The chemistry of **cyclobutanes**

The chemistry of cyclobutanes
Edited by Z. Rappoport and J. F. Liebman ISBN: 0-470-86400-1

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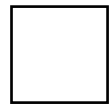

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Part 1

Edited by

ZVI RAPPOPORT

The Hebrew University, Jerusalem

and

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Dedicated to

Mario and **Tamar**

and to

Kifele

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Foreword

This is another volume in "The Chemistry of Functional Groups" series which deals with the chemistry of cyclic hydrocarbons and their derivatives. Earlier volumes dealt with "The Chemistry of Alkanes and Cycloalkanes" and "The Chemistry of the Cyclopropyl Group". The Cyclobutyl group occupies an intermediate position between these two groups.

The two parts of the present volume contain 23 chapters written by experts from 10 countries. They deal with theoretical and physical organic chemical aspects of cyclobutane derivatives including the aromaticity/antiaromaticity of derived unsaturated species, with their stereochemical aspects, their thermochemistry, and with the acidity and basicity of select derivatives. There are chapters on NMR, IR and mass spectra of cyclobutanes, on intermediates such as carbocations and cation radicals containing the cyclobutyl moiety and on the directing and activating effects of cyclobutane derivatives.

Several chapters deal with synthetic aspects of formation and use of cyclobutane derivatives, as well as with their rearrangements, their photochemistry, their organometallic derivatives and with their formation by solid state dimerization of olefins. The biomedically interesting pyrimidine dimers and their relevance to DNA damage is also discussed.

Special topics include highly unsaturated derivatives, arenocyclobutenes and cyclobutadiene, fluorocyclobutanes and polycyclic systems containing cyclobutanes such as cubanes, prismanes, ladderanes, bicyclo [2.1.0]pentanes and bicyclo [2.2.0]hexanes and other species. Unfortunately, two planned chapters, on cyclobutyl carbanions and anion radicals, and on structural chemistry did not materialize.

The literature coverage is up to 2004.

We would be grateful to readers who draw our attention to mistakes in the present volume, or to the omission of important chapters, which deserve to be included in such a treatise.

Jerusalem and Baltimore
August, 2004

ZVI RAPPOPORT
JOEL F. LIEBMAN

The Chemistry of Functional Groups Preface to the series

The series 'The Chemistry of Functional Groups' was originally planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the preparation, properties and reactions of the functional group treated and on the effects which it exerts both in the immediate vicinity of the group in question and in the whole molecule.

A voluntary restriction on the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series and in textbooks (i.e. in books which are usually found in the chemical libraries of most universities and research institutes), should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the topic. Therefore each of the authors is asked not to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level.

It is realized that no plan can be devised for a volume that would give a complete coverage of the field with no overlap between chapters, while at the same time preserving the readability of the text. The Editors set themselves the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters. In this manner, sufficient freedom is given to the authors to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter deals with the general and theoretical aspects of the group.

(b) Chapters discuss the characterization and characteristics of the functional groups, i.e. qualitative and quantitative methods of determination including chemical and physical methods, MS, UV, IR, NMR, ESR and PES — as well as activating and directive effects exerted by the group, and its basicity, acidity and complex-forming ability.

(c) One or more chapters deal with the formation of the functional group in question, either from other groups already present in the molecule or by introducing the new group directly or indirectly. This is usually followed by a description of the synthetic uses of the group, including its reactions, transformations and rearrangements.

(d) Additional chapters deal with special topics such as electrochemistry, photochemistry, radiation chemistry, thermochemistry, syntheses and uses of isotopically labeled compounds, as well as with biochemistry, pharmacology and toxicology. Whenever applicable, unique chapters relevant only to single functional groups are also included (e.g. 'Polyethers', 'Tetraaminoethylenes' or 'Siloxanes').

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the authors and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, some volumes may be published without giving consideration to the originally planned logical order of the chapters.

Since the beginning of the Series in 1964, two main developments have occurred. The first of these is the publication of supplementary volumes which contain material relating to several kindred functional groups (Supplements A, B, C, D, E, F and S). The second ramification is the publication of a series of 'Updates', which contain in each volume selected and related chapters, reprinted in the original form in which they were published, together with an extensive updating of the subjects, if possible, by the authors of the original chapters. A complete list of all above mentioned volumes published to date will be found on the page opposite the inner title page of this book. Unfortunately, the publication of the 'Updates' has been discontinued for economic reasons.

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editors.

The publication of this series would never have been started, let alone continued, without the support of many persons in Israel and overseas, including colleagues, friends and family. The efficient and patient co-operation of staff-members of the publisher also rendered us invaluable aid. Our sincere thanks are due to all of them.

The Hebrew University
Jerusalem, Israel

SAUL PATAI
ZVI RAPPOPORT

Sadly, Saul Patai who founded 'The Chemistry of Functional Groups' series died in 1998, just after we started to work on the 100th volume of the series. As a long-term collaborator and co-editor of many volumes of the series, I undertook the editorship and I plan to continue editing the series along the same lines that served for the preceeding volumes. I hope that the continuing series will be a living memorial to its founder.

The Hebrew University
Jerusalem, Israel
May 2000

ZVI RAPPOPORT

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
AIBN	azoisobutyronitrile
Alk	alkyl
All	allyl
An	anisyl
Ar	aryl
Bn	benzyl
Bu	butyl (C_4H_9)
Bz	benzoyl (C_6H_5CO)
CD	circular dichroism
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAH	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
EI	electron impact
ESCA	electron spectroscopy for chemical analysis
ESR	electron spin resonance
Et	ethyl
eV	electron volt

Fc	ferrocenyl
FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_3)
GLC	gas liquid chromatography
Hex	hexyl(C_6H_{13})
c-Hex	cyclohexyl(*c*-C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
i-	iso
ICR	ion cyclotron resonance
Ip	ionization potential
IR	infrared
LAH	lithium aluminium hydride
LCAO	linear combination of atomic orbitals
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	metal
M	parent molecule
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MNDO	modified neglect of diatomic overlap
MS	mass spectrum
n	normal
Naph	naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Pen	pentyl(C_5H_{11})
Ph	phenyl
Pip	piperidyl($C_5H_{10}N$)
ppm	parts per million
Pr	propyl (C_3H_7)
PTC	phase transfer catalysis or phase transfer conditions
Py, Pyr	pyridyl (C_5H_4N)

R	any radical
RT	room temperature
s-	secondary
SET	single electron transfer
SOMO	singly occupied molecular orbital
t-	tertiary
TCNE	tetracyanoethylene
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TLC	thin layer chromatography
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl or tetramethylsilane
Tol	tolyl(MeC_6H_4)
Tos or Ts	tosyl(*p*-toluenesulphonyl)
Trityl	triphenylmethyl(Ph_3C)
Xyl	xylyl($Me_2C_6H_3$)

In addition, entries in the 'List of Radical Names' in *IUPAC Nomenclature of Organic Chemistry*, 1979 Edition, Pergamon Press, Oxford, 1979, p. 305–322, will also be used in their unabbreviated forms, both in the text and in formulae instead of explicitly drawn structures.

CHAPTER 1

Cyclobutane — physical properties and theoretical studies

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I. INTRODUCTION

Cyclobutane is interesting because it provides a bridge between the very reactive (for a hydrocarbon) cyclopropane and the 'normal' cycloalkanes from cyclopentane to the larger cycloalkanes. Cyclopropane reacts readily with bromine to form 1,3-dibromopropane[1] and reacts with sulfuric acid to give 1-propylsulfuric acid[2]. Cyclobutane does not react with either of these reagents, but some cyclobutanes undergo C−C bond cleavage with transition metal species[3]. It is very difficult to cleave the C−C bonds of cyclopentane and the higher cycloalkanes.

II. CYCLOALKANE STRUCTURES AND BONDING

In order to understand these differences, it is helpful to examine the structures and energies of these compounds. Some data are given in Table 1. Cyclopentane undergoes

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TABLE 1. Structural data for some cycloalkanes

Compound	Observed			Calculated		
	r(C−C)	r(C−H)	H−C−H	r(C−C)	r(C−H)	H−C−H
Cyclopropane [a]	1.512(3)	1.083(3)	114.0(7)	1.509	1.083	115.1
Cyclobutane [b]	1.556(1)	1.091(1)		1.552	1.094 ax	109.3
					1.093 eq	
Cyclopentane [c]	1.546(1)	1.114		1.540	1.095	
Cyclohexane [d]	1.536(1)	1.097(2) ax		1.530	1.099 ax	106.9
		1.085(6) eq			1.096 eq	
Cyclopropene [e]	1.505(1)	1.085(1)		1.513	1.089	114.5
	1.293(1)	1.072(1)		1.304	1.077	
Cyclobutene [f]	1.566(3)	1.094(5)		1.568	1.094	109.2
	1.517(3)			1.517		
	1.342(4)	1.083(5)		1.351	1.086	

[a] Reference 5.
[b] Reference 6.
[c] Reference 4.
[d] Reference 9.
[e] R. J. Berry and M. D. Harmony, *Struct. Chem.*, **1**, 49 (1990).
[f] B. Bak, J. J. Led, L. Nygaard, J. Rastrup-Andersen and G. O. Sørensen, *J. Mol. Struct.*, **3**, 369 (1969).

pseudorotation in which the carbons undergo a motion perpendicular to the average plane without significant change in energy[4]. The average C−C bond length is only 0.013 Å greater than that of *n*-alkanes. In contrast, cyclopropane has markedly shorter C−C bond lengths[5] and cyclobutane has markedly longer C−C bond lengths[6].

The short bond lengths in cyclopropane are in part explained using the Coulson–Moffitt bonding model[7]. With nominal 60° C−C−C bond angles, it is not possible to form coaxial C−C bonds since the smallest interorbital angle for first row elements is 90°, corresponding to pure *p*-orbitals. The angle must be somewhat larger since a bond formed with just *p*-orbitals will be quite weak. They estimated an interorbital angle of 104°, corresponding to 80% *p*-character in the C−C bonds vs. the normal value of about 75% *p*-character. Thus, the bonds in cyclopropane are bent, and a better representation of the bond length would be given by the path of maximum electron density between the carbons (the bond path)[8] and it has been estimated to be 1.528 Å. It is approximately 0.008 Å shorter than the C−C bonds in cyclohexane[9].

The bent bonds in cyclopropane derivatives are readily observed in the results of X-ray crystallographic studies[10]. The output of such a study is an electron density map, and the maximum in electron density between two cyclopropane carbons lies outside the line of centers of the atoms. Bond angle bending based on *ab initio* calculations may be described in terms of the angle between the C−C bond paths at the C nucleus. With cyclopropane, the angle deviates from the conventional angle by 18.8° whereas the deviation for cyclobutane is only 6.7°[11].

The structure of cyclobutane presents some interesting questions. The C−C−C bond angle is 88°, indicating that it adopts a puckered structure[6]. This is probably due to a torsional interaction between two adjacent methylene groups. Ethane is known to prefer a staggered arrangement and the eclipsed arrangement is 3 kcal mol^{-1} higher in energy[12]. Planar cyclobutane, with a 90° C−C−C bond angle, has eclipsed methylene groups, resulting in considerable torsional strain. Puckering the ring leads to a reduction of this strain term, but at the same time the C−C−C bond angle is reduced, leading to increased bond angle strain. The equilibrium geometry is a result of the tension between these two

strain terms. The C−C−C bond angle (α) is related to the ring puckering angle (τ) by $\tan(\alpha/2) = \cos(\tau/2)$.

Another feature of the cyclobutane geometry is that the methylene groups are rotated inwards[13], whereas one might expect them to rotate outwards in order to reduce H···H non-bonded interactions. Bartell and Anderson have proposed that the methylene groups prefer a local C_{2v} geometry, and with bent C−C bonds this would result in the inward bend.

The most puzzling feature of the cyclobutane geometry is the long C−C bond length. This has been observed in a variety of cyclobutane derivatives, and C−C bond lengths cover a range of 1.521–1.606 Å depending on the substitution pattern, with an average of 1.554 Å[14]. With cyclobutane itself, the bond length is 1.556 Å[6].

The short C−C bond length in cyclopropane and the long length in cyclobutane may be explained by invoking a 1–3 C···C non-bonded repulsion[15]. It might be noted that this is contained in the Urey–Bradley force field[16]. Cyclopropane does not have such an interaction because all of the carbons are bonded to each other. Cyclobutane, on the other hand, has two 1–3 C···C non-bonded interactions with a relative small distance between the carbons. This repulsion will lead to a lengthening of the C−C bonds.

One might wonder if it would also lead to flattening of the ring in order to minimize this interaction. An *ab initio* calculation for cyclobutane gives a bond length of 1.555 Å and a CCC bond angle of 88°. If the C−C length is forced to be 1.536 Å (the cyclohexane bond length) and the geometry is again optimized, the CCC bond angle changes very little and the energy increases by only 0.4 kcal mol^{-1} [17]. Near their equilibrium values, bonds can initially be stretched with little increase in energy, but further extension become costly because of the quadratic nature of the bond stretching potential.

This proposal also explains why cyclopentane has C−C bonds a little longer than those in cyclohexane. The 1,3-C···C non-bonded distances are shorter in cyclopentane than in cyclohexane[18], leading to greater repulsion in the former. It also explains the observed 111° C−C−C bond angles in *n*-alkanes.

III. BOND STRENGTHS

The high *p*-character in the C−C bonds of cyclopropane must lead to high *s*-character in its C−H bonds. It is known that increasing *s*-character leads to shorter and stronger C−H bonds[19], and this is found with cyclopropane (Table 2). The force constant for stretching the C−H bond is significantly greater than for cyclobutane, the bond length is shorter, and the bond dissociation energy is greater than found with other cycloalkanes or open chain alkanes. The effect is further increased with cyclopropene. Here, the olefinic C−H bond would have an *s*-character approaching that of acetylene, and it is one of the few unsubstituted hydrocarbons that will undergo base catalyzed exchange of the vinylic C−H bonds with ROD to give C−D bonds[20].

The properties of the C−H bonds in cyclobutane are much closer to those of the other cycloalkanes, although there is an indication of somewhat increased *s*-character. The C−H bond lengths are somewhat shortened, and the bond dissociation energy is calculated to be 1.5 kcal mol^{-1} greater than in cyclohexane. Further information may be gained from the ^{13}C−H NMR coupling constants (see below).

TABLE 2. Cycloalkane C−H force constants and bond dissociation energies

Compound	k(C−H) [a]	BDE [b]
Cyclopropane	6.3	108.4
Cyclobutane	5.1 [c]	99.8 [c]
Cyclopentane	4.2 [c]	95.5 [c]
Cyclohexane	5.3 [c]	98.4 [c]

[a] Calculated at the B3LYP/6-311+G* level of theory.
[b] In kcal mol^{-1}; calculated at the G3B3 level of theory[17].
[c] Equatorial hydrogens.

IV. ENERGIES OF CYCLOALKANES

The heats of formation of a number of small cycloalkanes and related compounds have been determined via combustion calorimetry, and additional data have been obtained by measuring heats of hydrogenation. Some representative data are summarized in Table 3.

One item of interest with these compounds is the strain energy. This is defined as the difference in heat of formation between the compound of interest and that of an 'unstrained model'. The choice of this model has been the subject of some controversy, but almost any choice would be satisfactory as long as it is applied consistently. The values of the strain energies may differ, but the only quantities of importance are the relative values. The Franklin group equivalents[21] (Table 4) are frequently used for this purpose.

TABLE 3. Heats of formation and strain energies of cycloalkanes, gas phase, 25 °C, kcal mol^{-1}

Compound	ΔH_f	Strain energy	Reference
Cyclopropane	12.7 ± 0.1	27.5	a
Cyclobutane	6.6 ± 0.3	26.3	b
Cyclopentane	−18.3 ± 0.2	6.3	b
Cyclohexane	−29.5 ± 0.2	0.0	b
Cyclopropene	66.2 ± 0.6	52.2	c
Cyclobutene	37.4 ± 0.4	28.4	d
Cyclopentene	8.1 ± 0.3	4.0	e
Cyclohexene	−1.2 ± 0.1	0.4	f
1-Methylcyclopropene	58.6 ± 0.3	53.5	d
Methylenecyclopropane	29.1 ± 0.2	32.7	d
Bicyclo[1.1.0]butane	51.9 ± 0.2	63.9	d
Bicyclo[2.1.0]pentane	37.8 ± 0.3	54.8	g
Bicyclo[2.2.0]hexane	29.8 ± 0.3	51.7	g
Bicyclo[1.1.1]pentane	50.4	71.0	h
Cubane	148.7 ± 0.9	157.4	i
Bis(1,1′-bicyclo[1.1.1] pentane)	96.8 ± 1.2	126.9	j

[a] J. W. Knowlton and F. D. Rossini, *J. Res. Natl. Bur. Stand.*, **43**, 113 (1949).
[b] S. Kaarsaemaker and J. Coops, *Recl. Trav. Chim. Pays-Bas*, **71**, 261 (1952).
[c] K. B. Wiberg, W. J. Bartley and F. D. Lossing, *J. Am. Chem. Soc.*, **84**, 3980 (1962).
[d] K. B. Wiberg and R. A. Fenoglio, *J. Am. Chem. Soc.*, **90**, 3395 (1968).
[e] M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, *J. Am. Chem. Soc.*, **59**, 831 (1937).
[f] A. Labbauf and F. D. Rossini, *J. Phys. Chem.*, **65**, 476 (1961).
[g] W. R. Roth, F.-G. Klärner and H.-W. Lennartz, *Chem. Ber.*, **113**, 1818 (1980).
[h] Calculated energy: K. B. Wiberg, *J. Comput. Chem.*, **5**, 197 (1984).
[i] B. D. Kybett, S. Carroll, P. Natalis, D. W. Bonnell, J. L. Margrave and J. L. Franklin, *J. Am. Chem. Soc.*, **88**, 626 (1966). However, see V. V. Diky, M. Frenkel and L. S. Karpushenkava, *Thermochim. Acta* **408**, 115 (2003).
[j] V. A. Luk'yanova, V. P. Kolesov and V. P. Vorob'eva, *Russ. J. Phys. Chem.* (*Engl. Transl.*), **69**, 1908 (1995).

TABLE 4. Franklin's group equivalents, ΔH_f kcal mol^{-1} (25 °C)[a]

Group	Value
CH_3	−10.12
CH_2	−4.926
CH	−1.09
C	0.80
$=CH_2$	6.25
cis-CH=CH	18.88
C=CH	20.19

[a] Reference 21.

The strain energy of cyclobutane is then the heat of formation of cyclobutane less four times the CH_2 equivalent, or 26 kcal mol^{-1}. The strain energies of some compounds of interest are given in Table 3. Cyclohexane has essentially no strain energy; cyclopentane has a small strain energy which results from the partial eclipsing of adjacent C−H bonds plus some bond angle strain. Cyclopropane and cyclobutane have essentially the same strain energy, which at first appears surprising in view of the large difference in C−C−C bond angles, and the difference in hybridization. One factor that may contribute to the strain energy of cyclobutane is the cross-ring 1–3 repulsion between the methylene carbons[15]. This is not present in cyclopropane.

There is another important factor that contributes to the lack of difference in strain energies. The C−H bonds in cyclopropane are considerably stronger than those in cyclobutane. If the normal C−H bond dissociation energy (cyclohexane) is 98 kcal mol^{-1}, a C−H bond in cyclopropane is 10 kcal mol^{-1} stronger. With six C−H bonds, this could lead to a net stabilization that may approach 60 kcal mol^{-1}. The strain in the carbon skeleton of cyclopropane may approach 88 kcal mol^{-1}, and for cyclobutane, with 8 C−H bonds that are 1.5 kcal mol^{-1} stronger than those in cyclohexane, the strain may approach 38 kcal mol^{-1}. This is, of course, only a very rough approximation, but it does indicate that the strain in the skeleton of cyclopropane is significantly greater than that for cyclobutane, and that for the latter is still considerable.

The heats of hydrogenation of cyclopropene, methylenecyclopropane and cyclobutene are interesting. The heat of hydrogenation of cyclohexene (assumed to be unstrained) is just the difference in heat of formation between cyclohexene and cyclohexane, or 28 kcal mol^{-1}. Cyclobutene has a heat of hydrogenation of 31 kcal mol^{-1}, only a little larger than for cyclohexene, indicating that the introduction of a C=C bond does not lead to much of an increase in strain energy.

The value for cyclopentene is 26 kcal mol^{-1}, indicating that cyclopentene is less strained than cyclopentane because some of the methylene eclipsing strain in cyclopentane is relieved on going to cyclopentene.

Cyclopropene is remarkable, giving a heat of hydrogenation of 54 kcal mol^{-1}, 26 kcal mol^{-1} greater than that for cyclohexene. This effect is reduced somewhat in methylenecyclopropane and can be seen by comparing its heat of formation with the isomeric 1-methylcyclopropene. The origin of the high heat of hydrogenation has been attributed to the strong C−H bonds in cyclopropane that are lost on going to cyclopropene[22]. The effect is smaller with methylenecyclopropane since it has only one trigonal center in the ring.

V. NMR SPECTRA OF CYCLOALKANES

There are interesting differences between the NMR chemical shifts of cyclopropane, cyclobutane and the higher cycloalkanes (Table 5). The ^1H shift for cyclopropane is

TABLE 5. NMR chemical shifts (ppm)[a]

Compound	^{1}H		^{13}C	
	CH_2	=CH	CH_2	=CH
Cyclopropane	0.22		−2.6	
Cyclobutane	1.96		23.3	
Cyclopentane	1.51		26.5	
Cyclohexane	1.54		27.8	
Cyclopropene	0.93	7.06	2.3	108.9
Cyclobutene	2.57	6.03	31.4	137.2
Cyclopentene	2.28[b]	5.60	32.3[c], 22.7	130.2
Cyclohexene	1.96[b]	5.59	25.1[c], 22.6	126.9

[a] Reference 28.
[b] Protons adjacent to the double bond.
[c] Methylene carbons adjacent to the double bond.

TABLE 6. NMR ^{13}C−H coupling constants[a]

Compound	$J\,^{13}$C−H (Hz)	*%s*
Methane	125	25
Cyclopropane	161	32
Cyclobutane	134	27
Cyclohexane	123	25
Bicyclo[1.1.0]butane	153 (equatorial)	31
	169 (axial)	34
	205 (bridgehead)	41
Bicyclo[1.1.1]pentane	144 (methylene)	29
	164 (bridgehead)	33
Cubane	154	31
Cyclopropene[b]	228.2	46
Cyclobutene[b]	170	34
Cyclopentene[b]	162	32
Cyclohexene[b]	158	31

[a] Data were taken from Reference 28.
[b] Vinylic hydrogens.

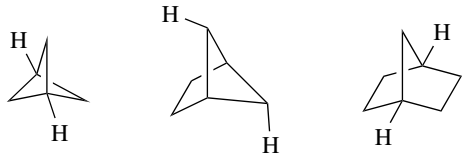
found to be remarkably upfield, and this has been used as a diagnostic for the presence of a cyclopropane ring[23]. Cyclobutane, on the other hand, has its ^{1}H band downfield from that in cyclohexane. The same trend is found with the ^{13}C shifts.

The upfield shift for cyclopropane has been attributed to a ring current associated with σ-aromaticity, and the downfield shift for the cyclobutane protons has been attributed to σ-antiaromaticity. The subject of σ-aromaticity has been the object of many studies. Recent work suggests that it is not a viable proposal[24]. Nevertheless, it is clear that cyclopropane has a higher than normal magnetic susceptibility[25]. In addition, the nucleus independent chemical shifts (NICS) at the center of the ring for cyclopropane is positive[26] and that for cyclobutane is negative[26, 27]. This quantity has been suggested as a test for aromaticity and antiaromaticity respectively, although the detailed origin of these shifts is not as yet understood.

The ^{13}C−H NMR coupling constants can be used to gain information on hybridization[28] and the empirical relationship $\%s = J\ ^{13}\text{C}-\text{H}/5$ has been proposed. The values of these coupling constants are given in Table 6 for cyclobutane and a number of other related

compounds, along with the empirically derived *%s* values. Again, the cyclobutane C−H bonds appear to have increased *s* character, but not as much as is found with cyclopropane.

Large long-range $^1H-^1H$ coupling constants are observed with cyclobutyl derivatives. One of the largest, 18 Hz, is found for the bridgehead hydrogens of bicyclo[1.1.1]pentane (**1**)[29]. With bicyclo[2.1.1]hexane (**2**), there is a 6 Hz coupling between the *endo* protons of the cyclobutane methylene groups[30]. When the distance is further increased as in bicyclo[2.2.1]heptane (**3**), the coupling between the bridgehead hydrogens is less than 1 Hz[31]. The coupling presumably involves the overlap of the backsides of the C−H bond orbitals which increases rapidly as the distance is decreased.

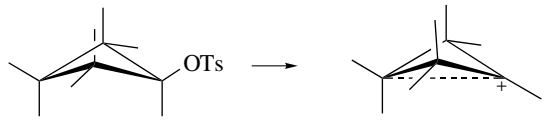


(1) **(2)** **(3)**

VI. CYCLOPROPYL AND CYCLOBUTYL CATIONS

In contrast to most reactions in which cyclopropane derivatives are more reactive than cyclobutanes, the opposite is true for solvolytic reactions. Cyclopropyl tosylate is relatively unreactive[32], and its lack of reactivity has been attributed to two factors. First, an S_N1 solvolytic reaction would normally lead to an increase in C−C−C bond angle at the reaction site as a carbocation is formed, and this is not possible with a cyclopropane ring[33]. As a result, there is an increase in strain energy. Second, the hybridization of the carbons in cyclopropane is close to that of ethylene, and vinyl halides are resistant to solvolytic reactions[34]. Despite its low reactivity, it is important to note that it is considerably more reactive than 7-norbornyl tosylate that has a 94° C−C−C bond angle[35]. It appears that the solvolysis of cyclopropyl tosylate is assisted by the development of allyl cation character in the transition state[36].

Cyclobutyl tosylate (**4**) would be expected to have reduced reactivity because it, again, will suffer an increase in strain on going to a carbocation due to the constrained C−C−C bond angles. However, it has a reactivity comparable to cyclopentyl tosylate[35b]. There is now much evidence that cyclobutyl cations are stabilized by an interaction with the cross-ring carbon, leading to a species that might be described as a 'bicyclobutonium ion' (**5**)[37] in which the cationic center is stabilized by an interaction with the cross-ring methylene group.

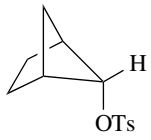


(4) **(5)**

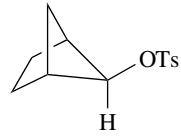
The cross-ring distance is important for such an interaction, and it increases in importance as the distance is decreased. Thus, 1-chlorobicyclo[1.1.1]pentane (**6**) is quite reactive[38].

5-Substituted bicyclo[2.1.1]hexane derivatives are interesting in that the *endo*-tosylate (**7**) is 10^6 times as reactive in solvolysis as the *exo*-tosylate (**8**)[39]. This indicates the need

(6)



(7)



(8)

for the remote carbon of the cyclobutane ring to be *anti* to the leaving group in order to have an assisted solvolysis. This appears to be a general feature of the solvolysis of bridged cyclobutyl derivatives[40].

In these solvolytic reactions, cyclopropylcarbinyl and cyclobutyl cations frequently are interconverted. B3LYP/6-311+G* calculations for the parent ions find both to be minima on the potential energy surface, with the cyclobutyl cation slightly lower in energy (1 kcal mol^{-1}). These ions are in rapid equilibrium, and substitution can easily shift the equilibrium composition[41].

VII. INTERACTION OF CYCLOPROPANE AND CYCLOBUTANE RINGS WITH ELECTRON-DEFICIENT CENTERS

The interaction of cyclopropane rings with a cationic site has been well studied. With dimethylcyclopropylcarbinyl cation, the 'bisected' conformer, in which the cationic *p*-orbital is aligned to interact with the bent C−C bonds of the cyclopropane ring, has a 14 kcal mol^{-1} lower energy than the 'perpendicular' conformer, with the latter being a transition state[42]. The ion can be observed by NMR spectroscopy. Methyl substitution at the cationic center is important since cyclopropylcarbinyl cation rearranges to a bridged cyclobutyl cation[38]. The interaction of the cyclopropane ring with an electron-deficient center is also seen with cyclopropylcarboxaldehyde where the rotational barrier is 6 kcal mol^{-1} [43]. The minimum energy conformers correspond to the 'bisected' arrangement and the transition state has the 'perpendicular' arrangement.

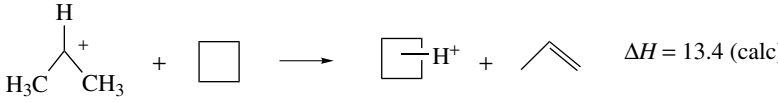
The interaction with a cationic site is much weaker with cyclobutane. The rotational barrier for cyclobutanecarboxaldehyde has not been measured, but calculations indicate it is only 0.8 kcal mol^{-1} [44]. There are two low energy conformers where the carbonyl group is eclipsed with either the adjacent hydrogen or one of the adjacent carbons. A rotamer corresponding to the perpendicular conformer is neither a minimum nor a transition state.

Dimethylcyclobutylcarbinyl derivatives (**9**) on solvolysis rearrange to cyclopentyl cations. Relief of strain energy is an important driving force, but this is reduced by the conversion of a tertiary cation to the usually less stable secondary cation[45]. In order to stabilize a cyclobutylcarbinyl cation enough to allow it to be observed by NMR, it was necessary to have two cyclopropane rings attached to the cationic center[46].

(9)

VIII. PROTONATED CYCLOPROPANES AND CYCLOBUTANES

As noted in the introduction, cyclopropanes are readily cleaved by electrophiles whereas this is not true with cyclobutanes. The reason is not thermodynamic since the overall heats of reaction are essentially the same. The proton affinity of cyclopropane has been measured and is 179 kcal mol^{-1} [47]. With cyclopropane, the interaction with protons is known to give a protonated cyclopropane intermediate[48]. The proton affinity of cyclobutane does not appear to have been measured, but B3LYP/6-311+G* calculations indicate its proton affinity to be about 10 kcal mol^{-1} lower than for cyclopropane. This is easily seen in the energies of transferring a proton from isopropyl cation to cyclopropane and cyclobutane:



The difference between these compounds has been studied by theoretical calculations. The protonation of cyclopropane may occur at either a corner or an edge, and experimental evidence suggests that both have comparable energies and can easily be interconverted. The structures of the two ions are shown in Figure 1, and are compared with the corresponding ions derived from cyclobutane[49]. Corner protonated cyclopropane is calculated to be the ground state, with the edge protonated ion being a transition state 4 kcal mol^{-1} higher in energy[17]. Edge protonated cyclobutane is calculated to be the ground state, with the corner protonated ion being a transition state 12 kcal mol^{-1} higher in energy.

Corner protonated cyclopropane is essentially a methyl cation coordinated with ethylene, whereas corner protonated cyclobutane appears like a methyl cation coordinated with a trimethylene diyl. Not surprisingly, the former has the lower energy. With the edge protonated ions, the proton in the C3 ion is able to achieve bonding with the strongly bent cyclopropane bonds thus remaining farther away from the carbons and not perturbing the geometry as much as is found with the C4 ion. Again, it is not surprising that the edge protonated cyclopropane has a lower energy than the edge protonated cyclobutane.

It should be noted that three- and four-membered rings may also be cleaved by nucleophiles with three-membered rings being more reactive than four-membered rings[50]. Here again, the overall change in energy is about the same for cyclopropane and cyclobutane, and the more facile cleavage of cyclopropanes must be due to an additional factor.

IX. THERMAL FORMATION OF CYCLOBUTANES BY CYCLOADDITION AND THERMAL CLEAVAGE

Cycloaddition of alkenes to form cyclobutanes normally does not occur thermally because at temperatures at which the reaction might occur the free energy of reaction is positive. This is a result of the unfavorable entropy effect that results from two molecules combining to form one. It can be overcome if the two C=C bonds are in the same molecule (**10**), and here the cyclobutane ring is formed on heating[51]. It is interesting to note that the free energy of cyclobutane at 25 °C is lower than that of two ethylenes, and if a suitable catalyst could be found, cyclobutane could be formed by the dimerization of ethylene.

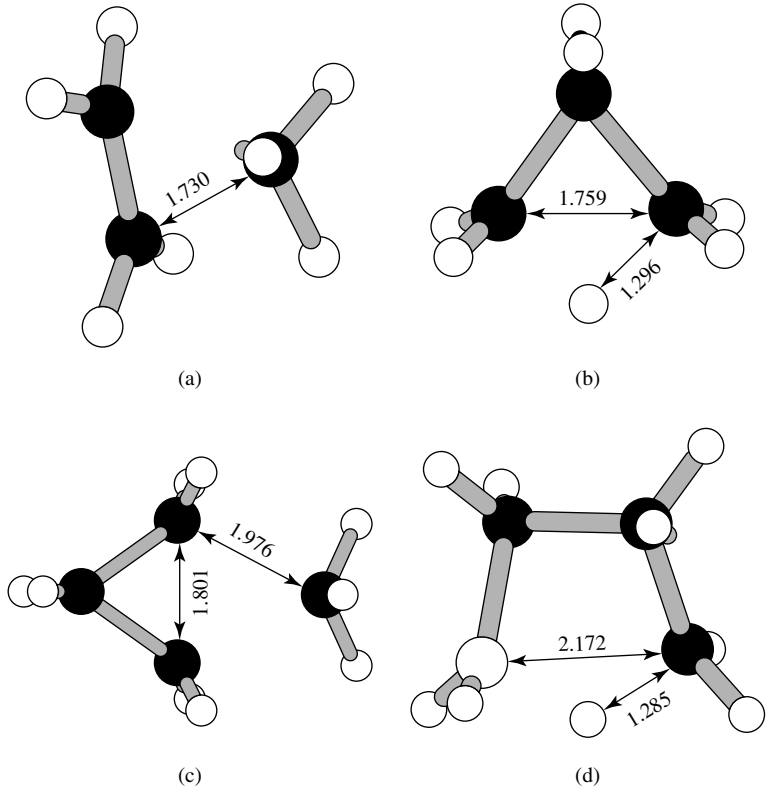
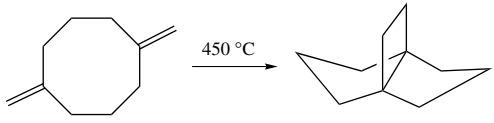


FIGURE 1. (a) Corner protonated cyclopropane, (b) edge protonated cyclopropane, (c) corner protonated cyclobutane and (d) edge protonated cyclobutane. The ground state structures are (a) and (d), whereas (b) and (c) are transition states. The structures are derived from B3LYP/6-311++G** calculations

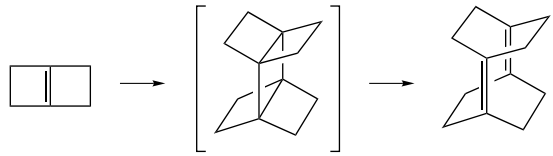
However, because of the negative entropy of dimerization, as the temperature is raised the free energy become less negative, and then positive at temperatures where cyclobutane is converted to ethylene.



(10)

This type of reaction can also occur if the double bond is sufficiently destabilized. As an example, bicyclo[2.2.0]hex(1,4)ene (**11**) undergoes dimerization at room temperature in dilute solution leading to a propellane (**12**) that undergoes cleavage to a diene (**13**). If the reaction is carried out using higher concentrations, the main product is a polymer.

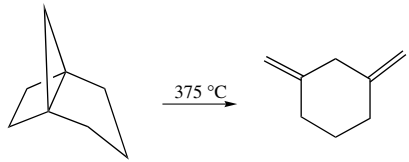
This is in accord with the initial combination of two molecules of the alkene to form a diyl. When the concentration is low, closure to the propellane predominates, but if the concentration is higher, the diyl can react with another diene to start polymerization.



(11) **(12)** **(13)**

The dimerization leading to a cyclobutane is best studied by examining the reverse process, the thermal cleavage of cyclobutanes. There is now good evidence that the reaction proceeds via the initial formation of a 1,4-diyl which then is cleaved to give two alkenes[52]. Thus, the thermolysis of cyclobutanes is initially very similar to the thermal cleavage of cyclopropanes[53], except that it occurs at higher temperatures.

The thermolysis of propellanes that contain a cyclobutane ring has received some study. There is a remarkable difference in the rates of reaction of the isomeric [3.2.1]propellane (**14**)[51] and [2.2.2]propellane (**15**)[54]. The former is quite unreactive whereas the known derivative of the latter undergoes cleavage at room temperature. One factor is the difference in strain energy, with the latter having the higher strain energy because it contains three small rings.



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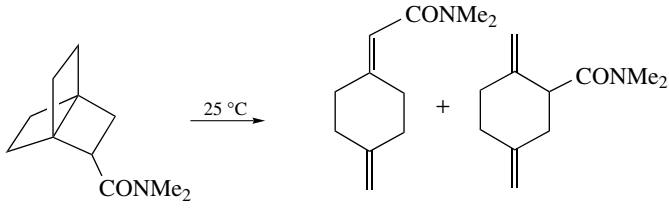


(15)

An examination of a series of [*n*.2.1]propellanes indicated that the rates of thermolysis are related to the relief of strain on going to a 1,4-diyl. However, there is possibly an additional factor that leads to the reactivity of [2.2.2]propellane. Stohrer and Hoffmann[55] have suggested that when the central propellane bond can be considerably extended as a result of the relative flexibility of the rings, the ground state will have an anti-symmetric combination of orbitals at the central carbons, and this could lead to an orbital symmetry allowed ring cleavage that would facilitate reaction. A related situation is found in the thermolysis of bicyclo[2.2.0]hexane[56].

It is interesting to note that the thermal reactivity of [2.2.2]propellanes is markedly reduced when the hydrogens are replaced by fluorines[57]. Fluorine substitution on a hydrocarbon can lead to either stabilization or destabilization, and with cyclobutane stabilization is found[58].

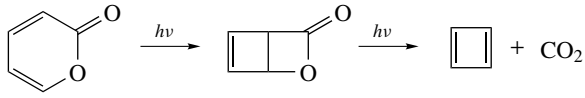
In contrast to the normal orbital symmetry forbidden ring opening of cyclobutanes, the thermal cleavage of cyclobutenes to butadienes occurs readily via a stereocontrolled reaction which provided one of the original pieces of evidence for orbital symmetry control[59].

The addition of ketenes to alkenes is a more facile process that occurs under relatively mild conditions. It has proven to be a useful method for the synthesis of cyclobutanones[60]. The mechanism of the reaction has received extensive study. A $[2\pi_s + (2\pi_s + 2\pi_s)]$ orbital symmetry allowed process has been proposed to account for the ease of reaction[61]. A recent study suggests that the reaction is relatively complex[62].

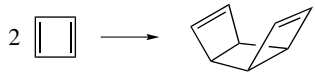
X. ANTIAROMATICITY IN CYCLOBUTADIENE

In 1967 Breslow and coworkers found that 1,2-diphenyl-3-benzoylcyclopropene undergoes base catalyzed H/D exchange at a slower rate than the corresponding cyclopropane by a factor of 6000[63]. This led to the proposal that the 4 π-electron cyclopropenyl anion is antiaromatic, i.e. it has an energy higher than that expected if it were simply non-aromatic[64]. This has been proposed to be a general feature of conjugated cyclic systems with $4n$ π-electrons[27].

Cyclobutadiene (**16**) is a $4n$ π-electron system, and thus potentially antiaromatic[65]. It has been a synthetic goal for many years, and it was finally observed via the photolysis of α-pyrone (**17**) in an argon matrix at 10 K[66,67]. It was found to be very reactive, and in the absence of other reagents it dimerizes to give the *syn* diene, **18**.



(17) **(16)**



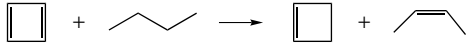
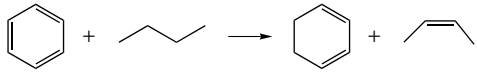
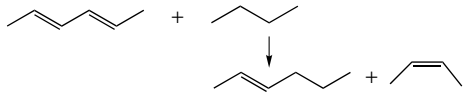
(18)

Subsequently, an iron carbonyl complex of cyclobutadiene was isolated and found to be stable at room temperature[68]. The diene could be regenerated by treatment with an oxidant, and if another compound were present, cycloaddition reactions could occur.

It has been possible to obtain an estimate of the heat of formation of cyclobutadiene via photoacoustic calorimetry[69]. This, along with theoretical estimates of its energy, allows the energy of the hydrogen transfer reaction to be calculated (Table 7). The enthalpy term for cyclobutadiene is large and negative, whereas with an aromatic compound such as benzene it is positive. A non-aromatic compound such as 2,4-hexadiene gives a small heat of reaction. The enthalpy change for the above reaction provides an estimate of the antiaromaticity of cyclobutadiene.

It is interesting to note that bicyclo[2.1.0]pent-2-ene has a heat of hydrogenation of 43 kcal mol^{-1} which is 10 kcal mol^{-1} larger than that for cyclobutene. This suggests that some antiaromatic character remains when one of the double bonds of cyclobutadiene is replaced by a cyclopropane ring[70].

TABLE 7. ΔH_f of several isodesmic reactions, kcal mol^{-1}

	ΔH obs[a]	calc[b]
	−41 ± 11	−34.4
	33.0 ± 0.4	34.4
	4.3 ± 0.6	5.3

[a] J. B. Pedley, *Thermochemical Data and Structures of Organic Compounds*, Thermodynamics Research Center, College Station, Texas, 1994. Hexenes: W. Fang and D. W. Rogers, *J. Org. Chem.*, **57**, 2294 (1992) and K. B. Wiberg and D. J. Wasserman, *J. Am. Chem. Soc.*, **103**, 6563 (1981).
[b] Derived from G2 energies, Reference 27.

Antiaromatic character is a major factor only with $4n$ systems such as cyclobutadiene, cyclopropentyl anion and cyclopentadienyl cation. The energetic effect decreases rapidly with increasing ring size[63]. A recent study of the origin of antiaromaticity concluded that the antisymmetry principle is a 'hidden variable' in the π-electron calculations and that it is responsible for the destabilization of the $4n\pi$-electron systems[71].

XI. SUMMARY

Cyclobutanes have a hybridization between that of cyclopropane and cyclopentane, and is closer to the latter. This is shown by the $^{13}C-H$ NMR coupling constants, the C−H bond lengths and the bond dissociation energies. Cyclobutanes are unique in that they can be formed from and be cleaved into two carbon species, and both orbital symmetry forbidden and allowed processes may occur. Cyclobutanes interact with electrophiles and electron deficient centers to a greater extent than cyclopentane, but to a much smaller degree than found with cyclopropanes.

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CHAPTER **2**

Antiaromaticity and aromaticity in carbocyclic four-membered rings

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I. INTRODUCTION AND SCOPE

Cyclobutadiene (**1**) has been a tremendous synthetic challenge for generations of organic chemists for more than one hundred years since the first unsuccessful attempts of Kekulé and Willstätter[1–5]. This small and deceptively simple, but extremely interesting molecular system was rightfully characterized by Cram and coworkers[6] as 'The Mona Lisa of Organic Chemistry', because of its ability to elicit wonder, to stimulate imagination and, last but not least, by its enigmatic elusiveness and numerous outstanding features. It is a highly reactive compound due to a very high energy content. The latter is a consequence of two fundamental notions contributing to destabilization of molecules: (i) Baeyer angular strain[7,8] and (ii) antiaromaticity of planar $4n\pi$ systems[9], where n denotes the number of π-electrons. Both of these facets are highly pronounced in archetypal cyclobutadiene. Neither of these two important concepts can be defined in an exact way, unfortunately, implying that deciphering the unusual properties of **1** in a quantitative manner is not an easy task due to unavoidable ambiguities. It is therefore not surprising that cyclobutadiene moiety was a subject matter of numerous experimental and theoretical studies and it is plausible to assume that this will be continued for good reasons in times to come. Namely, it turns out that this small molecule is a versatile building block in constructing larger molecular systems, exhibiting a full range of interesting novel properties.

It is the purpose of this chapter to describe the most important results pertaining to the spatial and electronic structure of **1** as well as compounds involving one or more cyclobutadiene subunits. After a brief history of the experimental work, which has led to various syntheses of **1** and its derivatives, particular emphasis will be laid on the physical nature of the chemical concept termed antiaromaticity. It will be shown that the latter has its origin in the facets of the 4π-electron network. Then, the effect of antiaromaticity of cyclobutadiene on the archetypal aromatic benzene moiety in some [4]annuleno[6]annulenes will be presented. It will be shown that juxtaposition of cyclobutadiene and benzene rings opens up the possibility of a fascinating phenomenon termed bond-stretch isomerism. Moreover, it will become apparent that derivatives of cyclobutadienes named [N]phenylenes represent a class of compounds, which offer a number of possibilities from the practical point of view, being theoretically very interesting at the same time. Finally, it will happen that in some fused systems as well as in some dications and dianions, cyclobutadiene exhibits highly pronounced aromatic character, implying that it represents an interesting case of molecular Janus. The emphasis is put on the 4π antiaromaticity of the cyclobutadiene ring, although there is some evidence about 8σ antiaromatic properties of the σ-framework in cyclobutane and larger molecules involving cyclobutane fragments. Studies of these systems are *in statu nascendi* and consequently they will be just briefly mentioned in the last paragraph.

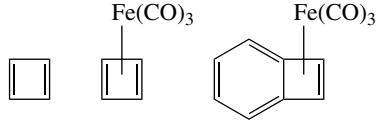
It should be mentioned that we shall focus on the theoretical results as a rule, which will be supported by the pertinent experimental findings whenever necessary. We would also like to emphasize that this is not a comprehensive review of all results published on

cyclobutadiene and related systems, since the literature is vast. Omission of some papers does not imply that they are uninteresting or irrelevant. Rather, they are not included due to space limitations.

II. ANTIAROMATICITY OF FOUR-MEMBERED RINGS

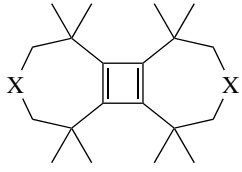
A. A Brief History of Cyclobutadiene

Cyclobutadiene C_4H_4 (**1**) was a synthetic target of many organic chemists. Their efforts were crowned in 1965 by brilliant preparative work of Pettit and coworkers,[10] who were able to obtain iron tricarbonyl complexes of cyclobutadiene (**2**) and benzocyclobutadiene (**3**). It is worth emphasizing that the former complex proved later to be a quite persistent compound surviving acidic, basic and reducing environments, as well as some mild oxidizing conditions. It turns out that **2** is sufficiently stable to tolerate a wide range of chemical transformations without destroying the cyclobutadiene skeleton, involving electrophilic substitution reactions[11] and deprotonation followed by trapping with electrophiles[12]. It is interesting to note that treatment of iron tricarbonylcyclobutadiene with cerium(IV) ammonium nitrate can oxidize the iron and liberate free cyclobutadiene[13–16].

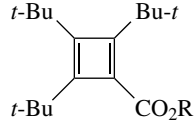


(1) **(2)** **(3)**

The next historical step toward trapping highly reactive **1** was its argon matrix isolation by Chapman and coworkers[17,18] and by Krantz and colleagues[19] at very low temperature (8 K). It turned out that cyclobutadiene was complexed with CO_2 imbedded in a matrix cavity, thus destabilizing the system. An important contribution to cyclobutadiene chemistry was made by Krebs and coworkers[20,21] by synthesizing cyclobutadiene moiety flanked by two seven-membered rings in **4** and **5** and by Masamune and coworkers[22,23] preparing esters **6** and **7**.



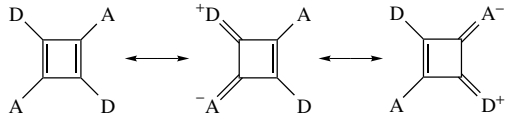
(4) X = S
(5) X = CH_2



(6) R = CH_3
(7) R = *t*-Bu

An interesting idea was also put forward by Roberts[24] as early as 1958, that cyclobutadiene moiety should be stabilized through a push–pull mechanism. It was realized in the laboratory later on by Gompper, Seybold and coworkers[25] by synthesizing tetrasubstituted cyclobutadiene **8** shown schematically in Figure 1, where the electron acceptor A and electron donor D are A = COOEt and D = NEt_2.

A partial electron transfer from the NEt_2 donating groups to the electron-withdrawing COOEt substituents is described by the corresponding resonance structures. It diminishes

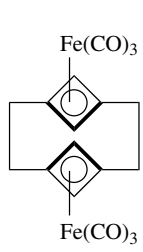


(8) A = COOEt
D = NEt_2

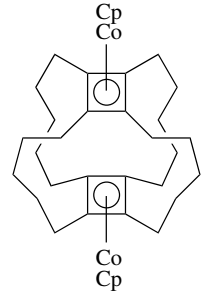
FIGURE 1. Push–pull resonance effect in donor–acceptor substituted cyclobutadiene

the local concentration of the π-electron density within the four-membered ring, thus alleviating its antiaromatic character. This mechanism is operative in spite of the fact that **8** is a nonplanar system. The X-ray structure[26] reveals that the acceptor substituents COOEt make a bending angle with the cyclobutadiene ring of 23°. This implies that the overlapping of the π-AOs in question is diminished by only 8% relative to the ideal planar case.

Cyclobutadiene moiety was found to provide an essential building block in metal-capped (cyclopentadienyl cobalt CoCp) cyclobutadienophanes and cyclobutadienosuperphanes[27] exemplified by **9** and **10**.

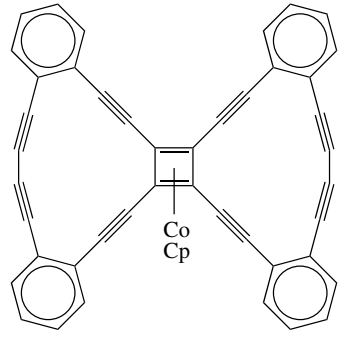


(9)

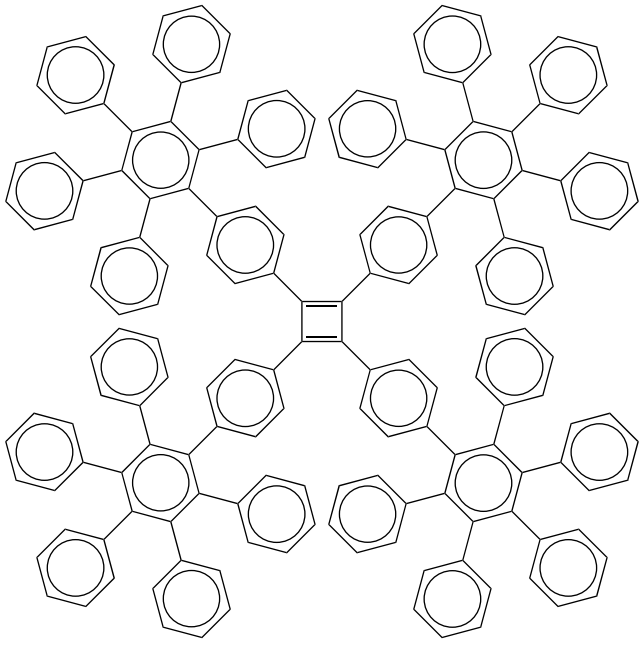


(10)

The cyclobutadienecyclopentadienylcobalt subunit is an essential ingredient of new carbon-rich structures, which lead to organometallic dendrimers and conjugated polyenes[28]. Characteristic examples are molecular butterfly **11** and dendrimer **12**.



(11)



(12)

Finally, it is worth noting that cyclobutadiene was also isolated inside Cram's hemicarcerand host container[29].

The spatial structure of cyclobutadiene and its symmetry was the subject matter of numerous deliberations in the past. Meticulous studies of its reactivity performed by Pettit and coworkers[10] provided a strong indication that the ground state is singlet and that the corresponding geometry is that of a planar rectangle. These ingenious conjectures were confirmed later by careful X-ray analyses of tetra-*t*-butylcyclobutadiene at low (−150 °C) temperature by Irngartinger and coworkers[30,31], and revealed a rectangular structure with alternating single and double CC bonds with a significant difference in their bond distances of 0.086 Å. A similar strong bond alternation was found in other substituted cyclobutadienes, such as **4**, **5** and **6**[32,33]. The rectangular four-membered ring structure was found to be consistent with photoelectron spectra (PES) of these molecules[34,35]. A more recent photoelectron spectrum of cyclobutadiene with partial resolution of the vibrational structure was reported by Kohn and Chen[36]. Their model calculations of the Franck–Condon envelope in the spectrum found very good accord for a transition from rectangular neutral cyclobutadiene to a rectangular radical cation $\mathbf{1}^{\bullet+}$. It is noteworthy in this respect that cyclobutadiene iron tricarbonyl complex does not form a symmetric top as assumed earlier[37,38]. Namely, this deceptively simple molecular system hides subtle secrets as revealed recently by its rotation–vibration spectrum. Indris[39] found that it belonged to a new point-symmetry group, which is homeomorphic, i.e. mathematically equivalent to the D_{6d} group.

Finally, it should be mentioned that automerization of cyclobutadiene from one rectangular structure (D_{2h}) to the other (D_{2h}) via a square transition structure of D_{4h} symmetry (Figure 2) was a topic of intensive discussions (see later) since Carpenter's hypothesis[40] that it could be realized through tunneling of the heavy carbon nuclei.

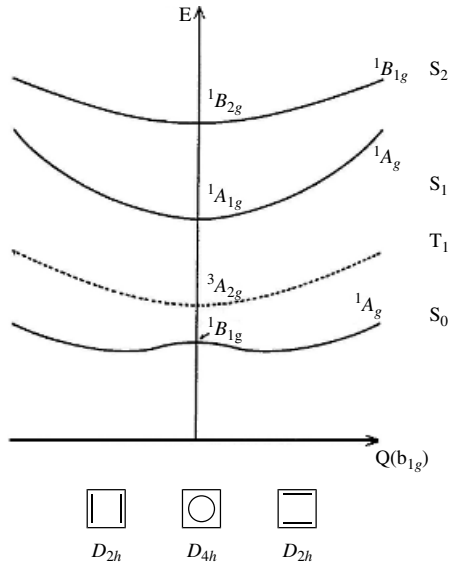


FIGURE 2. Schematic representation of the ground state S_0 and the lowest excited states T_1, S_1 and S_2 of cyclobutadiene and their change along the distortion coordinate related to the automerization reaction. Reproduced by permission of Elsevier B.V. from Reference 46

The barrier height was experimentally estimated[40,41] to be between $1.6 - 10$ kcal mol^{-1}. The ^{13}C NMR experiment shows that the equilibrium of two equivalent structures of tri-*t*-butylcyclobutadiene cannot be frozen out even at a very low temperature of 88 K, thus suggesting that the activation energy of this process is no more than 2.5 kcal mol^{-1} [42]. This experimental NMR work was the first spectroscopic proof of the conjecture that cyclobutadiene is not a resonance stabilized square structure, but rather a tautomeric equilibrium between two rectangular singlet ground-state structures.

B. Theoretical Investigations of the Structure of Cyclobutadiene

Theoretical description of the electronic structure of cyclobutadiene has been vividly discussed in the past. Most of the *ab initio* calculations have correctly predicted that the rectangular singlet is the ground state of this elusive molecule in accordance with the Jahn-Teller effect[43–46]. This obvious violation of Hund's rule was rationalized by Kollmar and Staemmler[46,47] by dynamical spin polarization, which is best understood if electrons with different spins are placed in different spatial molecular orbitals (MOs). Since repulsion between two electrons of the same spin placed in different MOs is smaller than that between α and β spin electrons, this simple mechanism introduces a specific correlation, which leads to a more stable singlet. The idea of dynamical spin polarization of Kollmar and Staemmler was an important contribution in a conceptual sense. Subsequent *ab initio* MO studies have convincingly shown that the ground state of **1** is rectangular singlet and that square geometry represents a transition state for bond flipping automerization[48,49]. Čarsky and coworkers[50] used several *ab initio* methods to estimate the barrier height for automerization of **1** and a variant of the coupled cluster approach gave 9.5 kcal mol^{-1} as the best estimate. A comprehensive study of the electronic structure of the ground state of **1** and several low-lying excited states was undertaken by Balková and Bartlett[51] by using

a multireference coupled cluster method with single and double excitations (MR-CCSD) augmented in a later stage by a noniterative inclusion of the triple excitations (MR-CCSD(T)). The energy barrier for the interconversion between the two rectangular ground-state structures was estimated to be 6.6 kcal mol^{-1}. It is remarkable that full inclusion of the triple excitations (CCSDT) lowered the barrier height by only 0.2 kcal mol^{-1} [51]. The ordering of electronic states for the square transition-state geometry is determined with the singlet being 6.9 kcal mol^{-1} lower than the triplet. These results were used as benchmark values for other theoretical treatments like a multireference Brillouin–Wigner coupled cluster (MR-BWCC) theory[52]. It was concluded that extension of the basis set is more important than going beyond CCSD(T) or MR-BWCCSD theory. We shall come back to the problem of the singlet–triplet splitting again in Section III.A, since it is a characteristic signature of antiaromaticity. A comparison of the density functional (DFT) procedures in deciphering energetic properties of **1** against the *ab initio* results was presented by Sancho-Garcia and coworkers[53]. The tunneling in the automerization of **1** was estimated to occur at the rate $k = 2.5 \times 10^{11}$ s^{-1} by the simple GVB/4-31G* method[54]. This and other theoretical estimates[55,56] seem to overestimate the influence of the carbon atom tunneling in splitting vibrational frequencies as revealed by neat analysis of the Raman spectrum of matrix-isolated cyclobutadiene as a function of temperature[57,58]. It is possible, however, that the matrix environment including CO_2 and CO ingredients contributes to hindering of the tunneling automerization and it might play a role in some other chemical transformation of **1** as elaborated recently by Zuev and coworkers[59].

With a renaissance of the valence bond (VB) theory[60] a lot of attention has been focused on the bonding features of cyclobutadiene. This conceptually simple theory, which is close to chemical intuition and the Lewis concept of the chemical bond, has been condemned for quite some time for two reasons: (a) computational complexities and (b) 'failures' in discussing bonding properties of some crown cases like cyclobutadiene and O_2 or in describing behavior of some aromatic and antiaromatic ions. The latter was refuted by Shaik and Hiberty[61a] in a convincing way. Shaik, Hoffmann, Hiberty, Cooper and others[61,62] rightfully point out that VB is equally as fundamental as MO theory, and that it is consequently justified to switch between the MO and VB representations when necessary, according to the nature of the particular problem being addressed. As to the computational feasibility of the VB methods, it is much improved by the recent development of the computational science. Consequently, VB theory became a viable alternative to the modern molecular orbital methods of quantum chemistry. Spin-coupled formulation of the valence bond theory contributed considerably to recent advances in this conceptually important theoretical approach[60,62], which is both accurate and pictorial. Briefly, it combines features of classical VB and self-consistent MO theories adopting the correlated one-electron-per-orbital model with simultaneous optimization of the orbital and spin part of the total molecular wave function[62]. A striking characteristic of the SC-VB method is that the orbitals are nonorthogonal and that they are unique once optimized, i.e. they are not invariant to any kind of linear transformations. Moreover, they are highly localized on the atomic centers. For example, the π-electron orbitals in aromatic benzene are atomic localized $2p\pi$-orbitals centered on each carbon exhibiting small but extremely important polarization to the two nearest-neighbor C atoms. In the antipodal cyclobutadiene in its symmetrical D_{4h} square structure and the lowest energy singlet $^1B_{1g}$ state, two electrons are coupled along a diagonal and form an 'almost perfect triplet'. Such highly unusual spin pairing is termed an 'antipair'[62]. Two such 'antipairs' along two diagonals of the square are combined to a net singlet. As the molecule distorts to its equilibrium rectangular geometry the spin-coupled orbitals rapidly assume spin coupling pattern expected for two separate C=C double bonds. It is found that this picture occurs in all antiaromatic molecules.

C. The Physical Origin of Antiaromaticity of Cyclobutadiene

The term antiaromaticity was introduced by Breslow, who found together with Brown and Gajewski[63] that 1,2-diphenyl-3-benzoylcyclopropene underwent base-catalyzed H/D exchange at a slower rate than the corresponding cyclopropane by a factor of 6000. This finding was rationalized by destabilization of the 4π anion formed within the cyclopropene moiety and was baptized accordingly as 'antiaromaticity' in contrast to aromaticity of 6π-electrons found, for example, in benzene. Both notions—aromaticity and antiaromaticity—evaded exact definition, because they cannot be reduced to a quantum mechanical expectation value in a direct and unique way. In spite of that, they affect a large number of properties of a myriad of molecules. Concomitantly, their quantitative description is very important and it is necessarily a matter of convention. Therefore, the problem of aromaticity and antiaromaticity should be reduced to the least arbitrary definitions of these features of immense importance. Thermodynamically, antiaromaticity of **1** is customarily estimated by a comparison with the open-chain strain-free polyenes. A good vehicle in exploring antiaromaticity is provided by homodesmotic chemical reactions introduced by George and coworkers[64]. The simplest such reaction related to **1** is equation 1,

$$\mathbf{1} + 2 \text{ ethylenes} = 2(\textit{trans}\text{-1,3-butadiene}) + E(\mathrm{d})_{\mathbf{1}} \tag{1}$$

Here, the names of the molecules entering the *gedanken* ring-opening reaction signify their total molecular energies. Since **1** is a small highly strained ring, the destabilization energy $E(\mathrm{d})_{\mathbf{1}}$ has two components (equation 2):

$$E(\mathrm{d})_{\mathbf{1}} = E(\mathrm{s})_{\mathbf{1}} + E(\mathrm{an})_{\mathbf{1}} \tag{2}$$

where $E(\mathrm{s})_{\mathbf{1}}$ and $E(\mathrm{an})_{\mathbf{1}}$ denote the angular strain and the antiaromatic decrease in stabilization energies, respectively, defined as positive quantities. It is convenient to break down the total destabilization energy into three contributions (equation 3):

$$E(\mathrm{d})_{\mathbf{1}} = E(\mathrm{d})_{\mathrm{HF}} + E(\mathrm{d})_{\mathrm{corr}} + E(\mathrm{d})_{\mathrm{ZPVE}} \tag{3}$$

where $E(\mathrm{d})_{\mathrm{HF}}$, $E(\mathrm{d})_{\mathrm{corr}}$ and $E(\mathrm{d})_{\mathrm{ZPVE}}$ stand for the Hartree–Fock, electron correlation and the zero-point vibrational energy, respectively. It can be shown that $E(\mathrm{d})_{\mathrm{corr}}$ and $E(\mathrm{d})_{\mathrm{ZPVE}}$ are small and of opposite sign, thus practically canceling out[65]. Consequently, they can be disregarded in the first approximation, implying that the analysis of antiaromaticity can be reduced to the HF level. For interpretative purposes, it is useful to resolve the total molecular HF energies into components (equation 4),

$$E(\mathrm{HF}) = E(\mathrm{T})_{\mathrm{HF}} + E(\mathrm{V})_{\mathrm{HF}} \tag{4}$$

where T and V denote the kinetic and potential energy terms, respectively. They can be further decomposed as shown in equations 5a and 5b,

$$E(\mathrm{T})_{\mathrm{HF}} = E(\mathrm{T})^{\sigma}_{\mathrm{HF}} + E(\mathrm{T})^{\pi}_{\mathrm{HF}} \tag{5a}$$

$$E(\mathrm{V})_{\mathrm{HF}} = V^{\sigma}_{\mathrm{ne}} + V^{\pi}_{\mathrm{ne}} + V^{\sigma\sigma}_{\mathrm{ee}} + V^{\pi\pi}_{\mathrm{ee}} + V^{\sigma\pi}_{\mathrm{ee}} + V_{\mathrm{nn}} \tag{5b}$$

The kinetic energy can be rigorously separated into the σ- and π-contributions due to the one-electron nature of the Laplacian. This is not the case for the potential energy $E(\mathrm{V})_{\mathrm{HF}}$, where one can distinguish two types of interaction between electrons. Whereas the nuclear–electron attractions can be exactly delineated for the σ- and π-electrons, the repulsions between the σ- and π-electrons $V^{\sigma\pi}_{\mathrm{ee}}$ and the nuclear term V_{nn} cannot

be dissected in a unique way into two contributions related to the σ- and π-electron frameworks. It should be pointed out that the nuclear repulsion V_{nn} is determined by the minima on the Born–Oppenheimer potential energy hypersurfaces, which in turn depend on both σ- and π-electrons in a complicated manner. The HF calculations[65] performed by Dunning's cc-pVDZ and cc-pVTZ basis sets[66] are summarized in Table 1. One should emphasize that the approximate HF wavefunctions are scaled in order to satisfy the virial theorem[67–69]. It appears that the kinetic energy of the σ-electrons stabilizes **1** relative to the open chain, while the opposite holds for the π-electrons. The σ-electrons prevail as far as the kinetic energy is concerned, yielding $\Delta E(\mathrm{T})_{\mathrm{HF}} = -83.5(-82.5)$ kcal mol^{-1} to the stability of **1** as obtained by the HF/cc-pVDZ (HF/cc-pVTZ) calculations, where Δ denotes contribution to $E(\mathrm{d})_{\mathbf{1}}$ according to equation 1. The potential energy terms, however, completely change this picture and lead to destabilization of **1** as discussed below.

In order to obtain manageable numbers, let us group the potential energy terms as $V^{\sigma} = [V_{ne}^{\sigma} + V_{ee}^{\sigma\sigma} + V_{nn}]$ and $V^{\pi} = [V_{ne}^{\pi} + V_{ee}^{\pi\pi} + V_{ee}^{\sigma\pi}]$. In other words, the nuclear repulsion V_{nn} is associated with the σ-framework, whereas the repulsion between the σ- and π-electrons is apportioned to the π-framework, exactly as assumed in the early theories of the π-electron systems[70]. Neither of these two assumptions is quite justified. The nuclei are indeed immersed in the σ-electron 'sea', while the π-electrons are subsequently imposed on the so-formed σ-skeleton. However, the role of the π-electrons in determining the geometries of the planar molecules cannot be neglected. The spatial structures of molecules are defined by the equilibrium distribution of the nuclei corresponding to true minima on the Born–Oppenheimer energy hypersurface (PES), implying that the π-electrons also participate in determining the amount of the nuclear repulsion V_{nn} at the equilibrium distances. However, their share is not easy to decipher and, to be more specific, it cannot be quantified in an unequivocal way. The simplest 'solution' is to attach V_{nn} to the σ-framework. By the same token, one cannot simply ascribe the σ/π electron repulsion to the π-electrons only. Nevertheless, it is of some interest to see the outcome of the σ/π potential energy partitioning defined above. It follows that the V^{σ} and V^{π} contributions to the destabilization energy $E(\mathrm{d})_{\mathbf{1}}$ are -133.1 (-140.9) and 300.2 (306.2) kcal mol^{-1}, meaning that the V^{π} term prevails. Moreover, it also overcomes the stabilization effect of the kinetic energy given by $\Delta E(\mathrm{T})_{\mathrm{HF}} = -83.5(-82.5)$ kcal mol^{-1}. The total potential energy contribution to the $E(\mathrm{d})_{\mathbf{1}}$ is 167.0 (165.0) kcal mol^{-1}, which is twice the absolute value of $\Delta E(\mathrm{T})_{\mathrm{HF}}$ as required by the virial theorem. Concomitantly, $E(\mathrm{d})_{\mathbf{1}}$ is 83.5 (82.5) kcal mol^{-1}. It follows that the destabilization energy of **1** is due to the unfavorable intramolecular interactions of the π-electron framework. Although the employed σ/π partitioning is not free of criticism as mentioned above, it qualitatively gives the right answer. Some other partitioning schemes have led to the same conclusions[65]. It is therefore fair to infer that cyclobutadiene **1** is destabilized relative to a zig-zag 1,3-butadiene open-chain polyene due to its specific π-framework.

It is interesting to point out that $E(\mathrm{d})_{\mathbf{1}}$ does not depend on the choice of the zig-zag polyene in the homodesmotic reactions. For example, the use of the all-*trans*-hexatriene in equation 6

$$\mathbf{1} + \text{ethylene} = \text{all-}trans\text{-1,3,5-hexatriene} + E(\mathrm{d})'_{\mathbf{1}} \tag{6}$$

gives $E(\mathrm{d})'_{\mathbf{1}} = 84.0$ kcal mol^{-1} for the HF/cc-pVDZ calculation, which is in good agreement with the earlier estimate at the same theoretical level $E(\mathrm{d})_{\mathbf{1}} = 83.5$ kcal mol^{-1}.

In order to pin down the antiaromatic part $E(\mathrm{an})_{\mathbf{1}}$ of the total destabilization energy, one has to estimate the strain energy $E(\mathrm{s})_{\mathbf{1}}$ of cyclobutadiene. This is possible by making use of homodesmotic reaction 7,

$$\text{cyclobutane} + 4 \text{ propanes} = 4\ anti\text{-butanes} + E(\mathrm{s})_{\mathbf{1}} \tag{7}$$

TABLE 1. The Hartree–Fock energy components of ethylene, *trans*-1,3-butadiene and cyclobutadiene (**1**) (in au) and their contributions to the destabilization energy $E(\mathrm{d})_{\mathbf{1}}$ (in kcal mol^{-1})

Energy Component	Ethylene	1,3-Butadiene	**1**	Ethylene	1,3-Butadiene	**1**	Contributions to $E(\mathrm{d})_{\mathbf{1}}$	
	cc-pVDZ			cc-pVTZ			cc-pVDZ	cc-pVTZ
$E(\mathrm{T})^{\sigma}_{\mathrm{HF}}$	76.10052	151.01005	149.51328	76.13541	151.06577	149.56455	−191.9	−185.8
$E(\mathrm{T})^{\pi}_{\mathrm{HF}}$	1.93969	3.92497	4.14314	1.92901	3.91303	4.13272	108.3	103.3
V^{σ}_{ne}	−232.87868	−526.02940	−512.84656	−233.36107	−527.17546	−513.94118	46092.9	46239.0
V^{π}_{ne}	−15.57667	−42.37382	−43.76151	−15.55955	−42.41022	−43.80953	6170.1	6207.1
$V^{\sigma\sigma}_{\mathrm{ee}}$	46.38920	119.31487	113.78523	46.60432	119.82970	114.27611	−20121.5	−20189.6
$V^{\pi\pi}_{\mathrm{ee}}$	0.44953	1.73034	1.96508	0.44651	1.72687	1.96211	−374.3	−375.6
$V^{\sigma\pi}_{\mathrm{ee}}$	11.98478	33.45378	34.18010	11.97669	33.49453	34.23045	−5495.6	−5525.3
V_{nn}	33.55143	104.03422	99.36483	33.76425	104.57698	99.88750	−26104.5	−26190.3

The HF/cc-pVDZ calculation yields $E(s)_{\mathbf{1}} = 26.8$ kcal mol^{-1} as the angular strain energy of cyclobutane (**13**). It is of some interest to dissect $E(s)_{\mathbf{1}}$ into separate kinetic and potential energy terms (equation 8),

$$E(s)_{\mathbf{1}} = \Delta E(T)_s + \Delta E(V)_s \tag{8}$$

where Δ signifies a difference between the corresponding terms of cyclobutane and four open-chain *anti*-butanes corrected by four propanes as required by equation 7. It appears that the total kinetic energy stabilizes cyclobutane just as was the case of the total destabilization energy $E(d)_{\mathbf{1}}$ (Table 1). More specifically, $\Delta E(T)_s = -26.5$ kcal mol^{-1}, whereas $\Delta E(V)_s$ is 53.3 kcal mol^{-1}, resulting in the total strain energy of 26.8 kcal mol^{-1}. Resolution of the $\Delta E(V)_s$ into three components $\Delta E(V_{ne})_s + \Delta E(V_{ee})_s + \Delta E(V_{nn})_s$ shows that the unfavorable nucleus–electron attraction is the cause of the angular strain in **13**. A comprehensive study has conclusively shown that this was generally the case[71] and that it can be reduced to bent bonds. A similar homodesmotic reaction (equation 9)

$$\text{cyclobutane} + 4 \text{ ethanes} = 4 \text{ propanes} + E(s)'_{\mathbf{13}} \tag{9}$$

shows that the strain energy $E(s)'_{\mathbf{13}} = 26.8$ kcal mol^{-1} at the HF/cc-pVDZ level is very close to $E(s)_{\mathbf{13}}$. Consequently, it is safe to conclude that strain is not strongly dependent on the choice of the homodesmotic reaction either. There is just one additional problem to be solved: the strain energy in **1** is larger than in **13**, since the bond bending in the former molecule is more pronounced due to the presence of the double bonds in the four-membered ring[72]. It occurs that bond bending is larger in cyclopropene vs. cyclopropane or in cyclobutene compared to cyclobutane. In order to get an idea about the increase in the strain energy of **1**, let us consider the heats of hydrogenation of cyclohexene and cyclobutene. The corresponding experimental values are -28.3 and -30.7 kcal mol^{-1}. The difference 2.4 kcal mol^{-1} corresponds to a strain energy release in going from cyclobutene to cyclobutane[73]. It follows that the strain energy in **1** is higher than that in **13** by some 5 kcal mol^{-1}. Thus we arrive at an estimate of $E(s)_{\mathbf{1}}$ being about 31.8 kcal mol^{-1}, which is in excellent agreement with the experimental result of 32 ± 2 kcal mol^{-1}, as reported by Deniz and coworkers[74]. Therefore, the antiaromaticity of **1** calculated relative to two *trans*-1,3-butadienes is $E(an)_{\mathbf{1}} = 51.8$ kcal mol^{-1}, in good agreement with the experimental value of 55 ± 11 kcal mol^{-1}, which unfortunately has a large error margin[74]. The antiaromatic destabilization per π-electron is 13 kcal mol^{-1} according to our calculation[71]. It follows that the π-electron antiaromaticity contribution is significantly larger than the σ-electron strain participation in the overall destabilization of **1**. It should be mentioned in this respect, however, that *trans*-1,3-butadiene does possess some π-electron delocalization energy, which was disregarded in the foregoing discussion. As a matter of fact, it is by no means negligible as shown by Carreira[75]. According to the spectroscopic measurements of the torsional potential of *trans*-1,3-butadiene, the conjugation energy is approximately 7 kcal mol^{-1}. If the conjugation energy of two *trans*-1,3-butadienes is subtracted from $E(an)_{\mathbf{1}}$, one obtains the antiaromatic destabilization of 38 kcal mol^{-1}, which is still larger than the σ-strain energy of **1**, albeit to a lesser extent. This is at variance with analysis of Mo and coworkers[76], who claimed that the destabilization energy $E(d)_{\mathbf{1}}$ was a direct outcome of the σ frame's ring strain. It is interesting to mention that our final estimate of $E(an)_{\mathbf{1}} = 38$ kcal mol^{-1} is in reasonable agreement with the G2 estimate of 40.6 ± 1.7 kcal mol^{-1} obtained by using localized C=C double bonds as a reference level[77]. On the basis of these results one concludes that the antiaromatic destabilization of **1** per π-electron is close to 10 kcal mol^{-1}. Finally, we would like to issue a caveat regarding the kinetic energy of the π-electrons as a good criterion of

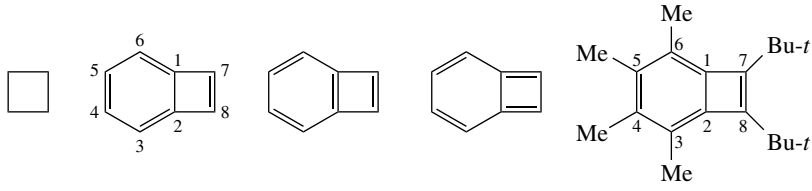
antiaromaticity used within the molecular virial theorem as suggested by Ichikawa and Ebisawa[78]. The reason for the criticism is that the virial theorem does not hold for the σ- and π-electrons separately. Consequently, the kinetic energy $E(\mathrm{T})^{\pi}_{\mathrm{HF}}$ taken with a negative sign cannot be identified with the total energy of the π-electrons. The same holds for the $E(\mathrm{T})^{\sigma}_{\mathrm{HF}}$ term and the σ-framework. If the σ- and π-components of the kinetic energy were considered as true energies of the σ- and π-electrons, then it would follow according to the virial theorem that the σ-electrons are a predominating factor in determining the total destabilization energy of **1**. This would be, however, erroneous, as our analysis expounded above has conclusively shown.

D. Fused Cyclobutadienes

1. The spatial and electronic structure of [4]annuleno[6]annulenes

Fused planar systems involving juxtaposed cyclobutadiene and benzene moieties provide an interesting class of the extended π-electron systems, which exhibit unusual properties. This is not surprising, because cyclobutadiene ring and benzene possess different structural and electronic demands. Since **1** is a small highly strained ring, its fusion to benzene(s) will undoubtedly lead to a spillover of the strain to the aromatic fragments(s). Moreover, **1** will try to release the unfavorable 4π antiaromatic destabilization at the expense of the neighboring benzene moiety. On the other hand, the aromatic fragment(s) will tend to diminish perturbation imposed by annelation of one or several cyclobutadiene small rings. The resulting geometries and the electronic properties will therefore be results of an interplay between the diametrically opposed tendencies—relief of antiaromaticity and retention of aromaticity—which promises a plethora of interesting results and new features. Some important consequences of these competing factors will be exemplified by considering the problem of the bond-stretch isomerism in benzocyclobutadiene (**14**), benzo[1,2:4,5]dicyclobutadiene and some related systems as well as a discussion of [*N*]phenylenes, which in turn aroused a lot of interest in the last two decades for very good reasons.

a. Benzocyclobutadiene: The Mills–Nixon effect. In order to take control over a highly pronounced reactivity of **1**, its annelation to larger and more stable rings has been attempted. The simplest example is given by benzocyclobutadiene **14**, which is still a quite reactive species. Hence, it has been trapped and isolated only in an Ar matrix at very low temperature (20 K) and its IR, UV-visible[79], photoelectron[80] and NMR[81] spectra have been recorded and examined. Much of the chemistry of **14** and its derivatives has been described by Toda and Garratt[82]. The X-ray structure of bis-(7,8)-*t*-butyl-tetramethylbenzocyclobutadiene **15** was determined by Winter and coworkers[83]. All experimental evidence was in favor of structure **14** with one notable exception: the chemical shifts were interpreted by making use of the distribution of the double bonds indicated



(13) **(14)** **(14a)** **(14b)** **(15)**

by the resonance structure **14b**[81], which turned out to be erroneous (*vide infra*). Benzocyclobutadiene is an intriguing planar antiaromatic 8π system possessing two annelated rings. Intuitively, one would expect that its ground state has a structure **14** involving a benzene fragment and an almost isolated double bond, instead of 8π electrons delocalized over the molecular perimeter as suggested by **14b**. The (resonance) structure **14a** does not look like a viable isomer either. Several theoretical studies show that this is indeed the case. The modern valence bond (VB) theory in its spin-coupled (SC) form based on the complete active space self-consistent field (CASSCF) optimized geometry is consistent with a distorted benzene ring and a peripheral localized double bond[84]. Each of the eight spin-coupled π-orbitals is found to be well-localized at one carbon atom only, with small distortions toward its nearest neighbors. Their inspection reveals that distortions are more pronounced within a strongly localized distal C(7)−C(8) double bond (cf. Figure 2 of Reference 84). In addition to the peripheral double bond belonging to the cyclobutadiene fragment, significant bond fixation is found in C(1)−C(6), C(2)−C(3) and C(4)−C(5) bonds. This is in harmony with the much-debated Mills−Nixon effect[85] *(vide infra)*. Karadakov and coworkers[84] concluded that benzocyclobutadiene **14** inherits neither the aromatic nor the antiaromatic character and that it should be regarded as a nonaromatic compound. A similar conclusion is reached by Hansen and coworkers[86] on the basis of magnetic shielding calculations. However, the best probe of antiaromaticity/aromaticity is provided by isodesmic or homodesmotic reactions. Kass and Broadus[87] have shown by using the isodesmic reaction 10

$$\text{benzocyclobutadiene} + \text{cyclobutane} = \text{benzocyclobutene} + \text{cyclobutene} + E(\text{d})_{\mathbf{14}} \quad (10)$$

that the antiaromatic destabilization $E(\text{d})_{\mathbf{14}} = 18 \pm 4$ kcal mol^{-1} (exp.), 19 kcal mol^{-1} (B3LYP/6-31G(d)) and 20 kcal mol^{-1} (MP2(fc)/6-31 + G(d)). Therefore, it is safe to say that benzocyclobutadiene **14** is antiaromatic. This result illustrates rather nicely a fact that the energetic (thermodynamic) criterion of antiaromaticity/aromaticity is superior to other indirect and qualitative indices, which in turn should be used with due care.

Recently, benzocyclobutadiene was carefully studied within the context of bond-stretch isomerism. The latter was introduced by Chatt and coworkers[88] as a distortional isomerism to characterize metallic complexes that differ only by the length of one or several bonds. Subsequently, this concept was studied in organic chemistry by Hoffmann and coworkers[89] and was renamed bond-stretch isomerism. It proved very elusive and has been questioned by several researchers, thus being controversial[90]. Indeed, some experimental results in favor of bond-stretch isomerism had to be reinvestigated and it turned out that some X-ray data were misinterpreted, because of serious disorder problems[90]. Hence, serious doubts were cast on the very existence of this phenomenon. It is important to point out that bond-stretch isomerism should not be confused with spin isomerism, which involves two isomers of the same compound differing in the total spin[91]. Instead, bond-stretch isomers should possess the same spin and differ in the bond lengths between the same types of atoms. The pioneering computational study of bond-stretch isomerism of **14** was performed by Schulman and Disch[92]. They examined the potential energy hypersurface (PES) by the Hartree−Fock HF/3-21G and MP2/6-31G models and found two minima corresponding to structures **14** and **14b**, the former being lower by 46.8 kcal mol^{-1}. The linear synchronous transit (LST) procedure was used to estimate the barrier height between the two possible isomers at the MP2/3-21G level and it occurred that the energy profile for the bond-stretching process was highly unsymmetrical. The barrier relative to **14** is quite high (44 kcal mol^{-1}), but it is only 3 kcal mol^{-1} in going from **14b** to **14**. Additional CASSCF(8,8)/STO-3G calculations have shown that **14b** was a false minimum, implying that benzocyclobutadiene does not exhibit bond-stretch isomerism. Further, it

was shown by Schulman, Disch, Jiao and Schleyer[93] by using the HF model and the gauge invariant atomic orbital approach (GIAO) employing the 6-31G* basis set that the proton chemical shifts are fully compatible with the structure **14**. Hence, it appears that the interpretation of Trahanovsky and Fischer[81] was not correct. Recently, the spatial and electronic structure of **14** was reexamined by a number of theoretical methods[94], including the HF/6-31G*, B3LYP/6-31G* and MP2(fc)/6-31G* treatments as well as the single-state SS-CASSCF(8,8)$^{\pi}$/6-31G* geometry optimization supplemented by the single-point SS-CASPT2 calculations in order to take into account both the nondynamical and dynamical correlation energy effects. The latter perturbational treatment of the second order (PT2), introduced by Roos and coworkers[95,96], gives a considerable portion of the dynamical correlation energy. It turns out that the single-configuration HF/6-31G*, B3LYP/6-31G* and MP2(fc)/6-31G* models predict the existence of both local minima corresponding to **14** and **14b** structures. Although the latter is a ghost minimum implying that extreme care has to be exercised in utilizing the single configuration models given above, they all indicate that **14** is by far more stable by 49.3, 46.7 and 49.0 kcal mol^{-1}, respectively. This is in accordance with chemical intuition, because **14** retains the aromatic sextet to a great extent avoiding the antiaromatic 4π pattern much more effectively than the **14b** (resonance) structure at the same time. The SS-CASSCF(8,8)$^{\pi}$/6-31G* search of the **14b** structure on the PES was performed by an artificial stretching of the annelated C(1)−C(2) bond to very large bond distances in a parametric way. By keeping the fused bond fixed at a particular value, the rest of the independent structural parameters were optimized. The single-point SS-CASPT2(8,8)$^{\pi}$/pVDZ//CASSCF/6-31G* and SS-CASPT2(8,8)$^{(\pi)+\sigma}$/pVDZ//CASSCF/6-31G* calculations were carried out, where π and $(\pi)+\sigma$ denote the π-electron only and all valence electron perturbational treatment of the dynamical correlation at the second order level, respectively. The single-point calculations employed Dunning's correlation consistent cc-pVDZ basis set[66]. It appeared that stretching of the annelated C(1)−C(2) bond did not provide another isomer[94]. Hence, one can safely conclude that **14** does not have a twin bond-stretch isomer, just as claimed by Schulman and Disch[92] by using a lower level of theory. It is interesting to mention that the nondynamical correlation of the π-electrons $E(\mathrm{ND})^{\pi}$ extrapolated to the infinite basis set limit for **14** is 66.3 kcal mol^{-1} [94], being in very good agreement with the additivity rule for this quantity[97,98]. This is interesting, since it was found that both aromatic and antiaromatic compounds exhibit remarkable nonadditivity effects albeit in different directions[99], both being counterintuitive. Thus the nondynamical correlation energy of the π-electron $E(\mathrm{ND})^{\pi}$ in benzene is smaller than predicted by the additivity rule, whereas the contrary holds for cyclobutadiene. The fact that **14** conforms to the additivity rule for $E(\mathrm{ND})^{\pi}$ indicates that it is a nonaromatic compound. This is in contradiction with result of Kass and Broadus[87], thus emitting a caveat that $E(\mathrm{ND})^{\pi}$ should not be used as an index of antiaromaticity/aromaticity in compounds involving fused cyclobutadiene and benzene rings.

The structural features of **14** deserve attention, because they have a decisive influence on its chemical properties. The characteristic bond distances[94] calculated for **14** are compared with X-ray data derived from the crystal structure of the derivative **15** in Table 2.

The Löwdin π-bond orders are obtained by the SS-CASSCF(8,8)$^{\pi}$/6-31G* method employing symmetrical partitioning of the interatomic mixed electron densities[100]. It is apparent that the calculated bond distances are in good agreement with experiment. The variation in bond distances is consistent with the Mills−Nixon effect[85], which implies shortening of *exo*-C(2)−C(3) bond distances and lengthening of the fused C(1)−C(2) bond relative to a free benzene value. Before discussing the importance of the Mills−Nixon effect in determining the structure and reactivity of annelated molecules[101], we would like to focus on the π-electron density distribution of **14**. Löwdin π-bond orders[100] assume a

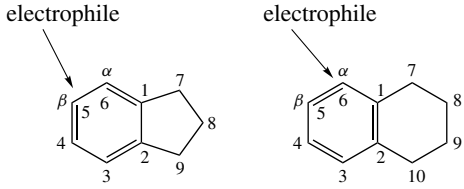
TABLE 2. Bond distances of **14** calculated by the MP2 and CASSCF methods and their comparison with the crystal structure data of **15** (in Å)

Molecule	Bond	MP2(fc)	SS-CASSCF/6-31G*	Exptl.[c]	BO(π)[d]
14	C(1)−C(2)	1.420[a] (1.429)[b]	1.434	1.416	0.41
	C(2)−C(3)	1.368 (1.378)	1.355	1.347	0.74
	C(3)−C(4)	1.429 (1.436)	1.446	1.435	0.43
	C(4)−C(5)	1.386 (1.396)	1.374	1.373	0.74
	C(1)−C(7)	1.521 (1.532)	1.509	1.531	0.19
	C(7)−C(8)	1.360 (1.372)	1.361	1.359	0.82

[a] MP2(fc)/6-31G*.
[b] MP2(fc)/cc-pVDZ.
[c] X-ray for **15** from Reference 83.
[d] Löwdin bond orders[100] obtained by the SS-CASSCF(8,8)π/6-31G* method.

very low 0.19 value in C(1)−C(7) and C(2)−C(8) bonds in an obvious tendency of the π-network to diminish the interaction between the six-π-electron moiety and the distal π-double bond. Concomitantly, the latter double bond has the highest value (0.82) in the system. Further, the bond orders within the benzene ring reveal a clear π-bond fixation, since the π-bond orders in C(2)−C(3) and C(4)−C(5) bonds assume an appreciable value of 0.74 while C(3)−C(4) and C(5)−C(6) bonds possess an intermediate value of 0.43. Similarly, the annelated C(1)−C(2) bond has the π-bond order 0.41. Closer scrutiny shows that this is a combined effect of the rehybridization of the carbon junction atoms and the π-electron interactions within the 8π network.

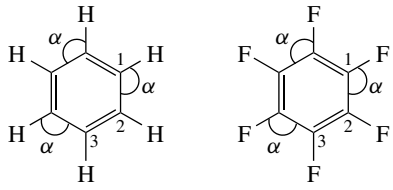
Since the Mills–Nixon effect was a matter of debate in the past, it is fitting to discuss the roots of the main misunderstandings present in the literature in more detail. Historically, the Mills–Nixon effect was discovered some seventy years ago[85] by the electrophilic substitution reaction studies of benzene fused to carbocyclic rings. Two illustrative examples are given by indan **16** and tetralin **17**.



(16) **(17)**

Since the molecular structure of indan was not known at that time, Mills and Nixon (MN) assumed the regular structure of the five-membered ring, which implied that the bond angle C(1)−C(2)−C(9) was 108°. Possessing at hand only the tetrahedral model for the carbon atom valencies of Van't Hoff and Le Bel, Mills and Nixon placed the single bond valencies of the carbon junction atom along the C(1)−C(2) and C(1)−C(7) bonds in order to conform to the almost tetrahedral C(1)−C(2)−C(9) bond angle. The double bond of benzene was laid down along the C(1)−C(6) link and was described by two bent bonds much in the sense of Pauling[102]. Consequently, the preferred resonance structure in **16** is the one involving the double bonds *exo* to the five-membered ring. Notice that the annelated CC bond in benzene should have sp^3–sp^3 hybridization according to the MN hypothesis. This prediction came true in systems involving highly strained, small fused rings, to be discussed later. The opposite should take place in tetralin **17**, leading to the

antipodal behavior in their reactivity[85], which was corroborated by the simple quantum mechanical treatment of Sutton and Pauling[103] and a number of *ab initio* calculations much later on (*vide infra*). It is fair to say that the partial bond localization in **16** and **17** is almost negligible. However, the bond fixation in benzocyclobutadiene **14** (Table 2) and in some other fused systems is considerable (*vide infra*). Obviously, small rings exert a profound influence on the structure and properties of annelated aromatic moieties. It is therefore of considerable interest to pinpoint the origin of the Mills–Nixon effect. The first reason is rehybridization of the carbon junction atoms as identified by us[104] and Stanger and Vollhardt[105]. An elegant and clear-cut proof is provided by model systems **18a** and **18b**[101, 105].



(18a) **(18b)**

The effect of a tris-annelation is mimicked by a simultaneous bending of three pairs of vicinal C−H/F bonds. The angle of bending α takes values from 90° to 120°. The results obtained by MP2(fc)/6-31G* calculations are presented in Table 3.

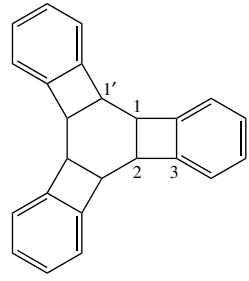
They provide conclusive evidence that forced deformation of the C−H/F bonds induces a pronounced shift of the s-character from the *ipso* bonds (participating in defining the deformation angle α) to the adjacent *ortho* bonds. For instance, in **18a** ($\alpha = 90°$), which

TABLE 3. Bond distances (in Å), NBO s-characters and Löwdin π-bond orders (bo) of deliberately distorted benzene **18a** and perfluorobenzene **18b** as obtained by the MP2(fc)/6-31G* model[a]

System	Bond	Distance	s-Character	π-bo	System	Bond	Distance	s-Character	π-bo
18a					**18b**				
	CC	1.397	35.1–35.1	0.66		CC	1.393	37.8–37.8	0.61
$\alpha = 120°$					$\alpha = 120°$				
	CH	1.087	29.6–100.0	—		CF	1.341	24.1–30.5	0.23
18a					**18b**				
	CC(i)	1.414	33.3–33.3	0.63		CC(i)	1.431	34.9–34.9	0.51
$\alpha = 110°$					$\alpha = 110°$				
	CC(o)	1.385	36.9–36.9	0.68		CC(o)	1.370	40.5–40.5	0.71
	CH	1.087	29.7–100.0	—		CF	1.343	24.3–30.3	0.23
18a					**18b**				
	CC(i)	1.446	31.0–31.0	0.59		CC(i)	1.557	30.0–30.0	0.33
$\alpha = 100°$					$\alpha = 100°$				
	CC(o)	1.374	38.7–38.7	0.72		CC(o)	1.340	44.4–44.4	0.82
	CH	1.087	30.1–100.0	—		CF	1.343	25.4–29.8	0.24
18a									
	CC(i)	1.515	27.4–27.4	0.49					
$\alpha = 90°$									
	CC(o)	1.357	41.1–41.1	0.80					
	CH	1.083	31.4–100.0	—					

[a] Taken from Reference 101. The *ipso* and *ortho* bonds are denoted by CC(i) and CC(o), respectively.

simulates triscyclobuta[*a*,*c*,*e*]benzene, the average s-character in CC(*i*) and CC(*o*) bonds is 27.4% and 41.1%, respectively. Concomitantly, the CC(*i*) and CC(*o*) bond distances are correspondingly 1.511 Å and 1.357 Å. Perfluoro model compound **18b** illustrates the fact that the effect can be amplified by deliberate choice of substituents. It is remarkable that perturbation in the σ-frame causes redistribution of the π-electrons, which act in concert with the hybridization. The increased π-bond orders in the *ortho* bonds and their decrease in the *ipso* bonds show that they contribute to the strengthening of the former and weakening of the latter linkages. This interesting result is in agreement with arguments put forward by Shaik and coworkers[106, 107] presented in a number of papers, claiming that the D_{6h} symmetry of benzene is due to the σ-electrons, whereas the π-electrons are distortive, preferring the localized D_{3h} structure. Another beautiful example which illustrates the importance of the rehybridization effect is provided by all-*cis*-tris(benzocyclobuta)cyclohexane **19**. The molecule resembles a rose with petals, given by three benzocyclobutenes, all being placed up in the molecular crystal relative to the plane of the central cyclohexane ring. The latter is the most striking feature of this compound, involving a unique, completely flat cyclohexane moiety[108] exhibiting a very strong alternation of CC bond lengths. The *ipso* C(1)−C(2) and *ortho* C(1)−C(1′) bond distances are 1.599 (1.595) and 1.511 (1.491) Å, respectively, where X-ray (semiempirical AM1[109]) values reveal a large anisotropy in lengths $d(\mathrm{CC})_i - d(\mathrm{CC})_o = 0.09(0.10)$ Å. It is worth noting that experiment and theory are in very good agreement. A very long *ipso* bond has very low s-character (21.4%−21.4%) as compared to 27.1%−27.1% s-character in *ortho* bonds. It should be also mentioned that the energy-partitioning technique within the AM1 method shows that the *ortho* bonds are much stronger than the *ipso* ones[109]. It is noteworthy that the AM1 calculation also shows that one petal in **19** is *trans* to the other two in the gas phase, as expected intuitively. However, all three are *cis* in the crystal, obviously due to crystal forces. Compound **19** is a crown case, which shows convincingly that the rehybridization effect is of paramount importance in determining bond alternation in a planar cyclohexane moiety, where π-electrons are completely absent. There is no reason why this should not hold in planar systems involving π-electrons too.



(19)

It would be of interest to find a fused system, where CC bonds have approximately the same hybridization and the partial bond fixation is induced by the π-electron network only. Fortunately, there is such a molecule (triphenylene) **20** depicted in Figure 3.

This compound exhibits reversed MN π-electron bond fixation as expected upon fusion of the central benzene ring with three peripheral benzenes, in some analogy with tetralin **17**. However, in the case of **20**, instead of a single cyclohexane carbocycle, three benzene rings are annelated in a symmetric D_{3h} manner (Figure 3). *Ab initio* MP2(fc)/6-31G* bond distances[101] are in good accord with X-ray and neutron diffraction[110] data. In particular,

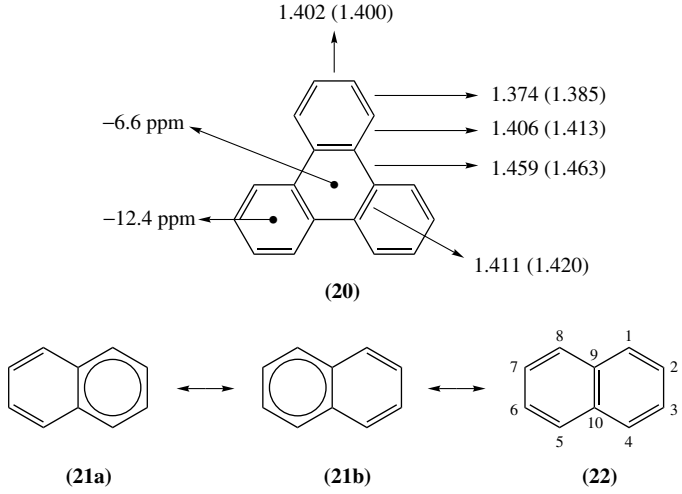


FIGURE 3. Bond distances (in Å) and NICS(1) values in triphenylene **20** and the resonance effect in naphthalene **22**

it was found that the annelated (*ipso*) bonds of the central benzene ring are considerably shorter 1.411 (1.420) Å than the *ortho* bonds 1.459 (1.463) Å, where the MP2 results are given within parentheses. Baldridge and Siegel[111] found this feature puzzling and argued that the *ipso* bonds were shorter because the peripheral benzenes tend to assume the aromatic 6π pattern implying regular six-membered rings. This interpretation is vague, since it does not take into account that distal benzene fragments exhibit partial π-electron localization too, as evidenced by alternating bond distances 1.406 (1.413) Å, 1.374 (1.385) Å and 1.402 (1.400) Å for *ortho, meta* and *para* positions, respectively (Figure 3). Namely, it will become clear later that partially localized benzene moieties retain a very large amount of their aromaticity despite moderate bond fixation. Hence, the situation is more subtle and it appears that a better explanation of the significant bond-fixation is offered by realizing that triphenylene **20** is composed by three naphthalene moieties coalesced in the central ring. It is important to recall in this respect that naphthalene itself exhibits partial π-electron localization by forming distal *cis*-1,3-butadiene patterns to some extent relative to the central CC bond as evidenced by both X-ray measurements[112] and theoretical calculations[113]. It happens that each of the twin-benzene fragments in naphthalene tends to preserve its aromaticity by localizing the other ring in the *cis*-1,3-butadiene fashion as illustrated by resonance structures **21a** and **21b**, resulting in the characteristic dominant bond fixation pattern of naphthalene **22** (Figure 3). It is worth mentioning that all three HF/6-31G*, MP2(fc)/6-31G* and MP3(fc)/6-31G* theoretical models give bond distances in good agreement with experiment. Interestingly, redistribution of the π-electron densities leads to a very moderate rehybridization in **22**[101]. Since the central benzene in triphenylene **20** is a part of three naphthalenes at the same time, it is expected that its *ortho* bonds are roughly three times more stretched than the C(1)−C(9) bond in the parent naphthalene (relative to free benzene). Additionally, the *ipso* bonds of the central benzene ring in **20** are shorter than the C(9)−C(10) bond in **22**, thus reflecting a collective effect of the three peripheral benzene rings through a naphthalene-like π-bonding pattern. It follows as a corollary that π-electrons can themselves produce significant bond alternation even if the angular distortions and the accompanying Baeyer strain destabilization are

absent. A degree of localization in **20** and **22** and a qualitative discussion of the aromatic character of their rings will be given later.

On the basis of the foregoing discussion it is possible to give a definition of the Mills–Nixon effect[101]: *It is a perturbation of the aromatic moiety exerted by fusion of one (or several) nonaromatic and angularly strained molecular fragment(s). This perturbation is reflected in the characteristic partial π-electron bond localization, leading to modification of a number of physical and chemical properties of the aromatic moiety*. Consequently, the notion of the Mills–Nixon effect is free of any preconceived underlying mechanism pertaining to the exerted perturbation. This is important to bear in mind, because the mechanisms and manifestations of the MN effect may be different in different molecular systems. To be more precise, the MN effect is generally a result of an interplay of several types of intramolecular interactions[101]. Furthermore, their relative contributions vary from one family of compounds to another. It should be also emphasized that the angularly strained fragments fused to an aromatic moiety do not necessarily have to be monocycles. Finally, a useful diagnostic tool for identifying the MN effect is the *ortho* bond placed next to the fused catenation bond: if the *ortho* bond is shortened upon annelation relative to free benzene, then the MN effect is operative. However, if the fused small ring is cyclopropene, then another criterion should be applied in view of the extremely high angular strain and short CC bonds of the three-membered fragment(s)[101].

It should be pointed out that there is some confusion in the literature concerning the very existence of the MN effect. It was claimed in some crystallographic papers[114, 115] that changes in the benzene ring induced by annelation are so small that they can be safely disregarded. This standpoint is based on the crystallographic criterion of what is a significant anisotropy in the bond lengths, derived from the standard deviation error σ. Since σ for all substituted benzenes is 0.013 Å, according to available crystallographic data, the significant CC bond changes in benzene are postulated to be only those which are equal to or larger than $\pm 3\sigma$, i.e. $\pm$ 0.04 Å according to Boese and colleagues[115]. This is, however, a very large number (i.e. error) for modern quantum chemistry computational standards. It should be recalled that the CC bond distances are very well correlated with the hybridization types sp^n-sp^m (n, $m = 1, 2, 3$). A decrease of n or m by 1 leads to a shortening of the CC bond by 0.04 Å (and *vice versa*)[116]. In other words, the distance between $C(sp^2)-C(sp^3)$ carbon atoms is smaller than that between $C(sp^3)-C(sp^3)$ carbons by 0.04 Å. This has important consequences, because a number of properties depend strongly on the bond distances and hybridization types of the participating atoms, to mention only the indirect spin–spin coupling constants $J(C^{13}-C^{13})$ between the directly bonded carbon nuclei. It was shown by Günther and Herrig[117] that the $J(C^{13}-C^{13})$ coupling constants in fused Mills–Nixon compounds varied in accordance with rehybridization taking place in the σ-frameworks. It follows that even if inaccuracies as large as a $\pm 3\sigma$ margin are acceptable in crystallography, they are definitely not tolerable in the modern theory of the electronic structure of molecules and computational chemistry. We shall see shortly that the MN effect has a decisive influence not only on the physical properties like $J(CC)$ coupling or force constants[101], but also on the electrophilic reactivity of annelated benzenes, and yet the variation in the CC bond distances of the aromatic nucleus is smaller than $\pm 3\sigma$.

A word on terminology is in place here, too. Some researchers prefer to use the term strain-induced bond localization (SIBL) instead of the MN effect[117–120]. Others choose better to pay a tribute to Mills and Nixon for their pioneering paper[85], which has triggered a number of studies over several decades. The latter contributed significantly to the understanding of the structure and properties of annelated aromatics, which has led to rationalization of their basic electronic facets[107, 121–127]. We would like to stick to the traditional terminology accepted by a majority of researchers in the field for two reasons:

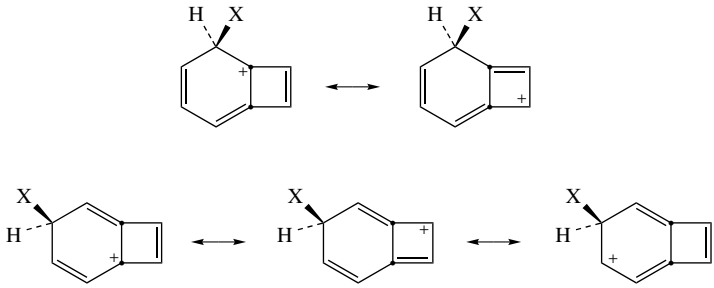


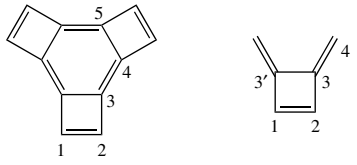
FIGURE 4. Cationic resonance effect in Wheland's σ-complexes triggered by the attack of the electrophile X at α- and β-positions. The critical carbon junction atoms are denoted by dots

(a) the argument used by Mills and Nixon in their original paper was that the angular strain of the cyclopentene carbocycles dictated the mode of π-bond fixation, and (b) the general definition of the MN effect (*vide supra*) includes not only the angular strain, but additionally the hyperconjugative interaction of the aromatic moiety with CH_2 group(s) of the fused carbocycle or a certain amount of conjugation with the localized distal double bond, thus going beyond the angular strain alone.

We are now in a position to discuss the electrophilic reactivity of benzocyclobutene. It is not surprising that the distribution of the π-electron density in **14** (and **15**) exhibiting a pronounced bond fixation has profound consequences on the chemical reactivity of the benzene ring. Examination of the electrophilic substitution reaction of **14** provides conclusive evidence of the regioselective MN effect, since the β-position is considerably more susceptible to the electrophilic attack with the proton[127] and methyl cation[128] as electrophiles. This finding is easily understood by inspection of the relevant Pauling's resonance structures (Figure 4), where the spin pairing schemes involving a cyclobutadiene distribution of the π-double bonds within the four-membered ring are omitted as less important.

It follows that the β-electrophilic attack is more compatible with the π-electron localization in the initial neutral molecule. In particular, the additional resonance structure occurring in the β-form retains the π-bond localization of the important dimethylenecyclobutene type in the *exo* C(1)−C(6) and C(2)−C(3) bonds. The actual MP2(fc)/6-31G**//HF/6-31G* calculations confirm this intuitive conjecture[127,128]. It should be strongly pointed out that the preference of the β-electrophilic substitution is one of the hallmarks of the Mills−Nixon effect and consequently it will be discussed in more detail later on in systems where the experimental data are more abundant.

Since fusion of cyclobutadiene ring to benzene moiety exerts a strong perturbation on the latter, it is of some interest to examine the effect of tris-annelation yielding **23**. It has been shown by the present authors and coworkers[129] and Streitwieser, Vollhardt and



(23) **(24)**

TABLE 4. Characteristic bond distances (in Å) in benzotricyclobutadiene **23** and 3,3′-dimethylenecyclobutene **24**, hybridization s-characters (in %) and Löwdin π-bond orders as calculated by the HF/6-31G* and MP2(fc)/6-31G* models[101]

		Bond lengths		s-Characters		Löwdin π-bond orders	
Molecule	Bond	HF	MP2	HF	MP2	HF	MP2
23	C(1)–C(2)	1.345	1.381	35.5–35.5	34.2–34.2	0.87	0.77
	C(2)–C(3)	1.483	1.470	29.6–32.0	30.6–33.0	0.28	0.33
	C(3)–C(4)	1.317	1.344	42.3–42.3	41.6–41.6	0.85	0.76
	C(4)–C(5)	1.500	1.509	25.6–25.6	25.3–25.3	0.23	0.24
24	C(1)–C(2)	1.337	1.366	35.4–35.4	34.4–34.4	0.88	0.80
	C(2)–C(3)	1.484	1.480	29.8–28.4	30.6–28.9	0.28	0.30
	C(3)–C(4)	1.316	1.338	43.1–39.2	42.3–38.8	0.92	0.85
	C(3)–C(3′)	1.509	1.508	28.4–28.4	28.6–28.6	0.21	0.23

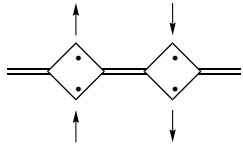
coworkers[130] that **23** possessed an almost frozen Kekulé structure with localized double bonds emanating from the four-membered ring at *exo* positions, thus resembling a triple 3,3′-dimethylenecyclobutene structure **24**. On the other hand, the annelated (*ipso*) bonds have essentially a single bond character. This is a conclusion based on the HF/6-31G* and MP2(fc)/6-31G* calculations of the geometries, local hybrid orbital s-characters and Löwdin π-bond orders presented in Table 4.

It appears that the HF/6-31G* model overestimates localization of the C=C double bonds, which is rectified by the post-Hartree–Fock MP2 model. This is reflected also in Löwdin π-bond orders, which are lower in double bonds and somewhat higher in essentially single bonds by the correlated MP2 calculations compared to the HF/6-31G* model. In contrast, the hybrid orbital s-characters change very little by explicit account of the correlation energy at the MP2 level. It is remarkable that the fused bonds are described by the sp^3–sp^3 hybridization despite the fact that they are parts of the planar σ-framework. This is in accordance with a bold Mills–Nixon hypothesis made in 1930 in indane[85]. In contrast, the *exo* bonds possess very high average s-character of 41.6%. It is noteworthy that the C=C double bonds in a central cyclohexatriene-like ring are moderately delocalized as evidenced by the π-bond order of 0.24 found in the formally CC single bonds. To put it in another way, it is fair to say that the central ring is best described by three weakly coupled π-double bonds. A considerable shift of the s-character into *exo* bonds accompanied by a pronounced drift of the π-electron densities to the same positions is a signature of a strong MN effect. Comparison of the bond distances, s-characters and π-bond orders between **23** and **24** shows that benzotricyclobutadiene can be rather closely represented by coalescence of three 3,3′-dimethylenecyclobutenes (Table 4).

It is well known that nucleus independent chemical shift (NICS)[131–134], customarily calculated at 1 Å above the ring critical point defined by Bader's[135,136] topological description of the electron distribution in molecules (NICS(1)), provides a useful index of antiaromaticity/aromaticity. They measure paratropic ring currents in antiaromatic and diatropic ring currents in aromatic molecules. The present calculations show that, for example, the HF/6-31G* model based on the gauge invariant atomic orbitals (GIAO) gives for the NICS(1) values −6.6 ppm and −12.4 ppm for the central and peripheral benzene ring in **20** (Figure 3), respectively, indicating an almost complete retention of the aromaticity in the latter moieties despite a partial bond fixation (*vide supra*). On the other hand, the central ring exhibits a decrease in aromaticity by approximately 50%. A closely related GIAO HF/3-21G calculation on benzocyclobutadiene **14** yields −6.0 and 10.4 ppm[93] for the aromatic and antiaromatic fragment, respectively. It should be

mentioned that NICS(1) values are not very sensitive to the basis set employed. Hence, results obtained by the GIAO HF/6-31G* and HF/3-21G calculations are comparable. The NICS(1) values for free benzene and cyclobutadiene are −12.5 and 15.1 ppm, respectively, obtained by utilizing the 3-21G set[93]. The NICS(1) values in a strongly localized system **23** are very interesting. The GIAO HF/3-21G calculation gives −2.6 and −4.2 ppm for the six- and four-membered ring, respectively[93], indicating that the aromatic stabilization of the benzene fragment is nonexistent. This is consistent with the picture of an almost frozen cyclohexatriene moiety (single Kekulé structure). In contrast, cyclobutadiene subunits exhibit—surprisingly enough—a mild aromaticity, which is comparable to that in 3,3′-dimethylenecyclobutene **24** (−4.5 ppm). This conclusion depends, of course, on a borderline drawn between the slightly aromatic and nonaromatic compounds. It follows that the π-electron part of the cyclobutadiene fragments in **23** contributes somewhat to the stability of this not yet synthesized compound, presumably due to its high angular strain.

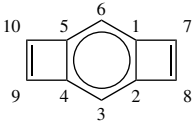
Another very interesting compound involving cyclobutadiene moiety deserving a few words of a comment is 1,3-dimethylenecyclobutadiene, which in turn is a non-Kekulé isomer of benzene. It has been synthesized and its EPR spectrum has shown that the ground state was planar triplet[137], in agreement with earlier calculations[138] and subsequent *ab initio* studies[139,140]. The spin-coupled VB treatment[141] described 1,3-dimethylenecyclobutadiene as a system of two *para* C=C double bonds and a diagonally triplet coupled 'antipair' of electrons. Its 'dimer' **25** is, on the other hand, a singlet due to the anti parallel alignment of two 'antipairs' via the so-called superexchange interaction[142] mediated by a common double bond.



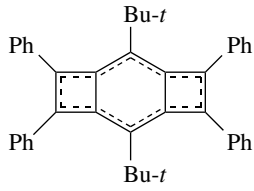
(25)

A straightforward generalization of this result has led to the conclusion that linear 1,3-dimethylenecyclobutadiene chains (polymers) should be triplets for any odd number of fragments[141]. This interesting finding might be useful in designing magnetic materials.

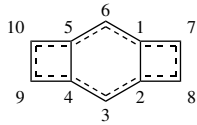
b. Benzo[1,2:4,5]dicyclobutadiene: A quasi-[10]annulene system. Benzodicyclobutadiene **26** is even less stable and more reactive than **14**[82]. Its derivative 3,6-di-*t*-butyl-7,8,9,10-tetraphenylbenzo[1,2:4,5]dicyclobutadiene **27** was synthesized by Toda and Ohi[143] and its crystal structure was determined by Boese and coworkers[144]. The molecular geometry possesses C_2 symmetry, with the annelated C(1)−C(2) bond distance, which is the longest



(26)



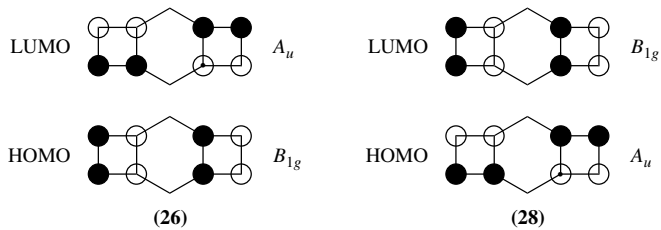
(27)



(28)

ever found in a benzene ring (1.540 Å). This is remarkable for two linked carbon atoms in a formally sp^2 hybridization state as is commonly assumed. As a matter of fact, this bond is of the sp^3-sp^3 type as we have seen in **14**, although it belongs to the planar σ-framework. It is a consequence of the MN effect. Hence, the electronic structure of **26** is of great theoretical importance. It was studied by Schulman and Disch[92], who found that **26** is a minimum on the Born–Oppenheimer PES at the MP2(full)/6-31G* level, but they were not able to locate the structure **28** of D_{2h} symmetry. Instead, the MP2(full)/6-31G* model gave as a local minimum just one of its resonance structures of C_{2v} symmetry, which was an artifact of the single-configuration method. Hence, a multiconfigurational approach is necessary and it was applied to settle the problem by Maksić and coworkers[94]. It was realized that **26** and **28** are two potential bond-stretch isomers *in spe* (in hopes) since their HOMO and LUMO orbitals are interconverted (Figure 5), implying that they might form a barrier by an avoided crossing in going from **26** to **28** and *vice versa*.

The corresponding π-electron ground-state configurations of **26** and **28** are $(B_{3u})^2(B_{3u})^2(B_{2g})^2(A_u)^2(B_{1g})^2$ and $(B_{3u})^2(B_{3u})^2(B_{2g})^2(B_{1g})^2(A_u)^2$, respectively. It appears that the ground-state π-electron configuration of **26** is the first excited state of **28**. The opposite holds for the ground state of **28** and the first excited state of **26**. Consequently, one should employ the two-state TWS-CASSCF procedure and a subsequent TWS-CASPT2 perturbation calculation. The first important result was that the nondynamical correlation of the π-electrons taken into account by the TWS-CASSCF$(10,10)^{\pi}$/6-31G* method did not yield an avoided crossing. The nondynamical π-electron correlation effect calculated at the single-point TWS-CASPT2$(10,10)^{\pi}$/cc-pVDZ//TWS-CASSCF$(10,10)^{\pi}$/6-31G* level did not introduce any improvement either. This drawback was circumvented by accounting for both σ- and π-electron dynamical correlation energy estimated by the TWS-CASPT2$(10,10)^{(\pi)+\sigma}$/cc-pVDZ//TWS-CASSCF$(10,10)^{\pi}$/6-31G* approach. In this case a barrier for interconversion of **26** into **28** was predicted to be 3.4 kcal mol^{-1} [94]. Obviously, the dynamical correlation of σ-electrons plays a very important role in benzo[1,2:4,5]dicyclobutadiene. It was also found that **28** is more stable than **26** by 3.2 kcal mol^{-1}. These results should be taken with due care, since it was not possible to optimize geometries at the TWS-CASPT2 level. Much more reliable in this respect is the multireference average coupled cluster (MR-AQCC) method, which is capable of reproducing the multireference character of the wavefunction and includes the size-extensivity corrections[145]. An additional important advantage of this approach is the availability of the analytic gradients[146], which makes geometry optimization at a post-CASSCF level possible. This is of great importance in locating the transition states (TS). In view of the controversial character of the concept of bond-stretch isomerism we deemed it worthwhile to examine structures **26** and **28** at the MR-AQCC(SA) level, where SA denotes the state-averaging approach. The structural parameters of **26** and **28** obtained by the state-averaged MR-AQCC(SA)/6-31G* calculations are summarized in Table 5.



(26) **(28)**

FIGURE 5. The highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals in bond-stretch isomers **26** and **28**

TABLE 5. Bond distances of compounds **26** and **28** calculated by MP2, TWS-CASSCF and MR-AQCC(SA) methods and their comparison with available experimental data (in Å)

System	Bond	MP2(fc)[a]	TWS-CASSCF[b]	MR-AQCC(SA)[c]	Exptl.[d]	BO(π)[e]
26	C(1)−C(2)	1.409 (1.419)	1.430	1.410	—	0.54
	C(2)−C(3)	1.394 (1.404)	1.394	1.394	—	0.60
	C(1)−C(7)	1.536 (1.547)	1.513	1.537	—	0.15
	C(7)−C(8)	1.355 (1.367)	1.367	1.357	—	0.82
28	C(1)−C(2)	1.555 (1.563)	1.54	1.550	1.540(5)	0.19
	C(2)−C(3)	1.390 (1.400)	1.392	1.392	1.407(5)	0.60
	C(1)−C(7)	1.397 (1.409)	1.415	1.401	1.401(5)	0.51
	C(7)−C(8)	1.439 (1.472)	1.442	1.458	1.471(5)	0.48

[a] MP2(fc)/6-31G* results. Numbers within parentheses refer to MP2(fc)/cc-pVDZ calculations. Results obtained by the MP2 method are taken from Reference 94.
[b] The TWS-CASSCF(10,10)$^{\pi}$/6-31G* method and results taken from Reference 94.
[c] MR-AQCC(SA)/6-31G* results, Reference 147.
[d] Experimental X-ray data of 3,6-di-*tert*-butyl-7,8,9,10-tetraphenylbenzo[1,2:4,5]dicyclobutadiene, Reference 144.
[e] Löwdin π-bond orders are obtained by SS-CASSCF(10,10)$^{\pi}$/6-31G* calculations, Reference 94.

Inspection of the presented results reveals a close semblance of the MP2(fc)/6-31G* single-reference and MR-AQCC(SA)/6-31G* multireference bond distances, which is both surprising and gratifying. Second, they are in good agreement with the experimental data, particularly if it is taken into account that the latter are obtained for a heavily substituted derivative **27** in the crystal. The largest deviation is found for the distal C(7)[C(9)]−C(8)[C(10)] bonds, where the theoretical estimates fall short of the experimental distance 1.471(5) Å. This is easily rationalized by the repulsion of the two substituted benzene rings and an additional conjugation effect between the π-electrons of the peripheral C=C bonds of the **1** fragment and the aromatic substituents[147]. Inspection of Löwdin π-bond orders is instructive. The aromatic character of the benzene moiety in **26** is preserved to a great deal. This is reflected in the π-bond order of the peripheral C(7)[C(9)]−C(8)[C(10)] bonds (0.82) and very low π-density over the C(1)−C(7) bond and its symmetry-related counterparts (0.15) which strongly indicates that their interaction with the aromatic fragment is at a minimum. Distribution of the π-bond orders in **28** on the other hand mirrors a highly pronounced delocalization over the molecular perimeter. Since the π-bond order of the fused bonds is fairly small (0.19), it follows that **28** represents a quasi-[10]annulene system. Analysis of the bond angles (not shown here) reveals that they are practically equal in both **26** and **28**, implying that these two systems provide excellent examples of bond-stretch isomers[147]. It is interesting to note in passing that both isomers conform to the Hückel $(4n + 2)\pi$ rule: isomer **26** preserves the central benzene moiety, whereas **28** involves the aromatic delocalization of all 10π electrons over the molecular perimeter. These conjectures are corroborated by the present GIAO HF/6-31G* calculations of NICS(1) values. In **26** the NICS(1) values are −3.3 ppm and 15.2 ppm for the benzene and cyclobutadiene moieties, respectively, indicating that antiaromaticity has overwhelming influence on the low stability of this compound. In a quasi-[10]annulene isomer **28**, NICS(1) values assume very high absolute values being −11.4 and −17.7 ppm over the six- and four-membered rings, respectively. Obviously, the π-network is a strongly stabilizing factor, which compensates for a bond-stretching strain inherent in the very long fused bonds. As a net effect, it turns out that both isomers are approximately of the same stability. A very high aromatic character of the cyclobutadiene fragments is astounding. Another striking feature is given by the apical C(1)−C(6)−C(5) angle, which is very small for a planar molecule (*ca* 111°), whereas the C(6)−C(1)−C(2) angle is enlarged to 124°, thus illustrating a considerable spillover of the angular strain

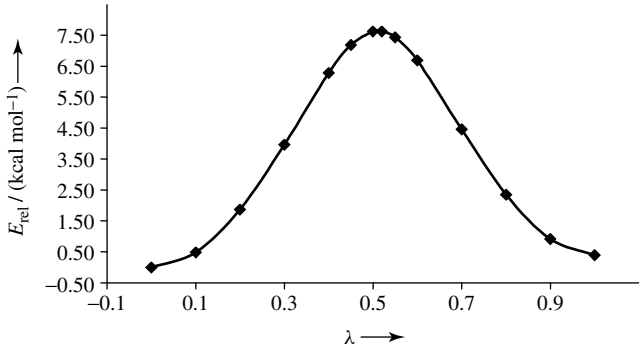


FIGURE 6. The barrier for the bond-stretch isomerization reaction leading from **26** to **28** as calculated by the MR-AQCC(SA-MO)/6-31G* method

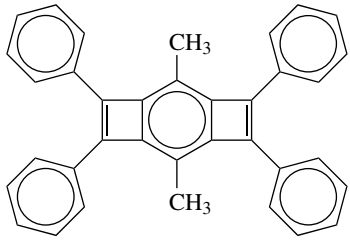
to the fused benzene ring. This is another structural detail, which is a direct consequence of the MN effect manifested through rehybridization. The MR-AQCC(SA)/6-31G* calculations show that isomers **26** and **28** are of the same stability within the accuracy of the method applied. In order to estimate the TS structure, an approximate reaction path has been examined[147] by considering internal coordinate $l_i(\lambda)$ (equation 11):

$$l_i(\lambda) = (1 - \lambda) \cdot l_i(\mathbf{26}) + \lambda \cdot l_i(\mathbf{28}) \tag{11}$$

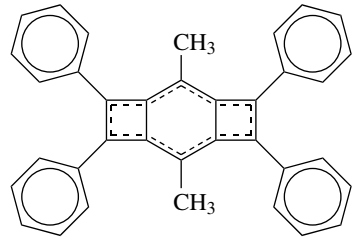
where λ is a parameter and l_i are bond distances C(1)−C(2), C(1)−C(7) and C(7)−C(8), because they are strongly coupled in the isomerization process. Internal coordinates $l_i(\lambda)$ correspond to respective coordinates in **26** and **28** for $\lambda = 0$ and $\lambda = 1$. For each value of λ along the reaction path, all other independent structural parameters were optimized. Finally, the TS structure was reoptimized allowing for a free relaxation of the C(1)−C(2), C(1)−C(7) and C(7)−C(8) bond distances. The potential energy curve computed at the MR-AQCC(SA) level is presented in Figure 6.

It appears that the TS is reached for $\lambda = 0.5$, implying that the curve is almost symmetrical and that the C(1)−C(2), C(1)−C(7) and C(7)−C(8) bond lengths are practically arithmetic means of their values in isomers **26** and **28**. It is important to emphasize that the bond angles in the TS are the same as in the structures **26** and **28**, implying that they are true bond-stretch isomers. The barrier height is 7.5 kcal mol^{-1}, which is diminished to 5 kcal mol^{-1} if the zero-point vibrational energy contribution is taken into account. In spite of the fact that the barrier of isomerization is rather low, it is quite possible that both isomers **26** and **28** are capable of existing. Their synthesis might be facilitated by judicious choice of substituents, which would favor one de/localization pattern over the other. This possibility was examined by Maksić and coworkers[94] by using approximate MP2(fc)/cc-pVDZ and B3LYP/cc-pVDZ methods. Some characteristic compounds are depicted below.

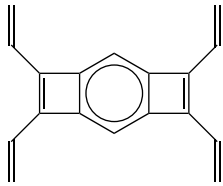
Their differences in stability are $E(\mathbf{29a}) - E(\mathbf{29b}) = 11.1(3.3)$, $E(\mathbf{30a}) - E(\mathbf{30b}) = -1.6(-7.0)$ and $E(\mathbf{31a}) - E(\mathbf{31b}) = 16.8(16.1)$ in kcal mol^{-1}. Here, the B3LYP/cc-pVDZ values are given in parentheses. It should be mentioned that the structure and energies for **29a** and **29b** were estimated at the MP2(fc) level by employing a slightly larger 6-31G* basis set. These two isomers differ from the synthesized compound **27** by two methyl groups, which replace the bulky *t*-butyls. It turns out that phenyl groups substituted at cyclobutadiene double bonds favor the delocalized structure **29b** for an



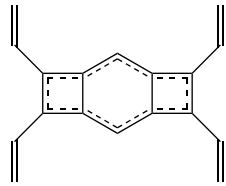
(29a)



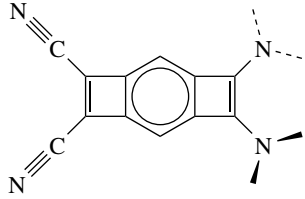
(29b)



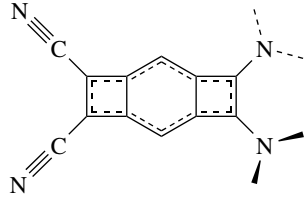
(30a)



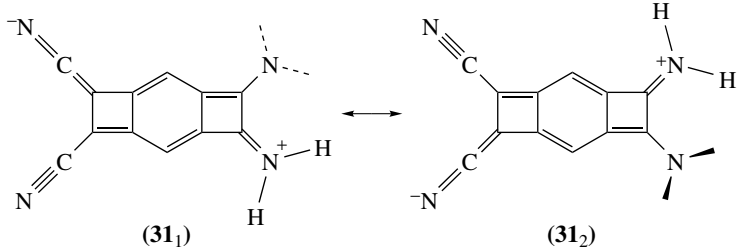
(30b)



(31a)



(31b)

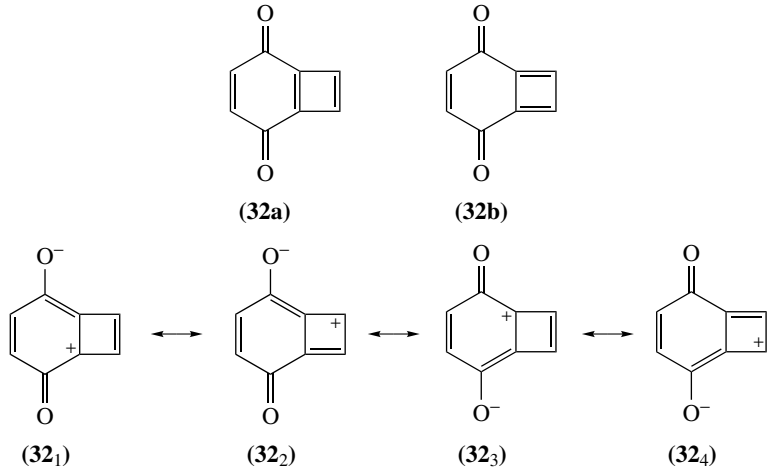


(31_1) **(31_2)**

obvious reason: their repulsion elongates the C(7)−C(8) and C(9)−C(10) bonds. Quite another effect is responsible for preference of the **31b** structure over the more localized system **31a**: It is a strong resonance effect between the π-electron donor NH_2 groups and π-electron acceptor C ≡ N groups. This is illustrated by two characteristic resonance structures $\mathbf{31_1}$ and $\mathbf{31_2}$. Obviously, a fully delocalized isomer **31b** should be energetically preferred. In contrast, calculations indicate that a 'localized' isomer **30a** should be slightly more stable than **30b**. The bottom line is that several substituted benzodicyclobutadienes exhibiting quasi-[10]annulene π-electron structures should be able to exist.

In concluding the topic of bond-stretch isomerism, it should be pointed out that benzo-[1,2:4,5]dicyclobutadiene is one of a very few molecular skeletons known so far for

enabling this elusive phenomenon in a realm of organic molecules (*vide infra*). An attempt to identify bond-stretch isomers in cyclobutadieno-*p*-benzoquinone **32a** and **32b** failed. It is expected that both possible isomers **32a** and **32b** are stabilized by a resonance effect indicated by resonance structures $\mathbf{32}_n (n = 1-4)$, albeit to a different extent. McKee and coworkers[148] found that **32a** and **32b** are indeed minima on the B3LYP/6-31G* potential energy hypersurface. Subsequent CASSCF(10,10)$^{\pi}$/6-31G*//GVB(2)/6-31G* and CASPT2(10,10)$^{\pi}$/ANO(3s2p1d,2s1p)//GVB(2)/6-31G* calculations have shown that this is indeed the case and that **32a** is by 5 kcal mol^{-1} more stable than **32b**[149]. However, the barrier height in going from **32b** to **32a** was found to be only 0.3 kcal mol^{-1}, if the ZPVE is taken into account. This is negligible and one can safely conclude that cyclobutadieno-*p*-benzoquinone does not exhibit bond-stretch isomerism. However, the angular strain and antiaromatic destabilization of **32a** is estimated to be comparable to that in the parent cyclobutadiene **1**[149]. Hence, it was concluded that **32a** should be prone to chemical synthesis, but in extreme conditions. In this context it should be mentioned that cyclobutadieno-*p*-naphthoquinone is synthesized and that Breslow and coworkers[150] estimated its antiaromatic destabilization exerted by the cyclobutadiene fragment employing electrochemical measurements. It was found to be in the range of 12–16 kcal mol^{-1}.



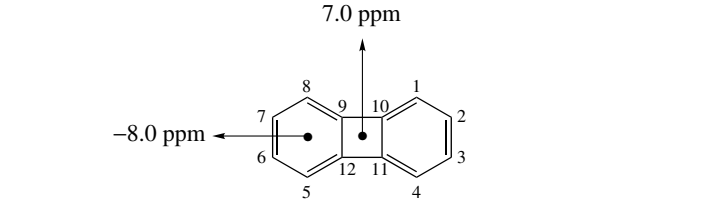
(32a) **(32b)**

(32_1) **(32_2)** **(32_3)** **(32_4)**

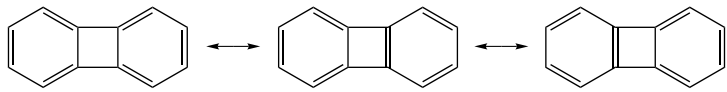
To summarize the bond-stretch isomerism discussion, it can be stated that it is a very rare phenomenon indeed. It does exist, however, as evidenced by 1,2- and 1,8-dichloroperfluoro derivatives of cyclooctatetraene[151], not to mention cyclobutadiene itself and possibly some of its substituted offsprings. Recent calculations strongly indicate that the number of systems exhibiting bond-stretch isomerization might be larger than supposed so far[94, 147].

c. [N]Phenylenes. i. The spatial and electronic structure of paradigmatic biphenylene. The [*N*]phenylenes contain alternating fused benzene [*N*] and cyclobutadiene [*N*-1] rings juxtaposed in a linear, angular or branched manner[152, 153]. The angular distribution of rings is unusual in the sense that it becomes helical for $N > 5$ and they are termed heliphenes for that reason[154, 155]. [*N*]Phenylenes have attracted a lot of attention in view of their possible practical applications[151, 156] and interesting electronic structure[130, 157] culminating with the icosahedral fullerene archimedene C_{120}[158], predicted by Schulman and Disch nearly a

decade ago[159], which may be regarded as spherical phenylene. These investigations were highlighted by estimates of the limiting features of linear and zig-zag phenylenes[160]. It should be noted that N denotes the number of benzene rings, whereas N-1 determines the number of cyclobutadiene moieties. The smallest is [2]phenylenes of biphenylene **33**, which can be considered as a progenitor of the large family or [N]phenylenes. Since it has cyclobutadiene ring flanked by two benzenes, it is substantially more stable than benzocyclobutadiene **14**. It was synthesized by Lothrop[161] in 1941 and independently by Rapson and Shuttleworth[162]. Its geometric and electronic structure is paradigmatic for all [N]phenylenes, because it reflects a strong interplay of the angular strain with aromaticity and antiaromaticity of catenated rings. *Ab initio* HF/6-31G* bond distances[101] are compared with the X-ray measurements of Trotter and coworkers[163] in Table 6.



(33)



(K1) **(K2)** **(K3)**

It appears that the HF/6-31G* bond lengths are in good agreement with experiment although they are systematically too low by 0.01 Å, which is a known drawback of the self-consistent field approximation in the description of the double bonds. Explicit inclusion of the electron correlation leads to their lengthening. However, the relative changes of the CC bonds in **33** are well reproduced. It is noteworthy that the bond angles are in perfect agreement with X-ray data (Table 6). The most interesting feature of **33** is alternation of bond distances around the molecular perimeter. Second, the bond angles deviate significantly from the ideal 120° value. For instance, the C(3)−C(4)−C(11) bond angle of 115.7° reveals that the benzene rings are somewhat strained too. Moreover, the C(4)−C(11)−C(12) angle is 147.6°, indicating a considerable redistribution of the s-character at the carbon junction atoms. This is indeed the case as evidenced by the NBO

TABLE 6. Bond distances (in Å) and bond angles (in deg) in biphenylene **33**, hybridization indices (in %) and Löwdin π-bond orders as calculated by the HF/6-31G* model

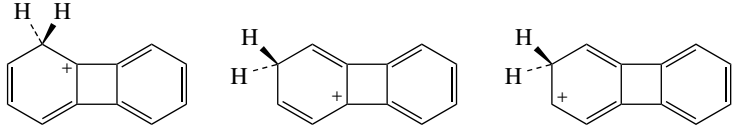
Bond	HF [a]	Exptl. [b]	s-Characters	Löwdin π-bo
C(1)−C(2)	1.417	1.423	34.2–34.0	0.56
C(2)−C(3)	1.373	1.385	36.3–36.3	0.74
C(4)−C(11)	1.357	1.372	35.4–40.3	0.72
C(11)−C(12)	1.507	1.514	30.2–30.2	0.21
C(10)−C(11)	1.414	1.426	29.3–29.3	0.52

[a] HF/6-31G* results from References 101 and 164.
[b] X-ray distances from Reference 163.

values given in Table 6. There is a substantial increase in the s-character of the hybrid AO emanating from C(11) and directed to the C(4) atom of the benzene ring (40.3%). On the other hand, the average s-character of the hybrids describing fused bonds is only 29.3%. This is a consequence of a well known fact that small rings prefer hybrids with high p-characters, since the bond bending is then smaller and the angular strain lower[116]. It is easy to see that the π-electron localization acts in the same direction as the result of a pure π-electron resonance effect. This is evident by inspection of the resonance structures **K1, K2** and **K3**, which suggest strong localization over the perimeter bonds and decreased π-bond orders in the fused bond. This conjecture is qualitatively correct as a comparison with the HF/6-31G* Löwdin π-bond orders shows. Thus, the bond order of annelated bonds (0.52) is smaller than in a free benzene which diminishes the antiaromatic character of the four-membered ring and perturbation of the six-membered ring at the same time. In contrast, C(1)−C(10) and C(2)−C(3) bonds exhibit enhanced π-bond density that is higher than in benzene. A preference of one Kekulé structure of benzene over the other is supported by a decreased π-bond order (0.56) in the C(1)−C(2) bond and its symmetry-related counterpart. The long C(11)−C(12) and C(9)−C(10) bonds possess a low π-bond order (0.21) as expected. Interestingly, the bridge bonds are appreciably shorter (1.507 Å) than in a free cyclobutadiene (1.565 Å at the same HF/6-31G* level), where perfectly localized peripheral double bonds are found. These data indicate that the antiaromatic character of the cyclobutadiene fragment in **33** is considerably smaller than in a free cyclobutadiene as a consequence of the fact that the π-bond order of the fused bonds is only 0.52. This is corroborated by the NICS(1) value for this ring, being 7.0 ppm (as compared with 15.1 ppm in **1**)[93]. Concomitantly, the aromatic character of the benzene moiety is also decreased as evidenced by NICS(1) = −8.0 ppm. It follows as a bottom line that both σ- and π-electrons act in concert in **33**, leading to alternation of the bond distances, π-bond orders and the average s-characters in the perimeter bonds. This effect is less pronounced than in **23** (Table 4), but one can nevertheless say that *the Mills–Nixon effect in biphenylene **33*** is rather strong[164]. The bonding pattern of biphenylene is very important for understanding the electronic structure of higher [*N*]phenylenes.

The electrophilic substitution reactions are strongly favored at position 2. Streitwieser and Schwager[165] were the first to investigate the relative rates of substitution at positions 1 and 2 of biphenylene by tritiodeprotonation in trifluoroacetic acid—70% perchloric acid (96.9:3.1 v/v) and obtained the ratio $(k_2/k_1) = 64$. Shortly afterwards, Blatchly and Taylor[166] obtained a much higher value $(k_2/k_1) = 135$ from experiments performed in anhydrous trifluoroacetic acid. It is noteworthy that only 2-substituted biphenylenes were isolated in acylation, halogenation and nitration reactions[167]. On the other hand, Streitwieser and coworkers[168] found that planar hydrocarbons, which have an aryl position adjacent to a fused strained ring, show enhanced acidity. Position 1 in biphenylene is a good illustrative example, since it was found in protodetritiation experiments with lithium cyclohexylamide in cyclohexylamine that position 1 is 79 times as reactive as position 2[169]. Subsequently, Taylor found that protodesilylation reaction by aqueous perchloric acid is undergone with the partial rate factors 27.8 and 0.52 for positions 2 and 1, respectively[170]. Hence, there is a remarkable dichotomy in the behavior of position 1, which is deactivated in the electrophilic substitution reactions and activated in the proton abstraction and metallation reactions. The opposite holds for position 2. These interesting findings call for rationalization. The regioselectivity in the electrophilic attack on the benzene positions in annelated systems involving small rings was studied in a number of model systems[171,172] and real compounds[127,128,173] by *ab initio* methods. The electrophilic group was modeled by the proton or by the CH_3^+ cation. The transition states (TS) were represented by Wheland's σ-complexes[174], which are metastable intermediates, and consequently they are generally accepted as a reasonable description of the nearest TS

according to Hammond's postulate[175]. In a nutshell, it happens that the difference in susceptibility to the electrophilic attack of β and α positions induced by small ring annelation can be resolved into two contributions[128, 171–173]: (1) the angular strain effect and (2) the cationic resonance contribution. The latter is the result of either the hyperconjugation in systems involving fused carbocycle with CH_2 groups next to the carbon junction atoms or conjugation, if the catenated ring is a part of the π-system like in benzocyclobutadiene **14** or biphenylene **33**. Therefore, the β positions are preferred in kinetically controlled electrophilic substitution reactions and the extent of discrimination is dependent on the ring size and the presence of the π-bonds in the fused fragment[101, 128, 173]. In qualitative terms, the more advantageous β electrophilic substitution in **33** is evident by examining the relevant resonance structures below.



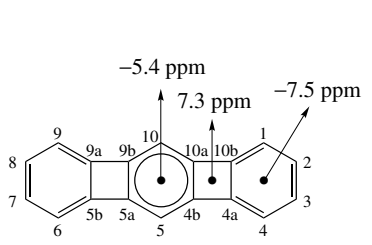
(R1) **(S1)** **(S2)**

It appears that the α-substitution has only one resonance structure (**R1**), which preserves the partial bond fixation in the neighboring unsubstituted benzene ring dictated by the MN effect, whereas in the case of the β-substitution there are two such resonance structures (**S1** and **S2**). Moreover, the **S2** resonance structure possesses a typical radialene distribution of the π-double bonds around the cyclobutadiene moiety found in the ground state of **33**. This 'memory effect' involved in the TS for the β-substitution, mimicked by the metastable Wheland's σ-intermediate, is one of the main reasons behind a more facile β-reaction. It follows as a corollary that the Mills–Nixon effect determines the regioselectivity in the electrophilic substitution reaction of aromatic compounds annelated to small rings in general. This directional feature is particularly strong if the annelated ring is a cyclobutadiene fragment. We note in passing that in anti-MN compounds the picture described above is just the opposite[101, 176]. It is very important to keep in mind that the rehybridization at the site of catenation is important, but it is just a part of a full mosaic. The cationic hyperconjugation or conjugation effect is the other side of the same coin.

Finally, it should be mentioned that in our *ab initio* description of the electrophilic reactivity of the MN compounds, we find that the α-positions are deactivated just like in Streitwieser's model[168]. Particularly strong deactivation is found in benzocyclobutadiene and biphenylene[101]. However, according to Streitwieser and coworkers[168] this site is deactivated in electrophilic substitution reactions and activated in the metallation reactions, because the α-carbon atom is deprived of some of its electron density, since the hybrid AO of the neighboring carbon junction atom has very high s-character, thus being strongly electronegative. Our calculations for benzocyclobutadiene show that both π-electron density and the total atomic charge of α- and β-carbons are the same, being 0.99 |e| and -0.17 |e|, respectively[101]. A negligible difference is found in some other MN systems. Hence, Streitwieser's model does not offer a credible interpretation of the reactivity of fused aromatic compounds.

ii. The limiting features of higher phenylenes. Higher [N]phenylenes with $N > 2$ will be briefly considered, since they exhibit some new and unexpected properties. We shall commence our discussion with linear (**34**) and bent [3]phenylenes (**35**) depicted below. Their bond distances, s-characters and Löwdin π-bond orders[157] are given in Table 7.

Comparison of the HF/6-31G* bond distances with the X-ray crystal structures[177] reveals a good accordance between theory and experiment in particular for the bent



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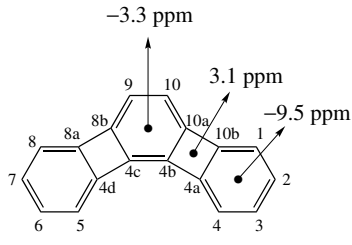


(35)

TABLE 7. Bond distances (in Å) in linear and angular [3]phenylenes **34** and **35**, NBO s-characters (in %) and Löwdin π-bond orders as calculated by the HF/6-31G* model

Molecule	Bond	d(HF/6-31G*)	d(Exptl.)	s-Character	π-Bond order
34	C(1)−C(2)	1.424	1.436 [a]	33.8–33.7	0.53
	C(2)−C(3)	1.368	1.397	36.4–36.4	0.76
	C(4)−C(4a)	1.352	1.359	35.5–40.6	0.74
	C(4a)−C(4b)	1.508	1.512	30.0–30.0	0.16
	C(4a)−C(10b)	1.417	1.397	29.0–29.0	0.50
	C(4b)−C(10a)	1.402	1.407	30.6–30.6	0.60
	C(4b)−C(5)	1.383	1.385	34.3–29.1	0.64
35	C(1)−C(2)	1.409	1.400 [a]	34.2–34.4	0.59
	C(2)−C(3)	1.379	1.370	35.9–35.9	0.71
	C(1)−C(10b)	1.363	1.368	39.8–35.1	0.70
	C(4)−C(4a)	1.363	1.365	35.1–40.0	0.70
	C(4a)−C(10b)	1.410	1.413	29.4–29.6	0.54
	C(4a)−C(4b)	1.498	1.503	30.1–31.6	0.23
	C(10b)−C(10a)	1.502	1.505	30.3–30.5	0.23
	C(4b)−C(4c)	1.335	1.345	40.7–40.7	0.77
	C(4b)−C(10a)	1.449	1.449	28.1–27.5	0.41
	C(10a)−C(10)	1.345	1.348	41.3–36.5	0.79
	C(9)−C(10)	1.451	1.446	33.0–33.0	0.45

[a] X-ray structure: B. C. Berris, G. H. Hovakeemian, Y. H. Loi, M. Mastagh and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **107**, 5670 (1985).

isomer **35**. Both molecules possess central and peripheral benzene rings, which differ in their degrees of the π-bond localization. In order to distinguish nonequivalent benzene fragments it is useful to introduce a simple measure of the partial π-bond fixation. It is given by the localization index, which is related to the aromaticity defect (equations 12a and 12b)

$$L_m(d_{CC}) = \sum_n |d_{CC}^{(n)} - \overline{d_{CC}}|(\text{Å}) \tag{12a}$$

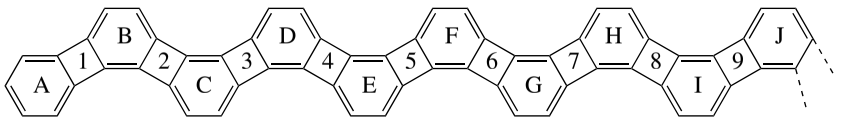
$$L_m(\pi) = \sum_n |\pi_{CC}^{(n)} - \overline{\pi_{CC}}| \tag{12b}$$

where $\overline{d_{CC}}$ and $\overline{\pi_{CC}}$ refer to the average bond distance and the average π-bond order in the ring under scrutiny, respectively. The summation is extended over all bond distances of the aromatic fragment and m denotes a fragment in question. Obviously, both $L_m(d_{CC})$ and $L_m(\pi)$ are 0 in the perfectly aromatic free benzene. As their values increase, both

the aromatic defect and bond fixation are higher. The maximal values of $L_m(d_{CC})$ and $L_m(\pi)$ are those of the central ring in **23**, which corresponds to an almost fully localized cyclohexatriene moiety. They read 0.55 and 1.86, respectively, thus defining the range of values one can encounter in fused benzenes. Let us consider the linear [3]phenylenes first. The $L_m(d_{CC})$ values for the central and peripheral benzenes (m = c, p) are 0.05 (0.06) and 0.19 (0.15), respectively, where the localization indices obtained by using the experimental bond distances are given within parentheses. The corresponding $L_m(\pi)$ (m = c, p) indices are 0.11 and 0.68, respectively. Therefore, the central ring retains a large part of its aromaticity according to the almost even bond length distribution and a low variation in the π-bond orders. This is at variance with the NICS(1) = −5.4 ppm value, which suggests a substantial decrease in aromaticity. On the other hand, the $L_p(d_{CC})$ and $L_p(\pi)$ indices strongly indicate a more pronounced localization of the peripheral benzene rings. Despite the increased localization, NICS(1) = −7.5 ppm would suggest a slight enhancement of the aromaticity compared with the central ring[93]. These results show that NICS(1) values in phenylenes should be taken with due care. The picture of the angular [3]phenylenes **35** is just the opposite to that found in its linear counterpart: the central ring is considerably more localized than that in **34** as evidenced by $L_c(d_{CC})$ = 0.32 (0.30) and $L_c(\pi)$ = 1.08. This is intuitively clear, because **35** can be imagined as if it were composed by two biphenylenes coalesced in the central benzene ring. Interestingly, this ring is more localized than the peripheral ring in **34** too. Analogously, the peripheral ring in angular [3]phenylenes **35** is somewhat more delocalized than its counterpart in **34**. The corresponding NICS(1) values, shown with the structures, are in qualitative agreement with this conclusion. It should be emphasized that the double bond C(4b)−C(4c) bridging two four-membered rings in **35** is the shortest and the most localized one, which is in accordance with its highest average s-character of 41% and a high π-bond order (0.77). Obviously, the σ- and π-electrons act in full concert in **35** as required by the Mills–Nixon effect leading *inter alia* to a decreased π-bond order in the fused bonds C(4a)−C(10b) and C(4b)−C(10a). This has an important consequence that the antiaromaticity of the cyclobutadiene rings is significantly smaller in **35** than in **34** as evidenced by the NICS(1) values of 3.1 ppm and 7.3 ppm, respectively. It comes as no surprise that bent [3]phenylene **35** is more stable than its linear counterpart **34**. The difference in the total molecular energy is, however, surprisingly small, being 1.2 kcal mol^{-1} at the MP2(fc)/6-31G*//HF/6-31G* level[157]. It is a result of a very subtle interplay between aromaticity and antiaromaticity mediated by the angular strain.

In their interesting B3LYP/6-31G* study of the limiting properties of large [N]phenylenes Schulman and Disch[160] have shown that the difference in stability between angular and linear phenylenes could be quite substantial. It is found that the zig-zag angular [19]phenylenes **36** is more stable than the linear isomer **37** by 40.4 kcal mol^{-1}, which makes 2.2 kcal mol^{-1} per cyclobutadiene ring.

It was found that NICS(1) values have converged for **36** and **37** systems, where only the left halves are explicitly shown. For the zig-zag form, which has nine unique six-membered and nine unique four-membered rings, they are (in ppm): A (−9.16), B (−3.95), C (−5.57), D (−5.08), E (−5.21), F (−5.17), G (−5.18), H (−5.18), I (−5.18), J (−5.18) for benzene fragments and $(5.37)_1$, $(2.59)_2$, $(3.48)_3$, $(3.24)_4$, $(3.31)_5$, $(3.29)_6$, $(3.30)_7$, $(3.30)_8$ and $(3.30)_9$ for cyclobutadiene rings. The latter are characterized by numbers given in the subscript. The corresponding values for the linear form **37** read: A (−6.90), B (−4.58), C (−4.47), D (−4.37), E (−4.36), F (−4.35), G (−4.35), H (−4.35), I (−4.35), J (−4.35) and $(9.27)_1$, $(9.43)_2$, $(9.80)_3$, $(9.85)_4$, $(9.88)_5$, $(9.88)_6$, $(9.89)_7$, $(9.89)_8$ and $(9.89)_9$. It appears that the fifth benzene and cyclobutadiene counted from the left terminus achieved NICS(1) values which did not change in the middle parts of the chains. Inspection of the data shows that the terminal ring is more aromatic in the angular zig-zag [19]phenylenes compared to its counterpart in linear isomer **37** as evidenced by NICS(1)



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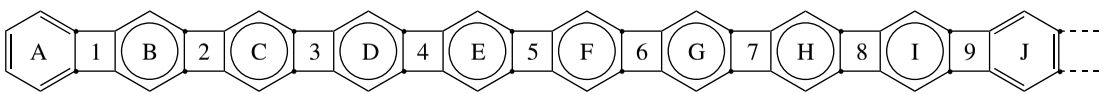


(37)

values (−9.16 vs. −6.90 ppm). Further, the cyclobutadiene rings in **37** are substantially more antiaromatic than their counterparts in **36**, whereas the overall aromaticity in both isomers is comparable. This conclusion is corroborated by the average NICS(1) values for the four-membered rings, which assume 3.5 ppm and 9.8 ppm in **36** and **37**, respectively. Somewhat surprisingly, the average NICS(1) value for benzene rings is slightly lower in the angular zig-zag [19]phenylenes than in its linear counterpart (−5.5 ppm vs. −4.6 ppm). In order to obtain a better insight into the energetic preference of the angular isomers, use of the homodesmotic reactions is appropriate. Let us consider biphenylene first[157] (equation 13).

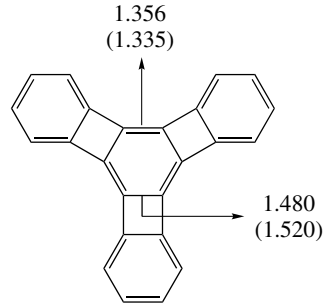
$$\mathbf{33} + 2 \text{ ethanes} = 2\ o\text{-xylenes} + E(\mathbf{33})_{\mathrm{d}} \tag{13}$$

The MP2(fc)/6-31G*//HF/6-31G* model yields $E(\mathbf{22})_{\mathrm{d}} = 52.2$ kcal mol^{-1}. Assuming that the angular strain energy is approximately the same as in free cyclobutadiene $E(\mathrm{s})_{\mathbf{1}} = 32$ kcal mol^{-1}, one concludes that the antiaromatic destabilization of the cyclobutadiene fragment in **33** is roughly 20 kcal mol^{-1}. This is lower than antiaromaticity of **1** by some 18 kcal mol^{-1}, since it was estimated in Section II. C that $E(\mathrm{an})_{\mathbf{1}}$ was 38 kcal mol^{-1}. This finding, taken together with the fact that biphenylene has two aromatic nuclei against only one cyclobutadiene fragment, explains the stability of this interesting compound and perseverance of its pattern in higher phenylenes. By using the corresponding homodesmotic reactions for linear and angular phenylenes, it was shown[157] that the destabilization energies $E([\mathrm{N}]\text{phenylene})_{\mathrm{d}}$ are approximately additive, being proportional to the $E(\mathbf{33})_{\mathrm{d}}$ destabilization in biphenylene and the number of cyclobutadiene rings $E([\mathrm{N}]\text{phenylene})_{\mathrm{d}} \cong (\mathrm{N}-1) \cdot E(\mathbf{33})_{\mathrm{d}}$. However, it should be stressed that it is a deviation from the additivity, which explains the greater stability of the angular phenylenes due to a somewhat diminished antiaromaticity of cyclobutadiene moieties and more orchestrated behavior of σ- and π-electrons. This difference becomes very large in higher [*N*]phenylenes assuming 40 kcal mol^{-1} in the limit as illustrated by **36** and **37**.

Results obtained by Maksić and coworkers[157] and Schulman and Disch[160] show convincingly that preservation of the biphenylene bonding pattern is very important for understanding the properties of higher [*N*]phenylenes. To reiterate, the underlying reason is that the σ- and π-electrons act in a cooperative way in producing a characteristic bond fixation, which in turn decreases the antiaromatic character of the cyclobutadiene rings. Hence, cyclobutadiene moiety appears to be the leading structural and electronic motif, which exerts a dominant influence on the electronic interactions and electronic density distributions in [*N*]phenylenes[157]. This feature explains a surprising finding that angular [*N*]phenylenes are more stable than the linear ones, in spite of the fact that they are more localized at the same time. They are simply better fitted to diminish the antiaromatic destabilization and to insure a concerted synaction of the σ- and π-electrons.

Everything said for angular phenylenes should hold to an even larger extent in branched polyenes exemplified here by starphenylene **38**.

Since the central benzene ring is a common part of three biphenylenes, it should be highly localized. This is indeed the case as confirmed by X-ray measurements[178] and MP2(fc)/6-31G* computations[101]. The bond distances of the annelated and *exo* bonds are 1.480 (1.520) Å and 1.356 (1.335) Å, respectively, where the experimental values are given within parentheses. It appears that the MP2(fc)/6-31G* method underestimates the length of fused bonds and overestimates the length of the *exo* bonds. Hence, the bond localization index $L(\mathrm{d})$ for the central benzene moiety is 0.37 and 0.55 obtained by the MP2 and X-ray methods, respectively. Whereas the theoretical value is rather low, the experimental structure shows that the π-electron localization pattern in the central ring is of the frozen cyclohexatriene type, which is comparable to that found earlier in **23**. It is interesting to mention that an extended starphenylene structure—the hexasilylated trigonal



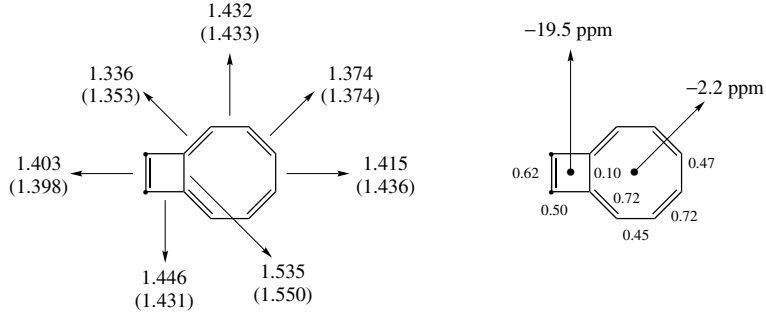
(38)

[7]phenylene—was prepared and its crystal structure was determined by Vollhardt and coworkers[179]. The central benzene ring exhibits the same almost ideal cyclohexatriene distribution of the double and essentially single bonds of the sp^3-sp^3 canonical type as evidenced by the $L_c(d)$ value 0.55 obtained by the experimental bond distances.

It is finally worth noting that biphenylene is not only a building block of higher phenylenes and heliphenes, but also a structural unit in constructing dimers[180,181], which in turn may lead to high-carbon materials exhibiting a number of outstanding properties. To summarize the field of [4]annuleno[6]annulenes in one sentence, it can be safely stated that phenylenes, biphenylene analogues[182] and related compounds represent a very rich field, which promises many fruitful harvests in the future.

As a final general comment, it should be emphasized that fusion of cyclobutadiene moiety into an aromatic π-system leads to a number of changes in the geometric and electronic structure of aromatic nuclei, which are sometimes dramatic. The cyclobutadiene fragment itself exhibits a full range of decreased antiaromaticities culminating in a strongly pronounced aromaticity in benzodicyclobutadiene **28**. It is less familiar that cyclobutadiene has an amazing ability to change properties of compounds by fusion which are not necessarily aromatic. This is exemplified here by bicyclo[6.2.0]decapentaene **39** (Figure 7), obtained by annelation of cyclobutadiene to cyclooctatetraene.

The resulting structure is planar as evidenced by X-ray analysis[183] and B3LYP/6-31G* calculation[184]. It appears that the tub structure of a free cyclooctatetraene possessing



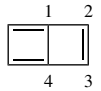
(39) **(39a)**

FIGURE 7. Comparison of bond distances in bicyclo[6.2.0]decapentaene **39** obtained by X-ray (B3LYP/6-31G*) methods and Löwdin π-bond orders presented together with NICS(1) values (**39a**)

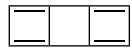
antiaromatic 8π electrons is converted into a planar structure due to the newly formed aromatic 10π-electron frame. Although the distribution of CC bonds over the perimeter exhibits a significant localization and concomitant anisotropy in bond distances and π-bond orders, this system illustrates rather nicely the importance of the concepts of antiaromaticity and aromaticity and the wealth of new features obtained by their interplay. It is remarkable indeed that the annelated bond has π-bond order as low as 0.1, which in turn is in harmony with enormous aromatization of the cyclobutadiene fragment evidenced by NICS(1) = −19.5 ppm as calculated by the GIAO HF/6-31G*//B3LYP/6-31G* level (Figure 7)[184]. The planar eight-membered ring is nonaromatic in contrast to antiaromaticity of free cyclooctatetraene in its planar transition state structure.

2. The spatial and electronic structure of [4]annuleno[4]annulenes

a. Butalenes: Aromatic or antiaromatic—That is not a question!. Butalenes represent a very interesting family of fused two or more cyclobutadiene rings. We consider here only the three smallest members **40**, **41** and **42**. It should be mentioned that single resonance structures are given only for each member of the series for the sake of simplicity. Butalene (**40**) was mentioned first as a possible stable species by Roberts, Streitwieser and Regan in 1952[185] on the basis of Hückel calculations, which gave a delocalization energy of 1.66β. Since the resonance integral is a negative β quantity, they surmised that **40** is aromatic and that it might be prone to chemical synthesis. It was not prepared as yet, but Breslow and coworkers[186, 187] reported trapping experiments which suggested that **40** might exist as a transient intermediate.



(40)



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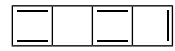
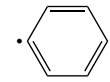


(42)



(43)

The stability of butalene has been the subject of numerous studies. The barrier to ring opening leading from **40** to its 'valence isomer' *p*-benzyne diradical (**43**) was estimated by several *ab initio* studies, albeit on relatively low theoretical levels[188–190]. Thus, Noell and Newton[188] performed generalized valence bond (GVB) calculation based on the 4-31G basis set and calculated that *p*-benzyne is more stable than **40** by some 77 kcal mol^{-1}. They used only a very limited geometry optimization. Thus their result should be considered as qualitative at best. Nicolaides and Borden[189] carried out complete HF/6-31G* geometry optimizations followed by single-point two-configuration SCF calculations and found that **40** was higher in energy by 60.7 kcal mol^{-1} than *p*-benzyne **43**. A more sophisticated QCISD(T) calculation lowered this difference to 37.0 kcal mol^{-1}. Finally, Ohta and Shima[190] reported GVB calculations with the 4-31G basis set, which put **40** 71.3 kcal mol^{-1} above **43** with an early transition state of only 1.6 kcal mol^{-1} in the C(1)−C(4) bond-stretching transformation from **40** to **43**. However, the barrier height is unreliable at this level of theory, since it requires a multireference coupled cluster treatment in order to obtain a reliable value. Warner and Jones[191] applied B3LYP/6-311 + G*//B3LYP/6-31G* calculations and obtained a difference in stability between **40** and **43** of about 39 kcal mol^{-1}. They concluded that DFT methods were not able to adequately treat diradical structures like **43** and used the experimental enthalpy of formation for the latter. They estimated the barrier height for the ring-opening reaction yielding **43** and obtained a very low hurdle of about 3 kcal mol^{-1} by the CCSD(T)/6-31G**//B3LYP/6-31G* method. One is tempted to conclude that such a barrier is too small to ensure

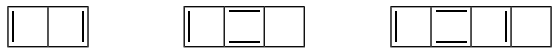
the existence of butalene **40**. Finally, Hess[192] executed B3LYP/cc-pVTZ calculations and scanned the potential energy hypersurface along the intrinsic reaction path with the result that the TS is higher by 6 kcal mol^{-1} than butalene **40** and about 43 kcal mol^{-1} above diradical **43**, implying that the latter is more stable than butalene by 37 kcal mol^{-1}. All calculations are consistent with the conclusion that butalene is considerably more unstable than its diradical isomer **43**. This finding coupled with a low barrier of about 3 kcal mol^{-1} casts serious doubts that **40** is amenable to chemical synthesis.

Calculated geometries of butalenes **40**–**42** are interesting. The progenitor of the series, molecule **40**, is planar with a very long central C(1)−C(4) bond (1.592 Å), which reflects a tendency of two four-membered rings to alleviate antiaromaticity[191]. In contrast, higher butalenes **41** and **42** are nonplanar, assuming tub structures (Figure 8), which is a consequence of a strong antiaromatic destabilization.

Warner and Jones[191] reckoned that stability of butalenes would be best described by isodesmic reactions, which could describe the energetic cost/benefit ratio by introducing a double bond at a previously saturated position. For example, an isodesmic reaction[193], which matches the formal single and double bonds in reactants and products and relates cyclobutadiene **1** with cyclobutene, is equation 14

$$\mathbf{1} + \text{ethane} = \text{cyclobutene} + \text{ethylene} + E(\text{an})_{\mathbf{1}}'' \tag{14}$$

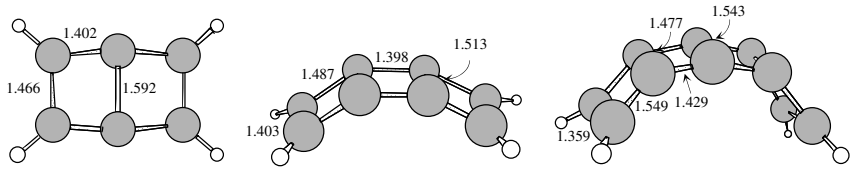
where $E(\text{an})_{\mathbf{1}}''$ denotes the antiaromaticity of **1.** The B3LYP/6-311 + G**//B3LYP-/6-31G* calculation gives $E(\text{an})_{\mathbf{1}}'' = 33.1$ kcal mol^{-1} [191], which is comparable with our estimate $E(\text{an})_{\mathbf{1}}'' = 38$ kcal mol^{-1} obtained by the homodesmotic reaction given in equation 1. The latter should be considered, of course, as a better estimate. To put it another way, $E(\text{an})_{\mathbf{1}}''$ is the price to be paid for the introduction of an additional double bond in cyclobutene, which leads to antiaromatic cyclobutadiene in equation 14. One can discuss antiaromaticity of **40**, **41** and **42** in an analogous way by using ancillary compounds **44**–**46**.



(44) **(45)** **(46)**

It is plausible to assume that **44** has antiaromaticity close to zero. Therefore, the isodesmic reaction in equation 15

$$\mathbf{40} + \text{ethane} = \mathbf{44} + \text{ethylene} + E(\text{an})_{\mathbf{40}}'' \tag{15}$$



(40) **(41)** **(42)**

FIGURE 8. Characteristic B3LYP/6-31G* CC bond distances[191] in planar **40** and tub structures **41** and **42**

will give some idea about antiaromatic destabilization of butalene **40**. It appears that $E(\text{an})_{\mathbf{40}}''$ is 32.5 kcal mol^{-1}, thus being just slightly smaller than the antiaromaticity of cyclobutadiene (equation 14). However, it should be noted that the corresponding strain in **40** is not exactly matched by the corresponding strain energy in **44**. The point is that the carbon atoms of the annelated central bond in **40** are more deformed owing to the presence of double bonds C(1)−C(6) and C(4)−C(5). Consequently, true antiaromaticity is lower than $E(\text{an})_{\mathbf{40}}''$. It is therefore fair to state that antiaromaticity of **40** is definitely lower than that in the parent cyclobutadiene. It is interesting to compare this result with the Hückel calculation of the resonance energy per electron (REPE) of Hess and Schaad[194]. They find that REPE for **1** and **40** is −0.268 and −0.067 (in β units), respectively, meaning that the latter molecule is less antiaromatic indeed. Further, an isodesmic reaction relating **41** and **45** takes the form of equation 16

$$\mathbf{41} + \text{ethane} = \mathbf{45} + \text{ethylene} + E(\text{an})_{\mathbf{41}}'' \tag{16}$$

If it is tacitly assumed that antiaromaticities of **40** and **45** are practically the same, then $E(\text{an})_{\mathbf{41}}'' = 8.6$ kcal mol^{-1} indicates that bicyclobutadienylene **41** is somewhat more antiaromatic than butalene **40**. This is again in qualitative accord with REPE of **41**, which assumes a value of -0.079β[194]. Finally, isodesmic reaction 17

$$\mathbf{42} + \text{ethane} = \mathbf{46} + \text{ethylene} + E(\text{an})_{\mathbf{42}}'' \tag{17}$$

yields $E(\text{an})_{\mathbf{42}}'' = 16.3$ kcal mol^{-1}, implying that **42** is more antiaromatic than **41**. This is once more in agreement with REPE(**42**) $= -0.122\beta$[194]. On the basis of B3LYP[191] and Hückel calculations of REPE[194] it is safe to conclude that butalenes **40–42** are antiaromatic systems. The antiaromatic destabilization increases along the series leading to severe nonplanarities in **41** and **42**. It would be advantageous to replace isodesmic equations 14–17 with more realistic homodesmotic reactions offering better estimates of the destabilization energies.

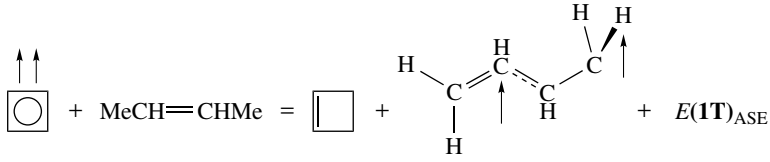
It is interesting to note as a final comment that Liebman and Van Vechten[195] compared the stability of the series of annelated four-membered rings commencing with cyclobutadiene and butalene, with that of polyacenes starting with benzene and naphthalene. In doing so Liebman and Van Vechten[195] derived first energies for $=CH_2$, $=CH-$and $=C<$ fragments using ethylene, benzene and graphite as reference systems. It was found that butalenes were less stable than the corresponding polyacenes.

III. CYCLOBUTADIENE IN EXCITED STATE

A. Aromaticity of the First Triplet State

The excited states of cyclobutadiene and its derivatives produced by fusion to aromatics are a large topic, which lies outside the scope of the present chapter. However, the lowest triplet state of the square transition structure of cyclobutadiene is important, since it exhibits aromaticity, which bears some relevance to the reactivity of this remarkable compound. It was shown by Borden and Davidson[196] that the D_{4h} structure of cyclobutadiene represents a minimum on the triplet potential energy hypersurface. At the same time, the D_{4h} structure is TS for the double-bond flipping interconversion of two equivalent D_{2h} minima on the singlet potential energy hypersurface (Section II.A). The single−triplet (S-T) splitting in the square transition state (TS) structure is low (Figure 2), thus being also a characteristic signature of antiaromaticity. The state-universal multireference coupled-cluster calculation at the two-determinant CCSD(T) level gives 6.6 kcal mol^{-1} for (S-T) splitting[51]. A more recent CCSD(T)/cc-pVDZ//B3LYP/6-311+G(d,p) study has shown

that the (S-T) splitting for the square geometry was 11.5 kcal mol^{-1} [197], which was in very good agreement with flash photolysis measurements performed on peralkylated cyclobutadiene by Wirz and coworkers[198]. Importantly, the first triplet state ($^3A_{2g}$) in the D_{4h} spatial symmetry of cyclobutadiene is aromatic, which is reflected in equal bond distances and a NICS(1) value of −5.3 ppm[197]. This is in accordance with earlier semiempirical results of Baird[199], who concluded that the rules of aromaticity and antiaromaticity are reversed in the lowest triplet states of annulenes. He suggested that the aromatic stabilization energy (ASE) of the lowest triplet state should be determined against the lowest triplet state of the open-chain polyene involving the same number of carbon atoms. By using this criterion and the homodesmotic reaction 18



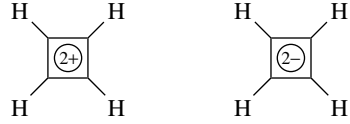
(18)

(1T) **(T)**

Schleyer and coworkers[197] found that the aromatic stabilization $E(\mathbf{1T})_{ASE}$ is −7.0 kcal mol^{-1}. A small singlet–triplet splitting between the first singlet and triplet states and a low interconversion barrier may well have a strong influence on the reactivity of cyclobutadiene. It was argued by Shaik and coworkers[200] that a very reactive molecule possesses low-lying excited states with spin-unpaired electrons, which are capable of forming new coupled pairs and additional covalent bonds. Triplet states of a conjugated molecule prepare the molecule to react with another molecule in its triplet state, e.g. in cyclodimerization or cycloaddition reactions[200], which are characteristic for cyclobutadiene. Consequently, Shaik and Shurki[200] concluded that a high reactivity of cyclobutadiene is a consequence of a kinetic instability associated with the existence of a low-lying triplet state. This plausible hypothesis deserves close scrutiny by high level post-Hartree–Fock methods.

IV. CYCLOBUTADIENE DICATIONS AND DIANIONS

In contrast to cyclobutadiene, its dication (**47**), possessing two π-electrons, and dianion (**48**), with six π-electrons, should be aromatic according to the Hückel rule. At the same time, considerable charge–charge repulsion arising from the dispersion of two positive (negative) charges over only four carbon centers is expected to diminish the stabilizing electronic features of the Hückeloid system.



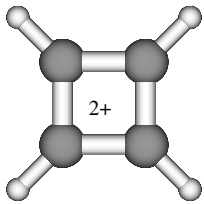
(47) **(48)**

Both ions **47** and **48** have been the subject of many theoretical studies, because they represent two paradigmatic cases of the electron-depleted and electron-rich monocycles, respectively. The most important, in chronological order, are those of Pittman and coworkers[201], Schleyer and colleagues[202], Hess, Ewig and Schaad[203], Skancke and

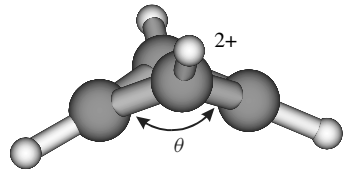
Agranat[204], Minkin and colleagues[205], Zandwijk and coworkers[206] and Sommerfeld[207]. The most recent publication of Schleyer[202d] offers a summary of the previous studies, which indicate that the parent dication is aromatic, but the parent dianion is non- or antiaromatic. Neither **47** nor **48** is observed experimentally in free forms. Moreover, **48** seems to be unstable toward electron loss according to B3LYP/6-311+G(d) calculations[202d].

A. Structural Features of Cyclobutadiene Dication and its Derivatives

It is generally accepted by now that dication **47** is not a planar molecule with D_{4h} symmetry (**47a**) as might be expected for an aromatic species, but rather a nonplanar D_{2d} structure (**47b**)[202a, 202d]. The geometric parameters of structures **47a** and **47b** calculated at the MP4/6-31G* level of theory are shown below for the sake of illustration[208].



(**47a**), D_{4h}
d_{CC} = 1.447 Å
d_{CH} = 1.097 Å



(**47b**), D_{2d}
d_{CC} = 1.425 Å
d_{CH} = 1.099 Å
θ = 134.9 °

The sizable puckering of the ring of 45.1° in **47b** is a result of the cooperative effect of favorable 1,3-homoallylic interactions and stabilization of several MOs upon a decrease in symmetry on going from D_{4h} to D_{2d} structure[202a, 202d]. The latter are shown in Figure 9.

The major stabilization occurs in the $3e_u$, $2b_{2g}$ and $2a_{1g}$ MOs. The last one is formed predominantly by 2s(C) atomic orbitals and its orbital energy is lowered primarily through enhanced overlapping in **47b**, because its C(1)−C(2) and C(1)−C(3) distances are shortened by 0.02 and 0.09 Å, respectively, as obtained by the HF/6-31G* calculations[202a]. A different situation is found in the $2b_{2g}$ and $3e_u$ MOs, where, e.g., the CH bond back lobes point toward each other (1,3-interaction) inside the ring in the former orbital (Figure 9). In the $2b_{2g}$ MO, two nodal planes bisect the next to nearest-neighbor CC bonds, resulting in a depleted electron density in the center of the ring. Puckering of the ring shifts these local hybrid AOs out of the initial molecular plane leading to a positive 1,3-electron density interference with concomitant pairwise stabilization. It is interesting to notice that the resulting stabilization is so large that the $2b_2\,(D_{2d})$ MO energy becomes practically degenerate with the $3a_1$ in the puckered structure at least within the RHF/STO-3G method (Figure 9). The pair of degenerate $3e_u$ MOs are strongly 1,3-antibonding. Thus, puckering decreases the unfavorable interaction by tilting the AOs, leading to a reduced overlapping. It should be strongly emphasized that not all features are advantageous in D_{2d} symmetry (**47b**). For instance, the $1b_{1g}$ MO composed of the tangential 2p(C) AOs represents a typical Walsh MO involving 1,2-bonding and 1,3-antibonding interactions as evidenced by positive and negative overlapping, respectively. Its orbital energy is somewhat increased in D_{2d} conformation. Furthermore, puckering leads to a loss in delocalization energy and an increase in the angular strain energy. It turns out, however, that pyramidalization in the puckered form leads to an overall stabilization, which is a result of a subtle interplay of

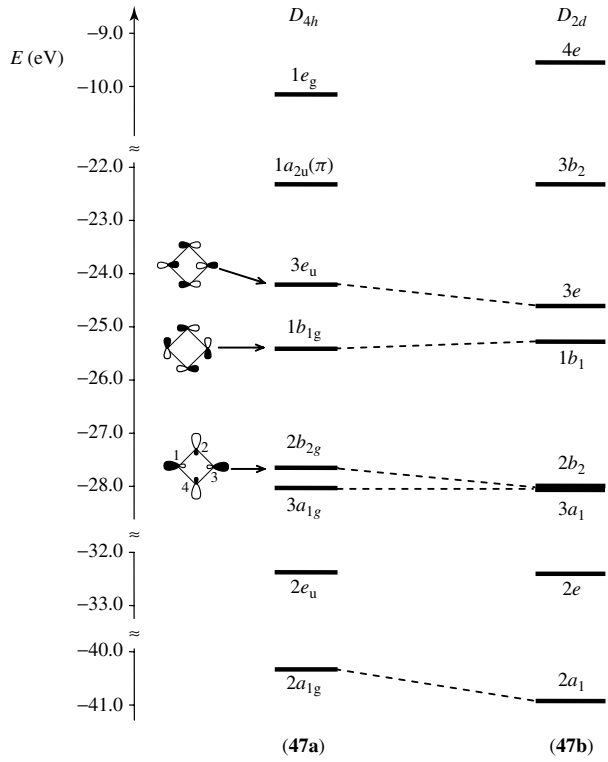


FIGURE 9. Comparison of orbital energies in **47a** (D_{4h}) and **47b** (D_{2d}) structures for cyclobutadiene dication calculated by the RHF/STO-3G method. Schematic representation of the $1b_{1g}$, $2b_{2g}$ and just one of the two $3e_u$ molecular orbitals of D_{4h} structure are also included

several effects. It appears that **47b** is more stable than **47a** by 9.6 kcal mol^{-1}, as obtained by MP4/6-31G(d)//HF/6-31G(d) calculation[202d]. The former is, however, above neutral cyclobutadiene **1** by 514 kcal mol^{-1}, as estimated at the same theoretical level.

In spite of appreciable puckering, dication **47b** is an aromatic species according to NICS(0) value of −9.0 ppm calculated by using the GIAO method with the HF/6-31G(d) model at the B3LYP/6-31G(d) optimized geometry[202d]. Likewise **47**, its tetramethyl- (**49**), tetra-*t*-butyl- (**50**) and tetrafluoro- (**51**) derivatives (Figure 10) were also found to be aromatic[202d].

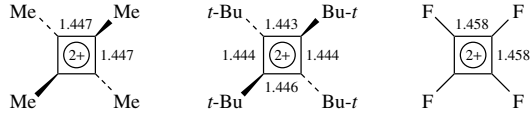


FIGURE 10. Calculated geometric parameters for dications **49**[202d], **50**[202d] and **51**[208] at the B3LYP/6-31G* level

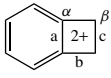
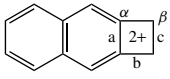
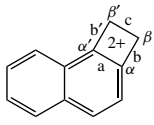
The minimum energy structures of **49** and **50** strongly resemble the structure of the parent dication, while for tetrafluorocyclobutadiene dication (at the STO-3G level) the planar structure was reported[202d]. We note in passing that the D_{4h} structure of the latter molecule was also found to be energy minimum at the B3LYP/6-31G* level of theory[208].

We have recently addressed a problem of aromaticity of cyclobutadiene dications annelated to an aromatic ring, **52–54**. The MP2/6-31G* optimized structures[209] and the NICS(1) values for the four-membered ring in these dications are summarized in Table 8. Comparison of the calculated structures with those of the neutral molecules reveals a less pronounced localization of the double bonds within the four-membered ring than in the neutral molecule. This effect appears to be most pronounced for naphtha[*b*]cyclobutadiene dication **53** (Table 8). The calculated NICS(1) values indicate that all considered ions are aromatic. In particular, the cyclobutadiene fragment exhibits a high aromaticity ranging from −10.6 to −14.7 ppm.

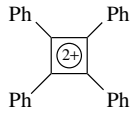
The aromaticity of substituted cyclobutadiene dications has also been challenged experimentally. Thus, preparation of a series of the substituted cyclobutadiene dications under superacidic stable-ion conditions was reported by Olah and Liang[210]. They include tetra methyl- (**49**), tetraphenyl- (**55**), 1,2-difluoro-3,4-diphenyl- (**56**) and 1,2-diphenylcyclobutadiene (**57**) dications.

Olah and Liang also described preparation of dimethyl benzocyclobutadiene dication (**52a**)[211]. Based on a comparison of ^{13}C NMR chemical shifts with those of the previously mentioned cyclobutadiene dications **49, 55, 57**, these researchers concluded that ion **52a** is aromatic, being thus in agreement with our theoretical predictions[209]. This work was soon followed by NMR studies of dibenzocyclobutadiene dications **58–61**[212]. In contrast, only UV-Vis data are known[213] for the parent biphenylene dication (**62**).

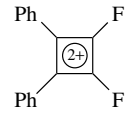
TABLE 8. Selected bond lengths (in Å), NICS(1) values and ^{13}C NMR chemical shifts of dications **52–54**[209]

Dication	Bond	Distance [a]	NICS(1) [b]	Atom	δ^{13}C [c]
	a	1.501	−11.5	C_α	176.36
	b	1.424		C_β	210.97
	c	1.453			
(52)					
	a	1.513	−14.7	C_α	158.34
	b	1.408		C_β	196.58
	c	1.464			
(53)					
	a	1.490	−10.6	C_α	171.00
	b	1.437		$C_{\alpha'}$	179.27
	b'	1.438		C_β	195.62
	c	1.427		$C_{\beta'}$	185.24
(54)					

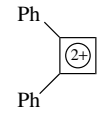
[a] Calculated at the MP2/6-31G* level.
[b] GIAO-B3LYP/6-31+G*//MP2/6-31G*; the NICS(1) value was calculated at 1 Å above the center of the four-membered ring.
[c] GIAO-B3LYP/6-31+G*//MP2/6-31G*.



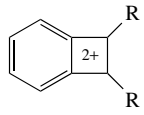
(55)



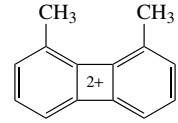
(56)



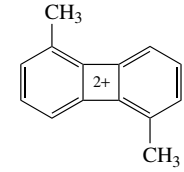
(57)



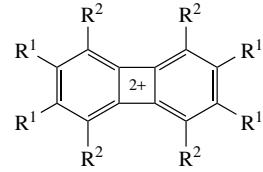
(52) R = H
(52a) R = CH_3



(58)



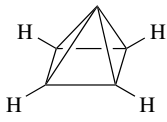
(59)



(60) $R^1 = CH_3$; $R^2 = H$
(61) $R^1 = H$; $R^2 = CH_3$
(62) $R^1 = R^2 = H$

B. Electronic Structure of Pyramidane

In connection with cyclobutadiene dication, it is also interesting to consider the electronic structure of pyramidane (tetracyclo[2.1.0.$0^{1,3}0^{2,5}$]pentane) C_5H_4 (**63**).



(63)

The molecule was first mentioned as a possible stable structure by Minkin and coworkers[214a], who performed semiempirical MINDO/3 calculations. Subsequent HF small basis set calculations supported this conjecture, providing some important clues for practical synthetic routes[214b]. The MP2 calculations of Balaji and Michl[214c] confirmed that pyramidane was indeed a local minimum. A comprehensive study of the pyramidane potential energy surface by Schaefer and coworkers[214d] at a high CCSD(T)/TZ2P theoretical level has shown conclusively that pyramidane was a true minimum with substantial barriers to isomerization. The aromatic character of pyramidane was briefly mentioned in a theoretical paper on lithium-capped annulenes by Jemmis and Schleyer[214] in 1982 and its potential aromatic character was briefly discussed by Lewars in a study of the C_5H_4 potential surface[215]. This study indicated that **63** has exceptionally long apex-to-base bonds (1.642 Å at the MP2/6-31G* level), with a total Löwdin bond

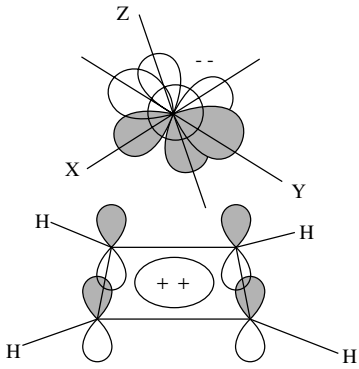


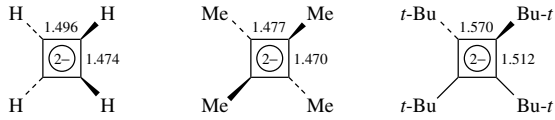
FIGURE 11. Schematic representation of the electronic structure of **63**. Reproduced by permission of Elsevier B.V. from Reference 215

order appreciably less than one (0.79). The peculiar electronic distribution was further substantiated by the natural bond orbital (NBO) analysis, which revealed that the apical carbon possesses six valence electrons, including a lone pair (1.998 electrons) placed largely in a 2s (82% s, 18% p) orbital. In other words, these results suggest that the electronic structure of pyramidane can be approximated as an unhybridized C^{2-} unit bonded to an aromatically stabilized cyclobutadiene dication (Figure 11).

The resulting representation shows that the three 2p orbitals on the apical carbon dianion occupied by four electrons overlap with the π-system of the cyclobutadiene dication possessing two electrons, thus forming four CC bonds. Each of these four CC bonds has $6/4 = 1.5$ electrons. Given that bond order is proportional to the number of electron pairs, it follows that the former is $(1.5/2) = 0.75$, which is close to the Löwdin bond order of 0.79 obtained by calculations mentioned above. However, application of the NICS criterion by varying positions of the probe nucleus gave no evidence for aromaticity of the cyclobutadiene dication-like base of pyramidane[216], leaving the definite answer to this question to more elaborate calculations in the future.

C. Cyclobutadiene Dianion and its Dilithium Salts

In spite of many efforts that have been directed toward studying cyclobutadiene dianion (**48**) in the past, its nature remains elusive. The early calculations indicated that the parent cyclobutadiene dianion should be regarded as a nonaromatic species. For example, based on results of the HF/6-31G(d) MO calculations, Hess and coworkers[203] predicted that **48** has bent structure of C_s symmetry, where the negative charge is delocalized over the allylic anion fragment and strongly localized at the C-4 atom. However, this highly unusual structure was not verified to be a minimum by vibrational analysis. Subsequent HF/6-31G* calculations supported by vibrational analysis have shown that the C_s structure corresponds to a saddle point on the potential energy surface of $C_4H_4^{2-}$ ion, while the global minimum has a C_2 symmetry at least at the HF level[202d]. It is interesting that the latter structure is also a false minimum, as revealed by the B3LYP/6-31G* calculations. It turned out that the true minimum had a more symmetrical C_{2h} structure **48** at the DFT B3LYP/6-31G* level[202d]. *Ab initio* and B3LYP calculated structures of tetramethylcyclobutadiene dianion (**64**) and tetra-*t*-butylcyclobutadiene dianion (**65**) were also reported[202d]. Within the HF/6-31G(d) formalism dianion **64** was found to have trapezoidal structure of C_2 symmetry, with one long C−C bond (1.570 Å), and one short (1.378 Å)

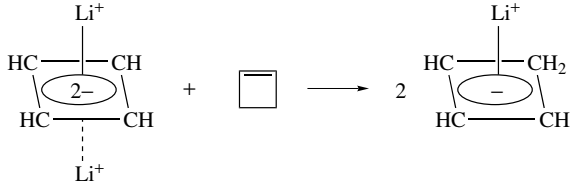


(48), C_{2h} **(64)**, C_{2h} **(65)**, C_2

FIGURE 12. Calculated geometric parameters for dianions **48**, **64**, and **65** at the B3LYP/6-31G* level[202d]

and two intermediate C−C bonds (1.473 Å). The latter structure optimizes back to C_{2h} symmetry at the B3LYP/6-31G* level. Interestingly, for tetra-*t*-butylcyclobutadiene dianion (**65**) both methods predict the C_2 structure to be the most stable. The B3LYP/6-31G* optimized structures of **48**, **64** and **65** are illustrated in Figure 12[202d].

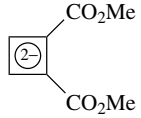
All these results should be taken with extreme care, since B3LYP/6-311+G(d) calculations of Schleyer and coworkers[202d] involving diffuse basis set functions indicate that cyclobutadiene dianion is probably not a stable molecule. This result is corroborated by the most recent calculations of Sommerfeld[207], which conclusively show that the parent dianion is unstable with respect to electron loss. Instead, it is a resonance state with an extremely short lifetime of 0.7 fs. Consequently, standard finite basis bound state methods cannot provide a reliable description of its structure and are condemned to fail. However, a stable system can be obtained by capping the parent ion with two lithium ions, as was first noted by Kos and Schleyer[217]. In the resulting charge-balanced $(C_4H_4{}^{2-})2Li^+$ complex, counteraction of the two Li^+ cations compensates for the dianionic electron repulsion, which leads to out-of-plane distortion of the hydrogens in the parent $C_4H_4{}^{2-}$, thus allowing for the aromatic stabilization of the complex. The results of early computational work by Schleyer and coworkers[202] and also by Zandwijk and colleagues[206] reveal indeed that $Li_2-C_4H_4$ (**66**) possesses a stable D_{4h} conformation with the Li^+ cation on either side of the ring above and below its center. The substitution by methyl and *t*-butyl groups lowers the symmetry of the complex to C_{2h} and D_2 symmetry, respectively, but the lithium-ring center distances remain similar, varying within the range 2.00–2.057 Å. The aromatic properties of the dianions **48**, **64** and **65** capped by two Li^+ cations are reflected in the NICS(0) values (−22 to −24 ppm), which are more negative than that of benzene, and by the calculated ^7Li chemical shifts which vary from −2.3 to −3.4 ppm with respect to free Li^+. Additional information on aromaticity of **66** is obtained by calculating its aromatic stabilization energy (ASE)[218] according to charge-balanced and strain-corrected homodesmotic reaction (equation 19).



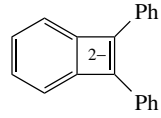
(66) (19)

The resulting ASE of 29.2 kcal mol^{-1} (calculated at the B3LYP/6-311+G**//B3LYP/6-311+G**+ZPE level) turned out to be comparable to the benzene value (33 kcal mol^{-1})[219a] obtained at the same theoretical level.

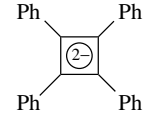
As to the experimental studies of cyclobutadiene dianions, some evidence for the formation of the parent dianion **48** as an intermediate was obtained by Pettit and colleagues[220]. In 1978, Garratt and Zahler used ester groups[221] to delocalize the negative charge and succeeded in obtaining the corresponding dianion **67** as a stable species at room temperature. Based on measurements of pK_a they concluded that the dianion **67** did not exhibit any aromatic stabilization. In 1982 and 1985, NMR studies of the dilithium salt of the 1,2-diphenylbenzocyclobutadiene dianion (**68**) and the dipotassium salt of tetraphenylcyclobutadiene dianion (**69**) were reported by Boche and coworkers[222].



(67)

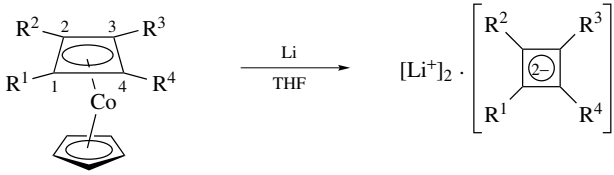


(68)



(69)

None of these studies indicated a preferred cyclic delocalization with formation of a six π-electron system. In 2000, Sekiguchi and coworkers[223, 224] reported the first experimental evidence in favor of aromaticity of a dilithium salt of tetrakis(trimethylsilyl)cyclobutadiene[223] dianion (**70**) and the *cis*-diphenyl-substituted cyclobutadiene dianion bridged by a [−$SiMe_2(CH_2CH_2)SiMe_2$−] chain (**71**)[224], respectively, which were prepared by reaction of the corresponding cyclobutadiene cobalt complexes (**70a** and **71a**) with lithium metal in THF.



(70a) ($R^1 = R^2 = R^3 = R^4 = SiMe_3$)
(71a) ($R^1 = R^2 =$ Ph, $R^3 = R^4 = Me_2SiCH_2CH_2SiMe_2$)
(72a) ($R^1 = R^2 =$ Ph, $R^3 = R^4 = SiMe_3$)
(73a) ($R^1 = R^3 =$ Ph, $R^2 = R^4 = SiMe_3$)

(70) ($R^1 = R^2 = R^3 = R^4 = SiMe_3$)
(71) ($R^1 = R^2 =$ Ph, $R^3 = R^4 = Me_2SiCH_2CH_2SiMe_2$)
(72) ($R^1 = R^2 =$ Ph, $R^3 = R^4 = SiMe_3$)
(73) ($R^1 = R^3 =$ Ph, $R^2 = R^4 = SiMe_3$)

Based on planarity of the four-membered ring, the lack of bond alternation and considerable upfield ^{7}Li chemical shifts, Sekiguchi and coworkers[223, 224] concluded that both ions should be aromatic species. More recently, the same authors reported preparation and X-ray crystal structure of 1,2-diphenyl-3,4-bis(trimethylsilyl)cyclobutadiene dianion dilithium (**72**) and 1,3-diphenyl-2,4-bis(trimethylsilyl)cyclobutadiene dianion dilithium (**73**)[225] from the complexes **72a** and **73a**, respectively. Similar to the cases of **70** and **71**, the ring geometry of the four-membered ring in these Li salts was found to be nearly planar. However, in contrast to the former species, the cyclobutadienediide ring in **72** exhibits trapezoidal structure, whereas that of **73** shows slightly rhomboid geometry (Table 9).

Comparison of the measured ^{7}Li chemical shifts for this series (Table 9) suggests that the degree of aromaticity of the four-membered ring in these species can be represented by inequalities **70** ($\delta = -5.07$) > **73**($\delta = -4.44$) $\geqslant$ **71** and **72** ($\delta = -4.21$ and -4.24 ppm),

TABLE 9. Selected bond distances (in Å) and ^{7}Li NMR chemical shifts (in ppm) of dilithium salts **70–73**[223–225]

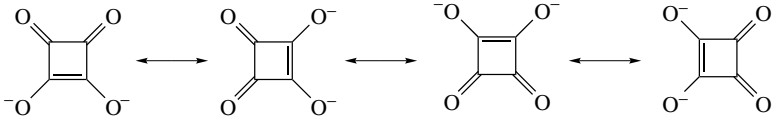
Dilithium salt	Bond distances[a] (Å) C(1)−C(2)	C(2)−C(3)	C(3)−C(4)	C(1)−C(4)	d(Li)[b] (Å)	δ^7Li (ppm)	Reference
70	1.507(9)	1.493(4)	1.485(10)	1.496(3)	1.901(1)	−5.07	223
71	1.470(2)	1.472(2)	1.482(2)	1.466(2)	1.959(6)	4.21	224
72	1.462(4)	1.488(4)	1.521(4)	1.479(4)	1.928(6)	−4.24	225
73	1.486(3)	1.488(3)	1.486(3)	1.488(3)	2.070(4)	−4.44	225

[a] X-ray results.
[b] The average Li distances from the ring centroid.

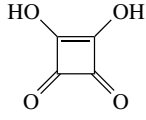
indicating that stabilizing cyclic electron delocalization in the ring decreases on the introduction of the benzene ring. It should be recalled in this respect that lower δ implies higher aromaticity. Finally, it is worth mentioning that **70** exhibits a negative Faraday A term in the magnetic circular dichroism spectrum[226]. The latter is interpreted by excitation from the degenerate e_g orbitals to the nondegenerate b_{2u} orbital in accordance with an earlier theoretical proposition by Michl[227]. It is interesting to mention that this is the first clear demonstration of a negative Faraday A term in an aromatic species. A more extensive description of the work on dilithium salts of the cyclobutadiene dianion substituted with silyl and phenyl groups can be found in a recently published review article by Matsuo and Sekiguchi[228].

V. SQUARIC ACID, ITS ANIONS AND RELATED COMPOUNDS

The 3,4-dioxo-cyclobutene-1,2-diol dianion, better known as the squarate dianion (**74**), was first mentioned by Cohen and colleagues[229] in connection with unusually strong acidity of the parent squaric acid (**74a**). These authors interpreted the high acid strength of **74a** as evidence that squarate dianion was greatly resonance-stabilized.



(74)



(74a)

The delocalized structure proposed for squarate dianion led West and coworkers[230] to suggest that the squarate dianion was aromatic and that oxocarbon anions of the general formula $C_nO_n^{2-}$ constitute a previously unrecognized class of new aromatic species. Experimentally, the D_{4h} symmetry[231] of **74** was first deduced by IR and Raman spectroscopy and later confirmed by X-ray analysis[232]. For a comprehensive overview of experimental and theoretical studies on **74** and other oxocarbon anions up to 1980, the reader is referred to Reference 233.

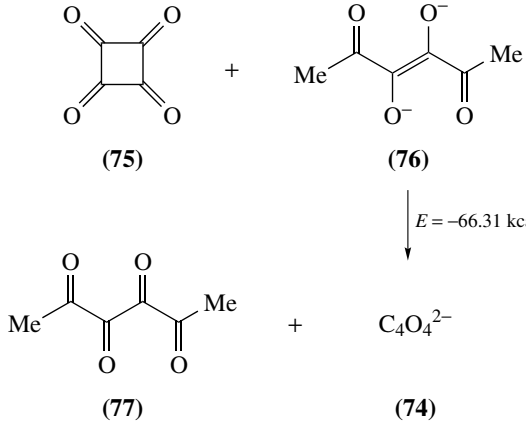
TABLE 10. Calculated and experimental structural parameters of squarate dianion (**74**)

Method	C−C/Å	C−O/Å	Ref.
Exp.	1.469	1.259	232
MP2/6-31G*	1.493	1.269	247
MP2/6-31+G*	1.489	1.272	247
MP2/6-311+G*	1.491	1.262	247
B3LYP/6-311+G*	1.487(1.469)	1.257(1.259)	246 (233)
RHF/6-311G**	1.467	1.237	246
RHF/4-31G	1.466	1.259	241b
RHF/STO-3G	1.491	1.269	241b
MNDO	1.487	1.253	244b

Due to their unique structure, the squarate dianion, its parent system, squaric acid **74a**, as well as their derivatives have found many applications[234]. They serve as coupling reagents in the synthesis of selective antitumor agents (squaric acid diethyl ester)[235], as templates for controlling the assembly of stable, highly organized two- and three-dimensional crystalline aggregates of interest for material sciences[236], as electron acceptors for nonlinear optic materials[237] and photovoltaic devices[238], etc.

From the theoretical point of view, the literature on squarate dianion has focused almost exclusively on its peculiar electronic structure and spectroscopic features, with emphasis on its aromaticity[239–246]. With the exception of the graph theoretical treatment[241], most of these studies have characterized squarate dianion as an aromatic species. This has been supported by geometric (bond length equalization, bond order indices)[244–247], energetic (aromatic stabilization energies)[244–246] and magnetic (magnetic susceptibility exaltation, nucleus-independent chemical shifts (NICS) and/or ^{17}O-chemical shifts) evidence[244–246]. Specifically, the structure of dianion **74** in the gas phase was found to be planar with high symmetry (D_{4h}) at several levels of theory, which is in agreement with a strong resonance effect (*vide supra*) and the experimentally determined structure[232]. A representative selection of the reported structural data is given in Table 10.

Recently, Schleyer and coworkers[244], and independently Frontera, Deyá and coworkers[245] discussed the reliability of various approaches in assessing aromaticity of monocyclic oxocarbon dianions $C_nO_n^{2-}$ ($n = 2–6$). Both groups of authors claim that the use of aromatic

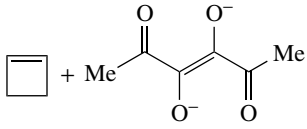


(75) **(76)** (20)

(77) **(74)**

stabilization energies (ASE) and exaltation of the diamagnetic susceptibility, Λ, as well as anisotropy of Λ, for assessment of aromaticity of oxocarbon derivatives, is not reliable due to the difficulty in finding suitable equations free from other effects. For instance, Schleyer and coworkers[244] considered three types of isodesmic reactions for evaluating ASE of **74**. The first (equation 20) involves the neutral oxocarbon C_4O_4 (**75**), the acyclic dianion **76** and polyketone **77**.

The second (equation 21) employs cyclobutene with **76** and *trans*-hex-3-ene as reference species.



$$+ \quad \xrightarrow{E = -60.82 \text{ kcal mol}^{-1}} \quad C_4O_4^{2-} + \textit{trans}\text{-hex-3-ene} \tag{21}$$

(76) **(74)**

The third type (equation 22) was based on carbon monoxide and the smallest member of oxocarbon dianions, $C_2O_2^{2-}$ (**78**), as the reference molecules.

$$C_2O_2^{2-} + 2\,CO \xrightarrow{E = -127.8 \text{ kcal mol}^{-1}} C_4O_4^{2-} \tag{22}$$

(78) **(74)**

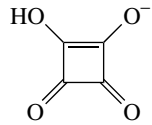
All three equations are exothermic, indicating that the squarate dianion is an aromatic species. However, it was argued that none of the employed equations modelled the strain and charge effects satisfactorily[244]. This skepticism is not justified since, for instance, in the first reaction (equation 20) all the carbons and oxygens in the cyclic neutral reference oxocarbon, C_4O_4, match those in **74**. Likewise, the acyclic dianion equivalent **76** is the same as polyketone **77**. Such comparison is allegedly imperfect, since the acyclic reference molecule, **76**, unlike the **74**, does not distribute the charge to the oxygen atoms in a uniform way. In our view this is exactly the reason why equation 20 is very good in estimating the stabilization of the $C_4O_4^{2-}$ dianion compared to the acyclic dianion **76**. Namely, **74** is exceptionally stable due to the anionic resonance effect present in cyclic $C_4O_4^{2-}$, which supports the aromaticity of the cyclobutadiene ring very effectively. It is interesting to note that cyclobutadiene ring possesses 2π-electrons. This obvious conclusion follows straightforwardly from inspection of the resonance structures of **74** (*vide supra*). We found the anionic resonance effect very efficient in determining the ultrahigh acidity of pentacyanocyclopentadiene[248] due to the substituent (CN group) assisted aromaticity of the conjugate base. Consequently, we feel that the calculated stabilization energy[244] employing equation 20 and the B3LYP/6-311+G* method of 66.3 kcal mol^{-1} for $C_4O_4^{2-}$ is an approximate, but good estimate. The same holds for equation 21, which yields 60.8 kcal mol^{-1} for ASE. The third equation (equation 22) predicts ASE = 127.8 kcal mol^{-1}, which is unrealistic. This is not unexpected in view of a poor modelling involved in equation 22. The Λ values, calculated according to equations 20–22, are -8.5, -10.6 and 12.5 in ppm, respectively. On the basis of good performance for the larger set of $C_nO_n^{2-}$ anions ($n = 2$–6), the first approach, resulting in $\Lambda = -8.5$ ppm, was proposed to be the most reliable, implying that **74** is aromatic. Poor performance of equation 22 is both obvious and expected.

The NICS criterion and calculated ^{17}O NMR chemical shifts were claimed to give satisfactory quantification of aromaticity[245]. The same should hold for the Wiberg bond index[249], which corresponds to the sum of the squares of the bond orders between the

bonded atoms in question. This was ascribed to the fact that none of these parameters requires an increment system or reference molecule for their evaluation in antiaromatic and aromatic molecules[245].

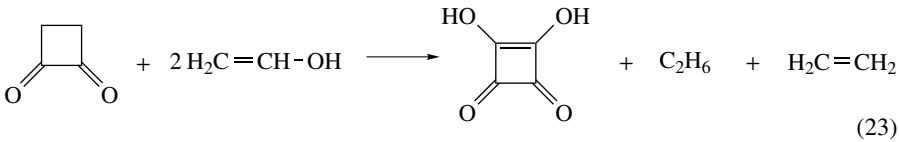
The calculated Wiberg bond index (WBI) for carbonyl CO bond in **74** is 1.403, as compared with WBI = 1.778 for acetone (both values calculated at the HF/6-311+G**//MP2/6-311+G** level), which is in accordance with considerable delocalization predicted by calculated structural features[245]. Furthermore, the calculated ^{17}O NMR chemical shift shows a high shielding of the oxygen atom ($\delta = 304$ ppm as compared to $\delta = 569$ ppm in, e.g., acetone)[245]. Moreover, the reported NICS values calculated at 0.6 Å[245] (NICS (0.6)) and 1 Å[244] (NICS(1)) over the ring plane are only slightly lower than in benzene. All these results are indicative of a highly pronounced aromatic character of **74**. We note in passing that it is not clear why Frontera, Deyá and coworkers[245] calculate NICS values at the point 0.6 Å above the center of the rings instead of the customary 1 Å distance.

Aromaticity of the parent squaric acid (**74a**) and its monoanion (**79**) have also been discussed[245,246]. Various criteria, including aromatic stabilization energies, magnetic susceptibility χ and diamagnetic susceptibility exaltation Λ, Wiberg bond indices (WBIs) and ^{17}O NMR chemical shifts, were used for this purpose[245,246]. The resulting values are summarized in Table 11.



(79)

For aromatic stabilization energies and diamagnetic susceptibility exaltations, two sets of data referring to equations 23 and 24, respectively, are included.



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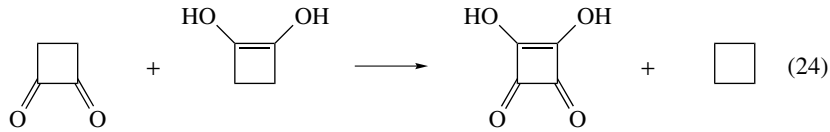


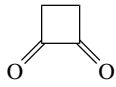
(24)

TABLE 11. Computed diamagnetic susceptibility (χ, ppm, cgs), diamagnetic susceptibility exaltation (Λ, ppm, cgs), aromatic stabilization energy (ASE, kcal mol^{-1}), NICS (ppm), Wiberg bond index (WBO) and ^{17}O chemical shift (δ, ppm, relative to water) of **74a**[245,246]

	χ	Λ	ASE	NICS(0.6)[a]	WBI(CO)[b]	δ
74a	−43.2	2.80[c] −2.07[d]	14.89[c] −15.2[d]	−5.7	1.736	463

[a] Calculated at the MP2/6-311+G** level.
[b] Calculated at the HF/6-31+G**//MP2/6-311+G** level.
[c] Calculated by using equation 23 (Reference 245).
[d] Calculated by using equation 24 (Reference 246).

Perusal of the results presented in Table 11 offers several interesting conclusions. First, it appears that the ASE and the Λ values are strongly dependent on the type of equation used for their evaluation. Equation 23 gives positive values, indicating that **74a** is antiaromatic! In contrast, equation 24 gives negative values, suggesting that **74a** is aromatic! It is extremely important to realize that adequate modelling of products and educts in isodesmic (homodesmotic) reactions is *conditio sine qua non* for obtaining reliable ASE values and some other characteristic properties like, e.g., Λ. Equation 23 is an example *par excellence* for unsatisfactory modelling. We shall substantiate this assertion by analogous isodesmic reaction used by Frontera, Deyá and coworkers[245] in considering aromaticity of $C_4O_4^{2-}$ dianion (equation 25).



(25)

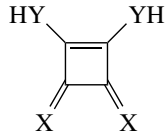
The aromatic stabilization of squarate dianion $C_4O_4^{2-}$ obtained by equation 25 is 11.4 kcal mol^{-1}, thus being grossly underestimated compared to 66.3 and 60.8 kcal mol^{-1} values obtained by Schleyer and coworkers[244] employing much more realistic isodesmic equations 20 and 21. In spite of that, Frontera, Deyá and coworkers[245] conclude: 'We consider that oxocarbon derivatives are examples where the use of ASE as a criterion of aromaticity is not applicable due to the difficulty in finding equations free from other influences'. This statement is dubious and therefore it is necessary to put forward on important *caveat emptor*: *isodesmic reactions might give misleading results unless great care is exercised in their design*. A molecule under scrutiny is one of the reactants. Its characteristic intrinsic property is 'measured' against a suitably selected reference molecule, which is one of the products. The rest of the educts and products should be chosen in such a way that stoichiometry is satisfied and that a 'noise' of other effects is kept at a minimum. In other words, we should not introduce any unnecessary complications in accordance with *Occam's razor* criterion. One should bear in mind that a system of isodesmic reactions defines a scale for a particular property under study. The quality of this scale depends on a skill of modelling. We would like to point out that better matching of educts and products leading to minimization of undesirable side effects can be obtained by the 'isomerization method' of Schleyer and Puhlhofer[219a] or by various homodesmotic, hyperhomodesmotic and homomolecular homodesmotic reactions[219b]. As an example of appropriate modelling of the aromatic stabilization in squaric acid, one should mention equation 24.

Let us return to the magnetic properties presented in Table 11. The NICS(0.6) is negative, but considerably smaller than that of benzene, thus indicating perhaps a moderate aromatic character of **74a**. To be more specific, since NICS(0.6) is about 50% of the corresponding value in benzene, one concludes that aromaticity of squaric acid is by 50% lower too. This is in qualitative agreement with ASE $= -15.2$ kcal mol^{-1} obtained by equation 24. The computed ^{17}O NMR chemical shift corresponding to the carbonyl oxygen atom of **74a** is $\delta = 463$ ppm, which is lower by 106 ppm than the corresponding value in acetone ($\delta = 569$ ppm). Similarly, the calculated Wiberg bond index for the carbonyl bond in **74a** is 1.736, which is by 0.042 lower than for carbonyl group in acetone (1.776) calculated at the same level of theory[245]. All these values are consistent with some aromaticity of squaric acid, but one is tempted to conclude that the magnetic properties and WBIs provide more qualitative than quantitative information about aromaticity and antiaromaticity.

For monoanion **79**, only results of geometry optimization are reported[246] and they clearly show that the C−C bonds within the four-membered ring have less pronounced single or double bond character than the corresponding bonds in the parent acid. In

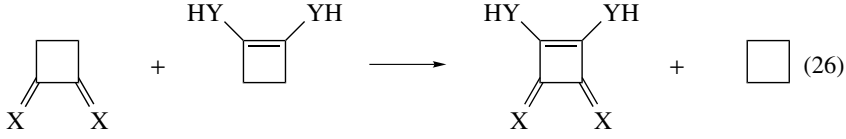
addition, the C=C and C=O double bonds in **79** are calculated to be longer by *ca* 0.015 Å and *ca* 0.05 Å, respectively, than the corresponding bonds in **75**. Both features suggest more pronounced π-electron delocalization than in the **74a**[246].

Considerable attention has been paid to aromaticity of squaric acid derivatives **80–86**[250] in which oxygen atoms are partially or completely replaced by sulfur and selenium.



(80) X = O; Y = S
(81) X = S; Y = O
(82) X = Y = S
(83) X = Se; Y = O
(84) X = Se; Y = S
(85) X = S; Y = Se
(86) X = Y = Se

Aromaticity of these compounds was probed by analysis of the optimized geometries and calculated aromatic destabilization energies, as well as by examining the diamagnetic susceptibility exaltations. As in the case of squaric acid, the ASE values were evaluated using the isodesmic approach employing equation 26.



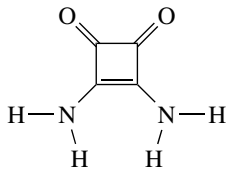
(26)

It appears that replacement of either carbonyl or hydroxyl oxygen by sulfur and selenium leads to changes in the ASEs and Λ values, which indicate that these compounds might be somewhat more aromatic than the squaric acid.

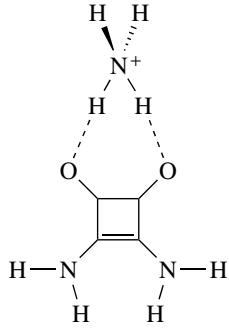
Zhou and coworkers[250] have also reported geometries (optimized at the HF and B3LYP level using various basis sets) of the corresponding mono- and dianions of compounds **80–86**. The calculated structures reveal that in both types of ions C−C and C−X bonds have no clear single or double bond character, suggesting that π-electron delocalization in these anions is stronger than in their parent acids, as expected intuitively. Based on the calculated deprotonation energies of **80–86**, the respective mono- and dianions were also predicted to be somewhat more aromatic than the mono- and dianion of the squaric acid[250].

More recently, aromaticity of squaramide **87** and a number of its complexes with anions and cations (**88–97**) was discussed by Frontera, Deyá and coworkers[251].

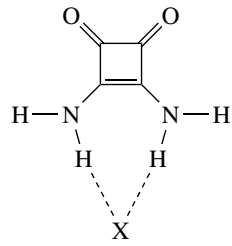
It is interesting to mention that the main impetus for undertaking this study was due to the authors' interest in the mechanism of host–guest complexation between squaramido-based receptors and a variety of biologically relevant compounds, including quaternary ammonium cations[252], choline containing phospholipides[253] and carboxylates[254]. The squaramide base receptors are particularly interesting in this regard due to the unique property of being both good hydrogen bond acceptors (due to the presence of carbonyl groups) and good hydrogen bond donors (due to the presence of the amino groups). The studied model compounds are shown below, while their NICS values, used as the main criterion for evaluating aromaticity, are summarized in Table 12, along with the corresponding NICS values for the squaric acid and benzene. The NICS values were calculated at the ring centers and at 0.6 Å above the ring centers, applying the HF/6-311+G**//MP2/6-311+G**



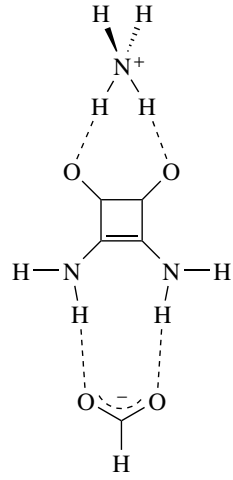
(87)



(88)



(89) X = $H_2PO_4^-$
(90) X = SO_4^{2-}
(91) X = HCO_2^-
(92) X = F^-
(93) X = Cl^-
(94) X = Br^-
(95) X = NO_3^-
(96) X = SH^-



(97)

TABLE 12. Nucleus-independent chemical shifts (NICS, ppm) computed at the geometrical centers (NICS(0), ppm) and 0.6 Å above them (NICS(0.6), ppm) of **87–97** calculated at the GIAO-MP2/6-31+G*//MP2/6311+G** level of theory[250b]

Compound	NICS(0)	NICS(0.6)	Compound	NICS(0)	NICS(0.6)
87	−1.9	−6.2	**93**	−4.2	−7.4
88	−5.0	−7.8	**94**	−3.7	−7.2
89	−4.2	−7.7	**95**	−3.5	−7.2
90	−5.4	−8.2	**96**	−3.8	−7.4
91	−4.2	−7.7	**97**	−6.6	−8.7
92	−4.2	−7.4	benzene	−7.9	−10.1

and MP2/6-311+G**//MP2/6-311+G** models. Both methods predict a qualitatively similar trend of changes in NICS values, therefore only the latter results are shown in Table 12.

Two important conclusions emerged from this work. First, squaramide was found to be only slightly more aromatic than the squaric acid[250]. Second, complexation (via hydrogen bonding interactions) with both anions and cations leads to enhancement of aromaticity. In particular, the 1:1:1 complex between squaramide, ammonium cation and formate anion was found to be more aromatic than any of the other squaramide−cation (anion) complexes. The increase in aromaticity on passing from the parent molecule to the complexes was also corroborated by the progressive equalization of the bond lengths within the four-membered ring. These results led the authors to conclude that the remarkable hydrogen bond acceptor and hydrogen bond donor capacities of squaramide might be due to the gain in aromaticity in the squaramide ring upon complexation. It is also noteworthy that a similar trend was observed upon diprotonation of the squaric acid (**74a**) and di-O-methylated squarate (**98**) leading to **99** and **100**, respectively, as for their complexes with NH_4^+ (**101** and **102**) (Figure 13)[245]. It is interesting to mention that dimethylsquarate

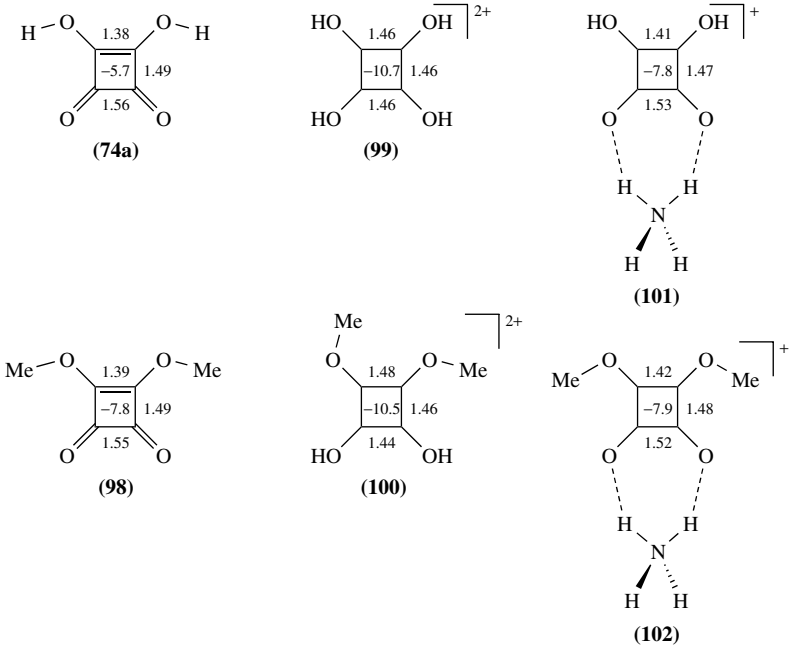


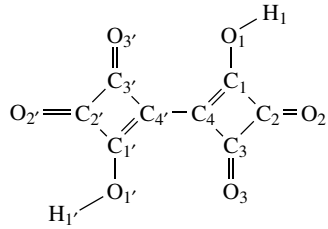
FIGURE 13. MP2/6-311+G* optimized structures and the NICS(0.6) values of squaric acid (**74a**) and dimethylsquarate (**98**), their di-O-protonated derivatives (**99** and **100**) and their complexes with ammonium cation (**101** and **102**). Bond distances are given in Å and NICS(1) values in ppm. The latter are written within the rings[245]

(**98**) is found to be somewhat more aromatic than the squaric acid, as indicated by the computed NICS(0.6), ^{17}O NMR chemical shifts and Wiberg bond index for the carbonyl group of −7.8 ppm, 468 ppm and 1.720, respectively[245]. It should be noted that structures **99** and **100** could also be considered as the tetrahydroxy and dimethoxy-dihydroxy cyclobutadiene dication, respectively[254].

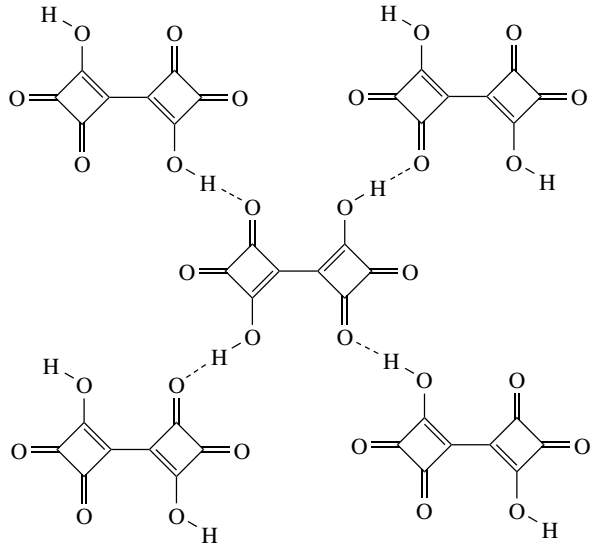
The evidence for the aromatic character of diprotonated squaric acid **99** was also provided by a subsequent NMR study and *ab initio*/IGLO calculated ^{13}C NMR chemical shifts[255].

Aromaticity of bisquaric acid (**103**) was briefly discussed by Dalal and coworkers[256]. Bisquaric acid is an extremely strong Brönsted acid and at room temperature exists as a hydrogen bonded solid **104**[257].

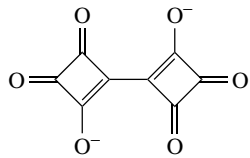
Based on the comparison of the B3LYP/6-31G* optimized geometries of the bisquaric acid (Table 13) with the parent squaric acid (Figure 13), the authors concluded that the former acid is less aromatic. This is what one would expect intuitively due to the absence of one of the O=C−C=O−OH chains in the bisquaric acid. In dianion **105**, however, the optimized bond distances C(1)−O(1), C(3)=O(3), C(1)=C(4) and C(3)−C(4) cannot be characterized as pure single and double bonds, thus indicating a strongly reinforced resonance along the O(3)=C(3)−C(4)=C(1)−O(1)−H chain (Table 13). Specifically, the C(3)=O(3) and C(1)=O(1) bond distances change from 1.204 Å and 1.315 Å in **103** to 1.234 Å in **105**, whereas the C(1)=C(4) and C(3)−C(4) bonds change from 1.382 Å and 1.507 Å calculated for **103** to 1.467 Å in **105**.



(103)



(104)



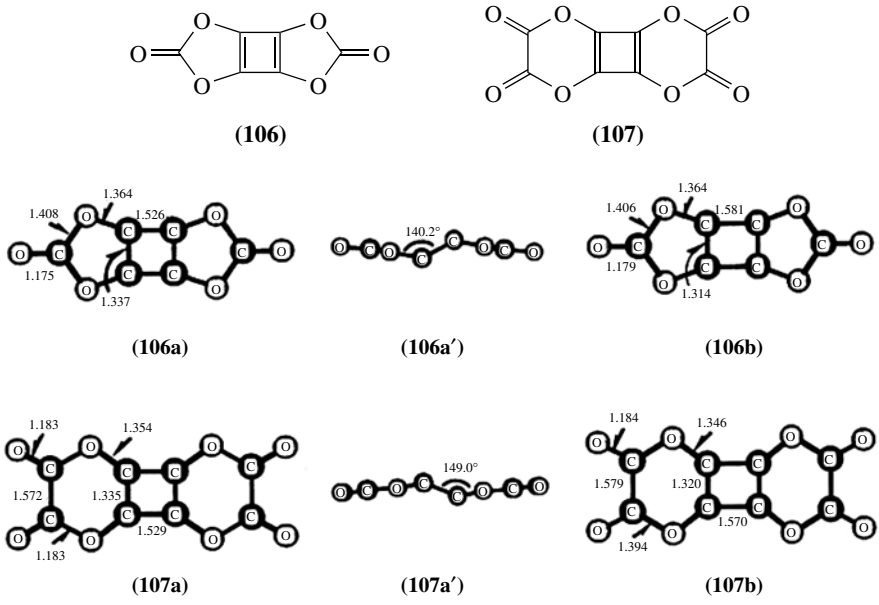
(105)

Finally, it is interesting to mention that Jiao and Wu[258] recently published a theoretical investigation on the structure and stability of two diannelated oxocarbons (**106** and **107**) containing a central cyclobutadiene ring. Their B3LYP/6-311+G* optimized structures are illustrated in Figure 14. In both cases the minimum energy structure exhibited nonplanar geometry (designated by letter **a**), while the planar structure (designated by letter **b**) was found to be a high-order saddle point on the potential energy surface. Based on calculated NICS(1) values (6.5 and 7.6 ppm for **106** and **107**), the energy minimum structures of both species were predicted to be weakly antiaromatic.

TABLE 13. Comparison of the B3LYP/6-31G* calculated bond distances (Å) of **103** and **105**[256] with X-ray data

Bond distances [a]	**103**	**105**	X-ray [b]
C(1)−C(2)	1.505	1.534	1.520
C(2)−C(3)	1.567	1.534	1.520
C(3)−C(4)	1.507	1.467	1.428
C(1)−C(4)	1.382	1.467	1.428
C(4)−C(4′)	1.422	1.425	1.435
C(1)−O(1)	1.315	1.234	1.244
C(2)−O(2)	1.204	1.228	1.198
C(3)−O(3)	1.202	1.234	1.244
O(1)−H	0.973		

[a] Numbering of atoms is shown in structure **103**.
[b] Reference 256.



(106) **(107)**

(106a) **(106a′)** **(106b)**

(107a) **(107a′)** **(107b)**

FIGURE 14. B3LYP/6-311+G* optimized structures of the nonplanar (**a**) and planar (**b**) forms of diannelated oxocarbons **106** and **107**. The critical dihedral angles in the nonplanar forms are indicated in structures **106a′** and **107a′**. Reprinted with permission from Reference 258. Copyright (2003) American Chemical Society

VI. SIGMA-ANTIAROMATICITY OF MOLECULES INVOLVING SATURATED FOUR-MEMBERED RING(S)

A question arises whether Hückel's $(4n + 2)\pi$ and $4n\pi$ rules hold for the σ-electrons in saturated systems. It seems that the answer to the posed question is positive, as discussed by several authors[259,260]. The story begins with a seminal Dewar's paper on the cyclic delocalization of six hybrid orbitals describing covalent bonding in cyclopropane[261]. It

stems from the fact that two geminal hybrid AOs placed on the same carbon atom have larger resonance integral than two nearest-neighbor π-AOs in the π-systems. According to Dewar, cyclopropane and benzene are isoconjugate systems. A very interesting discussion of the role of radial (hybrid AOs) and tangential (2p) orbitals in cyclopropane and larger carbocyclic rings was given by Cremer and Kraka[262–264]. It turned out that radial hybrid AOs led to a surface delocalization, whereas tangential AOs exhibited a π-type ribbon delocalization. Surface delocalization leads to a substantial increase in the electron density in the center of the ring and it is a strongly stabilizing factor. Analysis of Kraka and Cremer reveals[264] that six delocalized σ-electrons in cyclopropane are clearly delineated in two groups. The first is embodied by two electrons yielding a Hückel-aromatic σ-surface delocalization. The second class is formed by 4 electrons placed in a Möbius-aromatic system employing tangential AOs, thus leading to ribbon delocalization. The results of Dewar, Cremer, Kraka as well as more recent calculations of Exner and Schleyer[265] strongly suggest that cyclopropane is a σ-aromatic system. This conclusion is supported by large diamagnetic susceptibility and its anisotropy[266], upfield ^{1}H NMR chemical shifts[267] and a negative NICS value calculated above the cyclopropane ring[265].

If six σ-electrons in a cyclopropane ring are aromatic, then it is plausible to expect that eight σ-electrons in cyclobutane (**13**) should exhibit antiaromaticity. This is indeed the case, as shown by the NICS values calculated by Exner and Schleyer[265]. For this purpose, NICS quantities are partitioned into σ- and π-components employing Kutzelnigg's individual gauge for the localized orbitals (IGLO) method[268] and localized molecular orbitals obtained by the Pipek and Mezey[269] procedure. Final calculations were performed by using the IGLO-III TZ2P basis set available in the DeMon program[270]. It turns out that the NICS(CC)$^\sigma$ value computed at the cyclobutane center is positive and large, being 15.2 ppm. This is in accordance with depletion of the electron density in the central region of the ring due to 1,3-antibonding interaction of degenerate e_u MOs[264]. Hence, it can be safely concluded that the CC σ-frame in cyclobutane is antiaromatic. This is corroborated by abnormally low magnetic susceptibility in **13**[266] and a magnetic deshielding reflected in ^{13}C and ^{1}H chemical shifts[267]. A highly symmetric (O_h) cubane (**108**) composed of six planar cyclobutanes exhibits high paratropicity, as evidenced by NICS(CC)$^\sigma$ calculated at the cage center of 21.6 ppm[260].

(108)

Therefore, available evidence—albeit very scarce—shows that Hückel rules might well be operative in σ-electron frameworks too.

VII. CONCLUSION

Cyclobutadiene is a molecule with remarkable structural and electronic features. Its rectangular geometry inherits a high σ-electron angular strain. However, a neat theoretical analysis shows conclusively that the larger part of its lower stability is a direct consequence of antiaromaticity of the 4π-electron network. In spite of its elusiveness and highly pronounced reactivity, cyclobutadiene is a versatile building block of large (supra)molecular structures. If it is used in planar structures, cyclobutadiene takes control over behavior of extended π-systems like, e.g., in [*N*]phenylenes. Its annelation leads to changes consistent with the Mills–Nixon effect. However, it should be strongly pointed out that properties of cyclobutadiene are also changed upon fusion. Sometimes, these changes are quite

dramatic like in benzo[1,2:4,5]dicyclobutadiene (**28**), where the cyclobutadiene moieties exhibit a very strong aromaticity. It can be safely stated that annelation of cyclobutadiene fragments to aromatic molecules leads to systems exhibiting a wide range of interesting properties, which are results of a subtle interplay of the angular strain, aromaticity and antiaromaticity. It is important to mention that cyclobutadiene in its first triplet state and in some dications and dianions behaves like an aromatic system, thus representing molecular Janus. Its chameleon nature takes place in a number of complex compounds to mention only Pettit's cyclobutadiene-iron tricarbonyl, dilithium salts of various trimethylsilyl- or phenyl-substituted cyclobutadiene dianions, as well as squarate and squaramide dianions. In this way cyclobutadiene enriched both organic chemistry and the chemical bonding theory. It can be safely stated that cyclobutadiene chemistry is a highly promising field which will offer a plethora of new organic and organometallic systems and interesting novel features for many years to come.

VII. ACKNOWLEDGMENTS

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CHAPTER 3

Stereochemical aspects — conformation and configuration

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I. INTRODUCTION

This chapter deals with stereochemical aspects of cyclobutane and its derivatives. The scope is limited to molecules with sp^3-type ring carbon atoms with only few exceptions, and in those cases for the purpose of comparison. Certain structures containing the cyclobutane ring with interesting architectures are also included.

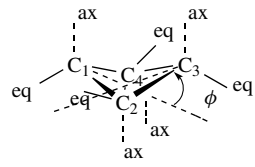
The stereochemistry of cyclobutane and its derivatives has attracted relatively little attention, especially if one compares it with cyclohexane. However, a comprehensive review by Moriarty of cyclobutane stereochemistry has appeared[1] and covers the literature up to 1974. Much of the fundamental aspects on cyclobutane stereochemistry had been considered at that time, in particular through information from spectroscopic studies. Since then the field has attracted increased interest as the photodimerization of nucleotides and the discovery of important natural products and molecules with intriguing electronic properties incorporating the cyclobutane ring have appeared. This chapter intends to report on information concerning the stereochemistry of cyclobutane and compounds bearing this ring system and on the factors that govern stereochemistry and reactivity.

II. CONFORMATION

A. Conformation of Cyclobutane

Cyclobutane (**1**) is a conceptually simple, symmetrical molecule. Intuitively, one would imagine cyclobutane should be planar, possessing a square geometry. The reason behind this idea is that any deviation from the already strained C−C−C bond angle of 90° in a square arrangement would further compress this angle. However, the situation is actually slightly more complicated. Thus, cyclobutane may be represented by two extreme conformations: a planar one (point group D_{4h}) and a puckered one (point group D_{2d}). Despite the fact that the angle strain in the planar form of cyclobutane is minimal, it has been known since the beginning of the 1950s that cyclobutane and most of its derivatives assume a puckered conformation. The first educated suggestion that cyclobutane may not be a planar molecule was due to Bell as early as 1945[2], but more definite experimental evidence appeared much later[3]. There are two alternative ways of defining the puckering of the cyclobutane ring system: one is the angle of pucker, ϕ, as defined by the acute angle between the planes $C_1C_2C_4$ and $C_2C_3C_4$; the other is known as the dihedral angle, which is equal to $180^\circ - \phi$ (Figure 1).

Cyclobutane itself does not have a dipole moment and thus is microwave inactive. The same is the case for the puckering mode vibration, and Raman spectroscopy has often been the spectroscopic method of choice. For substituted derivatives, infrared, microwave and diffraction methods have also been used for conformational studies. However, infrared spectroscopy can be used for other vibrations of cyclobutane, which can give information about the puckering vibration. Vibrational spectra of cyclobutane and monodeuteriocyclobutane were studied as early as in the 1960s with slightly divergent conclusions about



(1)

FIGURE 1. Structural parameters for cyclobutane showing the angle of pucker (ϕ) and the axial (ax) and equatorial (eq) substituents

the details of cyclobutane conformation, but agreed about a nonplanar structure[4,5]. The most recent structure determination of cyclobutane is a combined electron diffraction and FTIR study by Egawa and coworkers[6]. Their study includes a refinement compared to earlier studies, as it considers the coupling of the puckering vibration and other motions, especially the CH_2-rocking motion. The angle of pucker, ϕ, was given as 27.9° and the torsional angles are approximately 25°. The bond angles are contracted compared to the planar form to *ca* 86° as a result of the deformation. The average experimental C−C and C−H bond lengths are 1.554 and 1.109 Å, respectively, and the H−C−H bond angle 106.4°. Similar results have been obtained by other researchers[3,7–10]. The origin of this deformation has been the subject of much consideration, but it seems that the major contributions are the reduction of the torsional (Pitzer) strain and Dunitz–Schomaker strain (nonbonded 1,3 C−C interaction). This repulsive interaction was calculated to be 3.8 kcal mol^{-1} larger in the planar form[11–14]. Thus, the preferred conformation of cyclobutane belongs to the D_{2d} point group. A consequence of this deformation is that there are two types of hydrogen atoms, equatorial and axial, similar to the situation in cyclohexane, and thus two different conformations for monosubstituted derivatives. Inversion of the ring goes through a planar transition state, interchanging the hydrogen atoms or, in case of a substituted cyclobutane, the position of the substituents.

The 1,3-diaxial hydrogen atoms are slightly bent towards each other by an angle of 4°[15,16]. A similar tilt was determined for octafluorocyclobutane[17], whereas interestingly octahydroxycyclobutane has been reported to assume a planar D_{4h} structure in water solution according to the Raman spectrum[18], as well as in the crystal[19]. Thus, not all symmetrically octasubstituted cyclobutanes can be assumed to be puckered. The latest determination of the barrier to ring inversion in cyclobutane is 1.48 kcal mol^{-1} over a planar D_{4h} transition state geometry[10].

Microwave, infrared and Raman spectra can be analyzed by polynomic potential functions, originally proposed by Bell, describing the out-of-plane distortions of molecules such as cyclobutane[2]:

$$V = A\ z^4 + B\ z^2 \tag{1}$$

in which z is a dimensionless reduced coordinate or a puckering coordinate, such as half the orthogonal distance between the two diagonals. In the general case, a single potential minimum is obtained if B is positive or zero. If B is negative, a double potential energy minimum results. If B is zero or small, the molecule is planar. Function (1) is usually called a quartic-quadratic function. Higher-order polynomial functions have also been used (see Figure 2). Furthermore, for a monosubstituted cyclobutane the unsymmetrical potential can be represented by introducing an odd term:

$$V = A\ z^4 + B\ z^2 + C\ z^3 \tag{2}$$

Other models describing the ring puckering of cyclobutane have been proposed[20].

Cis- and *trans*-cyclobutane-1,2-d_2 (and cubane-d) have been studied by rotational spectra in the millimeter- and submillimeter-wave region[21]. *Trans*-cyclobutane-1,2-d_2 exists in an equatorial–equatorial and an axial–axial conformation, as expected from previous results on the structure of cyclobutane. The observed microwave spectrum exhibits the effect of puckering.

The use of ^{1}H NMR Karplus-type relations and molecular mechanics to link vicinal coupling constants to the cyclobutane dihedral angles has met with only moderate success[22]. Instead, four-bond couplings were suggested for studying cyclobutane stereochemistry rather than vicinal couplings, which showed variations with small distortions and ambiguity between the *cis* and *trans* values, except when the absolute coupling value

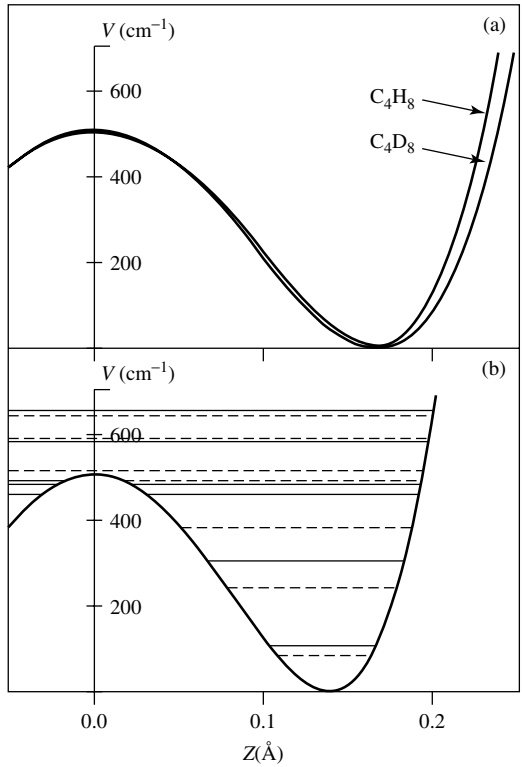


FIGURE 2. Puckering potential curves for cyclobutane, C_4H_8 and C_4D_8 using the expression $V = A\,z^6 + B\,z^4 + C\,z^2$, and assuming (a) no CH_2 rocking and (b) a rocking angle of 6.2°. Reproduced by permission of the American Institute of Physics from Reference 6

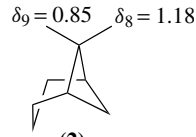
was <0.5 Hz. The ^4J coupling constant was positive when the two interacting protons were *cis* and negative when they were *trans* to one another[23].

Several quantum-mechanical-based methods for the computation of structure and of chemical shifts and coupling constants in cyclic and bicyclic compounds have been developed[24–31]. *Ab initio* IGLO (individual gauge for localized MO) methods of SCF-MO theory have been used to study and analyze the mathematical form of the conformational dependencies of the isotropic ^{13}C chemical shifts of cyclobutane and some derivatives[32].

Schleyer and coworkers calculated contrasting ring current effects, diatropic in three- and five-membered and paratropic in four-membered ring systems. In larger saturated rings these effects are negligible. The σ-antiaromaticity and deshielding effect of the cyclobutane C−C(σ) bonds is general: cubane and cages with four-membered rings are strongly deshielding (i.e. σ-antiaromatic)[26].

Anisotropy of the cyclobutane ring was claimed to be responsible for the difference in the chemical shifts ($\Delta\delta = 0.33$ ppm) of the protons of the 8-Me and 9-Me in 6,6-dimethylbicyclo[3.1.1]heptane (**2**)[33].

Earlier quantum-mechanical calculations, using methods such as CNDO/2, extended Hückel and minimum basis set *ab initio*, did not reproduce the puckered conformation unless rocking of the methylene groups was introduced[34,35].



(2)

Nonbonded 1,3 C−C interactions (Dunitz–Schomaker strain) in the cyclobutane system have been estimated based upon MINDO/3 and CNDO/1 and -/2 semiempirical SCFMO calculations[14,36]. All estimates of Baeyer strain in cyclobutane are *ca* 7–11 kcal mol^{-1}, i.e. too small to account for the large (26.4 kcal mol^{-1}) experimental cyclobutane strain. The calculations by Bauld and coworkers estimates 1,3 carbon–carbon repulsions (Dunitz–Schomaker strain) of approximately 20–30 kcal mol^{-1}. Even though the use of semiempirical methods makes the quantitative energy values uncertain, they suggest that Dunitz–Schomaker strain may be an important contribution to the total strain of cyclobutane. Calculated variation of the Dunitz–Schomaker strain with the pucker and methylene rocking angles is also in agreement with experimental observations. Even though puckering shortens the 1,3 C−C distance, the 1,3 carbon–carbon repulsion decreases by 4.0 kcal mol^{-1}. Dunitz–Schomaker strain in the cyclobutyl cation is 5.1 kcal mol^{-1} less than in cyclobutane, in agreement with the special stability of this cation.

Already the MM2 force field gave satisfactory reproduction of the conformation and barrier of cyclobutane[37–41]. Chen and Allinger later developed an MM4 force field and applied it to cyclobutane[42]. Structure, barrier and vibrational spectra were calculated and found to be in better agreement with experiment and *ab initio* and density functional calculations.

Hoffmann and Davidson constructed the orbital symmetry correlation diagram shown in Figure 3 and analyzed the valence orbitals of cyclobutane in terms of a $\sigma - \pi$ model

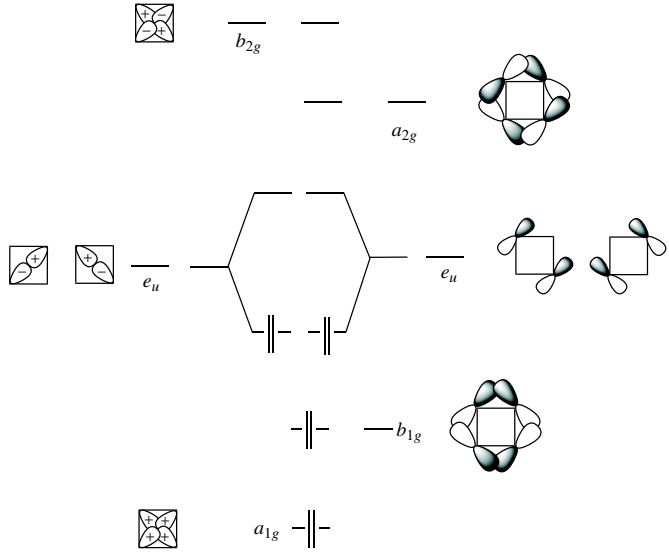
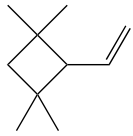


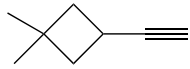
FIGURE 3. Orbital correlation diagram for cyclobutane[43]

analogous to that of Walsh for cyclopropane, assuming a planar ring[43]. The highest occupied MOs of cyclobutane are a degenerate pair of *e*(SA,AS) symmetry. While not as effective as the corresponding Walsh orbitals of cyclopropane, these valence orbitals of cyclobutane have unique symmetry properties. Thus, when two π-electron acceptor substituents are geminally substituted on a cyclobutane, one is expected to assume a bisected conformation, the other a perpendicular one. Geometrical distortions in cyclobutylcarbinyl cations are also predicted. Walsh-type orbitals in cyclobutane should be expected to stabilize the planar conformation, thus reducing the barrier.

Conjugation between cyclobutane and a π-system (e.g. **3** and **4**) was suggested from an interpretation of photoelectron spectra[44]. The interaction seemed to be independent of conformation, in contrast with the findings for the corresponding cyclopropyl compounds.



(3)



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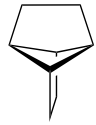


(5)

The unusual electronic spectrum of tricyclo[3.3.0.0^{2,6}]octane (**5**) is attributed to optimum interaction of the ethylene units with the valence orbitals of cyclobutane.

The puckering of four-membered rings is often solely described by the puckering amplitude. However, even though cyclobutane is the simplest molecule for which ring puckering can be studied, six internal coordinates are needed in order to specify the geometry of the ring atoms. Esteban and coworkers have theoretically analyzed the ring puckering[45]. The dependence of the intracyclic torsion angles and bond angles upon the puckering amplitudes has been calculated for a set of *ab initio* geometries of four-membered rings *c*-[$(CH_2)_3X$] as well as for a set of X-ray structures of their derivatives. The coefficients in the corresponding expressions have been estimated both theoretically, from the bond angles and bond lengths of planar reference conformations, and by parameterization. The equations calculated for the *ab initio* structures from the planar ring geometries are in good agreement with those obtained by parameterization. Likewise, the results from the analysis of X-ray structures are in reasonable agreement with the *ab initio* ones.

Allen has analyzed the molecular geometry, obtained by X-ray methods for 202 derivatives of cyclobutane, via the Cambridge Structural Database. For the cyclobutane ring a mean ring bond length of 1.554 Å was obtained, but the range (1.521–1.606 Å) is wide. Puckered conformations are preferred in the range $20 < \phi < 35°$, although a complete range to 67.2° is represented[46].

B. Heteracyclobutanes and sp^2-Hybridization

The mono heteracyclobutanes *c*-[$(CH_2)_3X$] possess a more or less puckered conformation with lower barriers than cyclobutane (see Figure 4). The following examples illustrate the effects of ring atom substitution and introduction of sp^2-hybridized carbon atom in the ring on the inversion barrier[47–49].

The oxetane molecule can be considered as planar, as the ground-state vibrational level is slightly above the inversion barrier according to microwave studies[50–53]. Microwave and infrared spectra[54,55] were matched by potential functions for ring puckering, leading to a barrier height of 15.3 cm^{-1} (0.1 kcal mol^{-1}).

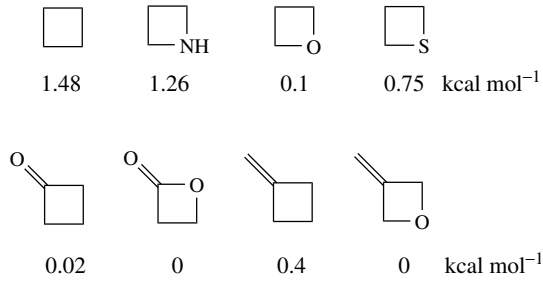


FIGURE 4. Inversion barriers of some heteracyclobutanes and derivatives with sp^2 ring carbon atoms. Values are taken from sources cited in the text

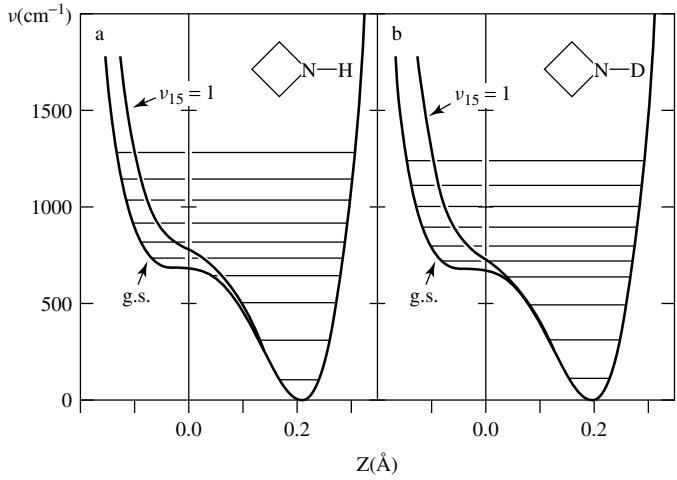


FIGURE 5. Ground-state (g.s.) potential and the ν_{15} excited-state potential for azetidine and azetidine-*d*. Z is one-half the distance between the C···N and C···C diagonals. Reprinted from Reference 65 with permission from Elsevier

The thietane molecule, on the other hand, is strongly puckered and has a barrier of 274 cm^{-1} (0.75 kcal mol^{-1}) and an angle of pucker (ϕ) of 40°[56,57]. The difference in structure between oxetane and thietane is probably due to the smaller C−S−C bond angle and the longer C−S bonds. In selenetane, the trend is maintained with a puckered ring ($\phi = 32.5°$) and an inversion barrier of 378 cm^{-1} (1.08 kcal mol^{-1})[58,59].

Azetidine is special in the sense that the two puckered conformations generated by ring flip are nonidentical, possessing an equatorial and axial N-hydrogen atom, respectively. In an early far-infrared study of this molecule and its N−D derivative, an analysis of the puckering potential had given a double-minimum shape while the energy difference between the conformers was 95 cm^{-1} (0.27 kcal mol^{-1}) and the barrier height was given as 441 cm^{-1} (1.3 kcal mol^{-1})[60]. Later investigators have argued that the data were better reproduced by a single-minimum potential[61,62], and this was confirmed by electron diffraction, microwave and infrared spectroscopy studies[63–65]. Figure 5 shows the potential for azetidine and its deuterio analog according to Egawa and Kuchitsu[65].

Silacyclobutane has been studied by infrared spectroscopy[5,66], microwave spectroscopy[67] and electron diffraction[68]. All studies agree that the molecule is puckered. The angle of pucker is calculated as 29–36° and the barrier as 440 cm^{-1} (1.26 kcal mol^{-1}).

Ground-state geometry optimization of oxetane, silacyclobutane, thietane, boracyclobutane and aluminacyclobutane has been carried out by *ab initio* SCF calculations at the 6-31G* level. Comparison with available experimental data confirms that this level of theory somewhat underestimates both the dihedral angles in these molecules and the barriers to ring inversion[69].

Changing the hybridization of a single carbon atom in cyclobutane to sp^2 reduces both ring puckering and inversion barrier. IR spectra of methylenecyclobutane, methylene-d_2-cyclobutane-2,2-d_2 and methylene-d_2-cyclobutane-d_6 have been studied with respect to occurrence of combination bands in the ring-puckering vibration[70]. A two-dimensional potential function yielded a barrier of 168 ± 10 cm^{-1} over the planar conformation, in good agreement with the barrier of 160 ± 40 cm^{-1} detected from the vibrational dependence of the rotational constants in the microwave spectrum[71].

Transitions for the ring puckering vibrations of methylenecyclobutane were found in the far-IR spectrum[72]. The barrier to ring inversion was given as 139 cm^{-1} (0.4 kcal mol^{-1}) and the distance between ring diagonals in the equilibrium conformation was estimated as 0.25 Å.

The electronic spectrum of benzylidenecyclobutane, seeded in a supersonic jet expansion, has been recorded using resonantly enhanced two-photon ionization spectroscopy[73], giving information about the potential energy surface in the excited state as well as in the ground state. A planar excited state with large amplitude motion of the phenyl ring was proposed. The ground state was found to be puckered with $\phi = 17–19°$ and the phenyl ring twisted *ca* 25° with respect to the vinyl moiety.

C. Monosubstituted Cyclobutanes

In monosubstituted cyclobutane derivatives the conformer with equatorial substituent is the more stable one. Some results chosen from work by Durig and other researchers, including simple substituents, are summarized in Table 1. These values follow a complicated pattern and, as far as they are reliable, indicate bonding interactions as well as steric and polar effects.

Raman and IR spectroscopy was used for an investigation of gaseous and solid methylcyclobutane and methyl-d_3-cyclobutane[81]. In the liquid state both the axial and equatorial conformers are present. The equatorial form is thermodynamically preferred and is the only form present in the solid form. A barrier as low as 161 cm^{-1} was deduced from the Raman spectra.

TABLE 1. Conformer stabilities (axial equatorial) and barriers for monosubstituted cyclobutanes (in cm^{-1}/kcal mol^{-1})[a]

Substituent	$\nu/\Delta H^\circ$ (gas)	$\nu/\Delta H^\circ$ (liquid)	Barrier	Reference
CH_3	295/0.84	354/1.01	641/1.83	74
F	413/1.18	413/1.18	713/2.04	75
Cl	449/1.28	328/0.94	827/2.36	76
		−/1.4		77
Br	*ca* 350/1.00	297/0.85	636/1.82	78
	−/1.9	−/2.1		77
CN	258/0.74	−/1.15	585/1.67	79,80

[a] The value 1 $cm^{-1} = 2.859$ cal mol^{-1} was used. Both values are given when the original values were given in cm^{-1}.

In the case of bromocyclobutane the difference is *ca* 1 kcal mol^{-1} (see also Reference 75). This is remarkably higher by a factor of 2 than the value for bromocyclohexane (0.49 kcal mol^{-1}). In cyclohexanes the conformational equilibria are more dependent upon 1,3-diaxial repulsions. The ring tends to be less puckered for axially substituted cyclobutanes and, in the case of bromocyclobutane, the axial form has been suggested to assume an essentially planar conformation[82]. Caminati and coworkers recently studied a series of monosubstituted cyclobutanes[79,83–87]. In chlorocyclobutane, both the equatorial and axial conformers are found to be present. Applying a model by introducing a separate Boltzmann-populated potential for two conformers vibrating harmonically for the puckering motion resulted in the following thermodynamic parameters: ΔH°(ax-eq) = 0.96 kcal mol^{-1}, ΔS°(ax-eq) = 0 cal mol^{-1} K^{-1}, $\phi_e = 30^\circ$ and $\phi_a = -21^\circ$[88].

The Raman and IR spectroscopy has also been applied to chloro- and bromocyclobutane as vapors, liquids and as amorphous and crystalline. IR spectra of the crystal phases were obtained at approximately 25 kbar pressure. Evidence from Raman and IR spectra shows that chloro- and bromocyclobutane have a second (axial) conformer existing in amounts <10% for chloro- and <3% for bromocyclobutane[77].

Jonvik and Boggs concluded from a computational study that electronegative substituents favor an equatorial position (the Jonvik and Boggs relationship)[89].

Cyanocyclobutane has been studied by several techniques. In an earlier investigation the infrared spectrum was interpreted in terms of a single conformation[90]. Infrared spectroscopy was also studied in various phases by Powell and coworkers and they concluded that less than 10% of the axial conformer was present at ordinary conditions[80]. The barrier to ring inversion was given as <1.2 kcal mol^{-1}. Nevertheless, it seems that it is the axial conformer that crystallizes at high pressure. The microwave spectrum of the axial conformer of cyanocyclobutane was assigned on the basis of its *ab initio* structure. From dipole moment and relative intensity measurements it was possible to determine the relative energy with respect to the previously assigned equatorial conformer: E(ax) − E(eq) = 258 ± 50 cm^{-1} (*ca* 0.7 kcal mol^{-1})[84]. Gas-phase electron diffraction of the molecular structure and conformation of cyanocyclobutane indicates 77% equatorial form. Cyanocyclobutane does not obey the Jonvik and Boggs relationship[89], in contrast to a variety of related monosubstituted cyclobutane homologs. Caminati and coworkers discuss possible electronic interactions between the CN group and the four-membered ring. In agreement with data for 1,1-dicyanocyclobutane, the adjacent C−C ring bond distance (1.557 Å) is larger than the distal C−C ring bond distance [1.547 Å (ax) and 1.551 Å (eq)]. The puckering angles are given as 19.1° and 27.0° for the axial and equatorial conformers, respectively[91].

Vinylcyclobutane was examined in an *ab initio* study and was found to be most stable in the s-*trans* form and predicted to possess shallow secondary s-*cis* and *gauche* minima as well (Figure 6). Substitution in the 2-position of the vinyl group by either π-acceptors or π-donors destabilizes the *gauche* structure relative to the other two. The C-1 substitution has little effect[92].

A combined analysis of electron diffraction and microwave spectroscopic study of ethynylcyclobutane reveals that this molecule exists in axial and equatorial forms with

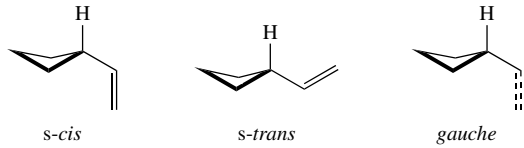
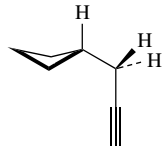


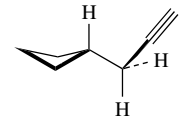
FIGURE 6. The three conformers of vinylcyclobutane[92]

the latter more stable by about 0.96 kcal mol^{-1} (corresponds to eg:ax = 84:16 at room temperature), which is in excellent agreement with the values observed by means of vibrational spectroscopy. This result is also in good agreement with the *ab initio* calculations. These methods predicted the equatorial form to constitute 81–88% in the conformational equilibrium. The results were compared with the isomeric molecule (2-propynyl)cyclopropane[93]. The Raman spectra of ethynylcyclobutane in the gaseous, liquid and solid phases are also consistent with two stable conformers existing at ambient temperature, and that the equatorial conformer is more stable than the axial form in both the gas and liquid phases, and is the only conformer present in the solid. Experimental values for the enthalpy difference between the two conformers were determined for both the gas (282 cm^{-1}/0.8 kcal mol^{-1}) and the liquid (181 cm^{-1}/0.5 kcal mol^{-1})[94]. Infrared, Raman and *ab initio* calculations were used to investigate the structure and conformational space of (2-propynyl)cyclobutane[95]. Four conformations could be identified at low temperatures in liquid krypton solution in order of decreasing stability: equatorial-*anti* (*Ea*), equatorial-*gauche* (*Eg*), axial-*anti* (*Aa*) and axial-*gauche* (*Ag*) (Figure 7).

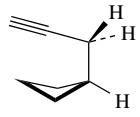
Aminocyclobutane presents a slightly more complicated situation as the amino group may assume *anti* or *gauche* conformations in both equatorial and axial positions yielding four possible conformers. Most stable in the gas phase is the *gauche*-equatorial conformer, shown in Figure 8, and the microwave spectrum and DFT computations of aminocyclobutane and its ND_2 and NHD derivatives give information about amino group inversion (856 cm^{-1}/2.4 kcal mol^{-1}) and internal rotation as well as ring inversion (712 cm^{-1}/2.0 kcal mol^{-1})[86, 87].



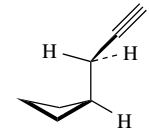
Ea = 0 cm^{-1}



Eg = 112 cm^{-1}



Aa = 271 cm^{-1}



Ag = 327 cm^{-1}

FIGURE 7. Conformations and relative energies of (2-propynyl)cyclobutane[95]

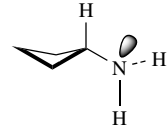


FIGURE 8. Equatorial-*gauche* conformation of aminocyclobutane[86, 87]

According to an electron diffraction study, bicyclobutyl (**6**) exists as a mixture of predominate equatorial–equatorial and minor equatorial–axial conformers with unperturbed cyclobutane units[96].

(6)

diequatorial axial-equatorial

D. 1,1-Disubstituted Cyclobutanes

A few 1,1-disubstituted cyclobutane derivatives have been investigated with respect to conformation. The microwave spectrum of the 1,1-difluoro derivative could be fitted to a quartic-quadratic expression, suggesting a puckered conformation with a barrier of 241 cm^{-1} [97]. Cyclobutane-1,1-dicarboxylic acid is also reported to be puckered[98,99]. A ^1H NMR spectrum of 1-chloro- and 1-bromo-1-methylcyclobutane and all their 2- and 3-mono-methyl homologs indicates that the halo substituents in geminal methylhalocyclobutanes prefer the equatorial position more than do methyl groups[100]. IR studies of cyclobutane monocarboxylic acid, cyclobutane-1,1-dicarboxylic acid and cyclobutane-*cis*-1,2-dicarboxylic acid have been reported[101].

The temperature dependence of the geminal F−F chemical-shift differences in unsymmetrically substituted difluorocyclobutanes was interpreted in terms of an equilibrium between axial and equatorial conformations[102–104]. The results indicate that the axial conformer in monosubstituted cyclobutanes may be nearly planar. The absence of temperature effects in the spectra of 1,1-difluoro-2-chloro-3,4-diphenylcyclobut-2-ene and 1,1-difluoro-3-methyl-3-phenylcyclobutan-2-one indicates that these systems are planar. The angle of puckering of 1,1-difluoro-3-phenylcyclobutane is estimated to be *ca* 27°.

E. 1,2-Disubstituted Cyclobutanes

With 1,2-disubstituted derivatives the stereochemistry becomes slightly more complicated, as such molecules may display *cis-trans* isomerism. The *trans* form may exist, when puckered, in two different conformations: diequatorial or diaxial, while the *cis* form exists in axial–equatorial conformations. The base-catalyzed equilibration of the methyl esters of *cis* and *trans* cycloalkane dicarboxylic acids has been reported (Table 2)[105].

Apparently, the *trans* isomer is preferred throughout, presumably since the molecules can assume a diequatorial conformation. However, the high value for the cyclopropane derivative indicates that polar effects may contribute significantly, although differences in relative direction of the substituents vary with the ring size. Eclipsing is also more pronounced

TABLE 2. Equilibrium composition of methyl 1,2-cycloalkanedicarboxylates[105]

Ester of	% *trans* isomer	% *cis* isomer
1,2-Cyclopropanedicarboxylic acid	99	1
1,2-Cyclobutanedicarboxylic acid	90	10
1,2-Cyclopentanedicarboxylic acid	90	10
1,2-Cyclohexanedicarboxylic acid	93	7

in cyclopropanes. Recently, a combined experimental and computational study found the same *trans* preference (by *ca* 7 kcal mol^{-1}) in the isomeric dimethyl fumarate–dimethyl maleate pair[106]. X-ray diffraction studies of *trans*-1,2-cyclobutanedicarboxylic acid show a puckered ($\phi = 31^\circ$) conformation with diequatorial substituents[107].

The crystal structure of *cis*-1,2-cyclobutanedicarboxylic acid shows that the cyclobutane ring is puckered with a dihedral angle of 24° and conformational deformations due to steric interaction between the carboxylic acid groups[108]. The *cis* isomer of 1,2-cyclobutanedicarboxylic acid is more acidic, since the monoanion may be stabilized by electrostatic and hydrogen bonding. Furthermore, the K_1/K_2 ratio is larger for the *cis* isomer (130) than for the *trans* isomer (41)[109].

The structures of *cis*-2-phenylcyclobutanecarboxylic acid and *cis*-3-(*p*-fluorophenyl)cyclobutanecarboxylic acid have been determined by X-ray diffraction. In both compounds the cyclobutane ring is puckered. In the latter compound both the carboxyl and *p*-FC_6H_4 substituents are close to the bisecting geometry, in contrast to the former compound[110].

The enantiomers of *trans*-1,2-bis(aryloxy)cyclobutanes were resolved by chiral high-performance liquid chromatography. A fluorescence spectrum indicated that *cis*-1,2-diphenoxycyclobutane formed an intramolecular excimer between two phenoxy groups[111]. The results led the authors to revise the configuration of some of the cyclobutane derivatives that they had previously reported on the basis of NMR data[112, 113].

NMR data on the methyl esters of *cis*- and *trans*-3-*tert*-butylcyclobutanecarboxylic acids and of *cis*- and *trans*-2(and 3)-*tert*-butylcyclobutanols indicate that the rings were puckered[114, 115].

^{1}H NMR vicinal coupling constants in *cis*- and *trans*-1,2-diphenylcyclobutane were compared with those obtained by the Barfield–Smith equations from existing structural data of cyclobutane derivatives[116, 117]. In the Barfield–Smith equations the vicinal coupling constant depends not only on the dihedral angle as in the classical Karplus equation, but also on the H–C–C bond angles. In the *trans* isomer, the conformation with the phenyls in the diequatorial positions is strongly preferred, in agreement with previous results on halocyclobutanes. As expected, the *cis* isomer fluctuates between the two equivalent eq-ax conformations[118].

F. 1,3-Disubstituted Cyclobutanes

As 1,3-disubstituted cyclobutanes have a plane of symmetry both *cis* and *trans* isomers are achiral (provided that the substituents do not brake the symmetry), although the C_1 and C_3 atoms in molecules such as the *cis* and *trans* 1,3-diols are stereogenic but not chirotopic. Electron diffraction studies of several 1,3-dihalo derivatives show exclusive diequatorial conformations for *cis* isomers and axial–equatorial conformations for *trans* forms[119]. The angle of pucker was given as 32–33°. *Cis–trans* equilibration of 1,3-dihalocyclobutanes through treatment with the corresponding halide salts was performed by Wiberg and Lampman[120]. The results are given in Table 3. The expected trend in terms of atom sizes is observed. The authors also estimated structural parameters from dipole moments.

TABLE 3. *Cis–trans* equilibration data of 1,3-dihalocyclobutanes at 124.4 °C[120]

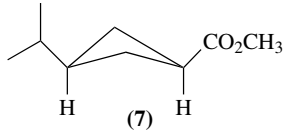
Dihalocyclobutane	$K_{cis/trans}$	ΔG° (kcal mol^{-1})
Dichloro-	1.44	0.29
Dibromo-	2.07	0.58
Diiodo-	2.18	0.62

Dipole-moment measurements of *trans*-1,3-dibromo-1,3-dimethylcyclobutane in which 1,3 interactions cannot be avoided were interpreted in terms of a flattening of the ring to reduce the magnitude of the interactions. The angle of pucker is estimated as small as 14°. Other examples where dipole moments have been used to estimate the conformation of 1,3-disubstituted derivatives have also appeared[121].

Infrared and Raman spectra of the two isomers of 1,3-dimethylcyclobutane in the temperature interval +20 to −100 °C show decisive differences[122]. Similar results were obtained by Lillien[123]. Symmetry properties of the planar *trans* isomer (C_{2h}) imply that the vibrational spectrum must obey alternation in IR Raman activity. Actually, considerable coincidence was observed indicating a nonplanar conformation. The *cis* isomer did not show any temperature dependence but the *trans* isomer gave new IR bands at low temperature, which coincided with the Raman bands. Thus, the *cis* isomer is exclusively diequatorial, whereas small amounts of planar conformation cannot be ruled out for the *trans* form.

Several cyclobutanecarboxylic acid derivatives have been studied[124–129]. In the crystal *trans*-1,3-cyclobutanedicarboxylic acid is planar, whereas the same molecule is puckered in a cocrystal with the disodium salt[126]. Surprisingly, the crystal is built up of one dianion containing a planar ring and one puckered neutral diacid molecule. These results indicate that crystal forces are of the order of 1 kcal mol^{-1} and that the potential for out-of-plane deformations is shallow. Equilibration of *cis*- and *trans*-3-*tert*-butylcyclobutanecarboxylic acid ethyl ester favors the *cis* form by 0.6 kcal mol^{-1} in an enthalpy-driven equilibrium, and the corresponding acid also favors the *cis* form[114].

The base-catalyzed *cis–trans* equilibration of 3-isopropyl- and 3-methylcyclobutanecarboxylic acid methyl esters (**7** and **8**, respectively) enables comparison between the methyl and isopropyl groups in the cyclobutane system[130], revealing a difference $\Delta\Delta G_{338\ K} = 0.2$ kcal mol^{-1}, slightly lower than the difference between the corresponding value (A-values) in the cyclohexane series. This is believed to primarily originate in the low penalty cost of ring flattening of the cyclobutane ring compared to cyclohexane as observed in several other derivatives[120].



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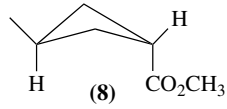

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For dimethyl 1,3-cyclobutanedicarboxylate $\Delta G^{\circ}_{338\ K} = 0.1$ kcal mol^{-1} in favor of the *trans*-ax,eq isomer, a preference that is probably governed by electrostatic interactions[127].

The aluminum isopropoxide-catalyzed *cis–trans* equilibration of 3-*tert*-butylcyclobutanol leads to $\Delta H^{\circ} = -1.6$ kcal mol^{-1}, $\Delta S^{\circ} = -1.1$ cal mol^{-1} K^{-1} and $\Delta G^{\circ}_{373\ K} = -1.15$ kcal mol^{-1} [129]. The NMR spectra of the *cis* and *trans* isomers of 3-isopropylcyclobutanols and 3-isopropylcyclobutylamines reveal the existence of both equatorial and axial substituents[131]. The isopropyl group is considered to be large enough to act as an equatorial anchor.

Equilibration of 1,3-di(phenylsulfonyl)cyclobutane in *t*-BuOK/*t*-BuOH shows that the *trans* isomer is more stable than the *cis* isomer by 2.1 kcal mol^{-1} [132], in contradiction to what is generally observed for 1,3-disubstituted cyclobutanes, for which the bulky substituent prefers the *cis* configuration in order to avoid 1,3-diaxial interactions. The effect was found to be enthalpic in nature. *Ab initio* 3-21G calculations also resulted in preference of the *trans* isomer by 2.6 kcal mol^{-1}. The cyclobutane rings were calculated to be nearly planar. An explanation could be found in terms of electrostatic interactions favoring the *trans* form.

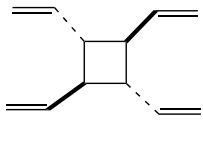
G. Polysubstituted Cyclobutanes

Cis-1,3-dibromo-1,3-dimethylcyclobutane and *trans*-1,3-dibromo-1,3-dimethylcyclobutane were analyzed in various states and by various spectroscopic methods[133]. The *trans* compound can only take one type of puckered conformation. The IR and Raman spectra of *cis*-1,3-dibromo-1,3-dimethylcyclobutane were interpreted in terms of only one conformer with diequatorial Br and C_{2v} symmetry. The spectra of *trans*-1,3-dibromo-1,3-dimethylcyclobutane were interpreted in terms of a planar or pseudo-planar cyclobutane ring and an effective C_{2h} symmetry in the condensed phases. *Trans*- and *cis*-1,3-dibromo-1,3-dimethylcyclobutane have been studied by gas electron diffraction. The *trans* isomer must exist in an equilibrium between two degenerate conformations. The puckering angle of the ring was determined as 18°. The *cis* isomer may exist as diequatorial and diaxial conformers with respect to the bromines. The diequatorial conformer is found to predominate at 40 °C with a population of 81%, corresponding to an energy difference of $\Delta G^{\circ}(\text{ax-eq}) = 1\ \text{kcal mol}^{-1}$ [134].

Vibrational spectra indicate that the barriers to ring inversion are high enough in 1-chloro-1,2,2-trifluoro- and 1,1,2-trichloro-2,3,3-trifluorocyclobutane for both conformers to be trappable in the matrix but not in the vapor state[135].

Comparison of the photoelectron spectrum of tetravinylmethane with that of all-*trans*-1,2,3,4-tetravinylcyclobutane (**9**) indicated that the interaction of the vinyl groups in these two compounds was similar and that they had S_4 symmetry[136].

The photodimers of cinnamic acid, truxillic acid (**10**) and truxinic acid (**11**), appearing in many sources of natural products, play an interesting role in cyclobutane stereochemistry. Truxillic acid may exist as five diastereomers, all remarkably achiral: α, γ, *peri, epi* and ε (Figure 9), whereas truxinic acid exists as six diastereomers of which two are *meso* and four chiral. The α-truxillic acid has no symmetry plane but a center of symmetry (S_2 point group) in the time-averaged planar conformation, which makes it achiral.



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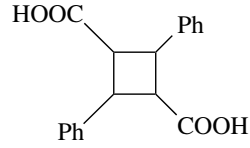

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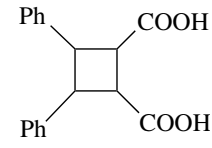


(11)

Truxillic acid is called α-type photodimer since it is formed regio- and stereospecifically from the α-modification of crystalline *trans*-cinnamic acid and truxinic acid (the β-form) is obtained from the β-modification[137]. Cocrystallization of *trans*-cinnamic amide with phthalic acid also gives the β-type photodimer, despite the fact that according to a single-crystal X-ray study the double bonds are nearly perpendicular to each other (Figure 10)[138].

Dynamic ^{1}H and ^{13}C NMR spectroscopy has been used to analyze restricted rotation of the phenyl groups in dimethyl 2,2′,6,6′-tetrachloro-β-truxinate, resulting in the following activation parameters: $\Delta H^{\ddagger} = 11.0\ \text{kcal mol}^{-1}$, $\Delta S^{\ddagger} = -4.4\ \text{cal mol}^{-1}\,\text{K}^{-1}$. In the transition state for rotation, the two Ph groups are perpendicular to one another and the act of rotation involves one phenyl group at a time. The origin of the barrier is the steric interactions of the chlorine atoms with their environment in the transition state for the rotation. X-ray analysis of the compound yields a structure with an angle of pucker of 14.3° for the cyclobutane ring in which one chlorine group hovers over the cyclobutane ring while the two chlorines of the other phenyl group avoid contact with the cyclobutane ring[139].

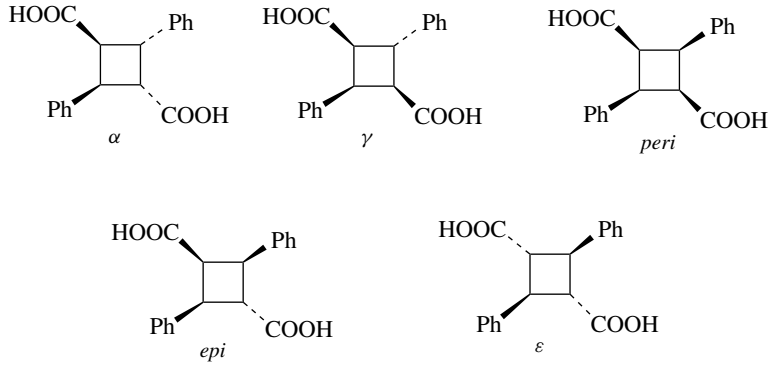


FIGURE 9. The five truxillic acids

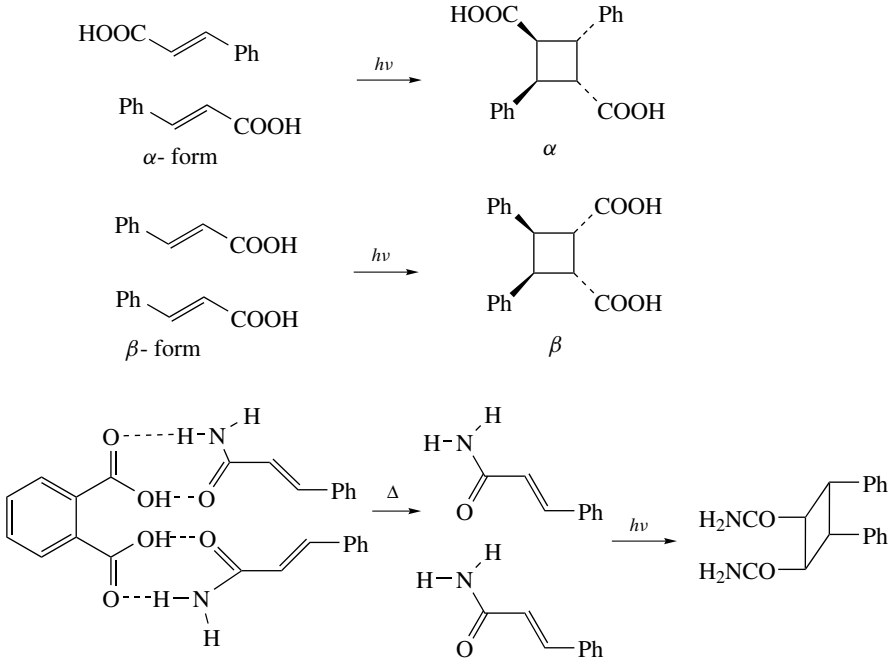
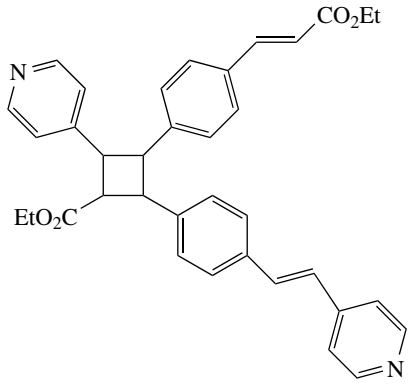


FIGURE 10. Formation of photodimers from cinnamic amide

Optically active dimer **12** was formed by topochemically controlled [2 + 2] photocyclodimerization of a single crystal of (pyridylvinyl)cinnamate (**13**). The regioselectivity is determined by the positions of the molecules in the crystal and the chirality of the dimer resulted only from the chiral environment of the crystal. Furthermore, amplification of asymmetry was achieved by seeding during the recrystallization of **13**. The optical purities of both enantiomers of **12** were more than 92%. The asymmetric induction mechanism

was interpreted by an X-ray structure analysis of **13**. The formation of a chiral space group was caused by the cisoid form of the monomer of **13**, which is very rare among photoreactive diolefinic molecules[140].



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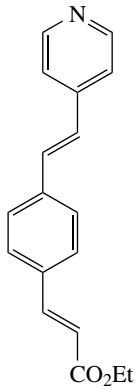


(13)

Irradiation of solid *trans*-β-nitrostyrene gave only the head-to-tail *r*-1-*t*-3-dinitro-*t*-2-*c*-4-diphenylcyclobutane[141].

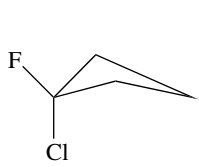
The chemo- and stereoselectivity of the cycloaddition of allene derivatives with diethyl fumarate and maleate shows that the reactions involve two steps and diradical intermediates. The product distribution reflects the preferred conformations of the diradical intermediates and the competition between ring closure, internal rotation and cleavage reactions of the diradical intermediates. The ^{1}H NMR spectroscopy was used to evaluate the conformation of the methylenecyclobutane cycloadducts[142].

The crystal structure and ^{1}H and ^{13}C NMR data of 1,1,2,2-tetracyano-3,3-dimethyl-4-(2′,2′-dimethylethenyl)cyclobutane show that the H−C−C−H dihedral angle of the vinyl group is *anti* both in the crystal and in solution and that the angle of pucker is 21.8°[143]. An analysis of the ^{1}H and ^{13}C spin–lattice relaxation times (T_1) show that the rotations of the two methyl groups in the three-position are hindered.

The Borodin–Hunsdiecker reaction (reaction with Br_2, Ag_2O) of *trans*-3,4-dibromocyclobutane-*cis*-1,2-tetracarboxylic acid gave 3 stereoisomeric 1,2,3,4-tetrabromocyclobutanes: 56% all-*trans*, 20% *cis,cis,trans* and 24% *cis,trans,cis*[144]. The stereochemical outcome could be explained by either intramolecular bromine shift of the intermediate radical, taking place without inversion, or a bromine *trans* attack leading to different tribromo intermediate radicals.

1-Chloro-1-fluorocyclobutane (**14**) and 1-chloro-1,2,2-trifluorocyclobutane (**15**) were investigated by IR and Raman spectroscopy in various phases and at different temperatures. Both compounds exist in two conformers. The argon matrix spectrum of **15** was consistent with an averaged structure at 13 K, suggesting a barrier lower than 1.2 kcal mol^{-1} between the conformers. Both the argon and nitrogen matrix spectra of **15** contained two conformers. The enthalpy difference ΔH^0 between the conformers was 0.5 kcal mol^{-1} for **14** in the liquid and 0.6 and 0.7 kcal mol^{-1} in the vapor and liquid, respectively, for **15**. The use of force constants from *ab initio* calculations at the 3-21G* and 6-31G* levels only reproduces the spectra if the fluorine atom is equatorial in the more stable confomer[145].

The substituent effects on the conformation of four 1,1-difluoro-2,2-dichlorocyclobutanes substituted at the 3-position were elucidated by NMR. The ring protons and fluorine



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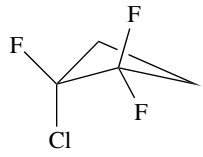


(15)

atoms gave rise to an ABXY spectrum, which markedly changed in complexity as the 3-substituents were varied. The author proposed that the appearance of the spectra depends upon the extent of puckering of the four-membered ring[146].

III. RESOLUTION AND DETERMINATION OF CONFIGURATION

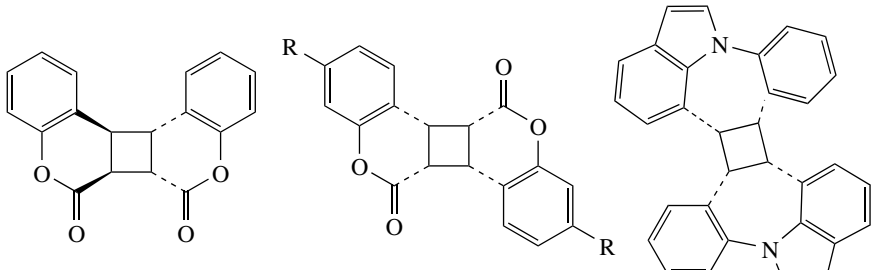
Since the synthesis of a chiral compound leads to racemic product unless a chiral handle is operating in the enantioselective step of the reaction, resolution of racemate is a vital technique for the preparation of pure or enriched enantiomers of synthetic compounds. A summary of the methods at hand can be found in the monograph by Eliel, Wilen and Mander[147]. If one is lucky, spontaneous resolution may occur enabling manual crystal picking. More often, the transformation of the racemate to a diastereomeric species in the enantiodiscriminating step has to be performed. Classical separation via diastereomers for chemical separation includes many variations and can be performed under either thermodynamic or kinetic control, preferentially using naturally occurring chiral resolving agents since they are often enantiopure. This is, however, not always the case. An example including a cyclobutane derivative is the use of α-pinene as a chiral auxiliary in enantioselective hydroboration. The enantiomeric excess (ee) of natural α-pinene is only *ca* 84%, although this does not necessarily mean that the ee of the resolving agent is the maximum possible ee of the product. This phenomenon, called the nonlinear effect, has been observed and utilized in asymmetric catalysis by the groups of Kagan and Noyori[148–151].

The use of various types of adsorption or inclusion complexes with chiral molecules has been successfully applied. In particular, chromatographic methods have been used for both analytical and preparative purposes. Under suitable conditions both enantiomers may be obtained in one experiment, although usually only in analytical or semipreparative scales[152].

The determination of the absolute configuration of a molecule is not an easy task. It was only in 1951 that this was achieved through the Bijvoet anomalous X-ray scattering method[153]. When the compound is not crystalline or when the crystals are not suitable for X-ray analysis, one is left with either indirect methods, e.g. comparison of chiral properties with other compounds of known configuration, or, in certain cases, application of empirical rules, such as the octant rules for carbonyl compounds. When the use of such methods fails, one must resort to the more elaborate theoretical computation of circular dichroism (CD), optical rotatory dispersion (ORD) or optical rotation. This method has been applied in a few cases for cyclobutane derivatives.

The photodimerization of coumarin has been the subject of interest for a long time, and the regiochemistry of the reaction is known to depend upon the conditions[154]. The racemic *anti* head-to-head coumarin dimer [(+)-**16**-(−)-**16**] was resolved by Saigo and coworkers through fractional crystallization of the lactone-opened diamides with (*S*)(−)-$PhCHMeNH_2$ followed by hydrolysis and relactonization. The absolute configuration was determined both by CD spectroscopy and crystallographically, initially giving opposite results[155]. However, the assignment was later corrected to (6a*R*, 6b*R*, 12b*R*, 12c*R*) for (+)-**16**, and the discrepancy was explained by a mirror reflection in the calculation of the stereostructure from the X-ray data[156, 157].

Chromatographic resolution of the *anti* head-to-head dimer **16** and the *syn* head-to-tail isomer **17** was performed on crossbound poly(ethyl (*S*)-2-(acryloylamino)-3-phenylproprionate) as the stationary phase and the absolute configurations were predicted by CD spectroscopy[157]. The CD spectra were found to agree with those calculated by the semiempirical matrix technique by Schellman and coworkers[158, 159], using transition moments and transition charge densities as input. The methoxy analog **17b** was resolved on the same stationary phase immobilized on a porous matrix[160]. Sandström and coworkers also resolved the C_2 symmetric photodimer of 5H-indolo[1,7-*ab*][1]benzazepine (**18**) and determined the absolute configurations from their CD spectra[157].



(**16**)

R = H (–)-(**17a**)
R = CH_3O (–)-(**17b**)

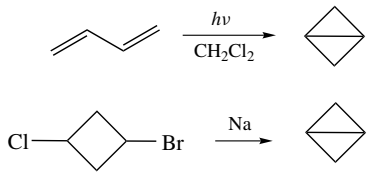
(+)-(**18**)

IV. CYCLOBUTANE IN BICYCLIC SYSTEMS

The smallest and most strained fused ring system is bicyclo[1.1.0]butane (**19**). A couple of the earlier syntheses are shown in Figure 11[161, 162]. Hoz has written a review on bicyclo[1.1.0]butane[163].

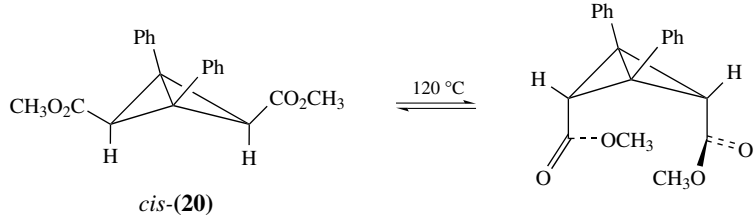
Among the examples of anomalous behavior noted for this bicyclic system is its propensity for flap inversion. Woodward and Dalrymple studied the diester **20** (Figure 12)[164]. The curious observation was that the di-*endo* ester isomer of *cis*-**20** was thermodynamically more stable in the equilibrium mixture ($K = 14$). Gassman and coworkers have taken up the case and ran X-ray analysis and performed computations on the PRDDO level of approximation, showing an unexpected flexibility of the bicyclo[1.1.0]butane skeleton[165]. An anti-parallel orientation of the ester groups as shown in Figure 12 seems to stabilize the di-*endo* isomer by electrostatic attraction.

Bicyclo[1.1.1]pentane was first prepared in 1964 by Wiberg and coworkers[166]. The strain of bicyclo[1.1.1]pentane (60–68 kcal mol^{-1})[167, 168], previously considered anomalously high, is clarified by the concept of Dunitz–Schomaker strain. Still, bicyclo[1.1.1]

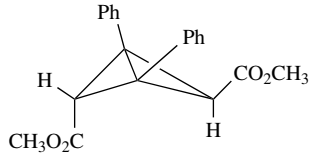


(**19**)

FIGURE 11. First syntheses of bicyclo[1.1.0]butane (**19**)[161, 162]



cis-(**20**)



trans-(**20**)

FIGURE 12. Configurational isomerization of **20**[164]

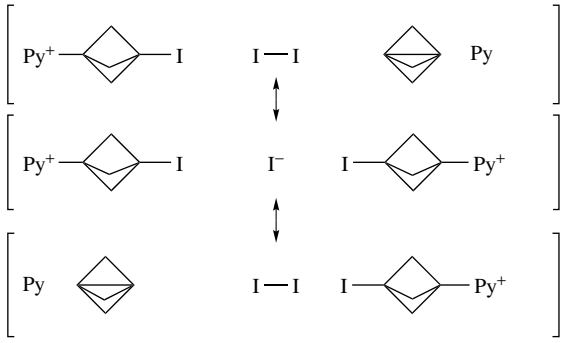


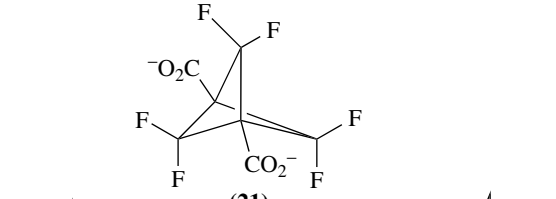
FIGURE 13. A pyridinium salt formed by pyridine substitution of the iodide in 1,3-diiodobicyclo[1.1.1]pentane, giving an iodide/triiodide salt represented by resonance structures

pentane is thermally stable up to 300 °C[169]. The molecular structure of bicyclo[1.1.1]pentane has been investigated in the vapor phase by electron diffraction[170] and vibrational spectroscopy[171, 172]. The molecule has an angle of pucker of 58° and its C−C bonds are unusually short, 1.498 Å[173]. The data support a D_{3h} conformation. The separation between the bridgehead C atoms (1.80–1.90 Å) is one of the shortest nonbonded C···C distances on record, leading to a very high value for the ^4J(H−H) coupling constant of 18 Hz[174–177]. Adcock and coworkers[174] prepared pyridinium salt by pyridine substitution of iodide in 1,3-diiodobicyclo[1.1.1]pentane, giving an iodide/triiodide salt with a C_1-C_3 distance of 1.80 Å (Figure 13).

Dimethyl bicyclo[1.1.1]pentane-1,3-dicarboxylate can be perfluorinated by direct fluorination, leading to various fluorinated compounds. Single-crystal X-ray diffraction analysis of hexafluorobicyclo[1.1.1]pentane-1,3-dicarboxylic acid (**21**) revealed an interbridgehead distance of 1.979 Å, long compared with the distance in the parent molecule, and very

short nonbonded F−F distances of 2.41 Å. The molecule has remarkably low pK_a values, 0.73 and 1.34, compared with 3.22 and 4.26 for the parent diacid originating in a direct field effect of the fluorine atoms, combined with an increased s character of the exocyclic hybrid orbital on the bridgehead carbon[178].

Reed and coworkers have shown that decarboxylation of 1-bicyclo[1.1.1]pentanecarboxylate anion (**22**) does not afford 1-bicyclo[1.1.1]pentyl anion, as previously assumed. Instead, a ring-opening isomerization leading to 1,4-pentadien-3-yl anion takes place. However, the 1-bicyclo[1.1.1]pentyl anion could be prepared via the fluoride-induced desilylation of 1-*tert*-butyl-3-(trimethylsilyl)bicyclo[1.1.1]pentane (**23**)[179].



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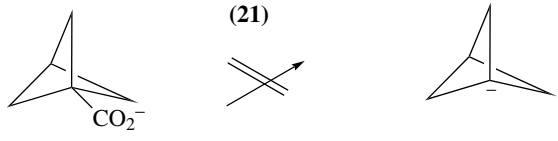

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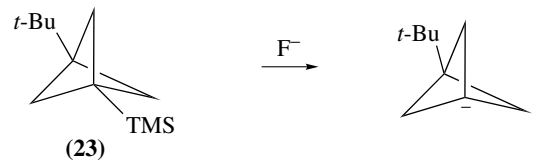


(23)

Bicyclo[2.1.0]pentane (**24**) has a calculated strain energy of 57.3 kcal mol^{-1}, which is approximately the sum of those of cyclopropane and cyclobutane[180]. This molecule has a remarkable structure. It is one of the few compounds in which the cyclobutane ring is planar and the zero bridge bond length is only 1.439 Å and the opposite CC distance is 1.622 Å[181–184]. The barrier to skeletal inversion of **24** and its methyl derivatives has been measured in the gas phase using appropriately deuteriated molecules (Figure 14)[185]. A barrier (E_a) of 37.8 kcal mol^{-1} was found for the parent molecule and the reaction is believed to proceed via a diradical intermediate. The potential energy surface for bicyclo[2.1.0]pentane has been calculated by semiempirical and *ab initio* MO calculations (6-31G** basis set and MP2 or MP4 perturbation theory)[186]. The predicted equilibrium geometry of **24** and of the 1,3-cyclopentanediyl radical, the barrier for the ring inversion and the fundamental frequencies of bicyclo[2.1.0]pentane were calculated. The calculated barrier was in excellent agreement with experiment.

The stereochemistry of bicyclo[2.1.0]pentane hydroxylation has been investigated by *ab initio* MO calculations and its relevance to cytochrome P-450 hydroxylation has been discussed (Figure 15)[187]. Both the *endo*- and *exo*-bicyclo[2.1.0]pent-2-yl radicals

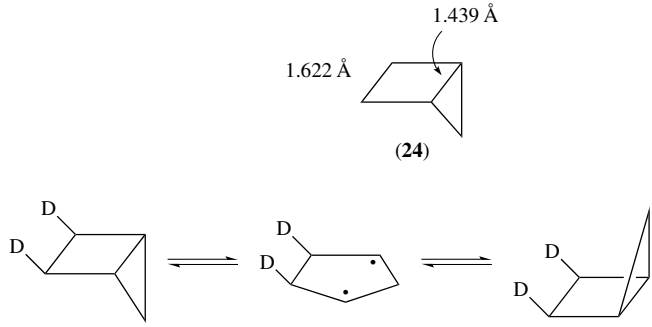


FIGURE 14. Deuteriated molecule for the study of the skeletal inversion of **24**[185]

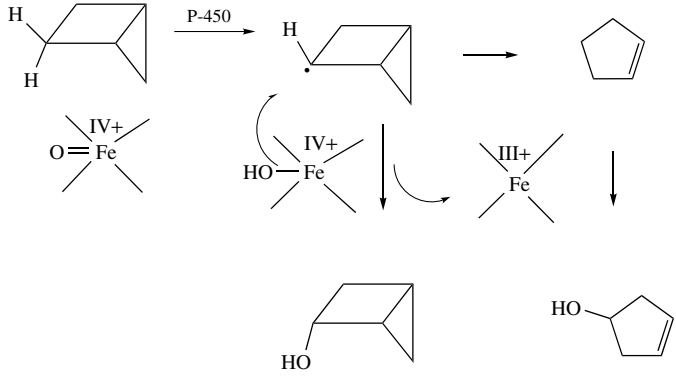


FIGURE 15. Reaction scheme for the hydroxylation of bicyclo[2.1.0]pentane by cytochrome P-450

are appreciably pyramidal, but are nearly equal in energy ($\Delta E < 0.3$ kcal mol^{-1}) and are separated by a very low (<0.4 kcal mol^{-1}) barrier. This small barrier disappears when corrections for zero-point energy are added. Even though the *endo* and *exo* bond strengths are nearly identical in bicyclo[2.1.0]pentane, abstraction of the *endo* hydrogen via the OH radical is favored over the *exo* hydrogen by 1.4 kcal mol^{-1}. The *endo* preference can be ascribed to stabilization by the cyclopropylcarbinyl moiety.

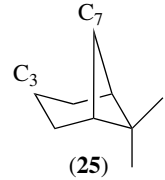
Bicyclo[2.1.0]pentane reacts with acetic acid to give cyclopentyl acetate and cyclopentene. Reactions with stronger acids are more rapid and give different product ratios[188].

Spin–spin coupling constants $^{13}C-^{13}C$ of bicyclo[2.1.0]pentane and bicyclo[2.2.0]hexane and several derivatives have been calculated within the self-consistent theory of finite perturbation SCPT INDO using previously optimized geometric parameters. The results show unusually small s-character of hybrid orbitals in the bridge bond: 4.8–8.8% in the derivatives of the bicyclo[2.1.0]pentane and 11.3–12.9% in those of bicyclo[2.2.0]hexane[189].

Bicyclo[2.1.1]hexane[190] and bicyclo[3.1.1]heptane[191] have also been analyzed by electron diffraction. The photoelectron spectrum[192] of bicyclo[2.1.1]hexane supports the revised structure given by Chiang.

The skeleton of bicyclo[3.1.1]heptane makes part of the pinane monoterpenes[193]. The ^{13}C NMR chemical shifts of bicyclo[3.1.1]heptane derivatives have been correlated with

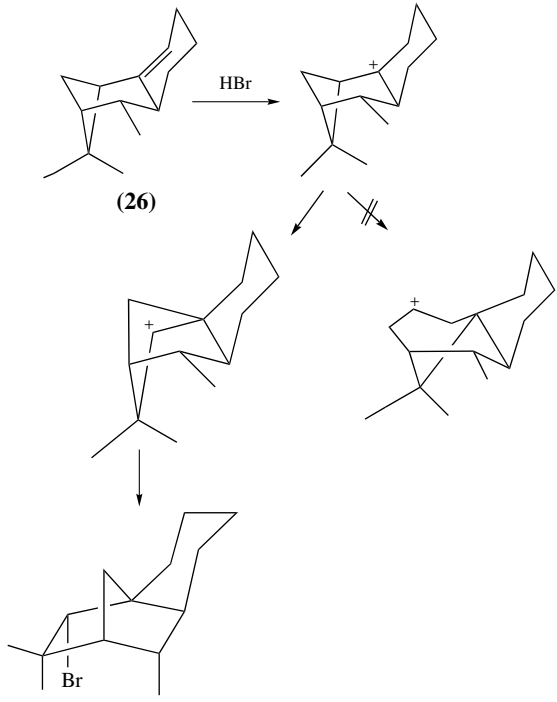
geometries obtained from molecular mechanics force-field calculations. For the parent hydrocarbon chair geometry minima were observed, although their interconversion is calculated to be rapid ($\Delta H^{\ddagger}$ *ca* 0.6 kcal mol^{-1}) so that an average flat Y form can be assumed for the ground state[194]. In 6,6-dimethylbicyclo[3.1.1]heptane (**25**), the C_3-atom is tilted towards the C_7-methylene group as expected from steric reasons[195].



(**25**)

Treatment of the β-pinene derivative **26** with HBr reveals an interesting selectivity in the formation of the product as shown in Figure 16, probably originating in a conformational effect[33,196]. The fused cyclohexane ring induces a conformation that facilitates the migration of the CH_2 moiety.

$^{13}C-^{1}H$ coupling constants have been correlated with electronic structure in bi- and polycycloalkanes[197], and with bond angles[198,199]. Quantum-chemical models have been used to generate Muller–Pritchard-type expressions [$^{1}J(^{13}C-^{1}H) = \text{const.} \times \%$ s-C, where s-C is the s-contribution to hybrid carbon orbital] for the prediction of one-bond C–H



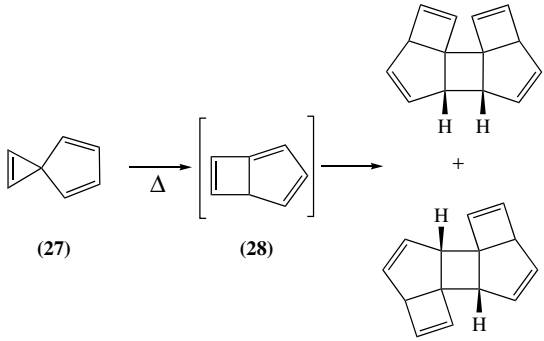
(**26**)

FIGURE 16. HBr-induced rearrangement of **26**[33,196]

spin–spin coupling constants, in a series of bi- and polycyclic compounds. The best fit was obtained when the model includes contributions from the atomic charges (q_H and q_C) along with the s character at carbon.

Nonbonded interactions between the bridgehead C atoms provide positive contributions to both $J(^{13}C-^{19}F)$ and $J(^{1}H-^{19}F)$ in bicyclic systems[31, 200, 201].

Thermolysis of spiro[2.4]hepta-1,4,6-triene (**27**) at 50 °C yielded bicyclo[3.2.0]hepta-1,3,6-triene as an unstable intermediate, **28**. This intermediate dimerizes exclusively to the two different cyclobutanes shown but not to the other isomers. *Ab initio* calculations indicate that the two strained olefins **27** and **28** have similar energies about 50 kcal mol^{-1} lower than norborna-1(7),2,5-triene, which thus could be excluded as a reaction intermediate[202].

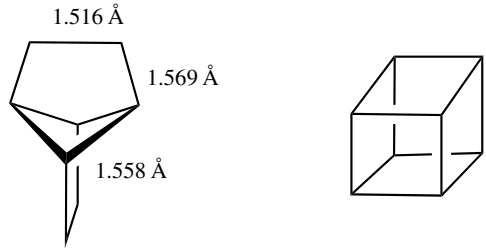


(**27**) (**28**)

V. CYCLOBUTANE IN POLYCYCLIC SYSTEMS

A. Some Highly Symmetrical Polycyclic Derivatives

In this section some symmetrical and strained polycyclic derivatives containing the cyclobutane ring are described. Wiberg has written a review about these simplest cage molecules[203], and Michl and coworkers another one on bicyclo[1.1.1]pentanes, [1.1.1]propellanes and staffanes[204].



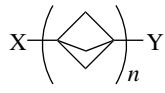
(**3**) (**29**)

Tricyclo[3.3.0.0^{2,6}]octane (**3**), mentioned earlier, contains a tetrasubstituted cyclobutane ring. The parent molecule has been prepared by photocyclization of *cis,cis*-1,5-cyclooctadiene[205–207] and its structure was determined by electron diffraction experiments[208]. The two carbon distances in the ethylene bridge are rather extreme. The perfluoro derivative was earlier prepared from hexafluorobutadiene[209] and has a disordered structure in the crystal with four different C–C bond lengths in the cyclobutane ring ranging from 1.439 to 1.514 Å according to X-ray diffraction data[210].

The electron-diffraction data of gaseous cubane (**29**) are consistent with O_h symmetry and the two geometrical parameters are $d_{C-C} = 1.575(1)$ Å and $d_{C-H} = 1.100(6)$ Å. Thus, the C−C bond is much longer than in cyclobutane[211].

Schleyer and coworkers have examined the concept of antiaromaticity applied to cyclobutane and cubane as well as the possibility of spherical homoaromaticity of symmetrical molecules such as the neutral dodecahedrane analog $C_{20}H_{12}$, possessing an inscribed cubic C_8 and eight π-electrons and thus satisfying the $2(n+1)^2$ rule for spherical aromaticity[26,212].

Polymerization of [1.1.1]propellanes gives the so-called [*n*]-staffanes (**30**), structures which have been proposed to exhibit potential electron-relaying properties[204,213,214].



(30)

Szeimies and coworkers have recently synthesized symmetrical 3,3′-disubstituted 1,1′-bi(bicyclo[1.1.1]pentanes) via a bridgehead-to-bridgehead homocoupling of bicyclo[1.1.1]pent-1-ylmagnesium halide catalyzed by palladium(II) (Figure 17)[215].

Only 1.1 mol percent of bis(acetonitrile)palladium(II) chloride and two equivalents of bromomethane were necessary to accomplish this reaction. The bromomethane formed in the first step is essential to convert Pd^0 to Pd^{II}. An X-ray structure of the diisopropyl derivative shows a nonbonded C_1-C_3 distance of 1.907 Å in the bicyclo[1.1.1]pentyl subunits.

B. Fenestranes

A molecule that has attracted considerable attention is the so-called fenestrane (also called windowpane), since the central carbon atom must have strongly distorted bonds. Nomenclature and stereochemistry of fenestranes is illustrated in Figure 18[216]. The *cis* and *trans* junction around the bonds from the central carbon atom defines the stereochemistry. No [4.4.4.4]fenestrane derivative has been prepared yet, but computations propose a strain energy of 177.5 kcal mol^{-1} [217]. Several homologs, e.g. **31**[218] and **32**[219], have been prepared, and *c*,*c*,*c*,*c*[5.5.5.5]fenestrane has D_2 symmetry according to an electron-diffraction study[220].

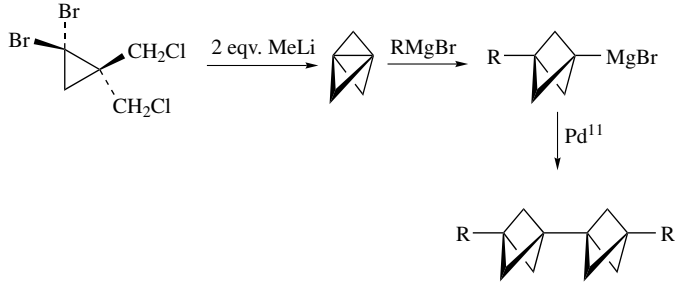
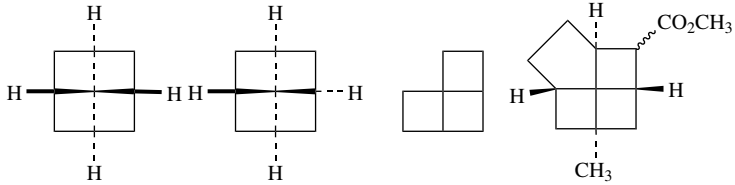


FIGURE 17. Synthetic sequence for the symmetrical 3,3′-disubstituted 1,1′-bi(bicyclo[1.1.1]pentanes)[215]

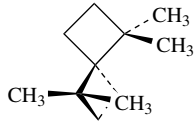


c,c,c,c-[4.4.4.4] fenestrane | *c,c,c,t*-[4.4.4.4] fenestrane | **(31)** | **(32)**

FIGURE 18. Various fenestrane analogs

(33) **(34)**

(*S*)-spiro[3.3]heptane-2,6-dicarboxylic acid (1*S*,*trans*-6)-spiro[3.3]heptane-1,6-dicarboxylic acid



(35)

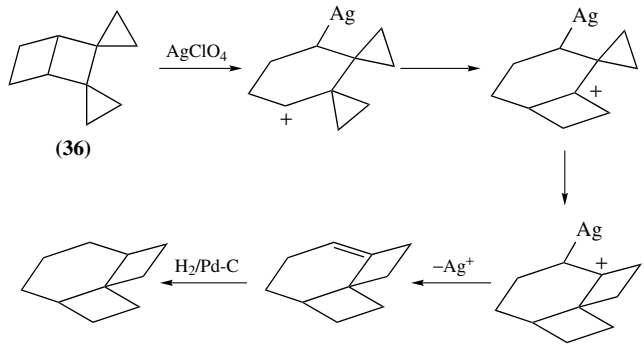
(*R*)-1,1,5,5-tetramethyl-spiro[3.3]heptane

FIGURE 19. Some chiral spiro[3.3]heptanes

C. Spiranes

Spiranes containing the cyclobutane moiety possess interesting stereochemical properties. The parent molecule, spiro[3.3]heptane, was obtained from spiro[3.3]heptane-2-carboxylic acid after treatment with $Pb(OAc)_4$ and iodine, and the product 2-iodospiro[3.3]heptane with Li and *tert*-BuOH[221]. If we consider the two dicarboxylic acid derivatives and the tetramethyl derivative in Figure 19, **33**, which displays axial chirality, has *S* configuration and **34** has four stereoisomers, two diastereomeric (*cis* and *trans*) pairs of enantiomers. **35** is confusing, since it would appear to have a stereo-axis, but for the purpose of nomenclature the central carbon is treated as a stereogenic carbon, one arbitrary substituted branch is given highest priority, the other branch in the same ring priority 3 and the corresponding branches in the other ring are given priority 2 and 4, respectively. This leads to *R* configuration for the central atom[147].

Treatment of the bicyclo[2.2.0]hexane derivative **36** with silver perchlorate produces a carbocation, which undergoes a cascade of rearrangements and the formation of a tricyclic system containing the spiro[3.3]heptane moiety[222].



D. Rotanes

[*m.n*]Rotanes are molecules which are composed of a central *m*-membered ring and *m* *n*-membered rings attached to the *m*-ring in a spiro fashion. One of the first examples is [4.3]rotane[223, 224] and other rotanes are given in Figure 20.

Fitjer and coworkers have prepared and conformationally characterized several rotanes containing cyclobutane rings[225–227]. The structures of the compounds were determined by X-ray analyses and by force-field calculations. They found that when the size of the central ring increased, the bond angles of this ring increase while the bond angles at the spiro center of the spiroannelated cyclobutane rings decrease. As a consequence, the cyclobutane rings undergo structural changes from a regular trapezoid in [4.4]rotane to a kite with the smallest angle at the spiro center in [5.4]rotane and [6.4]rotane. At the same time their puckering decreases, until in [6.4]rotane they are close to planar. Furthermore, the conformation of the cyclohexane ring and the barrier to inversion depended strongly upon the opening angle of the exocyclic substituent.

Hexaspiro[2.0.3.0.2.0.3.0.3.0.3.0]docosane (**37**) and hexaspiro[2.0.3.0.3.0.3.0.3.0.3.0]-tricosane (**38**) have been synthesized from spiro ketones **39** and **40**, respectively[226]. Chair conformations of the cyclohexane rings were found in the solid state and in solution. The activation parameters of the chair-to-chair interconversion were determined from dynamic ^{1}H-NMR and ^{13}C-NMR spectroscopy. The results were as follows: **37**: $\Delta H^{\ddagger} = 11.7\ \text{kcal mol}^{-1}$, $\Delta S^{\ddagger} = -5\ \text{cal mol}^{-1}\ \text{K}^{-1}$, $\Delta G^{\ddagger}_{298} = 13.1\ \text{kcal mol}^{-1}$; **38**: $\Delta H^{\ddagger} = 12.2\ \text{kcal mol}^{-1}$, $\Delta S^{\ddagger} = -2.9\ \text{cal mol}^{-1}\ \text{K}^{-1}$, $\Delta G^{\ddagger}_{298} = 13.1\ \text{kcal mol}^{-1}$. These barriers are only *ca* 2.5 kcal mol^{-1} higher than that of unsubstituted cyclohexane. Stereoselective labeling of [6.4]rotane in the α-position giving [1-^{13}C]-[6.4]rotane turned out to give conformationally stable isotopomers with the ^{13}C-atom in axial or equatorial position, respectively,

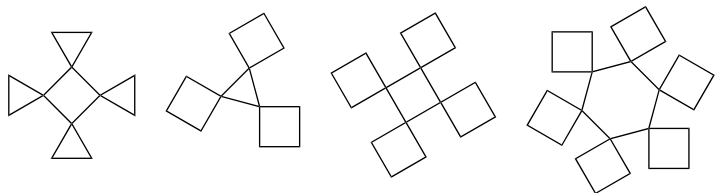
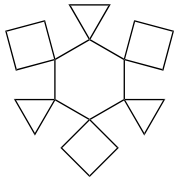


FIGURE 20. Some rotanes containing the cyclobutane ring

and the equilibration could be examined. A free energy of activation for the chair-to-chair interconversion of $\Delta G^{\ddagger} = 37$ kcal mol^{-1} was determined. This is the highest barrier of inversion ever reported for a cyclohexane derivative. A comparison of **38** with [6.4]rotane reveals a most remarkable difference of 24 kcal mol^{-1} only from expanding a single spirocyclopropane ring by one carbon unit.



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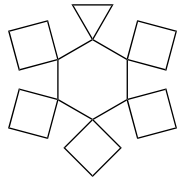

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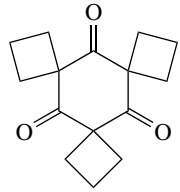

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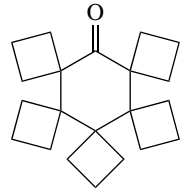


(40)

VI. STEREOCHEMISTRY OF RING CLOSURE AND RING-OPENING REACTIONS

The thermal suprafacial [2 + 2] cycloaddition of olefins is forbidden as a concerted reaction by orbital symmetry. Most thermal [2 + 2] cycloadditions take place via diradicals or zwitterions of the 1,4-tetramethylene type[228]. Quantum-chemical considerations indicate that diradicals and zwitterions are not alternatives, but the extremes of a continuous scale. Competition phenomena (ring closure, rotation, dissociation) observed for these tetramethylene derivatives are consistent with true intermediates. Trapping reactions of tetracyanoethylene and enol ethers show that the intermediates are best described as zwitterions. Huisgen argues that the widespread opinion that orbital control may be ignored in the discussion of two-step cycloadditions is erroneous in that the two-step reactions are likewise forbidden by orbital symmetry, although the activation energy should be lower than that for the concerted process.

The thermolysis of *cis*- and *trans*-1,2-dimethylcyclobutane is a classic kinetic study of cyclobutane decomposition[229, 230]. The stereochemistry of the fragmentation and isomerization of *cis*-1,2-dimethyl-*anti*-*cis*-3,4-dideuteriocyclobutane (**41**) and *trans*-1,2-dimethyl-*cis*-3,4-dideuteriocyclobutane (**42**) has been reported by Wang and Chickos[231]. At 510 °C compound **41** is fragmented to *cis*-/*trans*-MeCH:CHD (1.5:1, major pathway, Figure 21), *cis*-/*trans*-2-butene (1.4:1) and *cis*-/*trans*-DCH:CHD (1:1, minor pathway). Recovered cyclobutanes contained products in which one or both C·H−CH_3 groups had rotated with a relative frequency of *ca* 4:6. Compound **42** behaved similarly. Recovered **41** from **42** thermolysis consisted mainly of equal amounts of **41** and its *cis*-*syn*-*cis* isomer **43**. This thermochemical reaction was suggested to proceed via 2,5-hexanediyl (major pathway) and 3-methyl-1,4-pentanediyl (minor pathway).

Von Doering and coworkers explain the thermal rearrangements of cyclobutanes to ethene derivatives as an example of a 'not-obviously concerted' reaction—made possible due to their considerable strain energy. They have designed systems for the study of the stereochemistry of this kind of reaction (Figure 22)[232, 233]. The authors have performed an extensive kinetic study of the fragmentation, stereomutation and ring enlargement of the cyclobutane ring. The same stereoisomer was obtained regardless of whether starting from the *cis* or the *trans* isomer. An analysis of the results led the authors to draw conclusions that the diradical is removed from the 'caldera' of rotationally labile conformations whenever the two radical centers come within bonding distance and in an appropriate orbital orientation. Still the lifetime of the diradical is long enough for enabling conformational changes leading to the observed spectrum of products.

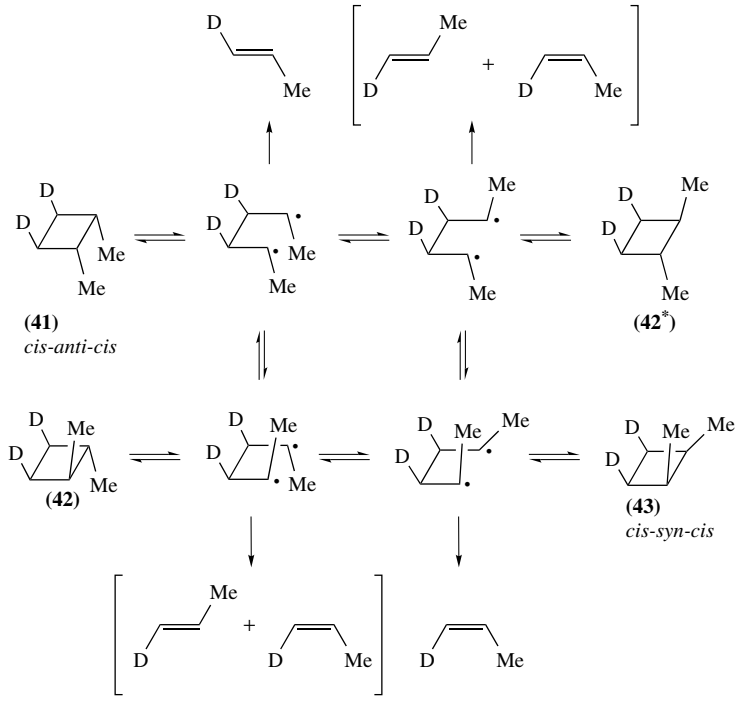


FIGURE 21. Thermolysis of *cis*- and *trans*-1,2-dimethylcyclobutane-d_2 via the major pathway. **42** and **42*** are enantiomers[231]

A constrained system, **44**, was designed to preclude an antiperiplanar conformation to the intermediate diradical (Figure 23). Comparison of stereomutation to fragmentation ratio with that of unconstrained 1,2-dicyanocyclobutane reveals that stereomutation (*trans*-**44** $\rightleftharpoons$ *cis*-**44**) is strongly favored compared to fragmentation (**44** $\rightarrow$ **45**)[233].

Intramolecular photocycloaddition of *cis*-1,2-bis(*m*-vinylphenyl)cyclobutane (**46**) gave three [2.2]metacyclophanes **47**–**49**[234]. According to X-ray analysis of **47** the aromatic rings were shown to be tilted 31–34° relative each other. Compounds **48** and **49** interconverted slowly in solution with an equilibrium ratio of 60:40. Reduction with sodium in ammonia converted **47**–**49** to **50**.

A series of metacyclophanes containing the cyclobutane ring has been prepared and their conformations studied[235]. Dimethoxy[*n*.2]metacyclophanes **51** ($n = 2$–6) were obtained stereoselectively in 61–87% yields via [2 + 2] photocycloadditions. The products were found to reside exclusively in *syn* conformations for $n = 3$–6, while the dimethoxy[2.2]metacyclophane exists as a 4:3 mixture of *syn* and *anti* isomers. Birch reduction of **51** gave the [*n*.4]metacyclophanes **52** ($n = 2$–6) in 59–94% yields. The conformations of **52** ($n = 2$–4) are *anti* and those of **52** ($n = 5$–6) are *syn*. Compound **51** could be demethylated and, after successive triflation, vinylation and stereoselective photochemical cycloaddition reactions, three-bridged [*n*.2.2](1,3,4)cyclophanes **53** were prepared. The two cyclobutane rings of **53** are located opposite to each other. Birch reduction/cyclobutane ring cleavage of **53** gave the corresponding [*n*.4.4](1,3,4)cyclophanes.

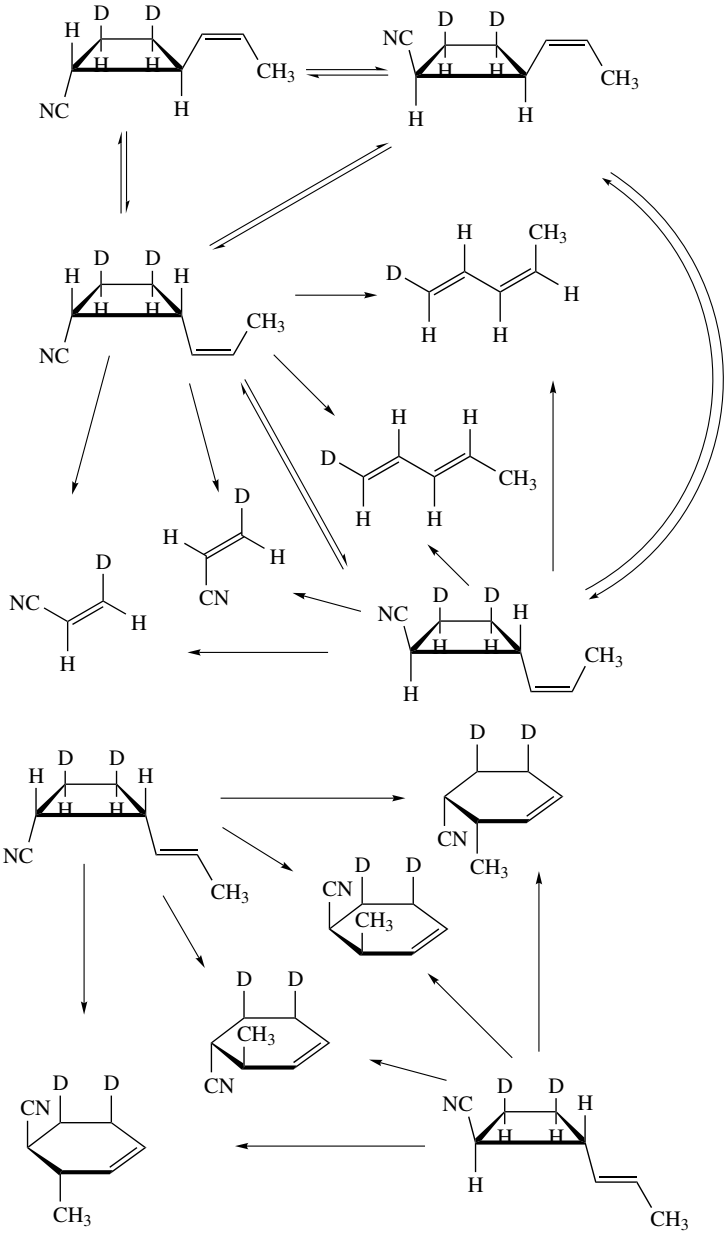


FIGURE 22. Reaction scheme for fragmentation of the *cis* isomer (upper reaction) and ring enlargement of the *trans* isomer (lower reaction) of 1-cyano-2-(*E* and *Z*)-propenyl-*cis*-3,4-dideuteriocyclobutane

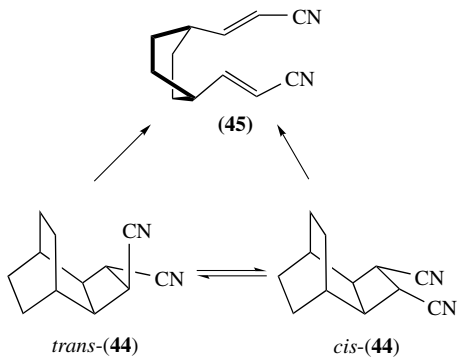
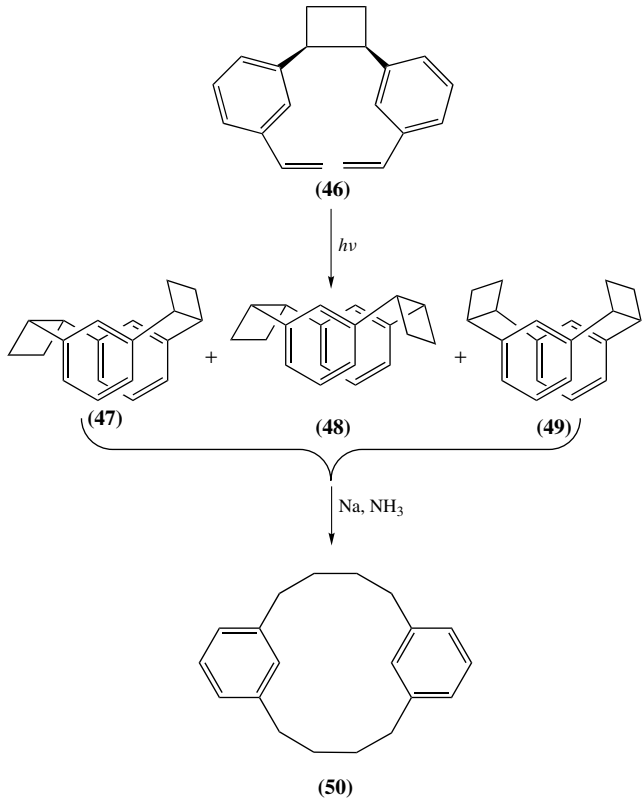
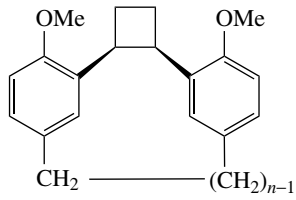


FIGURE 23. Stereomutation and fragmentation pathways of *cis*- and *trans*-**44**



Three-bridged [*n*.2.2](1,3,5)cyclophanes **54** ($n = 2$, 3, 4) were prepared stereoselectively in 31–78% yields via analogous photocycloaddition reactions. The configurations of the cyclobutane rings relative to the methoxyl groups in **54** were confirmed to be *anti* by NOESY experiments.



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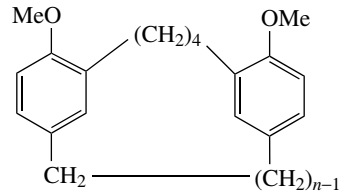

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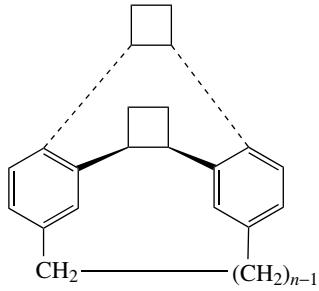

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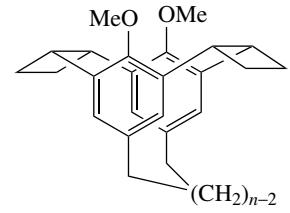


(54)

Allenes undergo [2 + 2] cycloaddition reactions with various alkenes such as $Cl_2C{:}CF_2$, $CH_2{:}CHCN$, $CH_2{:}CHCO_2Me$, *N*-phenylmaleimide and *cis*- and *trans*-$EtO_2CCH{:}CHCO_2Et$ [142, 236]. Product analysis indicated a two-step reaction of the general type shown in Figure 24. The differences in stereochemical preferences are ruled by differences in the degree of development of the transition states for diradical intermediate formation with different dominant steric interactions.

Pyrolysis of 1,8-divinylnaphthalene produces a mixture of 1,3-(1,8-naphthylene)cyclobutane (**55**) and 1,2-(1,8-naphthylene)cyclobutane (**56**)[237]. Labeling experiments and

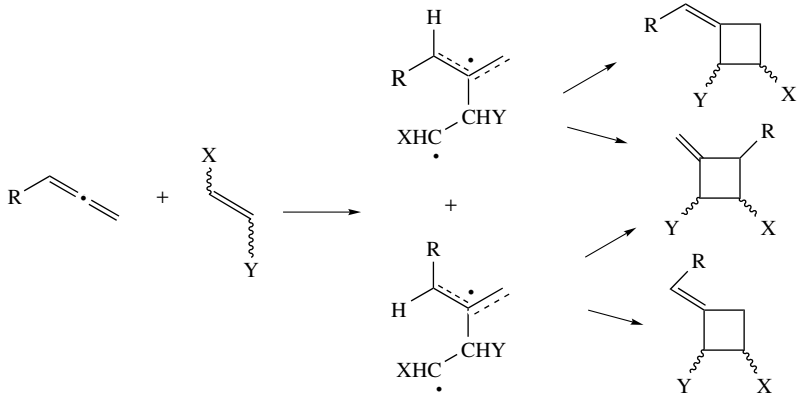
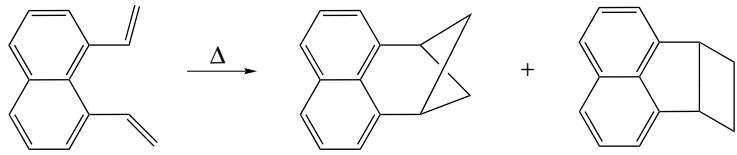


FIGURE 24. Mechanism of the [2 + 2] cycloaddition reactions indicating a two-step process via diradical intermediates[142, 236]

comparison with the photoinitiated reaction were consistent with a diradical pathway in which diradical formation from the *syn* conformer predominates over that from the *anti* conformation.



(55) **(56)**

On the other hand, photodimerization of olefins is an allowed concerted reaction in the singlet excited state, thus usually predicted to result in retention of the relative configuration. This is true for olefins such as *cis*- and *trans*-2-butene[238]. However, there exist exceptions where this stereospecificity is violated, particularly in the photocyclization of cycloalkadienes. These reactions are understood in terms of a *cis–trans* addition as a result of a Möbius orientation (**57**) of the alkenes[239]. Möbius arrangement in the ground state is found in certain strained cyclodienes such as *cis,trans*-cycloocta-1,5-diene[240, 241].

(57)

Thermolysis of vinylcyclobutanes produces two products given by a retro [2 + 2] cleavage and cyclohexenes[242]. The reaction involves a tetramethylene diradical able to adopt various conformations along a broad flat potential-energy surface leading to the different products (Figure 25).

The thermally induced retro [2 + 2] cleavage and rearrangement of the conformationally biased 5-methylenespiro[3.5]nonane and 5-methylenespiro[3.4]octane (**58**) revealed

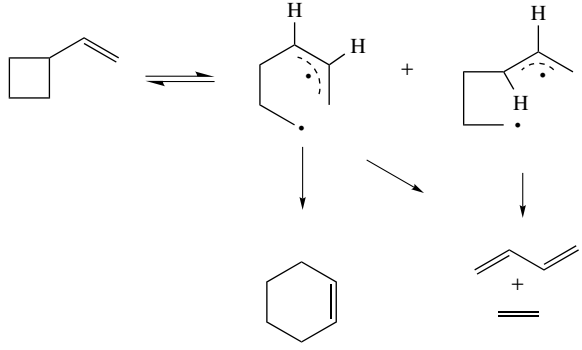


FIGURE 25. Reaction scheme showing the thermolytic pathways of vinylcyclobutane[242]

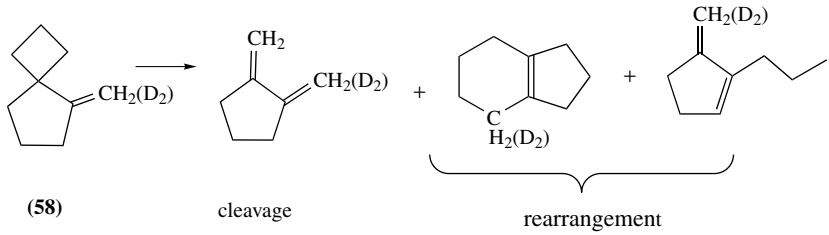


FIGURE 26. Products from thermal [2 + 2] retro reaction of **58**[243]

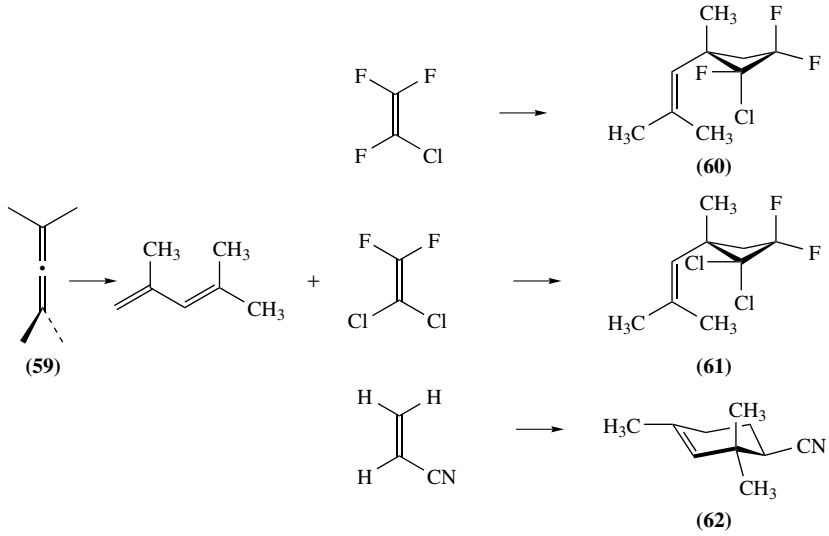


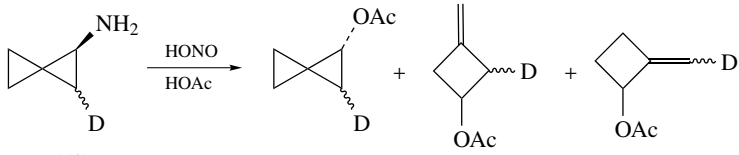
FIGURE 27. Cycloaddition of allene **59** to various alkenes[244]

different rearrangement to cleavage distribution compared to conformationally unbiased vinylcyclobutanes as shown in Figure 26[243]. The results of the kinetic analysis suggest that the rearrangement in unbiased systems results from an unfavorable entropy of activation, originating in a concerted rearrangement. The secondary deuterium kinetic isotope effect for the rearrangement of **58** was $k_H/k_D = 1.086 \pm 0.023$. This is also consistent with a concerted rearrangement, where *exo*-methylene rotation contributes to the reaction coordinate. The secondary KIE for cleavage was given as 1.025 ± 0.027.

Cycloaddition of the allene **59** to F_2C:CFCl, F_2C:CCl_2 and CH_2:CHCN gave *cis*- and *trans*-2-chloro-2,3,3-trifluoro-1-isobutenyl-1-methylcyclobutane (**60**), 2,2-dichloro-3,3-difluoro-1-isobutenyl-1-methylcyclobutane (**61**) and 4-cyano-1,3,3-trimethylcyclohexene (**62**), (respectively (Figure 27)[244]. The reaction was expected to be preceded by isomerization of **59** to the butadiene derivative prior to cyclization. ^{19}F NMR indicated that **60** is puckered with the isobutenyl group in an equatorial position.

Gajewski and Chang prepared and deaminated 2-deuteriospiropentylamine (**63**) in order to shed light on the possible existence of trimethylenemethane methyl cation as an intermediate. Three products were obtained, but not the 3-deuteriomethylenecyclobutyl acetate,

ruling out trimethylenemethane methyl cation as an intermediate[245]. The stereochemistry of the deamination of (−)-**63** in acetic acid was found to proceed with essentially complete inversion of configuration, suggesting that it is formed via an S_N2 displacement on the spiropentyldiazonium ion[246].



(63)

Lillien and coworkers studied the deamination of *cis*- and *trans*-3-methylcyclobutylamine and the corresponding isopropyl derivatives[247,248]. In the methyl case they obtained the same four products, but in significant different ratios for the two stereoisomers: 4-penten-2-ol (18% from *cis*, 59% from *trans*); 1-cyclopropylethanol (60% from *cis*, 20% from *trans*); *cis*-2-hydroxymethyl-1-methylcyclopropane (18% from *cis*, 0% from *trans*) and *trans*-2-hydroxymethyl-1-methylcyclopropane (2% from *cis*, 21% from *trans*). The stereospecificity in formation of 2-hydroxymethyl-1-methylcyclopropane was explained in terms of orbital-symmetry considerations over a concerted reaction, which is conformationally more facile for the *trans*-cyclobutyldiazonium intermediate.

In a mechanistic study Hoz and coworkers showed that acid-catalyzed addition reactions of methanol to derivatives of bicyclobutane are usually *syn* and in an equatorial fashion (Figure 28), and may proceed by more or less concerted attack of proton and nucleophile[249]. Reaction with hydride was also shown to favor equatorial attack[250].

Reaction of carbenes with bicyclobutane gives a pentadiene as the major product and, at best, traces of bicyclo[1.1.1]pentane[251,252]. The favored pathway is a concerted *endo* attack (pathway (1) in Figure 29). Product from pathway (2) corresponding to *exo* attack was not observed.

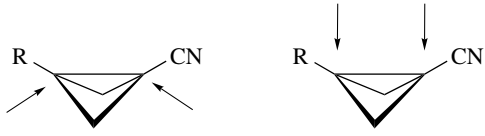


FIGURE 28. Preferred attack *syn*, equatorial, as shown in the formula on the left[249,250]

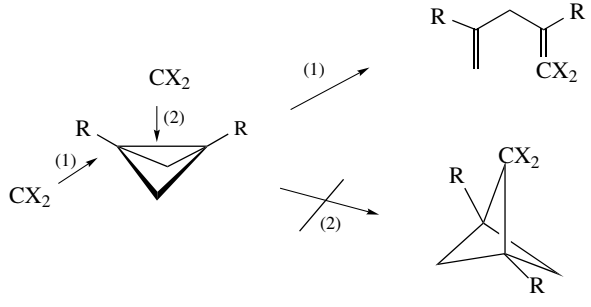
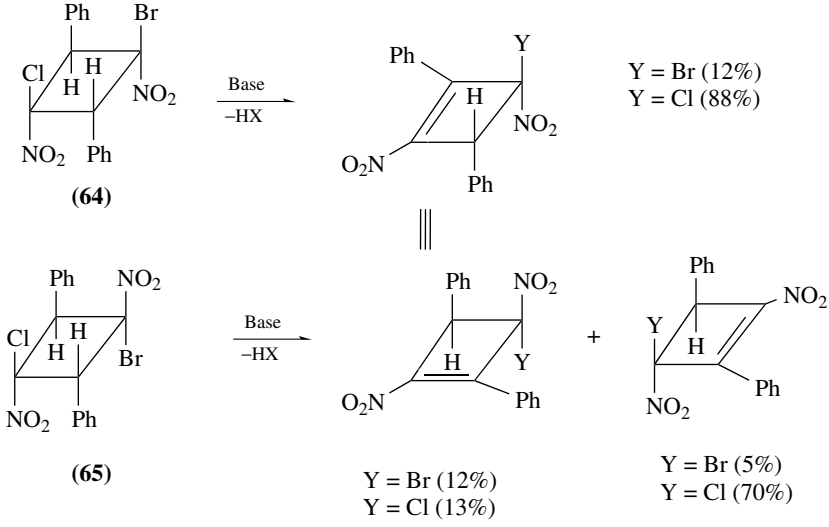


FIGURE 29. Reaction with carbenes follows preferably route (1). X = Cl or CO_2CH_3[251,252]

Trans-2,4-Diphenylcyclobutanes, **64** and **65**, undergo competitive *syn* and *anti* dehydrohalogenation. The *anti* dehydrohalogenation of **64** was suggested to be ruled by the preferred diequatorial conformations of the *cis* nitro groups in the puckered cyclobutane rings. In **65** both nitro groups cannot reside in an equatorial position, which leads to less puckered cyclobutane ring. Dehydrobromination is 5–7 times faster than dehydrochlorination[253].



In contrast to the five-membered analog, α-halo(or α-tosyloxy)cyclobutanone (**66**) undergoes ring contraction with high yields with various nucleophilic reagents (Figure 30)[254]. From mechanistic investigations, the semibenzilic pathway leading to undeuteriated **67** is proposed for these conformationally controlled rearrangements instead of a Favorskii-type rearrangement. Thus, neither carbanions nor carbocations are involved.

Even though Baeyer–Villiger oxidation with hydrogen peroxide normally selectively converts cyclobutanones to butyrolactones, this reaction has occasionally been found to lead to surprising results. A diastereomeric mixture of **68** gives the diacids **69** under these reaction conditions[255].

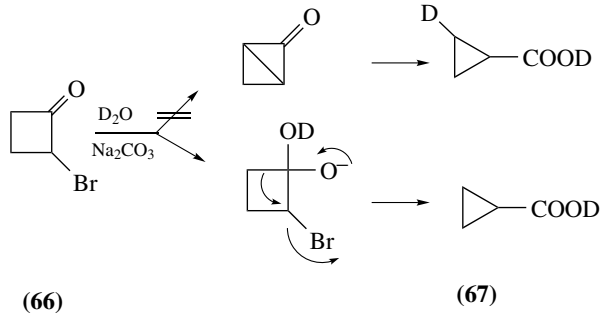
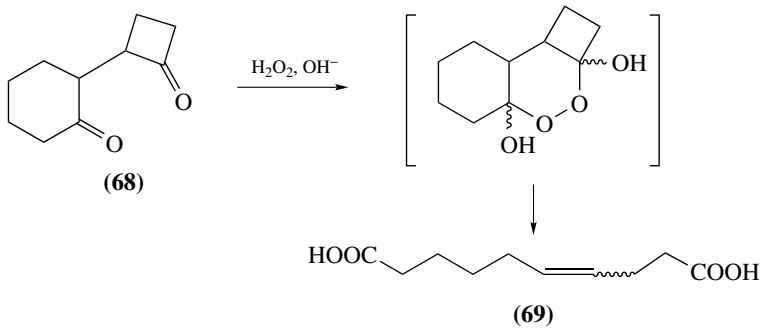


FIGURE 30. Alternative pathways for ring contraction of 2-bromocyclobutanone[254]



(68) **(69)**

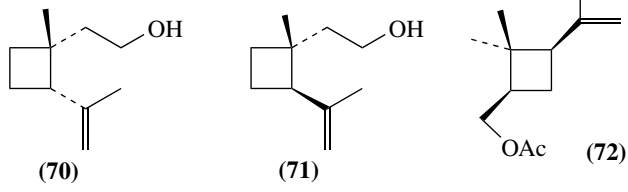
VII. NATURAL PRODUCTS

The cyclobutane ring is present in numerous naturally occurring molecules, many of which possess biological activity. Several of these cyclobutane derivatives are highly substituted and have intriguing stereochemical properties, often possessing complex polycyclic structures, which offer challenging synthetic targets. Hansen and Stenström have recently written a review on naturally occurring cyclobutanes[256]. This section presents examples from the field of natural products containing the cyclobutane ring without any ambition to cover the field.

A. Cyclobutane Derivatives in Nature. Structure and Synthesis

The cyclobutane ring frequently occurs in small, volatile molecules from the plant or insect kingdoms and often forms part of the chemical language of their host species. The stereochemistry is usually of vital importance for the biological effect.

Some simple examples are grandisol (**70**), the aggregation pheromone of the Cotton Boll Weevil and other insects, its *trans* stereoisomer fragranol (**71**), isolated from the roots of *Artemisa fragrans,* and the sex pheromone of the citrus mealy bug (**72**)[257].



(70) **(71)** **(72)**

The development of methodologies for the synthesis of functionalized four-membered rings is obviously of interest. An asymmetric synthesis of **70** has been described using kinetic resolution of a bicyclic allylic alcohol by Sharpless asymmetric epoxidation[258]. The synthesis of cyclobutane fused γ-butyrolactones has also been used for the synthesis of grandisol[259]. The two approaches are shown in Figure 31.

The stereoselective synthesis of highly functionalized cyclobutane derivatives has been reported by Paquette (Figure 32)[260]. The ring contraction induced by treating 4-vinylfuranosides (e.g. **73**) with zirconocene in the presence of boron trifluoride etherate was found to be sensitive to substitution pattern, giving products of high diastereoselectivity. A stereoselective synthesis of cyclobutane derivatives through a radical 4-*exo*-trig cyclization

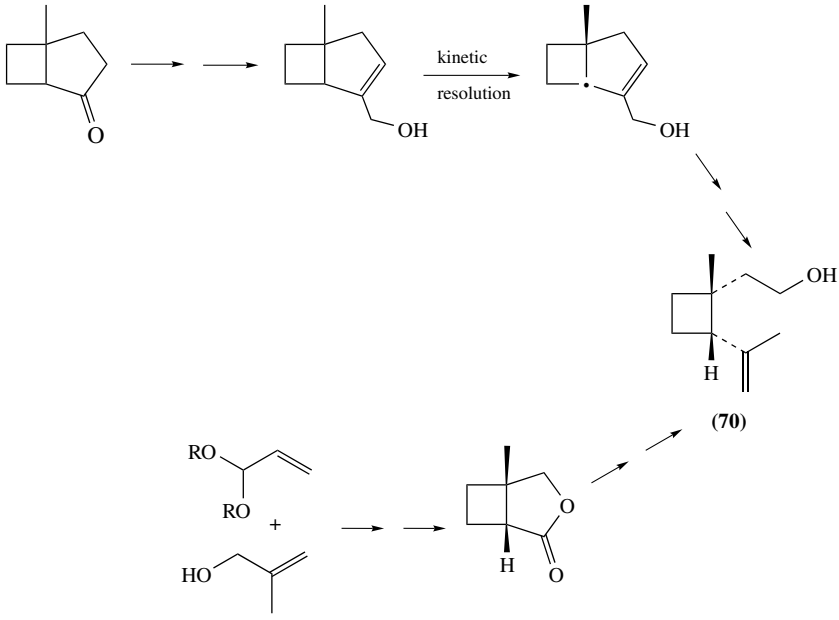


FIGURE 31. Synthetic strategies for preparation of grandisol (**70**)[258, 259]

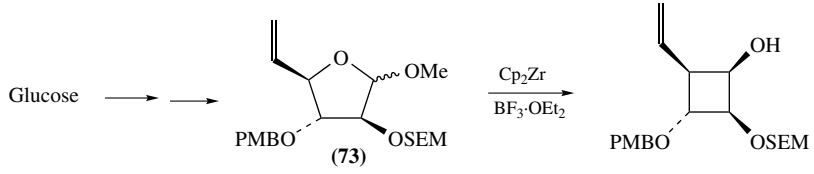
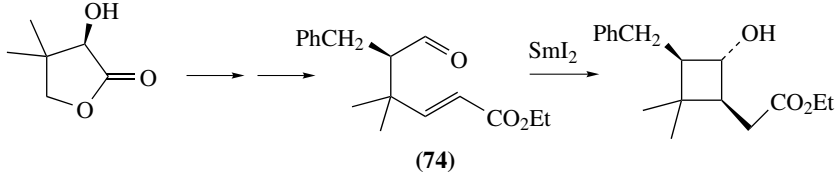


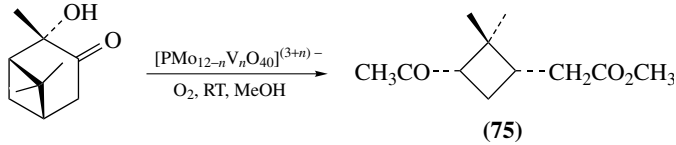
FIGURE 32. Reaction scheme for the synthesis of highly functionalized cyclobutanes[260] PMB = *p*-methoxybenzyl, SEM = 2-(trimethylsilyl)ethoxymethyl

with samarium(II) iodide has been described by Weinges and coworkers[261]. The key intermediate substrate, **74**, is easily obtained from enantiopure (−)-pantolactone.



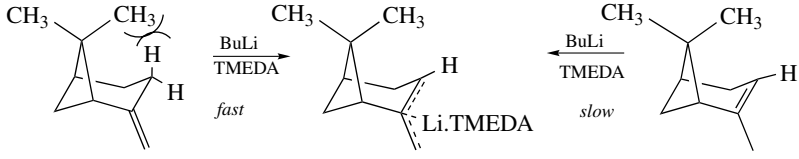
(74)

Pinane derivatives are a popular starting material for the stereocontrolled synthesis. Selective cleavage by the use of vanadium based heteropolyanion and oxygen gives excellent yields of pinonic acid ester (**75**)[262].



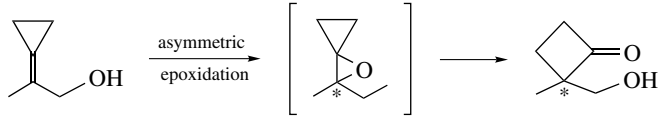
(75)

Allylic metalation of β-pinene (**76**) is much faster than for α-pinene (**77**) due to steric interactions in the initial state, which are relieved by metalation[263].



(76) **(77)**

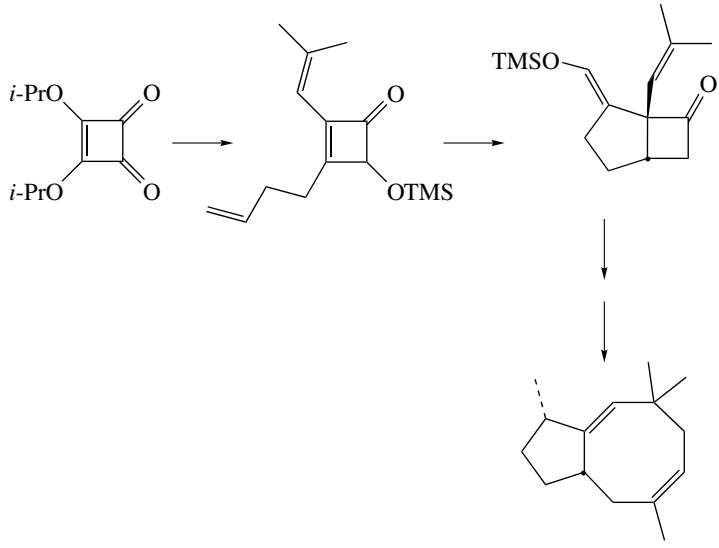
Chiral cyclobutanones, e.g. **78**, easily obtainable from cyclopropylene butanol, have been identified as versatile synthones for the syntheses of various cyclobutane containing natural products[264].



(**78**)

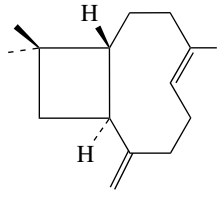
Squarate esters have found use in the synthesis of natural products and other compounds. Moore and coworkers developed a route to precapnelladiene (**79**), starting from diisopropyl squarate using an intramolecular [2 + 2] cycloaddition to the bicyclo[3.2.0] heptanone system as a key step[265].

The natural product caryophyllene (**80**) is a sesquiterpene possessing the bicyclo[7.2.0] undecane skeleton and has been known for a long time. The conformation and dynamics of β-caryophyllene has been investigated in a detailed low-temperature NMR study by Fitjer and coworkers[266]. Among the four considered conformations ($\alpha\alpha$, $\alpha\beta$, $\beta\alpha$ and $\beta\beta$, indicating the orientation of the exocyclic and intracyclic double bonds, respectively, where α referring to the group pointing upward and β downward in the average plane of the molecule), the following conformations were found: $\alpha\alpha$ (48%), $\beta\alpha$ (28%) and $\beta\beta$ (24%), while $\alpha\beta$ is not populated appreciably (Figure 33). It seems obvious that the *trans*-fusion between the rings plays a decisive role in the determination of the stability of the conformations. The highest barrier, $\alpha\alpha$ to $\beta\beta$ interconversion, was determined as 16.1 kcal mol^{-1} and the barrier $\alpha\alpha$ to $\beta\alpha$, measured on an *exo*-methylene ^{13}C-enriched compound, as 8.3 kcal mol^{-1}. Clericuzio and coworkers investigated the conformational space of β-caryophyllene on the *ab initio* 6-31G*/HF and MP2 levels and with density functional methods (B3LYP/6-31G*), for their relative thermodynamic stabilities[267]. The $\alpha\alpha$ is predicted to be the most stable geometry, in agreement with low-temperature NMR measurements. In the case of 6-hydroxycaryophyllene, the $\alpha\alpha$ is still the most stable



(79)

conformation when the configuration at C-6 is *S*, but when the configuration is reversed to *R* the $\beta\beta$ geometry becomes the most stable one. This is again in agreement with NMR data. The solvent effect (either chloroform or water) on the stability of the different conformers of β-caryophyllene and 6-hydroxycaryophyllene was studied by the polarizable continuum model.



(80)

Torsional equilibration between (*E*)-isomeric caryophyllene and the (*Z*)-isomeric isocaryophyllene occurs slowly in the presence of base at $-50\,^{\circ}C$ in THF and rapidly at $0\,^{\circ}C$ in hexane to afford *endo/exo* mixtures of about 95:5 (Figure 34)[268]. The intermediate salts could be trapped by consecutive treatment with fluorodimethoxyborane and hydrogen peroxide.

When β-caryophyllene is treated with sulfuric acid in ether, a multitude of products are obtained, including fourteen hydrocarbons and four alcohols. Product analysis together with MMP2 calculations allowed for an understanding of the complete rearrangement scheme of the intermediate cation[269].

The structure and biosynthesis of the dunniane class of sesquiterpenes has been published[270]. An example, illudosone (**81**), exists as a mixture of free aldehyde and hemiacetal[271].

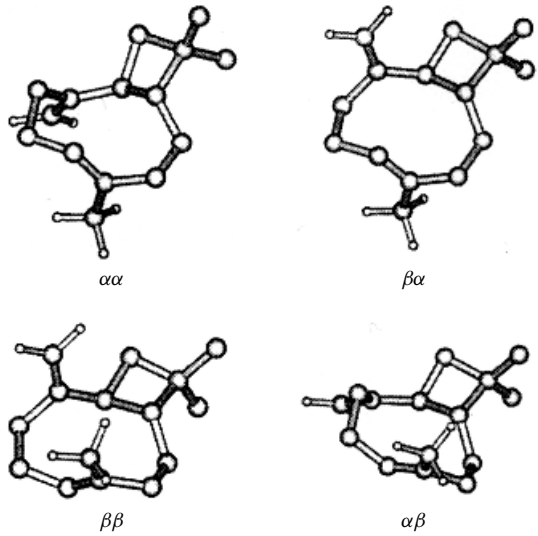


FIGURE 33. The four conformers of β-caryophyllene (**80**). Reprinted with permission from Reference 267. Copyright (2000) American Chemical Society

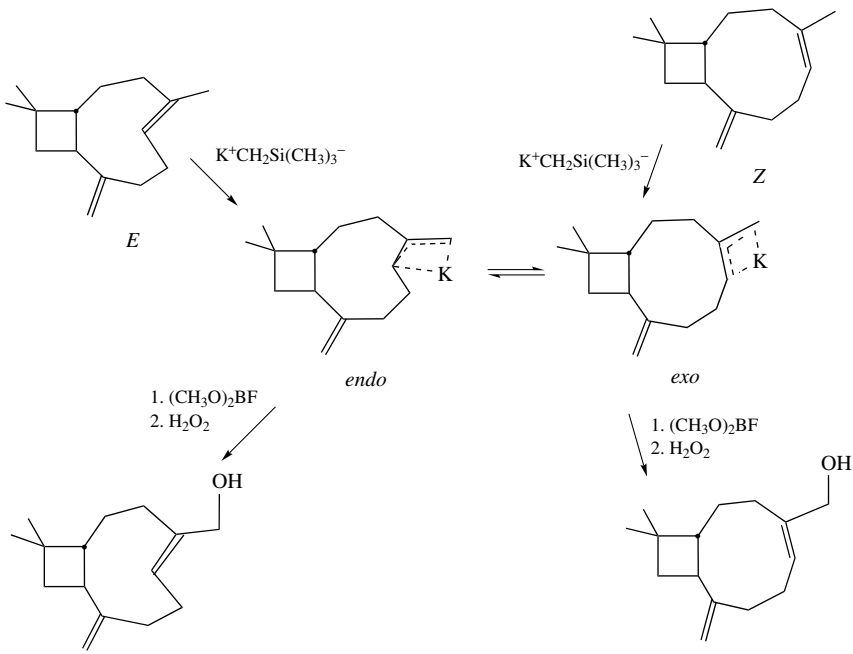
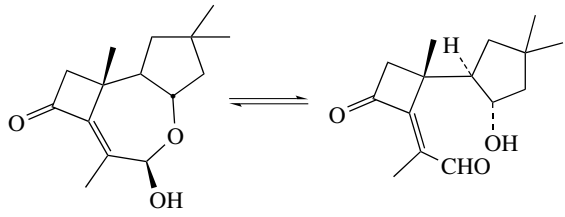
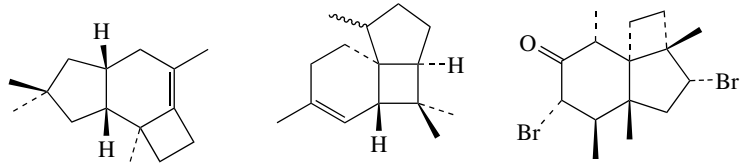


FIGURE 34. Base-induced equilibration of (*E*)- and (*Z*)-isomeric caryophyllene[268]



(81)

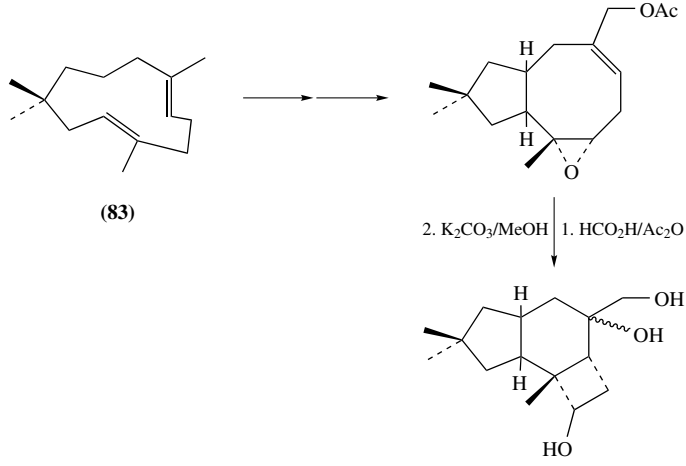
Δ^6-Protoilludene (**82**), isolated from various fungi, exhibit antibacterial activity as do some other illudane derivatives[272]. The ring skeleton has been the subject of synthetic approaches, one of which is a biomimetic synthesis from humulene (**83**) (Figure 35)[273]. Italicenes have a nonlinear 6/4/5 ring motif and several members of the class, e.g. both epimers of **84**, have been isolated from oil from *Helichrysum italicum* collected from the Mediterranean region[274]. Marine species occasionally contain halogenated products such as perforatone (**85**), isolated from an algae off the Canary Islands[275].



(82) **(84)** **(85)**

B. Natural and Artificial Cyclobutane Amino Acids

Peptide-based drugs have poor bioavailability and CNS penetration due to their susceptibility to metabolizing enzymes. Peptidomimetics are being increasingly used to

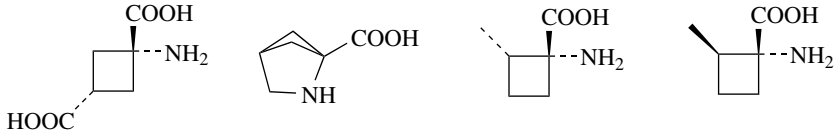


(83)

FIGURE 35. Schematic synthesis of the illudane skeleton from humulene (**83**)[273]

enhance the metabolic stability and oral bioavailability. The cyclobutane skeleton has been explored for this purpose, but also as a template for the distribution of pharmacophores in desired positions. The limited conformational freedom of the cyclobutane ring facilitates the design of peptide-based drug candidates. Conformational energy calculations have been conducted on model compounds containing 1-aminocyclobutanecarboxylic acid and derivatives substituted in the 2- and 4-positions using molecular mechanics methods[276]. The low-energy models adopt conformations characteristic of a variety of regular peptide structures.

1-Aminocyclobutane carboxylic acids, or 2,4-methanoamino acids, have been isolated from plants and received increasing attention in medicinal chemistry. *Cis*-2,4-methanoglutamic acid (**86**) and 2,4-methanoproline (**87**) were isolated and characterized in 1980[277]. Asymmetric Strecker synthesis of enantiopure 2,4-methanovalines, **88** and **89**, has been accomplished from racemic 2-methylcyclobutanone[278]. The *trans* α-amino acid (**88**) was obtained from cyanide addition carried out in methanol, whereas the *cis* 2,4-methanovaline (**89**) was accessible via reactions in hexane.

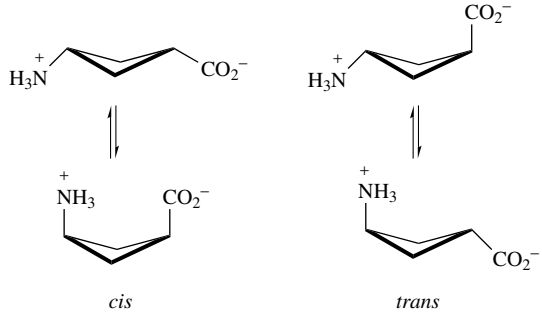


(86) **(87)** **(88)** **(89)**

(−)-(1*R*,2*S*)-2-Aminocyclobutane-1-carboxylic acid as well as some fully and partially protected derivatives have been synthesized in optically active form by means of a chemoenzymatic transformation[279].

Cis- and *trans*-3-aminocyclobutane-1-carboxylic acid have been synthesized as conformationally restricted analogs of GABA[280]. The *cis* isomer had weak to moderate GABA-like activity with respect to inhibition of GABA uptake. The lower activity of the *trans* form was explained in terms of unfavorable steric interactions between one of the methylene groups in the cyclobutane ring and a region of steric hindrance at the active sites of the receptor. The interpretation is hampered by the existence of two conformations in each isomer (Figure 36).

Enantiomerically enriched *N*-protected 1,3-cyclobutane amino acids have been prepared from α-pinene. Both enantiomers of (−)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-



cis *trans*

FIGURE 36. Conformational flexibility in *cis*- and *trans*-3-aminocyclobutane-1-carboxylic acid[280]

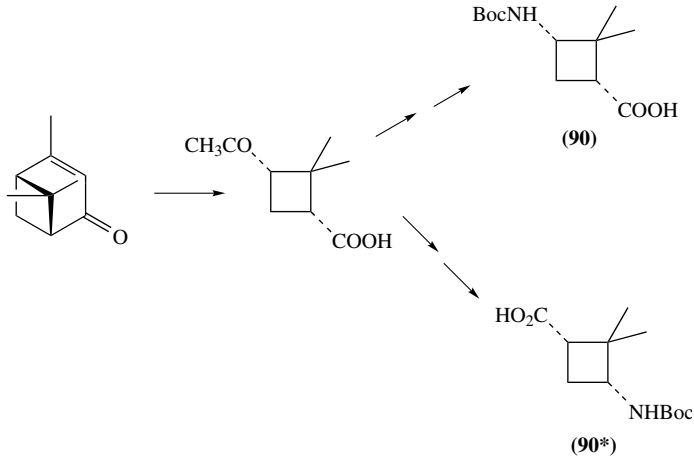


FIGURE 37. Schematic syntheses of the two enantiomers of **90** from α-pinene[281]

dimethylcyclobutanecarboxylic acid (**90**) were prepared from the same α-pinene (Figure 37)[281]. Single-crystal X-ray diffraction studies of derivatives of **90** reveal that these compounds can have extended conformations and give rise to sheet-like packing in the crystal.

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CHAPTER 4

Thermochemistry of cyclobutane and its derivatives

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I. INTRODUCTION, SCOPE AND DEFINITIONS

A. Thermochemistry

The current chapter will be devoted primarily to the relatively restricted property, the 'standard enthalpy of formation', a quantity more colloquially called the 'heat of formation'. Enthalpies of formation will be written as $\Delta_f H_m{}^0$ with an affixed s, lq or g to convey that the species of interest is found as a solid, liquid or gas, respectively. The temperature and pressure are tacitly 25 °C ('298 K') and 1 atmosphere (taken as either 101,325 or 100,000 Pa), respectively, and the energy units are kJ mol^{-1} where 4.184 kJ = 1 kcal. By intent, we forego discussion of other thermochemical properties such as Gibbs energy, entropy, heat capacity and excess enthalpy. Ionization processes (gain or loss of an electron or of a proton) will likewise be ignored. Enthalpies of reaction are only discussed within the context of deriving or otherwise discussing an enthalpy of formation. As such,

we will not particularly care whether the value arises from measurements of enthalpy of combustion, hydrogenation, rearrangement or some other chemical process. Phase change enthalpies (vaporization, liquid → gas; sublimation, solid → gas; fusion, solid → liquid and their reverse) will be ignored except to allow comparisons between species found in different phases.

B. Sources of Data

Unless otherwise said, following our practice in other chapters in this series, enthalpies of formation were taken from the evaluated archival source by Pedley, Naylor and Kirby[1]. If this lacked any necessary data, we turned to other sources, most notably those of Stull, Westrum and Sinke[2], Domalski and Hearing[3] and Kharasch[4]. When primary sources were difficult to access, data were obtained from the electronic database at the National Institute of Standards and Technology[5] and the original source cited. Where enthalpies of vaporization were not otherwise available, the 'CHLP protocol' was used to estimate these quantities, according to equation 1 where $\tilde{n}_c$ and n_Q refer to the number of non-quaternary and quaternary carbon atoms, respectively, and b is a value that is characteristic of the functional group on monosubstituted hydrocarbons[6].

$$\Delta H_{vap}(\text{kJ mol}^{-1}) = 4.69\tilde{n}_c + 1.3n_Q + 2.97 + b \quad (1)$$

Enthalpies of fusion were taken from the compendium[7] by Chickos, Acree and Liebman, and used without temperature correction to 298 K; enthalpies of sublimation were taken from the related compendium[8] by Chickos and Acree, again without temperature correction unless offered by these or the original authors.

C. Definition of Cyclobutane and its Derivatives

By the term 'cyclobutane and its derivatives', we mean a species containing a carbocyclic four-membered ring, saturated or not. However, not all polycyclic hydrocarbons containing four-membered rings so qualify. We employ the criterion of the 'smallest number of smallest rings' to decide whether a given species is a cyclobutane derivative. The number of rings is determined by cutting ring bonds until the species must be acyclic. The smallest sized rings are chosen that contain or 'span' all of the bonds in the polycycle. For example, bicyclobutane will not be considered a cyclobutane derivative in the current chapter because it has two rings, and these two rings can (and thus will) be chosen to be cyclopropanes. Little is lost by this choice because there are few determinations of the enthalpy of formation of bicyclobutane derivatives. (In fact, there is no chapter on bicyclobutanes in the current volume, these species having been relegated to a volume summarizing cyclopropane chemistry[9].) By contrast, both bicyclopentanes will be considered cyclobutane derivatives. The ring set chosen for the [1.1.1] isomer consists of two cyclobutane rings, and the set for the [2.1.0] isomer consists of one cyclobutane and cyclopropane (cyclobutane and cyclopropane are the smallest rings, as opposed to cyclobutane and cyclopentane or cyclopropane and cyclopentane). Had we not insisted on this last criterion of smallest rings, we might well have ignored cubane, an almost paradigmatic example of a polycyclic cyclobutane derivative.

II. RING-STRAIN ENERGIES OF CYCLIC COMPOUNDS

A. Cyclobutane and Other Cycloalkanes

The ring-strain energy (RSE) of a cyclic compound is manifested in its more positive enthalpy of formation relative to that estimated for an appropriate strain-free reference

compound (equation 2).

$$\mathrm{RSE} = \Delta H_\mathrm{f}(\text{experimental}) - \Delta H_\mathrm{f}(\text{estimated}) \tag{2}$$

There are a variety of approaches for calculating the RSE. Experimentally, one of the first[10] was the determination of the stability order of the simple cycloalkanes from their successively smaller enthalpies of combustion per methylene group (or more negative enthalpies of formation per methylene group): cyclohexane > cycloheptane > cyclopentane > cyclobutane > cyclopropane. Because each of these cycloalkanes is composed of multiple methylene groups, a strainless $-CH_2-$ group increment is required to calculate an additive ΔH_f (estimated). Although cyclohexane, which resembles the open-chain *n*-alkanes in stability, is not strain-free because of unavoidable non-bonded repulsions[11], it is nonetheless a convenient source for the idealized cyclic $-CH_2-$ reference group. Calculated as one-sixth of the enthalpy of formation of cyclohexane, the reference group quantities, $-26.1\ \mathrm{kJ\,mol^{-1}}$ (lq) and $-20.6\ \mathrm{kJ\,mol^{-1}}$ (g), are essentially identical to the enthalpy of formation values found for the methylene increment in the acyclic *n*-alkane homologous series, $CH_3\text{-}(CH_2)_n\text{-}CH_3$. The gas phase ring-strain energies for cyclopropane, cyclobutane, cyclopentane and cycloheptane are thus 115.1, 110.8, 26.6 and 26.1 $\mathrm{kJ\,mol^{-1}}$, respectively.

Especially desirable for computational comparisons, and useful generally, are homodesmic reactions in which the overall number of bond types and atom valence characteristics are identical in both reactants and products. A general homodesmic reaction for calculating the ring strain of a cycloalkane is equation 3:

$$(CH_2)_n + n CH_3CH_3 \longrightarrow n CH_3CH_2CH_3 \tag{3}$$

The enthalpy of reaction is exothermic and equal to the total ring-strain energy as the strained methylene groups in the cycloalkane are 'separated' in the strain-free propane[12]. The gas phase ring-strain energies calculated for the C_3-C_7 alkanes from equation 3 are 116.0, 112.0, 28.1, 2.0 and 28.2 $\mathrm{kJ\,mol^{-1}}$.

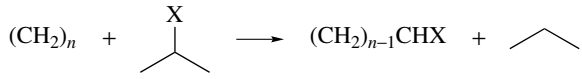
Cyclobutane is an unequivocally strained cycloalkane. Remarkably, the strain energy of cyclopropane is nearly identical to that of cyclobutane. The most apparent structural difference between these two is the deviation of their C−C−C bond angles from the ideal C−C−C bond angle in the open-chain hydrocarbon, propane. The smaller deviation for cyclobutane should result in smaller strain than for cyclopropane. However, this classically defined Baeyer-type ring angle strain[13] is not the only source of strain in small ring compounds. Contributions from torsional strain, hybridization and non-bonded interactions in the two compounds also are expected to be different. Perhaps most significantly, there is much evidence that cyclopropane is stabilized by σ-aromaticity[14], while a recent publication suggests destabilization of cyclobutane by σ-antiaromaticity[15]. It is because of these sometimes similar and sometimes dichotomous aspects of cyclopropane and cyclobutane that we frequently mention cyclopropane throughout this chapter about cyclobutane.

For monosubstituted rings, a group separation reaction resembling equation 3 can be formulated as in equation 4.

$$(CH_2)_{n-1}CHX + n CH_3CH_3 \longrightarrow (n-1)CH_3CH_2CH_3 + CH_3CHXCH_3 \tag{4}$$

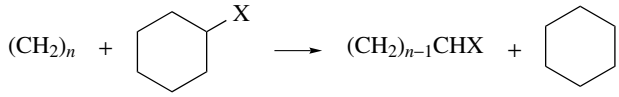
Two drawbacks to this approach are the lack of experimental enthalpy of vaporization data for ethane and propane and the number of species represented in the balanced equation, especially as the rings become larger. In order to cancel the latter effect, equations 3 and 4, with the same *n*, can be subtracted. Equation 5 is such an example. The enthalpy of reaction represents the relative ring-strain energy of the substituted and unsubstituted

cycloalkane. One limitation of this equation is the lack of an experimentally measured enthalpy of formation for liquid propane; however, it is easily estimated[16].



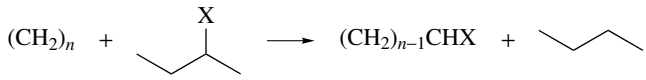
(5)

If equation 5 for $n = 6$ and the same equation for any other value of n are thermochemically summed, the result is equation 6 where the strain energies of the cycloalkanes are compared to the corresponding cyclohexanes.



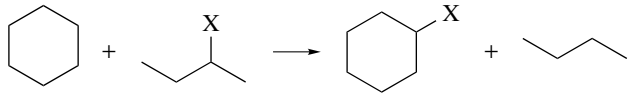
(6)

Where thermochemical data are lacking for the cyclohexyl and isopropyl reference species, there is often relevant data for the likewise secondary-substituted *sec*-butyl species for comparison in reaction 7.



(7)

Fortuitously, the gas phase enthalpies of reaction for equations 6 and 7 are nearly equal for a given substituent X because the enthalpies of formation of cyclohexane and *n*-butane are almost equal in the gas phase, as are the enthalpies of formation of identically substituted cyclohexane and butane. That is, gas phase reaction 8 is essentially thermoneutral for all experimentally available instances of X:

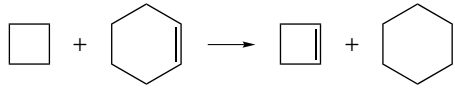


(8)

For all of these reactions, if the cyclobutyl species were to behave 'normally', that is strainless, then the enthalpy of reactions would be nearly zero. Deviations of the enthalpy of reaction from thermoneutrality provide a measure of comparative ring strain in the cyclobutane/cyclobutyl-X pair.

B. Cyclobutene and Other Cycloalkenes

The ring-strain energy of cyclobutene relative to other unsaturated reference compounds can be assessed using equations similar to 3 and 4. The (*Z*)-2-butene is chosen as the acyclic reference species. Because the gas phase enthalpies of formation of (*Z*)-2-butene and cyclohexene are the same within 2 kJ mol^{-1}, the enthalpies of reaction for equations 9 and 10 are also essentially identical, −9.9 and −9.8 kJ mol^{-1}, respectively.

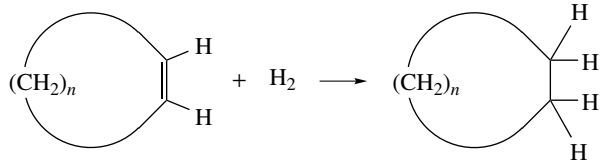


(9)

(10)

Although cyclobutane and cyclopropane have comparable ring-strain energies according to equations 2 and 3, the ring-strain energies for cyclobutene and cyclopropene are quite different according to equation 9 and a corresponding equation involving the C_3 species. For the latter reaction, the enthalpy of reaction is the very large $+105.4$ kJ mol^{-1}. For comparison, the corresponding reaction enthalpy for the C_5 species is -8.1 kJ mol^{-1}.

Another assessment of relative ring strain in the cycloalkanes is by their enthalpies of hydrogenation in the formal reaction 11.



(11)

The gas phase enthalpies of hydrogenation for the C_3, C_4, C_5 and C_6 cycloalkenes are -223.8, -128.3, -110.3 and -118.4 kJ mol^{-1}, respectively. Cyclopentene is the most stable cycloalkene relative to its saturated cyclic parent. The enthalpy of hydrogenation of the acyclic (*Z*)-2-butene is -118.5 kJ mol^{-1}. Compared to its acyclic analog, cyclobutene is *ca* 8 kJ mol^{-1} strained.

III. HYDROCARBON SUBSTITUENTS

A. Homologous Series

Cyclopropane, cyclobutane and the higher cycloalkanes form a homologous series with an increasing number of methylene groups incorporated into the ring. Unlike the acyclic *n*-alkane homologous series in which the enthalpy of formation difference between successive members (generally with more than three carbons) is about -20.6 kJ mol^{-1} (g), the thermochemical increment arising from the introduction of each methylene group in the cycloalkane series is not constant. The enthalpy difference between successive members of the series depends upon the effect of the methylene group on all components of ring strain.

For members of any homologous series $CH_3(CH_2)_nX$ in the same phase, except for the CH_3X and perhaps CH_3CH_2X members, there is a very nearly constant difference, the 'universal methylene increment', 20–21 kJ mol^{-1} for gaseous species and 25–26 kJ mol^{-1} for the corresponding liquids, depending on X. For hydrocarbon groups X such as $-CH{=}CH_2$ and $-C{\equiv}CH$, even the methyl/ethyl difference is found to be 'normal', as it is for X = cyclopropyl (lq) as well. The methyl/ethyl difference for X = cyclohexyl is slightly smaller than 'normal' in both the gaseous (-17.0 kJ mol^{-1}) and liquid (-21.8 kJ mol^{-1}) phases. However, for X = cyclobutyl, the liquid phase enthalpy of formation difference is but -14.5 kJ mol^{-1}. Furthermore, the liquid phase enthalpy of formation difference between the parent cycloalkane and the methylcycloalkane is 32.8 kJ mol^{-1} for cyclopentane, 33.7 kJ mol^{-1} for cyclohexane and 48.2 kJ mol^{-1} for cyclobutane (there is no measured liquid phase enthalpy of formation for cyclopropane). Are either or both of the archival methylcyclobutane or ethylcyclobutane enthalpies of formation incorrect or does the cyclobutyl series behave anomalously?

The enthalpy of formation of methylcyclobutane was determined from the enthalpy of combustion of the liquid[17]. The enthalpy of formation of ethylcyclobutane was determined from the enthalpy of combustion of the liquid[18] and, at that time, the enthalpy of vaporization was estimated. A more recent measured enthalpy of vaporization[19] resulted in a gas phase enthalpy of formation of -27.7 ± 0.7 kJ mol^{-1} that does not appear in

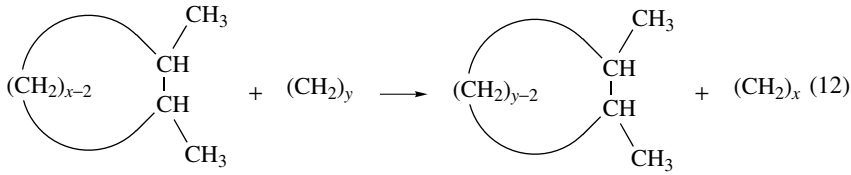
our archival source. Scrutiny should focus first on methylcyclobutane, because its value is included in both of the anomalous difference quantities discussed above. Assume the combustion-derived[18] enthalpies of formation for the liquid and gas methylenecyclobutane, respectively, are correct as shown in Table 1. Combining these with the enthalpy of hydrogenation of methylenecyclobutane[20] (-123.1 ± 0.3 kJ mol^{-1}, presumed phase and medium independent) results in -29.3 and -1.6 kJ mol^{-1} for the enthalpy of formation of liquid and gaseous methylcyclobutane, respectively. The former quantity is quite different from the one reported in the literature. Using these derived values, the enthalpy of formation differences between cyclobutane and methylcyclobutane of 33.0 (lq) and 30.0 (g) kJ mol^{-1} are more reasonable and consistent. The differences between methylcyclobutane and ethylcyclobutane, 29.7 (lq) and 26.1 (g) kJ mol^{-1}, are now greater than 'normal', however. It will be seen that the question of error or enigma will recur rather often in the study of cyclobutane derivatives.

B. Alkyl Substituents

There are only two alkyl-substituted cyclobutanes for which there are enthalpy of formation data, methyl- and ethylcyclobutane. They were discussed in the previous section where the accuracy of the enthalpy of formation of methylcyclobutane was questioned. From equation 5, for $X = CH_3$ and $n = 3$, 5 and 6 in both the liquid and gas phases, the enthalpies of reaction range from -0.3 to -2.1 kJ mol^{-1}. If the archival enthalpy of formation of liquid methylcyclobutane is used in equation 5 for $n = 4$, the enthalpy of this reaction is *ca* -15 kJ mol^{-1}. Using instead the liquid and gas enthalpies of formation derived above for methylcyclobutane, the enthalpies of reaction are -0.5 kJ mol^{-1}. If the derivation is accurate, none of the C_3-C_6 cycloalkane ring-strain energies are much changed upon methyl substitution. What about ethyl substitution? The enthalpies of reaction 5, for $X = CH_2CH_3$ and $n = 3$ and 5 in both the liquid and gas phases, are slightly negative, *ca* -3 ± 1.5 kJ mol^{-1}. For $n = 6$, the enthalpies are slightly positive in both phases. For $n = 4$, cyclobutyl, the enthalpies of reaction are a few kJ mol^{-1} more negative than for the cyclopropyl and cyclopentyl cases, *ca* -7 ± 1.0 kJ mol^{-1}. It is this small, but noticeable difference that likely accounts for the discrepancy in the methyl- and ethylcyclobutane enthalpy of formation difference, as discussed above. An ethyl substituent seemingly stabilizes a cycloalkyl ring, except for cyclohexyl, very slightly compared to a methyl group.

There is no measured enthalpy of formation for either stereoisomer of either 1,2- or 1,3-dimethylcyclobutane. The enthalpies of formation for the *cis* isomers can be derived differently in this section and the next, and the values shown to be consistent.

The enthalpies of the *cis*-1,2-dimethyl exchange reaction 12 with $x = 6$ are: -4.5 kJ mol^{-1} for $y = 3$ and -4.4 kJ mol^{-1} for $x = 5$. For $x = 5$ and $y = 3$, the reaction is thermoneutral. Assuming the same is true for $x = 5$ and $y = 4$, the gas phase enthalpy of formation of 1,2-dimethylcyclobutane is -24.7 kJ mol^{-1}. The same result is obtained using an enthalpy of reaction of -4.5 kJ mol^{-1} for $x = 6$ and $y = 4$.



(12)

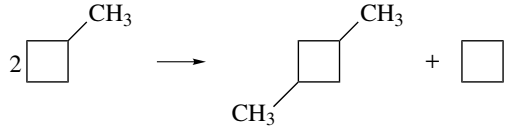
Reaction 13 is expected to be essentially thermoneutral. Using the previously derived gas phase enthalpy of formation for methylcyclobutane (-1.6 kJ mol^{-1}), the enthalpy of

TABLE 1. Enthalpies of formation of some monocyclic four-membered ring compounds (kJ mol^{-1})

Compound	$\Delta_f H_m^0$ (lq or s)	$\Delta_f H_m^0$ (gas)	Reference
Cyclobutane	3.7 ± 0.6 (lq)	28.4 ± 0.6	1
Cyclobutene		156.7 ± 1.5	1
Methylcyclobutane	−44.5 ± 1.4 (lq)		1 [a]
Ethylcyclobutane	−59.0 ± 0.8 (lq)	−27.7 ± 0.7	1
		−26.3	19
Methylenecyclobutane	93.8 ± 0.6 (lq)	121.5 ± 0.7	1
1,2-Bis(methylene)cyclobutane		204	21
Cyclobutyl amine	5.6 ± 0.6 (lq)	41.2 ± 0.8	1
Cyclobutanecarbonitrile	103.0 ± 1.2 (lq)	143.1 ± 1.3	1
3-Methylenecyclobutanecarbonitrile	207.9 ± 2.1 (lq)	252.5 ± 2.1	1
Cyclobutanol	−199 ± 0.7 (lq)	−145	25
Cyclobutanone	−130.8 ± 1 (lq)	−91.6	25
Cyclobutanemethanol	−268 (lq)		28 [a]
Cyclobutanecarboxylic acid	−425.3 ± 1.8 (lq)		30
1,3-Cyclobutanedione	−260.0 ± 2.1 (s)	−186.3 ± 3.0	1
3-Phenylcyclobutanone	−56.6 ± 1.5 (lq)	−10.2	32
3-Phenylcyclobutenone	27.8 (s)		32
4,6-Diisopropyl-2,2-dimethyl-1-phenylbenzocyclobuten-1-ol	−218.8 ± 1.7 (s)	−101.8 ± 9.2	34 [a]
1,1-Dimethoxycyclobutane	−351.0 ± 1.3 (lq)	−309.2 ± 1.7	38
Methyl cyclobutanecarboxylate	−395.0 ± 1.3 (lq)	−355.3 ± 1.4	1
	−371.9 ± 1.2 (lq)	−327.7 ± 1.3	46
Ethyl cyclobutanecarboxylate	−432 (lq)		28
	−413.5 ± 1.1 (lq)	−368.6 ± 1.2	46
Glyceryl tris(cyclobutanecarboxylate)	−1130 (lq)		28
1,1-Cyclobutanedicarboxylic acid	−835.7 ± 1.0 (s)	−724.5 ± 1.2	53
1,2-Cyclobutanedicarboxylic acid, *cis*	−838.1 ± 4.0 (s)	−718.1 ± 4.1	30,53
1,3-Cyclobutanedicarboxylic acid, *cis*	−838.1 ± 3.0 (s)		30
2,4-Diphenylcyclobutane-1,3-dicarboxylic acid (α-truxillic acid)	−651 (s)		56
2,4-Diphenylcyclobutane-1,3-bis(ethylene-2,2-dicarboxylic acid)	−1262 (s)		56
Dimethyl 1,2-cyclobutanedicarboxylate	−743.9 (lq)		51
Diethyl 1,1-cyclobutanedicarboxylate	−806.8 ± 0.7 (lq)	−741.0 ± 0.8	46
Dimethyl 2,2-dimethylcyclobutane-1,3-dicarboxylate, *cis* (dimethyl norpinate)	−825.9 (lq)		51
Methyl 3-carbomethoxy-2,2-dimethylcyclobutaneacetate (dimethyl pinate)	−869.4 (lq)		51

[a] See discussion in text.

formation of 1,3-dimethylcyclobutane is −31.6 kJ mol^{-1}. The 1,3-isomer, with no adjacent *non-bonded interactions*, is more stable than the 1,2-isomer

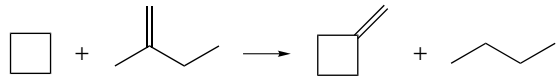


(13)

C. Methylenecyclobutanes

In considering the ring-strain energy of methylenecyclobutane with its exocyclic double bond, it is consequential whether methylenecyclohexane or 2-methyl-1-butene is chosen as a reference compound. Although the gas phase enthalpies of formation of cyclohexyl-X and *sec*-butyl-X are nearly identical when the substituent is singly bonded to carbon, that is not so when the substituent is double-bonded to the ring carbon. The enthalpies of formation of methylenecyclohexane and 2-methyl-1-butene differ by *ca* 10 kJ mol^{-1} and the enthalpies of formation of cyclohexanone and 2-butanone differ by *ca* 13 kJ mol^{-1}. In both cases, the *sec*-butyl derivative has a more negative enthalpy of formation. Because we might expect some ring strain in the cyclohexane due to the introduction of the trigonal carbon atom, we choose the acyclic alkene as the reference.

The gas phase enthalpy of reaction for equation 14 is $+4.6 \pm 1.4$ kJ mol^{-1} (lq) and $+2.8 \pm 1.5$ kJ mol^{-1} (g). Evidently, the exocyclic methylene group does not greatly increase the overall strain energy of the cyclobutane ring. Although there is expected to be an increase in ring angle strain due to the introduction of the trigonal ring carbon, non-bonded interactions in the parent cyclobutane may be relieved upon substitution.



(14)

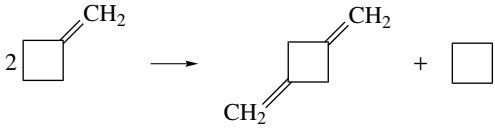
The enthalpies of reaction for the corresponding reactions of the C_3, C_5 and C_6 cyclic species are $+56.9$, -1.9 and $+7.9$ kJ mol^{-1}. It would appear that the energetics of cyclobutane are much less sensitive to substitution, at least of tetrahedral by trigonal carbon, compared to cyclopropane.

A comparison that takes into account the additional carbon atom in the methylenecyclobutane is with its isomer, 1-methylcyclobutene. The only thermochemical data available for the latter compound is the enthalpy of hydrogenation, -119.2 ± 0.04 kJ mol^{-1}, in acetic acid solvent[20]. Apart from any complications due to interactions with the solvent, there is some ambiguity as to whether the hydrocarbon is in the liquid or gaseous phase. However, enthalpies of hydrogenation of alkenes are not too different in the two phases. From the same source is found the enthalpy of hydrogenation of methylenecyclobutane, -123.1 ± 0.3 kJ mol^{-1}. The slightly more stable C_5H_8 isomer thus contains the more highly substituted endocyclic double bond even though the ring contains two trigonal carbon atoms that would presumably increase the RSE. The endocyclic 1-methylcyclopentene and 1-methylcyclohexene are *ca* 16 and 18 kJ mol^{-1}, respectively, more stable than their exocyclic isomers, while 1-methylcyclopropene is 43 kJ mol^{-1} less stable than its isomer.

It is thus clear that while cyclopropane and cyclobutane have comparable strain energies, the strain energy of cyclopropene and methylenecyclopropane are considerably greater than for cyclobutene and methylenecyclobutane. Indeed, the strain energies of these last two species are not particularly different from that for the parent cyclobutane. This suggests that cyclobutane is comparatively normal: the increase of strain energy on introduction of a trigonal carbon into the cyclopropane ring is legendary; into the cyclobutane ring seemingly of rather minor consequence.

Also found are the enthalpies of hydrogenation of 1,3-bis(methylene)cyclobutane (-251 kJ mol^{-1}) and 1-methyl-3-methylenecyclobutene (-230 kJ mol^{-1})[20]. The latter species is *ca* 21 kJ mol^{-1} more stable than its isomer, showing in addition to the *ca* 4 kJ mol^{-1} greater stability of the *endo* isomer, a substantial conjugative interaction of the double bonds. In that the enthalpy of hydrogenation of the 1,3-bis(methylene)cyclobutane is about twice that for methylenecyclobutane, there is apparently very little interaction of those bonds nor is there additional destabilization due to the introduction of the second trigonal carbon atom. Accordingly, reaction 15 should be approximately thermoneutral and the

enthalpy of formation of 1,3-bis(methylene)cyclobutane is *ca* +215 kJ mol^{-1}. From the enthalpy of hydrogenation, the enthalpy of formation of *cis*-1,3-dimethylcyclobutane is calculated as *ca* −36 kJ mol^{-1}, compatible with the value derived in the previous section.



(15)

The enthalpy of formation of 1,2-bis(methylene)cyclobutane is given as +204 kJ mol^{-1} from hydrogenation calorimetry to a mixture of *cis*- and *trans*-1,2-dimethylcyclobutane[21]. 1,2-Bis(methylene)cyclobutane is seemingly more stable than the 1,3-isomer by *ca* 10 kJ mol^{-1}, most likely due to a stabilizing conjugative interaction for the former species.

IV. NITROGEN-CONTAINING SUBSTITUENTS

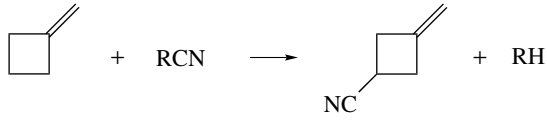
A. Cyclobutyl Amine

Cyclobutyl amine is the only amino-containing four-membered ring compound with thermochemical data. For both equations 5 and 6, where $n = 4$ and X = NH_2, the reaction enthalpies are identical in the liquid phase, −6.8 kJ mol^{-1}, and nearly so in the gas phase, −7.2 ± 1.0 kJ mol^{-1}. These exothermic reactions are in distinct contrast to those for $n = 3$ and 5 where the enthalpies are all positive and range from *ca* 1 to 5 kJ mol^{-1}. The amino group seemingly stabilizes only the cyclobutyl ring.

B. Cyanocyclobutane Derivatives

Let us compare the strain energy of cyclobutanecarbonitrile with that of cyclobutane itself. For both reactions 5 and 6 where X = CN, the exothermicity is *ca* −9 kJ mol^{-1} in the liquid phase and about −13 kJ mol^{-1} in the gas phase and so cyclobutanecarbonitrile is less strained than cyclobutane. Furthermore, the stabilization is greater than for cyclopentanecarbonitrile (*ca* −9 kJ mol^{-1}, gas) and cyclopropanecarbonitrile (<+1 kJ mol^{-1}, gas).

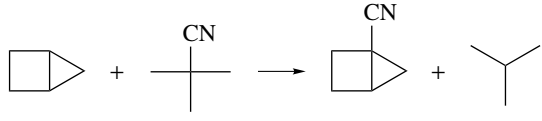
The enthalpies of formation for 3-methylenecyclobutanecarbonitrile are also known. For reaction 16, the enthalpies of reaction for R = cyclohexyl, *sec*-butyl[22] and isopropyl are comparable: *ca* +7 kJ mol^{-1} in the liquid phase and *ca* +4 kJ mol^{-1} in the gas phase.



(16)

Since methylenecyclobutane is only slightly more strained than cyclobutane, it is not apparent why cyclobutane and methylenecyclobutane should have such different behavior on formation of the cyano derivative[23].

The third cyclobutanenitrile for which there are thermochemical data is bicyclo[2.1.0]-pentane-1-carbonitrile, in which the cyano substituent is bonded to a tertiary carbon. Reaction 17 provides an assessment of the strain energy upon formation of the bicyclic nitrile.



(17)

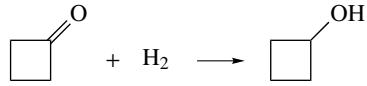
Taking the value of +158 kJ mol^{-1} for the gas phase enthalpy of formation of the parent bicyclic hydrocarbon[24], we find a reaction exothermicity of −17.6 kJ mol^{-1} and so conclude that the cyano group stabilizes the strained bicyclic ring even more than it stabilizes cyclobutane itself.

V. OXYGEN-CONTAINING SUBSTITUENTS

A. Alcohols and Ketones

1. Cyclobutanol, cyclobutanone and cyclobutanemethanol

The enthalpies of formation of cyclobutanol are from direct combustion calorimetric measurements of the liquid and an estimated enthalpy of vaporization[25]. From the same source are the enthalpy of combustion and an estimated enthalpy of vaporization for cyclobutanone. However, there are independent, and disparate by some 9 kJ mol^{-1}, values[26] for these two species, both with measured enthalpies of vaporization. There are values for the enthalpy of the formal hydrogenation reaction 18 of cyclobutanone (indirectly measured for a triethylborohydride reduction) of −67.9 ± 0.8 kJ mol^{-1} for the liquid and −53.3 ± 1.3 kJ mol^{-1} for gas, together with a measured enthalpy of vaporization[27].

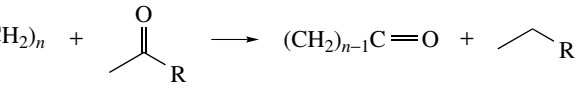


(18)

These independently determined reaction enthalpies for cyclobutanone reproduce the enthalpy of formation values for liquid and gaseous cyclobutanol from Reference 25 to within 1 kJ mol^{-1} and so are accepted by us; the values from Reference 26 remain disparate.

In assessing the ring strain of cyclobutanol, we choose to use reactions 5 and 7 because the experimental uncertainty for the enthalpy of formation of cyclohexanol is rather large, ±2.1 kJ mol^{-1}, and because of the effect of the hydroxyl group on the ring stability of cyclohexane as noted below. The hydroxyl group affects each of the cycloalkanes differently: the reaction enthalpies in both the liquid and gas phases are *ca* +1.5 kJ mol^{-1} for $n = 5$, *ca* +5 kJ mol^{-1} for $n = 6$ and *ca* −6 kJ mol^{-1} for $n = 4$ (there is no measured enthalpy of formation value for cyclopropanol). The hydroxyl group stabilizes only the cyclobutane ring, and to about the same extent as the amino group.

Cyclobutanone, like methylenecyclobutane, contains an sp^2-hybridized ring carbon. Also as with methylenecyclobutane, the acyclic reference species 2-butanone and acetone, R = Et and Me, are chosen in order to estimate the ring strain from reaction 19.



(19)

The oxo group, just like the hydroxyl group, affects each of the cycloalkanes differently: the reaction enthalpies in both the liquid and gas phases are *ca* −3 kJ mol^{-1} for $n = 5$, *ca* +11 kJ mol^{-1} for $n = 6$ and *ca* −7.7 kJ mol^{-1} for $n = 4$ (there is no enthalpy of formation measurement for cyclopropanone). Unlike the double-bonded methylene group that slightly destabilizes the cyclobutane ring, the double-bonded oxygen is stabilizing and to about the same extent as NH_2 and OH.

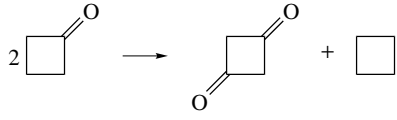
The enthalpy of formation of liquid cyclobutanemethanol was reported to be −268 kJ mol^{-1} [28]. From the same source comes the enthalpy of formation of liquid cyclohexanemethanol of −469 kJ mol^{-1}. A more recent (1929) value of −378.1 ± 8.4 kJ mol^{-1}

was reported for the latter species[29]. Casual inspection of the liquid phase enthalpies of formation of alkanes of the type RCH_3 and the corresponding alcohols, RCH_2OH, shows the alcohol species to have a more negative value by *ca* -180 kJ mol^{-1}. From the archival value of liquid methylcyclohexane of -190.1 ± 1.0 kJ mol^{-1}, we derive an enthalpy of formation of -370 kJ mol^{-1} for cyclohexanemethanol, in rough agreement with the more recent measurement and invalidating the result from the earlier study.

The enthalpies of reactions 5, 6 and 7 for $n = 4$ and $X = CH_2OH$ range from -50 to -62 kJ mol^{-1}, much too exothermic to be credible. Using our derived value of -29.3 (lq) for methylcyclobutane and the enthalpy of formation exchange value for CH_2OH/CH_3, we obtain a value of *ca* -209 kJ mol^{-1} for cyclobutanemethanol. The discrepancy is excessive. Similarly, the liquid phase enthalpies of formation of alcohols RCH_2OH are *ca* -207 kJ mol^{-1} more negative than for the corresponding carboxylic acids, RCOOH. From the liquid phase enthalpy of formation of cyclobutanecarboxylic acid[30], -425.3 ± 1.8 kJ mol^{-1}, the enthalpy of formation of cyclobutanemethanol would be *ca* -218 kJ mol^{-1}. Finally, comparing the isosteric RCH_2CH_3 and RCH_2OH where the CH_3/OH exchange quantity[31] is *ca* $+153$ kJ mol^{-1}, we expect enthalpies of formation of -365 and -212 kJ mol^{-1} for cyclohexanemethanol and cyclobutanemethanol, in acceptable agreement with our aforementioned estimates but not in agreement with the early value of the enthalpies of formation of these substances. Presumably these values are in error.

2. Cyclobutanedione

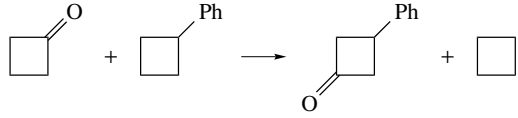
1,3-Cyclobutanedione has measured enthalpies of formation for the solid and gaseous phases. The gas phase disproportionation reaction 20 is endothermic by less than $+1$ kJ mol^{-1}. Evidently, the second oxo group destabilizes the cyclobutane ring to the same extent as the first oxo group in cyclobutanone stabilizes the ring.



(20)

3. Substituted cyclobutanones

The only species of this type for which we have data is 3-phenylcyclobutanone[32]. The enthalpy of vaporization as given in the original source, 46.4 kJ mol^{-1}, seems low compared to other species with the same number of carbon atoms. The phenylation enthalpy of cyclobutane is unknown as there are no reported enthalpies of formation of this, or any other arylated, cyclobutane. The phenylation enthalpy for cyclohexane, according to equation 5 where X = Ph, is essentially zero in either liquid or gaseous phase. In contrast, for cyclopropane the enthalpies are *ca* -16 kJ mol^{-1} (lq) and -12 kJ mol^{-1} (g) where the phenyl group stabilizes the bent cyclopropane bond[33]. Assuming the enthalpy of reaction for equation 5 is *ca* -7 kJ mol^{-1} for $n = 4$, the enthalpies of formation for phenylcyclobutane are *ca* $+91$ kJ mol^{-1} (lq) and $+144$ kJ mol^{-1} (g). The enthalpy of reaction for equation 21 is calculated to be -13 kJ mol^{-1} (lq) and -34 kJ mol^{-1} (g). In that enthalpies for similar disproportionation reactions are thermoneutral or endothermic, the result, at least for the gaseous phase, is implausible.



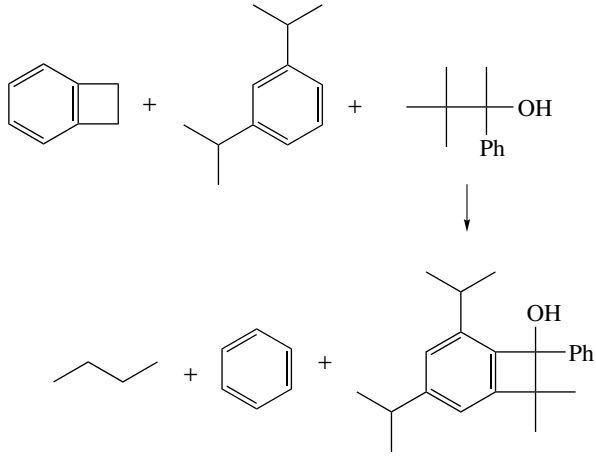
(21)

4. Cyclobutenones

A collection of data[32] includes enthalpies of formation for 3-phenylcyclobutenone and 3-phenylcyclobutene-1,2-dione. However, much of the interest in the latter compound arises from the possibility of aromaticity due to its 2 π electrons within the ring. Likewise, 3,4-dihydroxycyclobutene-1,2-dione (squaric acid) is recognized as a cyclobutenone as well. Aromaticity is again a possibility and discussion for all three species is accordingly deferred to a later section.

5. Cyclobutenols

A highly functionalized cyclobutenol species is 4,6-diisopropyl-2,2-dimethyl-1-phenylbenzocyclobuten-1-ol, a photocyclization product of 2,4,6-triisopropylbenzophenone. The gas phase enthalpy of formation[34] of this highly substituted benzocyclobutenol is suspected to be implausible by the following analysis that involves equation 22.

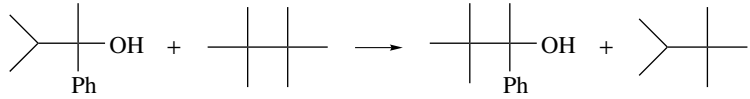


(22)

There is no measured gas phase enthalpy of formation of *m*-diisopropylbenzene. However, reaction 23 for both the *meta* and *para* isomers in the liquid phase is nearly thermoneutral[35]. Let us assume it as well for the gas phase and so derive the value of $-74.6\ \mathrm{kJ\,mol^{-1}}$ for gaseous *m*-diisopropylbenzene.

$$2\ i\text{-PrPh} \longrightarrow \mathrm{PhH} + m\text{- or } p\text{-}i\text{-}\mathrm{Pr_2C_6H_4} \tag{23}$$

Likewise lacking data on the hindered carbinol, 2-phenyl-3,3-dimethyl-2-butanol, its enthalpy of formation is approximated by assuming thermoneutrality for reaction 24 where the enthalpy of formation for the 2-phenyl-3-methyl-2-butanol is from Reference 36. The derived enthalpy of formation is $-232.1\ \mathrm{kJ\,mol^{-1}}$.



(24)

The enthalpy of reaction 22 is thus calculated to be $-37\ \mathrm{kJ\,mol^{-1}}$, using the reported experimental value for 4,6-diisopropyl-2,2-dimethyl-1-phenylbenzocyclobuten-1-ol. The

exothermicity suggests stabilization rather than the expected substituent-derived strain in the substituted cyclobutenol. Instead, if reaction 22 is roughly thermoneutral, the derived enthalpy of formation for 4,6-diisopropyl-2,2-dimethyl-1-phenylbenzocyclobuten-1-ol from equation 22 is -65 kJ mol^{-1}, a quantity that is very different from the experimentally derived value. We wonder if the benzocyclobutenol sample partially reverted to the precursor benzophenone, either through the *o*-quinodimethane from whence it immediately came, or some hydrogen atom or ion transfer process. As the benzocyclobutenol and benzophenone are isomers, such isomerization would be invisible to calorimetric investigation.

A potential cyclobutenol, 3-oxocyclobuten-1-ol, is an enol tautomer of cyclobutane-1,3-dione. Unlike acetylacetone that exists predominantly as the enolone[37], this β-diketone exists primarily as such. That is, the enthalpy of formation of the tautomeric cyclobutenol lies high above the -260.0 ± 2.1 kJ mol^{-1} and -186.3 ± 3.0 kJ mol^{-1} enthalpies of formation of the solid and gaseous dione, respectively.

B. Cyclobutyl Ethers

If cyclobutyl and cyclobutenyl alcohols have been relatively ignored by thermochemists, the ethers have been even more so. The sole cyclobutyl ether for which there is thermochemical data known to the authors is the dimethyl acetal of cyclobutanone, 1,1-dimethoxycyclobutane. The liquid phase enthalpy of formation was determined from the enthalpy of the acetalization reaction of cyclobutanone[38], the value for which was sandwiched (by a few kJ mol^{-1}) between the related acetal-forming reactions of acetone and cyclohexanone.

An interesting test of self-consistency makes use of estimated enthalpies of vaporization. It was earlier suggested that ethers with the generic structure ROR′ have enthalpies of vaporization very similar to the isosteric, isovalent hydrocarbons RCH_2R'[31]. Accordingly, the acetal, 1,1-dimethoxycyclobutane, would be related to 1,1-diethylcyclobutane and so have a predicted enthalpy of vaporization of *ca* 42 kJ mol^{-1}. Its measured enthalpy of vaporization was 41.6 kJ mol^{-1}, in fine agreement.

C. Cyclobutanecarboxylic Acids and their Derivatives

1. Cyclobutanecarboxylic acid

There are two, almost identical, values for the cyclobutanecarboxylic acid parent species in the liquid phase, -425.3 ± 1.8 and -426 kJ mol^{-1}, dating respectively from the recent 1984 measurement[30] and a really quite ancient measurement[39] from 1913. We know of no measurement of its enthalpy of vaporization. Results from equation 1 suggests a value of $+60.5$ kJ mol^{-1}. We thus have a predicted value of -364 kJ mol^{-1} for the enthalpy of formation of cyclobutanecarboxylic acid in the gas phase. For comparison, there are two measurements for the liquid phase enthalpy of formation of cyclopropanecarboxylic acid: -396 kJ mol^{-1} [40] and -424.3 kJ mol^{-1} [39]. Only the first value is compatible with that for the cyclobutanecarboxylic acid as it is unlikely that the enthalpy of formation of cyclopropanecarboxylic acid is the same as that of cyclobutanecarboxylic acid.

We are somewhat hampered from determining the ring-strain energy of cyclobutanecarboxylic acid by the lack of thermochemical data for reference species. The enthalpy of formation of cyclohexanecarboxylic acid is known only for the solid, -561.5 kJ mol^{-1} from Swietoslawski[28] in 1920 and -585.9 kJ mol^{-1} from a 1950 thesis[41]. Using a consensus value of -574 ± 13 kJ mol^{-1} and approximating the enthalpy of fusion as that of its aromatic counterpart[42], benzoic acid, we derive an enthalpy of formation of -556 ± 14 kJ mol^{-1} for liquid cyclohexanecarboxylic acid. From equation 6 where $X = CO_2H$,

there is thus an apparent decrease in strain energy, or a net stabilization, for cyclobutanecarboxylic acid of -29 ± 14 kJ mol^{-1}.

From equation 7, where X = CO_2H, and the liquid phase enthalpies of formation for 2-methylbutanoic acid (-554.5 ± 5.9 kJ mol^{-1}) and *n*-butane (-146.6 ± 0.7 kJ mol^{-1}), the decrease in strain energy for cyclobutanecarboxylic acid is calculated to be the comparable -21.3 ± 6.2 kJ mol^{-1}. We note that the enthalpy of formation of 2-methylbutanoic acid is slightly less negative than that of its straight chain isomer, pentanoic acid (-559.4 ± 0.7 kJ mol^{-1}), when we would expect the branched isomer to be slightly more stable. The stabilization of cyclobutanecarboxylic acid is likely somewhat less than that calculated above.

The enthalpy of formation of -553 kJ mol^{-1} for the liquid phase isobutyric acid (2-methylpropanoic acid) is from Longuinine's study[43] published in 1885. If the enthalpy of formation value, above, for 2-methylbutanoic acid is correct, then this almost identical value for isobutyric acid cannot be accurate. Alternatively, one may derive the enthalpy of formation of isobutyric acid as -535 ± 3 kJ mol^{-1} by summing the liquid phase enthalpy of hydrogenation[44], -118 ± 1 kJ mol^{-1}, and the enthalpy of formation of methacrylic acid[45] (2-methylpropenoic acid), -417 ± 3 kJ mol^{-1}. Accepting this value for the enthalpy of formation of liquid isobutyric acid, the enthalpy of reaction for equation 5 where X = CO_2H demonstrates an apparent decrease in strain energy of cyclobutanecarboxylic acid of -14.7 ± 5 kJ mol^{-1} relative to cyclobutane.

Combining all of the above, we conclude that cyclobutanecarboxylic acid is some 22 $\pm$ 10 kJ mol^{-1} less strained than cyclobutane.

2. Methyl cyclobutanecarboxylate

From two sources[23,46] there are extremely disparate enthalpies of formation for methyl cyclobutanecarboxylate. The earlier one also appears in our archival source. The enthalpy of vaporization from the later source is comparable to an independent measurement (44.7 $\pm$ 0.9 kJ mol^{-1})[19].

In the absence of any thermochemical data for methyl cyclohexanecarboxylate we assess the strain energy of methyl cyclobutanecarboxylate by reactions 5 and 7 where X = CO_2Me, which is complicated by the uncertainty of the accuracy of the reference species. The enthalpy of formation of liquid methyl isobutyrate[47] of -491 kJ mol^{-1} originally from a 1910 paper is in good agreement with a more contemporaneous value of -494 kJ mol^{-1} derived by summing the enthalpies of formation and hydrogenation of methyl methacrylate[48]. The liquid enthalpy of formation difference for methyl 2-methylbutanoate (-534.3 ± 7.1) and methyl isobutyrate is some 41 kJ mol^{-1}, much too large for a methylene increment. The enthalpy of reaction for equation 7 is -11.0 kJ mol^{-1} (lq) and -16.8 kJ mol^{-1} (g) using the methyl cyclobutanecarboxylate enthalpies of formation from the first study and $+12.1$ kJ mol^{-1} (lq) and $+10.8$ kJ mol^{-1} (g) kJ mol^{-1} from the second study. For comparison, the enthalpies of reaction 7 for $n = 3$, methyl cyclopropanecarboxylate, are -0.9 kJ mol^{-1} (lq) and $+3.8$ kJ mol^{-1} (g).

Using an average enthalpy of formation for liquid methyl isobutyrate in equation 5, liquid methyl cyclobutanecarboxylate is less strained than cyclobutane itself by either *ca* -27 or -4 kJ mol^{-1}, depending on which enthalpy of formation is chosen for methyl cyclobutanecarboxylate. These values are both different from that earlier obtained for the parent acid, cyclobutanecarboxylic acid, of -15 ± 5 kJ mol^{-1} as calculated by the same equation. For comparison, the enthalpy of reaction 5 for $n = 3$ is -16.6 kJ mol^{-1}.

The average of the two ring-strain calculations for methyl cyclobutanecarboxylate in the liquid phase is *ca* -21 kJ mol^{-1}, which is identical to that obtained for the average strain energy reduction calculated for the parent acid. It is quite clear that there is stabilization of cyclobutane by either $-$COO$-$ group.

3. Ethyl cyclobutanecarboxylate

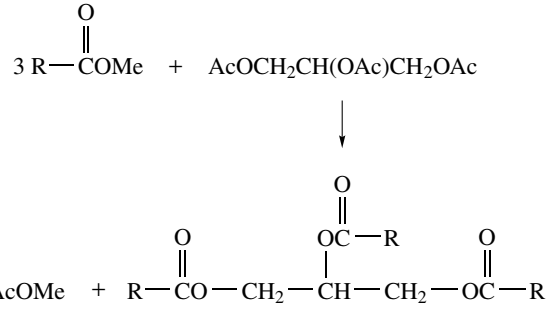
The trivial name for the ethyl ester of cyclobutanecarboxylic acid, ethyl tetramethylenecarboxylate, expresses[4] both a synthetic origin of carbocyclic four-membered rings as well as considerable instability relative to an acyclic assemblage of four saturated carbon atoms. Again, there are two very disparate measurements of the enthalpies of formation.

We ask first "are these values 'normal' for an ester of cyclobutanecarboxylic acid?" For a collection of methyl and ethyl esters from the archival source, both saturated and unsaturated, the enthalpy of formation difference in the liquid phase is *ca* -35 ± 3 kJ mol^{-1}. The enthalpy of formation difference between the earlier measurements of liquid methyl and ethyl cyclobutanecarboxylate (from different studies) is -37 kJ mol^{-1}; the difference between the later measurements, both from the same study, are -41.6 (lq) and -40.9 kJ mol^{-1} (g). These differences are only slightly larger than 'normal'.

There are no available enthalpies of formation for ethyl isobutyrate or ethyl cyclohexanecarboxylate. With the ethyl 2-methylbutanoate reference species[49], the enthalpy of reaction 7, where X = CO_2Et, is -18.7 ± 8.5 kJ mol^{-1} (lq) using the enthalpy of formation of the cyclobutyl ester from Reference 28. Using the enthalpies of formation from Reference 46 the enthalpies of equation 7 are (with the same error bars) -0.2 kJ mol^{-1} (lq) and -3.3 kJ mol^{-1} (g). For comparison[46], the equation 7 reaction enthalpies are (kJ mol^{-1}): -5.2 (lq) and -1.6 (g) for $n = 3$; $+13.5$ (lq) and $+12.8$ (g) for $n = 5$.

4. Glyceryl tris(cyclobutanecarboxylate)

The glyceryl triester of cyclobutanecarboxylic acid is known by the trivial name 'tricyclovalerin' that shows the connection with the aliphatic fatty acid, valeric acid. We lack enthalpy of formation data for direct evaluation of its strain energy: there are no available values for glyceryl tris(cyclohexanecarboxylate), glyceryl tris(2-methylbutanoate) or glyceryl tris(isobutyrate). So, instead, we ask "is this species a 'normal' glyceryl ester?" If so, equation 25 should be approximately thermoneutral.



(25)

For R = *n*-Pr, the only other example we know of, the enthalpy of reaction, normalized for three groups, is -4.0 kJ mol^{-1} [50]. For R = cyclobutyl, the normalized enthalpy of reaction is endothermic by $+16$ kJ mol^{-1} if the enthalpy of formation for methyl cyclobutanecarboxylate from Reference 1 is used, suggesting a rather large destabilization of the triglyceride relative to methyl cyclobutanecarboxylate. If the enthalpy of formation for the methyl ester from Reference 46 is used, the triglyceride, per R group, is stabilized by -7.0 kJ mol^{-1}.

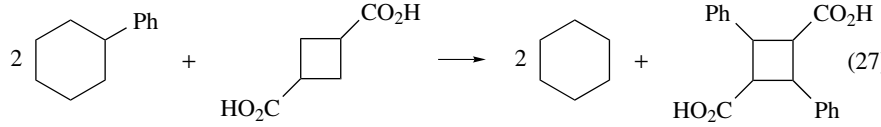
5. Cyclobutanedicarboxylic acids

There are five unsubstituted cyclobutanedicarboxylic acid isomers, the 1,1-; *cis*- and *trans*-1,2; and *cis*- and *trans*-1,3-. The 1,1-, 1,2- and 1,3-dicarboxylic acids were earlier

named the α, α; α, β; and α, γ-dicarboxylic acids. The enthalpies of combustion of each of the isomers were measured more than 90 years ago[51,52]. Table 1 shows more recent, and disparate, measurements[30,53]. What is the stability order of these isomers? Complications from substituent effects on strain, *geminal* vs. *vicinal* substitution, and intra- vs. intermolecular hydrogen bonding makes us unable and unwilling to rationalize the apparent stability order for the various cyclobutanedicarboxylic acids. In that the solid phase values for the three isomers are so close[54], a value of -838 ± 3 may be suggested for the enthalpy of formation of all of these species. Using this value, the disproportionation reaction 26 is endothermic by $+9$ kJ mol^{-1} [55]. This destabilization is not too different from that of other disubstituted cyclobutanes discussed here earlier.

$$2\ c\text{-}C_4H_7CO_2H \longrightarrow c\text{-}C_4H_6(CO_2H)_2 + c\text{-}C_4H_8 \qquad (26)$$

The enthalpy of formation of solid 2,4-diphenylcyclobutane-1,3-dicarboxylic acid, commonly named α-truxillic acid, is -651 kJ mol^{-1} [56]. Consider the solid phase reaction 27.



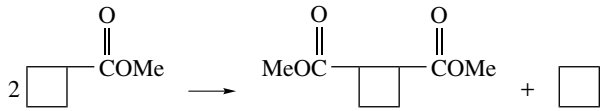
(27)

Accepting the consensus enthalpy of formation of solid 1,3-cyclobutanedicarboxylic acid (-838 ± 3 kJ mol^{-1}) and the derived enthalpies of formation of solid benzene and phenylcyclohexane from those of the liquids and enthalpies of fusion[42], the enthalpy of reaction is found to be endothermic by $+39$ kJ mol^{-1}.

We would like to ascribe the endothermicity to increased strain in the tetrasubstituted cyclobutane, although admittedly we lack thermochemical data on any other tetrasubstituted cyclobutane. We would also prefer to use phenylcyclobutane in the comparison rather than phenylcyclohexane but lack the requisite solid phase data. Then again, Kharasch[4] expresses concern about the enthalpy of the interconversion of α-truxillic acid and its photochemical precursor, cinnamic acid. This invites a related concern by the current authors for the reported enthalpy of formation of 3,4-diphenylcyclobutane-1,3-bis(ethylene-2,2-dicarboxylic acid), the putative photochemical dimer of cinnamylidenemalonic acid with the same pedigree[56].

6. Cyclobutanedicarboxylic acid esters

The above results refer to multiply substituted, hydrogen bonded species in the solid phase. What can be said about related esters that lack the hydrogen bonding and are also generally liquids? The thermochemical measurement[51] for the 1,2-dimethyl ester, of uncertain stereochemistry, is -743.9 kJ mol^{-1}. The liquid phase reaction 28 is endothermic by nearly $+50$ or $+3.6$ kJ mol^{-1} depending on whether the enthalpy of formation of methyl cyclobutanecarboxylate is from Reference 1 or from Reference 46. This very large disparity again hampers our understanding of strain in cyclobutyl esters.



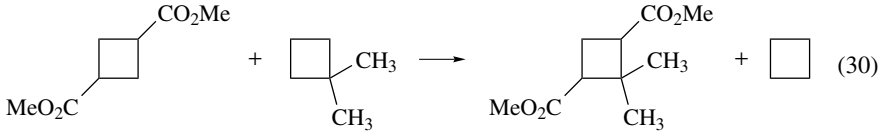
(28)

There are enthalpy of formation data for the diethyl 1,1-diesters of cyclopropane, cyclobutane and cyclopentane[46]. Equation 29 is a general disproportionation reaction for

these esters. The enthalpies of reaction in the liquid phase (the gas phase is comparable) are $n = 3$, $+0.44$; $n = 4$, $+24.6$; and $n = 5$, $+98.9$ kJ mol^{-1}. 1,1-Disubstitution is increasingly unfavorable as the ring size increases.

$$2\ (CH_2)_{n-1}CHCO_2Et \longrightarrow (CH_2)_{n-1}C(CO_2Et)_2 + (CH_2)_n \tag{29}$$

Dimethyl *cis*-2,2-dimethylcyclobutane-1,3-dicarboxylate, earlier known as dimethyl norpinate, reflecting the terpene, or more precisely pinene, origin of the compound, has a liquid enthalpy of formation[51] of -825.9 kJ mol^{-1}. We recall that the parent cyclobutane 1,2- and 1,3-dicarboxylic acids have very similar enthalpies of formation. Assuming this is true for their dimethyl esters (even though we have questioned the measured enthalpy of formation of the 1,2-diester), the difference between the enthalpies of formation of dimethyl norpinate and the parent dimethyl cyclobutanedicarboxylate would be the same as the difference between 1,1-dimethylcyclobutane and cyclobutane if equation 30 were thermoneutral.



(30)

The enthalpy difference between the esters is some 82 kJ mol^{-1}. However, we lack the enthalpy difference for the hydrocarbons—there is seemingly no measured enthalpy of formation for 1,1-dimethylcyclobutane. However, mimicking the cyclic structures by the pairs of acyclic hydrocarbons, neopentane and propane, or the substituted and parent cyclohexanes, or 2,2-dimethylbutane and butane, we find an enthalpy of formation difference for the hydrocarbons of *ca* 66 kJ mol^{-1}. Since the dimethyl norpinate should have additional strain because of CO_2Me/Me repulsion, that its enthalpy of formation is some 16 kJ mol^{-1} more negative than expected is disconcerting.

What about dimethyl pinate in which one carbomethoxy group in the norpinate ester is replaced by a CH_2COOMe group? Again using data from the same source[51], we find an enthalpy of formation difference between it and the norpinate of *ca* 40 kJ mol^{-1}. This difference is much larger than the 25 kJ mol^{-1} normally associated with insertion of a methylene group.

Summarizing, the thermochemical data for methyl esters of cyclobutanecarboxylic acids is no less enigmatic than for the acids themselves.

VI. HALOGENATED CYCLOBUTANES AND CYCLOBUTENES

Although the thermochemistry of halogenated organic compounds is relatively rich[57], at least compared to many other functionalized species, surprisingly little is known about the enthalpies of formation of such species containing carbocyclic four-membered rings.

A. Octafluorocyclobutane

There are three major sources of reaction data from which the enthalpy of formation of octafluorocyclobutane (perfluorocyclobutane) can be derived. The first is oxidative: the combustion of C_4F_8 in oxygen results in a mixture of CF_4, CO_2 and COF_2[58]. The same source presents the results from the oxygen calorimetry of tetrafluoroethylene, C_2F_4. Although the derived enthalpies of formation values are not accurate, assuming that the same products are formed in the same ratios in both oxidation reactions and that other

systematic errors also cancel, the dimerization of C_2F_4 is calculated to be exothermic by -207 kJ mol^{-1}. The measurements of the decomposition of perfluorocyclobutane[59,60] legitimize the above assumption as they report dimerization enthalpies of -211 and -209 kJ mol^{-1}, respectively. For comparison, the gas phase formal dimerization enthalpy of ethylene is only -76.6 kJ mol^{-1}.

The second method is reductive with elemental Na reducing perfluorocyclobutane according to reaction 31 where the original results were corrected to the carbon graphite standard state from the amorphous carbon formed in the reaction[61].

$$C_4F_8\ (g) + 8Na\ (s) \longrightarrow 8NaF\ (s) + 4C\ (\text{amorphous}) \tag{31}$$

The resulting enthalpy of formation measurement, -1488 ± 14.6 kJ mol^{-1}, should be corrected again for a more recently determined enthalpy of formation for NaF. There are two recommended values[62,63]: -573.6 kJ mol^{-1} and -575.4 kJ mol^{-1}. Although these values are compatible, the small difference is magnified by the comparatively large number of NaF reaction products. The enthalpy of formation range for perfluorocyclobutane is thus -1518 to -1532 kJ mol^{-1}. An enthalpy of formation for perfluorocyclobutane of -1542.6 ± 10.7 kJ mol^{-1} appears in Reference 1, taken from Reference 61. The origin of the *ca* 10 kJ mol^{-1} discrepancy is not clear. Accepting a consensus tetrafluoroethylene dimerization enthalpy of -209 kJ mol^{-1} and the archival enthalpy of formation of tetrafluoroethylene, -658.9 ± 4.9 kJ mol^{-1}, results in a suggested enthalpy of formation of octafluorocyclobutane of -1527 kJ mol^{-1}. A recent thermochemical/kinetics analysis suggested a value of -1542 kJ mol^{-1} [64]. Summarizing, the enthalpy of formation of octafluorocyclobutane remains uncertain but a value of -1530 ± 12 kJ mol^{-1} appears generally consistent with the available results.

Ring strain in perfluorocyclobutane and in perfluorocyclohexane (the only other perfluorocycloalkane for which there are calorimetric data) perhaps could be assessed by analogy with earlier equations for the perhydrocycloalkanes. For example, the enthalpies of formation per difluoromethylene group are -382.5 kJ mol^{-1} for perfluorocyclobutane and -395.0 kJ mol^{-1} for perfluorocyclohexane. For both fluorine and hydrogen substitution, the four-membered cycle is more strained. The strain energy difference per $-CF_2-$ group between the four- and the six-membered rings is about half the strain energy difference for the corresponding perhydrocycloalkanes of about 28 kJ mol^{-1}. The enthalpy of formation for the $-CF_2-$ increment derived from polytetrafluoroethylene is *ca* -405 kJ mol^{-1} [57], quite close to the presumably nearly strainless perfluorocyclohexane.

If all species are perfluorinated[65] as in equation 32, analogous to equation 3, the enthalpies of reaction for $n = 4$ and $n = 6$ are -226.8 and -265.2 kJ mol^{-1}, respectively.

$$(CF_2)_n + nCF_3CF_3 \longrightarrow nCF_3CF_2CF_3 \tag{32}$$

The ring strain in perfluorocyclohexane is seemingly greater than in perfluorocyclobutane. How can the contradiction between the two assessments be reconciled? The problem is the enthalpy of formation difference between C_2F_6 and C_3F_8, -440.8 kJ mol^{-1}, which is very different from the values for the strainless $-CF_2-$increment derived above and so cannot be used to calculate the ring strain energy. This has been termed the 'CF_3 terminal group problem'[66]. From a recent quantum chemical study, it appears probable that the earlier conclusion, that the strain energy of octafluorocyclobutane is less than that of the parent hydrocarbon, is affirmed regardless of the choice of values for its enthalpy of formation or of the approach used to evaluate its strain energy[67].

B. 1,2-Dichloro-1,2,3,3,4,4-hexafluorocyclobutane and Hexafluorocyclobutene

The dimerization enthalpy of trifluorochloroethylene has been determined[68] as -273 kJ mol^{-1}. Taking the enthalpy of formation of this olefin[69] to be -505 kJ mol^{-1} results

in a derived enthalpy of formation of 1,2-dichloro-1,2,3,3,4,4-hexafluorocyclobutane of $-1283\ kJ\,mol^{-1}$. This value is experimentally indistinguishable for formation of either the *cis*- or the *trans*-isomer as shown by their enthalpy of equilibration[68]. From this derivation, and the measured enthalpy of chlorination of hexafluorocyclobutene[70] of $-156.4 \pm 4.1\ kJ\,mol^{-1}$, the enthalpy of formation of the perfluorinated cyclobutene is $-1127\ kJ\,mol^{-1}$. Lacking the requisite data, it is not possible to appraise the strain energy of either hexfluorocyclobutane or 1,2-dichloro-1,2,3,3,4,4-hexafluorocyclobutane. However, the same recent calculational study of the strain energies of perfluoro- and perhydrocyclobutane shows the strain energy of octachlorocyclobutane to be smaller still[67].

C. Less Fluorinated Cyclobutanes

If highly fluorinated cyclobutanes are highly problematic, are less fluorinated cyclobutanes less problematic? Unfortunately, the answer to this question is in the negative. There are seemingly no calorimetric measurements on any of these less fluorinated species and but one energetics measurement study[71]. This involved determination of the appearance energy for various channels of the electron impact induced fragmentation of 1,1,2,2-tetrafluorocyclobutane. Without making any correction or revision, we cite the authors' upper bound of $-845\ kJ\,mol^{-1}$ for the enthalpy of formation of gaseous 1,1,2,2-tetrafluorocyclobutane.

VII. POLYCYCLIC COMPOUNDS CONTAINING CYCLOBUTANE

We have earlier discussed the thermochemistry of various monocyclic alkanes, including cyclobutane itself. Later in this chapter we discuss polycyclic compounds containing cyclobutane rings (along with other rings) that include prismanes and cubanes. Intermediate in complexity are those species that contain two and three rings. The various rings may be combined either in a 'spiro' or 'fused' manner, i.e. they may be joined by either a single carbon or by two carbons.

A. Spiro Species

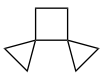
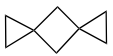
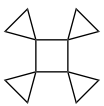
All of the most recent data for spiro species containing a cyclobutane come from one source[72] and are summarized in Table 2. We find no measurements from this or any other source for spiro[3.3]heptane, nor for any of its derivatives except for a reference to the structurally ambiguous 'dimethyl spiroheptane dicarboxylate' with an enthalpy of formation of $-714\ kJ\,mol^{-1}$ [28].

The total ring-strain energy of any spiro compound can be calculated as shown in equation 33, analogous to equation 4, where q equals the number of quaternary spiro carbons and m equals the number of methylene groups in the spiro compound.

$$(C)_q(CH_2)_m + (m + 2q)\ CH_3CH_3 \longrightarrow m\ CH_3CH_2CH_3 + q\ (CH_3)_4C \qquad (33)$$

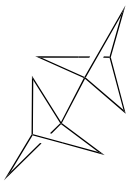
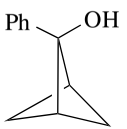
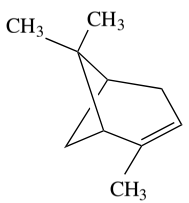
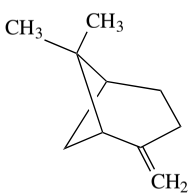
The difference between the ring-strain energies of spiro[2.2]pentane and two cyclopropane rings is $37\ kJ\,mol^{-1}$, a quantity that is essentially constant for all known [*n*]triangulanes[72]. The difference between the ring-strain energies of spiro[2.3]hexane and its constituent cycloalkanes, cyclobutane and cyclopropane, is only *ca* $2\ kJ\,mol^{-1}$. Lack of ring strain, exemplified by enthalpies of reaction 30 of *ca* $-3\ kJ\,mol^{-1}$ or less, is also found for the two dispirooctanes relative to their constituent cycloalkanes, normalized for the number of spiro fusions. For [4]rotane, the ring-strain energy difference, per spiro-fusion, is $9.6\ kJ\,mol^{-1}$. This non-negligible difference is most likely due to the forced planarization of the cyclobutane ring with the attendant increase in strain[72].

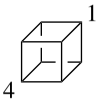
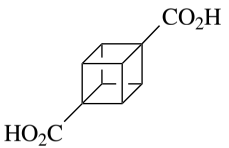
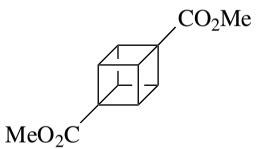
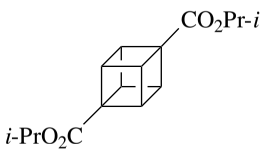
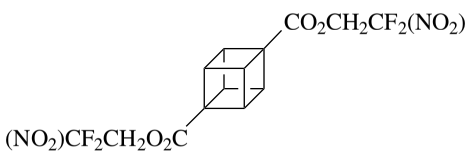
TABLE 2. Structures and enthalpies of formation of some polycyclic compounds with four-membered rings ($kJ\,mol^{-1}$)

Compound	Structure	$\Delta_f H_m^0$ (lq or s)	$\Delta_f H_m^0$ (gas)	Reference
Bicyclo[2.1.0]pentane-1-carbonitrile		227.8 ± 1.1 (lq)	272.1 ± 1.1	1
Spiro[2.2]pentane		157.7 ± 0.8 (lq)	185.2 ± 0.8	1
Spiro[2.3]hexane		88.3 ± 1.5 (lq) [a]	125.2 ± 1.7	72
Dispiro[2.0.2.2]octane		183.8 ± 0.6 (lq)	212.1 ± 0.9	72
Dispiro[2.1.2.1]octane		187.4 ± 0.9 (lq)	219.6 ± 1.3	72
[4]Rotane (tetraspiro[2.0.2.0.2.0.2.0] dodecane)		371.2 ± 2.3 (s)	446.1 ± 2.4	72
Bicyclo[2.1.0]pentane			158	24
Bicyclo[2.2.0]hexane			125	24
Bicyclo[2.2.0]hex-2-ene			261.2	24
Bicyclo[3.2.0]heptane			3	74
Bicyclo[4.2.0]octane		−68.1 ± 2.5 (lq)	−26.2 ± 2.7	1
Tricyclo[4.2.0.$0^{2,5}$]octane		*syn*: 193. ± 4. (lq)	*syn*: 235. ± 4.2	76

(*continued overleaf*)

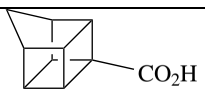
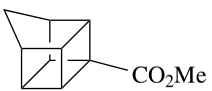
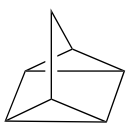
TABLE 2 (*continued*)

Compound	Structure	$\Delta_f H_m^0$ (lq or s)	$\Delta_f H_m^0$ (gas)	Reference
		anti: 169. ± 3. (lq)	*anti*: 211. ± 3.	
1,1′-Bis(bicyclo[1.1.1]pentyl)		347.0 ± 5.2 (s)	405.0 ± 5.2	77
2-Phenylbicyclo[1.1.1]pentane-2-ol		48.7 ± 3.0 (s)	135.8 ± 3.2	78
α-Pinene		−16.4 ± 2.1 (lq)	28.3 ± 2.5	1
β-Pinene		−7.7 ± 3.0 (lq)	38.7 ± 2.5	1

Cubane		541.8 ± 4.0 (s)	622.1 ± 4.2	81 [b]
Cubane-1,4-dicarboxylic acid		−318.5 ± 12.6 (s)		85
Dimethyl cubane-1,4-dicarboxylate		−231.2 ± 2.5 (s)		85
		−219.2 ± 2.1 (s)		82
Bis(isopropyl) cubane-1,4-dicarboxylate		−382.0 ± 2.1 (s)		85
Bis(2,2-difluoro-2-nitroethyl) cubane-1,4-dicarboxylate		−747.8 ± 6.3 (s)		85

(*continued overleaf*)

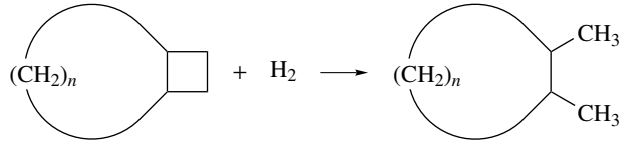
TABLE 2 (*continued*)

Compound	Structure	$\Delta_f H_m^0$ (lq or s)	$\Delta_f H_m^0$ (gas)	Reference
Homocubane-4-carboxylic acid		−79.4 (s)	3	88
		−77 (lq)		
Methyl homocubane-4-carboxylate		−54.0 ± 5.0 (lq)	26 ± 5.4	88
Quadricyclane (homotriprismane)		302.1 ± 2.3 (lq)	339.1 ± 2.4	1
			329.7 ± 5.0	94

[a] The liquid phase enthalpy of formation is incorrectly transcribed in the original publication.
[b] See discussion in text.

B. Bicyclo[*n*.2.0]alkanes and Related Tricyclo Species

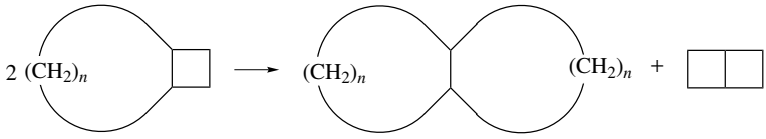
A simple thermochemical comparison for the bicyclo[*n*.2.0]alkanes is the difference between the enthalpies of formation of a given bicyclo[*n*.2.0]alkane and its formal hydrogenolysis product, the 1,2-dimethylcycloalkane, as in equation 34 where the bicycloalkane and the dimethylcycloalkanes are all of *cis* stereochemistry. However, some important thermochemical data are lacking for the analysis, principally the gas phase enthalpy of formation of 1,2-dimethylcyclopropane and any enthalpy of formation of 1,2-dimethylcyclobutane. The gas phase enthalpy of formation of the first substance is easily derived from the enthalpy of vaporization estimated from equation 1, which accurately predicts the experimental enthalpies of vaporization of 1,2-dimethylcyclopentane and 1,2-dimethylcyclohexane. In an earlier section we derived the gas phase enthalpy of formation of *cis*-1,2-dimethylcyclobutane (-24.7 kJ mol^{-1}). From these quantities, the enthalpies of reaction 34 are -157 ($n = 1$), -150 ($n = 2$), -133 ($n = 3$) and -146 kJ mol^{-1} ($n = 4$).



(34)

If it were not for the result for bicyclo[3.2.0]heptane, which looks surprisingly small compared to that for bicyclo[4.2.0]octane, it would appear that the reaction enthalpies decrease as the ring strain decreases, as expected.

Alternatively, we may compare bicyclic species with the same and different ring sizes as shown in reaction 35, where all the ring fusions are *cis*.



(35)

For $n = 1$, 2, 3 and 4, the reaction enthalpies are $+25$, 0, -26 and -8 kJ mol^{-1}. Once again, it is surprising that the $n = 3$ case is so different from $n = 4$. That the enthalpy of formation of the $n = 3$ species, bicyclo[3.2.0]heptane, reappears as problematic makes us somewhat suspicious of the value. There are numerous hydrogenation enthalpies for a plethora of olefins containing the bicyclo[3.2.0]heptane framework[24], but no enthalpy of combustion for any of these species that would allow us to derive the enthalpy of formation of the saturated species independent of computations[73]. However, interpolating the enthalpies of reaction 34 or 35 for the $n = 3$ case, we can derive the enthalpy of formation of bicyclo[3.2.0]heptane as $+18.5$ kJ mol^{-1} or $+18.0$ kJ mol^{-1}.

Related to the bicyclic compounds are tricyclo[3.2.0.0^{2,4}]heptane and tricyclo[4.2.0.0^{2,5}]-octane. Here, too, the ring fusions are *cis*, but the outer rings can be on the same or opposite sides of the center cyclobutane ring, that is, the species is either the '*syn*' or '*anti*' isomer. For neither isomer are there direct experimental measurements resulting in the enthalpy of formation of the tricycloheptane.

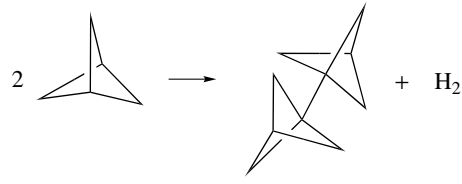
The enthalpies of hydrogenation[74] of the tricyclo[3.2.0.0^{2,4}]heptanes are -268 kJ mol^{-1} for the *syn*-isomer and -233 kJ mol^{-1} for the *anti*. Hydrogenation produces bicyclo[3.2.0]-heptane and therefore provides another reason to wish for the enthalpy of formation of this nominally simple hydrocarbon. The difference of *ca* 30 kJ mol^{-1} between the two isomers indicates a significant difference in stability between the two. The hydrogenation

enthalpy of -235 kJ mol^{-1} for converting bicyclo[2.1.0]pentane to cyclopentane[75] is very nearly the same as for the tricyclo *anti*-isomer, suggesting that it is the 'normal' isomer.

From a study that combined calorimetry and kinetics, the enthalpies of formation of *syn* and *anti*-tricyclo[4.2.0.0^{2,5}]octane are $+235 \pm 4$ and $+211 \pm 3$ kJ mol^{-1}, respectively[76]. Very much the same isomer enthalpy of formation difference is seen here for the tricyclooctanes as for the tricycloheptanes. However, neither isomer is 'normal' in resembling the enthalpy of hydrogenation of bicyclo[2.2.0]hexane to form the corresponding cyclohexane, -248 kJ mol^{-1}. More precisely, from the isomeric tricyclooctane enthalpies of formation and that of bicyclo[4.2.0]octane, we derive the hydrogenation enthalpies of -237 and -261 kJ mol^{-1}, values rather widely straddling the hydrogenation enthalpy of the bicyclic analog.

C. Bicyclo[*n*.1.1]alkanes

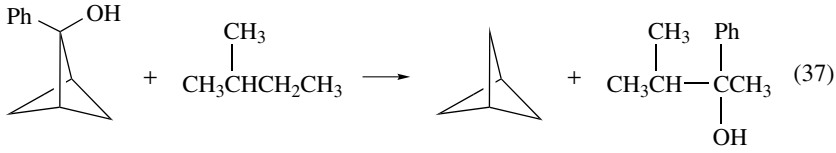
The first member of this series is bicyclo[1.1.1]pentane. Its enthalpy of formation has seemingly not been measured. Let us estimate this quantity from the 'formal dimerization' reaction 36 of bicyclo[1.1.1]pentane to its 'dimer', 1,1′-bis(bicyclo[1.1.1]pentyl)[77]. The dimerization reaction enthalpy might be approximated from analogous reactions of simpler hydrocarbons. For example, a reaction enthalpy of $+23$ kJ mol^{-1} is found for the gas phase 'dimerization' reaction (of secondary carbons) of the strained cyclopropane to form bicyclopropyl. Similarly calculated are reaction enthalpies of $+31$ kJ mol^{-1} for the unstrained, acyclic propane to form its dimer, 2,3-dimethylbutane, and the somewhat more endothermic, *ca* $+43$ kJ mol^{-1}, reaction of the unstrained acyclic isobutane to form 2,2,3,3-tetramethylbutane.



(36)

An enthalpy of $+33 \pm 15$ kJ mol^{-1} is plausible for reaction 36, resulting in a predicted enthalpy of formation of gaseous bicyclo[1.1.1]pentane of $+186 \pm 15$ kJ mol^{-1}.

Alternatively, we may make use of the functionalized derivative, 2-phenylbicyclo[1.1.1]-pentane-2-ol. In the same study[78] the enthalpy of formation of 3-methyl-2-phenyl-2-butanol was also reported, -278.7 ± 3.5 and -211.3 ± 3.5 kJ mol^{-1} for the liquid and gas, respectively. From the formal reaction 37, assumed to be thermoneutral, the gas phase enthalpy of formation of bicyclo[1.1.1]pentane may be deduced to be $+193$ kJ mol^{-1}, in agreement with the former result.



(37)

While there are no enthalpy of formation measurements for the next higher homolog, bicyclo[2.1.1]hexane, there is a calculated value[24] of $+80$ kJ mol^{-1}. There is also a hydrogenation enthalpy for the corresponding olefin[24], -171 kJ mol^{-1}. Were there a corresponding clean hydrogenation enthalpy for the related tricyclic benzvalene, one could

derive the enthalpy of formation of both bicyclo[2.1.1] species because the enthalpy of formation of benzvalene is derivable from literature reaction calorimetry results of its rearrangement to form benzene[79].

There are no thermochemical data for the next homolog, bicyclo[3.1.1]heptane, or any larger or multiple ring systems. However, we recognize trimethylbicyclo[3.1.1]heptene as α-pinene and its exocyclic methylene analog as β-pinene. The 10 kJ mol^{-1} enthalpy of formation difference between these isomers is somewhat small compared to the monocyclic counterparts, 1-methylcyclohexene/methylenecyclohexane, with their *ca* 18–20 kJ mol^{-1} difference. The liquid phase enthalpy of formation[80] of the saturated pinane (with no stereochemical (*exo/endo*) descriptors for the methyl group orientations) is -147 kJ mol^{-1}. The difference between the enthalpies of formation of the liquid α-pinene and pinane is 131 kJ mol^{-1}, rather much larger than the 109 kJ mol^{-1} for the monocyclic 1-methylcyclohexene and methylcyclohexane difference. However, in that we hesitate to estimate the effect of the multiple methyl substituents, much less the constraints of the bicycloheptane skeleton, we do not know how to derive a plausible enthalpy of formation for the parent bicyclo[3.1.1]heptane.

D. Cubanes and Prismanes

1. Cubane

Cubane is a highly symmetric species with but one type of C–C bond, one type of C–H bond and one type of ring. That all of the smallest rings are four-membered should add to its stability, or at least its kinetic stability, since saturated four-membered rings, despite their strain energy, are generally comparatively unreactive. These features suggest that cubane will be a relatively simple species to study and characterize, if not easy to synthesize or derivatize.

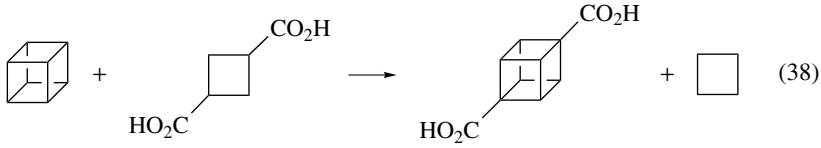
Almost forty years ago the enthalpies of combustion and sublimation were measured[81]. However, it was suggested recently that both of these measurements are problematic because of complications due to incomplete combustion[82] and solid–solid phase transitions[83], respectively. Calculations[82] suggest enthalpies of formation of +583.1 and +663.2 kJ mol^{-1} that are derived from estimated strain energies of 630.9 and 672.6 kJ mol^{-1} for the solid and gaseous cubanes. Nonetheless, in the analysis of the thermochemistry of cubane derivatives that follows in this section we will use the directly measured experimental enthalpy of formation values.

2. Cubene

Through a set of well chosen gas phase bond energies, electron affinities and gas acidity measurements and an *ab initio* calculation of the C–H bond energy, the enthalpy of the formal gas phase hydrogenation of cubene was experimentally determined[84] to be the very exothermic -377 ± 17 kJ mol^{-1}. From the enthalpy of formation of cubane, the derived enthalpy of formation of cubene is estimated to be $+999 \pm 18$ kJ mol^{-1}.

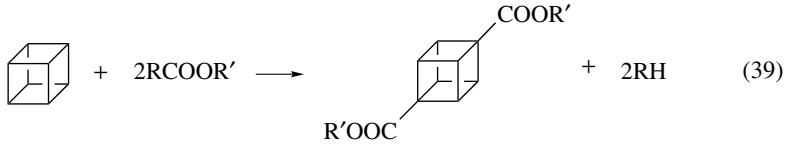
3. Cubane-1,4-dicarboxylic acid, its dimethyl ester and some other esters

There is one measured value[85] for the enthalpy of formation of cubane-1,4-dicarboxylic acid as a solid. The value is rather negative, much as that of cubane is rather positive. The comparison with cyclobutanedicarboxylic acid, reaction 38, is exothermic by -19.8 ± 14 kJ mol^{-1}, showing stabilization of the cubane, relative to cyclobutane, by the two carboxyl groups.



(38)

There is a dearth of data for solid carboxylic acid/hydrocarbon reference pairs to make comparisons with non-cyclic species, as in reaction 39 where $R' = H$. For R = 1-adamantyl and phenyl, the reaction enthalpies are endothermic by $+37.9 \pm 7.2$ and exothermic by -11 ± 6 kJ mol^{-1}, respectively. The deviation from thermoneutrality for the adamantyl substituent is larger than might be expected.



(39)

There are two reported solid phase enthalpies of formation for dimethyl cubane-1,4-dicarboxylate[82,85]. Rather than choosing between these rather disparate numbers, let us use a consensus value of -226 ± 8 kJ mol^{-1}: the large error bar for the cubane dicarboxylic acid and the aforementioned complications for the parent cubane justifies such an approach. The reference compounds for reaction 39 are the methyl esters of the carboxylic acids chosen previously, $R' = Me$ and R = 1-adamantyl and phenyl. The enthalpy of formation of solid methyl adamantane-1-carboxylate[86] is -577.8 ± 2.7 kJ mol^{-1}, and the enthalpy of formation of solid methyl benzoate is -346.2 kJ mol^{-1} (combining the liquid phase enthalpy[87], -332.3 ± 3.3 kJ mol^{-1}, and the fusion enthalpy[7], 13.9 kJ mol^{-1}). Both solid phase reaction enthalpies are almost precisely thermoneutral. While the error bars for the cubanes are admittedly large and the enthalpies of formation somewhat uncertain, it is thus plausible to suggest all of the values are roughly correct. However, the enthalpy of formation difference between the solid adamantyl acid and ester, *ca* 65 kJ mol^{-1}, seems much too large. It is likely that at least one of these enthalpies of formation is incorrect.

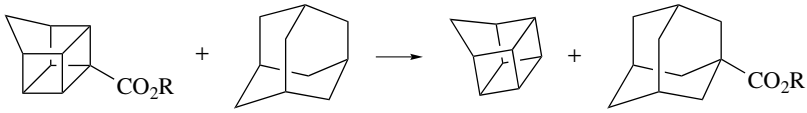
The enthalpies of formation of the solid bisisopropyl and bis (2,2-difluoro-2-nitroethyl) cubane-1,4-dicarboxylates have been reported[85]. However, we lack thermochemical data for any solid isopropyl or 2,2-difluoro-2-nitroethyl ester and so cannot evaluate these numbers other than to note that self-consistency of all of the values has been suggested based on the authors' analysis of the values[85].

4. Homocubanes

While there are no experimental thermochemical results for the parent species, homocubane, enthalpy of combustion, phase change and formation data are available for the 4-carboxylic acid and its methyl ester[88]. We admit that we are troubled by the values. The enthalpy of vaporization for the acid and ester are both 80 kJ mol^{-1}—it seems most unlikely that they would be so close. Calculations using equation 1 suggest that the enthalpies of vaporization of the acid and methyl ester should be *ca* 85 and 62 kJ mol^{-1}, respectively. The difference between the gaseous enthalpies of formation of *ca* 23 kJ mol^{-1}

is compatible with that of carboxylic acids and their methyl esters generally, although the identical difference is also found for their liquid enthalpies of formation—and that is uncharacteristically small.

Assuming thermoneutrality for equation 40 where R = H and all species are solids (there is no gaseous enthalpy of formation data for the adamantyl acid), the enthalpy of formation of solid homocubane is *ca* +370 kJ mol^{-1}. For the comparison using benzene and benzoic acid instead of the adamantyl species, the enthalpy of formation of solid homocubane is +345 kJ mol^{-1} and that of gaseous homocubane is +380 kJ mol^{-1}.



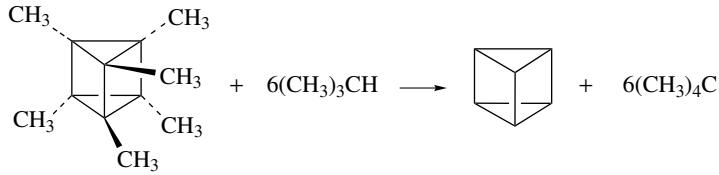
(40)

From the related reaction 40 where R = CH_3, the gas phase enthalpy of formation of homocubane is +386 kJ mol^{-1}. From these results, the sublimation enthalpy for homocubane would be between 10–41 kJ mol^{-1}. This is clearly wrong in that the enthalpy of sublimation would be smaller than the estimated enthalpy of vaporization of other C_9 hydrocarbons, *ca* 45 kJ mol^{-1}. Because we have previously questioned the accuracy of either the adamantyl acid or ester enthalpies of formation, it is difficult to discern the source of error.

5. Prismanes (triprismanes) and homoprismanes

The thermochemistry of prismanes, or more properly triprismanes, is relatively sparse. It is well-established from reaction calorimetry that hexamethylprismane is some 380 kJ mol^{-1} higher in energy than hexamethylbenzene[89] while the hexakis(trifluoromethyl)prismane is some 247 kJ mol^{-1} higher in energy than its aromatic counterpart[90]. We can derive the enthalpy of formation of the hydrocarbon species, hexamethylprismane, because we have the enthalpy of formation of hexamethylbenzene[91], but we cannot derive the enthalpy of formation of hexakis(trifluoromethyl)prismane because we lack the enthalpy of formation of hexakis(trifluoromethyl)benzene. Assuming the energy difference between the hexamethylprismane and hexamethylbenzene is independent of phase, the enthalpies of formation are *ca* +218 and +303 kJ mol^{-1} for the solid and gaseous hexamethylprismane, respectively.

What is the enthalpy of formation of prismane itself? This is unknown from experiment. G2 calculations[92] result in a value of +556 kJ mol^{-1}. Two simple formal reactions interrelating hexamethylprismane and prismane that maintain the number of tertiary and quaternary carbons on the two sides of the equation are equations 41 and 42. The reactions are endothermic by *ca* +49 or +111 kJ mol^{-1} using the above reaction calorimetry-derived value for the enthalpy of formation of hexamethylprismane and the G2-calculated enthalpy of formation of prismane.



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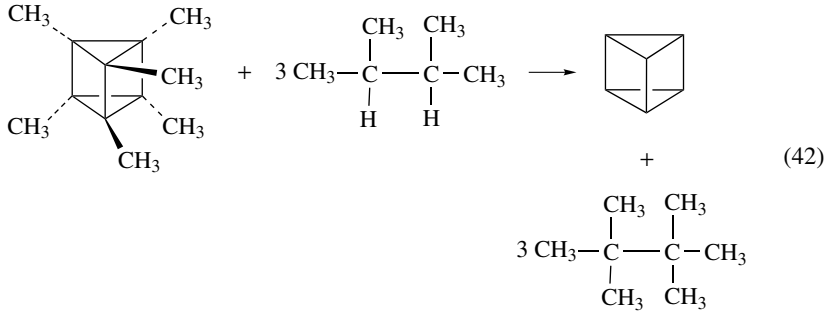
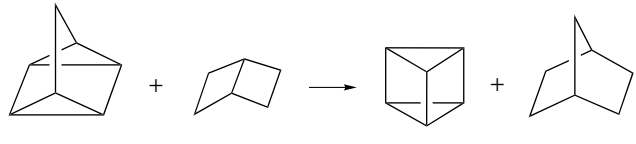


(42)

We certainly could not expect either reaction to be thermoneutral: the methylation of the central carbon in isobutane and a cyclopropane and/or cyclobutane-like carbon in prismane are rather different, we have ignored the multiple vicinal methyl–methyl interactions in hexamethylprismane, and there is scant thermochemical experience with species with multiple tertiary or quaternary carbons[93].

The unsubstituted homotriprismane, or quadricyclane, has long been known. The enthalpies of formation from a combustion measurement are $+302.1 \pm 2.3$ (lq) and $+339.1 \pm 2.4$ kJ mol^{-1} (g). An enthalpy of hydrogenation of quadricyclane to norbornane results in a gaseous enthalpy of formation of $+329.7 \pm 5.0$ kJ mol^{-1} [94]. G2 calculations result in a value of $+331$ kJ mol^{-1} [95]. The formal, plausibly thermoneutral, reaction 43 that connects prismane and quadricyclane is actually calculated to be endothermic by some 40 kJ mol^{-1} [96]. It is not clear what the source of strain is. The related reaction 44, using the various estimated and calculated enthalpies of formation in the gas phase, is nearly thermoneutral.



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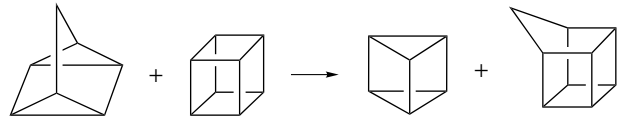


(44)

We are also disappointed because it makes us less confident in our understanding of homoprismanes and secoprismanes (bicyclo[2.2.0]hexane is a bis-seco-triprismane) in general and of quadricyclanes specifically[97].

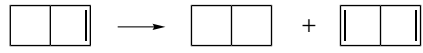
VIII. AROMATIC SPECIES AND FOUR-MEMBERED RINGS

A. Dewar Isomers

By a Dewar isomer, we mean a constitutional isomer derived from a conventional aromatic species in which two non-adjacent carbons have been saturated and joined by a covalent bond and the molecule deplanarized: we do not mean a resonance structure with a 'long-bond' connecting these non-adjacent carbons. As befitting the subject of this volume, the Dewar isomer contains a four-membered ring.

1. Dewar isomers of benzene and benzenoid hydrocarbons

Bicyclo[2.2.0]hexa-2,5-diene, also known as Dewar-benzene, is the Dewar isomer of benzene itself. Although the parent Dewar-benzene is the subject of numerous theoretical studies, there are no reported experimental thermochemical measurements for this species. Neither combustion nor rearrangement enthalpies provide a direct value for the enthalpy of formation of Dewar-benzene. However, there are measured values of the enthalpy of combustion and the rearrangement enthalpy of liquid hexamethyl-Dewar-benzene to the aromatic hexamethylbenzene. The combustion enthalpy[98] results in a liquid enthalpy of formation value of $+90.4 \pm 4.6$ kJ mol^{-1}. The rearrangement reaction enthalpies are the disparate values of -235 ± 3 kJ mol^{-1}[99] and -249 kJ mol^{-1} [100]. The consensus value is -242 ± 7 kJ mol^{-1}. Accepting the enthalpies of formation of solid and gaseous hexamethylbenzene[91] and assuming phase-independent reaction enthalpies, we derive enthalpies of formation of $+80$ and $+165$ kJ mol^{-1} for the solid and gas phase hexamethyl-Dewar-benzene. If we assume the enthalpy of rearrangement of Dewar-benzene to benzene is the same as for their hexamethylated derivatives[101], the enthalpy of formation of Dewar-benzene is predicted to be $+325 \pm 7$ kJ mol^{-1}. A different approach is to assume thermoneutrality for reaction 45 from which the enthalpy of formation of Dewar-benzene is calculated as $+39$ kJ mol^{-1}.



(45)

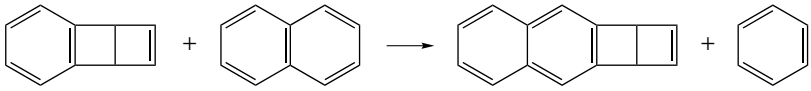
These two derived values of *ca* $+325$ and $+39$ kJ mol^{-1} are irreconcilably disparate. Then again, to assume no effect due to the six-methyl groups in the hexamethylbenzene and its Dewar isomer and to assume no cross-ring interaction between the two double bonds in the diene is at best simplistic. The latter value, however, is quite close to the enthalpy of formation of $+405$ kJ mol^{-1} obtained using G2 calculations[92].

There are two measurements of the rearrangement enthalpy of 1,4-Dewar-naphthalene to naphthalene, both in the non-polar solvent heptane[102,103]. In this case, both results are essentially the same and with comparable error bars, -249.2 ± 8.0 and -248.5 ± 8.0 kJ mol^{-1}. Applying these results to gas phase naphthalene, the enthalpy of formation of gaseous Dewar-naphthalene is derived to be $+399 \pm 8$ kJ mol^{-1}. From this and the assumption that reaction 46 is thermoneutral, an enthalpy of formation of Dewar-benzene is derived to be $+357$ kJ mol^{-1}, roughly interpolating the two values given above[104].

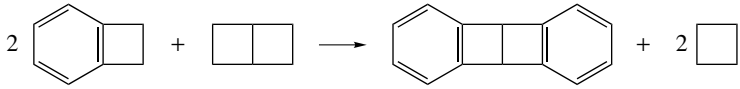
(46)

For anthracene, there are several Dewar isomers, of which the 1,4- and the 9,10- correspond to the original definition of creating a four-membered ring. For the former isomer, we find the rearrangement enthalpy[103] to anthracene of -324 ± 1 kJ mol^{-1} resulting in an enthalpy of formation of gas phase 1,4-Dewar-anthracene of $+555 \pm 2$ kJ mol^{-1}. There are two different measurements for the 9,10-isomer, or more properly for the 9-*tert*-butyl derivative thereof, one in decalin[105] and the other in the likewise non-polar hydrocarbon, hexane[106]. The two enthalpies of rearrangement are -172.3 ± 5.7 and -150 ± 8, for which a consensus value -161 ± 11 kJ mol^{-1} may be offered. Assuming that the *tert*-butyl group has no effect on the rearrangement enthalpy[107], the enthalpy of formation of 9,10-Dewar-anthracene is $+392 \pm 11$ kJ mol^{-1}. Are the enthalpies of formation for the isomeric Dewar-anthracenes plausible? It is entirely reasonable that the 9,10-isomer would be more stable than the 1,4- based on classical chemistry of anthracenes, but nevertheless, the difference between them of 163 kJ mol^{-1} seems large.

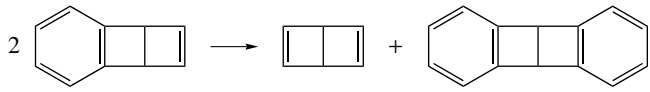
We would think that reaction 47 should be roughly thermoneutral. Using the above enthalpies of formation for 1,4-Dewar-anthracene and Dewar-naphthalene, we find the reaction is endothermic by 89 kJ mol^{-1}. No explanation, other than an inaccurate experimental measurement, is apparent.


(47)

We would likewise think that reaction 48 involving 9,10-Dewar-anthracene should be roughly thermoneutral.


(48)

So doing results in a predicted enthalpy of formation of 9,10-Dewar-anthracene of +457 kJ mol^{-1}. To ascribe to the *tert*-butyl group the 65 kJ mol^{-1} discrepancy between this value and the one derived earlier from the rearrangement enthalpy seems extreme. Can we corroborate either value for 9,10-Dewar-anthracene? Reaction 49 should also be roughly thermoneutral.


(49)

The derived enthalpy of formation is +405 kJ mol^{-1} using the G2-calculated enthalpy of formation of Dewar-benzene. This result is somewhat higher than the previously derived value of +392 ± 11 kJ mol^{-1}.

2. Dewar derivatives of other aromatic compounds

The first example is hexafluorobenzene and its Dewar isomer. The enthalpy difference has been measured by DSC in the liquid phase as 213 ± 13 kJ mol^{-1} [108,109]. Assuming phase independence of the result, the liquid and gas phase enthalpies of formation of hexafluoro-Dewar-benzene are −778 ± 13 and −742 ± 13 kJ mol^{-1}.

The second example is hexakis(trifluoromethyl)benzene and its Dewar isomer. As measured by DSC, their enthalpy of formation difference is 117.2 ± 5.9 kJ mol^{-1} [110]. The value is *ca* 125 kJ mol^{-1} less than the hexamethylbenzene/hexamethyl-Dewar-benzene enthalpy of formation difference of 242 kJ mol^{-1}. Perfluoromethylation has thermodynamically stabilized the strained species and/or destabilized the unstrained benzenoid form. A similar effect is seen for the substituted prismanes: the enthalpy of formation difference for hexakis(trifluoromethyl)prismane and hexakis(trifluoromethyl)-Dewar-benzene is *ca* 133 kJ mol^{-1} lower than the enthalpy of formation difference between hexamethylprismane and hexamethyl-Dewar-benzene.

Both strained species, the perfluoroalkylated prismane and perfluoroalkylated Dewar-benzene, have higher free-energy barriers to rearrangement to the aromatic isomer than their corresponding unfluorinated, merely methylated counterparts and so are kinetically stabilized. The enthalpy of activation barrier interconverting the prismane into the Dewar isomer of hexakis(trifluoromethyl)benzene is higher than its hydrocarbon counterpart, while the barrier interconverting the perfluoroalkylated Dewar isomer into its aromatic

counterpart is essentially unchanged from its hydrocarbon counterpart[110]. Both the thermodynamic and kinetic stabilization arising from the CF_3 and other perfluoroalkyl groups is quite general and this phenomenon has been labeled 'the perfluoroalkyl effect'.

Not discussing these fluorinated species because of lack of enthalpy of formation data also absolves us from a lengthy discussion of the relative stability of [*n*]paracyclophanes and their Dewar counterparts, the [*n*.2.2]propelladienes. As *n* becomes smaller and the benzene ring becomes increasingly non-planar, we may expect the Dewar counterpart to gain stability. This was quantitatively shown[103] for dicarboethoxycyclophanes, and more qualitatively (and long known) for the parent hydrocarbons[111]. We note that there are no [*n*]-paracyclophanes for which there are enthalpy of formation data: only for [*n*,*n'*]-paracyclophanes are there such data.

3. Dewar derivatives of non-benzenoid compounds

Most known Dewar isomers of the non-benzenoid aromatic compounds furan, pyrrole and thiophene are per(trifluoromethylated) but there are no thermochemical data for any of them. There are surprisingly few enthalpy of formation data available for any, even singly, substituted derivatives of the corresponding aromatic heterocycles and no data at all on any of their Dewar counterparts.

For the parent hydrocarbon cyclooctatetraene, the Dewar isomer of relevance is bicyclo-[4.2.0]octa-2,4,7-triene. The thermochemistry of the direct interconversion of these isomers has been measured[112] as 23 ± 3 kJ mol^{-1}. From this, an enthalpy of formation of the triene is $+319$ kJ mol^{-1}. Admittedly, this last species is not a Dewar isomer because cyclooctatetraene is not a conventional aromatic species. However, to the extent that benzene and cyclooctatetraene are recognizable as the related [6]- and [8]-annulene respectively, Dewar-benzene and this triene are likewise related. That the triene is energetically so much closer to cyclooctatetraene than Dewar-benzene is to benzene is due to both the relative stability of the new six- and four-membered rings found in the bicyclic species and to the lack of aromatic stabilization in the cyclooctatetraene.

B. Aromaticity and Antiaromaticity of Four-membered Ring Carbocycles

1. Cyclobutadiene and its benzoannelated derivatives

Cyclobutadiene with its 4π electrons is the archetype of antiaromatic species much as benzene with its 6 π electrons is the archetype for aromatic species[113]. Cyclobutadiene is too reactive to 'hang around' for classical combustion reaction calorimetric methods. From photoacoustic calorimetry and a set of semiempirically derived values for the enthalpy of formation of a variety of polycyclic precursors, a value of $+477 \pm 46$ kJ mol^{-1} was suggested for the enthalpy of formation of cyclobutadiene[114]. Using a collection of measurement techniques more commonly used by gas phase ion chemists, a value of $+406 \pm 17$ kJ mol^{-1} was determined[115] for the enthalpy of formation of the likewise ephemeral benzocyclobutadiene. The authors of this latter study suggested a value of $+427$ kJ mol^{-1} for the enthalpy of formation of cyclobutadiene. Although the two values are significantly disparate, both are included with the enthalpies of formation in Table 3. Rather than decide between them, we will use a consensus value of $+452 \pm 25$ kJ mol^{-1}.

The formal enthalpy of hydrogenation of gaseous cyclobutene (equation 11) of -128.3 kJ mol^{-1} is somewhat larger (by *ca* 10–15 kJ mol^{-1}) than the typical hydrogenation enthalpy of *cis*-alkenes or of cyclohexene, and the difference is attributed to ring strain. The formal enthalpy of hydrogenation of cyclobutadiene to cyclobutene is calculated to be *ca* -295 kJ mol^{-1}, a testament to the huge destabilization due to antiaromaticity. Only a portion of this could be assigned to ring strain in the cyclic diene[114]. In comparison,

TABLE 3. Structures and enthalpies of formation of aromatic and antiaromatic carbocycles with four-membered rings (kJ mol^{-1})

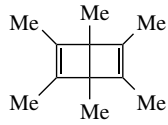
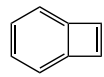
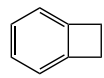
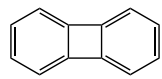
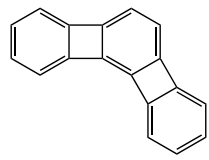
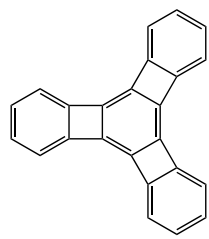
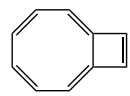
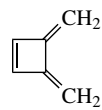
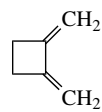
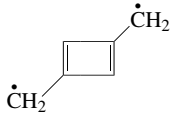
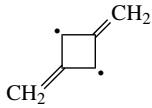
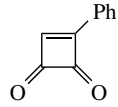
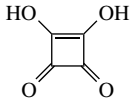
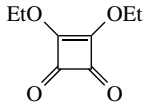
Compound	Structure	$\Delta_f H_m^0$ (lq or s)	$\Delta_f H_m^0$ (gas)	Reference
Hexamethyl-bicyclo-2,5-hexadiene (hexamethyl-Dewar-benzene)		90.4 ± 4.6 (lq)		98
Cyclobutadiene			477 ± 46	114
			427	115
Benzocyclobutadiene			406 ± 17	115
Benzocyclobutene		155.7 ± 0.9 (lq)	199.4 ± 0.9	104
Biphenylene		334.0 ± 3.3 (s)	417.9 ± 3.3	1
Angular [3]phenylene		614.2 ± 3.8 (s)	729.3 ± 3.8	119
C_3-Symmetric [4]phenylene		914.6 ± 6.6 (s)	1045.6 ± 7.9	119
Bicyclo[6.2.0]decapentaene			514	21
3,4-Dimethylenecyclobutene			336	21
1,2-Dimethylenecyclobutane			204	21

TABLE 3 (*continued*)

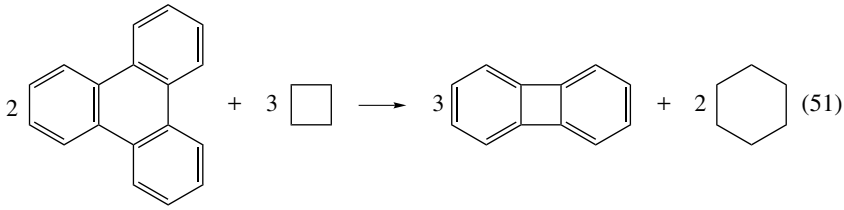
Compound	Structure	$\Delta_f H_m^0$ (lq or s)	$\Delta_f H_m^0$ (gas)	Reference
1,3-Dimethylenecyclobutene (2,4-dimethylenecyclobutene-1,3-diyl)			471	120
				
3-Phenylcyclobutendione		−84.2 ± 0.7 (s)	−29.8 ± 0.8	32,123
3,4-Dihydroxy cyclobut-3-ene-1,2-dione (squaric acid)		−598.2 ± 0.4 (s)	−514.5 ± 16.7	1
			−444	123
3,4-Diethoxycyclobut-3-ene-1,2-dione		−552.1 ± 1.4 (lq)	−478.5 ± 4.1	1

the formal enthalpy of hydrogenation of benzocyclobutadiene to benzocyclobutene is *ca* −207 kJ mol^{-1}. If the difference in ring strain between the two cyclobutanes and their effect on strain in the benzene ring are negligible, the decrease of the hydrogenation enthalpy signals a diminution of the antiaromaticity in the four-membered ring. Another indication of the antiaromaticity still inherent in the benzocyclobutadiene is the comparison of the exothermicity of −9.9 kJ mol^{-1} for equation 9 and the related reaction 50, which is *ca* 91 kJ mol^{-1} endothermic[116]. Even if the six-membered rings are not benzoannelated, the resulting enthalpy of reaction is the same, *ca* +88 kJ mol^{-1}.

 (50)

The dibenzo annelated derivative of cyclobutadiene, biphenylene, is well-known and would probably not belong in the current review had the thermochemistry of aromatic and antiaromatic species with four-membered rings not been relatively bleak. It is easy to document[113] considerable destabilization for this compound even though most of its resonance structures lack an offending cyclobutadiene central ring and X-ray analysis shows the major resonance contributor with no double bond in the cyclobutane moiety[117].

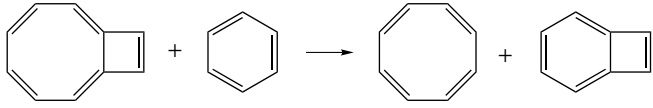
In the absence of additional strain and resonance destabilization derived from this ring, it is sensible to suggest that the enthalpy of reaction 51 of $+130$ kJ mol^{-1} per four-membered ring species may be taken as the contribution from the antiaromaticity[118].



(51)

Recently, the enthalpy of formation of some other annelated cyclobutadienes, angular [3]phenylene and C_3-symmetric [4]phenylene, have been reported[119]. Measurement of their enthalpies of hydrogenation (-279.4 ± 4.1 and -299.6 ± 6.3 kJ mol^{-1}) resulted in the conclusion that all aromaticity in the central, seemingly benzenoid, ring of the latter species is now gone.

We close with a brief note on bicyclo[6.2.0]decapentaene. Using hydrogenation calorimetry and molecular mechanics to deduce the enthalpy of formation for the related saturated bicyclodecane product, an enthalpy of formation of $+514$ kJ mol^{-1} was estimated[21]. In a formal sense, this species is related to cyclooctatetraene in the same way benzocyclobutadiene is related to benzene. The benzoannelation exchange reaction 52 is endothermic by 105 kJ mol^{-1}.



(52)

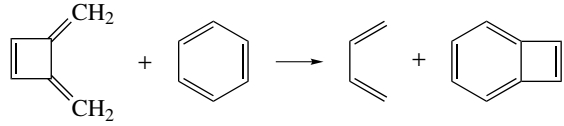
It is wishful thinking to ascribe this to the aromaticity of the pentaene, even though it is a cyclic 10 π system much as is naphthalene and azulene: the new, putative, aromatic is non-planar[21]. Rather, we assume this value is due to a small loss of aromaticity in the benzene ring and antiaromaticity in benzocyclobutadiene.

2. Methylenated species

There are two isomers of *cyclo*-$C_4H_2(CH_2)_2$, the 1,2-, more properly known as 3, 4-dimethylenecyclobut-1-ene, and, 1,3-dimethylenecyclobutadiene (also known as 2,4-dimethylenecyclobutene-1,3-diyl). The enthalpy of formation of the former has been determined by hydrogenation calorimetry and molecular mechanics to be $+336$ kJ mol^{-1} [21]. Gas phase ion chemistry methodologies, analogous to that used for the study of benzocyclobutadiene, have been used to study the energetics of the latter species: an enthalpy of formation for 1,3-dimethylenecyclobutadiene of *ca* $+471$ kJ mol^{-1} is offered in this reference 120. Indeed, both bismethylenated isomers have been suggested to be destabilized, the former by comparison with polyenes and other multiply unsaturated species[121], the latter by analysis of C$-$H bond strengths and electron affinities[120]. Regrettably, neither hydrogenation nor ion chemistry methodologies can seemingly be used for the 'other' isomer to confirm these conclusions. Hydrogenation calorimetry of the 1,3-isomer is precluded because of the excruciating reactivity and accompanying non-isolability of the hydrocarbon (cf. cyclobutadiene). By analogy to other simple polyenes, it is doubtful that the radical anion of the 1,2-isomer is stable to spontaneous loss of an electron (unlike the radical anions of benzocyclobutadiene or the stable radical anion of the 1,3-isomer), so the

necessary electron affinity measurement cannot be made that allows us to derive an independent, experimentally determined enthalpy of formation of 3,4-dimethylenecyclobut-1-ene. There are likewise no measured thermochemical data for either [4]radialene or 7,8-dimethylenebenzocyclobutadiene.

The energetics of the 3,4-dimethylenecyclobutene are similar to that of bicyclo[6.2.0]-decapentaene in that the reaction enthalpy of benzoannelation, reaction 53, corresponding to equation 52, is the comparable $+96.2\ \mathrm{kJ\,mol^{-1}}$.

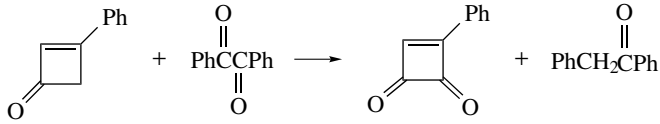


(53)

Since the enthalpy of formation of 1,2-dimethylenecyclobutane is also available from the same source, the enthalpy of formal monohydrogenation of 3,4-dimethylenecyclobutene is calculated as $-132\ \mathrm{kJ\,mol^{-1}}$, which is about the same as the $-128\ \mathrm{kJ\,mol^{-1}}$ found for hydrogenation of cyclobutene itself. However, the similarity of the two enthalpies of hydrogenation seems to indicate a lack of conjugative interaction in the 3,4-dimethylene-cyclobutene that was present in 1-methyl-3-methylenecyclobutene.

3. Cyclobutenediones

Cyclobutenediones may be also considered as cyclobutadienoquinones. By simple π-electron counting we conclude that they should be aromatic much as cyclobutadiene is deduced to be antiaromatic: they have but 2 π electrons. As with so many assertions about the energetics of molecules, this is hard to document. The first species we will discuss is phenylcyclobutenedione[32, 122]. A simple probe of its aromaticity is the energetics of the gas phase ketone/diketone interconversion reaction 54.



(54)

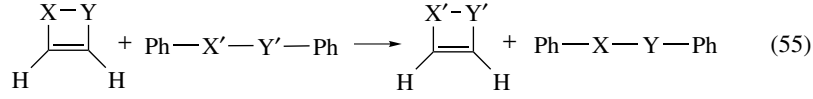
That this reaction is exothermic by $38.4\ \mathrm{kJ\,mol^{-1}}$ is suggestive of aromatic stabilization, not withstanding a contribution from the *gauche* geometry of the diketone reference, benzil, that is not possible for the four-membered ring.

3,4-Dihydroxycyclobut-3-ene-1,2-dione is more commonly known as squaric acid. While the enthalpy of formation of the solid is known to high precision, that of the gas is seemingly not. There are two measurements of the enthalpy of sublimation, the earlier one, $83.7 \pm 16.7\ \mathrm{kJ\,mol^{-1}}$, is totally disparate from a more recent one[123] of $154.3\ \mathrm{kJ\,mol^{-1}}$. Which value of sublimation enthalpy, and which enthalpy of formation, is more correct?

There are also data for the corresponding ethyl ester (ether), 3,4-diethoxycyclobut-3-ene-1,2-dione. The difference between the enthalpies of formation of phenol and its ethyl ether is but $5\ \mathrm{kJ\,mol^{-1}}$, while that between methanol (or ethanol) and its ethyl ether is larger, *ca* $17\ \mathrm{kJ\,mol^{-1}}$. Taking an average difference of $11\ \mathrm{kJ\,mol^{-1}}$ and doubling it for the two ethyl groups, suggests the value for the enthalpy of formation of squaric acid is *ca* $-500\ \mathrm{kJ\,mol^{-1}}$. The earlier value for the enthalpy of sublimation of squaric acid appears more likely.

4. The antiaromaticity of cyclobutadiene and the aromaticity of cyclobutenediones

The aromaticity of a variety of species with five-membered[124] and six-membered[125] rings was discussed within the context of an experimental realization of Dewar–Breslow logic[126], and then mathematically generalized[127]. If we wish to compare only species with four-membered rings containing a double bond, such as cyclobutadiene, cyclobutenedione, cyclobutenone and cyclobutene, a simpler approach may be offered. Let us assume that the strain energies of these four-membered ring compounds are essentially equal. In the absence of any additional stabilizing or destabilizing influences, the difference between the gas phase enthalpy of formation of these species, here denoted generically as *cyclo*-(X–CH=CH–Y), and the corresponding acyclic reference species, the diphenyl derivative PhXYPh, would be independent of the choice of X and Y. That is, equation 55 would be thermoneutral for all pairs of groups XY and X′Y′. Choosing $XY = CH_2CH_2$, the most electronically innocuous pair, as the four-membered ring reference species, any calculated exothermicity or endothermicity for equation 55 is a measure of the aromatic stabilization or antiaromatic destabilization, respectively, by any X′Y′ group within the four-membered ring.



(55)

First, let X′Y′ = CH=CH (cyclobutadiene and *trans*-stilbene). The calculated reaction enthalpy, +202 kJ mol^{-1}, may be understood as the antiaromaticity of cyclobutadiene.

We lack enthalpy of formation data for cyclobutenone and cyclobutenedione themselves, having values only for their phenylated derivatives. Let us accept as their dephenylation enthalpies the enthalpy of dephenylation of 2-phenylpropene, +93 kJ mol^{-1}. Accordingly, the enthalpies of formation of cyclobutenone and cyclobutenedione are derived to be −7 and −123 kJ mol^{-1}. The enthalpies of formation of their acyclic counterparts, deoxybenzoin and benzil, are +22.3 and −55.5 kJ mol^{-1}, respectively. The resultant stabilization energies are 43 kJ mol^{-1} for the cyclobutenone and 81 kJ mol^{-1} for the cyclobutenedione. It is perhaps surprising that the aromatic cyclobutenedione is only 38 kJ mol^{-1} more stable than the non-aromatic cyclobutenone. Perhaps the former species is destabilized by its enforced *cis*-arrangement of the adjacent carbonyl groups, while they are *gauche* in the reference α-diketone. Perhaps the latter species is stabilized by homoaromaticity. However, it is not obvious how—or even if—one should correct for these additional features. We exult in the confirmation of the definitive antiaromaticity of cyclobutadiene and the aromaticity of cyclobutenedione.

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CHAPTER 5

Acidity and basicity of cyclobutanes

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I. INTRODUCTION

'The cyclobutane class of molecules is an interesting subject to both experimentalists and computational chemists. Because [cyclobutanes] are highly strained structures, they have bond lengths and bond angles that are rather different from those in ordinary saturated hydrocarbons'[1]. These unusual geometrical features are mirrored by some interesting chemical properties. Here we focus attention on the acid–base properties of two members of this class, namely cyclobutane (CB) and cubane (pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane), (CUB), and some of their derivatives.

II. GEOMETRICAL STRUCTURES

The geometrical structures of CB and CUB have been determined experimentally and computationally. For our present purposes, geometrical structures obtained in the gas phase are preferred. Notice that gas-phase diffraction data lead to r_g values of bond lengths, that is to values averaged over the first vibrational levels. On the other hand, computational values provide equilibrium values r_e pertaining to the bottom of the potential energy well. The link between these values has been established[2,3]. Angles β_g and β_e have similar origins.

A. Cyclobutane (CB)

We summarize in Table 1 the experimental data and our own computational results[4] obtained at the MP2/6-311+G(3d,2p)[5], B3LYP/6-311+G(3d,2p)[6] and QCISD(T)/6-311+G (3d,2p)[7] levels. Also given are the values obtained with the MM4 molecular mechanics programme[1]. The experimental values are shown in Figure 1. Inspection of Table 1 shows that the agreement between experimental and computed values is rather good. For an in-depth discussion of this topic, see Reference 1. Notice that determining 'limiting r_e' values requires even higher computational levels, say TZ2P+fCCSD[2]. Our results, however, seem quite consistent with experiment. In particular, the difference between r_e and r_g for CH bonds, quite sensitive to anharmonicity effects, is close to 0.02 Å, the recommended[2] semiempirical correction. It is also clear that the computed β_e values are extremely sensitive to the computational level. This point has recently been emphasized in the case of 1,1-difluorocyclobutane and attributed to the presence of fluorine in the molecule[8]. The

TABLE 1. Experimental and computational geometrical parameters for cyclobutane (CB) [a]

Bond lengths and angles	Experimental $(r_g)^b$, $(\beta_g)^b$	B3LYP/6-311 + G(3df,2p) $(r_e)^{b,c}$, $(\beta_e)^{b,c}$	MP2/6-311 + G(3d,2p) $(r_e)^{b,c}$, $(\beta_e)^{b,c}$	QCISD(T)/6-311 + G(3d,2p) $(r_e)^{b,c}$, $(\beta_e)^{b,c}$	MM4[f] $(r_g)^b$, $(\beta_g)^b$
C−C	1.554(1) [d] (average)	1.551	1.543	1.553	1.554
C−H_{eq}	1.109(3) [d] (average)	1.090	1.094	1.092	1.109
C−H_{ax}	1.109(3) [d] (average)	1.091	1.094	1.094	
C−C−C	88.3 [e]	88.5	87.9	88.0	87.8
H−C−H	106.4(1.3) [d]	108.5	108.8	109.1	109.7
C−C−H_{eq}		117.8	118.4	118.3	116.6
C−C−H_{ax}		111.6	111.0	110.9	112.4
β [b]	27.9 (1.6) [d]	25.8	30.8	30.3	31.9
α [b]	6.2 (1.2) [d]	4.8	5.7	5.8	4.2
h [b]	0.269	0.248	0.295	0.292	0.308

[a] Distances in Å and angles in degrees.
[b] Defined in Figure 2.
[c] Computed in this work.
[d] Experimental values from Reference 12.
[e] From Reference 26.
[f] From Reference 1.

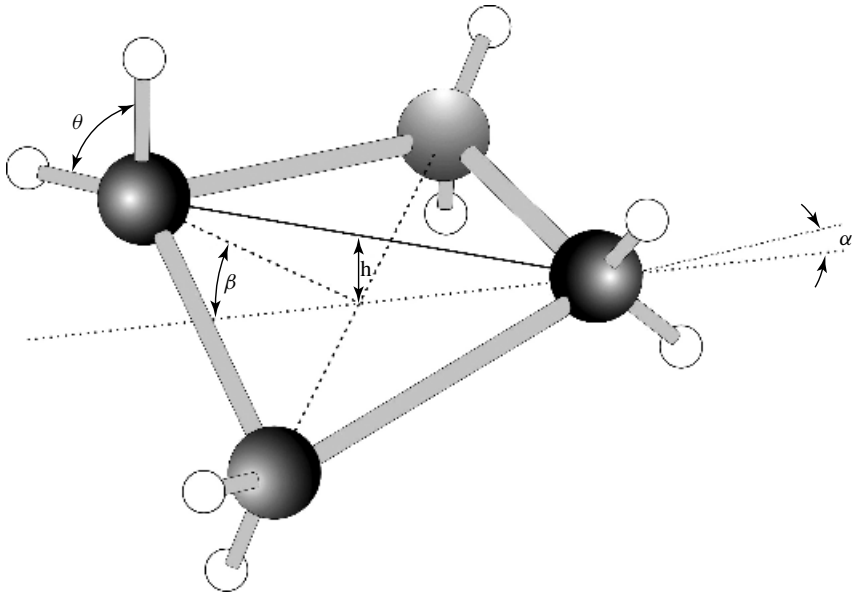


FIGURE 1. Geometric structure of CB. Values of the structural parameters are given in Table 1

present results tend to indicate that this computational shortcoming is more general and is likely a consequence of the very low energetic barrier associated to puckering.

The discovery of two distinctive features of the CB geometry, namely the ring puckering and the inward rocking of the methylene groups[9,10], is a fascinating example of the incept and interplay of the various methodologies currently (2003) available for structural analyses. Puckering minimizes torsional strain[11] but the inversion barrier is low, 1.28 kcal mol^{-1} [12]. Its existence (measured by the angle β) was originally revealed by gas-phase electron-diffraction studies[13,14] and was confirmed in solution by a classical proton NMR study in a nematic solvent[10]. It leads for CB to a D_{2d} symmetry, instead of the D_{4h} for a planar conformation. The rocking of the methylene groups (measured by the angle α)[9,10] was shown by computational techniques to be essential for the potential energy surface of CB to display a double minimum[9].

The contribution of the ring-puckering vibration to the experimental[15] entropy of CB was already examined by Pitzer and coworkers half a century ago[16]. For a recent discussion of this topic, see Reference 1.

As far as we know, the results of the most recent work on the crystal structure of CB (at 117 K)[17] are consistent with the main structural features reported above, although it is complicated by statistical disorder of bent molecules. An important, older review study of crystallographic data for cyclobutane derivatives is available[18].

B. Cubane (CUB)

The most recent experimental studies on the geometrical structure of gaseous cubane hydrocarbon[19] (Figure 2) include electron-diffraction experiments at 77 °C[20] as well as high-resolution IR spectra at 296 K[21]. As indicated in Reference 1, there is some disagreement between the C−C bond lengths obtained by both methods. We summarize in

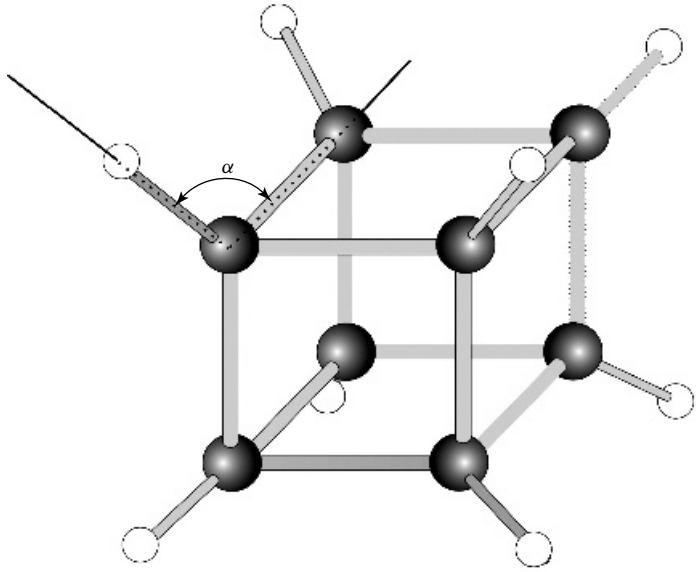


FIGURE 2. Geometric structure of CUB. Values of the structural parameters are given in Table 2

TABLE 2. Experimental and computational geometrical parameters for cubane (CUB)[a]

Bond lengths and angles	Experimental $(r_g)^b$, $(\beta_g)^b$	B3LYP/6-311+G(3d,2p) $(r_e)^{b,c}$, $(\beta_e)^{b,c}$	MP2/6-311+G(3d,2p) $(r_e)^{b,c}$, $(\beta_e)^{b,c}$	MM4[d] $(r_g)^{b,d}$, $(\beta_g)^{b,d}$
C−C	1.573(2)[e] 1.565(4)[f]	1.571	1.565	1.568
C−H	1.114(6)[e] 1.11(2) (fixed)	1.089	1.088	1.111
α		125.3	125.3	125.3

[a] Distances in Å and angles in degrees.
[b] Defined in the text.
[c] Computed in this work.
[d] From Reference 1.
[e] Experimental values from Reference 20.
[f] Far-IR r_α values from Reference 21, as corrected in Reference 1.

Table 2 this experimental information as well as the results of our own calculations at levels B3LYP/6-311+G(3d,2p) and MP2/6-311+G(3d,2p).

The quality of the agreement between experimental and computed values is comparable to that for CB.

To our knowledge, there is only one study by X-rays[22] of the geometry of solid CUB. Cubane molecules appear as slightly distorted. The C−C bond lengths determined by this technique, 1.551 ± 0.03 Å (average value), are significantly shorter than those obtained for isolated molecules in the gas phase (see Table 2). Recently, quantum-mechanical calculations were performed on solid CUB[23]. They reproduce the slight distortion of the

hydrocarbon framework and indicate that the deformation of the cubic structure and the shrinkage of C−C and C−H bonds in the solid state relative to the isolated molecule originates in crystal-field effects of the rhombohedral Bravais lattice.

III. SOME CONSEQUENCES OF THE GEOMETRICAL STRUCTURES

1. As indicated initially and shown in the previous section, these species have somewhat 'abnormal' bond lengths and bond angles. These features are more obvious in the case of CUB, because of the rigidity of the molecular framework. In particular, C−C bond lengths are longer than those found in, e.g., *n*-butane (in the *gauche* conformation). For example, the average C−C bond length for *n*-alkanes in the solid state as determined by X-ray is 1.521(1) Å[24]. The average C−C bond length in gaseous *n*-butane, as determined in the gas phase by electron diffraction, amounts to 1.533(3) Å[25].

It is interesting that these molecules are characterized by the existence of 'bent bonds' [27,28]. That is, in some of them, the path of maximum charge density between the bonded atoms is not colinear with the internuclear line[9]. This fundamental property of the electronic structure can be observed *experimentally* through X-ray studies (using difference Fourier synthesis). In the particular case of CB[17], the maxima of the electron density are located 0.10 Å[29] to the outside of the C−C bonds. Similar results have been obtained in the cases of CUB derivatives, notably dimethyl cubane-1,4-dicarboxylate[30] and, more recently, methyl 3,4-difluorocubane-1-carboxylate (Figure 3)[31]. For the latter, the maxima of electron density are obviously dependent on the position of the C−C bond, the average distance of the maxima to the centers of the corresponding C−C bonds being 0.14 Å. Notice that these values, while substantial, are still smaller than those found in cyclopropane (0.20 Å) and, even more so, in the tetrahedral moiety of tetra *(tert*-butyl) tetrahedrane (0.30 Å)[32].

Since this chapter is essentially experimentally-oriented, we simply mention here that quantum-mechanical calculations of electron densities and the Laplacians thereof lead to results nicely consistent with experiment[33,34]. Figure 4 is a computationally generated diagram of electron density around a face of cubane hydrocarbon, determined in this work at the B3LYB/6-311+G(d,p) level, and it shows indeed that charge density is concentrated slightly outside the internuclear line.

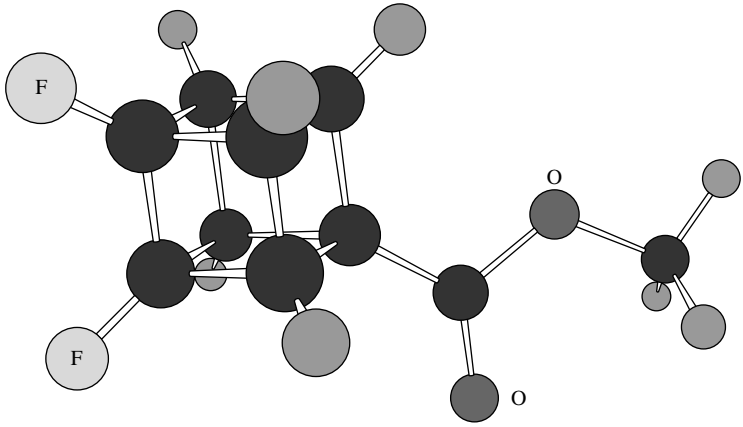


FIGURE 3. Structure of methyl 3,4-difluorocubane-1-carboxylate

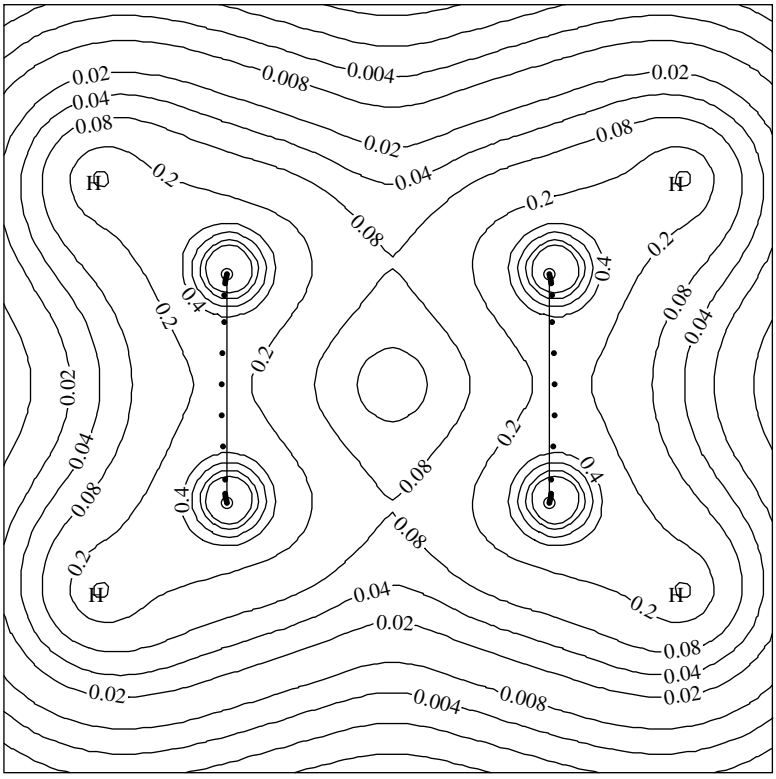


FIGURE 4. Computed (B3LYP/6-311+G(d,p) level) electron density (in atomic units) diagram for cubane. The plane bisects the cube. Straight lines are the shortest internuclear C−C distances. Dotted curves are electronic bond paths

2. These species are *strained*. CB is a nice example of the coexistence of classical Baeyer strain[35], Pitzer (torsional) strain[15,36] and, obviously, the 1,3 interactions (Dunitz–Schomaker strain)[13] which play, as indicated above, a great structural role. Other electronic effects further contribute to enhance or reduce this strain[37].

In what follows, we use the simple bond-dissociation scheme detailed below for the quantitative estimate of the strain in the species considered herein. Obviously, there are other possibilities. However, we agree[38] with Wiberg's concept[39] regarding the choice of a specific model, '*... this is of little consequence, since they are used in a comparative fashion and any reasonable and consistent definition is satisfactory*'. Notice that here we follow a procedure already used in important previous studies of strain in molecules and ions[40].

Let us consider cyclopropane (*c*-C_3H_6), CB and CUB, for which the standard enthalpies of formation in the gas phase amount to respectively 12.7 ± 0.1[41], 6.6 ± 0.3[41] and 148.7 ± 1.0 kcal mol^{-1}[42]. (The ancillary compounds, C_2H_6(g) and C_3H_8(g), for which $\Delta_f H^\circ_m$(g) values equal -20.04 ± 0.07 and -25.02 ± 0.12 kcal mol^{-1}[41], are considered by Burkert and Allinger[43] as suitable reference species for studies of strain.) We may construct equations 1–3 to determine their standard enthalpy changes in the gas phase, $\Delta_r H^\circ_m$(g),

TABLE 3. Standard enthalpy changes[a], in kcal mol^{-1}, for equations 1, 2 and 3

Reaction (n)	$\Delta_r H_m^\circ(n, g)$
1	-27.6 ± 0.4
2	-26.5 ± 0.6
3	-148.2 ± 1.2

[a] Defined in the text.

and take these values as quantitative estimates of strain.

$$c\text{-}C_3H_6(g) + 3C_2H_6(g) \longrightarrow 3C_3H_8(g) \qquad \Delta_r H_m^\circ(1, g) \qquad (1)$$

$$CB(g) + 4C_2H_6(g) \longrightarrow 4C_3H_8(g) \qquad \Delta_r H_m^\circ(2, g) \qquad (2)$$

$$CUB(g) + 20C_2H_6(g) \longrightarrow 16C_3H_8(g) \qquad \Delta_r H_m^\circ(3, g) \qquad (3)$$

These $\Delta_r H_m^\circ(g)$ values are presented in Table 3.

Notice that the standard enthalpy of formation of CUB presently available is most likely in error[44]. The size of $\Delta_r H_m^\circ(3,g)$ is so large, however, that this is not likely to affect the basis of the reasoning given below.

It is clear that there is a link between the $\Delta_r H_m^\circ(n, g)$ values and the geometrical structures discussed above. Attention has already been drawn to the fact that $\Delta_r H_m^\circ(1, g) \approx \Delta_r H_m^\circ(2, g)$. This remarkable feature[40d] has deep conceptual implications regarding the σ-aromaticity of cyclopropane and the σ-antiaromaticity of cyclobutane and cubane[45a]. It is interesting that perfluorination *increases* the strain energy of cyclopropane and *reduces* that of cyclobutane. These effects have been rationalized on the basis of a decrease in the σ-aromaticity of cyclopropane and an increase in the σ-antiaromaticity of CB[46]. Two main conclusions regarding reactivity can be drawn from the above:

1. C−C bonds are likely to be centers of at least the initial step of electrophilic attacks on CB and CUB.
2. The release of strain, particularly in the case of CUB, is a powerful driving force in a number of reactions.

In what follows we consider the interaction of CB and CUB with neutral and charged substituents as well as with positive and negative charges directly borne by the hydrocarbon frameworks.

IV. SELECTED REACTIONS

A. Stabilization of Negative Charges. Acidities of CB and CUB

1. Definitions, energetic and structural results in the gas phase and in solution

Consider a hydrocarbon, R-H. Its acidity in the gas phase[47] and in solution can be measured through the standard enthalpy or Gibbs energy changes for the ionization processes 4 and 4a:

$$R\text{-}H(g) \longrightarrow R^-(g) + H^+(g) \qquad \Delta_r H_m^\circ(4), \Delta_r G_m^\circ(4) \qquad (4)$$

$$R\text{-}H(soln) \longrightarrow R^-(soln) + H^+(soln) \qquad \Delta_r H_m^\circ(4a), \Delta_r G_m^\circ(4a) \qquad (4a)$$

2. In the gas phase

$\Delta_r H^\circ_m(4)$ is known as the proton affinity of $R^-(g)$, $PA(R^-)$, while $\Delta_r G^\circ_m(4)$ is the corresponding gas-phase acidity of RH(g), $\Delta G^\circ_{acid}(RH)$, or, alternatively, the gas-phase basicity of R^-, $GB(R^-)$.

Aliphatic and alicyclic hydrocarbons are extremely weak acids. Furthermore, a number of carbanions are unstable with respect to the autodetachment process (equation 5)[48]. This implies that the electron affinities (EA) of the corresponding radicals, $EA(R^\bullet)$, defined as $EA(R^\bullet) = \Delta_r H^\circ_m(5)$, are negative.

$$R^-(g) \longrightarrow R^\bullet + e^- \tag{5}$$

While this is not the case for methyl and phenyl anions[48,49], it is so for a variety of aliphatic and alicyclic carbanions. As strongly emphasized by Schleyer and coworkers[50], negative EA values are associated with short lifetimes as isolated species in the gas phase. However, as indicated below, the thermodynamic stability of many of them can be determined experimentally. It is important that the Hessian for a number of anions, including all those reported in Table 4, as obtained from calculations at the HF/6-31+G(d) level, indicate that the structures obtained at this level are true minima on the corresponding potential energy surfaces (PES)[49]. Furthermore, the corresponding PA values, computed at the MP2/6-31G//HF/6-31+G(d) level, are rather close to the experimental values[49]. More recently, Sauers[51] has carried out a thorough study at the R(U)B3LYP/6-311++G(2d,p) level on 28 hydrocarbons (including CB, CUB and all other molecules relevant to this study) as well as on the carbanions and radicals derived therefrom. It is important that, irrespective of the sign of the electron affinity, all of them appear as minima on their corresponding PES.

Extensively used methods for the experimental study of properties of carbanions in the gas phase, including the determination of their PA values, are as follows:

1. Activated unimolecular dissociation (through collision with an inert gas such as argon) of organic carboxylate ions[52,53], alkoxide ions[53] and ketone enolates[53] (equations 6, 7 and 8, respectively),

$$R\text{-}CO_2^-(g) \longrightarrow CO_2(g) + R^-(g) \tag{6}$$

$$R\text{-}CH_2O^-(g) \longrightarrow [R^- \ldots CH_2O](g) \begin{cases} \longrightarrow R^-(g) + H_2CO(g) \\ \longrightarrow HCO^-(g) + RH(g) \end{cases} \tag{7}$$

$$R\text{-}C(O)CH_2^-(g) \longrightarrow [R^- \ldots H_2C{=}C{=}O] \begin{cases} \longrightarrow R^-(g) + H_2C{=}C{=}O(g) \\ \longrightarrow HC_2O^-(g) + RH(g) \end{cases} \tag{8}$$

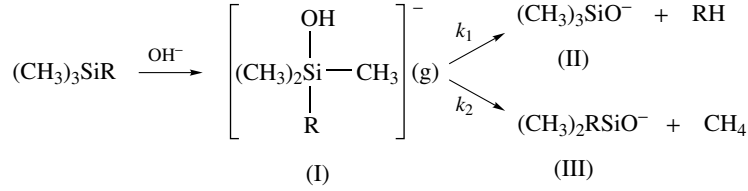
These processes provide reasonably consistent PA values for anions with positive EAs. An important mechanistic study of the unimolecular decomposition of alkoxide anions by infrared multiple photon (IRM) photochemical activation is available[48].

TABLE 4. Thermodynamic stabilities of selected carbanions in the gas phase [a]

Hydrocarbon	Anion	PA(G2) [b,c]	$\Delta_r G^\circ_{(acid)}$(G2) [b,c]	PA(exp) [b,c]	$\Delta_r G^\circ_{(acid)}$(exp) [b,c]
Methane	CH_3^-	418.4	410.1	416.7 ± 0.7 [d]	408.60 ± 0.08 [d]
				418.0 ± 3.5 [e]	409.9 ± 3.6 [e]
Ethane	$C_2H_5^-$	420.6	411.9	420.1 ± 2.0 [f]	411.7 ± 2.1 [f]
				421.0 ± 2.0 [g]	
				(420.6 ± 2.8) [h]	
Propane	n-$C_3H_7^-$	416.5	408.5	415.6 ± 2.0 [f]	407.2 ± 2.1 [f]
				(415.6 ± 2.0) [h]	
Isobutane	t-$C_4H_9^-$			412.9 ± 2.0 [g]	404.3 ± 2.1 [f]
				414.7 ± 2.4 [i]	
				(413.8 ± 3.1) [h]	
neo-Pentane	*neo*-$C_5H_{11}^-$	412.7	403.6	408.9 ± 2.0 [f]	400.1 ± 2.0 [f]
				411 ± 10 [e]	
c-Propane	*c*-$C_3H_5^-$	413.4	404.6	411 ± 7 [j]	401 ± 10 [j]
				410.7 ± 1.6 [k]	
				411.5 ± 2.0 [f]	
				412.0 ± 2.0 [g]	
				416.9 ± 4.9 [e]	
				(412.8 ± 2.8) [h]	
c-Butane (eq-H)	*c*-$C_4H_7^-$	414.7(eq-H)	406.4(eq-H)	417.4 ± 2.0 [f]	408.4 ± 2.1 [f]
				419.9 ± 2.4 [i]	
c-Butane (ax-H)		416.9(ax-H)	408.3(ax-H)	(418.7 ± 3.1) [h]	
c-Pentane (ax-H)	*c*-$C_5H_9^-$	413.4	406.1	416.1 ± 2.0 [f]	407.4 ± 2.1 [f]
(eq-H)		411.8	406.2	418.3 ± 2.4 [i]	
				(417.2 ± 3.1) [h]	
c-Hexane (eq-H)	*c*-$C_6H_{11}^-$	413.6	403.7	418.3 ± 2.4 [i]	
(ax-H)		415.9	405.8	404.0 ± 0.9 [l]	>398 [l]
c-Heptane	*c*-$C_7H_{13}^-$			415.6 [i]	
Cubane	$C_8H_7^-$	407.1	398.1	404.3 ± 3.1 [m]	396.5 ± 3.0 [m]
Ethylene	$C_2H_3^-$	408.5		409.40 ± 0.60 [n]	400.10 ± 0.50 [n]
				407.5 ± 2.0 [f]	
				407.0 ± 3.0 [e]	
				(408.0 ± 2.6) [h]	
Acetylene	C_2H^-	377.5	369.5	377.9 ± 0.70 [n]	369.70 ± 0.80 [n]
				378.0 ± 0.70 [o]	369.80 ± 0.60 [o]
				378.0 ± 0.50 [p]	369.80 ± 0.60 [p]
				379.8 ± 0.50 [q]	370 ± 6 [j]
				(378.4 ± 0.7) [h]	
				379 ± 5 [j]	
Benzene	$C_6H_5^-$	400.1	391.2	401.70 ± 0.50 [r]	392.90 ± 0.40 [r]
				401.80 ± 0.50 [s]	
				400.7 ± 2.5 [q]	390.9 ± 2.0 [q]
				(401.4 ± 1.8) [h]	

[a] All values in kcal mol^{-1}.
[b] Defined in the text.
[c] This work.
[d] From Reference 58.
[e] From Reference 53.
[f] From Reference 54.
[g] From Reference 59.
[h] Average of the experimental values taken from Reference 47.
[i] From Reference 55.
[j] From Reference 47.
[k] From Reference 60.
[l] From Reference 61.
[m] From Reference 56.
[n] From Reference 62.
[o] From Reference 63.
[p] From Reference 64.
[q] From Reference 65.
[r] From Reference 66.
[s] From Reference 67.

2. Reaction 9, namely the reaction between the relevant alkyltrimethylsilane, $(CH_3)_3Si\text{-}R$, and hydroxide ion[54,55].



(9)

The mechanism currently accepted for this reaction, as initially set forth by DePuy and coworkers[54], involves the formation of the pentacoordinate siliconate ion (I), followed by its decomposition to yield the ion–dipole complexes (II) and (III), respectively involving alkyl (R^-) or methyl (CH_3^-) anions. These complexes should readily decompose through internal proton transfer to yield either the hydrocarbon R-H or methane. According to experimental evidence, the statistically corrected relative rates of formation of ions $(CH_3)_3SiO^-$ and $(CH_3)_2RSiO^-$ and the gas-phase acidities of RH and CH_4 are related through equation 10:

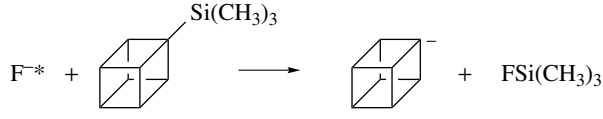
$$\ln(k_1/k_2) = -\beta[\mathrm{PA}(R^-) - \mathrm{PA}(CH_3^-)] \tag{10}$$

The scaling factor β is determined by using as anchoring values the PAs for methyl and phenyl anions for which independent, accurate PA values are available.

To our knowledge, there are two main experimental sets of gas-phase acidities for hydrocarbons relevant to this study, including CB. They are both based on the experimental study of reaction 9 but differ in the experimental techniques used and, hence, in the experimental conditions. They were respectively obtained by means of a flowing afterglow-selected ion flow tube[54], a 'high pressure' technique and by Fourier transform ion cyclotron resonance spectroscopy (FT ICR)[55]. Some representative results are presented in Table 4.

In the case of CUB, reaction 9 seems to proceed too slowly, perhaps because the rehybridization attending the formation of cubyl anion significantly slows down the formation of CUB and this precludes the use of equation 10. These difficulties were overcome in the elegant work of Hare, Kass and coworkers[56], who were able to generate cubyl anion in an FT ICR spectrometer through the reaction between (trimethylsilyl)cubane and kinetically excited fluoride anion (reactions 11 and 12). The kinetic (purely translational) excitation of F^- was achieved by means of the SORI[57] (sustained off-resonance irradiation) technique. The PA of cubyl anion (reported in Table 4) was estimated by bracketing the proton (or deuteron) exchange with a variety of proton donors and ND_3.

(11)



(12)

We have used the G2 computational method to determine the reliability of the experimental data in the case of negative EA values. This is important because, to our knowledge, cycloalkyl carbanions (with the exception of cyclopropyl anion) belong to this subset. To this end we have determined $\Delta_r H_m^\circ(4)$, $\Delta_r G_m^\circ(4)$ for a small group of ions having both

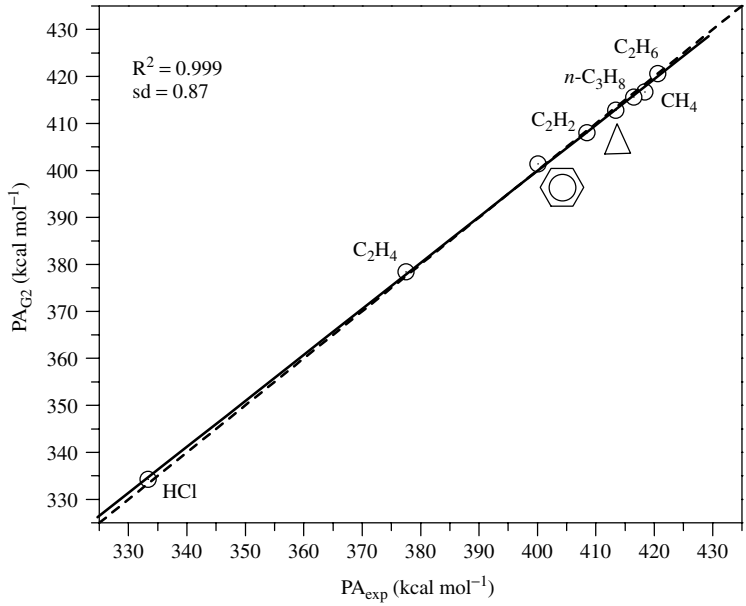


FIGURE 5. Correlation between computed (G2 level) and experimental proton affinities of selected anions. The structures shown pertain to the neutral acids. Dashed line: perfect coincidence

positive and negative EAs. We present in Figure 5 a comparison between the experimental and computed values for selected alkyl carbanions and other anions derived from stronger hydrocarbon acids (as well as HCl, added to widen the range of acidities). The agreement is remarkably good and lends confidence to the extension of the method to cycloalkyl carbanions. Similar excellent relationships have been described for a variety of acidic compounds studied at the B3LYP/6-311+G(d,p) level[68].

Inspection of the data presented in Table 4 shows the following:

1. The relative stabilities of the cyclic carbanions [in terms of $\Delta_r G^\circ_m(4)$] having the 'lone pair' in equatorial or axial positions are quite comparable and, under equilibrium conditions, a mixture of both isomers should be expected. The structures of the two isomeric cyclobutyl anions as optimized in this work at the MP2/6-311+G(3d,2p) level are presented in Figures 6 and 7. We have also computed here [at the B3LYP/6-311++G(d,p) level] the energetic barrier for the equatorial–axial interconversion in cyclobutyl anion. It amounts to 4.71 kcal mol^{-1}. In the case of cubyl anion, there is only one possible structure, portrayed in Figure 8.
2. The apparent experimental PA values for bulky aliphatic or alicyclic carbanions, irrespective of the sign of their EA, differ significantly from the computed values and this difference seems to increase with the bulk of the anion.

The latter feature as well as the very possibility of determining the stabilities of these species in the gas phase lend credence to the concept that the carbanions within complexes II and III (reaction 9) are 'solvated' by the trialkylsilanol molecule[54]. Because of the strong electrostatic interaction, the carbanion could avoid decomposition through electron loss. In this respect, Jorgensen's daring computational estimate of the aqueous pK_a of

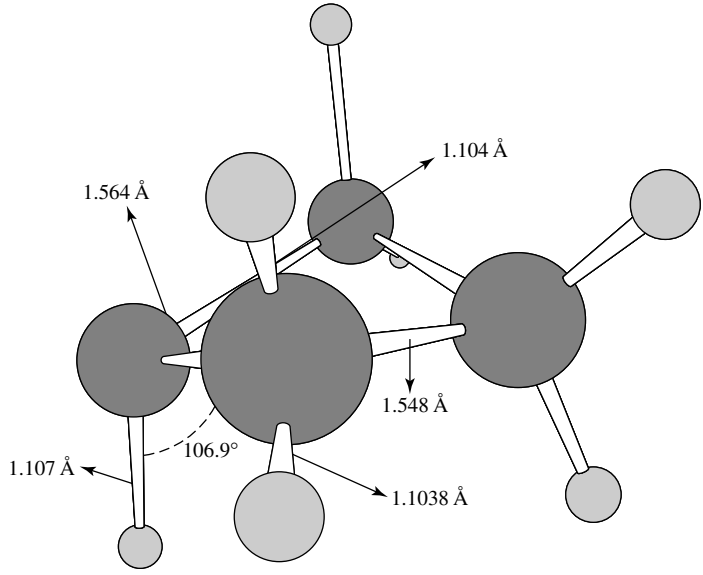


FIGURE 6. MP2/6-311+G(3d,2p)-optimized geometrical structure of the less stable isomer of cyclobutyl anion

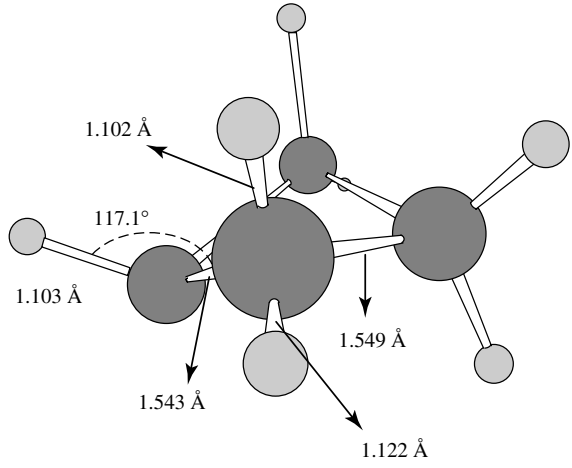


FIGURE 7. MP2/6-311+G(3d,2p)-optimized geometrical structure of the most stable isomer of cyclobutyl anion

ethane[69] indicates that even water can provide substantial stabilization to carbanions. That equation 10 holds requires that 'solvation' of the carbanions within the complexes be of identical strength. Obviously, this might apply to species of small steric requirements. It seems reasonable to infer that as the bulk of the carbanionic moiety increases, this

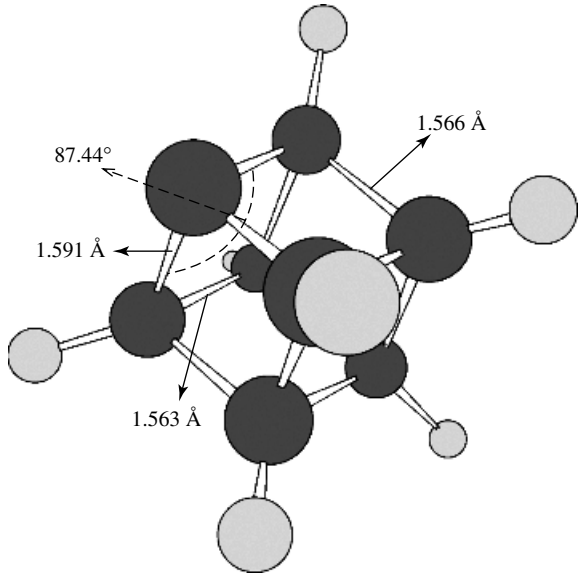


FIGURE 8. MP2/6-311+G(3d,2p)-optimized geometrical structure of cubyl anion

stabilizing effect decreases. This is in agreement with our results, but appears as an open invitation to carry out careful computational studies of the corresponding siliconate ions.

3. Structural considerations

The geometrical characteristics of the anions of CU and CUB do not differ significantly from those of the neutral hydrocarbons. In cubyl anion, a small lengthening (0.02 Å) of the C−C bonds attached to the charged atom is observed. A linear correlation has been found between the acidity and the percentage of s character of the carbon atom in a selected set of hydrocarbons[68]. Indeed, as seen in Table 4 and deduced from Figure 5, large increases in the s character of the acidic carbon bring about an important increase in acidity. However, when a large set of compounds of closely related structures is considered, the correlation is not so clear, probably due to long-range effects[51]. Notice also that the hybridization of the acidic carbons and their anions are generally different[70]. It is important that in the case of CUB and its anion, the s character is large[51] and increases on going from the neutral molecule to the anion. In the case of CB, the s character is smaller and slightly decreases on going from the neutral molecule to the anion. In the same sense, a good correlation has been found between the $^1J(^{13}C-^1H)$ spin–spin coupling constant and the s character of the carbon hybridization in 38 aliphatic hydrocarbons[71]. A large number of experimental values of these constants for CUB derivatives and other bridgehead hydrocarbons have been determined[72].

It has been pointed out that anionic hyperconjugation might play a stabilizing role in the case of carbanions[51,68,73] and leads to a lengthening of the corresponding C−H or C−C bonds. The importance of this interaction, involving the 'lone pair' and the antibonding C−H and C−C σ^* orbitals β to the anionic center, can be estimated by means of the NBO methodology. This has been done in previous studies[51,68] as well as in this work

with extremely consistent results. It is interesting that in the case of cubyl anion this effect is extremely small (<0.5 kcal mol^{-1}).

4. Solution acidity

As seen above, the proton acidities of saturated hydrocarbons are quite low and this has prompted the development of alternative experimental methodologies. Of great importance is Streitwieser kinetic technique. It is based on the study of the kinetics of the cyclohexylamide-catalyzed deuterium or tritium exchanges with cyclohexylamine (reaction 13)[74,75]:

$$\mathrm{RH}_{n-1}\mathrm{L(soln)} + \mathrm{R'NH_2(soln)} \xrightarrow{k} \mathrm{RH}_n\mathrm{(soln)} + \mathrm{R'NHL(soln)} \qquad \mathrm{L = D, T} \tag{13}$$

Lithium cyclohexylamide was initially used as a source of the cyclohexylamide anion [74,75]. Later on, and particularly in the studies relevant to this work, it was replaced by cesium cyclohexylamide[76–78]. Representative experimental results, in terms of relative rates referred to the ionization of c-C_6H_{12} are summarized in Table 5.

Comparisons between the intrinsic (thermodynamic) acidities in the gas phase and the kinetic acidities in solution are presented in Figures 9 and 10, wherein use was made of the experimental and computed (G2) PA values, respectively. In these plots we present the relative activation energies, $RT\ln(k/k_0)$ (k_0 stands for the reaction rate of c-C_6H_{12}).

Inspection of these plots indicates similar trends of structural effects on acidity in the gas phase and in solution. It is clear, however, that the solution kinetic acidities of cyclopropane and (to a lesser extent) CB seem to be affected by some different factors (including perhaps experimental difficulties). In particular, the seemingly higher solution acidity of cyclopropane relative to CUB does not reflect the ranking of intrinsic acidities of these compounds.

TABLE 5. Kinetic acidities in solution for selected hydrocarbons relative to cyclohexane

Hydrocarbon	k/k_0
c-C_3H_6 [a,b]	$(7.0 \pm 0.9) \times 10^4$
c-C_4H_8 [a,b]	28 ± 10
c-C_5H_{10} [a,b]	5.72 ± 0.27
c-C_6H_{12} [a,b]	(1.00)
c-C_7H_{14} [a,b]	0.76 ± 0.09
c-C_8H_{16} [a,b]	0.64 ± 0.06
c-C_9H_{18} [a,c]	1.01 ± 0.07
c-$C_{10}H_{20}$ [c,d]	0.73 ± 0.05
c-$C_{14}H_{28}$ [c,d]	0.345 ± 0.026
Cubane [e,f]	6.3×10^4
Benzene [e,f]	$(9.1 \pm 0.7) \times 10^7$

[a] At 50 °C.
[b] From Reference 76.
[c] From Reference 77.
[d] At 100 °C.
[e] At 25 °C.
[f] From Reference 78.

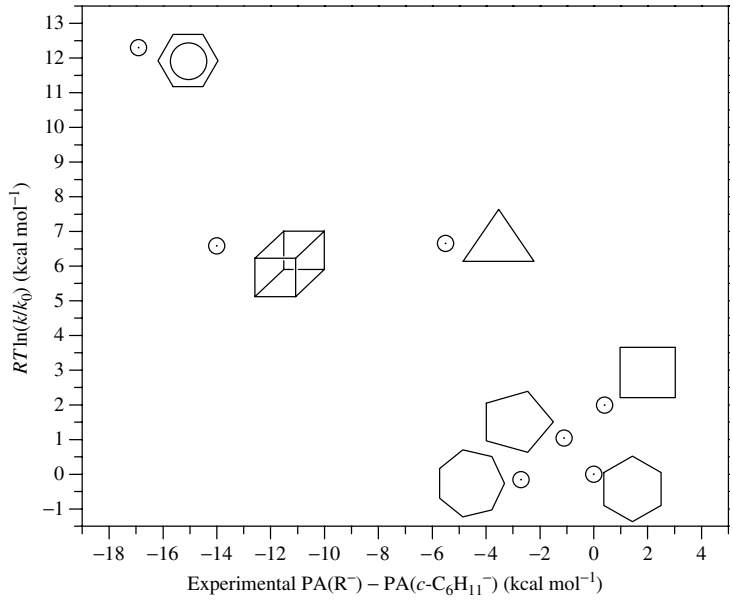


FIGURE 9. Experimental values of $RT\ln(k/k_0)$ [Differential Gibbs energy of activation] *vs.* experimental values of PA(R$^-$) − PA(c-C$_6$H$_{11}^-$)

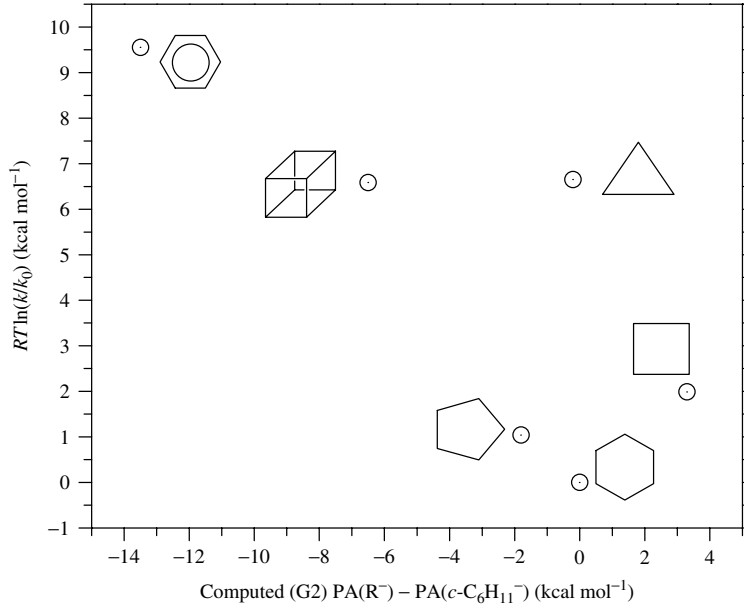


FIGURE 10. Experimental values of $RT\ln(k/k_0)$ [Differential Gibbs energy of activation] *vs.* computed values of PA(R$^-$) − PA(c-C$_6$H$_{11}^-$)

B. Stabilization of Positive Charges. Cyclobutylium and Cubylium Cations

1. Cyclobutylium cation (c-$C_4H_7^+$, $\mathbf{1}^+$)

Experimental evidence[79] as well as high level theoretical calculations[79–81] indicate that in solution at low temperature, $\mathbf{1}^+$ has a non-classical symmetrical puckered structure (bicyclobutonium ion, C_s point group) (Figure 11). It has also been experimentally established[79] that under the same conditions, $\mathbf{1}^+$ is in equilibrium with cyclopropylmethylium cation ($\mathbf{2}^+$, Figure 12), a species having a bisected (C_s point group) geometrical structure. The interconversion barrier is *ca* 2 kcal mol^{-1}. The presence of $\mathbf{1}^+$ and $\mathbf{2}^+$ in the gas phase has been reported[82].

In principle, the standard enthalpy of formation of $\mathbf{1}^+$(g) can be obtained from the experimental PA of cyclobutene and its experimental enthalpy of formation. However, as a consequence of the equilibrium between $\mathbf{1}^+$ and $\mathbf{2}^+$ (equation 14), the apparent experimental PA of cyclobutene does not pertain to a single species. This is why we have considered more reliable the values obtained from the computed (G2 level) PA of cyclobutene and its standard heat of formation (either experimental or computed at the G2 level)[81].

$$\mathbf{1}^+(\mathrm{g}) \longrightarrow \mathbf{2}^+(\mathrm{g}) \tag{14}$$

Furthermore, it has been found[81] that $\Delta_r G^\circ_m(14) \approx 0$ and $\Delta_r H^\circ_m(14) = -0.5$ kcal mol^{-1}. These results are in very good agreement with solvolytic data[79,83] and with the experimental observation that an equilibrating mixture of ions $\mathbf{1}^+$ and $\mathbf{2}^+$ in solution contains approximately 72 and 28% of these isomers, respectively.

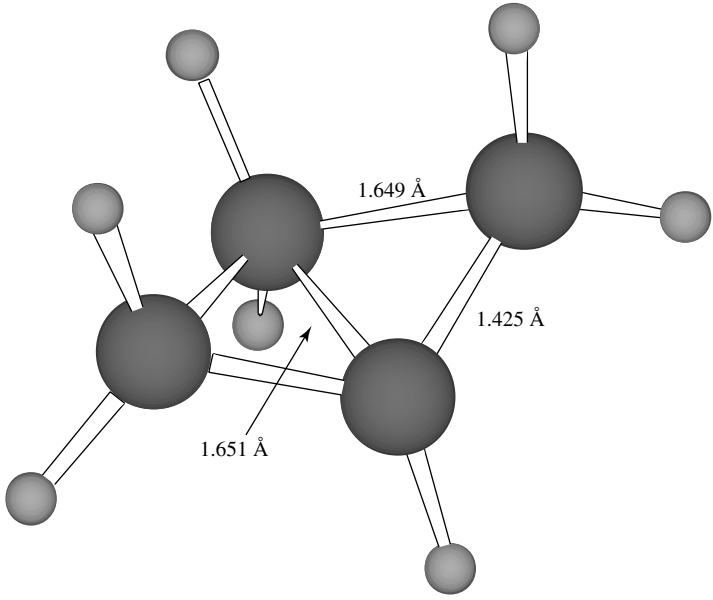


FIGURE 11. Geometrical structure of cyclobutyl cation ($\mathbf{1}^+$), optimized at the MP2(full)/6-31G(d) level

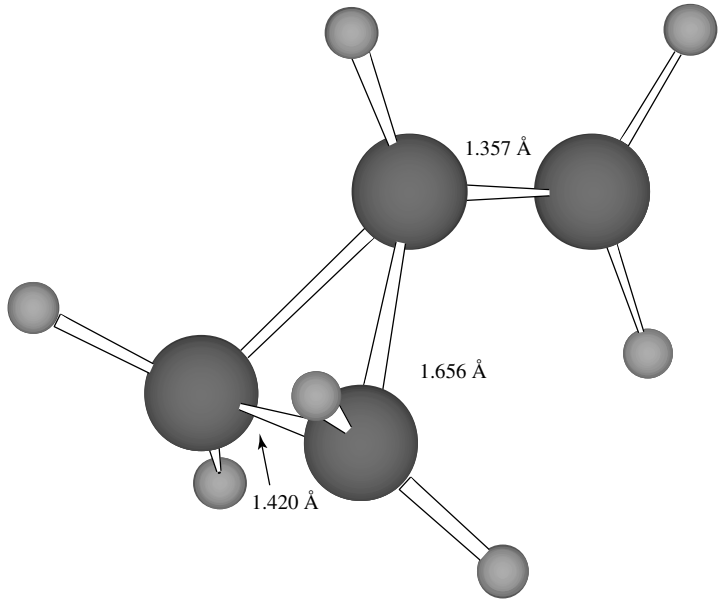


FIGURE 12. Geometrical structure of cyclopropylmethyl cation (**2**$^+$), optimized at the MP2(full)/6-31G(d) level

2. *Cubylium ion* ($C_8H_7^+$, **3**$^+$)

To our knowledge, the experimental geometrical structure of this ion is not yet available. We present in Figure 13 the geometrical structure optimized at the MP2/6-311+G(d,p) level.

A number of solvolytic processes suggesting the intermediacy of **3**$^+$ have been reported[84,85] although the ion itself does not seem to have been observed in solution. The fact that the solvolysis of cubyl triflate in hexafluoro-2-propanol at 60 °C is about 10^5 times faster than that of 1-norbornyl triflate under the same conditions was taken as indicative of significant positive charge delocalization over the cubic framework, particularly at positions 2 (there are three equivalent positions) and 4 (only one)[84].

The stability of **3**$^+$(g) was determined experimentally by means of FT ICR experiments[86,87]. Because the solvolytic rates of cubyl esters have been considered to be unexpectedly high with respect to those for the corresponding 1-norbornyl esters, it is interesting to compare the relative hydride affinities of 1-norbornyl (1-Nb$^+$), cubyl (**3**$^+$) and 1-adamantyl (1-Ad$^+$) cations relative to isopropyl (*i*-Pr$^+$). To this end, we construct equations 15–17:

$$i\text{-Pr}^+(\text{g}) + \text{Adamantane } (C_{10}H_{16,\,\text{g}}) \longrightarrow C_3H_8(\text{g}) + \text{1-Ad}^+(\text{g}) \qquad \Delta_r H^\circ_m(15) \quad (15)$$

$$i\text{-Pr}^+(\text{g}) + \text{Norbornane } (C_7H_{12,\,\text{g}}) \longrightarrow C_3H_8(\text{g}) + \text{1-Nb}^+(\text{g}) \qquad \Delta_r H^\circ_m(16) \quad (16)$$

$$i\text{-Pr}^+(\text{g}) + \text{Cubane } (C_8H_{8,\,\text{g}}) \longrightarrow C_3H_8(\text{g}) + C_8H_7^+ (\mathbf{3}^+, \text{g}) \qquad \Delta_r H^\circ_m(17) \quad (17)$$

Using experimental data from Reference 77 we obtain for $\Delta_r H^\circ_m(15)$, $\Delta_r H^\circ_m(16)$ and $\Delta_r H^\circ_m(17)$ −24.0, 3.9 and −6.5 kcal mol^{-1}, respectively. It is clear that 1-norbornyl

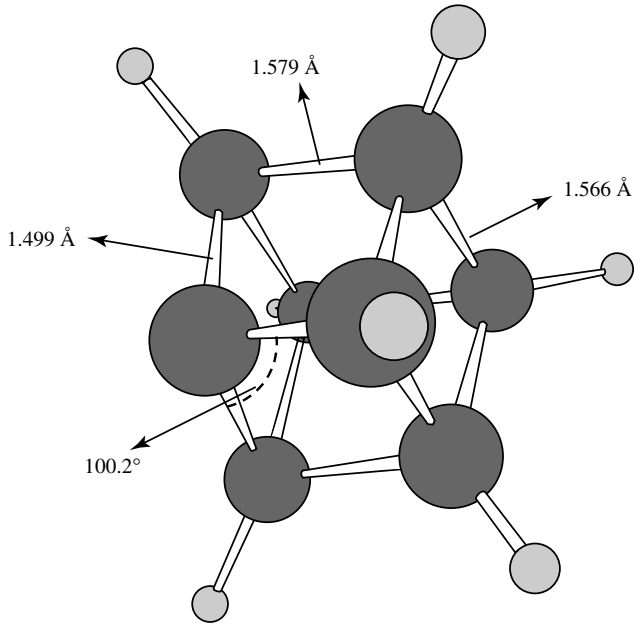


FIGURE 13. Geometrical structure of cubyl cation, optimized at the MP2/6-311+G(d,p) level

cation is less stable relative to its corresponding hydrocarbon than isopropyl cation, a secondary cation. Cubyl cation is somewhat more stable than both of them but it is still 17.5 kcal mol^{-1} less stable than 1-adamantyl cation, a typical, reasonably stable, well behaved tertiary cation. We further notice that there is a remarkably accurate, wide-range correlation (over 23 log units) between the logarithm of the solvolysis rates for the tertiary chlorides of bridgehead hydrocarbons (R-Cl) and the standard Gibbs energy changes for reaction 18 in the gas phase[81, 86, 87].

$$\text{R-Cl(g)} + \text{1-Ad}^+\text{(g)} \longrightarrow \text{R}^+\text{(g)} + \text{1-AdCl(g)} \qquad \Delta_r G^\circ_m(18) \qquad (18)$$

Both 1-Nb$^+$(g) and **3**$^+$(g) show excellent adherence to this correlation. It thus seems that the reactivities in solution and in the gas phase of **3**$^+$ are quite consistent.

We have carried out NBO calculations at the B3LYP/6-311++G(d,p) level on cubyl cation. We found that it is stabilized by the interaction of the six C−C bonds in β-position with respect to the positive charge. The calculated orbital interaction between each C−C and the antibonding lone pair on the positive carbon amounts to 23.9 kcal mol^{-1}. This value is substantial, but it is not indicative of any seemingly exceptional interaction. Thus, the same sort of calculation reveals that, in the case of 1-adamantyl cation, the three C−C bonds in β-position with respect to the positive charge contribute 25.6 kcal mol^{-1} to the stabilization of the ion. The main difference between the stabilization of **3**$^+$ and 1-Ad$^+$ originates in the number of stabilizing interactions (6 vs 3). It is interesting that the rate of solvolysis of 4-methyl-substituted cubyl triflate is about 1/3 of that for the unsubstituted cubyl triflate[85]. On the other hand, 4-methylcubyl cation is more stable by 2.0 kcal mol^{-1} than the parent cation according to B3LYP/6-311+G(d,p) calculations[88].

This difference obviously indicates differential solvent effects involving either or both neutral and ionic species.

V. CB AND CUB AS BASES

As indicated earlier, accumulation of negative charge outside the internuclear lines and release of strain are factors of potential relevance in electrophilic attacks on these compounds. Representative examples of this behavior follow.

A. The Case of CB

1. Reactions with Li^+

To our knowledge, no experimental information is available on the interaction between CB and Li^+, either in the gas phase or in solution. Recently, a computational study using the 'polarization-corrected electrostatic potential' (PMESP) methodology[89] was performed on some simple alkanes and cycloalkanes. In the case of CB, two critical points were found in the PMESP surface. They correspond to negative values of this property, leading to attractive interactions with Li^+. They are located either perpendicular to a C−C bond or on top of the center of mass of the molecule, the former being the most stable structure.

An intriguing possibility is presented by the reaction of our hydrocarbons with LiH, paralleling the suggested reaction between tetrahedrane and LiH that may lead to a species isoelectronic to the polyhedral boron anion $B_5H_5^-$ and related carborane $C_2B_3H_5$[90].

2. Protonation

It has long been established that CB can be protonated[91]. More recently, the reaction was studied experimentally by means of radiolytic experiments with gaseous mixtures of perdeuteriated CB and CH_4[92]. In these experiments, the protonated cycle was seen to open and isomerize. Under these experimental conditions, the proton donor was CH_5^+, an extremely strong acid. Likely, the protonation process released enough energy to lead to isomerization. Thus, up to now there seems to be no experimental determination (or estimate) of the PA or GB of CB. A computational study of the protonation of CB in the gas phase was carried out in 1975[93]. This pioneering study led to the conclusion that the protonation of CB can lead to edge- and corner-protonated structures of very similar stabilities. The computed PA was estimated at *ca* 127 kcal mol^{-1}. We are examining this matter both experimentally and computationally. Preliminary results at the MP2/6-311+G(d,p) level show at least one minimum on the potential energy surface of protonated cyclobutane, corresponding to an edge-protonated structure, possibly a non-classical species with a two-electron–three-center bond (Figure 14). The computed PA is close to 170 kcal mol^{-1}. Quite interestingly, this protonation process seems to be reversible. The existence of other structures is presently being investigated by our group.

B. The Case of CUB

1. Reaction with Li^+

To our knowledge, this reaction has not been studied so far in the gas phase. In solution, however, a recent study[94] shows that CUB isomerizes cleanly to yield cuneane (Figure 15) in the presence of Li^+. It has been known for a number years that Lewis acids such as Ag^+ and Pd^{+2} also catalyze the same reaction[95]. Recent experimental and computational evidence indicates that in the gas phase, the main contributor to the interaction between

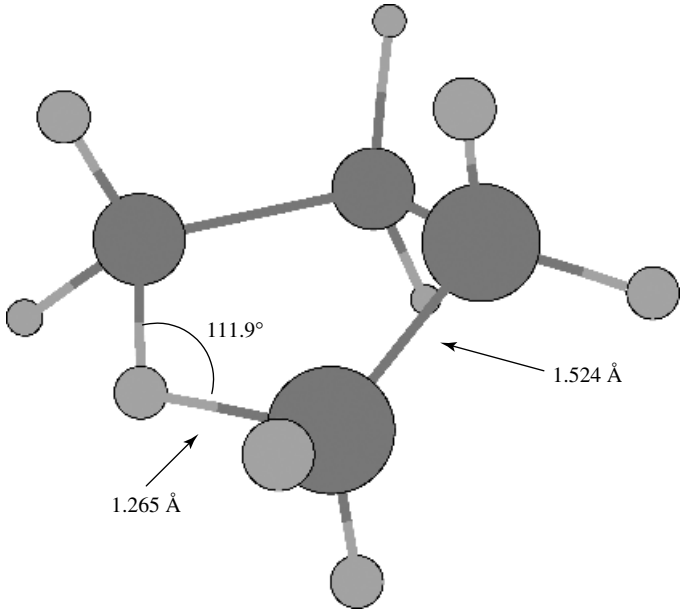


FIGURE 14. Geometrical structure of protonated cyclobutane, optimized at the MP2/6-311+G(d,p) level

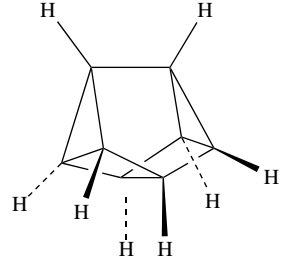


FIGURE 15. Cuneane hydrocarbon

Li^+ and a wide variety of aromatic hydrocarbons[96] is essentially electrostatic. We believe, therefore, that the Li^+-catalyzed reaction 19 is a process catalyzed by a strong electric field and not through the formation of a covalent bond. Clearly, this process requires a detailed computational study.

$$\text{Cubane (soln)} \longrightarrow \text{Cuneane (soln)} \tag{19}$$

2. Protonation

The protonation of cubane was studied experimentally by ICR in 1986[97]. The apparent GB value thus determined was 200.7 ± 3.0[97] (or 199.2 ± 3.0 kcal mol^{-1} [98]). Recently,

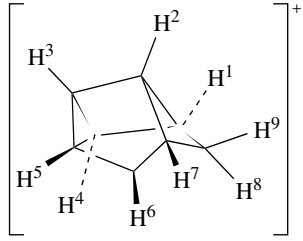


FIGURE 16. Tetracyclo[4.2.0.0^{2,4}0^{3,8}]oct-7-ylium cation

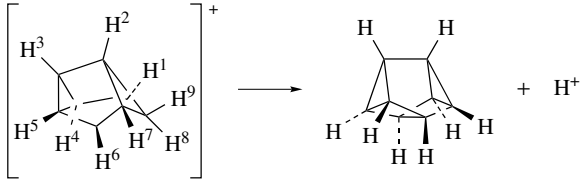
we carried out a computational study of reaction 20[99]. At the G2 level, we obtained $\Delta_r H^\circ_m(20) = -265.1$ and $\Delta_r G^\circ_m(20) = -258.8$ kcal mol^{-1}.

$$\text{Cubane (g)} + \text{H}^+\text{(g)} \longrightarrow \text{C}_8\text{H}_9^+\text{(g)} \tag{20}$$

The structure of the ion $C_8H_9^+$ was determined to be that of tetracyclo[4.2.0.0^{2,4}0^{3,8}]oct-7-ylium cation (Figure 16).

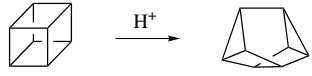
These results indicate that the gas-phase protonation of CUB is not reversible.

A preliminary exploration of the protonation of CUB at the B3LYP/6-311+G(d,p) level revealed that protonation at the center of the cube, as well as at its face, edge or corner, yields species (respectively belonging to the symmetry groups O_h, C_{4v}, C_{2v} and C_s) that are not minima on the potential energy surface of $C_8H_9^+$. Relaxation of these symmetry constraints leads in all cases to tetracyclo[4.2.0.0^{2,4}0^{3,8}]oct-7-ylium cation. The study of the energetics of the deprotonation of this ion was carried out at B3LYP/6-311+G(d,p) and MP2/6-311+G(d,p) levels. Both methods led to highly consistent results. Of all the possible neutral species derived from this process, cuneane is the most stable. The computed [G2(MP2)] $\Delta_r G^\circ_m(21)$ for reaction 21 amounts to 198.0 kcal mol^{-1}.



(21)

This value agrees well within the experimental error with the apparent experimental GB value of cubane. This, and the fact that the same isomerization takes place in solution in the presence of Li(I), Ag(I) and Pd(II), strongly suggest that the overall process observed in the gas-phase ICR experiments is the proton-catalyzed isomerization of cubane into cuneane (reaction 22).



(22)

VI. HYDROGEN BONDING (HB)

The abilities of CB and CUB as hydrogen bond acceptors and donors have been explored theoretically using as probe molecules hydrogen fluoride and ammonia. In Figure 17, the

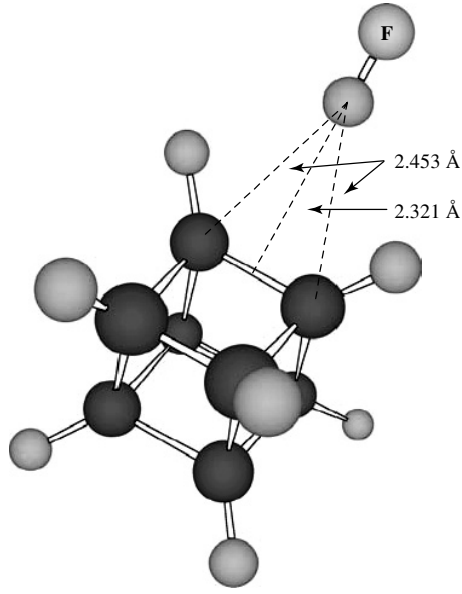


FIGURE 17. Optimized structure of the FH:cubane complex at the B3LYP/6-311++G(d,p) level

complex obtained between CUB and hydrogen fluoride shows the latter pointing towards the center of a C−C bond in a similar disposition to that found for other strained cyclic hydrocarbons as cyclopropane and tetrahedrane[100].

The electron density analysis using AIM methodology shows that the interaction is in fact between the hydrogen atom of HF and the C−H bonds (Figure 18) while in other cases it corresponds to a direct interaction of the hydrogen atom with the strained C−C bond[100]. The BSSE corrected interaction energy for the CUB:HF complex only accounts for -1.3 kcal mol^{-1} at the B3LYP/6-311++G(d,p) computational level.

CB and CUB are weak HB donors as in general is observed for saturated hydrocarbons. Thus, the interaction energies of the complexes of CB and CUB with ammonia at the B3LYP/6-311++G(d,p) level are -2.4 and -2.0 kcal mol^{-1}, respectively[101]. The enhancement of interaction energy in these complexes has been explained based on their structural strain. A correlation between the interaction energies of a number of strained hydrocarbons as hydrogen bond donors versus ammonia and their bond angles as a measure of their strain has been found[101].

VII. CB AND CUB AS SUBSTITUENTS

A. Carboxylic Acids

Consider the ionization of a carboxylic acid, R-COOH (equation 23):

$$\text{R-COOH} \longrightarrow \text{R-COO}^- + \text{H}^+ \tag{23}$$

Formally, the 'substituent effect' of R on the solution pK_a of this acid or on its ΔG°_{acid} in the gas phase will be determined by the difference in the interaction energy between

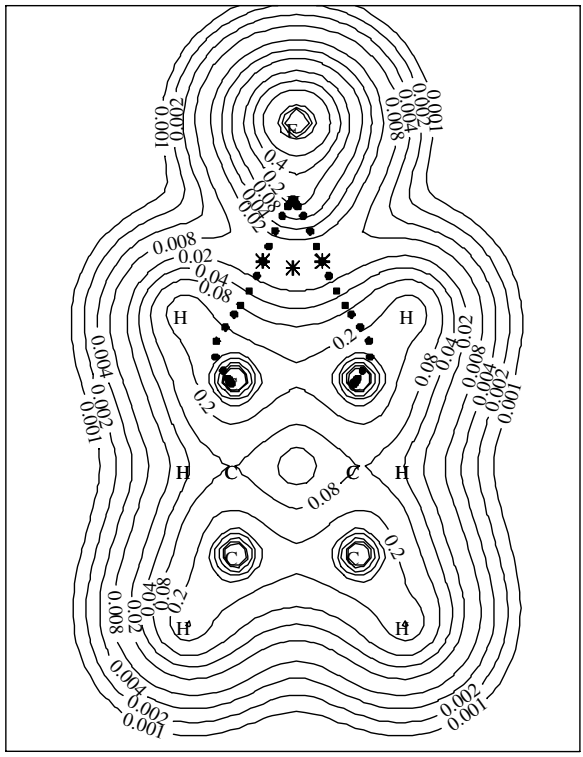


FIGURE 18. Electron density map (a.u.) of the FH:cubane complex calculated at the B3LYP/6-311++G(d,p) level. Stars indicate the position of the critical points and dots the bond path

R and COOH and R and COO^- with respect to some reference substituent, R^0. This is best seen by considering reaction 23a, wherein $R^0 = H$:

$$R\text{-}COO^- + H\text{-}COOH \longrightarrow R\text{-}COOH + H\text{-}COO^- \qquad (23a)$$

The general problem of substituent effects on the stability of substituted cyclobutanes[40b] was addressed after the first discussions of the molecular orbital diagram of CB[102].

Owing to the character of this chapter, we only consider here some representative experimental data and the energetic NBO analysis thereof. Table 6 collects representative gas-phase acidities relevant to our discussion.

The acidities of aliphatic carboxylic acids have been analyzed by means of different models. Here we use the Taft–Topsom methodology[103a]. According to this approach, the intrinsic (gas-phase) acidity of these species, R-COOH, is proportional to the polarizability of R, as measured by the polarizability parameter σ_α[103b]. Figures 19 and 20 are plots of $\Delta G^\circ_{\text{acid}}$ and $\Delta G^\circ_{\text{acid}}$ (DMSO) against σ_α.

Both plots are linear and the statistics of the correlations are excellent. However, the slopes have opposite signs. For gas-phase data, the slope is positive; that is, it follows the 'normal' pattern of increasing acidity with substituent polarizability. We use it to estimate

TABLE 6. Thermodynamic data for the gas-phase and solution ionization of selected carboxylic acids, RCOOH

R	ΔG°_{acid} [a,b]	ΔG°_{acid}(DMSO) [b,d]	σ_α [e]
Me	341.4	17.06 ± 0.14	−0.35
Et	340.4	—	−0.49
i-Pr	339.0	—	−0.62
t-Bu	337.8	17.75 ± 0.07	−0.75
c-Pr	339.0		−0.62
c-Bu	338.8		(−0.65) [f]
Bicyclo[2.2.2]octyl	337.2	12.90 ± 0.06	(−0.78) [f]
Cubyl	334.1 [a,c]	12.20 ± 0.05	
1-Adamantyl	336.0	13.09 ± 0.14	−0.95
Phenyl	333.0	11.0 ± 0.14	

[a] From Reference 47.
[b] All values in kcal mol^{-1}.
[c] From Reference 104.
[d] From Reference 104b and 105.
[e] Polarizability parameter; from Reference 103.
[f] Estimated as indicated in the text.

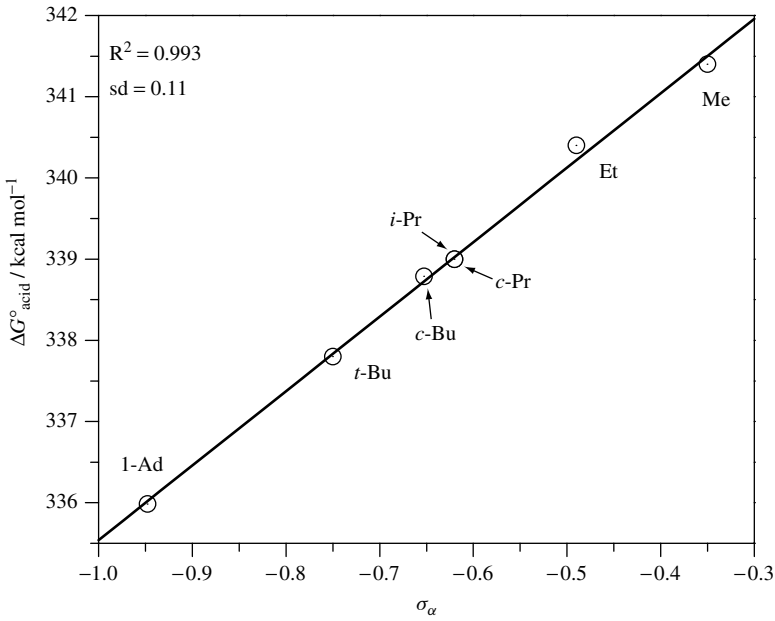


FIGURE 19. Plot of ΔG°_{acid} against σ_α

σ_α values for cyclobutyl and bicyclo[2.2.2]octyl-1 substituents. The slope for solution data is negative. This likely reflects the hydrogen bonding interaction between the neutral acids and DMSO, the low anion-solvating power of this solvent and, last, cavity effects (proportional to the volume of R).

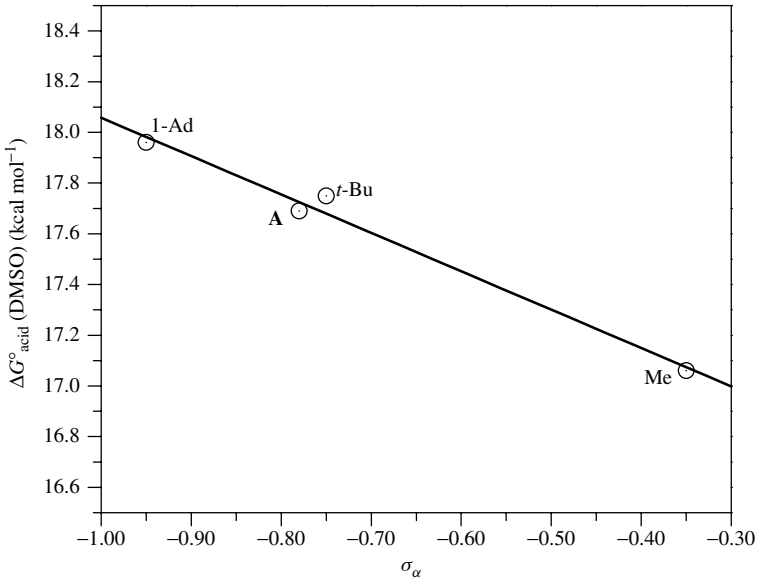


FIGURE 20. Plot of ΔG°_{acid}(DMSO) against σ_α for **A**, R = bicyclo[2.2.2]octyl

In Figure 19 we see that cyclopropanecarboxylic acid follows the 'normal' pattern. Interestingly, cyclobutanecarboxylic acid also displays such a behavior. This indicates that the differential interactions between the cyclobutyl substituent and the carboxyl and carboxylate groups are very close to those prevailing when the substituents are alkyl groups.

Figure 21 is a plot of ΔG°_{acid}(DMSO) against ΔG°_{acid}. As expected from the above, there is an excellent linear relationship of negative slope between these acidities. Two important exceptions are cubanecarboxylic and benzoic acids. The acidity of the latter is known to be affected by field and resonance effects. In the case of the former, evidence from other substituents (see below) tends to indicate that this effect likely originates in some transfer of the negative charge from the carboxylate ion into the cubyl moiety. Indeed, NBO calculations performed in this work (at the B3LYP/6-311+G(d,p) level) indicate that the amounts of charge transferred from the carboxylate to the cubyl and phenyl moieties are very similar, 0.197 and 0.186 electronic charges, respectively.

1. Substituent effects on the acidity of cubanecarboxylic acids

So far, there seems to be no substantial set of gas-phase acidities for these compounds. In solution, however, there is a group of six pK_a values in 50%(weight) EtOH–H_2O at 25 °C for 4-substituted-cubanecarboxylic acids (**B**). They are summarized in Table 7. Also given are data for 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids (**A**) obtained under the same experimental conditions.

The correlation between the two sets is given by equation 24:

$$\mathrm{p}K_a(\mathbf{A}) = 0.78(0.42) + 1.02(0.08)\mathrm{p}K_a(\mathbf{B}) \qquad (24)$$

$$n = 6, \quad \mathrm{sd} = 0.10, \quad R = 0.989$$

The statistical correlation is excellent. The most remarkable feature is the essentially unit slope. This indicates that the transmission of effects is not affected by the important

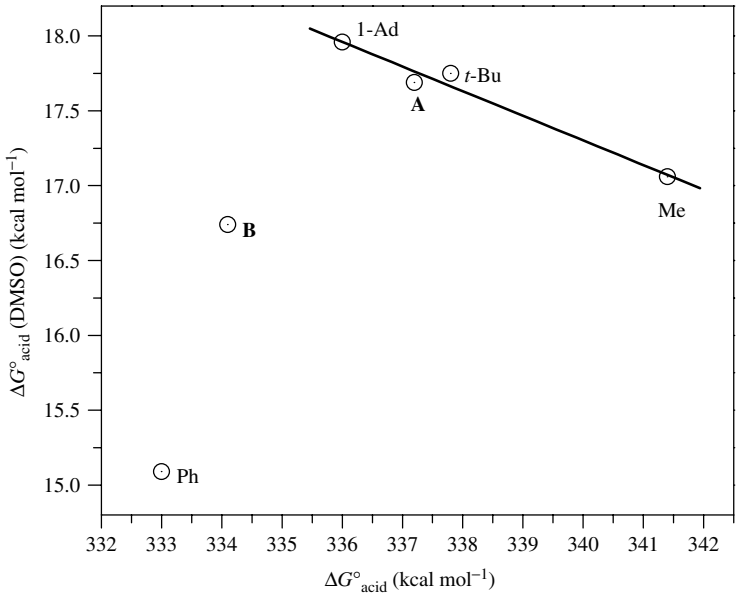


FIGURE 21. Plot of ΔG°_{acid}(DMSO) against ΔG°_{acid} for **A**, R = bicyclo[2.2.2]octyl; **B**, R = cubyl

TABLE 7. pK_a values for selected 4-X-substituted cubanecarboxylic acids (**B**) and 4-X-substituted bicyclo[2.2.2]octane-1-carboxylic acids (**A**) in 50%(weight) EtOH–H_2O at 25 °C

X	pK_a (**B**) [a]	pK_a (**A**) [b]
H	5.95	6.83
Br	5.32	6.14
COOH	5.13	6.10
COO^-	6.53	7.47
COOEt	5.40	6.40
CN	5.14	5.94

[a] From Reference 106.
[b] From Reference 107.

strain of the cubyl moiety. It is also known that substituent effects in 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids are essentially determined by field effects[103a, 108]. Although gas-phase data are missing, it seems reasonable to believe that something similar happens in the cubyl compounds. It is unfortunate, however, that no data seem to be available for relatively strong electron donors such as methoxy and amino groups.

2. The basicity of carboxylic acids

No information seems to be available on the protonation of cubanecarboxylic acid. On the other hand, the experimental proton affinity of cyclobutanecarboxylic acid has been determined experimentally by Cook's kinetic method[105]. We summarize in Table 8

TABLE 8. Experimental PA values for selected alicyclic carboxylic acids RCOOH[109]

R	PA (kcal mol^{-1})
c-C_3H_5	198.0 ± 0.2
c-C_4H_7	197.0 ± 0.2
c-C_5H_9	197.8 ± 0.2
c-C_6H_{11}	198.3 ± 0.2

experimental PA values for some alicyclic carboxylic acids. The range of structural effects is small, 1.3 kcal mol^{-1}. It seems that cyclobutanecarboxylic acid is the less basic of this group, and this is consistent with a small transfer of electron density from the carboxylic group to the four-membered ring.

B. Amines and Alcohols

1. Cyclobutylamine

Preliminary experimental results indicate that its GB is close to 211 kcal mol^{-1}[106a], in good agreement with the value calculated at the B3LYP/6-311+G(d,p) level (212 kcal mol^{-1})[110b]. It is known[98,104] that the correlation between GB and σ_α is excellent. Using the estimated σ_α value for the cyclobutyl group (−0.65) we can estimate a GB of *ca* 213 kcal mol^{-1} for cyclobutylamine, consistent with the values indicated above.

The experimental pK_a value of this base in DMSO-d_6, relative to isopropylamine, is −0.836 units, while that of *sec*-butylamine is −0.173. The difference, 0.66 units, indicates a basicity-weakening effect of the cyclobutyl moiety. The overall pattern of basicities for cyclic amines in DMSO-d_6 is too complicated, however, to draw significant structural conclusions.

2. Cubylamine

The protonation of this compound has recently been studied in the gas phase, in solution and computationally. Some results of this study are summarized in Table 9.

TABLE 9. Solution and gas-phase basicities of selected primary amines

Base	pK_a(H_2O) [a]	GB (R-NH_2) (kcal mol^{-1}) [b]
NH_3	9.24 [c]	195.7
CH_3NH_2	10.64 [c]	206.6
n-$C_3H_7NH_2$	10.53 [c]	211.3
Bicyclo[2.2.2]octyl-1-amine	10.66 [d]	217.8
1-Adamantylamine	10.55 ± 0.02 [e]	219.0
Cubylamine	8.66 ± 0.02 [e]	227.4 ± 2.3 [e,f] (211.7) [g]

[a] pK_a of the conjugate acid.
[b] From Reference 111.
[c] From Reference 112.
[d] From Reference 108.
[e] Experimental values from Reference 113.
[f] Apparent value.
[g] Computed (B3LYP/6-311+G(d,p) level) value from Reference 113.

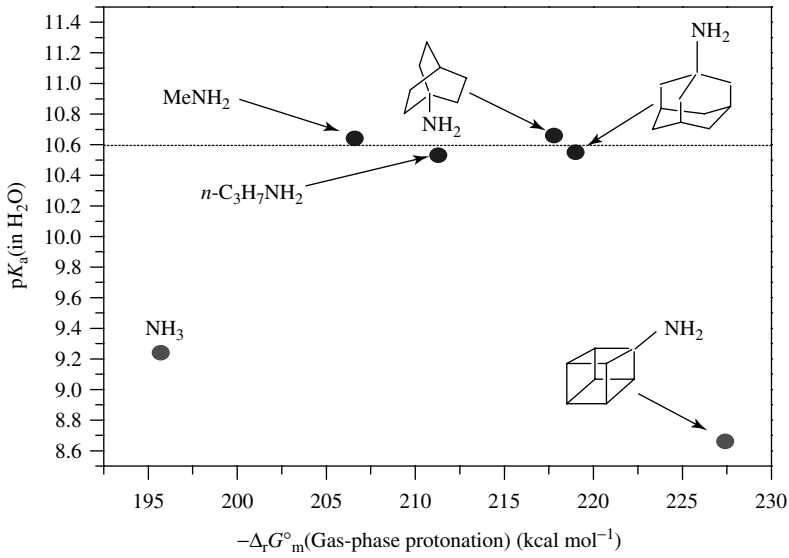


FIGURE 22. Plot of pK_a against GB for ammonia and selected primary amines

Figure 22 is a plot of pK_a against GB values for some aliphatic and alicyclic amines. Cubylamine seems 'too weak' in solution and 'too strong' a base in the gas phase.

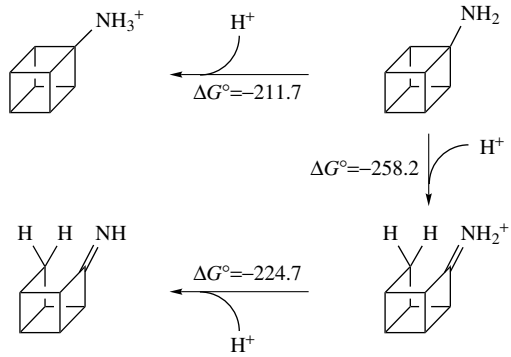
The solution result can be rationalized[113] on the basis of the stabilizing stereoelectronic interaction between the nitrogen lone pair and one of the C(α)-C(β) antibonding σ^* orbitals, antiperiplanar to the lone pair. This interaction leads to the transfer of electronic density from the lone pair to the cubyl moiety[114]. This phenomenon was predicted on theoretical grounds in 1991. From an experimental point of view, this hyperconjugative interaction leads to a selective lengthening of the C(α)-C(β) bond and a shortening of the C(α)-N bond. This has been confirmed computationally in the case of cubylamine[113, 114]. Experimentally, in dicubyl disulfide, X-ray studies reveal a substantial shortening of the C(α)-S bonds[115].

In the case of cubylamine, this interaction is strong (14.15 kcal mol^{-1} for the C−C bond in β-position) and substantially larger than in the case of cyclobutylamine (9.98 kcal mol^{-1} for the C−C in β position). This helps to explain the much weaker interactions with the amino group in the latter compound. Another significant factor is the important s character of the α carbon in cubylamine: 28.4% according to NBO calculations[113] and *ca* 31% on the basis of experimental NMR data[116].

A computational study of the protonation of cubylamine in the gas phase seems to involve the attack at the cubyl moiety[113]. Irrespective of the position of the attack (excepting C(α), which evolves without a significant barrier to nitrogen protonation), it liberates a substantial fraction of the internal strain. In all cases, a protonated imine is formed.

Equation 25 shows a representative example. C-protonation liberates some 258 kcal mol^{-1}. Protonation at other carbon sites, except at C(α), is even more exergonic. Hence, one would expect cubylamine to be a true super-base. However, all these imines are only moderately basic. Therefore, when studied in the presence of a reference base (as was the case in the original FT ICR experiments)[113], they will be deprotonated by species with a significantly lower GB. In the present example, any base with GB significantly larger

than 224.7 kcal mol^{-1} is able to deprotonate the imine.

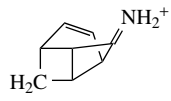
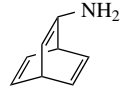
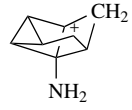
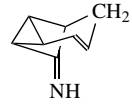
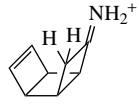
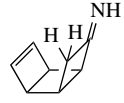
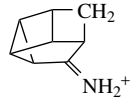
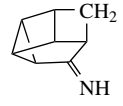
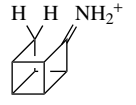
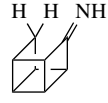


(25)

We present in Scheme 1 the various cationic products $\mathbf{P}_n$ obtained by C-protonation of cubylamine and the corresponding neutral bases $\mathbf{B}_n$ obtained by deprotonation of the former. Table 10 summarizes the standard Gibbs energy changes pertaining to reactions 26 and 27, respectively $\Delta_r G^\circ_m(26)$ and $\Delta_r G^\circ_m(27)$.

$$\text{Cubylamine (g)} + \text{H}^+\text{(g)} \longrightarrow \mathbf{P}_n\text{(g)} \qquad \Delta_r G^\circ_m\,(26) \tag{26}$$

$$\mathbf{P}_n\text{(g)} \longrightarrow \mathbf{B}_n\text{(g)} + \text{H}^+\text{(g)} \qquad \Delta_r G^\circ_m\,(27) \tag{27}$$

$\mathbf{P}_n$	$\mathbf{B}_n$	n
		1
		2
		3
		4
		5

SCHEME 1

TABLE 10. Standard Gibbs energy changes (in kcal mol^{-1}) for reactions 26 and 27[113]

n [a]	$-\Delta_r G^\circ_m(26)$ [a,b]	$\Delta_r G^\circ_m(27)$ [a,b]
1	283.4	205.1
2	250.5	179.2
3	262.4	222.5
4	283.0	228.5
5	258.2	224.7

[a] Defined in the text and in Scheme 1.
[b] Computed at the B3LYP/6-311+G(d,p) level.

All the species $\mathbf{P}_n$ and $\mathbf{B}_n$ were identified computationally. It is interesting that there are three different imines with GB values between 222.5 and 228.5 kcal mol^{-1} (corresponding to $n = 3$, 4 and 5 in Scheme 1). The experimental apparent GB value is 227.4 ± 2.3 kcal mol^{-1}. On account of the various sources of uncertainty, the experimental results are consistent with the observation of a mixture of the corresponding iminium ions. Obviously, they derive from the strongest bases $\mathbf{B}_n$.

3. Alcohols

As far as we know, no experimental information is available on cubanol. The gas phase basicity of cyclobutanol was recently determined by Cook's kinetic method[117]. Its value, 189.3 ± 1.5 kcal mol^{-1}, is slightly lower than those of 2-propanol and cyclopentanol, 190.2 ± 1.5 and 190.7 ± 1.5 kcal mol^{-1}, respectively. It is unfortunate that the size of the uncertainties discourages further discussion of structural effects.

VIII. ACKNOWLEDGMENTS

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CHAPTER 6

NMR spectroscopy of cyclobutanes

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I. INTRODUCTION

A. Data on NMR of Cyclobutanes

NMR parameters, such as chemical shifts and coupling constants, have been extensively investigated through the use of cyclic organic compounds. By the same token, NMR data are routinely used in determination of the stereochemistry of cyclic compounds and can help in the interpretation of many of the physical and chemical properties that are associated with different types of rings. Cyclobutanes were expected to play an important role in this type of investigation since their properties should fall between those of cyclopropane, which is highly strained, and cyclopentane or cyclohexane, where strain is minimal. Nevertheless, cyclobutanes do not seem to follow predictable NMR behavior of other ring systems[1].

When the first commercial NMR instruments became available around fifty years ago, a considerable amount of work on cyclobutanes was already under way. Physical Organic Chemistry was beginning to systematize a significant part of the empirical knowledge related to the structure and reactivity of organic compounds, and physical methods of analysis such as infrared spectroscopy and mass spectrometry had already simplified the identification of organic compounds to a considerable extent. Thus cyclobutanes were among the first compounds that were subjected to systematic studies by NMR. In fact, the generation of a large body of NMR data on cyclobutanes can be divided roughly into two quite distinct periods: an early one, which accompanied the development of NMR techniques, and a more recent one in which NMR data have been used to determine the stereochemistry of rather complex systems containing cyclobutane rings (but there are cases where the spectra are reported but no interpretation is given). The early data on NMR parameters of cyclobutane systems were generated in response to the application of chemical shifts and coupling constants to concepts associated with molecular structure such as strain, steric interactions, conformational effects and bond hybridization. Most of the experimental work was done on instrumentation having relatively low resolution, in the CW mode, and is limited to more abundant nuclei such as ^{1}H and ^{19}F. The use of cyclobutanes as synthetic intermediates has only flourished in the last two decades. Cyclobutane derivatives can be used as starting materials for the synthesis of both acyclic and cyclic systems and their easy accessibility by reliable preparative methods and through the use of novel organometalic reagents and procedures has generated more than 10,000 patents and papers in the field[2].

B. Scope and Limitation

In spite of the relatively large amount of work on the NMR of cyclobutanes, it seems that a comprehensive treatment of cyclobutane NMR parameters is still not at hand. Part of the problem of systematic studies of cyclobutanes was identified at a very early stage. Neat cyclobutane is nonplanar and undergoes rapid interconversion of puckered conformations at room temperature[3]. This results in nonequivalency of carbon and hydrogen atoms that can exchange in a process similar to that observed for cyclohexane. However, whereas substituents on cyclohexane stabilize one of the conformations, allowing studies

of dynamic equilibria of rather well-defined geometries, each type of substituted cyclobutane represents a new problem in stereochemical analysis. No attempt was made to check the stereochemistry reported in the original literature, and thus, unless it is based on X-ray structures or additional NMR data such as nuclear Overhauser effects or correlation experiments, this information must be treated with caution.

It it noteworthy that one of the most recent and comprehensive publications on the subject[4] questions one of the pillars of stereochemical assignment by NMR, namely the angular dependence of vicinal hydrogen coupling constants. In fact, reference is made to a 1967 article that states: '... data on cyclobutanes are scarce ... and appear rather erratic'[5].

C. Organization and Classification

The intimate relationship between NMR parameters such as chemical shifts and spin–spin coupling constants and molecular geometry is particularly evident for cyclobutane derivatives. Therefore, this aspect is treated first as a separate topic and then in conjunction with specific compounds. As data on cyclobutanes are not as extensive as those for other types of saturated ring systems, especially cyclopropanes and cyclohexanes, comparisons with their respective parameters or effects have also been included wherever they are considered relevant.

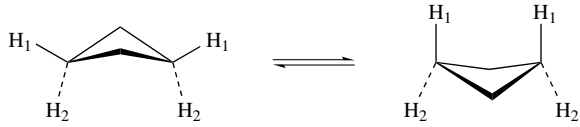
NMR data on different types of cyclobutanes have been organized according to the number and type of substituent on the ring systems. Monosubstituted cyclobutanes are used to exemplify general aspects of NMR data and are followed by di-, tri- and tetrasubstituted derivatives, and the fused ring systems. This material is arranged by parameter (chemical shifts, coupling constants) and then by nucleus, in their order in the periodic table. Wherever discussions of substituent or conformational effects are at hand, they are included along with the respective data on a certain structure.

Substitution patterns are classified relative to the cyclobutane moiety and referred to as geminal when they occur on the same atom and *cis* or *trans* according to their relative positions on the faces of the ring system, and ordered according to the degree of substitution.

II. STRUCTURAL AND CONFORMATIONAL EFFECTS

Hydrogen NMR played an important role in establishing that cyclobutane is nonplanar in the liquid state. At room temperature, the molecule appears to be undergoing rapid interconversion of puckered conformations (Scheme 1), in which there are two types of hydrogen atoms[3]. Fluorine NMR was successfully applied to the conformational analysis of substituted cyclobutanes[3].

In the work of Meiboom and Snyder[6] the hydrogen spectrum of cyclobutane was measured in a liquid crystal solvent (*p*,*p*′-di-*n*-hexyloxyazoxybenzene). The spectrum corresponds to a molecule undergoing rapid interconversion between two nonplanar conformations having D_{2d} symmetry. The lifetime of a single conformation was estimated to be less than 10^{-6} s. Assuming a C–C bond length of 1.548 Å, the spectrum was



SCHEME 1. Interconversion between puckered cyclobutane structures

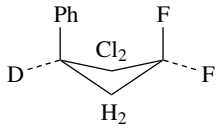
consistent with a H−C−H angle of 108°30′ and a dihedral angle of about 35°. The methylene groups are tilted 2°30′ in a direction which moves axial hydrogen atoms on the same side of the ring away from each other, as the planar conformation involves severe repulsive interactions between the hydrogen atoms attached to adjacent carbon atoms[3].

The conformation of unsubstituted cyclobutane in solution is firmly established. However, as has been pointed out, the conformation adopted by a substituted cyclobutane is variable, being sensitive to the number and nature of substituents. It seems, therefore, that the amount of puckering depends on the nonbonded interactions introduced by the particular substituent or substituents. In this respect, cyclobutane is similar to cyclopentane and cycloheptane, each substituted cyclobutane posing a slightly different problem in conformational analysis.

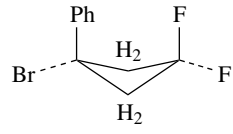
The ^{19}F chemical shift differences for geminal fluorine atoms in substituted cyclobutanes were determined by Lambert and Roberts[7,8]. Their temperature dependence is interpreted in terms of a conformational equilibrium. For a monosubstituted cyclobutane, it was suggested that the axially substituted conformation corresponds to an almost planar system. The angle of puckering for 1,1-difluoro-3-phenylcyclobutane was calculated from dipole moment measurements to be about 27°.

The ^{1}H and ^{19}F spectra of the four cyclobutanes (**1**–**4**) at −50 °C and +100 °C were also investigated by Lambert and Roberts[9]. Marked temperature variations of the ^{19}F chemical shift differences for geminal fluorine substituents and of the H−F coupling constants were observed. The temperature variation of the H−F coupling constants for 1,1-difluoro-2,2-dichloro-3-methyl-3-phenylcyclobutane, **5**, are given in Table 1. The magnitudes of the couplings appear to follow a dihedral angle Karplus-type $\cos^2\phi$ relationship.

The structural and stereochemical analysis of cyclobutanes as well as other four-, five- and seven-membered ring systems by ^{13}C NMR have been reviewed by Pihlaja



(1)



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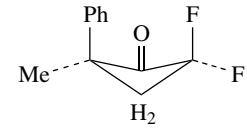

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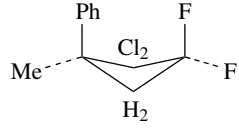

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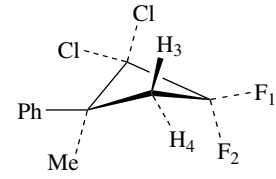


(5)

TABLE 1. Temperature dependence of H−F coupling constants (Hz) for **5**[9]

Temperature (°C)	J_{13}	J_{14}	J_{23}	J_{24}
−50	8.69	0.64	21.22	13.65
+30	8.79	0.91	21.02	13.93
+100	8.89	1.34	20.40	13.63

and Kleinpeter[10]. They report chemical shifts and discuss their application in structural analysis of cyclobutanes, their substituted derivatives and certain fused systems.

III. SPECTRAL PARAMETERS

There are several compilations of NMR parameters that include cyclobutanes. Representative examples are given here and compared with data on other saturated ring systems.

A. Chemical Shifts

Early work on chemical shifts of these systems[11] revealed that cyclobutane does not follow certain patterns related to the size of the ring. ^{1}H and ^{13}C chemical shifts are given in Table 2.

The ^{1}H NMR spectrum of cyclobutane gives a singlet at 1.94 ppm; cyclobutane hydrogens are thus less shielded than those of cyclopentane and cyclohexane. It did not escape early investigators in the field[13] that cyclobutane, in contrast to cyclopropane, shows decreased hydrogen shielding compared to the alkane chain value. Very recent theoretical work based on nucleus-independent chemical shift (NICS) analysis[1] has thrown some light on the factors involved in the shieldings that are observed for unsubstituted ring systems. Other theoretical calculations on chemical shifts of cyclobutane derivatives are seriously lacking, however.

The hydrogen spectra of a few monosubstituted cyclobutanes have been reported. The effect of substituents on the chemical shift of the ring hydrogens of cyclobutane was investigated by Weitkamp and Korte[14]. Nakagawa and coworkers[15] interpreted the downfield shift of axial-type hydrogens in puckered cyclobutanes in terms of magnetic anisotropy.

Hydrogen chemical shifts of cyclobutanes are included in a review on applications of ^{1}H NMR[3].

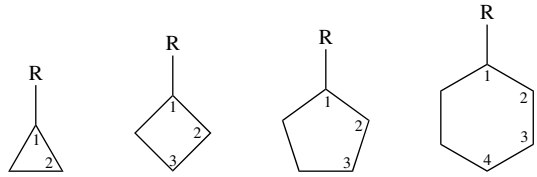
Carbon-13 chemical shifts for cyclobutane and monosubstituted cyclobutanes are compared to those of other saturated rings as can be seen in Scheme 2[16]. They do not appear to follow any systematic pattern.

Data on methyl-substituted cyclobutane derivatives are given in Table 3 and compared to the methyl substituent effects on cyclobutane ring carbons and those for cyclopropanes and cyclopentanes in Table 4[10].

The α- and β-effects of the methyl substitution in cyclobutane are comparable to these effects in cyclopropane and cyclopentane (Table 4)[10]. The geminal α- and β-effects are all negative (shielding), as expected. It should be noted that even in four-membered rings, the substitution provides evidence of some equatorial or axial character, the former probably predominating to some extent. It also appears that axial α-effects are less deshielding than equatorial α-effects. However, it is not possible to derive separate values for the axial and equatorial effects in four- or five-membered rings, indicating that, at least in the

TABLE 2. Chemical shifts of cycloalkanes (δ, in ppm)[12]

Compound	^{1}H (ppm)	^{13}C (ppm)
Cyclopropane	0.22	−2.8
Cyclobutane	1.94	22.4
Cyclopentane	1.51	25.8
Cyclohexane	1.44	27.0
Cycloheptane	1.54	28.7



Atom	R								
	---	–Me	$-CO_2H$	–Cl	–Br	–I	$-NH_2$	–OH	=O
Cyclopropanes									
C^1	–2.9	5.7	13.1	27.3	14.1	–20.2	24.0	45.7	
C^2		6.1	9.2	8.9	9.1	10.3	7.6	6.8	
C of R		19.9	181.9						
Cyclobutanes									
C^1	22.9	31.2	38.4	52.3	42.3	15.8		67.0	208.4
C^2		30.2	25.4	34.8	35.5	36.9		33.4	47.8
C^3		18.3	18.6	16.3	18.8	22.9		12.1	9.9
C of R		22.1	181.9						
Cyclopentanes									
C^1	26.2	35.1	43.9	61.8	53.0	28.1	52.5	73.6	219.6
C^2		35.1	30.1	37.3	38.0	39.8	35.5	35.4	38.2
C^3		25.6	26.0	23.2	23.4	23.9	23.0	23.5	23.4
C of R		20.9	183.5						
Cyclohexanes									
C^1	27.3	33.1	43.1	59.9	52.9	32.0	50.5	70.1	211.2
C^2		35.8	29.0	36.9	37.6	39.5	37.1	35.5	41.9
C^3		26.7	25.5	25.0	25.9	27.1	25.3	24.5	27.2
C^4		26.7	25.9	25.4	25.3	25.2	26.0	25.9	25.1
C of R		22.9	183.0						

SCHEME 2. Substituent effects on saturated ring systems

compounds studied, the magnitude of the α-effect also depends on the spatial orientation of the substituent.

The magnitude of γ-effects in cyclobutanes (−4.5 ppm), in contrast to the situation in cyclopentanes, is close to that of γ-axial or γ-*syn* effects in six-membered rings[10]. The estimates (Table 4) are based on the monomethyl substitution, which should be of a more equatorial than axial type. In cyclobutane as well as in other four-membered rings, γ-effects can operate from both directions. If this is the case, the magnitude of

TABLE 3. ^{13}C NMR chemical shifts (ppm) for cyclopropane, cyclobutane and cyclopentane and their methyl-substituted derivatives[10]

Compound	C-α	C-β	C-γ	Me		
Cyclopropane	−2.9	−2.9	−2.9			
1-Me	8.2	8.9	8.9	22.5		
1,1-Me_2	14.4	17.0	17.0	28.6		
c-1,2-Me_2	12.7	12.7	16.5	15.9		
t-1,2-Me_2	17.1	17.1	17.5	21.9		
Cyclobutane	22.86	22.86	22.86			
1-Me	31.24	30.18	18.32	22.11		
1,1-Me_2	35.93	34.87	14.82	29.44		
c-1,2-Me_2	32.22	32.22	26.55	15.36		
t-1,2-Me_2	39.17	39.17	26.83	20.49		
c-1,3-Me_2	26.87	38.51	26.87	22.47		
t-1,3-Me_2	26.10	36.44	26.10	22.00		
Me_{8-}	41.08	41.08	41.08	22.26		
Cyclopentanes	**C-1**	**C-2**	**C-3**	**C-4**	**C-5**	**Me**
	25.6	25.6	25.6	25.6	25.6	
1-Me	34.9	34.9	25.5	25.5	34.9	20.5
1,1-Me_2	39.2	41.4	25.0	25.0	41.4	29.1
c-1,2-Me_2	37.7	37.7	33.3	23.3	33.3	15.2
t-1,2-Me_2	42.8	42.8	35.1	23.4	35.1	18.8
c-1,3-Me_2	35.5	45.1	35.5	34.4	34.4	21.2
t-1,3-Me_2	33.6	43.2	33.6	35.3	35.3	21.5

TABLE 4. ^{13}C methyl substituent effects (in ppm) in cyclopropanes, cyclobutanes and cyclopentanes[10]

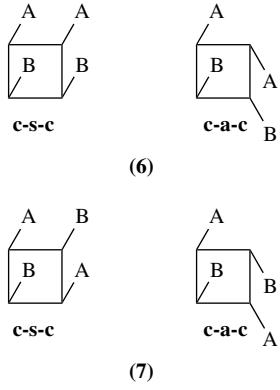
	Cyclopropanes		
	C-1	C-2	C-3
1-Me	8.2	8.9	8.9
1,1-Me_2	−2.0	−0.8	−0.8
c-1,2-Me_2	−4.4	−4.4	−1.3
t-1,2-Me_2			−0.3

	Cyclobutanes		
	C-α	C-β	C-γ
1-Me	8.4	7.3	−4.5
1,1-Me_2	−3.7	−2.6	1.0
c-1,2-Me_2	−6.4	−6.4	0.9
t-1,2-Me_2	0.6	0.6	1.2
c-1,3-Me_2	0.2	1.0	0.2
t-1,3-Me_2	−0.6	−1.1	−0.6

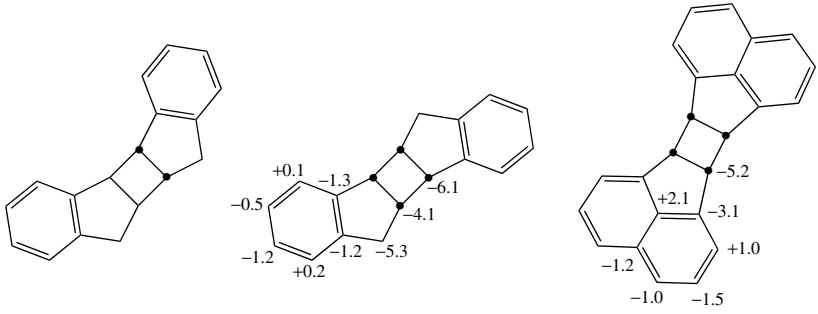
	Cyclopentanes				
	C-1	C-2	C-3	C-4	C-5
1-Me	9.3	9.3	−0.1	−0.1	9.3
1,1-Me_2	−5.0	−2.8	−0.4	−0.4	−2.8
c-1,2-Me_2	−6.5	−6.5	−1.5	−2.1	−1.5
t-1,2-Me_2	−1.4	−1.4	0.3	−2.0	0.3
c-1,3-Me_2	0.7	0.9	0.7	−0.4	−0.4
t-1,3-Me_2	−1.2	−1.0	−1.2	0.5	0.5

the γ-effects in cyclobutanes is, on the average, only -2.3 and -2.5 ppm, respectively, which emphasizes that in four-membered rings the equatorial and axial orientations are fairly close to each other energetically. In fact, chemical shifts of *cis*- and *trans*-1,3-dimethylcyclobutanes are very close. Small 1,3- and 2,4-disubstitution effects comparable to those found in several six-membered rings are present also in cyclobutanes and cyclopentanes[10]. The vicinal *cis* effects at C-1/2 are of the magnitude of about -6.5 ppm in cyclobutanes and cyclopentanes and about -4.4 ppm in cyclopropanes. These effects can slightly shield or deshield other carbons. The vicinal *trans* effects are small and usually positive (deshielding).

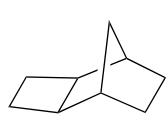
Browne and coworkers studied cyclobutane dimers formed photochemically from benzocycloalkenes and compared ^{13}C chemical shifts (Scheme 3) for the head-to-head, **6**, and head-to-tail, **7**, *cis-syn-cis* (**c-s-c**) and *cis-anti-cis* system (**c-a-c**, e.g. **8**). Model compounds such as **8** reveal shielding trends, which facilitate structural and stereochemical assignments (cf. **9** and **10**)[17]. Ishii and coworkers reported the ^{13}C NMR spectra of tricyclo[4.2.1.0^{2,5}]nonanes (**11**) and tetracyclo[5.4.1.0^{2,6}.0^{8,11}]dodecanes (**12**) and their dimethyl derivatives to demonstrate the four-membered ring annelation effects on the bicyclo[2.2.1]heptane skeleton, and the steric δ-*syn* effects of the methyls attached to the four-membered ring[18].



SCHEME 3. Head-to-head and head-to-tail cyclobutane dimers



(8) **(9)** **(10)**



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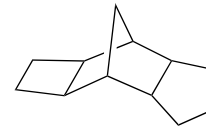


(12)

TABLE 5. Characteristic hydrogen–hydrogen coupling constants in cycloalkanes (Hz)[19]

Compound	J_{gem}	J_{cis}	J_{trans}
Cyclopropane	−4.5	9.2	5.4
Cyclobutane derivatives	−11 to −15	6 to 11	3 to 9
Cyclopentane derivatives	−11 to −17	7 to 11	2 to 8
Cyclohexane derivatives	−12 to −15	J_{ae} 2 to 5	J_{aa} 8 to 13 J_{ee} 1 to 4

TABLE 6. Characteristic carbon–hydrogen coupling constants in cycloalkanes (Hz)[13]

Compound	J_{C-H}
Cyclopropane	162 ± 2
Cyclobutane	136 ± 1
Cyclopentane	131 ± 2
Cyclohexane	127 ± 2

B. Coupling Constants

Hydrogen–hydrogen and carbon–hydrogen spin–spin coupling constants for cyclobutane are compared to those for other saturated ring systems in Tables 5 and 6, respectively.

1. Hydrogen–Hydrogen

From the spectrum of cyclobutane in a liquid crystal solvent, Meiboom and Snyder[6] deduced vicinal coupling constants of 10.4 Hz for J_{cis} ($J_{13} = J_{24}$) and 4.9 Hz for J_{trans} ($J_{14} = J_{23}$). The cross-ring coupling constants J_{16} and J_{15} were not detected.

Vicinal coupling constants cover a wide range of values. This is characteristic of four-membered and five-membered ring systems, due to the conformations which differ only slightly in the energy that they adopt. A geminal coupling constant of −13.95 Hz was reported[20] for the ring hydrogens at positions 4 of 1,1-dimethyl-*cis*-2,3-dichlorocyclobutane-2,3-dicarboxylic acid.

Coupling constants for two *cis*-1,1,2,3-tetra-R-substituted cyclobutanes in CD_3COCD_3[14] are given in Table 7.

The spectra of two *trans*-1,1,2,3-tetra-R-substituted cyclobutanes[14] gave the coupling constants in Table 8. J_{gem} was reported as −13 Hz for two *cis*-1,3-dimethyl-1,3-dihalogenocyclobutanes (halogen = Cl or Br) in CCl_4[21]. Lustig[22] showed that J_{gem} and J_{cis}, J_{trans} were of opposite sign in cyclobutanes, and recorded the coupling constants listed in Table 9 for two 1,1,2,2-tetrasubstituted cyclobutanes.

TABLE 7. Coupling constants of *cis*-1,1,2,3-tetra-R-substituted derivatives (Hz)[14]

R	J_{gem}	J_{cis}		J_{trans}	J(long range)	
	J_{12}	J_{14}	J_{34}	J_{24}	J_{13}	J_{23}
CO_2Me	−11.2	9.23	8.82	9.18	2.23	−0.82
CO_2H	−11.1	8.98	8.58	9.77	2.31	+0.4

TABLE 8. Coupling constants of *trans*-1,1,2,3-tetra-R-substituted cyclobutane derivatives (Hz)[14]

R	J_{gem}	J_{cis}		J_{trans}	J (long range)	
	J_{12}	J_{24}	J_{14}	J_{34}	J_{13}	J_{23}
CO_2Me	—	9.32	9.32	9.02	—	—
CO_2H	—	9.62	9.64	9.38	−0.53	−0.53

TABLE 9. Coupling constants for 1,1-di-R,2,2-di-R′-tetrasubstituted cyclobutane derivatives (Hz)[22]

R	R′	J_{gem}	J_{cis}	J_{trans}	
		J_{AB}, $J_{A'B'}$	J_{AB}, $J_{A'B}$	$J_{AA'}$	$J_{BB'}$
Cl	CN	−13.1	9.4	9.3	4.5
Br	CO_2Me	−12.0	6.2	10.0	8.4

One of the coupling constants reported[23] for dichlorocyclobutanedicarboxylic acid is only 6.3 Hz, the other being 10.6 Hz. For the same compound J_{trans} was 5.9 Hz, the 4-bond coupling being −1.5 Hz. A stereospecific 5-bond coupling between axial methyl hydrogens and the equatorial fluorine of *ca* 2.1 was detected by Roberts and coworkers[24] in 1,1-difluoro-2,2-dichloro-3-phenyl-3-methylcyclobutane.

The spectra of some 1,2,3,4-tetrasubstituted cyclobutanes were run by Kranch and coworkers[25]; J_{cis} values were in the range 9.4–10.6 Hz while J_{trans} values in the range 4.0–10.7 Hz and 4-bond coupling of 0.6 Hz (*trans*) were reported.

Hydrogen coupling constants in cyclobutanes are included in a review on applications of ^{1}H NMR[3].

2. Carbon–Hydrogen

Carbon–hydrogen spin–spin coupling constants of cyclobutane are included in a review by Hansen[26] and discussed in terms of ring strain, steric effects, electronegativity, lone pair effects and electric field effects. Additivity of substituent effects in a few systems was mentioned.

3. Fluorine–Hydrogen

Fluorine–hydrogen coupling constants in cyclobutanes are included in a review by Emsley, Phillips and Wray[27]. Their medium and temperature effects are analyzed.

TABLE 10. ^{13}C relaxation times T_1 in saturated rings[19]

Compound	T_1 (s)
Cyclopropane	37
Cyclobutane	36
Cyclopentane	29
Cyclohexane	20

4. Carbon–Carbon

Factors affecting carbon–carbon coupling constants of cyclobutane derivatives have been studied using ^{13}C-labeled compounds[28,29]. Small substituent effects on directly-bonded carbons are observed. Aliphatic vicinal $^{13}C-^{13}C$ couplings are shown to parallel vicinal $^{1}H-^{1}H$ couplings in similar geometric surroundings, suggesting a similar dependence on bond and dihedral angles.

One-bond carbon–carbon spin–spin coupling constants of cyclobutane are included in a review by Krivdin and Kalabin[30]. They are analyzed in terms of hybridization, substitution effects, lone pair effects and steric effects as well as their respective applications to structural determination. The carbon–carbon spin–spin coupling constants between carbons that are separated by more than one bond were reviewed by Krivdin and Della[31] and are discussed in terms of experimental techniques, the effects of hybridization, substituent effects, steric effects and respective additivity patterns.

C. Relaxation Times

Longitudinal relaxation times (T_1) for ^{13}C nuclei cover a large range of values. Those for cyclic ring systems (Table 10) are intermediate between the very short ones observed for macromolecules and the longer ones that are characteristic of quaternary carbons or those in highly symmetric molecules. For cyclobutanes, spin rotation is competitive with the dipolar mechanism for longitudinal relaxation[32].

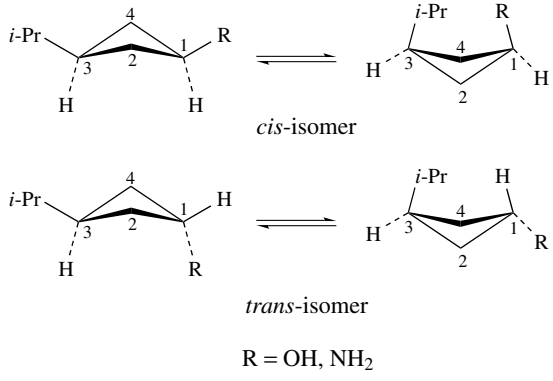
IV. SUBSTITUTED CYCLOBUTANES

A. Disubstituted Cyclobutanes

Geminal and vicinal effects on hydrogen chemical shifts of disubstituted cyclobutanes are exemplified by 1,1-diethoxycarbonylcyclobutane[14], where the chemical shifts of the ring hydrogens in CD_3COCD_3 are 2.55 and 2.97 ppm, for H_2 and H_3, respectively. While the methyl hydrogens of *trans*-1,3-dimethylcyclobutane are found at 1.1 ppm, the methylene hydrogens are at 1.7 ppm and the methine hydrogens at 2.3 ppm. Cyclobutane hydrogens are compared to cyclohexane hydrogens by Lillien and Doughty[33] in their work on 3-isopropylcyclobutanol and 3-isopropylcyclobutylamine. The *cis*-compounds exist almost entirely in one conformation and the *trans*-isomers reflect the presence of two forms, with one of them predominating (Scheme 4). Chemical shifts are given in Table 11. Arrows indicate averages between equatorial and axial positions.

B. Trisubstituted Cyclobutanes

Cis- and *trans*-2-methyl-1-phenylcyclobutanol, **13**(E) and **14**(Z), respectively, were differentiated by the chemical shift of their respective methyl hydrogens[34]. It was assumed

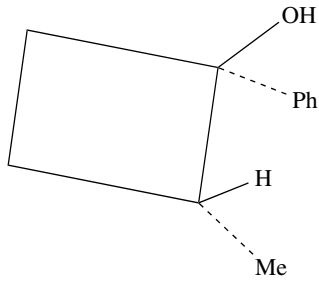


SCHEME 4. Steric interactions between substituents

TABLE 11. Chemical shifts for ring hydrogens of *cis*- and *trans*-3-isopropylcyclobutanol and *cis*- and *trans*-3-isopropylcyclobutylamine[33]

Compound[a]	Chemical shifts (centers of multiplets)[b,c]					
	H_1			H_2		
	e		a	e		a
cis-Alcohol (R = OH)	—		4.1	2.4		1.4
trans-Alcohol (R = OH)	←	4.3	→	←	2.1	→
cis-Amine ($R = NH_2$)	—		3.2	2.3		1.3
trans-Amine ($R = NH_2$)	←	3.4	→	←	1.9	→

[a] Structures and numbers of atoms are given in Scheme 4.
[b] e = equatorial, a = axial.
[c] Arrows indicate rapid equilibria and average chemical shifts.



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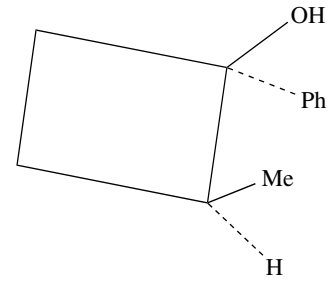
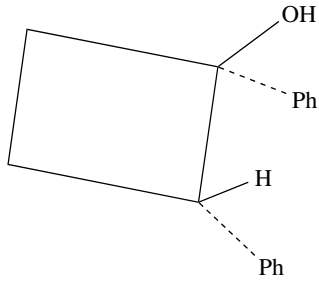


(14)

that the presence of an aromatic ring would shield the hydrogens of a *cis*-related methyl group (cf. three-membered rings). The alcohol for which the methyl doublet appeared at 0.67 ppm was assigned the *cis*-configuration, whereas the isomeric alcohol gave the methyl doublet at 1.06 ppm. Similar considerations were applied to the hydroxyl resonances in *cis*- and *trans*-1,2-diphenylcyclobutan-1-ol, **15**,(E) and **16**,(Z) respectively. Their configurations were assigned to the alcohols giving hydroxyl signals at 3.52 ppm and 1.75 ppm, respectively.



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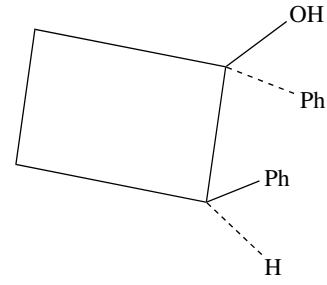
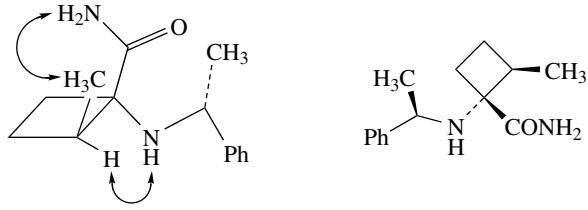


(16)

Cyclobutane aminoacids and their amides represent examples of trisubstituted systems that were analyzed by NMR and X-ray crystallography[35]. The relative stereochemistry of one of the corresponding α-amino amides (**17**) was determined by 2D NMR experiments carried out in $CDCl_3$. NOEs were measured between the carboxamide NH_2 hydrogens and the methyl group at position 2 of the cyclobutane on one side, and between the amino NH-hydrogen of the chiral moiety and the methyl hydrogen at position 2 on the other side, both indicating the *trans* configuration of the methyl and the 1-phenylethylamino substituents. The absolute stereochemistry of the *trans* compounds was obtained from X-ray analysis, which allowed unambiguous assignment of the αR, $1S$, $2S$ configuration to compound **18**. Consequently, the diastereomeric *trans* α-amino amide **17** must have the αR, $1R$, $2R$ configuration. Hydrogen and carbon-13 NMR data for **17** are **18** are given below. Similar NMR parameters for cyclobutane amino acids and other derivatives are also given in the article.



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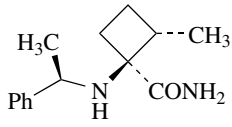
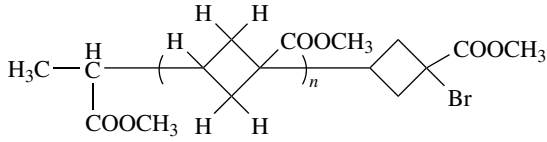


(18)

17: (αR, $1R$, $2R$)-2-Methyl-1-(1-phenylethylamino)cyclobutanecarboxamide. ^{1}H NMR ($CDCl_3$) δ: 0.98 (d, $J = 6.84$ Hz, 3H), 1.28 (d, $J = 6.59$ Hz, 3H), 1.46–1.62 (m, 2H), 1.67 (br s, 1H), 1.74–1.84 (m, 1H), 2.1–2.23 (m, 1H), 2.32–2.45 (m, 1H), 3.86 (q, $J = 6.59$ Hz, 1H), 5.5 (br s, 1H), 7.1 (br s, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$)δ: 15.9 (q), 22.7 (t), 23.8 (q), 26.5 (t), 43.4 (d), 54.7 (d), 67.2 (s), 126.3 (d), 127.0 (d), 128.4 (d), 146.5 (s), 177.5 (s).

18: (αR, 1*S*, 2*S*)-2-Methyl-1-(1-phenylethylamino)cyclobutanecarboxamide. ^{1}H NMR ($CDCl_3$)δ: 0.98 (d, $J = 6.84$ Hz, 3H), 1.41 (d, $J = 6.59$ Hz, 3H), 1.5–1.7 (m, 2H), 1.82–2.0 (m, 2H), 2.2–2.34 (m, 1H), 2.73–2.83 (m, 1H), 3.75 (q, $J = 6.59$ Hz, 1H), 4.9 (br s, 1H), 6.4 (br s, 1H), 7.15–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$)δ: 15.9 (q), 22.6 (t), 25.6 (q), 28.8 (t), 43.4 (d), 54.2 (d), 67.7 (s), 126.3 (d), 126.7 (d), 128.3 (d), 146.1 (s), 176.1 (s).

Polymers of methyl 1-bicyclobutanecarboxylate (MBC) represent examples of trisubstituted cyclobutanes. They are formed by head-to-tail addition when a 1-substituted bicyclobutane monomer such as MBC is polymerized[36]. The cyclobutane rings in the polymer chain can be either in a *trans* or *cis* configuration, that is, there are two types of methoxy groups, *trans*- or *cis*-OMe for the esters in the chain of the polymer **19**, that is, *trans*- or *cis*-CH_3 ester, which have chemical shifts at 3.65 or 3.68 ppm, respectively. The ratio of *trans* to *cis* is 66:34. Interestingly, two end-group signals corresponding to the two types of methoxy groups for the terminal esters end capped with Br were observed in the NMR spectrum of PMBC-Br synthesized by the ATRP initiation system. The signals for the *trans*- and *cis*-CH_3 ester group of the terminal MBC unit capped with an ω-end bromine were detected at 3.79 and 3.82 ppm, respectively.



(19)

C. Tetrasubstituted Cyclobutanes

Griesbaum and coworkers[21] recorded the hydrogen chemical shifts for *cis*- and *trans*-2,3-dihalogeno-1,3-dimethylcyclobutanes (Table 12). In the spectra of the *cis*-compounds the ring hydrogens gave AA′BB′ spectra whereas the spectra of the *trans*-isomers showed a singlet for the ring hydrogens.

The spectra of *cis*-1,3-dimethylcyclobutane-1,3-dicarboxylic acid and the related esters, anhydride and imide were discussed by LaLonde and Aksentijevitch[37]. The ring hydrogens of the acid and esters gave AX quarters, whereas the ring hydrogens of the anhydride and imide gave more complicated AA′BB′ patterns.

TABLE 12. Hydrogen chemical shifts (δ in ppm) of *cis*- and *trans*-2,3-dihalogeno-1,3-dimethylcyclobutanes in CCl_4[21]

2,3-Dihalogen	Me	H_A	H_B [a]
cis-Br	1.88	2.84	3.54
cis-Cl	1.69	2.72	3.10
	Me	Ring hydrogen	
trans-Br	2.13	3.21	
trans-Cl	1.86	2.88	

[a] H_B is *cis* to Me.

TABLE 13. Hydrogen chemical shifts (δ, ppm) for *cis*- and *trans*-1,1-dimethyl-2,3-di-R-substituted cyclobutanes in CD_3COCD_3

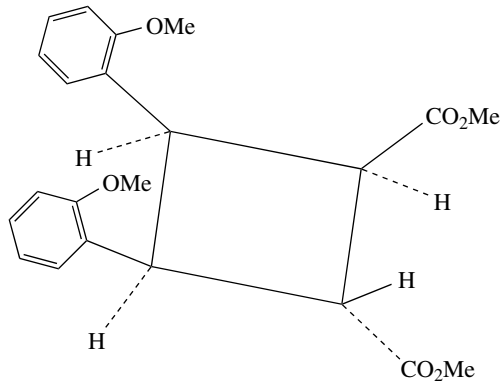
R	H_2	H_3	H_4 [a]	$H_{4'}$ [a]
cis-CO_2H	3.07	3.33	1.85	2.33
cis-CO_2Me	3.04	3.20	1.84	2.33
trans-CO_2H	3.08	3.31	1.94	1.94
trans-CO_2Me	3.04	3.31	1.89	1.89

[a] $H_{4'}$ is *cis* to R.

The ring hydrogen chemical shifts of *cis*- and *trans*-1,1,2,3-dimethyl-2,3-cyclobutanes-carboxylic acids and their esters[14] are given in Table 13.

Hydrogen chemical shifts of *cis*-3,4-dichlorocyclobutane-*cis*-1,2-dicarboxylic acid in pyridine were reported by Georgian and coworkers[23]. They correspond to an AA′XX′ pattern, H_A and H_X having shifts of 5.46 ppm and 4.18 ppm, respectively. Hydrogens of *trans*-3,4-dibromocyclobutane-*cis*-1,2-dicarboxylic acid gave a spectrum typical of an ABCD system, the chemical shifts being 5.79 (H_A), 5.16 (H_B), 4.45 (H_C) and 4.04 ppm (H_D). These were tentatively assigned, respectively, to H_3, H_4, H_1 and H_2 but H_3 and H_4 and H_1 and H_2 may be reversed.

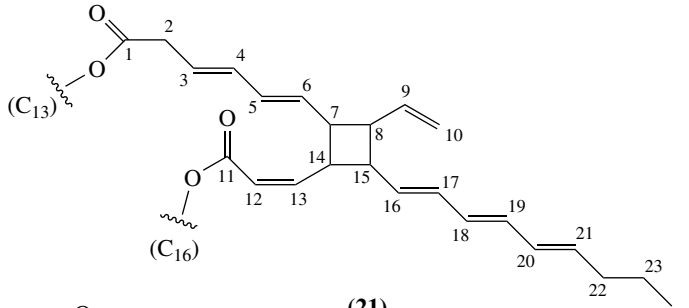
Anet[38] has successfully interpreted the spectrum of a 1,2,3,4-tetrasubstituted cyclobutane **20** for which eleven configurations are possible, taking into consideration the origin of the compound. The observation of four methoxy resonances allowed nine of the eleven configurations to be discarded and chemical evidence then eliminated one of the remaining configurations.



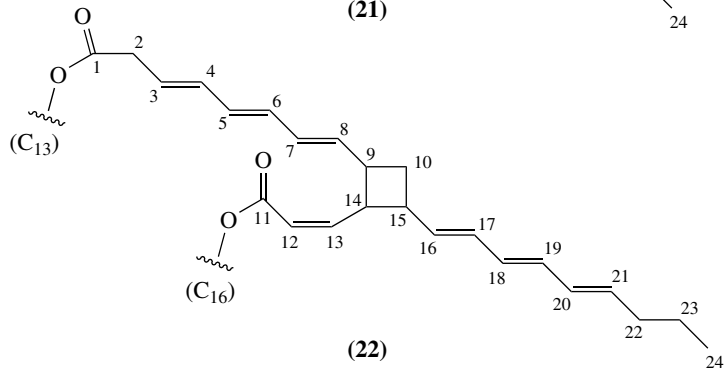
(20)

The isolation and structure elucidation of six phorbol esters from the seed oil of *Jatropha curcas* L (Euphorbiaceae), an oil-bearing shrub widely distributed in many Latin-American, Asian and African countries, yielded two new cyclobutanes, tetrasubstituted **21** and trisubstituted **22**[39]. Their respective hydrogen and carbon-13 NMR data are given in Tables 14 and 15. For **21**, $^1H-^1H$ COSY cross-peaks between H-7/H-8, H-8/H-15, H-14/H-7 and H-14/H-15 as well as coupling of each one of the hydrogens H-7, H-8, H-14 and H-15 with an olefinic signal led to the structure of the cyclobutane unit as **21**. Ambiguities in assignments, which result from the fact that the signals of H-7 and

H-15 have identical hydrogen shifts (δ_H2.91), were overcome by detailed analysis of the TOCSY and HMBC spectra. Structure elucidation of the carbon chains attached to C-8 and C-15 and of the ester chains linking the cyclobutane carbons C-7 and C-14 to C-13 and C-16, respectively, of the phorbol moiety was performed on the basis of NMR data.



(21)



(22)

The instability of compound **22** limited the number of experiments that could be performed. Thus, no NOE data could be measured to obtain information on the relative stereochemistry of **22**. NMR data were similar to those of **21**, with the exception that the ^{1}H NMR data of the dicarboxylic acid residue of **22** included only three aliphatic methine hydrogen signals at δ_H3.70 (H-9), 4.32 (H-14) and 2.98 (H-15) instead of the four signals displayed in the ^{1}H NMR spectrum of **21** and assigned to the cyclobutane hydrogens. Furthermore, the ^{1}H NMR spectrum of **22** exhibited additional signals of two nonequivalent aliphatic methylene hydrogens at δ_H2.21 (H-10a) and 2.12 (H-10b); the signals of two olefinic hydrogens at δ_H5.19 (H-10a) and 5.14 (H-10b) that appeared in the ^{1}H NMR spectrum of **21** were missing. Detailed analysis of 1D and 2D NMR spectra led to the determination of the structure of the acid moiety of **22**. Differences from the structure of the acid moiety of **21** consist in a tri- rather than tetrasubstituted cyclobutane unit and in the length of the ester chain leading from the cyclobutane unit to C-13. Neither the absolute stereochemistry of the molecule nor the relative configuration of the cyclobutane unit could be assigned.

The photochemical dimerization of styrylpyrones provides another interesting source of ^{1}H and ^{13}C data on tetrasubstituted cyclobutanes. Irradiation of 5-methoxy-2-styryl-4-pyrones yields **23a**–**23e** and **24a**–**24e** along with another product[40]. The ^{1}H NMR spectra together with ^{13}C NMR data of all the isolated dimeric products pointed to the symmetrical cyclobutane structure. Based on NOE experiments, combined with previously obtained

TABLE 14. ^{1}H NMR data (δ in ppm)[a,b] for the dicarboxylic acid moieties of compounds **21** and **22** (CD_2Cl_2, 500 MHz)[39]

Position	**21**	**22**
2a	3.22 dd (18.9, 5.1)	3.17 dd (17.9, 7.8)
2b	3.10 dd (8.9, 10.3)	3.12 dd (17.9, 7.1)
3	5.53 ddd (15.0, 10.3, 5.1)	5.57 dt (14.2, 7.3)
4	5.97 dd (15.0, 10.4)	6.04 o
5	5.89 dd (14.9, 10.4)	6.00–6.03 o[c,d]
6	5.62 dd (14.9, 9.5)	6.29 dd (13.9, 11.0)[d]
7	2.91 o	6.00–6.03 o[c]
8	2.85 q (8.7)	5.71 dd (10.1, 8.2)
9	6.25 ddd (16.9, 10.3, 8.7)	3.70 m
10a	5.19 dd (10.3, 1.7)	2.21 dt (11.5, 8.2)
10b	5.14 dd (16.9, 1.7)	2.12 o
12	2.61 dd (11.4, 1.3)	5.69 dd (11.4, 1.2)
13	6.27 dd (11.4, 9.3)	6.19 dd (11.4, 9.4)
14	4.57 br q (9.3)	4.32 br q (9.4)
15	2.91 o	2.98 m
16	6.02 dd (14.5, 9.4)	5.77 dd (14.2, 7.1)
17	6.20 o	6.00–6.03 o[c]
18	6.17 o	6.00–6.03 o[c]
19	6.17 o	6.00–6.03 o[c]
20	6.11 m	6.00–6.03 o[c]
21	5.75 dt (14.7, 7.4)	5.70 dt (14.2, 7.3)
22	2.10 q (7.4)	2.06 q (7.3)
23	1.44 tq (7.4)	1.40 tq (7.3)
24	0.93 t (7.4)	0.89 t (7.3)

[a]Multiplicities are indicated by their usual symbols; o, overlapped signal.
[b]J in Hz are given in parentheses.
[c]The large number of partly overlapping signals at δ 5.5–6.1 for **22** prevented an exact assignment of these hydrogens.
[d]These assignments may be interchanged.

data for stereochemical relationships of heterocyclic cyclobutanes, the stereochemistry of compounds **23** and **24** should correspond to structures **25** and **26**, respectively.

Some NMR data (δ, ppm) on the cyclobutyl ring for several members of the series in $CDCl_3$ are:

23a: ^{1}H NMR: δ 4.38 (m, 2H) and 4.28 (m, 2H) for cyclobutane H^a and H^b, respectively.

23b: ^{1}H NMR: δ 4.51 (m, 2H), 4.47 (m, 2H); ^{13}C NMR : δ 45.4 (d) and 43.6 (d) for the cyclobutane carbons.

23c: ^{1}H NMR: δ 4.33 (m, 2H, H^a), 4.17 (dd, 2H J = 8.65, 8.56 Hz, H^b); ^{13}C NMR : δ 45.6 (d), 43.1 (d).

23d: ^{1}H NMR: δ 4.57 (m, 2H), 4.52 (m, 2H); ^{13}C NMR : δ 44.2 (d), 42.2 (d).

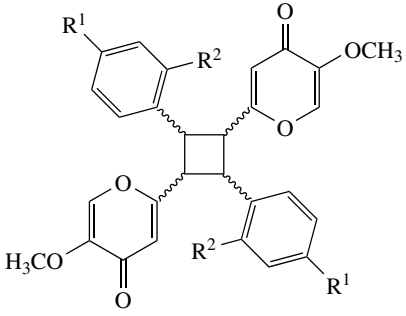
24d: ^{1}H NMR: δ 4.47 (s, 2H), 4.45 (s, 2H); ^{13}C NMR : δ 43.6 (d), 42.6 (d).

24e: ^{1}H NMR: δ 4.69 (s, 4H); ^{13}C NMR : δ 42.5 (d), 41.1 (d).

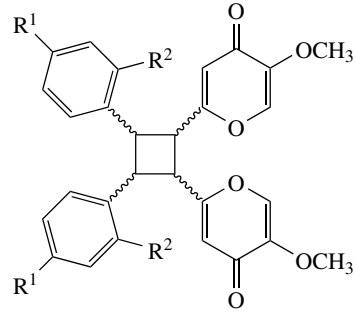
TABLE 15. ^{13}C NMR data for the dicarboxylic acid moieties of compounds **21** and **22** (δ, CD_2Cl_2, 125 MHz)[39]

Position	**21**[a]	**22**[a]
1	173.8	173.9
2	38.6	39.0
3	123.3	122.1
4	133.9	136.7
5	129.8	129.9–132.3[a]
6	131.6	130.6
7	48.9	129.9–132.3[b]
8	47.1	135.1
9	137.7	35.7
10	115.9	31.9
11	166.6	166.3
12	119.0	119.6
13	145.9	153.3
14	42.1	46.1
15	44.1	43.4
16	132.0	136.4
17	130.4 or 132.7[b]	129.9–132.3[b]
18	130.4 or 132.7[b]	129.9–132.3[b]
19	130.4 or 132.7[b]	129.9–132.3[b]
20	130.7	130.9
21	135.6	135.3
22	35.3	35.3
23	23.0	23.0
24	14.0	14.0

[a] Assignments are based on DEPT, HMQC and HMBC experiments.
[b] The large number of partly overlapping signals at δ 125–135 for **22** and 130–135 for **21** prevented an exact assignment of these carbons.

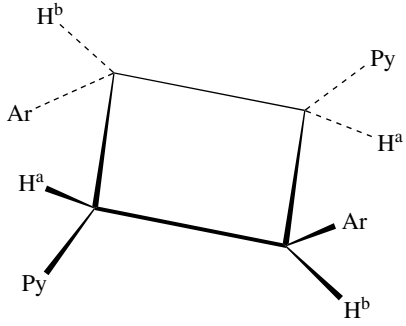


(23a–23e)

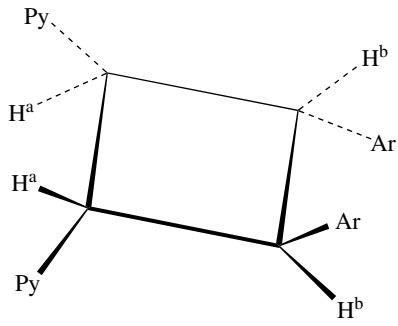


(24a–24e)

(a) $R^1 = R^2 = H$
(b) $R^1 = CH_3$, $R^2 = H$
(c) $R^1 = OCH_3$, $R^2 = H$
(d) $R^1 = Cl$, $R^2 = H$
(e) $R^1 = H$, $R^2 = Cl$



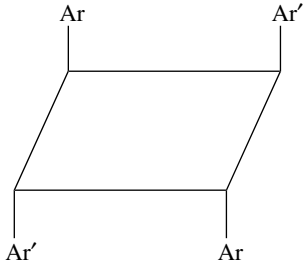
(25)



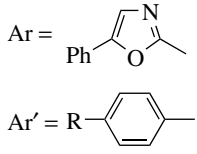
(26)

The authors also report the formation of 'half-cage' dimers containing a cyclobutane ring. However, the ^{1}H NMR data did not allow the distinction between isomers formed from 'head-to-head' or 'head-to-tail' dimerization.

Photodimerization of stilbazolium salts provides other examples of tetrasubstituted cyclobutanes **27**[41]. Their ^{1}H and ^{13}C NMR data for the cyclobutyl ring are reported without assignment as:



(27a–27d)



(a) R = H; **(b)** R = Cl;
(c) R = OMe; **(d)** R = *t*-Bu

27a: ^{1}H NMR($CDCl_3$): δ 4.90–4.75 (4H, m); ^{13}C NMR($CDCl_3$): δ 44.72 (CH), 41.26 (CH).

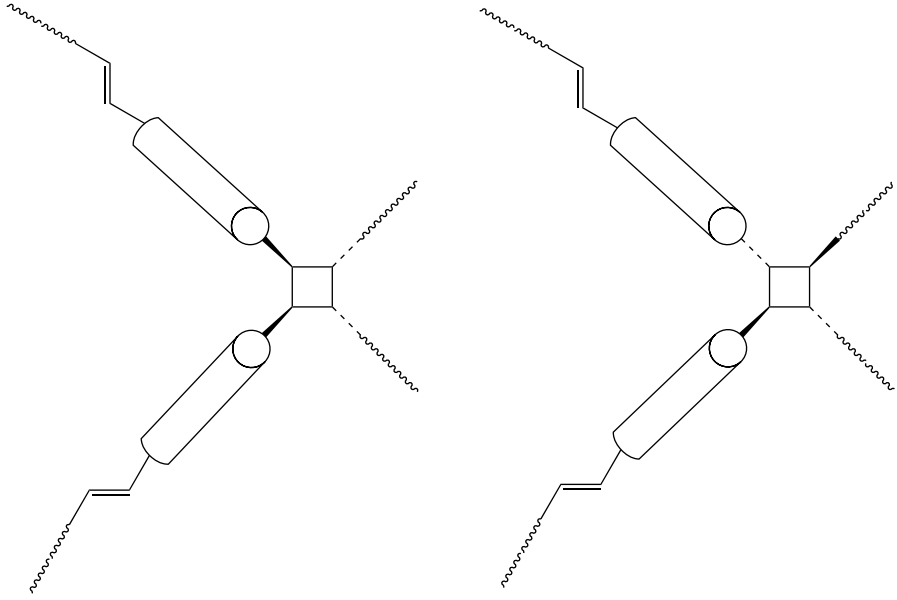
27b: ^{1}H NMR($CDCl_3$): δ 4.82–4.68 (4H, m); ^{13}C NMR($CDCl_3$): δ 44.42 (CH), 41.52 (CH).

27c: ^{1}H NMR($CDCl_3$): δ 4.82–4.64 (4H, m), 3.67 (6H, s); ^{13}C NMR($CDCl_3$): δ 44.33 (CH), 42.05 (CH).

27d: ^{1}H NMR($CDCl_3$): δ 4.83–4.72 (4H, m); ^{13}C NMR($CDCl_3$): δ 44.44 (CH), 41.33 (CH).

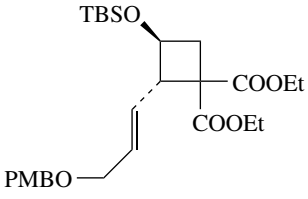
NMR was used to detect the presence of cyclobutane rings in photoproducts of liquid crystalline cinnamates[42]. The spectrum of **28** (cylinders represent aromatic diacid groups) reveals the presence of the *Z*-isomer characterized by two signals at 6.92 and 5.97 ppm with a $J = 12.7$ Hz. Additionally, two signals at 4.44 and 3.82 ppm are detected and correspond to the cyclobutane ring, which were assigned to a derivative of a β-truxinic acid

according to the reported values for different photoproducts of cinnamates. A new signal at 3.45 ppm together with a broadening of the signal at *ca* 3.8 ppm provides evidence of the existence of hydrogens corresponding to a new cyclobutane ring. The coupling of these signals at 3.45 and 3.78 ppm, respectively, were confirmed by decoupling experiments. By comparison with the literature, the new cyclobutane ring that appears on increasing the irradiation time was identified as a δ-truxinic derivative.

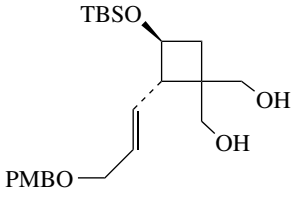


(28)

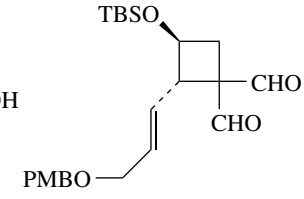
Tetrasubstituted cyclobutanes are also intermediates in the total synthesis of (+) laurenyne[43]. ^{1}H and ^{13}C NMR data of vinylcyclobutanes **29, 30** and **31** are given in Reference 43 without assignment.



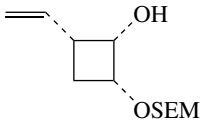
(29)



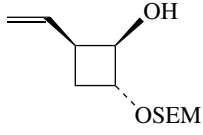
(30)



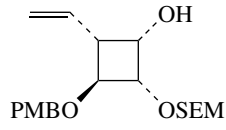
(31)



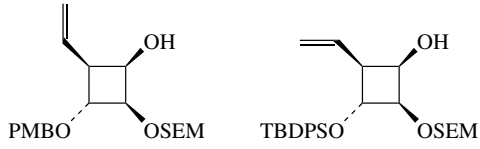
(32)



(33)



(34)



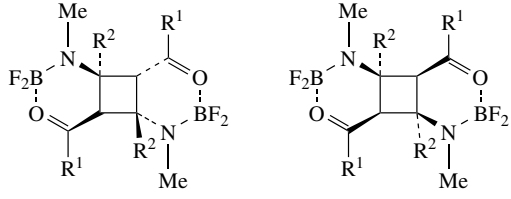
(35) **(36)**

PMB - p-Methoxy benzyl
SEM - 2-Trimethylsilylethoxymethoxy
TBDPS-t-Butyldiphenylsilyl
TBS - t-Butyldimethylsilyl

Ring contraction of 4-vinylfuranosides mediated by zirconocene leads to multiply functionalized cyclobutanes[44]. The ^{1}H and ^{13}C NMR spectra of trisubstituted **32** and **33** and tetrasubstituted **34**, **35** and **36** are reported without assignment in Reference 44.

D. Other Substituted Cyclobutanes

A number of photoadducts of enaminoketonatoboron difluorides were prepared taking advantage of the enhanced reactivity of these complexes[45]. Spectral data did not yield sufficient information to allow the structure of the photoproducts to be assigned, so X-ray crystallography was used to show that these products are the *anti* head-to-tail (**37**) and *syn* head-to-tail (**38**) dimers of the precursors. ^{1}H and ^{13}C NMR data are reported without assignment.



(37a–37b) **(38a–38b)**

(a) $R^1 = Ph$, $R^2 = Me$
(b) $R^1 = R^2 = Ph$

37a: ^{1}H NMR($CDCl_3$): δ 7.30–7.84 (m, 10H), 4.29 (s, 2H), 2.98 (s, 6H), 1.49 (s, 6H); ^{13}C NMR($CDCl_3$): δ 181.4, 142.2, 129.0, 128.8, 127.7, 126.6, 76.0, 35.2, 21.7.

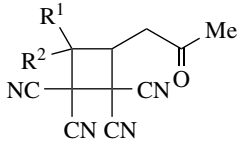
37b: ^{1}H NMR($CDCl_3$): δ 7.17–7.71 (m, 16H), 6.55 (d, $J = 7.4$ Hz, 4H), 4.80 (s, 2H), 3.12 (s, 6H); ^{13}C NMR($CDCl_3$): δ 178.9, 141.8, 131.5, 129.2, 128.6, 128.1, 127.7, 127.5, 127.3, 62.6, 37.4.

38a: ^{1}H NMR($CDCl_3$): δ 7.30–7.84 (m, 10H), 3.84 (s, 2H), 3.24 (s, 6H), 2.02 (s, 6H); ^{13}C NMR($CDCl_3$): δ 180.5, 144.6, 128.7, 128.0, 127.2, 126.5, 78.4, 34.0, 20.9.

38b: ^{1}H NMR($CDCl_3$): δ 7.17–7.71 (m, 20H), 4.14 (s, 2H), 3.32 (s, 6H); ^{13}C NMR($CDCl_3$): δ 171.3, 147.5, 133.3, 132.9, 132.7, 132.3, 130.8, 128.8, 127.5, 126.9, 96.0, 34.4.

1,1,2,2,3-Pentasubstituted-[46] and hexasubstituted-[14,24] cyclobutanes have been studied. Assignments are based on $J_{trans} > J_{cis}$.

A new synthesis of 1,1,2,2-tetracyanocyclobutanes via reactions of tetracyanoethylene with α,β-unsaturated ketones or β-bromoketones yielded hexa- and heptasubstituted cyclobutanes **39a**–**39d**[47]. Their ^{1}H NMR spectral data are given below. Note that the two hydrogens on the carbon neighboring the ketone are nonequivalent and coupled to each other.



(39a–39d)

(a) R^1 = Et, R^2 = H
(b) R^1 = Bu, R^2 = H
(c) R^1 = R^2 = Me
(d) R^1 = Ph, R^2 = H

39a: ^{1}H NMR, (300 MHz, DMSO-d_2 δ, ppm): 3.38 m (1H, C*H*CH_2CO), 3.25 m (1H, C*H*Et), 3.2 dd (1H, CHC*H*$_2$CO, *J* 6.5, 8.5 Hz), 2.99 dd (1H, CHC*H*$_2$CO, *J* 6.5, 8.5 Hz), 2.2 s (3H, COMe), 1.8 m (CHC*H*$_2$Me), 0.98 t (3H, CH_2CH_3, *J* 6.0 Hz).

39b: ^{1}H NMR, (300 MHz, DMSO-d_6 δ, ppm): 3.49 m (1H, C*H*CH_2CO), 3.2 m (1H, C*H*Bu), 3.08 dd (1H, CHC*H*$_2$CO, *J* 5.5, 8.0 Hz), 2.94 d.d (1H, CHC*H*$_2$CO, *J* 5.5, 8.5 Hz), 2.09 s (3H, COMe), 1.68–1.36 m (6H, $CH_2CH_2CH_2$Me), 0.98 t (3H, CH_2CH_3, *J* 7.0 Hz).

39c: ^{1}H NMR, (300 MHz, DMSO-d_6 δ, ppm): 3.53 dd (1H, C*H*CH_2CO, *J* 7.5, 8.5 Hz), 3.15 dd (1H, CHC*H*$_2$CO, *J* 6.5, 8.5 Hz), 2.95 d.d (1H, CHC*H*$_2$CO, *J* 6.5, 7.5 Hz), 2.22 s (3H, COMe), 1.5 s (3H, Me), 1.4 s (3H, Me).

39d: ^{1}H NMR, (300 MHz, DMSO-d_6 δ, ppm): 7.43 s (5H, Ph), 4.88 d (1H, C*H*Ph, *J* 10.5 Hz), 4.21 m (1H, C*H*CH_2CO), 3.09 dd (1H, CHCH_2CO, *J* 5.5, 8.0 Hz), 3.04 dd (1H, CHC*H*$_2$CO, *J* 5.5, 7.5 Hz), 2.818 s (3H, COMe).

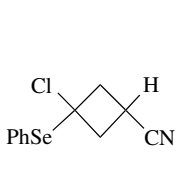
In studies on the internal displacement across a cyclobutane ring, two stereoisomers of 3-chloro-3-phenylselenocyclobutanecarbonitrite (**40**) were purified using a preparative HPLC column[48]. The ^{1}H and ^{13}C NMR data of these isomers **40a** and **40b** in $CDCl_3$ are reported below.

40a: ^{1}H NMR: δ 7.71 ((*o*), 2H), 7.48–7.36 ((*m* + *p*), 3H), 3.15 (qn under 2.4), 3.10 (m, 4H). ^{13}C NMR: δ 136.1 (*o*), 129.4 (*m*), 129.3 (*p*), 127.46 (*ip*), 123 (s), 50.8 (t), 17.2 (d).

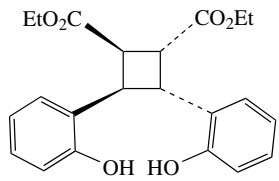
40b: ^{1}H NMR: δ 7.72 ((*o*), 2H), 7.48–7.36 ((*m* + *p*), 3H), 3.45 (qn, $J = 10$ Hz, 1H), 3.08 (m, 4H). ^{13}C NMR: δ 136.6 (*o*), 129.8 (*m*), 129.5 (*p*), 127.46 (*ip*), 123 (s), 49.3 (s), 46.1 (t), 18.3 (d).

A series of C_2-symmetric biphosphine ligands with a cyclobutane backbone was used to prepare tetrasubstituted cyclobutanes: **41**–**44**[49]. For the two former ^{1}H NMR data are reported, while for **43a**–**f** and **44a**–**f** ^{31}P NMR data are also reported. Structures **43a** and **44a** were selected to exemplify the NMR data (see below) without assignment.

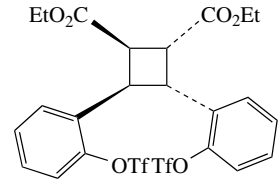
43a: ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 0.86 (t, $J = 7.1$ Hz, 6H), 2.95 (d, $J = 4.3$ Hz, 2H), 3.67–3.77 (m, 4H), 5.38 (d, $J = 4.3$ Hz, 2H), 7.00–7.80 (m, 28H). ^{31}P NMR (121.46 MHz, $CDCl_3$, δ, ppm) 31.1.



(40)

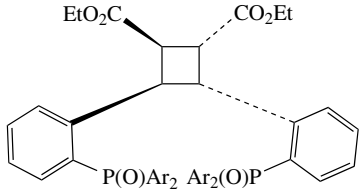


(41)

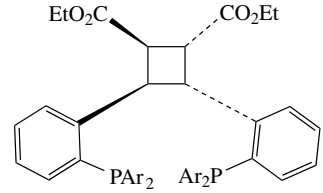


(42)

Tf - Triflate

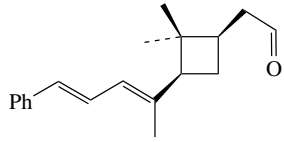


(43a–43f)

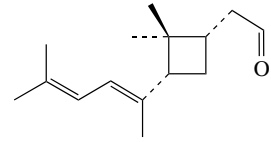


(44a–44f)

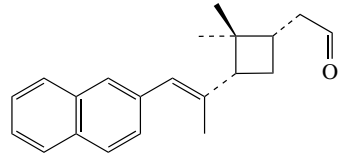
(a) Ar = C_6H_5
(b) Ar = 3,5–$(CH_3)_2C_6H_3$
(c) Ar = 4–$CH_3C_6H_4$
(d) Ar = 3–$CH_3C_6H_4$
(e) Ar = 4–$CH_3OC_6H_4$
(f) Ar = 4–$(CH_3)_3CC_6H_4$



(45)



(46)



(47)

44a: ^{1}H NMR (300 MHz, $CDCl_3$: δ, ppm) 0.77 (t, J = 7.2 Hz, 6H), 3.68–3.77 (m, 6H), 5.20–5.22 (m, 2H), 6.73–7.38 (m, 28H). ^{31}P NMR (121.46 MHz, $CDCl_3$: δ, ppm) −13.2.

Acid-catalyzed Grob fragmentation reactions of acetonides derived from terpenes yield tetrasubstituted cyclobutyl aldehydes **45**–**47**[50]. The ^{1}H NMR spectra of **45**–**47** are partially interpreted together with their ^{13}C NMR spectra which are reported below.

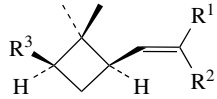
45: ^{1}H NMR (400 MHz, $CDCl_3$: δ, ppm): 9.71 (s, 1H, CHO), 7.50–7.15 (m, 5H, ArH), 7.08 (dd, J = 15.5, 11.0 Hz, 1H, C*H*CHPh), 6.51 (d, J = 15.5 Hz, 1H, PhC*H*), 5.90 (d,

J = 11.0 Hz, 1H, C*H*CMe), 2.59 (apparent t, J = 8.9 Hz, 1H, =CCH), 2.44 (dd, J = 18.0, 9.1 Hz, 1H, CH*H*CHO), 2.38–2.28 (m, 2H, C*H*HCHO and C*H*CMe$_2$), 2.11–2.00 (m, 1H, CH*H*CHC=), 1.89–1.69 (m, 1H, C*H*HCHC=), 1.81, 1.25, 0.78 (3s, 9H, 3Me), ^{13}C NMR (100 MHz, $CDCl_3$): 201.7, 138.9, 137.7, 130.0, 128.2, 126.6, 125.8, 124.9, 123.8, 50.9, 44.8, 42.7, 35.2, 30.2, 25.6, 17.2, 16.6.

46: ^{1}H NMR (200 MHz, $CDCl_3$: δ, ppm): 9.74 (t, J = 2.0 Hz, 1H, CHO), 6.03 (d, J = 11.4 Hz, 1H, C=CH), 5.82 (d, J = 11.4 Hz, 1H, C=CH), 2.65–0.60 (m, 6H, aliphatic CH_2 and CH), 1.80, 1.75, 1.66, 1.20, 0.74 (5s, 15H, 5Me). ^{13}C NMR (75 MHz, $CDCl_3$: δ, ppm): 202.1, 134.8, 133.0, 120.8, 119.7, 51.2, 45.0, 42.5, 35.4, 30.4, 26.2, 25.9, 18.0, 17.0, 16.7.

47: ^{1}H NMR (400 MHz, $CDCl_3$: δ, ppm): 9.78 (t, J = 1.9 Hz, 1H, CHO), 7.90–7.35 (m, 7H, ArH), 6.27 (s, 1H, =CH), 2.68 (apparent t, J = 9.0 Hz, 1H, =CCH), 2.49 (ddd, J = 18.8, 9.5, 1.9 Hz, 1H, CH*H*CHO), 2.46–2.35 (m, 2H, C*H*HCHO and C*H*CMe$_2$), 2.21–2.12 (m, 1H, CH*H*CHC=), 1.95–1.80 (m, 1H, C*H*HCHC=), 1.89, 1.29, 0.89 (3s, 9H, 3Me). ^{13}C NMR (100 MHz, $CDCl_3$: δ, ppm): 202.1, 138.8, 133.3, 131.7, 127.7, 127.6, 127.5, 127.3, 127.2, 125.9, 125.3, 124.1, 51.6, 45.1, 42.8, 35.5, 30.5, 26.2, 18.7, 16.8.

Tri- and tetrasubstituted cyclobutanes are reported in studies on the reaction between *N*-alkylhydroxylamines and chiral enoate esters[51]. ^{1}H and ^{13}C NMR data on cyclobutanes **48a–48d, 49a, 49b, 50a, 50b** and **51** were reported without interpretation. The data for **48a** are exemplified below.

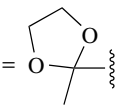


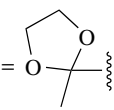
(48a–48d)

(49a–49b)

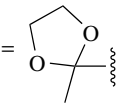
(a) R^1 = H, R^2 = R^3 = CO_2Me

(b) R^1 = CO_2Me, R^2 = H = R^3



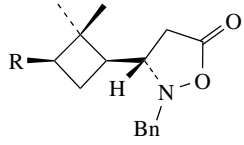


(a) R = CO_2Me

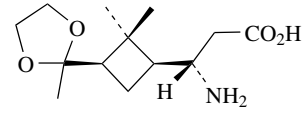


48a: ^{1}H NMR (acetone-d_6: δ, ppm) 1.06 (s, 3H), 1.13 (s, 3H), 1.17 (s, 3H), 1.80 (m, 1H), 2.00 (m, 2H), 2.22 (dd, J = 11.0 Hz, J' = 8.0 Hz, 1H), 3.64 (s, 3H), 3.70–4.00 (m, 4H), 5.75 (dd, J = 11.7 Hz, J' = 1.1 Hz, 1H), 6.22 (dd, J = 11.7 Hz, J' = 10.2 Hz, 1H); ^{13}C NMR (acetone-d_6: δ, ppm) 17.57, 22.76, 24.77, 30.82, 39.94, 43.72, 49.69, 48.89, 63.08, 64.81, 109.04, 119.36, 150.15, 165.65.

Photoproducts containing cyclobutyl rings are observed on irradiation of a benzodithia-18-crown-6-ether Pb complex[52]. The structures of the photolysis products **52** in their *syn*

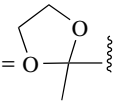


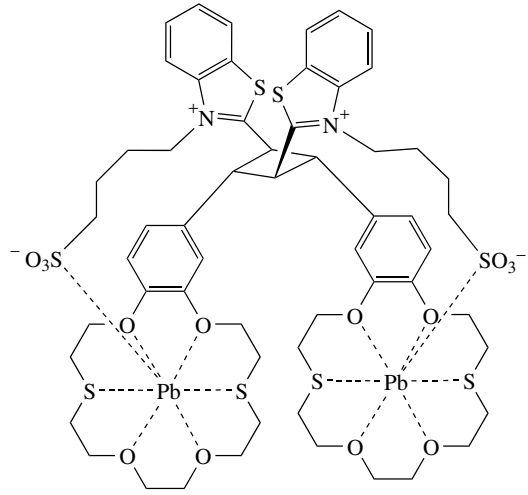
50(a) R = CO_2Me



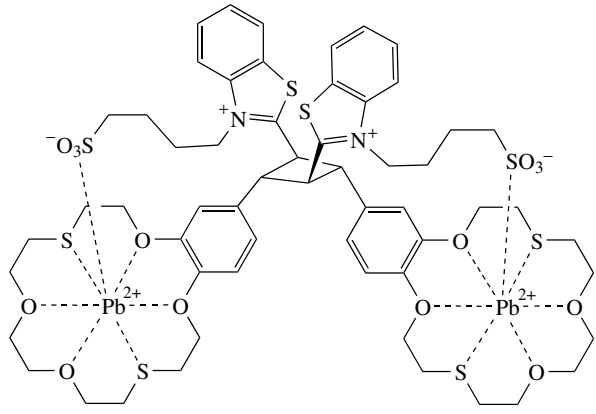
(51)

50(b) R =





syn-conformer



anti-conformer

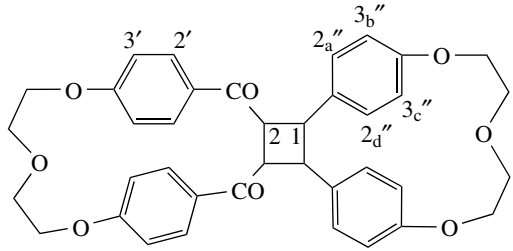
(52)

and *anti* conformations were analyzed by COSY and NOESY 2D techniques and by comparison with available ^{1}H NMR spectral data for the cyclobutanes of the benzothiazole series. The ^{1}H NMR spectrum of the photoproduct **52** in MeCN-d_3 exhibits two triplets at 4.44 and 4.98 ppm due to hydrogens of the cyclobutane ring. Each phototransformation yields only one isomer which is responsible for an A_2B_2-type spectrum with $^3J_{trans} = 9.6$ Hz. The quantity, position, multiplicity and spin–spin coupling constants of the cyclobutane ring hydrogens in **52**, constructed according to the *anti*-'head-to-tail' pattern, are similar to those obtained for cyclobutanes of the benzothiazole series.

V. CYCLOBUTANES AS PART OF RING SYSTEMS

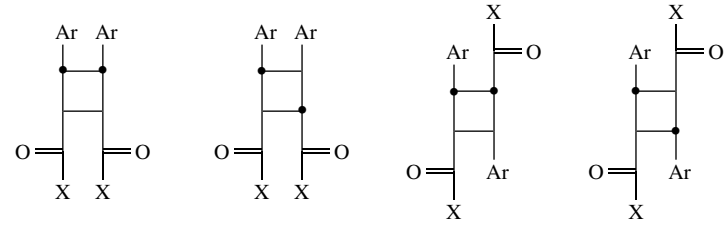
A. Cyclophanes

Cyclobutanes may provide a rigid nucleus for the insertion of different moieties in order to build ditopic cyclophanes, such as in **53**[53]. The cycloaddition of *trans*-chalcones may give four possible stereoisomers, namely *syn/anti*, head-to-head and head-to-head (Scheme 5). In face of difficulties in obtaining suitable crystals of these structures for X-ray studies, ^{1}H NMR spectroscopy provides a reliable source of information about their stereochemistry. Two symmetrical multiplets (AA′BB′ system) are observed for the cyclobutyl hydrogens. Simulation of these NMR patterns has allowed the estimation of the coupling constants of the cyclobutyl hydrogens: $J_{AA'} = 11.3$ Hz, $J_{AB} = 6.3$ Hz, $J_{AB'} = -0.8$ Hz, $J_{BB'} = 10.5$ Hz. The values of these coupling constants suggest head-to-head dimerization, but they do not allow a certain assignment with respect to the *syn/anti* stereochemistry. More accurate structural determination for **53** was attained by (H,H)-COSY, (H,C)-COSY and NOESY-Phase sensitive spectra. ^{1}H and ^{13}C NMR spectra showed that the *ortho* and *meta* hydrogens (and carbons) of the phenylene groups directly bonded to the cyclobutane ring of **53** are not chemically equivalent, because of the restricted rotation of the aromatic rings. The upfield shift of H-$2_d''$ and to a lesser extent of H-$3_{c'}''$ (Scheme 6) suggests that these hydrogens are directed inwards to the opposite phenylene group, and subject to its ring current shielding effect. The nonchemical equivalence of the H$-2''$ hydrogens was used to distinguish the through-space interactions of hydrogen $2_a''$ from those of $2_d''$. In particular, the NOESY spectrum of **53** reveals, inter alia, that hydrogen H-$2_a''$ is subject to a through-space coupling to hydrogens H-2, whereas hydrogens H-$2_d''$ only couple through the space with hydrogens H-1.



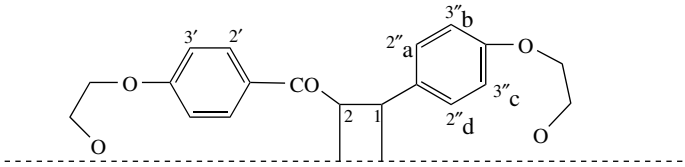
(53)

These results are in accordance with a *trans* relationship between H-1 and H-2, and with a *cis* relationship between the two H-1 hydrogens (and obviously between the two H-2 hydrogens), caused by a head-to-head *syn* junction. The NOESY pattern confirms that the head-to-tail junction (Scheme 5) does not occur, because in this case the H-2 hydrogens should correlate with both the H$-2''$ hydrogens, either in the *syn* structure or the highly



head-to-head *syn* head-to-head *anti* head-to-tail *syn* head-to-tail *anti*

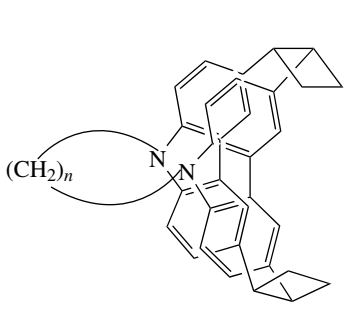
SCHEME 5. Stereoisomers formed from cycloaddition of *trans*-chalcones



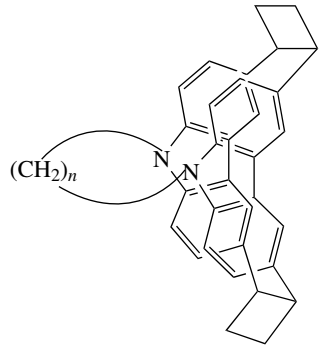
SCHEME 6. Nonequivalent hydrogens of phenylene groups and cyclobutane rings. Atoms on bottom half of the molecule (not shown) are numbered in the same way

strained *anti* structure. In particular, in **53** head-to-tail *syn*, symmetry considerations show that H-$2_a''$ and H-$2_d''$ (H-$3_b''$ and H-$3_c''$) (Scheme 6) hydrogens would be chemically equivalent, in contrast with the NMR results.

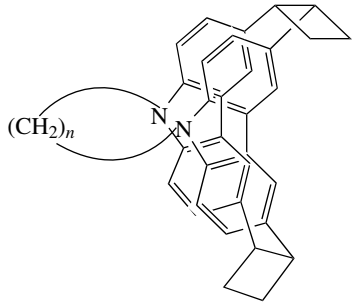
Triply-bridged *syn*-carbazolophanes containing cyclobutyl rings can be synthesized by intramolecular [2 + 2] photocycloadditions[54]. The structures of these carbazolophanes were characterized mainly by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of **54a** and **54b** gave a quite simple pattern, as demonstrated by the three aromatic and one methine hydrogen peaks. In the isomeric mixture, **55** also showed a pattern quite similar to **54a** and **54b**, but the aromatic H4 (or H5) and H2 (or H7) hydrogens were high-field ($\Delta\delta = -0.46$ ppm) and low-field ($\Delta\delta = 0.38$ ppm) shifted, respectively, compared with **54a**. Judged from the symmetry, **54a, 54b** and **55** obviously adopt *endo,endo* or *exo,exo* configuration. Since



(54a) $n = 4$
(54b) $n = 5$
(endo, endo)



(55) $n = 4$
(exo, exo)



(56a) $n = 4$
(56b) $n = 5$
(endo, exo)

the *endo*- and *exo*-directed cyclobutane rings induce the low-field shift of the H4 (or H5) and H2 (or H7) hydrogens, respectively, due to the steric compression effects, the configuration of the two cyclobutane rings in **54a** and **54b** was assigned as *endo*, and those in **55** as *exo*. The ^{1}H NMR spectra of **56a** and **56b** showed six aromatic and two methine peaks, apparently indicating *endo, exo* configuration.

Complete ^{1}H and ^{13}C NMR data are given as follows.

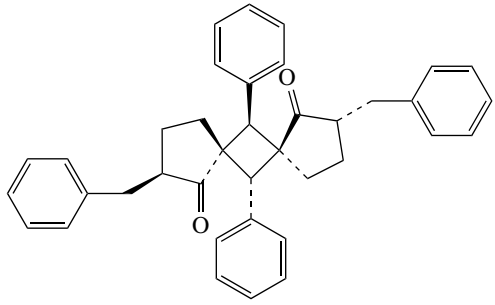
54a: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, $J = 1.7$ Hz, 4H), 6.68 (d, $J = 8.5$ Hz, 4H), 6.49 (dd, $J = 8.5$, 1.7 Hz, 4H), 4.33 (m, 4H), 3.94 (m, 4H), 2.89 (m, 4H), 2.75 (m, 4H), 1.35 (m, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 140.11, 132.41, 127.99, 123.52, 119.37, 109.22, 46.20, 43.40, 28.57, 21.46.

54b: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.03 (s, 4H), 6.68 (d, $J = 8.2$ Hz, 4H), 6.54 (d, $J = 8.2$ Hz, 4H), 4.31 (m, 4H), 2.89 (m, 4H), 2.77 (m, 4H), 1.50 (m, 4H), -1.05 (m, 2H); ^{13}C NMR (67.8 MHz. $CDCl_3$) δ: 139.43, 131.79, 126.85, 119.62, 108.46, 46.11, 41.48, 27.04, 22.30, 19.23.

B. Dispiro Cyclobutane Derivatives

In the course of an investigation of the reaction between 2,5-dibenzylidenecyclopentanone and 6-amino-1,3-dimethyluracil using phase transfer conditions[55], two interesting dispiro cyclobutane derivatives, **57** and **58**, were discovered. They are formed in solution along with the oxidized monoadduct, and were isolated in good yields and identified by spectroscopic methods. Using 2D high resolution NMR spectra, the structural identification of those compounds was made. The high resolution ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound **57** showed signals at $\delta = 6.86$, 2H-*ortho*, 7.10 1H-*para* and 7.17 2H-*meta* for the phenyl ring of the benzyl moiety. In addition, the aromatic hydrogens of the phenyls attached to the cyclobutane moiety were observed at $\delta = 7.35$ 2H-*ortho*, 7.32 2H-*meta* and 7.23 1H-*para* (the assignment was made through a HMBC experiment), a sharp singlet at $\delta = 4.25$, assigned to both methines of the cyclobutane ring and an AMX pattern at $\delta_A = 2.59$, dd, $J = 4.5$; -14.0; $\delta_M = 2.10$, m and $\delta_X = 1.08$, dd, $J = 11.0$ Hz; -14.0 Hz, assigned to the benzylic methylene and the methine where this was attached. The larger chemical shift difference between both hydrogens of each benzylic methylene ($\Delta\delta = 1.51$) suggested that the benzylic hydrogen at $\delta = 1.08$ suffered a

symmetrical diamagnetic shielding for only one hydrogen of each methylene through the magnetic anisotropy of the phenyl rings attached to the cyclobutane moiety. These NMR data matched well the structure previously established via X-ray crystallographic studies.



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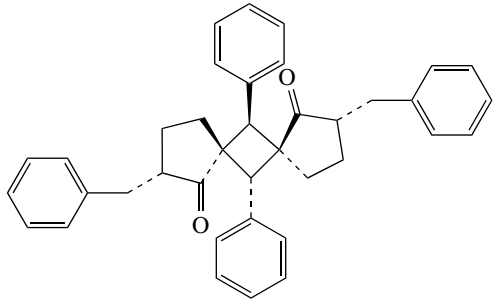


(58)

Using the vertical enhancement of the signal at $\delta = 4.25$, two additional singlets at $\delta = 4.23$ and 4.18 were observed and assigned to traces of a new asymmetric photoadduct **58**. Thus, the two cyclobutane hydrogens with these chemical shifts are magnetically nonequivalent and their coupling was not observed. As revealed by the COSY spectrum of the mixture of **57, 58** and another product, which displayed cross peaks for **58**, these signals provide evidence of the chemical shifts that correspond to the hydrogens of both benzylic methylenes at $\delta = 1.14$, dd, $J = 11.0$; -14.0 and 2.60 (overlapped) and $\delta = 2.91$, dd, $J = 4.5$ Hz; -14.0 Hz and $\delta = 2.30$, dd, $J = 10.0$, -14.0, respectively. These chemical shifts suggested an asymmetric structure, where only one hydrogen at $\delta = 1.14$ from both methylenes was shielded by one of the phenyl rings attached to the cyclobutane moiety with the remaining benzylic methylene hydrogens displaying the usual chemical shifts between $\delta = 2.91$ and 2.30. Thus, the two benzylic units were unambiguously *cis* to each other (preserving the center of symmetry as in compound **57**).

Photodimer **57** displayed a ^{13}C NMR signal at $\delta = 218.1$, assigned to the cyclopentanone carbonyls. Two signals of quaternary carbons are found at $\delta = 139.9$ and 138.0 for both *ipso* carbons of the different phenyl rings. In addition, the signals for the *ortho* and *meta* carbons of the phenyl rings (DEPT) at $\delta = 130.7$, 128.5, 128.3 and 128.4 (methines *ortho* and *meta*), and finally, the signals assigned to the *para* carbons at $\delta = 127.5$ and 126.0, were observed. At higher field, a quaternary carbon at $\delta = 59.6$, the methines at

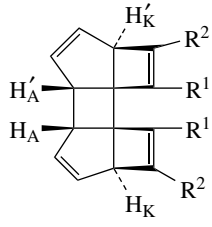
$\delta = 54.7$ and 49.7, with the three methylene carbons signals (DEPT) at $\delta = 35.2$, 34.7 and 25.4 are observed.

The HMQC experiment enabled the assignment of the hydrogen singlet at $\delta = 4.25$, which correlates with the carbon signal at $\delta = 54.7$ and the hydrogen multiplet at $\delta = 2.10$ with the methine carbon at $\delta = 49.7$. The benzylic methylene hydrogens displaying the higher chemical shift difference between both hydrogens at $\delta = 1.08$ and 2.59 correlated with the carbon signal at $\delta = 34.7$. Consequently, the methylene hydrogens at $\delta = 1.40$ and 1.82 correlated with the carbon signal at $\delta = 25.4$. At lower field, the hydrogen doublet at $\delta = 6.86$ was correlated with the carbon signal at $\delta = 128.5$; the hydrogen at $\delta = 7.10$ was correlated with the signal at $\delta = 126.0$ and the hydrogen triplet at $\delta = 7.17$ was correlated with the carbon signal at $\delta = 128.2$. The hydrogen triplet at $\delta = 7.23$ correlated with the carbon signal at $\delta = 127.5$ and the hydrogens at $\delta = 7.35$ and 7.32 with the carbons at $\delta = 130.7$ and 128.4, respectively.

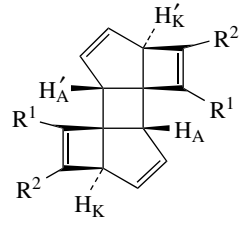
A HMBC experiment led to the assignment of the aromatic carbons which were quaternary or bound to hydrogens. For example, the singlet at $\delta = 4.25$ correlated through 3 sigma bonds with the carbonyl signal at $\delta = 218.1$, with the *ipso* carbon at $\delta = 138.0$ and with the methine carbon at $\delta = 130.7$. This experiment confirms the chemical shifts of the phenyl group carbons attached to the cyclobutane ring. Additional correlations through this methine signal were those observed at higher field with the quatenary carbon at $\delta = 59.6$ and the methylene carbon at $\delta = 35.2$. Using the benzylic hydrogens at $\delta = 1.08$ and 2.60, the 2σ and 3σ bond correlations with the carbonyl carbon at $\delta = 218.1$, the *ipso* carbon at $\delta = 139.9$ and the methine at $\delta = 128.5$, as well as with the methine carbon at $\delta = 49.7$ and the methylene carbon at $\delta = 25.4$, were observed. The triplet at $\delta = 7.17$ correlated with the *ipso* carbon at $\delta = 139.9$; the triplet at $\delta = 7.32$ was correlated with the *ipso* carbon at $\delta = 138.0$, and finally, the doublet at $\delta = 6.86$ correlated with the carbon signal at $\delta = 128.5$. The methylene hydrogens at $\delta = 1.60$ and 2.75 correlated with the quaternary carbon at $\delta = 59.6$, as well as the methines at $\delta = 54.7$ and 49.7 and the methylene at $\delta = 25.4$. The methylene hydrogens at $\delta = 1.40$ and 1.82 correlated with the quaternary carbon at $\delta = 59.6$, the methine at $\delta = 49.7$ and the methylene at $\delta = 35.2$.

C. Fused Cyclobutane Ring Systems

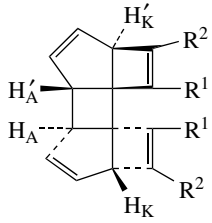
Cyclobutane dimers can also be formed from the thermolysis of strained spirotrienes. In principle, four different isomers, **59**–**62**, could be generated from cycloadditions of the strained bicyclo[3.2.0]hepta-1,3,6-triene. However, there were indications that only two of these were formed[56]. The symmetry of isomers **59b**–**62b** (C_s, C_2, C_2 and C_i, respectively) interfered with the usual application of 2D NMR correlation methods for determining regiochemistry and of NOE difference methods for determining stereochemistry. One consequence of the symmetry was the highly second-order nature of the ^{1}H NMR signal for the monoallylic methine H_A. The second-order character resulted from H_A being



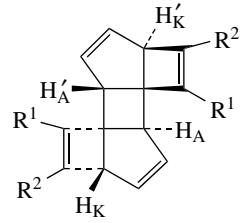
(59a–59c)



(60a–60c)



(61a–61c)



(62a–62c)

(a) $R^1 = R^2 = H$

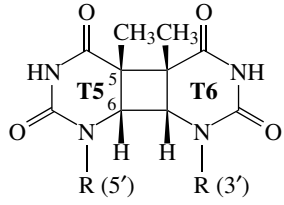
(b) $R^1 = R^2 = CH_3$

(c) $R^1 = H$, $R^2 = n$-Pr

coupled to its isochronous, symmetrical counterpart H_A', corresponding to the only significant $^1H-^1H$ scalar coupling between the two equivalent halves of each dimer **59b–62b**. The magnitude of the coupling between these hydrogens was not readily extracted from the H_A/H_A' resonance, but examination of the ^{13}C satellites showed first-order resonances for both dimers. The observed 9.4 and 4.4 Hz splittings, which did not appear in other resonances, were assigned as the H_A-H_A' couplings in the two dimers.

Tentative structure assignment of the two dimers was obtained from H_A-H_A' coupling, together with NOE difference data and molecular modeling. Geometries derived from molecular mechanics calculations were used to predict spin couplings and interatomic distances in dimers **59b–62b** for correlation with the observed NMR data. The thermolysis product showing a 9.4 Hz coupling could correspond to either dimer in which H_A and H_A' are vicinal (**59b** and **61b**), whereas the 4.4 Hz coupling is likely a four-bond coupling in **60b** or **62b**. Isomers **61b** and **62b** were ruled out for both isomeric products by the absence of any NOE between hydrogens only 2.3 Å apart. Patterns of chemical shifts for other thermolysis products were used to confirm these assignments.

Thymine and uracil cyclobutane dimers **63** and **64**, formed from B-type ultraviolet radiation (UVB) photosensitization of duplex DNA decamers (of particular interest here are the cyclobutane hydrogens H5 and H6; refer to Table 16 for abbreviations), were studied by NMR[57]. Assignments are based on previous work on the photochemically modified duplex with normal Watson–Crick base pairing at the T *cis-syn* (CBD) site[58,59]. Chemical shifts of the four central nucleotides in both the UU and the TT dimer duplexes are summarized and compared in Table 16. Exchangeable ^1H NMR spectra (6–14 ppm) and sequential NOE between imino hydrogens were used for assignment. Imino hydrogens of U5 and U6 appear at 11.87 and 13.16 ppm, respectively, and are similar to the frequencies of T5 and T6 in the TT CBD/AA[58,59]. Sequential NOE of imino hydrogens showed a relatively weak



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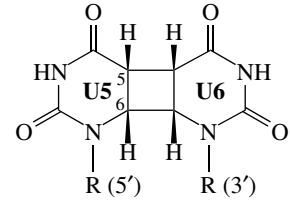


(64)

TABLE 16. ^{1}H chemical shifts of the central four nucleotides of the uracil *cis–syn* duplex decamer and the thymine *cis–syn* duplex decamer[58]

Residue	NH/NH_2	CH_3	H2/H5	H6/H8	H1′	H2′	H2″	H3′	H4′
UU dimer duplex									
5′									
A4	6.38	–	7.75	8.25	6.32	2.73	2.73	5.10	4.39
U5	11.87	–	3.10	4.84	5.93	2.01	2.63	4.73	4.18
U6	13.13	–	3.84	4.42	5.27	1.97	1.97	4.72	3.83
A7	–	–	7.36	8.23	6.13	2.45	2.73	4.92	4.37
3′									
3′									
T17	13.67	1.33	–	7.05	5.53	1.94	2.26	4.76	4.04
A16	5.63/6.45	–	7.46	7.97	6.01	2.42	2.64	4.88	4.31
A15	–	–	6.12	8.13	5.82	2.51	2.59	4.95	4.82
T14	13.44	1.49	–	7.13	5.77	2.05	2.51	4.82	4.16
5′									
TT dimer duplex									
5′									
A4	6.36	–	7.76	8.32	6.39	2.64	2.88	5.01	4.46
T5	12.02	0.57	–	4.44	5.57	1.97	2.63	4.75	4.21
T6	13.06	1.48	–	4.09	5.41	2.04	2.63	4.86	3.92
A7	–	–	7.35	8.31	6.22	2.51	2.79	4.99	4.30
3′									
3′									
T17	13.61	1.33	–	7.03	5.69	1.99	2.37	4.85	4.11
A16	–	–	7.56	8.03	6.17	2.50	2.83	4.96	4.42
A15	–	–	8.41	8.18	5.93	2.58	2.74	5.00	4.31
T14	13.38	1.56	–	7.22	5.87	2.20	2.62	4.89	4.25
5′									

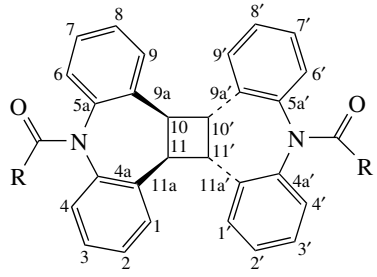
Abbreviations: A, adenosine; C, cytosine; CBD, cyclobutane dimer; G, guanine; T, thymine; TT CBD/AA, a DNA duplex containing thymine dimer base-paired with two adenines; U, uracil; UU CBD/AA, a DNA duplex containing uracil dimer base-paired with two adenines.

connectivity at the 3′ side of the dimer, although no disconnection was found. The imino and amino hydrogens were assigned after the standard analysis of the water-NOESY spectra. Typical strong NOE U5(NH) ↔ A16(H2), U6(NH) ↔ A15(H2), A7(H2) ↔ T14(NH) and A4(H2) ↔ T17(NH) were observed. The NOE cross peaks of U6(NH) ↔ A7(H2) and U6(NH) ↔ A16(H2) were not observed, whereas the NOE for U5(NH) ↔ A4(H2) was detected.

Sequential NOE of base hydrogens to H1′ and H2′/H2″ were used to assign base hydrogens and H1′, H2′/H2″ subsequently, as well as all other sugar hydrogens by the NOEs between them. In the complementary sequence, all sequential NOEs were normally observed in both the uracil dimer duplex and the thymine dimer duplex. The cross peak of A7(H8) ↔ U6(H1′) was the basis for identifying all the relevant hydrogens of the UU dimer strand. U6(H6) was found with the cross peak of U6(H1′) ↔ U6(H6) and finally confirmed with a sequential NOE, U5(H2″) ↔ U6(H6). The cross peak for U5(H1′) ↔ U6(H1′), probably produced from the spin diffusion effect, was used to find U5(H2′) and H5(H2″). The cross peaks of A4(H8) ↔ C3(H2″) were absent in the UU CBD/AA, although it was observed well in the TT CBD/AA. A cross peak of U5(H1′) ↔ U5(H6) and sequential NOE of U5(H1′) ↔ U6(H6) were used to locate the H6 of the U5. The

NOE distribution between the base hydrogens of the twisted puckering cyclobutane ring results in a cross peak of U5(H6) ↔ U6(H5) of a much stronger intensity than a cross peak of U6(H6) ↔ U5(H5).

Another type of dimer is formed from the sensitized photoreaction of *N*-acyl derivatives of iminostilbene (dibenz[*b*, *f*]azepine)[60]. The hydrogen NMR spectra of dimers **65a** and **65b** exhibit three characteristics absorption ranges: the CH_3 groups at $\delta = 2.39$ ppm, the cyclobutyl hydrogens (H-10, H-10′, H-11, H-11′) at $\delta = 3.89–4.11$ ppm and the aromatic hydrogens (H-1, H-4, H-1′, H-4′, H-6, H-9 and H-6′, H-9′) at $\delta = 6.85–7.47$ ppm. The fact that all signals are doubled in the spectrum suggests the existence of two nonequivalent isomers I and II in the solution with a ratio of 2:3 as determined by evaluating the corresponding integrals. The four cyclobutyl hydrogens generally appear as two AA′BB′ spin systems: In **65a**, one is formed by the symmetrical pattern centered at $\delta = 3.91$ and 4.09 ppm and the other one by the symmetric pattern at $\delta = 3.99$ and 4.01 ppm. Both spectra may be completely analyzed, using the standard rules for this spin system. At least three couplings between the four hydrogens are expected. Simulation of the spectrum provides values for the coupling constants $^3J_{HH}$ and $^4J_{HH}$ of the four cyclobutane hydrogens. The results of the simulations are shown (Tables 17 and 18).



(65a–65b)

(a) R = CH_3
(b) R = C_2H_5

TABLE 17. Chemical shifts δ (ppm) of **65a** from simulation for isomers I and II[60]

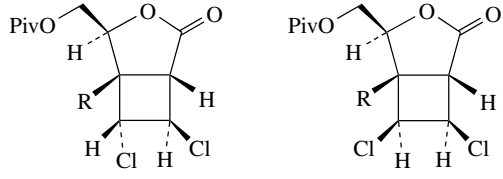
Isomer	$\delta_{H.10}$	$\delta_{H-10'}$	δ_{H-11}	$\delta_{H-11'}$
I	3.98	3.98	4.02	4.02
II	3.91	4.09	4.09	3.91

TABLE 18. Coupling constants J (Hz) of **65a** from simulation for isomers I and II[60]

Isomer	$^3J_{10.10'}$	$^3J_{11.11'}$	$^3J_{10.11}$	$^3J_{10'.11'}$	$^4J_{10'.11}$	$^4J_{10.11'}$
I	7.4	7.4	11.1	11.1	−1.3	−1.3
II	11.2	11.2	7.4	7.4	−1.2	−1.2

Two independent AA′BB′ spin systems which agree perfectly with the two spin systems in the experimental spectrum were obtained from the simulation. The differences in the coupling constants of the cyclobutyl hydrogens between isomers I and II reflects the different geometries of these two isomers. The origin of the two isomers was elucidated by further NMR experiments. NMR spectra of **65a** in toluene solution measured at different temperatures reveal a temperature dependence; the two AA′BB′ spin systems of the cyclobutyl signals observed at room temperature merge at a coalescence temperature of about $T_c = 75\,^{\circ}\mathrm{C}$. Above this temperature, an A_4 spin system appears in the spectrum exhibiting a singlet at $\delta = 3.95$ ppm. An analogous effect is shown for the aromatic hydrogens at *ca* $T_c = 70\,^{\circ}\mathrm{C}$. They take the shape of a spectrum of an *ortho*-substituted aromatic compound consisting of two doublets and two triplets. The doublets assigned to the methyl group change to one singlet at *ca* $T_c = 60\,^{\circ}\mathrm{C}$ with a chemical shift of $\delta = 2.19$ ppm. The NMR spectra of compound **65b** showed temperature dependence similar to that of **65a**.

The photochemical reaction of chiral furanones yields the corresponding dichloro adducts[61]. The four main structures that are formed (**66**–**69**) were established by ^{1}H and ^{13}C NMR. The value of the coupling constant between H-4 and H-5 is diagnostic for the *anti/syn* stereochemistry of the cycloadducts. A small value of $J_{4,5}$ is in agreement with a *trans* relationship between these two hydrogens, while larger values correspond to a *cis* relationship. For all compounds **66**–**69** the values of $J_{4,5}$ ranged from 0 to 2.9 Hz according to an *anti* stereochemistry, namely the cycloaddition proceeds with very high facial discrimination (84%). Relative stereochemistries of the C(1) substituents were inferred from the vicinal coupling constants $J_{1,7}$ and $J_{5,6}$.



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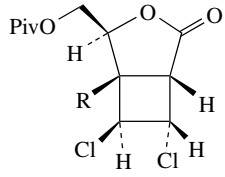

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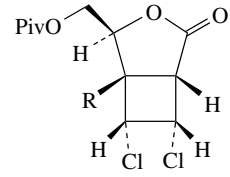
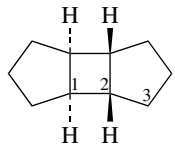


(69)

Piv - Pivaloyl

Tricyclic adducts containing cyclobutane rings can be prepared by photoaddition of cyclic enones to cycloalkenes. A wide variety of these adducts have been prepared but the assignment of their ^{13}C NMR spectra has not been straightforward. The *cis*–*anti*–*cis* tricyclic alkane **70** served as a model for a detailed investigation of a number of substituted tricyclo adducts (**71**–**75**) including the effect of different cyclobutane stereochemistries and α, β and γ substituent effects on ^{13}C chemical shifts[62]. The ^{13}C NMR assignments of the analyzed structures are given in Tables 19 and 20 and their hydrogen assignments are given in Table 21. Substituent effects on the cyclobutane carbons are often significantly reduced. Also, the different γ *gauche* effects for the *syn* and *anti* adducts are diagnostic. A number of changes to previously assigned systems is also proposed.



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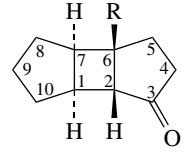
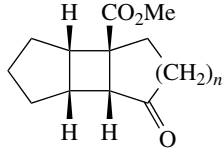


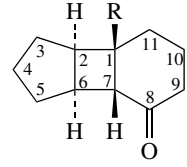
(71a–71g)

(a) R = H
(b) R = Me
(c) R = CO_2Me
(d) R = CN
(e) R = CH_2OH
(f) R = CH_2I
(g) R = OCOPh



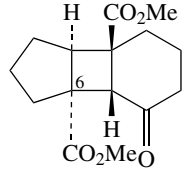
(72a–72b)

(a) $n = 1$
(b) $n = 2$



(73a–73c)

(a) R = H
(b) R = Me
(c) R = CO_2Me



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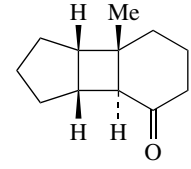
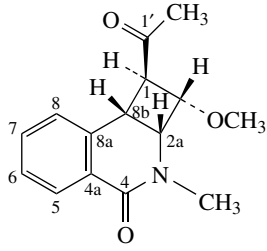
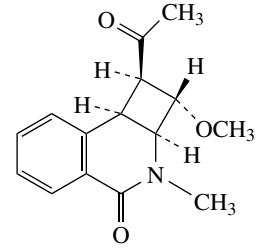


(75)



(76)



(77)

NMR can be instrumental in establishing the regioselectivity of photocycloadditions. A good example is provided by the analysis of two isomeric cyclobutanes **76** and **77** formed in this reaction[4]. The carbon-13 and hydrogen chemical shifts of **76** and **77** are given in Tables 22 and 23. The regiochemistry of each isomer is based on the assignment of H-2a and H-8b since the three-bond HMBC correlations between these hydrogens and the ketone carbonyl carbon C-(1′) confirm the carbon framework. In each isomer the HMBC correlations between the amide carbonyl carbon C-4 and H-2a and the HMBC correlations between C-8 and H-8b can be used to identify the key hydrogens. Both **76** and **77** exhibit only the requisite HMBC correlation between C-1′ and H-8b to establish that these compounds are stereoisomers of the same general structure and not regioisomers.

TABLE 19. ^{13}C NMR assignments of tricyclo[5.3.0.0^{2,6}]decane and decan-3-one adducts[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	Others
70	41.9	41.9	33.2	25.0	33.2	41.9	41.9	33.2	25.0	33.2	
71a	39.6	47.9	218.7	35.2	27.6	38.1	42.5	32.6	24.2	32.5	
71a(pred.)[b]	36.8	56.0	211.3	32.0	9.8	33.2	43.0	27.8	20.9	27.6	
71b	39.4	55.6 (+7.7)	221.3	37.6	37.8 (+10.2)	39.5 (+1.4)	46.7 (+4.2)	28.1 (−4.5)	25.8	32.5	20.3 (Me)
71c[c]	38.8	50.5 (+2.6)	217.1	36.6	32.5 (+4.9)	48.1 (+10.0)	47.5 (+5.0)	29.6 (−3.0)	24.7	32.5	51.5, 173.4 (CO_2Me)
71d[c]	39.7	52.7 (+4.8)	215.0	35.6	32.4 (+4.8)	35.6 (−2.5)	45.4 (+2.9)	30.4 (−2.2)	24.4	32.2	120.0 (CN)
71e[a]	39.9	51.5 (−4.1)	221.1	38.0	32.7 (−5.1)	44.0 (+4.5)	45.7 (−1.0)	28.1 (−4.5)	26.3	32.7	64.0 (CH_2OH) (+43.7)
71f[a]	38.0	55.1 (−0.5)	219.2	37.7	37.1 (−0.7)	42.7 (+3.2)	46.3 (−0.4)	27.8 (−0.3)	26.1	32.4	14.4 (CH_2I) (−5.9)
72a[c]	40.0	48.8	219	38.6	26.8	48.6	44.0	27.7	22.6	27.7	52.4, 177.5 (CO_2Me)

[a] δ in ppm. The values in parentheses are the α, β and γ shifts relative to the unsubstituted adduct **71**, except for compounds **71e** and **71f**, where the differences are relative to the methylated derivative **71b**.
[b] Computed chemical shifts[63].
[c] To facilitate comparisons with other adducts, the numbering of this compound does not adhere to IUPAC nomenclature rules.

TABLE 20. ^{13}C NMR assignments of tricyclo[5.4.0.0^{2,6}]undecan-8-one adducts[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	Others
72b	48.1	45.4	27.7	24.3	27.7	40.5	45.9	212.1	39.4	19.6	26.7	52.5, 178 (CO_2Me)
73a	37.1	41.4	32.0	24.4	32.7	40.8	47.3	214.0	39.3	19.6	27.5	
73b	37.3 (+0.2)	45.1 (+3.7)	27.2 (−4.8)	25.9	31.7	38.9	55.9 (+8.6)	214.2	38.1	19.3	37.4 (+9.9)	22.4 (Me)
73c	48.3 (+11.2)	46.8 (+5.4)	29.1 (−2.9)	25.2	32.5	39.8	49.0 (+1.7)	212.0	38.1	19.6	32.5 (+5.0)	51.6, 174.5 (CO_2Me)
74	47.8	50.4	28.9	25.6	36.3	55.9	51.9	210.2	38.4	19.6	31.0	51.5, 51.7, 174.3, 174.4 ($2CO_2Me$)
75	44.9	51.7	28.4	24.4	31.5	42.0	56.9	207.8	39.3	19.3	30.1	22.4 (Me)

[a] δ in ppm. The values in parentheses are the α, β and γ shifts relative to the unsubstituted adduct **73a**.

TABLE 21. ^{1}H NMR assignment of selected 5-4-5 and 5-4-6 ring adducts[a,b]

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9	H-10	H-11	Other
5-4-5 Adducts												
71a	1.81ddd, 7.0, 7.0, 2.8	1.40[c]		2.04, 1.51	1.38, 1.30	1.67	1.90 td, 6.4, 3.4	1.31, 0.90	1.19	1.30, 0.88		
71b	2.51	1.79[c]		2.26, 2.69 dt, 17.2, 9.2	1.97, 1.81		2.44 dd, 7.6, 6.8	1.78, 1.40	1.79, 1.44	1.61, 1.44		0.97s CH_3
71c	2.29	2.40[c]		2.48, 2.28	2.00, 1.51		2.48	1.47, 1.46	1.45, 1.44	2.02, 1.43		3.44 s CO_2CH_3
71d	2.56	2.46[c]		2.68, 2.40	2.41, 2.26 dd, 12.8, 3.6		2.70	2.00 dd, 13.6, 5.7, 1.62	1.89, 1.89	1.71 dd, 13.3, 5.7, 1.52		
71f	2.60 d, 6.4	2.03[c]		2.70 ddd, 18, 9.2, 9.2; 2.41	2.05–2.10		2.54	2.12, 1.64	1.87, 1.62	1.77, 1.60		3.24 d, 9.7 3.22 d, 9.7 CH_2I
5-4-6 Adducts												
73b		2.29 dd, 12.0, 12.0	1.75, 1.34	1.81, 1.72	1.60, 1.38	2.60 ddd, 4.8, 4.8, 4.8	5.6		2.45 dt, 9.2, 4.8, 2.14	2.10, 1.77	1.58, 1.32	0.88 s CH_3
73c		2.58 dd, 7.6, 7.6	1.58, 1.49	1.71, 1.65	1.69, 1.44	2.71 ddd, 6.8, 6.8, 6.0	2.95d, 6.8		2.41, 2.24	2.04, 1.78	1.96, 1.90	3.68 d CO_2CH_3

[a] δ in ppm.
[b] Reported as chemical shift splitting pattern, coupling constants. If no splitting is indicated, the signal is a multiplet.
[c] H-2 doublet buried under H-5 or H-7.

TABLE 22. ^{13}C and ^{1}H chemical shifts for **76** and the *n*-bond connectivity peaks from the HMBC experiment

Carbon	δ_C (ppm)	δ_H (ppm)[a]	*n*-Bond connectivity peaks (HMBC)
1	62.4	3.42 (br ddd, 8.4, 6.9, 1.1)	H-2, H-8b
2	79.1	4.11 (ddd, 6.9, 5.3, 1.0)	H-1, H-8b, O-CH_3
2a	57.3	4.33 (ddd, 7.8, 5.3, 1.1)	H-2, H-8b, N-CH_3
4	163.4		H-2a, H-5, N-CH_3
4a	126.9		H-6, H-8, H-8b
5	128.8	8.21 (dddd, 7.7, 1.5, 0.5, 0.50)	H-7
6	127.6	7.36 (ddd, 7.7, 7.5, 1.4)	H-8
7	132.1	7.42 (ddd, 7.5, 7.4, 1.5)	H-5
8	125.4	7.08 (dddd, 7.4, 1.4, 0.7, 0.5)	H-6, H-8b
8a	137.1		H-1, H-2a, H-5, H-7, H-8b
8b	31.8	3.58 (br t, *ca* 8.4)	H-1, H-2a, H-8
1′	206.0		H-1, H-2, H-2′, H-8b
2′	29.5	2.19 (s)	
O-CH_3	57.7	3.38 (s)	H-2
N-CH_3	34.9	3.15 (s)	H-2a

[a]In parentheses: multiplicity and *J* (Hz).

TABLE 23. ^{13}C and ^{1}H chemical shifts for **77** and the *n*-bond connectivity peaks from the HMBC experiment

Carbon	δ_C (ppm)	δ_H (ppm)[a]	*n*-Bond connectivity peaks (HMBC)
1	54.5	3.35 (dd, 9.9, 8.5)	H-2, H-8b
2	82.2	4.29 (ddd, 8.5, 7.0, 1.3)	H-1, H-2a, H-8b, O-CH_3
2a	58.6	3.93 (dd, 9.7, 7.0)	H-2, H-8b, N-CH_3
4	162.4		H-2a, H-5, N-CH_3
4a	128.0		H-6, H-8, H-8b
5	129.2	8.21 (dd, 7.7, 1.7)	H-7
6	127.6	7.33 (dddd, 7.7, 7.4, 1.4, 0.7)	H-8
7	131.8	7.39 (ddd, 7.5, 7.4, 1.7)	H-5
8	127.9	6.88 (ddd, 7.5, 1.5, 1.4)	H-6, H-8b
8a	134.8		H-1, H-2a, H-6, H-7, H-8b
8b	33.4	4.28 (br t, *ca* 9.8)	H-1, H-2a, H-8
1′	204.5		H-1, H-2, H-8b
2′	31.0	2.18 (s)	
O-CH_3	57.1	3.27 (s)	H-2
N-CH_3	34.3	3.18 (s)	H-2a

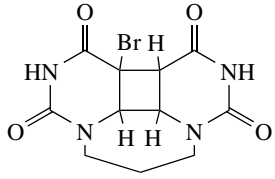
[a]In parentheses: multiplicity and *J* (Hz).

The symmetry-allowed [$\pi 2s + \pi 2s$] photocycloaddition implies that H-2a and H-8b are *cis* and that H-1 and H-2 are *trans*. In isomer **77**, the large coupling constants J(1,8b) (9.9 Hz) and J(2a,8b) (9.7 Hz) are consistent with *cis* stereochemistry and the smaller coupling constants J(1,2) (8.5 Hz) and J(2,2a) (7.0 Hz) suggested a *trans* relationship. However, the tendency for *cis* coupling constants to be larger than *trans* coupling constants in cyclobutanes is known to be unreliable for determining the stereochemistry owing to the large range of values observed for these couplings. In fact, this generalization fails completely to describe the vicinal coupling constants for cyclobutyl hydrogens in isomer **76**, where the largest vicinal coupling constant is J(1,8b) (8.4 Hz), a *trans* relationship, and the smallest vicinal coupling constant is J (2,2a) (5.3 Hz), a *cis* relationship.

Clearly, the coupling constants in these relatively rigid cyclobutanes are no more reliable for determining the stereochemistry than those reported for more flexible monocyclic molecules[5].

Single-crystal X-ray analyses established the relative substituent stereochemistry in each molecule. The anomalous high-field chemical shift for H-8b (δ 3.58 ppm) in **76** as compared with H-8b in **77** (δ 4.28 ppm) does not arise from the anisotropy of the aromatic ring. The crystal structures indicate that this hydrogen lies in almost identical environments relative to the aromatic π-system in each of the two isomers. More likely, H-8b in **76** is shielded by the proximal carbonyl group on a time-averaged basis, an interaction that is absent in **77**.

The structure of another photocycloaddition product that was determined by NMR is exemplified in **78**[64]. The spectral data for this 6b-bromohexahydro-1*H*-3a,5,8,9a-tetraaza-cyclohepta-[1,2,3,4-*def*]biphenylene-4,6,7,9(5*H*,8*H*)-tetrone is given as follows:



(78)

^{1}H NMR (600 MHz, DMSO-d_6): δ 10.90 (s, N3-H), 10.45 (s, N3′-H), 4.72 (d, C6-H, $J = 6.3$ Hz), 4.48–4.45 (dd, C6′-H, $J = 6.3$ Hz, $J = 10.12$ Hz), 4.11–4.05 (m, 3H, N1-CH*H*, N1′-CH*H* and C6-H), 2.89 (m, 1H, N1-C*H*H), 1.56 (m, 1H, C-C*H*H-C). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.65, 163.44, 150.48, 150.27, 64.44, 52.79, 48.05, 47.74, 46.60, 45.95, 24.06.

The close resemblance of the chemical shifts and splitting patterns of the cyclobutane ring hydrogens H6 and H6′ as well as those of the methylene hydrogens adjacent to the N1 and N1′ nitrogens to those of the previously obtained *cis–syn* cyclobutane photoadducts of other 1,1′-trimethylene-bridged pyrimidines indicated the *cis–syn* configuration of this adduct.

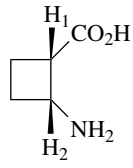
NMR data for the *cis*-cyclobutane β-aminoacid derivatives ($\pm$) **79**–**82** were reported without assignment[65]. ^{1}H chemical shifts and H–H coupling constants at 400 MHz and ^{13}C data at 100 MHz are given below.

79: ^{1}H NMR(D_2O)δ: 3.92 (m, 1H), 3.24 (m, 1H), 2.36 (m, 1H), 2.24 (m, 2H), 2.05 (m, 1H); ^{13}C NMR(D_2O)δ: 183.7, 48.2, 44.0, 27.7, 23.8.

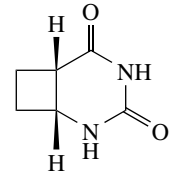
80: ^{1}H NMR (DMSO-d_6) δ: 10.02 (s, 1H), 7.68 (s, 1H), 3.90 (m, 1H), 3.11 (m, 1H), 2.18 (m, 2H), 1.92 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 173.3, 152.7, 44.8, 37.2, 30.6, 21.4.

81: ^{1}H NMR (DMSO-d_6) δ: 12.1 (bs, 1H), 6.19 (d, $J = 9.2$ Hz, 1H), 5.55 (s, 2H), 4.40 (quint, $J = 8.8$ Hz, 1H), 3.14 (m, 1H), 2.16 (m, 1H), 2.06 (quint, $J = 10.0$ Hz, 1H), 1.79 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 174.7, 157.4, 45.8, 44.9, 29.2, 17.4.

82: ^{1}H NMR (DMSO-d_6) δ: 12.15 (bs, 1H), 9.42 (d, $J = 7.3$ Hz, 1H), 9.10 (d, $J = 1.8$ Hz, 2H), 9.00 (d, $J = 1.8$ Hz, 1H), 4.81 (quint, $J = 8.3$ Hz, 1H), 3.40 (m, 1H), 2.52 (m, 1H), 2.31 (m, 1H), 2.14 (m, 1H), 1.98 (quint, $J = 8.8$ Hz, 1H); ^{13}C NMR (DMSO-d_6) δ: 173.5, 161.6, 148.1, 136.7, 127.5, 120.9, 45.8, 44.8, 25.7, 18.0.



(79)



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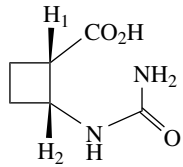

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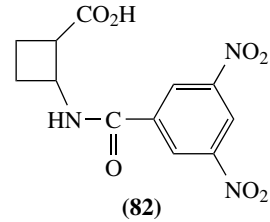
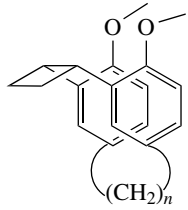


(82)

The *cis* relationship of the cyclobutane substituents was assigned by the nuclear Overhauser effects between the H_1 and H_2, the hydrogens on the substituted carbons of the cyclobutyl ring (**79**, 8%; **80**; 9%; **81**, 10%). Since these ^1H and ^{13}C NMR data for **79** differ from those of previous publications, the structure was confirmed by preparation of the 3,5-dinitrobenzamide **82**; 6% NOE between H_1 and H_2 was observed. The X-ray crystallographic structure of **82** reveals that both substituents on the cyclobutyl ring are *cis*.

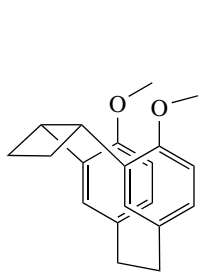
A series of [2, *n*] metacyclophane-fused cyclobutane rings **83**–**90** was prepared in order to verify if they can be functionalized by bromination[66]. The hydrogen NMR spectra of the structures **85**–**89** (δ, J) that contain cyclobutyl rings are reported in $CDCl_3$ without assignment as follows.



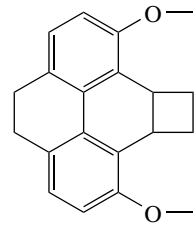
(a) $n = 1$
(b) $n = 2$
(c) $n = 3$
(d) $n = 4$
(e) $n = 5$

(83a–83e)

85: 2.08 (2H, m), 2.55 (2H, m), 2.84 (4H, m), 3.80 (6H, s), 3.91 (2H, m), 6.70 (2H, d, 8.1), 6.99 (2H, d, 8.1). **86** (in CD_2Cl_2): 2.10 (2H, m), 2.60 (2H, m), 3.10 (4H, m), 3.76 (6H, s), 3.92 (2H, m). **87b**: 1.50 (1H, m), 2.21 (1H, m), 2.33 (1H, m), 2.52 (2H, m), 2.63 (3H, m), 2.92 (2H, m), 3.54 (3H, s), 3.58 (3H, s), 4.50 (1H, m), 4.69 (1H, m), 6.32 (1H, d, 8.2), 6.65 (1H, dd, 2.0 and 8.2), 6.81 (1H, d, 1.8), 7.04 (1H, d, 1.8), 7.07 (1H, d, 2.0). **87c**: 1.37 (1H, m), 1.48 (1H, m), 1.92 (2H, m), 2.29 (3H, m), 2.56 (5H, m), 3.59 (3H, s), 3.62 (3H, s), 4.50 (1H, m), 4.63 (1H, m), 6.38 (1H, d, 8.2), 6.61 (1H, dd, 2.1 and 8.2), 6.81 (1H, d, 2.1), 7.09 (1H, d, 2.1), 7.14 (1H, d, 2.1). **87d**: 0.26 (1H, m), 0.94 (1H, m), 1.55 (2H, m), 1.79 (2H, m), 2.23 (1H, m), 2.44 (3H, m), 2.64 (2H, m), 2.74 (2H, m), 3.63 (3H, s), 3.64 (3H, s), 4.51 (1H, m), 4.63 (1H, m), 6.51 (1H, d, 8.2), 6.74 (1H, dd, 1.8 and 8.2), 6.93 (1H, d, 2.0), 7.17 (1H, d, 2.0), 7.18 (1H, d, 1.8). **88c**: 1.44 (2H, m),



(84)



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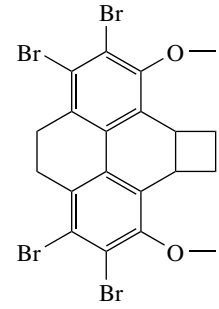

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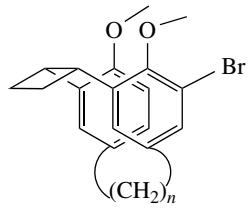
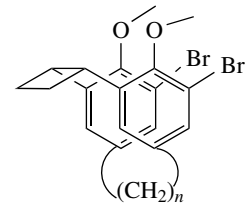
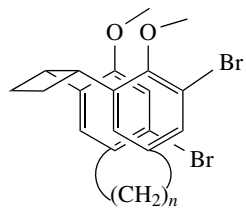


(87a–87e)

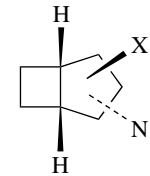


(88a–88e)

(a) $n = 1$
(b) $n = 2$
(c) $n = 3$
(d) $n = 4$
(e) $n = 5$



(89a–89e)



(90)

X = *exo*
N = *endo*

1.96 (2H, m), 2.29 (2H, m), 2.42 (2H, m), 2.59 (4H, m), 3.65 (6H, s), 4.56 (2H, m), 6.89 (2H, d, 2.1), 7.19 (2H, d, 2.1). **88d**: 0.29 (1H, m), 0.98 (1H, m), 1.58 (2H, m), 1.82 (2H, m), 2.44 (4H, m), 2.57 (2H, m), 2.75 (2H, m), 3.68 (6H, s), 4.56 (2H, m), 6.99 (2H, d, 2.0), 7.20 (2H, d, 2.0). **89c**: 1.47 (2H, m), 1.92 (2H, m), 2.24 (1H, m), 2.31 (1H, m), 2.38 (1H, m), 2.55 (4H, m), 2.90 (1H, m), 3.58 (3H, s), 3.62 (3H, s), 4.50 (2H, m), 6.62 (1H, s), 6.84 (1H, d, 1.9), 7.05 (1H, d, 1.9), 7.06 (1H, s). **89d**: 0.26 (1H, m), 1.02 (1H, m), 1.62 (2H, m), 1.86 (2H, m), 2.18 (1H, m), 2.40 (2H, m), 2.64 (3H, m), 2.78 (1H, m), 2.88 (1H, m), 3.62 (3H, s), 3.64 (3H, s), 4.44 (1H, m), 4.54 (1H, m), 6.71 (1H, s), 6.96 (1H, d, 2.0), 7.12 (1H, s), 7.21 (1H, d, 2.0).

The structures of these products were determined by ^{1}H NMR and mass spectrometry. Molecular symmetry was also used in this determination because of the C_1 symmetry for **87** and **89** or the C_s symmetry for **88**. The essential spectroscopic aspects are as follows: The tetrabromo compound **86** showed no Ar hydrogens. The tetrahydropyrene derivative **85** showed the two coupled *ortho* signals (δ 6.70 and 6.99, $J = 8.1$ Hz). Monobromide **87** shows two doublets (δ 6.81–6.93 and 7.04–7.17, $J = 1.82$–2.1 Hz) of Ar hydrogens with coupling between *meta* hydrogens on the substituted Ar ring. Dibromide **88** lost the couplings between *ortho* Ar hydrogens of **87** and only showed the two coupled *meta* signals (δ 6.89–6.99 and 7.19–7.20, $J = 2.0$–2.1 Hz). Dibromide **88** showed two peaks (δ 6.84–6.96 and 7.05–7.21, $J = 1.9$–2.0 Hz) of one Ar ring with coupling between *meta* signals and two singlets (δ 6.62–6.71 and 7.06–7.12) of the other Ar ring.

A compilation of ^{13}C chemical shifts of bicyclo[3.2.0]heptanes **90** is provided by Whitesell and Minton[16].

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CHAPTER 7

Mass spectrometry and gas-phase ion chemistry of cyclobutanes

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I. INTRODUCTION

Mass spectrometry and gas-phase ion chemistry of cyclobutanes is special and much less elaborated in detail than that of many other classes of compounds and functional groups. This is due to the fact that the four-membered ring is highly strained and that most ionization methods used in mass spectrometry transfer considerable amounts of additional internal energies to the molecular or quasi-molecular ion of the sample molecules. Therefore, the original constitution of the neutral precursor is lost particularly rapidly and the isomeric ions formed by ring opening often undergo further isomerization and/or

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fragmentation which is more alike the reactions of acyclic isomers of the cyclobutane ions of interest. Thus, a notorious weakness of mass spectrometry, that is, the sometime deep-seated chemical structure conversion of the initially formed molecular radical-cations or even-electron ions, is especially relevant to the strained precursors, such as cyclobutane and its derivatives.

On the other hand, gas-phase ion chemistry of cyclobutanes and the appearance of their mass spectra depending on this particular chemistry is special also in a positive sense, and distinct from that of other cyclic compounds. Cyclobutane ions have a much more facile channel to undergo fragmentation without the interplay of unimolecular isomerization. The reason for this lies in the fact that the facile cleavage of one C−C bond of the carbocycle triggers the cleavage of the opposite one to induce the direct formal [2 + 2] cycloreversion leading (irreversibly) to the fragments. Such particularly facile fragmentation of cyclobutane derivatives has been used in varied ways to probe for energetic irradiation; for example, aryl-substituted cyclobutanes have been utilized as a chemical actinometer[1].

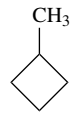
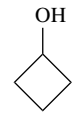
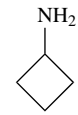
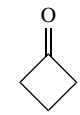
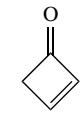
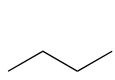
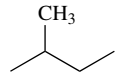
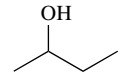
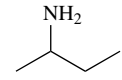
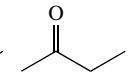
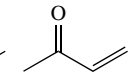
In turn, cyclobutane-type ions can also form easily by ion/molecule reactions in the gas phase by formal [2 + 2] cycloaddition. Hence, mass spectrometry can serve as a tool to generate ionized cyclobutane species in the plasma of a chemical ionization source or within the cell of an electric ion trap or an ion cyclotron resonance (ICR) mass spectrometer. When an olefinic reagent is added to the ionized olefin, 'orthogonal' *in-situ* cycloreversion of the newly formed four-membered carbocycle can then give rise to two new olefinic fragments which provide analytically useful information on the original position of the double bond in the sample olefin[2]. Also, ionized cyclobutanes form during isomerization of gaseous radical cations of dienes and polyenes[2], and cyclobutane can be used as a neutral partner in ion/molecule reactions with the radical cations of arenes in the mass spectrometer[3].

Thus, mass spectrometry of cyclobutanes is really special. This chapter will give an overview of the fundamentals of their gas-phase ion chemistry of mostly radical cations of cyclobutane and cyclobutane derivatives, including the typical unimolecular isomerization and fragmentation reactions as well as some bimolecular chemistry. Some analytical applications concerning cyclobutane derivatives will also be presented.

II. GASEOUS CATIONS DERIVED FROM CYCLOBUTANES: THERMOCHEMISTRY OF SOME TYPICAL SPECIES AND REACTIONS

Cyclobutane (**1**) and simple cyclobutane derivatives (**2**–**6**) have significantly lower ionization energies than the corresponding butanes (Chart 1)[4–7]. The photoelectron spectrum of **1** and its vertical ionization energies obtained by both photoionization[8,9] and electron ionization[10], as well as the structural details[8] of ion $\mathbf{1}^{\bullet+}$ have been presented. The difference of *ca* − 0.7 eV between the acyclic and the cyclic counterparts is not only found for the parent hydrocarbon but also for the methyl derivatives and the alcohols. Cyclobutanone (**5**) and cyclobutenone (**6**) have also lower IEs as compared to 2-butanone and 1-buten-3-one, but the difference is only *ca* − 0.3 eV. Interestingly, cyclobutanone has the highest ionization energy among the cycloalkanones[4,5,11]. This shows that removal of an electron from the strained carbocyclic ring is much easier than ionization of comparable strainless hydrocarbon skeletons. As can be seen from Chart 1, thermochemical data of simple cyclobutane derivatives are further from being complete as compared with the butane derivatives. For example, proton affinities are only known for cyclobutanone, again being lower than that of 2-butanone by *ca* − 25 kJ mol^{-1} (*ca* − 0.26 eV). One reason for the lack of PA data for cyclobutanes is obvious: Protonation of the four-membered ring may easily destroy the strained framework, impeding equilibrium measurements in the gas phase. The gas-phase acidity, given here as enthalpy of deprotonation $\Delta H_{\mathrm{acid}}{}^{\circ}$, of the cyclobutane framework is known to be the same within experimental error,

CHART 1. Gas-phase thermochemical data of cyclobutane and simple cyclobutane derivatives[a,b]

						
	(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**
IE (eV)	9.8	9.64	9.56 [c]	8.60 [c]	9.35	9.3
PA (kJ mol^{-1})	–	–	–	–	802.5	–
ΔH_{acid}° (kJ mol^{-1})	1746	–	–	–	1536	–
						
IE (eV)	10.53	10.32	9.88	(8.7)	9.52	9.65
PA (kJ mol^{-1})	–	–	815	929.7	827.3	834.7
ΔH_{acid}° (kJ mol^{-1})	1739	–	1565	–	1536	1520

[a] Data taken from Reference 4.

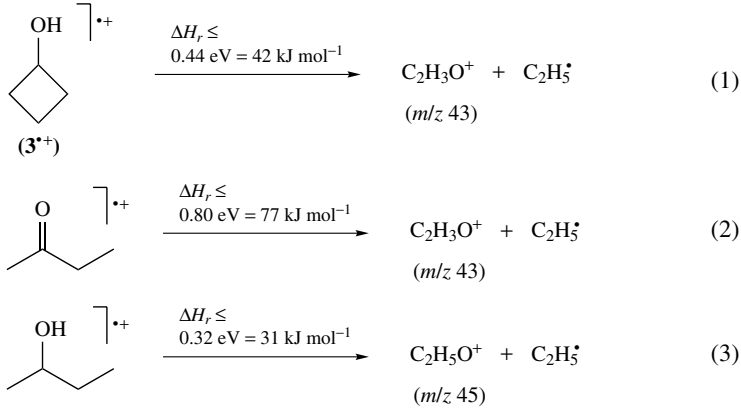
[b] For enthalpies of formations of neutral cyclobutanes, see Chapter 4.

[c] See also Reference 7.

$\Delta H_{acid}^{\circ}(\mathbf{1}) = 1746 \pm 8$ kJ mol^{-1}, as that of *n*-butane ($\Delta H_{acid}^{\circ} = 1739 \pm 8$ kJ mol^{-1}), in parallel to the identical values reported for deprotonation of cyclobutanone, $\Delta H_{acid}^{\circ}(\mathbf{5}) = 1536 \pm 17$ kJ mol^{-1}, and 2-butanone ($\Delta H_{acid}^{\circ} = 1536 \pm 12$ kJ mol^{-1})[4]. Hence, in contrast to the positive ions, the strain in the cyclobutane ring has no effect on the thermochemistry of formation of the $[M - H]^-$ anions. Thermochemical data concerning the radical anions of simple cyclobutanes have not been compiled yet, with the exception of the electron affinity (EA) of cyclobutanone. In fact, the radical anion $\mathbf{5}^{\bullet -}$ is an extremely labile species [$EA(\mathbf{5}) = EA(CH_3COC_2H_5) = 1.0$ meV ≈ 0.10 kJ mol^{-1}, cf., $EA(CH_3COCH_3) = 1.5$ meV ≈ 0.15 kJ mol^{-1}][4,12].

The hydrogen atom affinity of a radical cation reflects the negative of the reaction enthalpy gained by addition of H$^{\bullet}$ to it[13–15]. The hydrogen atom affinity of ionized cyclobutanone, $HA(\mathbf{5}^{\bullet +})$, can be determined from its ionization energy, its proton affinity and $IE(H^{\bullet}) = 13.598$ eV as $HA(\mathbf{5}^{\bullet +}) = IE(\mathbf{5}) - IE(H^{\bullet}) + PA(\mathbf{5}) = 393.0$ kJ mol^{-1} and compared to the hydrogen atom affinity of ionized 2-butanone, $HA(CH_3COC_2H_5^{\bullet +}) = 433.8$ kJ mol^{-1} (again using the data collected in Chart 1). Thus, the ionized carbonyl group of cyclobutanone is by more than 40 kJ mol^{-1} less 'aggressive' as an H$^{\bullet}$ abstractor group than the ionized carbonyl groups of aliphatic ketones. This may be important considering a McLafferty reaction occurring in the non-isomerized radical cations of derivatives of **1** (see below). Allowing for a first-order approximation, the hydrogen atom affinity of the radical cation of cyclobutenone, $\mathbf{6}^{\bullet +}$, can be assumed to differ from that of ionized methyl vinyl ketone, $HA(CH_3COC_2H_3^{\bullet +}) = 453.8$ kJ mol^{-1}, by the same ΔHA value as do ion $\mathbf{6}^{\bullet +}$ and ionized 2-butanone. Thus, addition of a hydrogen atom to ionized cyclobutenone should be exothermic by *ca* $(453.8 - 40.8) = 413.0$ kJ mol^{-1} and the radical cation $\mathbf{6}^{\bullet +}$ should be by *ca* 20 kJ mol^{-1} more aggressive an H$^{\bullet}$ acceptor than radical cation $\mathbf{5}^{\bullet +}$.

The thermochemistry of prominent fragmentation reactions of prototypical ionized cyclobutane derivatives has been determined experimentally in quite some detail[7,16,17]. Some of the relevant data will be discussed in the following section. One simple example may be mentioned here for comparison (Scheme 1). The energy required for the loss of an ethyl radical from ionized cyclobutanol, $\mathbf{3}^{\bullet+}$ (equation 1), can be estimated from the appearance energy (AE) determined for the $[M - C_2H_5]^+$ ions from neutral **3** and IE(**3**), by neglecting a possible activation barrier. [The appearance energy $AE(F^+)$ is defined as the minimum energy required for the detection of the fragment ion, F^+, formed along with the neutral fragment, N, from the neutral precursor, M, in the reaction $M + e^- \rightarrow F^+ + 2e^- + N$ in the case of an EI-induced fragmentation. In simple cases, it can be approximated from the corresponding heats of formation by the equation $AE(F^+) \geqslant \Delta H_f(F^+) + \Delta H_f(N) - \Delta H_f(M)$.] The experiment-based literature data suggest that $\Delta H_r(\mathbf{1}) \leqslant AE([\mathbf{3} - C_2H_5]^+ - IE(\mathbf{3}) = 0.44$ eV $= 42$ kJ mol^{-1}. Loss of $C_2H_5^{\bullet}$ from the radical cation of 2-butanone (equation 2) is significantly more endothermic. In the case of ionized 2-butanol (equation 3), however, the energy required for loss of $C_2H_5^{\bullet}$ is slightly less, $\Delta H_r(\mathbf{3}) \leqslant 31$ kJ mol^{-1}, than in the case of ion $\mathbf{3}^{\bullet+}$. Due to the intrinsic strain of the cyclobutane ring, the α-cleavage of the C(1)−C(2) bond in ion $\mathbf{3}^{\bullet+}$ should be less energy-demanding than in the corresponding α-cleavage of ionized 2-butanol. Therefore, the data suggest that a hydrogen rearrangement following the initial C−C bond cleavage of ion $\mathbf{3}^{\bullet+}$ represents the energy-determining step of their overall fragmentation. In turn, the considerably higher energy requirement for the loss of $C_2H_5^{\bullet}$ from the radical cations of 2-butanone suggests that the latter ions are much more stable than ion $\mathbf{3}^{\bullet+}$. In fact, the heats of formation of these isomeric $C_4H_8O^{\bullet+}$ radical cations, as determined from experimental data, are $\Delta H_f(\mathbf{3}^{\bullet+}) = 756$ kJ mol^{-1} and $\Delta H_f(CH_3COC_2H_5^{\bullet+}) = 677$ kJ mol^{-1} [5], reflecting mostly the different thermochemical stability of the neutral molecules. More detailed insight on the $C_4H_8O^{\bullet+}$ energy hypersurface has been elaborated (see below).



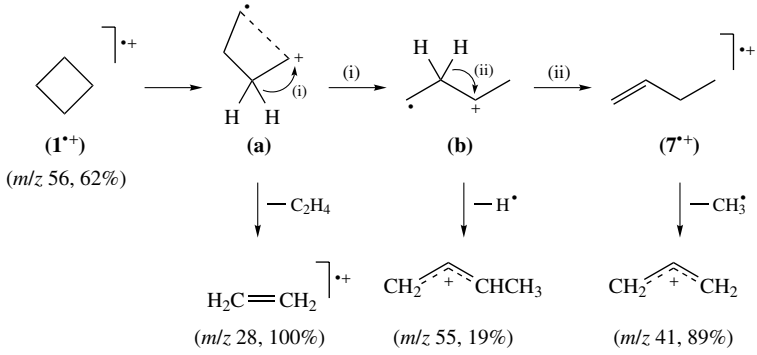
SCHEME 1

III. UNIMOLECULAR FRAGMENTATION REACTIONS OF CYCLOBUTANE RADICAL CATIONS AND SELECTED DERIVATIVES

A. Cyclobutane

The electron ionization (EI) mass spectrum of the parent cyclobutane recorded at 70 eV exhibits several intense peaks, the largest one of which (the 'base peak') appears at m/z 28 corresponding to the formal cleavage of the ring into two moieties, ionized ethene and

neutral ethene. The second largest peak at m/z 41 indicates the loss of a methyl radical, which inevitably requires a hydrogen rearrangement prior to the eventual fragmentation. Expulsion of $H^{\bullet}$ giving $C_4H_7^+$ ions (m/z 55) competes with $CH_3^{\bullet}$ loss, although a simple cleavage of a C−H bond is known to be more endothermic than cleavage of C−C bonds. Actually, at least a part of the $H^{\bullet}$ loss occurs after ring opening by C−C bond cleavage. As depicted in Scheme 2, cleavage of one of the C−C bonds in ion $\mathbf{1}^{\bullet+}$ would give a distonic carbenium ion (**a**) (see below) which, as a primary cation, should not correspond to an energy minimum. However, the incipient ion **a** is converted by 1,2-hydride shift to give another, secondary distonic carbenium ion **b** which, by a further 1,2-hydride shift, generates ionized but-1-ene ($\mathbf{7}^{\bullet+}$). Although the isomerization and fragmentation manifold of the isomeric $C_4H_8^{\bullet+}$ ions is much more complex and known to involve extensive H and C scrambling prior to decomposition through common fragmentation channels, the isomerization sequence $\mathbf{1}^{\bullet+} \rightarrow \mathbf{7}^{\bullet+}$ shown in Scheme 2 provides straightforward intermediates for the three primary fragmentation channels, viz. loss of C_2H_4, $H^{\bullet}$ and $CH_3^{\bullet}$. The first and the last reactions are the least energy consuming fragmentations, both requiring *ca* 116 kJ mol^{-1} above the ionization energy to be observable[4].



SCHEME 2

In fact, the isomerization and fragmentation processes of $C_4H_8^{\bullet+}$ ions have been studied in great detail for ions reacting within relatively long lifetimes ($\leqslant 1 \cdot 10^{-6}$ to *ca* $2 \cdot 10^{-5}$ s)[18–22] and extremely short lifetimes ($2 \cdot 10^{-11}$ s)[20–22]. Field ionization (FI) mass spectrometry was reported to reflect mainly unrearranged $C_4H_8^{\bullet+}$ isomers, and field ionization kinetics (FIK) of ionized cyclobutane indicated a lesser tendency of ion $\mathbf{1}^{\bullet+}$ to undergo isomerization, as compared to the other five $C_4H_8^{\bullet+}$ isomers[20]. This is certainly due to the particular ease of the incipient product, **a**, formed from $\mathbf{1}^{\bullet+}$ by the first C−C bond cleavage, to undergo a second C−C bond cleavage in a fast, consecutive step. In fact, the 'normal' FI mass spectrum of cyclobutane (**1**) is clearly distinct from the FI mass spectra of the other isomers: Only the former isomer yields an intense (*ca* 60%) peak for the loss of C_2H_4[20]. This difference is still evident in the conventional electron ionization (EI, formerly termed 'electron impact') mass spectra of the six C_4H_8 isomers[19]. In further agreement, the competition between fragmentation across structure-specific transition states of strained $C_4H_8^{\bullet+}$ ions and their isomerization to the olefinic counterparts was demonstrated by energy-selective ionization and fragmentation studies using threshold photoelectron-coincident photoion (TPE-CPD) mass spectrometry. At relatively high internal energies, both ion $\mathbf{1}^{\bullet+}$ and ionized methylcyclopropane show different fragmentation behaviour as compared to the olefinic $C_4H_8^{\bullet+}$ isomers[23].

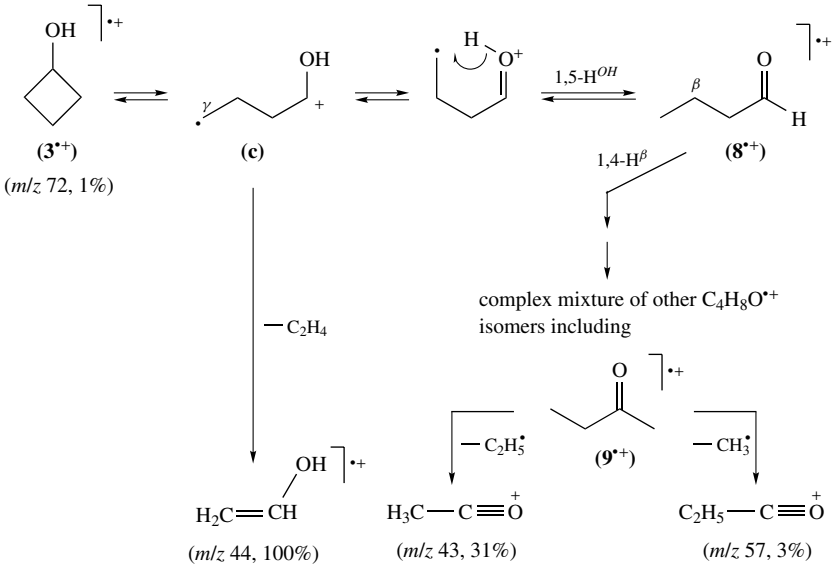
Long-lived ('metastable') $C_4H_8^{\bullet+}$ ions, including $\mathbf{1}^{\bullet+}$, eliminate not only C_2H_4 but also H_2 and CH_4. The metastable-ion spectra [e.g. the mass-analysed ion kinetic energy (MIKE) spectra] are indistinguishable, reflecting the conversion of the individual precursor ions to an equilibration mixture of $C_4H_8^{\bullet+}$ ions. Elimination of C_2H_4 from the metastable ions is only a minor process (*ca* 0.5% Σ) (Σ denotes sum of fragment ion currents), whereas loss of $CH_3^{\bullet}$ is by far the dominant fragmentation channel (*ca* 89% Σ)[18]. Clearly, the strained cyclobutane radical cation $\mathbf{1}^{\bullet+}$ cannot be the most energetically favourable isomer by which the ions find their way to eventual fragmentation. Rather, ionized but-1-ene $\mathbf{7}^{\bullet+}$ will take over this role for all the $C_4H_8^{\bullet+}$ ions that have sufficiently low excitation energy and, thus, sufficient time to undergo complete H scrambling and (in case of isobutene and methylcyclopropane) also C scrambling. Besides primary fragmentation of $\mathbf{1}^{\bullet+}$ and its isomers, secondary and further fragmentation has also been studied in detail[22].

A completely independent approach to probe the structure of $C_4H_8^{\bullet+}$ ions from cyclobutane (**1**) consists of performing bimolecular reactions. To this end, selective photoionization of **1** at $\lambda = 116.5$ nm (10.6 eV) in a mixture of various reactant gases was performed under 'high-pressure' conditions (i.e. *ca* 10^{-3} to 10^{-1} mbar), and the pressure-dependent relative ion abundances revealed that the reactive ionic species formed from **1** are acyclic and may even exist in two or more different ring-opened structures[24]. Similar results were obtained from an extended study on ion/molecule reactions in gaseous cyclobutane employing a high-pressure EI source[25]. Thus, the bimolecular reactivity of $C_4H_8^{\bullet+}$ ions from **1** are in agreement with the results obtained from the studies on their unimolecular reactivity discussed above.

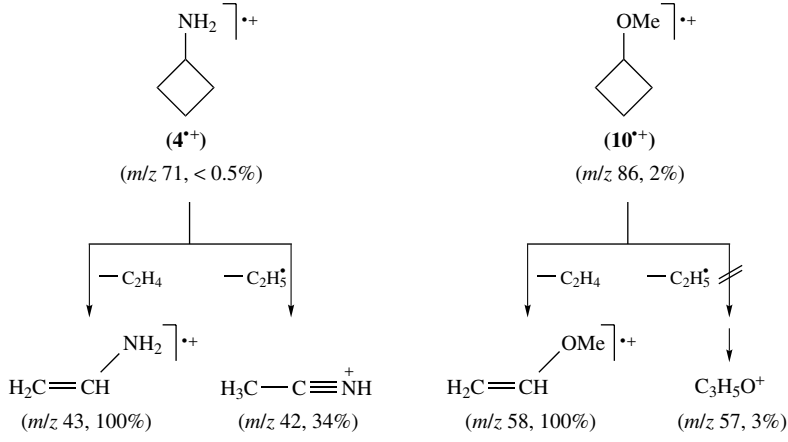
B. Cyclobutanol and Other *cyclo*-C_4H_7X Derivatives

Ring-opening reactions of cyclobutane derivatives under EI conditions occur even more easily if an electron-releasing group is present at the ring. For example, the EI mass spectra of methylcyclobutane (**2**) and ethylcyclobutane are even more strongly dominated by the corresponding $[M - C_2H_4]^{\bullet+}$ ions at *m/z* 42 and *m/z* 56, respectively, than is the case for the parent compound[4]. EI-induced loss of $CH_3^{\bullet}$ from the latter hydrocarbon has been studied by deuterium labeling[26]. However, electron-donating groups bearing non-bonding electron pairs, such as hydroxy and amino groups, dramatically labilise the carbocyclic framework. Thus, the EI mass spectra of cyclobutanol (**3**), cyclobutylamine (**4**) and cyclobutyl methyl ether (**10**) are governed by the formation of the $C_2H_3X^{\bullet+}$ ions (X = OH, NH_2, OMe) at *m/z* 44, *m/z* 43 and *m/z* 58, respectively (Schemes 3 and 4). Noteworthily, the relative abundances of the respective molecular ions, $M^{\bullet+}$, are very low ($\leqslant$2%). The only other significant fragment peaks are due to occurrence of $[M - C_2H_5]^+$ ions, 1 Th (Thomson, *m/z*) unit lower than the $[M - C_2H_4]^{\bullet+}$ ions. It is noteworthy that a combined photoionization and molecular orbital investigation of cyclobutanol and cyclobutylamine has shown that both ions $\mathbf{3}^{\bullet+}$ and $\mathbf{4}^{\bullet+}$, when formed by the vertical ionization process, do not represent energy minima on their potential hypersurface but are directly converted to the respective distonic ions, which then easily dissociate to ionized vinyl alcohol (*m/z* 44) and ionized vinylamine (*m/z* 43), respectively[7].

The major part of the fragmentation mechanism of ionized cyclobutanol ($\mathbf{3}^{\bullet+}$) is depicted in Scheme 3. In this case, both the intrinsic strain of the four-membered ring and the hydroxy group drive the α-cleavage. As mentioned above, ion $\mathbf{3}^{\bullet+}$ is not stable when generated by vertical ionization[7], but the γ-distonic ion **c** is a relatively stable species having its own chemistry[27,28]. It makes part of the large group of reactive intermediates formed by γ-$H^{\bullet}$ transfer during the McLafferty reaction of ionized carbonyl compounds[29]. In fact, besides fragmentation by cleavage of the central C–C bond (which corresponds to the final step of the McLafferty reaction) giving the extremely stable enol radical ion $CH_2CHOH^{\bullet+}$ (*m/z* 44), ion **c** can undergo



SCHEME 3



SCHEME 4

'reverse' 1,5-H$^{\bullet}$ transfer to give the molecular ion of butanal (**8**$^{\bullet+}$). Related stepwise isomerizations of ionized cycloalkanols to the respective ionized aldehydes were reported early[30,31]. A simple thermochemical approximation demonstrates that the isomerization step **c** → **8**$^{\bullet+}$ is almost thermoneutral: $\Delta H_r = PA(\mathbf{8}) - IE(\mathrm{H}^{\bullet}) - D(\mathrm{RCH_2} - \mathrm{H}) + IE(\mathbf{8}) = 793 - 1312 - 423 + 947 = +5\ \mathrm{kJ\,mol^{-1}}$ (R = alkyl)[4,5]. Ion **8**$^{\bullet+}$ undergoes further isomerization starting by 1,4-H shift from the β-methylene group to the carbonyl oxygen, which is an ubiquitous isomerization path in ionized carbonyl compounds in the gas phase[32–35]. The isomerization manifold includes further 1,2-H and

also 1,2-C shifts subsequent to the initial 1,4-H^{β} transfer[16,36–38]. In this way, ionized 2-butanone ($\mathbf{9}^{\bullet+}$) is formed, among further $C_4H_8O^{\bullet+}$ isomers, losing $C_2H_5^{\bullet}$ to give the acetyl cation (*m/z* 43) as particularly stable fragment ions. A weakly competing parallel fragmentation channel enables loss of $CH_3^{\bullet}$ giving propionyl cations (*m/z* 57) in very minor relative abundance.

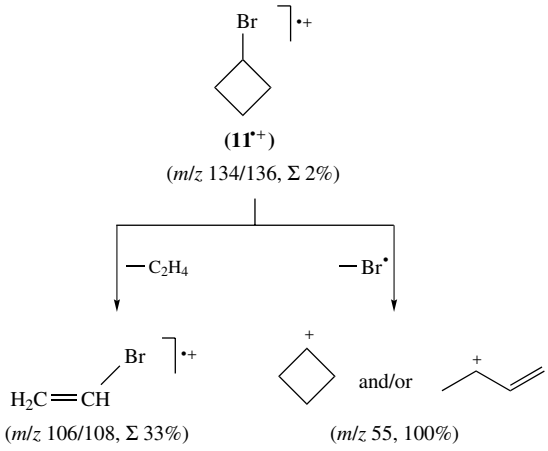
The excitation energies required to drive the two major fragmentation reactions have been determined experimentally and amount to *ca* 0.40 eV and 0.44 eV, respectively. Thus, only 39–42 kJ mol^{-1} are required to cleave the radical cations of cyclobutanol into the two pairs of ring fission fragments. Interestingly, the corresponding energies starting from ionized butanal $\mathbf{8}^{\bullet+}$ are not significantly higher[4,16].

Relief of strain in the very first, ring opening step of ionized cyclobutanol ($\mathbf{3}^{\bullet+}$) certainly put this isomer at the rim of the complex isomerization scenario of gaseous $C_4H_8O^{\bullet+}$ ions. However, it has been suggested[37] that the radical cation of butanal can undergo (re-)cyclization ($\mathbf{8}^{\bullet+} \rightarrow \mathbf{3}^{\bullet+}$, cf. Scheme 3). In fact, the possible formation of cyclobutanol-type radical cations by cyclization of the γ-distonic ion intermediates of type **c** during the McLafferty reaction has been examined previously for a number of aldehydes and diketones[39,40]. Bimolecular formation of γ-distonic ions has been achieved by reaction of ionized enols with ethene and propene but it was found that the cyclization step giving the corresponding cyclobutanol radical cations does take place[41].

It is worth noting in this context that the radical cations of cyclobutanol and cyclobutanol derivatives have been extensively used as precursors to generate enol radical cations by [2 + 2] cycloreversion. As the direct generation of these reactive species by ionization of *neutral* enols is difficult, although feasible by combined pyrolysis-mass spectrometry[42], the cycloreversion route from ionized cyclobutanols represents a convenient alternative, together with the McLafferty reaction, which has also been used frequently to generate radical cations of enols[35,41,43–45]. In turn, the directed generation of enol radical cations by cycloreversion of ionized cyclobutanols has enabled detailed studies of *neutral* enols in the gas phase. To this end, the enol ions were subjected to neutralization/re-ionization mass spectrometry (NRMS), by which the ions under investigation are neutralized by passing 'in-beam' through a reaction cell containing reducing vapours, such as mercury[43,44].

Cyclobutyl methyl ether **10** is another interesting example. In analogy to ions $\mathbf{3}^{\bullet+}$ and $\mathbf{4}^{\bullet+}$, α-cleavage of ion $\mathbf{10}^{\bullet+}$ followed by dissociation of the opposite C–C bond releases C_2H_4 giving methyl vinyl ether ion (*m/z* 58) and the base peak in the EI mass spectrum. However, in contrast to ions $\mathbf{3}^{\bullet+}$ and $\mathbf{4}^{\bullet+}$, the distonic ion intermediate $^{\bullet}CH_2CH_2CH_2CH{=}O^{+}CH_3$ formed by α-cleavage of $\mathbf{10}^{\bullet+}$ cannot undergo 1,5-H transfer from the functional group to the γ-CH_2 group because of the presence of the methyl group in place of a hydrogen atom. As a consequence, formation of an ionized carbonyl group is suppressed, as are the subsequent isomerization steps and the loss of $C_2H_5^{\bullet}$ (cf. Scheme 3). The residual minor peak at *m/z* 57 is probably due to $C_3H_5O^+$ ions formed along more energy-demanding pathways. The drastic decrease of the abundance of $[M - 29]^+$ ions in the EI mass spectrum of cyclobutyl methyl ether **10** is a nice proof for the isomerization mechanism of the radical cations of cyclobutane derivatives of the type *cyclo*-$C_4H_7YH^{\bullet+}$, e.g. $\mathbf{3}^{\bullet+}$ and $\mathbf{4}^{\bullet+}$.

Cleavage of cyclobutane ring under EI conditions into two olefinic fragments is also an important decomposition pathway when the stabilizing effect of the substituent is low and direct loss of the substituent by cleavage of its exocyclic bond is particularly facile. An example for this case is bromocyclobutane **11** (Scheme 5). Again, the molecular ion $\mathbf{11}^{\bullet+}$ is extremely labile. Here, the main reason for this is the weakness of the C–Br bond, the fission of which gives rise to most abundant $C_4H_7^+$ ions, probably as a mixture of isomers. However, loss of C_2H_4 is still prominent, leading to ionized bromoethene in



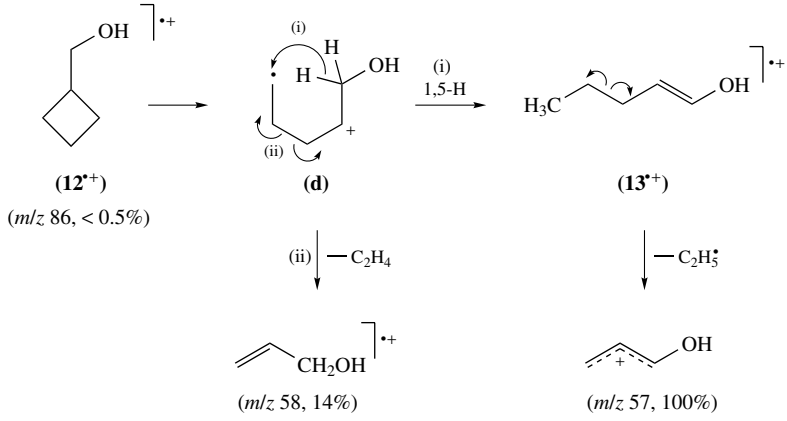
SCHEME 5

a combined relative abundance of 33%. In fact, two simple and irreversible C−C bond cleavages compete in this case.

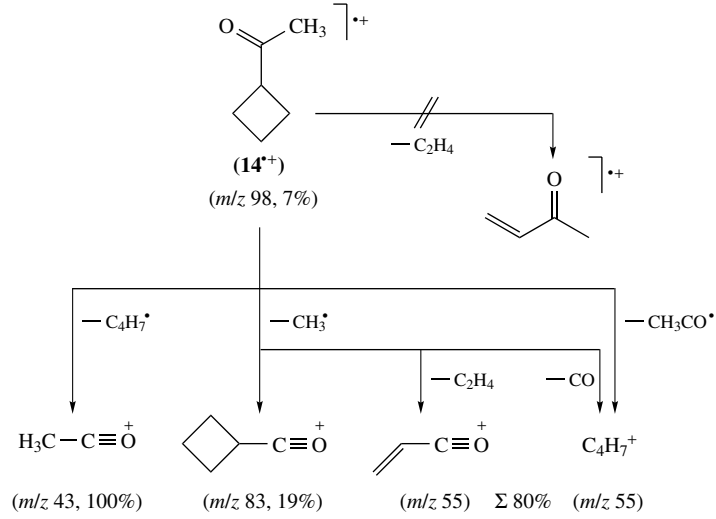
The ring fission of simple cyclobutane derivatives under electron impact has provided valuable examples for our understanding of a fundamental problem of organic mass spectrometry, namely, which of the fragments (X or Y) formed in the decomposition of a positive ion $[XY]^{\bullet+}$ retains the positive charge. In fact, the examples discussed in the cyclobutane series[46] show that the positive charge remains on the olefinic fragment having the lower ionization energy, in agreement with Stevenson's (or the 'Stevenson−Audier') rule[46−48]. In the case of the bromocyclobutane ion $\mathbf{11}^{\bullet+}$, ionization of the bromoethene fragment requires less energy than ionization of ethene [$IE(C_2H_3Br) = 9.82$ eV, $IE(C_2H_4) = 10.51$ eV][4]. Thus, the m/z 28 peak in the EI spectrum of **11** is of minor relative intensity (8%) as compared to the combined m/z 106 and m/z 108 peaks. Not surprisingly, the rule also applies to the formation of the $C_4H_7^+$ ions (m/z 55) from $\mathbf{11}^{\bullet+}$, as compared to the formation of Br^+ ions (m/z 79 and 81, Σ 3%): $IE(cyclo\text{-}C_4H_7^{\bullet}) = 7.54$ eV, $IE(CH_2CHCH^{\bullet}CH_3) = 7.49$ eV, $IE(Br^{\bullet}) = 11.81$ eV[4].

The EI mass spectrum of cyclobutylmethanol (**12**) represents another telling example. In this case, cleavage of the exocyclic C−C bond to lose $^{\bullet}CH_2OH$ should not be as facile as the loss of $Br^{\bullet}$ from $\mathbf{11}^{\bullet+}$ and, in fact, the by far dominating fragment ion formed from $\mathbf{12}^{\bullet+}$ is $[M - C_2H_5]^+$ (m/z 57), accompanied by minor amounts of $[M - C_2H_4]^{\bullet+}$ (m/z 58). The major fragmentation starts again with α-cleavage of the four-membered ring (Scheme 6). The γ-distonic ion **d** formed undergoes a 1,5-$H^{\bullet}$ transfer from the carbinol functionality to the remote radical position of the aliphatic chain, giving rise to ionized pent-1-en-1-ol ($\mathbf{13}^{\bullet+}$), which represents another particularly stable enol radical cation[49,50]. Nevertheless, allylic cleavage of the latter isomer of $\mathbf{12}^{\bullet+}$ is an energetically favourable reaction, releasing the $C_2H_5^{\bullet}$ radical from the remote part of the chain. Interestingly, this process dominates the spectrum in competition to the second C−C bond cleavage of intermediate ion **d** required to eliminate C_2H_4.

As a last example concerning a simple monosubstituted cyclobutane derivative, the EI mass spectrum of acetylcyclobutane **14** is discussed (Scheme 7). In this case, loss of the $cyclo\text{-}C_4H_7^{\bullet}$ radical and formation of the acetyl cation (m/z 43) by direct cleavage of



SCHEME 6

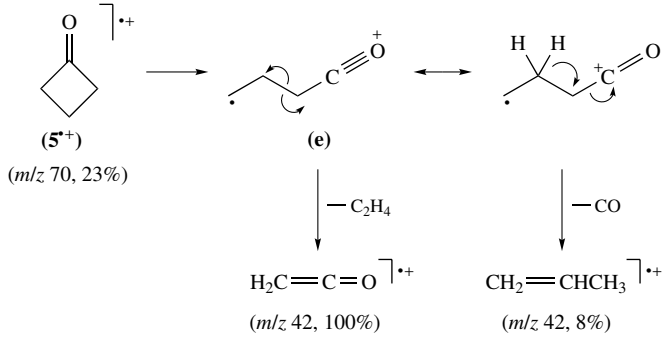


SCHEME 7

the exocyclic C−C bond is the dominating fragmentation path. As expected, the related loss of the smaller $CH_3^{\bullet}$ radical leaving the *cyclo*-$C_4H_7CO^+$ ion competes to a minor extent only. However, a relatively intense (80%) peak is found at *m/z* 55, which may be due to both isobaric acryloyl and $C_4H_7^+$ cations. Whereas the former may certainly form by [2 + 2] cycloreversion of the even-electron *cyclo*-$C_4H_7CO^+$ ion, the latter may be the product of either a primary or a secondary fragmentation. Interestingly, however, the molecular ion **14**$^{\bullet+}$ does not suffer direct [2 + 2] cycloreversion: loss of C_2H_4 is not observed. This can be attributed to the enhanced stability of the ring C−C bonds adjacent to the electron-withdrawing substituent, cleavage of which would give rise to energetically highly unfavourable distonic carbenium ions, viz. $CH_3COCH^+CH_2CH_2CH_2^{\bullet}$, and/or $CH_3COCH^{\bullet}CH_2CH_2CH_2^+$.

C. Cyclobutanones

Cyclobutanones have been studied by mass spectrometry to a relatively large extent since these cyclobutane derivatives are readily accessible by [2 + 2] cycloaddition reactions of ketenes and olefins. In fact, the formal [2 + 2] cycloreversion is by far the dominating fragmentation route of the corresponding radical cations under EI conditions. As mentioned above, this process obeys the Stevenson–Audier rule to perfection in substituted cyclobutanones[46,51]. Of course, the parent cyclobutanone decomposes accordingly, generating mainly ionized ketene and neutral ethene as the cycloreversion products via the distonic ion **e** as intermediate (Scheme 8). Given the strongly different ionization energies of the neutral cycloversion products, *IE*(ketene) = 9.62 eV and *IE*(C_2H_4) 10.51 eV[4], this is not surprising. The bimolecular gas-phase chemistry of the distonic ion **e**, being a Brønsted and Lewis acid and a radical at the same time, has been the subject of intense investigations[52–55]. The ring-opening process of the radical cation of cyclobutanone, $\mathbf{5}^{\bullet+} \rightarrow \mathbf{e}$, was used recently to demonstrate by femtosecond activation that dissociation of molecules can indeed proceed in a nonergodic manner, that is, *without* equilibration of the internal energy over all degrees of freedom prior to dissociation[56,57].

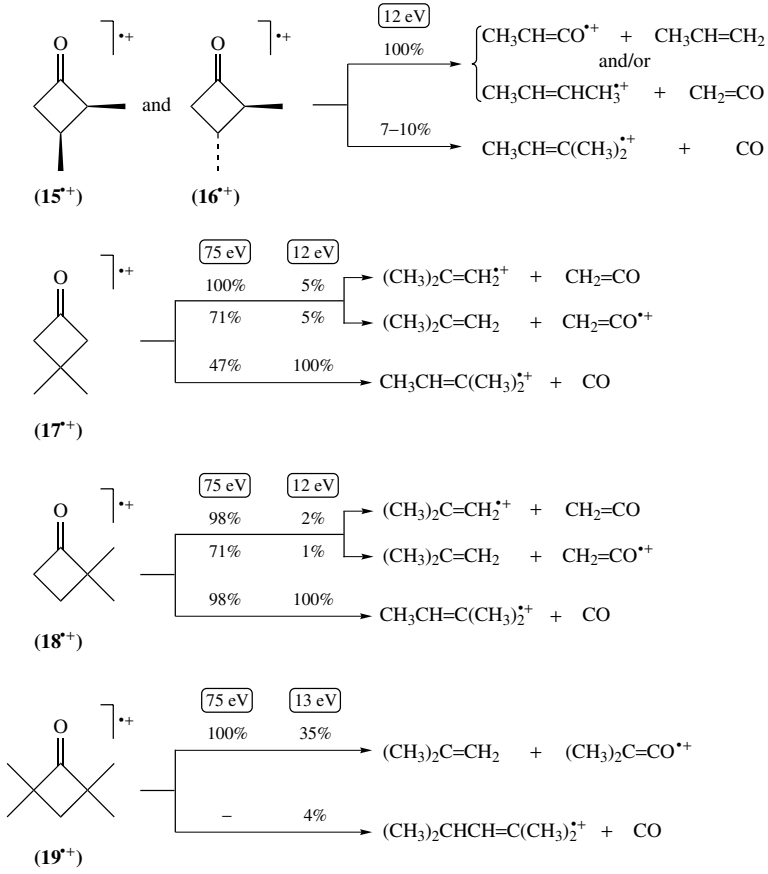


SCHEME 8

The first report on the EI-induced fragmentation of **5** suggested on the basis of exact mass measurements that formation of $CH_2CO^{\bullet+}$ was the predominant reaction channel to produce *m/z* 42 ions[58], in parallel to the behaviour of ionized cyclobutanol (see above). However, a positive proof of the competing formation of $C_3H_6^{\bullet+}$ ions, being isobaric with $CH_2CO^{\bullet+}$ at *m/z* 42, was provided later[59]. In fact, electron ionization at high electron energies (e.g. 70 eV) generates both fragment ions, $CH_2CO^{\bullet+}$ and $C_3H_6^{\bullet+}$, in a ratio of *ca* 13:1. Notably, however, at 'softer' ionization conditions, that is, using electron energies that just allow both fragment ions to be formed (e.g. 11 eV), the *m/z* 42 ion mixture consists predominantly of $C_3H_6^{\bullet+}$. Thus, while the signal at *m/z* 42 represents the base peak at all energy regimes, the elemental composition of the ions giving rise to it is inverted. Thorough measurements of the appearance energies of $CH_2CO^{\bullet+}$ and $C_3H_6^{\bullet+}$ from cyclobutanone (**5**) revealed that formation of the latter ion is more energetically favourable by 0.68 eV (66 kJ mol^{-1}). Thus, loss of carbon monoxide instead of ethene from $\mathbf{5}^{\bullet+}$ is the thermochemically much more favourable process but kinetically hindered at high excitation energies. It follows from the (relatively low) appearance energy that CO loss generates ionized propene but not ionized cyclopropane[59].

A systematic investigation concerning the competition between the two cycloreversion channels and the loss of carbon monoxide from a large number of methyl-substituted

cyclobutanones under EI conditions provides a broader overview[60]. These relatively simple fragmentation reactions of radical cations were also of interest with regard to the formally related photolytic decomposition of neutral cyclobutanones. From the variety of di-, tri- and tetramethylcyclobutanones, a small selection of results is reproduced in Scheme 9, illustrating the major cycloreversion channel and the CO loss but neglecting other fragmentation pathways. However, it is noted that metastable ion measurements had been carried out to corroborate the overall fragmentation[60].



SCHEME 9

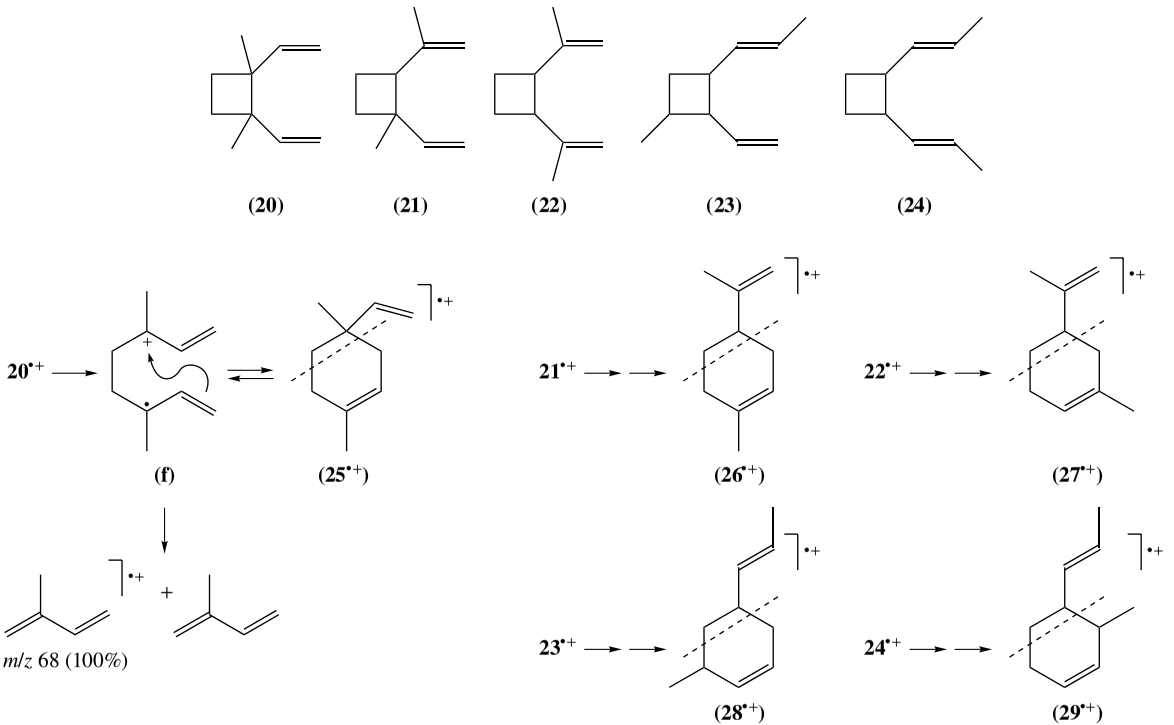
The fragmentation of the two stereoisomeric 2,3-dimethylcyclobutanones **15** and **16** is very similar and almost independent of the electron energies employed. Loss of CO is a minor process as compared to the formation of ions with *m*/*z* 56, which have been interpreted to be probably ionized methylketene formed by loss of propene. However, the formation of 'isobaric' ionized but-2-ene (*m*/*z* 56) and neutral ketene may compete as a higher-energy process because a loss of $CH_3^{\bullet}$ was reported for the metastable *m*/*z* 56 ions[60]. Formation of ionized ketene, as an even more energy-demanding fragmentation, represents a minor channel only. The results suggest that the cycloreversion reactions start

by α-cleavage of the more highly substituted C−C(O) bond. In contrast to the spectra of the former isomers, the EI spectrum of 3,3-dimethylcyclobutanone **17** is highly energy-dependent. Both cycloreversion reactions dominate at 75 eV ionization, according to the relatively close ionization energies of the neutral fragments [*IE* (isobutene) = 9.22 eV vs. *IE* (ketene) = 9.62 eV]. At low energies, however, CO elimination is by far the major fragmentation path. Obviously, expulsion of CO requires a Wagner–Meerwein rearrangement (1,2-C shift) of a methyl group; in the case of ion $\mathbf{17}^{\bullet+}$, this should be an energetically favourable but entropically unfavourable and thus time-consuming process. Interestingly, the isomeric 2,2-dimethylcyclobutanone **18** gives rather similar EI mass spectra, as compared to those of **17**, at both high and low electron energies. However, the relative rates of the CO loss are clearly increased, reflecting the fact that the same fragments are formed from ion $\mathbf{17}^{\bullet+}$ but without involving a 1,2-C shift prior to expulsion of CO. Finally, the fragmentation of the 2,2,4,4-tetramethylcyclobutanone **19** is mentioned. It appears that the molecular ion $\mathbf{19}^{\bullet+}$ is relatively stable because it gives rise to the base peak at low electron energies (13 eV). In fact, CO loss is completely suppressed at high energies and only of minor importance at low energies. Cycloreversion only gives rise to ionized dimethylketene. Clearly, in spite of the weak C−C(O) bonds in the carbocycle, the elimination of CO is strongly hampered because an unfavourable 1,2-hydride shift from a methylene group to a tertiary carbenium ion is required. Comparisons between mass spectrometric, photolytic and pyrolytic fragmentation of cyclobutanones are manifold and comprise also tetraalkyl-substituted cyclobutane-1,3-diones, where successive loss of two molecules of CO is the dominating decomposition pathway of the molecular radical cations[61,62].

D. Di- and Multiply Substituted Cyclobutane Derivatives

Ring opening of cyclobutane radical cations that bear vinyl or aryl groups at the four-membered ring is particularly easy. For example, phenyl-substituted cyclobutanes dissociate under EI conditions by cycloreversion to give ionized styrenes and stilbenes as the major fragment ions[63]. Similarly, the EI mass spectra of vinyl-substituted cyclobutanes exhibit base peaks which are due to the corresponding ionized 1,3-butadienes. A systematic study of the mass spectrometric fragmentation of 1,2-divinylcyclobutanes and isomeric vinylcyclohexenes is in line with this behaviour but also shows that olefinic substituents can form new C−C bonds after the first, ring-opening C−C bond cleavage[2,64]. Five different 1,2-divinylcyclobutanes, **20**–**24**, prepared by photodimerization of isoprene and 1,3-pentadiene, were studied (Scheme 10). The major fragmentation route of all molecular ions $\mathbf{20}^{\bullet+}$–$\mathbf{24}^{\bullet+}$ is the formal scission into two C_5H_8 moieties, one of them carrying the positive charge giving ions $C_5H_8^{\bullet+}$ (*m*/*z* 68). Losses of $CH_3^{\bullet}$, $C_2H_5^{\bullet}$ and $C_3H_7^{\bullet}$ give rise to minor but significant peaks, and ions $C_6H_7^{+}$ represent relatively small but likewise characteristic features, probably being due to the formation of protonated benzene[65–67].

The initially postulated direct [2 + 2] cycloreversion of ions $\mathbf{20}^{\bullet+}$–$\mathbf{24}^{\bullet+}$ [63] was revised[64] in favour of their isomerization to the corresponding cyclohexene ions $\mathbf{25}^{\bullet+}$–$\mathbf{29}^{\bullet+}$ (Scheme 10). The formation of distonic ions was assumed as the first step, corresponding to the general behaviour of ionized cyclobutanes. For example, cleavage of the doubly allylic C−C bond of ion $\mathbf{20}^{\bullet+}$ gives rise to the distonic intermediate **f**, followed by electrophilic C−C bond formation between the inner position of the allylic cation at the remote position of the allylic radical moieties to give the vinylcyclohexene-type ion $\mathbf{25}^{\bullet+}$. Formal [4 + 2] cycloreversion of this isomer, however, will again involve the distonic ion **f**. Although the formation of the cyclohexene-type isomers $\mathbf{25}^{\bullet+}$–$\mathbf{29}^{\bullet+}$ was proposed to explain the losses of $C_2H_5^{\bullet}$ and C_3H_6[63], the relative abundances of the 'monomeric' $C_5H_8^{\bullet+}$ ions were also found to correlate with the stabilities of the $C_5H_8^{\bullet+}$ fragments. Thus, the

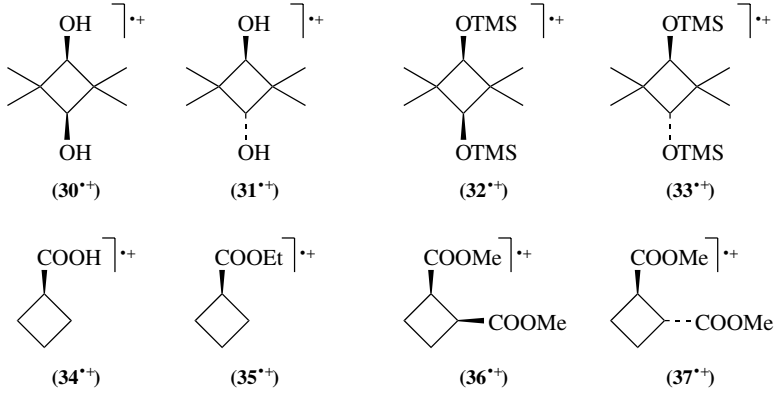


SCHEME 10

non-branched 1,3-pentadiene radical cation, formed by cleavage of ions **23**$^{\bullet+}$ and **24**$^{\bullet+}$, are thermochemically more stable than the (branched) isoprene radical cation, resulting from ions **20**$^{\bullet+}$–**22**$^{\bullet+}$. In fact, the ion $CH_2{=}CHCH{=}CHCH_3{}^{\bullet+}$ is by *ca* 24 kJ mol^{-1} more stable than ion $CH_2{=}C(CH_3)CH{=}CH_2{}^{\bullet+}$[4,5], and this should be the reason for the higher relative abundance of the *m/z* 68 ions in the EI mass spectra of **23** and **24** (55–60% Σ vs. 27–33% Σ). Overall, it appears that the endothermicity of the formal [2 + 2] cycloreversion of ions **20**$^{\bullet+}$–**24**$^{\bullet+}$ is the governing factor to explain the differences, disregarding the ring-expansion reaction.

Another systematic study comparing the EI-induced fragmentation of various cyclobutane derivatives concentrated on the stereoisomeric 2,2,4,4-tetramethyl-1,3-cyclobutanediols **30** and **31** and their trimethylsilyl ethers **32** and **33**[68]. As may be expected on the basis of the liability of radical cations of simple cyclobutanols (see above), the EI spectra exhibit no molecular ion peaks. Rather, scission into two moieties by formal [2 + 2] cycloreversion gives abundant enol ions $(CH_3)_2C = CHOH^{\bullet+}$ (*m/z* 72, 100%) from ions **30**$^{\bullet+}$ and **31**$^{\bullet+}$. Moreover, no significant differences were found with respect to the *cis*- and *trans*-stereoisomers; obviously, the initial α-cleavage sweeps out any energy differences in the stereoisomeric ions. Similar findings were reported for the TMS ethers **32** and **33**.

In the same study, the EI-induced fragmentation of cyclobutane carboxylic acid **34**, its ethyl ester **35** and some related esters was investigated[68]. Interestingly, and in agreement with the discussion on ionized acetylcyclobutane (**14**$^{\bullet+}$) presented above, the radical cation **34**$^{\bullet+}$ does not eliminate C_2H_4. Instead, rather cyclobutane-unspecific loss of H$^{\bullet}$, OH$^{\bullet}$, H_2O and $C_2H_3{}^{\bullet}$ are the primary fragmentation reactions. Of course, the ethyl ester ion **35**$^{\bullet+}$ does eliminate C_2H_4; however, this can safely be assumed to be eliminated from the ester group by McLafferty reaction but not to originate from the carbocyclic ring.



In this context, a further paper is mentioned which reports the EI mass spectra of the dimethyl *cis*- and *trans*-cyclobutane-1,2-dicarboxylates **36** and **37**, as well as those of some related cyclobutane derivatives including the 1,1-diester and a 1-cyano-1,2-diester[69]. In this case, the stereoisomeric ions exhibit clearly distinct fragmentation behaviour in that several characteristic fragment ion peaks show different relative intensities. For example, the abundance ratios of the fragment ion pairs [*m/z* 71] : [*m/z* 73] and [*m/z* 55] : [*m/z* 113] and [*m/z* 59] : [*m/z* 113] were found to be diagnostic. The greater tendency of the *cis* isomer **36**$^{\bullet+}$ to undergo fragmentation was traced to steric strain between the vicinal ester groups of this stereoisomer[69]. A later, more systematic and comparative study on the EI-induced fragmentation of the dimethyl esters of the cycloalkane 1,2-dicarboxylates including the cyclopropane to cyclohexane derivatives confirmed the quantitative but not

qualitative differences in the fragmentation behaviour of the cyclobutane diesters **36** and **37**[70]. However, in contrast to the previous report, only the loss of $OCH_3^{\bullet}$, one of the primary fragmentation steps, was reported to be faster in the ionized *cis* isomer $\mathbf{36}^{\bullet+}$ as compared to the *trans* isomer $\mathbf{37}^{\bullet+}$. It appears tempting to speculate whether in this case the loss of $OCH_3^{\bullet}$ from the ionized *cis* isomer is accelerated as a result of a neighbouring group interaction between the two ester groups. Such phenomena are known as '*ortho* effects' in organic mass spectrometry and occur frequently in the molecular ions of *ortho*-substituted aromatic compounds and (*Z*)-substituted olefins[71]. Noteworthily, this would imply that, in the case of the strained but electronically stabilized cyclobutane ion $\mathbf{36}^{\bullet+}$, this ring survives at least in part until the neighbouring group interaction has occurred.

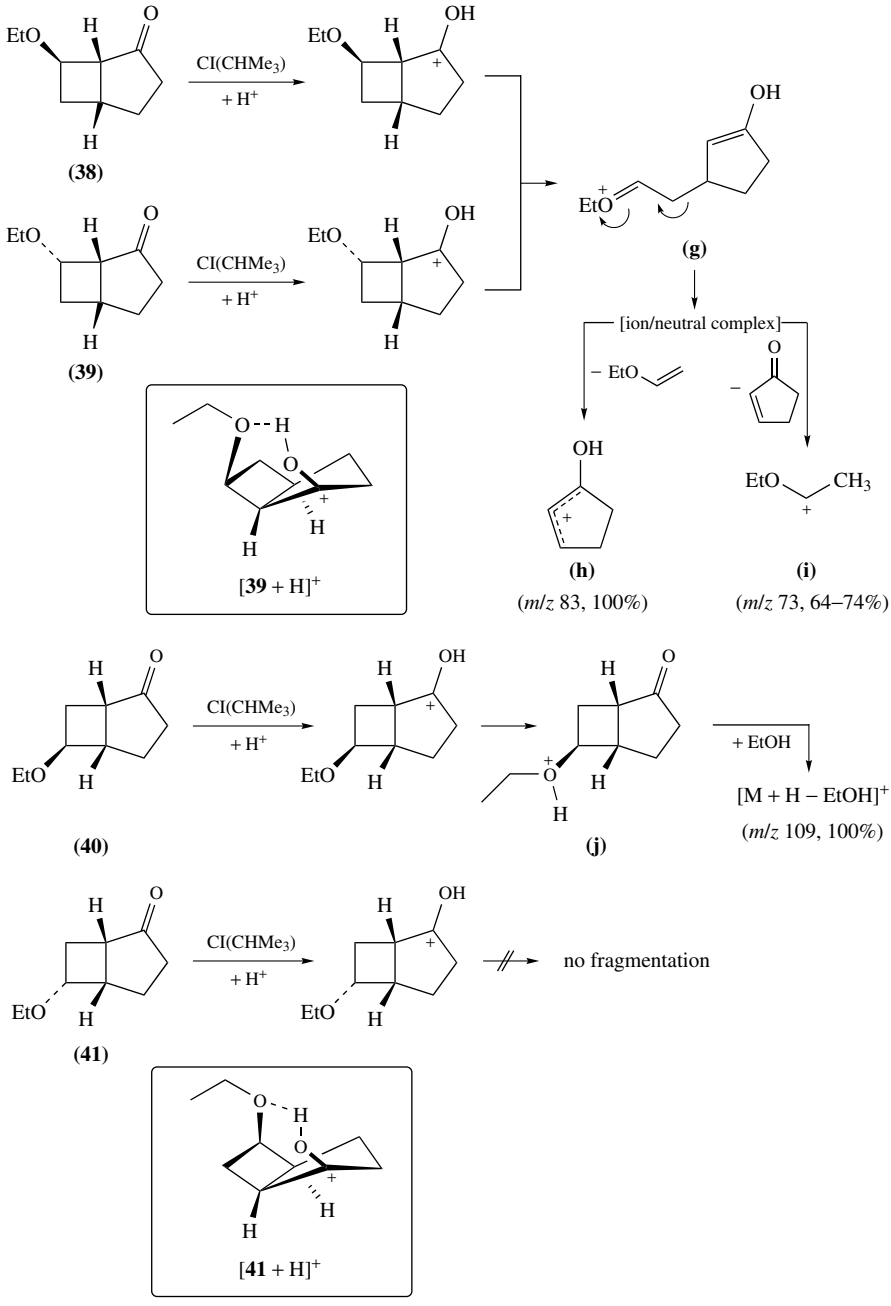
IV. ALTERNATIVE IONIZATION METHODS

The pronounced tendency of cyclobutane derivatives to undergo EI-induced fragmentation of the four-membered ring could be accommodated by milder ionization methods, such as chemical ionization (CI), fast atom bombardment (FAB), secondary ion mass spectrometry (SIMS) and electrospray ionization (ESI). In fact, addition of a proton or metal cation, generating an even-electron cationic species, should prevent the notorious α-cleavage process of radical cations of cyclobutanes. In this section, an example will be presented for the use of chemical ionization mass spectrometry, which demonstrates the usefulness but also the limits of the method for the analysis of cyclobutane derivatives. Also, some examples for analytical applications of 'soft' ionization methods for the mass spectrometric characterization of cyclobutane derivatives are collected here.

A. Chemical Ionization

Isobutane chemical ionization employs a reagent gas which generates mainly $t\text{-}C_4H_9^+$ ions (*m*/*z* 57) and, to a minor extent, $s\text{-}C_3H_7^+$ ions (*m*/*z* 43). The former reactant ions are relatively weak protonation agents, the latter are stronger ones. Both of them transfer a proton to ketones and other carbonyl compounds in an exothermic reaction, leaving a part of the energy gained on the protonated sample molecule. This can give rise to protonated ketones (hydroxycarbenium ions) which remain stable in the gas phase and enable the detection of the quasi-molecular ions $[M + H]^+$ in usually considerable relative abundance. Thus, fragmentation of the $[M + H]^+$ ions may be greatly suppressed under CI(isobutane) mass spectrometry. By contrast, singly bonded hydroxy or alkoxy substituents may easily be lost by protonation in the CI plasma.

In fact, such cases were encountered in the systematic CI-MS analysis of various isomeric derivatives of bicyclo[3.2.0]heptanones[72] and a telling set of examples is reproduced here (Scheme 11)[73]. The two stereoisomeric 6-ethoxybicyclo[3.2.0]heptanones **38** and **39** were found to give very similar CI mass spectra. The relative abundances of their $[M + H]^+$ ions amount to only 2.0% and 1.0%, respectively, of the total ion current (TIC). In both cases, the base peaks correspond to the formation of $C_5H_7O^+$ ions (*m*/*z* 83, *ca* 50% TIC) formed by loss of ethyl vinyl ether. Protonation of the carbonyl group gives rise to a (heterolytic) retro-aldol ether cleavage, again facilitated by the intrinsic strain of the four-membered ring, generating ion **g**. Subsequent (again diallylic) cleavage of the pendant side chain yields the stable protonated cyclopenten-2-one **h**. The only other prominent peak in each of the CI mass spectra indicates the formation of the 'conjugate pair' of fragments, viz. neutral cyclopentenone and protonated ethyl vinyl ether (**i**, *m*/*z* 73). As it is known that protonated ethers fragment through ion/molecule complexes (or, more generally, ion/neutral complexes)[74–79], it can be safely assumed that such an intermediate is also formed in the case of **38** and **39** on the way to both pairs of fragments. The


EtO
H
O
OH
CI(CHMe3)
+ H+
(38)
(39)
(g)
[ion/neutral complex]
– EtO
(h)
(m/z 83, 100%)
(i)
(m/z 73, 64–74%)
[39 + H]+
(40)
(j)
+ EtOH
[M + H – EtOH]+
(m/z 109, 100%)
(41)
no fragmentation
[41 + H]+

SCHEME 11

relative abundances of ions **h** and **i** for both stereoisomers may reflect the differences in internal energies of the stereoisomeric ions $[\mathbf{38} + H]^+$ and $[\mathbf{39} + H]^+$. In fact, protonation of the *syn* isomer **39** can generate a stable intramolecular proton bridge (cf. top insert). Therefore, the proton affinity of **39** should exceed that of **38** and the more exothermic formation of ion $[\mathbf{39} + H]^+$ may result in a somewhat faster decomposition as compared to ion $[\mathbf{38} + H]^+$.

However, those slight differences are minor as compared to the drastically distinct fragmentation behaviour of the regioisomers **40** and **41**, bearing the ethoxy substituent at C-5 instead of C-6, under the same CI conditions (Scheme 11). In these cases, retro-aldol-type fragmentation is not possible and the driving force for fragmentation of the cyclobutane ring cannot come into play. The *exo* isomer **40**, still being protonated most favourably at the carbonyl oxygen, cannot dissociate easily via this $[M + H]^+$ ion; rather, this tautomer has to isomerize to the less stable ethoxy-protonated ion **j** in order to find the most favourable fragmentation exit. In fact, heterolytic cleavage of tautomer **j** gives rise to extremely abundant fragment ions $[M + H - EtOH]^+$, comprising 59% TIC in the CI mass spectrum. No other fragment ions were observed. Thus, the behaviour of ion $[\mathbf{40} + H]^+$ may be considered normal for protonated alkyl cyclobutyl ethers. However, a 'hidden' isomerization by formation of a low-strain seven-membered isomer cannot be excluded.

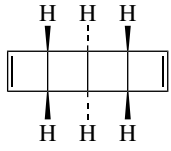
Again in contrast, the CI(isobutane) mass spectrum of the *syn*-isomer **41** is dominated by the $[M + H]^+$ ion (85% TIC), obviously reflecting its particular stability. Formation of the fragment ions *m/z* 73 and *m/z* 109 comprises only 3% TIC. Formation of an energetically favourable intramolecular proton bridge is possible (cf. bottom insert) but, for steric reasons, appears to be less stable than in the case of the isomeric ion $[\mathbf{39} + H]^+$. Nevertheless, the fact that the C−C bond cleavage is impossible in the 5-ethoxy regioisomers, combined with the internal stabilization by the proton bridge, gives rise to such a dramatically distinct CI mass spectrum of **41** as compared to those of the other three bicyclic cyclobutane derivatives **38, 39** and **40**. In the same work, a large number of other difunctionalized bicyclo[3.2.0]heptan-2-ones have been studied under CI conditions and many more interesting differences have been reported[72].

B. Miscellaneous Analytical Applications

Analytical applications of mass spectrometry to compounds bearing cyclobutane units are manifold but suffer from the intrinsic lability of the strained cyclocycle. As mentioned above, mild ionization methods can overcome this problem at least in part. In the following, miscellaneous examples are given where various ionization methods have been used to identify cyclobutane derivatives by mass spectrometry, without being exhaustive in any respect.

Exotic modifications within the large family of polycyclic cyclobutane derivatives are the 'ladderanes'[80–83]. Those compounds contain more than two cyclobutane units mutually fused to each other in a linear manner. Early attempts to analyse these multiply strained hydrocarbons by mass spectrometry have been acknowledged[81] but demonstrated the facile isomerization of polycyclic hydrocarbon ions to more stable species derived from benzene and other aromatic hydrocarbons[66,67,84]. As a relatively straightforward example, the base peak in the EI mass spectrum of the tetracyclic ladderane **42** corresponds to the loss of benzene, to give ions $C_4H_4^{\bullet+}$ (*m/z* 52), possibly ionized cyclobutadiene[82]. Related polycyclic [9]-, [11]- and [13]ladderanes (e.g. **43**), bearing the respective numbers of cyclobutane or cyclobutene units in linear orientation and several ester functionalities, have been characterized by FAB mass spectrometry[83].

FAB mass spectrometry proved also useful to characterize polymers obtained by polycondensation of various adipates and terephthalates with α-truxilloyl chloride (truxillic



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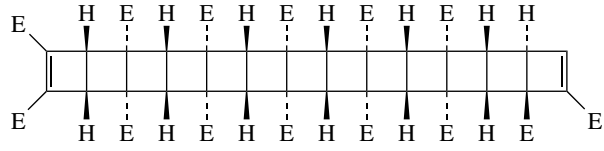
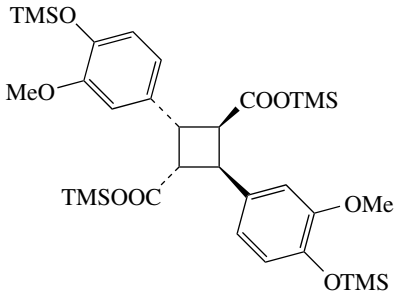


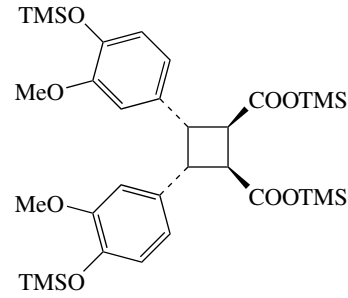
(43) E = COOMe

acid is 2,4-diphenylcyclobutane-1,3-dicarboxylic acid; for the stereochemistry of the α-series, cf. derivative **44**). Application of both the FAB(+) and also FAB(−) mode allowed the authors to confirm the alternating sequence of monomers in the polymers chains[85]. In a previous study, polyamides generated from cyclobutane 1,2-dicarboxylic acid and piperazine were analysed by use of pyrolysis combined with conventional EI mass spectrometry of the thermolytic fragments (Py/MS)[86]. In another study using FAB mass spectrometry, several palladium and platinum complexes were analysed, containing either *trans*-1,2-bis(diphenylphosphino)ethene or, as a single instead of two ligands, *cis,trans,cis*-1,2,3,4-tetrakis(diphenylphosphino)cyclobutane[87].

Photolysis of large-ring ketones was found to generate isomeric 1-hydroxybicycloalkanes. In the course of a thorough analysis of the product mixtures by mass spectrometry, the EI-induced fragmentation of the cyclobutanol derivatives was investigated and discussed along the lines presented in the sections above[88]. In another analytical study on isomeric organic products, the cyclobutane-type dimers of substituted cinnamic acids were identified as their bis(trimethylsilyl) esters, e.g. **44** and **45** derived from ferulic acid, by gas chromatography/mass spectrometry (GC/MS)[89]. The mass spectrometric analysis of the dimers lead to the assignment of the truxillic (**44**) and truxinic (**45**) structures by use of the distinct fragmentation behaviour. In the case of the truxillic acid TMS esters, McLafferty reaction was found to dominate the fragmentation and it was postulated that the 1,5-H transfer in ions of type $\mathbf{44}^{\bullet+}$ precedes the cleavage of the cyclobutane ring. This is in agreement with the fragmentation behaviour discussed above for other acyl-substituted cyclobutanes, e.g. $\mathbf{14}^{\bullet+}$, under EI conditions.



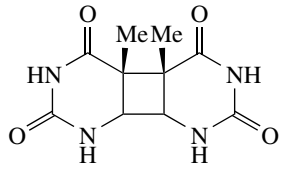
(44)



(45)

In a purely analytical context, cyclobutanol was identified and quantitatively determined (0.14%) by use of GC/MS among the volatile organic compounds (VOCs) present in human breath[90].

In a special context, it is noted here that the cyclobutane unit occurs frequently in the dimers formed by irradiation of DNA by formal [2 + 2] cycloaddition across the C−C bonds of the nucleobases. These adducts, e.g. the *cis,syn*-dimer **46**, were quantitatively

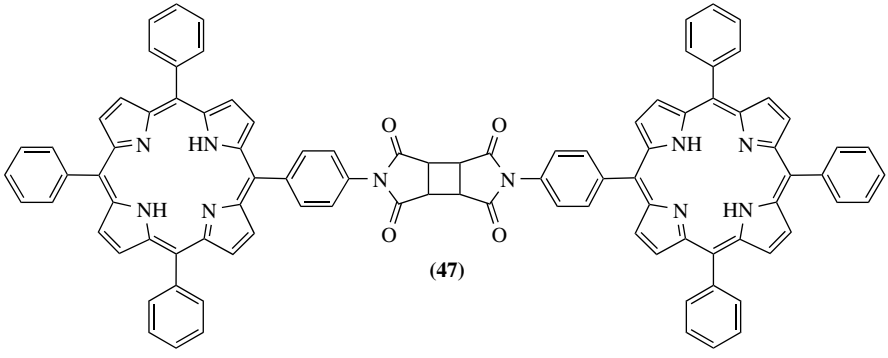


(46)

analysed by GC/EI-MS of their trimethylsilyl derivatives using a deuterium-labelled internal standard. As expected, splitting of the central cyclobutane ring was found to be the governing fragmentation route. In addition, ring-to-ring migration of a TMS cation was observed prior to fragmentation[91]. The photo-induced cleavage of a uracil cyclobutane dimer hapten was studied in detail including kinetic isotope effects by use of ESI mass spectrometry[92]. ESI mass spectrometry coupled with enzymatic digestion was used to analyse several photoproducts formed from dinucleoside monophosphates[93]. In a similar study published several years earlier, FAB mass spectrometry was used[94]. The sugar-free nucleobase dimers formed by far-UV-induced dimerization of thymine were analysed by ESI mass spectrometry[95].

The mass spectrometric analysis of organic or bioorganic compounds bearing annelated cyclobutane rings has also been a matter of diverse interest. The fragmentation of various cycloalkane-fused pyrimidines has been studied by EI mass spectrometry[96]. The formation of a cyclobuta-annelated derivative of pyrimidine-1-yl-2′-desoxynucleoside was analysed by FAB mass spectrometry[97].

Finally, the mass spectrometric analysis of a non-natural, large cyclobutane derivative, the diimide porphyrin dimer **47**, may be mentioned. The identity of this compound was determined by FAB(+) mass spectrometry employing a dithiothreitol/dithioerythritol matrix. Surprisingly, and in contrast to other diimide dimers bearing varied (e.g. a pyromellitic diimide) spacers, diimide **47** was found to be reduced under the ionization conditions, as shown by the presence of an $[M + 6\ H]^+$ peak as the largest signal in the molecular ion envelope. Possible reduction and/or cleavage of the cyclobutane unit under fast atom bombardment in the reducing matrix was briefly discussed[98]. Thus, the notorious propensity of cyclobutanes to undergo ring scission in one or the other manner, and induced by the often too-hard-for-cyclobutanes conditions of mass spectrometry, recurs at many points.



(47)

V. CONCLUSION

There are many other examples in the literature concerning mass spectrometry and gas-phase chemistry of cyclobutane derivatives. Mass spectrometric data on various compounds bearing benzoannelated cyclobutane rings have been reported but these cases have not been considered here. However, the energetic and mechanistic guidelines for the more interesting examples are the same as those discussed above. Either the cyclobutane rings are tightly fused between two intact benzene rings or larger aromatic π-electron systems (viz. in the biphenylenes or biarylidenes). In these case, the mass spectra are dominated by the peaks of the highly stable molecular ions. Alternatively, the annelated cyclobutane units are, formally, cyclobutene rings. In those cases the strained C−C bond at the 'non-aromatic' positions is cleaved even more readily than in simple cyclobutane radical cations because of the benzylic stabilization gained by this cleavage, leading to ionized *ortho*-quinodimethanes. For the same reason, substituents at those α-positions are also lost with particular ease, as known from the gas-phase ion chemistry of alkylbenzenes[66,67]. Facile retro-Diels–Alder reactions[99,100] of cyclohexenes and tetralins bearing the benzocyclobutane unit are another consequence of the special liability of the cyclobutane ring[101]. However, it has also been shown in this chapter that the gas-phase ion chemistry of cyclobutane derivatives can be understood in relatively simple terms concerning the strained four-membered ring. The presence of the latter unit in more complex molecules may have a dramatic effect on the fragmentation processes characterizing the mass spectra of cyclobutane derivatives.

VI. ACKNOWLEDGEMENTS

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CHAPTER 8

Synthesis of cyclobutanes

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I. INTRODUCTION

Since the earliest description of cyclobutanes obtained from the condensation of diethyl malonate with 1,3-dibromopropane (from C_3 and C_1 building blocks) as described by Perkin in 1883/84, and the homocondensation of ethyl 3-chloropropionate (from two C_2 building blocks) reported by Markovnikov and Krestikow in 1881, more than 120 years have elapsed[1]. However, it was only during the last four decades that cyclobutanes have emerged beyond the status of being mere curiosity, due to their unusual bonding and ring strain, to versatile intermediates in organic syntheses. Their diversity of reactions is the result of the inherent strain associated with the four-membered ring contributing to both angular and torsional effects. Thus cyclobutanes undergo reactions such as ring opening to acyclic products (*ca* 23–26 kcal mol^{-1} exothermic), ring enlargement to five- or six-membered ring products (*ca* 20 and 25 kcal mol^{-1}, respectively) and ring contraction to cyclopropanes. The latter reaction is energy neutral since cyclopropanes have strain energies comparable to those of cyclobutanes, but it is often exothermic since most of these products or intermediates possess the stabilizing conjugated cyclopropyl

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carbinyl unit. The principal strategies for formation of the four-carbon ring system involve [2 + 2] cycloadditions, cyclization of acyclic precursors and ring expansion of cyclopropanes. Cyclobutanones and cyclobutenones are the most readily available derivatives of cyclobutane[2]. Cyclobutanones offer a convenient four-carbon ring motif for further structural elaboration in that every center of the ring can be potentially functionalized. The application of chiral approaches to these useful intermediates has resulted in an increasing pool of chiral cyclobutanes, which have been used in enantioselective total syntheses[3]. Excellent reviews of specific methods for the preparation of cyclobutanes cover the literature to the early 1990s[4,5]. This review focuses on the most recent methods although brief summaries of more classical methods are also highlighted.

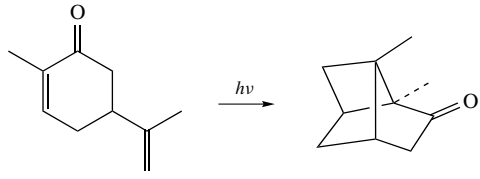
II. [2 + 2] CYCLOADDITIONS

Since two C−C bonds and four stereogenic centers are formed in a single step, the [2 + 2] cycloaddition between two alkene moieties represents the most popular method for the construction of cyclobutanes. This method, however, suffers from the inherent nonselectivity for the concerted thermal process, which is forbidden by orbital symmetry considerations[6], and thus proceeds via intermediates (biradicals or zwitterions depending on the nature of alkene substituents) which are sufficiently long-lived to undergo stereochemical equilibration. The photochemically induced cycloaddition is allowed by orbital symmetry. However, isolated alkenes possess chromophores which are not accessible to excitation by conventional light sources. On the other hand, conjugated alkenes and enones, which are conveniently excited by conventional UV sources, often undergo intersystem crossing to the triplet state[7], producing biradicals which can undergo stereochemical equilibration. An additional problem arises when nonsymmetrical alkenes with little stereoelectronic differentiation are used, giving rise to regioisomeric mixtures. This problem has been overcome by the use of ketene or ketene equivalents as reacting partners. Ketene cycloadditions with alkenes often occur with complete regio- and stereoselectivity as a result of the unusual electronic properties of this cumulene system[8]. The resulting cyclobutanones can be readily converted to other cyclobutane derivatives. Catalyzed [2 + 2] cycloadditions offer an alternative method for the construction of the cyclobutane ring[9]. These reactions often proceed in a selective fashion as a result of the mild reaction conditions minimizing stereochemical equilibration of the intermediates. Furthermore, many of the intermediates involve rigid complexes of the two reacting partners with a preferred geometry.

A. Photochemical [2 + 2] Cycloadditions

Photochemical [2 + 2] cycloadditions include both dimerization and the synthetically more useful reactions of two different alkenes. Some excellent reviews of the latter class have been reported[10,11]. The first [2 + 2] photocycloaddition reaction was reported by Ciamician and Silber in 1908 when they observed the formation of carvone camphor (**2**) on exposure of carvone (**1**) to Italian sunlight for one year! (Scheme 1)[12]. The potential for its use in the construction of complex molecular frameworks was not realized until the late 1950s.

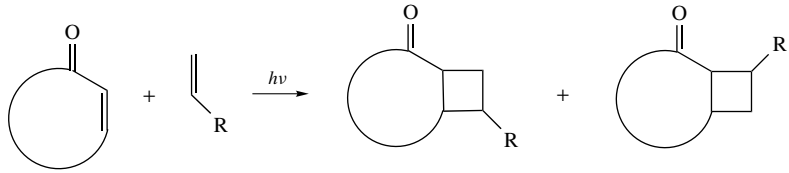
The [2 + 2] photocycloaddition is a rather complex set of transformations. Direct excitation of an alkene chromophore results in a singlet excited state from $\pi-\pi^*$ excitation. Since this state is rather short-lived, cycloaddition with another alkene partner can be realized within the lifetime requiring an alkene to be in close proximity, as in situations of concentrated solutions of the substrate for intermolecular reactions, or instances where the reacting substrate is tethered to the excited chromophore. Otherwise, *cis/trans* isomerization becomes the principal deactivation process for the excited alkene. Chromophores



(1) **(2)**

SCHEME 1

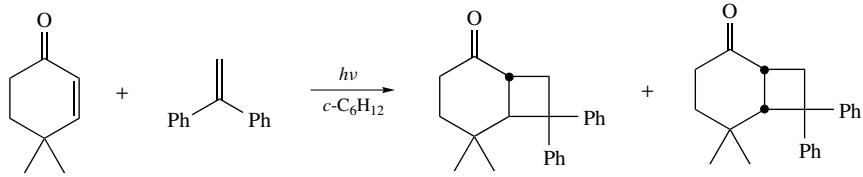
having an α,β-unsaturated carbonyl group are excited to the n-π^* state in which the initially formed singlet is efficiently transformed to a much longer-lived triplet state. The latter state resembling a biradical can react with an alkene partner to form a 1,4-biradical intermediate which ring closes to a cyclobutane. The long-lived nature of these radical intermediates can affect stereochemical equilibration resulting in mixtures of stereoisomers. The regioselectivity of enone cycloadditions with alkenes is largely determined by the substituents on the alkene and the conjugated unsaturated carbonyl group. The distribution of head-to-tail (h-t) and head-to-head (h-h) cycloadducts, **3** and **4** respectively (Scheme 2), is largely determined by the electronic nature of the alkene substituent.



(3) **(4)**

SCHEME 2

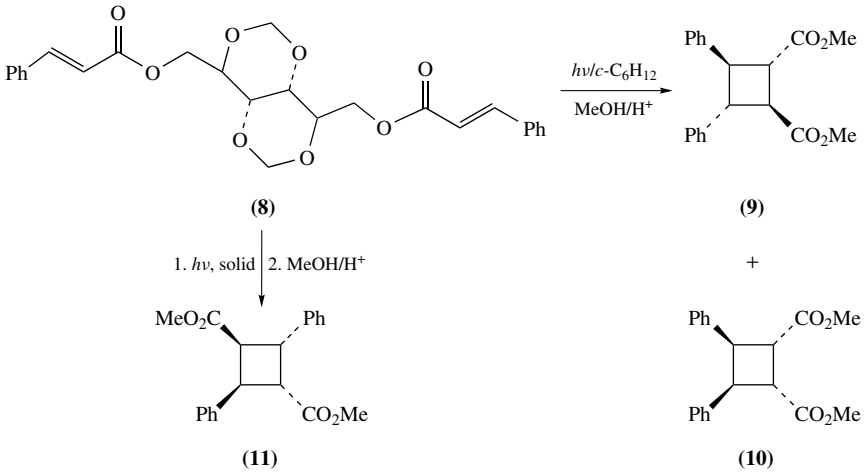
Electron-donating groups on the alkene favor **3** whereas electron-withdrawing groups favor **4**. This selectivity is largely due to stabilities of the 1,4-biradical formed on initial bonding of the alkene to the α- or β-carbon of the conjugated carbonyl group as well as their tendency to cyclize or revert back (partitioning) to starting materials[13,14]. Thus for geminally disubstituted alkenes such as **5**, exclusive h-t cycloadducts **6** and **7** are obtained[15]. It is interesting to note that in this case a mixture of stereoisomers is produced with the thermodynamic product formed as a minor component, suggesting that kinetic control associated with stereoelectronic factors may intervene in these processes (Scheme 3).



(5) **(6)** 35% **(7)** 6%

SCHEME 3

Another factor which influences regiochemistry is the charge distribution of the enone in its excited state which is reversed relative to its ground state electronic configuration. Thus, the β-carbon of the enone which is more negatively biased relative to the α-carbon will bond with the more substituted carbon of the alkene or the carbon to which an electron-donating substituent is attached[16]. Beside substituent effects, other parameters such as solvent and temperature can affect the regiochemical outcome of many photocycloadditions. The photodimerization of cyclopentenone results in a much larger proportion of the h-t dimer in less polar solvents[17]. The different product distributions are attributed to a polar excimer model which in more polar solvents loses its integrity. Organized media can also influence the regiochemical outcome in photocycloaddition reactions. For example, the solution phase photolysis of the tethered cinnamic acid diester **8** undergoes intramolecular photodimerization in a h-h regiochemistry as evident from the observed diastereomeric products **9** and **10** after cleavage of the tether. However, irradiation of the same substrate in the solid state gives the h-t dimer **11** (Scheme 4)[18].

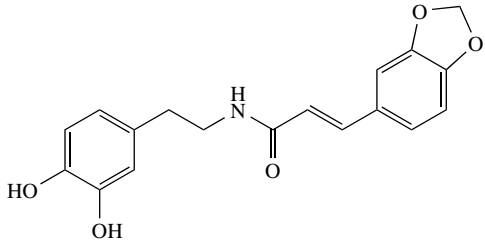


SCHEME 4

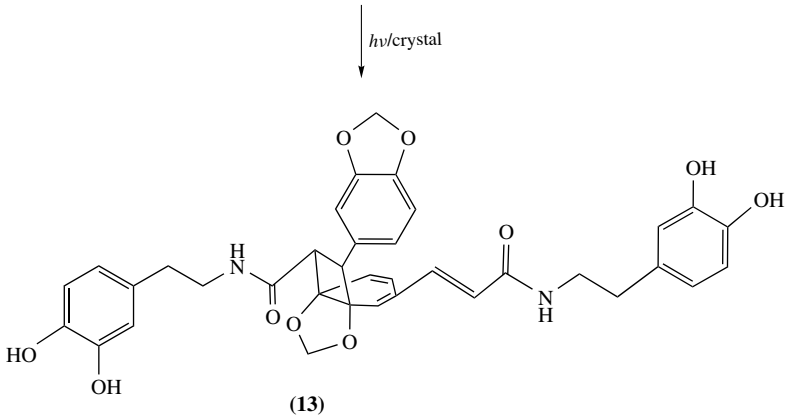
Photolysis of some substrates in the crystalline state can sometimes completely alter the reaction mode when compared to solution phase. For example, irradiation of cinnamide **12** in the crystalline state produces the [4.3.2]propellane dimer **13** resulting from the intermolecular cycloaddition of the double bond with the aryl ring (Scheme 5) in contrast to the solution phase *cis/trans* photoisomerization[19].

A similar phenomenon was reported for the photolysis of **14** in crystalline matrix giving exclusively the h-t dimer **15** (Scheme 6), whereas the solution reaction led to *cis/trans* isomerization[20].

Many of these differences between solid state and solution phase photochemistry are associated with the specific packing of molecules in a particular crystal matrix where topological control becomes dominant. Secondary effects such as hydrogen bonding can alter the regiochemistry. For instance, the cycloaddition of 2-cyclopentenone with a series of alkenols gives h-h addition products as a result of hydrogen bonding between the alcohol and carbonyl moieties which has the effect of 'tethering' the reacting partners (*vide infra*)[21]. Varying the temperature of the photoaddition reaction can also influence the regioselectivity with the trend towards the enhancement of the major regioisomer[22].

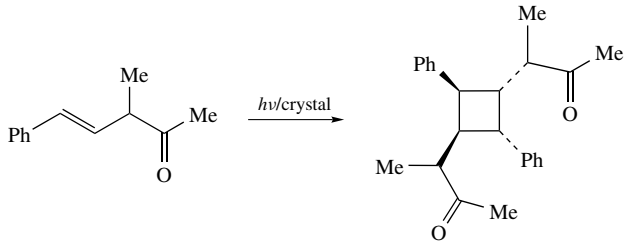


(12)



(13)

SCHEME 5

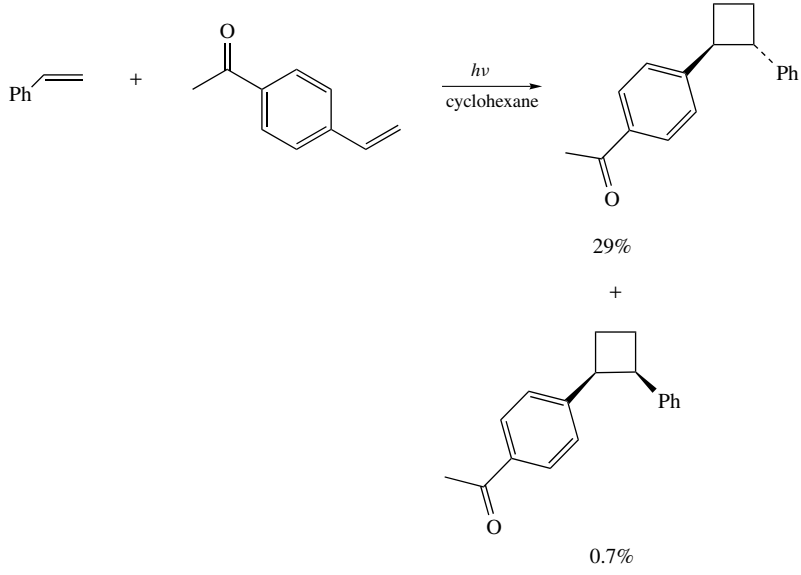


(14) **(15)**

SCHEME 6

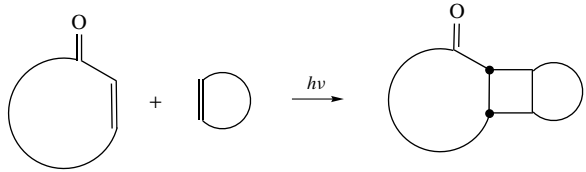
Since up to four new stereogenic centers can be produced in these cycloadditions, stereocontrol and predictability of stereoselectivity become extremely important when using such reactions in synthesis. The intermediacy of long-lived radical species at the stereogenic carbons in triplet reactions of unsaturated carbonyl chromophores will normally result in mixtures of stereoisomers. Thus, irradiation of 2-cyclohexenone with either *cis*- or *trans*-2-butene furnishes the same mixture of stereoisomeric photoadducts[23]. It is interesting to note that direct irradiation ($\lambda = 229$ or 214 nm) of either *cis*- or *trans*-2-butene

in neat phase results in stereospecific formation of their respective photodimers[24]. The latter observation is the result of concerted [2 + 2] cycloaddition from a much shorter-lived singlet state. Furthermore, photodimerization in the neat state is significantly more competitive than in solution where other modes, such as geometric isomerization, can take place. Some stereoselectivity is often observed in the ring closure of 1,4-biradicals where steric factors influence the predominance of one conformation. The photoaddition of styrene with 4-vinylacetophenone produces principally the *trans*-1,2-disubstituted cyclobutane (Scheme 7)[25].



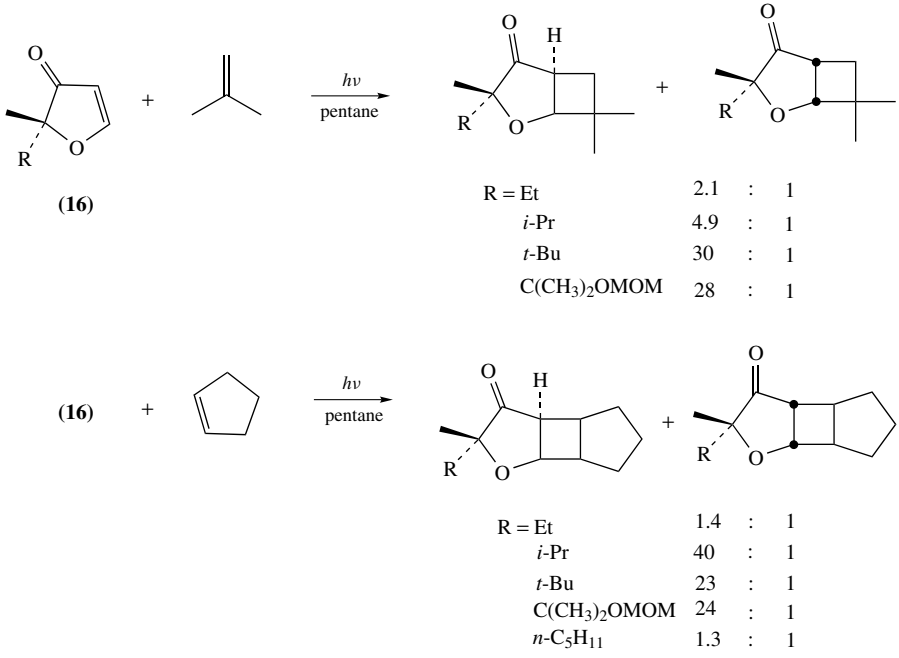
SCHEME 7

When five-membered or smaller-ring cyclic alkenes are used as substrates, stereochemical equilibration is not possible so that the bicyclo[*n*.2.0]alkane adducts are obtained with the *cis* ring fusion. Such is also the consequence of the cyclic enone incorporated in a small ring (five-membered or smaller). With six-membered rings, the enone–alkene cycloaddition can often produce the *trans*-fused bicyclo[4.2.0]octane as a byproduct[11]. In the cycloaddition of cyclic enones and acyclic or cyclic alkenes, the possibility of *endo*- or *exo*-cyclization can lead to further complexities. Where both substrate and enone are cyclic, *endo*-cyclization leading to the *syn-anti-syn* geometry of the tricyclic photoadduct is usually observed (Scheme 8), whereas the case for acyclic alkenes is not as predictable[11].



SCHEME 8

Facial stereoselectivity in cyclic systems can often be predicted on the basis of least hindered approach of the reactant. For example, the photocycloaddition of a series of unsymmetrical *gem*-disubstituted ketones **16** with either isobutylene or cyclopentene results in increasing discrimination of the product obtained from approach of the alkene from the less hindered face of the ring with increasing size of the R-group (Scheme 9)[26].

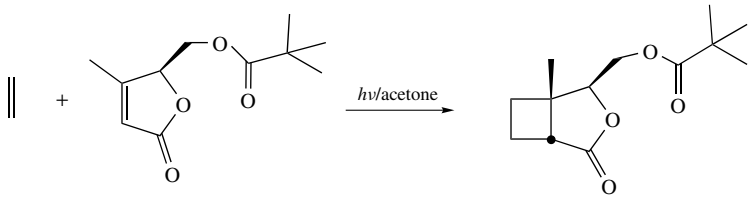


SCHEME 9

For other cyclopentenones, cyclohexenones and butenolides where a stereogenic center is located at the γ-position from the carbonyl group, bonding selectivities range from 2/1 to 5/1 in favor of the isomer derived from least hindered approach[11]. Thus, the photocycloaddition of ethylene to butenolide **17** results in the formation of the expected cyclobutane **18** (59%) as the major product accompanied by its diastereomer **19** (36%) (Scheme 10). The lactones are readily separated and cleaved to monocyclic stereospecifically substituted cyclobutane triols by methylation[27].

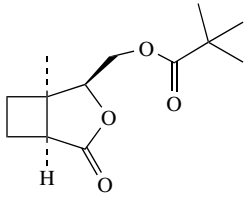
The facial selectivity for alkene cycloaddition to this butenolide with the pivaloyl ester is better than for the smaller methyl ester group[27b], consistent with the principle that larger differences in steric bulk give better differentiation. A stereogenic center located at the α'-position of the cyclic enone can exert significant differentiation between hydrogen and any alkyl group. The photocyclization of piperitenone **20** with cyclobutene **21** gives rise to a single diastereomer **22** in 73% yield (Scheme 11)[28].

Facial selectivity is also observed when a stereogenic center is located on the alkene. For example, the irradiation of cyclopentenones **23** with optically pure cyclopentene **24** gives predominant addition products originating from the approach of the enone to the less hindered side, although in this case no regioselectivity is observed, as was evident from the product distribution (1:1 mixture) (Scheme 12)[29].



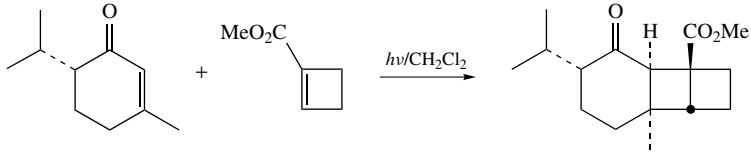
(17) **(18)** 59%

+



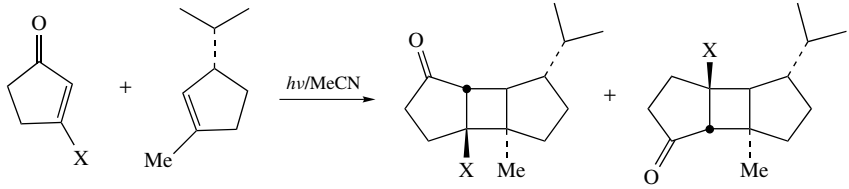
(19) 36%

SCHEME 10



(20) **(21)** **(22)**

SCHEME 11



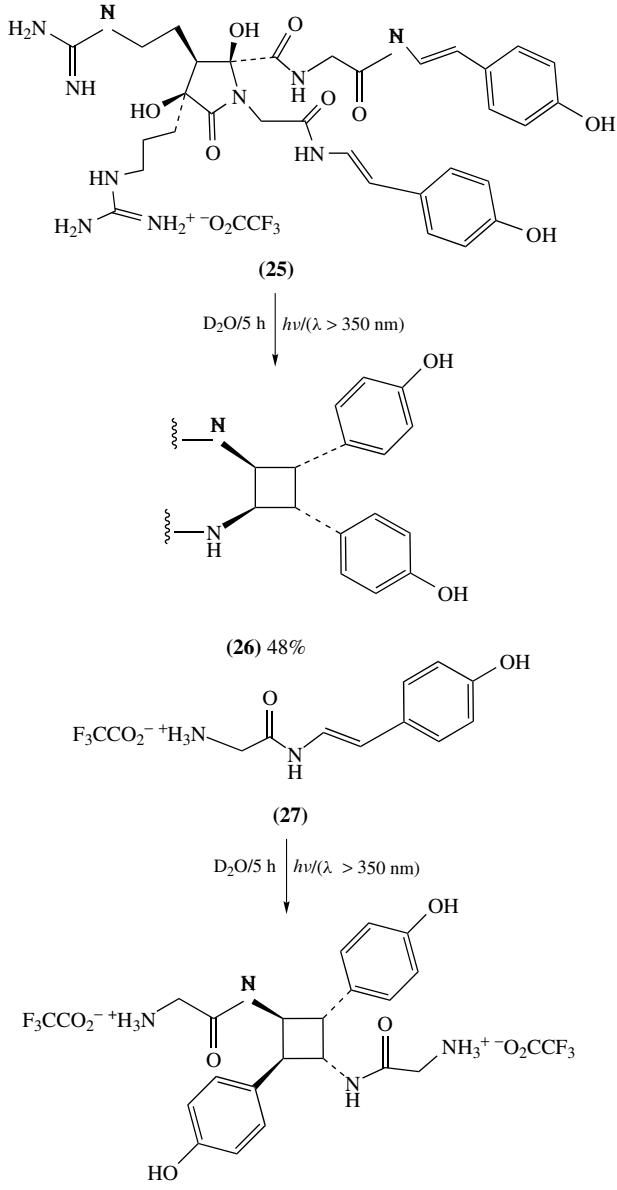
(23) **(24)**

X = OAc, OBz

SCHEME 12

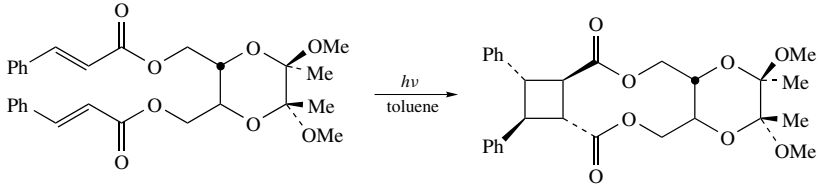
Unlike intermolecular [2 + 2] photocycloadditions, intramolecular cycloadditions between two alkene moieties generally exhibit much larger regio- and stereoselectivities. This is due to a decrease in mobility between reacting partners which are tethered together. Differences in photodimerization regioselectivities between the inter- vs. intramolecular versions are seen in the following examples. The bis-enamide **25** undergoes intramolecular cyclobutane formation by h-h *syn* geometry as seen in photoproduct **26**. By contrast,

the intermolecular photocycloaddition of the more simple analogue **27** under the same conditions gives the h-t dimer in 40% yield (Scheme 13)[30]. There is at the same time a decrease in the quantum efficiency for photodimerization.



SCHEME 13

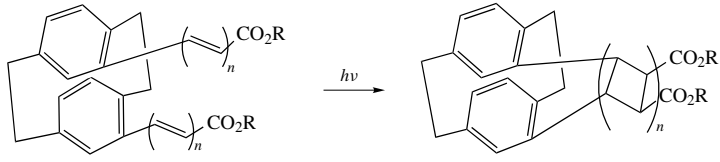
Similarly, the intramolecular photodimerization of the cinnamate diester **28** gives the h-h cyclobutane **29** (Scheme 14)[31]. The solution phase photodimerization of cinnamates generally yields a complex mixture of cyclobutanes (stereoisomers of truxinates from h-h and truxillates from h-t dimerization) due to photoisomerization preceding the dimerization[32].



(28) **(29)**

SCHEME 14

An extension of the intramolecular photodimerization of vinylogous cinnamates is seen in the conjugated derivatives **30** which leads to an interesting series of topologically rigid ladderanes **31** (Scheme 15)[33].



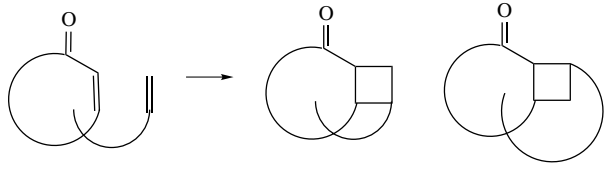
(30)
R = H, Me, Et
n = 1–3

(31) 80–100%

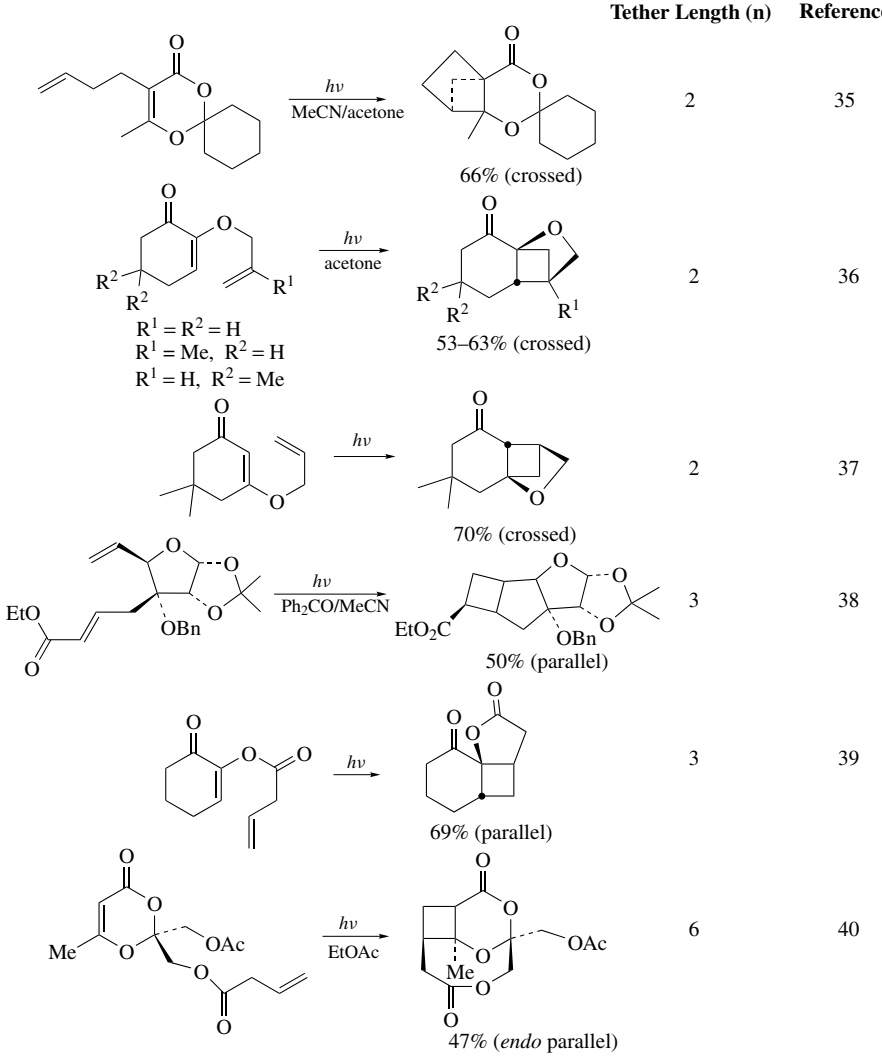
SCHEME 15

A similar increase in selectivity is observed for the intramolecular alkene–enone photocycloaddition. The parameters which influence selectivities are the tether length between enone and alkene, and the substitution pattern of the reacting functional groups. Two possible regioisomers can be produced as in the intermolecular version with one being the 'parallel' cyclobutane (1,2-disubstituted) and the other being the 'crossed' cyclobutane (1,3-disubstitution) (Scheme 16). The intramolecular version involving triplet enones goes through the same 1,4-biradicals with initial bonding occurring between either the α- or β-bond of the enone with the distal alkene unit. The selectivity between the 'parallel' and 'crossed' products depends largely on the tether length. Tether lengths possessing two centers between alkene units usually give the 'crossed' product whereas those of three or more centers give the 'parallel' product. This selectivity is associated with the 'rule of five' which is consistent with preferred modes of radical tethered olefin cyclization reactions[34]. This rule states that, if all other factors are equal, the 1,4-biradical formed from 1,5 carbon–carbon bond formation is preferred over any other mode of cyclization. Strain factors in product formation as well as substitution patterns also play a role in regioselectivities. Examples which follow these general principles are illustrated in Scheme 17.

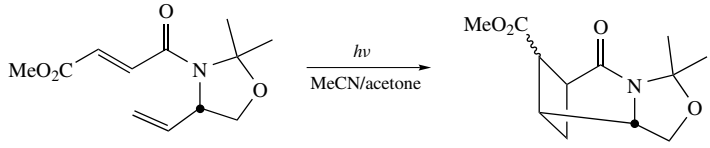
There are, however, exceptions to the rule in instances where conformational effects and biradical stabilities override 'the rule of five' as seen in the formation of the crossed



SCHEME 16



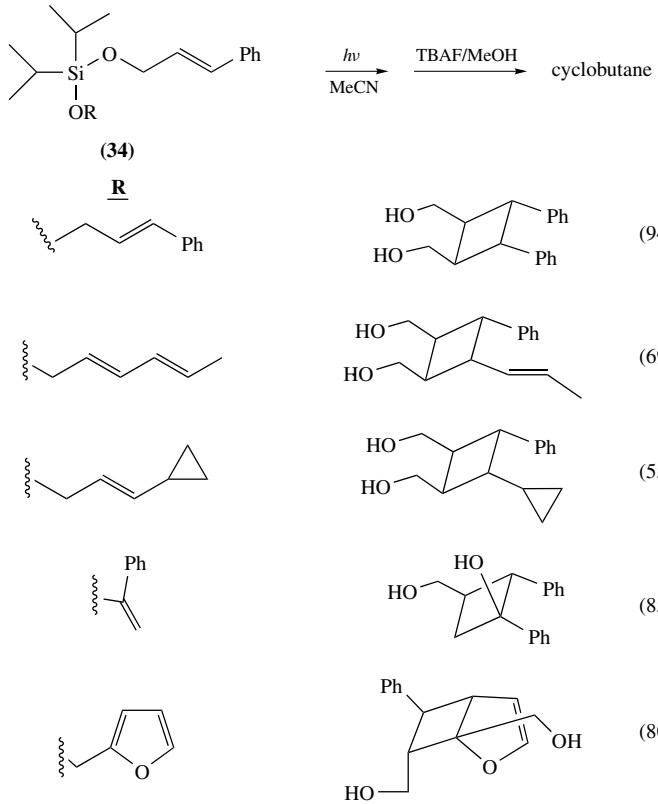
SCHEME 17



(32) **(33)** 73%

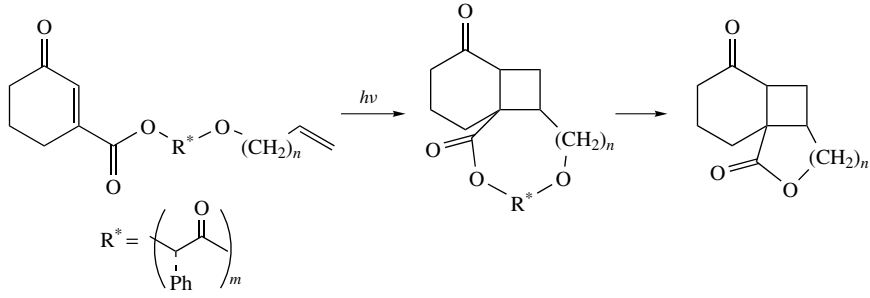
SCHEME 18

product **33** formed from oxazolidine **32** (Scheme 18)[41]. It is interesting to note that the cyclization is dependent on the use of a triplet sensitizer and that direct irradiation of **32** in the absence of acetone gives only *cis-trans* isomerization. The use of removable tethers in the application of intramolecular photocycloaddition of alkenes to prepare single defined stereospecifically substituted cyclobutane isomers has been quite effective. The use of a silyldioxy tether allows for easy removal of this group by fluoride ion cleavage. The photolysis of a series of bis(alkenoxymethyl) dialkyl silanes **34** gave intramolecular cyclization products which, upon treatment with fluoride ion, yields single diastereomers in good to excellent yields (Scheme 19)[42].



SCHEME 19

Using the same principle but incorporating a removable chiral tether allows for the enantioselective synthesis of certain bicyclic cyclobutanes. As shown below, the chiral tether is based on mandelic acid units which are commercially available in both antipodes (Scheme 20)[43,44]. Since the tether is linked by ester anchoring groups, it can be readily removed, giving enantiomerically enriched cyclobutanes in high yields. Such an approach was used to synthesize a tricyclic natural product in optically pure form[45].



SCHEME 20

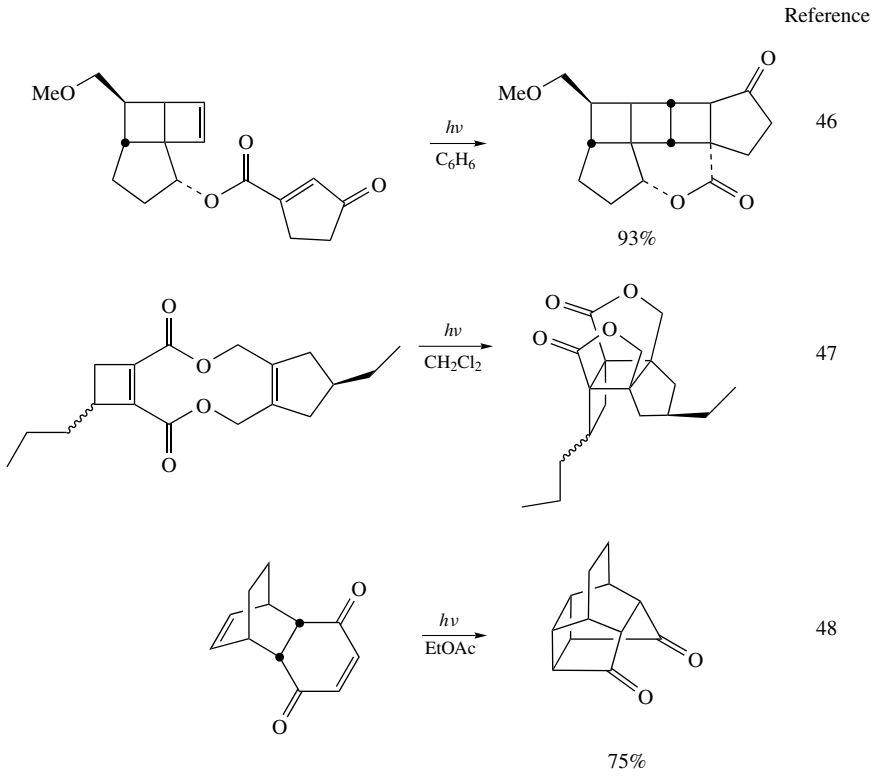
Intramolecular photocycloaddition provides a useful tool for the synthesis of unusual polycyclic and cage compounds not amenable by other approaches. Some examples of such enone–alkene cycloadditions giving interesting polycyclic derivatives are shown in Scheme 21.

In the absence of a conjugated chromophore or the use of a sensitizer, the intramolecular photocycloaddition of isolated alkene groups becomes inefficient. The copper catalyzed photocyclization of acyclic 1,6-dienes to bicyclo[3.2.0]heptanes using the commercially available bis[copper(I) trifluoromethanesulfonate]benzene complex has found general and synthetic utility. Good stereoselectivity is observed in the presence of one or more allylic ether or alcohol oxygen function. For example, the divinyl sugar derivatives **35** are transformed to single tricyclic diastereomers **36** in good yields (Scheme 22)[38]. The stereoselectivity is attributed to copper complexation by the two alkene and allylic oxygen ligands. Conversion of diallyl ethers such as **37** to 3-oxabicyclo[3.2.0]heptanes proceeds efficiently[49]. In one case of an optically active dienol **38**, such reaction gives excellent facial selectivity (Scheme 22)[50]. Experimental details and conditions have been described for these very useful transformations[51].

Chiral induction in the synthesis of cyclobutanes by the enone–alkene photochemical route can take place by placing chiral auxiliary groups on the enone or alkene reactants. These enantioselective syntheses have been reviewed[3] and only a few examples are presented. Chiral enones such as **39** and **40** give good to excellent facial selectivity in their photochemical addition of ethylene[52,53]. The *vicinal* diol derived from **39** can be readily cleaved to give identical halves representing a key intermediate in the synthesis of enantiomerically pure (+)-grandisol (Scheme 23)[52].

The chiral auxiliary in the photoproduct derived from **40** can be readily cleaved off giving the corresponding enantiomerically pure cyclobutane, which has also been used as an intermediate in the synthesis of (−)-grandisol (Scheme 23)[53].

Photochemical cycloadditions of allenes and alkynes to enones represent routes to alkylidene cyclobutanes and cyclobutenes, respectively, from which other cyclobutanes can be prepared. Irradiation of cyclopentenone or cyclohexenone with unsubstituted allene gives a mixture of h-h and h-t regioisomers of methylenebicyclo[*n*.2.0]alkanones with the

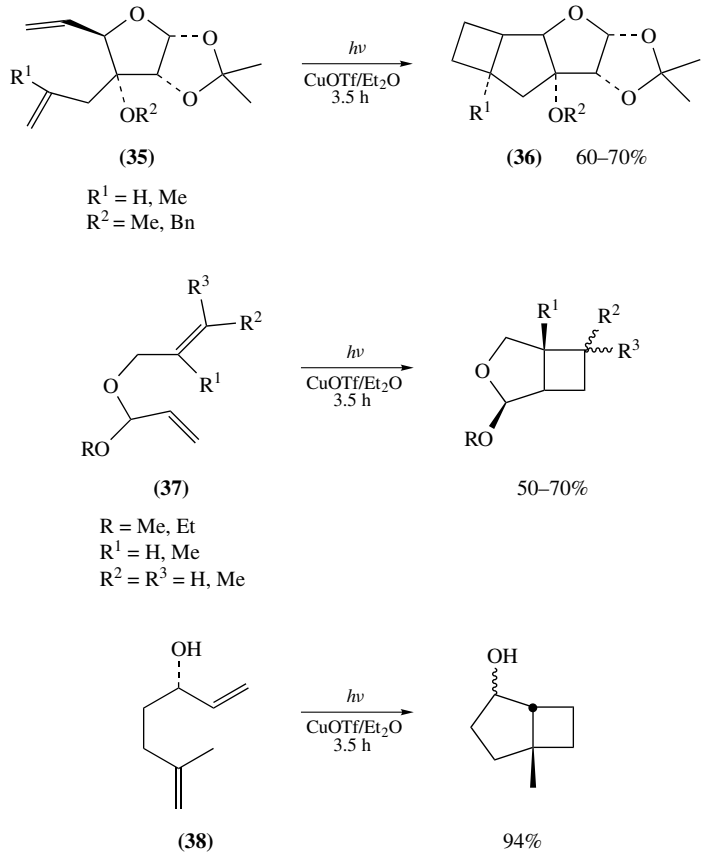


SCHEME 21

h-h isomer usually in greater abundance (Scheme 24)[54]. The regiochemistry can be rationalized in terms of the umpolung of the enone function in its excited state as mentioned above. The proportion of the h-t adduct can be significant to render such reactions of limited utility from a synthetic perspective. Few examples of regiospecific h-h cycloaddition have been reported such as the case of dioxalenone **41** (Scheme 24)[55]. Regioselectivity can also be improved by conducting such transformations at lower temperatures[56]. The complexity increases when nonsymmetrically disubstituted allenes are used and regioisomers associated with the allene moiety as well as stereoisomers originating from the alkylidene group (from nonidentical *gem*-substituents) are formed. The cycloaddition of acetylene with enones is a convenient method for the preparation of cyclobutenes, but of limited value when terminal or nonsymmetrically substituted alkynes are used because of the marginal regioselectivity observed for these substituted derivatives[54].

B. Thermal Cycloadditions

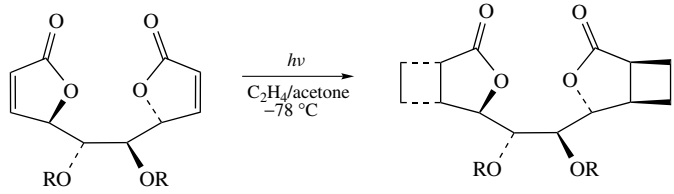
Concerted cyclodimerization or cycloadditions between nonidentical alkenes are forbidden according to symmetry conservation rules and do not occur unless certain structural



SCHEME 22

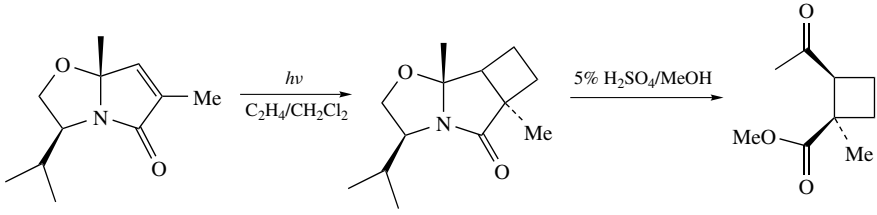
features permit the stabilization of 1,4-biradical or zwitterionic intermediates in nonconcerted processes. Strained alkenes such as methylenecyclopropanes, *anti*-Bredt bicycloalkenes, medium or small *E*-cycloalkenes and cyclobutadienes are capable of undergoing [2 + 2] cycloadditions by nonconcerted pathways[57]. Fluoroalkenes undergo mixed cycloadditions by way of biradical intermediates stabilized by the fluorine substituent when such radicals are pyramidal (by contrast to hydrogen substituted radicals which are planar). Donor–acceptor complexes formed from nucleophilic and electrophilic alkenes undergo facile cycloadditions, giving highly substituted cyclobutanes often with a high degree of regio- and stereoselectivity. In all of the latter class of reactions zwitterionic intermediates have been proposed, and the extent of stereoequilibration is dependent on the lifetime of these species which are affected by the nature of the reaction medium.

The strained bicyclopropylidene **42** reacts with conjugated dienes giving both [2 + 2] and [2 + 4] addition products; however, the major product obtained from addition with 1,3-butadiene is cyclobutane **43** (Scheme 25)[58]. The Diels–Alder product is not



(39)
R = TMS

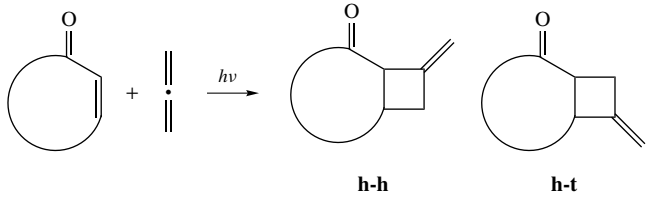
65% *de*
R = TMS



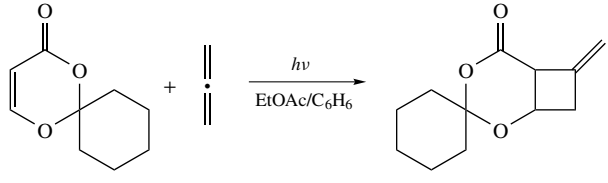
(40)

92% *de*

SCHEME 23



h-h **h-t**



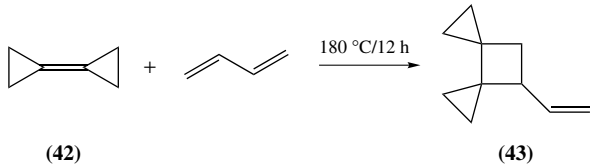
(41)

53%

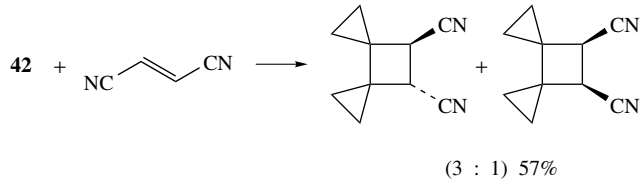
SCHEME 24

formed largely due to the conformational preference for the *s-trans* form in acyclic dienes. Oxygen-free conditions and elevated temperatures (sealed tube pyrolysis) are typical for such reactions.

The intermediacy of 1,4-biradicals is evident from the mixture of geometric cyclobutane isomers produced when **42** reacts with *trans*-dicyanoethylene[58]. Strained transient alkenes such as the anti-Bredt enone **44**, generated *in situ* from the dehydrobromination of the corresponding bridgehead bromoketone, react spontaneously with alkenes, giving the corresponding cyclobutanes (Scheme 26)[59]. The reaction efficiency in this particular



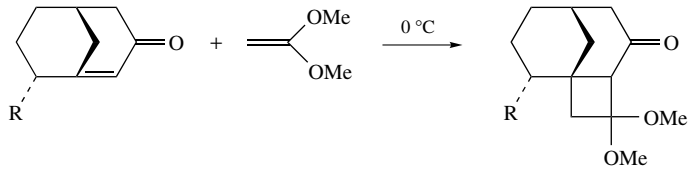
(42) **(43)**



(3 : 1) 57%

SCHEME 25

instance is likely due to the formation of donor–acceptor complexes (*vide infra*) as evident from the exclusive formation of a single regioisomer (Scheme 26).



(44) quant.

R = SPh, H

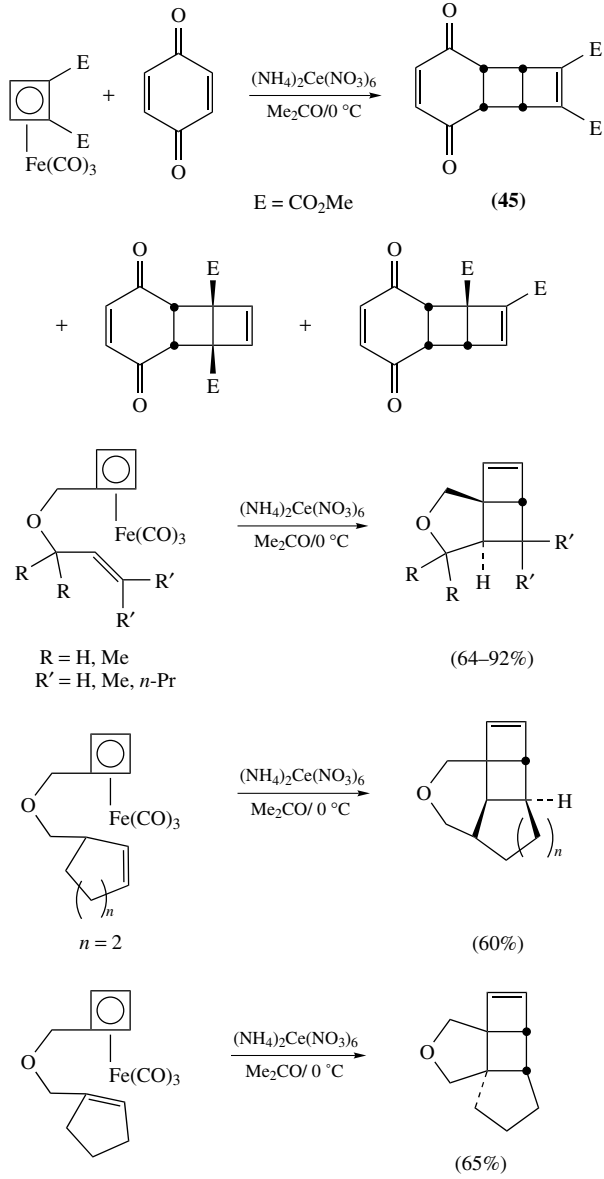
SCHEME 26

The antiaromaticity associated with cyclobutadiene makes this system a very good substrate for [2 + 2] cycloadditions with alkenes and the preparation of bicyclo[2.2.0]hexenes[5]. The less stable cyclobutadienes can be generated *in situ* in the presence of an alkene by either oxidative liberation from stable metal complexes such as cyclobutadienetricarbonyliron derivatives or from cyclobutadiene equivalents such as cyclobutenylaluminate salts. The latter precursors can be generated as stable intermediates from aluminum trichloride initiated dimerization of alkynes. Alkenes which undergo cycloaddition with cyclobutadienes are either electrophilic or strained.

Liberation of dimethyl cyclobutadiene-1,2-dicarboxylate from its iron tricarbonyl complex with ceric ammonium nitrate in the presence of benzoquinone furnishes three regioisomeric cyclobutanes in 50% yield with isomer **45** constituting the major fraction (Scheme 27)[60]. The presence of the other isomers suggests that Diels–Alder addition can also take place.

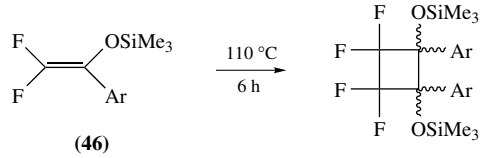
Alternatively, liberation of the iron complex can give in principle two regioisomers, dimethyl cyclobutadiene-1,2-dicarboxylate and dimethyl cyclobutadiene-1,4-dicarboxylate. The intramolecular version of this reaction produces some exotic tricyclic and tetracyclic structures not amenable by other methods of synthesis (Scheme 27)[61].

The dimerization (as well as mixed dimerization) of polyhalogenated alkenes with both activated and nonactivated alkenes has been well documented[5] and continues to represent a



SCHEME 27

convenient preparative method for polyhalogenated cyclobutanes. Of the polyhalogenated alkenes, the fluorinated ethenes are the most reactive towards [2 + 2] cycloadditions. The method is, however, limited by the nonstereoselectivity due largely to the formation of 1,4-biradical intermediates and the requirement for high temperatures. The cyclodimerization of fluoroalkene **46** giving a mixture of the two cyclobutane stereoisomers exemplifies

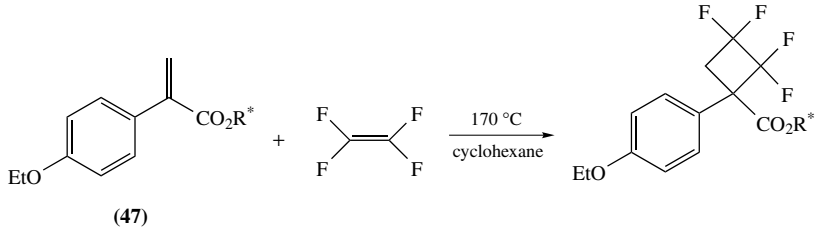


(46)

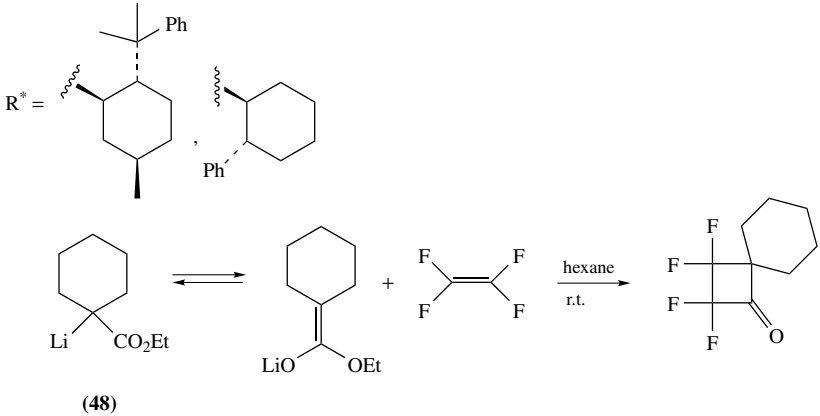
Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

SCHEME 28

this point[62]. The h-h dimerization is the exclusive regiochemistry observed as the result of fluorine stabilization of carbon radical sites (Scheme 28). Similar nonstereoselectivity is observed for mixed cycloaddition of fluorinated alkenes[63]. Among the fluorinated alkenes, tetrafluoroethylene is the most reactive in cycloadditions with other alkenes and provides a convenient route to fluorinated cyclobutanes. Tetrafluoroethylene cycloadds to chiral acrylates **47** to give the corresponding cyclobutanes with good diastereoselectivity[64]. Elevated temperatures (170 °C) are still required for this transformation. On the other hand, the same reactant in combination with the lithium enolate of ethyl cyclohexanecarboxylate, **48**, reacts at ambient temperatures[65]. In the latter case, the ketal is hydrolyzed to the cyclobutanone under the work-up conditions (Scheme 29).



(47)

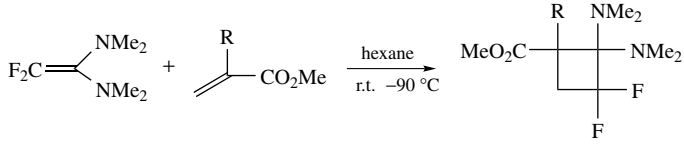


(48)

SCHEME 29

Nucleophilic alkenes such as enamines, enol and thioenol ethers will undergo cycloaddition with electrophilic alkenes giving cyclobutanes with high regioselectivity. Cycloadditions can take place with alkenes possessing a single electron-withdrawing group provided

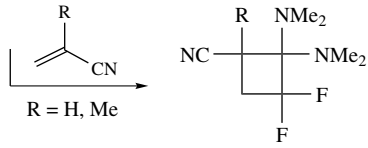
that the donor alkene is sufficiently nucleophilic. Ketene acetals thus react with acrylic esters, acrylonitrile and vinyl sulfones, and this route provides an alternative method for the preparation of cyclobutanones other than using the standard ketene to alkene cycloaddition (*vide infra*), which is limited largely to electron-rich alkenes. The cyclobutanone acetals formed are readily hydrolyzed to cyclobutanones[66]. Ketene aminals such as **49** react readily with methyl acrylates and acrylonitrile, giving the cyclobutanone aminals in good to excellent yields (Scheme 30)[67].



(49)

R = H, Me

84–87%



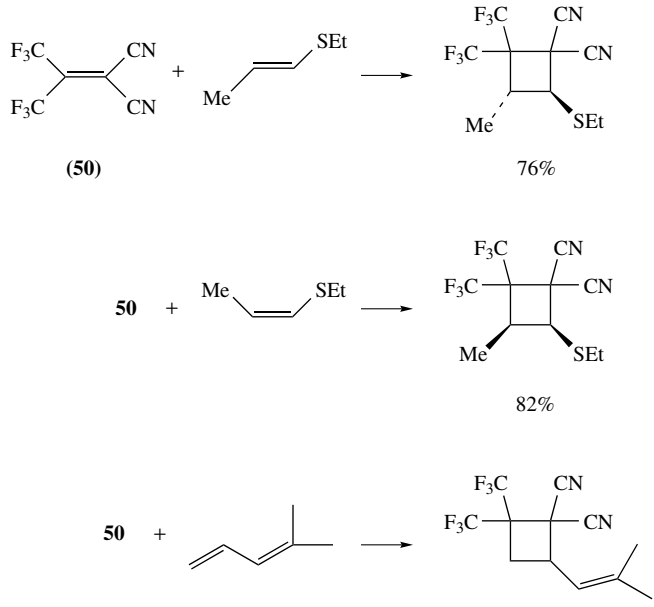
46–83%

SCHEME 30

Tetracyanoethylene (TCNE) is a very reactive electrophilic alkene and gives cycloaddition products even with moderately activated alkenes[68]. In addition to cycloadditions, TCNE reacts with alkenes to produce 'ene' products, the extent of which being dependent on the presence of allylic protons. The [2 + 2] cycloadducts of TCNE are formed via zwitterionic intermediates; evidence for this is based on trapping experiments and solvent dependence for stereoselectivity, which increases in nonpolar solvents. Cycloadditions are often preceded by formation of colored charge transfer complexes which can serve as an indicator for monitoring the reaction. The [2 + 2] cycloadducts are formed regiospecifically in nonsymmetrical conjugated alkenes with the regiochemistry corresponding to the most stable zwitterion (most stable positive charge site of the precursor alkene). Substrates which form cycloadducts with TCNE include strained alkenes, conjugated alkenes, enol ethers, thioenol ethers and enamines. More recently, it was found that salts such as lithium perchlorate accelerate the reaction by about 10^4 due to salt effect stabilization of the charge transfer complexes[69]. Stereoisomeric mixtures are the norm for TCNE cycloadditions to 1,2-disubstituted ethylenes[70].

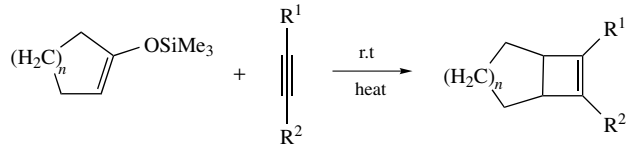
One of the most reactive electrophilic alkenes is 1,1-dicyano-2,2-bis(trifluoromethyl) ethene (**50**), which undergoes cycloaddition with enol ethers, thioenol ethers, ketene acetals and thioacetals even at temperatures as low as −78 °C. The cyclobutanes are formed as the sole products of the reaction (Scheme 31)[71–73]. These reactions are regiospecific and highly stereoselective even though evidence for zwitterionic intermediates has been obtained.

Electrophilic alkynes react with nucleophilic alkenes to produce cyclobutenes, which can be further elaborated to cyclobutanes. Dimethoxyalkenes and cyclic enol ethers react with acetylene carboxylates, giving cycloaddition products[74]. For example, the cyclic silyl enol ethers **51** react with ethyl propiolate and dimethyl acetylenedicarboxylate at



SCHEME 31

ambient temperatures yielding the corresponding cyclobutenes in excellent yields under solvent-free conditions (Scheme 32)[75].



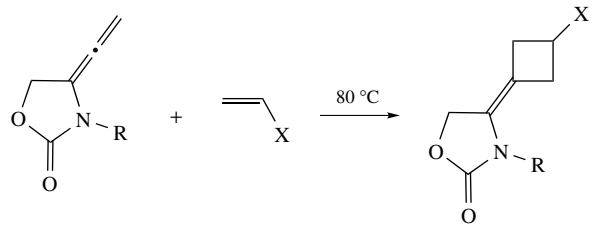
(51) 90–98%

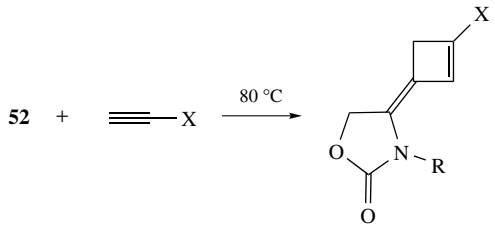
$n = 1, 2, 3$ $R^1 = CO_2Et$, $R^2 = H$

$R^1 = R^2 = CO_2Et$

SCHEME 32

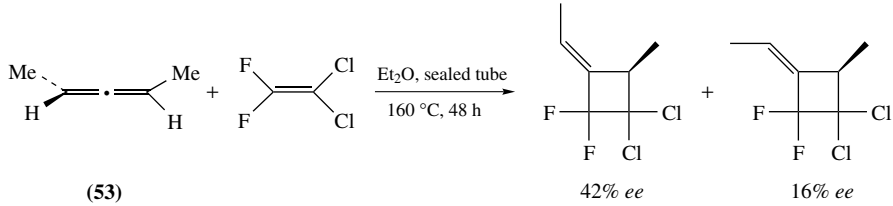
Allenes and cumulenes as a class are considerably more reactive than other alkenes in undergoing cycloadditions with isolated, nonactivated double bonds. According to their heats of hydrogenation allenes possess an additional strain energy of about 10–11 kcal mol^{-1} associated with their central *sp* carbon and this strain is relieved in any addition reaction including cycloadditions. The problem with using allene cycloadditions as a synthetic method for the preparation of cyclobutanes arises from the low regio- and stereoselectivities of these processes, which is largely associated with the occurrence of diradical and zwitterionic intermediates in these cases. An added complication with allene cycloadditions is the formation of *E*/*Z*-isomers with respect to the exocyclic methylene group in the product alkylidenecyclobutanes (see discussion on photocycloaddition of allenes above). Even when regiochemical and stereoselectivity occur, mixtures of isomeric cyclobutanes are obtained and separation of individual isomers is often not possible.





SCHEME 33

Several reviews on the field of allene chemistry, including cycloaddition reactions, are available[76]. There are, however, a number of examples reported where relatively clean reaction products of allenes with alkenes have been obtained and of synthetic potential. The oxazolidone allenes **52** react with electrophilic alkenes and alkynes giving alkylidene cyclobutanes and cyclobutenes, respectively[77]. The alkylidenecyclobutene is obtained from the alkyne addition as a single *Z*-regioisomer (Scheme 33). The cycloadditions of nonactivated allenes require neat samples heated to temperatures of 150–220 °C in sealed tubes for extended periods of time, which represents somewhat of a drawback with thermally sensitive materials. Typically, methyl methacrylate or methacrylonitrile with the parent allene has to be subjected to a temperature of 200 °C for cycloaddition to occur[78]. One rather unique feature of allenes as cycloaddition substrates is associated with the chiroptical properties which can be sometimes transferred to the cycloadducts[79]. As much as 42% of the enantiomeric excess of the starting allene can be transferred to the cyclobutane in the case of (+)-(*S*)-1,3-dimethylallene (**53**) cycloaddition with 1,1-dichloro-2,2-difluoroethene (Scheme 34).

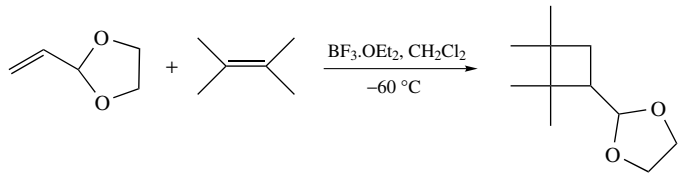


SCHEME 34

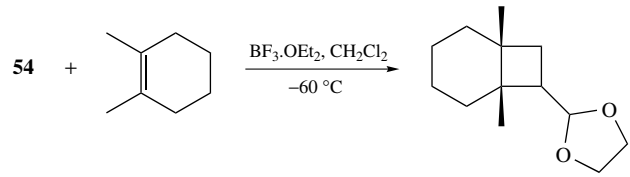
C. Catalyzed Cycloadditions

Alkenes which are thermally unreactive to cycloadditions can be induced to undergo such reactions by catalysts (metals, Lewis or Brønsted acids). In many instances, the substrates are converted to reactive intermediates such as metalated alkenes, cations or radical cations, which undergo cycloaddition more efficiently. The milder reaction conditions of the catalyzed process permit the extension of the scope of [2 + 2] cycloadditions to include alkene combinations which would not otherwise react. Nevertheless, a number of these catalysts can also cause the decomposition of the cyclobutanes formed in the initial reaction. Such catalyzed alkene cycloadditions previously reported were limited specifically to allyl cations, strained alkenes such as methylenecyclopropane, and donor–acceptor substituted alkenes. Many of such alkenes would possess a nucleophilic site for coordination with a metal or Lewis acid to generate a quasi-allylic cation sufficiently reactive for cycloaddition with another alkene. In such cases stereochemical equilibration can take place resulting in isomeric mixtures of products.

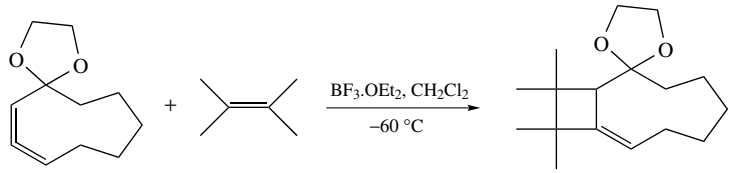
The Lewis-acid catalyzed cycloadditions of ketals **54** and **55** proceed quite efficiently at temperatures of −40 to −60 °C (Scheme 35). These transformations likely involve allylic cations[80].



(54) 71%



70% (stereochemistry not indicated)

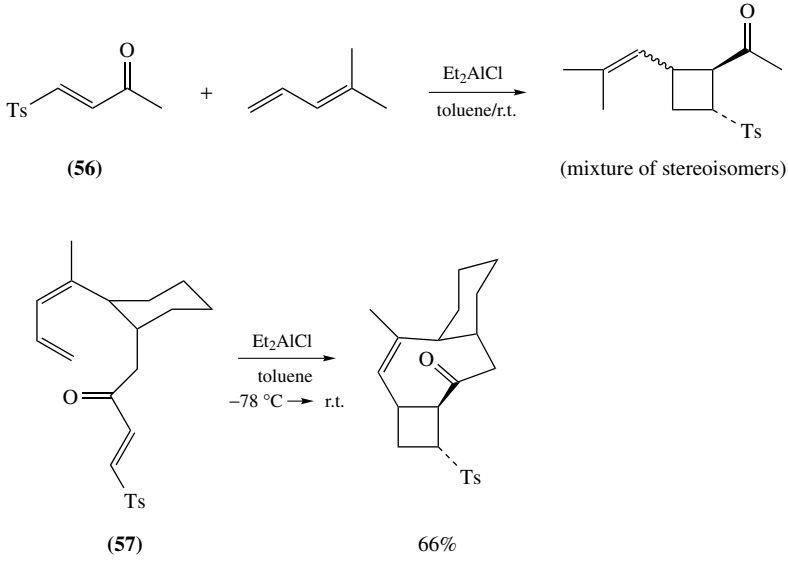


(55)

SCHEME 35

Thermal cycloadditions of these reactants could not have taken place in the absence of catalysts even at elevated temperatures. Stereochemical equilibration can take place when

an α,β-unsaturated carbonyl group is involved under Lewis-acid conditions as is evident from the mixture of stereoisomers obtained from the intermolecular cycloaddition of enone **56**, but **57** reacts by intramolecular cycloaddition with high selectivity (Scheme 36)[81]. Some Diels–Alder adducts are also observed, with percentages which depend on the conformational abundance of the *S-cis*-diene. The retention of stereochemistry of the enone substituents in the product is rationalized in terms of a double complexation by virtue of the presence of a β-tosyl group[81]. Other examples where high selectivity in product stereochemistry is exhibited include metal catalyzed cycloadditions of allyl and vinyl silanes to methyl methacrylate, and other electrophilic alkenes (Scheme 37)[82–84].

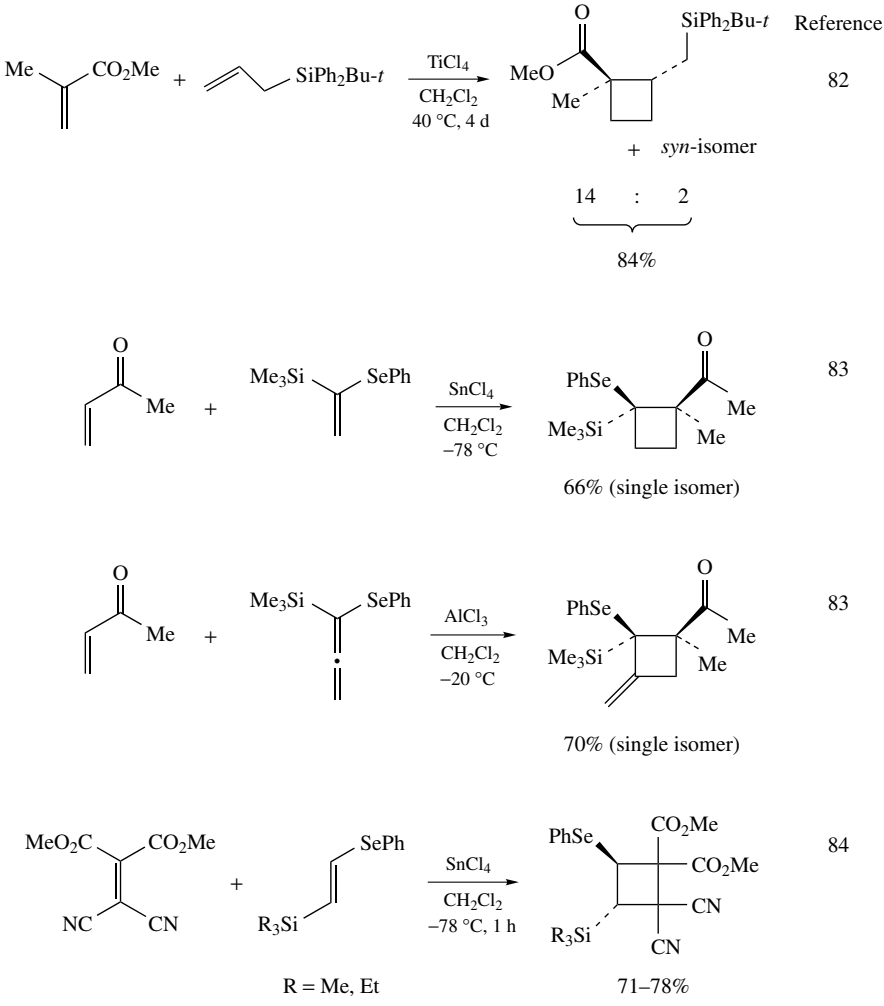


SCHEME 36

Zwitterionic intermediates have been proposed in some of these processes and the selectivity is often dependent on the nature of the metal catalyst.

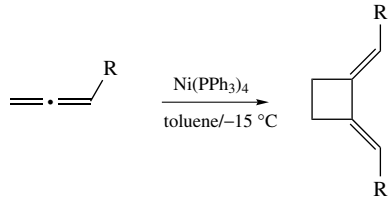
Certain transition metals are capable of catalyzing cycloadditions involving nonactivated alkenes. This latter class of reactions involves coordination of the metal to the π-binding site of the carbon–carbon double bond permitting the reaction of nonactivated alkenes[85]. Whereas allenes will dimerize at elevated temperatures to give mixtures of regioisomers with low selectivity, the nickel catalyzed reaction of allenes can take place at ambient or lower temperatures giving excellent regio- and chemoselectivity (Scheme 38)[86]. The selectivity was attributed to the intermediacy of nickelacyclopentanes formed in a chemoselective manner. Other relatively inert alkenes such as norbornenes can be induced to cycloadd to unactivated alkynes with certain ruthenium complexes (Scheme 38)[87].

The synthesis of chiral cyclobutanes by [2 + 2] cycloadditions can occur by the use of auxiliary groups on either of the reacting partners. The use of double chiral induction has been effectively applied for the diastereoselective synthesis of a chiral cyclobutanone. The cycloaddition of di-(−)menthyl fumarate with the ketene acetal, 1,1-dimethoxyethene, catalyzed by diethyl aluminum chloride, produces the corresponding cyclobutane with greater than 99% de[88]. This compound can be further structurally elaborated to the cyclobutanone

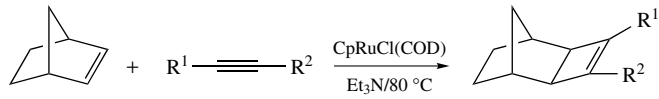


SCHEME 37

which serves as a key intermediate used in the preparation of a number of nucleosides with potential antiviral activity[89]. For the catalyzed cycloadditions, the use of chiral catalysts has extended the scope of these reactions and shown to be more effective in enantioselective synthesis of optically pure cyclobutanes[3]. One of the most efficient methods for enantioselective syntheses of cyclobutanes involves the use of chiral titanium complexes as a catalyst in donor–acceptor [2 + 2] cycloadditions developed by Narasaka and Hayashi[90]. The substituted tartaric acid derived complex **58** induces high stereoselectivity in the cycloaddition of ketene thioacetals, thioenol ethers and other electron-rich alkenes with oxazolidinone enamides to give enantiomerically pure cycloadducts (Scheme 39). For example, the enantioselective synthesis of a four-carbon ring nucleoside analog of oxetanocin involves the key intermediate **59** obtained in 83% yield with a >98% ee![90].

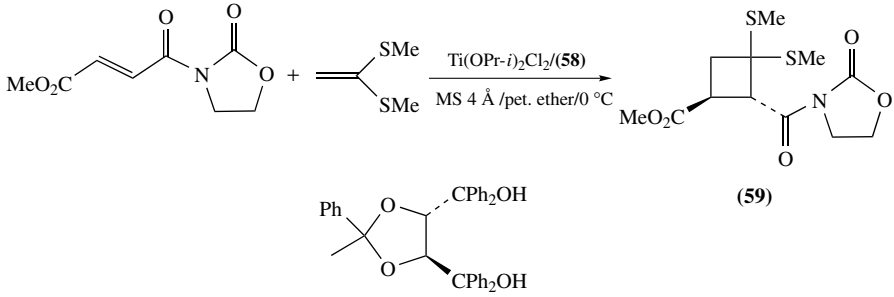


R = *n*-C_6F_{13}, C_6H_5, CO_2Et 71–81%



$R^1 = R^2$ = Ph, *n*-C_5H_{11}, CO_2Me
R^1 = Ph, R^2 = Me, CO_2Me
R^1 = Et, $R^2 = CH(OEt)_2$
R^1 = Me, $R^2 = CO_2Me$

SCHEME 38



(59) **(58)**

SCHEME 39

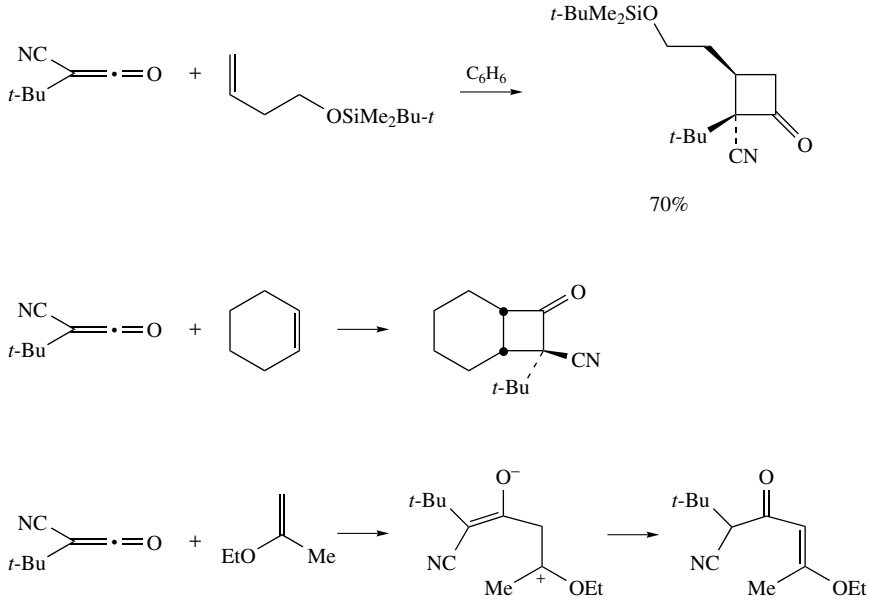
D. Cycloadditions with Ketenes or Ketene Equivalents

The uncatalyzed cycloaddition of nonactivated alkenes does not proceed efficiently, often requiring harsh conditions which result in regio- and stereochemical equilibration of the substituents in the cyclobutane ring. Thus, this class of reactions is not the method of choice in the construction of configurationally defined cyclobutanes. Ketenes represent a special class of reactive 'alkenophiles'[3,91]. Of all methods for the synthesis of four-membered carbocycles the cycloaddition of ketenes to alkenes remains one of the most popular for the preparation of cyclobutanes[4,92]. The availability of ketenes from different routes as well as the high regio- and stereoselectivity of these reactions are some of the important factors for the popularity of this method. Furthermore, the ease of ring-opening and ring-expanding transformation of the cyclobutanones obtained makes this route a very attractive one for *vicinal* carbofunctionalization of alkenes. Reactivities of ketenes differ widely depending on the substituents. Although these reactions have been described

as symmetry allowed concerted $[2\pi_a + 2\pi_s]$ process[6], theoretical analyses have pointed to an asynchronous pathway involving nonsymmetrical transition states[93]. Nevertheless, the regio- and stereochemistry can be predicted on the basis of the orbital symmetry approximation. The initial bonding interaction involves the ketene fragment acting as the electrophilic component and thus electron-withdrawing substituents on the ketene enhance reactivity. Most facile cycloadditions occur between electrophilic ketenes and nucleophilic alkenes. Sufficiently activated ketenes such as dichloroketene react with nonactivated double bonds such as cyclopentene and cyclohexene; however, electron-deficient alkenes do not undergo cycloaddition to ketenes. For these alkenes, ketene equivalents such as ketene acetals or thioacetals can be used (see Section II. B). An alternative ketene equivalent for cycloaddition to alkenes are the ketene iminium salts, which show greater tendency for reaction in [2 + 2] cycloaddition with alkenes. Nonactivated alkenes as well as certain electron-deficient alkenes will react with these salts, giving cyclobutanes. Further advantage with the use of ketene iminium salts is the absence of dimerization of these positive charged intermediates, a reaction which is common in ketene cycloadditions. Since dimerization is a common feature for ketenes, the cycloaddition is normally carried out by generating the species *in situ* in the presence of excess olefin at above ambient temperatures.

The cyclobutanones are formed regioselectively with the more nucleophilic carbon of the alkene bonded to the ketene carbonyl carbon. The stereochemical integrity of the alkene substituents is generally maintained in the product unless secondary equilibration of the cyclobutanone ensues. The relative stereochemistry of the ketene substituents with those of the alkene can be predicted on the basis of the concerted mechanism involving a symmetry allowed $[2\pi_a + 2\pi_s]$ process even though this rationalization has been superceded by a nonsynchronous or two-step mechanism. Thus, the product formed from unsymmetrical ketenes with cycloalkenes has the larger of the two substituents occupying the *endo* position in the bicycloalkane, which is the higher energy species indicating kinetic control as the dominant factor in these reactions. A similar prediction can be made for ketene cycloaddition with acyclic alkenes. The reaction of *tert*-butyl(cyano)ketene with an unsymmetrical *gem*-disubstituted alkenes results in the formation of the less stable cyclobutanone (Scheme 40)[94]. Cycloaddition of the same ketene with ethyl vinyl ether, however, gives a diastereomeric mixture of cyclobutanones favoring the kinetic product[95]. Furthermore, reaction of the same ketene with ethyl isopropenyl ether did not give any cycloaddition but led to acyclic products (Scheme 40). These latter results suggest that some ketene/olefin cycloadditions, especially with nucleophilic alkenes, may take place via the intervention of zwitterionic intermediates (Scheme 40)[95]. Independent evidence for the intervention of such species in cycloadditions was obtained by its generation by other means and observing products of cycloaddition[96]. The efficiency for ketene cycloadditions often depends upon their mode of preparation, with the most popular methods being base dehydrochlorination of α-mono or disubstituted acetyl halides, and zinc dechlorination of α-chloro acid halides, the latter being most effective in cycloadditions. The dehydrochlorination method for ketene generation is effective for activated nucleophilic alkenes such as enol ethers[97], but normally fails with nonactivated olefins. The use of soft bases of a highly hindered nature in combination with a soft Lewis acid has been found to vastly improve the efficiency of cycloadditions[98]. For the zinc dechlorination method, preparation of the activated zinc can be problematic in terms of the necessity for rigorous control and the exclusion of moisture and oxidizing conditions. The use of ultrasonication in the zinc dechlorination method[99], and the activation of zinc by heating (140–150 °C)[100] have been shown to improve yields further and in some cases promote cycloaddition in instances where no reaction would occur under ordinary circumstances. Other more esoteric methods for ketene generation,

such as deazotization of α-diazocarbonyl derivatives (Wolff rearrangement), have been effectively used in cycloadditions to alkenes[101]. Additional methods include pyrolysis of carboxylic acid anhydrides, ring opening of cyclobutenones (for vinyl ketenes), thermolysis of 4-azido-3-halofuran-2(5*H*)-ones (for cyano(halo)ketenes), 2,5-bisazido-3,6-dialkylbenzoquinones (for alkyl(cyano)ketenes), photolysis of trimethylsilyl α-diketones (for alkyl(trimethylsiloxy)ketenes and photolytically initiated carbon monoxide insertion in Fischer carbene complexes (*vide infra*)[8]. Carboxylic acids can be converted to ketenes via their mixed anhydrides such as acyl tosylates[102] which, upon detosylation with triethylamine, give the corresponding ketene in a one-pot reaction. Other mixed anhydrides such as α-hydroxyacyl acetates have been shown as effective ketene precursors in intramolecular cycloadditions[103].

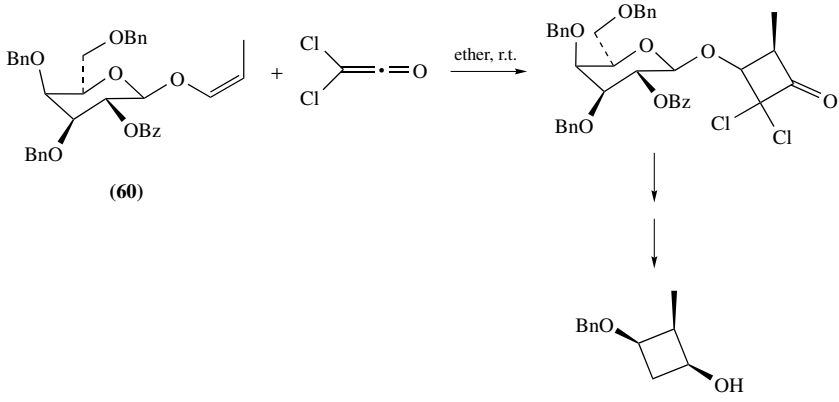


SCHEME 40

Parent ketene which can be economically obtained from the pyrolysis of acetone is quite inert towards cycloaddition with alkenes[91]. Dichloroketene is often used as a parent ketene equivalent because of its enhanced reactivity, and the facile dechlorination of the resultant α,α-dichlorocyclobutanones by metal (usually zinc) reductive cleavage. This route for the two-carbon annelation of alkenes remains the method of choice[104–108].

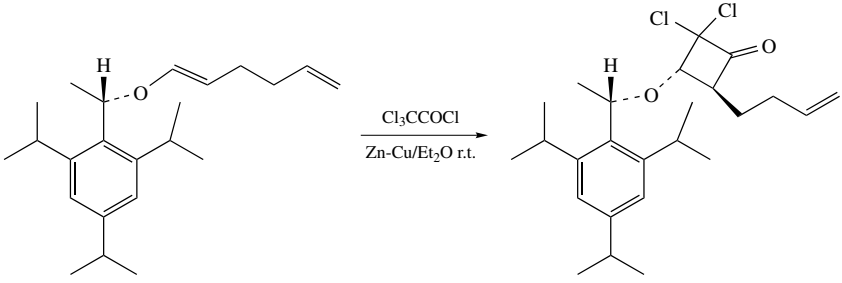
Optically active chiral cyclobutanones can be obtained from chiral alkene/ketene cycloadditions. Natural products with alkenes incorporated in a chiral carbon framework are abundant. Ketenes will add to terpenes[109], steroids[110,111] and dehydro cyclic acetals derived from sugars[112–115] to give the corresponding optically pure cyclobutanone. The use of removable chiral auxiliary groups on either the ketene or 'ketenophile' gives variable diastereoselectivity. A monosaccharide removable chiral auxiliary unit **60** was effectively used to prepare an optically enriched cyclobutane (Scheme 41). Attachment of a vinyl group at the anomeric position of galactose gives an electron-rich 'ketenophile' which reacts with dichloroketene to produce the corresponding α,α-dichlorocyclobutanone with

chiral induction resulting from preferential *si*-face attack of the olefin[115]. Reduction of the ketone followed by cleavage of the cyclobutane gives optically enriched cyclobutanols. In a related study, the chiral enol ether **61** was reacted with dichloroketene, giving ketone **62** with almost complete facial selectivity (95% de) (Scheme 42)[116]. The bulky substituted arylalkoxy group, which is responsible for the selectivity, can be readily removed by standard hydrogenolysis conditions.



(60)

SCHEME 41

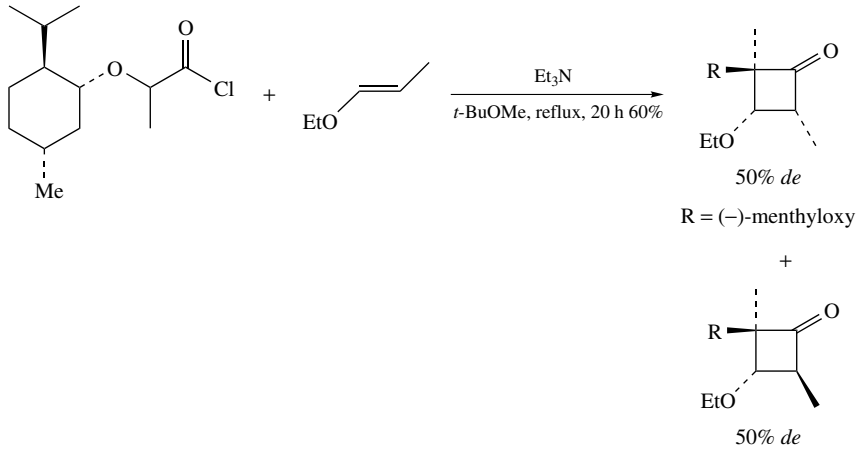


(61) **(62)**

SCHEME 42

The preferred cycloaddition to the enol ether over the terminal alkene exemplifies the chemoselectivity of ketene cycloadditions. This same chiral auxiliary group has been effectively used for the preparation of other optically enriched cyclobutanones[117]. Another chiral auxiliary group on a substituted alkene showing high diastereoselectivity includes the *Z*-2-phenylcyclohexyloxy group[118]. When the chiral auxiliary is attached to the ketene, such as in the case of [(−)-menthyloxy]methylketene, enantiomeric excesses of the final products are around 50–70% (Scheme 43)[119].

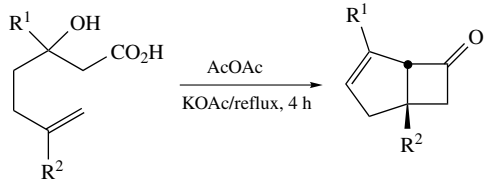
The reaction of ketenes with conjugated dienes are perispecific and give exclusively the [2 + 2] cycloadducts. Although vinylcyclobutanones are formed as initial products, these can undergo thermal or catalyzed rearrangements under the conditions of cycloaddition[8,92]. Addition of ketenes to allenes yields 2-alkylidenecyclobutanones with little chemoselectivity in the case of nonsymmetrical allenes[92]. In this reaction the ketene is the more



SCHEME 43

reactive species and homodimerization of ketene can be minimized by use of excess allene. Ketene cycloadditions with alkynes produces cyclobutenones. It should be noted that alkynes are more reactive than alkenes or even enol ethers. Thus conjugated enynes react with ketenes to give cyclobutenones as the exclusive products[92]. The regiochemistry for unsymmetrical alkyne additions follows the same pattern as for alkenes with the more nucleophilic carbon of the alkyne being bonded to the carbonyl carbon of ketene. Thus terminal alkynes form h-h cycloadducts with ketene[92].

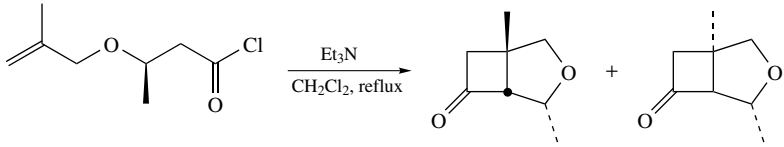
The intramolecular ketene to alkene cycloaddition is a very useful method for the production of ring-fused cyclobutanones and has been extensively reviewed[120] and only general trends are summarized. The efficiency for intramolecular cycloaddition depends on the nature and rigidity of the tether length. When the alkene and ketene functions are held rigidly and in close proximity, then good yields of the cycloadducts are obtained even with monosubstituted ketenes which are known to spontaneously dimerize. In such cases the presence of a proximal alkene moiety is equivalent to having a large concentration of alkene in intermolecular processes. Three-atom tethers between the ketene and alkene moieties give best results for such intramolecular cycloadditions. In the same manner as with the intermolecular version, intramolecular ketene to alkene cycloadditions proceed with retention of configuration of the alkene unit. The regiochemistry of these reactions depends on the substitution pattern of the alkene function. For a three-carbon tether, substrates in which the internal alkene carbon is more highly substituted give bicyclo[3.2.0]heptan-6-ones (h-h cycloaddition), while substrates in which the terminal alkene carbon is more highly substituted give bicyclo[3.1.1]heptan-6-ones. The orthogonal geometry required for the $[2\pi_a + 2\pi_s]$ cannot be attained in these intramolecular reactions, suggesting a mechanism involving an asynchronous transition state. Examples of such processes include the intramolecular cycloaddition of ketenes generated from 3-hydroxyhept-5-enoic acids **63** by the mixed anhydride method[103]. A chiral example of such a reaction is used in the enantioselective synthesis of grandisol. The base dehydrochlorination of chiral acid chloride **64** having a heteroatom incorporated in the tether gives bicyclic ketones **65** and **66** with a selectivity of 3.4:1 in favor of the former (Scheme 44)[121]. Limitations of the intramolecular ketene to alkene cycloaddition method for generating cyclobutanones is the



(63)

R^1 = H, Me
R^2 = H, Me

57–59%



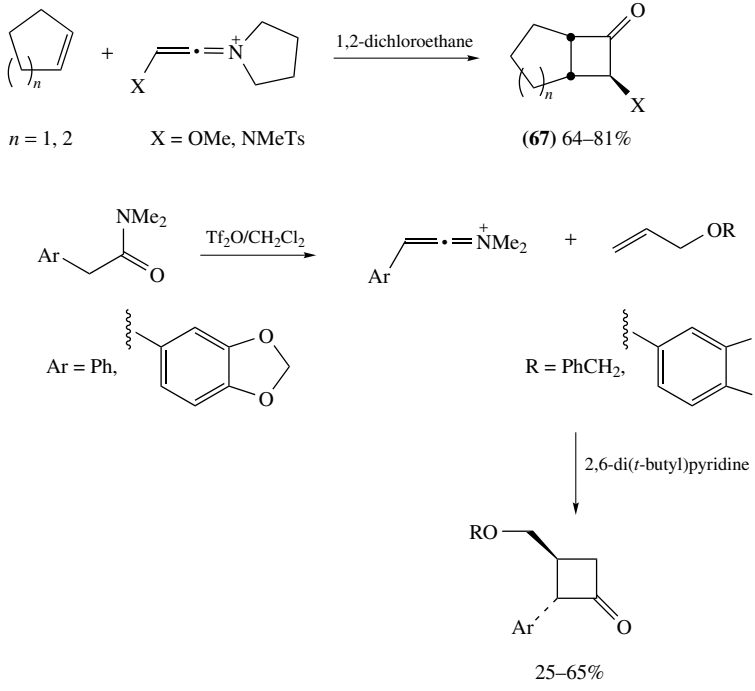
(64) **(65)** **(66)**

SCHEME 44

restriction of the tether length to three atoms (with a few exceptions[120]) and the competing intermolecular processes (i.e. ketene dimerization). It is suspected that the inability of monosubstituted alkenes to undergo intramolecular cycloadditions with reactive ketenes such as formyl ketenes and chloroketenes in flexible systems is due to competitive side reactions. Concentration effects can be used to a certain extent in minimizing the intermolecular pathway. Vinylketenes, however, do undergo intramolecular cycloadditions even with monosubstituted alkenes in modest yields (23–38%)[122]. It is believed that the vinyl group incorporated in the tether decreases the conformational flexibility, promoting the intramolecular process.

An alternative to ketene cycloadditions involves the reaction of ketene iminium salts with alkenes[123]. These reactive ketene equivalents are readily available from dehydration of carboxamides and avoid the problem of dimerization encountered in ketene reactions. Unlike ketene cycloadditions, very few mechanistic studies have been carried out with this class of reactions. The stereochemistry with respect to the ketene iminium salt in cases of monosubstituted or unsymmetrically disubstituted derivatives in cycloadditions to alkenes show differences from the ketene counterpart. In contrast to ketene cycloadditions of monosubstituted ketenes with cycloalkenes where the substituent in the bicyclic derivative ends up in the *endo* position, the cycloaddition of two monosubstituted ketene iminium salts with cyclopentene and cyclohexene gives the *exo*-substituted derivatives **67** (Scheme 45)[124]. Similarly, aryl-substituted ketene iminium salts will add to allyl ethers to give products with the opposite stereochemistry from ketene additions[125]. The formation of small amounts of the other epimers is indicative of a two-step process. Unlike ketenes, these salts are also capable of reacting even with electrophilic alkenes such as conjugated unsaturated esters and amides. However, differences in regiochemistry in these cycloadditions (the less nucleophilic β-carbon of the unsaturated ester bonds with the iminium carbon of the salt[4]) with those of ketene cycloaddition suggest that these

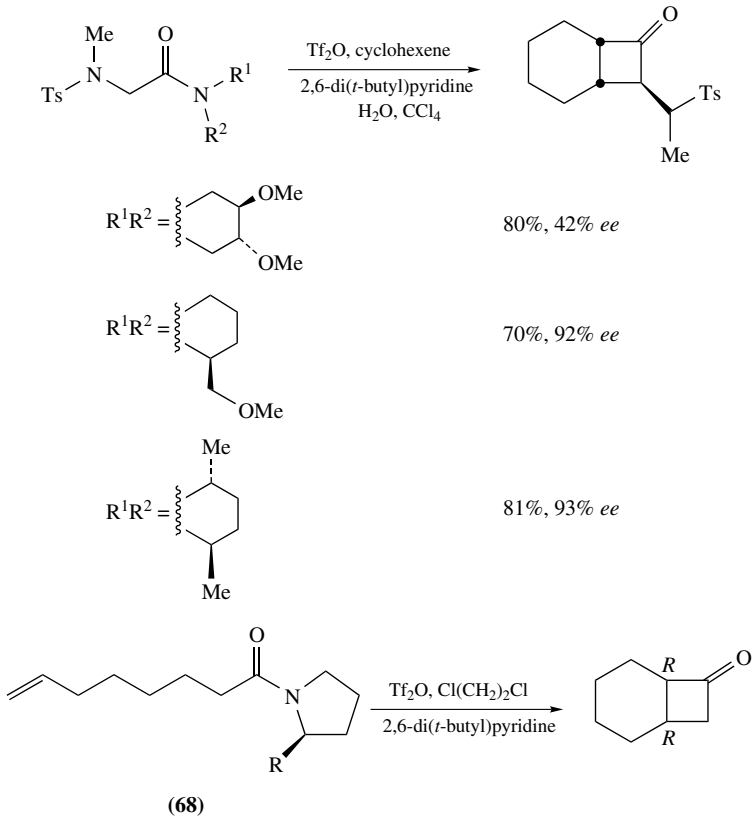
reactions involve different intermediates and transition states. The presence of a tetravalent iminium cation permits the placement of a chiral auxiliary group on the nitrogen. Enantiomeric enrichment of the cycloadducts depends on the substitution pattern of the ketene iminium salts with the more substituted salts giving greater asymmetric induction. This is seen in the examples in Scheme 46 of different chiral auxiliary groups attached to the precursor amide nitrogen with the proximal stereogenic centers closest to nitrogen showing largest induction[126].



SCHEME 45

An intramolecular version of asymmetric induction in these cycloadditions is seen for the enamide **68**, giving products with optical enrichment of up to 97.5%[127].

Photolysis of pentacarbonylcarbenechromium (Fischer) complexes produces species that react as if they were ketenes[128]. This class of reactions represents a rather unusual [2 + 1 + 1] cycloaddition of which one other type exists, namely, the sequential one-carbon homologation of ketenes with diazomethane to give cyclobutanones via the intermediacy of cyclopropanones. Photolysis of chromium (alkoxy) carbenes **69** in the presence of a range of simple alkenes produces cyclobutanones **70** in good yields (Scheme 47)[128c]. The reactions are highly regio- and stereoselective. The regiochemistry corresponds to that of ketene [2 + 2] cycloadditions with the more nucleophilic alkene carbon bonded to the ketene carbonyl carbon. The stereogenic center of the resulting products from **69** has the methyl group *cis* to the substituent on the alkene with the configuration of a disubstituted alkene maintained, again, in analogous fashion to ketene/alkene [2 + 2] cycloadditions. As in the case of ketene cycloadditions, electron-deficient alkenes are poor substrates



(68)

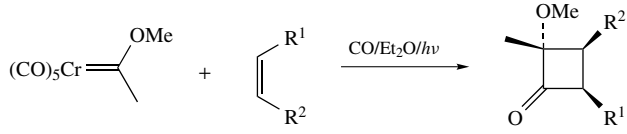
SCHEME 46

for this reaction. The intramolecular version of this reaction has also been shown to be successful. For example, the carbene complex **71** was transformed to 1-methyl-2-oxabicyclo[4.2.0]octan-8-one in 86% yield under anaerobic conditions (Scheme 48)[129]. Unlike intramolecular ketene cycloadditions, the reaction is not limited to a three-centered tether, and the use of a four-atom tether is still effective in bringing about cycloaddition. The use of alkenes with chiral auxiliary groups leads to chiral cyclobutanones **72**. Reaction yields of 50–70% and diastereomeric excesses of 86–97% were obtained for the 3-carbamylcyclobutanones, which were obtained from cycloaddition of the chromium carbene complexes with chiral ene carbamates (Scheme 49)[130].

Such approach was extended to cyclic carbene complexes for the synthesis of chiral spirocyclic cyclobutanones[130c].

In addition to the absence of ketene dimerization in these reactions, the mild reaction conditions associated with the use of chromium carbene complexes avoids epimerization and thermodynamic equilibration of 2-monosubstituted cyclobutanones.

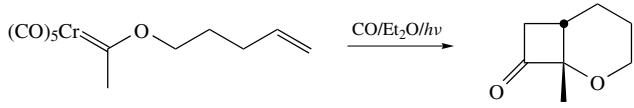
One of the classical methods for construction of cyclobutanones by the sequential [2 + 1 + 1] cycloaddition is the reaction of ketenes with diazoalkanes[5a] (Scheme 50) which proceeds via cyclopropanone intermediates. This type of reaction finds limited use



(69) **(70)**

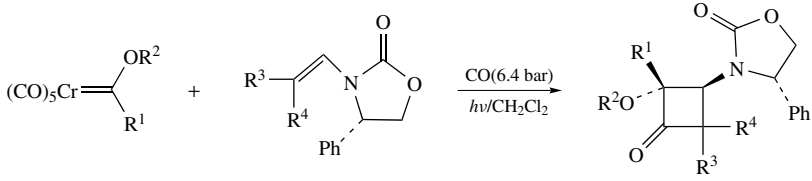
(70)	R^1	R^2	Yield %
a	H	OEt	85
b	H	Ph	30
c	H	NHAc	72
d	H	2-oxopyrolidin-2-yl	70
e	Me	Me	61
f	$-(CH_2)_3-O$		70

SCHEME 47



(71) 86%

SCHEME 48



(72)

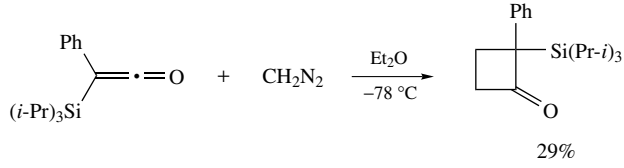
R^1 = Me, Bn
R^2 = Me, Ph, cyclopropyl
$R^1R^2 = -(CH_2)_4-$

$R^3 = R^4$ = H,
$R^3R^4 = -(CH_2)_2-, -(CH_2)_4-$

50–75%, 86–97% *de*

SCHEME 49

due to nonregioselective formation of substituted cyclobutanones as mixtures, although the use of diazomethane addition to substituted ketenes proceeds in a regioselective manner as illustrated below[131]. These homologation reactions generally proceed with the migration of the more substituted carbon.



SCHEME 50

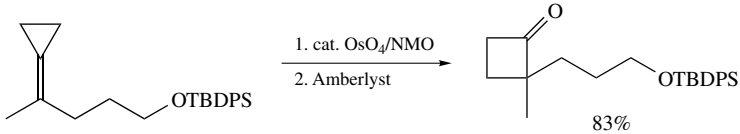
III. RING EXPANSION OF CYCLOPROPYLCARBINYL PRECURSORS

The rearrangement of cyclopropylmethyl to cyclobutyl cation proceeds through a common bicyclobutonium ion. This nonclassical cation intermediate on quenching with nucleophiles gives rise to a number of products with stereochemical scrambling and is not very useful as a method of cyclobutane synthesis. Placement of a donor group at C-1 of the cyclopropane ring enhances the selectivity for cyclobutane formation. The migration usually involves an inversion at the migrating terminus with retention of configuration of the migrating carbon, unless the cyclopropylcarbinyl cation is sufficiently long-lived to permit stereochemical equilibration. The regioselectivity in substituted cyclopropane derivatives is determined by the migration of the more substituted carbon. Substrates which can be used for such reactions include alkylidenecyclopropanes, vinylcyclopropanes, cyclopropylmethanol or any cyclopropylmethyl containing leaving group, cyclopropyl carbonyl derivatives, oxaspiropentanes and even spiropentanes. The synthetic applications of this class of reactions have been extensively reviewed covering the literature up to 1990[132], and only some key strategies for the synthesis of cyclobutanes are included with examples drawn from the more recent literature.

The transformation of alkylidenecyclopropanes to cyclobutanes is generally carried out by oxidation (epoxidation or hydroxylation) of the alkene group followed by a thermal (in the case of the strained oxaspiropentane) or cationic induced rearrangement. In most instances the oxidized intermediate is not isolated. Examples for such rearrangements are seen in the following illustrations (Scheme 51). Many of these substrates are prepared by Wittig reaction of aldehydes and ketones with the commercially available cyclopropyltriphenylphosphonium bromide. It is interesting to note that the epoxidation of allene **73** is chemoselective, giving the necessary oxaspiropentane intermediate for this rearrangement. Here again, the rearrangement is regioselective with migration of the more substituted carbon of the cyclopropane, giving preferentially cyclobutanones **74**[137]. With the availability of methods for enantioselective epoxidations and hydroxylations (e.g. the Sharpless method) such a protocol gives enantiomerically enriched cyclobutanones which are key intermediates in the enantioselective synthesis of natural products[138]. Sharpless epoxidation of alkylidenecyclopropanes **75** and **76** gives the corresponding optically enriched cyclobutanones (Scheme 52)[139, 140]. Enantiomeric excesses of up to 96% can be obtained with some of the products. Other methods which can be used for enantioselective epoxidation followed by ring expansion include Shi's method of oxone oxidation in the presence of fructose derived chiral ketone **78**[141], or Jacobsen's chiral (salen)Mn(III)complex **79** with NaClO[142], the latter being more effective in chiral induction of the ketone produced from **77**, a key intermediate for steroid synthesis[143].

Vinylcyclopropanes having an electron-releasing group at C-1 undergo regiospecific protonation or electrophilic addition to give cyclopropyl carbinyl cationic species, which are transformed to cyclobutanes[132a]. A rather unique reaction involving a tandem rearrangement starting from 1-hydroxy-1-vinylcyclopropanes **80** gives tricyclic cyclobutanones **81** (Scheme 53). This transformation involves the electrophilic addition to the vinyl group of the oxonium ion obtained from protonation of the aldehyde function in **80**[144].

Reference



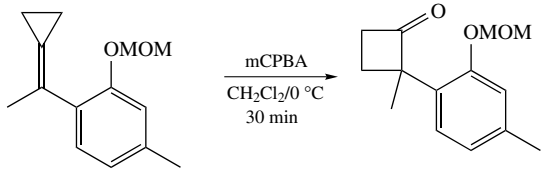
83%

133

NMO = *N*-Methylmorpholine oxide

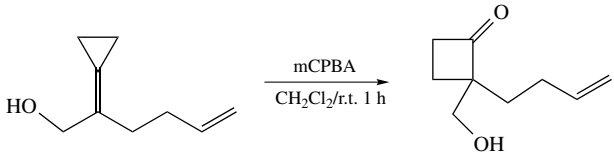
82%

134



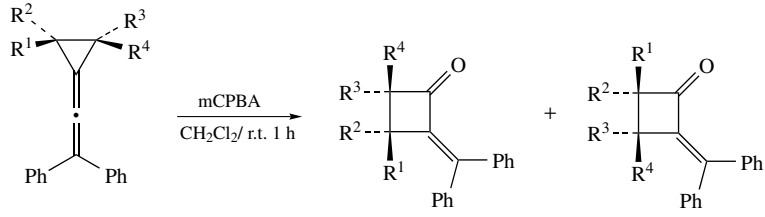
92%

135



52%

136



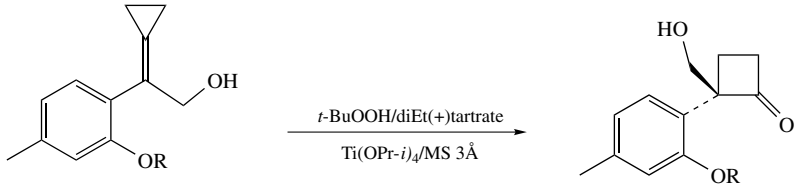
137

(73) **(74)**

R^1 = OEt, $R^2 = R^3 = R^4$ = H
R^1 = Me, R^2 = Ph, $R^3 = R^4$ = H
$R^1 = R^3$ = Me, $R^2 = R^4$ = H

37–72%

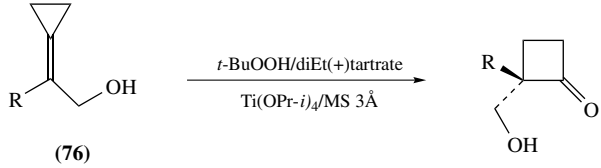
SCHEME 51



(75)

R = MOM, TMS, TBS

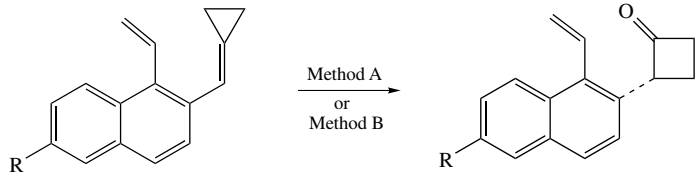
61–98%, 55–99% *ee*



(76)

R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, Toluene

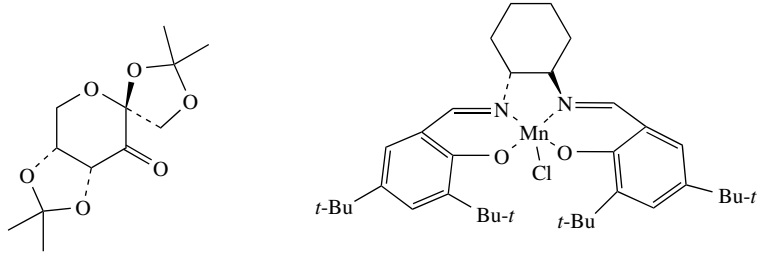
73–96% *ee*



(77)

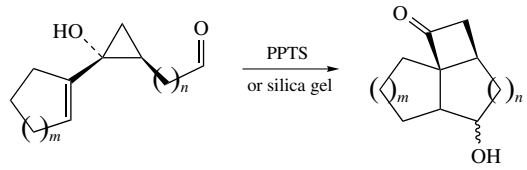
R = H, Me

Method A : Oxone, MeCN, NaOH (pH 9.0), **(78)**, Na(EDTA), 0 °C, 1 h
Method B : 5 mol%**(79)**, NaClO, 4-phenylpyridine N-oxide, CH_2Cl_2, 0 °C, 0.5 h



(78) **(79)**

SCHEME 52



$m = 1, 2$
$n = 1, 2$

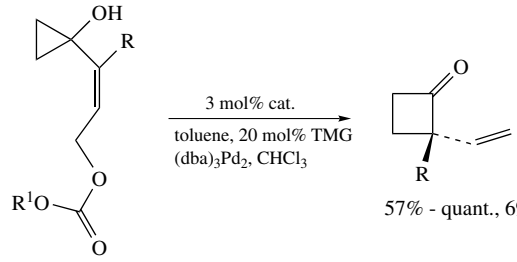
(80)

89–99%

(81)

PPTS = Pyridinium *p*-toluenesulfonate

SCHEME 53

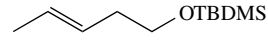


57% - quant., 69–93% *ee*

(82)

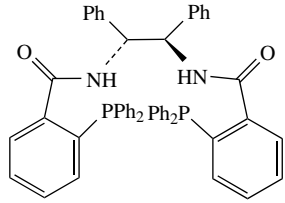
TMG = Thiomethyl *β*–*D*-galactopyranoside

R = Me, *n*-Bu, Ph, $(CH_2)_2Ph$,



$R^1 = CH_3$, CH_2CF_3

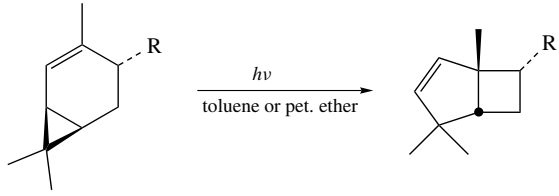
cat:



SCHEME 54

An interesting application of chiral induction to a vinylcyclopropane rearrangement was performed on a series of derivatives **82** in which palladium-catalyzed Wagner–Meerwein rearrangement in the presence of a chiral ligand gave good chiral induction in the vinylcyclobutanones produced (Scheme 54). The role of the metalated chiral ligand is to distinguish between the prochiral faces of the vinyl group in the stereoselective formation

of the metal olefin complex[145]. This reaction is equally effective for the homologous vinylcyclobutanols which give cyclopentanones. A somewhat unusual photochemical rearrangement involving a vinylcyclopropane to give cyclobutanes is seen for the natural product derived carene derivatives **83** (Scheme 55)[146]. These rearrangements likely involve biradical intermediates, since all chirality is lost with respect to ring formation of the bicyclo[3.2.0]heptenes.



(83) 60–91%

R = H, COMe, CH(OH)Me, CH_2O_2CMe, CO_2Me, OH, O_2CMe

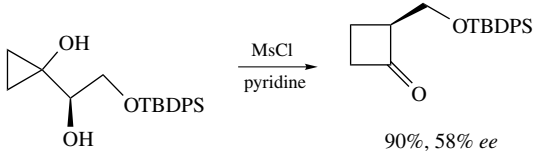
SCHEME 55

Dihydroxylations of alkylidenecyclopropanes give 1-hydroxycyclopropylmethanols from which 2-vinylcyclobutanones can be obtained in short order. This rearrangement can be induced by the use of Lewis or Brönsted acids, or thionyl chloride which involves formation of cyclic sulfites as intermediates. Since asymmetric dihydroxylation methods are known, enantiomeric synthesis of the *vicinal*-diols and their conversion to enantiomerically enriched cyclobutanones has been commonly used in enantioselective total synthesis protocols. The examples in Scheme 56 illustrate this basic strategy. Chiral induction is variable and depends on the reaction conditions and substitution pattern.

Cyclopropylcarbinyl cations with electron-donating groups such as sulfur or nitrogen are especially prone to the ring enlargement reaction due to formation of the corresponding immonium and thionium cyclobutanes. These groups are readily cleaved off under the acid conditions used, giving cyclobutanones.

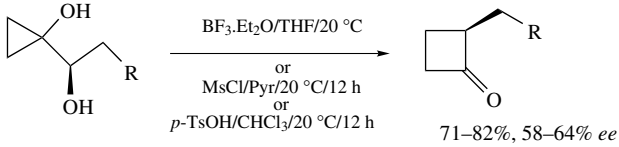
The 1-phenythio group is especially popular since 1-lithiocyclopropyl phenyl sulfide can be readily prepared from commercial cyclopropyl phenyl sulfide by deprotonation with butyllithium. The ease of this reaction is associated with the ability of sulfur to stabilize *geminal* carbanions. Thus, readily available lithiocyclopropyl phenyl sulfide can be used as a cyclopropyl anion for the addition to aldehydes and ketones to produce a variety of cyclopropylmethanols which, in turn, can be rearranged to cyclobutanones or cyclobutenes[132b]. In some cases the thionium cyclobutane intermediates can be trapped by annelation with proximal aryl groups (Scheme 57), lending this an effective method for the construction of benzo-annelated tricyclic compounds[151]. The thiophenyl substituent can be readily removed by standard methods of desulfurization. Similarly, the 1-phenylthiocyclopropylmethanols **84** rearrange in acid, giving the corresponding cyclobutanones in good yields (Scheme 58)[152]. In some cases the intermediate thionium ion is quenched by the tethered alkyne group, giving bicyclic derivatives (Scheme 58)[153]. Quenching of the thionium ion can take place with thiophenol, giving the cyclobutanone thioketal which, upon single desulfurization with copper (II) triflate and diisopropylethyl amine, gives cyclobutenes (Scheme 59)[154].

Ref



147

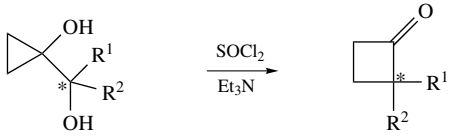
90%, 58% *ee*



148

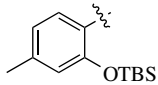
71–82%, 58–64% *ee*

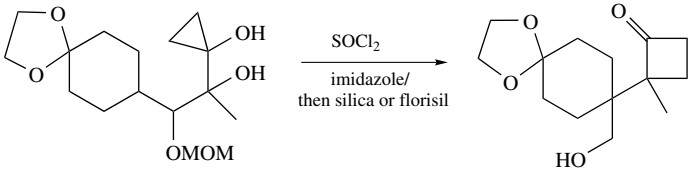
$R = C_7H_{15}, C_8H_{17}$



149

* = chiral

$R^1 = (CH_2)_6CH_3$, $R^2 = H$	91%, 5% *ee*
$R^1 = (CH_2)_7CH_3$, $R^2 = H$	100%, 3% *ee*
R^1 = Ph, $R^2 = H$	94.3%, 29% *ee*
R^1 = Ph, R^2 = Me	85%, 44% *ee*
R^1 =  , $R^2 = H$	96%, 55% *ee*



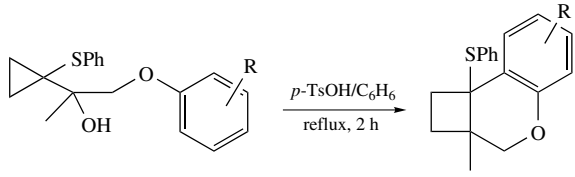
150

(±) (±) 88–91%

SCHEME 56

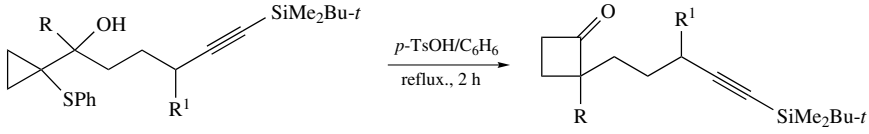
The presence of a nitrogen at C-1 in the form of an imino group in cyclopropylmethyl chloride or cyclopropyl cyanide promotes ring enlargement, as shown by the following examples of reductive dechlorination[155] and hydroboration (Scheme 60)[156].

Whereas oxaspiropentanes are easily transformed to cyclobutanones in acid, the homologous 4-oxaspiro[2.3]hexanes do not follow this pathway. An interesting Lewis acid



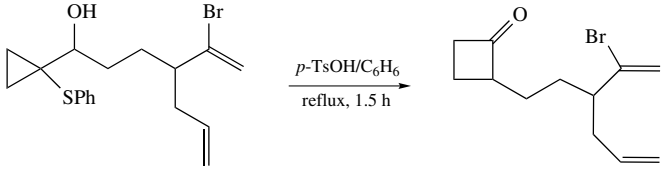
R = H, *p*-MeO, *p*-Me, *p*-Cl 67–80%

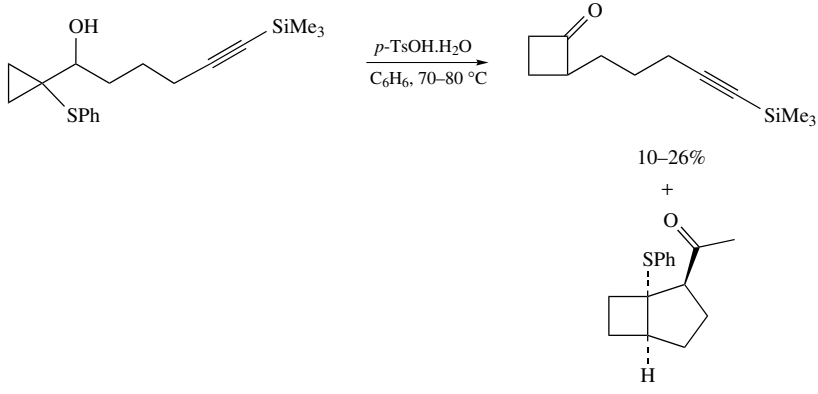
SCHEME 57



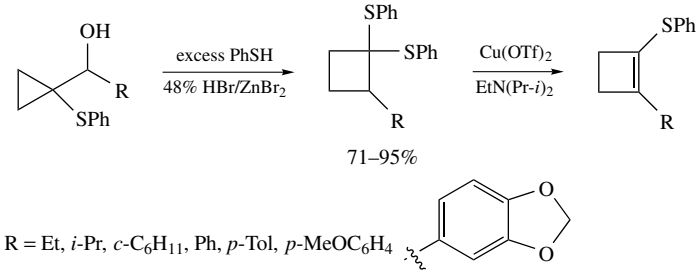
(84) 53–59%

R = H, Me
$R^1 = CH_2CH{=}CH_2$

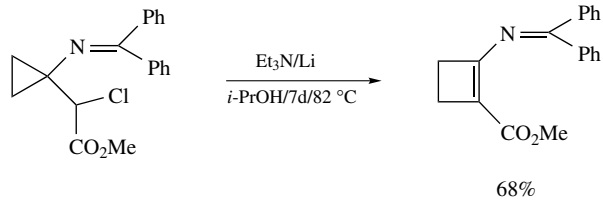


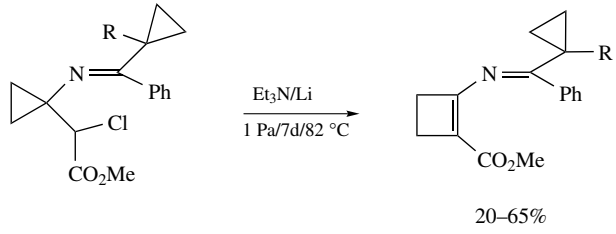


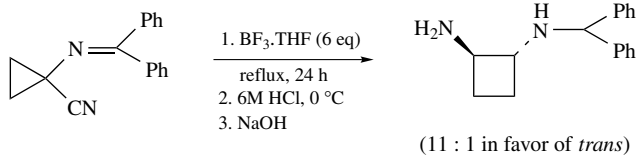
SCHEME 58



SCHEME 59



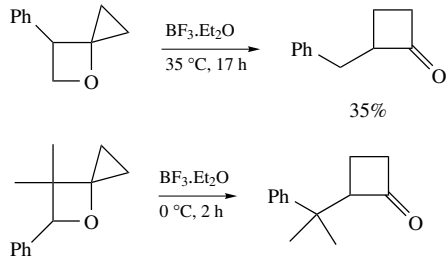




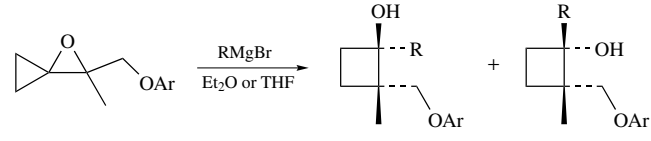
SCHEME 60

catalyzed rearrangement of 4-oxaspiro[2.3]hexanes to cyclobutanones was reported, involving a sequence of tandem migrations of hydride and phenyl groups (Scheme 61)[157].

Although oxaspiropentanes are not usually isolated and directly subjected to the ring expansion reaction under the condition of epoxidation of the alkylidenecyclopropanes, the alkylation of such intermediates frequently results in cyclobutanols (Scheme 62). Mixtures of stereoisomers are often obtained with selectivity reaching 80%, favoring the *Z*-isomer of the cyclobutanol products[158]. These processes are speculated to involve magnesium coordination to the two oxygen sites of the substituted spiropentanes resulting in coordinated cyclobutanone intermediates which are responsible for the observed selectivity.

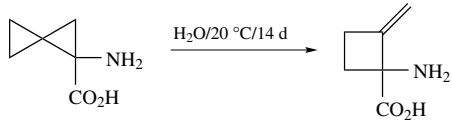


SCHEME 61

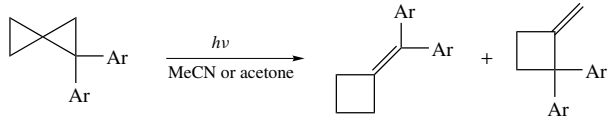


Ar = *p*-$MeOC_6H_4$, Ph R = Ph, *p*-Tol, $CH{=}CH_2$, Me, Bn

SCHEME 62



(85) (quant.)



Ar = C_6H_5	21%	27%
Ar = 4-$MeOC_6H_4$	21%	45%

SCHEME 63

The analogous ring enlargement of the carbocyclic spiropentane would yield methylenecyclobutane. While such thermal rearrangements are known, elevated temperatures are frequently required in the absence of activating groups on the rings[132]. With one or more activating groups such reactions can proceed in high yields, as illustrated by the preparation of an amino acid analog **85** (Scheme 63)[159]. Alternatively, photochemical activation of this rearrangement is possible when UV/visible chromophores are present on the spirocyclic ring system (Scheme 63)[160]. This photochemical process can also be induced by irradiation of the TCNE charge transfer complex, resulting in a different distribution of regioisomers[160].

IV. 1,4-CYCLIZATION OF ACYCLIC SUBSTRATES

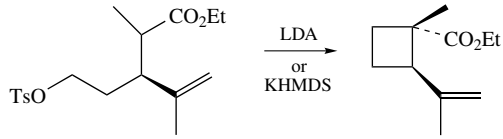
The 1,4-cyclization of acyclic precursors can take place by radical or ionic mechanisms. Such reactions often proceed with stereochemical equilibration of the stereogenic termini, especially in radical processes. Nevertheless, stereoelectronic factors sometimes lead to predictable selectivities. Several strategies have been developed for such ring closure reactions which include dehalogenation of 1,4-dihalobutanes, 1,4-dehydrohalogenations or dehydrotosylations, intramolecular electrophilic or nucleophilic additions to alkenes or alkynes, valence isomerization of 1,3-dienes and other conjugated systems, cyclization in homoallylic cations, radical cyclization by intramolecular addition to alkenes and alkynes, and photocyclization of carbonyl groups possessing a γ-hydrogen (Norrish–Yang photocyclization). These reactions have been extensively reviewed[161] and only recent examples covering the last decade are included.

The anionic intramolecular substitution of carbanions by S_N2 or S_N2' processes continues to be a popular method where such anions can be generated by deprotonation of acidic C–H functions (α-hydrogens to carbonyl, nitrile or aldimine groups[162]), or by metal halogen exchange processes. In order to enhance the C–H acidity, arylsulfonyl groups are attached which can be removed at a later stage[163, 164]. The electrophilic carbon center to which ring closure is enacted is bonded to an effective leaving group or is in the form of a carbonyl, an epoxide or some polarized conjugated enone. If carbons-2 and 3 are stereogenic centers, their stereochemical integrity is maintained during cyclization. Such examples include the dehydrotosylation of ester **86**[165] and the dehydroiodination of lactone **87** (Scheme 64)[166]. Even though planar enolates are intermediates in these processes, diastereoselectivity in both cases is excellent (19:1 in favor of the depicted stereoisomer). Similar diastereomeric selectivity is observed in the dehydrotosylations of **88**[167] and **89**[168], and the dehydroiodination of lactam **90** (Scheme 64)[169]. Other nucleofuge centers for carbanion attack include ketals, orthoesters and epoxides, although the possibility for regioisomers arises with the latter. The cyclization of substituted benzyl nitriles **91** under basic conditions can give cyclobutanes or cyclopentanes, depending on the substitution pattern about the epoxide (Scheme 65). Preferential nucleophilic attack takes place on the less substituted carbon of the epoxide and, where the degree of substitution is the same for the two sites, cyclopentanes are preferentially formed[170]. However, where the terminal epoxide is doubly substituted, attack at the less hindered carbon takes place giving cyclobutanes (Scheme 65)[171]. For epoxides derived from γ,δ-alkenes, nucleophilic cyclization to give cyclobutanes is preferred over cyclopropane formation[164].

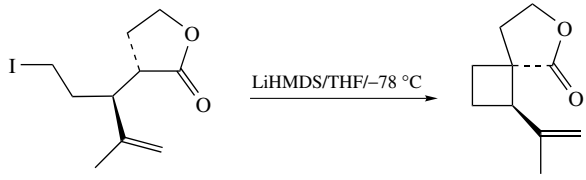
Ring closure usually involves an inversion of stereochemistry at the epoxide carbon. An 'umpolung' example of the 1,4-cyclization is seen for halogenated ketals and orthoesters (Scheme 66). Metal halogen exchange converts an electrophilic carbon site to a nucleophilic center and is a convenient method for generating carbanions where deprotonation is not possible. These ketals and orthoesters are sufficiently electrophilic for attack by carbanions[172]. The 'umpolung' of an electrophilic acyl group can be accomplished by conversion to a cyanohydrin acetal as in the case of aldehyde **92**. Deprotonation of the original aldehyde hydrogen with concomitant intramolecular nucleophilic substitution gives rise to a cyclobutane (Scheme 67)[173].

Fluoride ion desilylation of alkylsilanes represents an effective method for carbanion production and such functional groups can be used for the preparation of cyclobutanes by intramolecular S_N2 reactions or additions[174]. The fluoride ion source normally used is tetrabutylammonium fluoride (TBAF), which is soluble in most organic solvents. Examples of allyl silane precursors to an allylic carbanions are shown in Scheme 68[175].

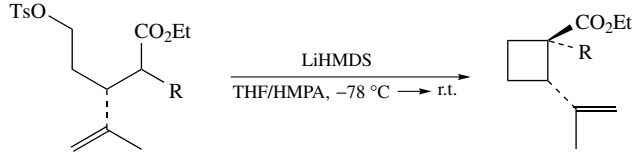
The use of acyl silanes as a carbanion source was exploited by the intervention of the Brook rearrangement. Thus, silylketoester **93** when subjected to alkylation proceeds to



(86) 85% (19 : 1 *de*)

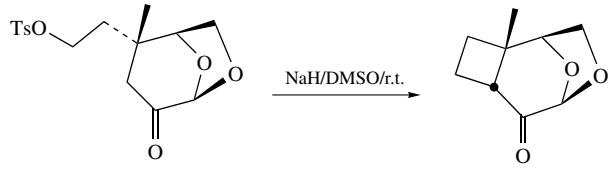


(87)

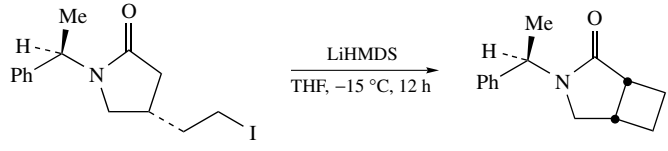


(88) 46–70%

R = $(CH_2)_3C(Me)=CH_2$

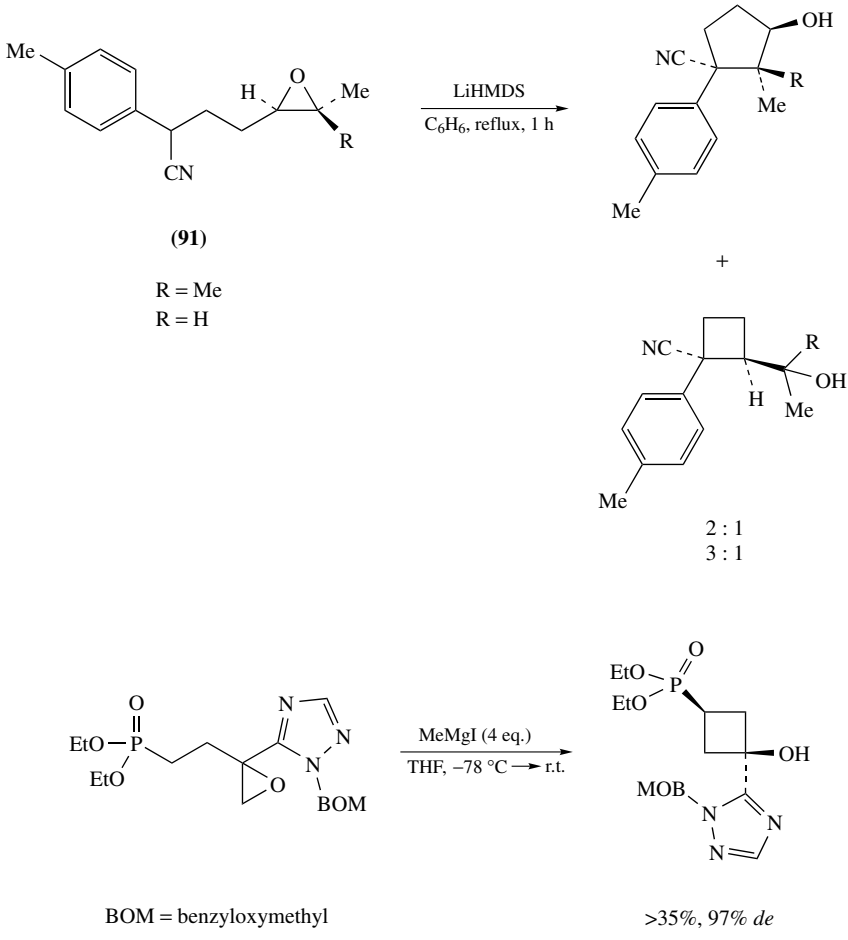


(89) 80%



(90)

SCHEME 64



(91)

R = Me
R = H

2 : 1
3 : 1

BOM = benzyloxymethyl

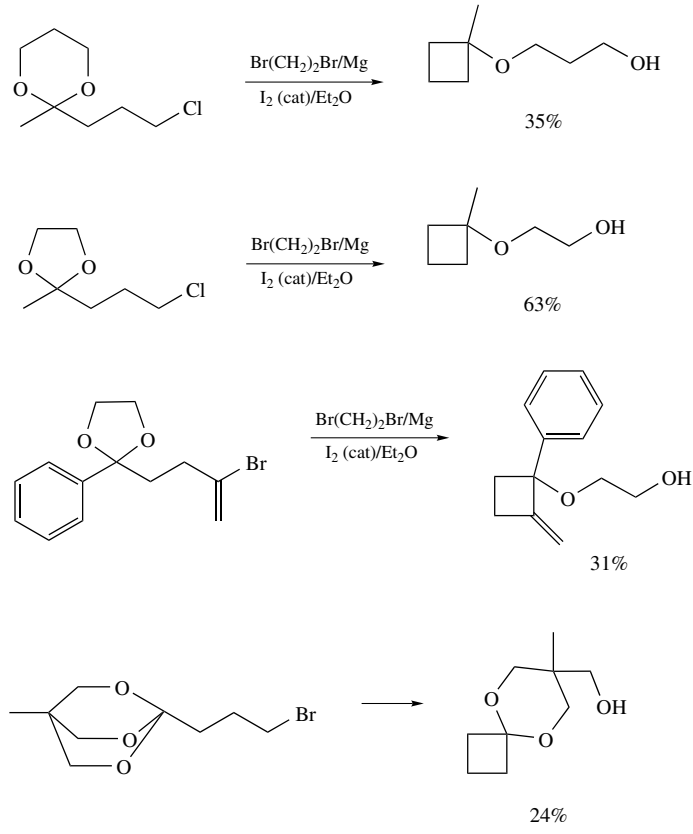
>35%, 97% *de*

SCHEME 65

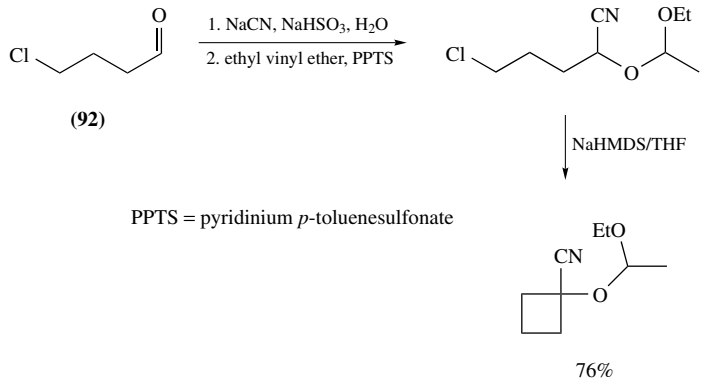
give an α-siloxycarbanion which ring closes by intramolecular Michael addition (Scheme 69)[176].

Desilylation can also take place by an electrophilic mechanism involving stabilized β-silyl carbocations, as seen from the acid-induced intramolecular cyclization of the silylated enal **94** (Scheme 70)[177].

Vinyl anions can be generated by a number of methods involving metal halogen exchange of halovinyl groups. One of the more facile generation methods of a metalvinyl functional group and its intramolecular addition to ketones uses Mori's stannylation method with stannylsilanes in the presence of fluoride ion[178]. This method has been effectively applied to the construction of four-membered rings, as is illustrated by the conversion of bromovinyl ketones **95** to methylenecyclobutanols.[179] Other vinyl stannanes undergo conjugate addition to alkynic esters mediated by copper(I) (Scheme 71)[180].

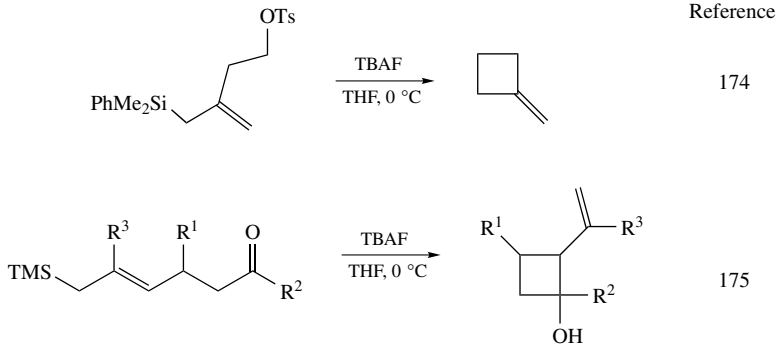


SCHEME 66

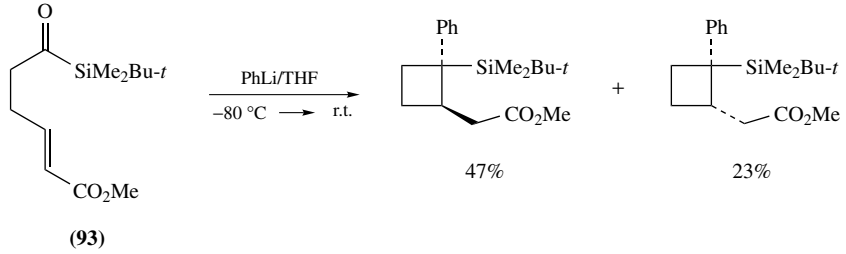


(92)

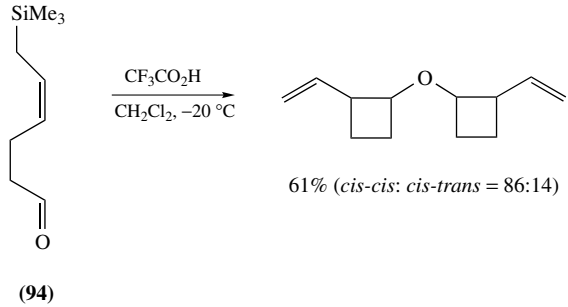
SCHEME 67



SCHEME 68

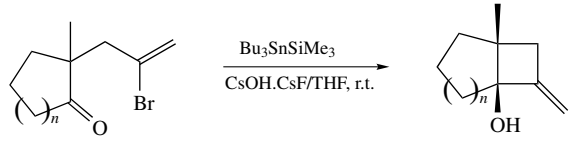


SCHEME 69



SCHEME 70

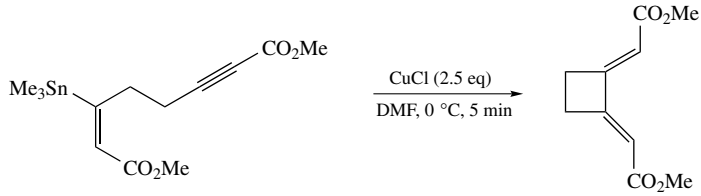
A general protocol involving alkyne/epoxide condensations, equivalent to a [2 + 2] cycloaddition, is applicable to the syntheses of cyclobutenes. The method involves the stannylcupration of an alkyne to give an alkyne dianion equivalent, which undergoes addition to epoxides. The vinylstannane alcohols are then tosylated and subjected to cyclization with butyl lithium (Scheme 72)[181].



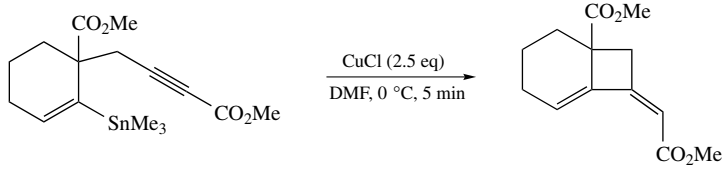
$n = 1,2$

(95)

42–47%

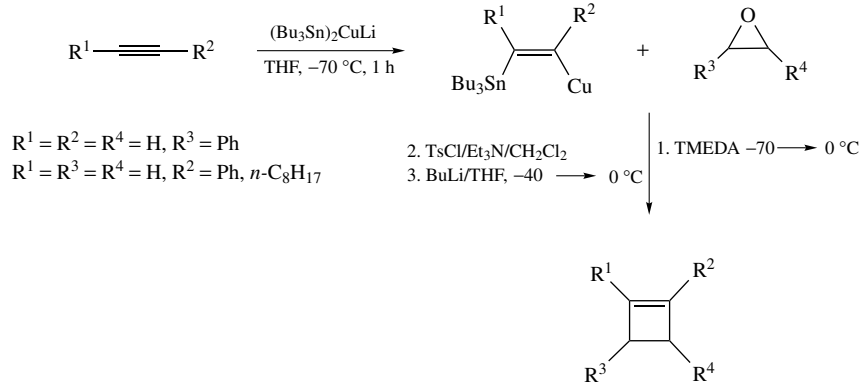


95%



94%

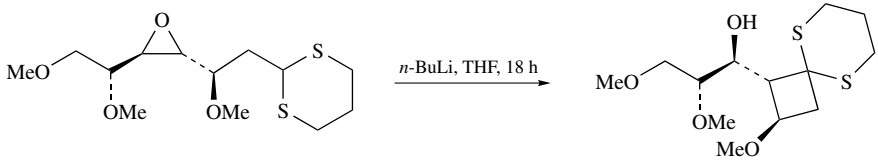
SCHEME 71



67–82%

SCHEME 72

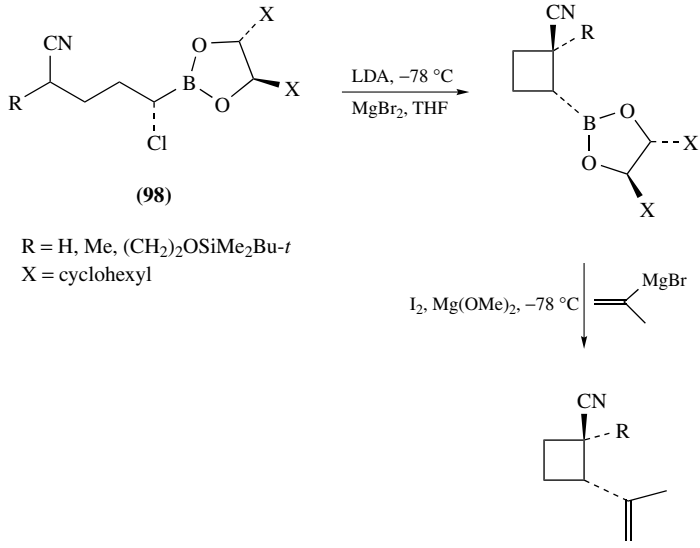
Although 1,4-cyclization by intramolecular nucleophilic substitution or addition is not usually the method of choice for the synthesis of chiral cyclobutanes due to stereochemical equilibration of the anion terminal, a number of such reactions have been effectively employed in the preparation of enantiomerically enriched cyclobutanes. This is especially true of substrates with a chiral sp^3-carbon center serving as the nucleofuge site and where inversion of stereochemistry is always observed in ring closure. For example, the sugar-derived dithianyl epoxide **96** is readily deprotonated and cyclizes to the chiral cyclobutane **97** in 34% yield with complete inversion of stereochemistry at the migrating terminus (Scheme 73)[182].



(96) **(97)** 34%

SCHEME 73

A similar inversion of stereochemistry is observed in the intramolecular cyclization of the chiral cyanoborinates **98** (Scheme 74). The resulting cyclobutanes are obtained with high diastereoselectivity and alkylated with retention of configuration[183].



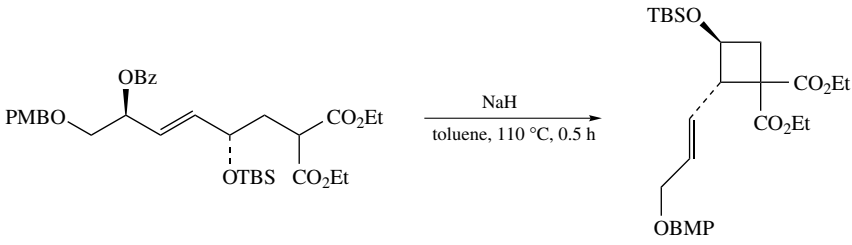
(98)

R = H, Me, $(CH_2)_2OSiMe_2Bu$-*t*
X = cyclohexyl

SCHEME 74

Inversion of stereochemistry also occurs in the intramolecular S_N2' reaction of the malonate ester **99**. It is interesting to note that *syn* ring closure (relative stereochemistry of the

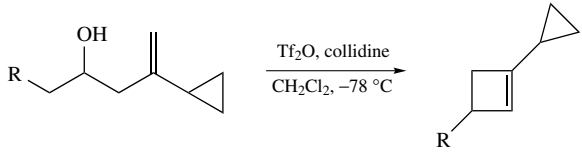
newly formed bond is the same as that for the carbon leaving group bond) is the exclusive process in the formation of enantiomerically pure cyclobutane **100** (Scheme 75)[184].



(99) **(100)**

SCHEME 75

The electrophilic pathway involving cyclization of homoallylic cations is not of general application since the bicyclobutonium ion intermediate can lead to several products, including those derived from the cyclopropylcarbinyl and cyclobutyl cations. Substituents such as cyclopropyl which stabilize cyclobutyl cations are effective in this ring closure reaction, as illustrated in Scheme 76[185, 186]. The cyclobutyl cations can be quenched with water or methanol to give cyclobutanols and cyclobutylmethyl ethers, or in the absence of nucleophilic solvents give cyclobutenes by deprotonation.



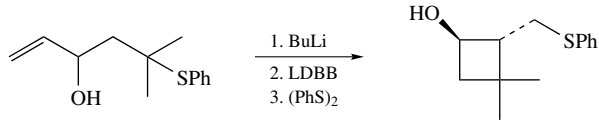
58–76%

R = $Ph(CH_2)_2$, *n*-C_8H_{17}, $MeO_2C(CH_2)_8$, $AcO(CH_2)_9$

SCHEME 76

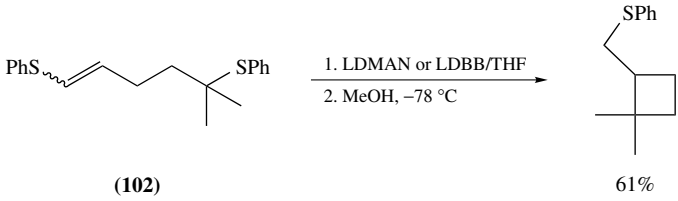
The intramolecular cyclization to terminal alkynes, allenes and alkenes has gained popularity in the preparation of cyclobutanes. A number of methods have been recently developed in this regard. The reductive lithiation and cyclization of acyclic δ-alkenylthioethers, such as **101** and **102**, produces cyclobutanes with excellent stereoselectivity, such as in the case of **101** (Scheme 77)[187, 188]. The intermediate cyclobutylmethyllithiated species can be quenched with a variety of electrophiles.

These reductive lithiations take place by the use of radical anion reagents such as lithium 4,4′-di-*t*-butylbiphenylide (LDBB) and lithium 1-(dimethylamino)naphthalenide (LDMAN). The sulfur substituent at the terminal alkene in **102** serves as an anion stabilizing group. The phenyl group can also delocalize negative charge, as is the case in the reductive alkylation and cyclization of oxazolines **103** and **104** (Scheme 78)[189]. The cyclobutanes are produced with excellent diastereoselectivity.

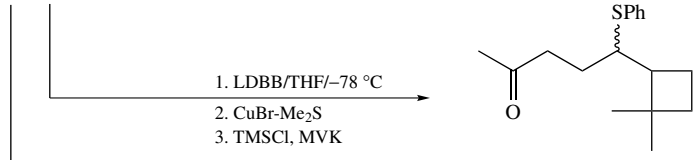


(101) 67%

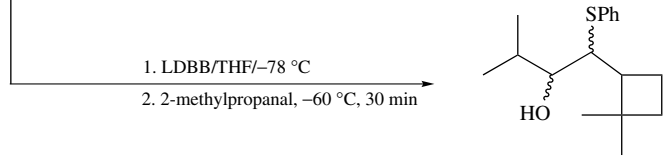
LDBB = Lithium 4,4′-di-*t*-butylbiphenylide



(102) 61%



67%



LDMAN = Lithium 1-(dimethylamino)naphthalenide

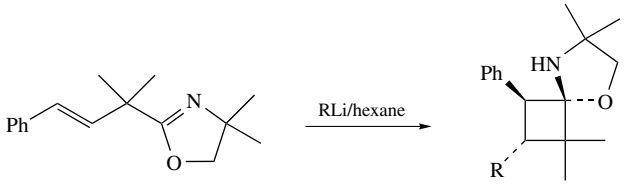
69%

SCHEME 77

Similar reductive alkylation of terminal phenyl alkynes give benzylidenecyclobutanes as depicted in the examples in Scheme 79[190–192]. The 4-*exo-dig*-cyclization takes place as seen from the predominantly *Z*-stereochemistry of the product obtained from alkyne **105**[191].

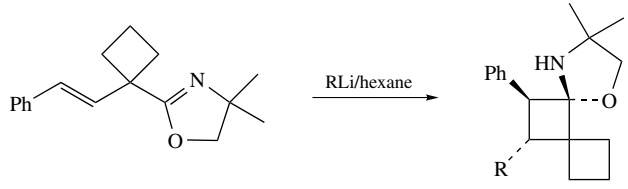
The anionic 1,4-cyclization of an alkyne by an S_N2' reaction was reported to give an allene (Scheme 80)[193].

The carbanion cyclization to a terminal allene by an allowed 4-*exo-dig* process can give both cyclobutenes and alkylidenecyclobutanes, depending upon the nature of the quenching electrophile. The 3,4-pentadien-1-yl lithium derivatives obtained from lithium iodide exchange give cyclized lithiated cyclobutenes and methylenecyclobutanes which are quenched by electrophiles, giving the corresponding products **106a** and **106b**, respectively[194]. The alkylation takes place at the central carbon of the terminal allene (Scheme 81).



(103) 37–90%

R = *n*-Bu, *t*-Bu, Me, Ph



(104) 55–63%

R = *n*-Bu, *t*-Bu

SCHEME 78

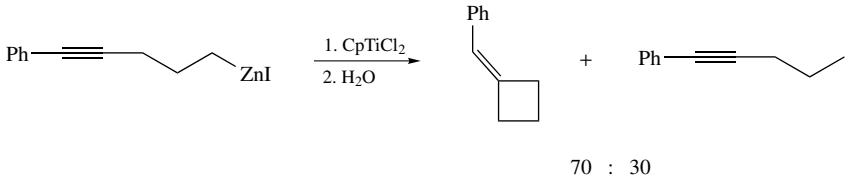
On the other hand, the malonate substituted allene **107** proceeds by palladium assisted alkylation of the proximal allene carbon (Heck reaction) (Scheme 82)[195].

Metal complexation of a terminal multiple C−C bond can activate such functional groups towards alkylation and be an effective route for 1,4-cyclizations. Titanium forms π-complexes with alkenes and alkynes. The ketal diene **108** forms a titanium π-allyl complex by reductive metallation which undergoes electrophilic cyclization[196]. The titanium complex of alkynyl butyl ketone **109** gives a cyclobutane by intramolecular addition to the carbonyl function (Scheme 83)[197].

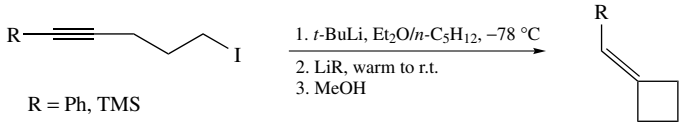
A rather interesting palladium-catalyzed cyclization of terminal diynes appears to have general synthetic application. The palladium-catalyzed borylstannylative carbocyclization of diyne **110** gives the 1,2-bisalkylidenecyclobutane, which can be further structurally elaborated (Scheme 84)[198].

Radical cyclization methods can be used for the preparation of cyclobutanes. Pent-1-en-5-yl radicals cyclize by the favorable 4-*exo-trig* route to give cyclobutylcarbinyl radicals[199]. These reactions are limited by unwanted side reactions associated with carbon radical chemistry. Nevertheless, a number of such reactions are used for the construction of the cyclobutane ring. Samarium diiodide is especially popular as a one-electron reducing agent and has been extensively used in reduction of carbonyl-containing compounds for the production of ketyl radicals which will cyclize with proximal alkene or other unsaturated functional groups. Examples of cyclizations mediated by samarium diiodide are depicted in Scheme 85.

The cyclization of γ,δ-unsaturated aldehydes produces up to three contiguous stereocenters with excellent stereocontrol. Evidence for the intervention of carbanions comes from deuterium incorporation in the product when methanol-O-*d* is used, suggesting a two-electron reduction mechanism[203]. Samarium reduction of carbonyl groups produces

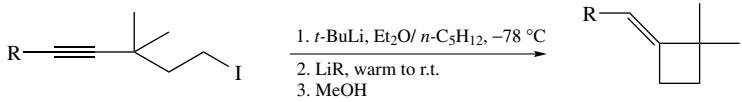


70 : 30



R = Ph, TMS

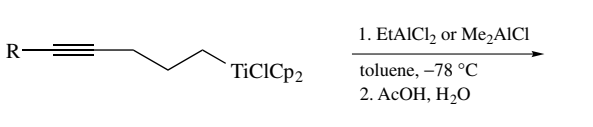
89–93%



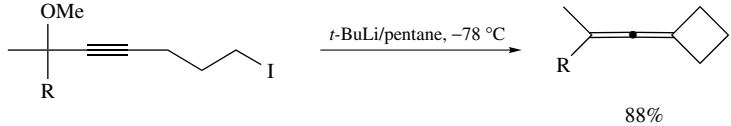
(105)

R = Ph, TMS

86–93%



SCHEME 79



88%

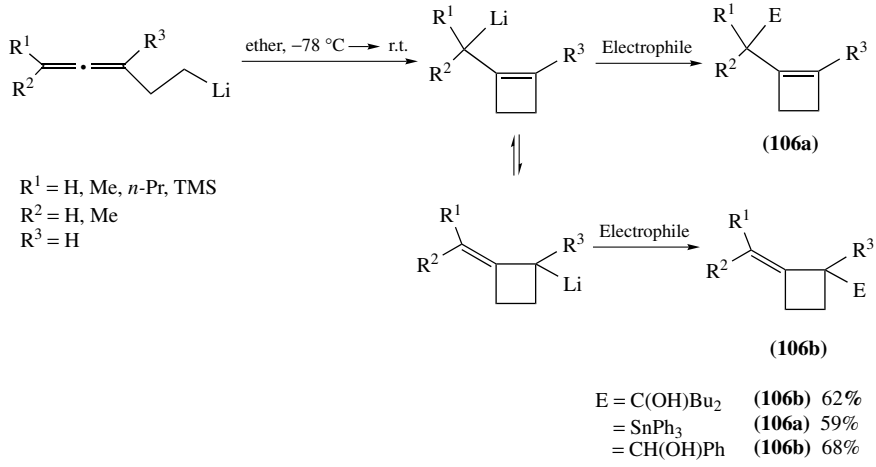
R = Ph, MeCH(Me)CH_2

SCHEME 80

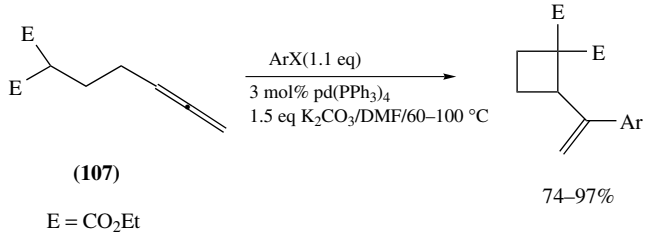
ketyl radicals which can result in 1,4-coupling with 1,4-diketones[204]. This reaction is highly selective, producing exclusively *Z*-cyclobutanediols (Scheme 86).

Tandem formation of bicyclic rings from acyclic precursors can be induced by samarium diodide reductions. The double cyclization of esters **111** and **112** occurs by nucleophilic acyl substitution followed by ketyl ring closure to the unsaturated bond (Scheme 87)[205].

A rather intriguing transformation from a mechanistic perspective involves a tandem three-step process of nucleophilic acyl substitution, cyclobutanone ketyl reaction with



SCHEME 81



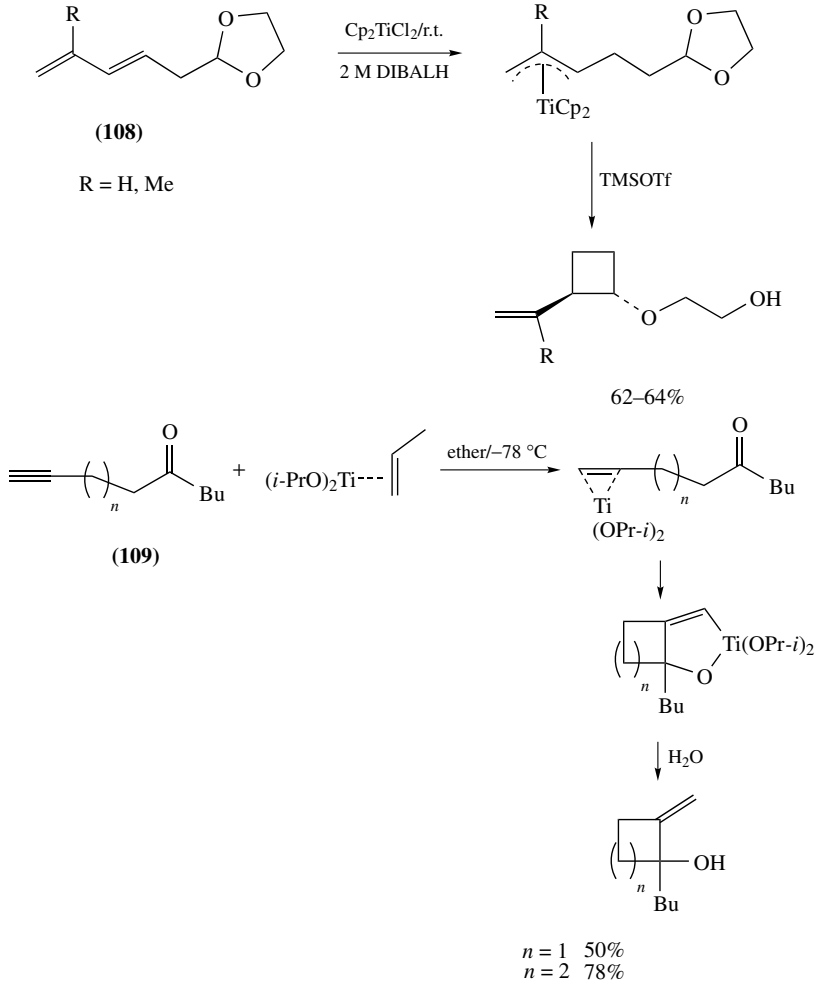
SCHEME 82

formation of a bicyclic intermediate, and termination by a β-elimination (alkenyl transfer for the last two steps) giving highly substituted cyclobutanols in a stereoselective manner (Scheme 88)[206].

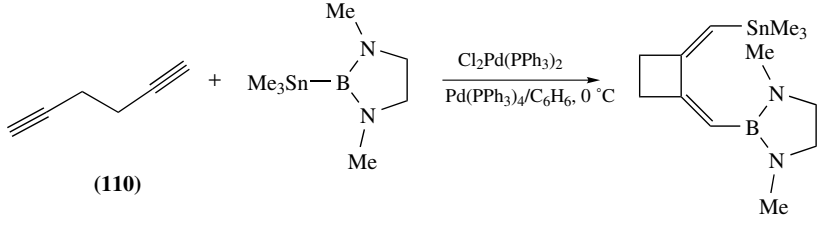
Pent-1-en-5-yl radicals can also be obtained from tributyltin/AIBN dehalogenations of 5-pent-1-enyl halides. The limitation of this process is the competitive reductive dehalogenation which accompanies the cyclization. As is illustrated in Scheme 89, the extent of cyclization of these radicals depends on the radical substitution pattern, with the more stabilized radicals favoring cyclization[207]. Conformational effects also affect this competition, as is observed in ketals **113**.

1,4-Cyclization involving acyl substitution of δ-iodoesters by samarium diiodide under mild conditions has been reported to give a cyclobutanone (Scheme 90)[208].

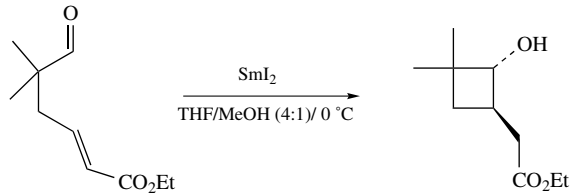
The reductive 1,4-coupling (Wurtz and acyloin reactions) of 1,4-dihalobutanes and 1,4-dicarbonyl compounds by reducing metals to form cyclobutanes is occasionally used but gives variable results, depending on the nature of the reducing metal. An effective method for 1,4-dehalogenations is the use of aromatic radical anions readily available by reduction with alkali metals (Scheme 91). Lithium naphthalenide prepared from lithium metal with naphthalene is effective in 1,4-dehalogenations under mild conditions[209]. The



SCHEME 83

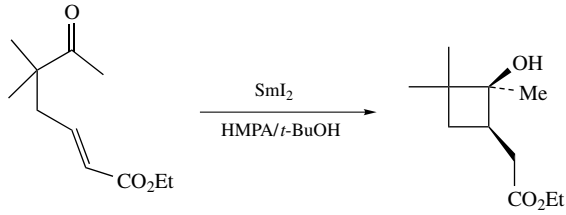


SCHEME 84



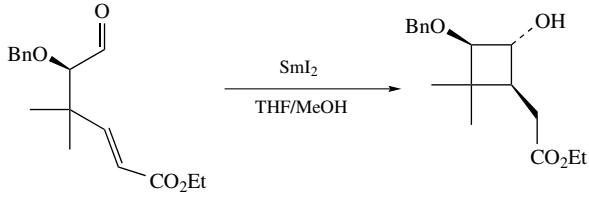
Reference 200

65%



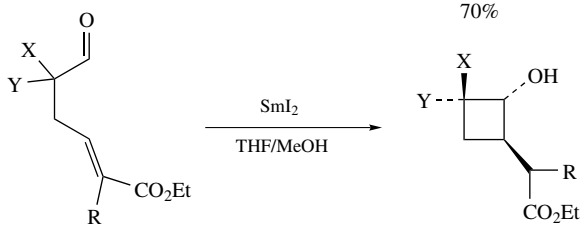
200

22%



201

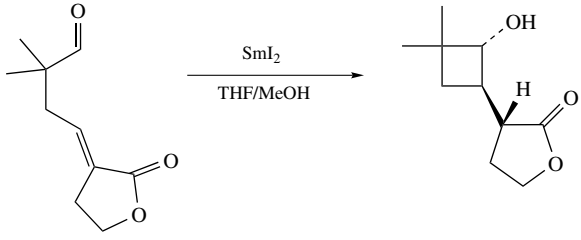
70%



201

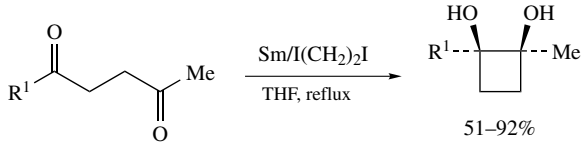
X = Me, OBn
Y = H, Me
R = H, Me

65%

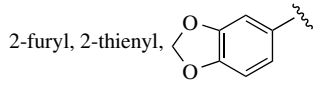


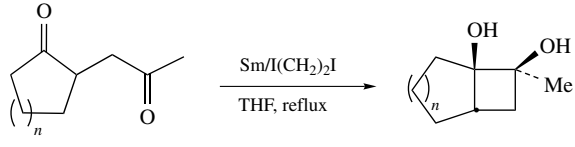
202

SCHEME 85



R^1 = Me, *n*-Pr, *n*-Hex, *i*-Pr, cyclohexyl, Bn, *i*-Bu, Ph, *p*-anisyl, *p*-ClC_6H_4,

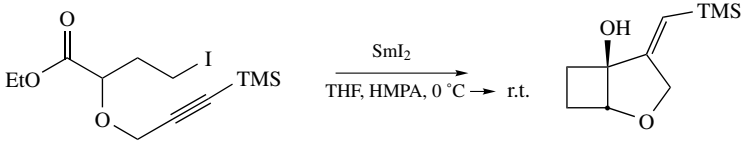




n = 1, 2, 3

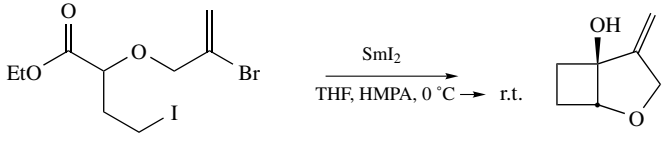
30–93%

SCHEME 86



(111)

55%



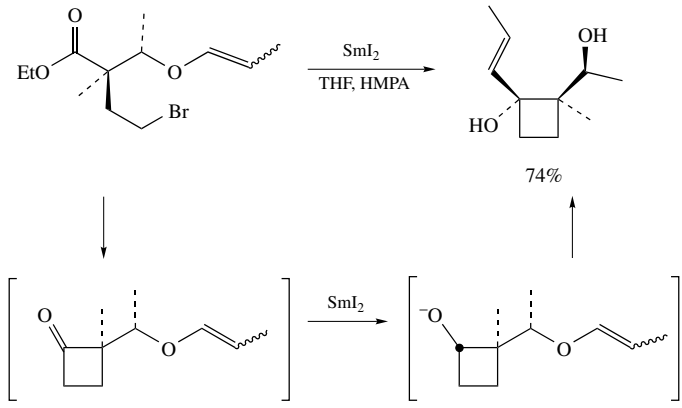
(112)

69%

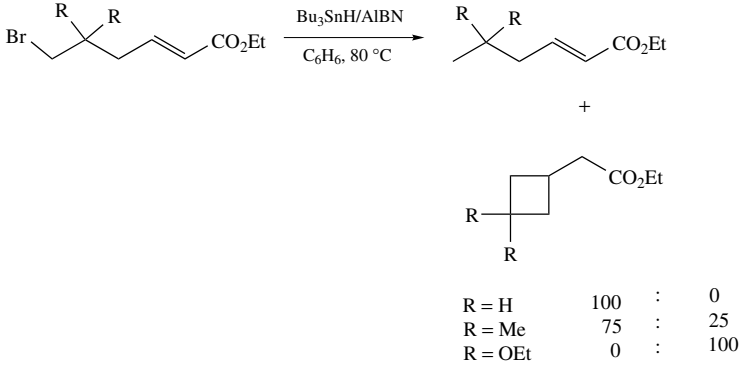
SCHEME 87

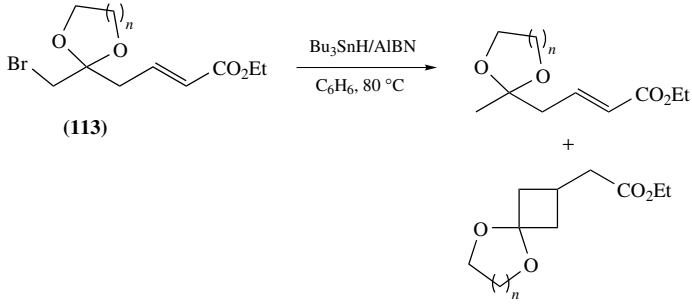
acyloin reaction of succinate esters remains popular for the preparation of cyclobutenes and cyclobutanones[210]. Although 1,2-bis(trimethylsiloxy)cyclobutene (**114**) is commercially available, its preparation from dimethyl succinate is more economical. The acid-catalyzed alcohol addition to **114** is a general route to 2-alkoxycyclobutanones (Scheme 91).

The photolysis of carbonyl compounds substituted by a γ-hydrogen gives cyclobutanes (Norrish–Yang photocyclization) by one of two principal decomposition pathways (Scheme 92). A 1,4-biradical is formed which can proceed to cyclobutanol or revert to starting material. Since radicals have trigonal planar geometries and the reaction is reversible, stereoisomeric mixtures are formed with relatively low quantum yields.

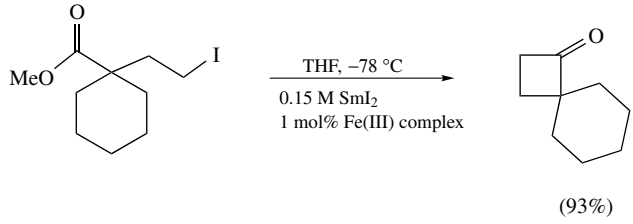


SCHEME 88



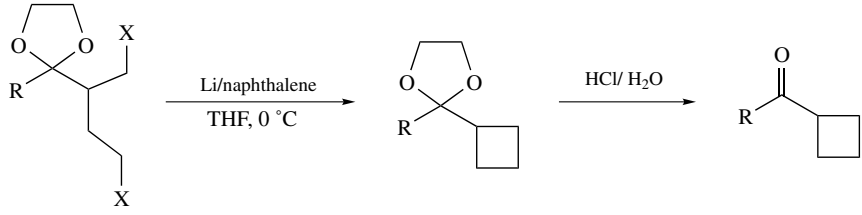


SCHEME 89

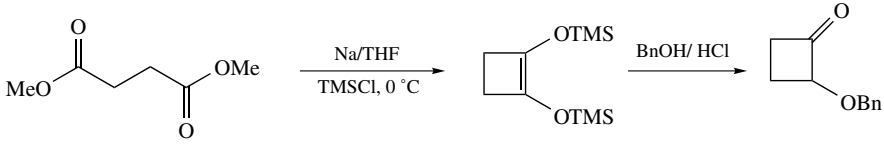


(93%)

SCHEME 90



R = Me, Et
X = I, Br



(114) 60% 61%

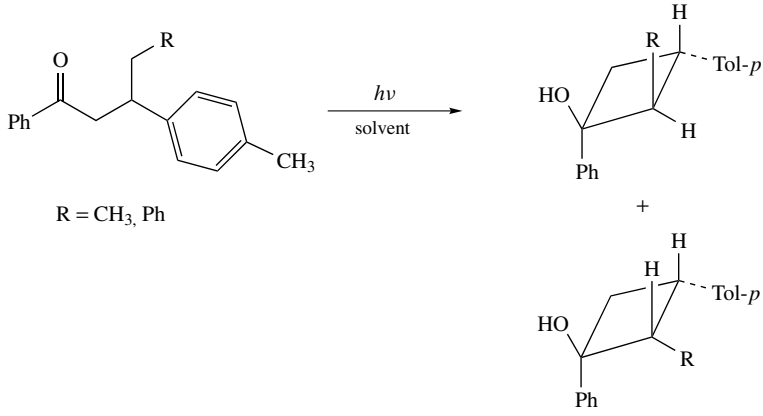
SCHEME 91

Stereoselectivity often depends on solvent effects which impinge on lifetimes and conformations of these biradicals[211].

The Norrish–Yang photocyclization method is not effective in chiral induction when a chiral γ-carbon is present. Any chirality information of their progenitors is lost in the biradical intermediates. The only instances for formation of chiral cyclobutanols are when the chiral centers are contained at the α- and β-carbons of the ketone. Exceptions are found when photolysis of these ketones takes place in rigid matrices, such as their crystalline matrix[3].

V. CYCLOBUTANES FROM C_3 AND C_1 BUILDING BLOCKS

One of the earliest reports of a cyclobutane synthesis was the condensation of diethyl malonate with 1,3-dibromopropane, and this method of [3 + 1] annelation continues to be used to some extent. Typically, the three-carbon unit has electrophilic centers located at C-1 and C-3, and the one-carbon unit represents a dianion equivalent, usually an acidic methylene group which becomes *geminally*-dialkylated. The 'umpoled' process involving the three-carbon unit as the donor with the one-carbon unit as the acceptor is not



R = CH_3, Ph

Solvent		Yield%
Cyclohexane	80 : 20	40
Benzene	82 : 18	31
MeOH	57 : 43	40
DMSO-d_6	52 : 48	35

SCHEME 92

common except for one notable exception. In one of the more useful preparations of parent cyclobutanone, a 1,3-bis(bromomagnesio)propane, prepared from 1,3-dibromopropane, is condensed with carbon dioxide[212]. The most common one-carbon unit used in these annelations is malonate ester. Advantages include the ease of sequential deprotonation of malonates under relatively mild conditions, as well as the ready decarboxylation of the resulting cyclobutane *gem*-dicarboxylates. Recent examples of diethyl malonate condensations with 1,3-dihalopropanes are shown in Scheme 93.

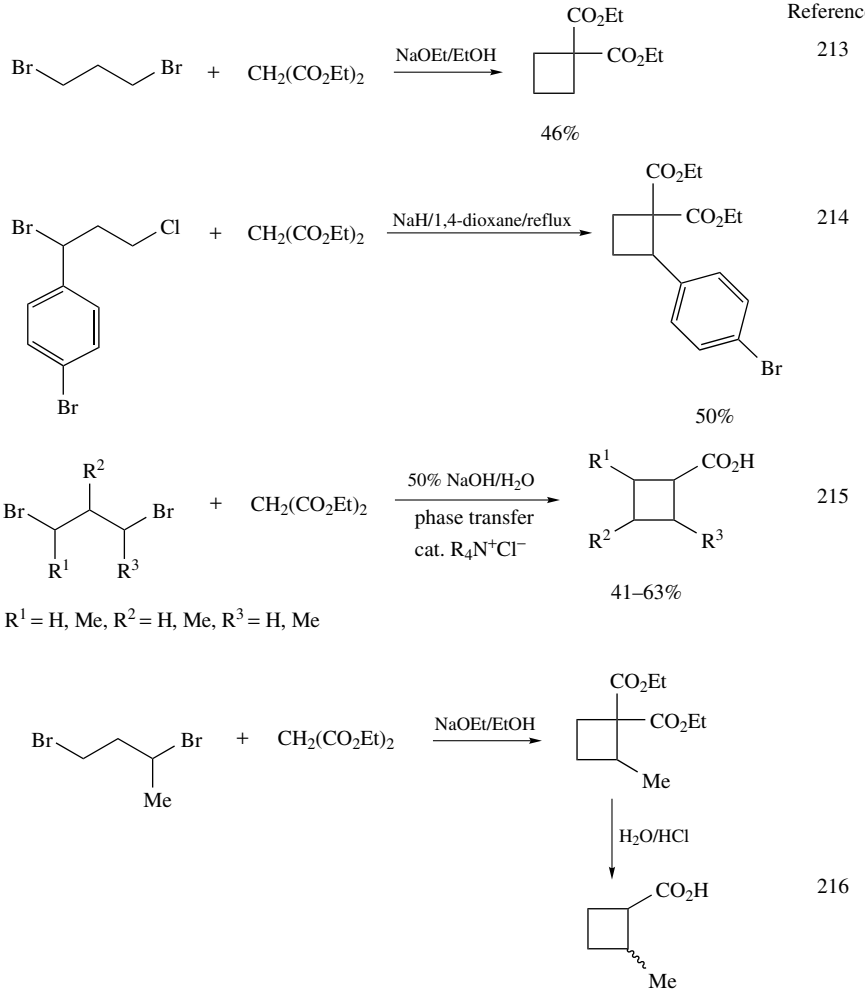
The use of a phase transfer catalyst is required when such reactions are carried out in aqueous phase[215]. Other one-carbon dianion equivalents include α-phosphonoacetates, sulfonylacetates, methanediphosphonates, arylmethyl cyanides and cyanomethanesulfones, examples of which are illustrated in Scheme 94.

Where a methylene group in the one-carbon unit is substituted by a single activating group, stronger bases are required for the deprotonation. The toluenesulfonylpropane **115** can be deprotonated to the dilithiodianion with *n*-butyllithium. Addition of 1,3-diiodopropane gives the sulfonylcyclobutane. The use of the sulfonyl substituent allows for ready dehydrosulfonylation (Scheme 95)[224].

Other three-carbon substrates used in this methodology include 1,3-diols, 1-bromo-3-hydroxypropane, epichlorohydrin and other epoxides. The construction of a cyclobutane from 1,3-diols can be effected by Mitsunobu-type condensations as shown in the examples in Scheme 96.

The advantage of using this type of annelation is the avoidance of strong bases which can be deleterious to other sensitive functional groups and cause unwanted stereoequilibration.

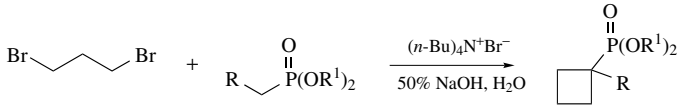
The use of a Wittig reagent as a one-carbon unit in the construction of cyclobutanes by this method was reported with epichlorohydrin as the three-carbon unit. Thus, reaction



SCHEME 93

of triphenylphosphonium methylide with epichlorohydrin under strong basic conditions produces a secondary cyclobutylidene Wittig agent, which can condense with aldehydes and ketones to give 3-alkylidenecyclobutanols (Scheme 97)[228].

A rather interesting method for cyclobutane synthesis involves the carbonylation of titanacyclobutanes with carbon monoxide at medium pressures[229]. The control of pressure is important in that the intermediate titanacyclopentanone can be carbonylated at high pressures of CO to give cyclopentanes. The titanacyclobutanes are readily prepared by reductive allylation of Cp_2TiCl and need not be isolated prior to the carbonylation (Scheme 98).

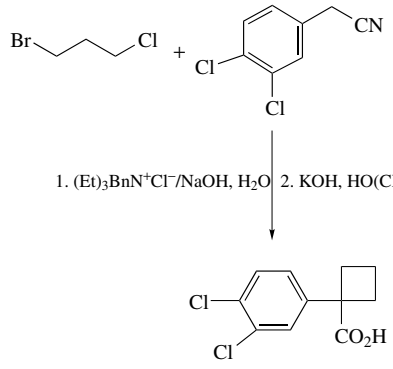


Reference

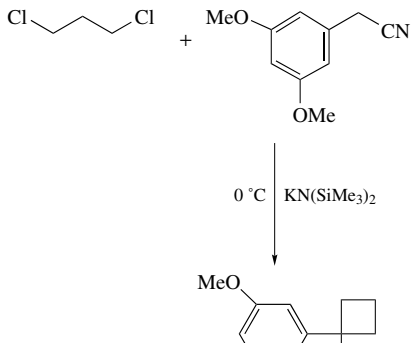
217

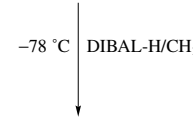
$R = CO_2$ Bu-*t*, P(O) OEt_2
R^1 = Et

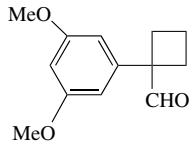
37–42%



218



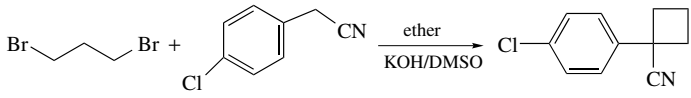




219

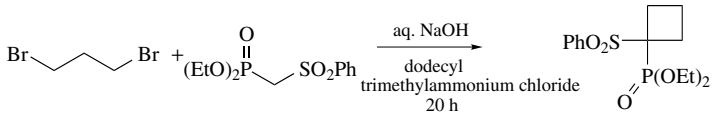
SCHEME 94

Reference

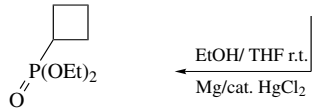


220

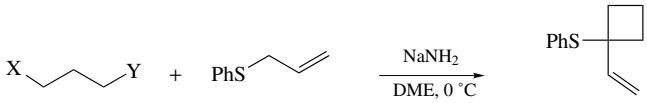
74%



96%

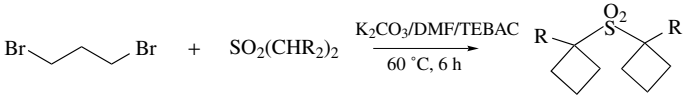


221



222

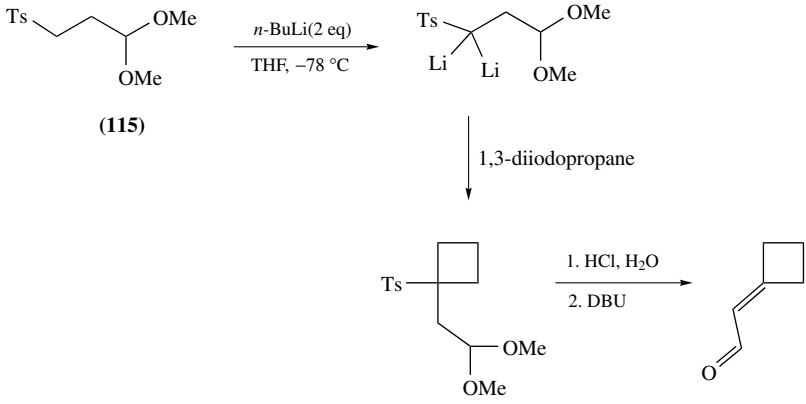
X = Y = Br 40%
X = Br, Y = Cl 55%



223

R = CN 60%
R = C(O)Ph 52%

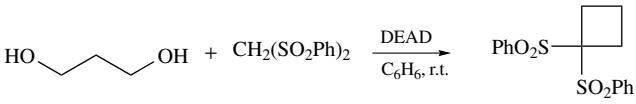
SCHEME 94. (*continued*)



(115)

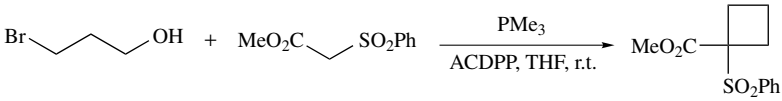
SCHEME 95

Reference



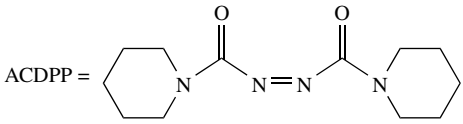
225

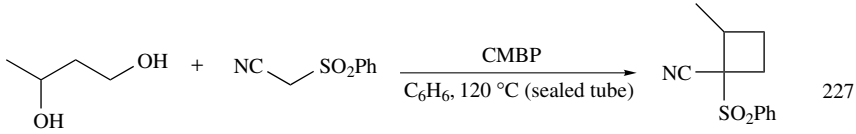
86%



226

55%



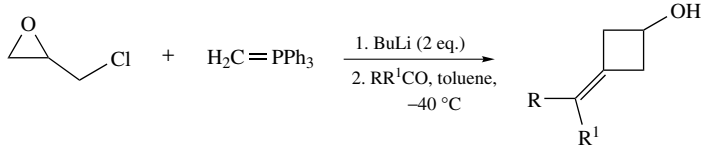


227

99%

CMBP = Cyanomethylenetributylphosphorane

SCHEME 96



RR^1CO = benzaldehyde, 4-Cl-benzaldehyde, propanal, hexanal, cyclohexanone

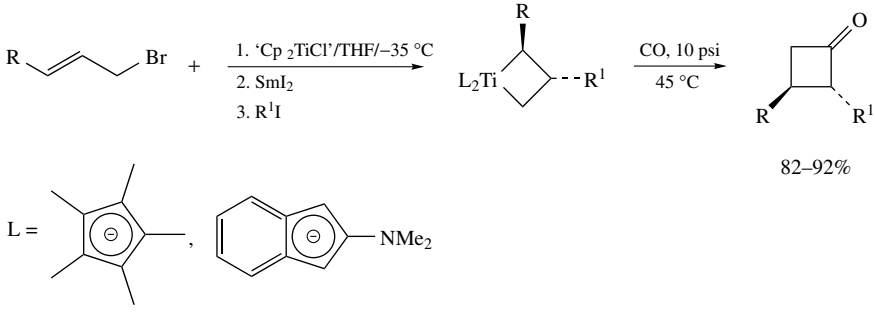
27–70%

SCHEME 97

In a related study the insertion of isocyanides to the titanacyclobutane produces cyclobutyl imines. It would appear that this is not a general reaction and depends on the nature of the isocyanide and titanacyclobutane substituents (Scheme 99)[230].

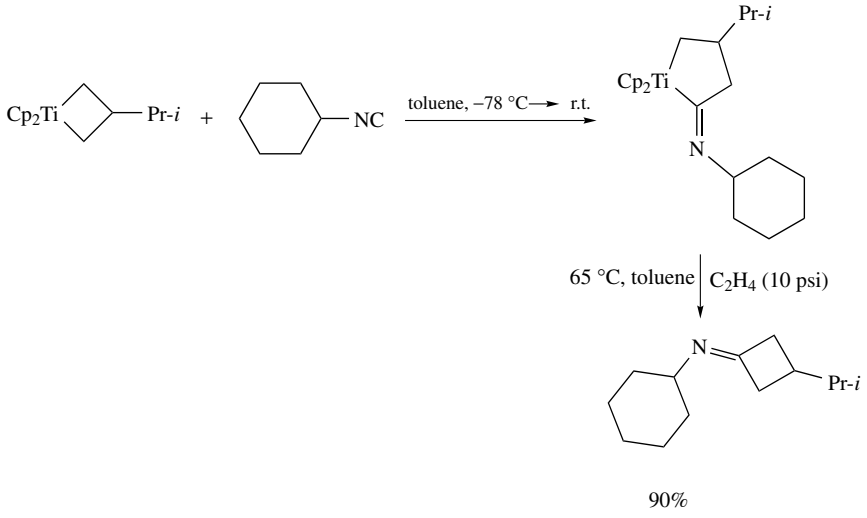
VI. OTHER METHODS

The ring contraction of five-membered and larger rings to cyclobutanes has been reviewed[231]. These methods include Wolff rearrangement of α-diazocyclopentanones, Favorskii rearrangement of α-halocyclopentanones, photodecarbonylation of cyclopentanones, and other rearrangements associated with carbenes, carbocations and radicals. With a few exceptions such as those used in the preparation of cubanes[232], none of these methods has



R = Ph, Me
R^1 = *i*-Pr, Bn

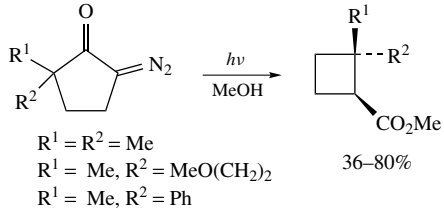
SCHEME 98



SCHEME 99

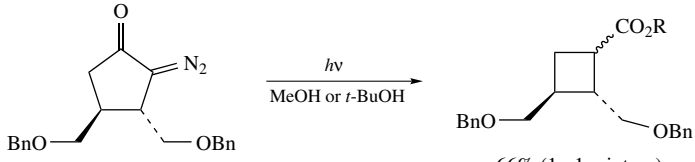
found wide application in synthesis with the majority of those giving other byproducts. The Wolff rearrangement of α-diazocyclopentanones has been shown to have some synthetic value in the preparation of cyclobutanes. These derivatives can be prepared from the corresponding ketones by standard methods and, when subjected to UV radiation in alcohol solvents, give cyclobutylcarboxylates in respectable yields as illustrated in the examples given in Scheme 100[233, 234].

The extrusion of a heteroatom from a five-membered heterocycle has found some useful synthetic application to cyclobutane synthesis. The thermal decomposition of 1,1-tetramethylene diazenes produces 1,4-biradicals which can ring close to cyclobutanes.



$R^1 = R^2 = Me$
$R^1 = Me, R^2 = MeO(CH_2)_2$
$R^1 = Me, R^2 = Ph$

36–80%



66% (1 : 1 mixture)

R = Me, *t*-Bu

SCHEME 100

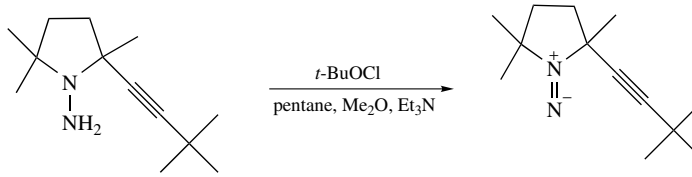
The reaction is somewhat limited in that the diazenes are not very stable and are usually formed as intermediates from oxidation of hydrazines or dehydrotosylation of tosyl hydrazines. Once formed, nitrogen extrusion can be effected thermally at elevated temperatures (>90 °C) or, more preferably, by low temperature photolysis[235, 236]. The similarity in product distribution from the nitrogen extrusion of **116** with that obtained from the thermal cycloaddition of 1,1-dimethylallene with styrene suggests a common 1,4-biradical intervening in the two processes (Scheme 101)[236].

An interesting and somewhat unusual oxygen extrusion from sugar-derived 4-vinylfuranose has been described. Such transformations give highly functionalized cyclobutanes in a stereoselective fashion. The method uses a zirconocene equivalent prepared from Cp_2ZrCl_2 and butyl lithium, and involves an intermediate zirconacycle which is conformationally restricted and accounts for the selectivity in these transformations (Scheme 102)[237–240].

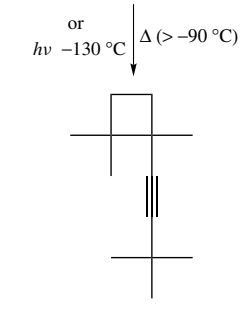
This method has also been used for the deoxygenation of pyranose derivatives in the preparation of highly functionalized cyclopentanes[237].

VII. SUMMARY

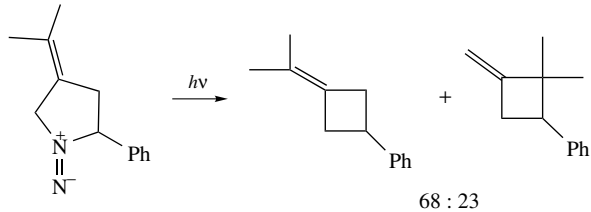
With the appreciation of the synthetic value of cyclobutane intermediates, the past forty years has seen the development of an arsenal of methods for their preparation. While each of the methods has limitations as to choice of substrates, limits of regio- and stereoselectivity and competitive byproduct formation, the [2 + 2] cycloaddition method remains one of the most popular in terms of simplicity of reaction and availability of starting materials. The thermal ketene (or ketene equivalent)/alkene (or alkyne) cycloadditions are especially useful in terms of predictability of regio- and stereoselectivity. With the development of new ketene equivalents, alkenes and alkynes, which are unreactive to regular ketene cycloadditions, can be made to react in this manner. Also, with the development of newer methods for the preparation of cyclopropanes and the chemodirection of their ring expansion, this method has gained popularity in cyclobutane synthesis. A variety



(116)

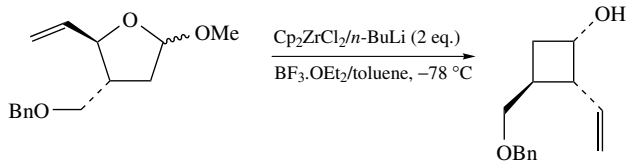


81%

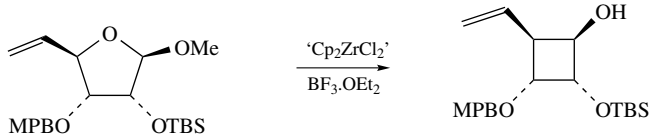


68 : 23

SCHEME 101



64%



65%

SCHEME 102

of natural products have been prepared by this route[241]. Some of the classical methods of 1,4-cyclization of acyclic precursors, and condensation of three- and one-carbon units have been advanced with milder conditions and stereochemical control. Many of these methods have been extended towards the preparation of chiral cyclobutanes[3] which serve as useful intermediates in the enantioselective synthesis of chiral natural products and materials of biological interest. The use of natural products such as sugar derivatives, chiral terpenes or steroids, as substrates in the preparation of cyclobutanes, has extended the scope of cyclobutane utility in organic synthesis.

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CHAPTER 9

The application of cyclobutane derivatives in organic synthesis

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I. INTRODUCTION

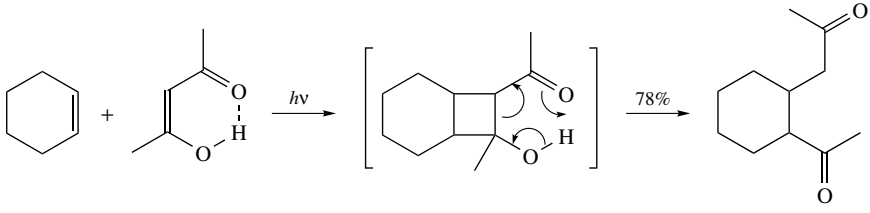
The construction of highly complex molecules in a regioselective and stereoselective manner remains a great challenge to synthetic organic chemists. In this connection, novel regio- and stereoselective synthetic transformations are still urgently required. Among these, the opening of small-ring systems, especially cyclobutane derivatives, to form more complex molecules is no doubt one of the most noteworthy[1,2]. The spectacular employment of cyclobutane derivatives has been very popular during the last several decades due mainly to two reasons. First, numerous methods are available for the regioselective as well as the stereoselective syntheses of extensively substituted four-membered ring carbocycles that are normally stable at room temperature so they can be handled conveniently in laboratories. Second, cleavage of cyclobutane rings is extremely facile due primarily to their inherent strain.

In 1986, we published an overview[3] on cyclobutane chemistry, focusing mainly on ring-opening reactions. Emergence of many useful new methods after the appearance of this article prompted us to summarize all the more encouraging achievements from 1985 up to the present. The contents of this account will still be organized as those of our previous review[3] according to a variety of routes for ring fission reactions in the presence of acids and bases, nucleophiles and electrophiles. Thermal, oxidative and reductive ring openings will also be presented. There are by all means an enormous number of articles in this area during this period of coverage but we do not intend to write a thorough account. We would like to attempt to screen the materials carefully and only those representative research works which could demonstrate the synthetic value of cyclobutane derivatives will be chosen and reviewed.

II. RING OPENING BY ACIDS, BASES, ELECTROPHILES OR NUCLEOPHILES

A. Retro-aldol Reaction (de Mayo Reaction) and Fragmentation

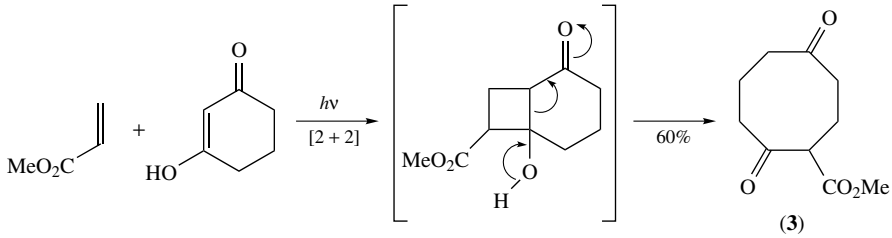
In 1963, de Mayo and Takeshita found that the process of photocycloaddition could be used to synthesize 1,5-diketones. A typical example reveals that the addition of acetylacetone to cyclohexene under irradiation gave diketone **2**[4]. This process should go through intermediate **1** following a retro-aldol reaction that is well known also as the de Mayo reaction. The inherent strain of the four-membered ring serves as the major driving force of this reaction.



(1) **(2)**

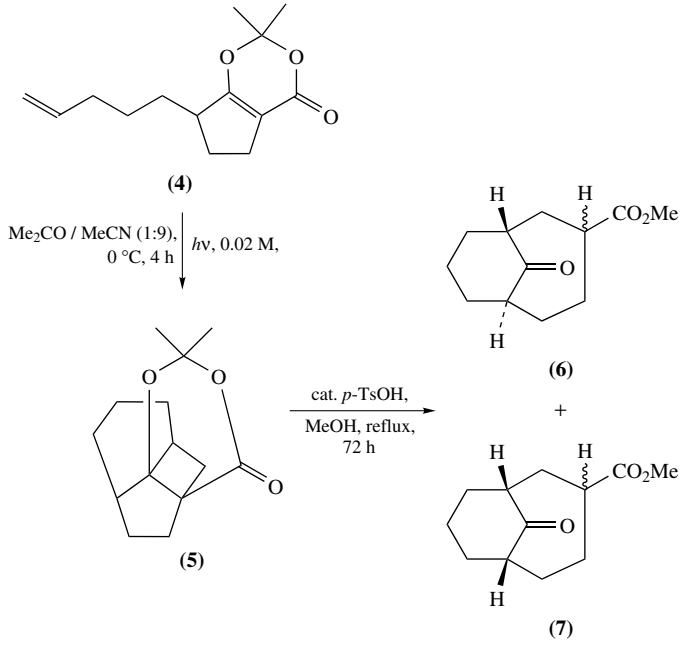
Because of its practical simplicity, this sequence has been utilized to realize 1,5-dicarbonyl compounds, including even a number of systems with seven- or eight-membered rings such as **3**[5].

The reaction mechanism and stereochemistry of the de Mayo reaction has already been comprehensively reviewed[6]. The scope of applications and variations has also been expanded during the last two decades. Some examples after 1985 will be discussed below.



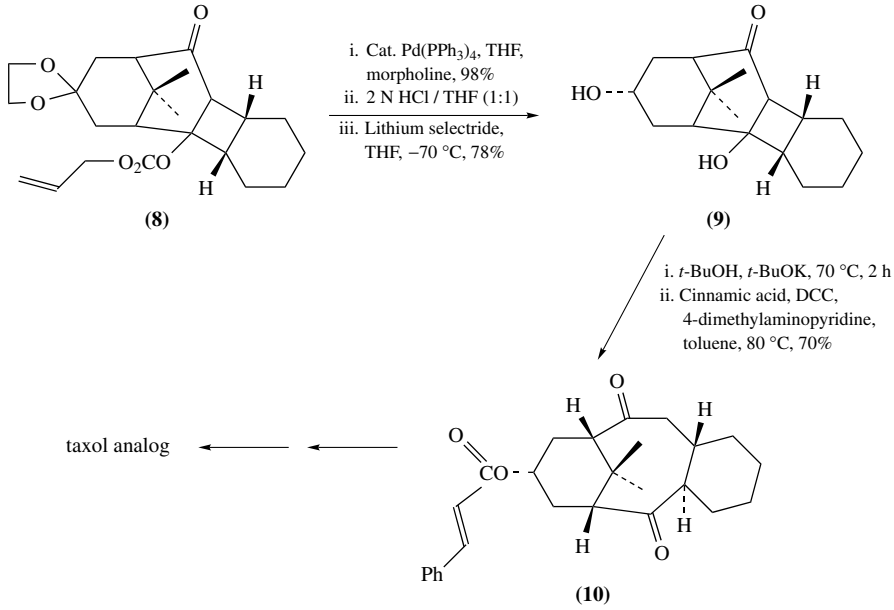
(**3**)

Irradiation of 0.02 M **4** in acetone/acetonitrile (1:9) at 0 °C for 4 h resulted in the formation of two diastereomeric photoadducts **5**, which, upon fragmentation catalyzed by 0.1 equivalent *p*-TsOH in MeOH under refluxing for 72 h, led to a 1:5 epimeric mixture of ketoesters **6** and **7** in 65% overall yield[7]. This method has been used in the synthesis of the carbocyclic skeletons of ingenane diterpenes, which contain the remarkable inside–outside intrabridgehead stereochemistry[8,9].



In the total synthesis of taxol analog containing an eight-membered ring skeleton, this synthetic strategy was also employed[10]. Thus, deprotection of ester **8** gave cyclobutanol **9**, which underwent retro-aldol reaction to afford ketone **10**.

Intramolecular photoaddition of 0.05 M **11a** in acetonitrile/acetone (9:1) with a 450 W Hanovia lamp for 30 min led to the formation of **12a** in 75% yield. On the other hand, reaction of **11b** under an identical condition led to photoadduct **12b** in 45% yield. Fragmentation of **12a** with 2 N KOH in MeOH at 25 °C led to the formation of **13a** as the only diastereomer. However, under the same condition, fragmentation of **12b** gave a mixture of **13b** and **14** with the ratio of 1:1[11].

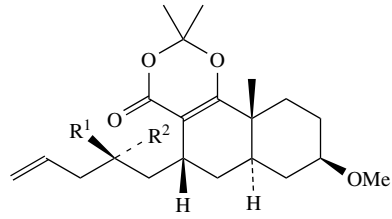


Irradiation of *O*-vinyl ethers **15a–c** in 10% Me_2CO/MeCN at room temperature with an Ace-Hanovia 450 W Hg medium-pressure UV lamp yielded the [2 + 2]-photoadducts **16a–c** and **17a–c** (50–70%) as *ca* 3:1 mixtures of diastereomers, which stereospecifically afforded tetrahydrofuran-3-ones **18a–c** (79–90%) and **19a–c** (79–84%) upon fragmentation in alkaline MeOH (K_2CO_3) at 0 °C. Similarly, the *O*-allyl homologs underwent [2 + 2]-cycloadditions to give cyclobutyl ring systems in 66–77% yields as mixtures of diastereomers. By treatment with alkaline MeOH (K_2CO_3) at 0–23 °C, these diastereomeric mixtures furnished diastereomeric mixtures of substituted tetrahydropyran-4-ones (65–81%)[12].

Irradiation of **20** and **21** in ethyl acetate under a 400 W high-pressure Hg lamp through a Pyrex glass filter for 7 h resulted in the formation of isomeric [2 + 2]-photocycloadducts, which directly rearranged to **22** and **23** in 77% and 2% yields, respectively, by treatment with aqueous Na_2CO_3[13].

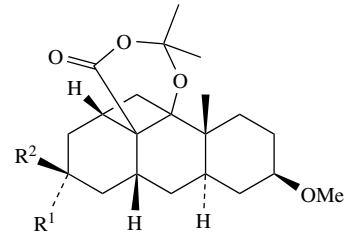
[2 + 2]-photocycloaddition of the enol silyl ether **24** to 2-cyclopentenone gave tricyclic trimethylsilyloxy carboxylate **25** in 35% yield. Methylation and reduction converted **25** to γ-lactone **26**. While stirring with 0.75 M solution of *n*-Bu_4NF under 0 °C, γ-lactone **26** underwent an intramolecular de Mayo reaction to give the desired product **27** in 97% yield, which was the key intermediate in the total synthesis of the (±)-asteriscanolide (**28**)[14].

Piva and coworkers reported a two-step photochemical process which allows an easy access to polycyclic compounds from oxoacids[15]. After irradiation in CH_2Cl_2 for a few hours, the expected [2 + 2]-cycloadducts **31** were afforded in quantitative yields from oxoacids **29** and cycloalkene **30**. In the presence of a small amount of acridine, cyclobutanecarboxylic acids **31** were decarboxylated by oxygen under irradiation to form presumably a cyclobutane hydroperoxide intermediate **32**. After stirring with Me_2S in



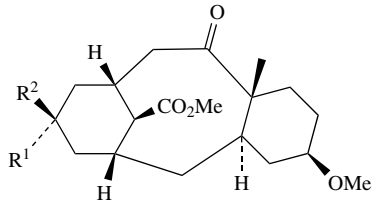
(11a) R^1 = OH; R^2 = H
(11b) R^1 = H; R^2 = OH

MeCN / Me_2CO (9:1), *hν*, 30 min



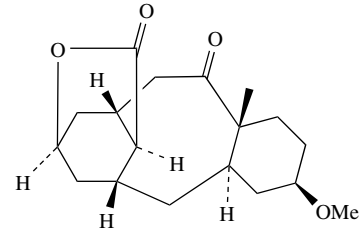
(12a) R^1 = OH; R^2 = H (75%)
(12b) R^1 = H; R^2 = OH (45%)

i. KOH, MeOH
ii. CH_2N_2



(13a) R^1 = OH; R^2 = H (82%)
(13b) R^1 = H; R^2 = OH (30%)

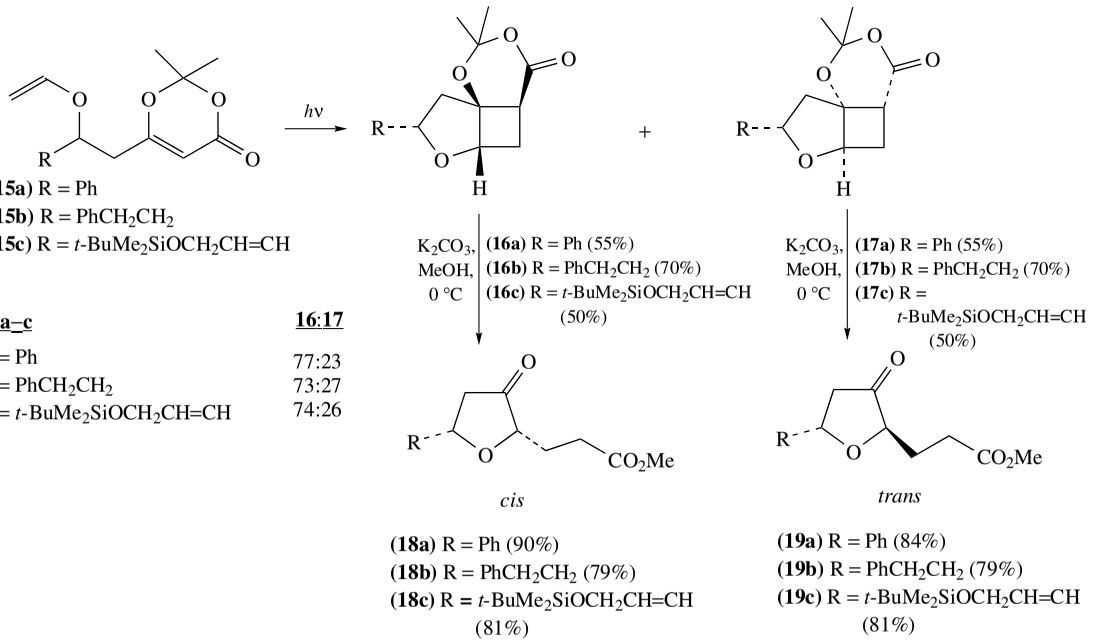
+



(14) (36%)

MeOH overnight, this intermediate could be reduced to the corresponding cyclobutanol which underwent a ring enlargement via a retro-aldol process to form **33**. This procedure provides a rapid access to bicyclic medium-ring diketones or ketolactones from the readily available oxoacids.

Highly substituted cyclic β-alkoxyvinylphosphonate **35** underwent thermal [2 + 2]-cycloaddition with activated ketene **34** to afford bicyclic phosphonate **36**. By treatment with



(15a) R = Ph
(15b) R = $PhCH_2CH_2$
(15c) R = *t*-$BuMe_2SiOCH_2CH{=}CH$

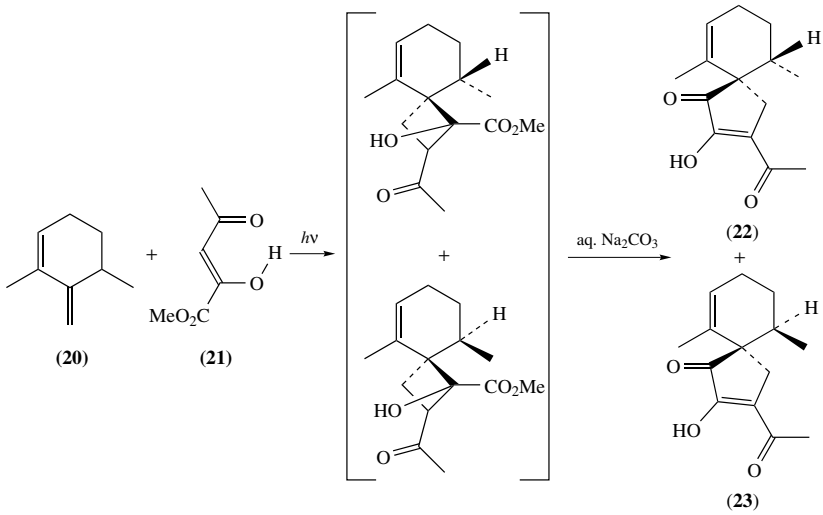
15a–c	**16**:**17**
R = Ph	77:23
R = $PhCH_2CH_2$	73:27
R = *t*-$BuMe_2SiOCH_2CH{=}CH$	74:26

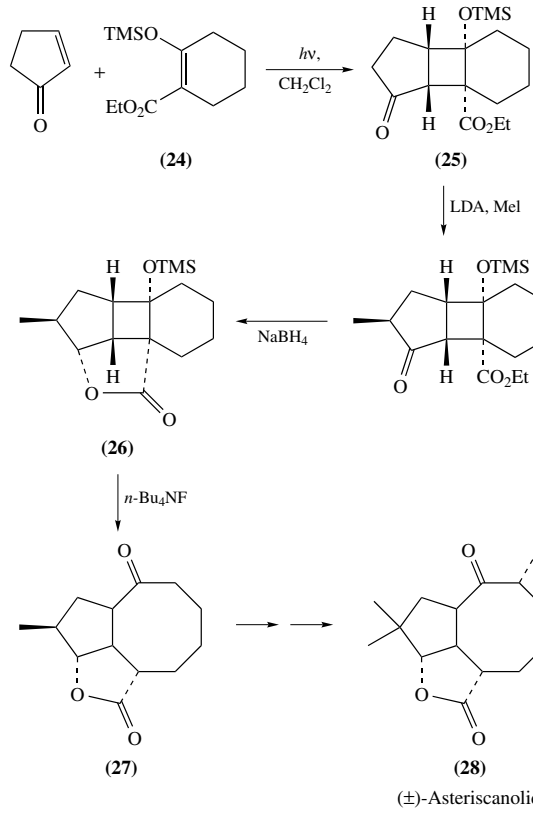
cis

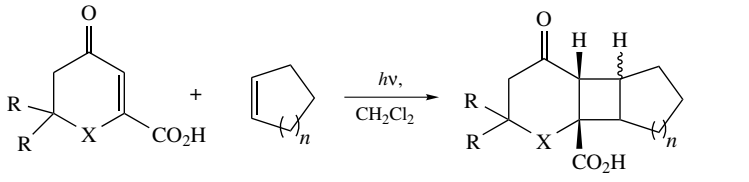
(18a) R = Ph (90%)
(18b) R = $PhCH_2CH_2$ (79%)
(18c) R = *t*-$BuMe_2SiOCH_2CH{=}CH$ (81%)

trans

(19a) R = Ph (84%)
(19b) R = $PhCH_2CH_2$ (79%)
(19c) R = *t*-$BuMe_2SiOCH_2CH{=}CH$ (81%)


(20)
(21)
hν
aq. Na2CO3
(22)
(23)


(24)
hν,
CH2Cl2
(25)
LDA, MeI
NaBH4
(26)
n-Bu4NF
(27)
(28)
(±)-Asteriscanolide



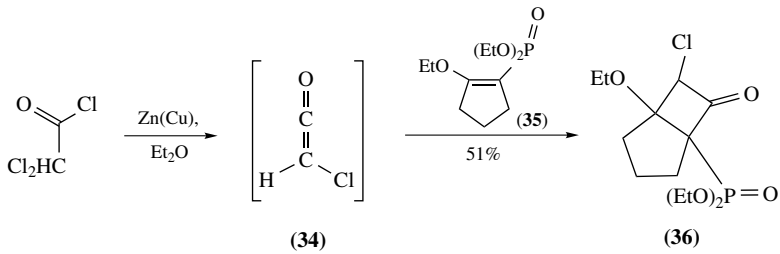
(29) **(30)** **(31)** **(32)**

i. $h\nu$, O_2, toluene, RT, acridine (0.3 equiv.)

ii. Me_2S, MeOH

(33)

R	*n*	X	Yield (%)
H	1	CH_2	48
H	2	CH_2	46
Me	1	O	48
Me	2	O	32



(34) **(36)**

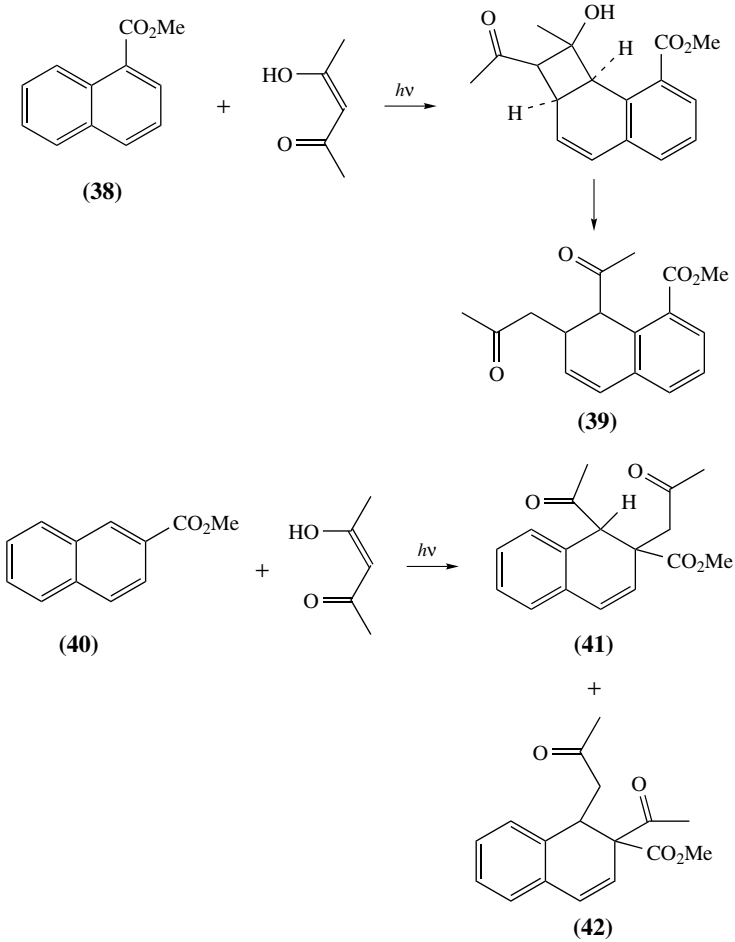
Zn, HOAc, RT, 1h

RT, 4 h, 73%

(37)

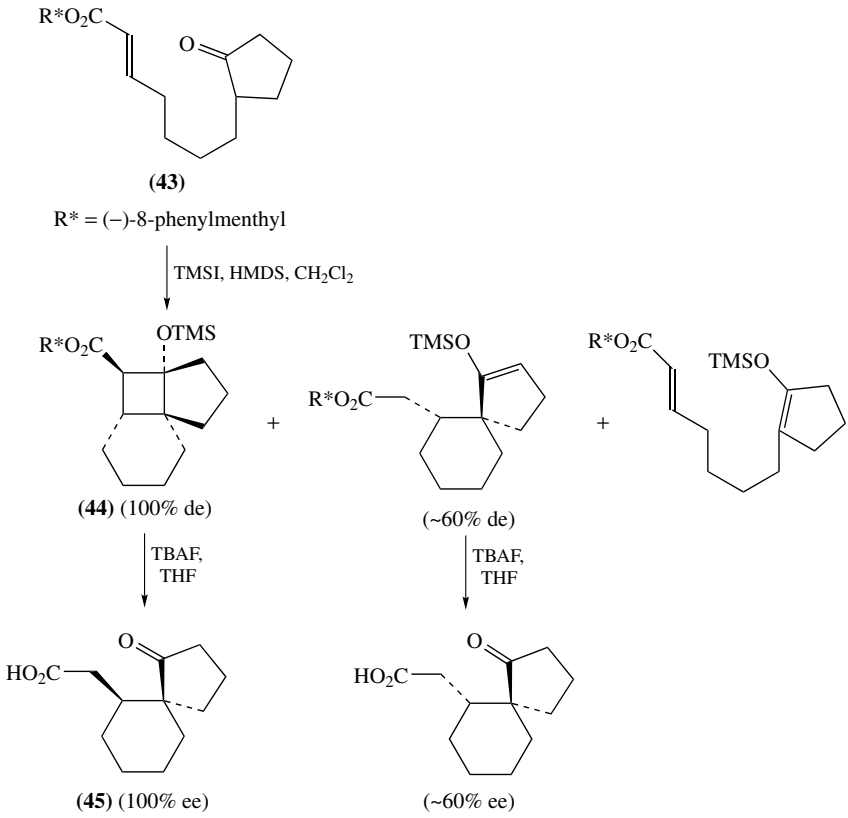
inactivated zinc dust in acetic acid at room temperature for 5 h, fragmentation of the central polarized bond of this bicyclic system occurred readily to give the expanded product **37**[16]. This method provides a shortcut to cycloheptane-1,3-diones with a phosphonate group at the 4-position that could undergo a Horner–Wadsworth–Emmons (HWE) reaction.

Photolysis of a mixture of methyl 1-naphthoate (**38**) and acetylacetone in CH_2Cl_2 gave diketone **39**, a process which was also believed to go through the de Mayo route. Higher ratio of acetylacetone to methyl 1-naphthoate was known to increase the efficiency of the diketone formation. For instance, with a 10:1 ratio, 60% of methyl 1-naphthoate was photolyzed in 8 h to give **39** with an isolated yield of 30%. However, under a similar condition, photolysis of acetylacetone and methyl 2-naphthoate (**40**) with the ratio of 10:1 in acetonitrile for 15 h caused 60% conversion, and diketones **41** and **42** were isolated in 37% and 3% yields, respectively[17].



Keto-α, β-unsaturated esters **43** could undergo Lewis acid–base co-mediated sequential Michael addition and aldol reaction to afford cyclobutane derivatives **44**. In the study of

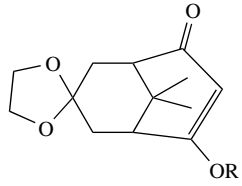
asymmetric intramolecular Michael-aldol reactions, Takasu and coworkers found that the diastereomerically pure **44** could be transformed into optically pure retro-aldol product **45** with a yield of 39% by treatment with 1 M TBAF–THF at room temperature for 12 h[18].



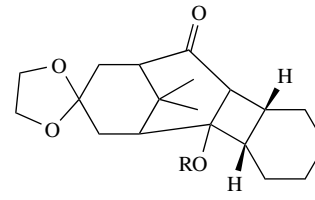
Treatment with 1 M KOH in EtOH under Ar overnight caused the fragmentation of **47**, which was a photoaddition product of 9,9-dimethylbicyclo[3.3.1]nonan-1,3-dione (**46**) and cyclohexene, and formed **48** through a de Mayo process[19].

In the construction of the [6.3.0]bicyclic skeleton of asteriscanolide, a cyclooctane sesquiterpene isolated from *Asteriscus aquaticus*, Booker-Milburn extended the de Mayo reaction to include the retro-Mannich process. Thus, refluxing with diphenylphosphoryl azide and triethylamine in dry dioxane for 2 h smoothly converted **49** to the corresponding isocyanate **50**, which was not isolated but was hydrolyzed by 2 M HCl at 100 °C for 2 h *in situ* to give the fragmented *cis/trans* cyclooctanone-lactones **51** and **52** as a 2.8:1 mixture in 61% yield[20, 21].

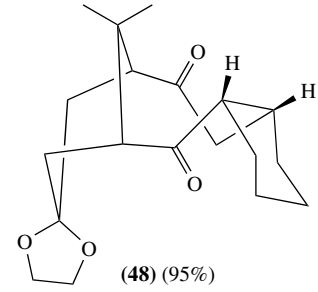
A similar methodology has also been employed as a pivotal step in the total synthesis of (±)-saudin which contains seven stereogenic centers and six oxygenated carbons in its 13-carbon core. Exposure of **53** to LiOH and cyclization of the corresponding carboxylic acid with pyridinium tosylate led to the formation of (±)-saudin **54** in 52% yield[22].



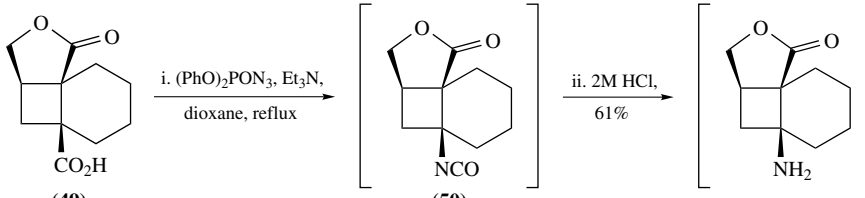
(46)



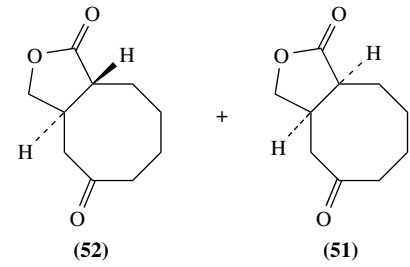
(47a) R = $COCH_3$ (65%)
(47b) R = CO_2CH_2Ph (70%)
(47c) R = $CO_2CH_2CH{=}CH_2$ (80%)
(47d) R = H (98%)



(48) (95%)

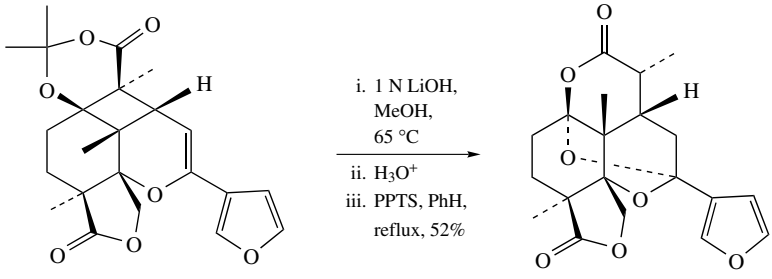


(49) **(50)**



(52) **(51)**

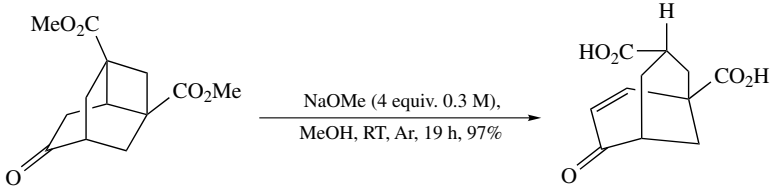
51:**52** = 2.8:1



(53) **(54)**

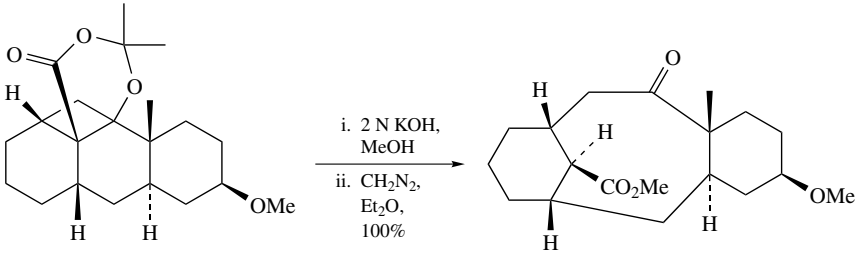
(±)-Saudin

In the stereoselective fragmentation of a tricyclic diester[23], a potent chorismate mutase transition state inhibitor, exposure of **55** to NaOMe–MeOH at room temperature produced enone-diacid **56** as an exclusive product in 97% yield.



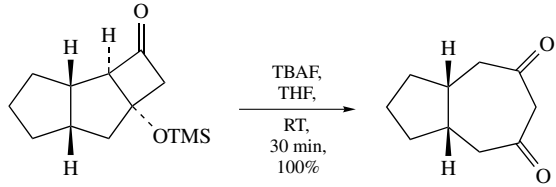
(55) Retro-Michael **(56)**

In the synthesis of the taxane diterpenes, fragmentation of cyclobutane played an important role in the formation of the tricyclic skeleton[24]. Reaction of **57** with 2 N KOH in MeOH and treatment of the resulting keto acid with ethereal diazomethane led to the formation of the keto ester **58** in quantitative yield.



(57) **(58)**

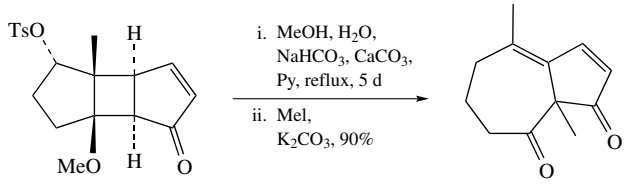
Hydroazulenones could be prepared efficiently from **59**[25] via two carbon annelation through the fluoride-induced fragmentation of the cyclobutane. When **59** was subjected to reaction with TBAF in THF at room temperature, a symmetric diketone **60** was obtained in an almost quantitative yield within 30 min.



(59) **(60)**

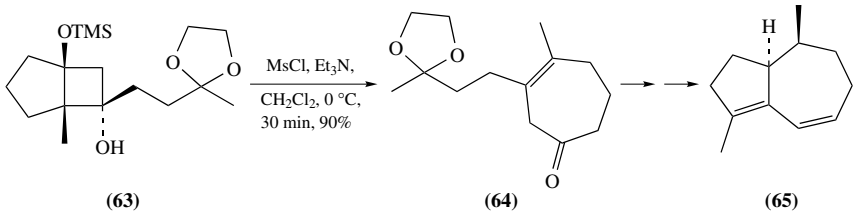
In addition, when an electron-donating group and a good leaving group are appropriately placed on a four-membered ring, the strain of the four-membered ring would assist the fragmentation so that a larger ring system can result. The mechanisms of this fragmentation reaction are believed to be of mostly E1 or E2 nature. Because some extremely complex cyclic systems can normally be obtained through the use of these fragmentation processes, they have been extensively used in the construction of larger ring skeletons applicable in the total synthesis of natural products.

In an approach towards the realization of pseudoguaianolides[26], a controlled fragmentation was furnished by a complete solvolysis of **61**. The cleavage of the required internal cyclobutane bond could be achieved by refluxing in MeOH containing a small amount of pyridine, aqueous $NaHCO_3$ and solid $CaCO_3$ to give the conjugated dienone in 90% yield. Then alkylation at the bridgehead carbon with iodomethane gave rise to **62** in high yield, which contains the requisite structural features necessary to serve as a pseudoguaianolide precursor.



(61) **(62)**

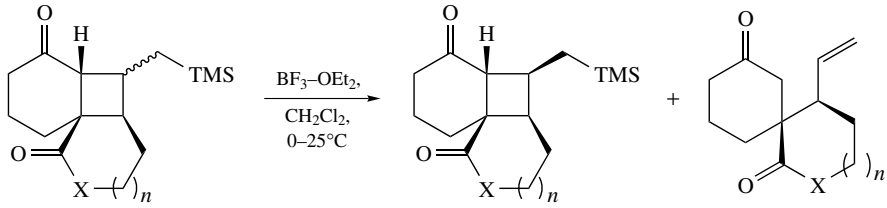
Thermal [2 + 2]-cycloaddition and carbon ring expansion reaction have been utilized as key steps in the total synthesis of (±)-clavukerin A[27]. The *endo* alcohol **63** was subjected to fragmentation conditions to afford cycloheptenone **64** in 90% yield. Then after consecutive acid-catalyzed deketalization, intramolecular aldol condensation, dehydration and decarbonylation, (±)-clavukerin A (**65**) was synthesized.



(63) **(64)** **(65)**

(±)-Clavukerin A

By treatment with BF_3-OEt_2 (3 equivalents) in CH_2Cl_2, a slow but clean transformation of compounds **66** into spiro compounds **68** was observed[28]. The lower reactivity of the *anti* isomers **67** could be attributed to an unfavorable arrangement of the keto group and the trimethylsilylmethyl unit which prevents the formation of a chair-like cyclic transition state. It is noteworthy that the yield was especially high in the case of lactam derivatives.



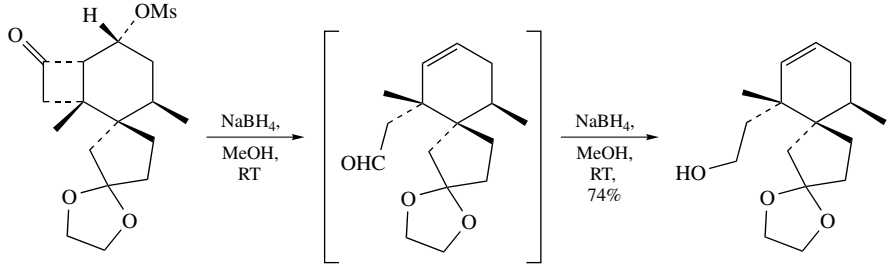
(66) *syn*
(67) *anti*

(67)

(68)

n	X	Conversion	Yield of **(68)**
1	O	> 90%	60%
2	O	64%	36% (+34% of **67**)
1	N-CH_3	> 95%	84%
2	N-CH_3	79%	70% (+21% of **67**)

In the first stereoselective total synthesis of (±)-subergorgic acid, reductive β-fragmentation was employed[29]. Mesylate **69** was reduced by $NaBH_4$ at room temperature and the corresponding aldehyde **70** was reduced further *in situ* to yield the alcohol **71** in 74% yield.



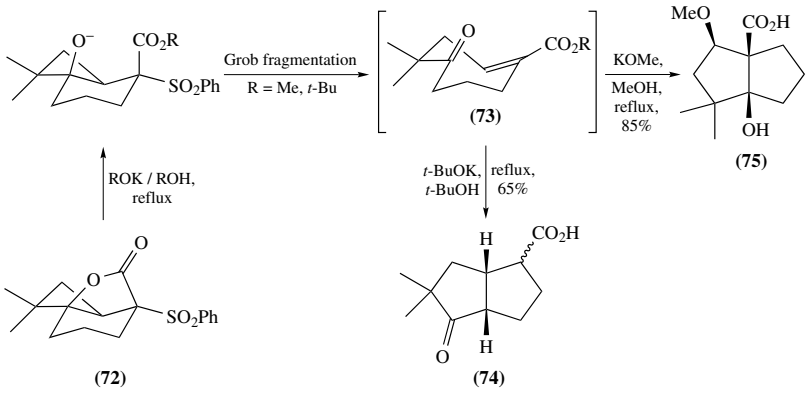
(69)

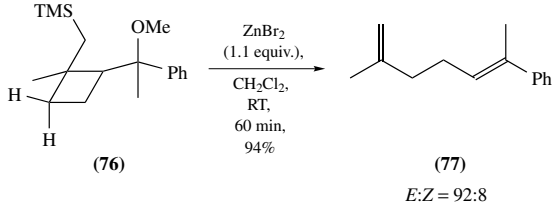
(70)

(71)

When lactone **72** was allowed to react with KOMe in dry MeOH at reflux for 2 h, carboxylic acid **75** was solely produced in 85–90% yields[30]. In contrast, when lactone **72** was refluxed in *t*-BuOH containing *t*-BuOK, keto acid **74** was formed as a 3:1 epimeric mixture in 65% overall yield. Such results could be attributed to the highly strained ester **73** resulting from the Grob fragmentation[31].

Cyclobutane could also participate in the stereoselective preparation of trisubstituted 1,5-hexadiene **77**[32]. The synthesis employed the $ZnBr_2$-catalyzed stereospecific 1,4-elimination of the 1-methoxymethyl-2-(trimethylsilylmethyl)cyclobutane (**76**), with high E/Z ratio.

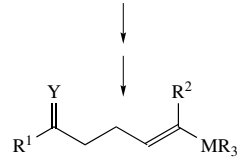




Fujiwara and coworkers have investigated the stereoselective synthesis of alkenylsilanes **83**–**85** utilizing cyclobutyl ketones **78** and **79** as starting materials[33]. This approach consisted of the addition of triorganosilyllithium to **78** or **79** and the subsequent ring opening reaction of the adduct **80** or **81**. The preparation of alkenylgermane **86** using cyclobutyl ketone **79** and triethylgermyllithium via intermediate **82** was also investigated. Alkenylgermanes have also been found to be useful precursors for the stereoselective synthesis of alkenyl halides.

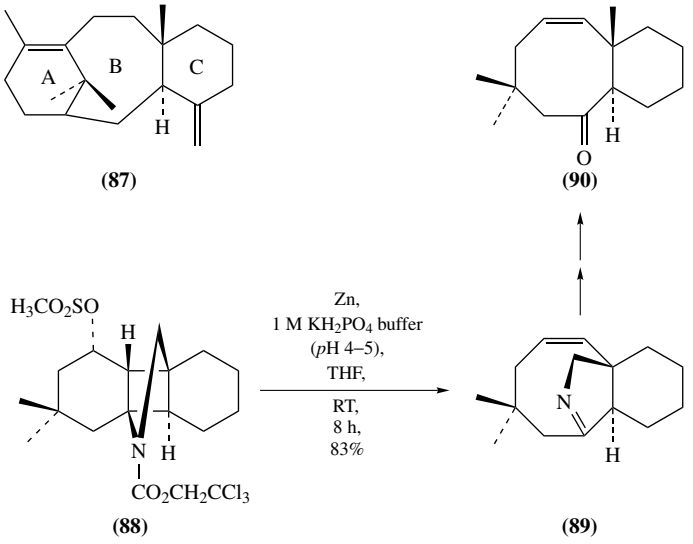
(78) X = SPh, R^1 = Me, R^2 = Me
(79) X = CH_2SiMe_3, R^1 = Bu, R^2 = Me

(80) X = SPh, MR_3 = $SiMe_2Ph$, R^1 = Me, R^2 = Me
(81) X = CH_2SiMe_3, MR_3 = $SiMe_2Ph$, R^1 = Bu, R^2 = Me
(82) X = CH_2SiMe_3, MR_3 = $GeEt_3$, R^1 = Bu, R^2 = Me

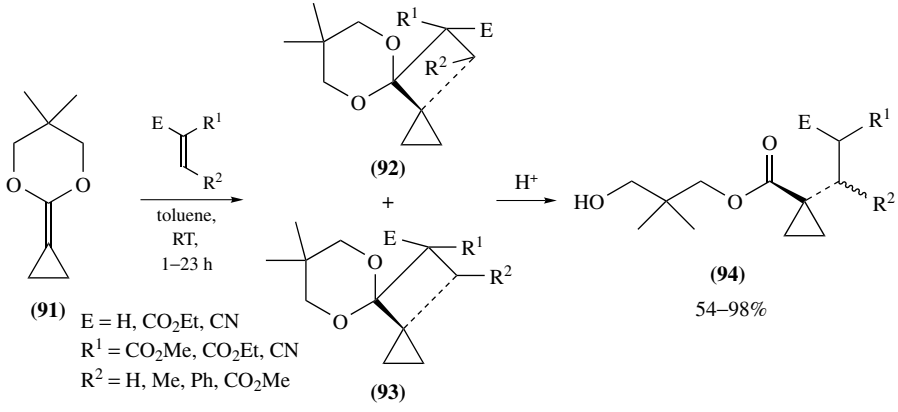


(83) Y = $(SPh)_2$, MR_3 = $SiMe_2Ph$, R^1 = Me, R^2 = Me
(84) Y = O, MR_3 = $SiMe_2Ph$, R^1 = Me, R^2 = Me
(85) Y = CH_2, MR_3 = $SiMe_2Ph$, R^1 = Bu, R^2 = Me
(86) Y = CH_2, MR_3 = $GeEt_3$, R^1 = Bu, R^2 = Me

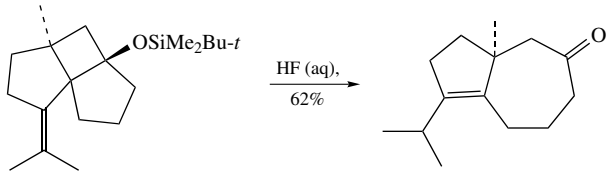
In the stereospecific construction of the carbon framework **87** of taxane diterpenes[34, 35], compound **88** was allowed to go through a Zn-triggered fragmentation under a very mild condition to yield **89** in 83% yield. Taxane BC intermediate **90** could then be prepared from **89** through a sequence of reactions.



The ketene acetal **91** reacted smoothly with electron-deficient olefins to give cyclobutanes **92** and **93**. Under an acidic condition, a fragmentation reaction occurred to afford a cyclopropane-containing compound **94** in 54–98% yields[36]. This method has been employed in the modification of C60 by Nakamura and coworkers.

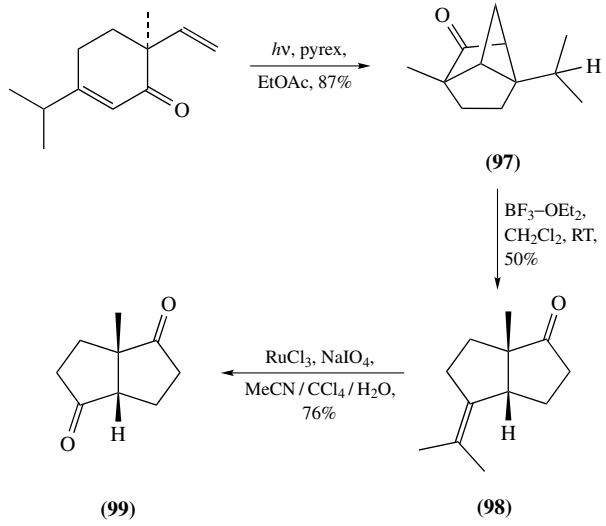


In the total synthesis of isoamijiol[37], fragmentation of cyclobutane **95** was easily accomplished by its brief treatment with aqueous HF[38], leading to the azulenone intermediate **96** in 62% yield.



(95) **(96)**

In the synthesis of diquinane chiron, exposure of tricyclic compound **97** to BF_3-OEt_2 resulted in a smooth regiospecific fragmentation to give **98** with an angular methyl group. After an oxidative cleavage of the isopropylidene group in **98**, (+)-*cis*-diquinane (**99**) was delivered[39].



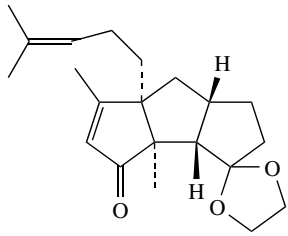
(97) **(98)** **(99)**

The fragmentation of cyclobutanes was also involved in the novel synthesis of tetraquinane diterpenes of the crinipellin group[40]. Thus, irradiation of a cyclohexane solution of enone **100** led to an intramolecular [2 + 2]-cycloadduct **101** in 83% yield. Exposure of pentacyclic ketone **101** to TMSI generated from TMSCl and NaI *in situ* then converted **101** to tetracyclic enedione **102** and the tricyclic dienedione **103** in a ratio of 4:1 in 81% yield.

In the synthesis of 3-isopropenyltropolones, alkylcyclopentadienes **104** were allowed to react with dichloroketene to form **105** in 50–58% yields. Cycloadducts **105** were then hydrolyzed in aqueous AcOH in the presence of NaOAc, providing 5-alkyl-3-isopropenyltropolones **106** in 60–82% yields[41].

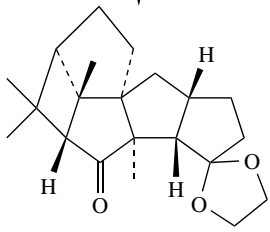
B. Ring Expansion to Five-membered Carbocycles and Heterocycles

The relatively high strain inherent in a cyclobutane ring is the main reason for the feasibility of cyclobutane derivatives to expand to other carbocycles. As such, the ring expansion from 4-membered carbocycles to 5-membered carbocycles and heterocycles serves to be one of the most powerful tools in synthetic organic chemistry.



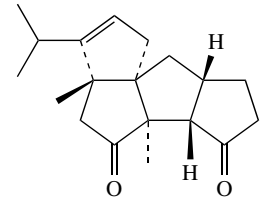
(100)

*h*ν,
cyclohexane,
40 min, 83%



(101)

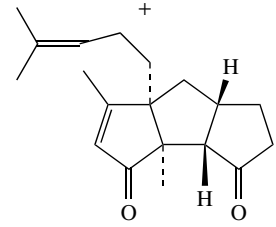
TMSCl,
NaI,
MeCN,
90 °C,
20 h,
81%



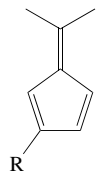
(102)

4 : 1

+



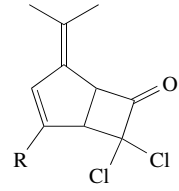
(103)



(104)

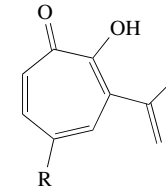
R = CH_3, $CH(CH_3)_2$, $CH(CH_3)C_2H_5$, $CH(C_2H_5)_2$

$CHCl_2COCl$,
Et_3N / hexane,
RT, 13 h,
50–58%



(105)

NaOH,
AcOH / H_2O,
reflux, 10 h,
60–82%

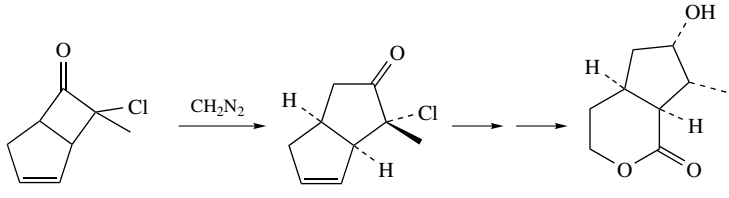


(106)

Cyclobutanones undergo a variety of carbocyclic ring expansions to give cyclopentanones. Among these, diazomethane methodology has been most extensively used. With unsymmetrical cyclobutanones, diazomethane ring expansions tend to favor the migration of the more-substituted α-carbon and disfavor the migration of α-positions bearing electronegative halogen groups. However, other factors including steric effect, ring strain, steric hindrance to the approach of the diazomethane and conformation of the intermediate

can all influence the stereochemistry of migration. For instance, Reeder and Hegedus discussed the influence of β-substituent on the regioselectivity[42].

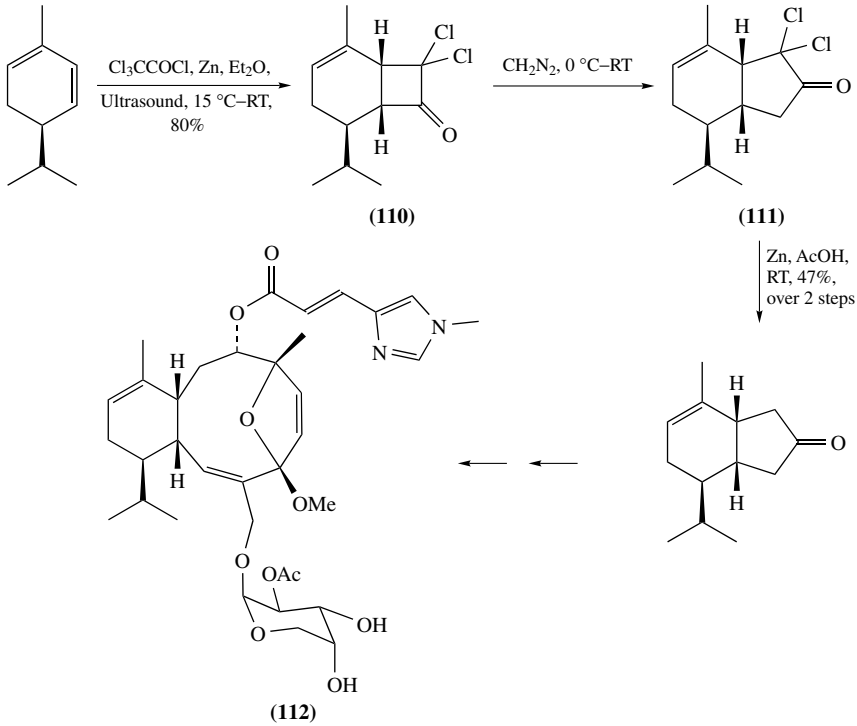
In Lee and coworkers' total synthesis of (±)-boonein (**109**), the bicyclic ketone **107** was ring expanded to the bicyclo-octenone **108** in 77% yield by treatment with diazomethane[43].



(107) **(108)** **(109)**

(±)-Boonein

The key step in Mann and coworkers' total synthesis of eleutherobin **112** also involved the ring expansion of **110** to **111** by treatment with diazomethane[44].

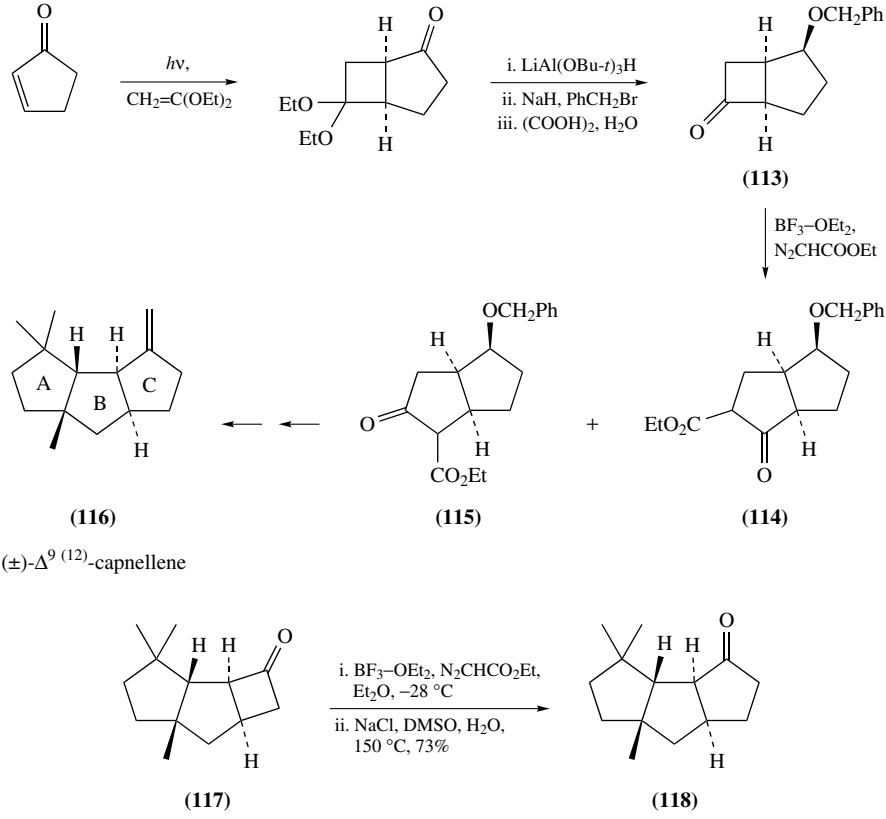


(110) **(111)**

(112)

Eleutherobin

In a more practical manner, treatment of ethyl diazoacetate and BF_3-OEt_2 at 0 °C in Et_2O overnight transformed the cyclobutanone **113** to **114** and **115**, which constitute the BC ring of (±)-$\Delta^{9(12)}$-capnellene (**116**)[45].

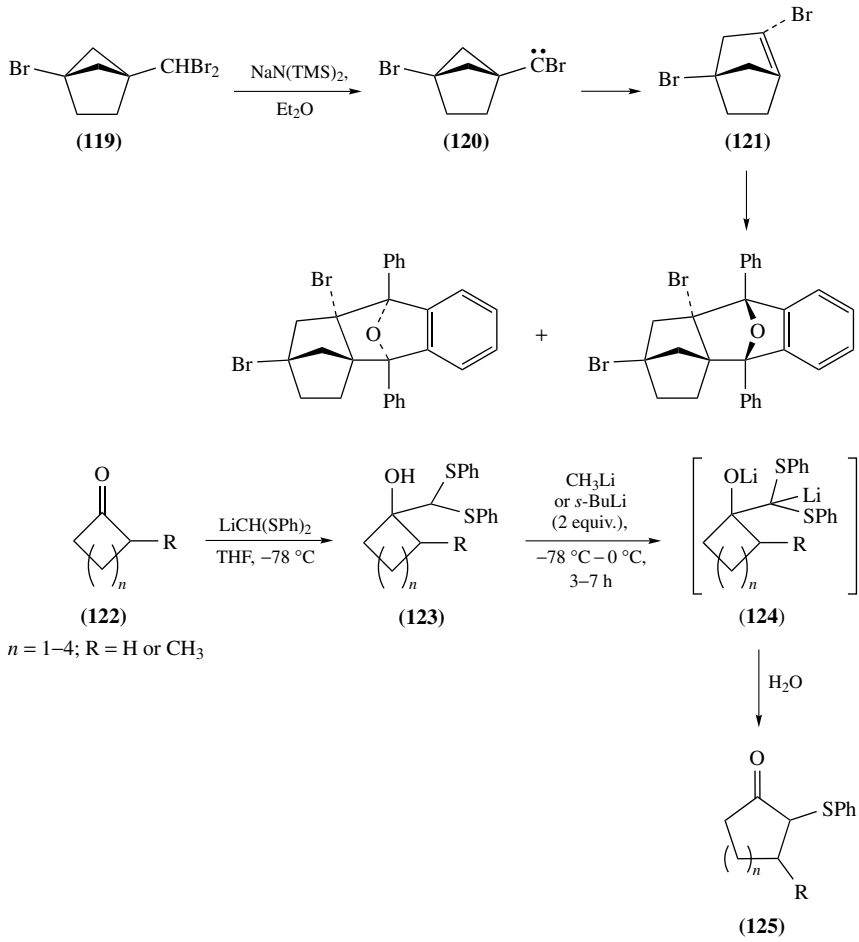


Stille and Grubbs also used the same method to complete the transformation of **117** to **118** which formed the basic structure of **116**[46].

The rearrangement of carbenes in which the carbenic carbon is linked to the bridgehead of a bicyclic or polycyclic carbon framework was thought to be a viable route to generate bridgehead alkenes. Szeimies and coworkers promoted this notion by constructing a 1-norbornene skeleton. (4-Bromo-1-bicyclo[2.1.1]hexyl)bromo carbene (**120**) was generated from **119** by metalation with sodium bis(trimethylsilyl)amide in Et_2O in the presence of diphenylisobenzofuran in a temperature range of -15 to $20\,^{\circ}C$. As expected, **120** rearranged with enlargement of the four-membered ring to give 2,4-dibromobicyclo[2.1.1]hept-1-ene (**121**) which was accordingly trapped by diphenylisobenzofuran[47].

Cohen and coworkers reported a ring-expansion method under a basic rather than a Lewis acid condition based on the fact that the conjugated base of a phenyl thioacetal exhibited carbenoid behavior in a molecule with a second negative charge. For example, treatment of **123**, formed by adding cyclic ketones **122** to bis(phenylthio)methyllithium in THF at $-78\,^{\circ}C$, with two equivalents of an appropriate alkyllithium in THF at $-78\,^{\circ}C$ and allowing the mixture to warm to $0\,^{\circ}C$ generated the dithio derivative **124**. The latter rearranged to the ring expanded ketones **125**. This method is a good complement of the Lewis acid induced procedure and is somewhat more general than the latter[48].

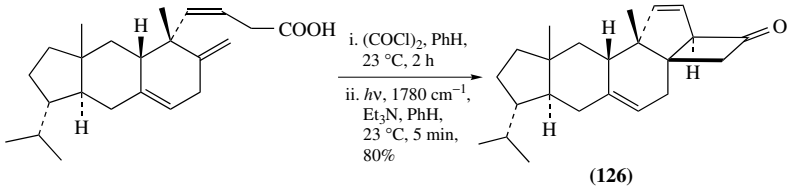
A similar method was applied to the total synthesis of (±)-retigeranic acid (**128**) by Corey and coworkers, completing the transformation from **126** to **127**[49].



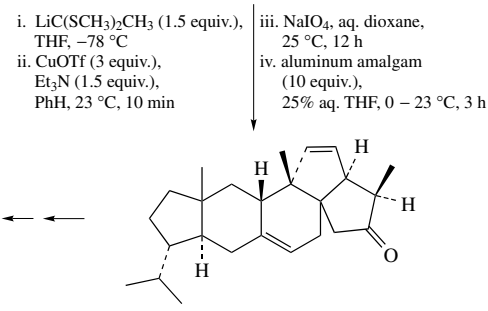
Upon treatment of the corresponding lithium alkoxide of a mixture of **129** and **130** with copper(I) perchlorate–acetonitrile complex, the same product **131** was obtained with equal efficiency. Subsequent desulfurization and methylation transformed **131** to α-cuparenone (**132**), a well-known synthetic precursor of cuparene[50].

Both Brønsted and Lewis acid promote the cyclization reaction of vinylcyclobutanols. The products are spirocycles consisting of a cyclopentanone derived from the ring expansion of the cyclobutanols, and the second ring being derived by attack of the terminator on the initiator. Spirocyclization to [4.5] and [4.6] systems proceeded smoothly, whereas spirocyclization to a [4.7] system was unfruitful. For example, cyclization of **133** proceeded smoothly to give the [4.5] spiro compound **134** with high diastereoselectivities. Under a standard cyclization condition consisting of 1.0 equivalent of TMSOTf and 0.7 equivalent of 2,6-di-*tert*-butylpyridine in CH_2Cl_2, a good diastereoselectivity of 9:1 (**134a:134b**) could be achieved[51].

Iodine is known also to promote the cyclization reaction of vinylcyclobutane derivatives. Thus, exposure of **135** to a catalytic quantity of iodine in PhH at room temperature

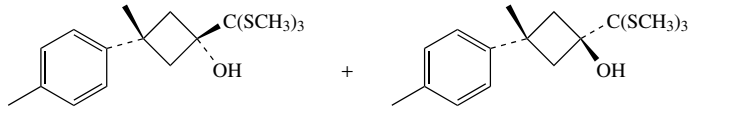


(126)

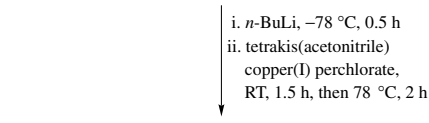


(128)
(±)-Retigeranic Acid

(127)

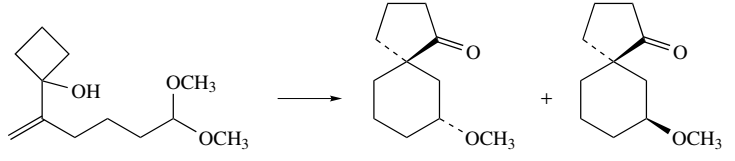


(129) **(130)**



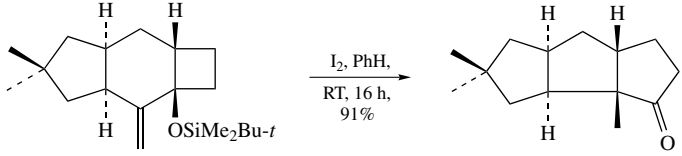
(132)
α-Cuparenone

(131)



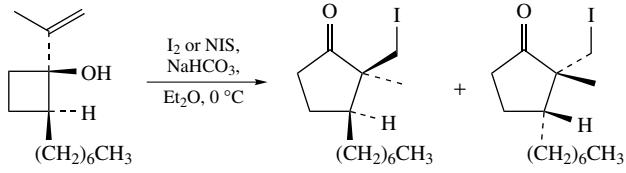
(133) **(134a)** **(134b)**

for 16 h was sufficient to induce its efficient conversion to **136** in 91% yield, a key step in the total synthesis of (±)-hirsutene[52].



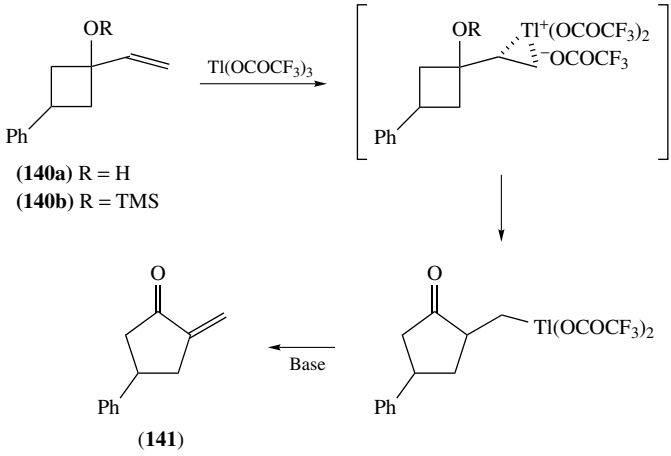
(135) **(136)**

A new strategy for the synthesis of iodoalkylated cyclopentanoids was also based on the iodonium ion mediated ring expansion of olefinic cyclobutanols. For example, after treatment of iodine or *N*-iodosuccinimide in the presence of $NaHCO_3$ in Et_2O at 0 °C, cyclobutanol **137** was converted to **138** and **139**[53].



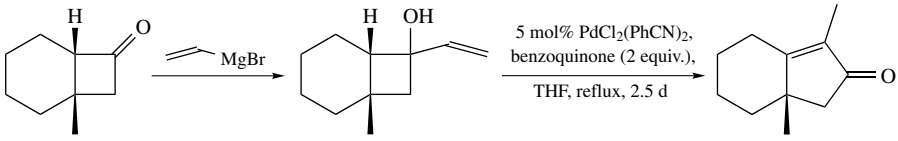
(137) **(138)** 40% **(139)** 39%

Thallium ion mediated ring expansion of 1-alkenyl-1-cycloalkanols has also been studied by Kim and Uh. Thus, treatment of **140a** with thallium(III) trifluoroacetate (TTFA) in acetonitrile at room temperature resulted in the slow consumption of the starting material. The resulting product, α-methylenecyclopentanone **141**, was isolated in 72% yield after 16 h. The use of trimethylsilylated substrate **140b** gave a much better result after treatment with aqueous $NaHCO_3$, yielding **141** in 82% yield[54].



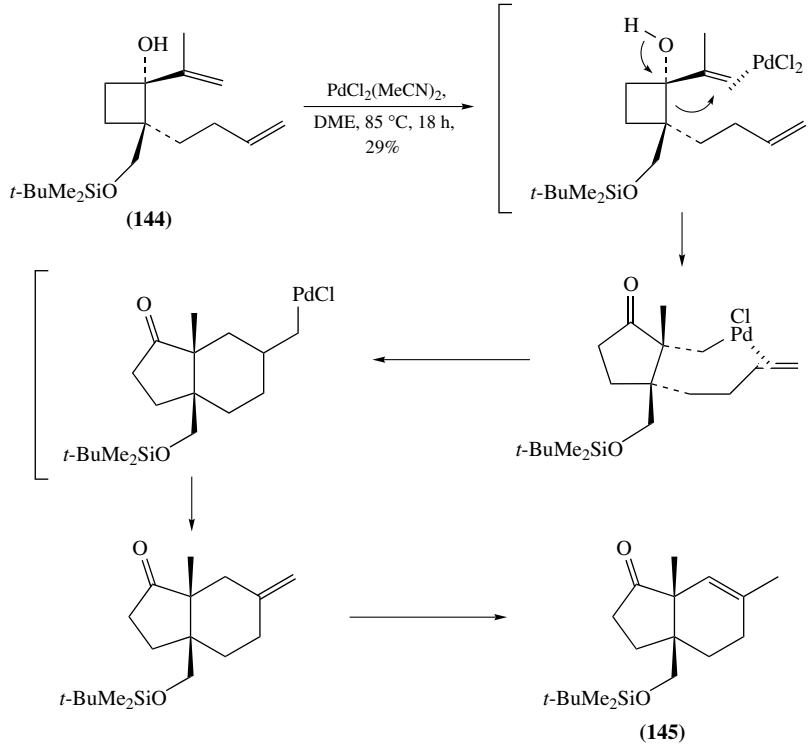
(141)

Palladium-promoted ring expansion of 1-alkenyl or 1-alkynyl cyclobutanols triggered by the release of strain in the four-membered ring system is also a useful methodology for the construction of five-membered carbocycles. In the presence of bis(benzonitrile)palladium dichloride, 1-vinylcyclobutan-1-ol **142** readily underwent ring expansion to give 2-methyl-2-cyclopenten-1-one **143**[55].



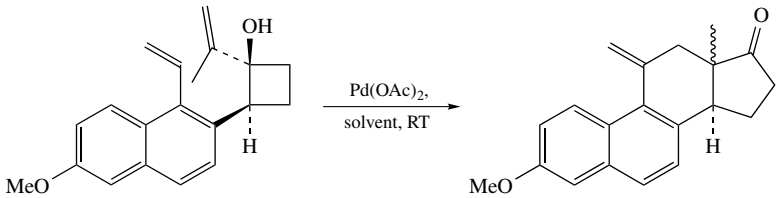
(142) **(143)**

Cyclobutanol **144** also underwent a tandem ring expansion and insertion reaction catalyzed by bis(acetonitrile)palladium chloride [$PdCl_2(MeCN)_2$] at 85 °C for 18 h, affording the hydrindane silyl ether **145** in 29% yield[56].

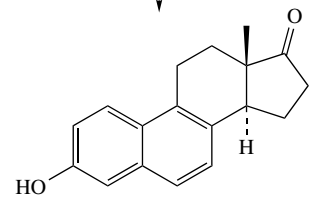


(144) **(145)**

This type of cascade ring-expansion reaction has been successfully deployed in an asymmetric synthesis of (+)-equilenin (**148**). It was found that solvent polarity is an important factor in controlling the diastereoselectivity of products in the Pd^{II}-mediated cascade ring expansion–insertion reaction. The *trans*-fused product **146** was selectively



(146) *trans*
(147) *cis*

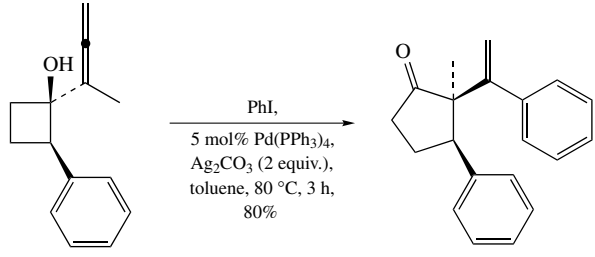


(148)
(+)-Equilenin

Entry	Solvent	*trans:cis*	Yield (%)
1	HMPA–THF (1:4)	73:27	60
2	$ClCH_2CH_2Cl$	0:100	63

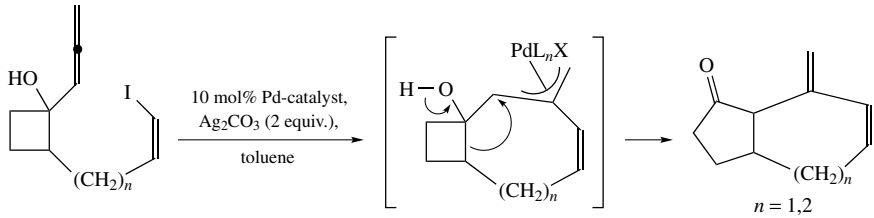
produced in HMPA–THF. On the other hand, the *cis*-fused product **147** was obtained as a sole product (63%) in 1,2-dichloroethane[57].

The palladium-catalyzed ring-expansion reaction of allenylcyclobutanols having a substituent at the 1-position of the allenyl moiety was delineated by Ihara and coworkers, who treated a mixture of **149** and PhI with 5 mol% of $Pd(PPh_3)_4$ in the presence of 2 equivalents Ag_2CO_3 in toluene at 80 °C for 3 h to exclusively generate **150** in 80% yield[58].



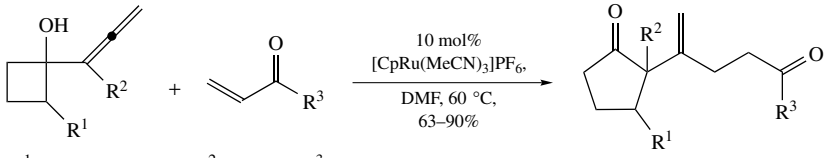
(149) **(150)**

Similarly, in the presence of $Pd(PPh_3)_4$, allenes underwent an intramolecular carbopalladation, in which the ring transformation of **151** was accompanied by the strain release of the cyclobutane ring to directly give the fused bicyclo [$n + 3.3.0$] ring system **152**[59].



(151) **(152)**

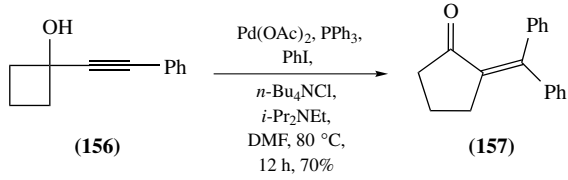
Treatment of allenylcyclobutanols **153** and α,β-unsaturated carbonyl compounds **154** with 10 mol% $[CpRu(MeCN)_3]PF_6$ in DMF at 60 °C for 0.5–2 h provided the cyclopentanones **155** in 63–90% yields[60].



R^1 = ph, $(CH_2)_6CH_3$, R^2 = H, Me, R^3 = H, Me

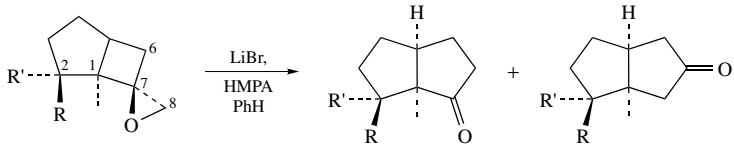
(153) **(154)** **(155)**

By treatment with 10 mol% $Pd(OAc)_2$, 20 mol% of PPh_3, 2 equivalents of aryl or vinylic iodide, 2 equivalents of diisopropylethylamine as the base and 2 equivalents of n-Bu_4NCl in DMF at 80 °C for 12 h, 1-(phenylethynyl)cyclobutanol (**156**) and PhI underwent a cross-coupling reaction to afford cyclopentanone **157** in 70% yield. High yields were also obtained from not only the electron-rich *o*-iodoanisole but also the electron-poor *o*-iodonitrobenzene. Neither electronic effects nor steric hindrance therefore appear to cause problems[61]. The reaction of 1-alkynylcyclobutanols with aryl iodides in the presence of $Pd(OAc)_2$ and Et_3N in acetonitrile at 80 °C for 24 h also gave 2-disubstituted methylenecyclopentan-1-ones in modest to good yields[62]. In addition, Pd^0 was also employed in the cascade ring-expansion reaction of 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanols with phenols[63].



(156) **(157)**

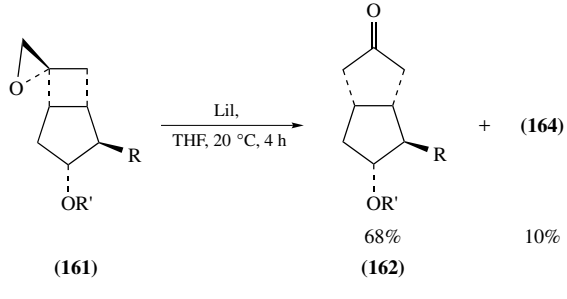
When **158a–d** were treated with 1 equivalent of LiBr and HMPA in boiling PhH, ketones **159a–d** were obtained as major products in 75–94% yields together with traces of **160b–d** in 0–4% yields. This remarkable abnormal selectivity in the rearrangement of **158**, in which the less substituted carbon C(6) migrated predominantly, resulted from the chelation of the *endo* oxygen atom at C(2) to the lithium cation in the transition state. Basically, the rotation around the C(7)–C(8) bond is hindered by the chelation, thus locking the conformation in which C(6)–C(7) and C(8)–Br bonds have *anti* periplanar alignment[64, 65].



(158a–d) **(159a–d)** **(160b–d)**

	R	R'	**159:160**	Yield (%)
a	OH	H	100:0	86
b	OMe	H	99:1	75
c	OCH_2OMe	H	98:2	88
d	$-OCH_2CH_2O-$		96:4	94

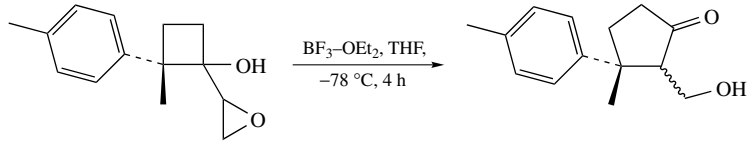
The rearrangement of α-epoxide **161** proceeded in a regioselective manner in the presence of LiI in THF at 20 °C for 4 h, affording ketone **162** in 68% yield and its isomer **164** in 10% yield. In contrast, the corresponding β-epoxide **163** underwent a slow, regioselective rearrangement in the presence of LiI in THF at 20 °C for 60 h, furnishing ketone **164** in 71% yield and with less than 10% yield of ketone **162**. The mechanistic mode of these epoxide–carbonyl rearrangements should be largely dictated by the considerable steric interactions and torsional strain inherent in the bicyclo[3.2.0]heptane system[66–68]. The key step in the total synthesis of pentalenolactone G also involved an intramolecular [2 + 2]-photocycloaddition and ring expansion of cyclobutyl epoxide in the presence of LiBr[69].



R′ = $SiMe_2Bu$-*t*; R = CH=CHCH($OSiMe_2Bu$-*t*)C_5H_{11}

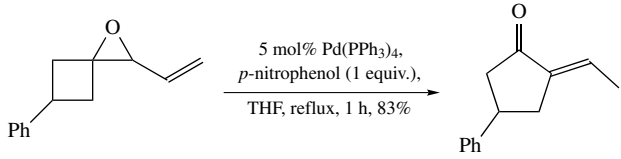
In the total synthesis of (+)-laurene, an enantiospecific ring expansion of a cyclobutanol followed by a tandem epoxide cleavage was employed as a key step. Thus, when treated with BF_3-OEt_2, the diastereomeric mixture of epoxides **165** underwent a ring expansion

of the cyclobutane ring to give the same cyclopentanone **166** as a mixture of diastereomers with the yield of 95%[70,71].



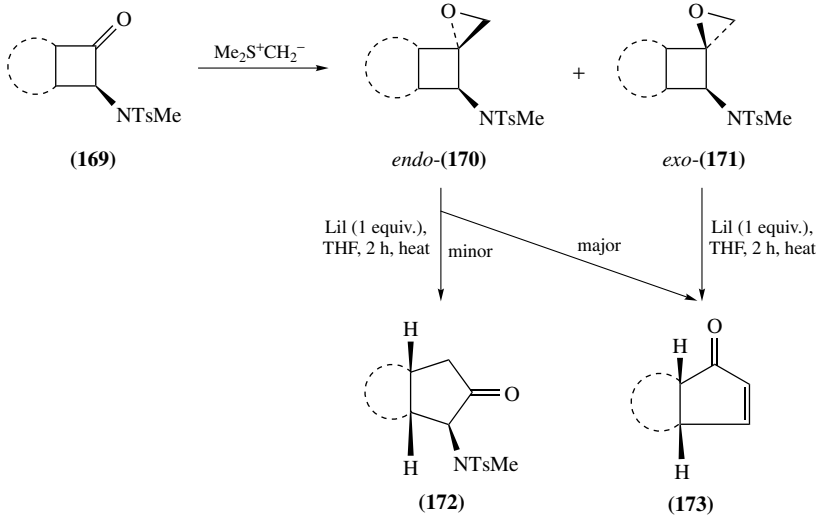
(165) **(166)**

In the presence of 1 equivalent of *p*-nitrophenol, the vinyl epoxide **167** reacted with 5 mol% $Pd(PPh_3)_4$ in THF at reflux for 1 h to afford the cyclopentanone **168** in 83% yield. Under a similar condition, vinyl oxaspirohexanes underwent facile ring expansion to yield 2-ethylidenecyclopentanones in high yields[72].



(167) **(168)**

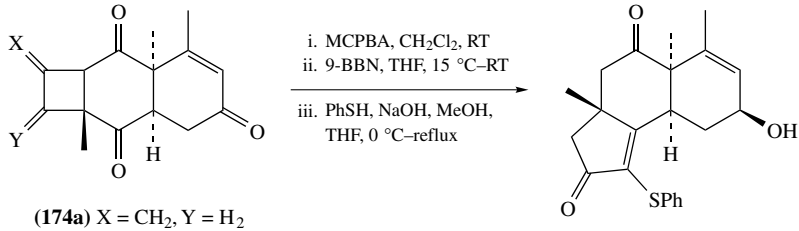
By reacting with dimethylsulfonium methylide generated from trimethylsulfonium tetrafluoroborate and *n*-BuLi, α-*N*-methyl-*N*-tosylcyclobutanones **169** were converted into the corresponding oxiranes **170** and **171**. The stereochemistry of this reaction was found to be influenced by the large NTsMe group and the methyl group at the ring junction. The *exo*-isomer **171** was selectively rearranged into **173** after refluxing in THF containing a stoichiometric amount of LiI. On the other hand, the *endo*-isomer **170** reacted more slowly and the ring expansion was less selective, the major product being still **173** with a substantial amount of **172**[73].



(169) *endo*-**(170)** *exo*-**(171)**

(172) **(173)**

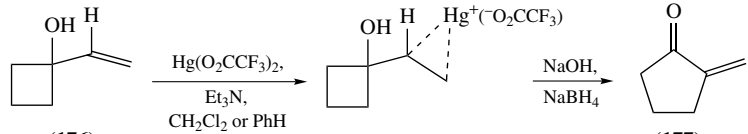
A 4:1 mixture of **174a** and **174b** was oxidized with MCPBA in CH_2Cl_2. After that, the resulting mixture of epoxides was dissolved in THF and the unsaturated ketone was selectively reduced with 9-BBN, and the excess borane was quenched by MeOH. After treatment with benzenethiol and base to induce epoxide ring opening, the resulting solution was refluxed with an excess of base to initiate cyclization. In this way, the mixture of photoadducts **174a** and **174b** could be converted into **175** in 75% overall yield in essentially a 'one pot' manner[74].



(174a) X = CH_2, Y = H_2
(174b) X = H_2, Y = CH_2

(175)

1-vinylcyclobutan-1-ols ring-expansion reaction of **176** with mercuric trifluoroacetate and Et_3N in CH_2Cl_2 or in PhH gave the ring-expanded cyclopentanones **177** in 40–60% yields after demercuration with $NaBH_4$ and NaOH. However, due to the reversibility of oxymercuration reaction and the lack of a ring strain, the mercurinium ion mediated ring expansion was much less effective with 1-vinylcyclopentan-1-ols[75].

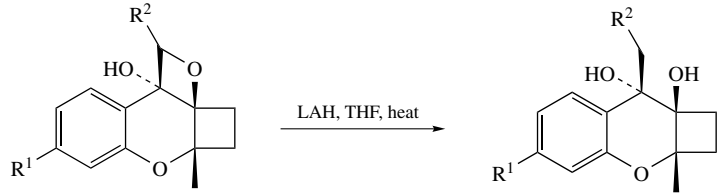


(176) **(177)**

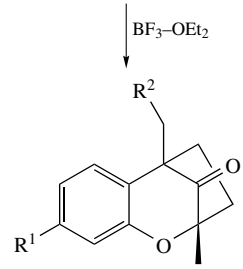
After reduction with LAH in refluxing THF, compound **178** (R^1, R^2 = H) was converted to the diol **179** (R^1, R^2 = H) in 94% yield, which is most suitable for a pinacol rearrangement. As such, treatment of a PhH solution of **179** with BF_3–OEt_2 at room temperature for 1 h resulted in a complete rearrangement to afford **180** (R^1, R^2 = H) with an isolated yield of 85%[76].

When stirred at room temperature with a catalytic quantity of camphorsulfonic acid (CSA) in CH_2Cl_2 for 2 h, **181** was stereoselectively transformed into **182** with a yield of 74%, presumably reflecting a steric control approach. On the contrary, stirring **183** with CSA for 4 h afforded a mixture of **184** (50%) and **185** (38%), revealing a likely half-boat conformation of the pyran ring in **184**. In contrast, the pyranose segment of **185** adopts the normal chair arrangement[77].

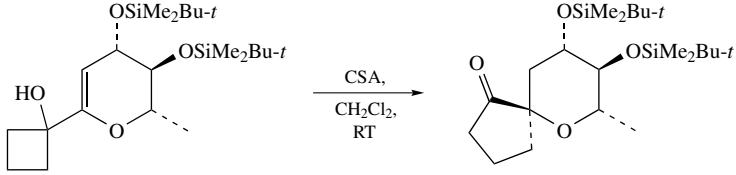
Subjecting cyclobutanol **186** to the action of CSA at 45 °C for 13 h resulted in its smooth expansion to cyclopentanones **187** and **188** in 81% yield in a ratio of 2.8:1. The diastereoselectivity of the ring-expansion reaction could be improved significantly at a lower temperature. The stereoselectivities of these reactions are thought to derive from transition states in which the substituents are pseudoequatorial. The diastereomeric transition states differ depending on whether the cyclic iminium ion reacted through a 'chair' or a 'twist-boat' conformation, with the chair orientation providing the major diastereomer **187** in preference to **188**[78].



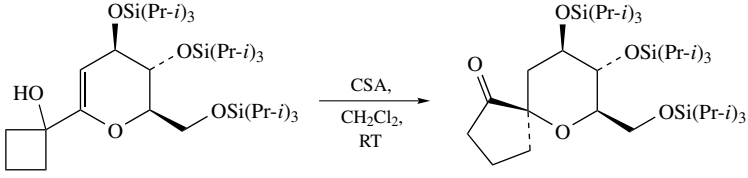
(178) **(179)**



(180)

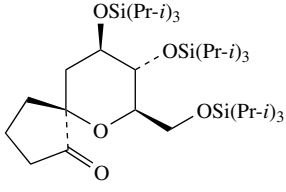


(181) **(182)**

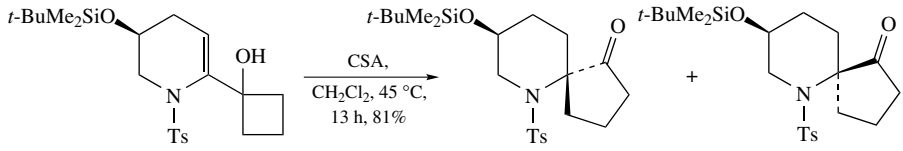


(183) **(184)**

+

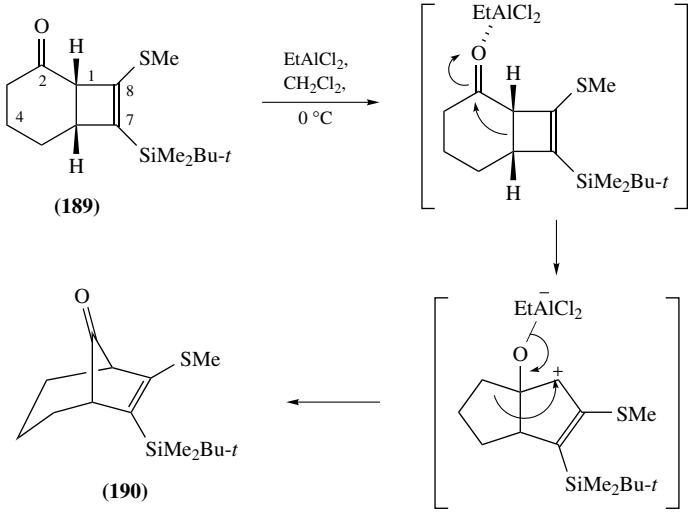


(185)



(186) **(187)** 2.8 : **(188)** 1

Treatment of bicyclo[4.2.0]octane derivative **189** with $EtAlCl_2$ in CH_2Cl_2 at 0 °C for 10 min led to the formation of the bicyclo[3.2.1]octane derivative **190** in 80% yield through the Cargill rearrangement, which proceeded selectively in the reaction of the bicyclo[*n*.2.0] derivatives ($n = 4, 5, 6$) having an oxo group at the 2-position. The methylthio group at the 8-position was known to enhance this rearrangement[79].



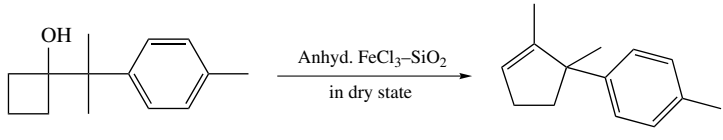
(189) **(190)**

Anhydrous ferric chloride adsorbed on silica gel induced the dehydration and the specific C4 → C5 ring enlargement of 1-(1-methyl-1-*p*-tolyl)ethylcyclobutanol (**191**), furnishing **193** in 85% yield and **192** in 15% yield. This synthetic protocol was used in the total synthesis of the sesquiterpenoid (±)-cuparene (**194**)[80].

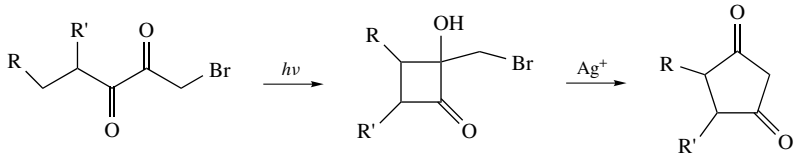
Hamer reported a Ag^+-induced solvolysis of 2-bromomethyl-2-hydroxycyclobutanones **196** via a photocyclization reaction of α-bromomethyl-1,2-diketones **195**, thus providing a simple route to 4 and 4,5 substituted cyclopentane-1,3-diones **197**[81].

In Paquette and coworkers' total synthesis of dimethyl gloiosiphone A, the key elements involved the condensation of bromide **198** with one equivalent of a squarate ester **199** and a subsequent deployment of a regio-controlled ring expansion to generate the critical spirocyclic center **200**[82].

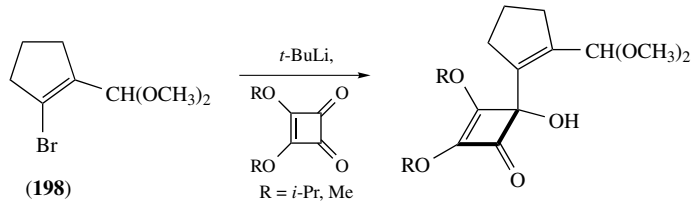
In the total synthesis of (±)-isokhusimone, Burnell and coworkers devised a method involving the Lewis acid-catalyzed reaction of a dimethyl or diethyl ketal **201** with 1,2-bis(trimethylsiloxy)cyclobutene (**202**), followed by rearrangement of the resulting



(191) **(192)**
15%
+
(193) **(194)**
85% (±)-cuparene



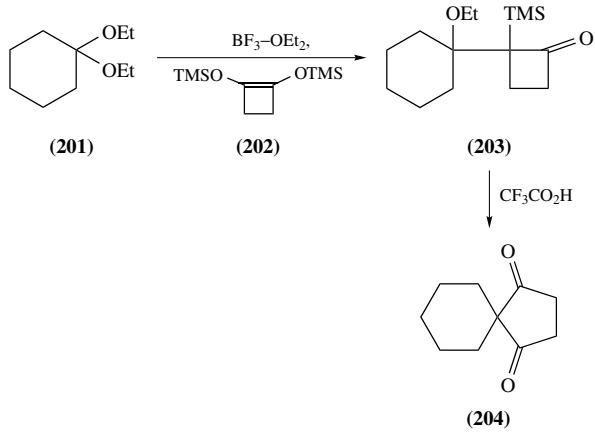
(195) **(196)** **(197)**



(**198**) (**199**)

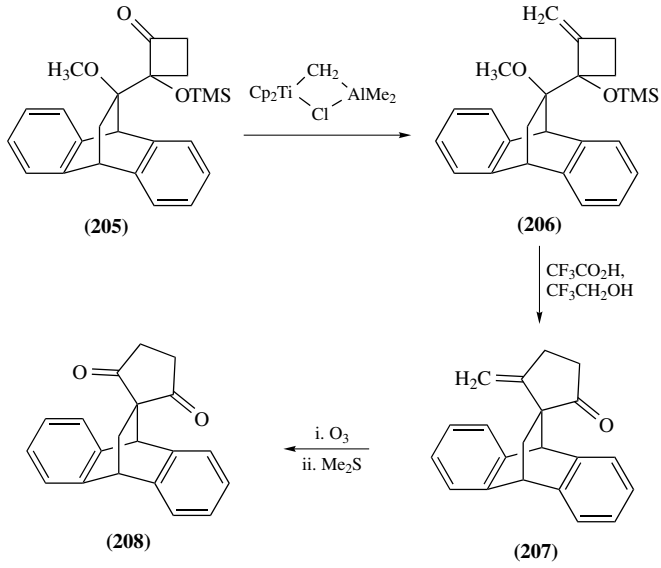
(**200**)

cyclobutanone **203** catalyzed by trifluoroacetic acid to afford the diketone **204**[83–85]. The Lewis acid-catalyzed geminal acylation of acetals with 1,2-bis(trimethylsiloxy)cyclobutene has also been employed in the construction of a tricyclic skeleton including the spiro[4.4]-nonane subunit[86].



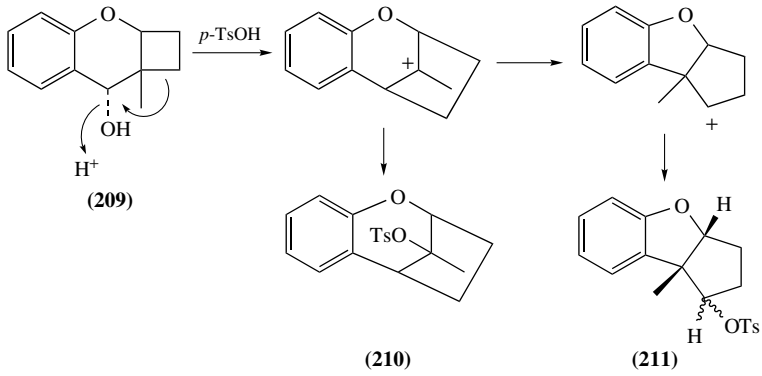
(201) **(202)** **(203)** **(204)**

Some spirodiketones such as **208** were highly sensitive to acids under pinacol rearrangement conditions. For this reason, a mild non-acid condition was applied to generate **208**. Methylenation of **205** was best accomplished with the Tebbe reagent, which provided **206** in 82% yield after chromatographic separation. Pinacolic ring expansion of **206** proceeded with clean migration of the vinyl group, smoothly providing the spiroannelated cyclopentanone **207** in 75% yield. Conversion of **207** to **208** was accomplished in high yield by ozonolysis, followed by work-up with dimethyl sulfide[87].

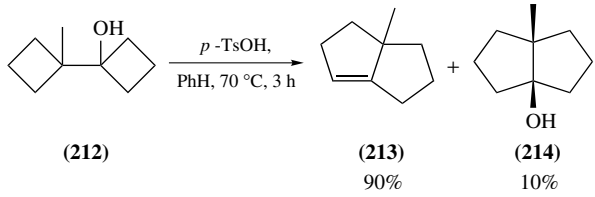


(205) **(206)** **(208)** **(207)**

Treatment of **209** with *p*-TsOH in boiling PhH for 3 h led to a mixture of *p*-toluenesulfonates in 70% yield, consisting of **210** and **211** in a ratio of 2:3. This rearrangement of α-hydroxycyclobutanes provided a facile route towards the carbocyclic skeleton of aplysin[88].



Quantitative rearrangements were observed when 1-methylcyclobutylmethanols were heated at 70 °C with solution of anhydrous *p*-TsOH in PhH (0.074 M) for 3 h. In all cases, the product formation involved a cyclobutylmethyl to cyclopentyl rearrangement. For example, **212** rearranged to **213** and **214** in 90% and 10% yields, respectively, under this general condition[89].

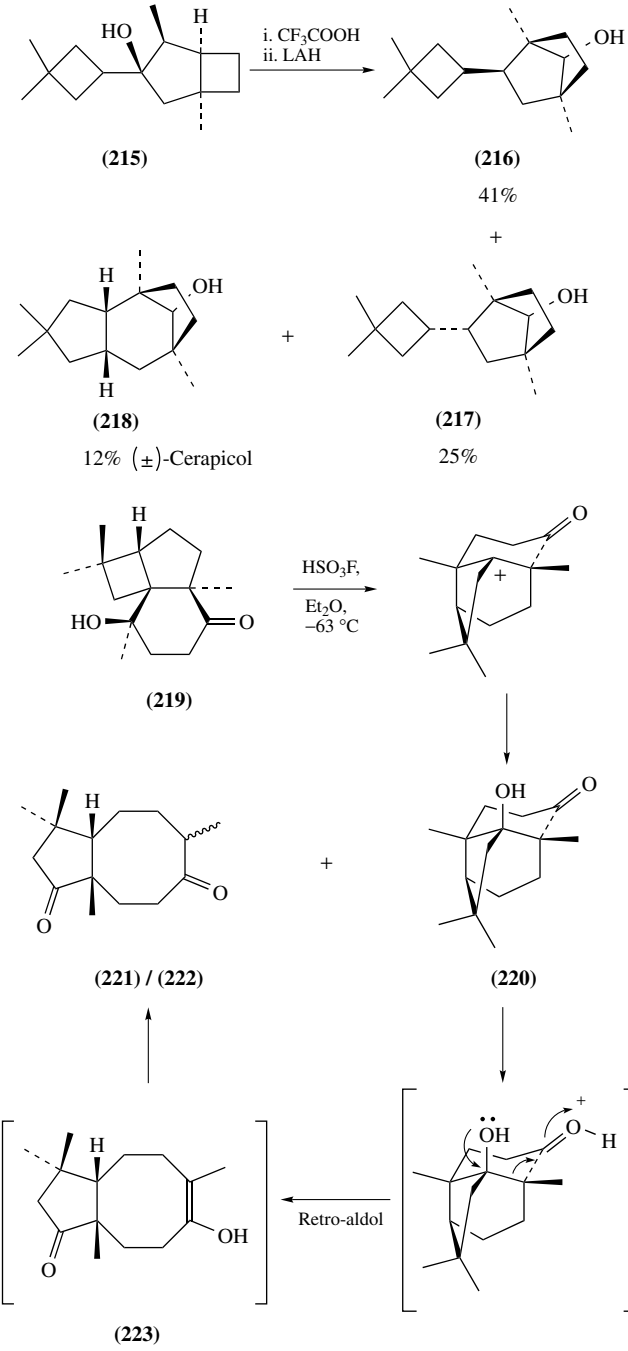


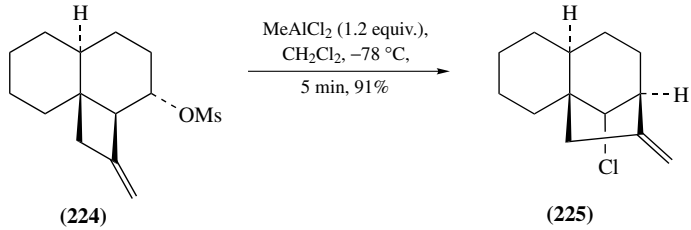
Upon treatment with trifluoroacetic acid, a similar rearrangement of cyclobutylmethanol **215** took place after reduction with LAH, leading to norbornanes **216** (41%) and **217** (25%) and the desired (±)-cerapicol (**218**) (12%)[90].

Treatment of compound **219** with HSO_3F in dry Et_2O at −63 °C gave a major product **220** and two minor products **221** and **222**. Formation of compounds **221** and **222** can be reasoned via a retro-aldol reaction of 8-oxoginsenol **220**, which would lead to an enol intermediate **223**[91].

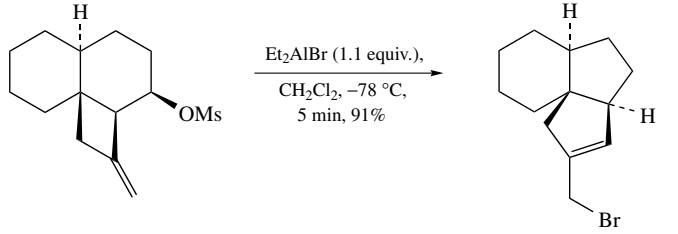
Reaction of mesylate **224** with $MeAlCl_2$ at −78 °C in CH_2Cl_2 proceeded by rearrangement of the β-olefinic carbon to give the rearranged chloride **225** in an essentially quantitative yield. In contrast, reaction of mesylate **226** with Et_2AlBr at −78 °C for 5 min provided in 91% yield the allylic bromide **227**, a product formed via shifting the 6/4 fusion bond in a 1,2-carbon rearrangement[92].

By treatment with a catalytic amount of concentrated H_2SO_4 and CF_3SO_3H (2 equivalents) in PhH at room temperature, the tricyclic ketone **228** afforded *cis,cis*-tricyclo-[6.3.0.$0^{1,5}$]undecan-4-one (**229**) in 74–83% yields instead of the Cargill rearrangement product. Moreover, a similar treatment of **228** with a Lewis acid (2 equivalents) [$AlCl_3$

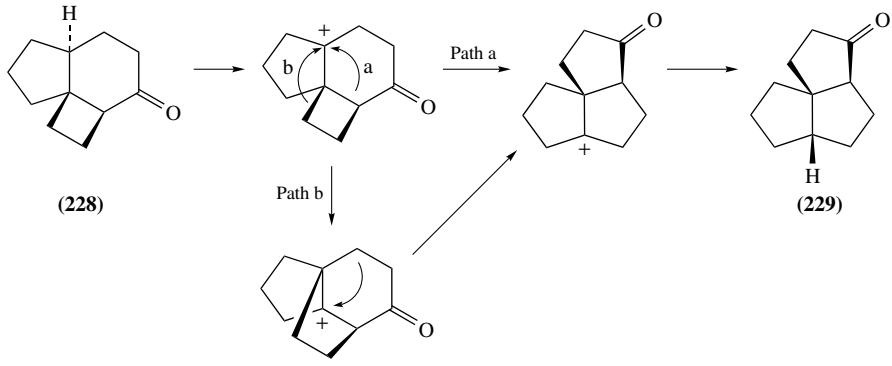

HO
H
i. CF_3COOH
ii. LAH
OH
(215)
(216)
41%
+
H
OH
H
(218)
12% (±)-Cerapicol
+
OH
(217)
25%
H
HO
O
(219)
HSO_3F,
Et_2O,
–63 °C
O
+
H
O
O
(221) / (222)
+
OH
O
(220)
H
OH
O
(223)
Retro-aldol
OH
O
H
+



(224) **(225)**



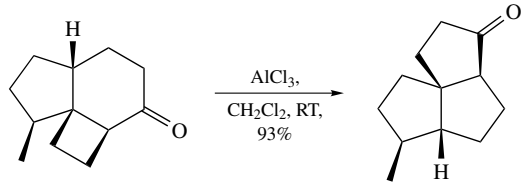
(226) **(227)**



(228) **(229)**

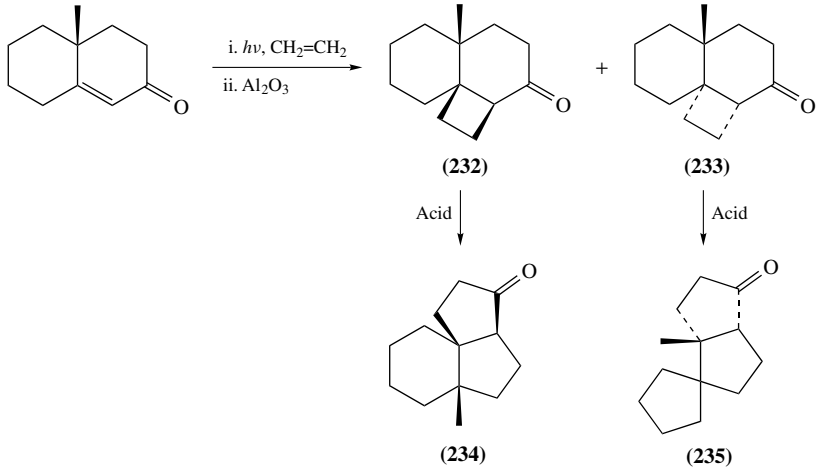
(97%); BF_3–OEt_2 (74%); $SnCl_4$ (63%); $FeCl_3$ (99%); $TiCl_4$ (99%)] in CH_2Cl_2 furnished **229** exclusively[93].

A novel rearrangement of **230** with $AlCl_3$ proceeded smoothly to give the desired angular ketone **231** in 93% yield, which was used in the total syntheses of (±)-5-oxosilphiperfol-6-ene and (±)-silphiperfol-6-ene[94]. The mechanism[95] was also discussed in detail.

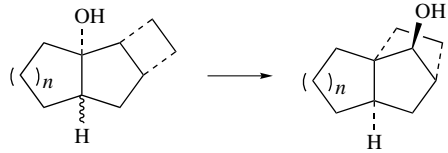


(230) **(231)**

Kakiuchi and coworkers studied the acid-catalyzed rearrangement of (1*R**, 4*S**, 8*R**)- and (1*S**, 4*R**, 8*R**)-8-methyltricyclo[6.4.0.0^{1,4}]dodecan-5-ones (**232** and **233**) and found that while **232** gave the angularly fused ketone **234, 233** produced the unique spiroannelated ketone **235**[96].



Solvolysis of the cyclobutyl carbinyl alcohols **236** in boiling 90% trifluoroacetic acid followed by saponification of the resulting trifluoroacetates afforded rearranged alcohols **237** in good yields (64–85%)[97]. Lange and coworkers also used the rearrangements of the strained cyclobutane ring in suitably functionalized photoadducts in the synthesis of tricyclo[6.4.0.0^{2,6}]dodecane skeleton (6-5-5 ring system) and tricyclo[6.3.0.0^{2,6}]undecane skeleton (linear triquinane system)[98].

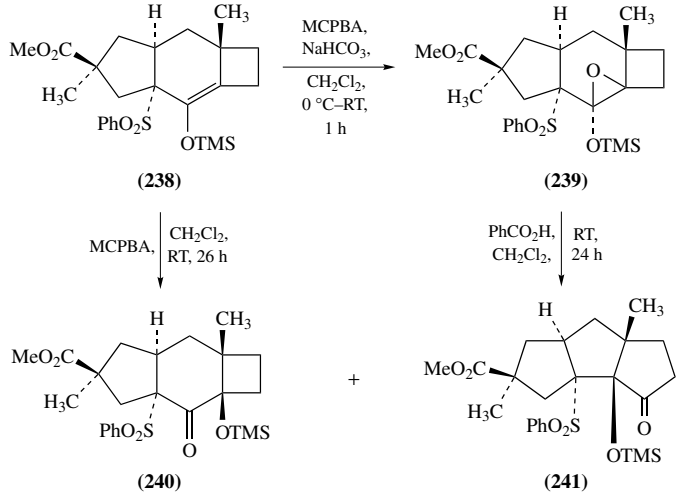


(236) *exo*-**(237)**

n = 1, 2, 3, 4

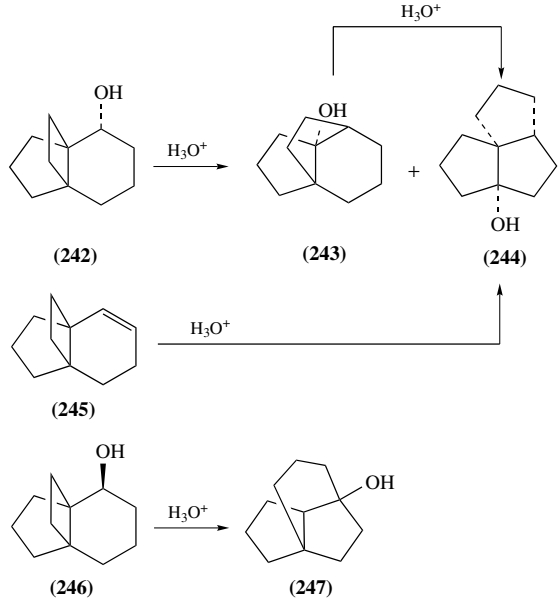
The susceptibility of **239** to acid was made evident by its quantitative conversion to a 77:23 mixture of **240** and **241** when stirred with a catalytic amount of benzoic acid in CH_2Cl_2 at room temperature for 24 h. Comparably, treatment of **238** with unbuffered MCPBA for a similar period of time gave rise directly to **240** in 76% yield alongside **241** ($\sim$ 10%). This synthetic protocol has already been utilized in the syntheses of sterpuric acid and sterpurene-3,12,14-triol, metabolites of the silver leaf fungus *Stereum purpureum*[99].

Treatment of α-alcohol **242** with 40% aqueous H_2SO_4 in THF [1:2 (v/v)] at room temperature for 3 d afforded a mixture consisting of the unreacted starting material and two isomeric alcohols **243** and **244**. At higher temperature (60 °C), **244** was isolated as the sole product. Pure **243** was also converted to **244** when subjected to a higher reaction temperature. Similarly, olefin **245** afforded **244** as the sole product when subjected to the



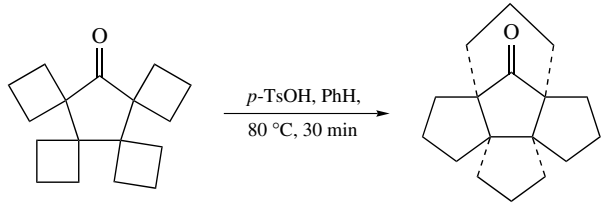
(238) **(239)** **(240)** **(241)**

rearrangement condition (40 °C). In both cases, the rearrangements are consistent with the expected initial peripheral bond migration leading to an intermediate which is then either captured by solvent (to give **243**) or undergoes a second rearrangement (to give **244**). However, when β-alcohol **246** was treated with 40% aqueous H_2SO_4 in THF (60 °C, 30 min), a new crystalline alcohol **247** was isolated in 93% yield. In this case an initial 1,2-migration of the central bond of the propellane ring took place[100].



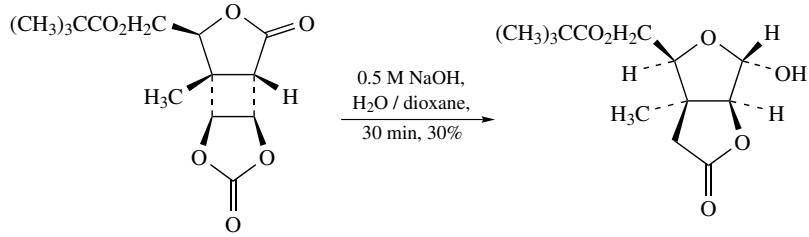
(242) **(243)** **(244)** **(245)** **(246)** **(247)**

A 0.25 M solution of anhydrous *p*-TsOH in PhH (molar ratio **248** : acid = 1:1) isomerized tetraspiroketone **248** quantitatively within 30 min at 80 °C to a new bridged ketone **249** via a fivefold 1,2-shift. The same ketone could also be obtained within 10 h at 80 °C by reaction of Nafion-H with a 0.25 M solution of **248** in PhH (w/w ratio of **248** : Nafion-H = 1:1)[101, 102].



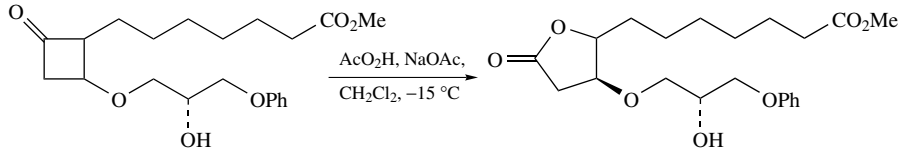
(248) **(249)**

Treatment of **250** with 0.5 M NaOH in water–dioxane for 30 min gave **251** in 30% yield. Similar results could be secured using either water/pyridine with reflux for 30 min or a catalytic amount of NaOMe in MeOH at room temperature for 3 h[103].



(250) **(251)**

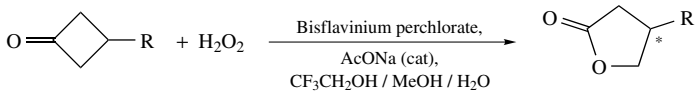
Baeyer–Villiger oxidation of cyclobutanones was employed extensively in natural product syntheses as a key synthetic route. In the synthesis of prostaglandin analogs[104], (±)-eriolanin[105], kempane diterpenes[106], (±)-ginkgolide B[107], pseudomonic acid C[108] and necine bases[109], the lactone rings embedded in these naturally occurring molecules were all obtained from cyclobutanones via a Baeyer–Villiger oxidation. For example, Taylor and coworkers oxidized **252** and **253** by using peracetic acid to yield the regiospecific γ-lactones **254** and **255**[104].



3,4-*trans*-isomer **(252)**
3,4-*cis*-isomer **(253)**

trans-isomer **(254)**
cis-isomer **(255)**

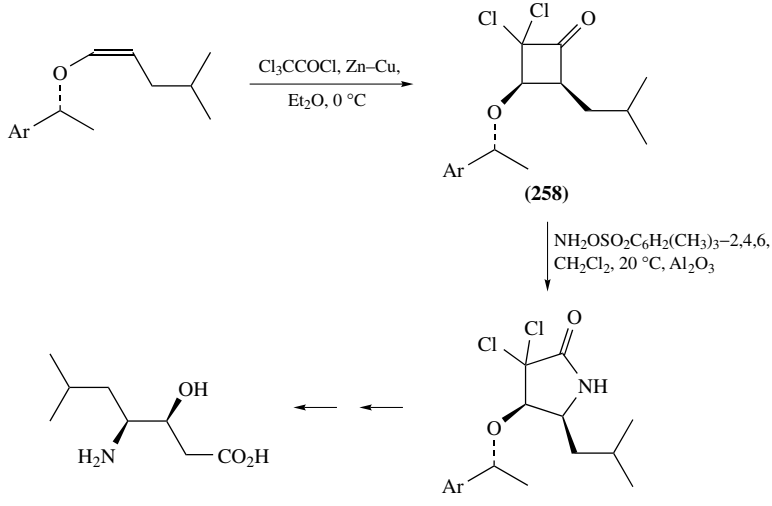
In addition to natural product syntheses, a combination of organometallic reagents[110] and Baeyer–Villiger condition can provide fruitful methods for the asymmetric synthesis of chiral lactones from prochiral cyclobutanones. Every (salen)cobalt(III) complex[111], Zr(salen) complex[112], magnesium complex[113] and palladium(II) 2-(phosphinophenyl)pyridine complex[114] has been shown to give very good enantiomeric results for the asymmetric synthesis of lactones. Recently, Murahashi and coworkers discovered that bisflavinium perchlorate could also serve as an asymmetric catalyst for the oxidation of cyclobutanones **256** to γ-lactones **257**[115] with up to 74% ee.



R=4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, Ph, 4-BrC$_6$H$_4$, 4-C1C$_6$H$_4$, 4-FC$_6$H$_4$

(256) **(257)**

In addition to lactone synthesis, lactams can also be synthesized through a Beckmann rearrangement[116] or a Schmidt reaction[117]. For example, in the preparation of β-hydroxy-γ-amino acid **260**, Beckmann ring expansion of cyclobutanone **258** with Tamura's reagent proceeded without apparent side reactions to give regioselectively a crude α,α-dichloro-γ-lactam **259**[118].



(258)

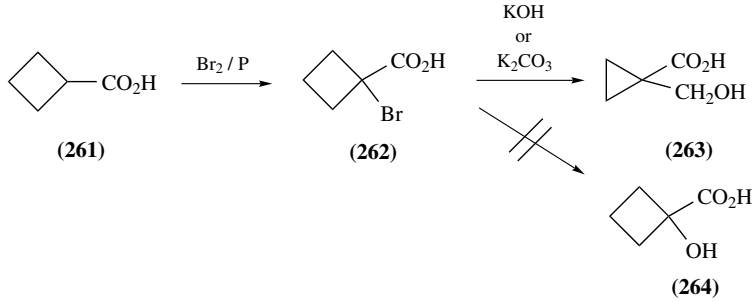
Ar = 2, 4, 6-[(CH$_3$)$_2$CH]$_3$C$_6$H$_2$

(260) **(259)**

C. Ring Contraction to Three-membered Carbocycles

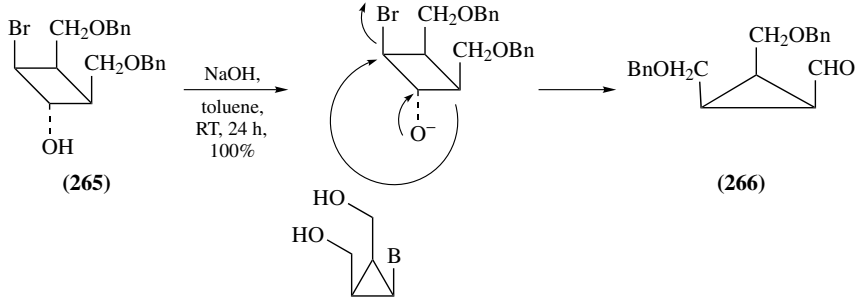
In an attempted synthesis of 1-hydroxycyclobutanecarboxylic acid (**264**) from cyclobutanecarboxylic acid (**261**), Salaün found that the α-bromination product of **261**, namely 1-bromocyclobutanecarboxylic acid (**262**), did not lead to **264**, but exclusively to 1-

(hydroxymethyl)cyclopropanecarboxylic acid (**263**) either in refluxing aqueous KOH or in an aqueous solution containing K_2CO_3[119].



(261) **(262)** **(263)** **(264)**

A quantitative and stereospecific C4 → C3 ring contraction was observed when bromohydrin **265** was treated with crushed NaOH in dry toluene under an atmosphere of Ar. A mechanistic hypothesis is shown in the following Scheme: The carbon bond migrated from the back of the bromine atom, which led exclusively to isomer **266**[120]. In addition, Gauvry and Huet also synthesized *cis,cis*-trisubstituted cyclopropane nucleosides **267** by using the same strategy[121].



(265) **(266)**

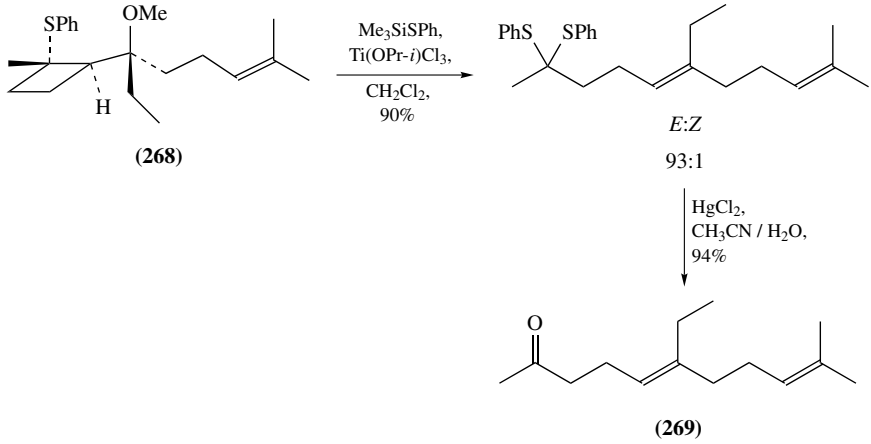
(267a) B = 1-thyminyl
(267b) B = 9-adenyl

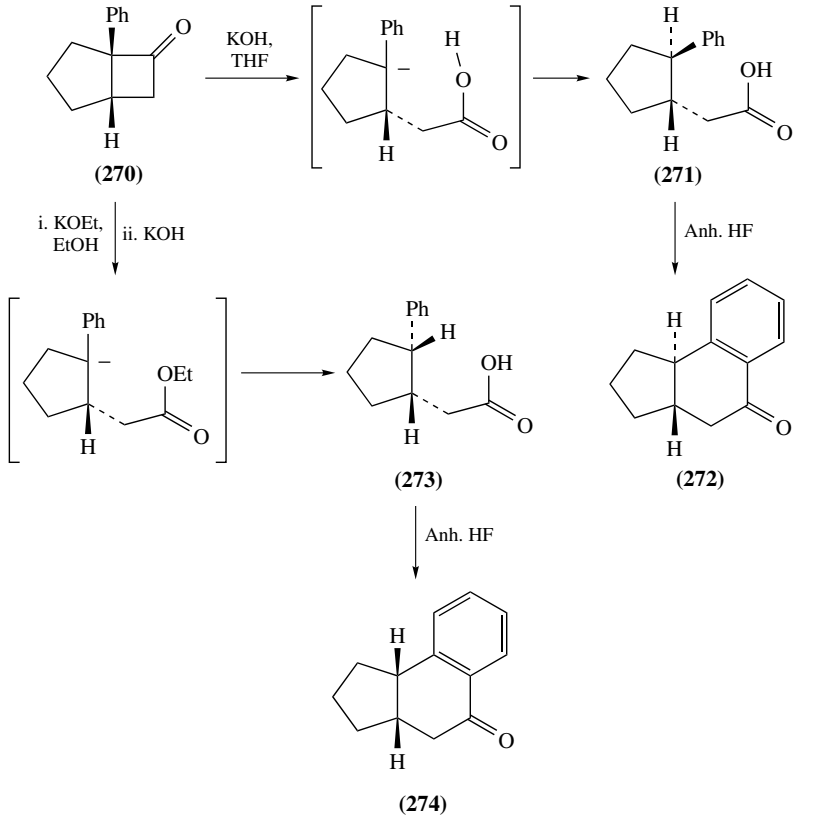
D. Ring Opening by Bases or Nucleophiles

As mentioned before, the cleavage of the cyclobutane ring is quite feasible. The substituents on the ring are not only responsible for facilitating the ring fission but also contributing to maintain the molecular stereochemistry during the course of nucleophilic attack.

As can be seen, the reaction of **268** with phenylthiotrimethylsilane followed by hydrolysis gave (*E*)- and (*Z*)-γ, δ-unsaturated ketones **269** with high *E*:*Z* ratio[122].

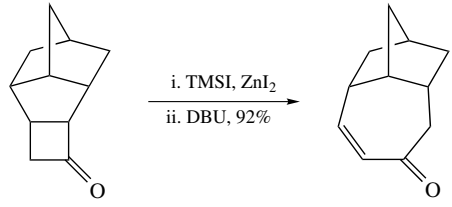
In the stereoselective synthesis of tricyclic compounds **272** and **274**, treatment of **270** with 2 equivalents of anhydrous KOH in THF (0.2 M) at reflux for 12 h gave a 94% yield of a 20:1 mixture of **271** and **273**. On the other hand, treatment of **270** with 5 equivalents of KOEt in EtOH (0.1 M) at reflux for 3 h, followed by addition of water and hydrolysis


SPh
OMe
H
(268)
Me3SiSPh,
Ti(OPr-i)Cl3,
CH2Cl2,
90%
PhS
SPh
E:Z
93:1
HgCl2,
CH3CN / H2O,
94%
O
(269)


Ph
O
H
(270)
KOH,
THF
Ph
H
O
O
H
H
Ph
OH
O
H
(271)
i. KOEt,
EtOH
ii. KOH
Anh. HF
Ph
OEt
O
H
Ph
H
OH
O
H
(273)
H
Ph
OH
O
H
(272)
Anh. HF
H
O
H
(274)

of the ester with heating, gave a 96% yield of a 3:1 mixture of **273** and **271**. Further acylations by using anhydrous HF provided the corresponding tricyclic compounds **272** and **274**[123].

When cyclobutanone **275** was treated with TMSI, ring opening occurred to yield a seven-membered keto iodide. Hydrogen iodide was then eliminated with DBU to give the corresponding enone **276**[124].

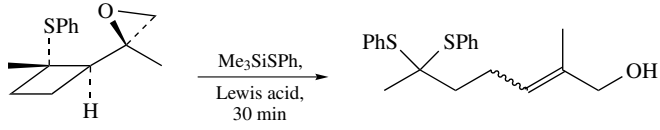


(275) **(276)**

E. Ring Opening and Rearrangement by Acids

Acid-promoted ring cleavage of cyclobutane rings inevitably involves carbenium ion intermediates, whose subsequent rearrangements to more stable carbon skeletons have been utilized widely in organic synthesis. The driving force for this rearrangement is again due to the ring strain of cyclobutanes. The prospect of applying this rearrangement to realize complex molecules is particularly encouraging, and this aspect of rearrangement will be exemplified by the following examples.

Takeda and coworkers chose a ring-opening reaction as a key step in their stereoselective synthesis of allyl and homoallyl alcohols. Cyclobutane **277** was fragmented to the corresponding alcohol **278** in the presence of a Lewis acid in 77–85% yields. It is noteworthy that the *E*:*Z* ratio could be controlled by using different Lewis acids as can be seen in the Table below[125].

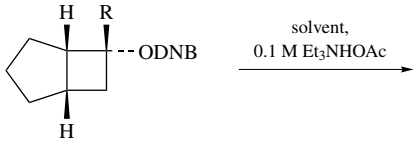


(277) **(278)**

Lewis acid	Yield (%)	*E*:*Z*
$TiCl_2(OPr\text{-}i)_2$	77	97:3
$EtAlCl_2$	85	8:92

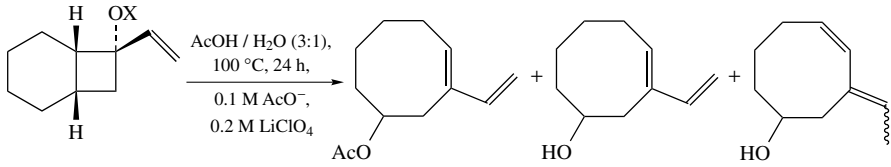
Seven- and eight-membered carbocyclic compounds **284**–**288** and **290**–**292** could be furnished by an acid-promoted solvolysis process starting from the 6-substituted *endo*-6-(3,5-dinitrobenzoyloxy)bicyclo[3.2.0]heptanes **279**–**283** and the vinyl-substituted bicyclo[4.2.0]octane analog **289**[126].

Kato and coworkers synthesized (+)-vernolepin (**295**), (−)-vernomenin (**296**)[127], (−)-kanshone A (**299**)[128], 7-oxo-Kolavenic acid (**302**) and Solidagonic acid (**303**)[129], via



(279–283) DNB = 3,5-dinitrobenzoyl **(284–288)**

Substrate (**274**)	Solvent	Temp (° C) / h	Products (Yield)
279:R = CH_3	AcOH	110 / 24	**284a** (72%) + **284b** (9%)
280:R = Et	AcOH	110 / 24	**285a** (88%) + **285b** (trace)
281:R = Ph	AcOH	110 / 24	**286a** (80%) + **286b** (6%)
282:R = $CH{=}CH_2$	AcOH	80 / 12	**287a** (66%) + **287b** (8%)
	AcOH / H_2O (3:1)	80 / 12	**287a** (54%) + **287c** (28%)
283:R = $CH_3CH{=}CH$ (E / Z = 2.5:1)	AcOH / H_2O (3:1)	110 / 12	**288a** (51%) + **288c** (14%)



(289)	**(290)**	**(291)**	**(292)**
X = DNB	43%	27%	trace
X = COPh	65%	23%	4%

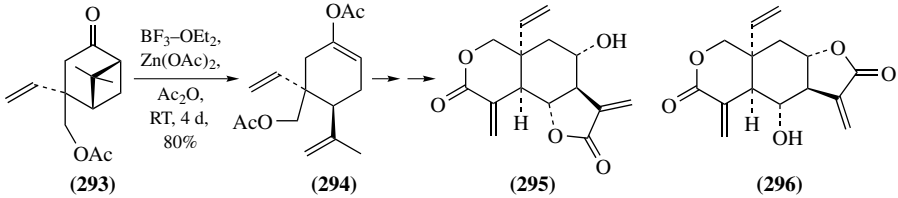
intermediates **294, 298** and **301**, respectively. Compounds **293, 297** and **300** all underwent $BF_3{-}OEt_2$-promoted cyclobutane cleavage to give the corresponding enol acetate **294, 298** and **301** in high yields.

In the total synthesis of the antimalarial natural product (+)-qinghaosu, the cyclobutane ring in ketone **304** also underwent a fragmentation reaction in the presence of *p*-TsOH and ethylene glycol in PhH under reflux condition to give **305**[130].

The Lewis acid-promoted reaction of 2-phenylthiocyclobutanemethanol derivative **306** with silyl nucleophiles gave the corresponding substituted olefins **307** with high stereoselectivity and in good yields[131].

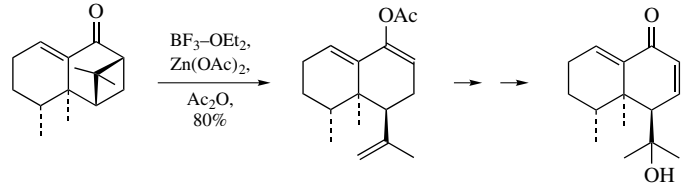
Stereoselective rearrangement of 6,7-epoxy-3-oxabicyclo[3.2.0]heptan-2-ones (**308** and **309**) in water afforded a *cis*-fused butyrolactone as a mixture of two epimers **310** and **311** in 35–37% yields, together with a minor amount of the unstable side product **312** in 7–11% yields[132].

In the synthesis of (+)-codeine, White and coworkers attempted to use an acid-induced ring-opening method. In this connection, the stereomeric mixtures **313** underwent a Wagner–Meerwein rearrangement in the presence of $BF_3{-}OEt_2$ to give the bridged tetracycle **314**, albeit in a low yield[133].



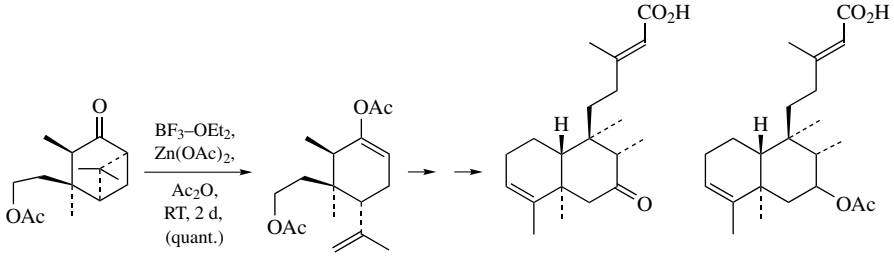
(293) **(294)** **(295)** **(296)**

(+)-Vernolepin (−)-Vernomenin



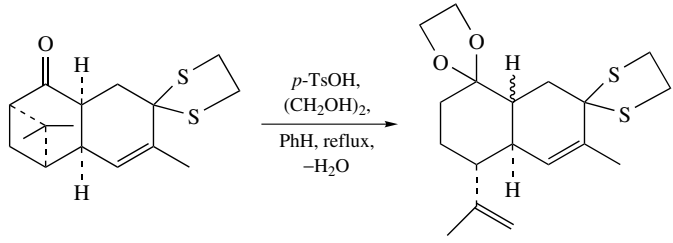
(297) **(298)** **(299)**

(−)-Kanshone A



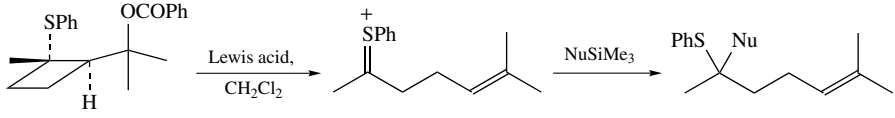
(300) **(301)** **(302)** **(303)**

7-oxo-Kolavenic acid Solidagonic acid



(304) **(305)**

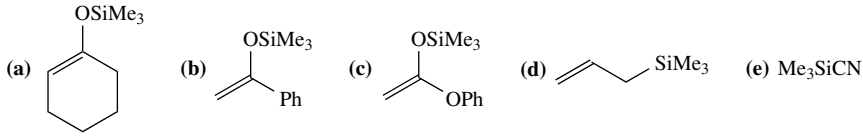
Irradiation of cyclopentenone **315** in the presence of allene in CH_2Cl_2 at $-78\,^{\circ}C$ gave the head to head adduct **316** in 84% yield. The rearrangement of **316** with $TiCl_4$ (5 equivalents) proceeded at room temperature to give bicyclo[3.2.1]heptanone (**317**) in 78% yield. This synthetic method was later used as a pivotal step in the construction of the AB-ring core of taxol[134].

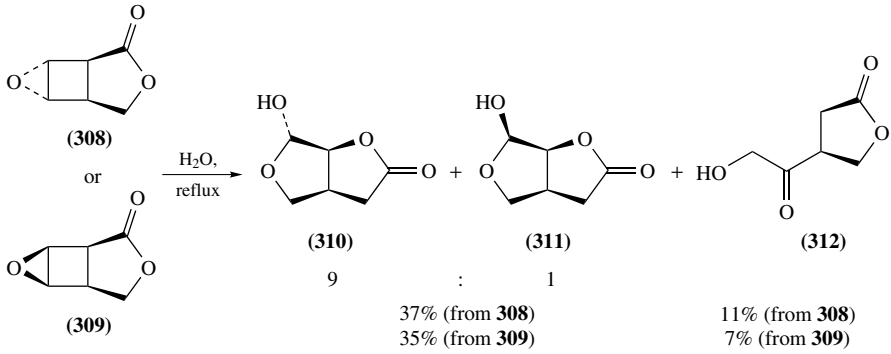


(306) **(307)**

Me_3SiNu	Lewis acid	Temp (°C)	Time (h)	Yield (%)
a	$(PhO)AlCl_2$	−78	2	55
b	$(PhO)AlCl_2$	−78	1.5	82
c	$EtAlCl_2$	−40	1.5	80
d	$EtAlCl_2$	−78	7	51
e	Et_2AlCl	−78–0	3.5	89

$NuSiMe_3$ =



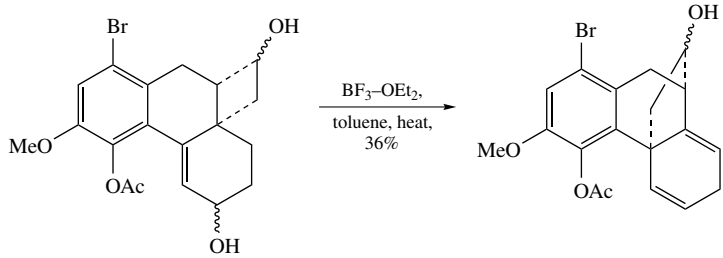


(310) **(311)** **(312)**

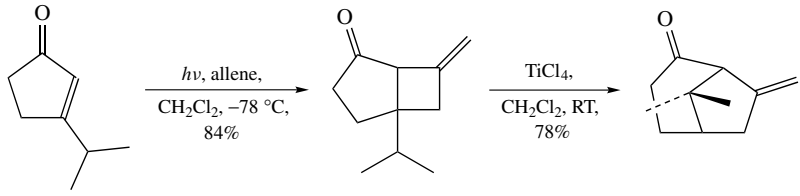
9 : 1

37% (from **308**)
35% (from **309**)

11% (from **308**)
7% (from **309**)



(313) **(314)**



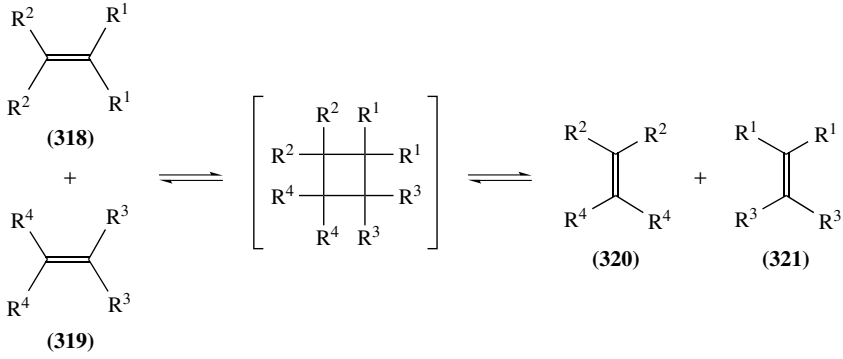
(315) **(316)** **(317)**

III. THERMAL RING OPENING

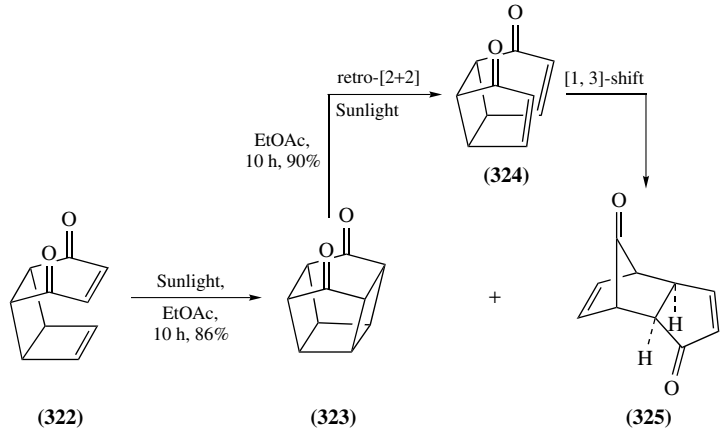
The inherent ring strain of cyclobutanes makes the thermal electrocyclic ring opening so feasible that sometimes such ring opening can even occur at room temperature. In Gourdel-Martin and Huet's synthesis of norcarbovir analogs, this facile thermal ring-opening process has ironically become the main difficulty in obtaining his target molecules[135]. On the other hand, a great number of synthetic strategies for realizing highly complex molecules nevertheless depend on this approach. Some cases in point are illustrated in the following sections.

A. Olefin Metathesis

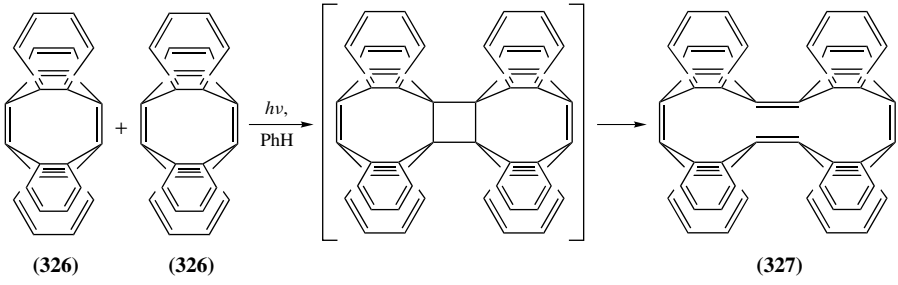
When alkene **318** is allowed to react with **319**, other alkenes **320** and **321** are obtained in a reaction in which the substituents on the alkenes formally interchange. This interconversion involving a cyclobutane intermediate is coined 'olefin metathesis'.



If the cycloaddition and cycloreversion steps occur under a similar condition, an equilibrium will be established and a mixture of alkenes will be obtained. As such, this complication would severely limit its synthetic use. The spontaneous transformation of metathesis products to more stable species will by all means shift the equilibrium and as a result the reactants would be consumed thoroughly. For example, irradiation of **322** under sunlight led to a 2:3 mixture of **323** and **325** in a total yield of 85%. Formation of **325** clearly indicated the intervention of the metathesis olefin **324** which further underwent a photochemical [1,3]-shift to furnish **325** in 90% yield[136]. This 'photo-photo metathesis' process was applied to the construction of polycyclic frameworks.

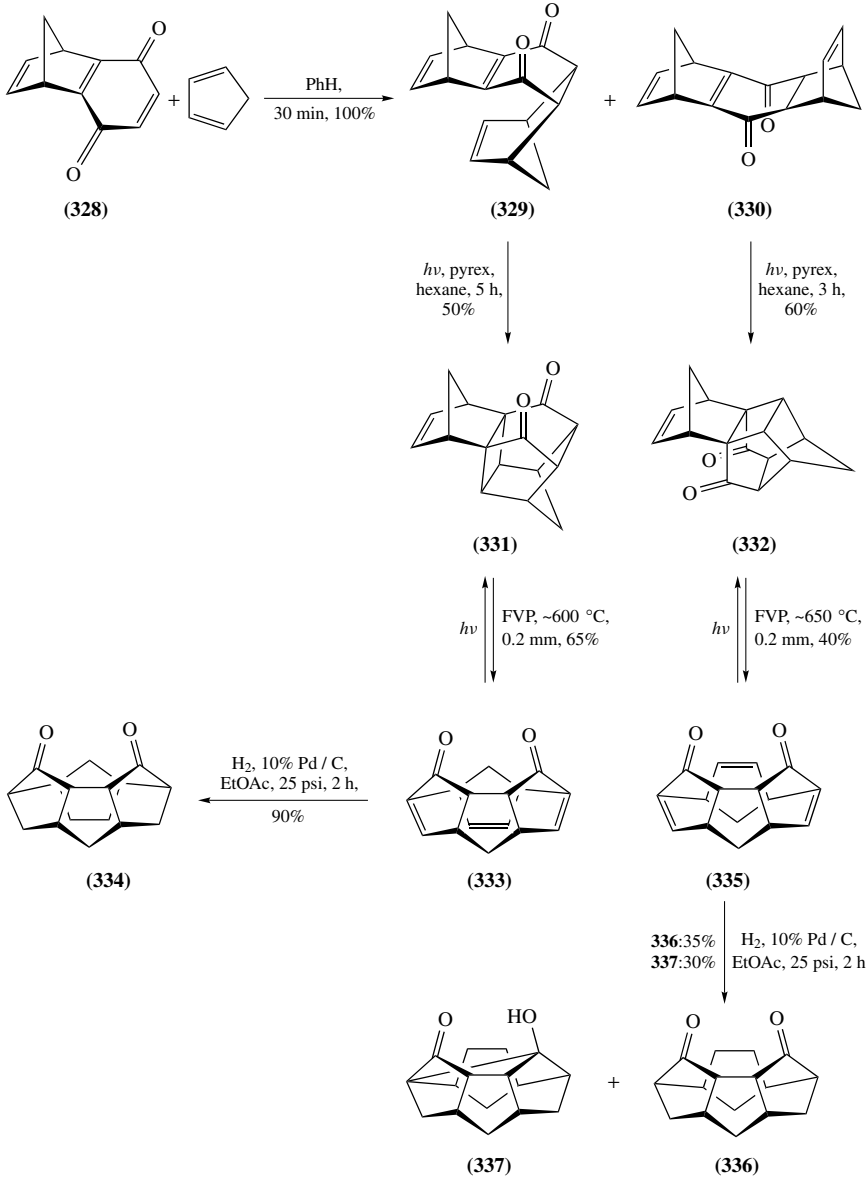


Fortunately, in many cases the two steps can proceed under very different conditions, thereby exhibiting pronounced regioselectivity. In this way many medium-sized rings were constructed based on ring-expanding metathesis reactions. For instance, photolysis of a suspension of tetradehydrodianthracene (**326**) in PhH with a high-pressure mercury lamp in a quartz apparatus led to the dimerizing metathesis and gave a beautiful tubelike compound **327**[137].

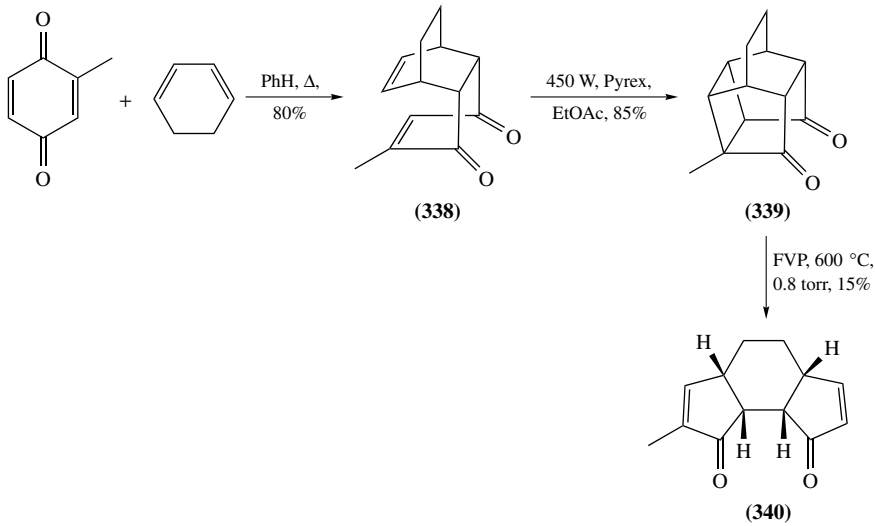


In the pursuit of dodecahedrane, a photo-thermal metathesis sequence was used as a key step in the synthesis of 'roofed' polyquinanes[138,139]. For example, reaction of cyclopentadiene and norbornenobenzoquinone (**328**) furnished the Diels–Alder adducts *endo,syn*-**329** and *endo,anti*-**330** (65:35) in high yields. Irradiation of **329** and **330** by UV light resulted in a smooth intermolecular [2 + 2]-cycloaddition to form the caged diones **331** and **332**, respectively. Passage of the major dione **331** through a quartz column under FVP (flash vacuum pyrolysis) conditions led to a regioselective [2 + 2]-cycloreversion of the cyclobutane ring [photo-thermal metathesis of **329**] to furnish *bis*-enone **333**. Catalytic hydrogenation of **333** gave the cyclopentane 'roofed' saturated dione **334**. In a similar manner, the minor caged dione **332** furnished the stereoisomeric *bis*-enone **335** on thermolysis (FVP). Hydrogenation of **335** led to an approximately 1:1 mixture of dione **336** and its internal aldol product **337**[140].

Another example revealed that the Diels–Alder adduct **338**, prepared from 1,3-cyclohexadiene and 2-methyl-*p*-benzoquinone, was photocyclized to the pentacyclic dione



339. Flash vacuum pyrolysis of **339** gave the required tricyclic *bis*-enone **340**, along with 2-methylhydroquinone[141]. *bis*-Enone **340** can serve as a key intermediate in an approach toward the tricyclic perhydro-as-indacene ring system found in the structurally novel antibiotics ikarugamycin and capsimycin.



(338) **(339)** **(340)**

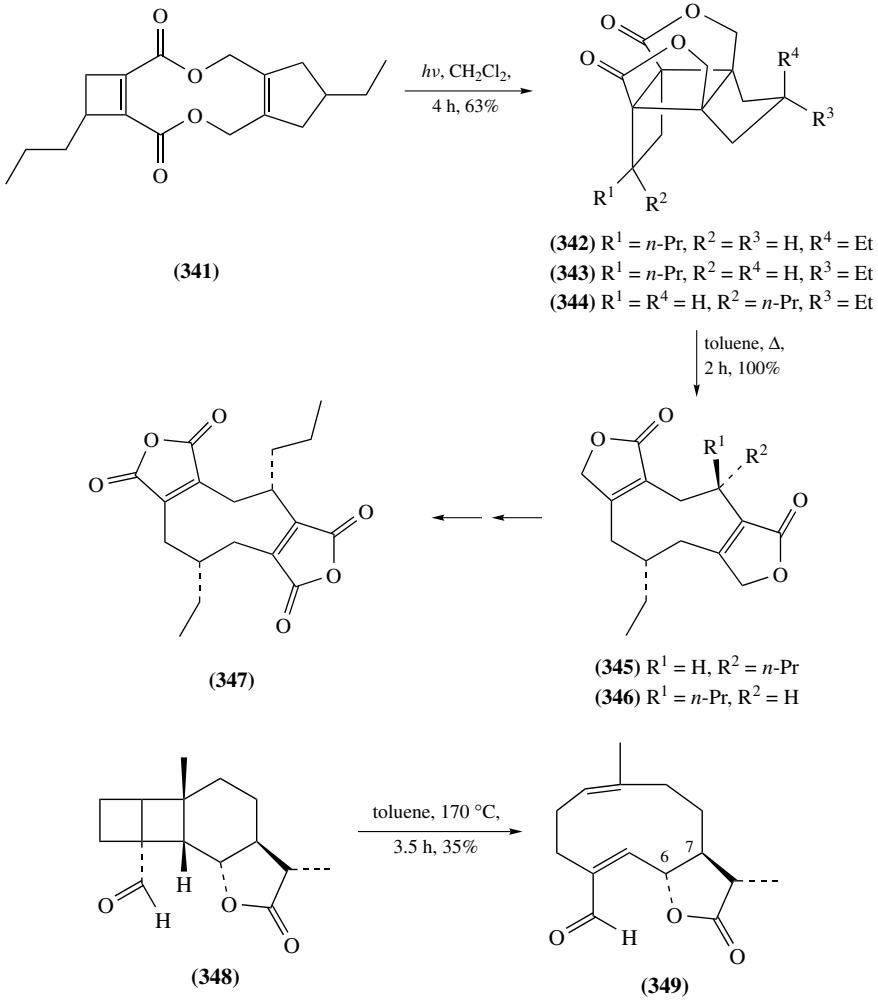
In White and coworkers' total synthesis of (±)-byssochlamic acid (**347**), characterized by the presence of a nine-membered carbocycle fused to two five-membered anhydride residues, a 'photo-thermal metathesis' strategy was also employed. Thus, irradiation of diolide **341** as a mixture of *syn* and *anti* stereoisomers in a dilute solution afforded the intramolecular photoadducts **342, 343** and **344** in the ratio 2:1.6:1. Thermolysis of the mixture of **342, 343** and **344** in refluxing toluene led to a quantitative cycloreversion of the central cyclobutane ring in a direction opposite to that from which it had been formed. As a result, a 2:1 mixture of *syn* and *anti* cyclononadienes **345** and **346** was produced[142, 143].

Upon thermolysis of aldehyde **348** at 170 °C for 3.5 h, *cis*-1,10-*trans*-4,5-cyclodecadiene (**349**) was obtained in 35% yield. This is another example in which the cycloaddition–thermolysis sequence was utilized. In addition, this approach also introduced a new concerted route to the formation of the *trans*-fused-γ-lactone ring bridging C-6 and C-7, a structural moiety present in most germacranolides[144, 145].

B. Cope Rearrangement

Heating of 1,5-dienes resulted in a [3,3]-sigmatropic rearrangement which is also known as the Cope rearrangement[146]. Although almost all 1,5-dienes undergo the Cope rearrangement at temperatures around 300 °C, the isomerization would take place more easily at lower temperature when the newly formed double bond can conjugate with other functional groups. Consequently, the energy difference between the two isomers should disturb the reversible reaction and the equilibrium therefore shifts towards the thermodynamically more stable one.

When a hydroxyl group is substituted at the 3-position of a 1,5-diene, the Cope rearrangement becomes irreversible due to the product's ability to tautomerize to a carbonyl compound. This reaction is generally called an oxy-Cope rearrangement, which can take place at a much lower temperature. Furthermore, when this transformation is accompanied

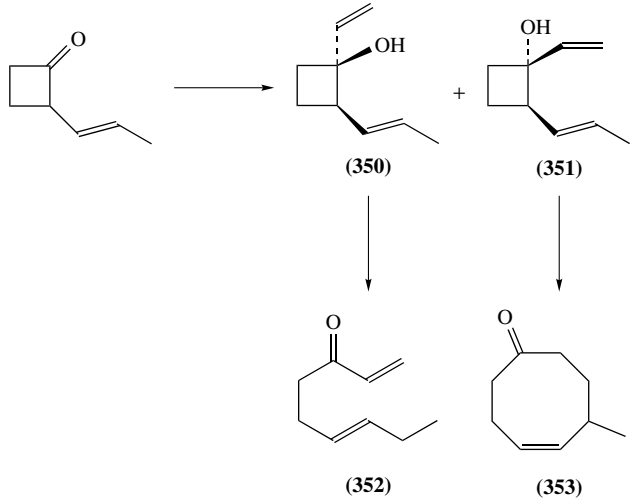


by a significant strain release, the process is irreversible and is also able to deliver a high level of chirality transfer and region control under very mild conditions.

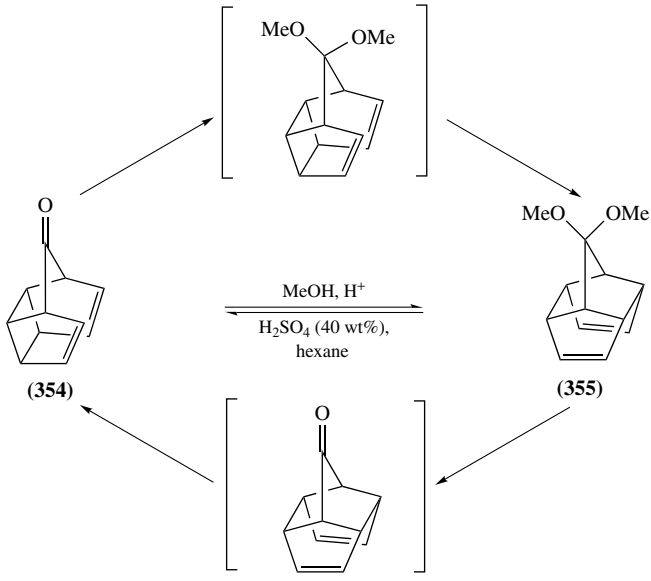
Substituent effects influencing the rate of oxy-Cope rearrangement to form cyclooctenones have been carefully studied by monitoring with NMR spectroscopy. The results show that in the absence of steric effects, all substituents would accelerate the rearrangement[147].

The influence of stereochemistry on the rearrangement of 1,2-dialkenylcyclobutanols was studied by Barnier and coworkers: While *trans*-1,2-divinylcyclobutanols **350** underwent a retro-ene ring opening to afford ketone **352**, the *cis* isomer **351** went through an oxy-Cope ring enlargement to afford ketone **353**[148]. It is therefore clear that the *cis*

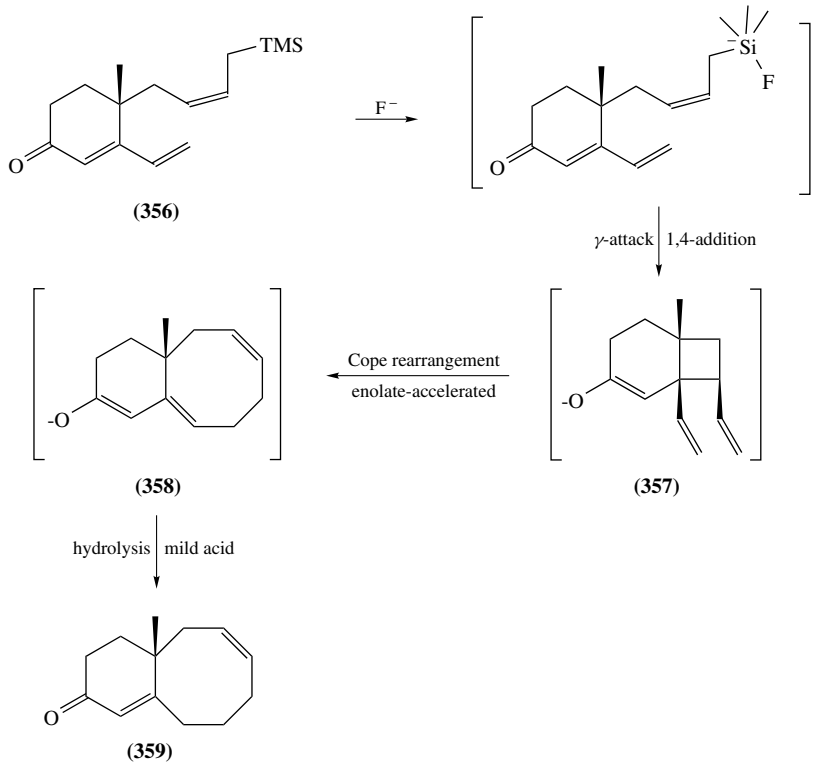
relationship between the two vinyl substituents of the cyclobutane is a prerequisite of the Cope rearrangement.



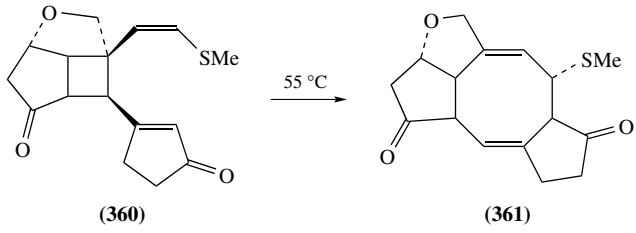
An intriguing Cope interconversion of the tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-diene (**354**) and tetracyclo[7.2.0.0^{4,11}.0^{6,10}]undeca-2,7-diene (**355**) was observed by Eaton and Yip. According to their experimental results, the molecular framework favored at equilibrium depended on the angle (hybridization) of the methylene bridge, which is in good agreement with calculated heats of formation[149].



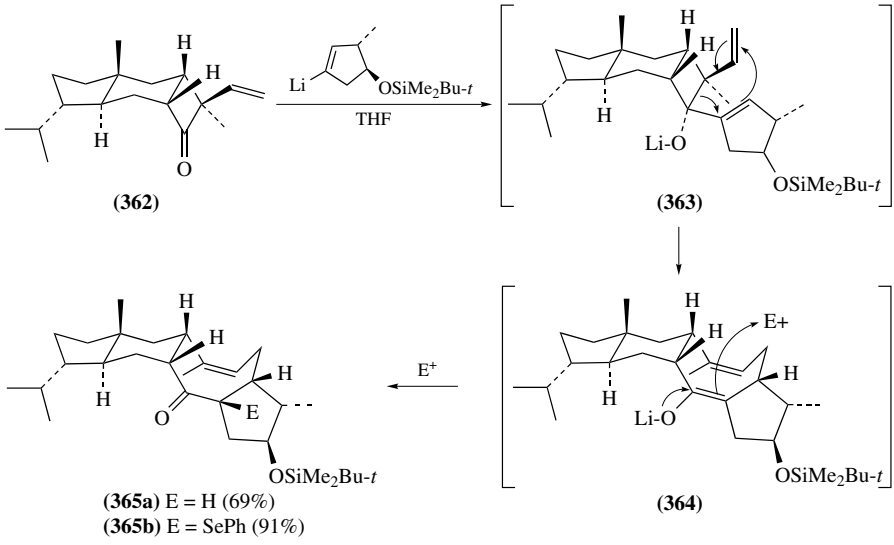
The Cope rearrangement of divinylcyclobutanes was intensively utilized in the construction of eight-membered ring systems. Some examples are illustrated below. Treatment of dienone **356** with fluoride ion at room temperature permitted a facile entry into 6,8-bicyclic skeletons. The reaction sequence was triggered by a conjugate addition of the allylsilane in a 1,4-fashion via an S_E2'-process, generating a 1,2-divinylcyclobutane intermediate **357**. A Cope rearrangement of **357** then provided diene **358** and hence enone **359** upon a subsequent acid treatment[150].



Thermolysis of compound **360** in PhH at 55 °C for 4 h led to its clean transformation to **361** in quantitative yield. Only a very mild condition was required, presumably because of the participation of the sulfur lone-pair or due to the ring strain of the divinylcyclobutane derivative **360**[151].



Upon treatment with cyclopentenyllithium at −78 °C, the tricyclic ketone **362** was transformed to intermediate **363**, which underwent a Cope rearrangement to form intermediate **364**. Following the addition of water or phenylselenenyl chloride, respectively, the tetracyclic ketones **365a** or **365b** were obtained. The ketone **365b** served as an intermediate in Paquette and Heidelbaugh's total synthesis of the antifungal antibiotic aleurodiscal[152].

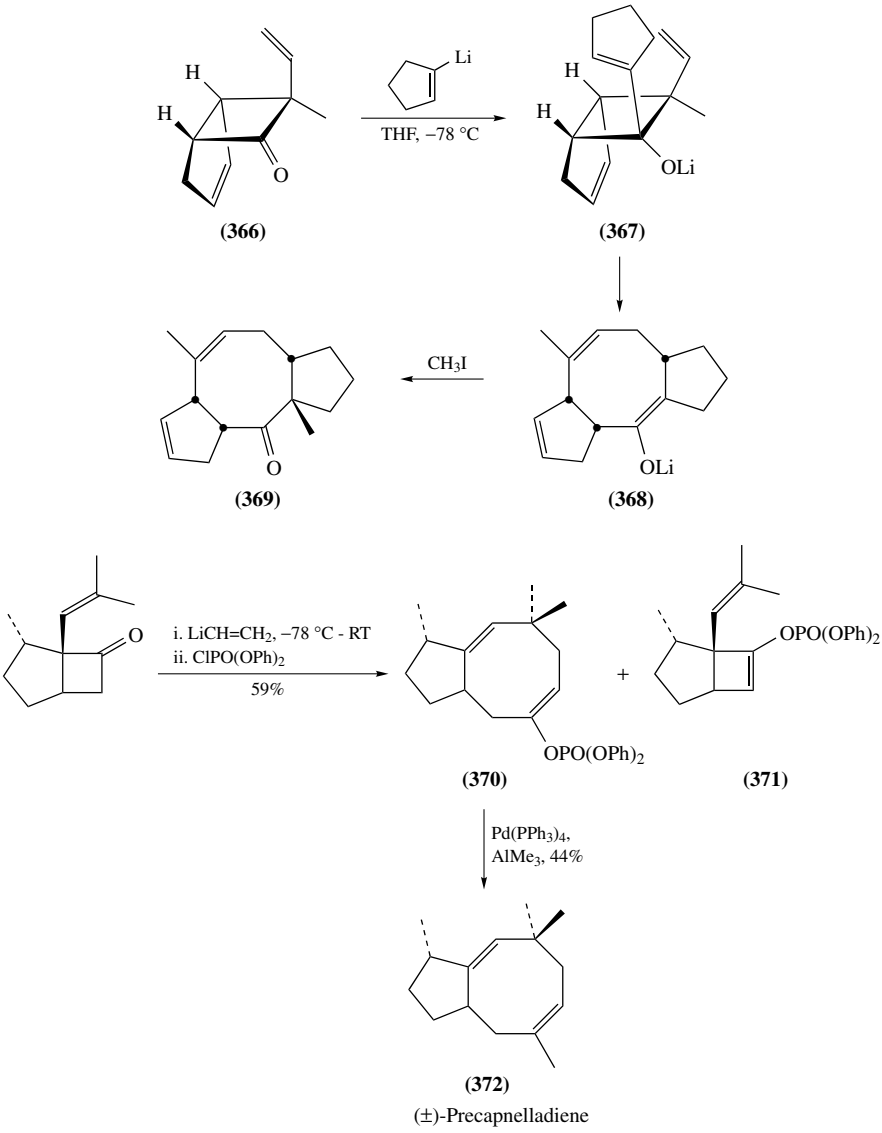


Addition of cyclopentenyllithium to **366** has previously been shown to direct to a spontaneous oxyanionic Cope rearrangement within **367**. The substantial relief of ring strain led stereospecifically to enolate anion **368**, which could be methylated to provide **369**, a functionalized all-*cis*-dicyclopenta[*a*,*d*]cyclooctane related to the ophiobolins, ceroplastols and fusicoccins[153].

The addition of vinyllithium, followed by an oxy-Cope rearrangement and trapping of the resulting enolate as its diphenyl phosphate derivative, afforded in 59% yield a 5:1 mixture of **370** and **371**. Exposure of **370** to $AlMe_3$ in the presence of a catalytic amount of $Pd(PPh_3)_4$ provided (±)-precapnelladiene (**372**) in 44% yield[154].

The intramolecular photocycloaddition of bis-dienes also provided the basis for an efficient and practical route to cyclooctadienes and triquinanes. Thus, photolysis of tetraene **373** followed by thermolysis of the photo-product gave in 60% overall yield cyclooctadiene **374**, which could be transformed to coriolin (**375**) after a number of steps[155].

Boeckman and Reeder found out that the dialdehyde derivatives of vinylcyclobutane could undergo a retro-Claisen rearrangement under thermal conditions to provide enantiomerically pure dihydrooxacenes, accompanied by the relief of the inherent strain of the four-membered ring[156]. They also employed this rearrangement procedure in the total synthesis of (+)-laurenyne. In Boeckman's programme, diester **376** was reduced with LAH under a standard condition to afford diol **377** in 93% yield. Upon Dess–Martin periodinane (DMP) oxidation and subsequent thermal equilibration at 45 °C, the desired dihydrooxocene **379** was obtained in 92% yield. Interestingly, in this synthesis, dialdehyde **378** could be isolated under a carefully controlled condition[157].

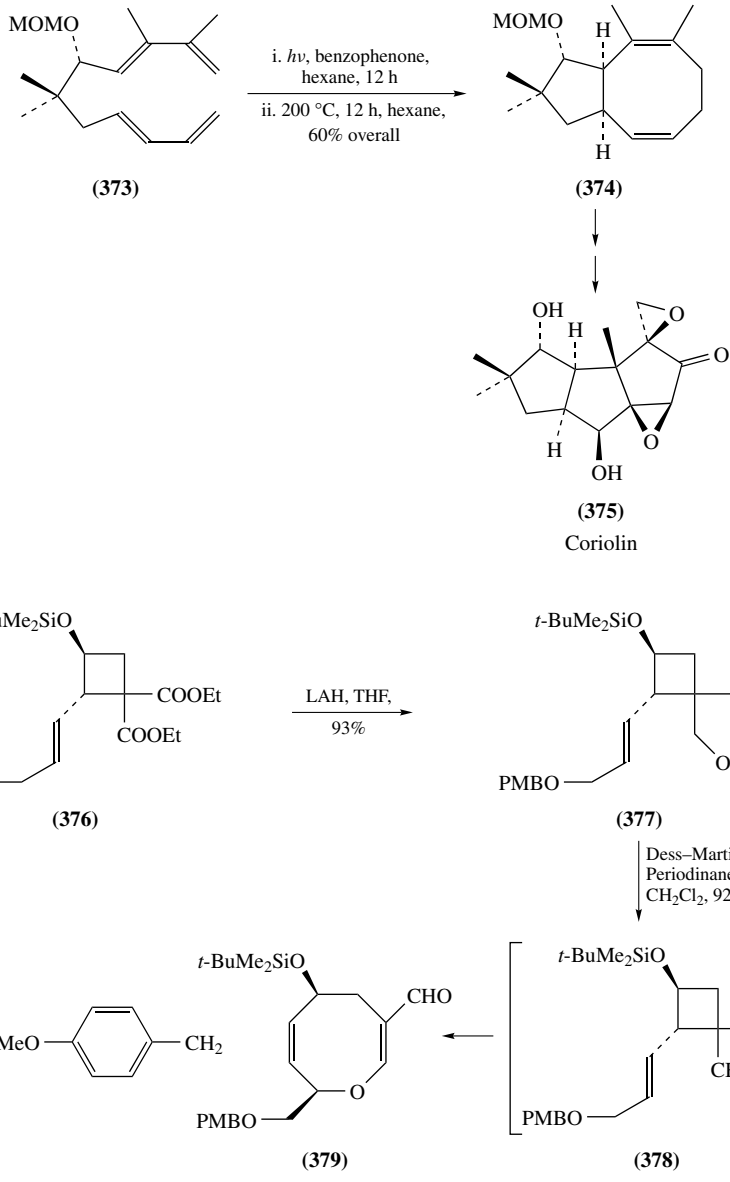


(366) **(367)** **(368)** **(369)** **(370)** **(371)** **(372)**

(±)-Precapnelladiene

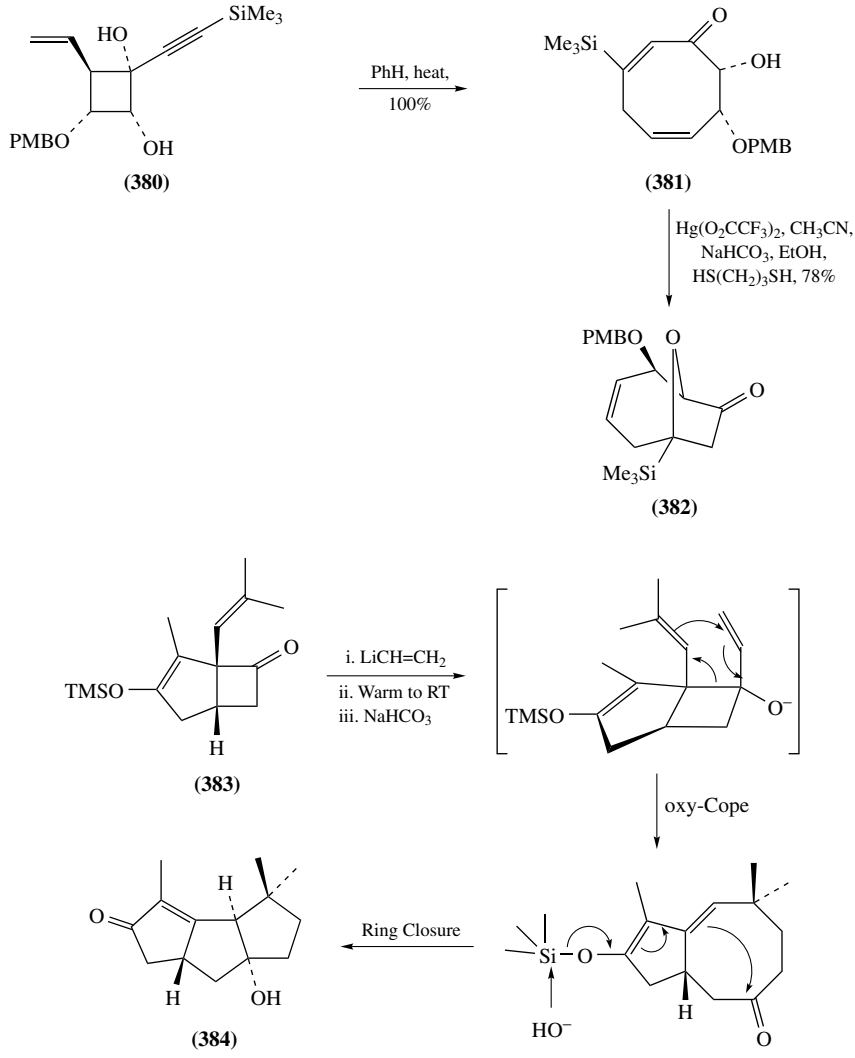
The Cope rearrangement, in connection with a transannular ring-closure reaction, is extremely useful in organic synthesis because the reaction sequence, starting from rather simple substrates, yields remarkably complex polycyclic structures. Some interesting examples are illustrated below.

Heating in PhH transformed **380** smoothly to **381** in a quantitative yield. When **381** was subjected to the action of mercuric trifluoroacetate, with subsequent reductive cleavage



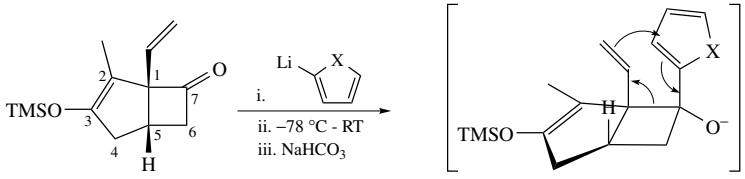
of the organomercurical, an oxygen bridge was installed to afford [4.2.1]bicyclic ketone **382** in 78% yield[158].

Upon addition of an appropriate vinyllithium reagent to bicyclo[3.2.0]heptenones such as **383**, followed by warming and subsequent basic workup, highly functionalized polycyclic products were formed (e.g. **384**) via also a tandem oxy-Cope transannular ring-closure reaction sequence[159].

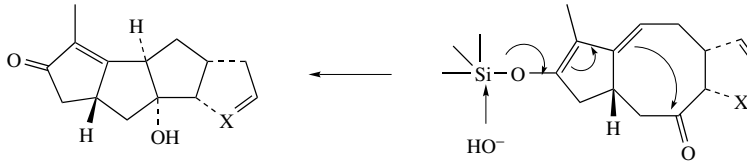


Addition of 2-lithiofuran or 2-lithiothiophene to **385**, followed by warming to room temperature with subsequent basic workup, gave the linearly fused polyquinane **388a** (60%) or **388b** (60%), respectively. Their formation is envisaged to stem from alkoxide **386**, which underwent an oxy-Cope ring expansion through a *cis*-boat conformational transition state. Subsequent hydrolytic desilylation of the resulting dienyl ether **387** accompanied by a concomitant transannular ring closure afforded **388**[160, 161].

Furthermore, treatment of the triquinanes **389** with *t*-BuOK in warm *t*-BuOH induced their remarkable rearrangement to the angular isomers **392** in 59–84% yields. This rearrangement is believed to involve the formation and equilibrium of the enolates **390** and **391** followed by an intramolecular Michael addition of the enolate ion in **391** to the enone moiety[162].

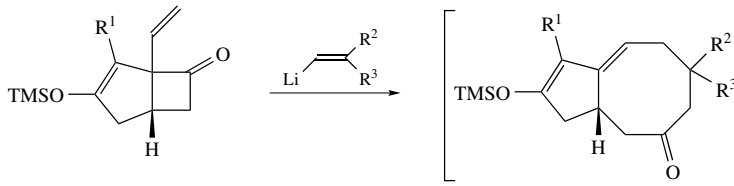


(385) **(386)**



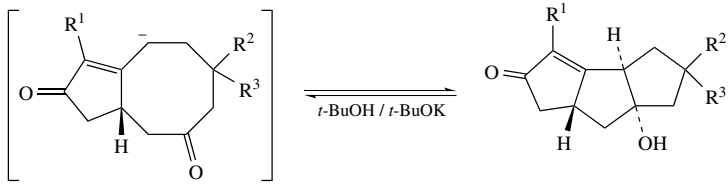
(388a) X = O (60%)
(388b) X = S (60%)

(387)

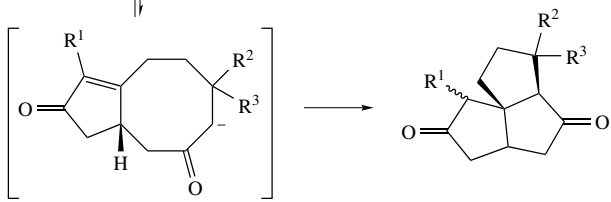


R^1 = OMe, Me, R^2 = R^3 = H, Me

H_2O

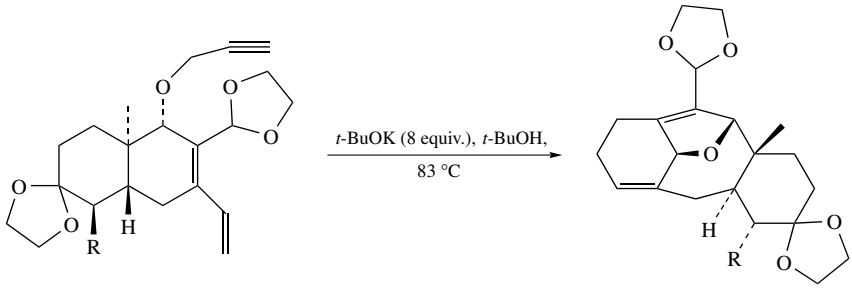


(390) **(389)**



(391) **(392)**

Another novel tandem intramolecular [2 + 2]-cycloaddition and [3,3]-sigmatropic rearrangement of the allenyl ethers led to the construction of tricyclic [*n*.3.1] carbon ring systems. For example, treatment of the bicyclic propargyl ethers **393a** or **393b** with *t*-BuOK (8 equivalents) in *t*-BuOH at 83 °C for 1 h afforded **394a** or **394b**, respectively, in an almost quantitative yield. This synthetic route was utilized to build the tricyclic[9.3.1.$0^{4,9}$]pentadecane skeleton, characteristic of the taxane diterepenes[163].



(393a) R = H
(393b) R = Me

(394a) 100%
(394b) 96%

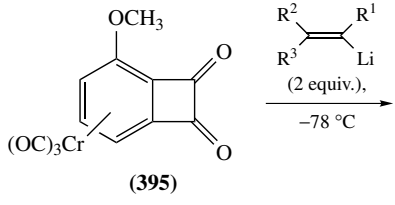
The chemistry of (arene)tricarbonylchromium complexes with functionalized annellated rings is dominated by a selective reagent attacked from the face opposite the tricarbonylchromium group[164]. This can facilitate the transfer of the planar chirality of the chromium complex to a center of chirality in the annellated ring. Butenschön and coworkers[165] utilized this synthetic protocol to study dianionic oxy-Cope rearrangements. In contrast to the dianionic oxy-Cope rearrangements starting from the unsubstituted benzocyclobutenedione complex which afforded symmetrical bis(enolates), treatment of **395** with a vinyllithium provided bis(enolate) **396** as a result of the rearrangement process. In the unsubstituted case the symmetry was destroyed by the subsequent intramolecular aldol addition, yielding a racemic mixture. Complex **395**, in contrast, would in principle afford two different products, namely **397** and **398**, as either one of the enolate moieties of **396** might, after hydrolysis, play the roles as an enol (or enolate) or the ketone component in the aldol addition.

In Limanto and Snapper's total syntheses of (+)- and (−)-asteriscanolide, cyclobutene **399** was treated with ruthenium benzylidene **401** (5 mol%, 50 °C, 10 h) in PhH under an ethylene atmosphere, and was followed by reflux for 10 h to produce cyclooctadiene **400** in 74% yield. Evidently, the dialkenyl cyclobutane formed initially in the ring-opening metathesis and then the Cope rearrangement proceeded under a relatively mild reaction condition[166].

A similar process was also utilized in a ring-opening cross-metathesis reaction between cyclobutene-containing substrates and terminal olefins in the presence of $(Cy_3P)_2Cl_2Ru{=}CHCH{=}CPh_2$. This reaction selectively afforded 1,5-diene-containing molecules[167].

A concise synthetic sequence towards 5-8-5 ring systems also involved a stereo- and regioselective [2 + 2]-photocycloaddition of functionalized cyclobutenes followed by thermolysis of the resulting photoadducts. For example, heating of photoadduct **402** with butylated hydroxytoluene (BHT) in PhH at 200–240 °C afforded tricyclic ketone **403** in 88% yield[168].

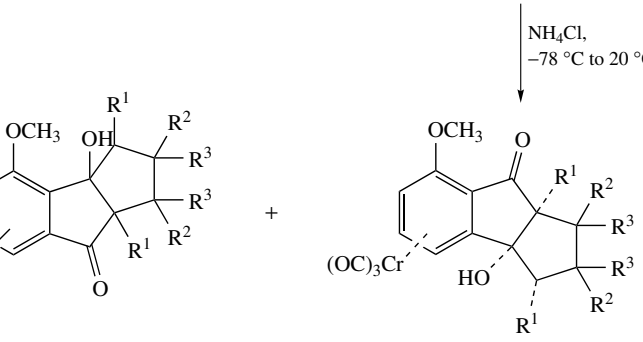
A similar intramolecular [2 + 2]-photocycloaddition/thermal fragmentation approach was used to construct 5-8-5 ring systems. However, when thermolysis of photoadduct



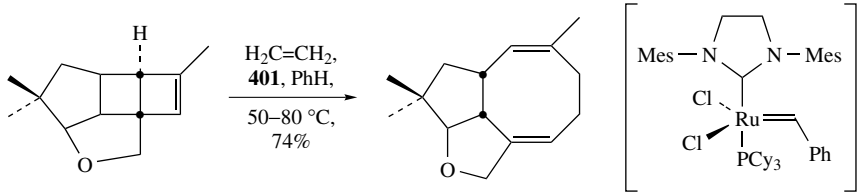
(395)

R^1, R^2=OCH_2CH_2, R^3=H

(396)

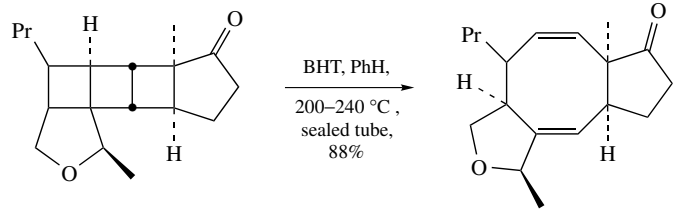


(398) **(397)**



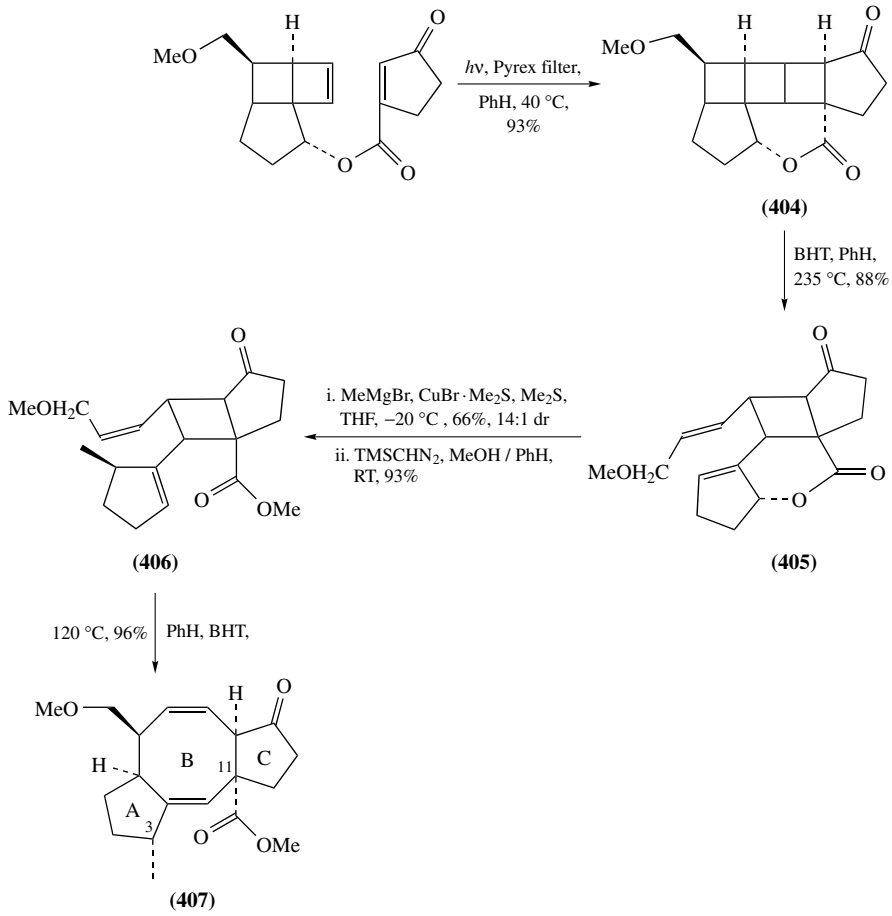
(399) **(400)** **(401)**

Cy = cyclohexyl
Mes = mesityl

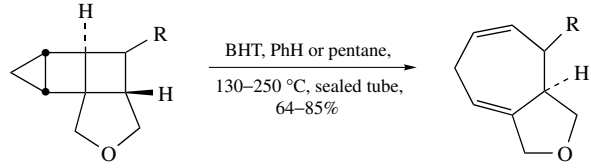


(402) **(403)**

404 was carried out at 235 °C in PhH, the thermodynamically more favorable dialkenylcyclobutane **405** was produced in 88% yield, instead of the formation of any cyclooctadiene products due to the geometric constraints imposed by the lactone. Treatment of **405** with methyl organocopper reagents and subsequently with trimethylsilyldiazomethane generated methyl ester **406** in 61% overall yield. A thermal Cope rearrangement of cyclobutane **406** furnished compound **407** in 96% yield with the desired C(3) methyl group installed on the A ring and an ester at C(11) in the corresponding 5-8-5 natural product framework[169].



This strategy was also employed in the construction of bicyclo[5.3.0]ring systems relying on the cyclopropanation of highly functionalized cyclobutenes followed by a selective fragmentation of the resulting adduct with exceeding strain. In general, heating of the cycloadducts **408** led to a desired 5–7 ring systems **409** in 64–85% yields[170].



(408) **(409)**

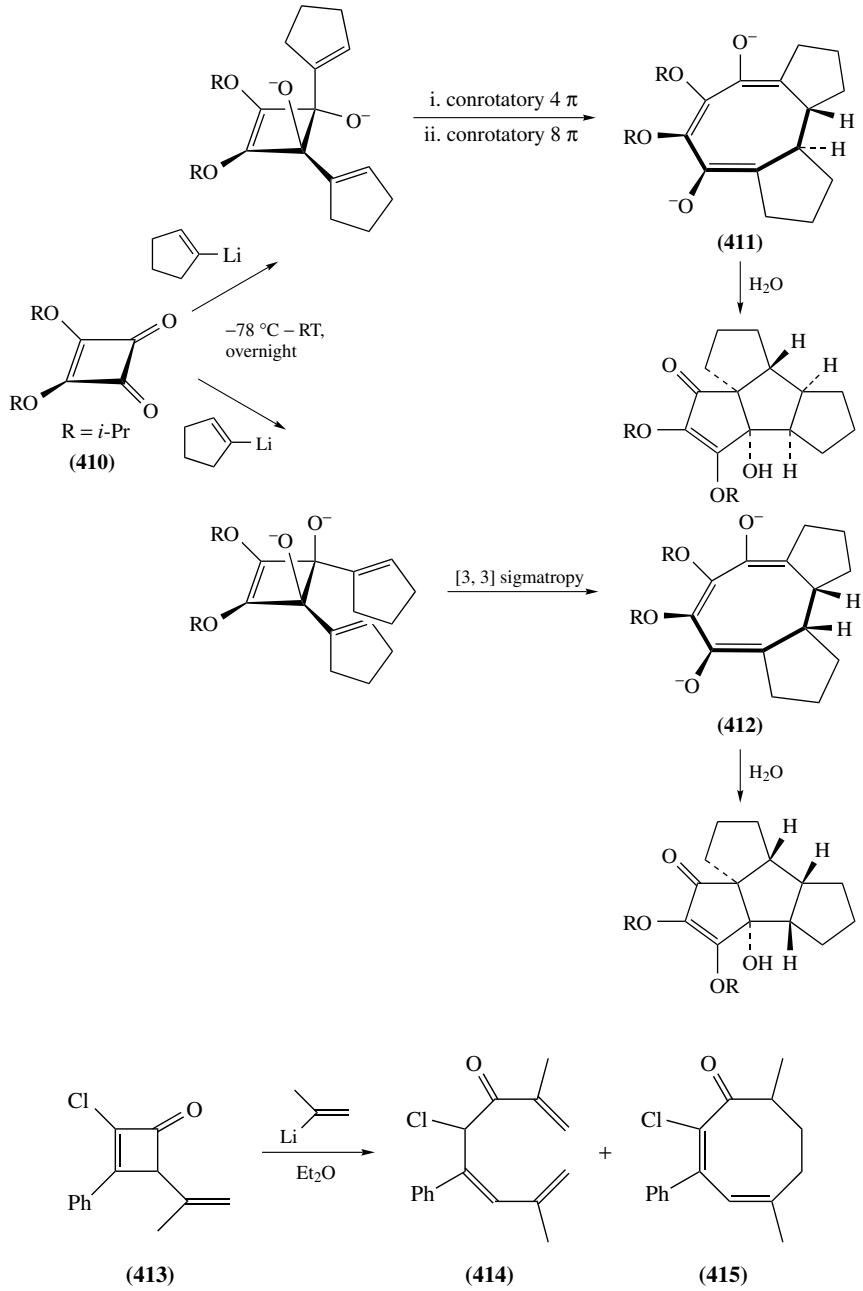
During the past 15 years, cyclobutene-1,2-diones have emerged convincingly from the class of theoretically interesting molecules to become useful synthetic precursors. This advancement has uniformly taken advantage of their complex functionalities and appreciable ring strain inherent in the four-membered dicarbonyl frameworks. The addition of 2 equivalents of the same alkenyl anion or 1 equivalent each of two different alkenyl anions to cyclobutene-1,2-diones **410** can serve as a very effective method for the highly stereocontrolled synthesis of di-, tri- and tetraquinanes, from which two reaction cascades have been identified. When *trans*-1,2-addition of two alkenyl anions occurs, sequential 4π and 8π electrocyclization would deliver *trans*-fused bis-enolates such as **411**. When a proper adjustment of stereoelectronic factors causes the *cis* addition to become kinetically favorable, a dianionic oxy-Cope rearrangement occurs spontaneously to generate the *cis*-diastereomers of type **412**. Subsequent protonation results in an irreversible ring closure via a transannular aldolization route. When the alkenyl anions are sufficiently substituted, the two pathways are distinguishable on stereochemical grounds[171].

For example, a single-step synthesis of cyclooctadienone derivatives by reaction of alkenylcyclobutenes with alkenyllithium through an 8π cyclization was observed by Suzuki and coworkers. Thus, upon treatment with 2-propenyllithium generated from $CH_2{=}C(CH_3)Br$ and *t*-BuLi in Et_2O at $-78\,^{\circ}C$, ketone **413** was rapidly consumed, and a direct warming of the resulting lithium alkoxide yielded the ring-expansion product **415** in 82% yield. By contrast, when the above reaction was immediately quenched with H_2O at $-78\,^{\circ}C$, the only product was the ring-opened ketone **414**, generated in 84% yield. These results reflect that the mechanistic process could comprise two consecutive electrocyclic reactions, namely the ring opening of the dialkenylcyclobutene and the subsequent closure of the resulting tetraene, among which the former step is facile, being already completed at $-78\,^{\circ}C$[172].

On the other hand, Paquette and Tae reported a new approach towards the extensively substituted 2,4-cyclooctadieneones by a combined reaction of a squarate ester, metalated enecarbamate and alkenyl- or cycloalkenyllithium reagent. For instance, addition of 1 equivalent of dimethyl squarate (**416**) to **417** in THF at $-78\,^{\circ}C$ was followed 1 h later by 2 equivalents of 2-lithiopropene. Slow warming to room temperature for 12 h gave a chromatographically inseparable 23:1 mixture of **418** and **419** (n = 1). This diastereomeric ratio reflected a kinetic-controlled generation of the *cis*-addition product and a tandem dianionic oxy-Cope sigmatropic rearrangement[171]. Interesting mechanistic details were discussed in several articles[173–176]. This synthetic method was successfully deployed in the total synthesis of bioactive triquinane sesquiterpene hypnophilin[177] and pentalenene[178].

C. Other Thermal Ring-opening Reactions

Interestingly, when α-pinene (**420**) was treated with dimethyl sulfoxide and phenyl dichlorophosphate or with dimethyl sulfoxide and phosphorous oxychloride in CH_2Cl_2 for


RO
RO
O
O
R = i-Pr
(410)
Li
Li
–78 °C – RT,
overnight
i. conrotatory 4 π
ii. conrotatory 8 π
(411)
H2O
[3, 3] sigmatropy
(412)
H2O
OR
OH H
Cl
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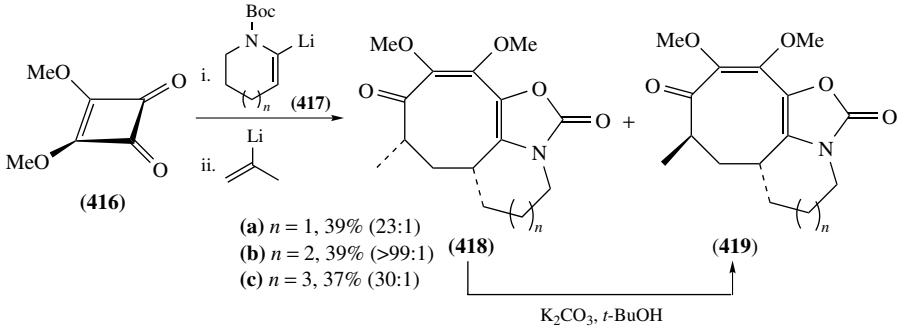
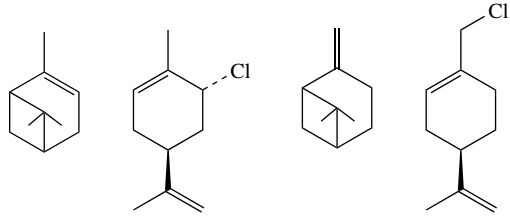
Li
Et2O
+
(413)
(414)
(415)



20 min over a temperature range of −20 to 20 °C, a rearrangement product **421** was formed in a virtually quantitative yield. Similarly, treatment of β-pinene (**422**) with dimethyl sulfoxide in the presence of phenyl dichlorophosphate or phosphorus oxychloride led also to the quantitative formation of the fragmentation product **423**. This facile rearrangement of pinenes induced by dimethyl sulfoxide and the phosphorus-containing reagents provides an efficient access to limonene derivatives[179].

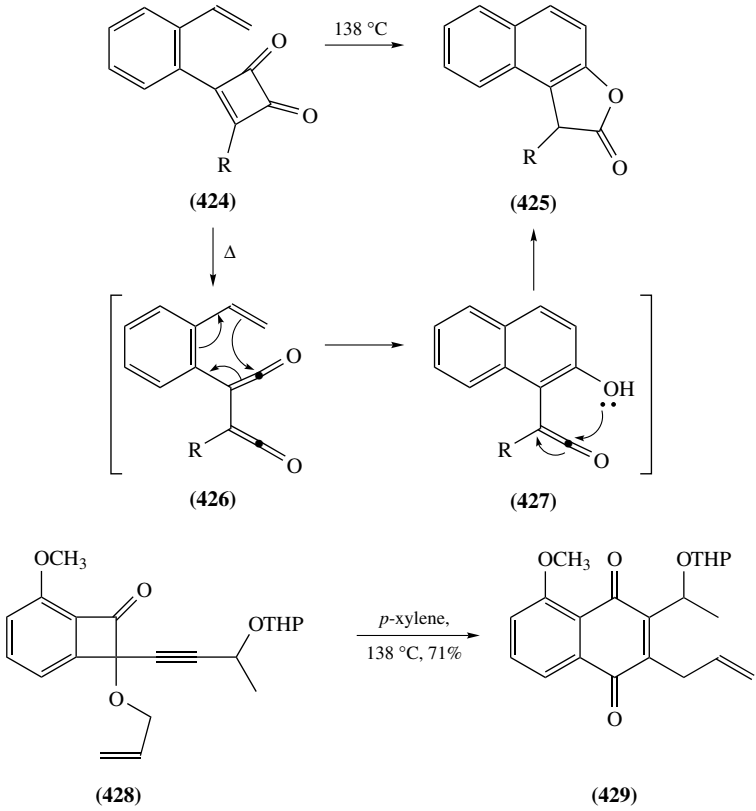


(420) **(421)** **(422)** **(423)**

Thermolysis of **424** at 138 °C gave naphthofuranones (**425**) in yields ranging from 47–76%. The rearrangement is envisaged to arise via a mechanism involving initial electrocyclic ring opening of the cyclobutenediones to the corresponding bisketenes **426**, which then underwent a 6π electrocyclization followed by aromatization to form naphthols **427**. Finally, addition of the naphthol hydroxyl group to the remaining ketene gave the observed products **425**[180].

Heat can also trigger the cleavage of cyclobutane rings[181,182]. Thermolysis of ether **428** in refluxing *p*-xylene at 138 °C gave the naphthoquinone **429** in 71% yield[183].

Hergueta and Moore reported a spontaneous rearrangement of 3-allenyl-2-(2-ethenylphenyl)-4,4-cyclobutenones to afford the corresponding bicyclo[4.2.0]octadiene systems at ambient temperature. Thus, treatment of a THF solution of **430** with 1-lithio-1-methoxyallene followed by quenching with an ammonium chloride solution gave the corresponding tetracyclic cyclobutenone **431**, which was used as a starting material for the synthesis of benza[*a*]anthracene-7,12-diones, compounds representing the framework of the angucycline group of natural products. Upon treatment with 2-lithioanisole in THF at −78 °C followed by hydrolysis of the acetal linkage, the tetracyclic cyclobutenone **431** was converted to **432**. Thermolysis in PhH at refluxing temperature followed by an oxidative workup (Ag_2O) provided the quinone **433** in 60% overall yield. Finally, addition



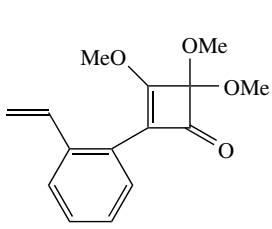
of bromine to the ethylidene group followed by photolysis with visible light completed the transformation of **433** to 6,11-dimethoxybenzo[*a*]anthracene-7,12-dione (**434**) in 77% yield[184].

Treatment of a mixture of **435** and **436** with 2,4-dinitrobenzenesulfenyl chloride and Et_3N in refluxing 1,2-dichloroethane provided **437** in 65% yield. This is a key step in Wang and Paquette's nine-step synthesis of 1,3-cyclooctatetraenophanes[185].

Treatment of **438** with 2,4-dinitrobenzenesulfenyl chloride and triethylamine resulted in a smooth dehydration to give **439** in 49% yield[186].

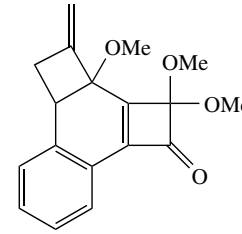
A transformation of the bicyclic adducts into the eight-membered ring compounds was reported by Takeda and coworkers. Initially, the diketone **440** was treated with 2 equivalents of LDA and chlorotrimethylsilane in THF at $-78\,^{\circ}C$ for 2 h to give a mixture of the trimethylsilyl enol ethers **441** and **442**. The mixture was heated in refluxing THF for 2 h and a mixture of cyclooctadienones **443** and **444** (87:13) was obtained in 70% yield after hydrolysis (KF/EtOH) of the resulting trimethylsilyl enol ether[187].

Fujiwara and Takeda reported a new method consisting of the conjugate addition of 1-alkenylmagnesium bromides to 1-cyclobutenyl ketones, with the ring-enlargement reaction of the resulting adducts. Compared with the Diels–Alder method, the merit of this method



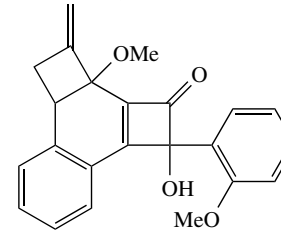
(430)

1-lithio-1-methoxyallene,
THF, −78 °C



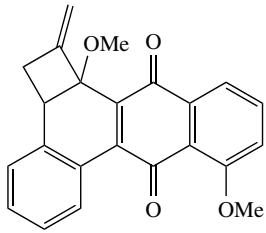
(431)

i. 2-lithioanisole, THF, −78 °C
ii. HCl, RT



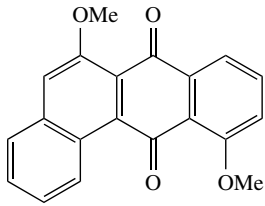
(432)

i. PhH, reflux
ii. Ag_2O, K_2CO_3

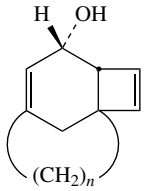


(433)

i. Br_2, $CHCl_3$, −10 °C
ii. visible light, $CHCl_3$, RT

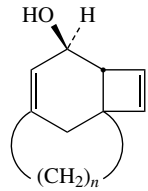


(434)



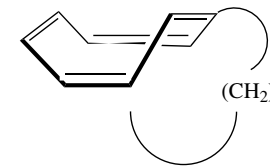
(435)

+

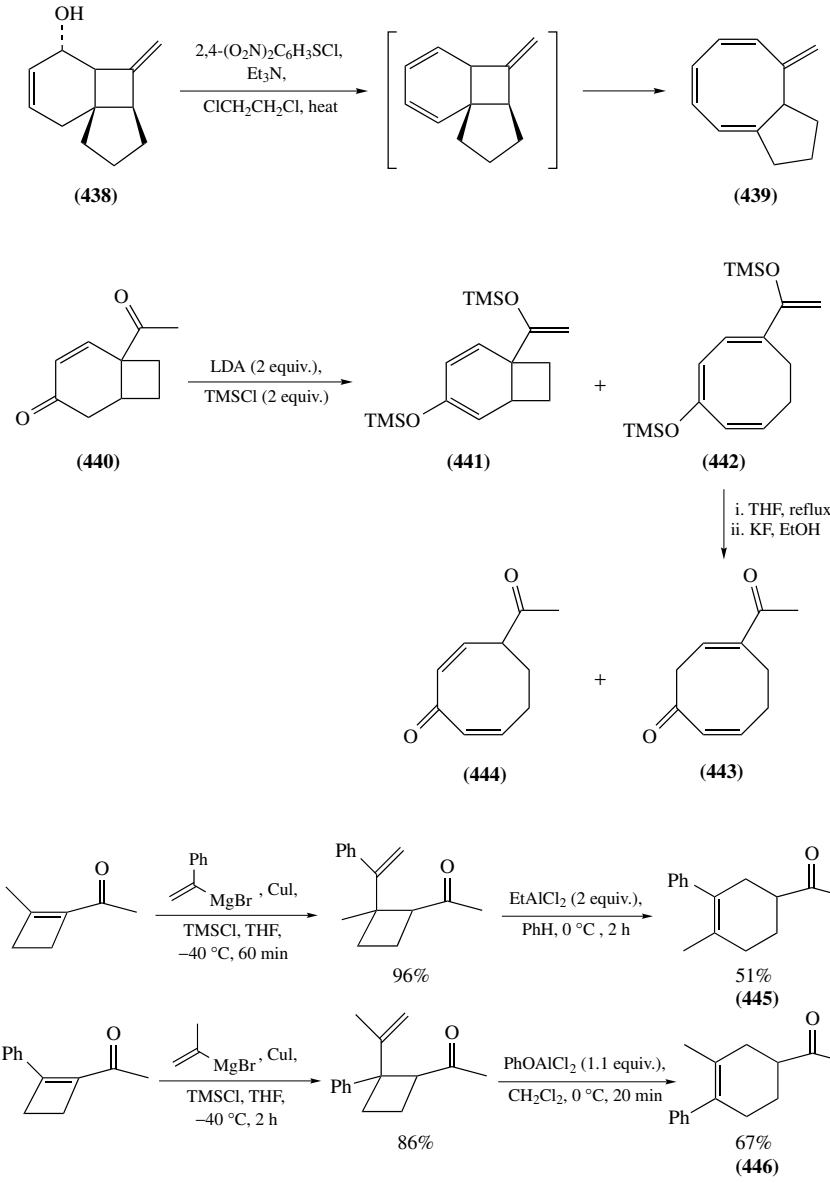


(436)

2, 4-$(O_2N)_2C_6H_3SCl$
Et_3N, $ClCH_2CH_2Cl$, heat

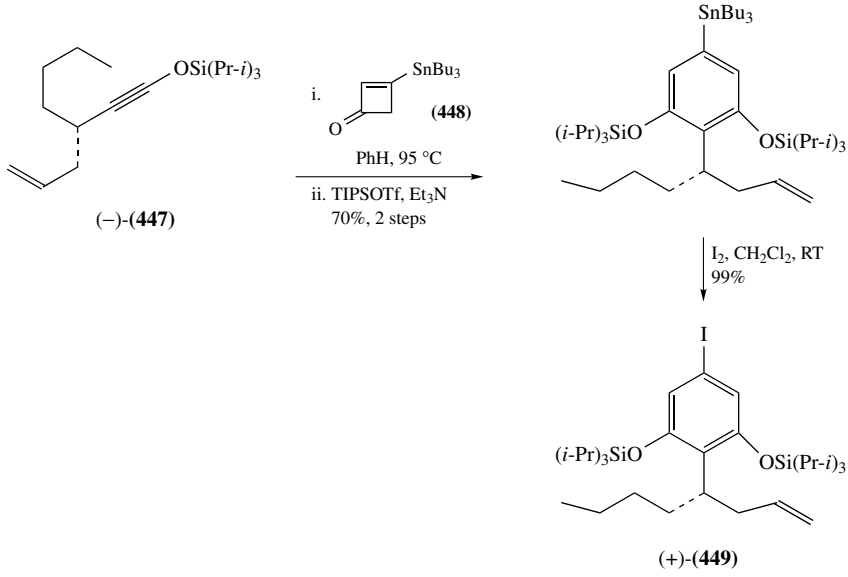


(437)

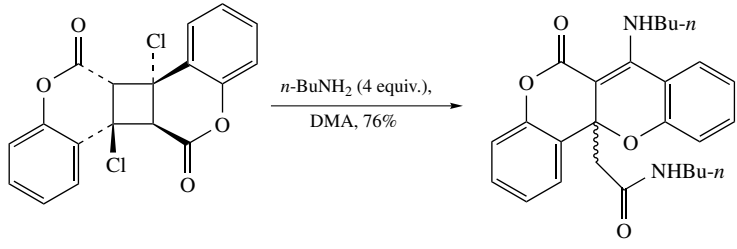


lies in its high regioselectivity and insensitivity towards steric hindrance. A case in point is illustrated above. The two position isomers **445** and **446** were synthesized selectively utilizing different cyclobutenyl ketones and Grignard reagents[188].

Siloxyalkyne (−)-**447** underwent a facile addition to known stannyl cyclobutenone **448**. Silylation, followed by iododestannylation, afforded aryl iodide (+)-**449** in 69% yield in three steps[189].



The reaction of **450** with 4 equivalents of *n*-butylamine was carried out in *N*,*N*-dimethylacetamide at 60 °C. After reacting for 2 h, the sole product **451** was isolated by precipitation from water, followed by recrystallization from carbon tetrachloride[190].

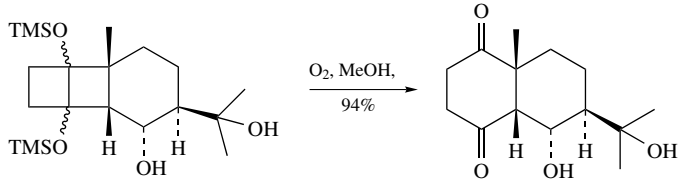


IV. OXIDATIVE AND REDUCTIVE RING OPENING

A. Oxidative Cleavage

Cyclobutane-1,2-diol can also be cleaved oxidatively and this route has been utilized in organic synthesis. This synthetic aspect is exemplified by the following examples.

In the synthesis of (+)-balanitol (**454**) and (+)-selin-4-(15)-ene-1β,11-diol (**455**), oxidative cleavage of the cyclobutane ring by gaseous oxygen was an important step. In this



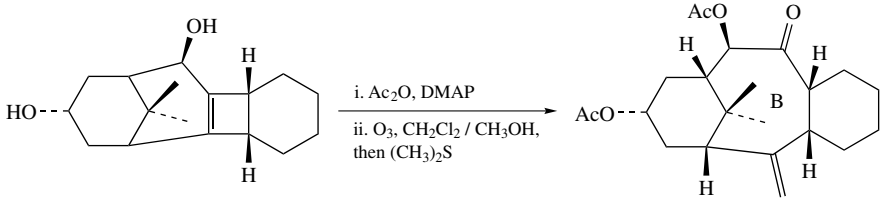
(452) **(453)**

(+)-Balanitol (+)-Selin-4-(15)-ene-1β,11-diol

(454) **(455)**

connection, oxygen was bubbled through a solution of **452** to form the corresponding diketone **453**[191].

In the synthesis of taxol derivatives, Blechert and coworkers employed the oxidative ring-opening method to synthesize the tricyclic taxane system with three oxygen-substituted centers in ring B. Cyclobutene **456** was oxidized by ozone in CH_2Cl_2/CH_3OH, yielding a stereochemically uniform compound **457**[192].

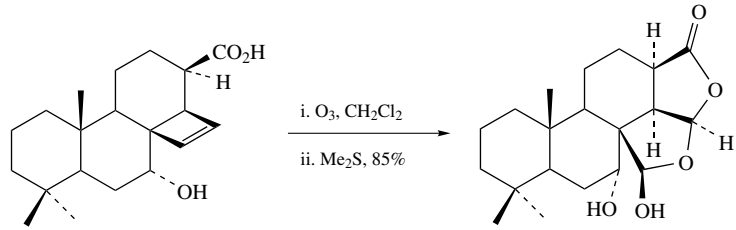


(456) **(457)**

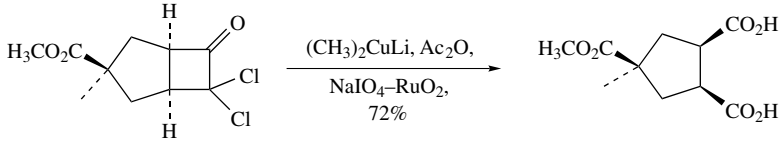
A similar method was also employed in the stereoselective synthesis of spongian pentacyclic diterpenes. Deacetylaplyroseol was synthesized through a cyclobutene intermediate **458** via the oxidative cleavage reaction that furnished a cyclic hemiactal **459** in 85% yield[193].

Oxidative ring opening of cyclobutane has also constituted a high-yield method for dicarboxylation. The dichlorocyclobutanone **460** was simply converted to the corresponding vicinal dicarboxylic acid **461** through successive treatment with lithium dimethylcopper, acetic anhydride and sodium metaperiodate-ruthenium dioxide[194].

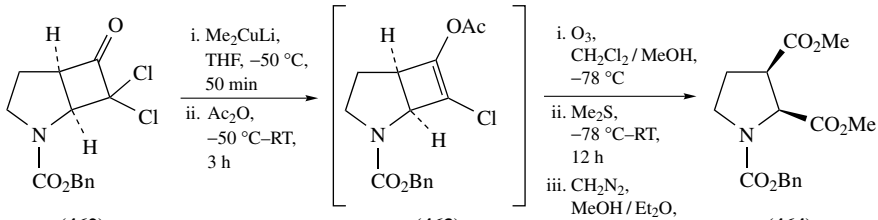
In the synthesis of the conformationally restricted analog of amino acids, the enol acetate **463**, formed from ketone **462** with Me_2CuLi/Ac_2O, was allowed to react with ozone and then Me_2S. Esterification with CH_2N_2 eventually furnished the *cis*-2,3-dicarbomethoxypyrrolidine (**464**) in high yield[195].



(458) **(459)**

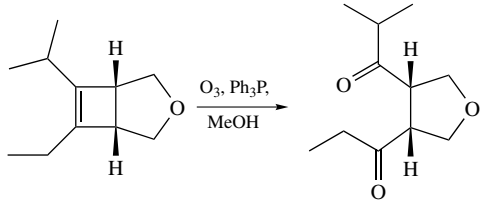


(460) **(461)**



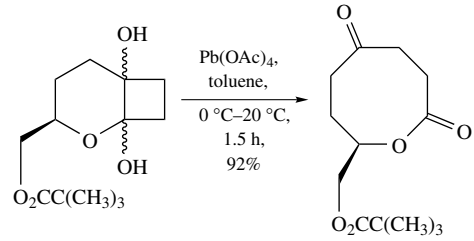
(462) **(463)** **(464)**

Mori and coworkers synthesized the antibiotic (+)-xanthocidin also through a cyclobutene intermediate **465**. Ozonolysis of (±)-**465** was executed by bubbling ozone into a solution of (±)-**465** in MeOH followed by reduction of the resulting ozonide with triphenylphosphine, providing the diketone (±)-**466**[196].

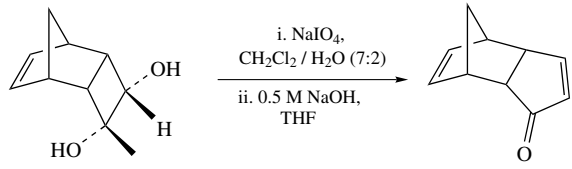


(465) **(466)**

Strong oxidizing agents can also be used to effect the oxidative cleavage of cyclobutane rings. In the first total synthesis of (+)-laurencin, the most representative marine natural product isolated from red algae, a facile oxidative cleavage procedure was the key step. As can be seen, oxidation of **467** with $Pb(OAc)_4$ in toluene afforded the desired lactone **468** in 92% yield[197].



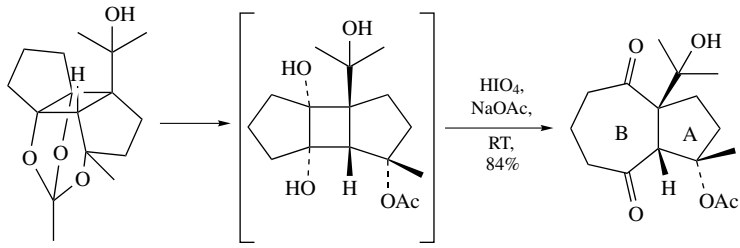
(467) **(468)**



(469) **(470)**

Taniguchi and Ogasawara synthesized the versatile chiral oxodicyclopentadiene **470**. The treatment of diol **469** with $NaIO_4$ and NaOH yielded the optically active (−)-oxodicyclopentadiene (**470**)[198].

Treatment of **471** with buffered periodic acid resulted in the hydrolysis of the orthoester to give a cyclobutane intermediate, which was oxidized by periodic acid to provide **472**, a comparable structure with abeotaxanes. After several more steps, the A/B skeleton of the 11(5-1)-abeotaxanes was finally obtained[199].

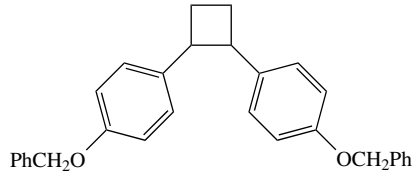


(471) **(472)**

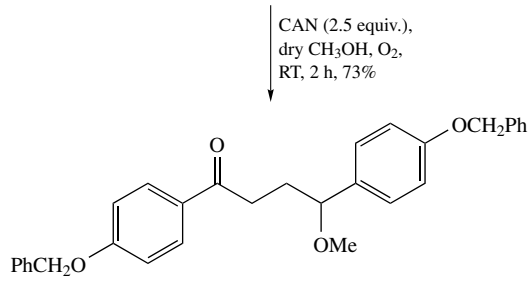
Cerium(IV) ammonium nitrate (CAN)-mediated oxidative rearrangement can also lead to the ring cleavage of alkoxyaryl cyclobutanes. For example, by treatment with a methanolic solution of CAN under an atmosphere of oxygen, cyclobutane **473** underwent an oxidative rearrangement to afford the 4-methoxy-1-butanone derivative **474** in 73% yield[200].

B. Reductive Cleavage

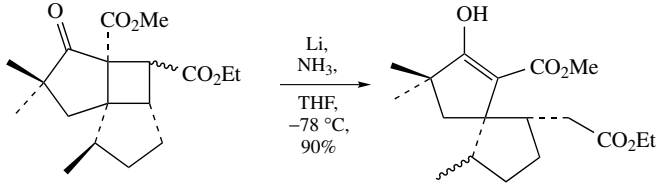
A cyclobutane ring can also be opened under electron-reduction conditions. Intramolecular cyclobutane reductive cleavage indeed plays an important role in the total synthesis of (±)-pentalenene (**477**), (±)-pentalenic acid (**478**) and (±)-deoxypentalenic acid glucuron



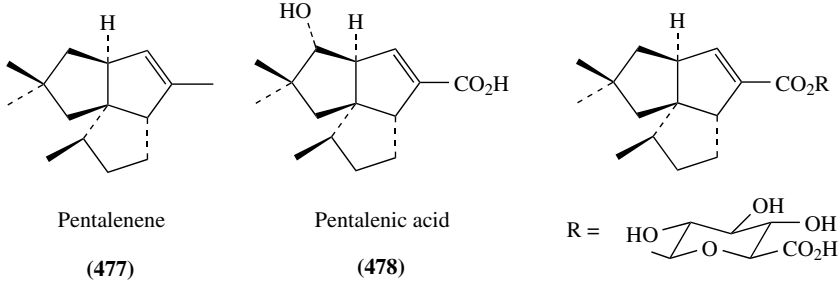
(473)



(474)



(475) **(476)**



Pentalenene

(477)

Pentalenic acid

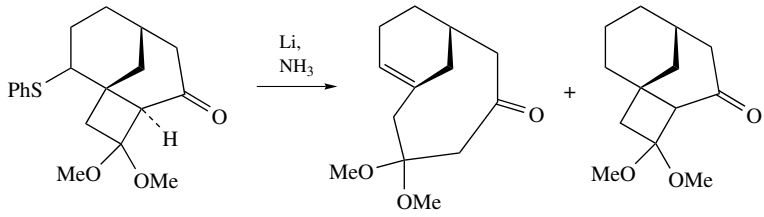
(478)

Deoxypentalenic acid glucuron

(479)

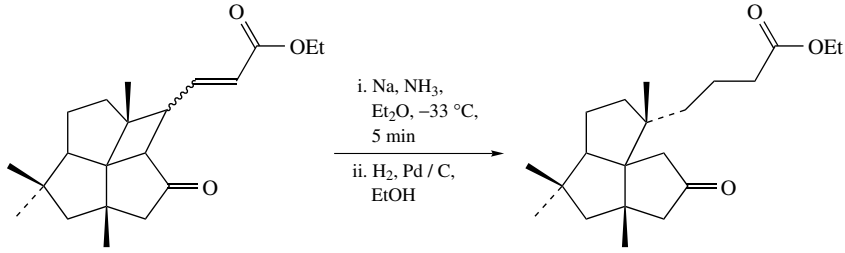
(**479**). Cyclobutane **475** was treated with lithium in liquid ammonia ($-78\,^{\circ}C$) to produce in 90% yield the β-keto ester **476**[201].

Alkali metal in liquid NH_3 as reductive cleavage reagent was also applied to the synthesis of the taxane skeleton **480**[202] and (±)-laurenene framework **481**[203].

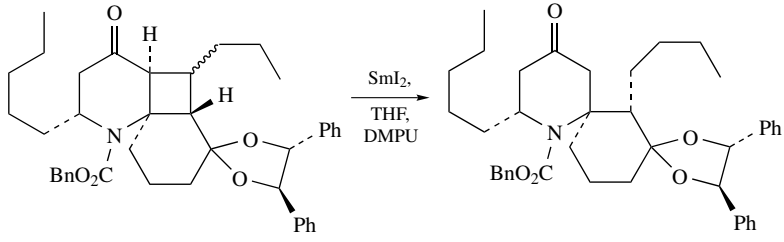


51% 10%

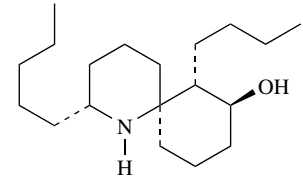
(480)



(481)



(482) **(483)**



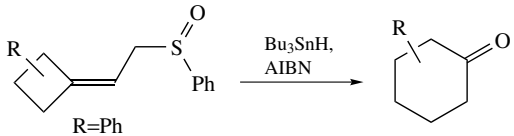
(–)-perhydrohistrionicotoxin

(484)

Comins and coworkers used SmI_2 as a reducing reagent for the opening of cyclobutane rings. Thus, treatment of **482** with SmI_2 in THF and DMPU was found to induce the ring opening of **482** to give the spirocyclic ketone **483** in 70% yield, which was then transformed to (−)-perhydrohistrionicotoxin (**484**)[204].

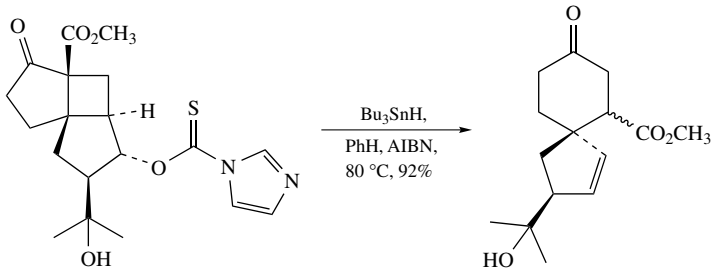
V. MISCELLANEOUS RING OPENINGS

Free-radical type ring cleavage has been extensively used as a synthetic tool for ring expansion[205–213]. For example, Renaud and coworkers made use of the cyclobutane **485** containing an allylic sulfoxide as a unique substrate for a two-carbon ring expansion of the four-membered ring based on a sequential radical-chain reaction, leading to the formation of cyclohexanone **486**[213].



R=Ph
(485) **(486)**

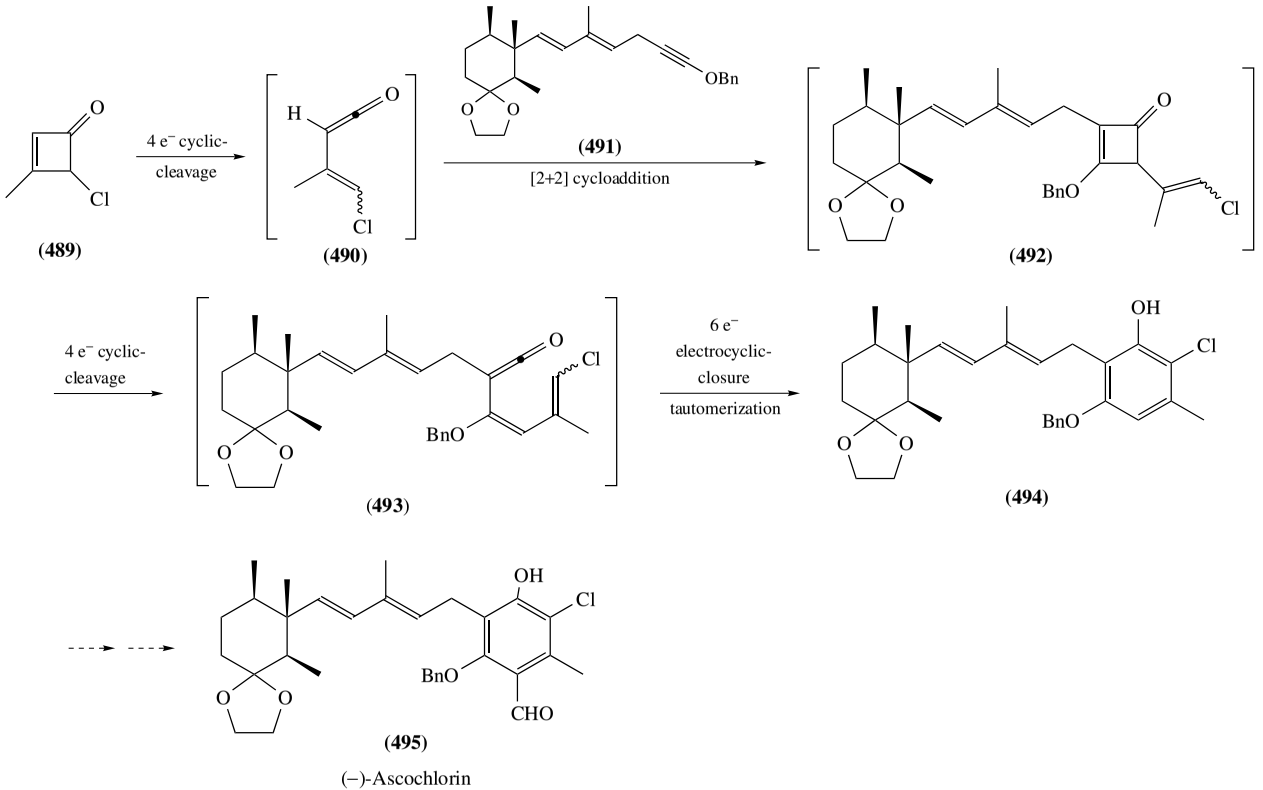
This type of reaction was also applied to the synthesis of natural products[214–218]. For example, in the total synthesis of (±)-lubiminol, slow addition of tributyltin hydride to thiocarbamate **487** over 5–6 h produced a mixture of the expected rearrangement products **488** in 92% combined yield[215].

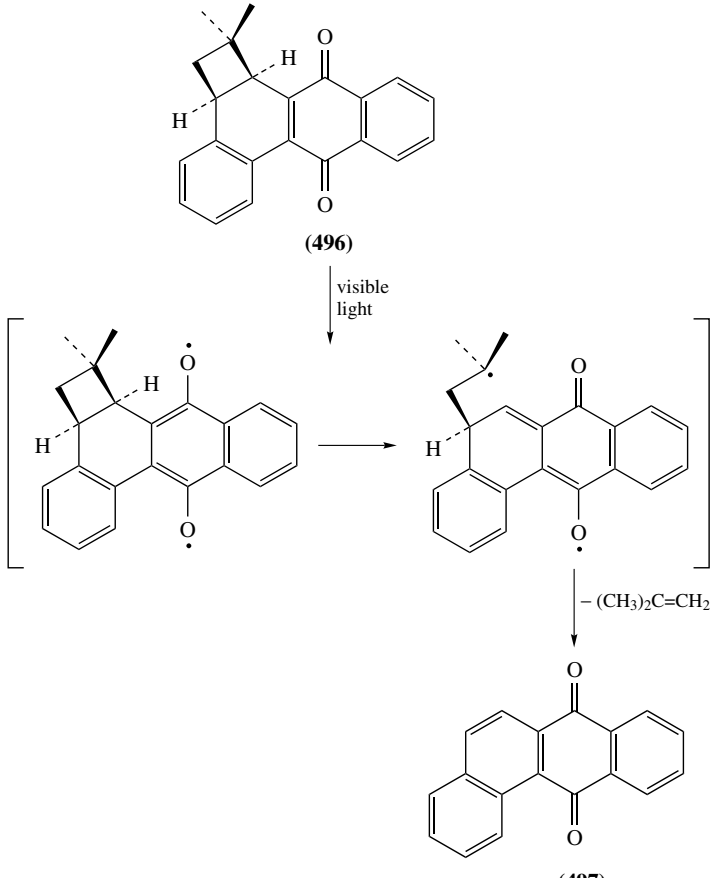


(487) **(488)**

In the total synthesis of (−)-ascochlorin (**495**), cyclobutenone played a key role in the benzannelation. Thus, irradiation of the cyclobutenone **489** in toluene at room temperature triggered four-electron electrocyclic ring opening to give vinylketene **490**, which combined with acetylene **491** in a regioselective [2+2]-cycloaddition to form **492**. Further irradiation at refluxing temperature then induced a second four-electron electrocyclic ring opening reaction to generate dienylketene **493**, which underwent a rapid 6π electrocyclization and tautomerization to afford the desired pentasubstituted benzene **494**[219].

Visible light can also trigger the radical-induced cleavage of cyclobutane rings. When the red-colored PhH solution of **496** was exposed to fluorescent laboratory light, it underwent an efficient photofragmentation reaction to yield the yellow benzo[*a*]anthracene-7,12-dione (**497**) in 87% yield[220].

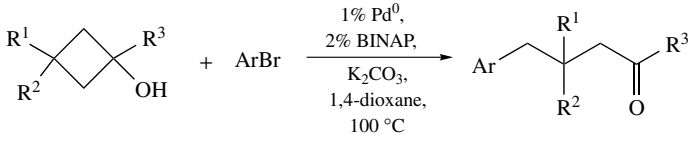

O
Cl
(489)
4 e⁻ cyclic-
cleavage
H
O
Cl
(490)
OBn
O
O
(491)
[2+2] cycloaddition
O
BnO
Cl
(492)
4 e⁻ cyclic-
cleavage
O
Cl
BnO
O
O
(493)
6 e⁻
electrocyclic-
closure
tautomerization
OH
Cl
BnO
(494)
OH
Cl
BnO
CHO
(495)
(–)-Ascochlorin



(496)

(497)

Nishimura and Uemura devised a new approach for the realization of γ-arylated ketones **499**. Their useful manipulation could be achieved by the palladium-catalyzed arylation of cyclobutanol **498** involving a selective β-carbon elimination from an aryl palladium alcoholate[221].



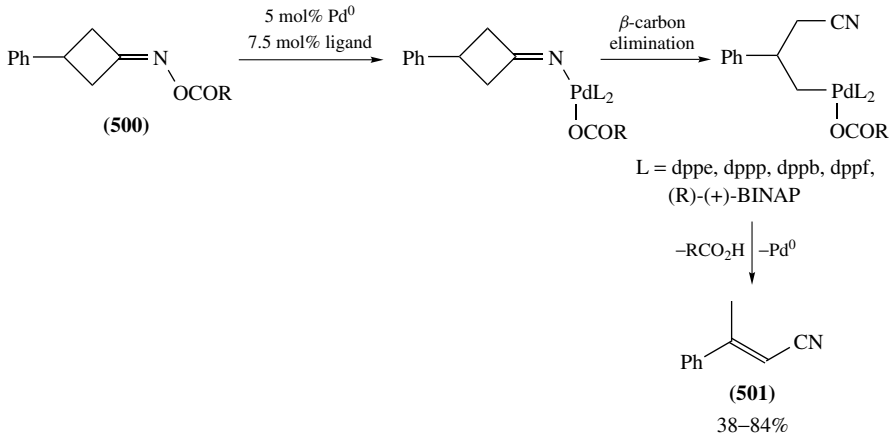
(498)

R^1, R^2, R^3 = CH_2Bu-*t*, H, *t*-Bu, Ph, CH_3

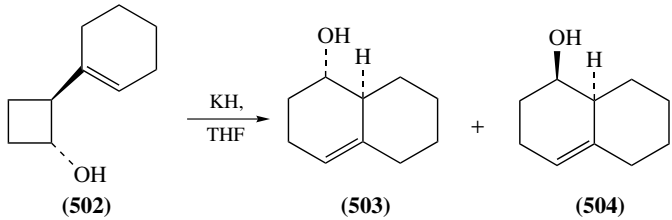
(499)

Ar = Ph, 2-naphthyl, *p*-MeC_6H_4, *p*-ClC_6H_4

The same research group also discovered that palladium(0)-catalyzed reaction of cyclobutanone *O*-acyloximes **500** led to various nitriles **501**, and the transformation is shown below[222].



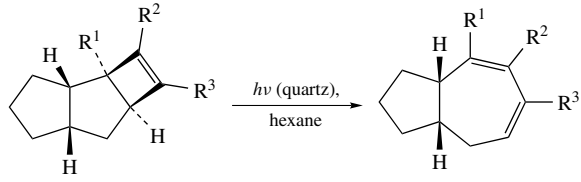
2-Vinylcyclobutanol **502** could undergo a [1,3]-sigmatropic rearrangement accelerated by both thermal and potassium hydride conditions to give alcohols **503** and **504**[223].



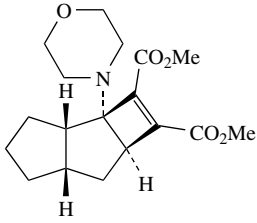
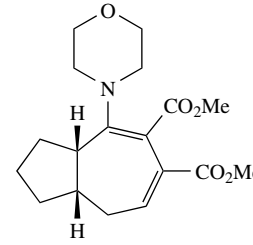
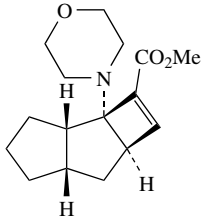
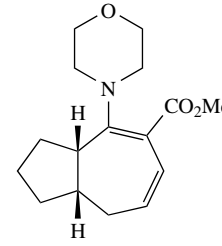
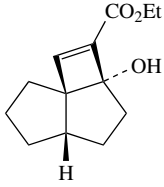
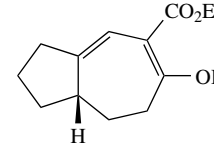
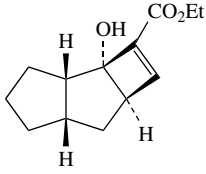
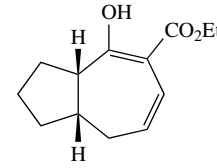
reflux (no additive)	3	:	7	88%
18-crown-6 RT	9	:	1	98%

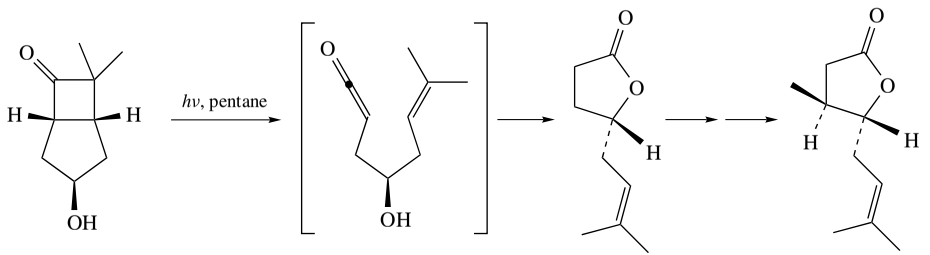
The photolytic ring opening of cyclobutenes condensed with a diquinane moiety has been used as a synthetic approach to synthesis of hydroazulene skeletons. When cyclobutenes **505** were irradiated in a quartz apparatus, ring-enlargement products **506** were isolated as expected in good yields[224].

Wakefield and coworkers reported that commencing from suitably functionalized bicycloheptanones, ring opening and intramolecular trapping of the derived alkenylketene provided viable routes towards natural products (+)-eldanolide (**507**) and (+)-leukotriene-B_4 (**508**)[225].



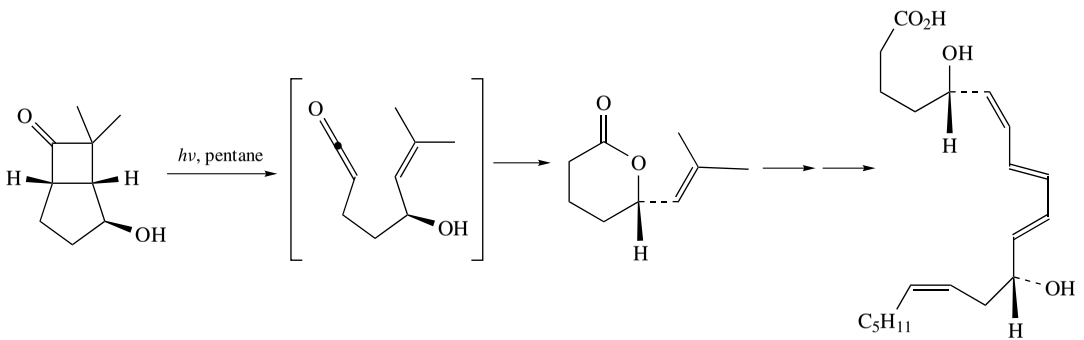
(505) **(506)**

Starting material	λ_{max} (ε)	Photolysis time	Product	Yields (%)
	330 nm (1000) 220 nm (7000)	20 min		90
	286 nm (1000) 218 nm (6400)	10 min		90
	218 nm (6300)	5 min		90
	213 nm (6400)	240 min		75



(507)

(+)-eldanolide



(508)

(+)-leukotriene-B_4

VI. ACKNOWLEDGMENT

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CHAPTER **10**

Structural Effects of the Cyclobutyl Group on Reactivity and Properties

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I. ALKYL AND CYCLOALKYL GROUPS

In this chapter we describe the effect of the cyclobutyl group as a substituent and the cyclobutane ring as a skeletal group transmitting substituent effects. Also described when

possible will be groups containing cyclobutyl rings such as 6-tricyclo[3.1.1.0^{3,7}]heptanyl and 1-cubyl derived from tricyclo[3.1.1.0^{3,7}]heptane (**1**) and cubane (**2**). The structural effects of the cyclopropyl group have long been known to be atypical when compared with those of alkyl groups and most cycloalkyl groups[1,2]. It has been suggested that this may also be true of the cyclobutyl group, though to a much lesser extent.

(1)

(2)

II. THE NATURE OF STRUCTURAL EFFECTS

A. Introduction

Models for the quantitative description of structural effects of substituents are described in this work. Also described are substituent effects of alkyl and cycloalkyl substituents.

The structural theory of organic chemistry was developed in the last half of the nineteenth century. It led to the concept that chemical, physical and biological properties of all kinds must be a function of structural change. The earliest structure–property relationships (SPR) were qualitative. An example is the directional effects of substituents on the benzene ring with respect to electrophilic aromatic substitution. With the development of methods of quantitative measurement of these properties, data such as ionization constants for acids and bases, and rate constants for reactions, accumulated, as did phase change properties such as melting and boiling points and solubilities. Attempts were then made to develop quantitative models of the structural dependence of these properties. It is these methods for the quantitative description of structural effects that will now be described.

B. Structure–Property Quantitative Relationships (SPQR)

Quantitative descriptions of the structural dependence of properties are called structure–property quantitative relationships (SPQR). There are four types of these relationships:

1. *Quantitative structure–chemical reactivity relationships* (QSRR). Chemical reactivities involve the formation and/or cleavage of chemical bonds. Equilibrium constants, rate constants, polarographic half-wave potentials and oxidation–reduction potentials are examples of chemical reactivity data.
2. *Quantitative structure–chemical property relationships* (QSCR). Chemical properties involve a difference in intermolecular forces between an initial and a final state. Equilibrium constants for hydrogen bonding, charge transfer complex formation, conformational equilibria, partition coefficients, chromatographic properties such as capacity factors in high performance liquid chromatography, retention times in gas chromatography and R_F values in thin layer and paper chromatography, melting and boiling points, solvent effects on equilibrium or rate constants and solubilities are examples of chemical property data.
3. *Quantitative structure–physical property relationships* (QSPR). Physical properties are either ground state properties or properties which depend on the difference in energy between the ground state and an excited state. Bond lengths, bond angles and dipole moments are ground state properties; infrared, ultraviolet, nuclear magnetic resonance and other types of spectra, ionization potentials and electron affinities are properties which depend on the energy difference between states.

4. *Quantitative structure–activity relationships* (QSAR). Any property associated directly or indirectly with a living organism is a biological activity. The bioactive substrates studied include pure enzymes, tissue homogenates, single-celled organisms, whole tissues and multi-cellular organisms. The data may be obtained in vitro or in vivo. They include rate and equilibrium constants for enzyme reactivity and for binding to receptor sites, various kinds of toxicity determinations such as lethal dose and lethal concentration, and minimum effective concentrations, a measure of activity used for a wide range of bioactivity type.

1. The nature of SPQR

There are several different types of chemical species, including molecules, ions, radicals, carbenes, nitrenes, benzynes etc. for which SPQR can be determined. Four kinds of structure are possible:

1. Species with the structure XGY, where X is a variable substituent, Y is a constant active site (an atom or group of atoms at which a measurable phenomenon takes place) and G is a constant skeletal group to which X and Y are bonded.
2. Species with the structure XY in which the variable substituent X is directly attached to the constant active site Y.
3. Species with the structure XG_Y in which the active site is part of the skeletal group.
4. Species in which substituent and active site are the same, the entire species is the active site and it varies. These species are designated X_Y.

SPQR is intended to provide a quantitative description of the change in some measurable quantity Q that occurs when a change is made in the structure of the species by varying the substituent X. All of the other pertinent variables, such as the conditions of the measurement, are held constant. Then equation 1 applies:

$$(\partial Q/\partial X)_{G,Y,T,P,Sv,I,\ldots} = Q_X \tag{1}$$

where Q_X is the measured quantity when the substituent is X, G is the skeletal group, Y the active site, T the temperature, P the pressure, Sv the solvent, I the ionic strength, and all of these are constant throughout the data set.

We **assume** that Q_X will be a linear function of some number of parameters which represent the effects of the structural variation of X. Then equations 2a and 2b apply:

$$Q_X = a_1 p_{1X} + a_2 p_{2X} + a_3 p_{3X} + \cdots + a_0 \tag{2a}$$

$$= \sum_{i=1}^{n} a_i p_{iX} + a_0 \tag{2b}$$

where the p_i are the parameters which account for the structural effect of X on Q. These parameters have been obtained in various ways:

1. From quantum chemical calculations[3]. This method is most suitable for electrical effect parameters.
2. From molecular mechanics calculations[4] for steric effect parameters.
3. From a reference set by definition (primary values). This method assumes that structural effects on the data set to be studied are a linear function of those which occur in the reference set. Secondary values of these parameters can be estimated by various methods.

4. From comparative molecular field analysis (COMFA)[5]. This method can be used for electrical, steric and polarizability parameters.
5. From molecular geometry for steric parameters.
6. From topological algorithms[6]. This method is best restricted to the steric effect and polarizability parameters. The nature of topological parameters has been described. They are composite parameters and result from a count of structural features[7].

When suitable parameters are available, the values of Q can be correlated with them by means of either simple linear regression analysis if the model requires only a single variable, or multiple linear regression analysis if it requires two or more variables. Such a correlation results in a SPQR. In this work we consider only those parameters that are defined directly or indirectly from suitable reference sets or, in the case of steric parameters, calculated from molecular geometries.

2. The uses of SPQR

SPQR have three major uses:

1. *Mechanistic*. QSRR and those QSAR which involve enzyme reactivity can provide information about the sensitivity of a reaction to electrical effects, its electronic demand, the composition of the electrical effect and the sensitivity to steric effects. QSAR which involve binding to receptor sites can provide information about the nature of the receptor site. Other QSAR can shed light on the bioactivity determining step.
2. *Predictive*. All SPQR can be used to predict reactivities, chemical and physical properties and bioactivities. There are manifold practical applications of such predictions. Particular examples include the design of bioactive molecules such as medicinal drugs and pesticides. In addition to the maximization of activity and minimization of side effects, desirable pharmaceutical properties such as improved solubility, longer shelf life and controlled release can be developed. They are also a major method in environmental science, where they can be used to predict toxicities, biodegradabilities and other properties of environmental interest. They may also be useful in materials science for the design of materials with specific properties.
3. *Archival*. SPQR provide a concise, efficient and convenient method for storing the results of experimental studies on the effect of structural changes upon properties.

C. The Types of Structural Effects

Structural effects are conveniently divided into three categories:

1. *Electrical effects*. These effects cause a variation in the electron density at the active site. They account for the ability of a substituent to stabilize or destabilize a cation, anion, radical, carbene or other chemical species.
2. *Steric effects*. These effects result from the repulsion between valence electrons in orbitals on atoms which are in close proximity but not bonded to each other, or by shielding an active site from a reactant or solvent.
3. *Inter- and intramolecular force effects*. These effects result either from the interactions between the substituent and its immediate surroundings such as the medium, a surface or a receptor site, or from the effect of the substituent on the interactions of the skeletal group G and the active site Y with their surroundings.

Electrical effects are the major factor in chemical reactivities and physical properties. Intermolecular forces are usually the major factor in bioactivities. Either electrical effects or intermolecular forces may be the predominant factor in chemical properties. Steric

effects only occur when the substituent and the active site are in close proximity to each other and even then rarely account for more than twenty-five percent of the overall substituent effect.

III. ELECTRICAL EFFECTS

A. Introduction

The earliest successful parameterization of electrical effects is due to Hammett[8–10]. Though Burkhardt reported the existence of QSRR two years before Hammett, he did not develop a general relationship[11]. Hammett defined the σ_m and σ_p constants using the ionization constants of 3- and 4-substituted benzoic acids in water at 25 °C as the reference set and hydrogen as the reference substituent to which all others are compared. For hydrogen, the values of the σ_m and σ_p constants were defined as zero. Thus

$$\sigma_X \equiv \log \frac{K_X}{K_H} \tag{3}$$

These parameters were intended to apply to XGY systems in which the skeletal group is 3- or 4-phenylene. Hammett found it necessary to define an additional set of parameters, σ_p^-, in order to account for substituent effects in 4-substituted benzene systems with an active site that has a lone pair on the atom adjacent to the benzene ring. The reference set was the ionization constants of 4-substituted phenols in water at 25 °C. Brown and his coworkers[12, 13] later defined another set of constants, σ_p^+, to account for substituent effects in benzene derivatives with electronically deficient active sites. The reference set was the rate constants for the solvolysis of 4-substituted cumyl chlorides in 90% aqueous acetone at 25 °C. Finally, Wepster and coworkers[14] and Taft[15] both independently proposed constants intended to represent substituent effects in benzene derivatives with minimal delocalized effect. Using the Taft notation these constants are written as σ_p°. The reference systems had a methylene group inserted between the benzene ring and the active site ($XGCH_2Y$ where Y is 1,4-phenylene), as it was argued that the methylene group acted as an insulator preventing conjugation between X and Y. These parameters all differ in electronic demand. They are used in the Hammett equation which may be written in the form

$$Q_X = \rho\sigma_X + h \tag{4}$$

where Q_X is the value of the quantity of interest when the substituent is X, and σ_X is either σ_{m}X, σ_{p}X, ${\sigma_p^{\circ}}_X$, ${\sigma_p^{+}}_X$ or ${\sigma_p^{-}}_X$; ρ and h are the slope and intercept of the line. In using the Hammett equation, it is necessary to make an *a priori* choice of parameters based on the location of the substituent and a knowledge of the electronic demand in the data set which is to be modeled. If such knowledge is unavailable, as is often the case, it is necessary to correlate the data set with each different parameter. The parameter which gives the best fit is then assumed to be the proper choice and the electronic demand associated with it is that of the data set.

Taft and his coworkers[16–18] developed a diparametric model that separates the electrical effect into contributions from the 'inductive' (actually the field) and resonance effects. This separation depends on the difference in the extent of electron delocalization when a substituent is bonded to an sp^3-hybridized carbon atom in one reference system and to an sp^2-hybridized carbon atom in another. As the first case represents minimal delocalization and the second extensive delocalization, we have referred to the two effects as the localized and delocalized electrical effects. This diparametric electrical effect model can be written in the form

$$Q_X = L\sigma_{lX} + D\sigma_{DX} + h \tag{5}$$

where σ_l and σ_D are the localized and delocalized electrical effect parameters respectively, L and D are their coefficients and h is the intercept. Taft and coworkers[18] stated that four σ_D constants are required in order to account for all types of electronic demand: σ_{RX}, ${\sigma_R}^{\circ}{}_X$, ${\sigma_R}^{+}{}_X$ and ${\sigma_R}^{-}{}_X$. They correspond to the σ_p constants described above. Charton noted that in cases of very large electron demand, two additional σ_D constants were required: ${\sigma_R}^{\oplus}$ for highly electron-deficient (positive) active sites[19] and ${\sigma_R}^{\ominus}$ for active sites that have a large electron excess (negative)[20].

An alternative diparametric model was proposed by Yukawa and Tsuno[21] for use with electron-deficient active sites. The equation was originally written as

$$Q_X = \rho\sigma_X + \rho r(\sigma_X^+ - \sigma_X) \tag{6}$$

A later version has the form[22]

$$Q_X = \rho\sigma_X + \rho r(\sigma_X^+ - \sigma_X^o) \tag{7}$$

A similar relationship:

$$Q_X = \rho\sigma_X + \rho r(\sigma_X^- - \sigma_X) \tag{8}$$

has been proposed for active sites with an electron excess[23]. These relationships are termed the YT equations. They resemble the Hammett equation in being able to include both *meta*- and *para*-substituted compounds in the same data set. To do this, it must be assumed that ρ_m is equal to ρ_p. This assumption is a reasonable approximation when the geometry of the data set of interest resembles that of the reference set from which σ_m and σ_p were defined, but in some cases the difference between ρ_m and ρ_p ($\Delta\rho$) is significant. The Yukawa–Tsuno and related models are therefore limited in scope.

Like the case of the Hammett equation, the use of the LD equation (equation 5) for the description of chemical reactivities required either an *a priori* knowledge of the type of σ_D substituent constant required, or a comparison of the results obtained using each of the available σ_D constants. The use of the YT equation has generally been restricted to electronically deficient active sites. Clearly, there was a need for a more general model of electrical effects that would avoid the *a priori* parameter choice. A triparametric model of the electrical effect has been introduced[24] that can account for the complete range of electrical effects on chemical reactivities of closed-shell species (carbenium and carbanions), that is, reactions which do not involve radical intermediates. The basis of this model was the observation that the σ_D constants differ in their electronic demand. On the assumption that they are generally separated by an order of magnitude in this variable, it is possible to assign to each σ_D type a corresponding value of the electronic demand, η. Thus, the equation

$$\sigma_{DX} = a_1\eta + a_0 = \sigma_e\eta + \sigma_d \tag{9}$$

is obeyed. The intercept of this linear relationship represents the intrinsic delocalized (resonance) effect, σ_{dX}. This is the delocalized effect observed when the electronic demand of the data set studied is zero. The slope represents the sensitivity of the X group to the electronic demand of the active site. On substituting equation 9 into equation 5, we obtain the triparametric LDR equation

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + h \tag{10}$$

The σ_l values are identical to σ_I. The symbol was changed in order to be consistent with the other symbols used in the equation.

When the composition of the electrical effect, P_D, is held constant, the LDR equation simplifies to the CR equation

$$Q_X = C\sigma_{ldX} + R\sigma_{eX} + h \tag{11}$$

where σ_{ld} is a composite parameter. It is defined by equation 12:

$$\sigma_{ldX} = l\sigma_{lX} + d\sigma_{dX} \tag{12}$$

Lower-case letters are used for the coefficients in equations that represent a substituent constant as a function of other substituent constants. The difference between pure and composite parameters is that the former represent a single effect while the latter represent a mixture of two or more. The percent composition of these parameters is given by

$$P_D = \frac{100d}{l + d} \tag{13}$$

If the constant value of P_D is written as k', then the σ_{ldX} parameter for a given value of k' is given by equation 14:

$$\sigma_{ldXk'} = \sigma_{lX} + [k'/100 - k']\sigma_{DX} \tag{14}$$

If we write

$$k^* = k'/(100 - k') \tag{15}$$

then we obtain

$$\sigma_{ldXk'} = \sigma_{lX} + k^*\sigma_{dX} \tag{16}$$

The Yukawa–Tsuno equation for 4-substituted benzene derivatives is approximately equivalent to the CR equation[25,26]. This observation has led to the development of a modified Yukawa–Tsuno (MYT) equation which has the form

$$Q_X = \rho\sigma_X + R\sigma_{eX} + h \tag{17}$$

with σ taking the value σ_m for 3-substituted benzene derivatives and σ_{50} for 4-substituted benzene derivatives, while σ_{eX} for 3-substituted benzene derivatives is 0. The σ_{50} constants have k' equal to 50 and η equal to zero; they are therefore equal to the sum of the σ_l and σ_d values.

If the sensitivity to electronic demand is held constant, the LDR equation reverts to the LD equation (equation 5). By means of an equation analogous to the MYT equation, the modified LD (MLD) equation 18 is obtained:

$$Q_X = \rho'\sigma_X + D\sigma_{DX} + h \tag{18}$$

where σ is σ_m for 3-substituted benzene derivatives and σ_l for 4-substituted benzene derivatives while σ_D is 0 for 3-substituents; 3- and 4-substituted benzene derivatives can be combined into a single data set. Again, the use of the MLD equation is restricted to systems for which $\Delta\rho$ is not significant.

When both the electronic demand and the composition of the electrical effect are held constant, a set of composite parameters having the form

$$\sigma_{k'/kX} = l\sigma_{lX} + d\sigma_{dX} + r\sigma_{eX} \tag{19}$$

with

$$k' = P_D = \frac{100d}{(l+d)} \tag{20a}$$

and

$$k = \eta = r/d \tag{20b}$$

is obtained. The Hammett substituent constants are special cases of these parameters.

The $\sigma_{k'/k}$ values describe the overall electrical effect of the X group. They are obtained from expressions 21a and 21b:

$$\sigma_{k'/kX} = \sigma_{lX} + [P_D/(100 - P_D)](\sigma_{dX} + \eta\sigma_{eX}) \tag{21a}$$

$$= \sigma_{lX} + k^*(\sigma_{dX} + k\sigma_{eX}) \tag{21b}$$

A plot of the $\sigma_{k'/kX}$ values for a group with P_D on the x-axis, η on the y-axis and $\sigma_{k'/k}$ on the z-axis produces a surface that characterizes the electrical effect of the X group.

B. Electrical Effects of Alkyl and Cycloalkyl Substituents

Values of electrical effect substituent constants for alkyl and cycloalkyl groups have been reported[27,28]; they are set forth in Tables 1, 2 and 3. Also reported in Table 1 are values for some other types of substituents[24,27] for purposes of comparison. It was pointed out quite some time ago that with very few exceptions the σ_l constants of alkyl and cycloalkyl groups are constant with a mean value of −0.01 and are therefore not significantly different from zero[28–30]. The σ_d and σ_e constants are also constant with mean values of −0.15 and −0.036, respectively.

TABLE 1. Electrical effect substituent constants for common substituents[a]

X	σ_l	σ_d	σ_e	$\sigma_{c14.3}$	$\sigma_{c16.7}$	σ_{c50}	σ_{c60}
***c*-Ak**							
Me	−0.01	−0.14	−0.030	−0.03	−0.04	−0.15	−0.22
Et	−0.01	−0.12	−0.036	−0.03	−0.03	−0.13	−0.19
c-Pr	0.01	−0.17	−0.069	−0.02	−0.02	−0.16	−0.25
Pr	−0.01	−0.15	−0.036	−0.04	−0.04	−0.16	−0.24
i-Pr	0.01	−0.16	−0.040	−0.02	−0.02	−0.15	−0.22
c-Bu	−0.01	−0.13	−0.048				
Bu	−0.01	−0.15	−0.036	−0.04	−0.04	−0.16	−0.24
i-Bu	−0.01	−0.14	−0.036	−0.03	−0.04	−0.15	−0.22
s-Bu	−0.01	−0.14	−0.036	−0.03	−0.04	−0.15	−0.22
t-Bu	−0.01	−0.15	−0.036	−0.04	−0.04	−0.16	−0.24
c-Pe	−0.01	−0.14	−0.036				
Pe	−0.01	−0.14	−0.036	−0.03	−0.04	−0.15	−0.22
CH_2Bu-*t*	0.00	−0.16	−0.040	−0.03	−0.03	−0.16	−0.24
c-Hx	0.00	−0.14	−0.036	−0.02	−0.03	−0.14	−0.21
1-Ad	−0.01	−0.12	−0.060	−0.03	−0.03	−0.13	−0.19
CH_2Z							
CH_2Br	0.20	−0.08	−0.026	0.19	0.18	0.12	0.08
CH_2OH	0.11	−0.10	−0.025	0.09	0.09	0.01	−0.04
CH_2Cl	0.17	−0.06	−0.024	0.16	0.16	0.11	−0.08
CH_2CN	0.20	−0.01	−0.011	0.20	0.20	0.19	0.18
CH_2OMe	0.11	−0.10	−0.041	0.09	0.09	0.01	−0.04
CH_2CH_2CN	0.09	−0.11	−0.024	0.07	0.07	−0.02	−0.08
CH_2Vi	0.02	−0.16	−0.039	−0.01	−0.01	−0.14	−0.22

(*continued overleaf*)

TABLE 1. (*continued*)

X	σ_1	σ_d	σ_e	$\sigma_{c14.3}$	$\sigma_{c16.7}$	σ_{c50}	σ_{c60}
CH_2X							
CH_2OEt	0.11	−0.10	−0.041	0.09	0.09	0.01	−0.04
CH_2GeMe_3	−0.02	−0.31	−0.028	−0.07	−0.08	−0.29	−0.49
CH_2SiMe_3	−0.03	−0.30	−0.029	−0.08	−0.09	−0.27	−0.48
CH_2SnMe_3	−0.03	−0.16	−0.028	−0.06	−0.06	−0.19	−0.29
$CH_2CH_2CO_2Et$	0.08	−0.12	−0.027	0.06	0.06	−0.04	−0.10
$CH_2CHMeCO_2Me$	0.07	−0.12	−0.027	0.05	0.05	−0.05	−0.11
CH_2NEt_2	0.03	−0.12	−0.038	0.01	0.01	−0.09	−0.15
CH_2Ph	0.03	−0.13	−0.057	0.01	0.00	−0.10	−0.17
CZ_3							
CF_3	0.40	0.13	−0.026	0.42	0.43	0.53	0.60
CCl_3	0.36	0.10	−0.018	0.38	0.38	0.46	0.51
$C(SiMe_3)_3$	−0.09	−0.21	−0.028	−0.13	−0.13	−0.30	−0.41
Ar							
C_6F_5	0.31	0.08	−0.068	0.32	0.33	0.39	0.43
Ph	0.12	−0.12	−0.12	0.10	0.10	0.00	−0.06
C_6H_4Z (PnZ)							
4-$PnNMe_2$	0.09	−0.32	−0.12	0.04	0.03	−0.23	−0.39
4-$PnNEt_2$	0.08	−0.27	−0.12	0.04	0.03	−0.19	−0.34
4-PnCl	0.15	−0.01	−0.070	0.15		0.14	
4-PnMe	0.10	−0.12	−0.041	0.08		−0.02	
4-PnOMe	0.11	−0.15	−0.062	0.08		−0.04	
4-$PnNO_2$	0.23	−0.01	−0.045	0.23		0.22	
(CO)Z							
CHO	0.30	0.27	−0.10	0.35	0.35	0.57	0.71
CO_2H	0.30	0.17	−0.041	0.33	0.33	0.47	0.56
Ac	0.30	0.25	−0.095	0.34	0.35	0.55	0.68
CO_2Me	0.32	0.16	−0.070	0.35	0.35	0.48	0.56
CO_2Et	0.30	0.18	−0.064	0.33	0.34	0.48	0.57
$CONH_2$	0.28	0.12	−0.055			0.40	
$CONMe_2$	0.28	0.05	−0.060			0.33	
Bz	0.30	0.22	−0.11			0.52	
CN	0.57	0.12	−0.055	0.59	0.59	0.69	0.75
N							
N_3	0.43	−0.27	−0.12	0.38	0.38	0.16	0.02
NH_2	0.17	−0.68	−0.13	0.06	0.03	−0.51	−0.85
NHMe	0.13	−0.67	−0.18	0.02	0.00	−0.54	−0.88
NHAc	0.28	−0.35	−0.088			−0.07	
NMe_2	0.17	−0.66	−0.24	0.06	0.04	−0.49	−0.82
NEt_2	0.15	−0.65	−0.18	0.04	0.02	−0.50	−0.83
NO	0.37	0.31	−0.056	0.42	0.43	0.68	0.84
NO_2	0.67	0.18	−0.077	0.70	0.71	0.85	0.94
O							
OH	0.35	−0.57	−0.044	0.25	0.24	−0.22	−0.51
OMe	0.30	−0.55	−0.064	0.21	0.19	−0.25	−0.53
OAc	0.38	−0.24	−0.005	0.34	0.33	0.14	0.02
OEt	0.28	−0.55	−0.070	0.19	0.17	−0.27	−0.55
OPr-*i*	0.27	−0.55	−0.067	0.18	0.16	−0.28	−0.56
OBu	0.28	−0.55	−0.067	0.19	0.17	−0.27	−0.55
$OSiMe_3$	0.25	−0.44	−0.053	0.18	0.16	−0.19	−0.41
OPh	0.40	−0.51	−0.083	0.31	0.30	−0.11	−0.37

TABLE 1. (*continued*)

X	σ_1	σ_d	σ_e	$\sigma_{c14.3}$	$\sigma_{c16.7}$	σ_{c50}	σ_{c60}
S							
SH	0.27	−0.40	−0.098	0.20	0.19	−0.13	−0.33
SMe	0.30	−0.38	−0.13	0.24	0.22	−0.08	−0.27
SAc	0.39	−0.08	−0.057			0.31	
SEt	0.26	−0.39	−0.12	0.19	0.18	−0.13	−0.33
SPh	0.31	−0.34	−0.17	0.25	0.24	−0.03	−0.20
SOMe	0.54	−0.01	−0.037			0.53	
SOPh	0.51	−0.02	−0.052			0.49	
SO_2Me	0.59	0.13	−0.052	0.31	0.62	0.72	0.79
SO_2Ph	0.56	0.08	−0.082	0.57	0.58	0.64	0.68
SF_5	0.59	0.04	−0.040			0.63	
Other							
H	0	0	0	0	0	0	0
Br	0.47	−0.27	−0.028	0.42	0.42	0.20	0.06
Cl	0.47	−0.28	−0.011	0.42	0.41	0.19	0.05
F	0.54	−0.48	0.041	0.46	0.44	0.06	−0.18
I	0.40	−0.20	−0.057	0.37	0.36	0.20	0.10

[a] For abbreviations see Appendix II.

TABLE 2. Values of σ_D for common substituents [a]

X	$\sigma_R^{\ominus}$	σ_R^{-}	σ_R^{o}	σ_R	σ_R^{+}	$\sigma_R^{\oplus}$
Ak, *c*-Ak						
Me	−0.03	−0.09	−0.16	−0.16	−0.16	−0.25
Et	−0.01	−0.07	−0.14	−0.14	−0.14	−0.28
c-Pr	0.01	−0.08	−0.15	−0.19	−0.27	−0.43
Pr				−0.16		
i-Pr	−0.04	−0.09	−0.16	−0.16	−0.16	−0.34
Bu				−0.16		
i-Bu				−0.16		
s-Bu				−0.16		
t-Bu	−0.05	−0.11	−0.18	−0.18	−0.18	−0.33
Pe				−0.16		
CH_2Bu-*t*				−0.17		
c-Hx				0.15		
Oc				0.16		
1-Ad						
Vinyl						
$CH{=}CH_2$	0.45	−0.08	−0.15	−0.15	−0.15	−0.56
$CH{=}CH{-}CH{=}CH_2$	−0.02	−0.23	−0.29	−0.38	−0.57	−0.91
CH=CHPh	0.02	−0.23	−0.30	−0.30	−0.30	−1.01
Ethynyl						
C≡CH	0.28	0.13	−0.04	−0.04	−0.12	−0.45
C≡C−C≡CH	0.34	0.19	0.02	0.01	−0.17	−0.36
C≡CPh	0.16	−0.14	−0.21	−0.21	−0.21	−1.03
Aryl						
Ph	0.28	−0.04	−0.11	−0.11	−0.17	−0.69
C_6H_4Ph-4	0.18	0.00	−0.14	−0.20	−0.36	−0.68
1-Nh	0.12	−0.07	−0.18	−0.26	−0.57	−0.75

(*continued overleaf*)

TABLE 2. (*continued*)

X	$\sigma_R^{\ominus}$	σ_R^{-}	σ_R^{o}	σ_R	σ_R^{+}	$\sigma_R^{\oplus}$
2-Nh	0.19	0.01	−0.13	−0.20	−0.50	−0.67
C_6F_5	0.28	0.20	−0.02	−0.02	−0.08	−0.19
C_6H_4Z (PnZ)						
4-PnCl	0.05	0.00	−0.07	−0.03	−0.15	−0.30
4-PnMe	0.00	−0.07	−0.12	−0.13	−0.20	−0.32
4-PnOMe		−0.01		−0.19	−0.27	
4-PnNO_2	0.29	0.04	−0.03	0.03	−0.18	−0.21
CH_2Z						
CH_2Br				−0.10		
CH_2OH				−0.07	−0.15	
CH_2Cl				−0.08		
CH_2CN				−0.04		
CH_2OMe				−0.10		
CH_2Vi				−0.14		
CH_2SiMe_3				−0.23	−0.30	
CH_2Ph				−0.13		
CZ_3						
CCl_3				0.08		
CF_3	0.20	0.18	0.11	0.11	0.15	0.00
Carbonyl						
CHO	0.57	0.53	0.15	0.15	0.15	−0.04
Ac	0.56	0.41	0.20	0.20	0.06	−0.05
$CONH_2$	0.28	0.23	0.08	0.08	0.08	−0.10
CO_2Me	0.37	0.30	0.11	0.11	0.11	−0.12
CO_2Et	0.37	0.31	0.11	0.11	0.11	−0.06
CN	0.26	0.26	0.08	0.08	0.08	−0.10
N						
NH_2	−0.30	−0.55	−0.42	−0.80	−1.10	−1.05
NHAc	−0.09	−0.28	−0.25	−0.35	−0.47	−0.75
NMe_2	0.05	−0.30	−0.44	−0.88	−1.22	−1.38
NO_2	0.41	0.37	0.10	0.10	0.10	−0.08
N_3	0.08	−0.11	−0.21	−0.31	−0.47	−0.67
P						
PMe_2	0.30	−0.14	−0.35	−0.55	−1.03	−1.63
$POMe_2$	0.24	0.22	0.08	0.12	0.14	0.00
$PO(OMe)_2$	0.34	0.33	0.15	0.21	0.25	0.12
O						
OH	−0.45	−0.45	−0.46	−0.62	−0.64	−0.71
OMe	−0.36	−0.51	−0.44	−0.58	−0.66	−0.83
OEt	−0.35	−0.51	−0.44	−0.57	−0.65	−0.86
OAc	−0.23	−0.16	−0.22	−0.23	−0.26	−0.32
OPh	−0.27	−0.44	−0.42	−0.48	−0.64	−0.96
S						
SH	−0.11	−0.29	−0.32	−0.41	−0.56	−0.81
SMe	0.01	−0.24	−0.31	−0.38	−0.55	−0.97
SAc	0.09	0.00	−0.08	−0.09	−0.13	−0.34
SEt	−0.04	−0.10	−0.30	−0.30	−0.59	−0.99
SPh	0.16	−0.11	−0.24	−0.34	−0.65	−1.00
SOMe	0.13	0.05	0.00	0.00	−0.10	−0.70
SOPh	0.03	0.06	−0.07	−0.07	−0.21	−0.81

TABLE 2. (*continued*)

X	$\sigma_R^{\ominus}$	σ_R^{-}	σ_R^{o}	σ_R	σ_R^{+}	$\sigma_R^{\oplus}$
SO_2Me	0.18	0.35	0.11	0.11	0.11	−0.12
SO_2Ph	0.32	0.22	0.12	0.12	−0.16	−0.42
SF_5				0.03		
Se						
SeMe	0.01	−0.23	−0.31	−0.42	−0.65	−1.02
Other						
F	−0.61	−0.58	−0.44	−0.48	−0.37	−0.25
Cl	−0.25	−0.30	−0.25	−0.25	−0.21	−0.41
Br	−0.21	−0.28	−0.25	−0.25	−0.19	−0.44
I	−0.06	−0.18	−0.16	−0.16	−0.16	−0.57
H	0	0	0	0	0	0

[a] Values are from References 24, 25 and 27, unless otherwise noted.

TABLE 3. Values of Hammett substituent constants

X	σ_m	σ_p^{-}	σ_p^{o}	σ_p	σ_p^{+}
Ak, *c*-Ak					
Me	−0.06	−0.15	−0.15	−0.17	−0.31
Et	−0.06	−0.09	−0.12	−0.15	−0.28
c-Pr	−0.08	−0.09	−0.15	−0.22	−0.46
Pr	−0.06			−0.17	
i-Pr	−0.04	−0.12	−0.12	−0.15	−0.28
t-Bu	0.00	−0.15	−0.14	−0.19	−0.26
CH_2Bu-*t*	−0.05			−0.17	
c-Hx	−0.05			−0.17	
Vinyl					
$CH{=}CH_2$	0.02	0.21	0.02	−0.05	−0.30
$CH{=}CH{-}CH{=}CH_2$	−0.08	−0.17	−0.20	−0.33	−0.76
CH=CHPh	−0.06	0.13	−0.16	−0.28	−0.68
Ethynyl					
C≡CH	0.24	0.50	0.26	0.21	0.05
C≡C−C≡CH	0.36	0.72	0.41	0.37	0.26
C≡CPh	0.26	0.39	0.11	0.12	−0.39
Aryl					
Ph	0.09	0.08	0.00	0.01	−0.51
C_6H_4Ph-4	0.06	0.11	−0.03	−0.09	−0.42
1-Np	−0.02	0.05	−0.07	−0.17	−0.28
2-Np	0.01	0.13	−0.03	−0.11	−0.25
CH_2Z					
CH_2Br	0.17			0.10	
CH_2OH	0.10			0.04	
CH_2Cl	0.15			0.09	
CH_2CN	0.20			0.16	
CH_2OMe	0.08			0.01	
CH_2SiMe_3	−0.11			−0.26	
CH_2Ph	−0.01			−0.10	
CX_3					
CF_3	0.46	0.74	0.52	0.53	0.61
CCl_3	0.40			0.44	

(*continued overleaf*)

TABLE 3. (*continued*)

X	σ_m	σ_p^-	σ_p^o	σ_p	σ_p^+
Carbonyl					
CHO	0.36	0.91	0.50	0.45	0.53
Ac	0.38	0.82	0.46	0.50	0.51
$CONH_2$	0.31	0.62	0.37	0.37	0.39
$CONMe_2$	0.31	0.62	0.37	0.37	0.39
CO_2Me	0.36	0.74	0.46	0.44	0.49
CO_2Et	0.35	0.74	0.46	0.44	0.49
Bz	0.36			0.41	
CN	0.61	1.02	0.69	0.65	0.66
N					
NH_2	−0.21	−0.51	−0.40	−0.63	−1.30
NHAc	0.11	0.03	0.00	−0.12	−0.46
NMe_2	−0.22	−0.35	−0.44	−0.67	−1.50
NO_2	0.74	1.29	0.82	0.77	0.79
N_3	0.27	0.38	0.20	0.08	−0.25
P					
PMe_2	−0.25	−0.18	−0.37	−0.61	−1.40
$POMe_2$	0.35	0.65	0.42	0.43	0.50
$PO(OMe)_2$	0.46	0.87	0.56	0.59	0.73
O					
OH	0.13	−0.24	−0.10	−0.38	−0.61
OMe	0.11	−0.25	−0.12	−0.28	−0.78
OEt	0.07	−0.27	−0.16	−0.29	−0.73
OAc	0.31	0.20	0.21	0.16	0.06
OPh	0.23	−0.04	−0.01	−0.08	−0.57
S					
SH	0.07	−0.04	−0.06	−0.19	−0.58
SMe	0.09	0.04	−0.02	−0.17	−0.60
SAc	0.34	0.50	0.33	0.28	0.18
SEt	0.16	−0.01	−0.07	−0.04	−0.63
SPh	0.23	0.18	0.01	−0.15	−0.64
SOMe	0.47	0.74	0.47	0.54	0.21
SOPh	0.50	0.75	0.51	0.44	0.44
SO_2Me	0.63	1.13	0.71	0.70	0.75
SO_2Ph	0.62	0.95	0.68	0.68	0.48
Other					
SeMe	0.05	0.03	−0.06	−0.21	−0.68
F	0.34	0.03	0.17	0.06	−0.07
Cl	0.37	0.28	0.27	0.22	0.11
Br	0.34	0.30	0.26	0.22	0.15
I	0.35	0.35	0.27	0.24	0.13
H	0	0	0	0	0

1. Classification of substituent electrical effects

Substituents are frequently classified as either electron acceptor (electron withdrawing, electron sink), EA; or electron donor (electron releasing, electron source), ED. There is a small third category as well that consists of groups whose electrical effect is not significantly different from zero (NS groups). Groups vary in the nature of their electrical effect to a greater or lesser extent depending on the electronic demand of the phenomenon

being studied, the skeletal group, if any, to which they are bonded, and the experimental conditions. Very few groups are in the same category throughout the entire range of P_D and η normally encountered. We have observed earlier that a plot of the $\sigma_{k'/k,X}$ values for a group with $X = P_D$, $Y = \eta$ and $Z = \sigma_{k'/k}$ produces a surface that characterizes the electrical effect of the X group. A matrix of these values can be obtained by calculating them for values of P_D in the range 10 to 90 in increments of 10 and values of η in the range -6 to 6 in increments of 1. The resulting 9 by 13 matrix has 117 values. We define $\sigma_{k'/k,X}$ values greater than 0.05 as EA, $\sigma_{k'/k,X}$ values less than -0.05 as ED and $\sigma_{k'/k,X}$ values between 0.05 and -0.05 as NS. The variability of the electrical effect of a group can be quantitatively described by the percent of the matrix area in the $P_D-\eta$ plane in which the group is in each category (P_{EA}, P_{ED} and P_0). Approximate measures of these quantities are given by the relationships in equation 22:

$$P_{EA} = \frac{n_{EA}}{n_T}, \quad P_0 = \frac{n_{NS}}{n_T}, \quad P_{ED} = \frac{n_{ED}}{n_T} \tag{22}$$

where n_{EA}, n_{NS}, n_{ED} and n_T are the number of EA, the number of NS, the number of ED and the total number of values in the matrix. Matrices for a number of substituents are given in Table 2; values of P_{EA}, P_{ED} and P_0 for many substituents are reported in Table 3. We may now classify groups into seven types:

1. Entirely electron acceptor (**EA**) ($P_{EA} = 100$). Examples: CF_3, $PO(OMe)_2$, $POPh_2$.
2. Predominantly electron acceptor (**PA**) ($100 > P_{EA} \geqslant 75$). Examples: NO_2, HCO, CN.
3. Largely electron acceptor (**LA**) ($75 > P_{EA} \geqslant 50$). Examples: Cl, C_2Ph, OCN.
4. Ambielectronic {**AM**) ($50 > P_{EA}$ or P_{ED}). Examples: SH, CH_2Ph, $SiMe_3$.
5. Largely electron donor (**LD**) ($75 > P_{ED} \geqslant 50$). Examples: Me, OH, NH_2.
6. Predominantly electron donor (**PD**) ($100 > P_{ED} \geqslant 75$). Examples: *P=PMe*, *P=POMe*.
7. Entirely electron donor (**ED**) ($P_{ED} = 100$). Example: *P=PNMe*$_2$.

The values in italics are based on estimated substituent constants.

2. The nature of substituent electrical effects

The overall electrical effect of a substituent as was noted above is a function of its σ_l, σ_d and σ_e values. It depends on the nature of the skeletal group G, the active site Y, the type of phenomenon studied, the medium and the reagent, if any. These are the factors that control the values of P_D and η, which in turn determine the contributions of σ_l, σ_d and σ_e.

IV. STERIC EFFECTS

A. Introduction

The concept of steric effects was introduced by Kehrmann[30] over a century ago. V. Meyer[31] and Sudborough and Lloyd[32] shortly thereafter presented kinetic results supporting the steric effect explanation of rate retardation in the esterification of 2-substituted and 2,6-disubstituted benzoic and 3-*cis*-substituted acrylic acids. Major early reviews of steric effects were given by Stewart[33] and Wittig[34]. Somewhat later reviews are that by Wheland[35], and in a volume edited by Newman[36].

B. The Nature of Steric Effects

1. Primary steric effects

Primary steric effects are due to repulsions between electrons in valence orbitals on adjacent atoms which are not bonded to each other. They are believed to result from the

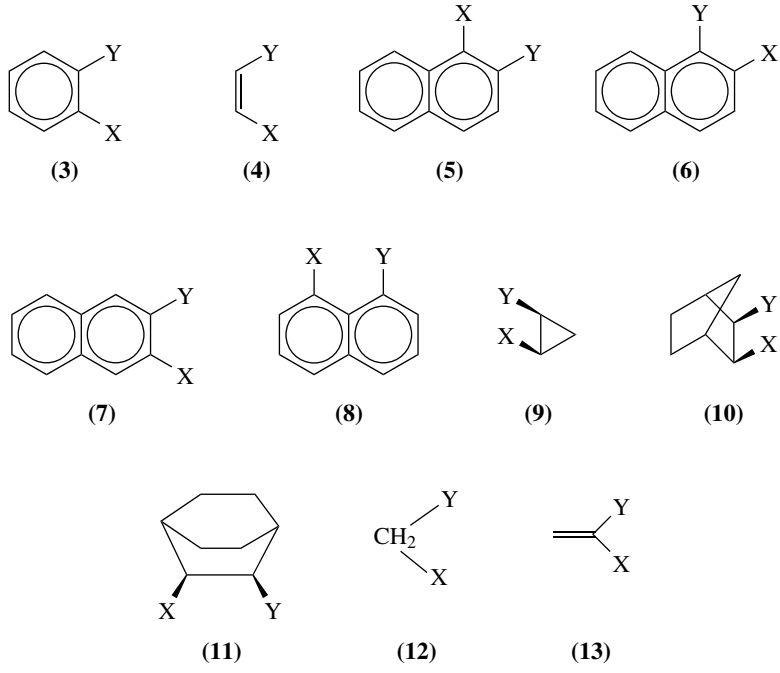
interpenetration of occupied orbitals on one atom by electrons on the other, resulting in a violation of the Pauli exclusion principle. **All steric interactions raise the energy of the system in which they occur.** Their effect on chemical reactivity is to either decrease or increase a rate or equilibrium constant, depending on whether steric repulsions are greater in the reactant or in the product (equilibria) or transition state (rate).

2. Secondary steric effects

Secondary steric effects on chemical reactivity can result from the shielding of an active site from the attack of a reagent, from solvation, or both. They may also be due to a steric effect on the reacting conformation of a chemical species that determines its concentration.

3. Direct steric effects

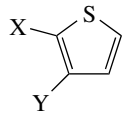
These effects can occur when the active site at which a measurable phenomenon occurs is in close proximity to the substituent. Among the many systems exhibiting direct steric effects are *ortho*-substituted benzenes (**3**), *cis*-substituted ethylenes (**4**) and the *ortho* (1,2-; 2,1-; and 2,3-) and *peri* (1,8-) substituted naphthalenes (**5**, **6**, **7** and **8** respectively). Other examples are *cis*-1,2-disubstituted cyclopropanes, *cis*-2,3-disubstituted norbornanes and *cis*-2,3-disubstituted [2.2.2]-bicyclooctanes (**9**, **10** and **11**, respectively). Some systems generally do not show steric effects. Vicinally substituted systems, such as disubstituted methanes (**12**) and 1,1-disubstituted ethenes (**13**), are examples. 2,3-Disubstituted heteroarenes with five-membered rings such as thiophenes and selenophenes (**14a–14c**) are also generally free of steric effects. This is probably due to the larger XCC angle in these systems as compared with benzenoid systems.



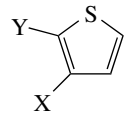
(3) **(4)** **(5)** **(6)**

(7) **(8)** **(9)** **(10)**

(11) **(12)** **(13)**



(14a)



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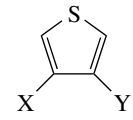

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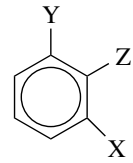


(15)

4. Indirect steric effects

These effects are observed when the steric effect of the variable substituent is relayed by a constant substituent between it and the active site, as in **15**, where Y is the active site, Z is the constant substituent and X is the variable substituent. This is a type of buttressing effect.

5. The directed nature of steric effects

There is a regrettable tendency to regard steric effects as being related to 'bulk'. Regrettably, the word bulk is invariably used without a precise definition of its meaning. The most popular form of this atrocity is the use of the phrase steric bulk. Presumably, this is intended to imply group size in some undefined way. Steric effects are vector quantities. This is easily shown by considering, for example, the ratio r of the steric parameter for any five-carbon alkyl group to that for 1-pentyl(Pe). Values of r are: 1-Pe, 1; 2-Pe, 1.54; 3-Pe, 2.22; CH_2Bu-*s*, 1.47; CH_2Bu-*i*, 1.00; CH_2Bu-*t*, 1.97; CMe_2Et, 2.40; CHPr-*i*Me, 1.90. All of these groups have the same volume and therefore the same bulk, but they differ in steric effect. In order to account for this it is necessary to consider what happens when a nonsymmetric substituent is in contact with an active site. Take as an example the simple case of a spherical active site Y in contact with a nonsymmetric substituent, $CZ^LZ^MZ^S$, where the superscripts L, M and S represent the largest, the medium-sized and the smallest Z groups, respectively. There are three possible conformations of this system. Top views of them are shown in Figure 1. As all steric repulsions raise the energy of the system, the preferred conformation will be the one that results in the lowest energy increase. This is the conformation which presents the smallest face to the active site, conformation **C**. From this observation is obtained the minimum steric interaction (MSI) principle which states: **a nonsymmetric substituent prefers that conformation which minimizes steric interactions**. The directed nature of steric effects results in a conclusion of vital importance: that in general **the volume of a substituent is not an acceptable measure of its steric effect**[37–39]. There are still some workers who are unable to comprehend this point. It is nevertheless true that group volumes are not useful as steric parameters. They are actually measures of group polarizability. In short, for a range of different substituent shapes in a data set **steric effects are not directly related to bulk, polarizability is**.

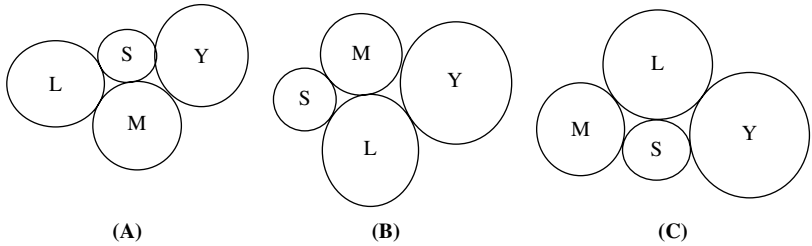


FIGURE 1. Top views of possible conformations of a nonsymmetric tetrahedral group interacting with a symmetric active site

C. The Monoparametric Model of Steric Effects

Stewart[33] proposed a parallel between the rate of esterification of 2-substituted benzoic acids and the molecular weights of the substituents. The nitro group strongly deviated from this relationship. It is the first attempt to relate the steric effect of a group to some property that might at least in part be a measure of size. Kindler[40] made the first attempt at defining a set of steric parameters. These parameters were later shown to be a function of electrical effects. The first successful parameterization of the steric effect is due to Taft[41], who defined the steric parameter E_S for aliphatic systems by the expression

$$E_{S,X} \equiv \delta \log \frac{k_X}{k_{Me}} \tag{23}$$

where k_X and k_{Me} are the rate constants for the acid catalyzed hydrolysis of the corresponding esters XCO_2Ak and $MeCO_2Ak$, respectively. The value of δ is taken as 1.000 for this purpose. The $E_{So,X}$ parameters intended to represent the steric effects of substituents in the *ortho* position of a benzene derivative were defined for a few groups from the rates of acid-catalyzed hydrolysis of 2-substituted alkyl benzoates. These parameters are a mix of electrical and steric effects with the former predominating, and are therefore of no use as steric parameters.

The original Taft $E_{S,X}$ values suffered from several deficiencies:

1. Their validity as measures of steric effects was unproven.
2. They were determined from average values of rate constants obtained under varying experimental conditions, often in different laboratories.
3. They were available only for those groups in which the atom bonded to G or Y (the first atom of the substituent) is an sp^3-hybridized carbon atom, and for hydrogen. Values were therefore unavailable for many, if not most, of the substituents generally encountered.
4. The use of the methyl group as the reference substituent meant that they were not compatible with electrical effect substituent constants, for which the reference substituent is hydrogen.

The first problem was resolved when it was shown that the E_S values for symmetric groups are a linear function of van der Waals radii[42]. The latter have long been held to be an effective measure of atomic size. The second and third problems were solved by Charton, who proposed the use of the van der Waals radius as a steric parameter[43] and developed a method for the calculation of group van der Waals radii for tetracoordinate symmetric top substituents MZ_3, such as the methyl and trifluoromethyl groups[44]. In later

work the hydrogen atom was chosen as the reference substituent and the steric parameter υ was defined as

$$\upsilon_X \equiv r_{VX} - r_{VH} = r_{VX} - 1.20 \tag{24}$$

where r_{VX} and r_{VH} are the van der Waals radii of the X and H groups in Angstrom units[45]. Expressing r_V in these units is preferable to the use of picometers, because the coefficient of the steric parameter is then comparable in magnitude to the coefficients of the electrical effect parameters. Whenever possible, υ parameters are obtained directly from van der Waals radii or calculated from them. Recently, an equation has been derived which makes possible the calculation of υ values for nonsymmetric tetrahedral groups of the types $MZ_2^SZ^L$ and $MZ^SZ^MZ^L$ in which the Z groups are symmetric. These are considered to be primary values. For the greater number of substituents, however, υ parameters must be calculated from the regression equations obtained for correlations of rate constants with primary values. The values obtained in this manner are considered to be secondary υ values. All other measures of atomic size are a linear function of van der Waals radii. There is, therefore, no reason for preferring one measure of atomic size over another. As values of υ were developed for a wide range of substituent types with central atoms including oxygen, nitrogen, sulfur and phosphorus as well as carbon, these parameters provide the widest structural range of substituents for which a measure of the steric effect is available.

1. Steric classification of substituents

Substituents may be divided into three categories based on the degree of conformational dependence of their steric effects:

1. *No conformational dependence* (NCD). Groups of this type include monatomic substituents such as hydrogen and the halogens, cylindrical substituents such as the ethynyl and cyano groups, and tetracoordinate symmetric top substituents such as the methyl, trifluoromethyl and silyl groups.
2. *Minimal conformational dependence* (MCD). Among these groups are: (a) nonsymmetric substituents with the structure $MH_n(lp)_{3-n}$ such as the hydroxyl and amino groups (lp is a lone pair), and (b) nonsymmetric substituents with the structure $MZ_2^SZ^L$, where S stands for small and L for large.
3. *Strong conformational dependence* (SCD). These groups have the structures: (a) $MZ_2^LZ^S$ and $MZ^LZ^MZ^S$, where the superscript M indicates medium; (b) planar π-bonded groups MZ^LZ^S, where M and either or both Zs are sp^2-hybridized, such as phenyl, acetyl, nitro ($X_{p\pi}$ groups) (Figure 2); and (c) quasi-planar π-bonded groups, such as dimethylamino and cyclopropyl.

The steric parameter for NCD groups can be obtained directly from van der Waals radii or calculated from them. The values for MCD groups are often obtainable from van der Waals radii, although in some cases they must be derived as secondary values from regression equations obtained by correlating rate constants for groups with known values of the steric parameter. Steric parameters for SCD groups of the nonsymmetric type are usually obtainable only from regression equations. In the case of planar π-bonded

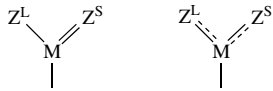


FIGURE 2. Planar π-bonded groups

groups, the maximum and minimum values of the steric parameter are available from the van der Waals radii. These groups are sufficiently common and important to require a more detailed discussion.

2. Planar π-bonded groups

These $X_{p\pi}$ groups represent an especially difficult problem, because their delocalized electrical effect depends on the steric effect when they are bonded to planar π-bonded skeletal groups, $G_{p\pi}$. An approach to the problem has been developed[45,46]. The σ_d and σ_e electrical effect parameters are a function of the dihedral angle formed by $X_{p\pi}$ and $G_{p\pi}$. The relationship generally used has the form

$$P = P_0 \cos^2 \theta \tag{25}$$

where P is the property of interest, P_0 is its value when the dihedral angle is zero and θ is the dihedral angle. Thus equations 26 and 27 apply:

$$\sigma_{dX,\theta} = \sigma_{dX,0} \cos^2 \theta \tag{26}$$

$$\sigma_{eX,\theta} = \sigma_{eX,0} \cos^2 \theta \tag{27}$$

where $\sigma_{dX,0}$ and $\sigma_{eX,0}$ are the values of σ_d and σ_e when the substituent and skeletal group are coplanar ($\theta = 0$). The steric parameter does not depend on equation 25; the effective value of υ, which is derived from the geometry of the system, is given by the expression

$$\upsilon = d' \cos\theta + r_{VZS} - 1.20 \tag{28}$$

where Z^S is the smaller of the two Z groups attached to the central atom M of the $X_{p\pi}$ group, and d' is the distance between the center of Z^S and the perpendicular to the line joining that center with the group axis. There is no simple *a priori* way to determine θ. It could conceivably be estimated by molecular mechanics calculations, but there is some reason to believe that θ is a function of the medium. Alternatively, the $X_{p\pi}$ group can be included in the data set by means of an iteration procedure. The method requires an initial correlation of the data set with all $X_{p\pi}$ and other SCD groups excluded. This constitutes the basis set. The correlation equation used for this purpose is the LDRS equation, which takes the form

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + S\upsilon + h \tag{29}$$

The correlation is then repeated for each $X_{p\pi}$ group using υ values, increasing incrementally by some convenient amount from the minimum, which represents the half-thickness of the group, to the maximum, which occurs when $X_{p\pi}$ is nearly perpendicular to $G_{p\pi}$. The proper value of θ is that which:

1. Results in the best fit of the data to the correlation equation. The best fit is indicated by the minimal value of the S_{est} and S^o statistics, and the maximal value of the F and $100R^2$ statistics. The statistics used in this work are described in Appendix I.
2. Has the L, D, R, S and h values that are in best agreement with those of the basis set.

D. Bond Length Difference as a Factor in Steric Effects

The steric effect exerted by some group X is a function of the lengths of the substituent-skeletal group (X−G) and active site-skeletal group (Y−G) bonds[47]. The steric parameters described above function best when they are of comparable length. In that case the contact

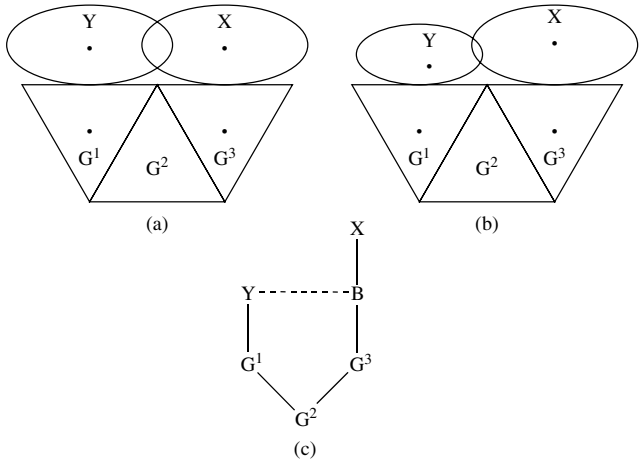


FIGURE 3. The effect of bond length difference on the steric effect. G^1, G^2 and G^3 are consecutive atoms of the skeletal group, X is a substituent and Y is an active site

between X and Y is that shown in Figure 3a. If the YG bond is much shorter than the XG bond, the contact is as shown in Figure 3b. In that case, the distance from Y to the X−G bond is less in Figure 3b than it is in Figure 3a although the XY distance in both Figures 3a and 3b is the sum of the Van der Waals radii, r_{VX} and r_{VY}. The effective size of the van der Waals radius of X is reduced. Steric parameters were originally derived for systems like that in Figure 3a. In a system like that in Figure 3b, corrected steric parameters are needed. An approximate value of the effective van der Waals radius of X, $r^c{}_{VX}$, can be calculated for the case in which the X−G and Y−G bonds are parallel to each other from a consideration of Figure 3c and Scheme 1, where l_{XG} and l_{YG} are the lengths of the X−G and Y−G bonds, respectively.

$$\overline{XY} = r_{VX} + r_{VY}$$
$$\overline{XB} = l_{XG} - l_{YG}$$
$$\overline{BY} = [(\overline{XY})^2 - (\overline{XB})^2]^{1/2}$$
$$\overline{BY} = [(r_{VX} + r_{VY})^2 - (l_{XG} - l_{YG})^2]^{1/2}$$
$$\overline{BY} = r_{VY} + r^c_{VX}$$
$$r^c_{VX} = [(r_{VX} + r_{VY})^2 - (l_{XG} - l_{YG})^2]^{1/2} - r_{VY}$$

SCHEME 1

Values of steric effect substituent constants for typical groups are presented in Table 4.

E. Multiparametric Models of Steric Effects

In some cases a simple monoparametric model of the steric effect is insufficient. Examples are when the active site is itself large and nonsymmetric, or alternatively when the phenomenon studied is some form of bioactivity in which binding to a receptor is

TABLE 4. Steric effect parameters for common substituents[a]

X	υ	υ_1	υ_2	n_1	n_2
Ak, *c*-Ak					
Me	0.52	0.52	0	0	0
Et	0.56	0.52	0.52	1	0
Pr	0.68	0.52	0.52	1	1
i-Pr	0.78	0.78	0	2	0
Bu	0.68	0.52	0.52	1	1
i-Bu	0.98	0.52	0.78	1	2
s-Bu	1.02	0.78	0.52	2	1
t-Bu	1.24	1.24	0.52	3	0
Pe	0.68	0.52	0.52	1	1
i-Pe	0.68	0.52	0.52	1	1
c-Hx	0.87			1.5	0.74
Hx	0.73	0.52	0.52	1	1
Oc	0.68	0.52	0.52	1	1
1-Ad	1.33	1.33			
CH_2Z					
CH_2Br	0.64	0.52	0.65		
CH_2Cl	0.60	0.52	0.55		
CH_2OMe	0.63				
CH_2CH_2CN	0.68	0.52	0.52		
CH_2GeMe_3	1.53				
CH_2SiMe_3	1.46				
$CH_2CH_2CO_2Et$	0.68	0.52	0.52		
$CH_2CHMeCO_2Me$		0.52	0.78		
CH_2NEt_2		0.52	0.63		
Vn					
Vi	0.57	0.57	0.57		
2-VnVi	0.57	0.57	0.57		
2-VnPh	0.57	0.57	0.57		
Ar					
C_6F_5	0.57	0.57	0.57		
Ph	0.57	0.57	0.57		
C_6H_4Z (PnZ)					
4-$PnNMe_2$	0.57	0.57	0.57		
4-$PnNEt_2$	0.57	0.57	0.57		
4-PnCl	0.57	0.57	0.57		
4-PnMe	0.57	0.57	0.57		
4-PnOMe	0.57	0.57	0.57		
4-$PnNO_2$	0.57	0.57	0.57		
N					
NH_2	0.35	0.35			
NHAc	0.35	0.50	0.32		
NMe_2	0.35	0.52	0		
NO_2	0.35	0.35	0.32		
N_3	0.35	0.35	0.35		
O					
OH	0.32	0	—		
OMe	0.32	0.32	0.52		
OEt	0.36	0.32	0.52		
OAc	0.48	0.32	0.52		
$OSiMe_3$	0.50	0.32	1.40		
OPh	0.57	0.32	0.57		

TABLE 4. (*continued*)

X	υ	υ_1	υ_2	n_1	n_2
S					
SH	0.60	0.60	0		
SMe	0.64	0.60	0.52		
SAc	1.09	0.60	0.50		
SEt	0.94	0.60	0.52		
SPh	1.00	0.60	0.57		
SOMe	0.76	0.74	0.52		
SOPh	1.10	0.74	0.57		
SO_2Me	1.13	1.03	0.52		
SO_2Ph		1.03	0.57		
Se					
SeMe	0.74	0.70	0.52		
Other					
H	0	0	—		
F	0.27	0.27	—		
Cl	0.55	0.55	—		
Br	0.65	0.65	—		
I	0.78	0.78	—		

[a] For abbreviations see Appendix II.

the key step. The failure of the monoparametric model is due to the fact that a single steric parameter cannot account for the variation of the steric effect at various points in the substituent. The use of a multiparametric model of steric effects that can represent the steric effect at different segments of the substituent is required. Five multiparametric models are available: that of Verloop and coworkers[48], the simple branching model and the expanded branching model[47,49,50], the segmental model and the composite model. The Verloop model suffers from the fact that its parameters measure maximum and minimum distances perpendicular to the group axis. These maxima and minima may occur at any point in the group skeleton (the longest chain in the group). The steric effect, however, may be very large at one segment of the chain and negligible at others. If a data set is large, as it must be if a multiparametric model is to be used, the likelihood that the maximum and minimum distances of all groups are located at the same segment and that it is this segment at which the steric effect is important is very small. The Verloop model will therefore not be discussed further.

1. The branching equations

The simple branching model[45,47] for the steric effect is given by the expression

$$S\psi = \sum_{i=1}^{m} a_i n_i + a_b n_b \tag{30}$$

where $S\psi$ represents the steric effect parameterization, a_i and a_b are coefficients, n_i is the number of branches attached to the i-th atom and n_b is the number of bonds between the first and last atoms of the group skeleton. It follows that n_b is a measure of group length. Unfortunately, it is frequently highly collinear in group polarizability, which greatly limits its utility. For saturated cyclic substituents it is necessary to determine values of n_i from

an appropriate regression equation[50]. For planar π-bonded groups, n_i is taken to be 1 for each atom in the group skeleton. For other groups, n_i is obtained simply by counting branches. The model makes the assumption that all of the branches attached to a skeleton atom are equivalent. This is at best only a rough approximation. Distinguishing between branches results in an improved model, called the expanded branching equation:

$$S\psi = \sum_{i=1}^{m}\sum_{j=1}^{3} a_{ij}n_{ij} + a_b n_b \tag{31}$$

which allows for the difference in steric effect that results from the order of branching[45,49]. This difference follows from the MSI principle. The first branch has the smallest steric effect, because a conformation in which it is rotated out of the way of the active site is preferred. In this conformation the active site is in contact with two hydrogen atoms. The preferred conformation in the case of a second branch has the larger of the two branches directed out of the way. The smaller branch and a hydrogen atom are in contact with the active site. When there are three branches, the largest will be directed out of the way and the other two will be in contact with the active site.

The problem with the expanded branching method is that it requires a large number of parameters. Data sets large enough to permit its use are seldom seen. It has been applied to a number of studies in which only alkyl groups are the varying substituents. In this case electrical effects are constant, thus only steric effects need be considered.

2. The segmental model

As both branching methods have problems associated with them, the segmental method[49] is often the simplest and most effective of the multiparametric models. In this model, each atom of the group skeleton together with the atoms attached to it constitutes a segment of the substituent. Applying the MSI principle, the segment is considered to have that conformation which presents its smallest face to the active site. The segment is assigned the υ value of the group which it most resembles. Values of the segmental steric parameters υ_i, where i designates the segment number, are given in Table 4. Numbering starts from the first atom of the group skeleton, which is the atom that is attached to the rest of the system. The segmental model is given by the expression

$$S\psi = \sum_{i=1}^{m} S_i \upsilon_i \tag{32}$$

When only steric effects are present, then

$$Q_X = S\psi_X \tag{33}$$

In the general case, electrical effects are also present and the general form of the LDRS equation

$$Q_X = L\sigma_{DX} + D\sigma_{dX} + R\sigma_{eX} + S\psi_X + h \tag{34}$$

is required.

3. The composite model

The composite model is a combination of the monoparametric υ model with the simple branching model. This method has proven useful in modeling amino acid, peptide and

protein properties[51]. It is an improvement over the simple branching model and requires only one additional parameter.

V. INTERMOLECULAR FORCES

A. Introduction

Inter- and intramolecular forces (imf) are of vital importance in the quantitative description of structural effects on bioactivities and chemical properties. They can make a significant contribution to chemical reactivities and some physical properties as well. Types of intermolecular forces and their present parameterization are listed in Tables 5 and 6[52].

B. Parameterization of Intermolecular Forces

1. Hydrogen bonding

Hydrogen bonding requires two parameters for its description, one to account for the hydrogen atom donating capacity of a substituent and another to account for its hydrogen atom accepting. A simple approach is the use of n_H, the number of OH and/or NH bonds in the substituent, and n_n, the number of lone pairs on oxygen and/or nitrogen atoms as parameters[20,53]. The use of these parameters is based on the argument that if one of the phases involved in the phenomenon studied includes a protonic solvent, particularly water, then all of the hydrogen bonds the substituent is capable of forming will indeed form. For such a system, hydrogen-bond parameters defined from equilibria in highly dilute solution in an 'inert' solvent are unlikely to be a suitable model. This parameterization accounts only for the number of hydrogen-donor and hydrogen-acceptor sites in a group. It does not take into account differences in hydrogen-bond energy. A more sophisticated

TABLE 5. Intermolecular forces and the quantities upon which they depend[5] [a]

Intermolecular force	Quantity
Molecule–molecule	
Hydrogen bonding (hb)	q_{M^H}, q_{M^E}, orbital type
Agostic bonding	
Dipole–dipole (dd)	dipole moment
Dipole–induced dipole (di)	dipole moment, polarizability
Induced dipole–induced dipole (ii)	polarizability
Charge transfer (ct)	ionization potential, electron affinity
Ion–molecule	
ion–dipole (Id)	ionic charge, dipole moment
ion-induced dipole (Ii)	ionic charge, polarizability

[a] Abbreviations are in parentheses. dd interactions are also known as Keesom interactions; di interactions are also known as Debye interactions; ii interactions are also known as London or dispersion interactions. Collectively, dd, di and ii interactions are known as van der Waals interactions. Charge transfer interactions are also known as donor–acceptor interactions.

TABLE 6. ΔP_M and α values of the atoms M [a]

M, ΔP_M, α: **H**, 0, 0; **F**, −0.11, −0.001; **Cl**, 1.513, 0.0510; **Br**, 2.383, 0.079; **I**, 4.033, 0.129; **O**, 0.135, 0.015; **S**, 2.233, 0.082; **Se**, 3.103; 0.114; **N**, 0.433, 0.038; **P**, 2.963, 0.107; **C**, 1.093, 0.039

[a] P_M values are from T. M. Miller, in *Handbook of Chemistry and Physics*, 67th Edn. (Gen. Ed. R. C. Weast) (Eds. M. J. Astle and W. H. Beyer), CRC Press, Boca Raton, 1986, pp. E66–E75.

parameterization than that described above would be the use of the hydrogen-bond energy for each type of hydrogen bond formed[52]. Thus for each substituent the parameter E_{hbX} would be given by equation 35,

$$E_{hbX} = \sum_{i=1}^{m} n_{hbi} E_{hbi} \tag{35}$$

where E_{hbX} is the hydrogen-bonding parameter, E_{hbi} is the energy of the i-th type of hydrogen bond formed by the substituent X and n_{hbi} is the number of such hydrogen bonds. The validity of this parameterization is as yet untested. In any event, the site number parameterization suffers from the fact that, though it accounts for the number of hydrogen bonds formed, it does not differentiate between their energies and can therefore be only an approximation. A definition of a scale of hydrogen-bond acceptor values from 1-octanol–water partition coefficients of substituted alkanes shows that the site number method strongly overestimates the hydrogen-acceptor capability of the nitro group and seriously underestimates that of the methylsulfoxy group[54]. It is now apparent that there are many weak types of H donors and H acceptors that are capable of contributing significantly to the intermolecular forces that are responsible for many properties involving a change of phase. Green has reported[55] evidence many years ago for the H-donor activity of CH groups, and in a more recent work Nishio, Hirota and Umezawa have reviewed evidence for CH-π interactions[56]. No really satisfactory parameterization of hydrogen bonding is available at present.

2. van der Waals interactions

These interactions (dd, di, ii) are a function of dipole moment and polarizability. It has been shown that the dipole moment cannot be replaced entirely by the use of electrical effect substituent constants as parameters[57]. This is because the dipole moment has no sign. Either an overall electron-donor group or an overall electron-acceptor group may have the same value of μ. It has also been shown that the bond moment rather than the molecular dipole moment is the parameter of choice. The dipole moments of MeX and PhX were taken as measures of the bond moments of substituents bonded to sp^3- and sp^2-hybridized carbon atoms, respectively, of a skeletal group. Application to substituents bonded to sp-hybridized carbon atoms should require a set of dipole moments for substituted ethynes.

The polarizability parameter used in this work, α, is given by the expression

$$\alpha \equiv \frac{MR_X - MR_H}{100} = \frac{MR_X}{100} - 0.0103 \tag{36}$$

where MR_X and MR_H are the group molar refractivities of X and H, respectively[49,52]. The factor 1/100 is introduced to scale the α parameter, so that its coefficients in the regression equation are roughly comparable to those obtained for the other parameters used. There are many other polarizability parameters including parachor, group molar volumes of various kinds, van der Waals volumes and accessible surface areas, any of which will do as well as they are all highly collinear in each other[57]. Proposing other polarizability parameters was a popular occupation in the past.

Values of α can be estimated by additivity from the values for fragments or from group molar refractivities calculated from equation 37,

$$MR_X = 0.320n_c + 0.682n_b - 0.0825n_n + 0.991 \tag{37}$$

where n_c, n_b and n_n are the number of core, bonding and nonbonding electrons, respectively, in the group X[57]. They can also be calculated from a relationship between ΔP_M and α. Values are given in Table 6.

For alkyl and cycloalkyl groups, the number of carbon atoms in the group is a good polarizability parameter when no other type of substituent is present in the data set. Improved results are obtained on using corrected values of n_C for cycloalkyl groups[50].

3. Charge transfer interactions

These interactions can be roughly parameterized by the indicator variables n_A and n_D: n_A takes the value 1 when the substituent is a charge transfer acceptor and 0 when it is not; n_D takes the value 1 when the substituent is a charge transfer donor and 0 when it is not. An alternative parameterization makes use of the first ionization potential of MeX (ip_{MeX}) as the electron-donor parameter and the electron affinity of MeX as the electron-acceptor parameter. Usually, the indicator variables n_A and n_D are sufficient. This parameterization accounts for charge transfer interactions directly involving the substituent. If the substituent is attached to a π-bonded skeletal group, then the skeletal group is capable of charge transfer interaction the extent of which is modified by the substituent. This is accounted for by the electrical effect parameters of the substituent.

4. The intermolecular force (IMF) equation

A general relationship for the quantitative description of intermolecular forces, called the intermolecular force (IMF) equation, is given by equation 38:

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + M\mu_X + A\alpha_X + H_1 n_{HX} + H_2 n_{nX} + Ii_X + B_{DX} n_{DX} + B_{AX} n_{AX} + S\psi_X + B^o \quad (38)$$

Some values of the IMF parameters for alkyl and cycloalkyl substituents and for a few other groups of interest are given in Table 7.

TABLE 7. Intermolecular force substituent constants[a]

X	α	$\mu(sp^2)$	$\mu(sp^3)$	n_H	n_n	n_C
Ak, *c*-Ak						
Me	0.046	0.37	0	0	0	1
Et	0.093	0.37	0	0	0	2
c-Pr	0.125	0.48		0	0	
Pr	0.139	0.37	0	0	0	3
i-Pr	0.140	0.40	0	0	0	3
Bu	0.186	0.37	0	0	0	4
i-Bu	0.186		0	0	0	4
s-Bu	0.186		0	0	0	4
t-Bu	0.186	0.52	0	0	0	4
Pe	0.232		0	0	0	5
CH_2Bu-*t*	0.232		0	0	0	5
c-Hx	0.257		0	0	0	
Hx	0.278		0	0	0	6
Oc	0.372		0	0	0	8
1-Ad	0.396		0	0	0	

(*continued overleaf*)

TABLE 7. (*continued*)

X	α	$\mu(sp^2)$	$\mu(sp^3)$	n_H	n_n	n_C
CH_2Z						
CH_2Br	0.124	1.87	2.069	0	0	
CH_2Cl	0.095	1.83	1.895	0	0	
CH_2OH	0.062	1.71	1.58	1	2	
CH_2CN	0.091	3.43	3.53	0	0	
CH_2OMe	0.114			0	2	
CH_2CH_2CN	0.145	3.92		0	0	
CH_2Vi	0.135	0.364	0.438	0	0	
CH_2OEt	0.160			0	2	
$CH_2CH_2CO_2Et$	0.256		1.84	0	4	
$CH_2CHMeCO_2Me$	0.256		1.84	0	4	
CH_2NEt_2	0.278		0.612	0	1	
CH_2Ph	0.290	0.22	0.37	0	0	
CZ_3						
CF_3	0.040	2.86	2.321	0	0	
CCl_3	0.191		1.95	0	0	
$C(SiMe_3)_3$	0.760			0	0	
Other						
H	0	0	0	0	0	
Br	0.079	1.70	1.84	0	0	
Cl	0.050	1.70	1.895	0	0	
F	−0.001	1.66	1.8549	0	0	
I	0.129	1.71	1.618	0	0	

[a] For abbreviations see Appendix II.

VI. APPLICATIONS

A. Introduction

Examples of the application of correlation analysis to cyclobutane derivative data sets are considered below. Both data sets in which the cyclobutane is directly substituted and those in which a phenylene group lies between the substituent and the cyclobutane ring group have been considered. In some imaginary perfect world, all data sets have a sufficient number of substituents and cover a wide enough range of substituent electronic demand, steric effect and intermolecular forces to provide a clear, reliable description of structural effects on the property of interest. In the real world this is frequently not the case. We will therefore try to show how the maximum amount of information can be extracted from small data sets.

1. The choice of correlation equations

In choosing a correlation equation there are several factors that must be considered. They include the number of data points in the set to be studied, the experimental conditions, the type of data to be correlated and the possibility of steric effects.

a. *The number of data points*. The number of data points, N_{DP}, and the number of independent variables, N_V, determine the number of degrees of freedom, N_{DF}. Thus

$$N_{DF} = N_{DP} - N_V - 1 \tag{39}$$

In order to obtain reliable models (minimize the probability of chance correlations), it is necessary to consider the ratio $r_{DF/V}$:

$$r_{DF/V} = \frac{N_{DF}}{N_V} \tag{40}$$

The minimum value of $r_{DF/V}$ required for a reliable model depends on the quality of the determination of the data to be correlated. The smaller the experimental error in the data, the smaller the value of $r_{DF/V}$ required for dependable results. Experience indicates that in the case of chemical reactivity data, $r_{DF/V}$ should be not less than three. For bioactivity studies, $r_{DF/V}$ depends heavily on the type of data; for rate and equilibrium constants obtained from enzyme kinetics, a value of not less than three is reasonable, while for toxicity studies on mammals at least seven is required.

b. *Steric effects*. If substituent and active site are proximal, then steric effects may occur. In that event it is necessary to include a steric effect parameterization in the correlation equation. The choice of parameterization depends on the number of data points in the set. If N_{DF} is sufficiently large, then the segmental method is a good choice of parameterization. If this is not the case, then it is best to use a monoparametric method.
c. *Intermolecular forces*. If intermolecular forces are likely to be significant, as is the case with bioactivity data and many types of chemical properties, then it is necessary to use the intermolecular force equation or some relationship derived from it. If N_{DF} is too small, it may be necessary to use composite parameters such as log P in order to get a reliable model.
d. *Small chemical reactivity data sets*. Chemical reactivity data sets which involve only electrical effects are best modeled by the LDR equation. Although data sets are often encountered which are too small to give reliable results with the LDR equation, it is still possible to extract from them useful information regarding structural effects. There are two ways to handle this problem. The best approach is to combine two or more small data sets into a single large data set. This can be done if all of the data sets to be combined have been studied under experimental conditions such that all but one are kept constant and the variation in that one can be parameterized. Consider, for example, the case in which the data are rate constants that have been determined at various temperatures. Addition to the correlation equation of the term $T\tau$, where

$$\tau \equiv \frac{100}{t} \tag{41}$$

and t is the absolute temperature, makes possible the combination of rate constants at different temperatures into a single data set. Thus, the LDR equation becomes the LDRT equation

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + T\tau_X + h \tag{42}$$

If the data sets were studied in aqueous organic solvents, they can be combined into a single large set by the addition of the term $F\varphi$, where φ is the mole fraction of organic solvent in the medium. Thus, the LDR equation becomes the LDRF equation.

VII. AN OVERVIEW OF ALKYL AND CYCLOALKYL SUBSTITUENT AND STRUCTURAL EFFECTS

From the previous discussion, it can be seen that a substituent can exert three types of effect:

(1) electrical,

(2) steric and
(3) intermolecular force.

The electrical effects of alkyl and cycloalkyl groups are generally constant. Further evidence for this conclusion is presented in Table 3, where values of the composite substituent constants, σ_m, σ_p, σ_p^+, σ_p^- and σ_p^o, are given when available for a number of alkyl and cycloalkyl groups.

As was noted above, steric effects of alkyl and cycloalkyl groups depend primarily on the number of C−C bonds at the first and second atoms of the substituent (n_1 and n_2, respectively). For ring systems that exhibit conformational isomerism, this is an additional factor in the steric effect. For any ring system that is capable of exerting a resonance effect, such as the cyclopropyl group, the dihedral angle between the group and the active site or skeletal group to which it is bonded is a factor in determining the extent of delocalization.

Dipole moments of XY, where X is alkyl or cycloalkyl, are generally constant. In view of the previous observation that dipole moments can be modeled by electrical effect parameters, this is not surprising. Polarizability of alkyl and cycloalkyl groups can be modeled using MR_X, the group molar refractivity, usually rescaled and then written as α, or n_C, the number of C atoms in the group. As can be seen from the α and n_C values in Table 7, α for cycloalkyl groups is generally less than that for the corresponding alkyl group with the same number of carbon atoms. This problem has been addressed by Charton[50].

Alkyl and cycloalkyl groups are not involved in hydrogen bonding unless a strong electron-acceptor group is bonded to the carbon atom bearing the hydrogen atom involved. No charge transfer interactions occur in any case.

The ring strain energies of cycloalkyl groups may be an important structural factor in those reactions in which the ring opens. Correlations of solvolysis rates with ring strain have been reported[58]. This does not necessarily mean that there is a direct relationship between the two phenomena. There is a distinct possibility that both are related to some third phenomenon. Consider the following:

1. Ring strain can result in a change in ring orbital hybridization.
2. Electronegativity has been shown to be a function of hybridization[59]. The electronegativities of sp^3, sp^2 and sp orbitals on carbon have been reported as 2.50, 2.78 and 3.19, respectively. It is interesting to note that the σ_I values of the Et, Vi and C_2H groups are −0.01, 0.11 and 0.29, respectively. σ_I is linear in χ. It follows then that the dependence of solvolysis rates on the ring strain energies may actually be due to a dependence of σ_I on χ.

VIII. THE CYCLOBUTYL AND RELATED GROUPS AS SUBSTITUENTS

A. Introduction

The cyclobutyl group does not seem to be as atypical in its behavior as is the cyclopropyl group. If we are to detect atypical behavior, it would be best to study XY systems in which the effect is likely to be largest. There are two different systems of interest:

1. Y has a positive electronic demand.
2. Y has a negative electronic demand.

B. Y with Positive Electronic Demand

1. Radical cation XY systems

XY systems are the most sensitive for detecting atypical behavior of cycloalkyl groups as they are the most sensitive to structural effects. The transmission of electrical effects

depends on $1/r^n$, where r is the distance between X and the atom of Y at which the measured phenomenon takes place.

A method has been developed for the detection of atypical *c*-Ak behavior[60]. It is based on the nature of the alkyl group substituent effects. In the general case, the σ_I, σ_d and σ_e values of alkyl groups are constant and therefore the electrical effects of alkyl groups are constant. Intermolecular forces depend primarily on hydrogen bonding, polarizability, dipole moment and occasionally on charge transfer interactions as well. For alkyl groups, dipole moment and hydrogen bonding are constant; charge transfer interactions are as well. Polarizability does vary with the number of C atoms, n_C, in the group, in fact, n_C is a suitable polarizability parameter. Steric effects vary with the number of C−C bonds to the first atom of the group. This is a good steric parameter. Thus, any quantity Q_{Ak} which varies with the structure of alkyl and cycloalkyl groups should be modeled by equation 43:

$$Q_{Ak} = A_c n_C + A_1 n_1 + A_0 \tag{43}$$

It has been shown[60] that equation 43 is obeyed by both the adiabatic and, in some cases, the vertical first ionization potentials of XY, where X is Ak or *c*-Ak and Y is Cl, Br, I, CH_2, Vi, Ph, HCO and Ac. All acyclic alkyl groups fit this equation. Among the cycloalkyl groups that fit this equation are cyclohexyl, cyclododecyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, 1-adamantyl and 2-adamantyl. Those that show atypical behavior:

1. Lie $\geqslant 3$ standard deviations from the correlation line.
2. Give a much improved correlation when the atypical groups are excluded from the data set, as is shown by the statistics.

Atypical cycloalkyl groups are cyclopropyl, cyclobutyl, 6-tricyclo[3.1.1.$0^{3,6}$]heptyl and cubyl. These groups give calculated IP values that differ from the observed values by three or more standard deviations. The data used in the correlations are given in Table 8, the results of the correlations in Table 9 and the comparison of calculated and observed IP values in Table 10.

TABLE 8. $XY^{\cdot+}$ data sets[a]

1. IP, XCl. X, IP: Me, 11.265; Et, 10.98; Pr, 10.82; *i*-Pr, 10.78; Bu, 10.67; *i*-Bu, 10.66; *s*-Bu, 10.65; *c*-Hx, 10.10; 1-Ad, 9.30; *c*-Dod, 9.04.
2. 2v. IP, XBr. X, IP: Me, 10.54, *10.54*; Et, 10.30, *10.29*; Pr, 10.18; *i*-Pr, 10.12; Bu, 10.13; *i*-Bu, 10.09; *s*-Bu, 9.98; *t*-Bu, 9.95, *10.05*; Pe, 10.10; *c*-Hx, 9.85, *10.00*: 1-bc[2.1.1]Hx, 9.5, *9.72*; 1-bc[2.2.1]Hp, 9.6, *9.76*; 1-bc[2.2.2]Oc, 9.4, *9.67*; 1-Ad, 9.30; 2-Ad, 9.30, *9.633*.
3. 3v. IP, XI. X, IP: Me, 9.538, *9.53*; Et, 9.346, *9.35*; Bu, 9.229, *9.23*; *i*-Bu, 9.202, *9.4*; *s*-Bu, 9.09, *9.4*; *t*-Bu, 9.02, *9.04*; *c*-Pe, 9.076; Pe, 9.201; *i*-Pe, 9.192; *t*-Pe, 8.93; *c*-Hx, 9.003; Hx, 9.178; 1-bc[2.1.1]Hx, 8.80, *8.98*; 1-bc[2.2.1]Hp, 8.80, *8.96*; 1-bc[2.2.2]Oc, 8.70, *8.87*; 1-Ad, 8.60, *8.79*; 6-trc[3.1.1.$0^{3,8}$]Hp, 8.60, *8.79*; 1-Cb, 8.60, *8.76*.
4. 4v. IP, XOH. X, IP: Me, 10.85, *10.97*; Et, 10.49, *10.65*; Pr, 10.22, *10.52*; *i*-Pr, 10.10, *10.44*; Bu, 9.99, *10.44*; *i*-Bu, 10.09, *10.47*; *s*-Bu, 9.88, *10.35*; *t*-Bu, 9.97, *10.25*; 2-Pe, 9.78, *10.27*; 3-Pe, 9.73, *10.25*; *c*-Dod, 9.26; 1-Ad, 9.09; 2-Ad, 9.09; *c*-Bu, 9.56; *c*-Pr, 9.10.
5. IP, XC_2H. X, IP: Me, 10.33; Et, 10.178; Pr, 10.10; *i*-Pr, 10.05; Bu, 10.07; *s*-Bu, 9.923; Pe, 10.044; Hp, 9.93; Dc, 9.91; Und, 9.90; Dod, 9.90; Trid, 9.90; Ted, 9.89.
6. 6v. IP, XVi. X, IP: Me, 9.73, *9.91*; Et, 9.59, *9.77*; Pr, 9.52, *9.68*; *i*-Pr, 9.533, *9.5*; Bu, 9.47, *9.65*; *i*-Bu, 9.45; *t*-Bu, 9.45, *9.7*; Pe, 9.442; Hx, 9.427, *9.60*; Oc, 9.417, *9.59*; neoPe, 9.399, *9.6*; *c*-Pr, 8.7, *9.15*.
7. 7v. IP, XPh.X, IP: Me, 8.82, *8.90*; Et, 8.76, *8.77*; Pr, 8.72; *i*-Pr, 8.69, *8.71*; Bu, 8.69, *8.69*; *i*-Bu, 8.69, *8.71*; *s*-Bu, 8.68, *8.68*; *t*-Bu, 8.63, *8.74*; *c*-Bu, 8.4, *8.77*.

(*continued overleaf*)

TABLE 8. (*continued*)

8. IP, XCHO. X,IP: Me, 10.22; Et, 9.953; Pr, 9.836; *i*-Pr, 9.705; Bu, 9.748; *i*-Bu, 9.697; *t*-Bu, 9.50; Pe, 9.722; neoPe, 9.610
9. IP, XAc. X, IP: Me, 9.709; Et, 9.529; Pr, 9.383; *i*-Pr, 9.298; Bu, 9.331; *i*-Bu, 9.296; *s*-Bu, 9.209; *t*-Bu, 9.117; Pe, 9.298; neoPe, 9.226; 2-Pe, 9.19; *t*-Pe, 9.019.

[a] Values of IP are in eV. For abbreviations see Appendix II.
Vertical IP values are given in italics.

TABLE 9. Results of correlations with equation 43

Set/Y	A_C	S_{A^C}	A_1	S_{n^1}	A_o	S_o	$100R^2$	A$100R^2$	F	S_{est}	S^o
1 Cl	−0.194	0.00726	−0.0669	0.0300	11.48	0.0352	99.59	99.54	855.9	0.0526	0.0763
2 Br	−0.104	0.00897	−0.127	0.0238	10.66	0.0405	97.10	96.90	217.9	0.0678	0.189
2v Br	−0.0613	0.0162	−0.129	0.0421	10.59	0.0629	96.13	95.48	62.08	0.0760	0.249
3 I	−0.0599	0.00563	−0.135	0.0117	9.62	0.0232	98.47	98.35	386.1	0.0340	0.138
[a]	−0.637	0.0103	−0.147	0.0215	9.64	0.0422	95.57	95.28	151.2	0.0634	0.232
3v I	−0.0445	0.00588	−0.103	0.0144	9.55	0.0211	99.16	99.02	294.0	0.0276	0.116
[a]	−0.0483	0.0130	−0.111	0.0321	9.56	0.0472	95.61	95.06	76.16	0.0620	0.251
4 OH	−0.118	0.0153	−0.179	0.0601	10.80	0.0954	93.30	92.69	69.66	0.147	0.295
[b]	−0.0876	0.0303	−0.284	0.120	10.74	0.198	70.99	68.76	14.68	0.305	0.602
4v OH	−0.110	0.0134	−0.115	0.0201	11.02	0.0370	97.68	97.39	147.6	0.0380	0.182
5 C_2H	−0.0268	0.00325	−0.105	0.0215	10.32	0.0377	89.44	88.48	42.37	0.0510	0.370
[c]	−0.0539	0.00572	−0.0895	0.0119	10.39	0.0244	97.44	97.01	94.97	0.0271	0.203
6 Vi	−0.0573	0.00803	−0.0271	0.0152	9.75	0.0327	90.18	88.95	32.12	0.0349	0.375
[d]	−0.0164	0.0697	−0.138	0.0979	9.67	0.207	20.02	12.01	1.125	0.244	1.033
6v Vi	−0.0410	0.0106	−0.0163	0.0285	9.88	0.0530	77.24	73.45	8.484	0.0613	0.603
[e]	−0.0184	0.0319	−0.112	0.0784	9.83	0.165	26.52	17.34	1.263	0.193	1.025
7 Ph	−0.0321	0.00459	−0.0292	0.00564	8.85	0.0117	97.64	97.25	103.5	0.0105	0.194
[f]	−0.0479	0.0423	−0.0397	0.0524	8.89	0.108	47.11	39.56	2.672	0.0979	0.891
7v Ph	−0.0465	0.00867	−0.0461	0.0146	8.93	0.0217	97.08	96.34	49.79	0.0191	0.242
[g]	−0.0516	0.0221	0.00047	0.0278	8.91	0.0570	65.79	60.09	4.808	0.0510	0.740
8 CHO	−0.104	0.0123	−0.34	0.0197	10.30	0.0433	96.76	96.30	89.54	0.0319	0.221
9 Ac	−0.0825	0.00888	−0.112	0.0126	9.78	0.0303	97.38	97.11	166.9	0.0327	0.187

[a] Includes 6-trc[3.1.1.$0^{3,8}$]Hp, 1-Cb.
[b] Includes *c*-Pr, *c*-Bu.
[c] Includes Ak groups with $n_C \geqslant 8$.
[d] Includes *i*-Pr, Oc.
[e] Includes *c*-Pr, *i*-Pr.
[f] Includes *c*-Bu.
[g] Includes *c*-Bu, *t*-Bu.

2. Carbenium ion XY systems

The relative rates of acetolysis of (*c*-Bu)$_2$CHCH$_2$OBs (**16**) and *c*-BuMeCHCH$_2$OBs (**17**) are 16,800 and 3000, respectively[61]. Peters[62] states that the relative rates of acetolysis of **17** and *i*-PrMeCHCH$_2$OBs (**18**) are 85.5 and 1, respectively. Then the relative rates for **16**, **17** and **18** are 371, 85.5 and 1, respectively. With some data sets we can only draw qualitative conclusions regarding the atypical behavior of a cycloalkyl group. If the group in question exhibits a rate or equilibrium constant differing from that of an alkyl group in the same data set by at least one log unit (one or more orders of magnitude), it is behaving atypically. If the difference in a number of related data sets is consistently either greater or less than that of an alkyl group by at least 0.6 log unit, then it is probably exhibiting atypical behavior. Thus, the relative rates for acetolysis show that the *c*-Bu group stabilizes a positive charge much more effectively than does a typical alkyl or

TABLE 10. Atypical cycloalkyl groups

c-Ak	Set	Y	IP_{calc}	IP_{obs}	ΔIP	S_{est}	N_{SD}
c-Pr	4	OH	10.09	9.10	0.99	0.147	6.73
	12	Vi	9.52	8.7	0.82	0.0349	23.6
	12v		9.72	9.15	0.57	0.0613	9.30
c-Bu	4	OH	9.97	9.56	0.41	0.147	2.79
	13	Ph	8.66	8.4	0.26	0.0105	24.8
	13v		8.05	8.77	0.12	0.0191	6.28
6-trc[3.1.1.$0^{3,7}$]Hp	3	I	8.80	8.60	0.20	0.0340	5.88
	3v		8.93	8.79	0.14	0.0276	5.05
Cb	3		8.74	8.60	0.14	0.0340	4.12
	3v		8.89	8.76	0.13	0.0276	4.71

cycloalkyl group. It follows then from the relative rates of **15**, **16** and **17** that the *c*-Bu group is exhibiting atypical behavior.

The difference in ρ values ($\Delta\rho$, equation 44) obtained from correlation of rate constants for the solvolysis of (XPn)RMeCOPnNO_2-4 (**19**), where R is *i*-Pr, *c*-Bu or *c*-Pr, has been proposed as a means of determining the extent to which R stabilizes a carbenium ion[63,64].

$$\Delta\rho = \rho_{c\text{-Ak}} - \rho_{i\text{-Pr}} \tag{44}$$

In this method, the larger the value of $\Delta\rho$ the greater the stabilization by R. The correlations were carried out with the Hammett equation using the σ^+ constants. As the only statistic reported was the correlation coefficient, we have repeated the correlations in order to make sure that the standard error of ρ was small enough to give reliable results. The data sets are 10, 11 and 12 in Table 11; the results are reported in Table 12. The method is valid, showing that stabilization is in the order *c*-Pr >> *c*-Bu > *i*-Pr. The $\Delta\rho$ values are 1.86, 0.66 and 0, respectively.

TABLE 11. Carbenium ion XY^+ data sets

10. 10^6k_1: *i*-PrMe(XPn)COPnNO_2-4′, 80% aq. Me_2CO, 25°.
X, 10^6k_1: **4-OMe**, 65.5; H, 0.00951; **4-CF_3**, 0.0000136; **3,5-$(CF_3)_2$**, 0.000000261.
11. 10^6k_1:*c*-PrMe(XPn)COPnNO_2-4′, 80% aq. MeAc, 25°.
X, 10^6k_1: **4-OMe**, 33,000; H, 241; **4-CF_3**, 3.88; **3,5-$(CF_3)_2$**, 0.315.
12. 10^6k_1; *c*-BuMe(XPn)COPnNO_2-4′, 80% aq. MeAc, 25°.
X, 10^6k_1: **4-OMe**, 63.2; **H**, 0.0545; **4-CF_3**, 0.000123; **3,5-$(CF_3)_2$**, 0.00000460.
13. 10^5k_t: 1-(XPn)-1-CH_2OBs-*c*-Bu, AcOH, various *T*.
X, *T*, 10^5k_t: **4-OMe**, 45°, 8.8; 55°, 24.0; 65°, 74.4; 75°, 180; **4-Me**, 45°, 1.23; 55°, 4.9; 65°, 5.5; 75°, 49; **H**, 45°, 0.62; 55°, 1.97; **4-Cl**, 45°, 0.26; 55°, 0.92; 65°, 2.9; 75°, 9.5; **4-NO_2**, 55°, 0.186; 65°, 0.66, 75°, 2.4.
14. 10^7k_t: 1-(XPn)-1-CH_2OBs-*c*-Bu, 97% aq. TFE, various *T*.
X, *T*, 10^7k_t: **4-OMe**, 25°, 25; 35°, 74; 45°, 183; 55°, 400; **4-Me**, 45°, 49; 55°, 126; 60°, 200; 65°, 330; **H**, 35°, 5.0; 45°, 15.5; 55°, 45.8; 65°, 107; **4-Cl**, 45°, 5.6; 55°, 13.7; 60°, 21; 65°, 30; **4-NO_2**, 45°, 0.45; 75°, 12.2.
15. 1-(XPn)-1-CH_2OTs-*c*-Pe, AcOH, various *T*.
X, *T*, 10^8k_t: **4-OMe**, 25°, 900; 35°,4000; 45°,14,000; 55°, 40,000; **4-Me**, 35°, 270; 45°, 920; 55°, 3700; 75°, 40,000; **H**, 25°, 6.2; 35°, 23; 45°, 120; 65°, 1600; **4-Cl**, 45°, 18; 55°, 66; 65°, 260; 75°, 810; **3,5-$(CF_3)_2$**, 65°, 5.4; 75°, 20; 85°, 71.

(*continued overleaf*)

TABLE 11. (*continued*)

16. 1-(X-Pn)-1-CH_2OTs-*c*-Pe, 97% aq. TFE, various T.
X, T, 10^7k_t: **4-MeO**, 15°, 1600; 20°, 2700; 25°, 4500; 30°, 7600; **4-Me**, 25°, 640; 30°, 1200; 35°, 1900; 45°, 5300; **H**, 30°, 110; 35°, 200; 45°, 650; 55°, 1900; **4-Cl**, 30°, 12; 35°, 24; 45°, 65; 55°, 200; **3,5-$(CF_3)_2$**, 35°, 0.11; 45°, 0.45; 55°, 1.2; 65°, 3.9.
17. $XPnMe_2$-*c*-CH_2OBs, AcOH, various T.
X, T, k: **4-MeO**, 75°, 6050; **4-Me**, 50°, 29.1; 75°, 497; **4-Ph_2CH**, 50°, 10.1; 75°, 183; **3-Me**, 75°, 131.8; 100°, 1720; **H**, 75°, 68.4; **3-MeO**, 75°, 47.5; **Br**, 75°, 10.9; 100°, 152; CO_2Me, 75°, 1.32; 100°, 21.4.
18. k_S: 4-$XPnCH_2CH_2OTs$ in AcOH, various T.
X, T, k_S: **MeO**, 65°, 3.2; 75°, 8.5; 90°, 35; **Me** 75°, 2.0; 90°, 8.4; 115°, 79.3; **H**, 75°, 2.07; 90°, 8.92; 115°, 79.3; **Cl**, 75°, 1.97; 90°, 7.96; 115°, 28.9.
19. k_Δ. 4-$XPnCH_2CH_2OTs$, AcOH, various T.
X, T, k_Δ: **MeO**, 65°, 77.7; 75°, 228; 90°, 998; **Me**, 75°, 19.0; 90°, 92.3; 115°, 997; **H**, 75°, 2.39; 90°, 11.8; 115°, 128; **Cl**, 75°, 0.39; 90°, 2.19; 115°, 28.9.
20. k_Δ; *c*-$AkCH_2OTs$.
X, k_Δ: *c*-**Bu**, 42; *c*-**Pe**, 0.99; *c*-**Hx**, 0.27; *c*-**Hp**, 1.67; *c*-**Oc**, 1.98; *c*-**No**, 2.42; *c*-**Dc**, 2.57; *c*-**Udc**, 1.67; *c*-**Ddc**, 0.78; *i*-**$PrCH_2$**, 0.32.

Overall rate constants k_t for the solvolysis in AcOH and in 97% aqueous 1,1,1-trifluoroethanol of 1-(XPn)-1-CH_2OBs-Bu-*c* (**20**) and 1-(XPn)-1-CH_2OTs-Pe-*c* (**21**) have been determined at various temperatures[65,66]. Overall (titrimetric) rate constants k_t for the solvolysis in AcOH at various temperatures of $XPnCMe_2CH_2OBs$ (**22**) and rate constants k_S and k_Δ for $XPnCH_2CH_2OBs$ (**23**) under the same conditions[67,68] are given in equation 45:

$$k_t = k_S + k_\Delta \tag{45}$$

where k_S is the solvent-assisted rate constant and k_Δ is the nucleophilic hydrogen-assisted rate constant. The rate constants were correlated with a form of equation 46 in which the electrical effect is described by the σ^+ constants:

$$Q_X = \rho^+\sigma_X^+ + T\tau + h \tag{46}$$

The data sets (sets 13 through 18) are given in Table 11; the results of the correlations are presented in Table 13.

All of these systems have the structure $XPnGCH_2Lg$, where G is *c*-Bu, *c*-Pe, CMe_2 or CH_2 and Lg is a leaving group. As noted above, we have shown that unless the angle θ between the X−C bond and the line joining X and the C atom of CH_2Lg, C^{Lg}, is very large, transmission of electrical effects depends on n^{-m}, where n is the number of bonds between X and C^{Lg} and m is a constant for a given reaction type. As the value of n is the same for **20**, **21**, **22** and **23**, transmission will be the same for all of them. Then the variation in ρ^+ measured by $\Delta\rho^+$ must be due to differences in electronic demand. Defining the reference system as **22**, G^o is CMe_2 for which ρ^+ is −2.97; the system **20** with a ρ value of −1.33 has $\Delta\rho^+$ of −1.64. This is indicative of significant stabilization by the *c*-Bu group. Assuming that replacement of OBs as leaving group by OTs has a minimal effect, *c*-Pe has little if any effect on the electronic demand. The results of solvolysis in aqueous TFE are in accord with the acetolysis results. Comparison of ρ^+ for **22** with that for **23** supports the conclusion that −3 is the value for maximal electronic demand, although it must be noted that the data set for **23** (set 18) does not include an electron-acceptor group.

The acetolysis of cycloalkyl carbinyl tosylates, *c*-$AkCH_2OTs$ (**24**), from cyclobutane to cyclododecane and of *i*-$PrCH_2OTs$ has been studied[69–71]. Values of k_Δ are given in

TABLE 12. Results of correlations with equations 4 and 46

Set	ρ	S_ρ	T	S_T	h	S_h	$100R^2$	A$100R^2$	F	S_{est}	S^0	N_{dp}	N_{df}	$r_{df/iv}$	$C_\sigma{}^+$	C_T	$r_{\sigma T}$
10	−4.64	0.130			−1.90	0.0930	99.84		1284.	0.177	0.0558	4	2	2			
11	−2.78	0.0428			2.35	0.0307	99.95		4226	0.0585	0.0308	4	2	2			
12	−3.98	0.109			−1.31	0.0781	99.85		1334	0.149	0.0547	4	2	2			
13	−1.33	0.0551	−56.5	2.92	17.5	0.877	98.40	98.29	430.7	0.127	0.139	17	14	7.0	6.57	92.4	0.118
14	−1.66	0.0845	−45.5	3.29	15.4	1.01	96.52	96.52	208.3	0.147	0.204	18	15	7.5	9.82	90.2	0.452
15	−2.50	0.150	−58.3	5.17	20.4	1.59	94.64	94.33	141.3	0.297	0.252	19	16	8.0	11.4	88.6	0.59
16	−2.89	0.147	−49.4	6.77	18.1	2.18	96.40	96.20	227.6	0.288	0.206	20	17	8.5	14.9	85.1	0.684
17	−2.97	0.161	−56.8	4.20	18.0	1.20	97.43	97.20	189.9	0.172	0.183	13	10	5.0	13.5	86.5	0.422
18	−0.836	0.161	−50.6	4.55	14.7	1.24	93.20	92.52	61.69	0.180	0.301	12	9	4.5	4.71	95.3	0.461
19	−3.08	0.267	−60.7	7.17	17.5	1.95	94.19	93.61	72.97	0.283	0.278	12	9	4.5	13.2	86.8	0.461

TABLE 13. Results of correlations with equation 43

Set	A_{nC}	S_{Anc}	A_{n1}	S_{An1}	A^0	$S_A{}^0$	$100R^2$	A$100R^2$	F	S_{est}	S^0	N_{dp}	N_{df}	$r_{df/iv}$	r_{ncn1}	c_{nC}	C_{n1}
20	−0.00799	−0.07009	—	—	0.258	0.570	0.16	—	0.0127	0.644	1.12	10	8	80	—	100	—
[a]	0.0709	0.0387	—	—	−0.519	0.323	32.39	—	3.354	0.321	0.932	9	7	20	—	100	—
[b]	0.0960	0.0254	—	—	−0.579	0.204	74.04	—	214.26	0.176	0.603	7	5	5.0	—	100	—
29	2.70	0.724	2.33	2.94	24.0	5.32	70.50	67.56	10.76		0.627	12	9	4.5	0.449	74.3	25.3
[c]	2.18	0.519	3.74	2.06	25.4	3.66	82.15	80.17	18.41	4.28	0.495	11	8	4.0	0.480	59.3	40.7
[d]	2.24	0.558	3.54	2.19	25.2	3.86	82.80	80.65	16.85	4.49	0.496	10	7	3.5	0.500	61.3	38.7
30	4.07	0.411	3.83	2.51	3.83	5.27	93.12	92.35	54.12	3.50	0.308	11	8	4.0	0.164	72.7	27.3
[e]	4.17	0.434	—	—	10.9	2.66	91.12	—	92.33	3.75	0.329	11	8	8.0	—	100	—
31	0.0587	0.0107	0.0878	0.0652	5.87	0.159	74.49	72.52	17.52	0.110	0.565	15	121	6.0	0.149	62.6	37.4
[f]	0.0482	0.00429	0.182	0.0246	5.78	0.0637	95.60	95.16	97.71	0.0368	0.242	12	9	4.50	0.077	39.9	60.1
32	—	—	0.0587	0.0176	4.75	0.0329	52.72	—	11.15	0.0517	0.753	12	10	10.0	—	—	100
[g]	—	—	0.0312	0.0485	4.78	0.0312	12.87	—	1.625	0.0785	1.01	13	11	11.0	—	—	100
[h]	—	—	0.0197	0.0310	4.79	0.0615	3.539	—	0.403	0.0997	1.07	13	11	11.0	—	—	100
[i]	—	—	0.0114	0.0362	4.80	0.0717	0.889	—	0.098	0.116	1.08	13	11	11.0	—	—	100
[j]	—	—	0.00416	0.0462	4.82	0.0914	0.007	—	0.008	0.148	1.09	13	11	11.0	—	—	100
[k]	—	—	0.0412	0.0709	4.86	0.140	2.978	—	0.338	0.227	1.07	13	11	11.0	—	—	100
37	−0.204	0.185	0.219	0.392	0.995	0.515	20.90	7.72	0.66	0.555	1.12	8	5	2.5	0.707	70.0	30.0
[c]	−0.0444	0.156	−0.165	0.341	0.867	0.390	24.80	9.76	0.66	0.416	1.15	7	4	2.0	0.775	40.2	59.8
[d]	−0.0280	0.0395	−0.434	0.0906	0.857	0.0960	94.04	91.55	23.66	0.102	0.345	6	3	1.5	0.786	13.9	86.1
38	−0.0855	0.0986	−0.121	0.137	0.700	0.304	37.14	26.66	1.477	0.293	1.00	8	5	2.5	0.482	63.9	36.1
[c]	−0.0457	0.0647	−0.197	0.0915	0.611	0.197	69.45	63.35	4.548	0.188	0.731	7	4	2.0	0.513	36.7	63.3
[d]	−0.0578	0.0449	−0.223	0.0640	0.638	0.136	88.68	85.85	11.75	0.130	0.476	6	3	1.5	0.482	39.4	60.6

[a] Excluding *c*-Bu.
[b] Excluding *c*-Bu.
[c] Excluding *c*-Pr.
[d] Excluding *c*-Pr, *c*-Bu.
[e] Dropping n_1 as a variable.
[f] Excluding *c*-Pr, *c*-Bu, *endo*-trc[2.2.1.$0^{2,5}$]Hp.
[g] Including 1-bc[2.1.0]Pe.
[h] Including 1-trc[4.1.0.$0^{2,5}$]Hp.
[i] Including 1-bc[1.1.0]Bu.
[j] Including Cb.
[k] Including 1-bc[1.1.1]Pe.

TABLE 14. XGY^+ and $XY^{\Delta+}$ data sets[a]

21. k_{hydr}, 1-NhCH$(OCH_2)_2$-*c*-Akn, 20% v/v aq. dioxane, 34.3°
c-Akn, log k_{hydr}: **c-Prn**, 0.623; **cBun**, −0.553; **cPen**, −0.943; **cHxn**, −1.046
22. k_{hydr}, 2-NhCH$(OCH_2)_2$-*c*-Akn, 20% v/v aq. dioxane, 34.3°
c-Akn, log k_{hydr}: **c-Prn**, −0.633; **c-Bun**, −0.650; **cPen**, −0.845; **cHxn**, −1.167
23. k_{hydr} 1-NhCMe$(OCH_2)_2$-*c*-Akn, 20% v/v aq. dioxane, 34.3°
c-Akn, log k_{hydr}: **c-Prn**, 0.536; **c-Bun**, −0.495; **c-Hxn**, −1.456
24. K_e, 1-NhCH$(OCH_2)_2$-*c*-Akn, aq. dioxane containing HCl, 34.3°
c-Akn, log K_e: **c-Prn**, −0.027; **c-Bun**, 1.04; **c-Pen**, 1.418; **c-Hxn**, 1.785
25. K_e, 2-NhCH$(OCH_2)_2$-*c*-Akn, aq. dioxane containing HCl, 34.3°
c-Prn, 0.104; **c-Bun**, 0.982; **c-Pen**, 1.425; **c-Hxn**, 1.820
26. K_e, 1-NhCMe$(OCH_2)_2$-*c*-Akn, aq. dioxane containing HCl, 34.3°
c-Akn, log K_e: **c-Prn**, −2.699; **c-Bun**, −1.678; **c-Hxn**, −0.620
27. ^{13}C NMR, 4-Ak/cAkPnC$^+$Me$_2$, $SbF_3/FSO_3H/SO_2ClF$, −80°
Ak/c-Ak, δC^+: **Me,** 243.6; **Et,** 243.7; ***i*-Pr**, 244.0; ***t*-Bu**, 244.5; **c-Pe**, 241.6; **c-Hx**, 242.8; **2-*exo*-bc[2.2.1]Hp,** 241.0; **2-*endo*-bc[2.2.1]Hp,** 241.8; **2-*exo*-trc[2.2.1.3^{5,6}]Dc,** 241.0; **2-*endo*-trc[2.2.1.3^{5,6}]Dc,** 241.3; **c-Pr**, 231.6; **c-Bu**, 241.6
28. **Ak/c-Ak**, ^{13}C NMR, 4-Ak/*c*-AkPnC$^+$Me$_2$, $SbF_3/FSO_3H/SO_2ClF$, −80°
Ak/c-Ak, δC^4: **Me,** 175.2; **Et,** 180.1; ***i*-Pr,** 183.9; ***t*-Bu,** 185.7; **c-Pe,** 183.8; **c-Hx,** 183.0; **2-*exo*-bc[2.2.1]Hp,** 183.3; **2-*endo*-bc[2.2.1]Hp,** 181.9; **2-*exo*-trc[2.2.1.3^{5,6}]Dc,** 183.8; **2-*endo*-trc[2.2.1.3^{5,6}]Dc,** 182.2; **c-Pr,** 184.7; **c-Bu,** 181.6
29. **Ak/c-Ak,** ^{13}C NMR, 4-Ak/*c*-AkPnC$^+$Me$_2$, $SbF_3/FSO_3H/SO_2ClF$, −80°
Ak/c-Ak, $\delta C^{1'}$: **Me**, 25.1; **Et**, 32.6; ***i*-Pr**, 38.1; ***t*-Bu**, 39.4; **c-Pe**, 50.2; **c-Hx**, 48.7; **2-*exo*-bc[2.2.1]Hp**, 51.7; **2-*endo*-bc[2.2.1]Hp**, 51.5; **2-*exo*-trc[2.2.1.3^{5,6}]Dc**, 51.5; **2-*endo*-trc[2.2.1.3^{5,6}]Dc**, 50.8; **c-Pr**, 23.7; **c-Bu**, 43.8
30. **Ak/c-Ak**, ^{13}C NMR, 4-Ak/*c*-AkPnC$^+$Me$_2$, $SbF_3/FSO_3H/SO_2ClF$, −80°
Ak/c-Ak, $\delta C^{2'}$: **Et**, 13.9; ***i*-Pr**, 22.9; ***t*-Bu**, 29.7; **c-Pe**, 36.1; **c-Hx**, 33.4; **2-*exo*-bc[2.2.1]Hp**, 43.2; **2-*endo*-bc[2.2.1]Hp**, 45.4; **2-*exo*-trc[2.2.1.3^{5,6}]Dc**, 49.6; **2-*endo*-trc[2.2.1.3^{5,6}]Dc**, 49.4; **c-Pr**, 21.1; **c-Bu**, 30.0
31. pK_a, *c*-Ak/AkCO_2H, 50% v/v aq. EtOH
Ak, pK_a: **c-Bu**, 6.21[b], **c-Pe**, 6.43(6.48[b]); **c-Hx**, 6.42 (6.49[b]); **c-Hp**, 6.50; **c-Oc**, 6.54; **c-No**, 6.59; **c-Dc**, 6.66; **c-Udc**, 6.65; **c-Ddc**, 6.68; ***i*-PrCH$_2$**, 6.24
32. pK_a, *c*-AkCO_2H, water, 25°
c-Ak, pK_a: **c-Pr**, 4.827; **c-Bu**, 4.785; **c-Pe**, 4.987; **c-Hx**, 4.903
33. pK_a, *c*-AkCO_2H, MeOH, 25°
c-Ak, pK_a: **c-Pr**, 9.830; **c-Bu**, 9.889; **c-Pe**, 10.146; **c-Hx**, 10.035
34. pK_a, *c*-AkCO_2H, EtOH, 25°
c-Ak, pK_a: **c-Pr**, 10.462; **c-Bu**, 10.627; **c-Pe**, 10.762; **c-Hx**, 10.770
35. *c*-AkCO_2H, 50% v/v aq. EtOH, 25°
c-Ak, pK_a: **c-Pr**, 6.21; **c-Bu**, 6.21; **c-Pe**, 6.49;, **c-Hx**, 6.49
36. log k_2, *c*-AkCO_2H + Ph_2CN_2, EtOH, 30°
c-Ax, log k_2: **c-Pr**, −0.282; **c-Bu**, −0.299; **c-Pe**, −0.441; **c-Hx**, −0.45

[a] Akn = Alkenyl (applies also to *c*-Prn, *c*-Bun, *c*-Pen, *c*-Hxn).
[b] From Reference 86.

Table 14 (set 20). All of the members of this data set have about the same value of n_1. The rate constants were therefore correlated with equation 43 in the form

$$\log k_\Delta = A_C n_C + A_o \tag{47}$$

Best results were obtained on exclusion of the data points for *c*-Bu, *c*-Hx and *c*-Ddc. The rate constant for *c*-Hx is much smaller than expected. That for *c*-Ddc suggests that polarizability effects fall off or reach a limit after $n_C > 10$. The behavior of *c*-Bu is clearly atypical, as $N_{SD} = 10.3$.

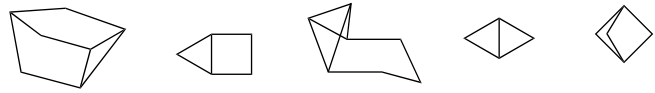
3. Carbenium ion XGY systems

Rate constants for the acid-catalyzed hydrolysis of the acetals and ketals $ArCZ(OCH_2)_2$-1,1-*c*-Ak (**25**), where Z is H or Me, have been determined[72]. The Ar groups are 1- or 2-naphthyl, the cycloalkylidene groups are *c*-Pr, *c*-Bu, *c*-Pe and *c*-Hx (sets 21, 22 and 23, Table 14). The rate-determining step is thought to be dissociation into protonated aldehyde and *c*-$Ak(CH_2OH)_2$, thus G is CH_2. It follows that the *c*-Ak group is not directly bonded to either of the two atoms carrying partial positive charges in the transition state. The rate constants for *c*-Pr show atypical behavior in all three data sets; those for *c*-Bu do so only in set 23. Also determined were equilibrium constants for the formation of **25** (sets 24, 25 and 26, Table 14). Again, equilibrium constants for *c*-Pr show atypical behavior in all three data sets; those for *c*-Bu do so only in set 26.

^{13}C NMR chemical shifts δ of C atoms in 4-$RPnCMe_2^+$ (**26**), where R is alkyl or cycloalkyl, have been reported[73]. Those of interest are for the carbenium C^+ atom, for C^4 of the benzene ring, the atom to which R is attached, and to $C^{1'}$, the atom of R that is bonded to C^4, and $C^{2'}$, the other C atom bonded to $C^{1'}$ (sets 27 through 30, respectively, in Table 14). The δ values for C^2 are identical to those of C^6 and are essentially constant, as are also those of C^3 and C^5 and those of C^{Me}. The δ values of C^1 also show little variation. The $\delta^{1'}$ (set 29) and $\delta^{2'}$ (set 30) values were correlated with equation 43; results are reported in Table 13. The *c*-Pr group shows atypical behavior for δ C^+, and δ $C^{1'}$ shifts; the *c*-Bu group shows no atypical behavior.

4. Low positive electronic demand XY systems

A number of authors have considered the variation of the pK_a of carboxylic acids with ring size; pK_a values for RCO_2H in 50% aqueous ethanol at 25° and in water (where R is alkyl or cycloalkyl)[70, 74–78] are given in Table 14 (sets 31 and 32); the results of correlation with equation 43 are presented in Table 13. No clear-cut evidence of atypical behavior is found for either the *c*-Pr or the *c*-Bu group. This is not surprising because the electronic demand of CO_2H is too small, as is also the magnitude of the delocalized effect of X in XCO_2H. The 3-*exo*-trc[2.2.1.$0^{2,6}$]Hp group (**27**) in set 31 seems to exhibit atypical behavior with $N_{SD} = 11.1$. In set 32, the 1-bc[2.1.0]Pe (**28**), 1-trc[4.1.0.$0^{2,7}$]Hp (**29**), 1-bc[1.1.0]Bu (**30**), Cb (**2**) and 1-bc[1.1.1]Pe (**31**) groups all exhibit atypical behavior with N_{SD} values of 4.45, 6.31, 7.66, 10.2 and 16.2, respectively. The results are in accord with pK_a values of these acids in a number of other solvents (sets 33 through 35, Table 14)[79].



(27) **(28)** **(29)** **(30)** **(31)**

C. Y with Negative Electronic Demand

Little has been done in the way of studies on the ability of a cyclobutyl group to stabilize a species with negative electronic demand.

1. Radical anion XY systems

The reaction of RPhC=O (**32**) with (*t*-BuO)$_2$ in *s*-BuOH is thought to occur via a mechanism involving the radical anion with the contributing structures $RPhC^{\cdot}\text{-}O^- \leftrightarrow$

TABLE 15. XY^{+-}, XY^{-} and $XY^{\delta-}$ data sets

37. RCOPh + $(t\text{-BuO})_2$ in 2-BuOH, 130°.
Ak/c-Ak, k_{rel}: **Me**, 7.60 ± 0.80; **Et**, 3.33 ± 0.20; ***i*-Pr**, 2.00; ***i*-Bu**, 3.16 ± 0.50; ***c*-Pe**, 1.84 ± 0.27; ***c*-Hx**, 1.23 ± 0.10; ***c*-Bu**, 11.30 ± 1.20; ***c*-Pr**, 36.00 ± 1.00.
38. $NaOD/D_2O + RCH_2Bz$ in pyridine.
R, k_{rel}: ***i*-Pr**, 1.0; **Me**, 2.9; **Et**, 2.9; ***t*-Bu**, 0.49; ***i*-Bu**, 1.8; ***c*-Bu**, 2.0; ***c*-Pr**, 4.8; ***c*-BuCH₂**, 1.2.
39. pK_b, *c*-$AkNH_2$, 50% v/v aq. EtOH, 25°.
Ak, pK_b: ***i*-Pr**, 8.66; ***c*-Bu**, 9.34; ***c*-Pe**, 9.95; ***c*-Hx**, 9.83.
40. pK_b, *c*-$AkNMe_2$, 50% v/v aq. EtOH, 25°.
Ak, pK_b, ***c*-Pr**, 7.70; ***c*-Bu**, 8.77; ***c*-Pe**, 8.94; ***c*-Hx**, 9.16.

$RPhC:^{-}\text{-}O^{\cdot}$ (**33**), where R is alkyl or cycloalkyl[80]. The relative rates that were reported (set 37, Table 15) were correlated with equation 43; the results are presented in Table 13. Both *c*-Pr and *c*-Bu exhibit atypical behavior with N_{SD} values of 14.5 and 9.33, respectively.

2. Carbanion XY systems

Relative rates for $H \rightleftarrows D$ exchange in RCH_2Bz (**34**), in pyridine—D_2O containing NaOD at 33 °C (set 38, Table 15), have been determined[81]. Correlation with equation 43 gave the results presented in Table 15. The *c*-Pr group shows atypical behavior, the *c*-Bu does not. The N_{SD} values are 17.1 and 2.62, respectively. In the case of both groups, exclusion from the data set results in a much improved fit to equation 43.

3. Intermediate electronic demand XY systems

The pK_b values of XNH_2 (**35**) and $XNMe_2$ (**36**) have been determined (sets 39 and 40, respectively, Table 15). Both the *c*-Pr and *c*-Bu groups exhibit atypical behavior in **35**, only the *c*-Pr group does in **36**.

D. Conclusion

Our results for atypical behavior in sets 10 through 38 are presented in Table 16. They lead to the following conclusions:

1. In $XY^{\cdot+}$ and XY^{+} systems, both *c*-Pr and *c*-Bu show atypical behavior.

TABLE 16. Atypical behavior of cycloalkyl groups[a]

System	*c*-Pr	*c*-Bu	trc[3.1.1.0^{3,6}] Hp	Cb	bc[2.1.0] Pe	bc[2.1.1] Hx	trc[4.1.0.0^{2,7}] Hp	bc[1.1.0] Bu	bc[1.1.1] Pe
$XY^{\cdot+}$	3/3	3/3	2/2	2/2					
XY^{+}	2/2	4/4							
XGY^{+}	8/10	2/10							
		0							
$XY^{\delta+}$	0/5	0/5	1/1	1/1	1/1	1/1	1/1	1/1	1/1
$XY^{\cdot-}$	1/1	1/1							
XY^{-}	1/1	1/1							
$XY^{\delta-}$	2/2	0/2							

[a] Number of data sets in which *c*-Ak is atypical/Number of data sets studied.

2. In XGY^+ systems, *c*-Pr usually behaves atypically while *c*-Bu does so only occasionally.
3. Neither the *c*-Pr nor the *c*-Bu group behaves atypically in $XY^{\delta+}$ systems.
4. What little data are available suggest that both *c*-Pr and *c*-Bu can stabilize $XY^{\bullet-}$ and XY^- systems.
5. It seems likely that *c*-Pr behaves atypically in $XY^{\delta-}$ systems while *c*-Bu does not.
6. The evidence clearly implies that *c*-Pr is more likely to exhibit atypical behavior than is *c*-Bu.

To explain the capacity of *c*-Pr and *c*-Bu groups for stabilization of both XY^+ and XY^- systems, consider their electrical effect substituent constants σ_l, σ_d and σ_e in Table 1. Their values differ significantly from the average values for alkyl and cycloalkyl groups only in the σ_e values. These are -0.069 and -0.048 for *c*-Pr and *c*-Bu, respectively, while the mean *c*-Ak/Ak value is -0.036. We have redetermined the σ_d and σ_e constants as follows:

By definition,

$$\sigma_{50,\eta} \equiv \sigma_l + \sigma_D \tag{48}$$

where $\sigma_{50,\eta}$ is the Hammett-type σ_p constant for the reaction with the electronic demand η. Values of σ_p, σ_p^+ and σ_p^- are available; a value of σ^o can be obtained from a value of σ_R^o in the literature and the σ_l value in Table 1 by means of equation 48. Then, from equations 9 and 48, for a given substituent X,

$$\sigma_{50,\eta} = \sigma_e\eta + \sigma_d + \sigma_l \tag{49}$$

As σ_l and σ_d are constant, this is the equation of a line with slope σ_e and intercept $\sigma_d + \sigma_l$. Values of η have been determined for the σ_p, σ_p^+, σ_p^- and σ^o; the σ_p, σ_p^+, σ_p^- and σ^o constants are 0.330, 2.04, -1.40 and -0.374. Correlation of the $\sigma_{50,\eta}$ values with equation 49 by means of simple linear regression analysis gave the regression equation 50:

$$\sigma_{50,\eta} = -0.0635(\pm 0.00714)\eta + 0.151(\pm 0.00901) \tag{50}$$

$100R^2$, 97.54; F, 79.17; S_{est}, 0.0179; S^o, 0.222; N_{dp}, 4; N_{df}, 2; $r_{df/iv}$, 2.

Thus σ_d and σ_e for *c*-Bu are -0.14 and -0.064, respectively. The former is in excellent agreement with the previous value of -0.13; the latter is somewhat larger than the previous value of -0.048. In Table 17, values of $\sigma_{50,\eta}$ are reported for *c*-Pr, *c*-Bu, *c*-Pe, *c*-Hx, Me and the typical alkyl group Ak as well as for methyl and phenyl with η values ranging from -4 to $+4$. These values show clearly that at high positive or negative electronic demand, *c*-Pr and *c*-Bu are much more effective at stabilizing a reaction site than are typical alkyl groups, and the difference is due to the larger value of σ_e. The σ_e constants are themselves a function of the electronegativity of the atom of the substituent X that is bonded to Y or GY and of the group polarizability.

TABLE 17. Values of $\sigma_{50,\eta}$ calculated from equation 49

X/η	-4	-3	-2	-1	0	1	2	3	4
c-Pr	0.12	0.05	-0.02	-0.09	-0.16	-0.23	-0.30	-0.37	-0.44
c-Bu	0.05	0.00	-0.04	-0.09	-0.14	-0.19	-0.24	-0.28	-0.33
	0.12	0.05	-0.01	-0.08	-0.15	-0.22	-0.29	-0.35	-0.41
c-Pe	0.00	-0.03	-0.07	-0.10	-0.14	-0.18	-0.21	-0.25	-0.28

TABLE 17. (*continued*)

X/η	−4	−3	−2	−1	0	1	2	3	4
c-Hx	0.00	−0.03	−0.07	−0.10	−0.14	−0.18	−0.21	−0.25	−0.28
Ak	−0.02	−0.05	−0.09	−0.12	−0.16	−0.20	−0.23	−0.27	−0.30
Me	−0.03	−0.06	−0.09	−0.12	−0.15	−0.18	−0.21	−0.24	−0.27
Ph	0.40	0.36	0.24	0.12	0.00	−0.12	−0.24	−0.36	−0.48

IX. THE CYCLOBUTYL AND RELATED GROUPS AS SKELETAL GROUPS. THE TRANSMISSION OF DELOCALIZED ELECTRICAL EFFECTS

A. Transmission Through the Cycloalkyl Group. XGY Systems Where G Has At Least One 3- or 4-Membered Ring

The *trans*-2,1-cyclopropylene group was found to transmit the delocalized effect to some extent quite some time ago[1,82,83]. Up to the present time, with the exception of the solvolysis of the 2-norbornyl derivatives, no other examples of transmission of the delocalized effect had been observed. We have re-examined the cyclopropane derivatives. The method we have used involves the correlation of data sets XGY where X is *trans*- or *cis*-cyclopropylene with the LDR, LD, L and C equations. The LD equation results when the term in σ_e is dropped as a variable. The L equation results when both σ_d and σ_e are dropped from the LDR equation. The C equation results when σ_e is dropped as a variable from the CR equation. The need for the latter three equations ensues from the poorly characterized data sets available in most cases. The number of data points is often quite small and frequently there is only one substituent with a negative σ_d value. The data are given in Table 18 and the results of the correlations with the LDR equation and relationships derived from it are given in Table 19.

TABLE 18. Electrical effect transmission data sets

41. *trans*-2-Substituted cyclopropanoic acids, water, 25°
X, pK_a: **H**, 4.84; **Me**, 4.98; **Br**, 4.09; **EtO**, 4.46; **Ac**, 4.08; **CO_2Me**, 4.09; **CO_2Et**, 4.10; **CN**, 3.73; **Cl**, 4.12; **MeO**, 4.47; **Ph**, 4.57.
42. *trans*-2-Substituted cyclopropanoic acids, 50% aq. EtOH, 25°
X, pK_a: **H**, 6.44; **Me**, 6.62; **Br**, 5.41; **Ac**, 5.36; **CO_2Et**, 5.35; CN, 4.63; **MeO**, 5.76.
43. *trans*-1,2-Dimethyl-2-substituted 1-cyclopropanoic acids, water, 25°
X, pK_a: **H**, 4.964; **Br**, 3.777; **CO_2Me**, 3.932; **CN**, 3.430; **CO_2H**, 3.9332[a]; **$CONH_2$**, 4.102.
44. 3-Substituted bicyclo[3.1.0]hexane-1-carboxylic acids, water, 25°
X, pK_a: **H**, 5.066; **Br**, 4.215; **CO_2Me**, 4.154; **CN**, 3.903; **$CONH_2$**, 4.778.
45. 3-Substituted-bicyclo[2.1.0]pentane−1-carboxylic acids, water, 25°
X, pK_a: **H**, 4.696; **CO_2Me**, 4.168; **CN**, 3.58; **$CONH_2$**, 3.962.
46. 3-substituted bicyclo[1.1.0]butane-1-carboxylic acids, water, 25°
X, pK_a: **H**, 4.53; **CO_2Me**, 3.316; **CN**, 3.176; **$CONH_2$**, 3.727.
47. *trans*-2-Substituted-3,3-dimethylcyclopropanoic acids, 80% aq. methyl cellosolve, 25°
X, pK_a: ***i*-Bu**, 7.90; **Ph**, 7.12; ***i*-PrO**, 7.55; **CO_2H**, 6.31[a].
48. 3-Substituted bicyclo[1.1.1]pentane-1-carboxylic acids, 50% v/v aq. EtOH, 25°
X, pK_a: **Me**, 5.67; **Ph**, 5.38; **OH**, 5.14; **CO_2H**, 4.90; **CO_2Me**, 4.85; **OAc**, 4.84; **CN**, 4.35; **NO_2**, 4.12.
49. 4-Substituted cubane-1-carboxylic acids, 50% w/w aq. EtOH, 25°
X, pK_a: **H**, 5.94; **CO_2H**, 5.43; **Br**, 5.32; **CO_2Me**, 5.40; **CN**, 5.14.
50. 6-Substituted spiro[3.3]heptane-2-carboxylic acids, 50 w/w aq. EtOH, 25°
X, pK_a: **H**, 6.266; **CN**, 5.956; **Br**, 5.980; **CO_2Me**, 6.062; Me, 6.321; **CO_2H**, 6.096[a]; **$CONH_2$**, 6.110.
G, n: 4, 1-Cb, 4.7; 1,3-bc[1.1.1] Pe, 4.4; 6,2-sp[3.3] Hp, 5.8; [*E*]-1,2-*c*-Pr, 4.

[a] A statistical factor of 1/2 is used.
[b] 50a1, 50a2, 50a3. Number of bonds between X and CO_2H.

TABLE 19. Results of correlations with the LDR equation and relationships derived from it

Set	L	S_L	D	S_D	R	S_R	h	S_h	100 R^2	A100 R^2	F	S_{est}	S^0
41	−1.87	0.0735	−0.439	0.0493	1.33	0.380	4.87	0.0334	99.07	na [a]	298.4	0.0433	0.121
42	−2.82	0.237	−0.586	0.176	2.47	1.67	6.51	0.0935	98.52	na [a]	69.60	0.116	0.182
43	−2.63	0.204	−0.546	0.236	—	—	4.90	0.0771	98.24	97.81	83.93	0.0879	0.187
	−2.58	0.292	—	—	—	—	4.86	0.108	95.10	—	77.68	0.127	0.271
	−2.64	0.177	—	—	—	—	4.90	0.0763	98.24	—	222.9	0.0763	0.163
44	−2.03	0.524	—	—	—	—	5.086	0.200	83.20	—	14.86	0.228	0.529
	−2.06	0.501	—	—	—	—	5.106	0.192	84.89	—	16.85	0.216	0.502
45	−1.93	0.359	—	—	—	—	4.665	0.128	93.49	—	28.72	0.145	0.361
	−1.85	0.358	—	—	—	—	4.675	0.150	93.03	—	26.71	0.150	0.373
46	−2.38	0.563	—	—	—	—	4.426	0.211	89.96	—	17.92	0.236	0.448
	−2.44	0.647	—	—	—	—	4.401	0.230	87.69	—	14.25	0.261	0.496
47	−3.28	2.45	—	—	—	—	7.78	0.517	47.17	—	1.786	0.610	1.03
	−4.04	1.36	—	—	—	—	7.78	0.259	81.60	—	8.871	0.360	0.607
	−3.75	0.770	—	—	—	—	7.66	0.148	92.22	—	23.72	0.234	0.394
	−3.19	0.440	—	—	—	—	7.50	0.0891	96.34	—	52.64	0.161	0.271
48	−2.07	0.0605	−0.454	0.0527	−0.305	0.386	5.56	0.0352	99.76	99.67	556.3	0.0328	0.0692
	−2.08	0.0577	−0.440	0.0476	—	—	5.58	0.0233	99.72	99.68	901.5	0.0315	0.0665
	−2.25	0.211	—	—	—	—	5.67	0.0834	95.00	—	114.0	0.122	0.250
49	−1.38	0.110	−0.258	0.129	—	—	5.91	0.0427	98.75	98.33	78.96	0.0472	0.177
	−1.35	0.154	—	—	—	—	5.90	0.0592	96.25	—	77.02	0.0667	0.290
	−1.38	0.0877	—	—	—	—	5.91	0.0341	98.80	—	247.4	0.0377	0.141
50	−0.757	0.0555	−0.143	0.0870	−0.925	0.721	6.273	0.0238	98.83	98.24	84.39	0.0243	0.165
	−0.717	0.0498	−0.060	0.0629	—	—	6.296	0.0167	98.19	97.82	108.3	0.0262	0.178
	−0.724	0.0489	—	—	—	—	6.296	0.0166	97.77	—	219.5	0.0260	0.177
	−0.700	0.0486	—	—	—	—	6.293	0.168	97.65	—	207.5	0.0267	0.182
	−0.713	0.0440	—	—	—	—	6.294	0.0150	98.14	—	263.1	0.0238	0.162

Set	r_{ld}	r_{le}	r_{de}	N_{dp}	N_{df}	$r_{df/iv}$	P_D	S_{PD}	η	S_η	Correlation equation	C_l	C_d	C_e
41	0.003	0.020	0.174	11	7	2.33	19.1	2.26	3.02	0.296	LDR			
42	0.054	0.391	0.304	7	3	1.00	17.2	5.38	4.21	2.55	LDR			
43	0.120	—	—	6	3	1.00	17.2	7.60	—	—	LD			
	—	—	—	6	4	4.00	0	—	0	—	L			
	—	—	—	6	4	4.00	16.7	—	0	—	C			
44	—	—	—	5	3	3.00	0	—	0	—	L			
	—	—	—	5	3	3.00	16.7	—	0	—	C			
45	—	—	—	4	2	2.00	0	—	0	—	L			
	—	—	—	4	2	2.00	16.7	—	0	—	C			
46	—	—	—	4	2	2.00	16.7	—	0	—	C			
	—	—	—	4	2	2.00	0	—	0	—	L			
47	—	—	—	4	2	2.00	0	—	0	—	L			
	—	—	—	4	2	2.00	16.7	—	0	—	C			
	—	—	—	4	2	2.00	25	—	0	—	C			
	—	—	—	4	2	2.00	33.3	—	0	—	C			
48	0.334	0.010	0.320	8	4	1.33		—		—	LDR	81.0	17.8	1.20
	0.334	—	—	8	5	2.50	17.5	1.96	0	—	LD	82.5	17.5	—
	—	—	—	8	6	6.00	0	—	0	—	L	100	—	—
49	0.101	—	—	5	2	0.67	15.8	8.06	0	—	LD	84.2	15.8	—
	—	—	—	5	3	3.00	0	—	0	—	L	100	—	—
	—	—	—	5	3	3.00	16.7	—	0	—	C	—	—	—
50	0.144	0.486	0.712	7	3	1.00	15.9	9.84	6.48	3.15	LDR	76.3	14.4	9.33
	0.144	—	—	7	4	2.00	7.72	8.13	0	—	LD	92.3	7.72	—
	—	—	—	7	5	5.00	0	—	0	—	L	100	—	—
	—	—	—	7	5	5.00	16.7	—	0	—	C	—	—	—
	—	—	—	7	5	5.00	10	—	0	—	C	—	—	—

[a] Not available.

1. Trans-cyclopropylene

Set 41 is a well-characterized data set of pK_a values in water at 25°. Correlation with the LDR equation gave excellent results. We have a P_D value of 19.1 and an η value of 3.02. For a much smaller data set of the same acids in 50% ethanol, the correlation with the LDR equation gave a P_D value of 17.2 and η was not significant. A very poorly characterized set of pK_a values of these acids in 80% aqueous methyl cellosolve (set 47) could not of course be correlated with the LDR equation as it had only four data points. Therefore, it was correlated with the L equation and with the C equation using composite constants with P_D values of 16.7, 25 and 33.3. Best results were obtained for correlation with the C equation using 33.3 as the P_D constants. Also studied was a data set in water consisting of pK_a values of *trans*-2-substituted 1,2-dimethylcyclopropane-1-carboxylic acids (set 43). This data set was correlated with the LD, L and C equations. Best results were obtained with the C equation using constants with P_D equal to 16.7. It is clear from these results that the cyclopropylene group can transmit the delocalized electrical effect to some extent. No such behavior has been observed for alicyclic systems such as the bicyclo[2.2.1]heptane and the bicyclo[2.2.2]octane rings. In fact, the latter system has been used as the basis for the definition of localized electrical effect substituent constants.

2. Cis-cyclopropylene systems

We have examined three data sets for these systems by correlations with the L and C equations. The possibility of steric effects in these systems certainly exists. Because of the very limited number of data points in the data sets, we have ignored the steric effects. The first of these sets (set 44) consists of pK_a values of 3-substituted bicyclo[3.1.0]hexane-1-carboxylic acids. Best results were obtained with the C equation using constants with P_D equal to 16.7. pK_a values for 3-substituted bicyclo[2.1.0]pentane-1-carboxylic acids (set 45), on correlation with the L and C equations, also gave somewhat better results with the C equation using the same P_D constants. pK_a values for the 3-substituted bicyclo[1.1.0]butane-1-carboxylic acids (set 46) gave somewhat better results with the L equation, suggesting that perhaps no transmission of the delocalized electrical effect occurs in this case. It must be noted, however, that this data set had only four points, insufficient to permit parameterization of the steric effect. It also lacked sufficient variation in substituent type.

3. Cyclopropylidene

In previous work, we had examined a data set of cyclopropylidene that had only four data points. This data set included an ionic substituent. While the results suggested transmission of the delocalized electrical effect, we now believe that ionic substituents should not be included in a data set because they are highly dependent on the ionic strength and nature of the solvent. Unfortunately, no further data sets of the type have become available.

4. Skeletal groups containing a four-membered ring

Data sets are available for three such skeletal groups; the first of these consists of pK_a values for 3-substituted bicyclo[1.1.1]pentane-1-carboxylic acids (set 48). This data set is comparatively well characterized. Correlation with the LDR equation gave excellent results but η was not significant. When correlated with the LD equation, the P_D value is 17.5. The results were much poorer after correlation with the L equation. Clearly, transmission of the delocalized electrical effect occurs in this system. The pK_a values

of 4-substituted cubane-1-carboxylic acids (set 49) are not a well-characterized data set. Correlation with the LD equation gave a P_D value of 15.8. Correlation with the L and C equations gave much better results with the C equation using the constants for P_D equal to 16.7. It seems that in this case we again have some transmission of the delocalized electrical effect.

The last set we studied is of pK_a values for 6-substituted spiro[3.3]heptane-2-carboxylic acids (set 50). Correlation with the LDR equation showed that η was not significant. Correlations were then carried out with the LD, L and C equations, in the latter case with both P_D equals 16.7 and P_D equals 10. Best results were obtained with P_D equals 10. We have previously shown that D, the measure of electrical effect transmission, is a function of the distance between the substituent X and the atom of the reaction site Y that is reacting[84,85]. It is also dependent on the cosine of the angle made by that distance with the XY or XG bond. It is therefore transmitted by a modified field effect. In order to provide further insight into the delocalized effect in these systems, we have correlated the D values for sets 42, 48, 49 and 50 with equations 51–53:

$$-D = \frac{a_1}{n^2} + a_o \tag{51}$$

$$-D = \frac{a_1}{n} + a_o \tag{52}$$

$$\log(-D) = -m \log n + \log a_o \tag{53}$$

where n is the number of bonds between the substituent X and the O atom bonded to H in the carboxyl group. The results are reported in Table 20. The distance between C^1 and C^3 in the bc[1.1.1]Pe system was taken to be $\sqrt{2}\ n$, that between C^4 and C^1 of 4,1-Cb as $\sqrt{3}\ n$ and that in 6,2-sp[3.3]Hp as $2\sqrt{2}\ n$, giving n values of 4.4, 4.7 and 5.8 for these systems while that for the *trans*-cyclopropylene system is 4. The correlations with equations 51 and 52 support the existence of delocalization of the electrical effect. The coefficient of equation 53 suggests that the magnitude of m may be as large as 5.

We regard these results as probable, but not certain, insofar as delocalized electrical effect transmission is concerned.

B. Transmission Through XG_Y Systems

In XG_Y systems the alicyclic moiety is also the reaction site. The reaction studied is solvolysis, thus the substituent X is bonded to the i-th C atom of the alicyclic skeletal group and the leaving group to the j-th atom. Data sets studied include adamantylene, bicyclo[2.2.2]octylene and cyclobutanylene skeletyl groups. For purposes of comparison, solvolysis of $XCH_2CH_2{-}c\text{-}Me_2Cl$ was also examined. The data sets studied are reported in Table 21, and results of the correlations in Table 22.

TABLE 20. Results of correlation with equations 51, 52 and 53 [a]

Set [b]	a_n/m	Sa_n	$a^0/\log a^0$	$S_a{}^0$	$100r^2$	F	S_{est}	S^0
50a1.	6.63	1.02	−1.08	0.221	95.49	42.38	0.0578	0.300
50a2.	16.0	2.05	−0.410	0.100	96.79	60.31	0.0488	0.253
50a3.	−5.62	0.525	3.196	0.353	98.28	114.3	0.0622	0.185

[a] In all sets $N_{dp} = 4$, $N_{df} = 2$, $r_{df/iv} = 2.0$.
[b] Results for sets 50a1, 50a2 and 50a3, are with equations 51, 52 and 53, respectively.

TABLE 21. Alicyclic solvolysis data sets [a]

51. 3-Substituted 1-adamantyl bromides in 80% aq. dioxan at 100 °C[27]. X, 10^5 k_1: 4′-$O_2NC_6H_4$, 0.389; CH_2Br, 0.464; CH_2CO_2Me, 2.19; CH_2CO_2H, 2.17; $CH_2C_6H_4NO_2$-4′, 1.43; CO_2Me, 0.218; Br, 0.013; H, 10.7.

52. 3-Substituted 1-adamantyl bromides in 80% aq. EtOH at 75.0 °C[28]. X, 10^5 k_1: H, 13.8; Me, 9.76; Et, 13.4; *i*-Pr, 19.3; *t*-Bu, 29.0; Ph, 2.39; CN, 0.00241; CO_2Me, 0.115.

53. 3-Substituted 1-adamantyl bromides in 80% aq. EtOH at various temperatures[29]. X, 10^5 k_1, T (°C): H, 7.16, 70.00; Me, 5.31, 70.00; Et, 7.28, 70.00; *i*-Pr, 10.9, 70.00; *t*-Bu, 16.6, 70.00; 45.8, 80.00; 116, 90.00; CH_2Br, 13.4, 110.0; 31.1, 120.0; 63.3, 130.0; CO_2H, 11.1, 120.0; 27.4, 130.0; 58.7, 140.0; Br, 5.57, 140.0; 12.0, 150.0; 24.3, 160.0; CN, 1.17, 135.0; 5.08, 155.0; NO_2, 0.556, 150.0; 4.13, 180.0; $CMe{=}CH_2$, 18.4, 90.0; 49.1, 100.0; 109, 110.0; Ph, 28.8, 100.0; 67.3, 110.0; 157, 120.0; SMe, 5.04, 100.0; 11.8, 110.0; 26.4, 120.0; OMe, 0.974, 70.0; OH, 3.37, 70.0; 25.1, 90.0; 65.1, 100.0; CH_2NH_2, 34.6, 90.0; 86.5, 100.0; 199, 110.0; $CONH_2$, 8.17, 110.0; 19.4, 120.0; 44.0, 130.0; CH_2OH, 31.1, 90.0; 78.4, 100.0; 183, 110.0; NH_2, 267, 70.0; NMe_2, 8500, 70.0; SH, 4.52, 110.0; 9.43, 120.0; 18.9, 130.0; 4′-HOC_6H_4, 23.2, 90.0; 57.8, 100.0; 136, 110.0; 4′-$MeOC_6H_4$, 16.8, 90.0; 39.9, 100.0; 93.3, 110.0; 4′-$H_2NC_6H_4$, 12.4, 80.0; 32.0, 90.0; 80.2, 100.0; 4′-$Me_2NC_6H_4$, 13.9, 80.0; 36.5, 90.0; 89.5, 100.0; 4′-$O_2NC_6H_4$, 14.5, 110.0; 34.2, 120.0; 76.1, 130.0.

54. 3-Substituted 1-adamantyl tosylates in 80% aq. EtOH at various temperatures[30]. X, 10^5 k_1, T (°C): H, 63.0, 9.45; 232, 20.00; 756, 30.00; Me, 50.3, 9.50; 187, 19.95; 592, 30.00; *i*-Pr, 27.4, 0.00; 109, 9.98; 386, 20.05; CH_2OAc, 36.6, 30.06; 116, 40.05; 323, 50.13; CH_2OTs, 29.9, 40.07; 91.9, 50.12; 255, 60.00; CH_2OH, 29.0, 10.00; 109, 20.00; 376, 30.00; CO_2Me, 31.2, 50.00; 92.1, 59.85; 260, 70.00; OAc, 35.3, 60.03; 99.4, 70.00; 261, 80.00; Cl, 6.04, 80.13; 151, 90.27; 334, 99.60; Br, 16.0, 70.00; CN, 44.2, 89.95; 104, 100.00; 229, 109.72; NO_2, 24.7, 100.05; 57.2, 110.13; 131, 120.28; OMe, 23.6, 20.00; 84.5, 30.00; 276, 40.00.

55. 3-Substituted 1-adamantyl tosylates in 80% aq. EtOH at 75.0 °C[31]. X, 10^4 k_1: H, 0.192; Me, 4.10; Ph, 1.64; 4′-$MeOC_6H_4$, 2.70; 4′-$CF_3C_6H_4$, 0.186, 4′-$O_2NC_6H_4$, 0.0790; Et, 12.3; *i*-Pr, 28.6; *c*-Pr, 8.32; *t*-Bu [b], 506.

56. 4-*exo*-Substituted 2-*exo*-adamantyl tosylates in 80% aq. v/v EtOH at various temperatures[32]. X, 10^5 k_1, T (°C): H, 46.8, 70.00; 138, 80.02; 375, 60.02; Me, 56.7, 70.00; 165, 80.00; 444, 90.00; CH_2OH, 22.7, 70.00; 66.8, 80.00; 188, 90.00; CH_2OMe, 35.0, 80.00; 97.8, 90.00; 265, 100.00; CH_2OAc, 12.6, 80.00; 37.5, 90.00; 98.4, 100.00; CH_2Br, 30.0, 90.00; 80.1, 100.00; 207, 110.00; CO_2H, 39.4, 100.00; 106, 110.01; 260, 119.92; CO_2Me, 39.4, 100.00; 72.8, 110.00; 177, 120.00; $CONH_2$, 31.0, 90.00; 85.5, 100.03; 203, 109.40; Cl, 28.6, 110.05; 72.9, 120.16; 169, 129.40; Br, 7.74, 100.30; 21.4, 110.74; 52.6, 120.60; CN, 1.49, 100.00; 12.5, 110.00; 30.3, 120.00; 73.5, 130.00.

57. 6-*exo*-Substituted 2-*exo*-bicyclo[2.2.2]octanyl tosylates in 80% v/v aq. EtOH at various temperatures[33]. X, 10^5 k_1, T (°C): H, 25.6, 40.45; 67.5, 50.31; 154, 59.80; Me, 21.9, 48.62; 66.0, 58.27; 181, 68.02; CH_2OMe, 36.5, 70.30; 105, 80.38; 269, 90.69; CH_2OAc, 22.8, 80.28; 62.7, 90.52; 148, 99.88; CH_2OTs, 17.1, 90.51; 40.5, 99.85; 93.2, 109.78; CO_2Me, 29.5, 99.80; 71.8, 110.02; 169, 120.15; CN, 15.8, 120.43; 36.9, 130.64; 66.4, 138.91; CH_2OH, 22.3, 38.80; 96.2, 71.10; 273, 80.28.

58. 6-*exo*-Substituted 2-*exo*-bicyclo[2.2.2]octanyl tosylates in 97% w/w aq. 1,1,1-trifluoroethanol at various temperatures[33]. X, 10^5 k_1, T (°C): H, 25.1, 11.74; 64.9, 19.94; 186, 30.62; Me, 39.5, 20.04; 123, 30.62; 353, 40.54; CH_2OMe, 248, 70.00; CH_2OAc,43.8, 70.00; CH_2OTs, 7.83, 70.00; CO_2Me, 4.65, 70.00; CN, 2.50, 99.76; 5.69, 109.87; 12.3, 119.88.

59. 4-Substituted 1-bicyclo[2.2.2]octanyl brosylates in AcOH at 74 °C[28]. X, 10^5 k_1: H, 11.3; Me, 3.38; Et, 4.04; *i*-Pr, 4.75; *t*-Bu, 6.24; Ph, 0.874; CO_2Ak, 0.0789; CN, 0.0025.

60. 4-Substituted 1-bicyclo[2.2.2]octanyl 4′-nitrobenzenesulfonates in 80% v/v aq. EtOH at 75.00 °C. X, 10^6 k_1: H, 4620; Me, 4790; Et, 1300; *i*-Pr, 1530; *t*-Bu, 1850; $MeC{=}CH_2$, 487; Ph, 277; Me_2N, 74.0; $NHCO_2Et$, 18.0; OMe, 10.2; CO_2Et, 13.7; CN, 0.547; Br, 2.18; CO_2NH_2, 35.6; CO_2Me, 12.6.

(*continued overleaf*)

TABLE 21. (*continued*)

61. 6-*exo*-Substituted 2-*endo*-bicyclo[2.2.2]octanyl tosylates in 80% v/v aq. EtOH at various temperatures[33]. X, 10^5 k_1, T (°C): H, 25.6, 40.45; 67.5, 50.31; 154, 59.80; Me, 48.2, 49.17; 131, 58.19; 303, 66.84; CH_2OMe, 51.2, 59.66; 156, 69.78; 397, 79.87; CH_2OAc, 25.9, 65.29; 77.6, 75.47; 208, 85.64; CH_2OTs, 17.6, 72.19; 41.5, 80.33; 137, 92.56; CO_2Me, 25.3, 80.33; 69.0, 90.53; 168, 99.84; CN, 20.8, 110.20; 49.3, 120.40; 115, 130.58; CH_2OH, 47.4, 53.07; 102, 59.96; 204, 66.52.

62. 6-*exo*-Substituted 2-*endo*-bicyclo[2.2.2]octanyl tosylates in 97% w/w aq. 1,1,1-trifluoroethanol at various temperatures[33]. X, 10^5 k_1, T (°C): H, 25.1, 11.74; 64.9, 19.94; 186, 30.62; Me, 23.4, 11.74; 62.2, 19.94; 208, 30.62; CH_2OMe, 3.53, 19.94; 15.4, 30.62; 52.0, 40.24; CH_2OAc, 261, 70.00; CH_2OTs, 74.7, 70.00; CO_2Me, 44.5, 70.00; CN, 8.07, 99.77; 19.2, 109.87; 43.0, 119.89.

63. *Z*-3-Substituted 1-cyclobutyl tosylates in 80% v/v aq. EtOH at 25.8 °C[35]. X, 10^5 k_{rel}: H, 1; Ph, 267; 4-MeC_6H_4, 400; 4-ClC_6H_4, 130; *t*-Bu, 800; *i*-Pr, 6250; OEt, 43.5; Cl; 2.00.

64. *E*-3-Substituted 1-cyclobutyl tosylates in 80% v/v aq. EtOH at 25.8 °C[35]. X, 10^3 k_{rel}: H, 1; Ph, 200; 4-MeC_6H_4, 333; 4-ClC_6H_4, 90.9; *t*-Bu, 143; *i*-Pr, 333; OEt, 5.26; Cl; 0.0667.

65. 4-Substituted 2-chloro-2-methylbutanes in 80% v/v aqueous EtOH at various temperatures[36]. X, 10^5 k_1, T (°C): H, 10.4, 40.13; 30.5, 49.86; 86.9, 59.57; Me, 35.6, 52.05; 152, 66.00; 262, 71.90; Et, 8.75, 40.00; 52.5, 56.25; 251, 71.75; *i*-Pr, 47.2, 56.00; 337, 76.00; *t*-Bu, 21.2, 50.00; 60.8, 60.00; 164, 70.00; CH_2NMe_2, 18.7, 50.00; 54.5, 60.00; 157, 70.01; CH_2Cl, 21.4, 59.94; 52.6, 69.95; 118, 79.77; CH_2OH, 34.7, 50.10; 94.9, 59.94; 252, 70.00; CO_2Et, 23.2, 69.97; 61.8, 79.97; 153, 90.02; CO_2H, 35.0, 69.87; 86.2, 79.93; 202, 89.95; Cl, 6.18, 70.01; 16.6, 79.97; 41.5, 90.00; CN, 37.7, 100.07; 86.5, 110.00; 182, 119.55; NMe_2, 35.7, 56.00; 304, 76.00; NO_2, 0.242, 60.00; 7.84, 90.37; 20.2, 99.80; 56.2, 110.15; SMe, 7.55, 56.00; 21.7, 66.00; 58.8, 76.00; OMe, 10.4, 56.00; 30.5, 66.00; 85.7, 76.00; OH, 16.4, 52.05; 48.6, 62.00; 141, 71.90.

65A. 4-Substituted 2-chloro-2-methylbutanes in 80% v/v aqueous EtOH at 60.00 °C[36]. X, 10^6 k_1: H, 902; Me, 820; Et, 779; *i*-Pr, 712; *t*-Bu, 608; NO_2, 2.42; MeS, 116; Me_2N, 559; OMe, 161; CO_2Et, 84.1; CN, 8.38; Cl, 22.0; CH_2Cl, 216.

[a] Set designations in boldface are well characterized.
[b] This value was excluded from the correlation.

1. Adamantyl systems

There is no detectable delocalized effect in 3-substituted 1-adamantyl tosylates and bromides and in 4-*exo*-substituted 2-*exo*-adamantyl tosylates. There may be delocalization in 1-substituted 2-adamantyl tosylates.

Bicyclo [2.2.2]octyl systems. There is no detectable delocalized effect in 4-substituted 1-bicyclo[2.2.2]octanyl 4-bromobenzenesulfonates and 4-nitrobenzenesulfonates or in 6-*exo*-substituted 2-*exo*-bicyclo[2.2.2]octanyl tosylates. Delocalization may occur in 6-*exo*-substituted 2-*endo*-bicyclo[2.2.2]octanyl tosylates.

2. Cyclobutyl systems

There is no detectable delocalized electrical effect in *E*-3-substituted 1-cyclobutyl and *Z*-3-substituted 1-cyclobutyl tosylates.

3. Acyclic systems

There is a significant delocalized effect in 4-substituted 2-chloro-2-methylbutanes.

Values of P_D are much less than that normally encountered in carbocation-forming reactions in which the substituent is either directly bonded to positive carbon or conjugated with it. η values tend to be large, indicating considerable electronic demand. L values

TABLE 22. Results of correlations of solvolysis data sets with the LDRT, LDR, LD, LT, L, CR and C equations

Set	L	S_L	D	S_D	R	S_R	T	S_T	h	S_h	$100R^2$	A$100R^2$	F	S_{est}	S^0
51	−5.82	0.610	—	—	—	—	—	—	0.988	0.147	93.83	—	91.20	0.234	0.287
52	−2.71	0.301	—	—	—	—	—	—	1.167	−0.687	98.81	—	498.3	0.168	0.126
53	−54.1	0.241	—	—	—	—	−44.7	3.02	14.15	0.840	98.51	88.26	173.3	0.200	0.350
54	−5.66	0.509	—	—	—	—	−39.1	3.71	15.6	1.27	81.54	80.90	61.85	0.195	0.452
55	−3.40	1.66	−10.2	2.22	—	—	—	—	−0.538	0.316	88.51	86.59	19.26	0.353	0.429
56	−3.86	0.203	—	—	—	—	−51.4	3.09	16.7	0.874	92.37	92.12	181.5	0.122	0.290
57	−5.95	0.727	—	—	—	—	—	—	2.228	0.187	91.77	—	66.93	0.384	0.348
58	−7.95	0.950	—	—	—	—	—	—	3.315	0.258	93.34	—	70.03	0.472	0.305
59	−5.84	0.338	—	—	—	—	—	—	0.691	0.0783	98.03	—	298.5	0.189	0.162
60	−6.58	0.301	—	—	—	—	—	—	3.412	0.0968	98.07	—	169.5	0.202	na[b]
61	−5.03[a]	0.415	—	—	—	—	—	—	2.555	0.109	96.07	—	146.8	0.225	0.229
	−5.41	0.452	—	—	—	—	—	—	2.644	0.126	95.98	—	143.3	0.227	0.231
62	−7.55[a]	0.418	—	—	−8.89	3.47	—	—	3.532	0.106	99.13	98.96	228.4	0.169	0.123
63	−7.84	1.05	—	—	—	—	—	—	2.848	0.218	90.33	—	56.07	0.456	0.359
64	−6.26	0.849	—	—	—	—	—	—	3.257	0.189	91.59	—	54.66	0.347	0.343
65	−3.39	0.149	−0.472	0.161	0.699	0.656	—	—	−2.826	0.0524	98.07	na[b]	227.5	0.114	0.137

Set	r_{ld}	r_{le}	r_{de}	N_{dp}	N_{df}	$r_{df/iv}$	P_D	S_{PD}	η	S_η	Correlation equation	C_l	C_d	C_e	C_τ
51	—	—	—	8	6	6.00	—	—	—	—	L	100	—	—	—
52	—	—	—	8	6	6.00	—		—	—	L	100	—	—	—
53	—	—	—	48	45	22.5	—		—	—	LT	na[b]	—	na[b]	0.825
54	—	—	—	31	28	14.0	—	—	—	—	LT	—	—	—	0.792
55	0.392	—	—	8	5	2.50	75.0	22.4	—	—	LD	na[b]	—	—	—
56	—	—	—	33	30	15.0	—	—	—	—	LT	—	—	—	0.827
57	—	—	—	8	6	6.00	—	—	—	—	L	—	—	—	—
58	—	—	—	7	5	5.00	—	—	—	—	L	—	—	—	—
59	—	—	—	8	6	6.00	—	—	—	—	L	—	—	—	—
60	—	—	—	14	12	12.0	—	—	—	—	L	—	—	—	—
61	—	—	—	8	6	6.00	14.3	—	—	—	C	—	—	—	—
	—	—	—	8	6	6.00	—	—	—		L	—	—	—	—
62	—	—	—	7	4	2.00	10.0	—	10.6	4.09	CR	—	—	—	[c]
63	—	—	—	8	6	6.00	—	—	—	—	L	—	—	—	—
64	—	—	—	8	6	6.00	—	—	—	—	L	—	—	—	—
65	0.154	0.066	0.511	13	9	3.00	13.9	na[b]	0.00	na[b]	LDR	—	—	—	—

[a] Correlated with the CR equation L = C; r_{ld} should be r_{ce}.
[b] na = not available.
[c] This is r_{ce}.

seem to be a function of the distance between X and C^j. If this is the case, then they behave like other molecular ionization (Mi) reactions.

C. Conclusions

The results for solvolysis are best explained by a partial charge on the reacting C atom resulting from a transition state closer to reactants than to products. That would reduce the electronic demand, making the delocalized electrical effect harder to detect. In those cases where it seems to occur, the number of bonds between substituent and reaction site is four or less. Detectable delocalized (resonance) electrical effects occur in saturated systems when the electronic demand of the reaction site is large enough and the number of bonds separating substituent and reaction site is small enough. The electrical effect is transmitted by a modified field effect; its dependence on distance is a function of n^{-m}, where n is a measure of the distance between substituent and reaction site. The reason that transmission of the delocalized electrical effect is so often found when G_S is a small ring alicyclic system is because the X to Y distance is small.

D. Transmission in 4-XPnG_SY Systems Where G_S is a Small Ring Alicyclic Group

The small D values observed in XG_SY systems in which delocalized electrical effect transmission occurs implies that the delocalized electrical effect due to G_S in 4-XPnG_SY is probably undetectable. Thus, in 2-(4′-XPn)-*c*-Pr-1-CO_2H the number of bonds between X and the reacting atom of Y is 8. It is possible to improve the situation to some extent by choosing systems XGG_SY in which G is *trans*-vinylene or ethylene. Study of such systems, especially when the data set is poorly characterized with regard to substituent number and variety, is of very limited use.

X. APPENDIX I. GLOSSARY

This appendix is an updated, corrected and slightly modified version of one we have published elsewhere[50].

General

X A variable substituent.

Y An active site. The atom or group of atoms at which a measurable phenomenon occurs.

G A skeletal group to which X and Y may be attached.

Parameter An independent variable.

Pure parameter A parameter which represents a single effect.

Composite parameter A parameter which represents two or more effects.

Modified composite parameter A composite parameter whose composition has been altered by some mathematical operation.

Monoparametric equation A relationship in which the effect of structure on a property is represented by a single generally composite parameter. Examples are the Hammett and Taft equations.

Diparametric equation A relationship in which the effect of structure on a property is represented by two parameters, one of which is generally composite. Examples discussed

in this work include the LD, CR and MYT equations. Other examples are the Taft, Eherenson and Brownlee DSP (dual substituent parameter), Yukawa–Tsuno YT and the Swain, Unger, Rosenquist and Swain SURS equations. The DSP equation is a special case of the LDR equation with the intercept set equal to zero. It is inconvenient to use and has no advantages. The SURS equation uses composite parameters which are of poorer quality than those used with the LDR and DSP equations. The MYT equation has all the advantages of the YT equation and gives results which are easier to interpret.

Multiparametric equation An equation which uses three or more parameters all of which may be either pure or composite.

Electrical effect parameterization

σ_{I} The localized (field) electrical effect parameter. It is identical to σ_{I}. Though other localized electrical effect parameters such as $\sigma_{\mathrm{I}}{}^{\mathrm{q}}$ and σ_{F} have been proposed, there is no advantage to their use. The σ^* parameter has sometimes been used as a localized electrical effect parameter; such use is generally incorrect. The available evidence is strongly in favor of an electric field model for transmission of the effect.

σ_{d} The intrinsic delocalized (resonance) electrical effect parameter. It represents the delocalized electrical effect in a system with zero electronic demand.

σ_{e} The electronic demand sensitivity parameter. It adjusts the delocalized effect of a group to meet the electronic demand of the system.

σ_{D} A composite delocalized electrical effect parameter which is a function of σ_{d} and σ_{e}. Examples of σ_{D} constants are the $\sigma_{\mathrm{R}}{}^{+}$ and $\sigma_{\mathrm{R}}{}^{-}$ constants. The $\sigma_{\mathrm{R,k}}$ constants, where k designates the value of the electronic demand η , are also examples of σ_{D} constants.

σ_{R} A composite delocalized electrical effect parameter of the σ_{D} type with η equal to 0.380. It is derived from 4-substituted benzoic acid pK_{a} values.

$\sigma_{\mathrm{R}}{}^{\mathrm{o}}$ A composite delocalized electrical effect parameter of the σ_{D} type with η equal to -0.376. It is derived from 4-substituted phenylacetic acid pK_{a} values.

$\sigma_{\mathrm{R}}{}^{+}$ A composite delocalized electrical effect parameter of the σ_{D} type with η equal to 2.04. It is derived from rate constants for the solvolysis of 4-substituted cumyl chlorides.

$\sigma_{\mathrm{R}}{}^{\oplus}$ A composite delocalized electrical effect parameter of the σ_{D} type with η equal to 3.31. It is derived from ionization potentials of the lowest energy π orbital in substituted benzenes.

$\sigma_{\mathrm{R}}{}^{\ominus}$ A composite delocalized electrical effect parameter of the σ_{D} type with η equal to -2.98. It is derived from pK_{a} values of substituted nitriles.

$\sigma_{\mathrm{R}}{}^{-}$ A composite delocalized electrical effect parameter of the σ_{D} type with η equal to -1.40. It is derived from pK_{a} values of substituted anilinium ions.

$\sigma_{k'/k}$ A composite parameter which is a function of σ_{I}, σ_{d} and σ_{e}. Its composition is determined by the values of k and k'. The Hammett σ_m and σ_p constants are of this type.

$\sigma_{\mathrm{C}k'}$ A composite constant that is a function of σ_{I} and σ_{d}; its composition is determined by the value of k'.

σ° An electrical effect modified composite parameter.

σ Any electrical effect parameter.

η The electronic demand of a system or of a composite electrical effect parameter that is a function of both σ_{d} and σ_{e}. It is represented in subscripts as k. It is a descriptor of

the nature of the electrical effect. It is given by R/D, where R and D are the coefficients of σ_e and σ_d, respectively.

$\boldsymbol{P_D}$ The percent delocalized effect. It too is a descriptor of the nature of the electrical effect. It is represented in subscripts as k'.

LDR equation A triparametric model of the electrical effect.

$\boldsymbol{P_{EA}}$ The percent of the $\sigma_{k'/k}$ values in a substituent matrix which exhibit an electron acceptor electrical effect.

$\boldsymbol{P_{ED}}$ The percent of the $\sigma_{k'/k}$ values in a substituent matrix which exhibit an electron donor electrical effect.

$\boldsymbol{P_0}$ The percent of the $\sigma_{k'/k}$ values in a substituent matrix which do not exhibit a significant electrical effect.

Steric effect parameterization

$\boldsymbol{r_V}$ The van der Waals radius. A useful measure of group size. The internuclear distance between two nonbonded atoms in contact is equal to the sum of their van der Waals radii.

$\boldsymbol{\upsilon}$ A composite steric parameter based on van der Waals radii. For groups whose steric effect is at most minimally dependent on conformation, it represents the steric effect due to the first atom of the longest chain in the group and the branches attached to that atom. The only alternative monoparametric method for describing steric effects is that of Taft, which uses the E_S parameter. This was originally developed only for alkyl and substituted alkyl groups and for hydrogen. Kutter and Hansch[86] have estimated E_S values for other groups from the υ values using a method which in many cases disregards the MSI principle. It is best to avoid their use.

Simple branching equation (SB) A topological method for describing steric effects which takes into account the order of branching by using as parameters n_i, the number of atoms other than H that are bonded to the ith atoms of the substituent.

$\boldsymbol{n_i}$ The number of branches on the ith atoms of a substituent. These are the steric parameters used in the SB equation.

Expanded branching equation (XB) A topological method for describing steric effects which takes into account the order of branching by using as parameters n_{ij}, the number of jth branching atoms bonded to the ith atoms of the substituent.

$\boldsymbol{n_{ij}}$ The number of jth branches on the ith atoms of a substituent. These are the steric parameters used in the XB model of steric effects.

$\boldsymbol{n_b}$ The number of bonds in the longest chain of a substituent. It is a steric parameter which serves as a measure of the length of a group along the group axis.

Segmental equation A steric effect model that separately parameterizes each segment of a substituent. It requires fewer parameters than the XB equation and is generally more effective than the SB equation.

$\boldsymbol{\upsilon_i}$ A steric parameter based on van der Waals radii that is a measure of the steric effect of the ith segment of a substituent. The ith segment consists of the ith atom of the longest chain in the substituent and the groups attached to it. The MSI principle is assumed to apply and the segment is assigned the conformation that gives it the smallest possible steric effect.

MSI principle The principle of minimal steric interaction which states that the preferred conformation of a group is that which results in the smallest possible steric effect.

Intermolecular force parameterization

α A polarizability parameter defined as the difference between the group molar refractivities for the group X and for H divided by 100. Many other polarizability parameters, such as the van der Waals volume, the group molar volume and the parachor, can be used in its place. All of these polarizability parameters are very highly linear in each other.

n_H A hydrogen-bonding parameter which represents the lone-pair acceptor (proton donor) capability of a group. It is defined as the number of OH and/or NH bonds in the group.

n_n A hydrogen-bonding parameter which represents the lone-pair donor (proton acceptor) capability of the group. It is defined as the number of lone pairs on O and/or N atoms in the group.

i A parameter which represents ion–dipole and ion-induced dipole interactions. It is defined as 1 for ionic groups and 0 for nonionic groups.

n_D A charge transfer donor parameter which takes the values 1 when the substituent can act as a charge transfer donor and 0 when it cannot.

n_A A charge transfer acceptor parameter which takes the values 1 when the substituent can act as a charge transfer acceptor and 0 when it cannot.

IMF equation A multiparametric equation which models phenomena that are a function of the difference in intermolecular forces between an initial and a final state.

Statistics

Correlation equation An equation with which a data set is correlated by simple (one parameter) or multiple (two or more parameters) linear regression analysis.

Regression equation The equation obtained by the correlation of a data set with a correlation equation.

N_{dp} The number of data points in a data set.

Degrees of freedom (N_{df}) Defined as the number of data points, N_{dp}, minus the number of parameters (N_p), plus 1 [$N_{df} = N_{dp} - (N_p + 1)$].

***F* statistic** A statistic which is used as a measure of the goodness of fit of a data set to a correlation equation. The larger the value of F, the better the fit. Confidence levels can be assigned by comparing the F value calculated with the values in an F table for the N_p and DF values of the data set.

$100R^2$ A statistic which represents the percent of the variance of the data accounted for by the regression equation. It is a measure of the goodness of fit.

$A100R^2$ A statistic that corrects $100R^2$ for the number of independent variables.

S_{est} The standard error of the estimate. It is a measure of the error to be expected in predicting a value of the dependent variable from the appropriate parameter values.

S^o Defined as the ratio of S_{est} to the root mean square of the data. It is a measure of the goodness of fit. The smaller the value of S^o, the better the fit.

N_{dp} The number of data points in the data set.

N_{df} The number of degrees of freedom in the data set.

N_{iv} The number of independent variables in the regression equation.

$r_{df/p}$ Defined as the ratio of N_{df} to N_p. It is a measure of the reliability of the data set in the absence of clustering.

XI. APPENDIX II. ABBREVIATIONS[a]

Ak	alkyl	*c*-Pe	cyclopentyl	bc[4.1.0]Hp	bicyclo[4.1.0] heptyl
c-Ak	cycloalkyl	Hx	hexyl	bc[3.2.0]Hp	bicyclo[3.2.0] heptyl
c-Akn	cycloalkylene	*c*-Hx	cyclohexyl	bc[2.2.1]Hp	bicyclo[2.2.1] heptyl
Me	methyl	Hp	heptyl	bc[3.1.1]Hp	bicyclo[3.1.1] heptyl
Et	ethyl	Oc	octyl	bc[2.2.2]Oc	bicyclo[2.2.2] octyl
Pr	1-propyl	No	nonyl	bc[4.1.1]Oc	bicyclo[4.1.1] octyl
i-Pr	2-propyl	Dc	decyl	3-*exo*-trc[2.2.1.$0^{2,6}$] Hp	3-*exo*-tricyclo [2.2.1.$0^{2,6}$]heptyl
c-Pr	cyclopropyl	Udc	undecyl	trc[4.1.0.$0^{2,7}$]Hp	tricyclo[4.1.0.$0^{2,7}$] heptyl
1-*c*-Prn	cyclopropylidene	Ddc	dodecyl	trc[2.2.1.$3^{5,6}$]Dc	tricyclo[2.2.1.$3^{5,6}$] decyl
2-E-*c*-Prn	*trans*-cyclopropylene	Trd	tridecyl	2-sp[3.3]Hp	2-spiro[3.3] heptyl
2-Z-*c*-Prn	*cis*-cyclopropylene	Ted	tetradecyl	6,2-sp[3.3]Hpn	2-spiro[3.3] heptylene
Bu	butyl	Pdc	pentadecyl	1-sp[4.3]Oc	spiro[4.3]octyl
i-Bu	2-methyl-1-propyl	Hxd	hexadecyl	2-dsp[3.1.1.3]Dc	2-dispiro[3.1.1.3] decyl
s-Bu	1-methyl-1-propyl	Hpd	heptadecyl	Cb	cubyl
t-Bu	2-methyl-2-propyl	Ocd	octadecyl	Ad	adamantyl
c-Bu	cyclobutyl	Ndc	nonadecyl	Nh	naphthyl
1-*c*-Bun	cyclobutylidene	Eic	eicosanyl	Nn	naphthalene
2-*E*-*c*-Bun	2-*trans*-cyclobutylene	*c*-Hp	cycloheptyl	Ant	anthracenyl
2-*Z*-*c*-Bun	2-*cis*-cyclobutylene	*c*-Oc	cyclooctyl	Pht	phenanthracenyl
3-*E*-*c*-Bun	3-*trans*-cyclobutylene	*c*-Nn	cyclononyl	Py	pyridyl
3-*Z*-*c*-Bun	3-*cis*-cyclobutylene	*c*-Dc	cyclodecyl	Vi	vinyl
1-Pe	1-pentyl	*c*-Udc	cycloundecyl	1-Vn	vinylidene
2-Pe	2-pentyl	*c*-Ddc	cyclododecyl	2-Vn	vinylene
3-Pe	3-pentyl	bc[1.1.1]Pe	bicyclo[1.1.1] pentyl	Bz	benzoyl
i-Pe	3-methylbutyl	bc[2.1.0]Pe	bicyclo[2.1.0] pentyl	Ts	4-toluenesulfonyl
t-Pe	2,2-dimethylpropyl	bc[3.1.0]Hx	bicyclo[3.1.0] hexyl	C_2H	ethynyl
neo-Pe	3,3-dimethylpropyl	bc[2.2.0]Hx	bicyclo[2.2.0] hexyl	C_2	ethynylene
Pn	phenylene	bc[2.1.1]Hx	bicyclo[2.1.1] hexyl	Bs	4-bromobenzene-sulfonyl

[a] The prefixes c, bc, trc, sp, and dsp mean cyclo, bicyclo, tricyclo, spiro and dispiro, respectively. The suffix n indicates the ene ending meaning a bivalent fragment.

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CHAPTER **11**

Rearrangements of cyclobutanes

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I. INTRODUCTION

Because of the 111 kJ mol^{-1} of ring strain[1] associated with cyclobutane, virtually every rearrangement of a cyclobutyl-containing system involves ring opening or ring expansion at some point in the sequence of mechanistic steps. In many cases, cyclobutane

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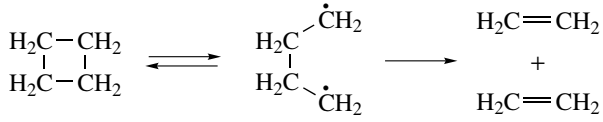
ring-opened products are formed, and the relief of ring strain provides the thermodynamic driving force for the overall reaction. By virtue of the fact that the C−C bond of a cyclobutane is weak relative to the C−C bond of an acyclic hydrocarbon, low activation energy pathways are available for cyclobutane rearrangements involving bond cleavage and the generation of reactive intermediates; similar pathways are inaccessible for analogous reactions involving unstrained systems. This chapter focuses mainly on rearrangements involving relatively simple cyclobutanes. Rearrangements of polycycles containing cyclobutanes (e.g. cubane → cuneane, Dewar benzene → benzene etc.) have generally been excluded.

II. THERMAL REARRANGEMENTS OF CYCLOBUTANES

A. Thermally-induced Ring Opening of Cyclobutanes

Because of ring strain, the C−C bond of cyclobutane is considerably weaker than a 'normal' C−C bond of an alkane. Thermolysis of cyclobutane (and derivatives) leads to a diradical intermediate. Two pathways exist for reaction of this diradical: a) reversion back to the cyclobutane, or b) fragmentation to yield two olefins (equation 1). For substituted cyclobutanes (e.g. 1,2-dimethylcyclobutane), this reversible ring opening/ring closing can lead to *cis*/*trans* isomerization if the diradical is sufficiently long-lived to allow rotation about the C−C bonds. Activation energies for stereomutation provide an estimate of the strength of the C−C bond and are easily rationalized on the basis of radical stability: Cyclobutane (260 kJ mol^{-1})[2] > 1,2-dicyanocyclobutane (200 kJ mol^{-1})[3] > 1,2-divinylcyclobutane (140 kJ mol^{-1})[4]. (For $XCH_2^{\bullet}$, radical stabilization energies are 29, 50 and 79 kJ mol^{-1} for X = alkyl, CN and CH=CH$_2$, respectively)[5].



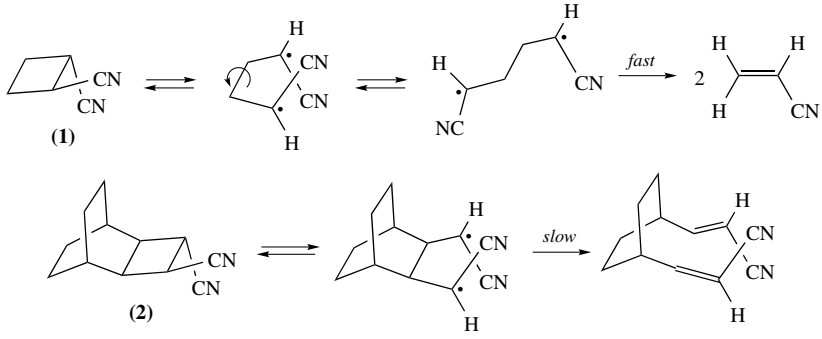
(1)

There has been considerable interest in the mechanistic details of the fragmentation process. It was suggested that for fragmentation to occur, the diradical may need to adopt an antiperiplanar conformation[6,7]. More recent calculations suggest that while the *anti* conformation is not required, fragmentation from the *anti* conformation is more favorable than from the *syn* conformation[8].

To test this hypothesis, Doering and DeLuca compared the rates and activation parameters for stereoisomerization and fragmentation of 1,2-dicyanocyclobutane (**1**) and its constrained counterpart 3,4-dicyanotricyclo[4.2.2.0^{2,5}]decane (**2**, Scheme 1). Because of the fusion of the bicyclic ring system, **2** cannot achieve the *anti* conformation. Although the activation energies for stereoisomerization of **1** and **2** are comparable, the inaccessibility of the *anti* conformation for **2** results in about ten times less fragmentation (relative to stereoisomerization)[3]. Three isomeric *cis*-1,4-bis-β-cyanovinylcyclohexanes are formed from **2**: *Z*,*Z* (4.9%), *E*,*E* (3.1%) and *E*,*Z* (28%). The major thermolysis product is the *cis* isomer of **2** (64.2%).

B. The Vinylcyclobutane → Cyclohexene Rearrangement

The vinylcyclobutane (**3**) → cyclohexene (**4**) rearrangement has been extensively studied, and is the topic of several excellent reviews[9−11]. The vinylcyclobutane rearrangement is 'simply' a 1,3-alkyl shift (equation 2). Mechanistically, however, this reaction is far

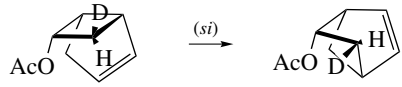


SCHEME 1

from simple and years of research have led to remarkable insight into what has been often described as a 'not obviously concerted' reaction.

(2)

Orbital symmetry considerations such as the Woodward–Hoffmann rules[12], frontier molecular orbital theory[13] and the principle of isoconjugate transition states[14, 15] all predict that the concerted pathway will occur suprafacially with inversion of configuration at the migrating carbon (*si*), or antarafacially with retention (*ar*). The two other modes, suprafacial with retention (*sr*) and antarafacial with inversion (*ai*), are symmetry forbidden. Early results were entirely consistent with prediction. For example, 6-*endo*-acetoxy-7-*exo*-d-bicyclo[3.2.0]hept-2-ene (**5**) was found to isomerize preferentially in the *si* mode (equation 3)[16].



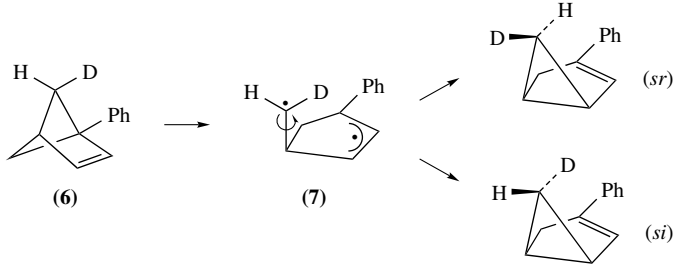
(3)

However, it soon became apparent that this reaction might not be totally controlled by orbital-symmetry considerations. For the bicyclo[3.2.0] system above, the switch from D to CH_3 results in a detectable yield of the *sr* product (*si*/*sr* $\geqslant$ 9.3); the 7-*endo*-methyl substrate forms *mainly* the *sr* product (equation 4)[16, 17]. For other systems, the *si*/*sr* ratio was found to be temperature-dependent, suggesting the existence of a second (likely diradical) pathway for the rearrangement[18].

(4)

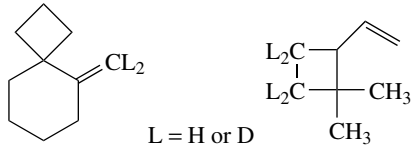
$R^1 = CH_3$, $R^2 = H$	9.3	:	1
$R^2 = CH_3$, $R^1 = H$	1	:	7.2

As the role of a diradical pathway became increasingly evident, the challenge was to explain the high stereoselectivity associated with the reaction. For example, the stepwise rearrangement of 1-phenyl-5-*endo*-d-bicyclo[2.1.1]hex-2-ene (**6**) gave a product ratio $si/sr = 10^{19}$. For a diradical pathway (Scheme 2), free rotation about the C−C in **7** is expected to result in stereorandomization. To explain these and related results, Newman-Evans and Carpenter suggested that the stereoselectivity in this diradical pathway is a consequence of dynamic issues, i.e. because of the momentum associated with the trajectory from reactant → intermediate → product, there is not enough time for bond rotation to occur[20]. Subsequent experimental and computational studies have generally confirmed and extended this hypothesis[9].



SCHEME 2

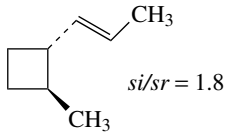
An exception to this generalization though is a report by Gajewski and Paul who, based upon an unfavorable entropy of activation and secondary deuterium isotope effects at the *exo* methylene of **8**, argue for a concerted pathway[21]. (A normal secondary isotope effect of this magnitude suggests a change in hybridization $sp^2 \rightarrow sp^3$ in the progression from reactant → transition state; no change in hybridization at the *exo* CH_2 is needed for diradical formation.) Conversely, a slight inverse isotope effect *was* observed for the rearrangement of **9** → 4,4-dimethylcyclohexene, a result which was interpreted on the basis of a diradical mechanism[22].



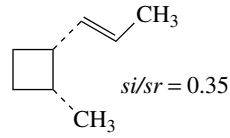
(8) $k_H/k_D = 1.086(23)$ **(9)** $k_H/k_D = 0.95(4)$

For rearrangement of monocyclic vinylcyclobutanes, all possible stereochemical outcomes (*si, ar, sr* and *ai*) have been observed (depending on the specifics of the system). Some generalizations can be made: 1) The suprafacial mode is always preferred, but the antarafacial pathway becomes increasingly important with smaller substituents at the migrating carbon, 2) for *trans* monosubstituted vinyl cyclobutanes, the *si*/*sr* ratio is greater than one, but not as high as observed in the bicyclic systems; for *cis*, the *si*/*sr* ratio is less than one (e.g. for **10**, $si/sr = 1.8$; for **11**, $si/sr = 0.35$). For both *cis*- and

trans-monosubstituted vinylcyclobutanes, the *trans*-3,4-disubstituted cyclohexene is the major product[9].



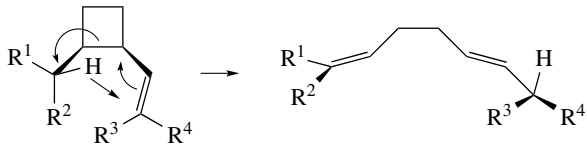
(10)



(11)

In summary, the prevailing view seems to be that the vinylcyclobutane rearrangement is a diradical, stepwise process. In some cases, the intermediate diradicals are short-lived, resulting in an overall reaction which exhibits high stereoselectivity reminiscent of a concerted reaction. When the diradical is longer-lived (allowing time for bond rotation, conformational interconversion etc.), stereorandomization results.

As a final note, in addition to the vinylcyclobutane rearrangement, *cis*-2-alkyl-1-vinylcyclobutanes undergo a 1,5-hydrogen shift (reverse ene reaction). Consistent with orbital-symmetry considerations for a concerted process, this reaction proceeds with high stereospecificity and occurs suprafacially as illustrated in equation 5[23,24].



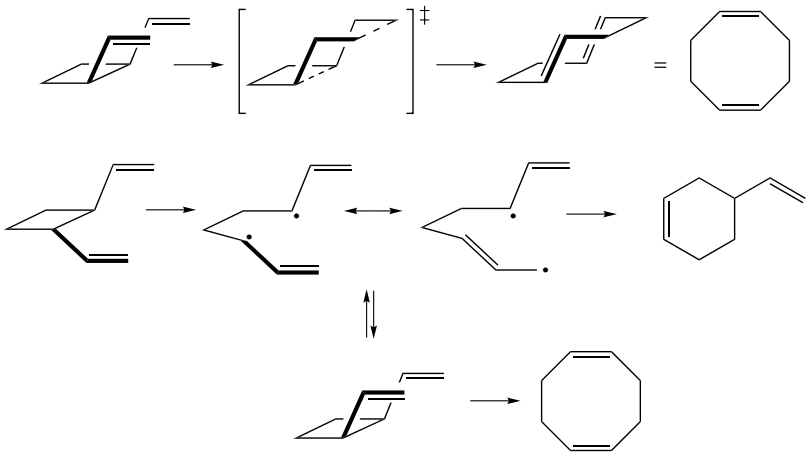
(5)

C. 1,2-Divinylcyclobutane (Cope) Rearrangement

The conversion of 1,2-divinylcyclobutane to cyclo-1,5-octadiene is a specific example of a Cope rearrangement[25]. For the *trans* starting material, a concerted pathway is precluded for geometric reasons, and a diradical pathway is the only viable mechanistic option, yielding 4-vinylcyclohexene and *cis, cis*-1,5-cyclooctadiene as the major products (Scheme 3)[26]. In contrast, for the *cis* isomer, the vinyl groups are in close proximity. Consequently, the extremely low activation energy observed for rearrangement (100 kJ mol^{-1}) and negative entropy of activation[27] suggest a concerted pathway proceeding via a boat-type transition state yielding *cis, cis*-1,5-cyclooctadiene (Scheme 3)[11,28]. It is likely that during the reaction, *trans*-1,2-divinylcyclobutane first isomerizes to the *cis* isomer en route to *cis, cis*-1,5-cyclooctadiene.

Recent contributions to this field include high level *ab initio* calculations (RHF/6-31G* and MP2(full)/6-31G*//RHF/6-31G*) of the transition states and energetics for the Cope rearrangement of 1,2-divinylcyclobutane[29]. A recent study by Gajewski and coworkers examined secondary H/D isotope effects for *cis*-1,2-divinylcyclobutane (**12**) and *cis*-1,2-divinylcyclopropane (**13**)[30]. The miniscule secondary isotope observed for the cyclobutane (vs. cyclopropane) suggests that little bonding occurs at the transition state for rearrangement of the cyclobutane (compared to divinylcyclopropane).

In an extremely intriguing study, Doering and coworkers examined the effect of pressure on the rate of the Cope rearrangement as a diagnostic tool for differentiating concerted vs. stepwise pathways. Thus while *cis*-1,2-divinylcyclobutane had a volume of activation of



SCHEME 3

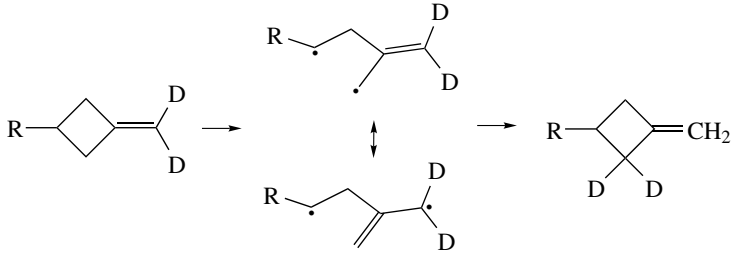
-13.4 cm^3 mol^{-1}, consistent with an organized (cyclic) transition state, the *trans* isomer had $\Delta V^{\neq} = +4.2$ cm^3 mol^{-1}. Like an increased entropy, the increased volume of the transition state was taken to be diagnostic of the diradical pathway[31].

(12) (a) L = H
(b) L = D
$k_{\mathbf{12a}}/k_{\mathbf{12b}} = 1/1.04(2)$

(13) (a) L = H
(b) L = D
$k_{\mathbf{13a}}/k_{\mathbf{13b}} = 1/1.29(9)$

D. Methylenecyclobutane and 1,2-Dimethylenecyclobutane Degenerate Rearrangements

The degenerate rearrangements of methylenecyclobutane and 1,2-dimethylenecyclobutane were the topic of a 1970 review by Baldwin and Fleming[32]. These reactions likely involve diradical intermediates. Since that review, Roth and Paschmann examined the temperature and oxygen dependence of the rate of trapping of the intermediate diradical, and discuss the decreasing stereoselectivity observed for radical stabilizing substituents (equation 6, R = Ph) on the basis of increased lifetime for the diradical[33].



(6)

Gajewski and coworkers reported the kinetics and H/D isotope effects for rearrangement and interconversion of *cis*- and *trans*-2,3-dimethylmethylenecyclopropane, and interpreted the results on the basis of a diradical mechanism[34]. Dolbier and Cooke examined the effect of *gem*-difluoro substituents (equation 7) and concluded that the CF_2 group increases the C−C bond strength of cyclobutane by 20−25 kJ mol^{-1} [35].

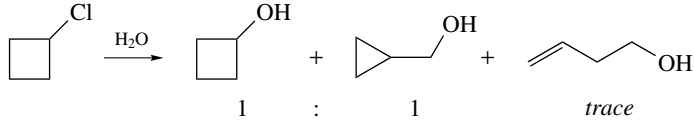
(7)

III. REARRANGEMENTS OF CYCLOBUTYL-CONTAINING REACTIVE INTERMEDIATES

A. Cyclobutyl Cations

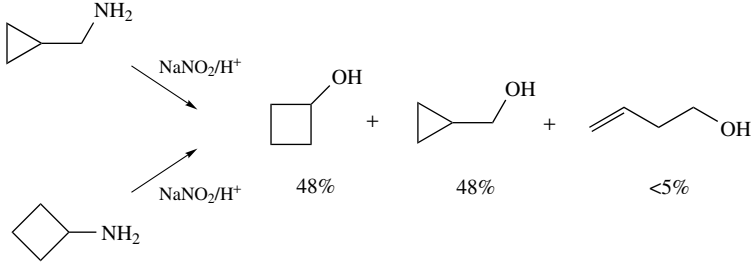
The chemistry of cyclobutane (and related) carbocations is covered extensively in Siehl's chapter in this book. Consequently, this section will provide only a brief (mostly historic) overview of this fascinating system.

Hydrolysis of cyclobutyl chloride was found to be significantly faster than for other secondary systems (e.g. cyclohexyl chloride), suggesting that there was something unique about the cyclobutyl cation. The products of the reaction (equation 8) clearly show that the cyclobutyl cation undergoes rearrangement, resulting in formation of the expected cyclobutyl and corresponding cyclopropylcarbinyl products in about a 1:1 ratio, and to a lesser extent, the ring opened homoallyl products[36, 37].



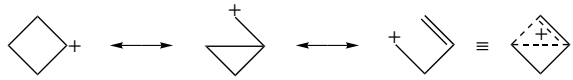
(8)

Roberts and coworkers demonstrated in the 1950s that the isomeric cyclobutyl cation and cyclopropylcarbinyl cation are intimately related. Diazotization of either cyclopropylcarbinyl amine or cyclobutyl amine (Scheme 4) was observed to produce the same products in nearly the same ratio, suggesting that common carbocationic intermediates are involved in both systems[36]. Initially, a symmetric tricyclobutonium ion was suggested, but such an intermediate was inconsistent with the results of ^{13}C labeling studies.



SCHEME 4

Instead, to explain both the observed products and the enhanced reactivity of cyclobutyl and cyclopropylcarbinyl systems, Roberts and coworkers proposed that a highly delocalized, non-classical carbocation (bicyclobutonium ion) intermediate was formed (Scheme 5)[36,38]. Recent spectroscopic results[39,40] and *ab initio* calculations[41,42] seem to confirm this proposal. Wiberg and coworkers have suggested that ionization leads to a bridged cyclobutyl cation, which subsequently rearranges to the cyclopropylcarbinyl cation. The cyclobutyl and cyclopropylcarbinyl cations are of comparable energy and separated by a low energy barrier[43].



SCHEME 5

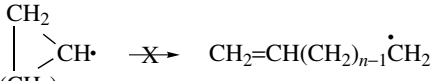
B. Cyclobutyl Anions

Unlike cyclopropanes, there is nothing remarkable about the chemistry of carbanions involving cyclobutane or cyclobutylcarbinyl systems. The proton affinities of cyclobutyl, cyclopentyl and cyclohexyl anions are nearly identical (1750 ± 10 kJ mol^{-1}). In contrast, the proton affinity of cyclopropyl anion is considerably lower (1708 kJ mol^{-1})[44]. Similarly, as a substituent attached to an electron rich center, the cyclobutyl group is unremarkable. For instance, the rate of base-catalyzed H/D exchange in cyclobutylcarbinyl phenyl ketones is similar to that of other alkyl phenyl ketones, demonstrating that the cyclobutyl group does not stabilize (or for that matter, destabilize) an adjacent carbanionic center[45].

C. Paramagnetic Intermediates

1. Cyclobutane systems

a. Neutral free radicals. Despite the ring strain associated with a four-membered ring, the cyclobutyl radical (**14**) is unremarkable and behaves much like any other simple alkyl or cycloalkyl radical. In fact, neither the cyclopropyl radical (**15**) nor the cyclobutyl radical exhibits any tendency to undergo ring opening in order to relieve ring strain (equation 9).



(9)

(14) $n = 2$

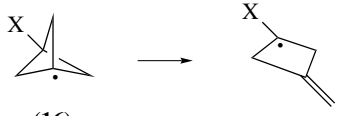
(15) $n = 1$

The highly strained 1-bicyclo[1.1.1]pentyl radical (**16**) is also reluctant to ring open. Maillard and Walton report that the EPR spectrum of **16** can be recorded at temperatures as high as 40 °C, and estimate a lower limit for the activation energy for ring opening (equation 10) to be 59 kJ mol^{-1} [46]. Della and Schiesser report that even with strategically placed radical-stabilizing substituents, the activation energies for ring opening are still exceptionally high (Table 1)[47]. Finally, even the cubyl radical (**17**) is stable at temperatures up to 150 °C, despite possessing a ring strain approaching 700 kJ mol^{-1} [48]. (Readers are directed to Hashemi and Higuchi's chapter on cubanes and prismanes.)

TABLE 1. Activation energies for ring opening of bridgehead-substituted 1-bicyclo[1.1.1]pentyl radicals (**16**, equation 10)[47]

X	E_a(kJ mol^{-1})
H	110
CO_2CH_3	105
Ph	88

Of course, cyclobutyl radicals *do* ring open when C−C bond cleavage is a natural consequence of *another* radical rearrangement. For example, the bicyclo[2.1.0]pent-2-yl radical (**18**) rapidly ring opens to cyclopent-2-en-1-yl radical (**19**, equation 11). Formally, this is best viewed as a cyclopropylcarbinyl → homoallyl radical rearrangement (**20** → **21**, equation 12) resulting in rupture of the bond shared by the cyclopropane and cyclobutane rings in this fused system. However, relief of cyclobutane ring strain does impart additional driving force for this reaction, manifested in a rate constant for ring opening (equation 11, $k = 2.1 \times 10^9$ s^{-1}, $E_a = 22$ kJ mol^{-1}) which is nearly one order of magnitude greater than that of the unsubstituted cyclopropylcarbinyl radical (equation 12)[49].

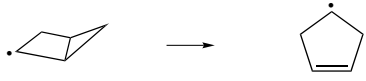


(10)

(16)

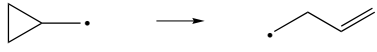
(17)

Because of its high rate of ring opening, and the fact that the rate constant has been well-characterized, the bicyclo[2.1.0]pent-2-yl radical rearrangement can be used as a so-called 'free radical clock'[50] to estimate rates of competing bimolecular reactions. Specifically, this rearrangement has been used to estimate the rate of the oxygen rebound step in the cytochrome P-450 catalyzed oxidation of hydrocarbons[51,52].



(11)

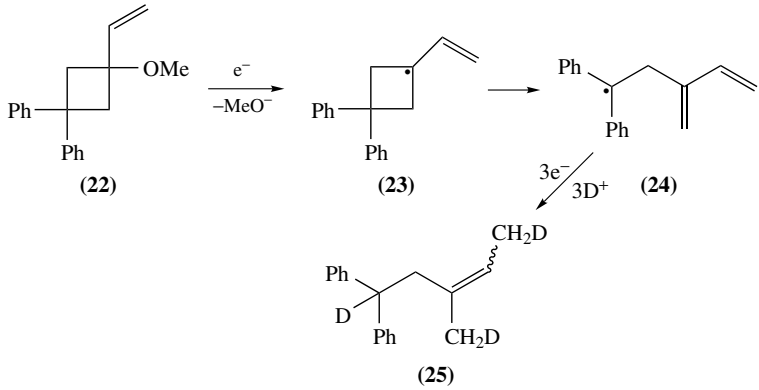
(18) **(19)**



(12)

(20) **(21)**

Finally, reduction of **22** with Li or Na yields **25** after workup with D^+. It was suggested that one-electron reduction of **22** yields vinylcyclobutyl radical **23**, which undergoes ring opening to **24** as depicted in Scheme 6 to afford the final products[53].

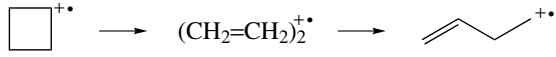


SCHEME 6

b. Radical cations. Under oxidative conditions, cyclobutanes undergo ring opening both in solution and in the gas phase[54–57]. Most of the examples of this chemistry in solution involve cyclobutanes with other (typically electron-donating) substituents on the cyclobutyl group, and proceed in a stepwise manner (rather than a concerted [2 + 2] cycloreversion) to yield an olefin/olefin radical cation. For example, treatment of cyclobutane **26** with the one-electron oxidant Ce(IV) ammonium nitrate (CAN, Scheme 7) yields cyclobutane ring-opened products **27** and **28** arising from trapping of a ring-opened distonic radical cation **29** by (a) intramolecular cyclization, and/or (b) reaction with methanol[58].

Johnston and coworkers have shown by laser flash photolysis that structurally related radical cation **30** (Scheme 8) has a lifetime on the order of 100 ns, and decays by rearrangement yielding **31** (which is spectroscopically observable at 500 nm) rather than by cycloreversion to **32**[59]. Other examples of oxidative cyclobutane ring openings are discussed in subsequent sections of this chapter.

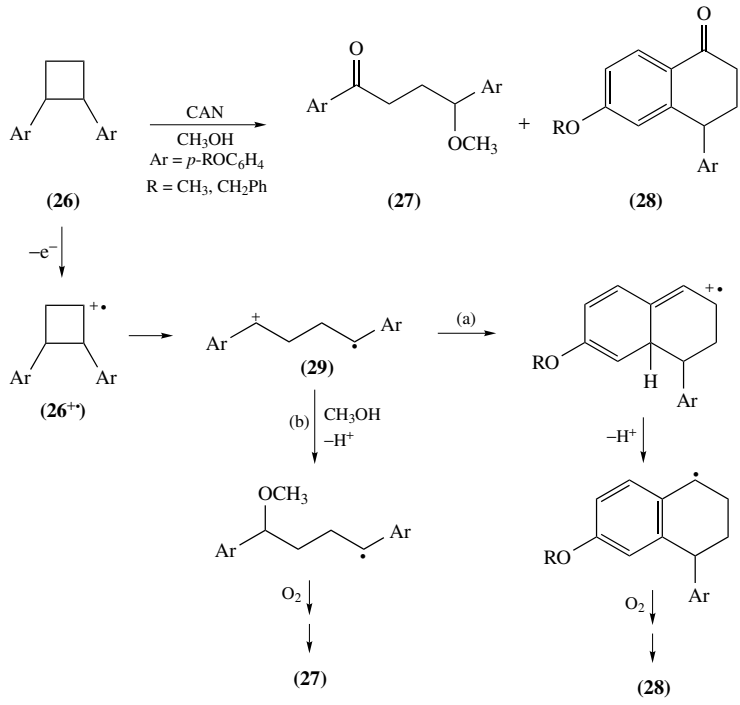
Without an electron donor on the cyclobutyl group, a (likely concerted) [2 + 2] cycloreversion appears to become an important pathway. Jungwirth and Bally have studied the entire $C_4H_8^{+\bullet}$ potential surface computationally at the QCISD(T)/6-32G*//UMP2/6-31G* level and concluded that ethylene dimer (formed via a [2 + 2] cycloreversion) is an intermediate in the path to ring-opened products (equation 13). A tetramethylene radical cation ($CH_2CH_2CH_2CH_2^{+\bullet}$) does not appear to be an intermediate in the ring-opening process[60].



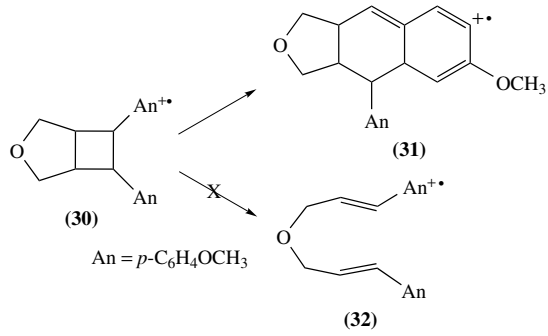
(13)

Herges and coworkers have suggested that the [2 + 2] cycloreversion of quadricyclane radical cation (equation 14) proceeds via a concerted, though not synchronous, pathway as well[61].

(14)



SCHEME 7

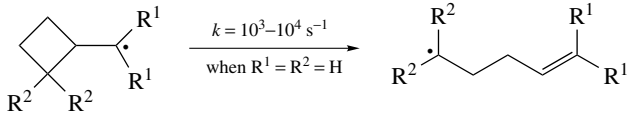


SCHEME 8

2. Cyclobutylcarbinyl (and related) systems

a. Neutral free radicals. Ring opening of the cyclobutylcarbinyl radical (equation 15) has been extensively studied by Beckwith and Moad[62] and more recently by Walton[63]. From their results, it is clear that alkyl groups at the α-carbon slightly retard the rate

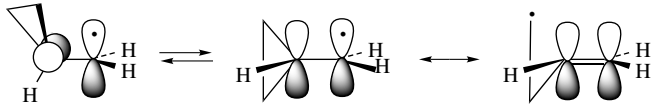
of rearrangement. For example, when $R^1 = CH_3$, the rate is about 25% slower than for $R^1 = H$. Alkyl groups on the cyclobutyl group have a more pronounced effect: When $R^2 = CH_3$, the rate is 300 times faster than for $R^2 = H$. Because alkyl groups stabilize a radical center, these results suggest that this reaction is characterized by a fairly late (more product-like) transition state.



(15)

It is particularly noteworthy that the rates for ring opening of cyclobutylcarbinyl-type radicals are about 4 - 5 orders of magnitude slower than analogously substituted cyclopropylcarbinyl radicals (equation 12)[64–74]. Because the ring strain of cyclobutane and cyclopropane are nearly identical, the thermodynamic driving force for ring opening is similar for both these systems.

The difference in the rate of ring opening seems to be related to the extent of interaction of a cyclopropyl groups vs. a cyclobutyl group with the radical center. In the bisected conformation[75, 76], the highest occupied molecular orbital of the cyclopropyl group is properly aligned with the singly occupied molecular orbital of the cyclopropyl group[77]. This stabilizes the radical center, increases the spin density at C_2 and C_3 and results in a diminished bond order between C_1-C_2 and C_1-C_3 of the cyclopropyl group. Qualitatively, this can be envisioned in a resonance context (i.e. C–C hyperconjugation) as shown in Scheme 9.



perpendicular conformation *bisected conformation*

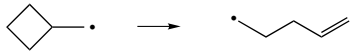
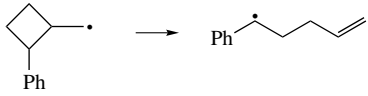
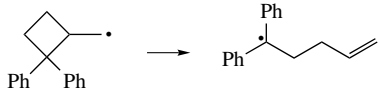
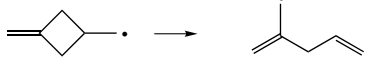
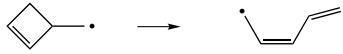
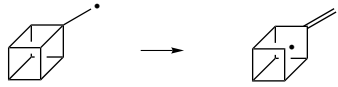
SCHEME 9

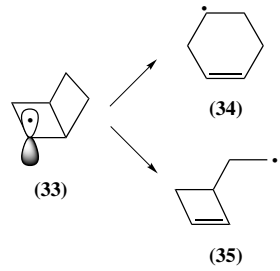
For the cyclopropylcarbinyl radical, the barrier to rotation about $C_\alpha-C_2$ is 11.5 kJ mol^{-1}, and from this, a stabilization energy on the order of about 10 kJ mol^{-1} has been suggested[78]. For the cyclobutylcarbinyl radical, although the bisected conformation is still preferred, the barrier to rotation is only 5 kJ mol^{-1}[79], suggesting less interaction with the radical center. (For larger cycloalkylcarbinyl radicals, the perpendicular conformation is preferred and the rotational barrier is <2 kJ mol^{-1}.)[79] Hence for the cyclobutylcarbinyl radical, C–C hyperconjugation is less important, resulting in a higher barrier to ring opening.

It is noteworthy that in some cases at least, relief of ring strain can overcome the stereoelectronic requirements for ring opening. For example, ring opening of the bicyclo[2.2.0]hexan-2-yl radical (**33**) yields the more stable cyclohex-2-enyl radical (**34** rather than **35**) despite the fact that the C_1-C_4 bond is in the nodal plane of the SOMO (Scheme 10)[80].

Table 2 summarizes some of the kinetic data pertaining to ring opening of cyclobutylcarbinyl and related neutral free radicals. Entries 1–3 clearly show that phenyl substitution at C_2 of the cyclobutyl dramatically increases the rate of ring opening; the phenyl group(s) stabilizes the ring-opened form by direct resonance interaction[62, 81–83]. However, entries 4 and 5 clearly illustrate the stereoelectronic requirements of the reaction. Although both

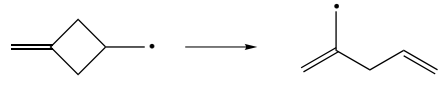
TABLE 2. Absolute rate constants and activation energies for ring opening of cyclobutylcarbinyl and related free radicals

Entry	Reaction	k (s^{-1})	E_a (kJ mol^{-1})	Reference
1		2.3×10^4 4.3×10^3	49.8 51.0	81 62
2		4.9×10^6	33.0	83
3		2.5×10^8	21	82
4		2.8×10^4	48.1	84
5		3.9×10^3	52.3	84
6		2.9×10^{10}	15	85

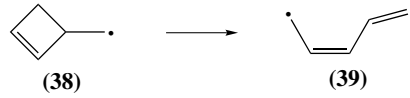


SCHEME 10

36 and **38** ring open to yield highly resonance-stabilized radicals (**36** → **37** and **38** → **39**, equations 16 and 17, respectively), the rate constant and activation energies are similar to those for the unsubstituted cyclobutylcarbinyl radical[84].

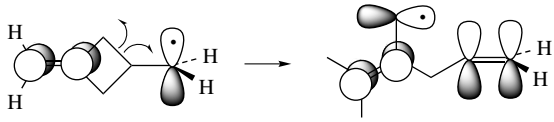


(16)



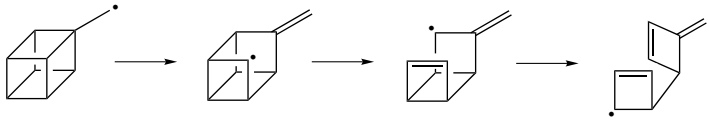
(17)

In both cases, resonance stabilization is not realized in the transition state because the rupturing C−C bond is orthogonal to the π-system of the C=C (illustrated in Scheme 11 for the ring opening of **36**). This phenomenon was discussed by Walton in the context of the principle of non-perfect synchronization (i.e. bond cleavage occurs before rotation, leading to resonance stabilization)[84].



SCHEME 11

The final entry in Table 2 involves ring opening of the cubylcarbinyl radical (**40**), which emerges as 'one of the fastest radical rearrangements ever reported'[85]. What is especially intriguing about this system is that it undergoes three consecutive rearrangements (equation 18)[86]; the rate constant and activation energy reported in Table 2 refer to the first step in the sequence.

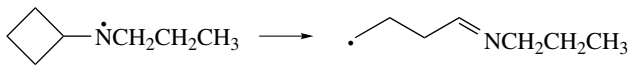


(40) (18)

Somewhat surprisingly, both the structurally related 9-homocubyl (**41**) and the 9-basketyl radical (**42**) ring open at a rate at least six orders of magnitude slower than the cubyl radical. (The 9-homocubyl radical does not rearrange; the 9-basketyl radical rearranges with a rate constant and activation energy similar to the unsubstituted cyclobutylcarbinyl radical.)[87] Borden and coworkers analyzed this system in detail employing *ab initio* calculations and concluded that the difference in the exothermicities for reactions of **41** and **42** vs. **40** accounts for most of the difference in the activation energy for ring opening (i.e. a plot of E_a vs. ΔH° for **40, 41, 42** and related cyclobutylcarbinyl radicals is linear with no obvious deviations for any of these radicals)[88].

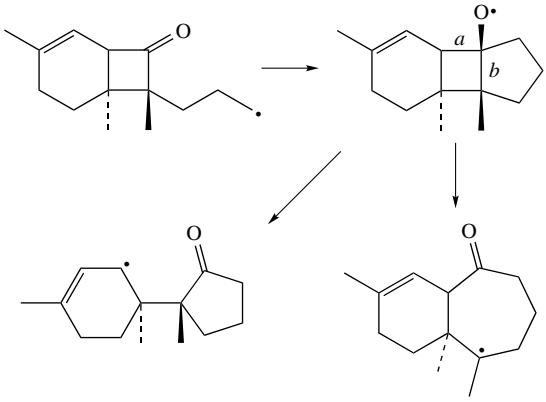
(41) **(42)**

There are several other rearrangements related to the cyclobutylcarbinyl system which have been examined. In the context of a 'free radical clock' for aminyl radical reactions, Maeda and Ingold reported that the *N*-cyclobutyl-*N*-*n*-propylaminyl radical (**43**) ring opens at a 'useful rate' (equation 19, $k = 1.2 \times 10^5$ s^{-1}, $E_a = 43.9$ kJ mol^{-1})[89].



(43) (19)

While the kinetics of ring opening of the cyclobutyloxyl radical has not been fully characterized, it is likely significantly faster than that of the cyclobutylcarbinyl radical. (The cyclopentyloxyl radical ring opens with $k = 9 \times 10^7\ s^{-1}$.)[90] Ring openings of cycloalkyloxyl radicals are frequently used to induce ring expansion in organic synthesis. An example from the Ziegler group is presented in Scheme 12. In this example, the preference for the cleavage of bond *b* (despite the fact that cleavage of bond *a* leads to a more stable radical) was rationalized on the basis of an early transition state[91]. (Note: The older literature refers to $RO^{\bullet}$ as an alkoxy radical. More recently, it has become common to refer to this as an alkoxyl radical.)



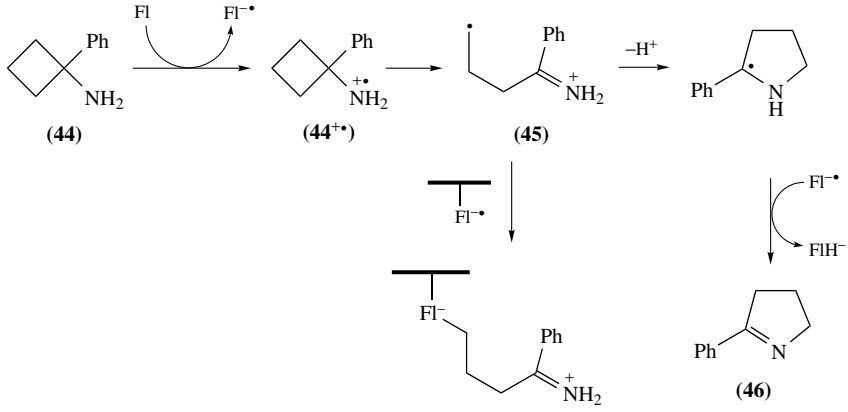
SCHEME 12

b. Radical ions. Radical ion variants of the cyclobutylcarbinyl radical rearrangement have proven to be of particular significance in mechanistic biochemistry. Silverman and coworkers have used rearrangements involving cleavage of 3- and 4-membered rings to probe for radical ion intermediates in enzyme-catalyzed oxidations involving monoamine oxidase (MAO) and cytochrome P-450. For example, 1-phenylcyclobutylamine (**44**) is found to inactivate MAO. The suggested mechanism (Scheme 13) is that oxidation of **44** yields radical cation $\mathbf{44}^{+\bullet}$, which in analogy to neutral cyclobutylaminyl radical **43** (equation 19) is suggested to undergo rapid ring opening. Presumably, the reactive 1° radical portion of distonic radical cation **45** disrupts the active site, perhaps via trapping by a flavin semiquinone (Fl). Consistent with the proposed mechanism is the fact that 2-phenyl-1-pyrroline (**46**) is formed, presumably via intramolecular cyclization of radical cation **45**[92].

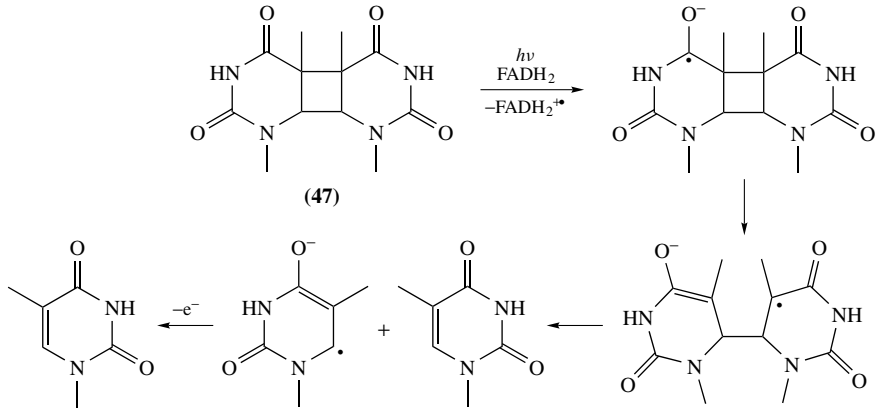
Another system which may involve radical ion intermediates involves DNA photolyase enzymes, which repair pyrimidine dimers in DNA damaged by visible light. In a model reaction, Falvey and coworkers demonstrated that the photochemical reaction of **47** with $FADH_2$ results in a stepwise retro [2 + 2] cycloaddition (Scheme 14)[93,94].

The rate of ring opening appears to be quite slow in these systems. For the conversion $\mathbf{48} \rightarrow \mathbf{49} + \mathbf{49}^{-\bullet}$ (equation 20), a global rate constant of $3.0\ s^{-1}$ was obtained via cyclic voltammetry[95]. (Part of the reason for the low rate of reaction is undoubtedly attributable to stabilization of **48** from extended conjugation.)

It was suggested that rearrangement does not occur if there are no radical-stabilizing substituents on the cyclobutane ring. For example **50**, generated from the carbonyl precursor via photoinduced electron transfer using *N*,*N*-dimethylaniline as an electron donor, was found to neither ring open nor isomerize (equation 21)[96].

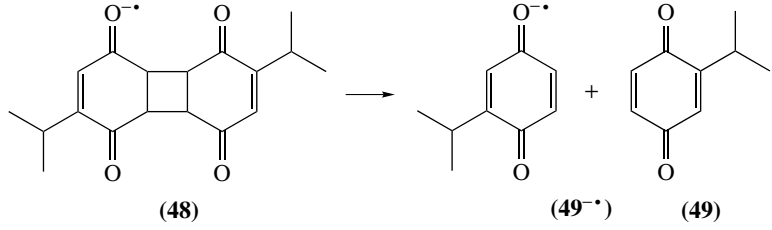


SCHEME 13

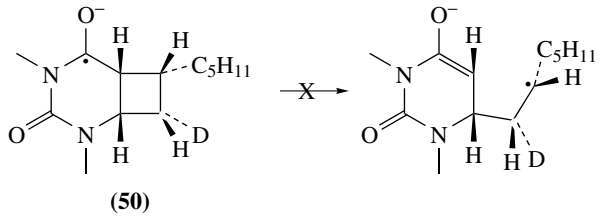


SCHEME 14

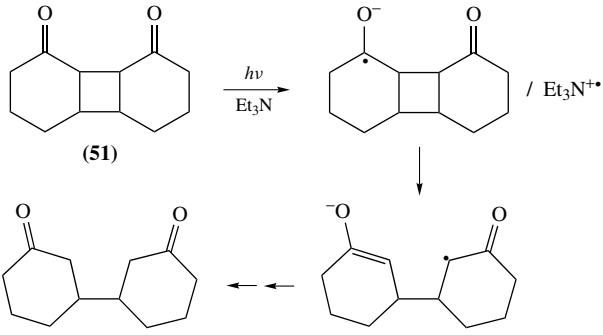
However, closely related radical anion **51** does in fact undergo rearrangement (Scheme 15)[97]. Clearly, resonance stabilization in the ring-closed radical anions, relief of ring strain, and resonance in the ring-opened, distonic radical ions all play a role in determining the rate of the reaction.



(20)



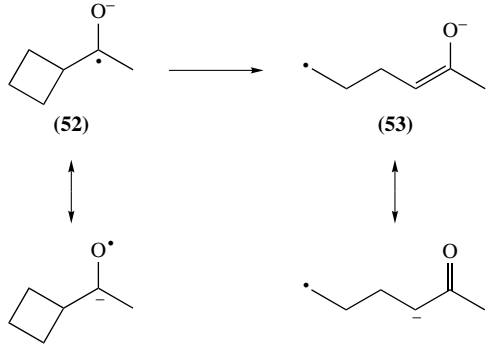
(50) (21)



(51)

SCHEME 15

Recently, Tanko and coworkers discussed the relative importance of these various factors and their effect on the rate of cyclopropylcarbinyl- and cyclobutylcarbinyl-type ring opening of ketyl anions. For example, radical anion **52** undergoes ring opening (Scheme 16) with a rate constant greater than that of the neutral cyclobutylcarbinyl radical[98,99].



(52) **(53)**

SCHEME 16

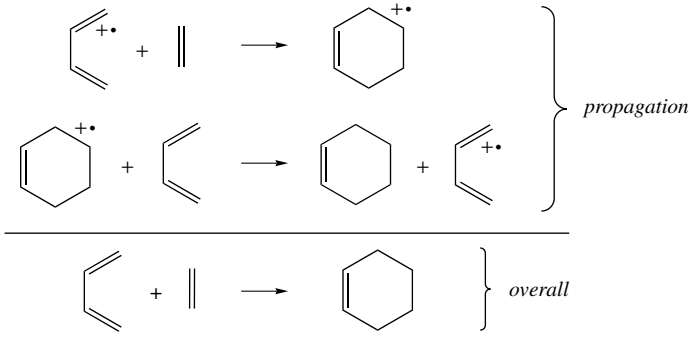
These results suggest that the aliphatic ketyls are at least (and likely more) reactive in comparison to alkyl radicals in β-scission-type processes, despite the fact that the former are thermodynamically much more stable (by as much as 113 kJ mol^{-1}). Essentially, the O^- group, being a potent electron donor, is able to stabilize a radical center. The

reason that aliphatic ketyls undergo such rapid rearrangement is that the O^- group *also* stabilizes the double bond in **53**, possibly to an even greater extent. (An equivalent and indistinguishable argument is that the O^- is stabilized by an adjacent radical center in the ring-closed form, and by a double bond in the ring-opened form.)[99]

3. The radical cation vinylcyclobutane → cyclohexene rearrangement

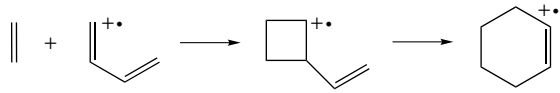
One of the most fascinating discoveries in mechanistic organic chemistry in the past twenty years is that certain pericyclic reactions can be catalyzed by single electron transfer. The so-called 'hole catalyzed' (radical cation) Diels–Alder reaction is likely the most recognized example of such a process. Bauld and coworkers have shown that under oxidative (single electron transfer) conditions, Diels–Alder reactions proceed readily, even for substrates which fail to react under 'normal' reaction conditions[100, 101].

The mechanism of the radical cation Diels–Alder reaction is depicted in Scheme 17 for the hypothetical reaction of ethylene and butadiene. This process is a free radical chain reaction, and can be initiated by most common methods which accomplish a single electron oxidation (e.g. chemical oxidants, electrochemistry and photoinduced electron transfer)[100, 101].



SCHEME 17

Under some conditions, and with certain substrates, competing with the $[4 + 2]^{+\bullet}$ cycloaddition is a $[2 + 2]^{+\bullet}$ cycloaddition yielding a vinylcyclobutane radical cation. The vinylcyclobutane radical cation can subsequently undergo a 1,3-sigmatropic rearrangement (the radical cation variant of the vinylcyclobutane rearrangement) yielding the Diels–Alder adduct (Scheme 18). This chapter will only briefly review this fascinating rearrangement; the interested reader is directed to Bauld's chapter for more information.

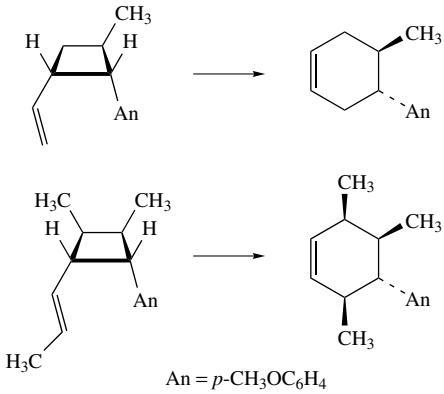


SCHEME 18

Like the 'hole-catalyzed' Diels–Alder reaction, the radical cation variant of the vinylcyclobutane rearrangement nicely illustrates the potency of single electron transfer as a means of catalyzing chemical reactions. The thermal vinylcyclobutane → cyclohexene

rearrangement has an activation energy of 210 kJ mol^{-1} [102]. For the radical cation, recent high level MO calculations suggest that the barrier is reduced to a mere 59 kJ mol^{-1} [103].

An interesting question is whether the vinylcyclobutane → cyclohexene rearrangement is a concerted process. Early MO studies (MP2/6-31G*/3-21G) suggest a concerted process characterized as suprafacial, with retention of configuration at the migrating carbon[104]. More recent calculations support this view[103]. Product studies are also consistent with this formulation, as illustrated in Scheme 19[100].

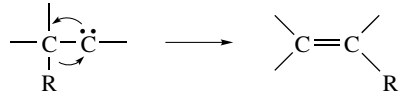


An = *p*-$CH_3OC_6H_4$

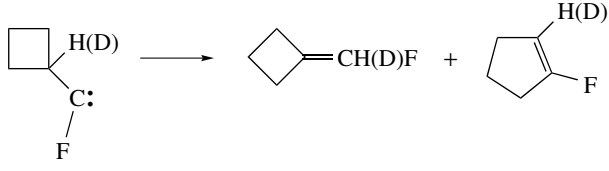
SCHEME 19

D. Singlet Carbenes

Unimolecular rearrangements of singlet carbenes typically involve a 1,2 migration of hydrogen or carbon (equation 22)[105–107], and cyclobutane-containing systems are no exception. For cyclobutylfluorocarbene (**54**), both pathways are observed leading both to fluoromethylenecyclobutane and to 1-fluorocyclopentene (equation 23)[108]. The observed H/D isotope effect for the hydrogen migration process suggests that this reaction may involve quantum mechanical tunneling, similar to what has been suggested for rearrangement of other carbenes such as chloromethyl[105–107].



(22)

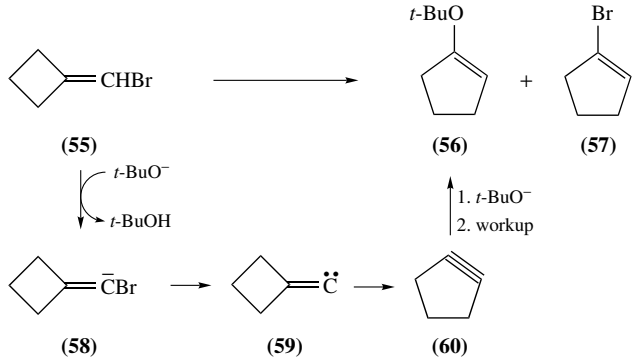


(23)

(54)

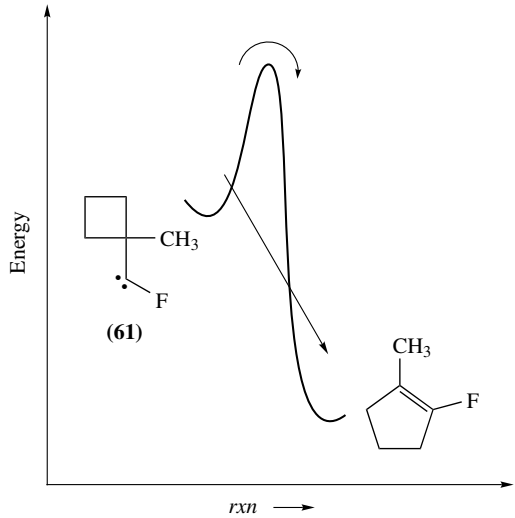
In another example of an alkyl shift involving a cyclobutane-type system, treatment of (bromomethylene)cyclobutane (**55**) with base (*t*-BuO^-) yields rearranged products **56** and **57** (Scheme 20). Formation of **56** was attributed to a 1,2-alkyl shift in **59**, resulting in

ring expansion and a cyclopentyne intermediate (**60**)[109, 110]. The mechanism for formation of **57** is a bit more complicated, potentially involving rearrangement of carbene **59**, or a simultaneous migration of carbon and bromide in vinyl anion **58**[111].



SCHEME 20

Returning to the issue of quantum mechanical tunneling, Borden and coworkers have recently provided results from both theory and experiment to show that the 1,2-alkyl shift of 1-methylcyclobutylfluorocarbene (**61**) involves tunneling of carbon (Scheme 21)[112]. (Quantum mechanical tunneling of heavy atoms such as carbon is exceptionally rare, and may arise in this case because the rearrangement requires only a small movement, resulting in a thin reaction barrier that facilitates tunneling.) At low temperature (8 K), it is estimated that the rate 'through the barrier' (i.e. tunneling) is >150 times faster than the rate 'over the barrier' (i.e. normal, thermal reaction)[112].



SCHEME 21

IV. CLOSING REMARKS

As is the case for cyclopropanes, the ring strain associated with the cyclobutane group opens up novel, low energy pathways for molecular rearrangements. While there are similarities between the two systems (e.g. nearly identical strain energies), there are also differences. Cyclopropanes do not have anything analogous to the [2 + 2] cycloreversion of a cyclobutane. As a substituent, the cyclobutyl group does not interact as strongly with an electron-deficient center; as a consequence, bond breaking in cyclobutylcarbinyl systems is slower than in cyclopropylcarbinyl systems. While this chapter has focused mainly on the mechanistic aspects of cyclobutane rearrangements, several of these reactions have proven extremely useful in organic synthesis.

V. ACKNOWLEDGMENT

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CHAPTER **12**

Cyclobutyl, cyclobutyl-substituted and related carbocations

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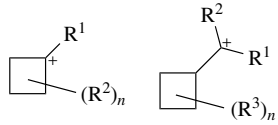
I. INTRODUCTION

This chapter deals with carbocations in structures containing a cyclobutyl ring. Cyclobutyl carbocations and related carbocations (**A**) and cyclobutyl-substituted carbocations (**B**) are reviewed.



(A) **(B)**

A comprehensive coverage of the field has not been attempted. Only selected solvolytic investigations are described. Synthetic applications such as polymerization[1] and biosynthetic

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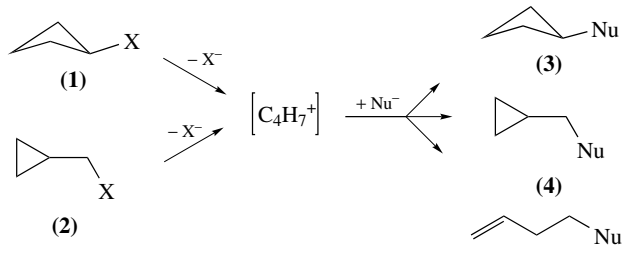
aspects[2] have been omitted in favor of reviewing investigations of these types of carbocations by contemporary methods including NMR spectroscopy and quantum chemical calculations. Emphasis is placed on description of the basic features of unusual structure, dynamics and bonding which are quite common in these systems.

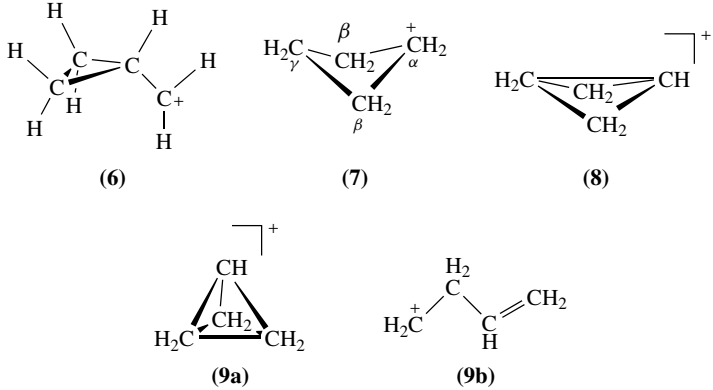
II. CYCLOBUTYL CATIONS $[C_4H_7]^+$ AND SUBSTITUTED CYCLOBUTYL CATIONS $[C_4H_6R]^+$

The cyclobutyl/cyclopropylmethyl cation system ($C_4H_7^+$) most likely has been the focus of more studies than any other carbocation system except the 2-norbornyl cation. Cyclobutyl substrates **1** as well as cyclopropylmethyl substrates **2** solvolyse at high rates and give similar substitution products (**3**, **4** and **5**).



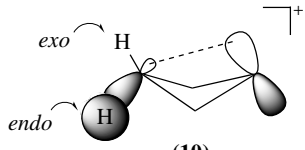
The observed mixture of cyclobutyl (**3**) cyclopropylmethyl (**4**) and homoallyl (**5**) substitution products could result from a single cationic intermediate $C_4H_7^+$ [3] that may be attacked at different sites by a nucleophile or may involve two or more rapidly equilibrating cations. The structure and dynamics of the parent cyclobutyl cation $C_4H_7^+$ has been an intriguing problem for more than half a century[4].

Several isomeric structures have been proposed to account for the experimental results. The considered structures are bisected cyclopropylmethyl cation **6**, a puckered cyclobutyl cation **7**, a hypercoordinated bicyclobutonium ion **8**, tricyclobutonium ion (**9a**) and the homoallylcation (**9b**).



The puckered cyclobutyl cations **7** and **8** are related in symmetry and distinguished only according to whether the transannular carbons C^{α} and C^{γ} are in bonding distance or

not. The bicyclobutonium cation **8** has a pentacoordinated C^{γ} carbon. It can be called a protonated bicyclobutane. The bridging interaction can formally be drawn as an interaction of the backside of the $C^{\gamma}-H^{endo}$ sp^3 orbital with the empty carbon p orbital at C^{α} as shown in **10**. Theoretical calculations predict similar energies for **6**, **7** and **8**, but indicate that **9a** is less likely. In any case, the exactly threefold symmetric tricyclobutonium ion **9a** must be a maximum in energy as a consequence of the Jahn–Teller theorem[5a].



(10)

All experimental and computational evidence indicate that the open homoallyl cation **9b** is significantly higher in energy than the other structures and does not have to be considered for the parent system[5b]. Gas phase reactivity studies of the $C_4H_7^+$ ions suggest that bicyclobutonium ion **8** and cyclopropylmethyl cation **6**, which are initially generated from corresponding precursors such as **1** and **2**, share a common reactivity outlet[6].

A major difficulty in understanding the ionic intermediates involved in solvolysis and gas phase reactions is that the nature of the intermediate cations involved and their interconversion is not directly accessible but is inferred from rate studies, kinetic isotope effects and product analysis.

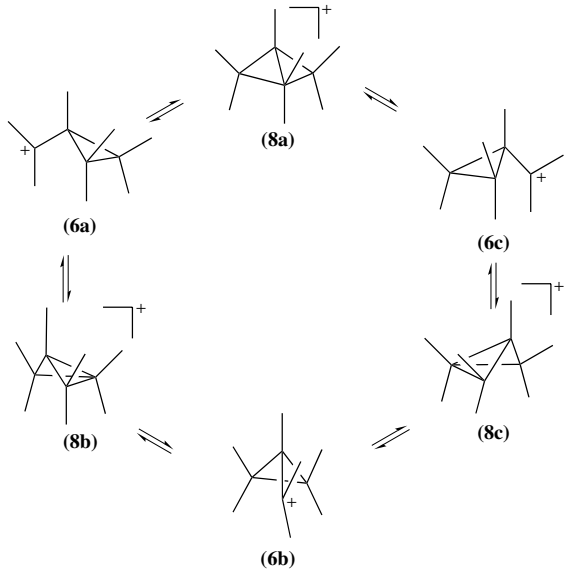
Experimental NMR investigations of $C_4H_7^+$ cations generated in solution as long-lived intermediates in superacid media from cyclobutyl substrates and cyclopropylmethyl substrates afforded additional insight.

Assignment of the experimental ^1H and ^{13}C NMR spectra to a single structure is not straightforward because the $C_4H_7^+$ cations are highly fluxional molecules undergoing fast rearrangements on a very flat energy surface. These give rise to averaged peaks for the three methylene carbons. No line broadening could be observed at the lowest accessible temperature in solution. The six hydrogens at the three methylene groups are averaged as two separate sets of three hydrogens, keeping the vicinal related hydrogens distinct. This indicates that the interconversion process for the parent $C_4H_7^+$ cation is stereospecific. A cyclobutyl cation structure without significant $C^{\alpha}-C^{\gamma}$ bridging was excluded as a contributor to the equilibrium of $C_4H_7^+$ cations.

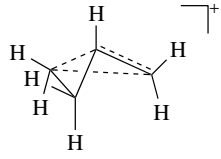
The extremely small energy differences and the flat potential energy surface in this system make it impossible to reach unambiguous conclusions concerning the actual structure on the basis of a single experimental or computational method alone. However, a fruitful combination of experimental and computational methods finally helped to resolve the controversial questions regarding the structure of the $C_4H_7^+$ cation system: These involve the analysis of the temperature dependence observed for the ^{13}C NMR chemical shifts in solution[7,8], solid state ^{13}C CPMAS NMR spectra at cryogenic temperatures as low as 5 K[9], the size and sign of equilibrium isotope effects observed in NMR spectra of CHD- and CD_2-methylene labeled $C_4H_6D_1^+$, $C_4H_5D_2^+$[8] and $C_4H_4D_3^+$[10] cations and quantum chemical calculations of energies, geometries, vibrational frequencies[11] and IGLO and GIAO computed chemical shifts[12,13].

The parent system $C_4H_7^+$ is now best described as a degenerate set of rapidly interconverting symmetric bicyclobutonium ions (**8**) with minor contributions from a set of degenerate, rapidly equilibrating cyclopropylmethyl cations **6** which are only marginally higher in energy.

A set of three symmetric bicyclobutonium ions **8a**, **8b** and **8c** interconverting via a set of three cyclopropylmethyl cations **6a**, **6b** and **6c** accounts for the rapid averaging of the methylene carbons observed in solution-state NMR studies.



Other structural representations with different symmetries have been suggested for hypercoordinated cyclobutyl cations. The so-called unsymmetrical parent bicyclobutonium ion **11** has recently been suggested again to be an important contributor in the equilibrium of $C_4H_7^+$ cations[14].



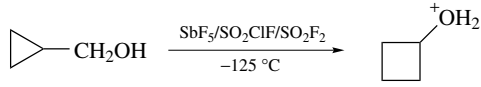
(11)

The computational results, however, were obtained using DFT methods and the B3LYP functional and are in contrast to calculations done at high level of electron correlation, including MP4 and CCSD calculations. The study reports differential solvent effects for different cyclic isomers of $C_4H_7^+$ cations which are, however, rather small. DFT and MP2 methods have also been used to investigate solvent-cation complexes of unsymmetrical bicyclobutonium cations embedded in a bicyclo[3.1.1]heptyl framework[15,16].

The interpretation of experimental results on deuterium equilibrium isotope effects (EIE) on NMR spectra of $C_4H_7^+$ cations is in accord with the major species having a bridged symmetric bicyclobutonium structure and gives no evidence for an unsymmetrical bicyclobutonium ion. The splitting pattern of $C_4H_7^+$ cations mono- or dilabeled with deuterium in the methylene groups shows that the equilibration process is between two

different sites, one singly and one doubly populated. The singly populated site is attributed to the pentacoordinated C^{γ} carbon. The bond to the *exo*-hydrogen on the pentacoordinated carbon has a larger force constant than the bond to the *exo*-hydrogens at the tetracoordinated carbons. The force constant of the *endo*-hydrogen bond on the pentacoordinated carbons is lower than those of the *endo*-hydrogen bonds at the tetracoordinated carbons. This gives rise to two isotope effects different in sign and magnitude for the sterically distinct *exo*-D and *endo*-D CHD-deuteriated $C_4H_6D_1^+$ cations. The experimental isotope effect results in deuteriated $C_4H_7^+$ cations, in full agreement with theoretical calculations of EIE for bicyclobutonium ions using *ab initio* force constants[17].

When cyclopropylmethanol **12** is reacted with SbF_5 at low temperatures under carefully controlled conditions, a protonated cyclobutyloxonium ion **13** is observed which cleaves off H_2O only at higher temperatures, to yield the $C_4H_7^+$ cation.

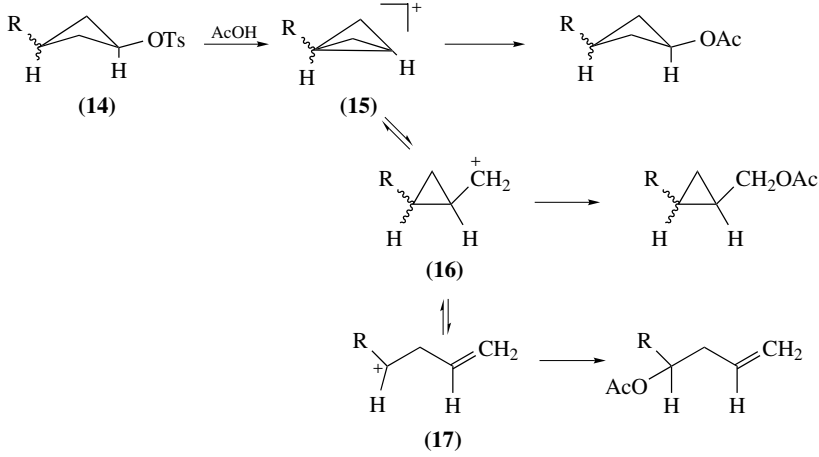


(12) **(13)**

III. SUBSTITUTED CYCLOBUTYL CARBOCATIONS

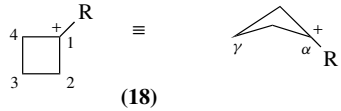
The structure and stability of substituted cyclobutyl cations depends on the nature and the position of the substituent.

Separating transition state effects and product-forming effects is a common problem in the interpretation of substituent effects in solvolysis reactions. An investigation of the acetolyses of 3-substituted cyclobutyl tosylates **14** accompanied by quantum chemical MO calculations at the MP2/6-31G(d) theoretical level indicated that the formation of the transition state which has essentially a bridged cyclobutyl cation structure **15** (bicyclobutonium ion) is the rate-determining step, and that only after this step rearrangements to cyclopropylmethyl and homoallyl ions **16** and **17** take place[17].



(14) **(15)** **(16)** **(17)**

1-Substituted cyclobutyl cations $1\text{-}RC_4H_6^+$ may have the structure of a tricoordinated cyclobutyl cation **18** or a bicyclobutonium ion structure **19** with a pentacoordinated $C\gamma$ carbon.



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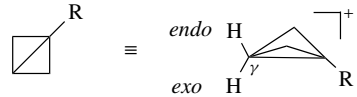
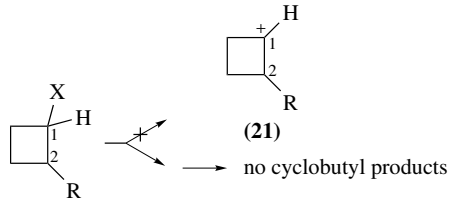


(19)

2-Substituted cyclobutyl substrates **20** generally give only cyclopropylmethyl derivatives in solvolysis and deamination reactions[18]. Thus 2-substituted cyclobutyl cations **21** have not been considered as short-lived intermediates and also could not be generated in superacid media[19].



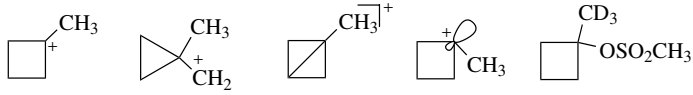
(21)

no cyclobutyl products

(20)

IV. NMR SPECTROSCOPIC AND COMPUTATIONAL INVESTIGATIONS OF SUBSTITUTED CYCLOBUTYL CATIONS

The dominant structure in the dynamic equilibrium of the 1-methylcyclobutyl/1-methylcyclopropylmethyl cation 1-$CH_3C_4H_6^+$ has been in dispute for a long time[7b, 20, 21]. 1-Methylcyclobutyl- (**22**), 1′-methylcyclopropylmethyl- (**23**) and 1-methylbicyclobutonium cation (**24**) structures have been suggested.

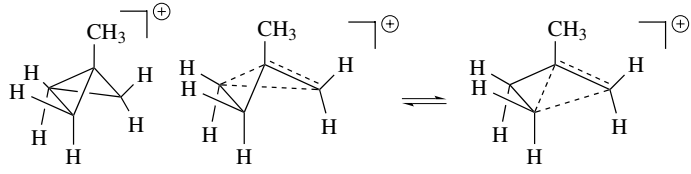


(22) **(23)** **(24)** **(25)** **(26)**

The reduced magnitude of the secondary deuterium isotope effects in the solvolysis of 1-CD_3-cyclobutyl methanesulfonate **26** was suggested to originate from a transition state structurally closely related to an intermediate 1-methylbicyclobutonium ion (**24**-CD_3)[22].

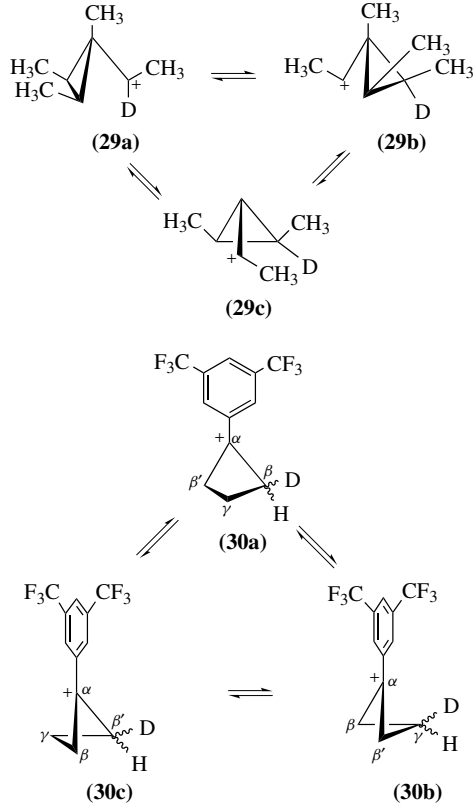
On the basis of ^{13}C NMR spectroscopic studies two different structures have been suggested, an sp^3-hybridized cyclobutyl cation **25** and a bicyclobutonium **24**, considered to be either a single minimum **27** or a set of fast equilibrating less symmetric cations **28a** and **28b** claimed to be indistinguishable from a symmetric one[20c, 21].

Further experimental NMR studies and quantum chemical calculations showed that the 1-methylcyclobutyl cation 1-$CH_3C_4H_6^+$ is best described similarly to the parent $C_4H_7^+$ cation **8** as a symmetric bicyclobutonium ion **27**, undergoing a fast threefold degenerate methylene rearrangement leading to averaged methylene carbon signals. However, contrary



(27) **(28a)** **(28b)**

to the parent cation the corresponding isomeric cyclopropylmethyl cation structure **23** is calculated to be a transition structure and does not contribute to the averaged chemical shifts. Equilibrium isotope effects (EIE) on 1-$CH_3C_4H_6^+$ cations, mono- or dideuteriated[23] at one methylene carbon, were measured by ^{13}C and ^1H NMR spectroscopy[24]. A comparison with the isotope effects and the intensity/shift ratio in slow exchange ^{13}C NMR spectra of methine C(CH_3)D-deuteriated β,β',1-trimethylcyclopropylcarbinyl cations **29a**, **29b**, **29c** and methylene CDH-deuteriated-1-phenylcyclobutyl cations **30a**, **30b**, **30c** and the EIEs in the methylene CHD-deuteriated parent bicyclobutonium ion proves that $C_4H_6CH_3^+$ has the symmetric methylbicyclobutonium ion structure **27**[25].

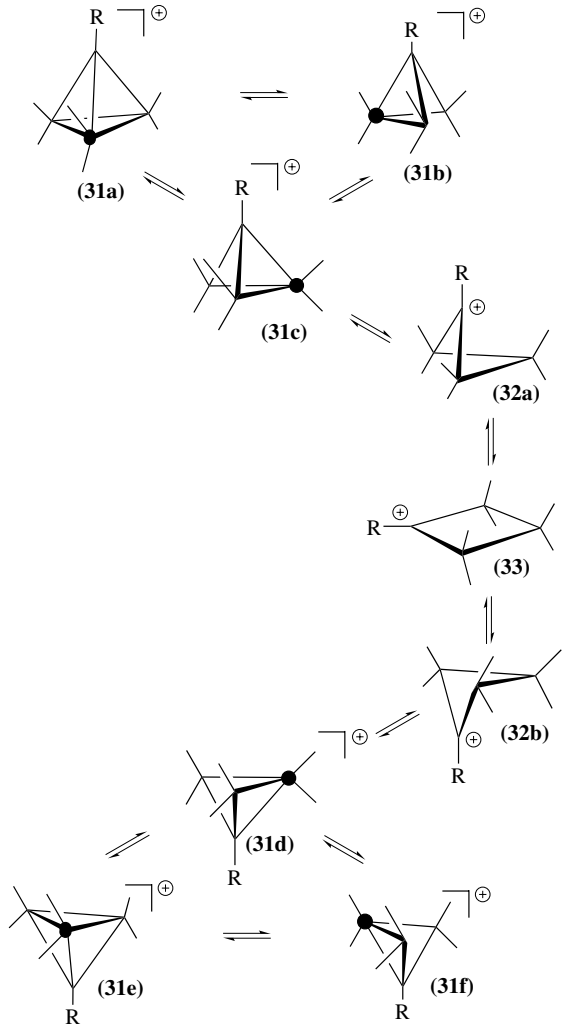


(29a) **(29b)** **(29c)**

(30a) **(30c)** **(30b)**

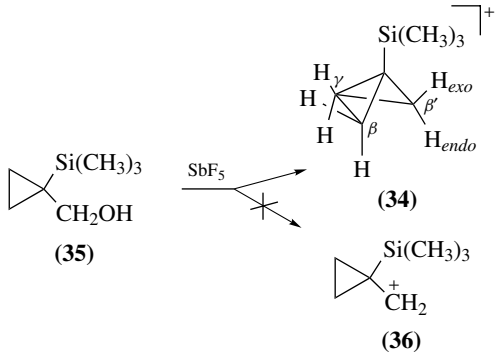
Contrary to the parent system, the 1-methylbicyclobutonium cation **27** undergoes a ring inversion process via a planar cyclobutyl cation transition state averaging the vicinal

related *exo*- and *endo*-hydrogens at the methylene groups. Therefore, in contrast to the parent ion **8** only averaged isotope effects for *endo*- and *exo*-C(H)D methylene groups are observable in **27**. At −153 °C, the equilibrium averaging the methylene groups in **27** is frozen out. EIEs are no longer observable. The averaged ^{13}C NMR signal for the three methylene carbons is separated into two broad peaks in 2:1 ratio at *ca* 71 and −3 ppm. In the course of this conformational averaging, bridged 1-methylbicyclobutonium ion structures **31a**, **31b** and **31c** (R = CH_3) change to a puckered 1-methylcyclobutyl cation **32a** (R = CH_3) which undergoes ring inversion via a planar 1-methylcyclobutyl structure **33** (R = CH_3) and another puckered 1-methylcyclobutyl cation structure **32b** to form a set of mirror images **31d**, **31e** and **31f** (R = CH_3) of bicyclobutonium ions.



The hypercoordinated carbon in **31a**–**31f** is symbolized as a black dot.

The 1-(trimethylsilyl)bicyclobutonium ion **34** is formed exclusively when (1′-(trimethylsilyl)cyclopropyl)methanol **35** is reacted with SbF_5. The 1′-trimethylsilylcyclopropylmethyl cation **36** is not formed.



(35) **(34)** **(36)**

The ^{13}C- and ^{1}H-NMR spectroscopic data show that **34** has a bridged puckered bicyclobutonium structure and undergoes a threefold rapid degenerate rearrangement via **31a**, **31b** and **31c** [R = $Si(CH_3)_3$] that renders the two β- and one γ-methylene groups equivalent, leading to one averaged ^{13}C NMR signal for the CH_2 groups at 48.9 ppm. Kinetic line broadening is not observed at temperatures as low as $-130\,^{\circ}C$. This sets the upper limit for the barrier to methylene interconversion at about 4–5 kcal mol^{-1}.

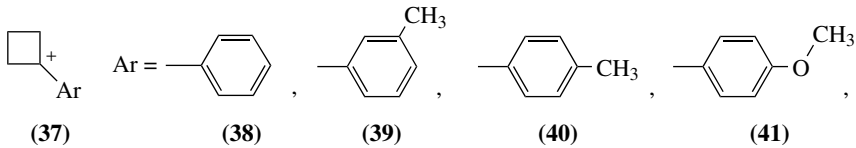
Like in the parent bicyclobutonium ion **8** [**31**, R=H] conformational ring inversion for **34** [**31**, R = $Si(CH_3)_3$] does not occur and two separate signals for the three averaged *endo*-CH_2 (4.04 ppm) and three averaged *exo*-CH_2 hydrogens (3.24 ppm) are observed. Equilibration via a planar transition structure for ring inversion [**33**, R=H or $Si(CH_3)_3$] is energetically not accessible at temperatures where these cations are stable. In the case of the 1-CH_3-substituted bicyclobutonium ion **27** (**31**, R = CH_3) the planar cyclobutyl cation structure **33** (R = CH_3) is lower in energy owing to better stabilization of the positive charge by an α-CH_3 group as compared to an α-H or α-$Si(CH_3)_3$-group. This is in accord with earlier findings that the α-trimethylsilyl group stabilizes a positive charge less than an α-methyl group but better than an α-hydrogen[26].

The deuterium EIE for *exo*- and *endo*-CHD-monolabeled cations **34**-d_1 are different in sign and magnitude and are rationalized by different *endo*- and *exo*-C−H bond force constants at the pentacoordinated carbon.

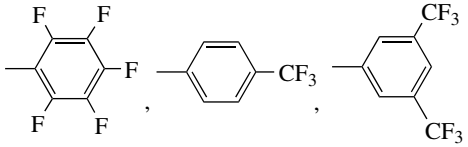
At MP2/6-31G(d) level of theory, the 1-silylcyclobutyl cation $[1\text{-}SiH_3C_4H_6]^+$ (**34**-SiH_3) which serves as a model compound for $[1\text{-}Si(CH_3)_3C_4H_6]^+$ (**34**) has a hypercoordinated puckered 1-silylbicyclobutonium structure **34**-SiH_3 which is about 2.8 kcal mol^{-1} lower in energy than the (1′-silylcyclopropyl)methyl cation (**36**-SiH_3) which is a transition state. ^{13}C NMR chemical shift calculations for the 1-silylbicyclobutonium ion **34**-SiH_3 with the GIAO-MP2 method satisfactorily reproduce the experimentally observed shifts for the 1-silylbicyclobutonium structure **34**, whereas chemical shifts calculated for the (1′-silylcyclopropyl)methyl cation **36**-SiH_3 are not in accord with the experimental data for **34**. The good agreement between calculated and experimental chemical shifts supports a threefold degenerate set of interconverting 1-(trimethylsilyl)bicyclobutonium ions **34** and excludes contributions from other isomers to the observed equilibrium process. The geometric and electronic properties of the 1-(trimethylsilyl)bicyclobutonium cation **34** are intermediate between those of the parent bicyclobutonium ion **8** and the methyl substituted bicyclobutonium ion **27**.

1-Aryl substituted cyclobutyl cations **37** have been investigated by ^{13}C NMR spectroscopy[27].

The electron demand of cations **37** has been varied by choosing different substituents at the aryl ring (**38**–**44**).

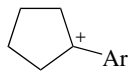


(37) **(38)** **(39)** **(40)** **(41)**



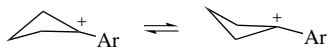
(42) **(43)** **(44)**

A linear correlation of the ^{13}C NMR chemical shift of the cationic carbon C^{α} of **38**–**44** with the shift of C^{α} in analogously substituted 1-arylcyclopentyl cations **45** was observed. This indicates that 1-arylcyclobutyl cations **38**–**44** are benzylic-type cations, structurally similar to other 1-arylcycloalkyl cations, and that contrary to 1-H-,1-alkyl- and 1-silyl-substituted cyclobutyl cations **8**, **27** and **34**, bicyclobutonium ion structures, i.e. transannular bridging and hypercoordination, do not contribute to stabilization of the positive charge in 1-aryl substituted cyclobutyl cations **37**.



(45)

The cyclobutyl cations **38**–**41** with electron-donating aryl substituents as well as the pentafluoroaryl-substituted cation **42** are static over the temperature range studied (0 to −140 °C). In **42**, the *ortho*- and *para*-fluorine atoms, besides their inductive electron-withdrawing ability, also delocalize charge through resonance interaction with the nonbonded electron pair. A conformational equilibrium of type **37a/37b** has no effect on the ^{13}C NMR spectra of **38**–**44**.

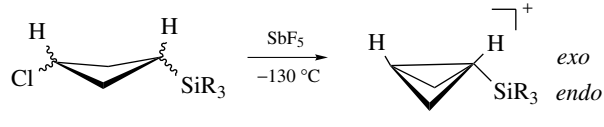


(37a) **(37b)**

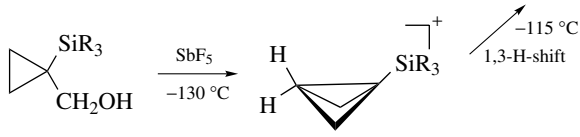
The (4-trifluoromethylphenyl)cyclobutyl cation **43** and the 3,5-bis(trifluoromethylphenyl)cyclobutyl cation **44** show dynamic line broadening in the ^{13}C NMR spectra. The β,β'- and γ-methylene carbon signals are averaged by a cyclobutyl–cyclopropylmethyl–cyclobutyl rearrangement process (analogous to that shown for **30a**, **30b** and **30c**). The corresponding 1′-substituted cyclopropylmethyl cation isomer does not contribute to the averaged chemical shifts, therefore it is unpopulated in the Boltzman distribution. The barriers for the equilibrating processes were estimated from the coalescence temperatures and

were found to be $\Delta G^{\#}$ (203 K) = 8.8 kcal mol^{-1} for **43** and $\Delta G^{\#}$ (173 K) = 7.4 kcal mol^{-1} for **44**.

Endo-3-silyl-substituted bicyclobutonium ions **46** is directly accessible by ionization of 3-(trimethylsilyl)cyclobutyl chloride **47** with SbF_5. An indirect route to **46** was via a rearrangement from 1′-trialkylsilylcyclopropylmethanol **48**. Ionization of **48** at low temperatures led to formation of the 1-trialkylsilyl bicyclobutonium cation **49**. Sterically bulky alkyl groups at silicon prevent cleavage of the silyl group at higher temperatures. Controlled warming up to −115 °C led to clean formation of the *endo*-3-silyl-substituted bicyclobutonium ions **46**. The rearrangement **49** → **46** was suggested to occur by a 1,3-hydride shift[19, 28].



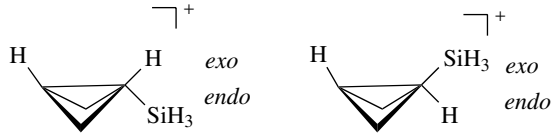
(47) **(46)**



(48) **(49)**

The 3-*endo*-(*tert*-butyldimethylsilyl)bicyclobutonium ion **46** (R_3 = Me_2Bu-*t*) is the first static bicyclobutonium ion. The 1D and 2D NMR spectra of this carbocation are a direct proof for the hypercoordinated and puckered structure of bicyclobutonium ions.

The model structure 3-*endo*-silylbicyclobutonium ion **50** calculated at MP2/6-31G(d) level of theory is an energy minimum, being 7.9 kcal mol^{-1} lower in energy than the 3-*exo*-silylbicyclobutonium ion **51** which is characterized by frequency calculations as a transition state.



(50) **(51)**

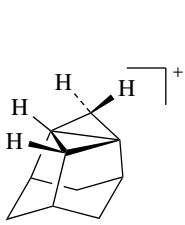
The *endo* conformation for the observed bicyclobutonium cation **46** was confirmed by comparison of the measured ^{13}C NMR chemical shifts with calculated chemical shifts (GIAO-MP2/tzpdz) of the model structures **50** and **51**.

The assignment was also confirmed by FPT (Perdew/IGLO-III) calculation of the transannular ^3J(H,H) spin−spin coupling constant, which is 5.5 Hz measured experimentally and 5.9 Hz calculated for the *endo*-silyl isomer **50**, but is only 1.2 Hz calculated for the *exo*-silyl isomer **51**.

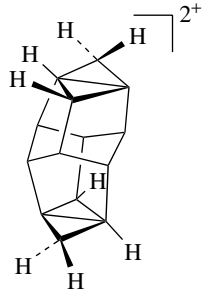
The calculated distance between the C^{α} and C^{γ} carbon in cation **50** (164.1 pm) is shorter than the C^{α}−C^{γ} distance calculated for the unsubstituted bicyclobutonium ion **8** (165.4 pm). This indicates a stronger bonding interaction between C^{α} and C^{γ} for **50**, which

is due to the stronger stabilizing interaction of the *endo*-silyl group at the C^{γ} carbon with the formally positively charged carbon C^{α} as compared to the C^{γ}-*endo*-H$-C^{\alpha}$ interaction in **8**.

Trisubstituted bicyclobutonium cations built into a polycyclic hydrocarbon were generated from polycyclic cyclopropylmethyl-type precursors by reaction with SbF_5 and were characterized by ^{13}C NMR spectroscopy and DFT calculations of structure and chemical shifts. Both the triaxanemethyl cation **52** and the 2,10-*para*-[$3^2.5^6$]octahedranedimethyl dication **53** were described as a twofold or triply degenerate set of equilibrating bicyclobutonium ions[29]. Other polycyclic cyclobutyl and bicyclobutonium ion intermediates have been investigated experimentally and computationally[30].



(52)



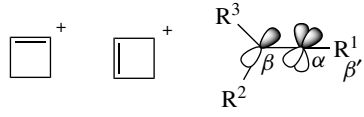
(53)

V. CYCLOBUTENYL AND CYCLOBUTADIENYL CARBOCATIONS

A. The 1-Cyclobuten-1-yl Cation

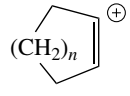
Two monocharged cyclobutenyl carbocation isomers ($C_4H_5^+$) are known: the 1-cyclobuten-1-yl cation **54** has formally a cyclic vinyl cation structure and the 1-cyclobuten-3-yl cation **55** has formally a cyclic allyl cation structure.

Cation (**54**) is formally a vinyl cation (**56**)[31] embedded in a four-membered ring. Vinyl cations have an sp-hybridized C^{α} carbon. The formally vacant p-orbital at C^{α} lies in the plane of the two substituents R^2 and R^3 at the sp^2-hybridized β-carbon, thus is perpendicular to the $C^{\alpha}-C^{\beta}$ double bond.



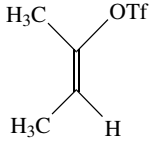
(54) **(55)** **(56)**

The vinyl cation subunit $C^{\beta}=C^{\alpha}-R^1$ prefers a linear structure. Cyclic vinyl cations (**57**) such as 5-, 6- and 7-membered-ring 1-cycloalkenyl cations (**57**, $n = 1, 2, 3$) cannot adopt a linear structure and are higher in energy than comparable linear vinyl cation structures.



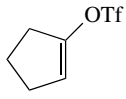
(57)

Five- to eight-membered-ring cycloalkenyl trifluormethansulfonates (triflates; -OTf) such as **59**–**62** undergo much slower heterolytic bond cleavage as compared to acyclic alkenyl triflates such as **58**, because the intermediate vinyl cations formed in the rate-determining step from the cyclic progenitors cannot adopt a linear structure. The relative solvolysis rates are given below the structures.



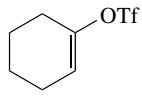
(58)

rel. k_{sol} : 1



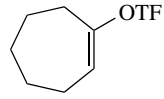
(59)

1.0×10^{-9}



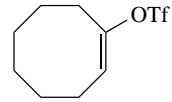
(60)

1.1×10^{-8}



(61)

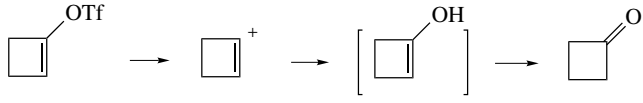
3.3×10^{-5}



(62)

5.5×10^{-4}

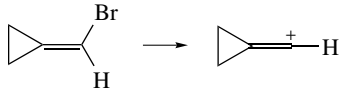
1-Cyclobutenyl triflate (**63**), however, exhibits a high solvolytic reactivity compared to 5- and 6-membered-ring homologous triflates[32]. This is attributed to the stabilization of the transition state leading the 1-cyclobutenyl cation (**54**), which is better described as a hypercoordinated cyclobuten-1-yl cation structure (**64**)[33]. Cyclobutanone (**65**) is the main product formed in the solvolysis reaction of 1-cyclobutenyl-derivatives such as **63**.



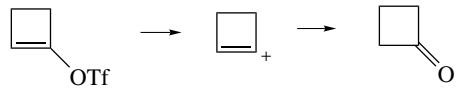
(63) **(54)** **(65)**

(64)

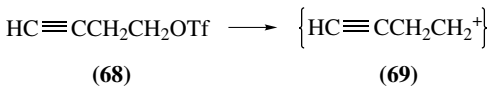
The same main product, cyclobutanone (**65**), is formed from the structural isomeric progenitors, the cyclopropylidenemethyl bromide (**66**) and the homopropargyl triflate (**68**)[34] in solvolysis reaction in aqueous solvent mixtures.



(66) **(67)**



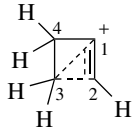
(63) **(54)** **(65)**



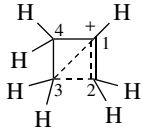
(68) **(69)**

The cyclobuten-1-yl cation (**54**) was suggested as a common intermediate in the course of the solvolysis reaction of **63**, **66** and **68**.

The cyclobuten-1-yl cation ($C_4H_5^+$) **54**, better depicted as **64**, can formally be regarded as an unsaturated analogue of an unsymmetrical bicyclobutonium ion structure ($C_4H_7^+$) (**70**).

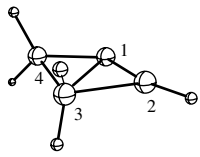


(64)

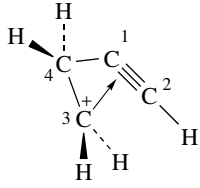


(70)

In the 1-cyclobutenyl cation, the formally vacant p-orbital at C^1 interacts in the plane of the ring with the C^2-C^3 bond. This results in a planar bicyclic structure **71**, where C^3 is pentacoordinated. According to quantum chemical calculations, the cyclobutyl ring is heavily distorted[35]. The transannular distance C^1-C^3 is 1.69 Å. The C^2-C^3 distance (1.74 Å) is very long for a formal single bond. The C^1-C^2 double bond is short (1.26 Å). An alternative but equivalent way of representing the 1-cyclobutenyl cation structure is a π-complex of a primary carbocation with the terminal triple bond, which is a heavily distorted homopropargyl cation **72**.



(71)



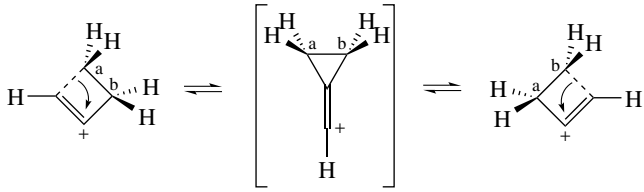
(72)

In collision-activated mass spectroscopy, 1-cyclobutenyl cations (**54**) are formed from the corresponding 4-ring precursor as well as from cyclopropylidenemethyl and homopropargyl compounds similar to those observed in the solvolysis reactions of **63**, **66** and **68** in solution[36].

The 1-cyclobutenyl cation (**54**) is the lowest energy isomer of the three ($C_4H_5^+$) isomeric cation structures **54**, **67** and **69**[37]. The 1-cyclobutenyl cation **54** is calculated to be 5.1 kcal mol^{-1} more stable than cyclopropylidenemethyl cation **67**. The homopropargyl cation (**69**) is 25.2 kcal mol^{-1} higher in energy than **54** as determined both from computations and from gas phase experimental studies. One experimental gas phase study reported a metastable peak indicating the cyclopropylidenemethyl cation **67** to be a stable species[38]. However, quantum chemical calculations with inclusion of electron correlation indicates that **67** is not a stable structure but a transition state[39].

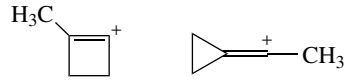
Similar to the cyclobutyl/cyclopropylmethyl rearrangement, which equilibrates the three methylene groups in bicyclobutonium cations **8a**, **8b** and **8c** via cyclopropylmethyl cations **6a**, **6b** and **6c**, the cyclopropylidenemethyl cation **67** is a transition state structure for scrambling of the two methylene groups (a and b) in 1-cyclobutenyl cations **54A** and **54B**.

The 1-methyl substituted 1-cyclobutenyl cation **73** is still somewhat more stable than the isomeric cation **74**, but the relative energy difference is very much reduced (E = 0.9 kcal mol^{-1}) compared to the parent structures **54** and **67**. The 1-methyl substituted



(54A) **(67)** **(54B)**

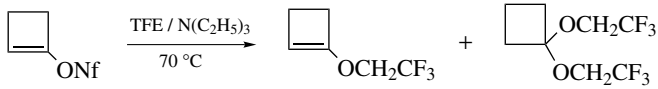
cyclopropylidenemethyl cation **74** is calculated to be an energy minimum. The preference of **73** over **74** is consistent with the fact that the major solvolysis product of corresponding precursors in aqueous solvent mixtures is 2-methylcyclobutanone.



(73) **(74)**

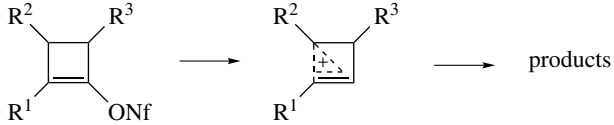
The solvolysis reaction of homopropargyl compounds such as **68** leads to appreciable amounts of four-membered-ring products.

The nonafluorobutanesulfonate group ('nonaflate'; $CF_3(CF_2)_3SO_2O$; 'ONf') is a very good leaving group and has been widely used to investigate the solvolysis reactions proceeding via 1-cyclobutenyl cations. 1-Cyclobutenyl nonaflate (**75**) solvolyses in the highly ionizing and slightly nucleophilic solvent 2,2,2-trifluoroethanol (TFE) with a high rate via an S_N1 mechanism with the formation of only four-membered-ring products **76** and **77**[40,41].



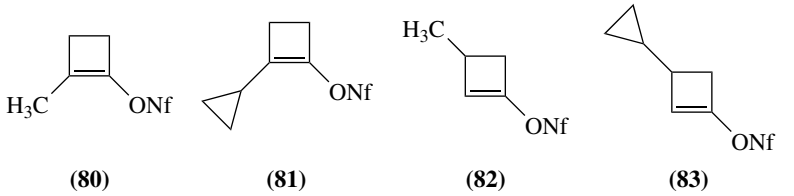
(75) **(76)** **(77)**

Systematic solvolytic studies of substituted 1-cyclobutenyl nonaflates (**78**) were performed using 2-, 3- and 4-substituted cyclobutenyl derivatives as well as bicyclic cyclobutenyl nonaflates **80**–**92**.

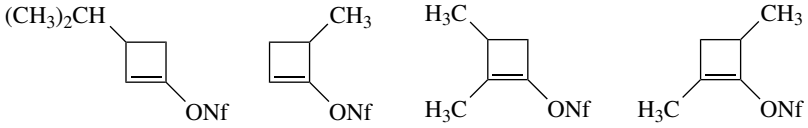


(78) **(79)**

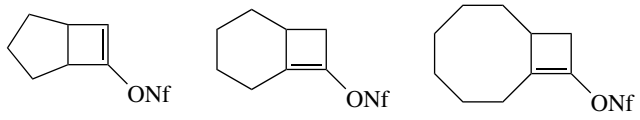
The kinetics of the solvolysis reactions of 2-, 3- and 4-substituted nonaflates **80**–**87** indicate that the rate is strongly dependent on the substituent pattern of the cyclobutenyl system. The substituent effects on the rates and the product ratios are in accord with the hypercoordinated structure **79** of the intermediate 1-cyclobutenyl cations with partial positive charge at C^2 and C^3. For the solvolysis of the bicyclic nonaflates **88**–**92**, the



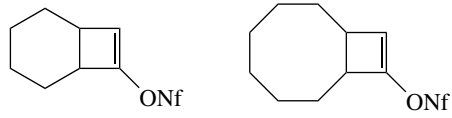
(80) **(81)** **(82)** **(83)**



(84) **(85)** **(86)** **(87)**



(88) **(89)** **(90)**



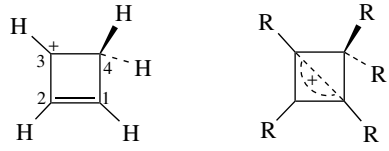
(91) **(92)**

reaction rate and the ratio of unrearranged and rearranged products vary characteristically with the substitution pattern and ring strain of the intermediate vinyl cations[42, 43].

The formation of 1-cyclobutenyl cations in the course of the homopropargyl rearrangement has been extensively reviewed[34, 44].

B. The 1-Cyclobuten-3-yl Cation

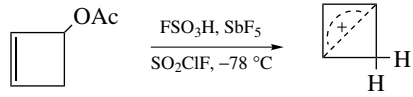
Two isomeric monocharged four-membered ring unsaturated carbocation isomers are found on the $C_4H_5^+$ potential energy surface, the vinylcation structure **54** and the 1-cyclobuten-3-yl cation (**55**), which formally has a cyclic allyl cation structure.



(55) **(93)**

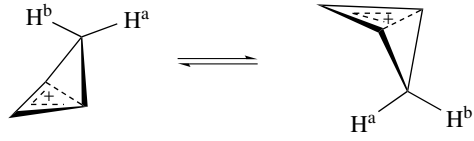
Various alkyl-, phenyl and halogen-substituted 1-cyclobuten-3-yl cations **93** have been generated at low temperatures in solution[45, 46] and have been characterized by physical methods, in particular by NMR spectroscopy[47].

The parent 1-cyclobuten-3-yl cation **95** can be generated from the corresponding acetate **94** with superacids at low temperatures in solution.



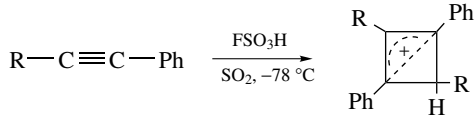
(94) **(95)**

The experimental ^{1}H and ^{13}C NMR data are consistent with a highly delocalized structure. The methylene protons H^a/H^b give rise to one averaged signal in the ^{1}H NMR spectrum at temperatures above *ca* $-80\,^{\circ}C$. At lower temperatures, coalescence and splitting of two separate peaks is observed. Line shape analysis leads to a barrier of 8.4 kcal mol^{-1} for this process. This barrier has been attributed to the ring inversion process of puckered 1-cyclobuten-3-yl cation structures **95a** and **95b**.



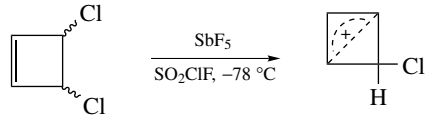
(95a) **(95b)**

Alkyl- and aryl-substituted 1-cyclobuten-3-yl cations **97** can be generated by dimerisation of the correspondingly substituted alkynes **96** in superacids.



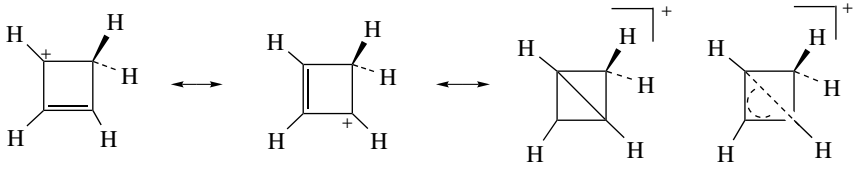
(96) **(97)**

Chloro-substituted 1-cyclobuten-3-yl cation **99** was prepared from dichloro-substituted cyclobutenes **98**.



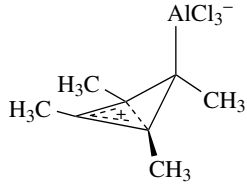
(98) **(99)**

The 1-cyclobuten-3-yl cation, **55**, owes its stability to homoaromaticity[48]. A cross-ring orbital interaction, with a C^1-C^3 distance considerably longer than a single C–C bond, and bond lengths between the CH groups which are similar to those in the allyl cation are the characteristic features. In valence bond theory representation, cation **55** can be depicted as a hybrid of resonance limiting structures **55a** ↔ **55b** ↔ **55c**; the corresponding dotted line formula is **95**.



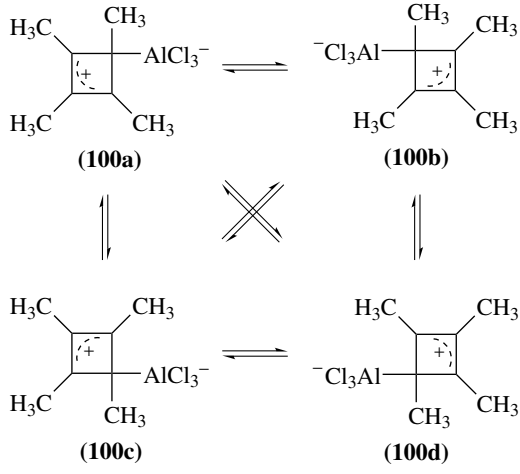
(55a) **(55b)** **(55c)** **(95)**

The $AlCl_3$ complex of tetramethylcyclobutadiene **100** is an intermediate in the trimerisation of but-2-yne to yield hexamethyl-Dewar-benzene. The crystal structure of **100** shows a nonplanar 1-cyclobuten-3-yl cation moiety with a puckering angle of 149° and a relatively short 1,3-distance, indicating significant transannular interaction in agreement with the concept of homoaromaticity of a homocyclopropenylium cation. The aluminum chloride is coordinated via a σ-aluminum carbon bond (1.979 Å). The bond length pattern of the C−C bonds indicates charge dislocation within the four-membered ring[49].



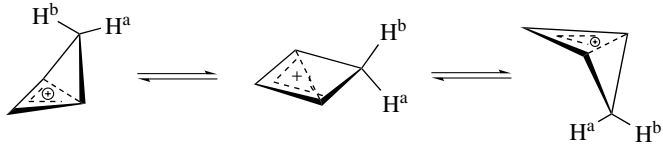
(100)

In solution, substituted cyclobuten-3-yl cation $AlCl_3$-σ-complexes such as **100** show dynamic processes, which have been investigated by ^1H NMR spectroscopic techniques and found to consist predominantly, if not exclusively, of consecutive 1, 2 shifts of the $AlCl_3$ group in cations **100a**, **100b**, **100c** and **100d**[50].



(100a) **(100b)** **(100c)** **(100d)**

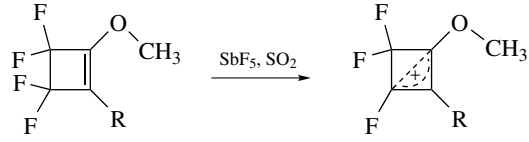
The 1-cyclobuten-3-yl cation **95** has been the subject of numerous theoretical studies[51]. Recent extensive computational studies have applied correlated wave functions to study the stability and the proton-donating power of **95**, the planar structure **101** and the inversion barrier **95a** → **101** → **95b**[52–55], also called homoaromatization energy. The ring inversion barrier for the parent 1-cyclobuten-3-yl-cation **95**[56], determined experimentally by ^{1}H NMR spectroscopy, could be reproduced by quantum chemical calculations when sufficient electron correlation was taken into account.



(95a) **(101)** **(95b)**

The best quantum chemical description of the 1-cyclobuten-3-yl cation **95** was achieved with a combination of the 6-311G(d,p) basis set, geometries optimized at the MP2 or MP4(SDQ) level, MP2 calculated ZPE effects, and a correlation method that handles triple excitation in a balanced way, e.g. CCSD(T). Calculated NMR chemical shifts verify the nonequivalence of the CH_2 protons, and indicate that the assignments of the experimental shifts of H^a and H^b in **95** may have been reversed. The experimental ^{13}C NMR chemical shifts of the 1-cyclobuten-3-yl-cation **95** are reproduced using the GIAO-MP2 method and DZP and TZP basis sets and the MP2(full)/6-311G(d,p) geometry within 3–5 ppm, while using an MP4(SDQ)/6-31G(d) geometry the agreement is within 1.9 ppm.

1-Methoxy-2-*R*-3,4,4-trifluorocyclobuten-3-yl cations **103** have been prepared from **102** and studied by ^{1}H and ^{19}F NMR spectroscopies. The hexafluoroantimonate salts of **103** are isolable solids, which are stable at room temperature. In solution, each cation exists as an equilibrating pair of isomers, which differ only by the 1-methoxy group conformation. The barrier to rotation of the methoxy group was determined for various R groups to be 15–16 kcal mol^{-1} [57].



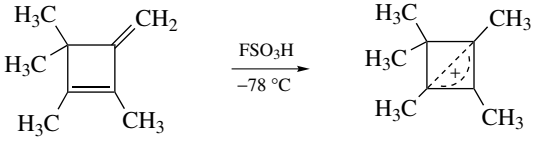
(102) **(103)**

The energy barrier for the ring inversion in substituted 1-cyclobuten-3-yl cations **93** is dependent on the substitution pattern of the four-membered ring and the ability of the substituents to stabilize positive charge.

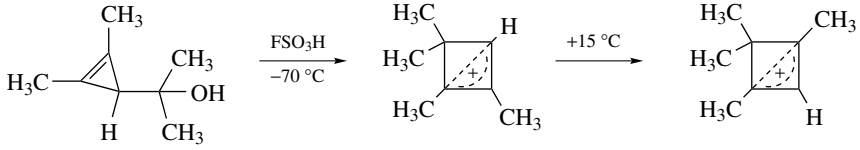
The 1,2,3,4,4-pentamethylcyclobuten-3-yl **104** and 1,2,4,4-tetramethylcyclobuten-3-yl **106** cations were obtained by reaction of HSO_3F with the corresponding precursors **107** and **108** at −70 °C. 1,3,4,4-Tetramethylcyclobutenyl cation **105** was obtained from **106** via rearrangement at +15 °C[46e,58].

For cation **106** at −142 °C, slow exchange conditions were reached and separate signals for the 4-Me and 4′-Me groups were observed. The experimental energy barrier for ring inversion of **106** was determined as $\Delta G^{\#} = 5.6$ kcal mol^{-1}.

An unusually strong temperature dependence over a range of *ca* 120 °C for the ^{13}C NMR chemical shifts of the signal for the C^1/C^3 carbons of the carbocation **104**–**106**

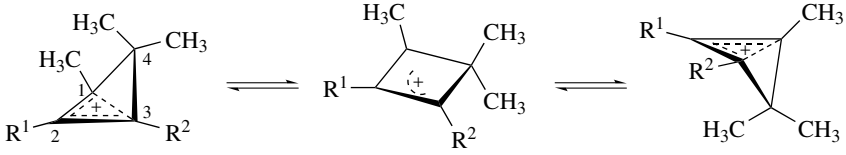


(107) **(104)**



(108) **(106)** **(105)**

was observed[59]. The shift of the other carbon signals remains almost constant between −100 and +20 °C. The temperature dependence is most pronounced for the C^1/C^3 signal of **105** (0.071 ppm K^{-1}), intermediate for **104** (0.048 ppm K^{-1}) and less pronounced for **106** (0.016 ppm K^{-1}).



(104a–106a) **(104-TS–106-TS)** **(104b–106b)**

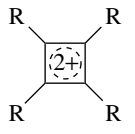
(104) $R^1 = R^2 = CH_3$
(105) $R^1 = H$, $R^2 = CH_3$
(106) $R^1 = CH_3$, $R^2 = H$

The calculated barrier for ring inversion decreases significantly on going from **106** to **104** to **105**. The planar structures **104-TS–106-TS** are transitions states. Thus the temperature dependence cannot be explained assuming a nondegenerate equilibrium process including populated structures **104-TS–106-TS**. The ring inversion is a degenerate process between two equally populated sites **104a–106a/104b–106b**. The energy levels of an oscillator with such a potential with two symmetric shallow minima are very close, so that even at low temperatures higher vibrational states, including those situated above the energy barrier, are populated. The potential wells of such an anharmonic oscillator are highly asymmetric. At high energy levels, greater contributions to the mean chemical shift are made by the structures which are similar to the planar transition state structures **104-TS–106-TS**. An increase in temperature leads to the occupation of higher vibrational states and, as a result, to an increase in the contribution from such structures. This influences the averaged values of chemical shifts of the C^1/C^3 positions, which are significantly different in the planar and the bent conformations. The chemical shift of C^4 is not significantly different in the puckered and the planar structure, therefore this peak position shows no significant temperature shift. This explanation suggests that the temperature dependence of the chemical shift is due to changes in the vibrational level

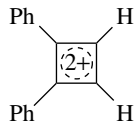
occupation and should be most pronounced for the system with the lowest ring inversion barrier. This is in accord with experiment.

C. The Cyclobutadienyl Dication

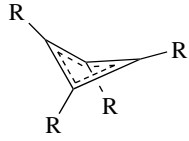
The cyclobutadienyl dication **109** is a Hückel 2π aromatic system. Numerous derivatives, such as **110** and **111**, have been characterized by NMR spectroscopy in superacid solution[60]. In contrast to the expectation that 2π electron Hückel aromatics should prefer planar geometries, *ab initio* calculations have shown the puckered structures such as **112** and **112a** to be more stable than planar structures **109** and **110**[61]. The IGLO-HF/DZ calculated ^{13}C NMR chemical shifts, computed for the puckered structure of the tetramethylcyclobutadienyl cation **112b** (209 and 18.7 ppm), are in good agreement with the experimental chemical shifts (209.7 and 18.8 ppm), whereas the chemical shifts calculated for a planar structure **110** show large deviations[62]. The puckering of four-membered 2π-electron Hückel ring systems does not lower the strong π-stabilization in these systems. The energies of the π-MOs are lowered by the orbital mixing possible in the lower symmetry and from the shorter C−C distances. The 2π systems **109** and **110** enjoy 1,3- as well as 1,2-stabilizing interactions and strive to achieve three-dimensional aromaticity[61c,63].



(109) R = H
(110) R = CH_3



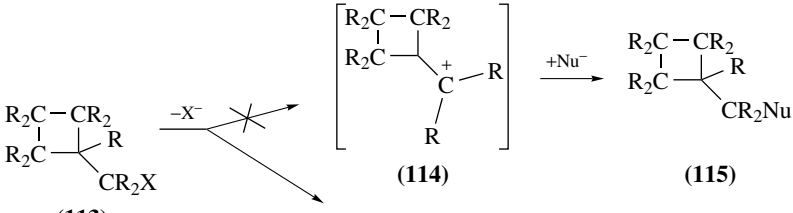
(111)



(112) R = H
(112a) R = CH_3

VI. CYCLOBUTYL-SUBSTITUTED CARBOCATIONS

Nucleophilic substitution reactions of cyclobutylmethyl substrates **113** are well documented[64]. However, cyclobutylmethyl derivatives **115**, the products of the direct reaction of a cyclobutylmethyl cation **114** with a nucleophile, were not generally observed.



(113)

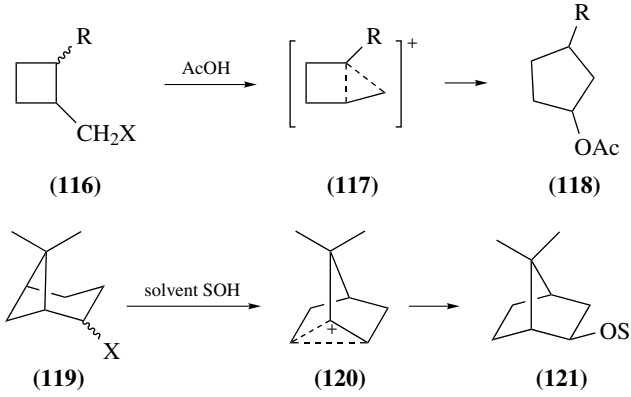
(114)

(115)

rearranged products

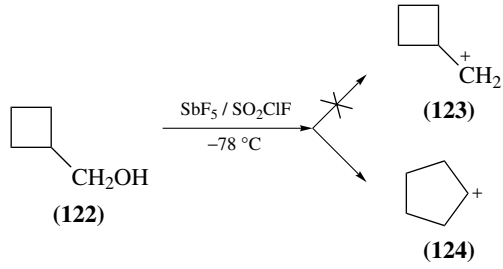
Solvolysis reactions of cyclobutylmethyl derivatives such as **116** and **119** lead to rearranged products, via ring expansion (**116** → **117** → **118**) and Wagner–Meerwein-type (**119** → **120** → **121**) rearrangement reactions.

Rate acceleration observed in kinetic studies was interpreted as anchimeric assistance of the four-membered ring in forming the transition state analogous to the intermediates **117** and **120**. Stereochemical studies of **116-Z** and **116-E** confirmed the involvement of



a transition state structurally close to the hypercoordinated carbocation intermediate such as **117** in the course of the solvolysis of cyclobutylmethyl substrates.

The ionization of cyclobutylmethyl substrates in superacidic media to form cyclobutyl substituted carbocations has been attempted[65]. Treatment of the primary alcohol **122** with the Lewis acid SbF_5 at $-78\,^{\circ}C$ did not yield the parent cyclobutylmethyl cation **123** but led to ring enlargement, and only the cyclopentyl cation **124** was observed.



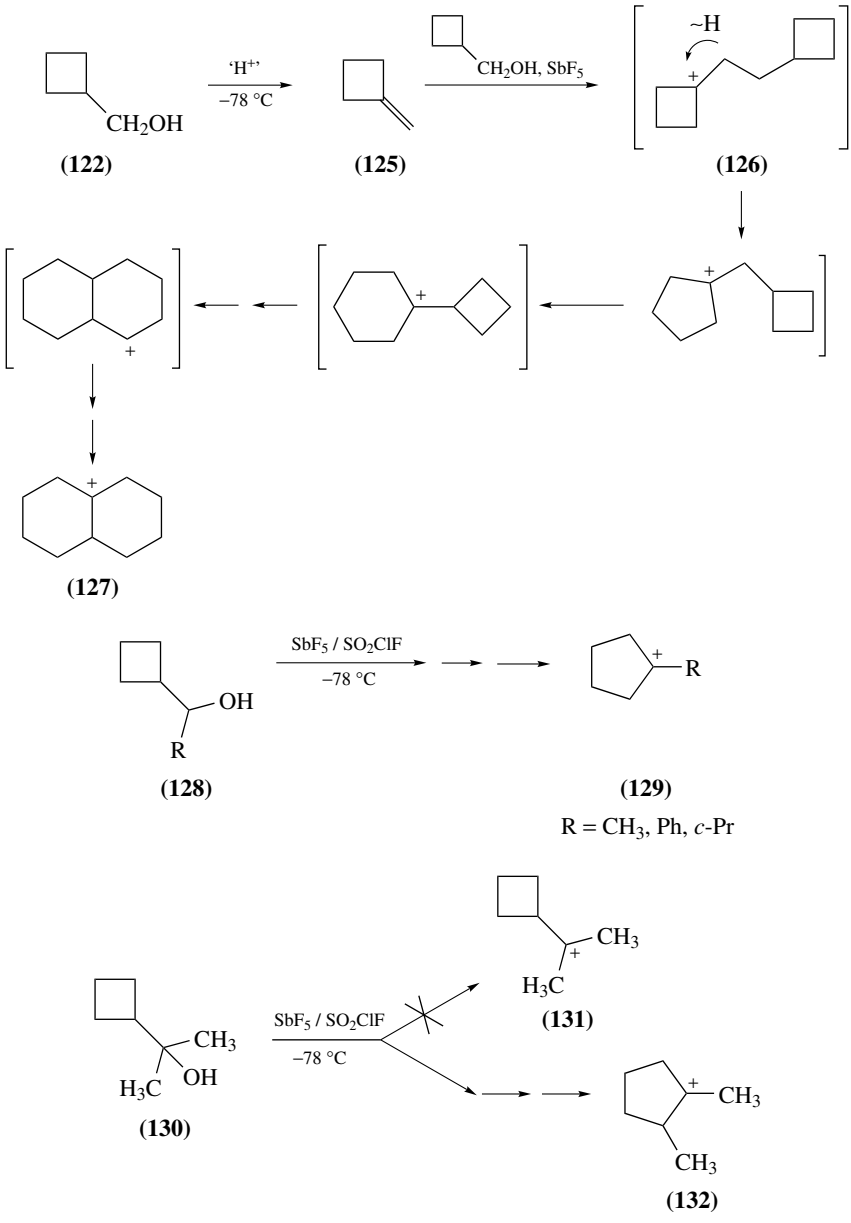
The reaction of cyclobutylmethanol **122** with a Brønsted superacid unexpectedly gave the bicyclo[4.4.0]decan-1-yl cation **127**. The reaction was suggested to occur by dehydrative dimerisation (**122** → **125** → **126**) followed by a series of Wagner–Meerwein rearrangements to yield **127**.

Secondary alcohols **128** are converted to the corresponding substituted cyclopentyl cations **129**.

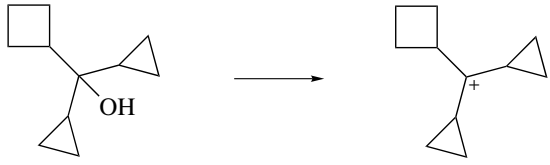
Quantum chemical calculations (B3LYP/6-31G(d)) showed the primary cyclobutylmethyl cation **123** not to be a minimum, whereas the dimethylcyclobutylmethyl cation **131**, the cyclopropylcyclobutylethyl cation **136** and the dicyclopropylcyclobutylmethyl cation **134** are stable structures at that computational level. However, the dimethylcyclobutylmethyl cation **131** could not prepared from **130** under the experimental conditions and only the ring enlarged cyclopentyl cation **132** is formed.

Cyclobutyldicyclopropylmethanol **133** on reaction with FSO_3H in SO_2ClF at $-90\,^{\circ}C$ cleanly forms the cyclobutyldicyclopropylmethyl cation **134**.

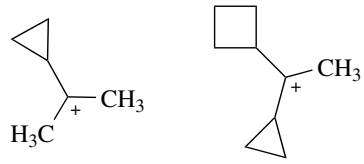
The two cyclopropyl rings in **134** are preferentially arranged in the bisected conformation. The C_s symmetric structure of cation **134** is the main species present. Quantum chemical calculations (B3LYP/6-31G(d)) and NBO charge calculations for **134** indicate that a propeller conformation allows for partial delocalization of positive charge in the



cyclobutyl and the two cyclopropyl rings. The perpendicular conformation of **134** is calculated not be a minimum at B3LYP/6-31G(d) level of theory. A barrier for rotation of the cyclopropyl rings in **134** was estimated to be 11 kcal mol^{-1} at −40 °C. This barrier is similar to that in the α,α-dimethylcyclopropylmethyl cation **135** (13 kcal mol^{-1}, −21 °C)[66].



(133) **(134)**



(135) **(136)**

Chemical shift calculations (IGLO-HF/DZ/B3LYP/6-31G(d)) for **136** gave deviations from the experimentally observed chemical shifts of +25 ppm for the C^+ carbon, −10 ppm for carbon C^1 and deviations of up to 7 ppm for the other ring carbons.

VII. CONCLUSION

Contrary to the alleged simplicity of low molecular weight structures of cyclobutyl and related carbocations reviewed in this chapter, it has been recognized that conventional bond formulas with single, double and triple bonds are inadequate to account for the structure, dynamics and properties of these (and many other) electron-deficient compounds.

The conundrum of the structures of the $C_4H_7^+$ cation has been termed a molecular will-o′-the-wisp[8]. For over half a century, this area of physical organic chemistry has triggered the development for better tools and methods. A fruitful interplay of experimental and computational methods has guided the further development of the field. NMR spectroscopy in superacid solution combined with today's state-of-the-art of quantum chemical calculations have been particularly useful. The everlasting need for better tools and methods has already given birth to new methods, such as spectroscopy on a femtosecond time scale, which allows quite direct experimental approaches towards the structures of transition states. The chemistry of hypercoordinated carbocations, such as bicyclobutonium ions, has again served as a forerunner for close integration of experimental and computational approaches applicable to all areas of chemistry.

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CHAPTER **13**

Cation radicals in the synthesis and reactions of cyclobutanes

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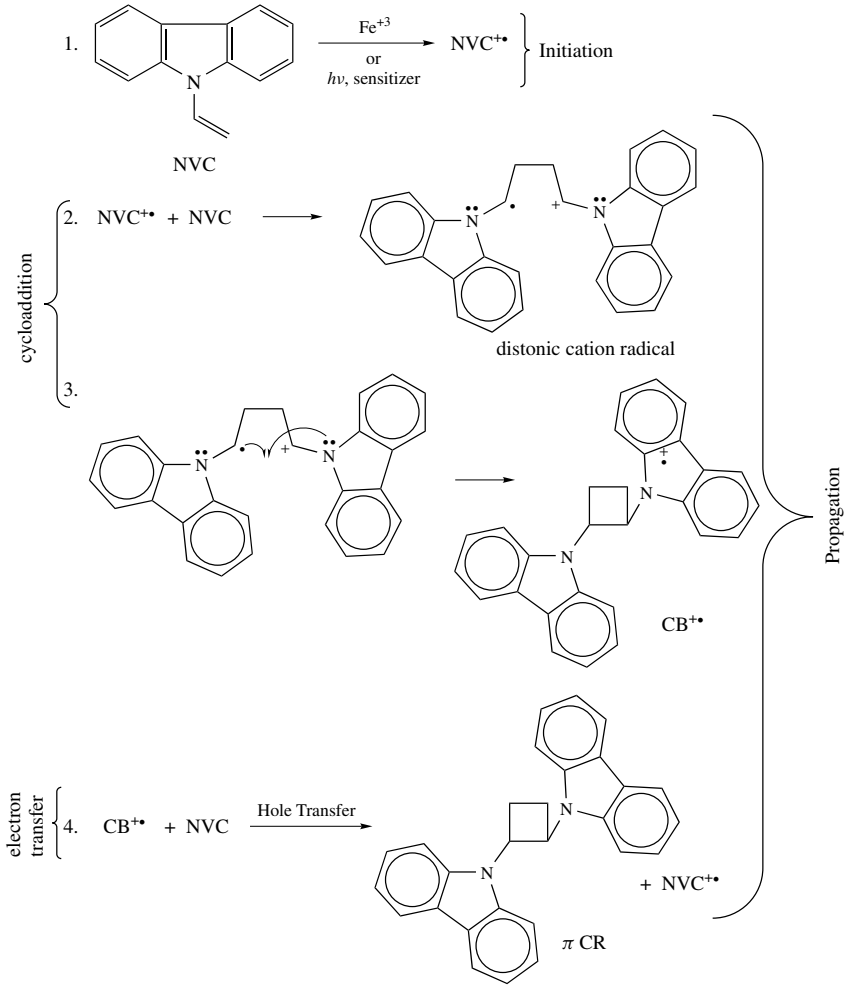
I. INTRODUCTION

Historically, the advent of synthetically useful cation radical chemistry is intimately linked to the cyclobutane structural moiety. The specific linkage is the discovery of the cation radical chain mechanism for the cyclodimerization of *N*-vinylcarbazole[1]. This work established the first example of a then completely new mechanistic type, the cation radical chain reaction, but further provided a powerful, new method for the synthesis of cyclobutane rings which has continued to expand in scope during the subsequent four decades. As a further outgrowth of the pioneering vinylcarbazole work, the general proclivity for π-type cation radicals to undergo cycloadditions of various types began to emerge and has resulted in the development of an extensive body of cation radical Diels–Alder cycloaddition chemistry as well as cyclopropanation chemistry[2].

II. HISTORICAL

The cyclodimerization of *N*-vinylcarbazole under photosensitized electron transfer (PET) conditions, using chloranil as the sensitizer, was initially observed by Ellinger[3]. The mechanism of this reaction was then extensively investigated by the Ledwith group, which found that the reaction could also be carried out using metal ion oxidants such as ferric ion. Under both PET and metal ion oxidation conditions the exclusive product is *trans*-1,2-bis(*N*-carbazolyl)cyclobutane, the cycloaddition occurring with essentially complete regiospecificity and anti diastereoselectivity. Under both chemical and photochemical conditions a relatively efficient chain process (chain lengths of 30–100) was found to operate and to be inhibited by dioxygen. The mechanism proposed by the Ledwith group is illustrated in Scheme 1. Step 1 represents the initiation step of a cation radical chain mechanism, in which the cation radical of *N*-vinylcarbazole is formed by single electron transfer (SET), to ferric ion in the chemical process or alternatively to excited state chloranil in the photosensitized process. The cycloaddition reaction (Steps 2 and 3) between this cation radical and a molecule of neutral *N*-vinylcarbazole was proposed to proceed in a stepwise fashion via a distonic cation radical intermediate (see Step 2), i.e. a cation radical in which the positive charge and the electron spin are largely or completely separated. The distonic cation radical intermediate was then envisioned as forming the second covalent bond in a discrete step (Step 3), generating the cation radical of the product, in which the cation radical moiety is assumed to move to and reside on the π-electron system of the relatively ionizable carbazole ring. A crucial part of this mechanism is the final step (Step 4) in which the product cation radical is neutralized by single electron transfer from a molecule of *N*-vinylcarbazole, regenerating another *N*-vinylcarbazole cation radical and setting up the cation radical chain. Steps 2, 3 and 4 thus constitute the propagation cycle of this cation radical chain mechanism. The propagation cycle therefore consists of alternating cycloaddition and electron (or hole) transfer stages. The term cyclobutanation is used in the present review to describe the formation of a cyclobutane ring generally, and the more specific term cyclobutadimerization[4] to describe cases in which a single type of monomer molecule undergoes cyclobutanation to yield a dimer. Hole transfer (HT) is considered to be a specific type of electron transfer (ET), in



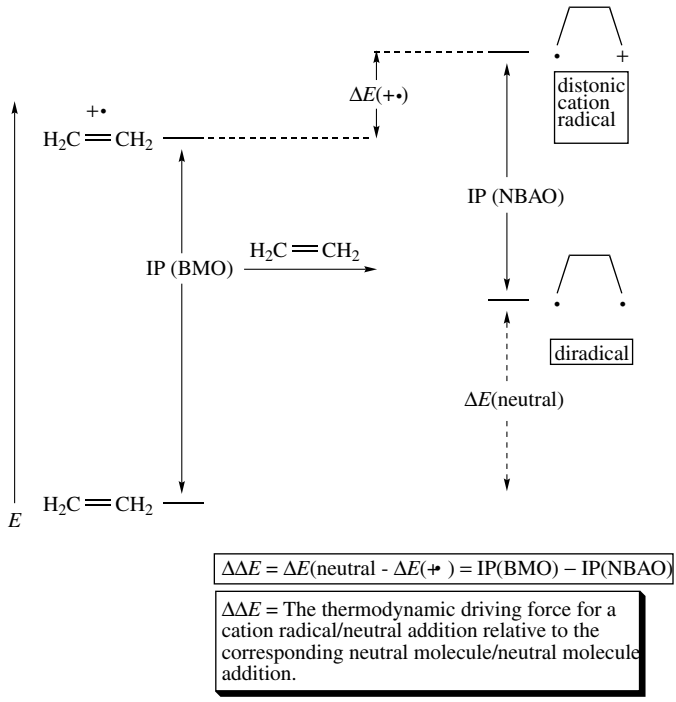
SCHEME 1. Cation radical chain mechanism for the cyclobutadimerization of *N*-vinylcarbazole

which a neutral molecule transfers an electron to a cation radical. Viewed alternatively, the hole corresponding to the cation radical is transferred to the originally neutral molecule.

III. ENERGETIC CONSIDERATIONS FOR CATION RADICAL/NEUTRAL CYCLOADDITION REACTIONS

Although concerted cycloadditions between two neutral alkene molecules are symmetry-forbidden, such reactions nevertheless can occur via stepwise mechanisms involving the formation of either diradical or zwitterionic intermediates. Stepwise additions involving diradical intermediates, in particular, typically require a large amount of activation because

the intermediate diradicals are much higher in energy than the starting alkene moieties. In contrast, the activation requirement for the addition of a cation radical to a neutral alkene moiety is not nearly so great, in part because the energy of the distonic cation radical intermediate is not so elevated relative to the starting materials (one neutral molecule plus one cation radical) as in the case of the neutral/neutral addition. These relationships are illustrated in Scheme 2, which compares the initial cycloaddition steps for the neutral/neutral and cation radical/neutral reactions of two ethene moieties. The ethene cation radical is at a much higher energy than the ethene molecule because an electron has been removed from the π-bonding molecular orbital (BMO) of ethene. The gas-phase energy required for this conversion is, of course, the ionization potential (IP) of ethene. On the product side, the distonic 1,4-butanediyl cation radical is also at a higher energy than the 1,4-butanediyl diradical by an amount equal to the ionization potential of the latter. However, this ionization potential relates to the removal of an electron from a nonbonding 2p atomic orbital on carbon (NBAO), which is much less than the ionization potential for the BMO of an alkene. Consequently, the energy change corresponding to the cation radical/neutral cycloaddition is less unfavorable than that for the neutral/neutral addition by an amount equal to this (large) difference in ionization potentials. Since the excess activation energy for reactions of positively charged (electron-deficient) species is usually relatively small, the overall activation energies for cation radical/neutral cycloadditions are typically dramatically decreased in comparison to the corresponding neutral/neutral reactions.



SCHEME 2. Energetic relationships between cation radical/neutral additions and the corresponding neutral molecule/neutral molecule reactions illustrated for the case of ethene: BMO = bonding molecular orbital; NBAO = nonbonding atomic orbital

IV. NOVEL CATION RADICAL STRUCTURES ENCOUNTERED IN CATION RADICAL/NEUTRAL CYCLOADDITIONS

In the specific context of cation radical/neutral cycloadditions, three different types of structure are most commonly encountered. The distonic cation radical, in which the positive charge and the spin are largely separated (or uncoupled), is nicely illustrated in the Ledwith mechanism for the cyclobutadimerization of *N*-vinylcarbazole. A second type is also illustrated in the Ledwith mechanism, viz. the π-type cation radical, in which the cation radical moiety is situated on a (usually delocalized) π-electron system, such as the carbazole moiety of the product. A third type, the long, one-electron bond will be illustrated in the context of the cyclobutadimerization of *trans*-anethole, which is discussed further on.

V. MECHANISTIC CONSIDERATIONS

Because the aforementioned reaction is the prototype example of a mechanism which has proved to be quite general for cation radical cyclobutanation, it appears appropriate to consider the individual steps at somewhat greater length. The initiation step is essentially a single electron transfer (SET) reaction which converts neutral *N*-vinylcarbazole to the corresponding cation radical. The relatively low oxidation potential of this particular substrate renders cation radical formation facile by a variety of methods, including both PET and chemical ionization methods. The resulting cation radical, being highly electron-deficient, is able to add to electron-rich π-bonds with great facility, in a reaction which can be loosely regarded as analogous to the addition of tetracyanoethylene to electron-rich alkenes. In addition to the generic thermodynamic facilitation of cation radical/neutral reactions previously discussed, the initial addition step of the carbazole dimerization is facilitated by the formation of a carbocation center which is highly stabilized by an adjacent electron-donating group, i.e. by the nonbonded electron pair of the nitrogen atom of the carbazole ring. In the case of cation radical cycloadditions it is also usually important for the radical site to have some degree of extra stabilization. Usually, this is provided by conjugation, such as in a benzylic or allylic type radical, but in the carbazole case this is evidently provided by three-electron bonding, involving overlap of the filled 2p AO on nitrogen with the half-filled 2p AO of the radical center. It is interesting to note that cation radical/neutral cycloadditions having rates of up to and even greater than 10^9 s^{-1} have been observed[5].

The driving force for the cyclization of the distonic cation radical to a cyclobutane cation radical (Step 3) is obviously the formation of a new carbon–carbon bond (albeit a strained cyclobutane bond), but this must be accomplished at the expense of removal of an electron from somewhere in the molecule, to form a new cation radical center. In the case of the *N*-vinylcarbazole cycloaddition, the most readily ionizable site is the *N*-carbazolyl moiety of the product. Because of the relatively low oxidation potential of the *N*-cyclobutylcarbazole moiety of the product cyclobutadimer, covalent bond formation is evidently energetically favorable and facile in this case.

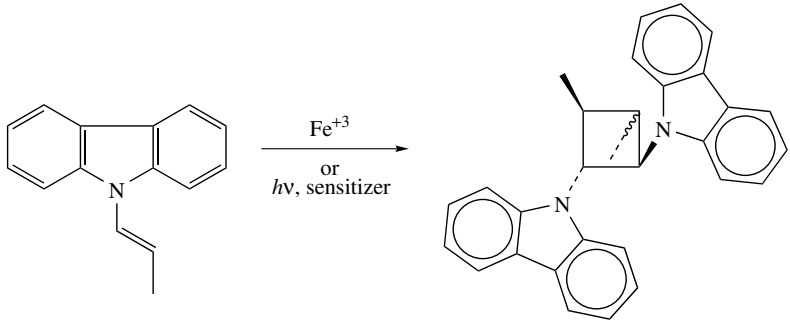
The electron transfer step (Step 4) is clearly exergonic, because the product cation radical has a less extensive conjugated system over which to delocalize the cation radical moiety than does the starting substrate. Since cycloaddition always removes a π-bond from the substrate, the exergonicity and thus rapidity of this electron transfer step is assured for virtually any cycloaddition reaction.

As a consequence of these considerations, and in view of extensive further studies of cation radical cycloadditions, it has become apparent that efficient propagation cycles

typically require both a carbocation stabilizing functionality and a radical stabilizing functionality in the distonic cation radical intermediate, along with a cation radical stabilizing moiety in the cyclobutane product. Depending upon the method of ionization, a wide range of substrates can potentially be ionized to the corresponding cation radical.

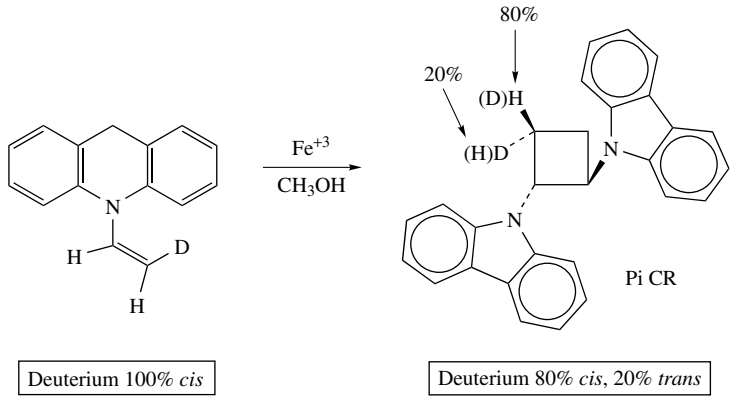
VI. STEREOCHEMISTRY OF CATION RADICAL CYCLOBUTANATION

In the pioneering work of the Ledwith group, the analogous cyclobutadimerization of *N-trans*-1-propenylcarbazole was also studied. This reaction afforded a single cyclodimer, the *trans,anti,trans* dimer shown in Scheme 3. The corresponding reaction of *N-cis*-1-propenylcarbazole failed, however, presumably as a consequence to the inability of the *cis*-propenyl group to achieve planarity with the carbazole ring. As a result of this steric prohibition of planarity, the oxidation potential of the *cis* isomer is evidently increased substantially and ionization is more difficult. It may also be the case that with a twisted *cis*-propenyl group attached to the carbazole nitrogen, the great preponderance of the cation radical moiety exists upon the aromatic ring, with little electron deficiency in the propenyl π-bond. It may be worthwhile to note that although the author's research group has subsequently observed a wide variety of efficient cation radical cycloaddition reactions of *N-trans*-1-propenylcarbazole, no cycloaddition chemistry of the cation radical of the *cis* isomer has even yet been observed. As a consequence of the failure of the *cis* isomer to undergo cyclobutadimerization, the stereochemistry of the reaction could not be determined at that time, so that the proposal of a two-step cycloaddition involving a distonic cation radical intermediate, as opposed to the possibility of a concerted cycloaddition, had no direct confirmation.



SCHEME 3. Cyclobutadimerization of *N-trans*-1-propenylcarbazole

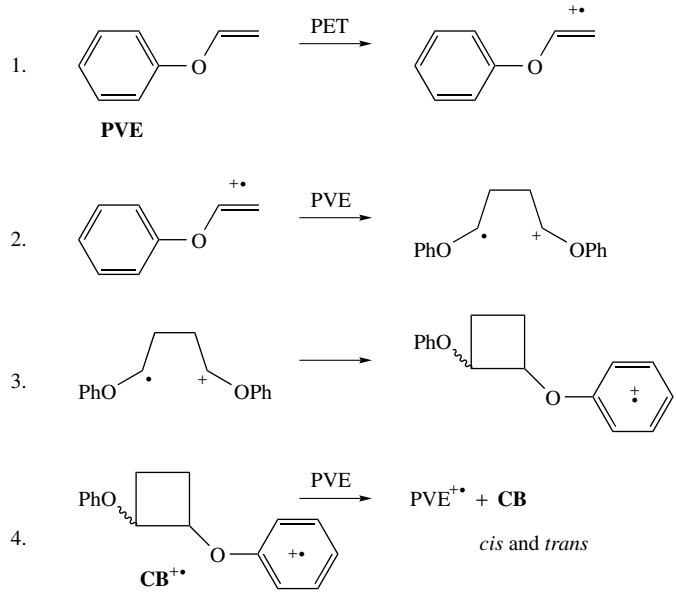
Much more recently, the author's research group has provided more direct evidence supporting the original postulate of the Ledwith group with regard to the stepwise nature of the cycloaddition[6]. The cyclobutadimerization of *N-cis*-2-deuteriovinylcarbazole was observed, under both PET and ferric ion initiation conditions, to result in extensive scrambling of the deuterium label (Scheme 4). Using both the ferric ion and PET methods of initiation, the product was observed to have 20% of the deuterium scrambled to the position *trans* to the carbazolyl moiety, under conditions where unreacted starting material was recovered stereochemically intact. These observations are inconsistent with a concerted cycloaddition mechanism, but are fully consistent with the proposed stepwise mechanism.



SCHEME 4. Stereochemistry of the cyclobutadimerization of *N*-vinylcarbazole

VII. OTHER EARLY CATION RADICAL CYCLOBUTANATION PRECEDENTS

The cyclobutadimerization of phenyl vinyl ether under photosensitized electron transfer conditions (Scheme 5) constitutes another early example of a thoroughly studied cation radical chain mechanism for cyclobutadimerization[7]. The reaction was again observed to be highly head-to-head regiospecific, but, in contrast to the cyclodimerization of *N*-vinylcarbazole, afforded a mixture of the *cis* and *trans* diastereoisomers. Further, the *cis/trans* ratio was observed to change during the course of the reaction, and this was



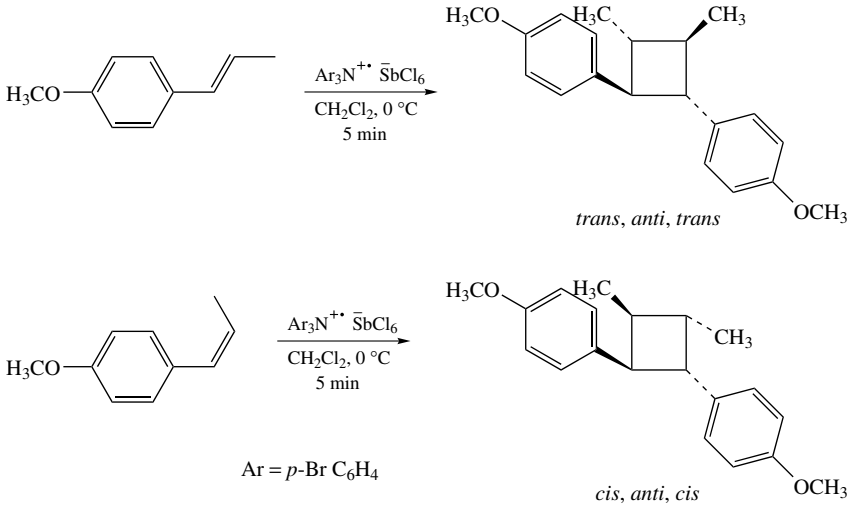
SCHEME 5. Cyclobutadimerization of phenyl vinyl ether

interpreted in terms of re-ionization of the cyclobutane product under photosensitized electron transfer conditions, followed by reversal of Step 3 to regenerate the distonic cation radical intermediate. Subsequent rotation and re-cyclization results in the partial equilibration of the *cis* and *trans* isomers.

The important role of the phenyl ring in the cyclization step is evident from Scheme 5, i.e. the electron-rich phenoxy ring provides a low energy venue for the cation radical moiety in the cyclobutane product. Interestingly, although ethyl vinyl ether has a lower oxidation potential than phenyl vinyl ether and is also more nucleophilic (in the sense of being more reactive toward an electron-deficient species), no analogous cyclobutadimerization reaction of it or any other alkyl vinyl ether has ever been reported. Presumably the second bond-forming step (Step 3) may be unfavorable in the case of an alkyl vinyl ether, since there would not be a sufficiently ionizable functionality present in a dialkoxycyclobutane product. However, it should be noted that cross additions of cation radicals to alkyl vinyl ethers are often facile, since the cation radical component can potentially provide the necessary venue for the cation radical moiety in the adduct cyclobutane cation radical.

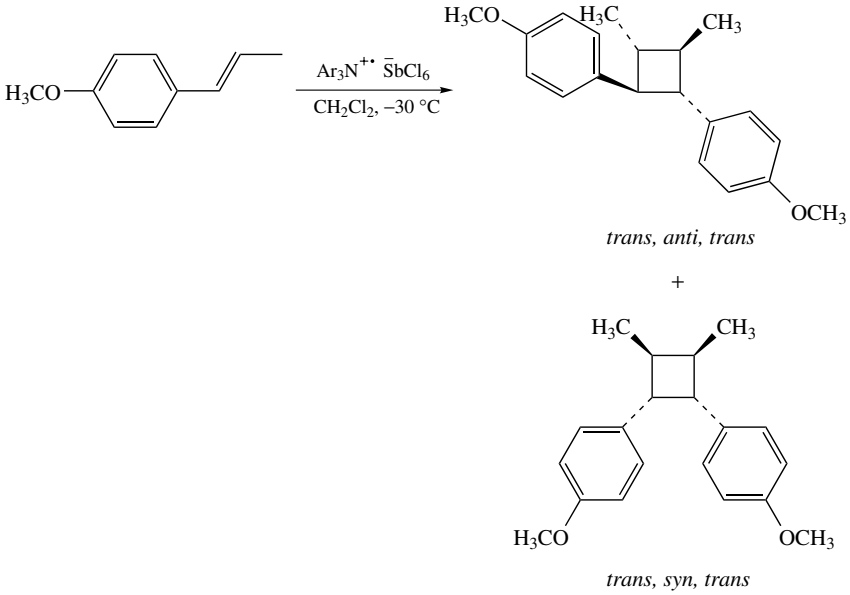
VIII. MECHANISTIC DIVERSITY

The convenience, and ultimately the scope, of cation radical cyclobutanation reactions was enhanced by the discovery that many of these reactions could be initiated by shelf-stable and readily available organic cation radicals, such as tris(4-bromophenyl)aminium hexachloroantimonate[8]. It was found that in dichloromethane solvent, at 0 °C, catalytic quantities of the latter salt could effect the conversion of *trans*-anethole (Scheme 6) to its corresponding cyclobutadimer in 40% yield in less than 5 minutes. When a hindered amine base was included in the reaction medium to suppress the competing Bronsted acid-catalyzed side reactions of the monomer, the yield was increased to 70%. The corresponding cyclobutadimerization of *cis*-anethole was found to yield only the *cis,anti,cis* isomer in a *syn* stereospecific cycloaddition. Subsequently, the corresponding PET-initiated cyclobutadimerizations of *trans*- and *cis*-anethole were also investigated and confirmed to be highly *syn* stereospecific[9].

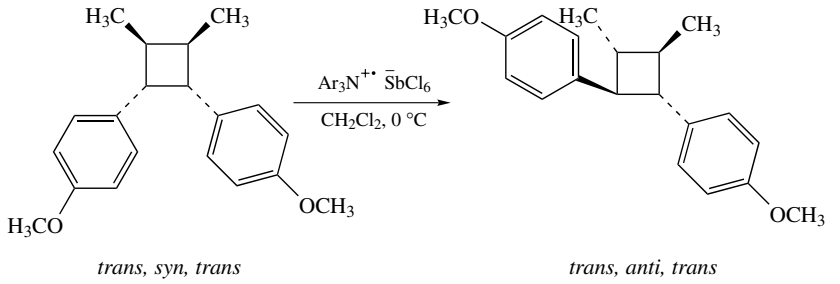


SCHEME 6. *Syn* stereospecific cyclobutadimerization of *cis*- and *trans*-anethole

Of still further interest is the observation that, when carried out at −30 °C, the cyclobutadimerization of *trans*-anethole yielded an approximately 50:50 mixture of the *trans,anti,trans* and *trans,syn,trans* stereoisomers, both formed via *syn* stereospecific, head-to-head regiospecific cycloadditions (Scheme 7). Finally, the thermodynamically less stable *trans,syn,trans* isomer was found to be converted to the *trans,anti,trans* isomer quantitatively when subjected to the aminium salt conditions at 0 °C (Scheme 8). None of the other possible stereoisomers was formed, indicating that the retrocyclobutanation of the cation radical of the less stable isomer is also concerted. Presumably the long bond cation radical is also involved in this reversal.



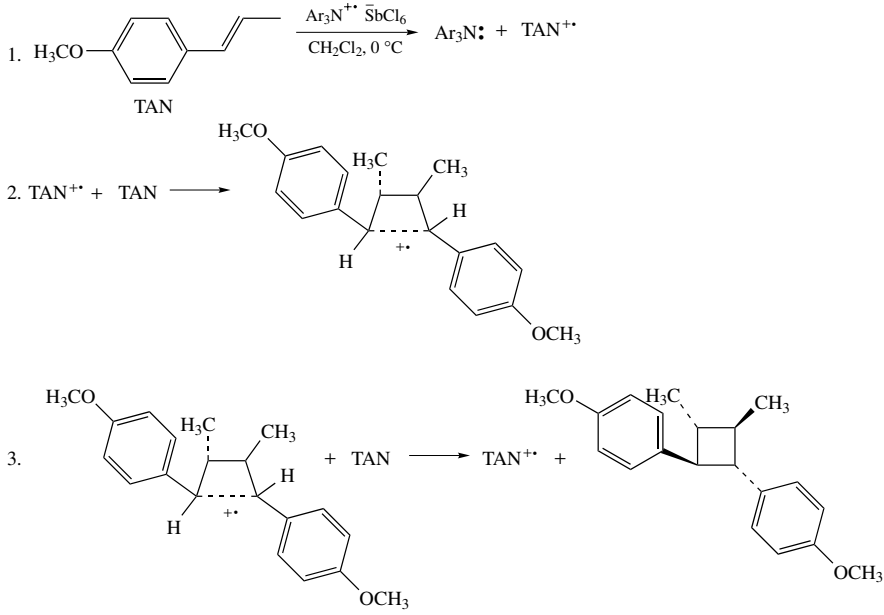
SCHEME 7. Formation of two diastereoisomeric cyclobutadimers, both by *syn* stereospecific addition



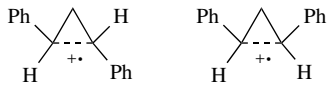
SCHEME 8. Stereospecific retrocyclobutanation of the *trans,syn,trans* cyclobutadimer and re-cycloaddition to yield the thermodynamically more stable *trans,anti,trans* dimer exclusively

IX. THE CONCERTED (OR QUASI-CONCERTED) CYCLOADDITION MECHANISM

Since a distonic cation radical intermediate would be expected to engender at least some stereorandomization, and especially so for the cyclodimerization of *cis*-anethole and the retrocyclobutanation of the *trans,syn,trans* cyclodimer, it appears appropriate to postulate a mechanism which differs from that for the cyclodimerization of *N*-vinylcarbazole, and specifically one in which both new carbon–carbon bonds are at least partially formed in the first cycloaddition step. The proposed mechanism (Scheme 9) may be considered a concerted or a quasi-concerted mechanism. The latter term recognizes that the second cyclobutane bond is not fully formed even in the product of the first step (as opposed to the transition state). This product contains a one-electron bond analogous to that in the dihydrogen cation radical or, more aptly, the long, one-electron bonds found to be present in the *trans*- and *cis*-1,2-diphenylcyclopropane cation radicals and to be capable of maintaining the separate stereochemical identities of these two geometric isomers (Scheme 10)[10].



SCHEME 9. The concerted mechanism for the cyclobutadimerization of *trans*-anethole



SCHEME 10. The isomeric *cis*- and *trans*-1,2-diphenylcyclopropane cation radicals: the long, one-electron bond

X. MECHANISTIC CONSIDERATIONS IN AMINIUM SALT INITIATED CYCLOBUTADIMERIZATIONS

A. Inner vs Outer Sphere Electron Transfer

Under photosensitized electron transfer (PET) conditions, the single electron transfer reaction which results in the ionization of the substrate is assumed to be of the outer sphere type, in which an electron in the highest occupied MO (HOMO) of the substrate jumps to the excited state of the electron-deficient sensitizer without any close contact or covalent interaction between the sensitizer and the substrate. Consequently, the relative ease of ionization of substrates should normally correlate with their oxidation potentials. However, it has been established that, at least in many cases, the ionization of substrates by the tris(4-bromophenyl)aminium hexachloroantimonate salt is of the inner sphere type. In a number of cases, very strong covalent interactions have been inferred[11]. Consequently, rates of ionization of different types of substrate molecule by aminium salts are not so directly related to the oxidation potentials of the substrates. For example, nucleophilic atoms such as sulfur present in the ionizable substrate could sharply accelerate the rate of ionization relative to the corresponding oxygen analogue.

B. Relationship Between the Oxidation Potential of the Tris(4-bromophenyl)aminium Hexachloroantimonate Salt and That of the Substrate

The aminium salt most commonly used to initiate these reactions, viz. tris(4-bromophenyl)aminium hexachloroantimonate, has an oxidation potential of 1.05 V vs SCE (actually, that is the oxidation potential of the corresponding neutral amine, tris(4-bromophenyl)amine)[12]. Virtually all of the substrates which have been successfully ionized via this aminium salt for the purpose of cyclobutanation have oxidation potentials greater than this, so that the single electron transfer is endergonic. This appears to be highly appropriate for an initiation step, since the too rapid generation of cation radicals would probably result in cation radical/cation radical reactions, such as coupling. A range of substrate oxidation potentials has been used in this chemistry, but the highest oxidation potential which afforded successful cation radical chemistry was that of stilbene (1.60 V SCE). Indeed, instead of the usual 3–5 minutes, the reactions of stilbene typically require hours[13].

C. Chain vs Catalytic Mechanisms

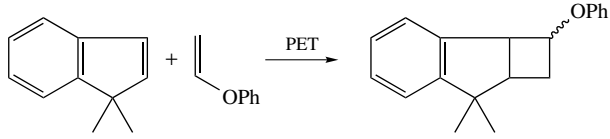
In the context of aminium salt initiated cycloadditions, a potential mechanistic ambiguity arises. The Ledwith cation radical chain cycloaddition mechanism requires the neutralization of the adduct cation radical by the neutral substrate, thus affording a new substrate cation radical to continue the chain. If, instead, a molecule of the neutral triarylamine (generated progressively during the reaction by the gradual decomposition of the initiator) acts as the single electron donor, the original aminium cation radical is regenerated, leading to a catalytic mechanism. Although both the chain and catalytic mechanisms lead to the same product, the former is more efficient, because the ionization of substrate molecules by adduct cation radicals is exergonic and thus very fast, while the ionization of substrate molecule by the tris(4-bromophenyl)aminium ion, required in the catalytic method each time the catalytic cycle is repeated, is endergonic and much slower. Consequently, it has frequently been observed that the rates of cation radical cycloadditions slow down significantly in later stages of the reaction, as a result of the generation of neutral triarylamine and the change, at least in part, to a catalytic mechanism[14]. If this amine is added at the outset of the reaction, reaction rates are substantially retarded[15].

D. Competition with Acid-catalyzed Reactions

Finally, it is noteworthy that the progressive decomposition of the aminium salt also results in the formation of strong Bronsted acids. For substrates which are highly acid-sensitive, competing Bronsted acid-catalyzed, carbocation-mediated reactions, including cationic polymerization, can overwhelm the cation radical reactions. In such cases the addition of a hindered amine such as 2,6-di-*tert*-butylpyridine to the dichloromethane solvent usually inhibits the carbocation-mediated processes[16]. Another option is the use of a two-phase, dichloromethane/water solvent[17]. Apparently, the aqueous phase acts to continuously extract the strong Bronsted acids from the organic phase, where the cycloaddition reactions take place.

XI. CROSS CYCLOBUTANATION

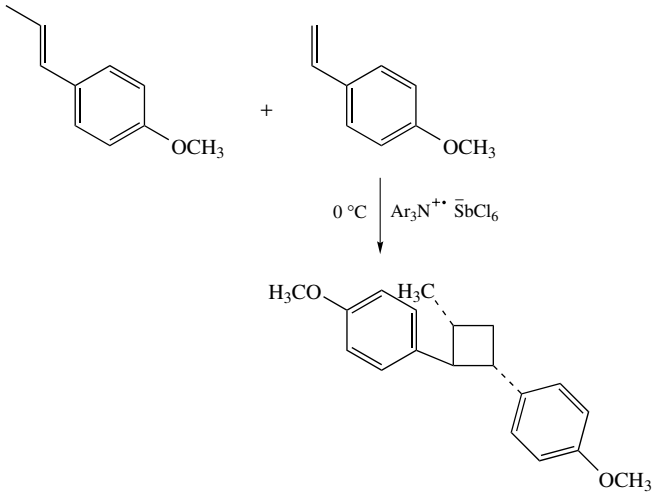
In cation radical cyclobutanation reactions between two different substrates, three types of cyclobutane product are possible, including a cross adduct and the two possible symmetrical cyclobutadimers. In some cases, as a result of specific role preferences (role selectivity), the cross adduct may sometimes be formed with a high degree of selectivity. An early example of an efficient cross addition is the reaction between phenyl vinyl ether and dimethylindene, studied under photosensitized electron transfer conditions (Scheme 11)[18]. The oxidation potential of dimethylindene is less than that of phenyl vinyl ether, resulting in the preferred formation of the dimethylindene cation radical. This latter cation radical selectively reacts with phenyl vinyl ether to yield the cross adduct, which constitutes 91% of the adducts. The rates of reaction of the dimethylindene cation radical with dimethylindene and phenyl vinyl ether were estimated to be 10^6 and 10^8, respectively. Presumably the greater reactivity of the vinyl ether toward cation radicals reflects, at least in part, the greater nucleophilicity of this substrate (ability to stabilize the cationic moiety of the distonic cation radical). However, steric effects are also a major factor in this reactivity order, especially since phenyl vinyl ether presents an unsubstituted β-carbon for reacting with the cation radical, whereas dimethylindene not only has a β-substituent but also additional steric effects derived from the circumstance that the β-carbon, the position of reactivity, is a neopentyl-like carbon. In addition to the cross adduct, small amounts of the two homodimers are also formed.



syn:*anti* = 60:40

SCHEME 11. The efficient cross addition between dimethylindene and phenyl vinyl ether

A more recent example of the efficient formation of a cross adduct is available in the reaction of *trans*-anethole and 4-vinylanisole under tris(4-bromophenyl)aminium hexachloroantimonate salt conditions (Scheme 12)[19]. The presence of the β-methyl substituent on the styryl double bond of *trans*-anethole renders this substrate more ionizable, but this same methyl substituent present in the neutral molecule renders it less reactive toward cation radicals. Consequently, the cation radical of *trans*-anethole is formed selectively, and the latter cation radical reacts selectively with vinylanisole to yield the cross adduct to the virtual exclusion of the two homodimers.

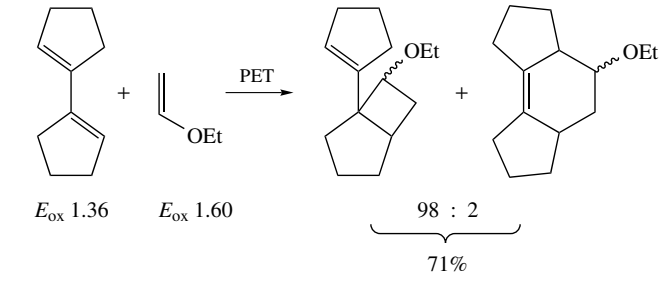


SCHEME 12. Efficient cross cyclobutanation between similar substrates

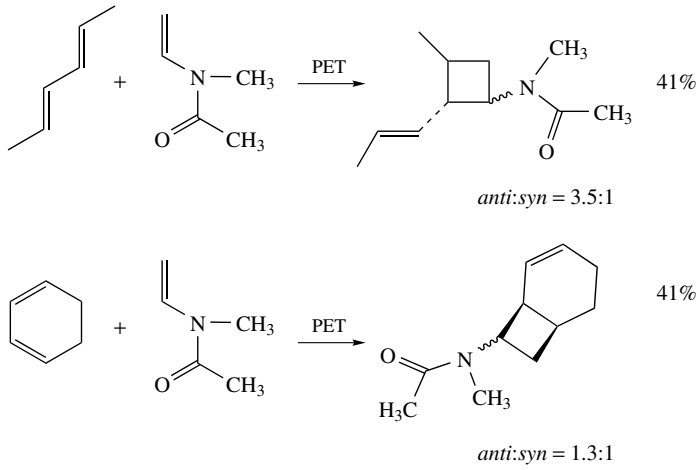
XII. CYCLOBUTANE PERISELECTIVITY IN CROSS ADDITIONS TO CONJUGATED DIENES

The cross addition of 1,1′-dicyclopentenyl with ethyl vinyl ether (Scheme 13) is another relatively efficient example of cross addition involving role selectivity[20]. In this case, the diene is revealed by oxidation potentials to be substantially more readily ionized than ethyl vinyl ether. On the other hand, ethyl vinyl ether is a more reactive nucleophile with respect to reaction with the diene cation radical. The sterically unhindered β-position of this substrate is also effective in enhancing its reactivity toward cycloaddition. Under photosensitized electron transfer conditions, the cyclobutane cross adduct is obtained in good yield (e.g. 71% under PET conditions, using acetonitrile as the solvent and 1,4-dicyanobenzene as the sensitizer). Also obtained is a small amount (1.9% of the cycloadducts) of the corresponding Diels–Alder adduct. The strong preference for cyclobutanation over Diels–Alder addition (periselectivity) is noteworthy. It is also noteworthy that ethyl vinyl ether can efficiently participate as a component of a cross addition because the ionizable component (the conjugated diene) can provide the necessary site for the cation radical moiety in the adduct. In this reaction the site is presumably the trisubstituted alkene moiety of the adduct. Other ionizable substrates which have been found to afford relatively efficient cross-cyclobutanation of 1,1-dicyclopentenyl are phenyl vinyl ether (82% cyclobutanation vs 20% Diels–Alder addition) and phenyl vinyl sulfide (69% cyclobutanation vs 31% Diels–Alder addition).

The highest cyclobutane periselectivity, interestingly, is observed for the substrate which is perhaps the most highly nucleophilic of all those mentioned thus far, viz. *N*-methyl-*N*-vinylacetamide[21]. This enamide reacts, under PET conditions, with both acyclic and cyclic conjugated dienes to yield exclusively (within the limits of detection) cyclobutane adducts. Several examples of such reactions are illustrated in Scheme 14. It is noted that the yields given are isolated yields and that often a considerable amount of starting material remained unreacted. Mechanistically, it appears reasonable to assume that these cross additions occur via reaction of the diene cation radical with the neutral nucleophile, since the enamide cation radical should selectively react with the neutral enamide as the



SCHEME 13. Selective cyclobutanation vs Diels–Alder addition



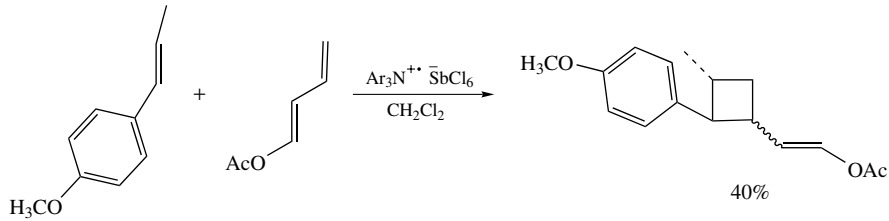
SCHEME 14. High cyclobutane periselectivity in the reaction of a cyclic diene with an enamide

more nucleophilic and less sterically hindered substrate. In the cyclohexadiene case, this scenario is also consistent with the relative oxidation potentials, which are 1.53 for the diene and 1.55 for the enamide. The oxidation potential of 2,4-hexadiene (1.59), however, appears to be slightly less than that of the enamide, according to our measurements.

XIII. THE COMPETITION BETWEEN CATION RADICAL CYCLOBUTANATION AND DIELS–ALDER CYCLOADDITION

In rather sharp contrast with the foregoing cyclobutane selective reactions, the reaction of a much more readily ionizable substrate, *trans*-anethole, with 1,3-cyclopentadiene appears to be strongly Diels–Alder periselective[22]. No cyclobutane adducts at all can be detected in this reaction, at any stage. Since this reaction clearly involves the *trans*-anethole cation radical reacting with the neutral diene, as opposed to the opposite role sense, which appeared to be operative in the previously discussed cyclobutane periselective reactions, the shift to Diels–Alder periselectivity might appear to be somehow connected to the

inverted role sense. However, the reactions of this same *trans*-anethole cation radical with conformationally flexible, acyclic dienes are not similarly Diels–Alder periselective[23]. Rather, the cyclobutane adducts usually predominate, at least initially. The complications which can arise from the subsequent cation radical vinylcyclobutane rearrangement of the initially formed cyclobutane adducts will be discussed below. In instances in which the vinylcyclobutane adducts are resistant to the vinylcyclobutane rearrangement, exclusive formation of the cyclobutane adducts has been observed even in the reactions of the *trans*-anethole cation radical with acyclic dienes (Scheme 15)[24].

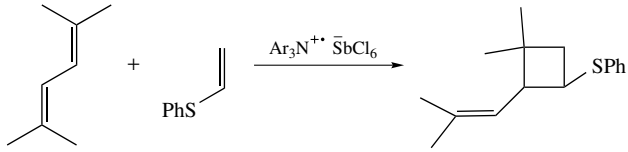


SCHEME 15. Cyclobutane periselectivity in a reaction of the *trans*-anethole cation radical

XIV. STERIC EFFECTS IN CATION RADICAL CYCLOBUTANATION

The very high degree of regioselectivity observed in cation radical cycloadditions is a reminder that cation radicals, although they are highly reactive species, can nevertheless often be quite selective in their reactions. Another selectivity element is their preference for cycloaddition, as opposed to linear addition or other reaction modes. In this connection, the reactions are also frequently rather periselective, i.e. selective in regard to cyclobutanation or Diels–Alder addition. The selectivity of reactions of cation radicals is not so surprising when it is considered that these reactions are not highly exergonic, as would be expected if the reactants were on a high energy, cation radical, energy surface and the products were on a much lower energy, neutral molecule surface. Rather, the cycloadditions occur on a cation radical surface, i.e. both reactants and products are cation radicals. Consequently, these cation radical cycloadditions are usually at best modestly exergonic, not unlike the more common reactions on a neutral potential energy surface. In fact, cation radical/neutral cycloadditions are commonly less exergonic than the corresponding neutral/neutral reactions, since the ionization potential (or oxidation potential) of the ionizable reaction partner is lower than that of the adduct. This follows as a direct result of the circumstance that the cation radical of the adduct is less highly delocalized than that of the reactant. As a result, cation radical reactions tend to be surprisingly selective. One result of this is their much more rapid reaction with an unsubstituted, vinyl double bond than with a propenyl group, and very slowly indeed (if at all) with a terminally disubstituted double bond. The very strong preference of cation radicals for reaction at electron-rich (nucleophilic) and conjugated double bonds has already been noted, as has the high regiospecificity observed in such cycloadditions.

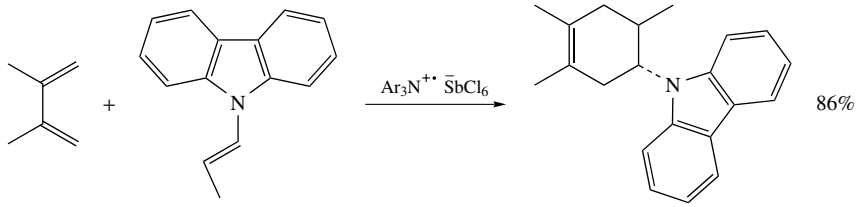
On the other hand, it has been observed that 2,5-dimethyl-2,4-hexadiene reacts rather smoothly with phenyl vinyl sulfide in the presence of tris(4-bromophenyl)aminium hexachloroantimonate (Scheme 16)[25]. In this instance, the hindered diene is the more ionizable component, and this hindered diene cation radical is evidently able to react with an unhindered, nucleophilic substrate. Since this diene has extreme difficulty in accessing an s-*cis* conformation, also for steric reasons, Diels–Alder addition is not competitive with cyclobutanation.



SCHEME 16. Addition of the cation radical of a hindered diene to an electron-rich substrate

XV. DIELS–ALDER PERISELECTIVITY IN REACTIONS WITH ACYCLIC DIENES

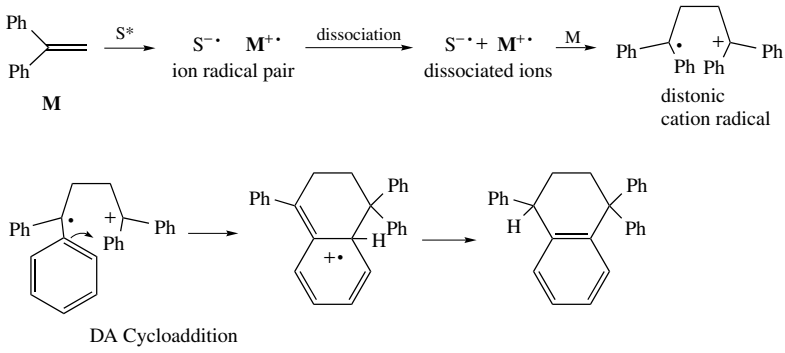
When a substrate is employed which is even more readily ionizable than *trans*-anethole, viz. *N*-propenylcarbazole, cycloaddition becomes Diels–Alder periselective even with acyclic conjugated dienes[26]. The reactions of this cation radical, formed under tris(4-bromophenyl)aminium hexachloroantimonate salt conditions, with a wide variety of cyclic and acyclic conjugated dienes is efficient as well as Diels–Alder periselective (Scheme 17). In these instances it appears possible that the carbocation center of the intermediate distonic cation radical is so well stabilized by the strongly electron-donating nitrogen functionality, and the radical site stabilized by allylic resonance, that cyclization to a (strained) cyclobutane cation radical is thermodynamically unfavorable, resulting either in preferential cyclization to the more stable Diels–Alder adduct or in reversion of the distonic cation radical to give back the *N*-propenylcarbazole cation radical and the neutral diene. Reversal would presumably be the exclusive result if the *N*-propenylcarbazole cation radical adds to the s-*trans*-conformation of the diene. Incidentally, stereochemical evidence has been presented that these reactions do, in fact, proceed in a stepwise fashion, via the distonic cation radical[27].



SCHEME 17. Diels–Alder periselectivity in a cycloaddition to an acyclic diene

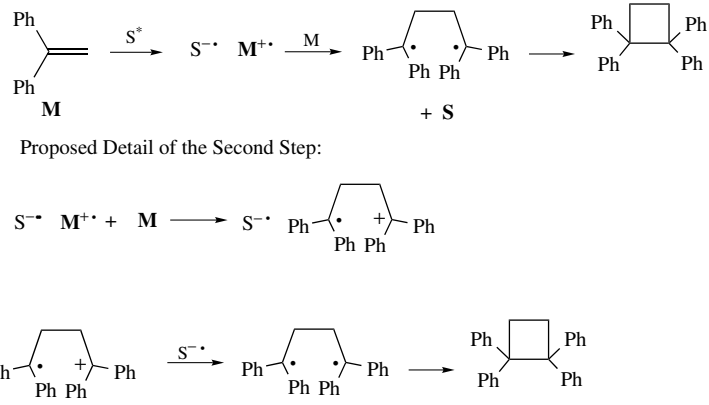
XVI. DIELS–ALDER/CYCLOBUTANATION COMPETITION IN CATION RADICAL CYCLOADDITIONS TO STYRENES

In another pioneering study of a PET induced cation radical cycloaddition reaction, the cyclodimerization of 1,1-diphenylethene was found to yield a mixture of cyclobutadimers and Diels–Alder dimers (Scheme 18)[28]. The special novelty of the Diels–Alder reaction in this instance is that a styrene moiety of the monomer serves as the dienic component. The Diels–Alder cyclodimer and the corresponding dehydrodimer were found to be formed primarily via reaction of the *dissociated* diphenylethene cation radical with neutral diphenylethene to yield a distonic cation radical intermediate which cyclizes mainly in the Diels–Alder sense. This Diels–Alder periselectivity presumably arises from a combination of the steric hindrance inherent in the formation of a bond between the two distonic benzhydryl moieties, the relative difficulty of forming a strained cyclobutane bond and the relatively high energy of the fully cyclized tetraphenylcyclobutane cation radical, which presumably would have a benzene-like cation radical moiety.



SCHEME 18. Mechanism for the Diels–Alder cyclodimerization of 1,1-diphenylethene using 9,10-diphenylanthracene as the photosensitizer (S)

In contrast, the cyclobutadimer is considered to be predominantly formed via reaction of ion paired diphenylethene cation radical (ion paired with the sensitizer anion radical) with neutral diphenylethene, leading to a diradical intermediate, which cyclizes to give predominantly the cyclobutadimer (Scheme 19). It appears reasonable to suggest that a distonic cation radical intermediate is also formed in this latter process, but in the presence of the sensitizer anion radical the cationic center of this intermediate is reduced to a second radical center. The highly exergonic diradical coupling then leads to the cyclobutadimer and also to a small amount of the Diels–Alder dimer.



SCHEME 19. Mechanism for the cyclobutadimerization of 1,1-diphenylethene using 9,10-diphenylanthracene as the photosensitizer

XVII. CONFORMATIONAL EFFECTS UPON PERISELECTIVITY IN CATION RADICAL/NEUTRAL CYCLOADDITION REACTIONS

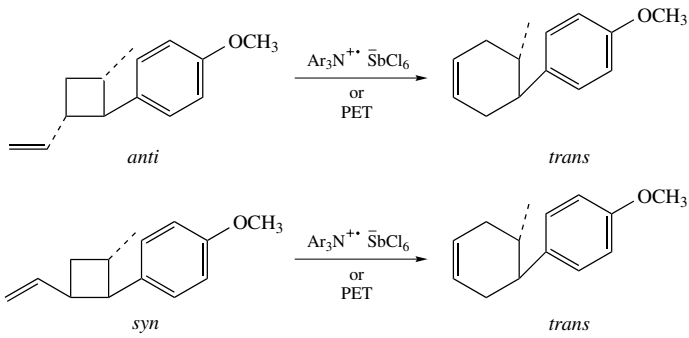
The tendency of simple, acyclic dienes such as 1,3-butadiene and 1-acetoxy-1,3-butadiene to undergo preferential cyclobutanation as opposed to Diels–Alder addition in their reactions with cation radicals is presumably based, at least in part, upon their preference for the s-*trans* conformation, which cannot undergo Diels–Alder addition *per se*. The same preference holds *a fortiori* for dienes such as 2,5-dimethyl-2,4-hexadiene, which are sterically

prevented from accessing their s-cis conformations. On the other hand, the observation of high cyclobutane periselectivity in additions to dienes which have substantial s-cis conformational populations, such as 1,1-dicyclopentenyl and 2,3-dimethyl-1,3-butadiene, and even to rigidly s-*cis* cyclic dienes, such as 1,3-cyclohexadiene (in the case of enamides), suggests that another factor is probably at work. In the case of PET induced reactions, a mechanism similar to that proposed for the cyclodimerization of 1,1-diphenylethene might be involved. That is, the cationic site of the distonic cation radical intermediate might be reduced to a radical site by electron transfer from the sensitizer anion radical, followed by a diradical coupling to yield the cyclobutane adduct. In the aminium salt initiated reactions an analogous mechanism might conceivably be involved in which the neutral amine neutralizes the cationic site, but simultaneously with the second, ring-closing, bond formation. In this hypothetical mechanism the ring closure provides the thermodynamic driving force for the modestly endergonic electron transfer.

XVIII. THE CATION RADICAL VINYLCYCLOBUTANE (VCB) REARRANGEMENT

Since successful cation radical cyclobutanation typically requires some relatively ionizable function to be present in the cyclobutane adduct upon which to center the cation radical moiety, it is perhaps not so surprising that, under appropriate conditions, the adduct can be re-ionized, once again placing the cation radical moiety upon the same functionality, an occurrence which could lead to reversal of the second, cyclobutane-forming step, i.e. re-formation of the distonic cation radical intermediate (or the long-bond intermediate if that is involved). Potentially the first step of the cycloaddition might even be reversed. This latter was, in fact, observed in the conversion of the *trans,syn,trans* cyclobutadimer of *trans*-anethole to the more stable *trans,anti,trans* dimer. More commonly, only the second step of the cycloaddition, the cyclization step, is reversed, leading to a re-formation of the intermediate distonic cation radical. In the case of the cyclobutadimer of phenyl vinyl ether, this leads to *cis/trans* isomerization of the adduct via rotation and re-closure of the cyclobutane ring. In the case of vinylcyclobutane adducts, an additional possibility presents itself and is often realized for those cyclobutane cycloadducts which have ionizable functionalities, viz. the vinylcyclobutane rearrangement.

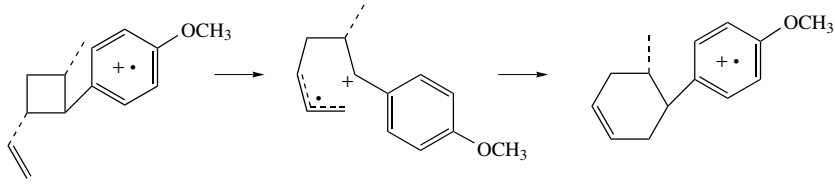
When the cycloaddition of *trans*-anethole to 1,3-butadiene is carried out at $-35\,^{\circ}C$, only the cyclobutane adducts ($anti > syn$) are formed, at least initially[29]. When the reaction is carried out for synthetic purposes at $0\,^{\circ}C$ for a few minutes, typically a 1:1 mixture of (*anti* and *syn*, but mostly *anti)* cyclobutane and Diels–Alder adducts is obtained. When this 1:1 mixture of the two types of cycloadduct are subjected to aminium salt conditions for 1.5 minutes, 30% of the cyclobutane adducts are converted to Diels–Alder adducts with 100% efficiency (Scheme 20)[30]. When the pure *syn* cyclobutane adduct, prepared by direct irradiation of a mixture of *trans*-anethole and 1,3-butadiene, is treated with the aminium salt for 2 minutes or under PET conditions for 10 minutes, a 90% conversion to the Diels–Alder adduct is observed. The possibility of a retrocyclobutanation mechanism (re-forming the *trans*-anethole cation radical, followed by eventual re-cycloaddition in the Diels–Alder sense) was excluded by the observation that the inclusion in the reaction mixture of a large (800%) excess of 2,3-dimethyl-1,3-butadiene did not result in the formation of even traces of the *trans*-anethole/2,3-dimethyl-1,3-butadiene adduct, even though the *trans*-anethole cation radical is at least 3 times more reactive toward the latter diene than toward 1,3-butadiene (competition experiments). These rearrangements are sharply retarded by added *trans*-anethole, which retardation accounts for the ability to observe cyclobutane adducts at all, and for the extremely rapid and efficient rearrangement of these cyclobutane cycloadducts to Diels–Alder adducts when purified and subjected to aminium salt or PET conditions. Presumably the reason for this rate retardation is that *trans*-anethole is more readily ionizable than the cyclobutane adduct, and any cyclobutane



SCHEME 20. The cation radical VCB rearrangement of the *trans*-anethole/1,3-butadiene cyclobutane adducts

cation radical which is formed in competition with formation of the t*rans*-anethole cation radical would be quenched by exergonic electron transfer from *trans*-anethole.

In every case, only the *trans* Diels–Alder adduct was formed. This would be consistent with an effectively concerted vinylcyclobutane rearrangement, but since the *trans* Diels–Alder isomer is undoubtedly more stable than the *cis* isomer, a stepwise mechanism involving a distonic cation radical intermediate is not necessarily excluded. The stepwise mechanism (Scheme 21) would simply require that the cyclization step be considerably faster than rotation around the C−C bond which connects the anisyl and methyl moieties.

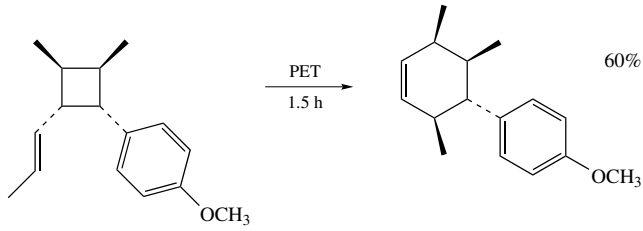


SCHEME 21. A possible stepwise mechanism of the cation radical vinylcyclobutane rearrangement

XIX. STEREOCHEMISTRY OF THE CATION RADICAL VINYLCYCLOBUTANE REARRANGEMENT

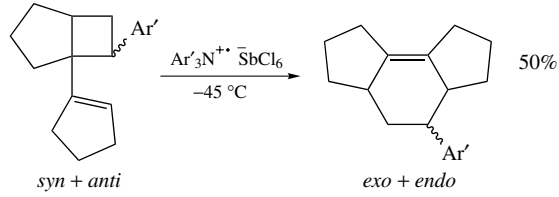
The mixture of cyclobutane adducts initially formed in the aminium salt-initiated reaction between *trans*-anethole and *trans,trans*-2,4-hexadiene (Scheme 19) are detectable by GCMS but rearrange with such facility to Diels–Alder adducts that it is impractical to obtain useful amounts of the pure cyclobutane isomers for stereochemical studies. On the other hand, direct uv irradiation (presumably via exciplex formation) of a mixture of these substrates afforded a small amount of the pure *trans,syn,trans* diastereoisomer (Scheme 22). Under photosensitized electron transfer conditions, this adduct rearranged predominantly to the *exo* Diels–Alder isomer shown, i.e. via a suprafacial shift across the pendant double bond with retention of configuration at the migrating carbon (sr stereochemistry). This result is consistent either with a concerted rearrangement or with a stepwise rearrangement, via a distonic cation radical, in which the final cyclization step is very rapid in relation to rotation around the C−C bond which connects the anisyl and methyl moieties. Since the *trans* relationship of these moieties is the more stable one, it would not be surprising if rotation into a *cis* or *gauche* relationship were slower than

cyclization to the Diels–Alder adduct. The aminium salt-initiated reaction initially forms the same *syn* cyclobutane isomer as was obtained from direct irradiation along with an approximately equal amount of the corresponding *anti* isomer. The rapidly ensuing vinylcyclobutane rearrangement then generates the same *exo* Diels–Alder adduct obtained from the pure *syn* cyclobutane isomer obtained via the PET procedure, along with an equal amount of the corresponding *endo* Diels–Alder isomer. Presumably the latter is formed from the *anti* cyclobutane stereoisomer, again presumably via a predominantly sr stereochemical course.



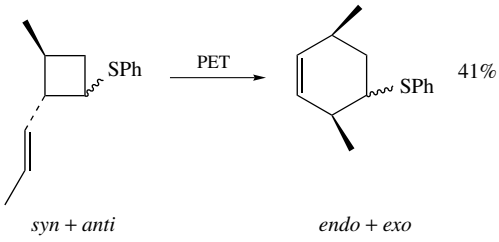
SCHEME 22. Stereoselective cation radical vinylcyclobutane rearrangement

The vinylcyclobutane rearrangements of the initially formed cyclobutane adducts of *trans*-anethole with 1,3-butadiene and 2,4-hexadiene show rather clearly that the anisyl moiety, at least in the context of an attached cyclobutane moiety, is ionizable under both PET and aminium salt conditions. Other, less readily ionizable substituents are capable of activating vinylcyclobutanes to cation radical vinylcyclobutane rearrangement, but the reactions may proceed more efficiently when the more powerful initiator, tris(2,4-dibromophenyl)aminium hexachloroantimonate, is employed or when the inherently more powerful PET ionization method is used[30]. An example of the former is the rearrangement depicted in Scheme 23 which involves ionization of a phenoxy group. In the case of the still less readily ionizable phenylthio moiety, the PET ionization method is preferred (Scheme 24).



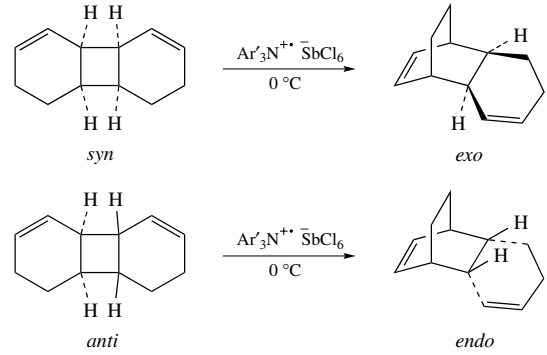
SCHEME 23. A vinylcyclobutane rearrangement activated by the ionization of a phenoxy group

In some cases, even alkenyl substituents can activate the rearrangement, particularly if the alkene is tri- or tetrasubstituted by alkyl groups. Especially interesting in this regard is the rearrangement of the *endo* and *exo* isomers of the cyclobutadimers of 1,3-cyclohexadiene (Scheme 25). The tris(4-bromophenyl)aminium hexachloroantimonate initiated cyclodimerization of 1,3-cyclohexadiene gives a 70% yield of cycloadducts, 98% of which are the Diels–Alder adducts. The cyclobutadimers are, of course, more readily



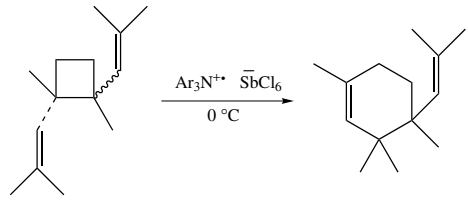
SCHEME 24. A vinylcyclobutane rearrangement activated by a phenylthio substituent

prepared by triplet sensitized cyclodimerization of this diene. These are quite stable in the presence of tris(4-bromophenyl)aminium hexachloroantimonate, but when the more powerful aminium salt initiator is used they rearrange smoothly into the Diels–Alder dimers. In particular, the *syn* cyclobutadimer rearranges exclusively to the *exo* Diels–Alder dimer, while the *anti* cyclobutadimer rearranges exclusively to the *endo* Diels–Alder dimer[30]. Although these reactions are highly sr (suprafacial, retention) stereospecific, they provide no direct evidence in regard to the concerted vs stepwise nature of the reaction. Because of the rigidity of the cyclic systems, no other stereochemical result is plausible even for a stepwise process. The cyclobutadimers of 2,4-dimethyl-1,3-pentadiene rearrange quantitatively to the Diels–Alder cyclodimer even in the presence of the milder aminium salt initiator (Scheme 26).



Ar′ = 2, 4-dibromophenyl

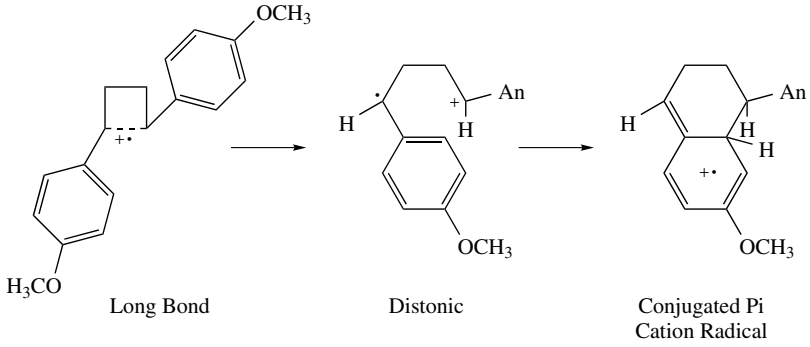
SCHEME 25. The sr stereospecific cation radical vinylcyclobutane rearrangements of the *syn* and *anti* cyclobutadimers of 1,3-cyclohexadiene



SCHEME 26. A highly efficient vinylcyclobutane rearrangement activated by an alkenyl moiety

XX. THE CATION RADICAL ARYLCYCLOBUTANE REARRANGEMENT

It was previously noted that a formal double bond of an aryl ring can serve as a reactive cycloaddition site in the context of cation radical cycloadditions to a styrene-type double bond. In a similar manner, rearrangements analogous to the vinylcyclobutane rearrangement have been observed for 1,2-diarylcyclobutane cation radicals (Scheme 27). The rearrangement of the cation radical of *trans*-1,2-di-(4-methoxyphenyl)cyclobutane, generated by photoionization and studied by nanosecond and picosecond transient absorption spectroscopy, involves the cleavage of this (presumably long-bond) cation radical to a distonic cation radical intermediate (rate constant, $k = 2.5 \times 10^8\ s^{-1}$), with subsequent rapid cyclization to the *ortho* position of one of the anisyl rings in what amounts to a stepwise 1,3-sigmatropic shift[31]. Importantly, this distonic intermediate was found not to be involved in the cation radical cyclodimerization of 4-methoxystyrene, which forms this cyclobutane derivative. The cycloaddition of the 4-methoxystyrene cation radical to neutral 4-methoxystyrene occurs with a rate constant of $1.4 \times 10^9\ M^{-1}\ s^{-1}$. The latter reaction was considered to occur through the previously postulated long-bond cyclobutane cation radical.



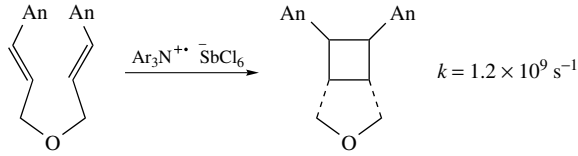
SCHEME 27. A cation radical arylcyclobutane rearrangement (1,3 sigmatropic shift)

XXI. INTRAMOLECULAR CATION RADICAL CYCLOBUTANATION

A. Observation and Calibration

Intermolecular cation radical/neutral cyclobutanations, in the absence of pronounced steric effects, have been seen to be capable of proceeding extremely rapidly, in favorable cases at a rate differing from the diffusion rate by less than a factor of ten. In view of the inherent entropic advantage of intramolecularity, it appeared of interest to synthesize and study examples of intramolecular cation radical cyclobutanation. A specific goal of these studies was to develop a cation radical mechanistic probe, i.e. a molecule which, if ionized to a cation radical in the course of a given transformation, would undergo a uniquely cation radical reaction at a rate competitive with that of the 'normal' reaction of the substrate, thus confirming the intermediacy of the cation radical. Since cyclobutanation, under very mild conditions, and in the absence of light quanta, appears to be a uniquely cation radical process, and since intramolecular cation radical cyclobutanation would appear likely to be fast enough to compete with virtually any intermolecular reaction, a cation radical probe involving intramolecular cyclobutanation was sought. Although a number of such substrates have been studied, the probe which has been studied in the most detail is shown

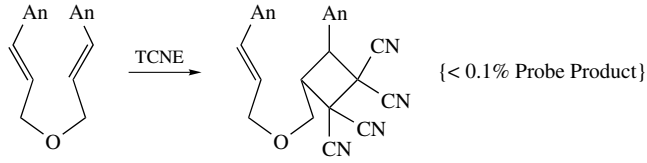
in Scheme 28. Picosecond spectroscopic studies of this reaction, in which the appropriate cation radical is generated by photoionization and photosensitized electron transfer, reveal a rate constant for cyclization of 1.2×10^9 s^{-1}, easily fast enough to compete with any intermolecular reaction and indeed with most intramolecular reactions[32].



SCHEME 28. Intramolecular cation radical cyclobutanation: a cation radical mechanistic probe

B. Use as Mechanistic Probes

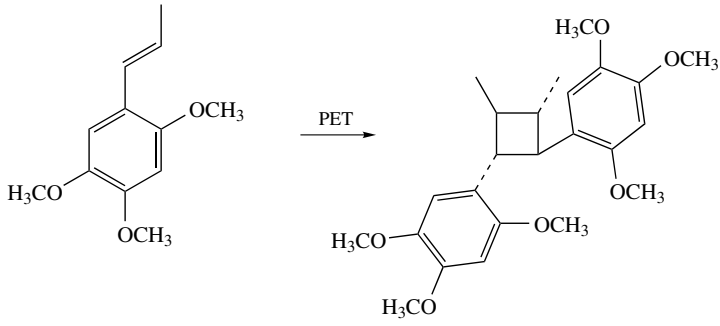
This and analogous cation radical probes were used to investigate the possibility of an electron transfer mechanism for the addition of tetracyanoethylene (TCNE) to electron-rich alkenes, a mechanism which had been considered by early investigators[33]. This mechanism involves electron transfer from the alkene to TCNE, forming the TCNE anion radical and the alkene cation radical, which then couple to form a zwitterion, followed by cyclization of the latter to form the cyclobutane adduct. If this mechanism were operative in the case of the probe depicted in Scheme 29, the probe cyclization product should be formed in competition with TCNE adduct formation. In fact, TCNE reacts rapidly with the probe and generates only the TCNE cross adduct and no detectable amount of the probe product[34]. Since this probe product could have easily been detected in 0.1% yield, it appears highly unlikely that an anion radical pair is involved in this cycloaddition. To further confirm this conclusion, the relevant ion radical pair was generated by selective irradiation of the probe/TCNE π-complex at the charge transfer wavelength. Under these conditions, the adduct and the probe product were both generated in substantial quantities. An analogous study of the hypothetical electron transfer mechanism for the metalloporphyrin-catalyzed epoxidation of this same probe substrate also fails to yield any probe product, suggesting that a cation radical intermediate is not involved in these reactions[35].



SCHEME 29. Cation radical probe test for an electron transfer mechanism for the cycloaddition of tetracyanoethylene to electron-rich alkenes

XXII. NATURAL PRODUCT SYNTHESIS VIA CATION RADICAL CYCLOBUTANATION

Cation radical cyclobutanation has not yet been used extensively for the synthesis of natural products. However, one such instance has been reported, the synthesis of magnosalin (Scheme 30)[36].



Magnosalin

SCHEME 30. Synthesis of the natural product magnosalin by means of PET-induced cation radical cyclobutadimerization

XXIII. CATION RADICAL CHAIN CYCLOADDITION POLYMERIZATION

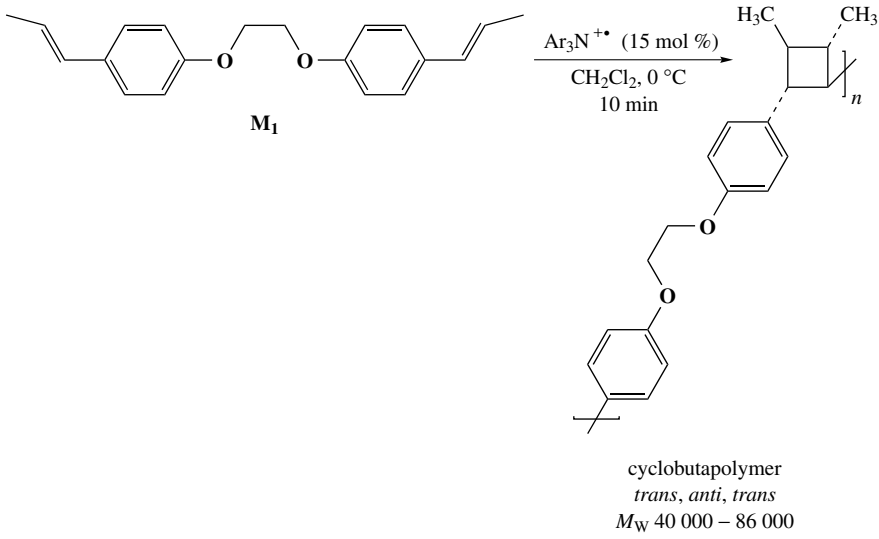
A. General Considerations

For readily ionizable, difunctional monomers which are not too highly disposed to undergo intramolecular cycloaddition, polymerization is a theoretically possible result. A chain polymerization mechanism based upon the cycloaddition reactions of cation radical intermediates at every step of the propagation cycle would represent a fundamentally new mechanism for polymerization, and the linkage of monomers via cycloaddition, and especially cyclobutanation, is particularly intriguing and unique. Such a polymerization method should be capable of polymerizing electron-rich monomers which are not readily polymerizable by other means and of yielding polymer structures which are inaccessible by other means. As will be seen below, the polymerization format for cation radical cycloadditions has the especially empowering advantage of providing an intramolecular, as opposed to an intermolecular, electron transfer step.

B. Initial Exemplification

The choice of monomers and initiation methods for investigating this possibility was assisted by the experience of this research group in the area of monofunctional cation radical chain cycloaddition chemistry. The cyclodimerization of *trans*-anethole, as has been noted, had already been extensively studied in this laboratory using tris(4-bromophenyl)aminium hexachloroantimonate as the chemical initiator. These and additional studies using photosensitized electron transfer initiation have strongly supported a cycloaddition mechanism which differs from that established for *N*-vinylcarbazole in that the cycloaddition appears to be concerted, instead of stepwise, directly yielding a long-bond cation radical structure and avoiding a distonic cation radical intermediate and the attendant nonstereospecificity. Building upon *trans*-anethole as a model monofunctional compound, difunctional monomer $\mathbf{M_1}$ was selected for study. Polymerization of a 0.056 M solution of $\mathbf{M_1}$ in dichloromethane solution at 0 °C for 10 minutes in the presence of 15 mol% of tris(4-bromophenyl)aminium hexachloroantimonate yielded a soluble polymer having M_W 37 000 and a polydispersity index (PDI) of 7.31. Subsequently, a very pure sample of $\mathbf{M_1}$ was obtained and polymerized under similar conditions (0.03 M, 16 mol%

of initiator, 12 min), affording a polymer of M_W85 500(PDI = 2.3)[37]. The anticipated cyclobutapolymer structure was confirmed by both ^1H and ^{13}C NMR spectroscopy and by the very close similarity of these spectra to those of the corresponding *trans*-anethole cyclodimer (Scheme 31).



SCHEME 31. Cation radical chain cyclobutapolymerization of bis-1,2-[4-(1-propenyl)phenoxy] ethane (M_1) using tris(4-bromophenyl)tris(4-bromophenyl)aminium hexachloroantimonate hexachloroantimonate as the initiator

The formation of a cyclobutapolymer is novel and decisively implicates a cation radical mechanism, since cyclobutane formation does not occur at all thermally under these conditions, nor are cyclobutadimers formed via acid-catalyzed processes. Further, the virtually exclusive formation of *trans,anti,trans* cyclobutane linkages exactly parallels that found for the authenticated cation radical chain cyclodimerization of the closely analogous monofunctional compound, *trans*-anethole.

C. Chain Growth vs Step Growth

Although a chain growth process involving intramolecular electron transfer would appear to represent by far the most efficient mechanism conceivable for cation radical cycloaddition polymerization, it appeared possible *a priori* that polymerization could occur via a step growth process in which the electron transfer step is intermolecular and the single electron donor is the neutral triarylamine generated in the initiation process. This would regenerate the tris(4-bromophenyl)aminium ion at each step, and thus constitute a catalytic, not a chain, mechanism. The question of whether the postulated chain-growth mechanism or the conceivable catalytic, step-growth mechanism is actually operative was addressed in several experiments[38,39]. The principal criterion employed was that step-growth polymerization cannot yield high polymers until essentially all of the monomer is consumed, whereas in chain-growth polymerization polymeric material is formed from the outset, even at relatively low monomer conversions. Quantitatively, this is expressed in the equation $M_W = M_o(1 + P)/(1 - P)$, where M_W is the weight average molecular

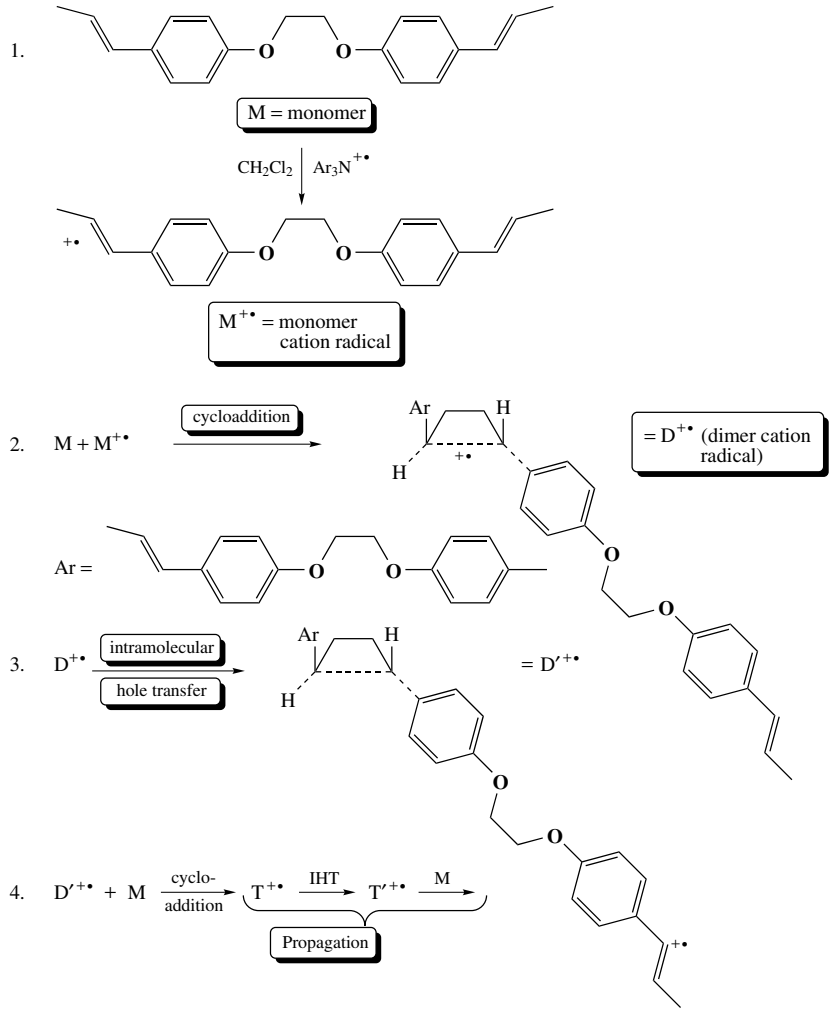
weight, M_o is the molecular weight of the monomer and P is the fraction of the monomer consumed. In one polymerization experiment at a monomer concentration of 0.03 M, and using 10 mol% of the initiator, the reaction was quenched after 30 s, yielding a polymer having M_W15 300(PDI = polydispersity index = 2.2). The monomer conversion was found to be 82%, leading to a predicted value of M_W2 969(PDI = 1.82) for a step-growth process. In a separate experiment at a monomer concentration of 0.022 M and using only 5 mol% of the initiator, the reaction was quenched after 2.5 minutes (50% monomer conversion), yielding a polymer having M_W10 000(PDI = 1.8). These stand in sharp contrast to the values calculated for a pure step-growth process: $M_W = 882; \text{PDI} = 1.5$.

D. The Cation Radical Chain Mechanism for the Cycloaddition Polymerization

The proposed mechanism for the cation radical chain cycloaddition polymerization is illustrated for monomer $\mathbf{M_1}$ in Scheme 32. Considering first the initiation step, the peak oxidation potentials of $\mathbf{M_1}$ and tris(4-bromophenyl)amine (1.23 and 1.05 V, respectively, vs SCE) indicate that the required initiating electron transfer is mildly endergonic (4.2 kcal mol^{-1}). The activation free energy for the closely related oxidation of *trans*-anethole to its cation radical by the same tris(4-bromophenyl)aminium hexachloroantimonate salt has been measured in this laboratory and is 10.6 kcal mol^{-1}. The ionization of monomer $\mathbf{M_1}$ is therefore plausibly expected to occur at a moderate rate, appropriate for steady initiation, but not generating a high steady-state concentration of monomer cation radicals, which would favor coupling reactions between two monomer cation radicals. The rate of cycloaddition of *trans*-anethole cation radicals to *trans*-anethole has also been measured and been found to be extremely fast ($k = 2.0 \times 10^7$ M^{-1} s^{-1}). The intermediacy of a long-bond cation radical has also been confirmed in the latter cycloaddition. The key aspect of the polymerization of $\mathbf{M_1}$ which makes the chain mechanism feasible is rapid intramolecular electron transfer from the cyclobutane long bond to the terminal propenyl groups (or, equivalently, hole transfer from the propenyl π-bond to the cyclobutane cation radical long bond). That this transfer should be substantially exergonic is indicated by comparison of the peak oxidation potentials of $\mathbf{M_1}$ (1.23 V) and the cyclobutadimer of *trans*-anethole (1.60), which should be a good model for the cyclobutane ring present in the polymers. The difference in peak potentials would suggest an approximate exergonicity of 8.5 kcal mol^{-1}. It is not presently clear whether the electron transfer is through bonds or through space.

E. The Novelty of the Cation Radical Chain Cycloaddition Mechanism

Prior to the report of the polymerization of $\mathbf{M_1}$ by the author's laboratory, no precedent had existed in the literature for the propagation of polymerization chains via cation radicals. It is important to note, however, that important roles had previously been established for cation radical intermediates in polymerization processes in at least two distinct ways. The first is illustrated by the ionization of *N*-vinylcarbazole to the corresponding cation radical, followed by coupling of two such cation radicals to give a dication. Polymerization of *N*-vinylcarbazole then results from a cationic polymerization mechanism initiated by the dimer dication. This type of polymerization, then, is of the strictly linear addition type, as opposed to cycloaddition, and does not involve cation radicals at all in the propagation cycle. The second significant role of cation radicals in polymerization is illustrated by the polymerization of pyrrole by oxidative means (anodic oxidation or oxidation by a metal ion oxidant, e.g.). In this case, cation radicals appear to be involved in every step of a step-growth polymerization. The polymerization is not of the linear addition or cycloaddition type, but of the substitution type and is neither catalytic nor



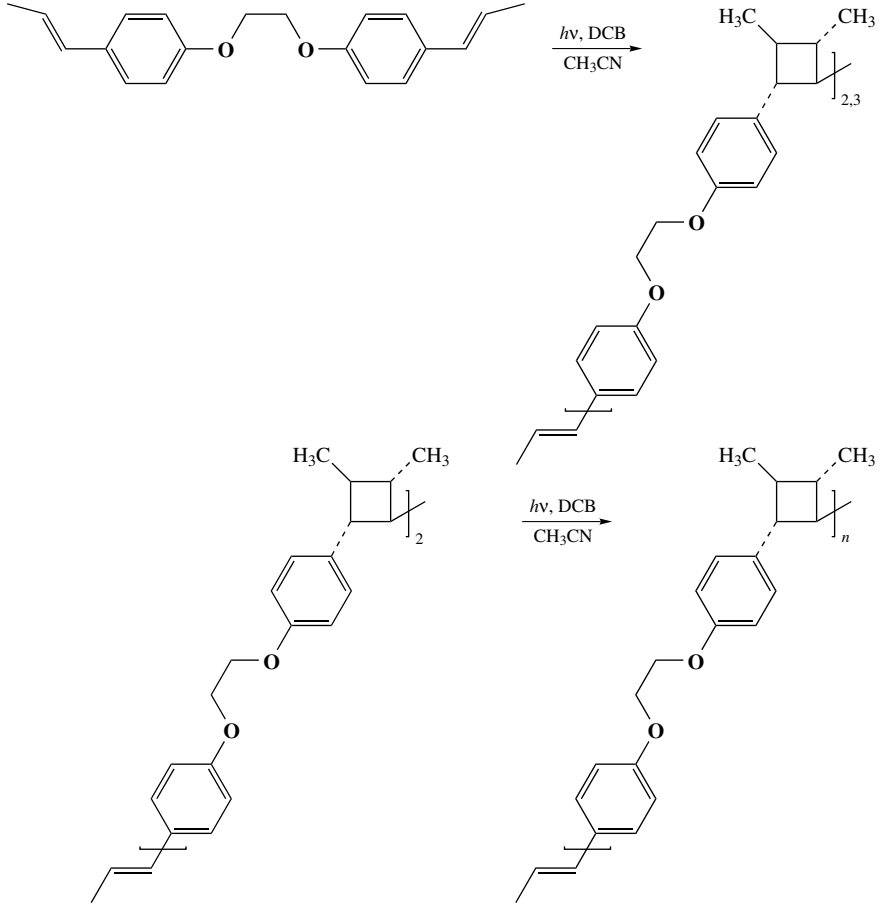
SCHEME 32. The cation radical chain cycloaddition mechanism for the polymerization of monomer $\mathbf{M_1}$

chain. Each monomer unit must be oxidized to the corresponding cation radical by the appropriate oxidant.

F. Polymerization by Photosensitized Electron Transfer Initiation

In the author's laboratory, the use of a chemical initiator, tris(4-bromophenyl)aminium hexachloroantimonate, has been found to be not only the most convenient method of initiation, but also to be the method which generates the highest molecular weight polymers.

This dark blue salt, a stable cation radical salt, is shelf-stable and commercially available. Nevertheless, it was of interest to investigate other initiation methods, including photosensitized electron transfer (PET) and anodic oxidation. The typical PET procedure used in this laboratory for accomplishing cation radical cycloadditions consists of irradiation of the appropriate substrate dissolved in a dry acetonitrile solution, which also contains the sensitizer 1,4-dicyanobenzene (DCB), with a mercury vapor lamp using a pyrex filter so that only the sensitizer absorbs the ultraviolet light. When this standard procedure was applied to monomer $\mathbf{M_1}$, only the cyclobutadimer and trimer of $\mathbf{M_1}$ (Scheme 33) were obtained, presumably because back electron transfer from the sensitizer anion radical is relatively efficient in quenching the intermediate long-bond cation radicals. These adducts represent the first and second stages of propagation, and as such still have ionizable terminal propenyl groups.



SCHEME 33. Photosensitized cycloaddition polymerization of the cyclodimer of monomer $\mathbf{M_1}$, using 1,4-dicyanobenzene (DCB) as the sensitizer

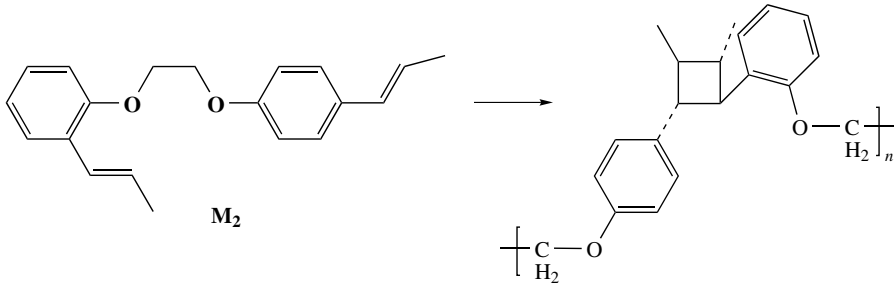
Significantly, when the purified cyclodimer of $\mathbf{M_1}$ was subjected to PET conditions, the polymerization occurred much more efficiently, yielding a polymer the NMR spectrum of which was essentially identical to that obtained in the aminium salt method, except that the M_W was 11 400(PDI = 2.0). It is also noted that the lower molecular weight polymers show stronger NMR absorptions from the terminal propenyl groups than do the polymers obtained from the aminium salt method.

G. Electrochemical Initiation

Initiation of the polymerization of monomer $\mathbf{M_1}$ could also be accomplished by anodic oxidation of $\mathbf{M_1}$ to its cation radical. In this way a cycloaddition polymer was again obtained which was virtually identical to that obtained from both the aminium salt and PET methods except for M_W (3 366 and PDI = 2.5) and the intensity of the propenyl end group absorptions.

H. Cycloaddition Polymerization of Other Monomers Having Structures Related to That of $\mathbf{M_1}$

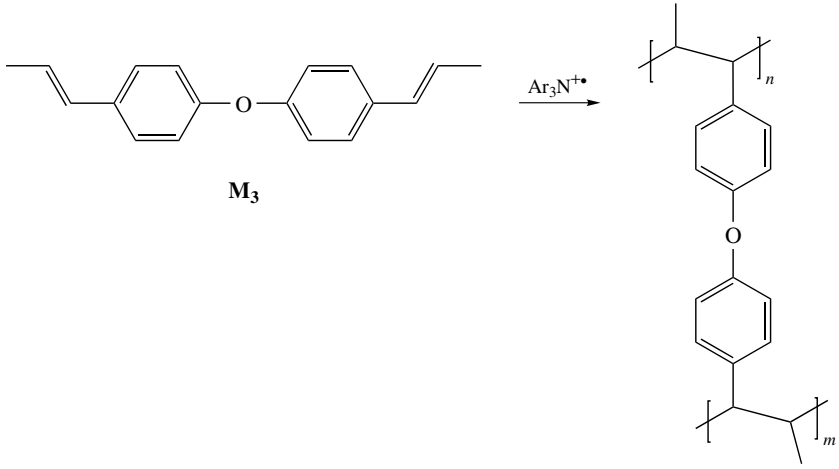
The aminium salt-initiated cation radical chain cycloaddition polymerization of monomer $\mathbf{M_2}$ was also found to be quite efficient, yielding a cyclobutapolymer having M_W 86 700 (PDI = 1.84) when the monomer is polymerized at a concentration of 0.192 M for 8 minutes, using 10 mol% of the initiator (Scheme 34).



SCHEME 34. Cation radical chain cyclobutapolymerization of the *o*, *p* isomer ($\mathbf{M_2}$) of $\mathbf{M_1}$

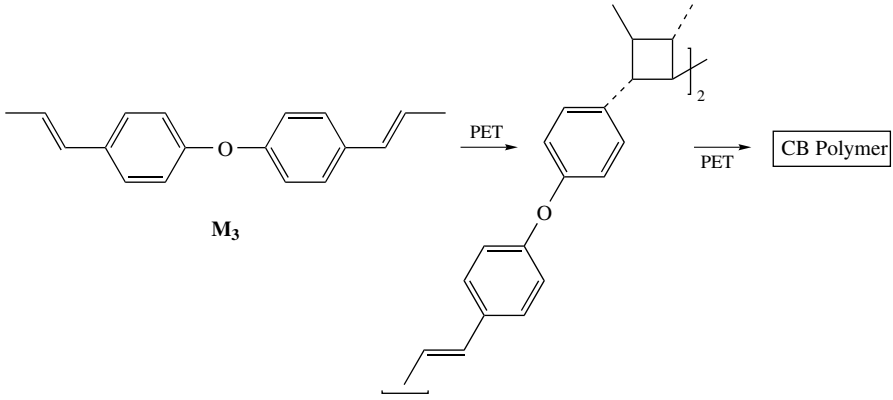
The polymerization of 4,4′-bis(*trans*-1-propenyl) diphenyl ether ($\mathbf{M_3}$) was also investigated (Scheme 35). The application of the standard aminium salt procedure to this monomer yielded an insoluble, evidently highly cross-linked polymer as the major product[40]. Solid state ^{13}C NMR spectroscopy revealed that this was not primarily a cyclobutapolymer, but a linear addition polymer, cross-linked through the second propenyl functionality. Since cation radicals are known to be able to act as strong acids, and since a virtually identical polymer could be prepared by an acid-catalyzed, carbocation-mediated route using triflic acid as a catalyst, the polymer generated under aminium salt conditions is considered to arise via a cationic polymerization mechanism. The failure of the cation radical chain cycloaddition method to prevail with $\mathbf{M_3}$, as it does with $\mathbf{M_1}$ and $\mathbf{M_2}$ is evidently not the inability of the initiator to ionize $\mathbf{M_3}$, since the peak oxidation potential of the latter is 1.36 V, which is well within the range of the ability of this initiator to ionize substrates at a rate sufficient to support efficient cation radical chain chemistry. Instead, it is postulated that the intramolecular transfer from the long-bond cation radical site to the propenyl group may not be sufficiently exergonic in this system, as a result

of the more difficultly ionizable propenyl groups in $\mathbf{M_3}$. As in the case of monomer $\mathbf{M_1}$, the photosensitized reaction of $\mathbf{M_3}$ gave primarily the dimer. Once again, purification of the cyclodimer and initiation under PET conditions (Scheme 36) afforded moderately efficient cycloaddition polymerization (M_W7 220; PDI = 6.7).



$\mathbf{M_3}$

SCHEME 35. Carbocation-mediated, cationic linear/cross-link polymerization of 4,4′-bis(*trans*-1-propenyl)diphenyl ether under aminium salt conditions



$\mathbf{M_3}$

SCHEME 36. Photosensitized electron transfer (PET) initiated polymerization of the cyclodimer of monomer $\mathbf{M_3}$

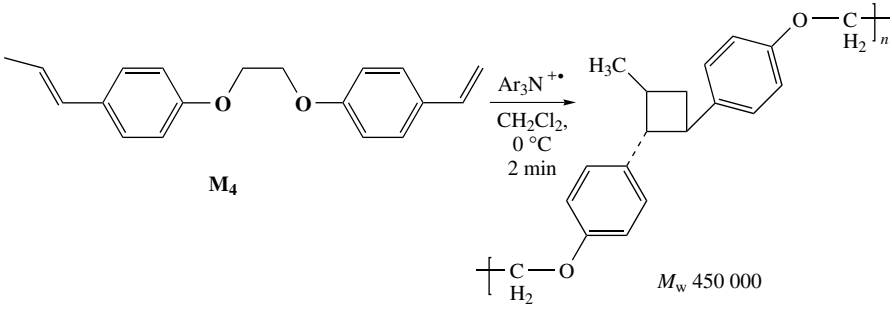
I. Propenyl vs Vinyl Monomers

In contrast to most polymerization methods, which proceed most efficiently when vinyl monomers are employed, cation radical cycloaddition polymerization and cation radical cycloadditions in general tend to work better with propenyl monomers. In some cases, and to some extent, this is the result of the greater ease of ionization of propenyl as compared to

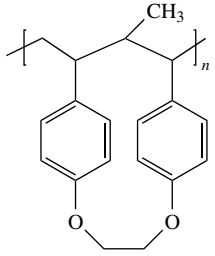
vinyl groups, a consequence of the electron-releasing ability of alkyl groups. Perhaps more generally, propenyl monomers are favored over vinyl monomers because of the tendency of the latter to undergo rapid cationic polymerization induced either by protonation of vinyl groups by strong Bronsted acids generated during the aminium salt-initiated reactions or by direct electrophilic reaction of the aminium ion with the sterically unhindered vinyl groups to generate carbocations. On the other hand, the corresponding propenyl monomers appear to be much less subject to either acid-catalyzed or electrophilically catalyzed carbocation-mediated polymerization. When the alkene moiety is disubstituted by, for example, methyl groups (isobutenyl moieties), ionization is even more facile, but both carbocation and cation radical polymerizations are sharply retarded. It should, however, be noted that relatively efficient monofunctional cation radical cycloadditions have been established for phenyl vinyl sulfide and phenyl vinyl ether, so that these functionalities could also prove to be effective in the bifunctional, polymerization context.

As an example of the sharply differing behavior of propenyl vs vinyl substrates, the cation radical cycloadditions (both cyclobutadimerization and Diels–Alder additions) of *trans*-anethole are typically quite facile and efficient under aminium salt conditions; those of 4-vinylanisole are completely overwhelmed by cationic polymerization of this reactive monomer. To take advantage of both the greater ease of ionization of propenyl groups and the intrinsically higher reactivity of vinyl groups as the neutral cycloaddition component, the synthesis and polymerization of mixed vinyl/propenyl monomers was proposed. It was presumed at the outset that the propenyl moiety of the monomer would be preferentially ionized and that this propenyl cation radical would react preferentially with the unhindered vinyl moiety of a neutral monomer molecule. It has previously been established that cation radicals add much more rapidly to 4-vinylanisole than to *trans*-anethole, presumably as the result of steric repulsions engendered by the terminal methyl group.

Consequently, the unsymmetrical monomer **M$_4$** was prepared and its polymerization was carried out (Scheme 37)[41]. The polymerization (0.04 M, 10 mol% initiator) was



But also containing cyclopolymerization linkages:

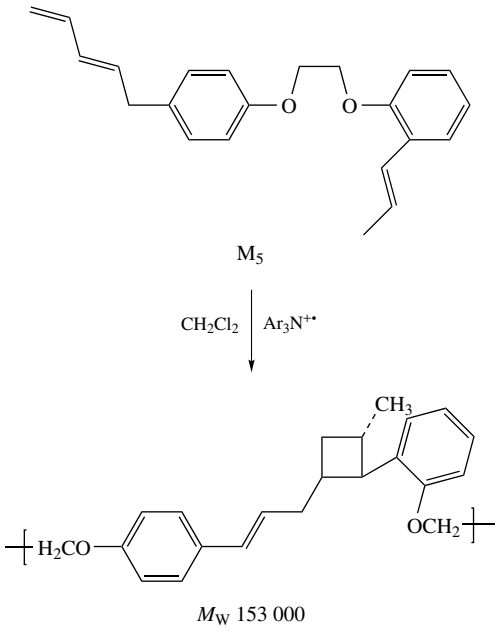


SCHEME 37. Mixed cycloaddition/cyclopolymerization of an unsymmetrical vinyl/propenyl monomer under aminium salt conditions

impressively facile, leading to the formation of a soluble polymer having M_W450 000 (PDI = 4.9) after only two minutes of reaction. The similarity of the NMR spectrum of this polymer to that of the cross adduct of *trans*-anethole and vinylanisole was striking, indicating the presence of an abundance of these unsymmetrical cyclobutane linkages. However, very careful NMR studies (including 500 MHz ^{1}H NMR and both H−H and C−H correlation spectra) revealed the additional presence of moieties formed by cyclopolymerization. The ratio of cyclobutapolymerization to cyclopolymerization was found to be approximately 1:1. Evidently, linear addition was not a major competitor, since no insoluble polymer was formed, and linear polymerization would be expected to result in crosslinking. The observation of efficient macrocyclopolymerization (ring size = 15) is also noteworthy, especially for a propenyl monomer.

J. Cyclobutapolymerization vs Diels–Alder Cycloaddition Polymerization

The polymerization of a monomer which contains a readily ionizable moiety of the anethole type and a conjugated diene moiety represents an interesting opportunity to examine the competition between cyclobutapolymerization and Diels–Alder polymerization. The monomer **M$_5$**, when subjected to the standard aminium salt conditions, affords the cyclobutapolymer shown in Scheme 38[38, 39]. At longer reaction times, however, the cyclobutapolymer rearranges to a Diels–Alder polymer via a cation radical vinylcyclobutane rearrangement.

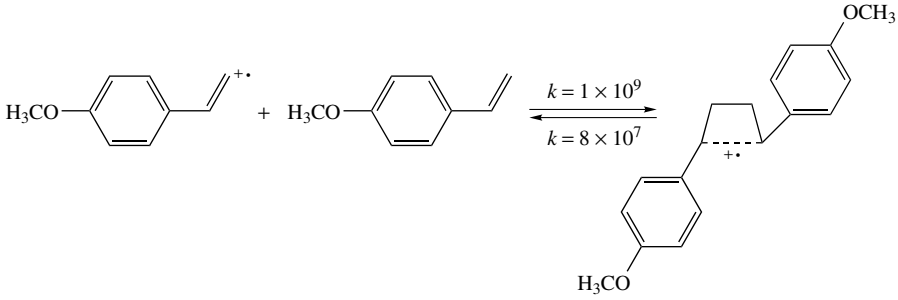


SCHEME 38. Vinylcyclobutane rearrangement of a cyclobutapolymer

XXIV. RETROCYCLOBUTANATION

The cycloreversion of a cyclobutane derivative to two alkene moieties via a cation radical mechanism, i.e. the reverse of the cation radical/neutral cycloadditions which have been

discussed in considerable detail, is also sometimes quite facile. The conversion of the *trans,syn,trans* cyclobutadimer of *trans*-anethole to the *trans,anti,trans* isomer, which was discussed in an earlier section of this chapter, is an especially interesting example of cycloreversion, in this case followed by re-addition to yield a thermodynamically more stable cyclobutadimer. Presumably this cycloreversion is facilitated by the relief of steric repulsions between the *cis* anisyl groups and also between the *cis* methyl groups. However, it appears likely that the cycloreversion may still be reasonably facile even for the *trans,anti,trans* isomer. In support of this, Schepp and Johnston have measured the rate constants for both the cycloaddition of the 4-vinylanisole cation radical to 4-vinylanisole and of the cycloreversion of the corresponding cyclobutadimer cation radical (Scheme 39)[31]. The cycloreversion rate constant was found to be 8×10^7 s^{-1}. This was only a little slower than the corresponding arylcyclobutane rearrangement, which has a rate constant of 1.5×10^8 s^{-1}. That cycloreversion is slower than rearrangement is consistent with the observation that several cation radical vinylcyclobutane rearrangements have been found to occur without competing cycloreversion.

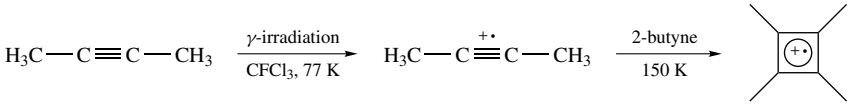


SCHEME 39. The rate of a cation radical retrocyclobutanation

XXV. CATION RADICAL CYCLOADDITIONS INVOLVING ALKYNES

A. The Formation of Cyclobutadiene Cation Radicals

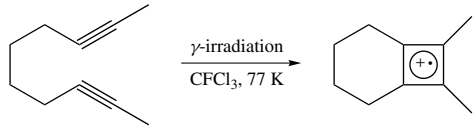
The employment of alkynes in either cation radical cyclobutadimerizations or cross cyclobutanations has not yet proved very successful in an organic synthetic sense (e.g. using the aminium salt or PET methods). However, the γ-irradiation of 2-butyne in a solid matrix of $CFCl_3$ at 77 K, followed by annealing the sample up to *ca* 150 K, has been reported to yield the tetramethylcyclobutadiene cation radical (Scheme 40)[42]. Apparently the 2-butyne cation radical is generated by the low temperature irradiation and then reacts with neutral 2-butyne under the annealing conditions.



SCHEME 40. An alkyne cation radical/alkyne cyclobutadimerization

B. An Intramolecular Cation Radical Cycloaddition Reaction of a Bis(alkyne)

An interesting intramolecular version of the alkyne cation radical/neutral alkyne cycloaddition was also observed at 77 K by γ-irradiation of 2,8-decadiyne (Scheme 41).



SCHEME 41. An intramolecular version of the alkyne cation radical/alkyne cyclobutanation

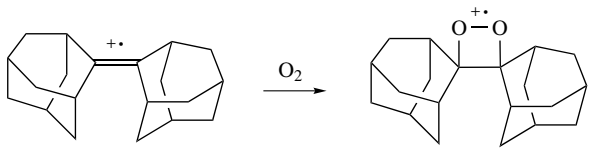
C. Theoretical Calculations of Cation Radical Cycloaddition Paths

Incidentally, the structure of the cyclobutadiene cation radical has been found to be rectangular, not square, but closer to square than in the case of neutral cyclobutadiene[43]. Theoretical studies provide a rather clear picture of the reaction of the ethyne cation radical with ethyne, indicating a concerted collapse of an intermediate T-shaped cation radical/neutral complex to the cyclobutadiene cation radical[44]. Analogous studies have been carried out for the reaction of the ethene cation radical with ethyne[45]. However, the corresponding reaction of the ethene cation radical with ethene preferentially leads to the formation of the 1-butene cation radical[46].

XXVI. CATION RADICAL CHAIN REACTIONS OF ALKENE CATION RADICALS WITH DIOXYGEN

In the pioneering research of the Ledwith group, the cation radical cyclobutadimerization of *N*-vinylcarbazole was found to be strongly inhibited by molecular oxygen. The majority of cation radical cycloaddition reactions studied under aminium salt conditions in this research group, however, appear to occur rather smoothly in the presence of atmospheric oxygen (i.e. even when an inert atmosphere is not provided). This suggests that the reactions of many cation radicals with their corresponding neutral molecules are faster than their reactions with dioxygen at these low concentration levels. However, in the case of sterically hindered substrates which can readily form cation radicals, efficient cation radical chain cycloadditions to dioxygen (dioxacyclobutanation) can sometimes be observed as a consequence of the relative slowness of the additions of cation radicals to hindered neutral substrates.

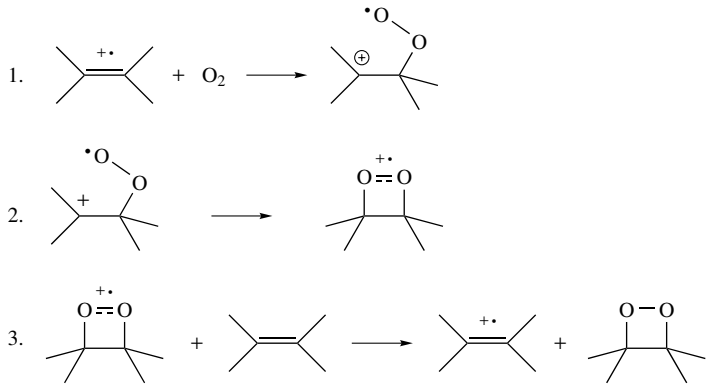
The elegant work of the Nelsen group has demonstrated that the bisadamantylidene cation radical, generated by anodic oxidation, reacts efficiently with dioxygen to form the corresponding 1,2-dioxetane via the cation radical of this latter 1,2-dioxetane (Scheme 42)[47]. The ESR spectrum of the latter cation radical reveals it to have a ring-closed structure which presumably has a three-electron oxygen–oxygen bond. When the reaction of bisadamantylidene with dioxygen is initiated by 'magic green', tris(2,4-dibromophenyl)aminium hexachloroantimonate, efficient conversion to the dioxetane occurs with a chain length of as much as 800 at −78 °C. Analogous cycloadditions



Bisadamantylidene
Cation Radical

SCHEME 42. Cation radical cycloaddition of the bisadamantylidene cation radical to dioxygen

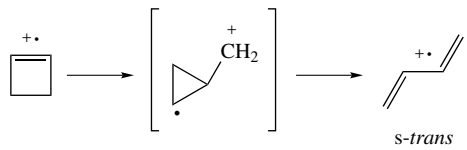
have been observed for a variety of hindered, highly substituted alkenes. Even isopropylidene adamantane and 1,1-diisopropyl-2,2-dimethylethene undergo the reaction, but 2,3-dimethyl-2-butene and 1,2-dimethylcyclohexene do not. The chain mechanism proposed for these reactions is illustrated in Scheme 43.



SCHEME 43. The stepwise mechanism for the cation radical chain dioxygenation of alkenes

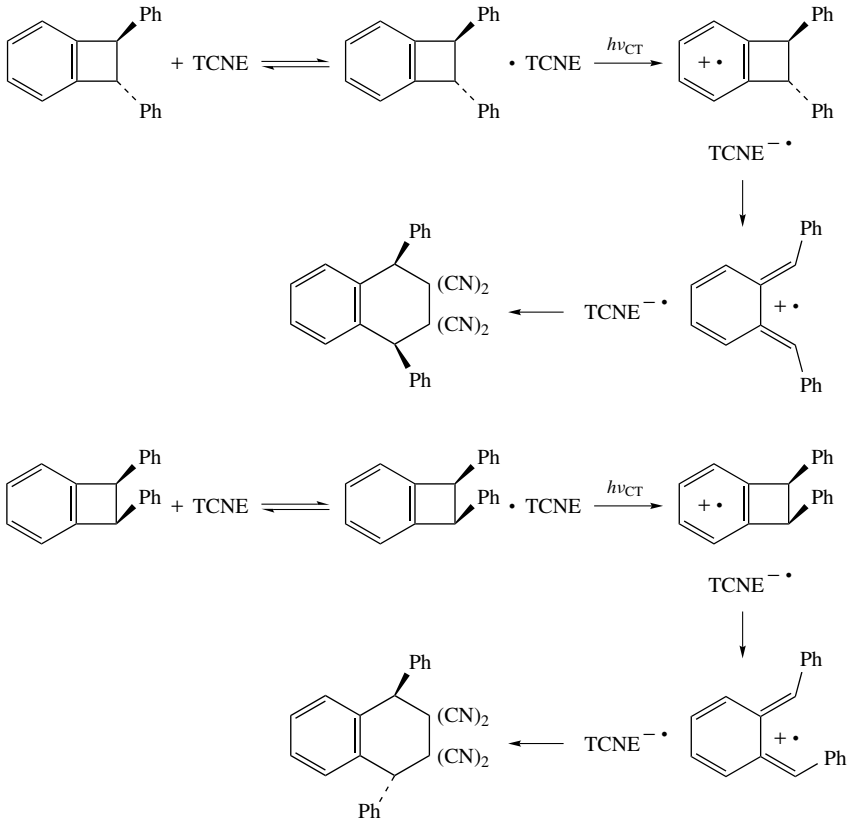
XXVII. RETROELECTROCYCLIC REACTIONS OF CYCLOBUTENE CATION RADICALS

Although cation radicals of cyclobutenes could potentially undergo cycloreversion to an alkyne and an alkene cation radical, it appears that more often the preferred pericyclic reaction is a retroelectrocyclic reaction affording a diene cation radical. The parent cyclobutene cation radical has been observed to undergo such a reaction both in the gas phase[48] and in a solid matrix[49]. The latter study is especially interesting in that, instead of forming the cation radical of s-*cis*-1,3-butadiene, as might have been expected, the only observed product is the s-*trans*-1,3-butadiene cation radical (Scheme 44). This result had previously been predicted on the basis of molecular orbital calculations, which envisioned a reaction path involving a cyclopropylcarbinyl cation radical intermediate, rather than a true retroelectrocyclic path[50]. Subsequently, more sophisticated theoretical studies have provided strong support for a reaction path involving a cyclopropylcarbinyl cation radical structure, which is, however, not an energy minimum on the path[51].



SCHEME 44. The formal retroelectrocyclic reaction of the cyclobutene cation radical to the s-*trans*-1,3-butadiene cation radical

The cleavage of the *cis*- and *trans*-1,2-diphenylbenzocyclobutene cation radicals is another especially elegant example of a retroelectrocyclic reaction of a cyclobutene derivative[52]. The cation radicals of these two substrates were generated by irradiation



SCHEME 45. The conrotatory retroelectrocyclic cleavage of the *cis*- and *trans*-1,2-diphenylbenzocyclobutene cation radicals

of the charge transfer complexes of these substrates with tetracyanoethylene at the charge transfer band of the complexes, resulting in the formation of an ion radical pair consisting of the substrate cation radical and the TCNE anion radical. The retroelectrocyclic reactions which followed were facile, forming cation radicals of the diphenyl-*o*-xylylene type (Scheme 45). The subsequent reactions of these latter cation radicals with the tetracyanoethylene anion radical were found to form adducts of the tetrahydronaphthalene type via what amounts to an anion radical/cation radical Diels–Alder reaction. Evidently, both the retroelectrocyclic cleavage and the subsequent Diels–Alder cycloaddition are highly stereospecific. Since the *cis* substrate results in the formation of the Diels–Alder adduct having *trans* phenyl groups and the *trans* substrate forms only the adduct having *cis* phenyls, the cleavage reaction must have been conrotatory, i.e. it has the same stereochemical bias as the retroelectrocyclic cleavage of neutral cyclobutenes.

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CHAPTER **14**

Highly unsaturated cyclobutane derivatives

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I. INTRODUCTION

Cyclobutane (**1**) and cyclobutene (**2**) have strain energies of 26.5 and 28.4 kcal mol^{-1}, respectively[1–3]. These substances and their many derivatives generally are stable and isolable. The scope of the present chapter includes structures which contain two or more (!) double bonds or a *triple* bond in a four-membered ring. As will be apparent, many of these substances lie on the fringe of existence.

Systematic dehydrogenation beyond cyclobutene (C_4H_6) yields a small but remarkable collection of C_4H_n structures, as shown in Scheme 1. C_4H_4 isomers in this series include

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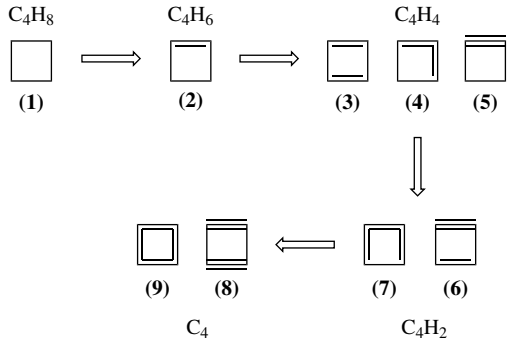
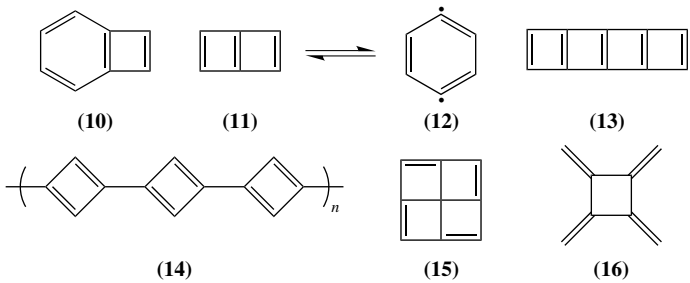


SCHEME 1

1,3-cyclobutadiene (**3**), 1,2-cyclobutadiene (**4**) and cyclobutyne (**5**). 1,3-Cyclobutadiene is one of the most famous molecules in organic chemistry but its isomeric brethren **4** and **5** are almost unknown. Much has already been written about the fascinating chemistry of 1,3-cyclobutadiene[4–12] and only some recent developments will be highlighted here. The series is completed by C_4H_2 and C_4; both are expected to be highly reactive. Structures **6** and **7** are almost certainly just formal resonance structures. Neither resonance structure **8** nor **9** inspires confidence in the existence of cyclic C_4. Of course substances with odd numbers of hydrogen (e.g. C_4H_5) also exist as radical or ionic intermediates. Best known in this series is the $C_4H_5^+$ homocyclopropenyl cation studied decades ago by Winstein[13] and by Olah and coworkers[14].

The collection of more exotic but related structures (Scheme 2) is not large. These range from substances that are isolable and well studied to others that currently exist only as a gleam in the eye of theoreticians. For example, benzannelated cyclobutadienes (e.g. **10**) are well known[15]; this topic is reviewed elsewhere in this volume. The relationship between C_6H_4 isomers butalene (**11**) and *p*-benzyne (**12**) remains a question of active investigation[16]. More elaborate structures which build on some of the frameworks in Scheme 1 have been considered but remain unknown. For example, polybutalenes[17] (**13**) and polycyclobutadienes[18] (**14**) might be expected to have unusual electronic properties. Structure **15** could engender a planar central carbon atom amidst a ring of cyclobutadienes[19]. Highly unsaturated 'fenestrane' structures such as this remain a subject of great interest[20]. Following a very different motif, quite a variety of derivatives of radialene **16** are known and isolable[21]. Moore and Yerxa have reviewed the



SCHEME 2

diverse synthetic applications of cyclobutenediones and related structures[22]. Finally, many heterocyclic variants on these structures are possible. Aza-, phospha- and silacyclobutadienes have received considerable study. These are discussed in a later section in this chapter.

II. 1,3-CYCLOBUTADIENE

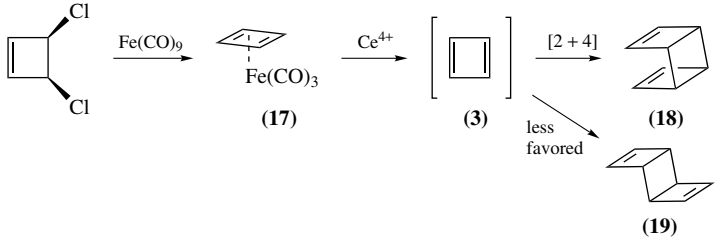
A. Synthesis of 1,3-Cyclobutadienes

At the beginning of a classic paper entitled (in the English version) 'The Taming of Cyclobutadiene', Cram noted: 'Cyclobutadiene $(CH)_4$, is the *Mona Lisa* of organic chemistry in its ability to elicit wonder, stimulate the imagination and challenge interpretive instincts'[23]. The first attempts to prepare a 1,3-cyclobutadiene derivative are described in 19th century reports by Kekulé[24] and by Perkin[25]. Soon thereafter, Willstätter and von Schmaedel[26] prepared cyclobutene (**2**) and made the first attempt to prepare parent diene **3**. The field lay largely dormant for decades until Longuet-Higgins and Orgel predicted in 1956 that cyclobutadiene would form stable transition metal complexes[27]. This prediction was soon realized by Criegee, who prepared a nickel(0) complex of tetramethylcyclobutadiene[28]. Several years later, Pettit reported the synthesis of **17**, the iron tricarbonyl complex of the parent hydrocarbon[29]. Subsequent work showed that the parent diene is easily released by oxidation (Scheme 3) with cerium ammonium nitrate (CAN) and this is now a widely used synthetic approach[30]. In the absence of trapping agents, **3** dimerizes to **18** rather than **19**.

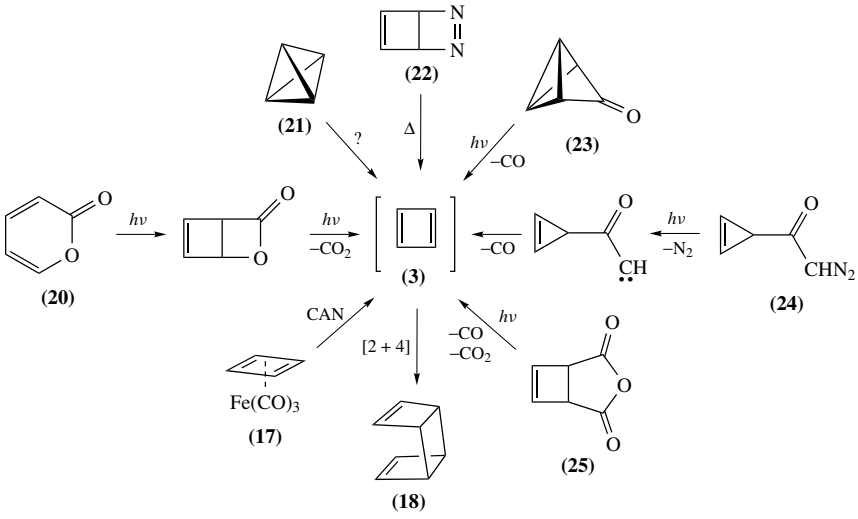
This early work stimulated a lively international effort which led to rapid development of numerous routes to **3**. Most of the known methods are summarized in Scheme 4[7,8,10,31]. Synthetic routes to intermediate **3** generally involve cycloreversion to release some stable molecular fragment such as CO, N_2 or CO_2. This is exemplified by the thermal or photochemical reactions of **20** and **22**–**25**. Although tetra-*t*-butyl-tetrahedrane rearranges to the isomeric cyclobutadiene[32], it is uncertain if the parent structure **21** will do the same since tetrahedrane remains unknown.

Dimerization of **3** yields the *endo* dimer **18**, even though this is the less stable product. Li and Houk studied this process by *ab initio* SCF and complete active space SCF calculations, which predict no potential energy barrier[33]. Along the *syn* dimerization pathway toward **18**, calculations show a novel second-order stationary point of D_{4h} symmetry which resembles two symmetrically-stacked cyclobutadienes.

An impressive collection of metal complexes of 1,3-cyclobutadiene now exists and this area has been reviewed[34,35]. For example, a routine search in the *Cambridge Crystallographic Structure Database*[36] under the term 'cyclobutadiene' brought up over 200 entries, most of them metal complexes of cyclobutadiene derivatives with nickel, cobalt, iron, rhodium, platinum and other metals.



SCHEME 3



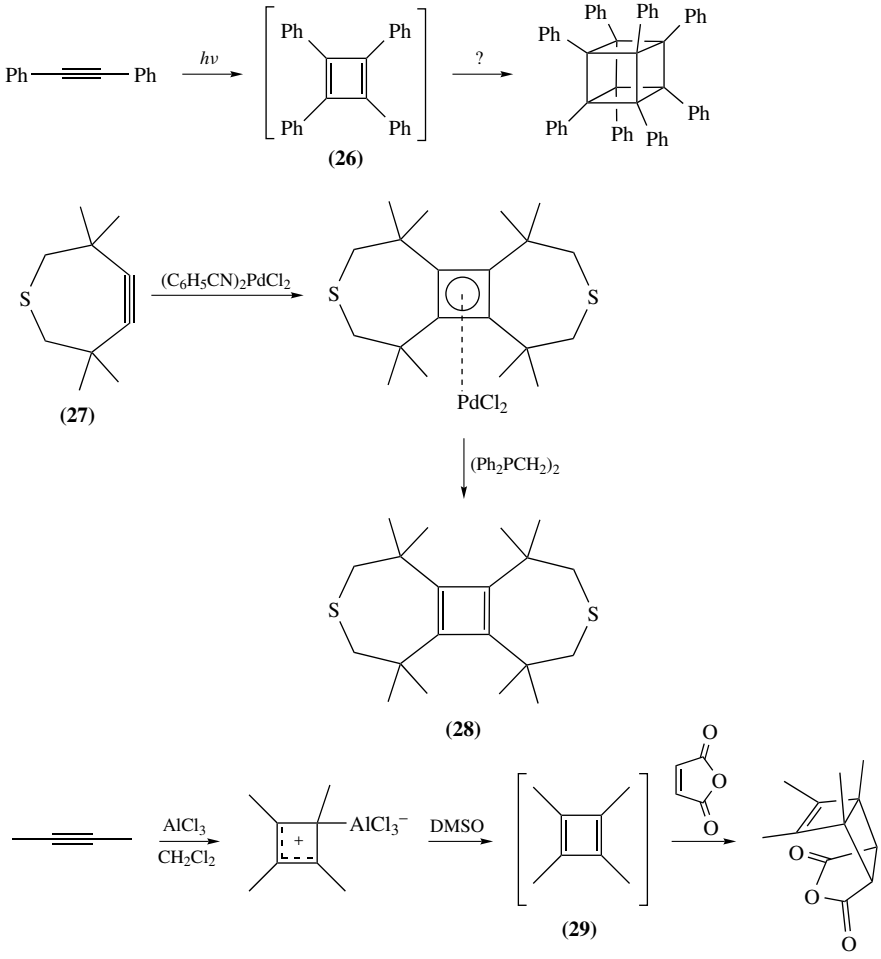
SCHEME 4

Before the end of the 1970s, the existence of 1,3-cyclobutadiene as a 'free' species had been well established by several groups[37,38] while numerous derivatives of **3** were prepared as intermediates. Cava and Mitchell's classic 1967 book *Cyclobutadiene and Related Compounds* collects a vast array of science on this topic[4], but the authors summarily conclude on page 1 that there seems '. . .little hope that a stable cyclobutadiene can be synthesized'. However, contrary to expectations, the authors also noted that Dewar and Gleicher had recently predicted a singlet ground state for **3**[39].

Dimerization of alkynes presents another logical route to cyclobutadienes. Photodimerization is known to occur in limited cases but complex products may result from secondary reactions. For example, irradiation of diphenylacetylene is reported to give a low yield of octaphenylcubane and Büchi and coworkers speculated that tetraphenylcyclobutadiene (**26**) may be an intermediate[40]. Thermal dimerization of a strained alkyne was used in Kimling and Krebs' brilliant route (Scheme 5) to an isolable cyclobutadiene[41,42]. Reaction of strained cycloalkyne **27**—itself a landmark structure—with Pd(II) afforded a metal complex. Subsequent ligand exchange with $(Ph_2PCH_2)_2$ gave **28**, the first isolable cyclobutadiene. In a better explored [2 + 2] route, reaction of simple alkynes with $AlCl_3$ yields a zwitterionic species which liberates cyclobutadienes such as **29**[43,44]. Trapping yields an *endo* adduct. This has not been applied to the parent diene. Matrix photolysis of 1,3-cyclobutadiene yields two molecules of acetylene, but only recently has a reversal of this process been reported by Maier and Lautz[45]. Bally and coworkers have studied the addition of acetylene radical cation to another acetylene to give cyclobutadiene radical cation[46].

B. Structure, Stability and Spectroscopy

Cyclobutadiene has played an important role in the theory of aromaticity and antiaromaticity[47–49]. A square planar structure for **3** (D_{4h} symmetry) is expected to be antiaromatic, with two formally nonbonding molecular orbitals. According to Hund's rule, this should preferentially exist as a triplet. The molecular orbital energy levels are shown in Figure 1. Jahn–Teller distortion to a rectangular geometry (D_{2h} symmetry) lifts



SCHEME 5

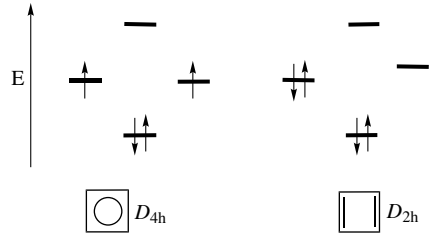


FIGURE 1. Orbital energies for 1,3-cyclobutadiene

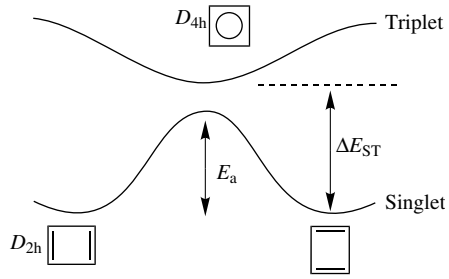


FIGURE 2. Potential surfaces for singlet and triplet 1,3-cyclobutadiene

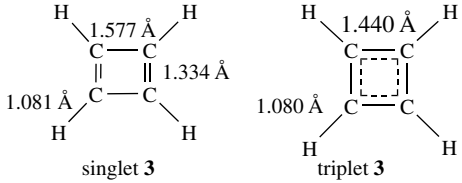


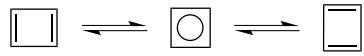
FIGURE 3. B3LYP/6-311+G** structures

the orbital degeneracy and allows for spin pairing in the singlet species. This may also be expected to localize the double and single bonds.

The current view of parent 1,3-cyclobutadiene—hard-won from decades of outstanding research—is summarized in Figure 2. Singlet 1,3-cyclobutadiene has a rectangular (D_{2h}) equilibrium structure with a small barrier (E_a) to automerization through a D_{4h} transition state. Based on theory and experiment, the best estimate for E_a is *ca* 5–6 kcal mol^{-1} [50–54]. By contrast, for the triplet state, a D_{4h} geometry is preferred. The difference between singlet and triplet **3,** ΔE_{ST}, is believed to be *ca* 7 kcal mol^{-1}.

In hindsight, this diagram makes eminent sense; nevertheless, the accumulation of information leading to such a simple description has posed many challenges. During the early 1970s, Krantz[55] and Chapman[56] and their coworkers independently reported the first photochemical generation of parent **3** in an argon matrix. Photolysis of α-pyrone (**20**, Scheme 4) yields **3** in two steps. Krantz did not initially commit to a structural assignment but Chapman concluded: 'The simplicity of the cyclobutadiene infrared spectrum consisting of four fundamentals. . .leads us to the tentative conclusion that cyclobutadiene has D_{2h} symmetry'. Later analysis by several groups revised this interpretation in favor of *seven* fundamental vibrations and thus a rectangular structure[57–61]. High-level computational studies now uniformly predict a rectangular structure for singlet **3** and a square geometry for the triplet[54,62]. For example, B3LYP/6-311+G** geometries for singlet and triplet **3** are given in Figure 3[54].

Peters and coworkers have used photoacoustic calorimetry to estimate the antiaromaticity of **3** as 55 ± 11 kcal mol^{-1} [63]. This number is derived from a combination of calculations and an experimental heat of reaction, as measured by the laser photoacoustic method. More recently, Suresh and Koga employed a novel homodesmotic scheme to estimate a ring strain of 34.7 kcal mol^{-1} (MP4 theory) and antiaromatic destabilization of 40.3 kcal mol^{-1} [64]. DFT theory gave very similar values. Rogers and coworkers have estimated the heat of formation for **3** at various levels of theory[65,66]. The best current value for the heat of formation of **3** is 106.3 kcal mol^{-1}. No completely experimental



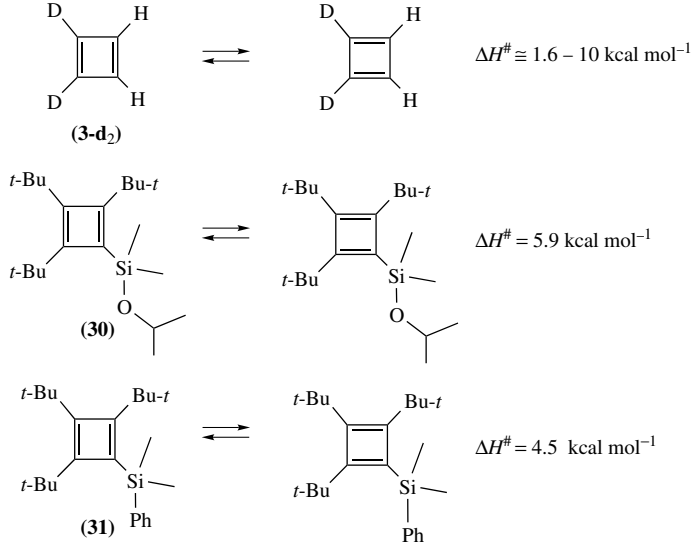
SCHEME 6

value is available. Kass and Broadus have reported an experimental heat of formation for benzocyclobutadiene (**10**) and predicted a value of 102 kcal mol^{-1} for **3**[67].

The process of automerization in cyclobutadiene (Scheme 6) still holds some mysteries. The barrier to double bond switching is expected to be quite small and reliable experimental data are sparse. To date, the best computational efforts predict a value around 6–7 kcal mol^{-1} but this requires a well correlated wavefunction; many computational methods yield values that are probably much too high[53,54,62,68,69].

The experimental barrier for parent **3** remains a subject of uncertainty. Carpenter studied the trapping of **3-d$_2$** (Scheme 7) generated from labeled **22** to provide one quantitative estimate. Based on rapid scrambling of the isotopic label, he concluded that the automerization barrier was between 1.6 and 10 kcal mol^{-1}, with a large negative entropy of activation[70]. Carpenter further postulated that automerization in **3** is dominated by heavy atom tunneling. This idea has attracted considerable attention[71–75]. Grant, Michl and coworkers studied the NMR spectrum of ^{13}C labeled **3** in an argon matrix and concluded that rapid equilibration between tautomeric forms occurs even at 25 K[76]. This would seem to argue for an effective barrier lower than that calculated. Maier's group has used dynamic NMR to measure more accurate values for E_a in derivatives **30** and **31** and ruled out the participation of heavy atom tunneling in these reactions[52]. In these cases, differences in steric effects in the transition state may play a major role. At present, it seems that more reliable experimental data are needed on the parent structure **3** and the role of the matrix is still unclear. Redington has provided a detailed analysis of this possibility[69,77].

Wannere and Schleyer have reported the most detailed analyses of the NMR properties of **3**[78]. According to DFT calculations, the predicted ^{1}H chemical shift for **3** is 5.9 ppm,



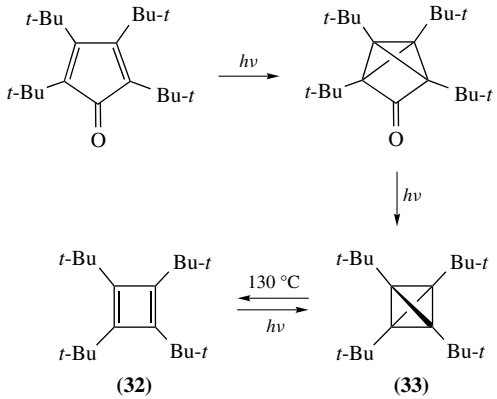
SCHEME 7

somewhat downfield from the value expected for a paramagnetic ring current[78,79]. Surprisingly, Schleyer's analysis shows that paratropic contributions from the π bond in **3** are nearly zero. The experimental chemical shift of **3** as a carceplex[23] is 1.51 ppm; by comparison to benzene in the same clathrate environment, this gives an estimate of 5.76 ppm, in good agreement with theory. The vinyl hydrogen in tri-*t*-butyl-**3** appears at 5.38[80]. According to calculations, structure **3** shows a strongly positive NICS (nucleus-independent chemical shift) value consistent with the expected antiaromaticity[81,82].

The ultraviolet spectrum of **3** is surprisingly difficult to measure because the longest wavelength band at >300 nm is optically forbidden and thus quite weak[9,83,84]. In tetra-*t*-butyl-1,3-cyclobutadiene, which is slightly yellow, this band is shifted to 425 nm but it is still a weak transition with $\varepsilon = 38$[32].

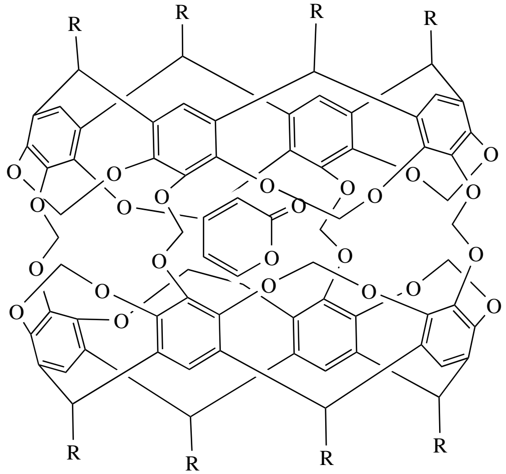
C. Isolable Cyclobutadienes

In addition to the cryogenic matrix studies described above, several extraordinary strategies have led to room-temperature *isolable* 1,3-cyclobutadienes. In the first approach, several research groups steadily worked toward the preparation of cyclobutadienes bearing bulky substituents. As shown in Scheme 5 above, Kimling and Krebs first prepared kinetically stabilized cyclobutadiene **29** in 1972[41]. A hydrocarbon version was reported later[42]. Unfortunately, this impressive milestone was not deemed to resolve the square/rectangular structure dilemma because of the two fused rings, which might bias an equilibrium. Tri-*t*-butyl-1,3-cyclobutadiene was soon made independently by the group of Masamune[85] and by Maier and Sauer[86]. This amazing substance is isolable, although it readily dimerizes at room temperature and reacts quickly with alcohols or water. Soon afterward, Maier's group prepared tetra-*t*-butyl-1-3-cyclobutadiene (**32**) by the method shown in Scheme 8[32]. Apart from oxygen sensitivity, this substance proved to be remarkably stable at room temperature. The thermal and photochemical interconversion of **32** and **33** is extraordinary. As expected, the X-ray crystal structure supported a rectangular geometry for **32**, but the geometry was less distorted than expected[87]. At −150 °C, the measured bond lengths were 1.441 and 1.527 Å[88]. Additionally, according to the reported crystal structure, this substance is nonplanar with a slight twist in the ring structure. Bond lengths in **32** may be distorted in the crystal lattice; as a consequence, Schleyer and coworkers suggest that DFT calculated values of 1.354 and 1.608 Å may be more accurate[89].



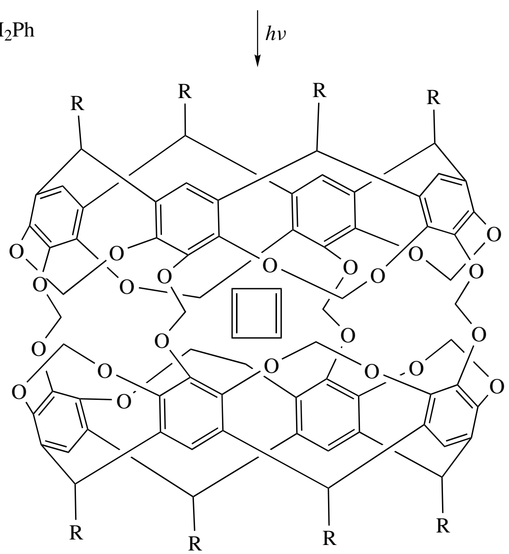
(32) **(33)**

SCHEME 8



(carceplex—**20**)

$R = CH_2Ph$

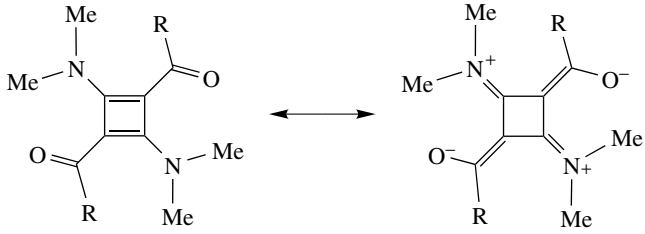


(carceplex—**3**)

SCHEME 9

In a second, even more extraordinary approach to an isolable cyclobutadiene, Cram and coworkers sequestered α-pyrone (**20**) in the interior of a hemicarcerand[23]. Photolysis of this complex (Scheme 9) in solution led to disappearance of the NMR signals for α-pyrone, with appearance of a new singlet at 2.27 ppm. This resonance was assigned to **3** as a carceplex in the molecular cavity. Heating resulted in the formation of cyclooctatetraene, presumably the consequence of escape of **3** from the hemicarcerand, dimerization to **18** and then ring opening.

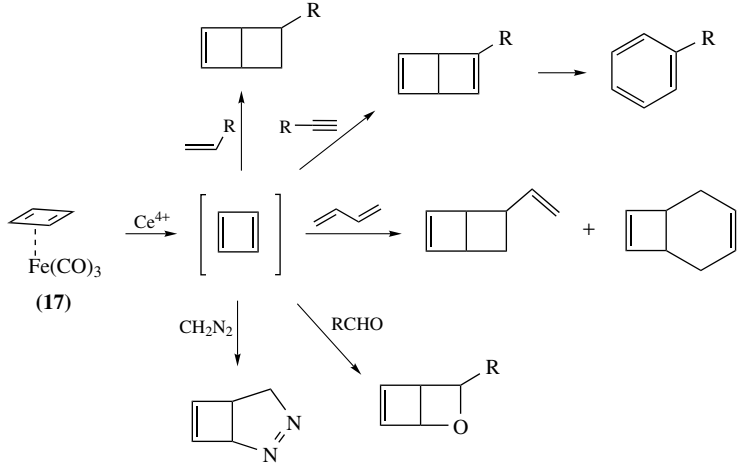
One other strategy that has led to isolable cyclobutadienes is the 'push–pull' concept in which substituents of opposite polarity are attached to the ring. As described by Breslow and coworkers in 1965, '...a compound may be stable if a cyclobutadiene structure is only one of the important resonance forms...'[90]. Efforts by the same authors to prepare such substances were unsuccessful. A few years later, Neuenschwander and Niederhauser reported the synthesis of **34a** and **34b** as moderately stable crystalline substances[91,92]. Hoffmann has noted that the push–pull effect results from stabilization of one pair of degenerate molecular orbitals and destabilization of the other pair[93].



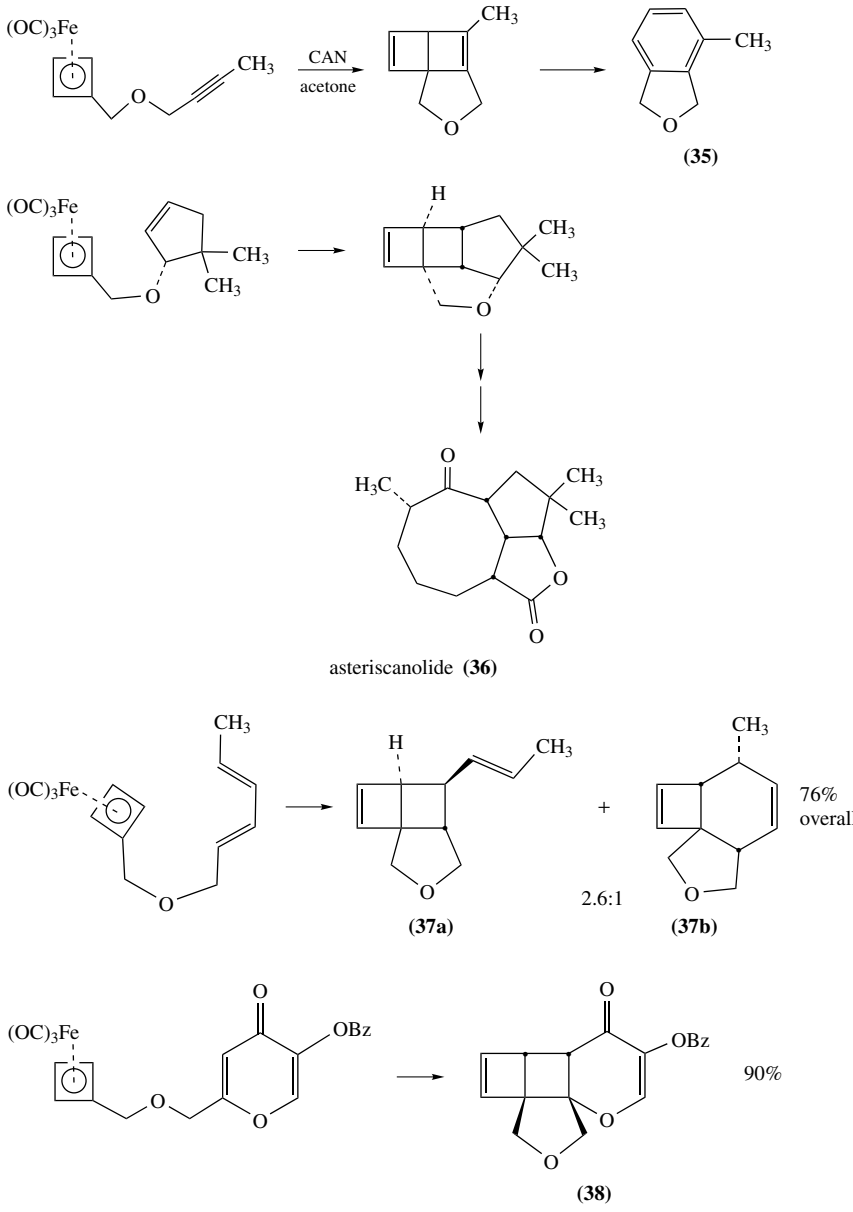
(34a) R = CH_3
(34b) R = OCH_3

D. Cyclobutadiene in Synthesis

In addition to its fascinating questions of structure, 1,3-cyclobutadiene may now be considered an important reagent in organic synthesis[10,94,95]. This substance is both a potent diene *and* dienophile, thus it is not surprising to see a growing number of creative synthetic applications. Common reaction modes are shown in Scheme 10. In most reactions, **3** plays the formal role of a 1,3-diene. Regitz and coworkers have published an extensive series of papers on synthesis with cyclobutadiene and have explored many modes of cycloaddition[96–101].



SCHEME 10

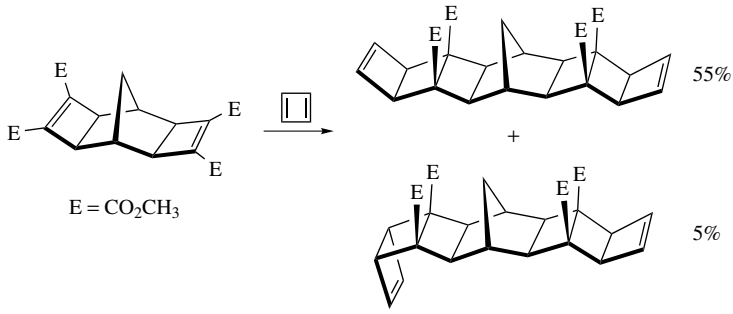


SCHEME 11

Scheme 11 shows a few of the applications of cyclobutadiene in synthesis. Grubbs and coworkers initially demonstrated that intramolecular [2 + 2] addition to a tethered alkyne will result in a bicyclic aromatic derivative (**35**), after ring opening of the intermediate Dewar benzene[102]. Limanto and Snapper employed an intramolecular [2 + 4]

cycloaddition in the total synthesis of asteriscanolide (**36**)[103]. More recently, Snapper, Houk and coworkers have reported extensive experimental and theoretical studies on intramolecular trapping of a tethered cyclobutadiene by alkenes and dienes[104, 105]. Two of the many examples from this work are shown. Cycloadducts such as **37a** and **37b** can result from competing [2 + 4] modes of addition or from secondary rearrangements. The efficient formation of cycloadduct **38** illustrates how optimal tether length and an electronically activated cycloaddition component result in high yield.

One other unique application of cyclobutadiene has been the synthesis of 'ladderanes' which has been reported (Scheme 12) by several groups[106–109]. These methods also rely on the unusual cycloaddition reactions of **3** to build novel frameworks of four-membered rings.



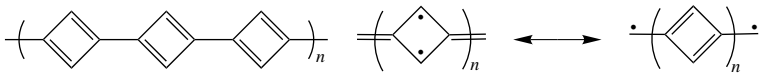
SCHEME 12

E. More Complex 1,3-Cyclobutadienes

Several more complex cyclobutadiene derivatives have been considered theoretically but not yet synthesized. In principle, the unusual structure of **15** might favor a planar tetracoordinate carbon atom, either for the neutral substance or some ionic variant. Following an earlier suggestion by Hoffmann, Alder and Wilcox[110], Schleyer and coworkers used MNDO calculations to predict the structure for neutral **15**[19]. The resulting geometry (**15a**) has a highly pyramidalized central carbon atom with alternating bond lengths. A few years later, Glidewell and Lloyd predicted a similar geometry for ionic variants of this structure[111]. They concluded that the geometry remains relatively constant because electrons are removed from or added to a nonbonding molecular orbital. This problem needs to be revisited at a higher level of theory.

(15) **(15a)**

Linear polycyclobutadiene (**14**) has been the subject of several theoretical studies. In the most thorough analysis, Dougherty and coworkers concluded that such structures will have high radical character (cf. **14** and **14a**) and thus novel electronic properties[18, 112].

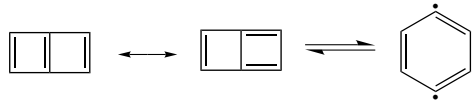


(14) **(14a)**

No synthetic efforts have been reported but we speculate that the strategy of peripheral *t*-butyl substitution might be successful at stabilization of these compounds.

III. BUTALENE CHEMISTRY

Butalene (**11**) may be considered a 'bond-stretch' isomer of the well-characterized intermediate *p*-benzyne (**12**) (Scheme 13). The interesting structure of butalene has been the subject of numerous theoretical studies[16, 17, 113–116]. In addition to its substantial ring strain, it is easy to see that butalene has both a six π electron aromatic component and two antiaromatic 1,3-cyclobutadiene rings. Amazingly, a *SciFinder* sub-structure search of the butalene ring substructure in early 2004 yielded 287 hits, but only 53 of these had an attached reference and none of these structures has proven to be isolable! The modern history of butalene began in 1974 when Dewar and Li predicted that both **11** and **12** represent energy minima, with a 4.6 kcal mol^{-1} barrier for rearrangement of **11** to **12**[113]. A year later, Breslow, Napierski and Clarke reported the first experimental evidence for **1** as a reactive intermediate[117]. Treatment of Dewar benzene **39** with $LiNMe_2/DNMe_2$ (Scheme 14) afforded primarily aniline derivative **40**. Partial label scrambling to the *ortho* and *para* positions was also observed. Reaction in the presence of diphenylisobenzofuran gave 10–15% of adduct **41**. The authors reasoned that butalene is formed and trapped, with further rearrangement or cycloaddition providing the observed products. The only troubling feature of these results is the above-mentioned deuterium label scrambling, which has not yet been explained.

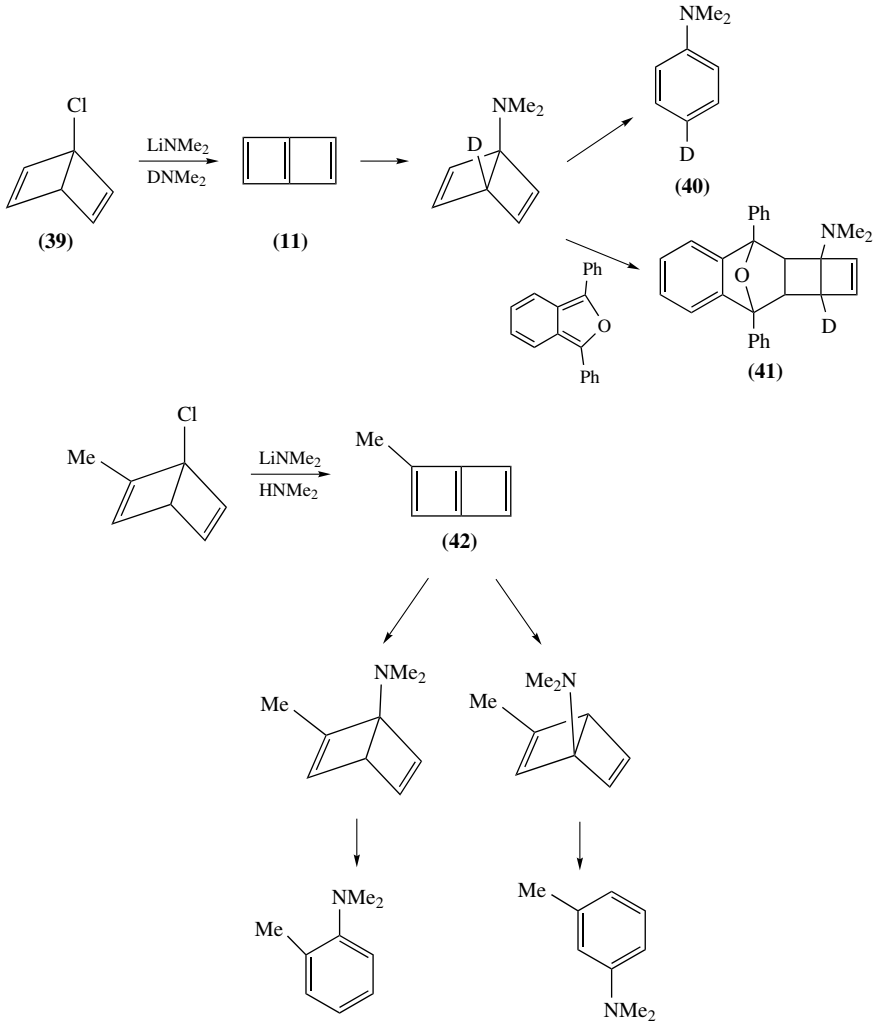


(11) **(12)**

SCHEME 13

Further support for this mechanism came from the observed chemistry (Scheme 14) of methyl derivative **42**[118]. In this case, both *meta* and *ortho* substituted anilines are observed, consistent with nucleophilic addition to methylbutalene **42**.

Computational studies on butalene (**11**) predict a planar structure with an elongated (*ca* 1.58 Å) central bond[16, 17, 113–116]. The question of aromaticity in butalene remains somewhat controversial. Most authors favor antiaromatic character based on various resonance or topological criteria[17]. By contrast, one recent study by Warner and Jones predicted a modest level of aromaticity[116]. This conclusion is based on an isodesmic scheme, a large predicted singlet/triplet gap, no evidence of diradical character and a slightly positive magnetic susceptibility exaltation. Rearrangement to *p*-benzyne (**12**, Figure 4) is predicted to be exothermic by *ca* 40 kcal mol^{-1} and this substantial exothermicity has led to questions about whether butalene even exists as an energy minimum or will spontaneously rearrange to *p*-benzyne. As with most such highly strained species, the estimated barrier to rearrangement is quite dependent on the level of theory. Predicted activation barriers range from Dewar's initial semiempirical prediction of 4.6 kcal mol^{-1}, through the first



SCHEME 14

ab initio prediction by Ohta and Shima of only 1.6 kcal mol^{-1} [115]. Nicolaides and Borden noted that ring opening of butalene involves a change in symmetry of the HOMO and thus is symmetry forbidden[114]. The transition state has C_2 symmetry with an out-of-plane twist. Indeed, the geometric hindrance to a fully conrotatory transition state is probably the only reason that butalene might exist at all.

In 2001, two groups addressed this reaction barrier at high levels of theory. Warner and Jones report '. . . the barrier . . . can confidently be placed between 3.5 and 5.5 kcal mol^{-1}' [1, 116]. This was based on B3LYP/6-31G* geometries and energetics calculated at several higher levels of theory. In the same year, Hess reported a B3LYP/cc-pVTZ value of 5.9 kcal mol^{-1}

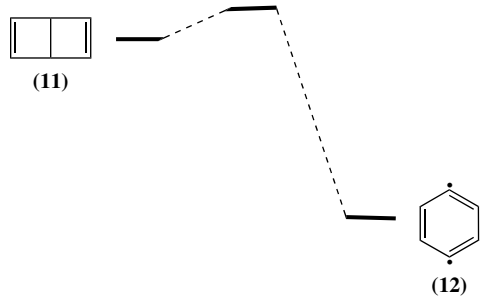
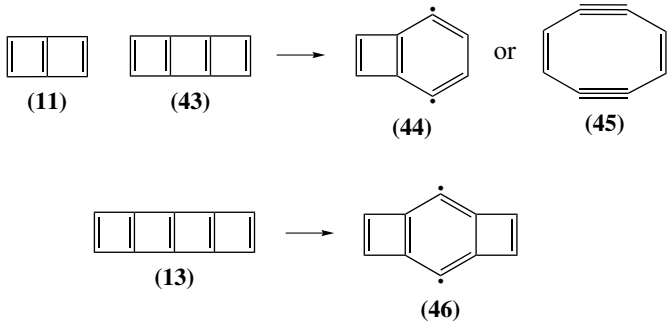


FIGURE 4. Ring opening of butalene

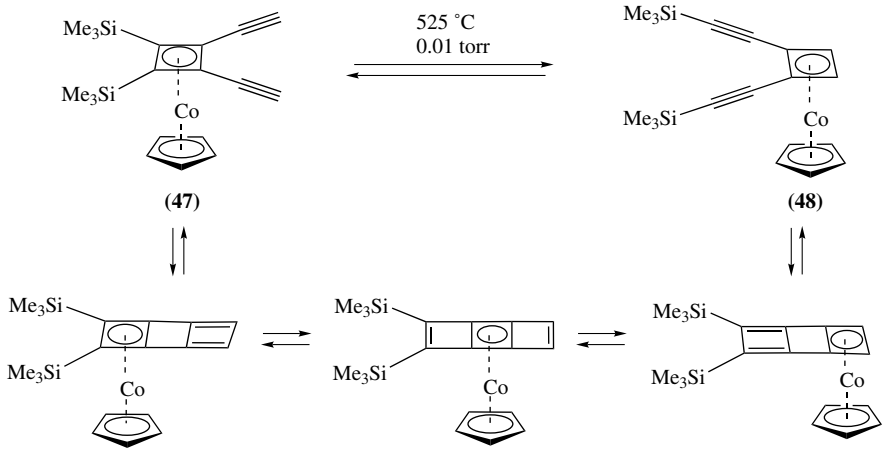
and predicted the infrared spectrum for butalene at this same level of theory[16]. Hess offered the view: 'it is suggested that butalene is a good candidate for low temperature isolation. . .'. As of this writing, that prediction remains to be realized.

Beyond butalene lies a fascinating collection of homologues with multiple rings; these have been the subject of occasional theoretical study. Warner and Jones used DFT theory to predict a *cis*-puckered geometry for **43** with a barrier to opening of 11–12 kcal mol^{-1} [116]. Their calculations suggested a pathway to **45** rather than the diradical **44** but they did not follow an intrinsic reaction coordinate. The tetra-ring structure **13** also optimized to a *cis*-bent geometry but the authors were unable to locate a transition state for ring opening to **46**.



As another assessment of aromaticity, Hess and Schaad have applied the REPE (resonance energy per electron) method to butalene and its homologues[17]. They predict that all members of this series (**11**, **43** etc.) will be modestly antiaromatic, although much less so than their parent 1,3-cyclobutadiene, and attribute the nonplanarity of **43** and **13** to a driving force for minimizing conjugation. The predicted degree of antiaromaticity varies systematically with the number of rings.

Finally, we note that no stable metal complexes of butalene or its homologues have been reported. Just as 1,3-cyclobutadiene is stabilized by complexation with $Fe(CO)_3$, we speculate that butalene complexes analogous to **17** might be prepared. Fritch and Vollhardt reported that isomers **47** and **48** interconvert upon flash vapor thermolysis and they suggested a mechanism that passes through three intermediate cobalt complexes (Scheme 15)[119].

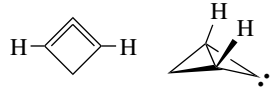


SCHEME 15

IV. OTHER C_4H_4 ISOMERS

A. 1,2-Cyclobutadiene

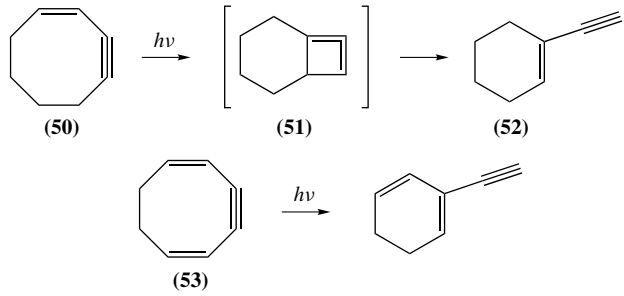
1,2-Cyclobutadiene (**4**) is the smallest member of the cyclic allene series[120]. For decades, *Chemical Abstracts* did not bother to include a '1,3-' prefix on cyclobutadiene, presumably because only one isomer appeared possible. Chapman drew this structure as one interesting C_4H_4 isomer in an early review on matrix isolation spectroscopy[121] but reported no relevant experiments. In 1975, Hehre and Pople included **4** in a study of C_4H_4 chemistry[122]. Unfortunately, their closed-shell Hartree–Fock wavefunction optimized to bicyclopropylidene (**49**) and this was concluded to represent the structure of **4**. This error has been repeated in more recent literature[123].



(4) **(49)**

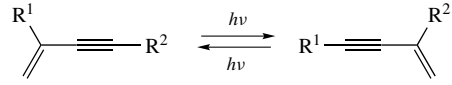
The experimental history of 1,2-cyclobutadiene began in 1986 with a brief report on enyne photochemistry by Meier and König[124]. Irradiation of **50** in the solution phase (Scheme 16) yielded **52** and the authors reluctantly suggested **51** as one potential intermediate. A similar rearrangement was observed for **53**. In 1993, Johnson and coworkers studied enyne photoreactions in search of experimental evidence for 1,2-cyclobutadiene[125]. They showed the enyne photorearrangement to be a general singlet excited state process and reported a variety of new examples, including those shown in Scheme 17. Importantly, the photoreaction is both facile and often *reversible* for simple enynes. For enediyne **56**, this process is unidirectional. In one case, four different enynes appear to give the same intermediate **57**, which opens thermally by preferential 1,4-bond cleavage. Efforts to trap a 1,2-cyclobutadiene intermediate have been unsuccessful. This reaction is best described as a four-electron homologue of the thermal Bergman rearrangement[126].

While the structural mystery for 1,3-cyclobutadiene may now be solved, the structure of its isomer 1,2-cyclobutadiene remains uncertain. The various structures that might be



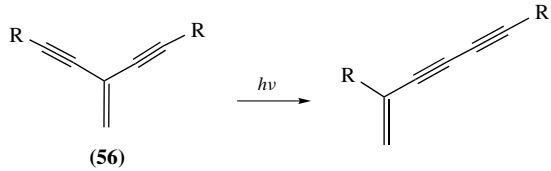
(50) (51) (52) (53)

SCHEME 16



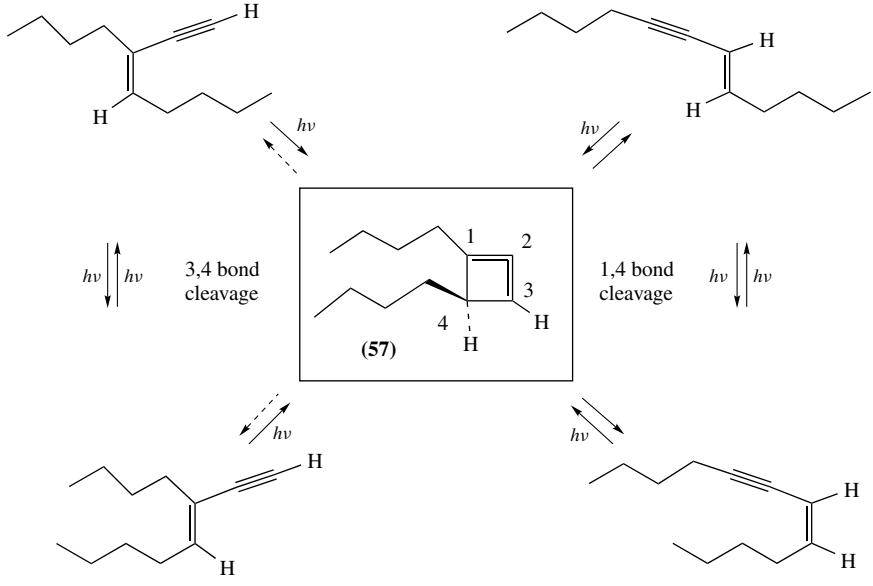
(54) (55)

R^1 = Me, R^2 = *n*-Bu



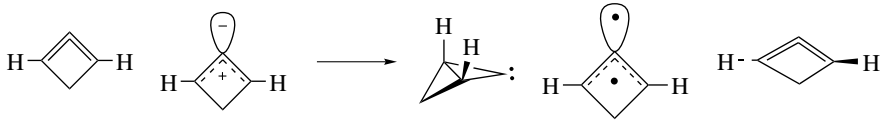
(56)

R = *n*-Bu



SCHEME 17

proposed are shown below. Line structure **4** is too simplistic. Electronic states for a bent planar allene may have diradical or zwitterionic character[120]. Zwitterion **58** is found to be a transition state for ring inversion of carbene **49**; not surprisingly, closed-shell Hartree–Fock calculations optimize to this carbene. MCSCF and MP4//MP2 calculations on 1,2-cyclobutadiene by Johnson and coworkers[125] showed an energy minimum for a diradical structure (**59**) which lies *ca* 74 kcal mol^{-1} above vinylacetylene, but this may not be the final answer. More recent studies indicate yet another minimum energy structure (**60**) which is chiral[127].



(4) **(58)** **(49)** **(59)** **(60)**

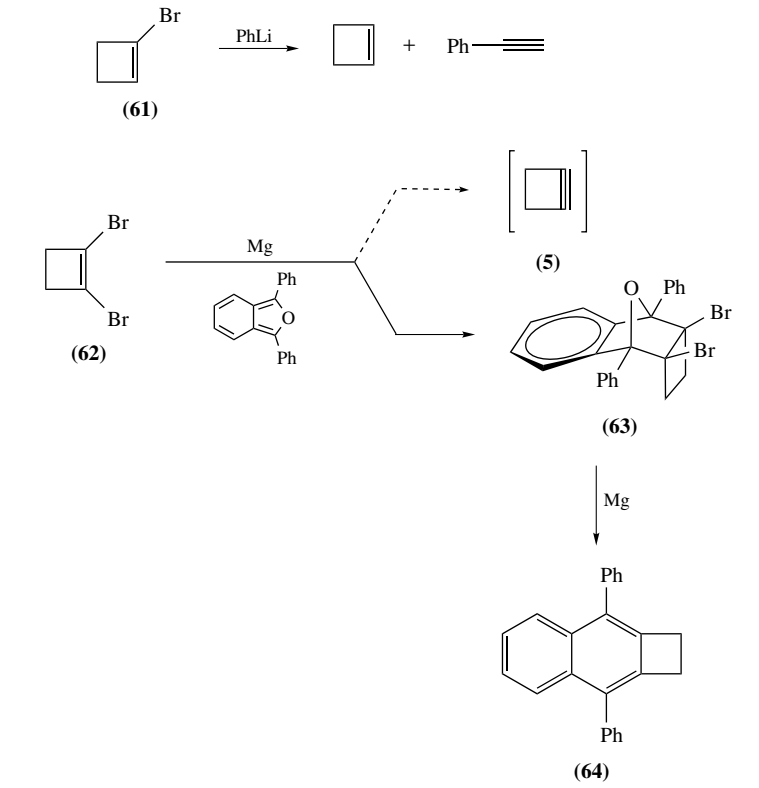
Simple homodesmic reactions predict a strain energy of 99.2 kcal mol^{-1} for 1,2-cyclobutadiene[128]. For the enyne photorearrangements, CI calculations along excited state surfaces suggest a straightforward mechanism in which S_1 of the enyne relaxes toward an energy minimum which is poised above **4**[125]. Internal conversion to the ground state surface is followed by ring opening in either direction. Clearly, this area needs more theoretical and experimental studies to sort out the true nature of **4**.

B. Cyclobutyne

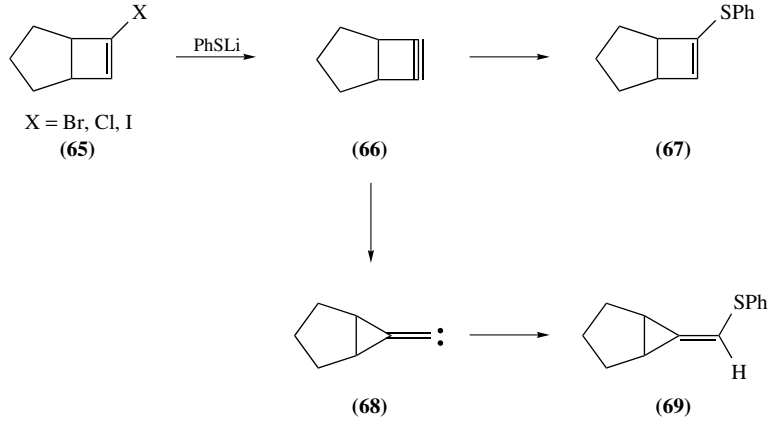
In the concluding section of their classic 1960 paper on cyclopentyne, Montgomery and Roberts described an unsuccessful attempt to find evidence for the smaller homolog cyclobutyne (**5**)[129]. Treatment of 1-bromocyclobutene (**61**) with phenyllithium (Scheme 18) yielded cyclobutene and phenylacetylene as isolable products. No evidence for the intermediacy of cyclobutyne was observed. Five years later, this cause was taken up by Wittig and coworkers who treated 1,2-dibromocyclobutene (**62**) with magnesium in the presence of diphenylisobenzofuran[130]. Although the expected [2 + 4] cycloadduct **64** was obtained, control experiments showed that **62** also reacted with diphenylisobenzofuran to give **63** and thus no firm conclusion could be drawn about the intermediacy of cyclobutyne.

This question lay dormant for almost 20 years until Baumgart and Szeimies studied routes (Scheme 19) to bicyclic cyclobutyne derivative **66**[131]. Reaction of **65** with lithium thiophenoxide yielded **67** and **69**, products consistent with trapping of both cyclobutyne **66** and its expected rearrangement product **68**. Increasing the concentration of base yielded a greater percentage of **67**. However, later isotopic labeling experiments carried out by Düker and Szeimies did not support a symmetrical intermediate such as **66**, but instead favored an ionic mechanism[132].

In principle, theory should resolve this question but computational studies have provided somewhat conflicting results even on the *existence* of cyclobutyne. The structure has considerable strain and diradical character in the triple bond and requires well correlated wavefunctions and a good atomic orbital basis set for accurate calculations. In 1983, Schaefer and coworkers used two-configuration *ab initio* SCF theory to predict that cyclobutyne lies in an energy minimum *ca* 78 kcal mol^{-1} above butatriene[133]. A few years later, in a paper that curiously evades *Chemical Abstracts* searches on cyclobutyne, Skell and coworkers studied the addition of C_2 to ethylene and noted that isomeric carbene **71** lies *ca* 23 kcal mol^{-1} lower than **5**[134]. The electrocyclic ring opening of cyclobutyne to butatriene (**70**, Figure 5) was later studied by Schaefer and coworkers who predicted a



SCHEME 18



SCHEME 19

barrier of 25 kcal mol^{-1} and suggested that '... cyclobutyne should be makeable under suitable conditions...'[135]. Li and coworkers optimistically predicted a significant lifetime for **5**[136]. Unfortunately, Schaefer's paper did not consider a much lower reaction pathway leading toward **71**; this is shown on the right side of Figure 5. A few years later, Dewar and coworkers used AM1 calculations with 3×3 configuration interaction to predict that cyclobutyne will exist as 'orbital isomer' rather than 'classical cyclobutyne'. Later computational studies examined the $[2 + 2]$ addition of cyclobutyne with ethylene[137]. Unfortunately, these results relied on semiempirical methods, which do not adequately describe highly strained molecules.

In 1995, Johnson and Daoust used *ab initio* MCSCF and MP2 theories to predict that cyclobutyne should easily rearrange to carbene **71** along a pathway (Figure 5) that is much lower than electrocyclic ring opening[138]. Although the structure for **5** was predicted to be an energy minimum, at the highest level theory examined and with zero point corrections, the authors concluded '... cyclobutyne must exist in a very shallow minimum and will rearrange with little or no barrier to carbene...'. This process is predicted to be exothermic by 20–25 kcal mol^{-1}. An isodesmic scheme was used to predict a π bond strain energy for **5** of 73.4 kcal mol^{-1}. The near equivalence of this value with the π bond strength in acetylene indicates that the in-plane π bond in cyclobutyne is essentially broken.

More recent studies cast further doubt on the existence of cyclobutyne. Calculations by Wiberg and coworkers with high levels of electron correlation and larger basis sets predicted negligible or nonexistent barriers to rearrangement for cyclobutyne. Indeed, calculations with QCISD and density functional (B3LYP) theories predicted cyclobutyne to be a transition state[123, 139].

Perfluorination often has dramatic effects on reaction energetics and the availability of suitable experimental precursors to perfluorocyclobutyne (**73**) prompted a study by Wiberg and Marquez. Treatment of chlorocyclobutene **72** with phenyllithium (Scheme 20), followed by the addition of D_2O, yielded **76**[140]. These results imply that perfluorocyclobutyne might have been the intermediate that reacted with phenyllithium to give **74**. Theoretical studies by the same group predicted barriers of up to 5 kcal mol^{-1} for rearrangement of **73**

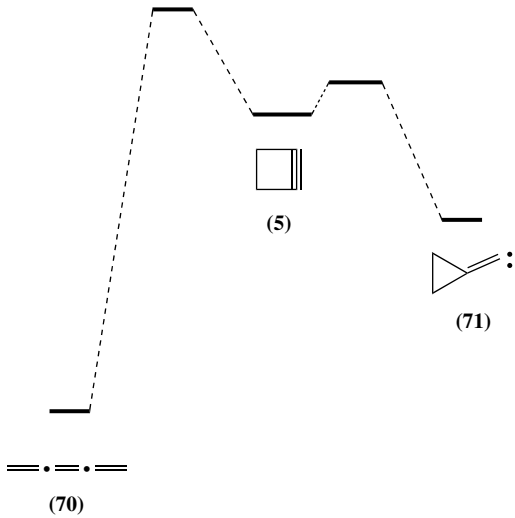
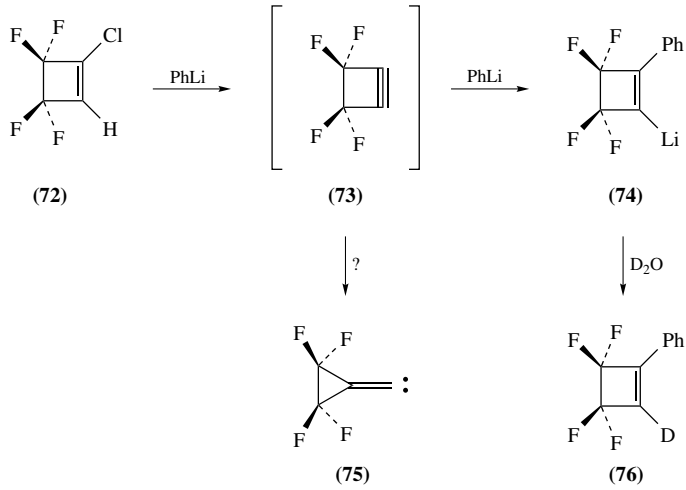


FIGURE 5. Rearrangements of cyclobutyne



SCHEME 20

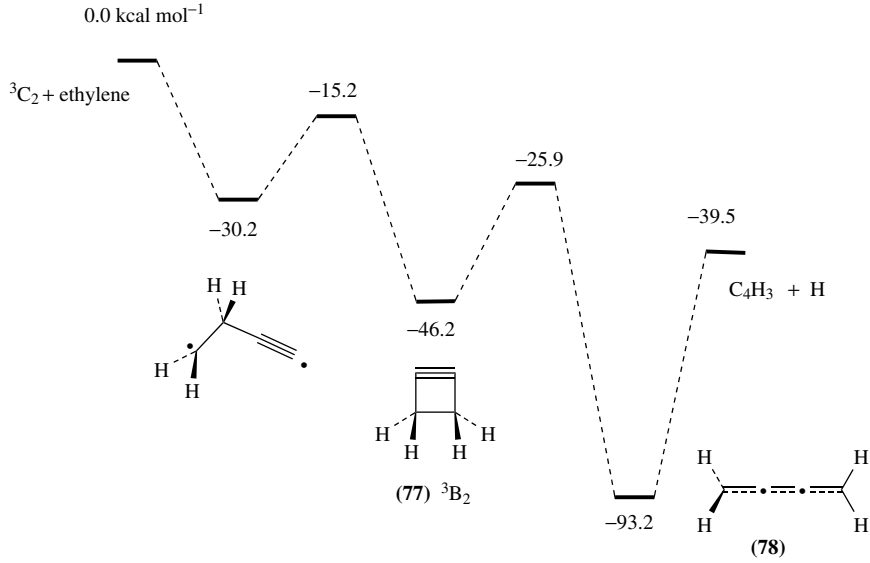


FIGURE 6. Triplet potential energy surfaces for cyclobutyne

to **75**. However, the highest levels of theory again predicted spontaneous rearrangement to the isomeric carbene **75**[139]. Thus, while perfluorination clearly alters the energetics, the intermediacy of **73** remains an open question.

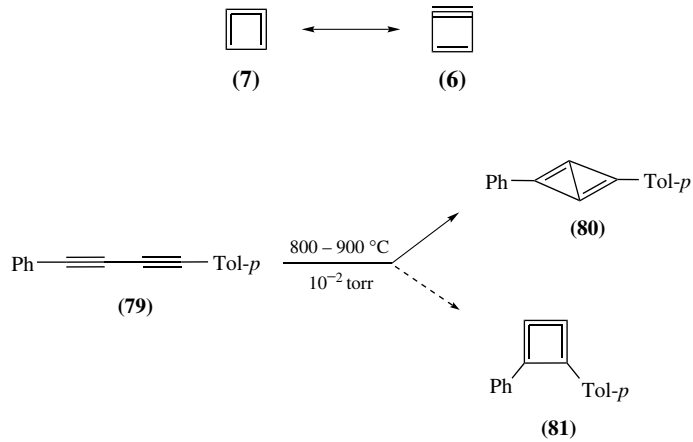
Although its existence as a singlet now seems improbable, *triplet* cyclobutyne has recently emerged as a potentially important species. According to calculations (Figure 6), triplet cyclobutyne lies in a fairly deep energy minimum[141]. The singlet/triplet gap in

cyclobutyne is *ca* 10 kcal mol^{-1}, with the singlet lower, but the triplet (**77**) clearly is an energy minimum while the singlet is more likely a transition state. Lee and coworkers have studied the reactions of triplet C_2 with ethylene in a molecular beam. This reaction may occur in some combustion reactions where these are common species. The energetics predicted for these processes are shown in Figure 6. Based on their experimental results and associated RRKM calculations, Lee and coworkers concluded that triplet cyclobutyne may be an important intermediate in the reaction of triplet C_2 with alkenes[142]. Ultimately, this leads toward triplet **78** and fragmentation products. Skell, Shevlin and coworkers had considered some of these pathways in earlier work[134].

V. MORE HIGHLY UNSATURATED C_4 STRUCTURES

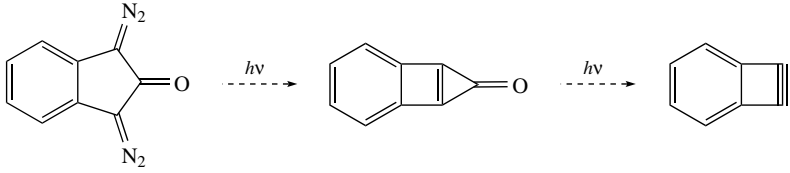
A. C_4H_2 Chemistry

The only C_4H_2 isomer that is isolable under ordinary conditions is 1,3-butadiyne. However, a number of novel cyclic structures have been considered as reactive intermediates. In principle, C_4H_2 might be represented as 1,2,3-cyclobutatriene (**7**) or cyclobutenyne (**6**). These are almost certainly just formal resonance structures. Mabry and Johnson considered the intermediacy of these structures in thermal skeletal rearrangements of diaryl 1,3-butadiyne **79** (Scheme 21). In **79**, carbon atom scrambling within the diyne chain occurs at high temperature[143]. Computations with DFT or Moller–Plesset theory afforded conflicting results. DFT theory indicated that this geometry, which more closely resembles cumulene **7** than alkyne **6**, represents only a transition state, while MP2 theory predicted an energy minimum. However, the computed structure for **7** lies >120 kcal mol^{-1} above 1,3-butadiyne. This led to the conclusion that high temperature rearrangement of **79** occurs through **80** rather than **81**. Trialene structure **80** is predicted to lie only *ca* 66 kcal mol^{-1} above **79**.



SCHEME 21

Benzocyclobutyne (**83**) should be considered a benzannelated C_4H_2 structure. Tomioka and coworkers hoped to prepare **83** by matrix photolysis of bis-diazo indanone **82** (Scheme 22) but saw no evidence for this intermediate[144, 145]. It is easy to show by B3LYP/6-311+G* calculation that **83** is not an energy minimum because this structure has two imaginary vibrational modes at this level of theory[146].

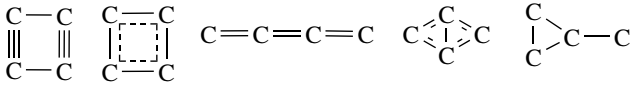


(82) **(83)**

SCHEME 22

B. C_4 Chemistry

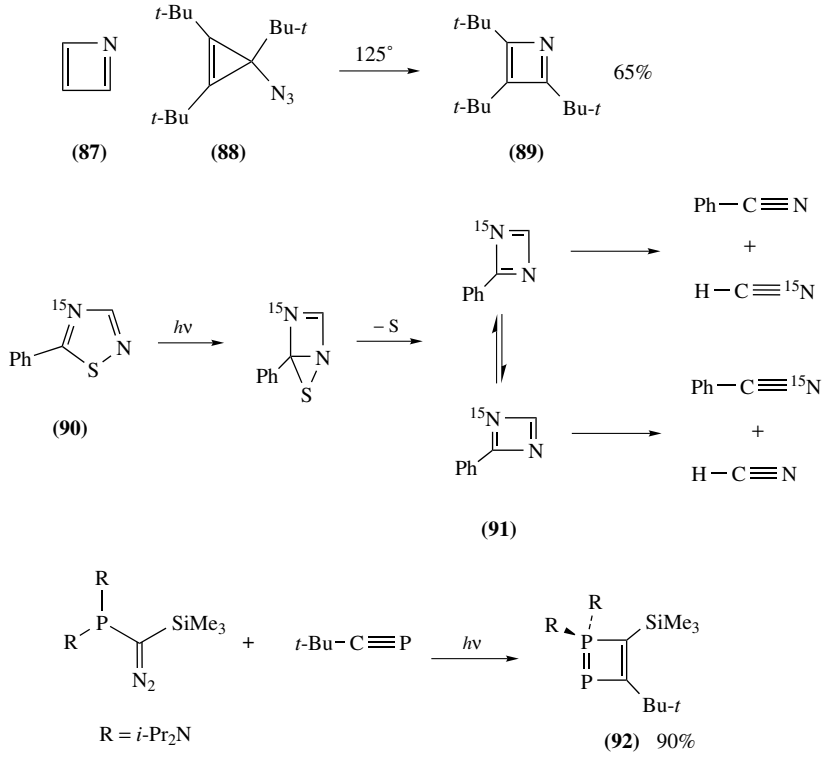
There is a substantial literature on the chemistry of small carbon clusters; among these, C_4 has been well studied[89,147–150]. The principal isomeric structures that have received active consideration include **8**, **9** and **84**–**86**. Results to date indicate that linear (**84**) and rhombic (**85**) forms of C_4 are close in energy, with **84** the global minimum. Square and rectangular forms **9** and **8** are transition states rather than energy minima.



(8) **(9)** **(84)** **(85)** **(86)**

VI. HETEROCYCLIC ANALOGS

A small but interesting collection of heterocyclic analogs of some of these substances has been reported. The majority of this effort has focused on derivatives of 1,3-cyclobutadiene. Schoeller and Busch have reported analysis of the bonding and energetics in aza- and phosphacyclobutadienes[151]. The aza structures were lower in energy than isomeric tetrahedranes, while the reverse was true for phospha-derivatives. Bonacic-Koutecky and coworkers have predicted that for protonated azacyclobutadiene, 'critical biradicaloid' geometries exist where the S_0/S_1 energy gap nearly vanishes[152]. As noted in a recent review by Regitz and coworkers, azacyclobutadiene (azete, **87**) should be more stable thermodynamically than its carbocyclic parent **3**; nevertheless, numerous attempts to make this substance have been unsuccessful[153]. This may be due to facile fragmentation to HCN and acetylene, although the barrier to that process is unknown. However, the tri-*t*-butyl derivative **89** is produced in good yield (Scheme 23) by thermolysis of azide **88**[154]. Azete derivative **89** is quite stable and Regitz and coworkers have explored much of the chemistry of this interesting substance[12,153]. In more recent work, Pavlik and coworkers have suggested that diazacyclobutadiene **91** is formed as an intermediate in the photochemistry of **90**[155]. In this case, benzonitrile is the major isolable product and an observed 1:1 ^{15}N label distribution in fragmentation products is consistent with equilibration of the two isomers of **91**. Phosphorus derivatives of 1,3-cyclobutadiene are also well known[156–159]. For example, Bertrand and coworkers reported the synthesis of stable diphosphete **92** according to the reaction in Scheme 23[157]. Sila derivatives of **3** have been well studied theoretically[160,161] and pose a tempting target for synthesis but attempts to make sila-1,3-cyclobutadiene have been unsuccessful[162,163]. On the Si_4H_4 singlet potential energy surface, the lowest-energy isomer is predicted to have a D_{2d} puckered ring structure, with four equal Si−Si bond lengths and an axial arrangement of the four hydrogen atoms[164].



SCHEME 23

Much is also known about Si_4 clusters which adopt a structure similar to **85** rather than a simple four-membered ring[165].

Beyond cyclobutadiene, a literature search revealed only a few theoretical studies on azabutalene derivatives[166, 167]. Clearly, there remains much work to be done in this field.

VII. CONCLUSIONS

Speculation and controversy surround many of the structures in this chapter! 1,3-Cyclobutadiene (**3**) is one of the most famous molecules in organic chemistry and has been compared by Cram to the *Mona Lisa*[23]. The structure, antiaromatic character and facile automerization of **3** have posed many fascinating challenges; its matrix isolation, synthesis of isolable crystalline derivatives and 'taming' by imprisonment in a carcerand all rank as extraordinary accomplishments. In spite of several attempts and a few convincing trapping studies, butalene (**11**) remains uncharacterized. The best computations to date indicate that butalene will have a very low barrier for ring opening to *p*-benzyne. In the C_4H_2 isomer series, enyne photochemistry points toward the existence of 1,2-cyclobutadiene (**4**) as a reactive intermediate but much more work remains to be done on this problem, which generally has escaped the attention of the chemical community. Cyclobutyne (**5**) remain mysterious; the best computations suggest that singlet **5** may not exist as an energy minimum. However, triplet cyclobutyne may be formed from the addition of triplet C_2 to

acetylene and could be an important intermediate in combustion! Finally, current theory provides evidence that four-membered ring structures do not represent minima on the C_4H_2 and C_4 potential energy surfaces.

VIII. ACKNOWLEDGMENTS

I am grateful to Professors Joel Liebman and Zvi Rappoport for the invitation to write this chapter and for their enduring and good-natured patience.

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CHAPTER **15**

Cyclobutarenes[§]

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I. INTRODUCTION

The fusion of an aromatic ring (e.g. benzene) and a four-membered carbocyclic ring (e.g. cyclobutene and cyclobutadiene) to produce cyclobutarenes offers unique systems within the cyclobutane family of compounds. Sterically, the fusion of a strain-free six-membered ring with a highly strained four-membered ring offers an opportunity to study the mutual effects of these groups, and the special chemistry resulting from this situation. Benzocyclobutene (**1**) is the basic system on which the effect of strain that is perpendicular to the benzene's π-system affects the aromaticity of the latter (Mills–Nixon effect or SIBL) is studied, and benzocyclobutadiene **2** (and its benzo derivative biphenylene, **3**) are the

[§] Dedicated to Professor Yitzhak Apeloig on the occasion of his 60th birthday.

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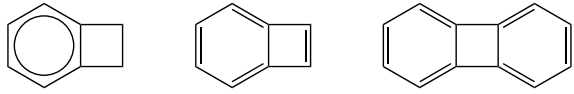
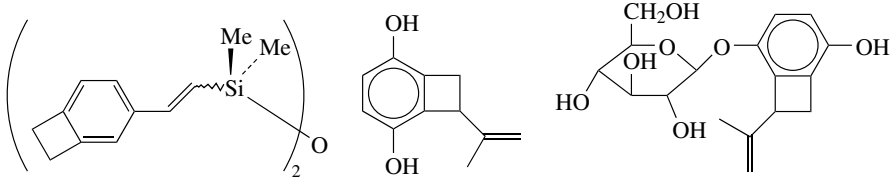
simplest systems that contain fused aromatic and antiaromatic moieties. Inherently, there is a built-in problem in understanding such systems. Thus, whereas strain is thought about in classic terms (i.e. force-field terms), aromaticity is a phenomenon which even intuitively is understood in quantum-mechanical terms, either valence bond terms (e.g. canonic forms) or molecular orbital terms (e.g. Hückel theory). Therefore, for the understanding of strained aromatic compounds in general and benzocyclobutenes and benzocyclobutadienes in particular, the concept of strain has to be 'translated' to quantum-mechanical terms. Section IV.B which discusses the Mills–Nixon effect will offer such a translation.

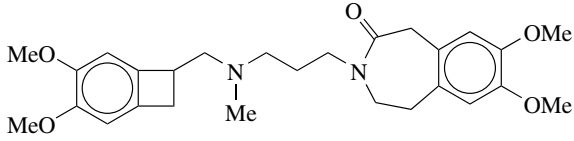


(1) **(2)** **(3)**

A comprehensive review of the benzocyclobutenes that include preparation methods, their uses in organic chemistry and some structural aspects was published recently[1]. Two more recent reviews and book chapters[2] and several older ones[3] make the successive review of the literature here redundant at this stage. Instead, the reader will find here the principal ways for making the systems and some of their reactions followed by selected examples. Benzocyclobutadienes and their derivatives (e.g. phenylenes) will be presented and discussed briefly in Section V due to their electronic structure which is very different from that of benzocyclobutenes. Bi- and tricyclobutabenzenes will be presented in Section II.B.2. Finally, the Mills–Nixon effect, which was last reviewed a few years ago[4], will be presented in a more comprehensive way in Section IV.B.



(4) **(5a)** **(5b)**



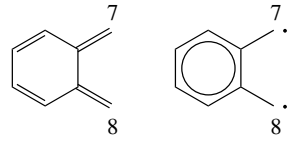
(6)

The benzocyclobutene moiety is a part of polymers (such as the one based on the monomer **4**) and some natural products and drugs (for example, **5a**[5], **5b**[5] and **6**[6], respectively). The macromolecular systems, polymers and drugs will not be discussed in this chapter. Benzocyclobutenes and benzocyclobutadiene have a rich organometallic chemistry which is covered in another chapter in this book.

II. PREPARATION OF BENZOCYCLOBUTENES

A. Bonding Considerations

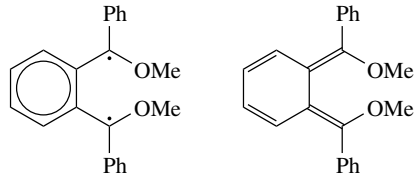
There are quite a few methods for preparing benzocyclobutenes, mostly based on forming the four-membered ring on an existing six-membered ring. A frequently used group of methods is based on forming *ortho*-quinodimethane (*ortho*-xylylene, **7**), which is a structural isomer of benzocyclobutene. Series of experiments have shown that **1** is more stable than **7** by *ca* 11–12 kcal mol^{-1} and the thermal barrier for the ring closure is *ca* 23 kcal mol^{-1}[17]. Thus, once **7** (or its derivative) is formed it can thermally conrotatorily ring-close or photochemically disrotatorily ring-close to form **1**.



(7) **(8)**

Substituents at the 7 and 8 positions of **1** (and **7**) affect the electronic structure of **7**, the barriers for the four-membered ring closure and the relative stability of **1** and **7**. Thus, **8** represents a singlet diradical resonance form of **7**, which is close in energy to **7**[8]. In a very detailed investigation Roth and coworkers showed on the basis of stereochemical experiments that several substituents stabilize the diradical form[9]. Similarly, a theoretical investigation on other systems reached a similar conclusion[10]. Clearly, a diradical should be less stable than a bond; however, both radicals in **8** are benzylic and the six-membered ring is aromatic, and these two factors diminish the difference between **7** and **8**, while additional stabilization of the radical (for example, by phenyl substituents) may further diminish this difference between them. Note, however, that **8** is also a canonic structure of **1**, although usually not being considered as contributing substantially to its structure. Nevertheless, there may be cases in which it does (see Section IV). Interestingly, the above discussion regarding the different stabilities of **1** and **7** does not apply to the triplet state. Thus, at the B3LYP/6-31G* theoretical level singlet **1** is more stable than singlet **7** by 13.8 kcal mol^{-1}, whereas triplet **1** is less stable than triplet **7** by 48.5 kcal mol^{-1}. This result has an experimental support: photochemical reactions that involve derivatives of triplet **7** as intermediates do not yield even traces of the respective derivatives of **1**[11].

As a result of the biradical nature of the *ortho*-quinodimethane, the activation barrier for the 'forbidden' thermal disrotatory ring closure is lowered, and the products are obtained as mixtures of *cis* and *trans* isomers, depending on the substituents. The substituents also affect the activation barrier for the 'allowed' process and the relative stability of **1** and **7** (or **8**)[9,10]. Thus, it had been suggested that **9** is more stable than **10**[12].



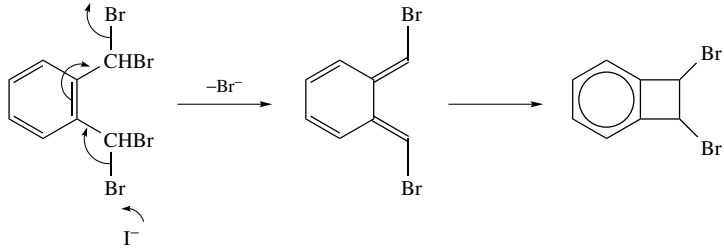
(9) **(10)**

The ring closure of **7** to give **1** is usually stereospecific. However, substituted systems may suffer from lack of stereoselectivity of this process. As a result, using the *ortho*-quinodimethane approach for preparing benzocyclobutenes may result in some cases in a mixture of stereoisomeric products.

B. Methods

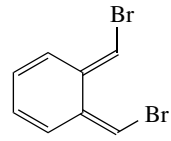
1. Systems with one four-membered ring

An example for the preparation of such a system is the synthesis of 7,8-dibromobenzocyclobutene (**11**) that was published by Cava and coworkers in the 1950s[13]. They reacted $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*ortho*-xylene (**12**) with I^- in a dipolar-aprotic solvent (originally acetone and later DMF) and obtained **11** in good yields. The reaction mechanism (Scheme 1) is thought to be a halophilic attack of I^- on one of the bromine atoms to eliminate IBr. The shuffling of electrons and the expulsion of a Br^- yields the 7,8-dibromo-*ortho*-quinodimethane (**13**) which ring-closes to **11**. Although the major product is the *trans*-dibromo derivative, the product contains a considerable amount of *cis*-7,8-dibromobenzocyclobutene, in addition to *cis* and *trans* isomers of bromoiodo and the diiodo derivatives. The *E*,*Z*-isomer of 7,8-*ortho*-quinodimethane (**14**), which may be formed after the elimination of IBr and Br^-, is sterically hindered, but is probably stabilized by hydrogen bonding between the hydrogen at C-7 and the bromine atom at C-8. Thus, at B3LYP/lanl2dz the difference between the two isomers is *ca* 1.8 kcal mol^{-1} and **13** is not planar whereas **14** is[14]. At higher level of theory (B3LYP/6-311G*) the difference between the two increases slightly to 2.1 kcal mol^{-1} and **14** also deviates from planarity. However, the hydrogen bond discussed above still persists[14]. It is thus reasonable to assume that *cis*-**11** is formed through the allowed conrotatory pathway, although the forbidden disrotatory pathway cannot be excluded. In any event, this route is not stereoselective.



(12) **(13)** **(11)**

SCHEME 1

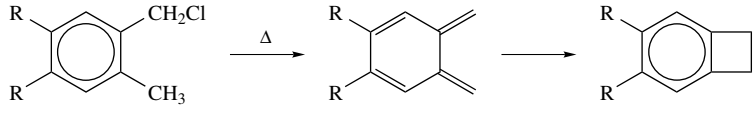


(14)

Actually, any 1,4-elimination from *ortho*-xylene derivative that forms an *ortho*-quinodimethane can be used for the synthesis of benzocyclobutenes. This elimination has been

demonstrated for the case of simple substituted *ortho*-xylenes or in systems where the two benzylic carbon atoms are part of a ring. A few examples are presented below.

Thermally induced (usually under gas-phase pyrolytic conditions) 1,4-elimination of HCl has been demonstrated for some derivatives. α-Chloro-*ortho*-xylene (**15**) undergoes this elimination to produce **7** as an intermediate which ring-closes to **1**[15]. When this system is substituted by two additional methyl groups (**16**), the reaction works equally well to produce **18** via the intermediate **17** (Scheme 2)[16]. Even heavily substituted benzocyclobutenes can be prepared using this method. Thus, pyrolysis of **19** yields the respective tetramethyl-*ortho*-quinodimethane **20** which ring-closes to **21** (Scheme 3)[17].

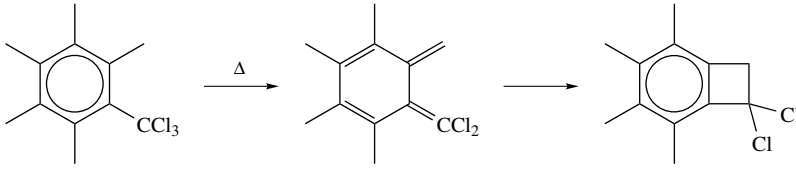


(15) R = H
(16) R = Me

(7) R = H
(17) R = Me

(1) R = H
(18) R = Me

SCHEME 2



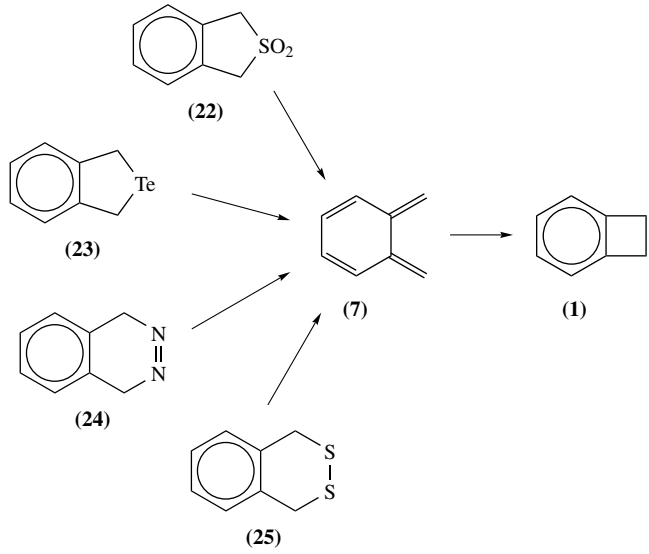
(19) **(20)** **(21)**

SCHEME 3

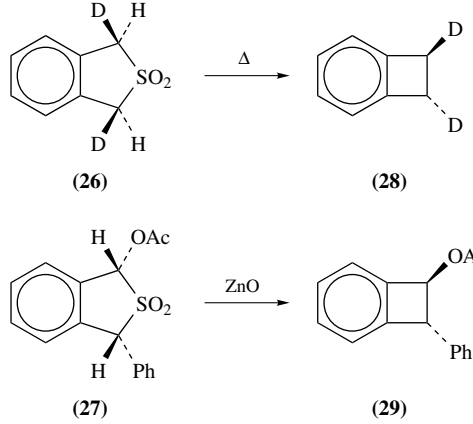
Arenes annulated to five- and six-membered ring heterocycles have been also used as precursors for **7**. Thermal decomposition of the sulfone **22**[18], the telluride **23**[19], the diazene **24**[8] and the disulfide **25**[20] all lead to **7**, and **1** is isolated (Scheme 4). The defined stereochemistry of the ring closure was shown by the thermal decomposition of **26**[21] and ZnO-mediated decomposition of **27**[22] which result only in **28** and **29**, respectively (Scheme 5). This defined stereochemistry implies that both the formation of **7** and the ring closure to **1** are stereoselective under the conditions applied.

Organometallic chemistry can be used as well for the production of **7** (and **1**). Two examples are given here. The reaction of $Fe_2(CO)_9$ with α,α'-dibromo-*ortho*-xylene (**30**) leads to the $Fe(CO)_3$ complex of **7**, i.e. **31**, which can be heated to produce **7** (Scheme 6)[23]. An F^- mediated elimination of a trimethylsilyl group from **32** accompanied by the loss of trimethylamine leads also to **7**[24].

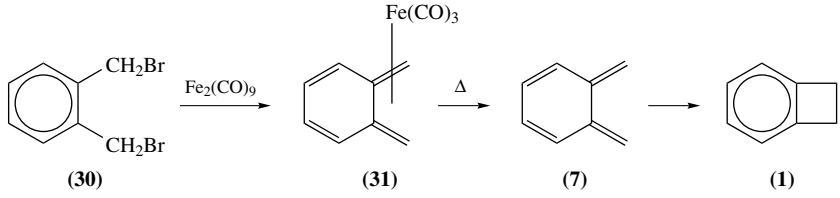
There are two types of ionic routes to prepare benzocyclobutenes. One is an intramolecular anion addition to benzyne (Scheme 7), which is formed *in situ* by elimination of HX (R is usually an electron-withdrawing group and X is a halogen). The reaction is usually carried out in liquid ammonia. Thus, treating **33** with a base in liquid ammonia produces **34**, R = CN, SO_2Ph, where both the nitrile and the sulfone groups can be manipulated using standard procedures of organic chemistry to form a variety of 7-substituted benzocyclobutenes[25]. The second ionic synthetic approach is intramolecular as well, and is based on forming the Li salt of an aryl anion in α-position to an alkyl chain containing a β-leaving group. The starting material for this method (known as



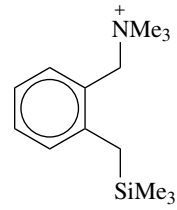
SCHEME 4



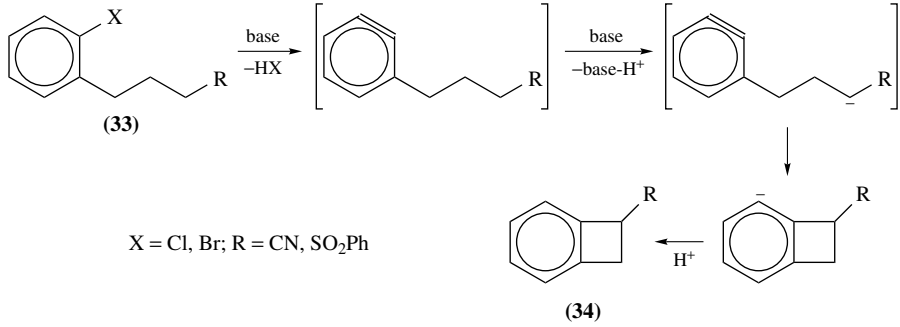
SCHEME 5



SCHEME 6



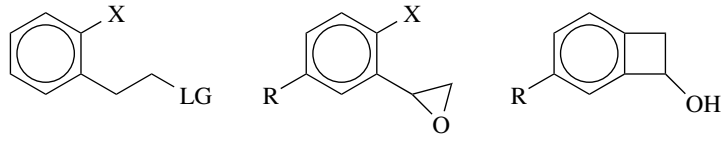
(32)



(33) **(34)**

SCHEME 7

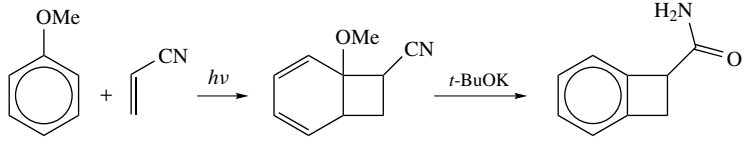
Parham cyclization) is an iodo or bromo benzene (e.g. **35**, X = I, Br), which is converted to the Li salt by metal–halogen exchange with *n*-BuLi. The leaving group (LG) in **35** is usually also a halogen, but other groups have been used as well[26]. For example, an oxirane ring as a substituent in an α-position to X (**36**, R = H, OMe, X = Br, I) leads to 7-hydroxybenzocyclobutene derivatives **37**[27].



(35) **(36)** **(37)**

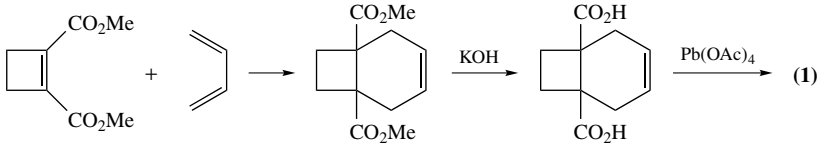
Photochemical [2+2], Diels–Alder (i.e. [4+2]) and CpCo-mediated [2+2+2] cyclizations have also been used for the synthesis of benzocyclobutenes. A few examples are given in Schemes 8–10. Irradiation of anisole and acrylonitrile yields the 1-methoxy-7-cyano dihydrobenzocyclobutene **38** as a *cis/trans* mixture, which on treatment with *t*-BuOK gives **39** (Scheme 8)[26a]. Reaction of dimethylcyclobutene-1,2-dicarboxylate with 1,3-butadiene yields the diester **40**, which after hydrolysis and treatment with lead tetraacetate yields **1** (Scheme 9)[28]. The reaction of disubstituted acetylene with a 1,5-hexadiyne in the presence of $CpCoL_2$ (Cp = cyclopentadienyl, L = CO, C_2H_4) yields the respective benzocyclobutene derivative **41** (Scheme 10)[29].

Benzocyclopropene derivatives were also used for the synthesis of benzocyclobutenes. Oxidation of **42** with Br_2 in aqueous THF yields **43**[30], and addition of dihalocarbene to



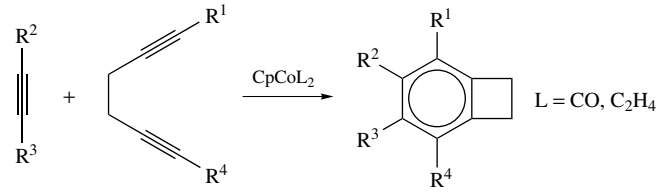
(38) **(39)**

SCHEME 8



(40)

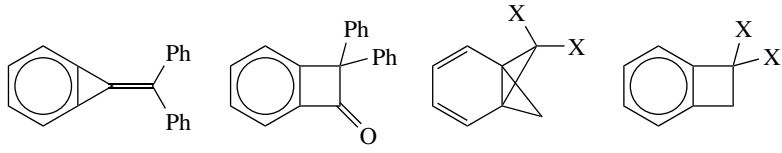
SCHEME 9



(41)

SCHEME 10

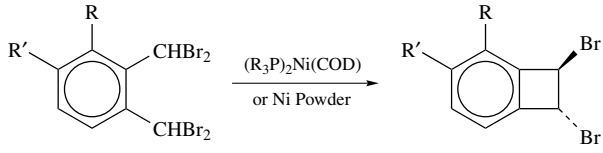
benzocyclopropene yields **44** which rearranges to 7,7-dihalobenzocyclobutene **45**[31]. Other methods have been used occasionally, depending on the kind of chemistry that was of interest to the authors, and the reader is referred to Reference 1 for a comprehensive compilation of these methods.



(42) **(43)** **(44)** X = Cl, Br **(45)** X = Cl, Br

Another method which seems to be useful for the synthesis of *trans*-7,8-dibromobenzocyclobutenes is the nickel-mediated cyclization. It is based on the formation of the four-membered ring from $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*ortho*-xylene (**12**) which is then cyclized by nickel (Scheme 11)[32]. Although it uses the same starting material as Cava's I^--mediated synthesis, the reaction has some advantages since it is general (i.e. R or R′ differs from H) and produces mainly or only the *trans*-dibromo isomer, which is the useful isomer for using the system as a synthon for a diene (see below). The mechanism of the cyclization reaction is unclear, but surely it does not involve the formation of

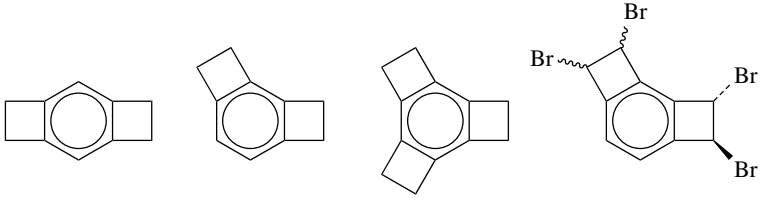
ortho-quinodimethane (see Section II.B.2), and therefore it is suitable for the synthesis of substituted benzocyclobutenes, bicyclobutabenzenes and tricyclobutabenzenes.



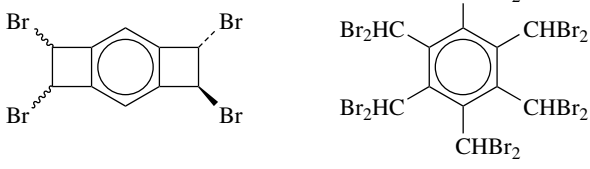
SCHEME 11

2. Systems with two and three four-membered rings

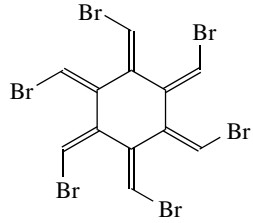
Some, but not all of the methods presented above for the preparation of benzocyclobutenes have been used for the preparation of the two isomers of bicyclobutabenzene (the linear **46** and angular **47**) and tricyclobutabenzene **48** and their derivatives. Cava's synthesis was used for the preparation of **49** in 61% yield as a mixture of the two *trans* isomers[33], but **50** was obtained in only 2% yield (also as a mixture of the two *trans* isomers)[33]. The analogous hexabromo derivative of **48** was not obtained at all when reacting **51** with I^-. Instead **52**, i.e. its structural isomer, was isolated[33]. Pyrolytic elimination of HCl (such as presented in Schemes 2 and 3) from **53** or **54** yielded **55** (R = H, Br, CH_3)[34], and Parham cyclization was used to convert **56** to **46**[35], and **57** and **58** to **59**[36]. Thermal extrusion of SO_2 from **60**, **61** and **62** yields **46**[37], **47**[38] and **48**[39], respectively. Diels–Alder reactions have been used to build the skeleton of **48** in two ways. One is the reaction between **63** and dimethyl cyclobutene-1,2-dicarboxylate which yields **64**, that after hydrolysis and reaction with lead tetraacetate yields **48** (Scheme 12)[40]. The second is by reacting **63** with dimethyl acetylenedicarboxylate to yield **65**, which after aromatization with DDQ, reduction to the diol and reaction with PBr_3 gives **66**[39]. The dibromide **66** is reacted with Na_2S to yield **67** and, after oxidation with *m*-chloroperbenzoic acid, **62** is obtained, and is further thermolyzed to **48** (Scheme 13). Finally, bromination of hexamethylbenzene yields **51**, which is reacted with nickel powder to yield **68** along with **51** (Scheme 14)[41].



(46) **(47)** **(48)** **(49)**



(50) **(51)**



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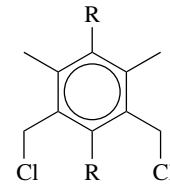

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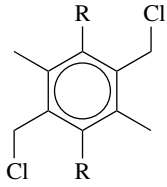

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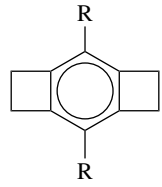

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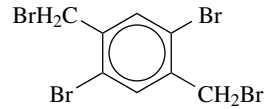

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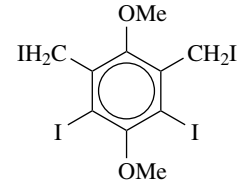

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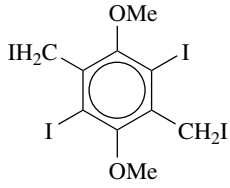

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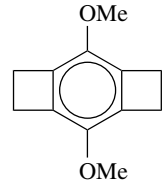

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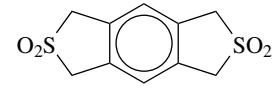

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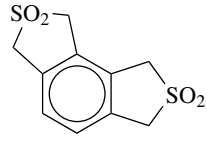

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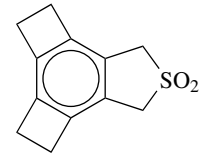

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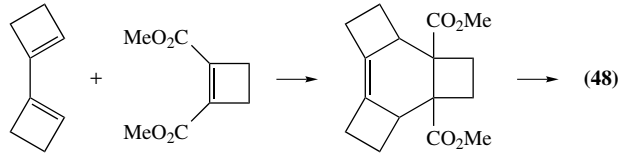
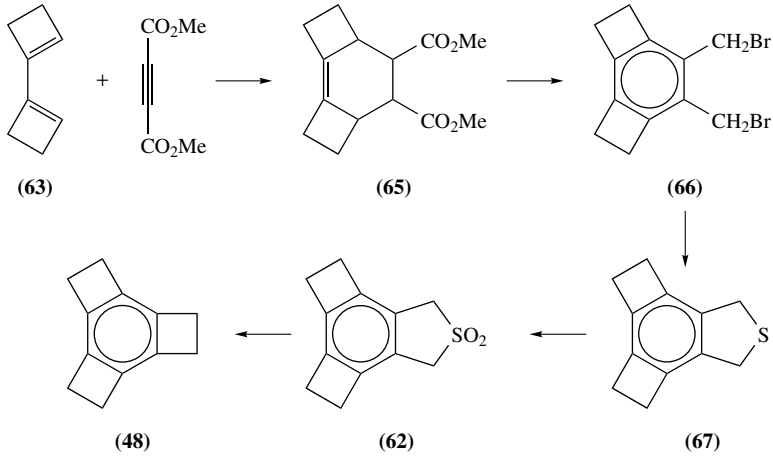


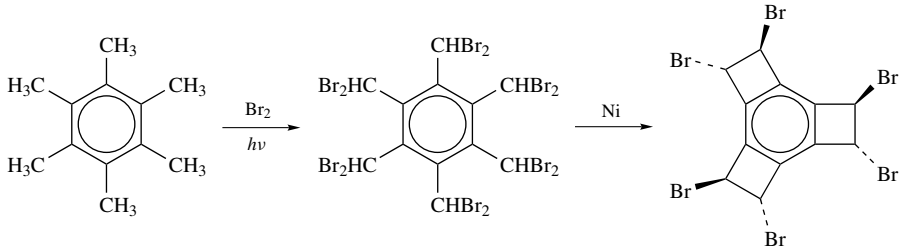
(63) **(64)**

SCHEME 12



(63) **(65)** **(66)** **(48)** **(62)** **(67)**

SCHEME 13



(51) **(68)**

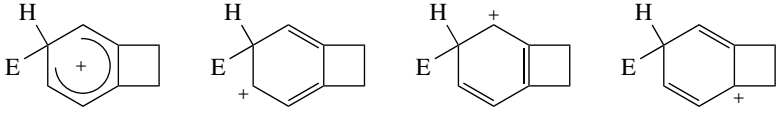
SCHEME 14

In summary, the preparation of benzocyclobutenes have been achieved using many different types of methods. The different approaches include different reaction conditions and solvents, probably enabling the synthesis of any desired derivative of benzocyclobutene.

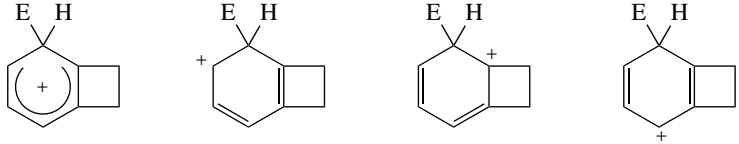
III. REACTIONS OF BENZOCYCLOBUTENES

The strain energy of benzocyclobutene relative to *ortho*-xylene is 23–26 kcal mol^{-1}[42], but it seems that the four-membered ring is quite resistant to ring-opening. Although the major use of benzocyclobutenes in organic synthesis is by trapping their structural isomer *ortho*-quinodimethane (see below), the latter is far less stable than the former. Reactions that break the benzylic bonds of benzocyclobutenes occur only under forcing conditions (e.g. nitration under HNO_3/H_2SO_4 conditions or the use of a strong Lewis acid, such as $AlCl_3$ which is usually used in Friedel–Crafts acylations)[43]. Thus, benzocyclobutene undergoes usual chemistry at the aromatic moiety and the benzylic four-membered ring carbon atoms, including electrophilic substitution on the aromatic ring, whereas nucleophilic or radical substitution can be carried out on benzocyclobutene without opening of the four-membered ring. Some examples are given below.

Electrophilic substitution with E^+ normally yield the 4-substituted product as the major or the only product, while the 3-substituted product is the minor product or not obtained at all. A straightforward explanation emerges from looking at the two isomeric σ-complexes **69a–c** and **70a–c**. Whereas in **70** a double bond exists at the annulated bond in two of the most important resonance structures (**70a** and **70c**), enforcing a high cyclobutene character on the four-membered ring, the respective resonance structure of **69** has only a respective single resonance structure with a double bond at the annulated bond. Since cyclobutene is more strained than cyclobutane, **69** is more stable than **70**. Indeed, at B3LYP/6-311G* theoretical level **69** (E = H) is more stable than **70** (E = H) by 3.5 kcal mol^{-1}[42] (4.5 and 3.7 kcal mol^{-1} at HF/6-31G* and MP2(fc)/6-31G*)[44], and the annulated bond lengths are 1.419 and 1.379 Å in **69** and **70**, respectively. A difference of 2.2–2.4 kcal mol^{-1} was predicted for the respective difference when E = Me[44].

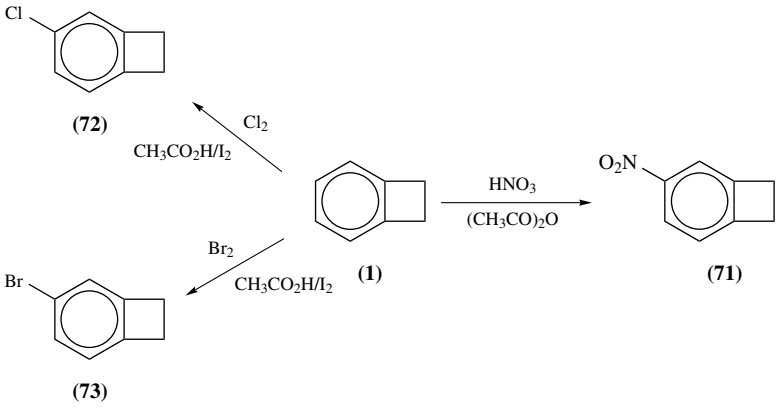


(69) **(69a)** **(69b)** **(69c)**



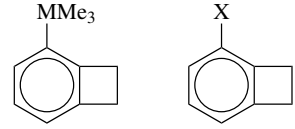
(70) **(70a)** **(70b)** **(70c)**

Three examples of electrophilic substitution are described in Scheme 15. Reaction of **1** with HNO_3 in acetic anhydride under the catalysis of clay (K10) leads to **71**[45]. In acetic acid and in the presence of iodine, **1** reacts with Cl_2 and Br_2 to yield **72** and **73**, respectively[46].

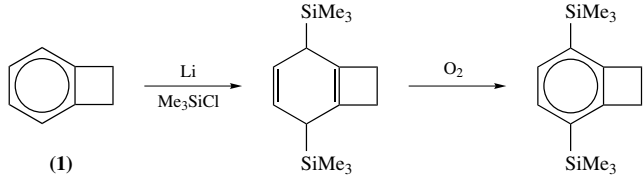


SCHEME 15

The ring protons have different acidity[44]. Thus, the 3-proton is more acidic than the 4-proton by *ca* 3.2 kcal mol^{-1}. Indeed, treatment of **1** with *n*-BuLi and quenching with Me_3MCl (M = Si, Sn) yields only **74**[47]. The reaction of **74** with electrophilic halogen (ICl or Br_2) yields **75**, which is a typical product of Me_3M-phenyl chemistry[47]. Other reactions that the aromatic moiety undergoes are Birch-type reduction and oxidation of the product (Scheme 16)[48] and DDQ oxidation of the 1,4-bis-phenol **76** to **77**[49]. However, catalytic (Pd/C) hydrogenation of **78** yields **79**[50], probably by the intermediacy of **10** which is an activated olefin and therefore very reactive towards hydrogenation.

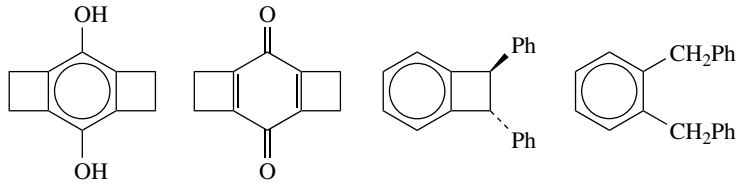


(74) M = Si, Sn **(75)** X = I, Cl



(1)

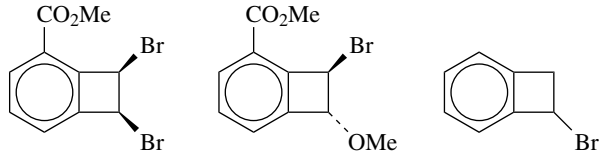
SCHEME 16



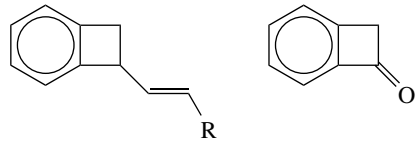
(76) **(77)** **(78)** **(79)**

In summary, although the four-membered ring is sensitive to acid and is in equilibrium with the *ortho*-quinodimethane isomer (and therefore hydrogenolysis does not yield the cyclohexane derivative), benzocyclobutene undergoes a typical aromatic chemistry. The four-membered ring acts as a strong directing group, a subject that was dealt with already in 1930 by Mills and Nixon[51]. This is the Mills–Nixon effect, which will be discussed in Section IV.B.

The four-membered ring undergoes typical chemistry of benzylic carbon atoms. For example, **11** can be reduced to **1** by $Bu_3SnCl/LiAlH_4$[52]. This radical type reaction is not suitable for the reduction of **68** to **48** since the tricyclobutane opens to hexaradialene in the presence of radicals. However, 'super hydride' ($LiEt_3BH$), which reduces through nucleophilic substitution, cleanly transfers **68** to **48**[41]. A nucleophilic substitution of the Br by MeO^- in methanol converts **80** to **81**[32b]. Heck or nickel catalyzed coupling of substituted ethylenes $H_2C{=}CHR$ with **82** yield **83**, where R can be a variety of substituents[53]. Oxidation of **37** (R = H) yields **84**[54].

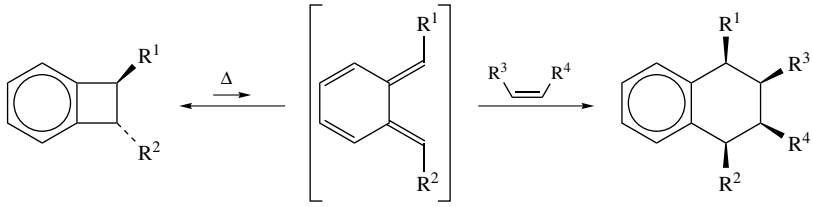


(80) **(81)** **(82)**



(83) **(84)**

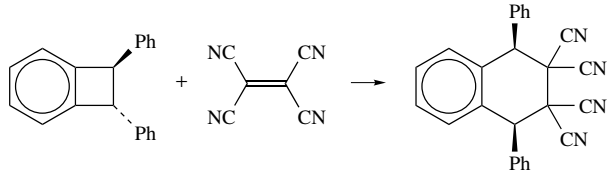
However, the vast majority of the reactions reported for benzocyclobutene are Diels–Alder reactions, where the benzocyclobutene serves as a synthon to *ortho*-quinodimethane that can be trapped by an intramolecular or intermolecular dienophile (Scheme 17). These reactions have been used as key steps in the synthesis of natural products, drugs and other organic compounds. A few selected examples are given below.



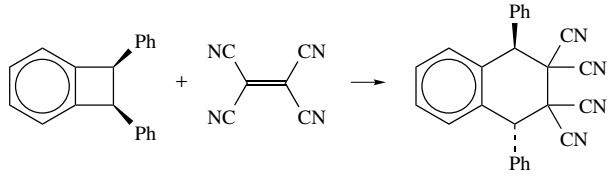
SCHEME 17

The stereochemistry described in Scheme 17 is for the thermally allowed reaction. Thus, the ring opening of the benzocyclobutene is conrotatory, leading to the *E*, *E*-*ortho*-quinodimethane, and the Diels–Alder reaction yields the *endo* product. The photochemical ring-opening is, of course, reversed, i.e. it is disrotatory. For example, under thermal conditions, the reaction of **78** with tetracyanoethylene (TCNE) yields **85**, whereas **86** yields with TCNE **87** (Scheme 18)[55]. The same products are obtained from the same starting materials when the reaction is photochemically induced[56]. However, the authors claim that the mechanism does not involve photochemical induced ring-opening, but charge transfer between the thermally opened 7,8-diphenyl-*ortho*-quinodimethane and TCNE, which react to form the product. Thus, under their conditions the ring opening is thermal, and therefore the thermally allowed products are formed.

When the substituents at the 7 and 8 positions of the benzocyclobutene are good leaving groups (LG) and the hydrogen atoms on the dienophile are acidic, the conrotatory ring-opening and the *endo* addition cause the formation of a product that has two pairs of antiperiplanar leaving group and acidic hydrogen atoms, which leads to spontaneous elimination of two equivalents of HLG and formation of the respective naphthalene. For example, reaction of styrene with **88** yields **90**, presumably through the intermediate **89** (Scheme 19)[57]. This product suggests that the addition is also regioselective. Reaction of

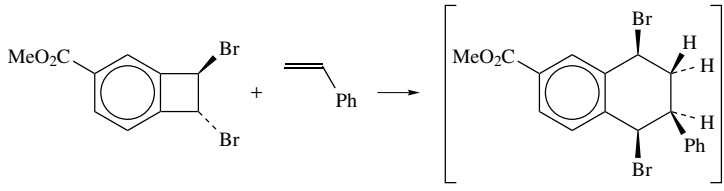


(78) **(85)**



(86) **(87)**

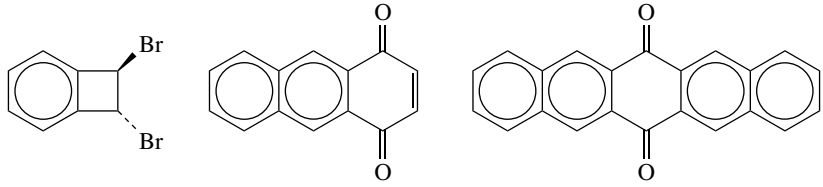
SCHEME 18



(88) **(89)** **(90)**

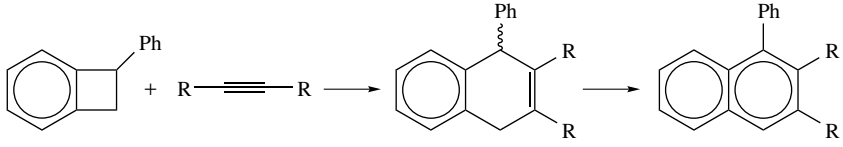
SCHEME 19

91 with 1,4-benzoquinone in a 1:1 molar ratio yields **92**, and in a 1:2 molar ratio **93**[58]. These reactions may be explained by the formation of the initial Diels–Alder product that contains two pairs of antiperiplanar H and Br atoms, which spontaneously eliminate two equivalents (or four in the case of **93**) of HBr to yield the aromatic product.



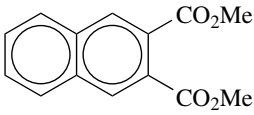
(91) **(92)** **(93)**

Alkynes add to the *ortho*-quinodimethanes to produce the respective 1,4-dihydronaphthalene derivatives. For example, the reaction of **94** with **95** yields a stereoisomeric mixture **96**, which can be aromatized to **97** on treating with Pd/C (Scheme 20)[59]. However, in some cases the products aromatize spontaneously. For example, reaction of **88** with phenylacetylene yields mainly **90** and the reaction product of **91** and dimethyl acetylenedicarboxylate is mainly **98**[58]. Also, 7-methoxybenzocyclobutenes yield the respective naphthalenes (and not the 1,4-dihydronaphthalenes) when reacting with substituted alkynes[60]. The mechanism of the aromatization is not clear, but the high yields of these reactions make them a good alternative for the preparation of substituted naphthalenes.



(94) **(95)** R = $CO_2CHMeCO_2Me$ **(96)** **(97)**

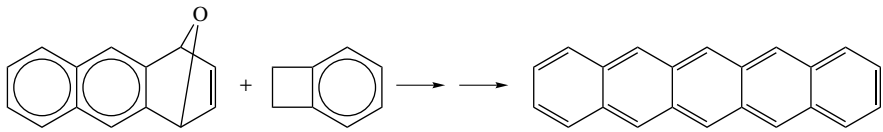
SCHEME 20



(98)

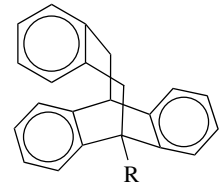
Benzocyclobutenes have been extensively used as synthetic intermediates in the preparation of various compounds ranging from polyaromatics to natural products and drugs. An extensive literature compilation of these can be found in Reference 1. Below are listed some representative examples that were chosen by the author of this chapter.

Reacting **99** with **1** followed by treatment with methanolic hydrochloric acid and dehydrogenation with Pd/C yields the pentacene **100** (Scheme 21)[61]. 9-*R*-Substituted anthracenes react with **1** to yield tribenzo[4,2,2]bicyclodecane derivatives **101**[62]. One of the key steps in the total synthesis of xestoquinone and xestoquinol is the Diels–Alder reaction between 1,4-dimethoxybenzocyclobutene **102** and **103** which, after treating the product with DDQ, yields **104** (Scheme 22). Four synthetic steps lead to the xestoquinone **105**, and reaction of **105** with thiosulfate in aqueous acetone yields the xestoquinol **106**[63]. Tetracyclic diterpenes have been prepared by an intramolecular Diels–Alder reaction of a benzocyclobutene derivative. Thus, thermolysis of **107** gave **108a** and **108b** in 75:15 ratio when X = CO_2Me and Y = H, and 82:8 when X = Y = CO_2Me[64].



(99) **(1)** **(100)**

SCHEME 21



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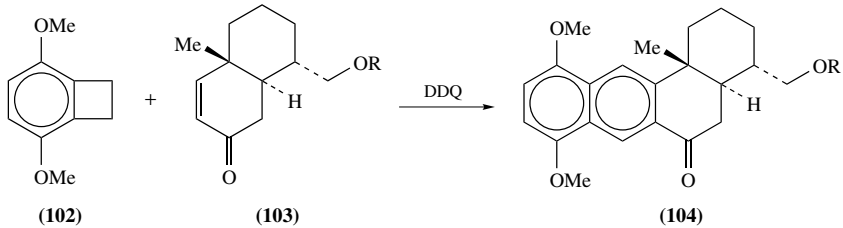
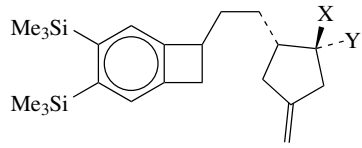


(102) **(103)** **(104)**

$R = CH_2OCH_3$

(106) **(105)**

SCHEME 22



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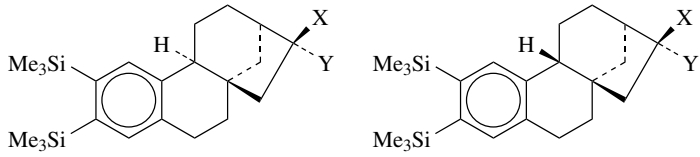
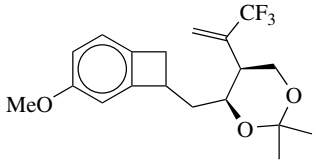


(108a) **(108b)**

The first enantiocontrolled total synthesis of 18,18,18-trifluorosteroids used a benzocyclobutene derivative in one of the key steps. Thus, refluxing **109** or **110** in dichlorobenzene yielded **111a** and **111b** and **112a** and **112b**, which were converted to the target molecule (and its enantiomer)[65]. The synthesis of the steroid **113** was achieved by heating **114** in dichlorobenzene to obtain **115**, which was converted to **113** by decarboxylation[66]. *Trans*-isoindolines **116** were prepared by intramolecular Diels–Alder reaction of **117**[67]. A key step in the synthesis of (+)-19-nordeoxycorticosterone **118** is the intramolecular Diels–Alder reaction of **119** to give **120**[68]. The synthesis of 25-hydroxy Windaus–Grundmann ketone (**121**, an active metabolite of vitamin D_3) was achieved by thermolysis of **122**, which yielded **123** after Birch reduction and deprotection. Nine additional synthetic steps lead to **121**[69]. The basic skeleton of the kaurane family natural products was prepared by refluxing **124** in decane; after six hours **125** was the main product, while after 72 hours **126** was isolated in 92% yield[70].



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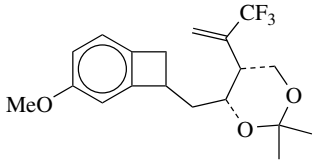

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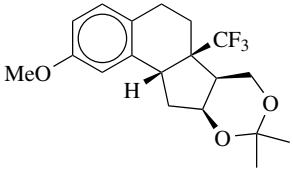

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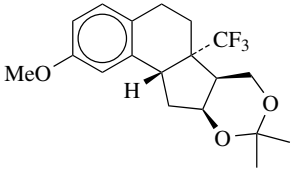
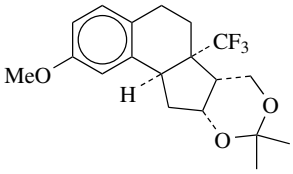


(111b)



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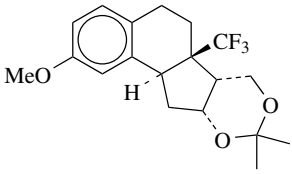

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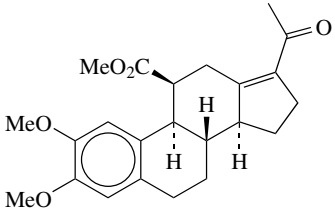

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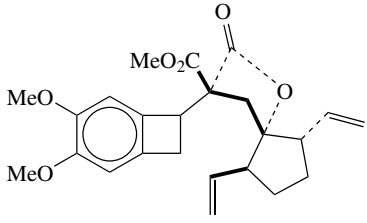

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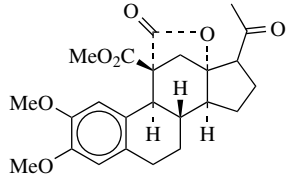

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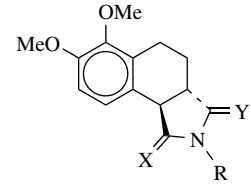
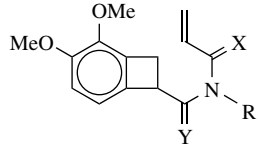


(116)

X = H_2, Y = O; X = O, Y = H_2



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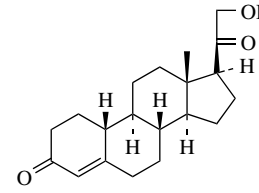

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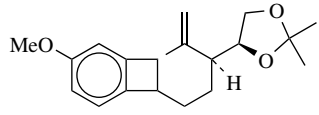

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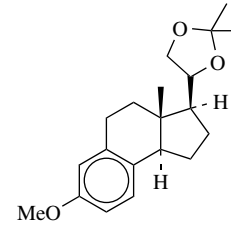

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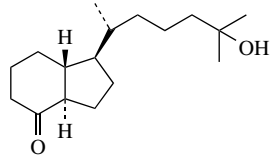

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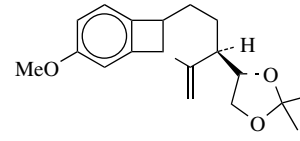

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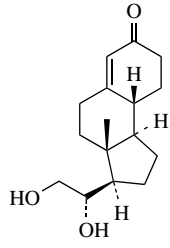

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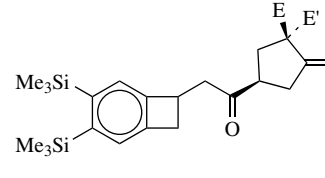
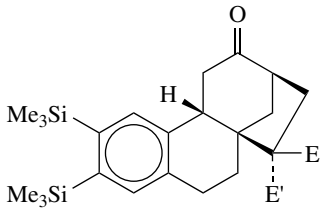


(124)

E = COi Pr, E′ = CO_2t-Bu;
E = CO_2t-Bu, E′ = COi Pr



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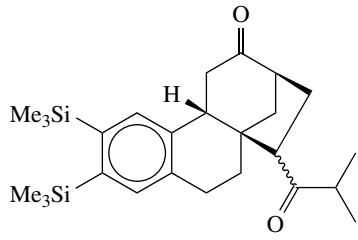


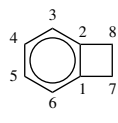
(126)

In summary, the few examples listed above, which consist of only a small part of the literature describing the use of benzocyclobutenes in organic synthesis, exemplify the versatility of benzocyclobutenes as intermediates in the synthesis of different types of organic molecules, in particular their usefulness in constructing polycyclic systems.

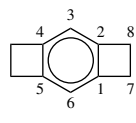
IV. STRUCTURAL ASPECTS

The structure of benzocyclobutene **1**[71] and of the higher homologs, the bis-annulated systems **46**[71] and **47**[72], the tris-annulated system **48**[72] and some other derivatives (mainly halogenated) of these systems were determined. Table 1 specifies the bond lengths and some bond angles of these systems. X-X-Electron density deformation analysis which was performed for the three structures shows that the benzylic and aromatic bonds are bent.

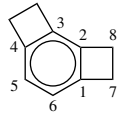
TABLE 1. Bond lengths (in Å) and angles (in deg) of unsubstituted benzocyclobutenes **1** and **46**–**48**



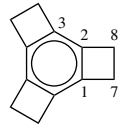
(1)



(46)



(47)



(48)

	1	**46**	**47**	**48**(HT) [a]	**48**(LT) [a]
C(1)–C(2)	1.391	1.399	1.402	1.401	1.413
C(2)–C(3)	1.385	1.394	1.385	1.383	1.390
C(3)–C(4)	1.400				
C(4)–C(5)	1.399		1.392		
C(5)–C(6)			1.413		
C(1)–C(7)	1.518	1.521	1.522	1.519	1.527
C(2)–C(8)			1.518		
C(7)–C(8)	1.576	1.575	1.582	1.566	1.579
C(1)–C(2)–C(3)	122.3	124.0	118.1	120.0	120.0
C(2)–C(3)–C(4)	116.0	112.1	124.3		
C(3)–C(4)–C(5)	121.7		117.7		
C(2)–C(1)–C(7)	93.5	93.4	93.2	93.0	93.0
C(1)–C(2)–C(8)			93.8	87.0	87.0
C(1)–C(7)–C(8)	86.5	86.6	86.8		
C(2)–C(8)–C(7)			86.5		

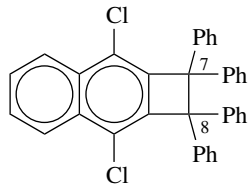
[a] **48** exists in high temperature (HT) and low temperature (LT) phases with slightly different structures.

We will concentrate here on two features of the structures of benzocyclobutenes: the C(7)−C(8) bond length and the geometry of the aromatic moieties.

A. The C(7)−C(8) Bond

The C(7)−C(8) bond length in **1** (1.566–1.582 Å, Table 1) is somewhat long relative to a standard C(sp^3)−C(sp^3) bond (1.54 Å) and the C−C bond distance in cyclobutane (1.548 Å)[73] but similar to that of cyclobutene (1.566 Å)[74]. At B3LYP/6-31G* and B3LYP/6-311G* the respective bond length of **1** is 1.581 Å[75]. At these levels of theory, the calculated respective bond lengths of cyclobutane and cyclobutene are 1.553 and 1.572 Å, respectively. Considering that the structures reported for cyclobutane and cyclobutene were obtained from NMR (coupling constants) and microwave spectra, it can be concluded that the C(7)−C(8) bond length in benzocyclobutenes is only slightly longer than that of cyclobutene. The B3LYP/6-31G* and B3LYP/6-311G* levels of theory reproduce well the experimental geometries, suggesting that they can be safely used for the study of such molecules. Indeed, much of the geometrical information about benzocyclobutenes comes from theoretical studies.

Substitution at this bond modifies, sometimes dramatically, its length[76]. The longest observed C−C single bond ever found (1.720 Å) is the C(7)−C(8) bond of **127**. Theoretical studies suggested that the reason for the exceptional long bond is the four phenyl substituents at the four-membered ring, and a very similar bond length (1.718 Å) was calculated for **128**. The effects that cause this bond length are unclear. Siegel and coworkers[76] suggest that classic steric interactions are responsible, whereas Bettinger, Schleyer and Schaefer[77] suggest that the long bond is a sum of three effects: about a 1/5 is due to the cyclobutene ring strain, while steric interactions and through-bond coupling are each responsible for *ca* 2/5 of the effect. Another possibility which has not been examined so far is a biradical character of the C(7)−C(8) bond. As mentioned earlier, **8** is considered to be a contributing resonance structure of **7** in some substituted benzocyclobutenes, but (although never considered as such) is also a resonance structure of **1**. Normally, **8** is not expected to contribute much to the structure of **1**. However, in the case of the very long C(7)−C(8) bond it may well be that this bond has a biradical character, i.e. the canonic structure **8** contributes significantly. Indeed, the C(7)−C(8) bond lengths in **129a–f** are 1.633, 1.637, 1.607, 1.648, 1.698 and 1.674, respectively, at the B3LYP/6-311G* theoretical level[14]. However, when some of the systems are allowed to mix their HOMO and LUMO, the function loses its singlet character. Thus, it is clear that the steric effect is important in determination of the C(7)−C(8) bond length (see, e.g., the bonds in **129d** vs. **129e**), but it is certainly not the only factor (e.g. **129a** has a shorter C(7)−C(8) bond than **129b** although Me is bulkier than NH_2, and **129f** has a very long bond in the series although it is certainly not the most hindered one). Moreover, a non-singlet function yields lower energy (in a slightly different geometry) and indicates that the contribution of a diradical character to this bond is important. The issue is currently under study.



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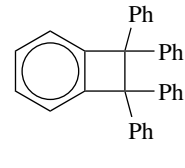
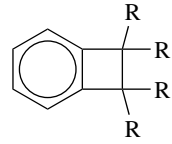


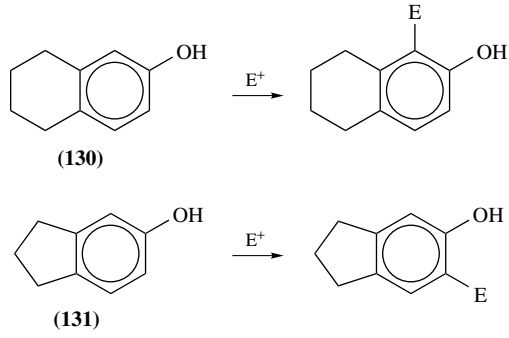
(128)



(**129**)(**a**) R = Me
(**b**) R = NH_2
(**c**) R = NO
(**d**) R = SiH_3
(**e**) R = $SiMe_3$
(**f**) R = CN

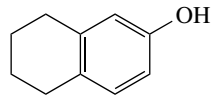
B. Strain-induced Bond Localization (SIBL) or the Mills–Nixon Effect

In 1930, Mills and Nixon published a paper[51] that describes and explains the regioselectivity of electrophilic aromatic substitution of 2-hydroxytetraline (**130**) and 2-hydroxyindane (**131**) by several diazo derivatives and bromine (Scheme 23), and integrating other relevant experimental data known then[78]. They offered an explanation for the opposite regioselectivity of the two compounds based on the following three theories: (1) Van't Hoff's model, namely that all carbon atoms in a molecule are tetrahedral, and therefore the strainless bond angles near a double bond are tetrahedral (*ca* 109.47°). (2) The aromatic moiety consists of two equilibrating structures. (3) The mechanism for electrophilic aromatic substitution is addition-elimination. The first and second assumptions led to the conclusion that the isomer **130a** is more stable than **130b**, but **131b** is more stable than **131a**. Addition-elimination across the double bond α to the OH explained coherently the observed product within the three theories mentioned above, which are realized to be wrong.

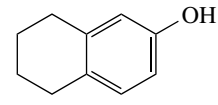


SCHEME 23

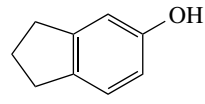
Although based on erroneous theories, the Mills–Nixon effect still retained its name to explain the effect of strain on the structure and properties of aromatic systems. We have shown (see below) that in some cases the same strain effect can cause the opposite deformation of the aromatic skeleton. Traditionally, this is called anti-Mills–Nixon effect, causing the system 'anti-Mills–Nixon' distortion. However, since they both arise from the same reasons, and since the explanation of Mills and Nixon about the kinetic



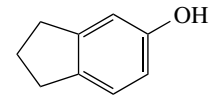
(130a)



(130b)



(131a)



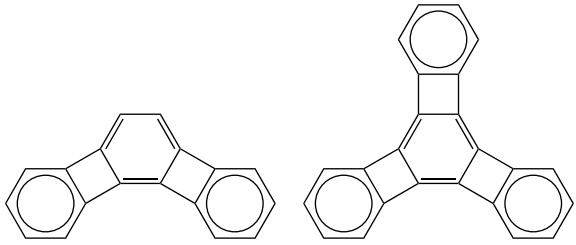
(131b)

effect discussed above is based on erroneous theories, we suggested another name, SIBL (abbreviation for Strain-Induced Bond Localization), and ΔR (defined as the bond-length difference between the bond annulated to the small ring and the bond exocyclic to the small ring of the aromatic system) as a quantitative measure for the effect. The effect is not directly related to benzocyclobutenes; however, since most of the compounds that have been used to study the effect are benzocyclobutene derivatives, and, as a matter of fact, some benzocyclobutene systems were made in order to study this effect, it is only appropriate to discuss it here.

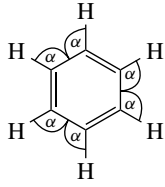
The Mills–Nixon effect issue is one of the more controversial topics in today's organic chemistry. Two basic approaches exist: One is the π-approach which claims that in order to localize the aromatic moiety, π-interactions of the antiaromatic type are required, and strain is not enough for causing localization. The second approach suggests that strain alone is enough to localize aromatic moiety, and antiaromaticity is not needed. Two chapters were written about the topic by two authors that represent the two approaches, where most of the relevant literature is cited[4]. The following describes the approach of the present author, which contains elements of both approaches.

Until the mid-eighties, the basis for the debate as to whether or not there is a Mills–Nixon effect, or anti-Mills–Nixon effect (i.e. a strain effect, but in the opposite direction), was based mainly on theoretical calculations, which naturally, at that time, were based on crude approximations and therefore yielded different answers. The first localized benzene derivatives, the angular[3]-phenylene **132**[79] and the triangular[4]-phenylene **133**[80], were introduced in the mid-eighties by Vollhardt and coworkers. To explain the bond localization in these molecules one can invoke two orthogonal explanations: One is based on the Mills–Nixon effect which results from strain in the σ-plane, and the second is based on π-interactions, which suggest that if the central ring would be delocalized, three cyclobutadienoid antiaromatic moieties (two in **132**) would be formed, and the system thus 'prefers' to give up the aromatic stabilization in order not to obtain the antiaromatic destablization. Note that even here, the approach that uses the π-explanation is somewhat incoherent. Thus, aromaticity and antiaromaticity are properties of the number of electrons in a cyclic conjugated π-system. A system may be aromatic or antiaromatic on having $4n + 2$ or $4n$ π-electrons, respectively. Applying the avoidance-of-antiaromaticity explanation to the bond localization in **132** and **133** suggests that the central six-membered ring in both should have had the same localization. The fact is that ΔR in **132** is 0.095 Å, whereas in **133** ΔR is 0.143 Å. The effect is completely additive: Thus, $(0.143\ \text{Å}/3) \times 2 = 0.095$ Å. The difference in bond localization between **132** and **133** and the complete additivity of the effect argues strongly against the explanation which relies on the avoidance of antiaromaticity.

In order to get more insight into this problem, one needs to study system(s) in which only one factor (i.e. strain or antiaromaticity) is present. This was done by bending the



(132) **(133)**

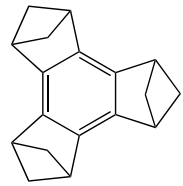


(134)

C−H bonds in benzene in pairs (keeping D_{3h} symmetry) to mimic annulation of three small rings and optimizing the rest of the geometrical parameters (cf. **134**)[81]. The results clearly showed that strain is enough to localize the aromatic bonds, and that antiaromaticity is not essential for this. A quantitative formula that connects ΔR to the bond angles α (equation 1) was given. However, since **48** showed a much smaller bond localization than expected by its bond angle, it was necessary to invoke 'bent' bonds. If the formation of bent bonds cannot be efficient (for example, in the studied model or in **133**, where there are less orbitals available for the necessary re-hybridization), then the aromatic carbon atoms undergo re-hybridization to produce different sp lobes at each direction, causing a different bond length at each direction, i.e. localization. There is numerous experimental evidence that is consistent with this view: The experimental X-X-electron density deformation of **48** shows very clearly that the bonds are bent[72]. The agreement between the theoretically predicted effective bond angle and the experimentally found bond angle is also quantitative. Thus, calculating the effective bond angle (i.e. the angle formed by the two respective paths through the maximum electron densities) from the experimentally found ΔR (0.030 Å) by equation 1 yields an angle of 111°, which is within 1° of the experimental angle of 112°. Other evidence comes from the structure of **135**: The bridgehead carbon atoms, although tetravalent, cannot efficiently re-hybridize, and are therefore expected to produce a bond localized benzene derivative. Indeed, the ΔR that was found is 0.089 Å, and the bond angle is 102.3°[82]. Unfortunately, the X-X-electron density deformation of **135** was not reported, but calculating the effective bond angle by equation 1 yields 103.3°, indicating that the bonds are indeed not (or almost not) bent.

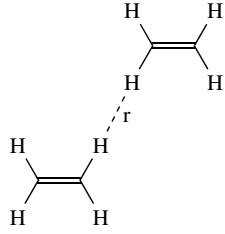
$$\Delta R = 0.9414 \times \sin^2 \phi + 6.81 \times 10^{-3} \quad \phi = 120 - \alpha \tag{1}$$

Although this approach is strongly consistent with results published before and after its publication, it received some criticism. One criticism was worrying, because if correct, it can actually make the investigation meaningless. It claims that the reason that **134** shows localization is the H–H repulsion which increases on bringing these protons to a closer proximity when decreasing α[83]. In order to probe this question, an estimation of



(135)

H–H repulsion (preferably on a hydrogen bound to an sp^2-hybridized carbon) should be undertaken. This was done by calculating the energy of two ethylene molecules that are brought together as a function of the distance r (Scheme 24). Table 2 shows the energy of the 'ethylene dimer' as a function of distance, and for comparison, the energy of **134** at different α values, together with the respective H–H distance, at the same theoretical level (B3LYP/6-31G*). Clearly, the rise in energy due to H–H repulsion is far smaller than that due to the α bending in **134**. Thus, it may well be that a part (a smaller percentage with decreasing α) of the energy rise is due to H–H repulsion but the latter cannot be the cause for the former. Furthermore, the physical behavior of the changes in the two is different. Thus, whereas the H–H distance in the ethylene dimer shows good linear correlation with the logarithm of the energy (Figure 1a), it correlates to the square root of the energy in the 'bent benzene' (Figure 1b). Thus, this criticism seems to be unjustified.



SCHEME 24

The basic work on the 'bent benzene' was carried out using the HF/3-21G theoretical level with single point calculations at HF/6-31G* and MP2/6-31G* for four bending angles in the range of $\alpha = 120$ to 90°. The advance in computers and software allowed repetition of this work at different theoretical levels on a 1° grid, testing the conclusions reported in 1991[81a]. The conclusions of this re-examination are as follows:

(a) As shown in Figure 2, equation 1 does not lead to a good linear correlation in the whole range. However, at a range of *ca* 95–110° it is close to linear, explaining the success of predicting the effective bond angles in compounds such as **48** and **135**.

(b) The calculation of varying α values was carried out for 5 different basis sets at the HF level (ranging from STO-3G to 6-311G**), and three basis sets using the B3LYP hybrid DFT functional. Each theoretical level produces different ΔR as a function of α. However, at all these levels ΔR can be almost perfectly correlated with α via a three-parameter equation (equation 2), where ϕ is the deviation from the sp^2 angle in radians (see, for example, Figure 3).

$$\Delta R = \mathrm{a} \times \phi^3 + \mathrm{b} \times \phi^2 + \mathrm{c} \times \phi \quad \phi = 2.0944 - \alpha(\text{radians}) \tag{2}$$

TABLE 2. The change in energy (B3LYP/6-31G*, kcal mol^{-1}) as a function of distance in ethylene dimer and in bent benzene (Å)

Ethylene dimer			Bent benzene	
R(H–H)	ΔE	α	R(H–H)	ΔE
2.5	0.0	120	2.4837	0.0
2.4	0.0	115	2.3239	3.21
2.3	0.096	110	2.1597	12.97
2.2	0.200	105	1.9935	29.70
2.1	0.331	100	1.8291	53.93
2.0	0.565	95	1.6713	86.28
1.9	0.862	90	1.5280	127.03
1.8	1.31			
1.7	1.97			
1.6	2.91			
1.5	4.22			

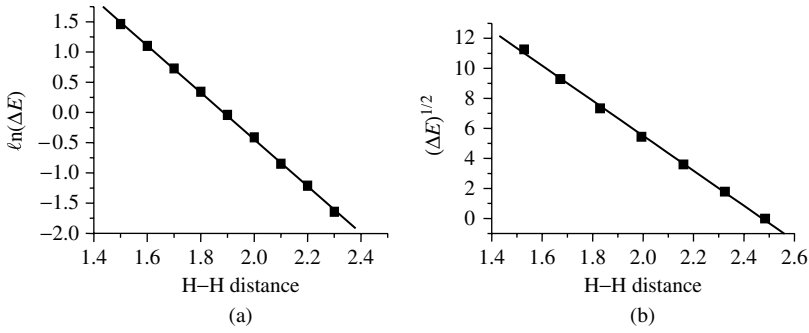


FIGURE 1. Linear correlation between H–H distance (Å) and (a) ln ΔE of the ethylene dimer (correlation coefficient = 0.99978) and (b) $(\Delta E)^{1/2}$ in the bent benzene

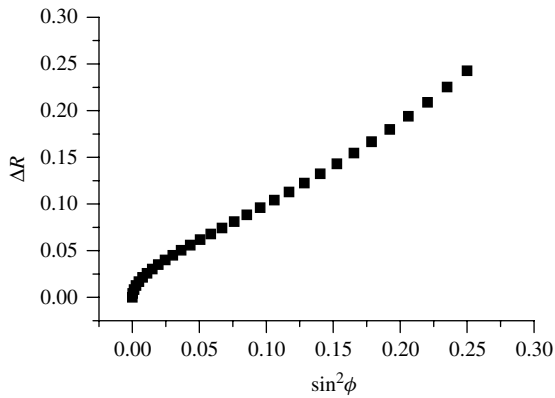


FIGURE 2. ΔR (Å, HF/3-21G) as a function of $\sin^2\phi$ for **134** where ϕ (radians) is the sp^2 angle (120° or 2.0944 radians $-\alpha$)

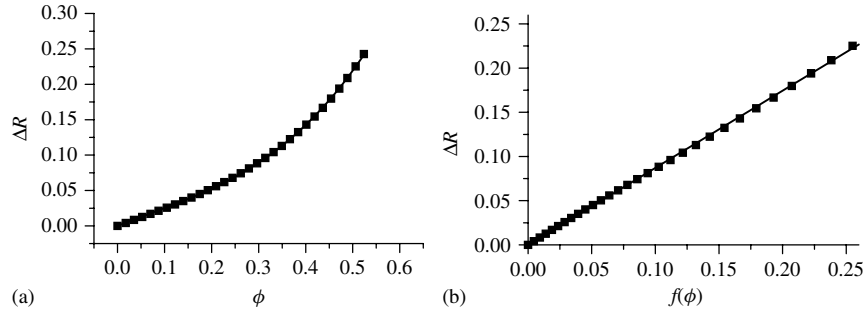


FIGURE 3. (a) A plot of ΔR as a function of ϕ (HF/3-21G) with the best-fit line according to equation 2: $a = 1.17594$, $b = -0.23821$, $c = 0.26365$. (b) A linear fit representation of the same plot. $f(\phi)$ is equation 2; a, b and c are the parameters specified above. Correlation coefficient = 0.99976

Using equation 2 and the experimentally observed ΔR of **48** and **134**, the effective bond angle can be calculated and compared with the experimental value. It turns out that the HF/3-21G theoretical level is indeed the best choice for calculating the 'bent benzene' model. STO-3G does not describe well enough the carbon atoms, while basis sets which are larger than 3-21G (and the B3LYP functional) allow some extend of C−H bent bonds. Certainly, allowing C−H bonds to bend is more realistic (i.e. in real molecules), but is not in accordance with what the chosen model is supposed to describe. Thus, not only is the principal understanding of the behavior of benzene under strain is understood, but also the quantitative predictions regarding the relations between effective bond angles and ΔR are valid for experimentally accessible molecules.

Since this basic concept was introduced, numerous publications have studied it. Currently, it seems that there is no other approach which coherently explains all the data obtained through the years. Lately, the SIBL concept was applied also to kinetics and found to explain nicely the regiochemistry of the products and the rates of oxidation of vitamin E[84].

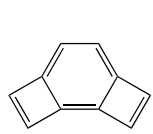
In summary, the structural and chemical properties of strained aromatic compounds (among which benzocyclobutenes are the largest group) is governed by the σ-frame, and affected by strain and bond curvature (which is affected by the electronegativity of the atoms forming the bond). Antiaromaticity seems to be unnecessary for localizing aromatic bonds. Furthermore, trying to explain the structural and energetic properties of strained aromatic compounds by using the $4n\pi/(4n+2)\pi$ argument does not yield a coherent explanation for all the systems studied[42, 85].

V. BENZOCYCLOBUTADIENES AND PHENYLENES

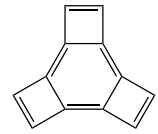
The uniqueness of the title compounds **2** and **3** is that they are built from aromatic and antiaromatic moieties fused together. Thus, they have been subjected to intensive experimental and theoretical basic research, mainly focusing on the balance between aromaticity and antiaromaticity.

Let us examine the aromaticity and antiaromaticity in **2** and its higher homologs **136** and **137** by three different indices: Structural (HOMA—Harmonic Oscillator Model of Aromaticity)[86], NICS (Nucleus Independent Chemical Shift)[87] and resonance structures.

At B3LYP/6-311G* ΔR values in **2, 136** and **137** are 0.0667, 0.1384 and 0.1811 Å. The difference in the ΔR between **136** and **2** is therefore 0.0717 Å, and between **137** and



(136)



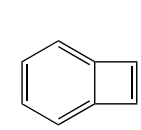
(137)

136 is 0.0427 Å. Thus, ΔR is not additive (in contrast to what was claimed)[83], although according to HOMA the order of aromaticity of the six-membered rings is **2**>**136**>**137**. Note also that the reduction in aromaticity (according to HOMA) is larger between **2** and **137** than between benzene and **2**. Thus, according to structural criteria the behavior is counter-intuitive: One would expect the largest effect in the first annulation, and a decreased effect in each successive annulation, or an additive behavior. The actual behavior of the systems is that the largest effect results from the second annulation.

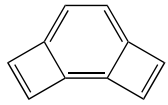
NICS(1.0) (i.e., NICS values calculated 1.0 Å above the center of the rings) values give a completely different picture: At GIAO-HF/3-21G//B3LYP/6-311G* (in parentheses the GIAO-HF/6-31+G*//B3LYP/6-311G* values are given) the NICS(1.0) of benzene and cyclobutadiene (the prototypes aromatic and antiaromatic systems) are −12.56 (−11.54) and 14.8 (18.2), respectively. The NICS(1.0) values of the six-membered ring in **2, 136** and **137** are −6.12 (−4.37), −1.12 (0.74) and −2.58 (−1.38), respectively, and those of the four-membered rings are 10.16 (12.77), −0.67 (1.33) and 4.23 (−2.4), respectively. Thus, NICS suggests that the six-membered ring in **2** is slightly aromatic, in **136** is non-aromatic and in **137** non-aromatic as well, but slightly more aromatic than in **136**, in contrast to the HOMA conclusions. The four-membered ring in **2** is antiaromatic, in **136** non-aromatic and in **137** it is slightly antiaromatic or non-aromatic at the larger basis set.

NRT (Natural Resonance Theory)[88] analysis reveals yet another picture: This analysis (at B3LYP/6-311G*) for benzene assigns 89.1% to the two Kekulé structures, 24 structures having an H^+ and a negative charge on one of the carbon atoms, each contributing 0.22% (total −5.3%), and 24 structures having one C−C bond broken, each contributing 0.21% (total −5%). The remaining 54 resonance structures contribute a total of *ca* 0.4%. At the same theoretical level, the Kekulé structures **a** are the most important canonic structure of the three systems, and accounts for 46.4, 39.1 and 21.1% of the structure of **2, 136** and **137**, respectively. The second Kekulé structure is insignificant and does not appear at all in the analyses of the three systems. All the other significant structures are zwiterionic. In **2**, the structure **b** containing a cyclobutadiene moiety accounts for 8.8%, whereas it is 13.3% in **136** and does not exist at all in **137**. Thus, the order of antiaromaticity is different than that obtained from NICS analysis. The charged structures of the type **c** and **d** are only 7.4% in **2**, but are 45.3% and 53.8% in **136** and **137**, respectively. The picture that emerges from the NRT analysis is that the six-membered ring is non-aromatic in the three systems, whereas the four-membered rings are somewhat antiaromatic in **136**, less so in **2** and not at all in **137**. The most electronically localized system is **2** (exactly the opposite is concluded from the HOMA analysis), and the delocalization through charged structures of the respective bridged annulenes ([8]-, [10]- and [12]-annulenes for **2, 136** and **137**, respectively) increases although the uncharged canonic structure is insignificant. This can be understood in light of the large strain that exists in these molecules when viewed as annulenes due to the [0.0] bridges. Thus, NRT predicts increase in delocalization on annulating cyclobutadiene rings to benzene, but through the annulenic form rather than through benzene-cyclobutadiene forms.

Even energetically it is difficult to determine whether benzocyclobutadienes are aromatic or antiaromatic. An attempt to investigate resonance energies of the three systems



(2a)



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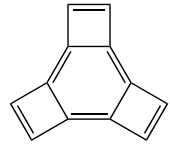
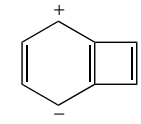
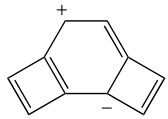


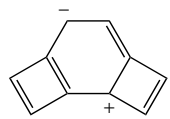
(137a)



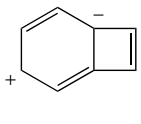
(2b)



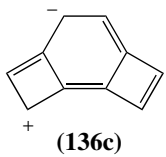
(136b)



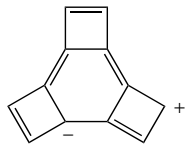
(136b′)



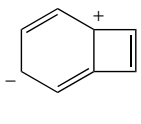
(2c)



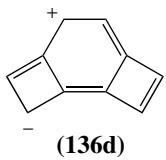
(136c)



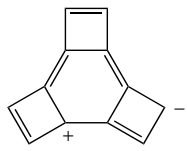
(137c)



(2d)

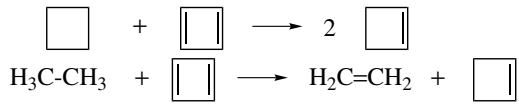


(136d)



(137d)

resulted in two different conclusions, depending on the reference systems chosen[89]. One method suggests that all three compounds have aromatic stabilization, and the other suggested that **2** is aromatic while **136** and **137** are non-aromatic.



ΔE (kcal mol^{-1})

−35.62 (3a)

$H_3C\text{-}CH_3$ + → $H_2C{=}CH_2$ +

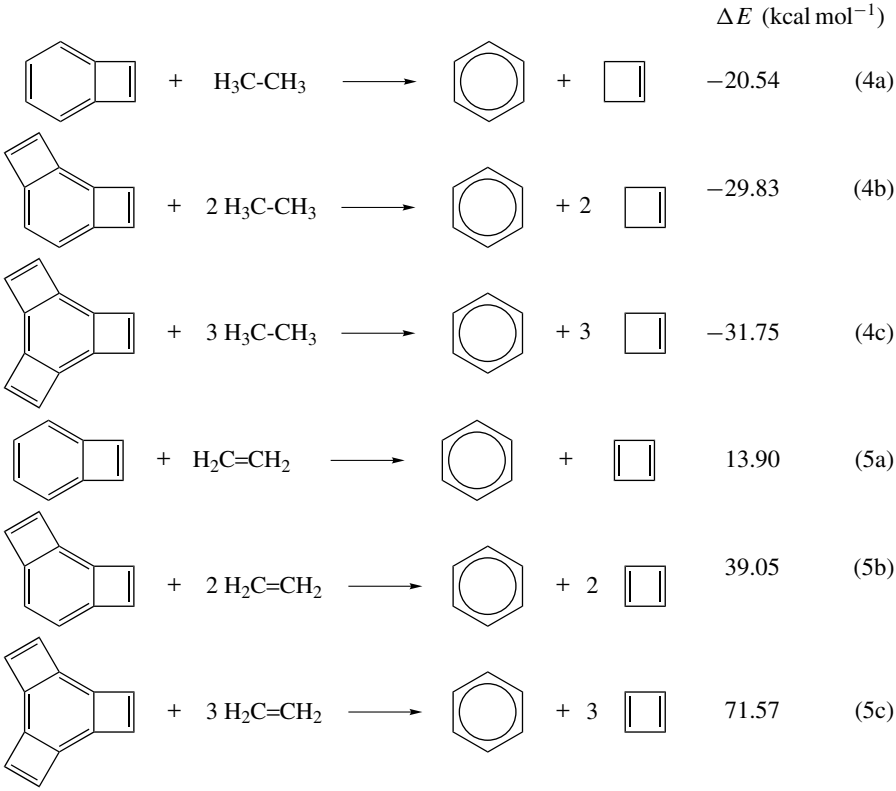
−34.44 (3b)

Let us try to compare the energetics of the systems. To do this we first need to know the antiaromatic energy cost in cyclobutadiene. Equation 3a compares cyclobutadiene to cyclobutene and cyclobutane, and suggests that the antiaromaticity in cyclobutadiene is 35.6 kcal mol^{-1}. A similar comparison, but with ethane and ethylene (equation 3b), yields a similar number (34.4 kcal mol^{-1}), suggesting that the strain on both sides of the equation is similar, and that the energy reflects the antiaromaticity destabilization. Benzocyclobutadienes can be compared to aromatic (benzene) and non-aromatic (cyclobutene, equations 4a–c) or to aromatic and antiaromatic (cyclobutadiene, equations 5a–c). The

TABLE 3. Energies of equations 4 and 5 (B3LYP/6-311G*)

Equation	ΔE (kcal mol^{-1})
4a	−20.54
4b	−29.83
4c	−31.75
5a	13.90
5b	39.05
5c	71.57

results (Table 3) suggest that benzocyclobutadienes are destabilized relative to benzene and stabilized relative to cyclobutadienes.



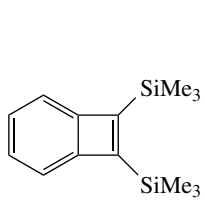
The experimental results for equations 3a, 3b, 4a and 5a are −45.6, −44.0, −20.1 and 24.3 kcal mol^{-1}, respectively[90]. It appears that there is a 10 kcal mol^{-1} disagreement between the experimental and theoretical results for equations 3a, 3b and 5a, whereas theory and experiment show good agreement for equation 4a. This probably results from the large uncertainty (±11 kcal mol^{-1}) in the determination of the heat of formation of cyclobutadiene that appears in equations 3a, 3b and 5a but not in equation 4a.

To conclude, it seems that there is no definite answer to the question posed above. Clearly, benzocyclobutadienes are neither simply aromatic nor simply antiaromatic, nor

are they 'localized' or 'delocalized' systems. There is no good simple description of their exact character, at least with the rather modern indices that have been used here. It appears also that despite the apparent structural homology, it is wrong to treat **2, 136** and **137** as a homologous series since the nature of the systems change upon successive annulation.

The parent system **2** is kinetically unstable and tends to dimerize. It can be studied in Ar matrix[91] or by fast flow techniques[92], but due to its kinetic instability the data have to be treated carefully. For example, the ^{1}H-NMR spectrum of **2** (taken using flow techniques)[92] shows three signals at 6.36, 6.28 and 5.77 ppm. At a slower flow rate the two higher-field signals are partially resolved to AA′BB′, allowing the assignment of the lowest-field signal to the vinylic proton, the highest-field signal to the proton β to the four-membered ring and the middle signal to the proton α to the four-membered ring. The calculated NMR spectrum (at GIAO-HF/6-31+G*//B3LYP/6-311G*) suggests that the vinylic protons resonate at 6.68 ppm, H_α at 5.95 ppm and H_β at 6.39 ppm[14]. The different trend between the calculated and experimental numbers, and the fact that the splitting was measured at a low flow rate (thus, perhaps dimerization may have occurred) may suggest wrong assignment. In addition, the aromatic protons of **138** resonate at 6.30 and 5.75 ppm[93], supporting the miss-assignment of the protons in **2**. The high-field shift of all the protons was attributed to a paratropic shift resulting from an 8π-electron system. Note, however, that whereas the chemical shifts of H_α and H_β in **1** are 7.18 and 7.05 ppm, respectively, the chemical shift of the vinylic protons in cyclobutene is 5.95 ppm[94]. Thus, if indeed the experimental assignment of the protons[92] is not correct, the vinylic proton actually experiences a downfield shift relative to that of cyclobutene. Both assignments, however, suggest a strong annulenic character of **2**, in best accord with the NRT picture obtained (see above).

Substituted derivatives of **2** (such as **138**[93], **139, 140**[95] and **141**[96]) or organometallic complexes of **2** (such as **142**[97] and **143**[98]) are more stable towards dimerization, and the stability depends on substitution. Thus, replacing the mesityls groups in **139** or the *t*-Bu groups in **140** by Ph, Me or H causes destabilization towards dimerization[95].



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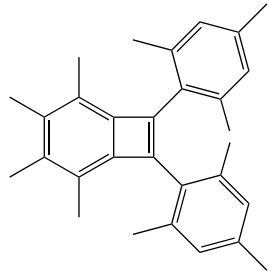

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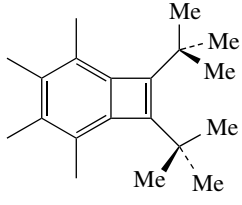

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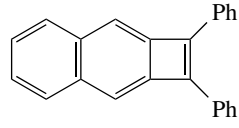

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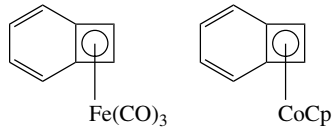
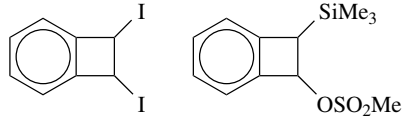


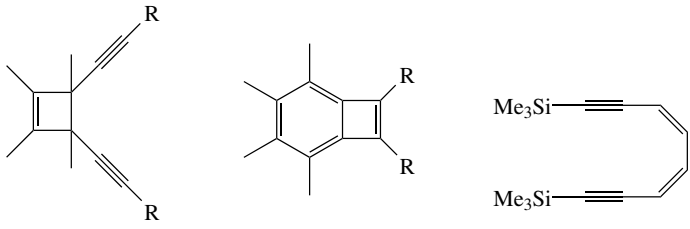
(142) **(143)**

Two principal methods have been used for the preparation of **2** and its derivatives: Elimination and rearrangement. Reaction of **30** with Mg at high temperature results in elimination of two HBr equivalents and the formation of **2**[91a]. Zn reacts with **11** or **144** to yield **2**[99]. F^--mediated desilylation of **145** yields **2** after the expulsion of the mesylate anion[92]. The complex **142** can be prepared from **30** and $Fe_2(CO)_9$, which serve as both the Br_2 eliminator and the source for $Fe(CO)_3$[97].

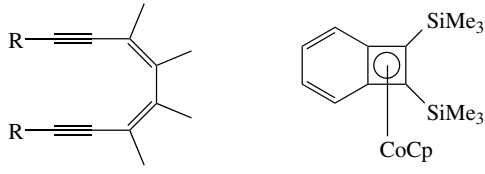


(144) **(145)**

Thermal rearrangement of **146** yields **147**[95], whereas the rearrangement of **148** yields **138**[93]. Note that the carbon skeletons of **146** and **148** are isomeric, and the positions of the substituents R are on the alkyne in **146** but on the four-membered ring in **147**. Thus, it is feasible to assume that the first step in the **146** → **147** rearrangement is the electrocyclic opening of the four-membered ring to **149**. The reaction of **148** with (or in the presence) $CpCo(CO)_2$ yielded the CpCo complex of **138** (namely **150**) which could be desilylated with F^- to yield **143** (i.e. the CpCo complex of **2**)[98]. It is unclear whether the CpCo actually catalyzes the reaction or is just forming a π-complex with **138** or with one of the intermediates. The complex **143** is stable, and attempts to liberate **2** from it failed.

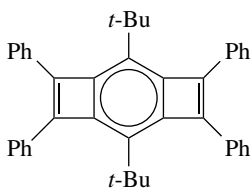


(146) **(147)** R = H, Me, Ph **(148)**



(149) R = H, Me, Ph **(150)**

The only higher homolog of **2** known experimentally is a substituted [1,2][4,5]-bis-cyclobutadienobenzene **151**[100], and its mono $Fe(CO)_3$ and bis- $Fe(CO)_3$ complexes **152** and **153**[101], respectively. Compound **151** is prepared by the thermal rearrangement of **154**, obtained by the coupling of **155** with CuCl in DMF. For many years the structure of **151** was unknown, and its properties were deduced from spectral data, reactivity studies and the structures of **152** and **153**[100b, 102]. Recently, the X-ray structure of **151** was determined, and the results show that this system is best described as a doubly bridged [10]-annulene rather than a bis(cyclobutadieno)benzene, i.e. as an average of the two resonance structures **156a** and **156b**. DFT calculations suggested that this system is a candidate for bond-shift isomerism, changing its character between [10]-annulene and bis-(cyclobutadieno)benzene, both having similar energy but having different geometries, separated but an energy barrier[103].



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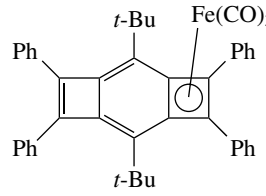

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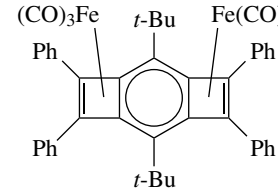

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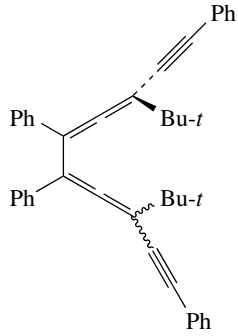

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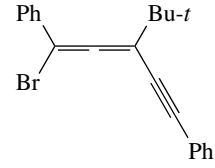

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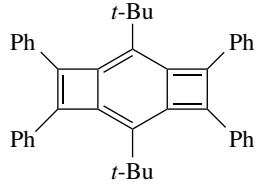
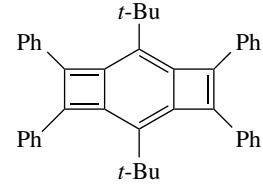


(156a)



(156b)

Phenylenes are benzo derivatives of benzocyclobutadienes. The fact that the cyclobutadiene is a part of two benzene rings stabilizes the systems, and many of these compounds have been prepared. The parent system **3** can be prepared efficiently by the dimerization of

benzyne, but substituted biphenylenes and higher phenylenes are mainly prepared by the CpCo-catalyzed [2+2+2} cyclization of three alkynes, a method developed by Vollhardt and used extensively by his research group to prepare many different linear and angular phenylene. Perhaps the most exciting system prepared is the triangular[4]phenylene **133** which exhibited the first cyclohexatrienic system, i.e. a bond-localized benzene[80, 104].

Due to the number of phenylenes known and their interesting properties, they deserve a chapter of their own. The latest review on phenylene is written in Serbian[105], and an earlier one in English was published in 1996[106]. Other literature sources include a somewhat older review about bis(methylene)cyclobutene and tetrakis(methylene)cyclobutane which include sections on benzocyclobutadienes and phenylenes[107], a review that deals with the reaction of phenylenes with transition metals[108] and the latest papers of Vollhardt (and references cited therein)[109].

VI. SUMMARY

In this chapter I have tried to show the significance of benzocyclobutabenzenes in organic chemistry. The message is to show that these somewhat unfashionable molecules are very significant in different fields of organic chemistry: concerning basic concepts such as SIBL (Mills–Nixon effect) in particular and the understanding of aromaticity, in synthetic organic chemistry mainly as synthons for *ortho*-quinodimethanes and the higher annulated systems (bi- and tricyclobutabenzene) and as potential building blocks for higher molecular weight systems. It is clear that the potential of these systems in all the above-mentioned areas is far from being fully explored, and there is still much to do with these systems, both in the basic as well as in the applied sense.

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CHAPTER **16**

Organometallic derivatives

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I. INTRODUCTION AND SCOPE

The organometallic chemistry of cyclobutane derivatives is rather diverse. As saturated cyclobutanes due to their lack of π electrons cannot coordinate to transition metals, their organometallic chemistry includes σ bound systems, and their reactivity is mainly a result of their ring strain resulting in ring opening reactions. Cyclobutenes, in contrast, have π electrons and can therefore act as ligands in organometallic complexes. Like their saturated analogues they are strained and undergo ring opening reactions. Cyclobutadienes are a more special class of compounds: Due to their antiaromatic character they are unstable in most cases, but they can be stabilized as ligands in organometallic complexes. In benzocyclobutenes the cyclobutane is anellated to a benzene ring, and complexes of these systems display a rich organometallic chemistry, which is determined by the steric as well as the electronic effects of the metal involved. Benzocyclobutadienes have a highly extended π system, which allows them to realize a number of coordination modes. Although some of their organometallic chemistry resembles that of cyclobutadiene complexes, there are aspects which are unique to this class of compounds.

This chapter will include the organometallic chemistry of the classes of compounds mentioned. Not included are heteracyclobutanes such as oxetanes, nor are metallacyclobutanes included. These compounds have their own diverse chemistry.

The chemistry of cyclobutanes
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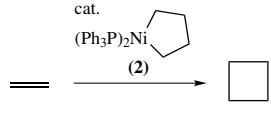
II. CYCLOBUTANES

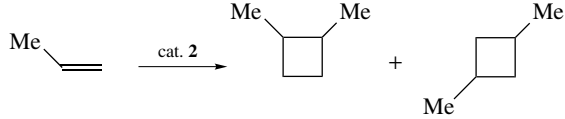
In addition to 1,4 dehalogenation reactions with activated metals[1] transition metal mediated reactions leading to cyclobutanes usually involve a [2 + 2] cycloaddition of double bonds. While such reactions of simple alkenes are rare, strained substrates such as methylenecyclopropanes or cyclopropenes are possible substrates. Norbornene and norbornadiene derivatives are also frequently used in these cycloadditions. Substrates with more extended π systems involve 1,3-dienes, allenes or other cumulenes. These reactions are known as dimerizations, but also as cross reactions when two different substrates are being involved[2–4].

Unactivated alkenes such as ethene (**1**) or propene (**4**) usually do not undergo a metal catalyzed [2 + 2] cyclization to give a cyclobutane **3** (equation 1). However, Grubbs reported nickelacyclopentane **2** to catalyze the [2 + 2] cyclodimerization of **1** to give **3** and that of **4** to give a regioisomeric mixture of **5** and **6** (equation 2)[5]. This is clear evidence that metallacyclopentanes like **2** play a key role as intermediates in transition metal catalyzed [2 + 2] cyclizations. Diversi and coworkers reported the thermal decomposition of several palladacyclopentanes to yield the respective cyclobutanes[6]. Dzhemilev and coworkers observed the reductive elimination reaction of aluminacyclopentanes to cyclobutanes in the presence of palladium complexes[7].



(1)

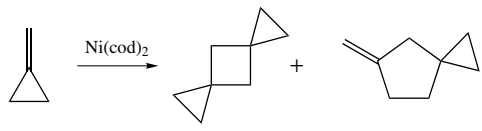
(1) **(3)**



(2)

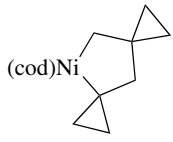
(4) **(5)** **(6)**

The first metal catalyzed [2 + 2] dimerization of an alkene was reported by Binger. Treatment of methylenecyclopropane (**7**) with bis(cyclooctadiene)nickel(0) [Ni(cod)$_2$] gave a mixture of oligomers containing dimers **8** (9%) and **9** (29%) (equation 3). Metallacyclopentane **10** was regarded as an intermediate in the reaction, from which **8** is generated by reductive elimination[8]. Whitesides and coworkers reported the thermolysis of a platinacyclopentane to yield cyclobutane in addition to a cyclobutene complex[9].



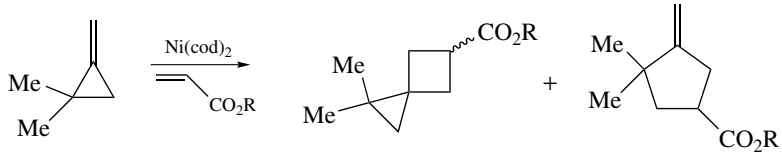
(3)

(7) **(8)** 9 % **(9)** 29 %



(10)

Whereas experiments directed to a codimerization of methylenecyclopropane with other alkenes lead to cyclopentane derivatives, small yields of spiro anellated cyclobutanes **12** were obtained when 2,2-dimethyl-1-methylenecyclopropane (**11**) was treated with acrylates in the presence of $Ni(cod)_2$ in addition to **13** (equation 4)[10].

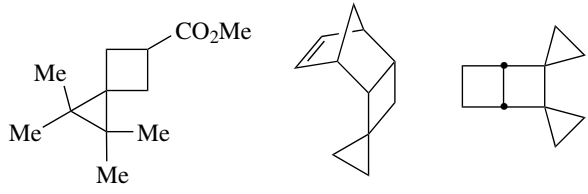


(4)

(11) **(12)** 19–40% **(13)** 81–60%

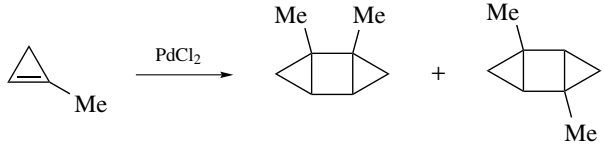
R = Me, Et, *i*-Pr, *n*-Bu, *t*-Bu

An even higher yield of 75% was achieved in the corresponding reaction of 2,2,3,3-tetramethyl-1-methylenecyclopropane with methyl acrylate, which leads to **14** in addition to a small amount of a ring opened side product[10]. Noyori and coworkers obtained cycloadduct **15** in 50% yield by treatment of methylenecyclopropane with norbornadiene in the presence of a catalytic amount of $Ni(cod)_2$ and triphenylphosphine[11]. A highly strained cycloadduct **16** was obtained from cyclobutene and bicyclopropylidene[12].



(14) 75% **(15)** **(16)**

In addition to methylenecyclopropanes, cyclopropenes can act as substrates for metal catalyzed [2 + 2] cyclization reactions. This is remarkable, because transition metals often undergo oxidative addition with ring opening of strained small ring compounds. In 1970 Baird and coworkers reported the reaction of 1-methylcyclopropene (**17**) with a catalytic amount of palladium dichloride to result in the formation of a regioisomeric mixture of the highly strained tricyclic cyclobutanes **18** and **19**, presumably formed as the sterically less hindered *anti* isomers (equation 5)[13].

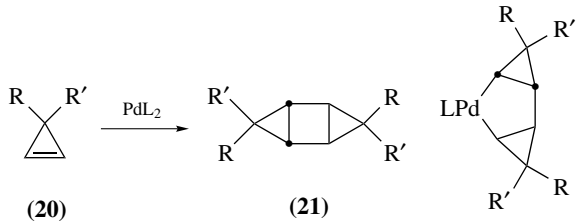


(5)

(17) **(18)** **(19)**

Binger and coworkers investigated the metal catalyzed [2 + 2] cyclization of 3,3-dialkyl- and 3,3-dimethoxycyclopropenes **20** in the presence of palladium(0) catalysts such as $Pd(dba)_2$ and found that the cyclobutane **21** (R = Me) was formed in up to 80% yield.

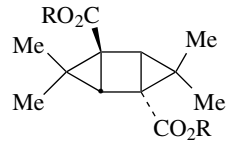
The *trans* anellation is explained by obvious steric reasons. In these reactions tricyclic palladacyclopentanes **22** are considered as key intermediates (equation 6)[14–16]. A similar reaction sequence was reported by Isaeva and coworkers, who used tris(triphenylphosphine) nickel(0) and isolated the nickelacyclopentane, which released **21** (R = Me) upon oxidation with oxygen[17].



(20) **(21)** **(22)** (6)

L = dba, (*t*-Bu)$_3$P, η^3-allyl, cod
R, R′ = Me, Et, OMe
RR′ = –(CH$_2$)$_4$–

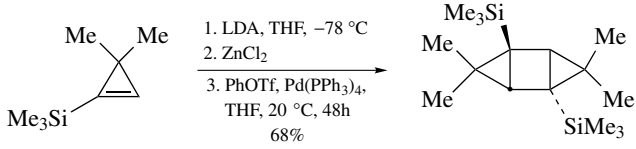
Baird and coworkers reported the [2 + 2] dimerization of methyl-3,3-dimethylcyclopropenecarboxylate or of the corresponding carboxylic acid to give dimer **23**, which has been characterized crystallographically in the case of the acid[18].



(23)

R = H, Me

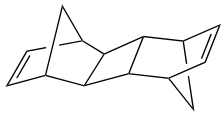
More recently, Untiedt and de Meijere published the analogous products of 3,3-dimethyl-1-(trimethylsilyl)cyclopropene (**24**). Deprotonation with lithium diisopropylamide (LDA) followed by transmetallation with zinc chloride and treatment with phenyl triflate and Pd(PPh$_3$)$_4$ unexpectedly afforded a 68% yield of cyclobutane **25** (equation 7). Remarkably, **25** is formed much slower in the absence of phenyl triflate. Without the deprotonation step, no **25** was formed[19].



(24) **(25)** (7)

In addition to the formation of **15** there is a number of reports describing the metal catalyzed [2 + 2] cycloaddition of norbornadiene and related systems[7, 20–40]. The earlier ones of these describe the dimerization of norbornadiene in the presence of metal carbonyls

as catalysts leading to different ratios of stereoisomers **26**–**28**[20–22,30]. Later, a variety of nickel catalysts was found to be efficient for this reaction. These catalysts include bis(acrylonitrile)nickel(0)[23,33].



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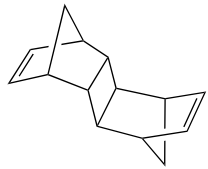

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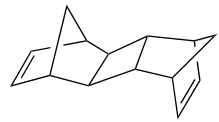
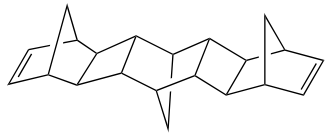


(28)

Catalysts derived from other metals than nickel are hexacarbonylbis(triphenylphosphine) dicobalt(0)[24], dicarbonyldinitrosyliron(0)[25], rhodium on carbon[26–28] and bis[dichloro(1,5-cyclooctadiene)iridium(II)][31].

Jennings and coworkers reported a related trimerization of norbornadiene leading to **29** in 5% yield as a side product in addition to 93% of **26**, when norbornadiene was treated with dicarbonylbis(triphenylphosphine)nickel(0)[32].



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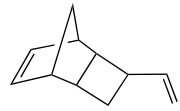
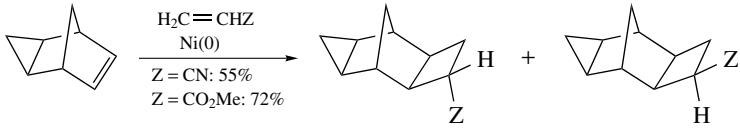


(30)

In addition to dimerization and trimerization reactions of norbornadiene, there are also metal catalyzed codimerizations involving norbornadiene or a related compound and different alkenes. A cycloadduct **30** (configuration undefined) was obtained in addition to other products upon treatment of norbornadiene and butadiene in the presence of a catalytic amount of tris(acetylacetonato)iron and chlorodiethylaluminum[29]. Treatment of cyclopropanated norbornene **31** and acrylonitrile with bis(acrylonitrile)nickel(0) as the catalyst afforded a diastereomeric mixture of **32** and **33** (63:37), and the corresponding reaction with methyl acrylate and bis(cyclooctadiene)nickel(0) as catalyst led to **34** and **35** (78:22) (equation 8). Similar reactions with 1,2-disubstituted alkenes are reported to proceed more sluggishly[34].

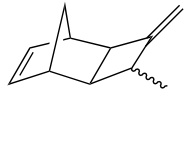


(31) **(32)** Z = CN **(33)** Z = CN
(34) Z = CO_2Me **(35)** Z = CO_2Me

(8)

Unusual coupling products **36** and **37** were obtained upon treatment of norbornene and dicyclopentadiene, respectively, with butadiene and dibromobis(triphenylphosphine)nickel (0) as the catalyst[35].

Another interesting reaction in this context is the 'trimerization' of cyclopentadiene in the presence of $Pd(acac)_2$, triphenylphosphine and acetic acid, which leads in 70% yield to a 1:1 isomeric mixture of tetracycles **38** and **39**, which have not been fully characterized with respect to the configuration of the cyclobutane carbon atoms[36].



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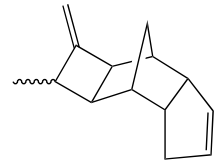

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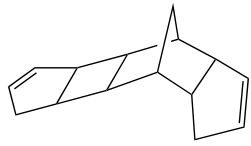

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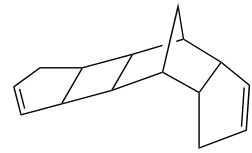
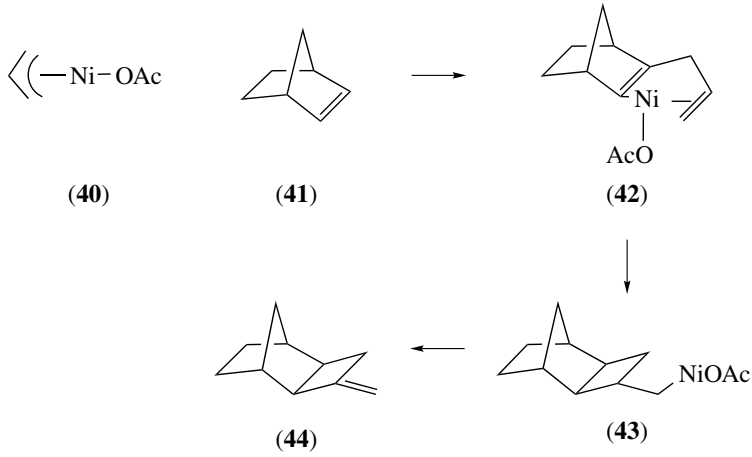


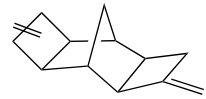
(39)

There are some reports of nickel or palladium catalyzed reactions of norbornene and related substrates with allylic acetates or esters leading to cyclobutane derivatives[37–40]. The results are explained by formation of an allyl nickel acetate **40**, which undergoes a carbometallation with a norbornene (**41**) double bond giving the chelate stabilized complex **42**. A following intramolecular carbometallation forms **43**, which after reductive elimination results in **44** in addition to nickel(0) and acetic acid (equation 9).



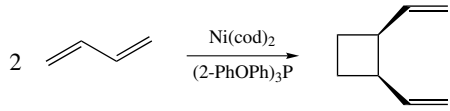
(**40**) (**41**) (**42**) (**43**) (**44**) (9)

Dzhemilev and coworkers reported a similar reaction of norbornadiene resulting in a 54% yield of tetracyclic **45**. The regioselectivity of the reaction was not completely assigned[38].



(**45**)

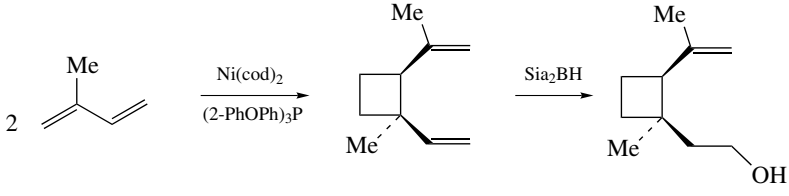
Conjugated dienes such as 1,3-butadiene (**46**) dimerize in the presence of nickel catalysts with formation of *cis*-1,2-divinylcyclobutane (**47**) (equation 10). Nickel catalysts used include $Ni(cod)_2$/tris-(2-biphenylyl)phosphite[41,42]. While these reactions usually led to 1,5-cyclooctadiene, a modification of the reaction conditions led to the discovery that **47** can be obtained catalytically in 40% yield. More highly substituted *cis*-1,2-divinylcyclobutane derivatives were obtained, when *cis*-1,3-pentadiene (piperylene) was used as the starting material[43]. Similar reactivity of 1,3-butadiene was observed in the presence of palladium salts (ClO_4, BF_4)[44].



(10)

(**46**) (**47**)

Billups and coworkers applied this type of reaction in a two-step synthesis of the monoterpene (±)-grandisol (**50**), a key constituent of the male boll weevil pheromone. Nickel catalyzed dimerization of isoprene (**48**) gave the substituted cyclobutane **49**, which after hydroboration with disiamylborane gave **50** (equation 11)[45]. This chemistry has been reviewed by Heimbach[46].

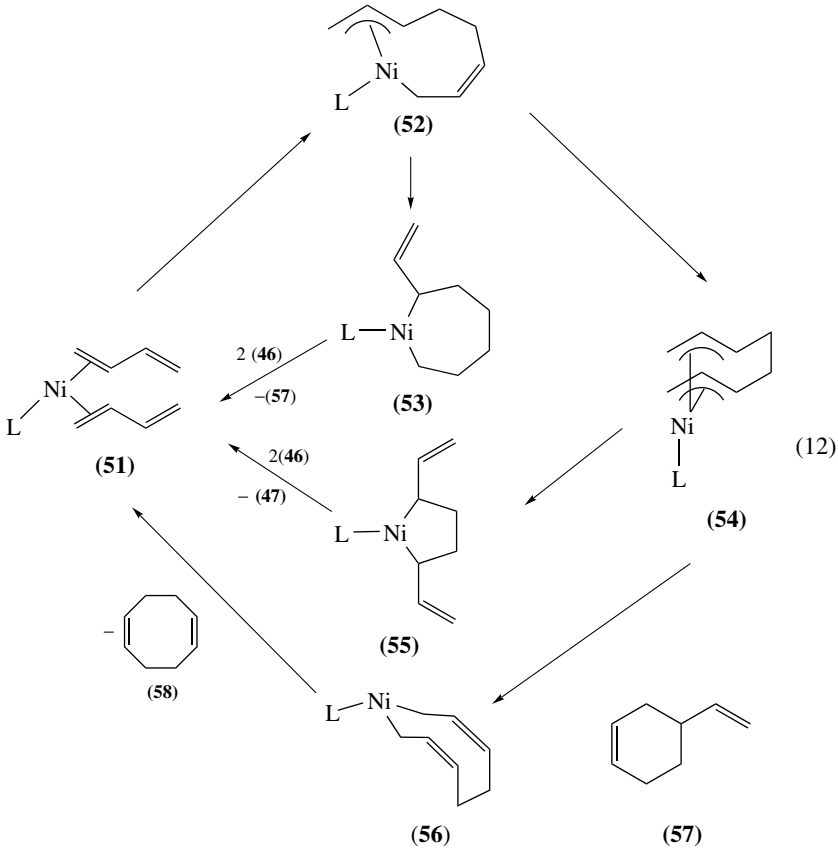


(11)

(**48**) (**49**) (**50**)

Later, some intermediates of these reactions were characterized spectroscopically. On the basis of these investigations a catalytic cycle involving some coordinatively unsaturated intermediates was formulated, according to which two molecules of butadiene (**46**) coordinate at nickel with formation of the bis(olefin) complex **51**. Coupling yields the η^3:η^1 intermediate **52**, from which the metallacycle **53** and the bis(allyl) complex **54** are

formed. While **52** gives vinylcyclohexene (**57**), **54** either terminally couples with formation of metallacycle **56**, which results in the formation of 1,5-cyclooctadiene (**58**), or forms the metallacyclopentane **55**, which is the basis for the formation of *cis*-1,2-divinylcyclobutane (**47**) (equation 12)[47].



(12)

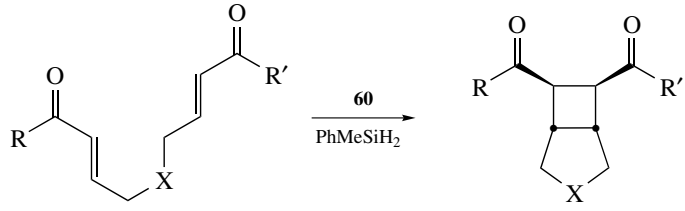
L = additional Ligand, e.g. phosphine or phosphite

Cannell has reported a cocyclization of ethene and 1,3-butadiene, which takes place with titanium catalysts and leads to vinylcyclobutane[48]. A diastereoselective intramolecular metal catalyzed [2 + 2] cycloaddition of bis-enones **59** has recently been reported by Krische and coworkers[49]. **59** reacts in the presence of the cobalt catalyst **60** with formation of the cyclobutane **61** in up to 73% yield (equation 13).

Another interesting case of an intramolecular [2 + 2] cycloaddition is the photolytic reaction of a diene with an olefin in the presence of copper triflate. For the reaction of **62** to give **63** (equation 14) a cationic copper diene complex has been proposed as the key intermediate[50].

Fischer-type carbene complexes are often regarded as analogues of esters. Of interest in this context are the results of Dötz and coworkers, who reported [2 + 2] cycloaddition

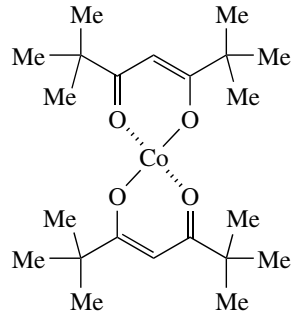
reactions of chromium or tungsten carbene complexes **64** with acyclic or cyclic enol ethers **65** to give spirocyclobutane derivatives **66** in up to 81% yield with high diastereoselectivity (equation 15)[51].



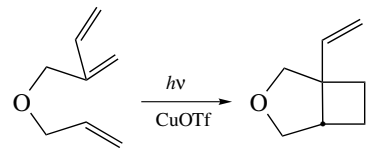
(**59**) (**61**)

R, R′ = Ph, Me, cyclopropyl, 2-furanyl, 3-indolyl
X = CH_2, $C(CO_2Me)_2$, NTs, CHOTBS

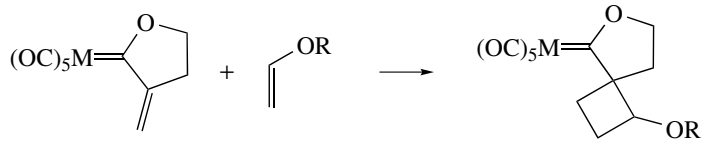
(13)



(**60**)



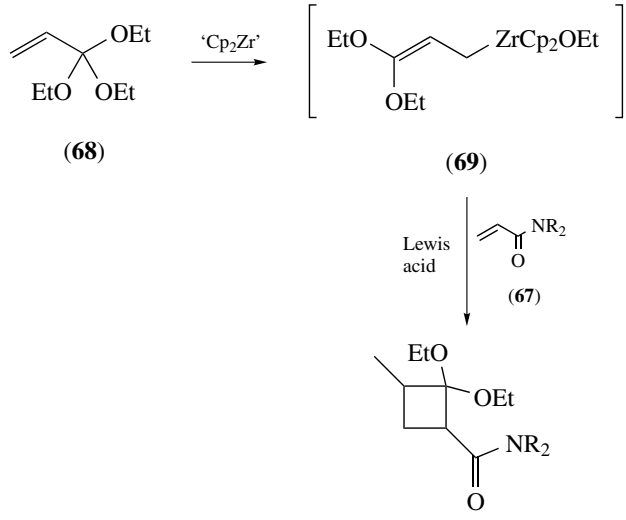
(**62**) (**63**) (14)



(**64**) (**65**) (**66**) (15)

M = Cr, W
R = Bu, *t*-Bu, 2-propenyl

Another [2 + 2] cycloaddition of an α,β-unsaturated carbonyl compound is the reaction of acrylamides **67** with the alkylzirconium intermediate **69**, which is formed by reaction of the ortho ester **68** in the presence of a zirconocene, leading to spiro anellated cyclobutanes **70** (equation 16)[52].

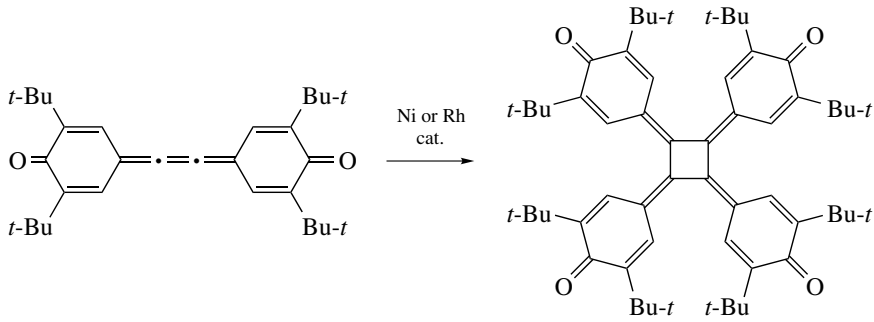


(**68**) (**69**) (**67**) (16)

(**70**)

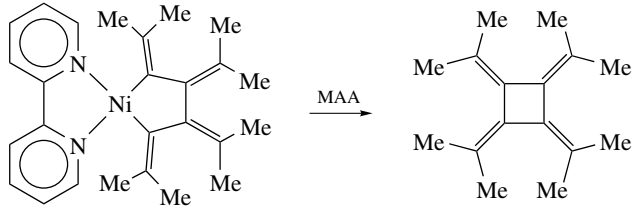
R = Me, Bn, *i*-Pr, Ph

Another class of metal catalyzed reactions leading to cyclobutane derivatives is the [2 + 2] cyclization of cumulenes. The cumulene **71** reacts in the presence of nickel and rhodium catalysts with formation of the cyclobutane derivative **72** (equation 17)[53,54], which is interesting because of the extended cross conjugated π system.



(**71**) (**72**) (17)

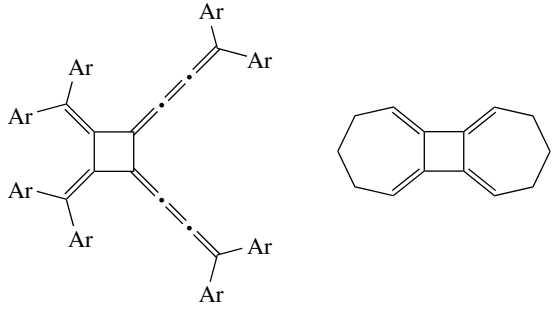
These reactions presumably proceed via a nickelacyclopentane intermediate. Stehling and Wilke succeeded in isolating **73** as a product of the reaction of tetramethylbutatriene with (bipyridyl)(cyclooctadiene)nickel(0) and showed it to give the [4]radialene **74** upon treatment with maleic acid anhydride (MAA) (equation 18)[55]. In a similar way Iyoda and coworkers obtained **74** starting from a dimethylbutatriene precursor in the presence of a Cu(I) compound[56]. The reactions of 1,1-dimethylallene with nickel(0) complexes have been investigated mechanistically by Pasto and Huang[57].



(18)

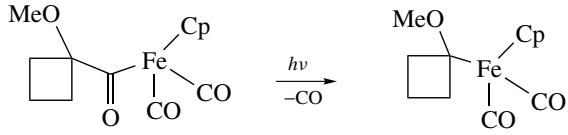
(**73**) (**74**)

Later, Iyoda and coworkers reported a nickel(0) catalyzed cocyclization of 1,1,6,6-tetraarylhexapentaenes leading to [4]radialenes **75**[58–61]. An especially interesting case of such a cyclization was reported by Szeimies and coworkers, who trapped 1,2,3-cycloheptatriene, which was generated by thermal isomerization of tricyclo[4.1.0.$0^{2,7}$]hept-1(7)-ene, with $Ni(PPh_3)_4$ as catalyst and obtained 32% yield of the tricyclic [4]radialene **76**, which was structurally characterized[62]. Recently Saito, Yamamoto and coworkers reported the nickel(0) catalyzed [2 + 2] cyclization of electron-deficient allenes to occur regioselectively with formation of 1,2-dimethylenecyclobutanes[63].



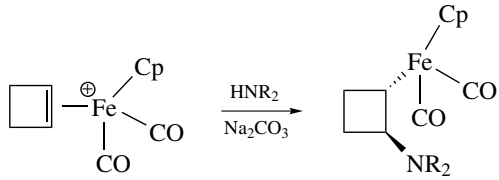
(**75**) (**76**)

In addition to more trivial compounds like cyclobutyl Grignard reagents, cyclobutyl metal complexes with a σ bond between the cyclobutane ring and the metal atom were reported by Stenstrøm and Jones. Photolysis of the cyclobutanoyl iron complex **77** caused a decarbonylation with formation of **78** as an intermediate (equation 19)[64]. Later, the formation of the amino substituted cyclobutyl iron complexes **80** (R = Me, Et) was reported by reaction of the cationic cyclobutene complex **79** with dimethyl or diethyl amine (equation 20)[65].



(19)

(**77**) (**78**)

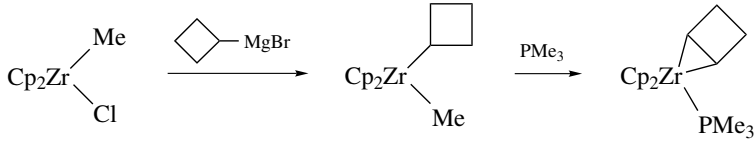


(20)

(**79**) (**80**)

R = Me, Et

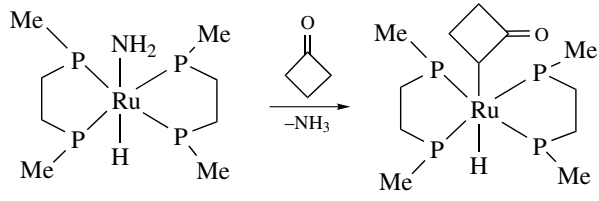
Fisher and Buchwald reported the formation of cyclobutyl complex **82** by treatment of methyl zirconocene chloride **81** with cyclobutylmagnesium bromide. Subsequent treatment with trimethylphosphine caused elimination of methane and formation of the cyclobutene complex **83**, which has to be regarded as a metallacyclopropane (equation 21)[66].



(21)

(**81**) (**82**) (**83**)

More recently, Bergman and coworkers observed the formation of a η^1 C-bonded enolate complex **85** by treatment of the basic amido ruthenium complex **84** with cyclobutanone (equation 22)[67].



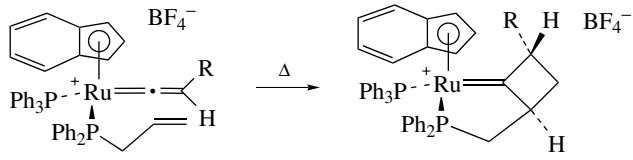
(22)

(**84**) (**85**)

Another ligand associated with cyclobutanes is the cyclobutylidene ligand. Bassetti and coworkers reported the thermal reaction of the cationic vinylidene ruthenium complex **86** to result in the cyclobutylidene chelates **87** (R = Ph, *p*-MeC_6H_4, 70%) (equation 23)[68].

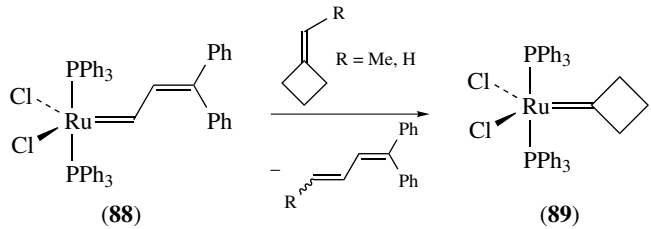
Grubbs and coworkers obtained a ruthenium complex bearing the unsubstituted cyclobutylidene ligand by metathesis starting from the vinylcarbene complex **88**. Treatment

with methylenecyclobutane or with ethylenecyclobutane gave **89** in 62% yield, which was characterized crystallographically (equation 24)[69].



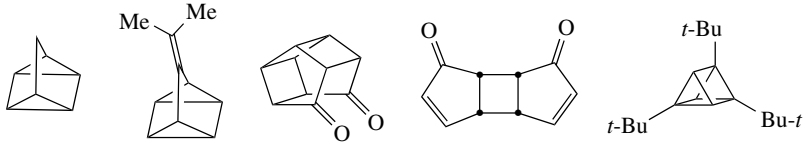
(**86**) (**87**) (23)

R = Ph, 4-MeC$_6$H$_4$



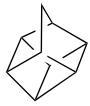
(**88**) (**89**) (24)

Most reactions of cyclobutane derivatives involving organometallics are ring opening or cycloreversion reactions. King and Harmon described the synthesis of (1,2-dimethylenecyclobutane)tricarbonyliron, a usual diene metal complex, by reaction of the organic ligand with $Fe_3(CO)_{12}$[70]. However, a more important organometallic reaction of cyclobutane derivatives is the cycloreversion of cyclobutanes creating two alkene units. This reaction was realized with strained cyclobutane structures such as quadricyclane (**90**) or its derivative **91**, which isomerized to the respective norbornadiene in the presence of a number of organometallic catalysts, e.g. rhodium(I), palladium(II) or platinum(I) complexes[71–73]. Eaton and Cerefice reported the isomerization of the cage diketone **92** to the tricycle **93** in the presence of rhodium(I)[74]. Hogeveen and Volger observed the result of the catalyzed valence isomerization of triprismanes to be highly dependent on the reaction conditions[75]. Maitlis and coworkers published an investigation about the kinetics of the catalyzed isomerization of triprismane **94** to Dewar benzene or benzvalene derivatives and later to the corresponding aromatic system, in which a number of Lewis acids were shown to be suitable catalysts[76].

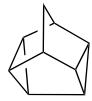


(**90**) (**91**) (**92**) (**93**) (**94**)

Homocubane (**95**) was reported to isomerize to **96** in the presence of silver cations[77]. Only a short time after this, the corresponding valence isomerization of a cubane derivative was communicated, which led to derivatives of cuneane (**97**) or **98**[78,79].

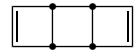


(95)



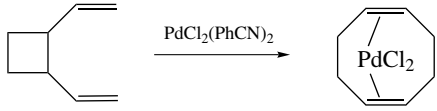
(96)

(97)



(98)

There are a few reports about metal catalyzed ring expansion reactions with vinyl or 1,2-divinylcyclobutane derivatives. Fujiwara and Takeda reported some vinylcyclobutene–cyclohexene rearrangements catalyzed by ethyl or phenoxy dichloroaluminum[80]. Heimbach and Molin reported that stoichiometric amounts of nickel(0) and palladium(II) complexes promote the ring enlargement reaction of 1,2-divinylcyclobutane derivatives with formation of the respective 1,5-cyclooctadiene complexes. For example, treatment of 1,2-divinylcyclobutane (**99**) with $PdCl_2(PhCN)_2$ gave the cyclooctadiene complex **100** (equation 25)[81].

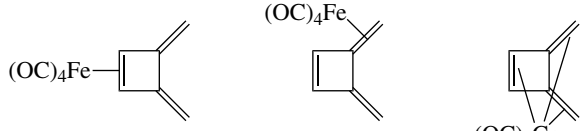


(25)

(99) **(100)**

III. CYCLOBUTENES

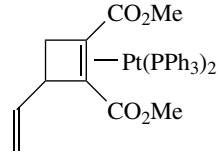
Cyclobutenes can act as ligands for organometallic complexes. Among the more interesting complexes are those of 3,4-dimethylenecyclobutene. **101** is generated upon treatment of the ligand with pentacarbonyliron and it undergoes a haptotropic rearrangement at 40 °C giving the isomer **102**[70]. Chromium complex **103** is obtained by treatment of the ligand with $Cr(MeCN)_3(CO)_3$ in 36% yield and was characterized crystallographically[82, 83].



(101) **(102)** **(103)**

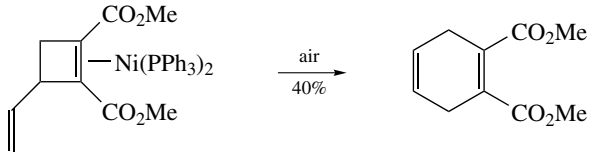
In addition to more trivial metal induced reductive dehalogenation reactions of 1,2-dihalocyclobutanes, the formation of cyclobutenes is performed by cycloaddition reactions usually involving an alkene and an alkyne component, by reactions of alkynylcarbene or vinylidene complexes and by some more special reactions.

Pinhas and coworkers reported the formation of 3-vinylcyclobutene metal complexes, **104** and **105**, which are complexed at the more strained endocyclic double bond. Remarkably, when oxidized with air, the nickel complex undergoes a vinylcyclobutene-cyclohexadiene rearrangement giving the 1,4-cyclohexadiene **106** in 40% yield (equation 26)[84, 85].



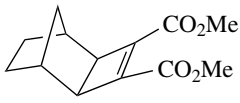
(104)

(26)

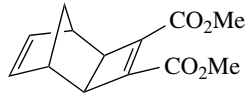


(105) **(106)**

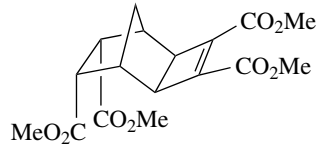
Mitsudo and coworkers found that $H_2Ru(PPh_3)_4$ catalyzes the [2 + 2] cycloaddition of norbornene or some of its derivatives and dimethyl butynedioate, resulting in anellated cyclobutenes **107–112** in up to 57% yield[86]. The authors propose the respective ruthenacyclopentene as the key intermediate[87].



(107)



(108)



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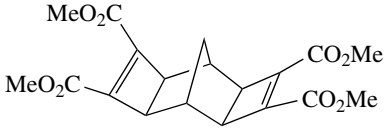

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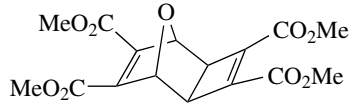

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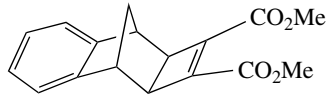
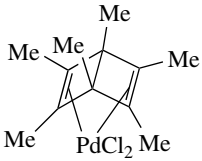
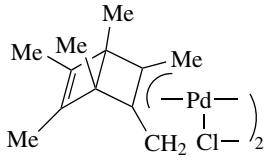


(112)

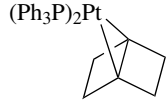
Complexes such as **113** based on the hexamethyl Dewar benzene ligand were prepared by treatment of the ligand with suitable complexation reagents. While **113** reacts to give **114** in poor yield upon treatment with sodium methoxide, treatment of hexamethyl Dewar benzene with anhydrous $PdCl_2$ makes **114** available in 62% yield[88]. Metalla[2.2.1]propellane **115**, which was characterized structurally, was described by Wiberg and coworkers[89].



(113)

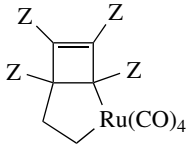


(114)



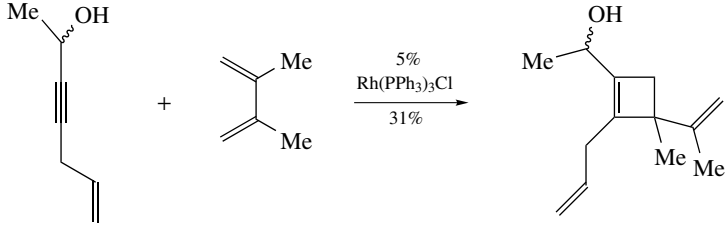
(115)

A remarkable stoichiometric [2 + 2] cycloaddition was reported by Lindner and coworkers, who found tetracarbonyl(ethene)ruthenium to react with hexafluoro-2-butyne, 1,4-dichloro-2-butyne or 1,4-dibromo-2-butyne with formation of metallacyclic cyclobutenes **116**–**118** in good yields[90]. Although the relative configuration was not assigned it should be *cis* for obvious reasons of ring strain.



(116) Z = CF_3
(117) Z = CH_2Cl
(118) Z = CH_2Br

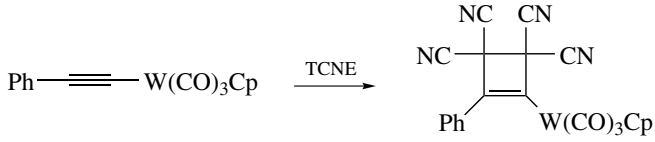
Dolor and Vogel observed the formation of cyclobutene **121** upon treatment of **119** with 2,3-dimethyl-1,3-butadiene (**120**) in the presence of Wilkinson's catalyst $Rh(PPh_3)_3Cl$ as a main product along with [4 + 2] cycloadducts (equation 27)[91].



(27)

(119) **(120)** **(121)**

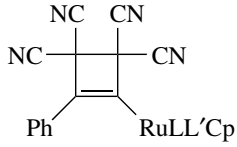
Another possibility for the construction of cyclobutene systems is the reaction of transition metal σ acetylides with electron-poor alkenes such as tetracyanoethylene (TCNE). This chemistry has been put forward by Bruce and coworkers[92,93], who found the reaction of the tungsten acetylide **122** with TCNE to result in the formation of cyclobutenyl complex **123** via a dark green paramagnetic intermediate (equation 28). This intermediate has been investigated by ESR; although it could not be completely characterized, the authors propose a structure in which the TCNE interacts in symmetrical fashion with the acetylide ligand. After some time the color changes to yellow with formation of **123**[92–94].



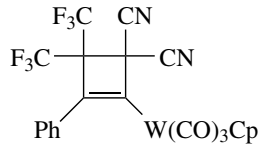
(28)

(122) **(123)**

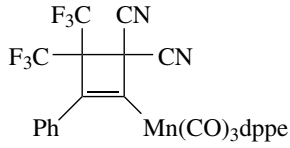
In a subsequent publication Bruce and coworkers describe similar reactions of ruthenium acetylides leading to complexes **124** [L, L′ = CO, PPh_3, $P(OMe)_3$, dppe][95]. In addition to TCNE, 1,1-dicyano-2,2-bis(trifluoromethyl)ethene [$(NC)_2C{-}C(CF_3)_2$, DCFE] reacted in a similar way when treated with **122**, $Mn(C_2Ph)(CO)_3$(dppe) or $Fe(C_2Ph)(CO)_2Cp$ giving cyclobutenyl complexes **125**–**127**, which were characterized structurally[96].



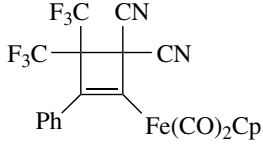
(124)



(125)



(126)

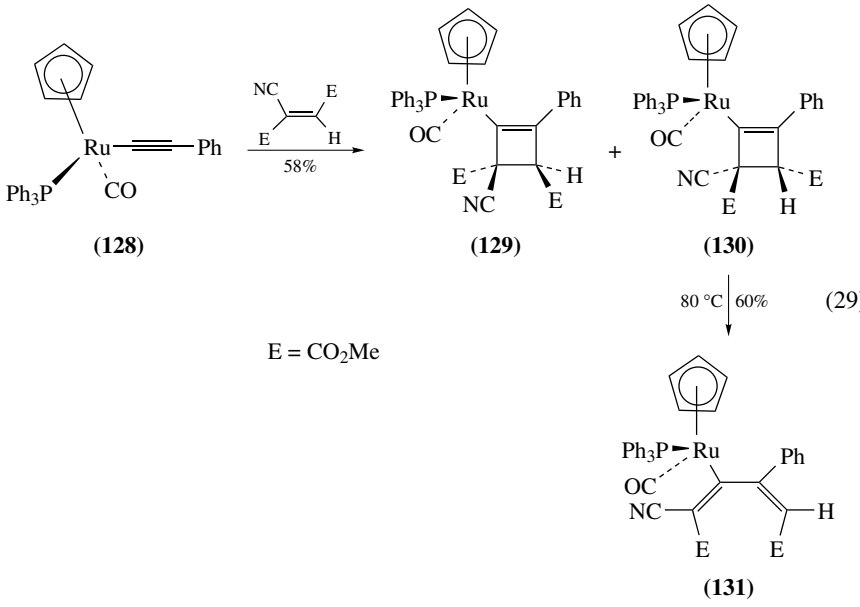


(127)

Remarkably, the bond length of the single bond opposite to the double bond is shorter than in some complexes derived from a TCNE cycloaddition. The authors correlate this observation with the reluctance of **125**–**127** to undergo a ring opening reaction. Later, Bruce and coworkers reported the reaction of the chiral ruthenium acetylide **128** with *trans*-2,3-di(methoxycarbonyl)acrylonitrile to give a diastereomeric mixture of **129** (59%) and **130** (27%), which were characterized structurally (equation 29)[97].

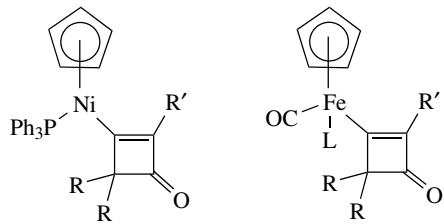
The chemistry of 1-cyclobutenyl metal complexes has been investigated by Bruce and coworkers, who showed that a ring opening reaction with formation of a 2-(1,3-butadienyl)

ligand system is the most prominent reaction pathway[92,95,96,98–101]. For example, thermolysis of **129/130** at 80 °C afforded complex **131** in 60% yield (equation 29)[97].



(29)

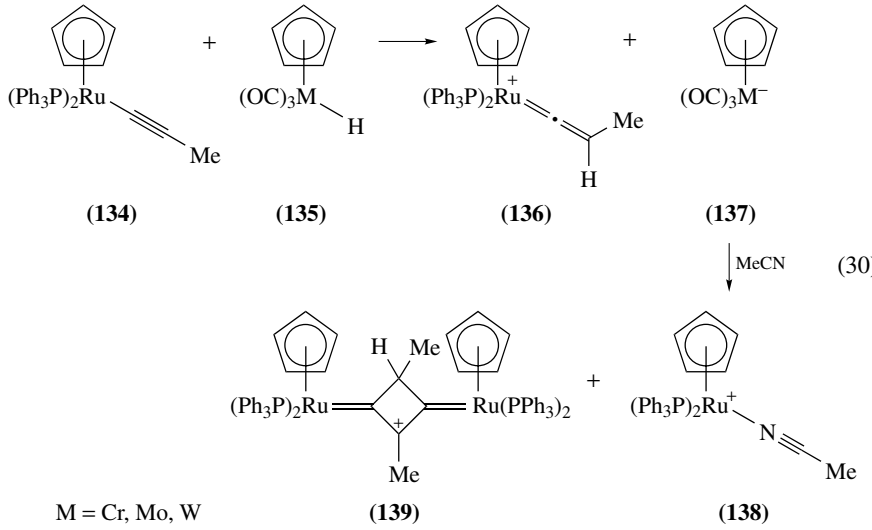
In a similar way the reaction of nickel or iron acetylides with ketenes afforded 3-oxocyclobutenyl complexes **132** and **133** (R, R′ = H, Ph, Me)[102].



(132) **(133)**

Barrett and coworkers treated a variety of iron acetylides with ketenes, acyl halides (which are ketene precursors), 2-chloroacrylonitrile, diketene and dimethyl methylenepropanedioate and obtained the respective [2 + 2] cycloadducts, some of which were characterized structurally, in yields up to 96%[103]. Bullock reported an interesting bimetallic cyclobutenyl complex derived from a ruthenium acetylide. Treatment of the acetylide **134** with the metal hydride **135** resulted in a proton transfer and formation of a cationic vinylidene ruthenium intermediate **136** and the anionic carbonyl complex **137**. Subsequent reaction with acetonitrile gave **138** in addition to the cationic complex **139** (equation 30)[104]. Similar iron complexes were earlier prepared by similar routes[105–108]. All these reactions

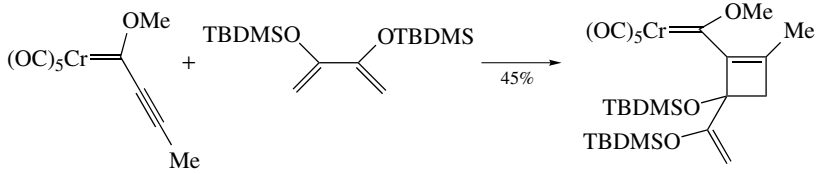
show that the reaction of transition metal acetylides with a variety of electron-poor alkenes is a general route to the respective 1-cyclobutenyl complexes.



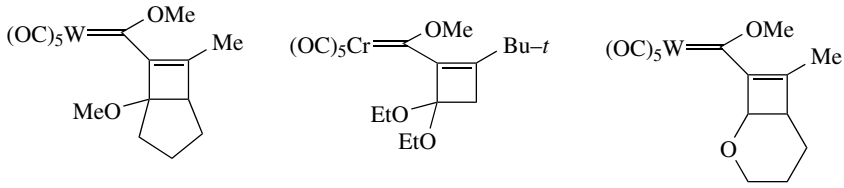
(134) (135) (136) (137) (30)

M = Cr, Mo, W (139) (138)

An important class of compounds, which serves to form cyclobutene derivatives, are alkynylcarbene complexes. Wulff and coworkers found that these complexes can undergo [2 + 2] cycloadditions with olefins bearing at least one alkoxy substituent. Alkynylcarbene complexes **140** react with 2,3-bis(*tert*-butyldimethylsilyl)butadiene (**141**) with formation of cyclobutene derivative **142** in 45% yield. The reaction works with chromium and tungsten complexes with a variety of substituents at the alkynyl group and at the alkene. Representative reaction products are **143**–**145** (equation 31)[109, 110].

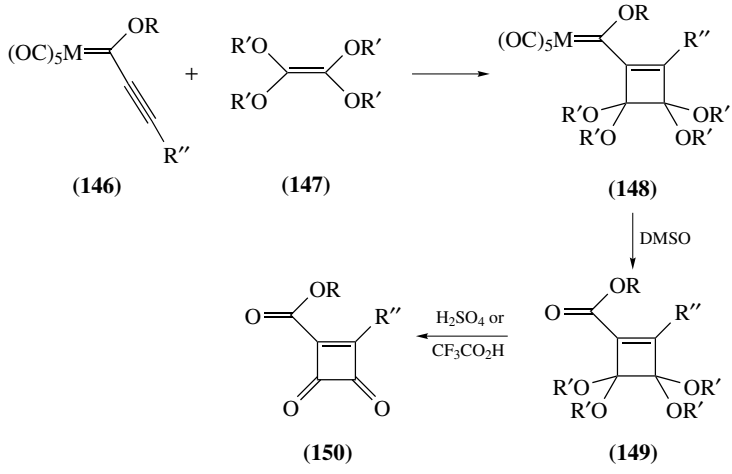


(140) (141) (142) (31)



(**143**) 87% (**144**) 73% (**145**) 97%

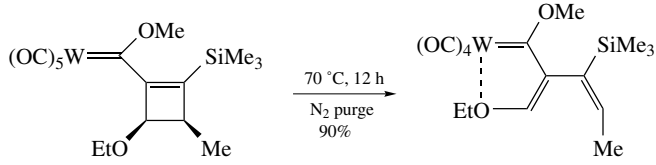
An interesting example in this context was provided by Moretó and coworkers, who treated complexes **146** with tetraalkoxyethenes **147** and obtained **148**, which was oxidized to the metal-free cyclobutenones **149**, which after acetal hydrolysis gave cyclobutenedione carboxylates **150** (equation 32)[111].



(32)

M = Cr, W; R = Me, Et; R′ = Me, Et; R″ = Pr, Ph, $SiMe_3$

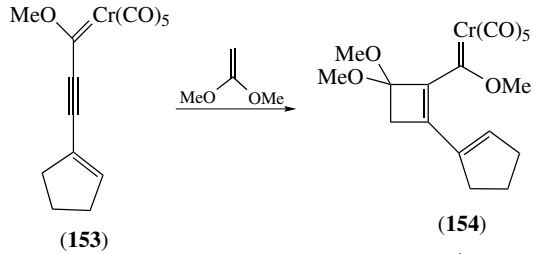
Cyclobutenylcarbene complexes undergo electrocyclic ring opening reactions with formation of 2-butadienylcarbene complexes. For example, tungsten complex **151** gave **152** in 90% yield upon heating at 70 °C with nitrogen purging through the reaction mixture in order to remove the CO (equation 33)[110].



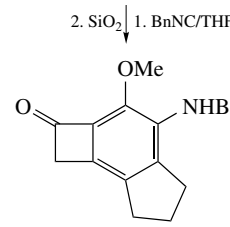
(33)

This chemistry was recently extended by Barluenga, Aznar and Palomero, who used alkynenyl carbene complexes such as **153**. The [2 + 2] cycloaddition gave dienylcarbene complexes such as **154**, from which amino substituted benzocyclobutenones like **155** were obtained upon treatment with isocyanides. By variation of the substituents a large number of dienylcarbene complexes and benzocyclobutene derivatives were made available in high yields (equation 34)[112, 113].

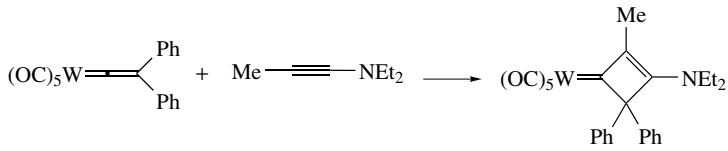
Fischer and coworkers showed that chromium or tungsten vinylidene complexes react with a variety of electron-rich alkynes with the formation of cyclobutenylidene complexes. For example, vinylidene complex **156** reacted with 1-diethylaminopropyne (**157**) to give **158** in 85% yield (equation 35). There is NMR evidence that complexes like **158** can be described by resonance formulas **158** and **159**[114]. Other examples of this type of complexes include bimetallic derivatives **160** and **161** or the cation **162**[115, 116]. A number of these complexes were characterized crystallographically.



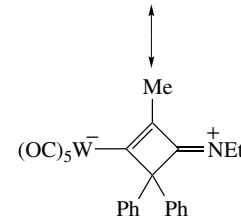
(**153**) (**154**)



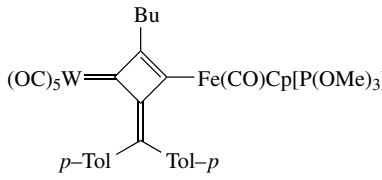
(**155**) (34)



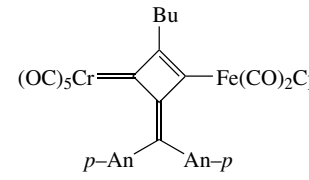
(**156**) (**157**) (**158**)



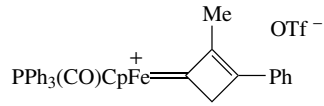
(**159**) (35)



(**160**)

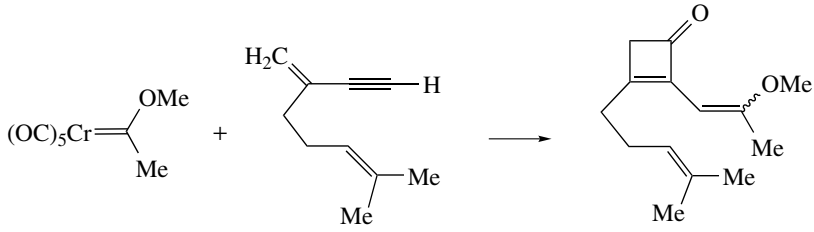


(**161**)

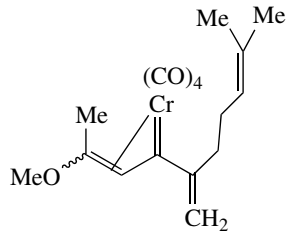


(**162**)

A reaction sequence starting from carbene complex **163**, which was treated with enyne **164**, resulted in the formation of cyclobutenone **165**. This sequence includes carbene complex **166** as an intermediate, which undergoes a CO insertion and a ring closure reaction (equation 36)[117].

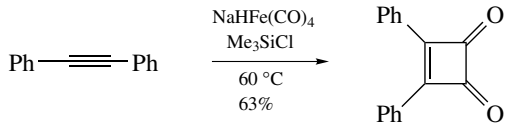


(**163**) (**164**) (**165**) (36)



(**166**)

Periasamy and coworkers reported an interesting cyclodicarbonylation reaction of alkynes in the presence of $NaHFe(CO)_4$/RX, where RX are halides such as CH_2Cl_2 or Me_3SiCl, to give cyclobutenedione derivatives in good yields. Ferracyclobutenones and ferracyclopentenediones are likely intermediates in these reaction sequences. For example, diphenylethyne (**167**) gave diphenylcyclobutenedione (**168**) in 63% yield (equation 37)[118, 119].

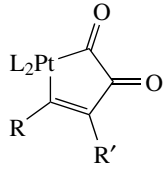


(**167**) (**168**) (37)

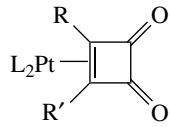
The reaction of some cyclobutenediones with platinum(0) complexes was reported to result in the formation of platinacyclopentenones **169**. The authors did not observe a cyclobutenedione complex intermediate and showed that a complex such as **170** does not undergo the insertion[120].

Weiss and coworkers treated triphenylcyclopropenylium chloride with $Na[Fe(CO)_3NO]$ and obtained among other products the oxocyclobutenyl complex **171**, which can also be described by resonance formula **172**[121].

Cyclobutenylpalladium complexes can be prepared in good yields from cyclobutadiene complexes. A number of cyclobutenyl complexes has been reported and their chemistry

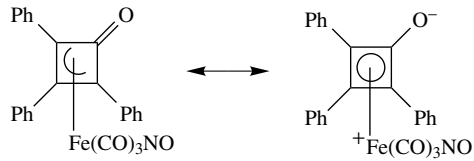


(169)



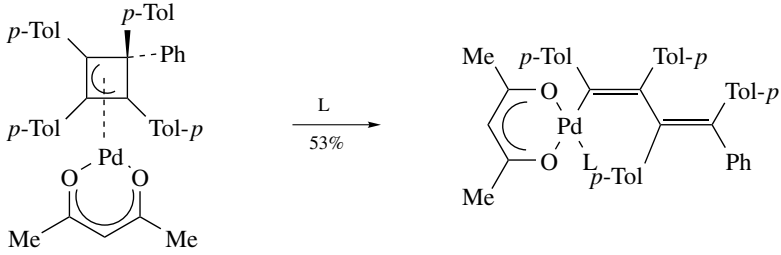
(170)

R, R′ = Ph, OMe, H
L = PPh_3, PAs_3, stilbene



(171) **(172)**

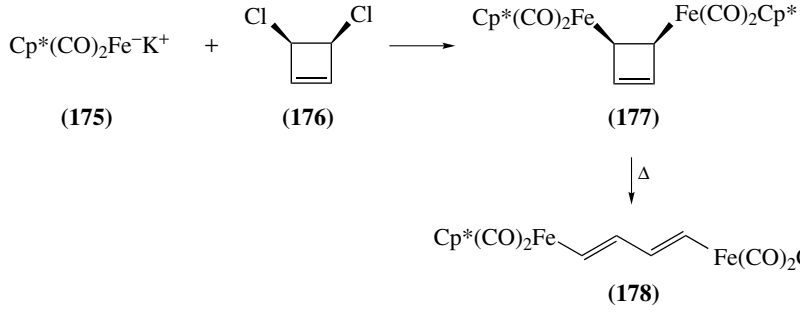
has been studied. This chemistry is dominated by ring opening reactions yielding σ-1-butadienyl complexes in stereospecific equilibrium reactions[122–124]. For example, Taylor and Maitlis reported the reaction of cyclobutenyl complex **173** with dimethylphenylphosphine to give **174** in 53% yield (equation 38)[124].



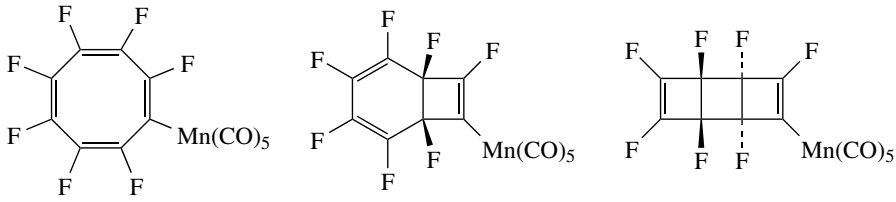
(173) L = PMe_2Ph **(174)** (38)

The formation of a dinuclear cyclobutenediyl complex was reported recently by Zubieta and Sponsler, who treated the potassium ferrate **175** with *cis*-3,4-dichlorocyclobutene (**176**) and obtained as a result of a twofold nucleophilic substitution the bimetallic cyclobutene complex **177** in 22% yield. The latter underwent a thermal ring opening to give **178** upon heating (equation 39)[125].

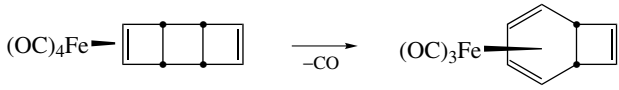
A rather special case of cyclobutenyl complex formation was published by Hughes and coworkers, who treated octafluorocyclooctatetraene with sodium pentacarbonylmanganate and obtained an equilibrium mixture of **179** and **180**, the latter being the minor component. In a similar way the synthesis of the tricyclic system **181** was achieved[126]. Related chemistry was reported by Pettit and coworkers as early as 1974, who found that complex **182** forms by treatment of the ligand system with $Fe_2(CO)_9$. Upon loss of CO a ring opening to **183** takes place (equation 40)[127]. Later, this reaction was explained by Pinhas and Carpenter by using the principles of frontier molecular orbital theory[128].



(175) **(176)** **(177)** **(178)** (39)

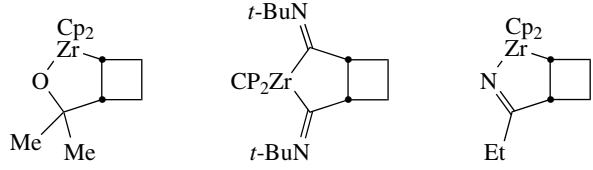


(179) **(180)** **(181)**



(182) **(183)** (40)

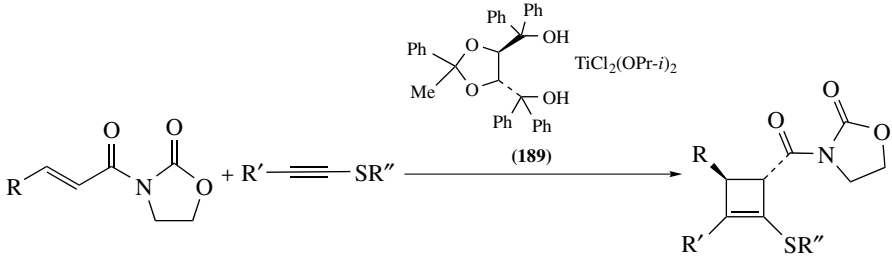
Fisher and Buchwald showed that C,H activation can be used to form cyclobutene complexes. The reaction of cyclobutylmagnesium bromide with di(cyclopentadienyl)methylzirconium(IV) chloride (**81**) gave cyclobutylzirconium(IV) complex (**82**). Subsequent treatment with trimethylphosphine caused the elimination of methane with formation of the cyclobutene zirconium(II) complex (**83**) in 58% yield. The crystallographic analysis revealed this compound to be a zirconacyclopropane. **83** undergoes reactions with unsaturated reactants, which usually insert into a zirconium–carbon bond. Typical examples are **184**–**186**[66].



(184) **(185)** **(186)**

Although the Lewis acid catalyzed [2 + 2] cycloaddition of alkynes and alkenes is slightly beyond the scope of 'organometallic' cyclobutene chemistry, some work of

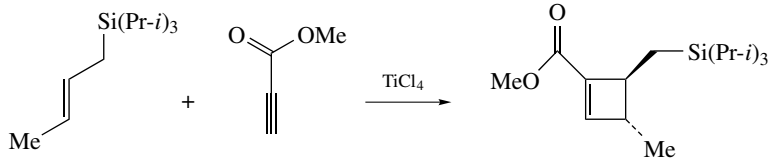
Narasaka and coworkers deserves mention here. The authors observed the cycloaddition of α,β-unsaturated carbonyl compounds such as **187** with alkynyl sulfides **188** in the presence of the enantiomerically pure chiral titanium Lewis acid **189** to give cyclobutenes **190** in good chemical yields with up to >98% *ee* (equation 41)[129].



(187) **(188)** **(190)**

$$R = H, CO_2Me, Me;\ R' = H, Me, Bu, Cy;\ R'' = Me, Ph \qquad (41)$$

Knölker and coworkers showed that the allylsilane **191** reacts with methyl propynoate (**192**) in the presence of $TiCl_4$ to give cyclobutene **193** in 70% yield (equation 42)[130].

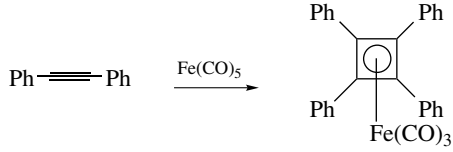


(191) **(192)** **(193)** (42)

IV. CYCLOBUTADIENES

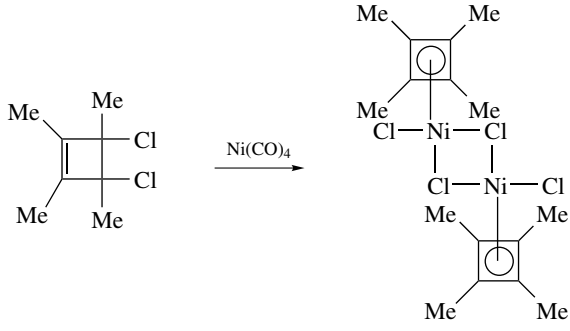
Due to their antiaromaticity, cyclobutadienes[131] readily decompose unless they are stabilized by a matrix[132, 133], in a carcerand[134, 135], by bulky substituents[136–138] or as a ligand in an organometallic complex.

The possibility of a stabilization of cyclobutadiene derivatives as ligands in organometallic complexes had first been theoretically predicted by Longuet-Higgins and Orgel in 1956[139]. Three years later Hübel and coworkers reported the first synthesis of the cyclobutadiene complex **195**, which was obtained by the reaction of diphenylethyne (**194**) with $Fe(CO)_5$ (equation 43)[140, 141].



(194) **(195)** (43)

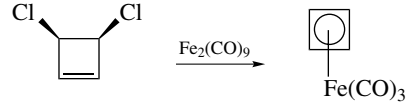
In the same year Criegee and Schroeder reported the synthesis of the nickel tetramethylcyclobutadiene complex **197** by treatment of 3,4-dichloro-1,2,3,4-tetramethylcyclobutene (**196**) with $Ni(CO)_4$ (equation 44)[142].



(44)

(196) **(197)**

The first synthesis of a complex of the unsubstituted cyclobutadiene complex was achieved by Pettit and coworkers in 1965, who treated *cis*-3,4-dichlorocyclobutene (**176**) with $Fe_2(CO)_9$ and obtained complex **198** (equation 45)[143]. In contrast to the free cyclobutadiene, which is rectangular, the cyclobutadiene ligand in complexes like **198** forms a regular square[144]. The history of the first cyclobutadiene complexes is an interesting case, in which the successful experiment followed stimulating predictions of theory. Very recently this has been summarized in a highly instructive essay by Seyferth[145].



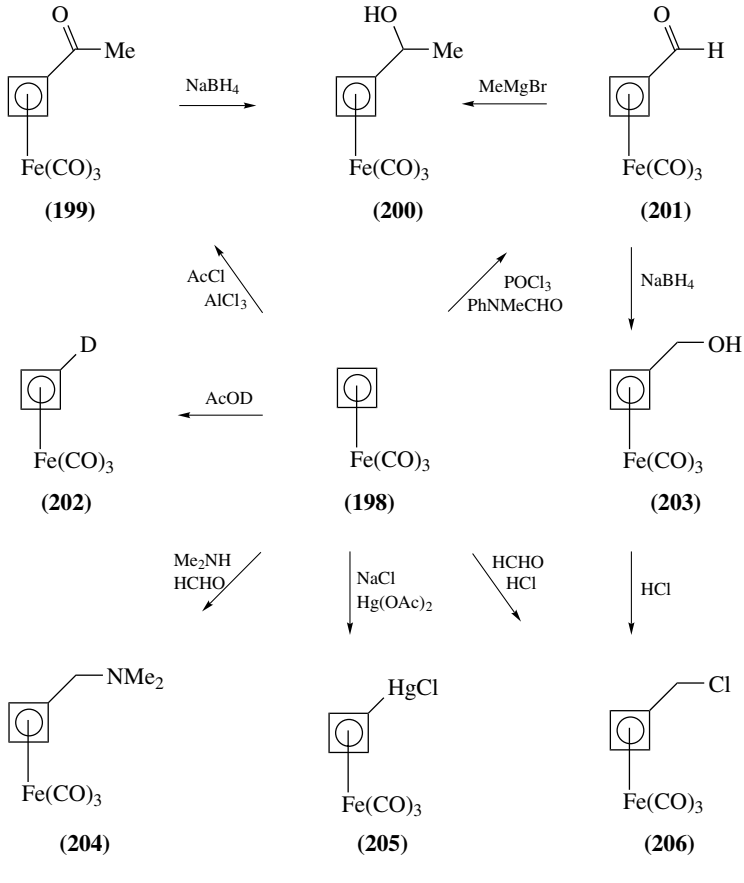
(45)

(176) **(198)**

The synthesis of **198** raised important questions, e.g. concerning the chemistry of this new class of compounds and the possibility of a liberation of free cyclobutadiene from **198**. It was concluded that the chemistry of **198** is that of an aromatic compound[146]. In this context Bursten and Fenske put forward a theoretical concept of metalloaromaticity[147].

Friedel Crafts acylation with acetyl chloride gives **199**. Vilsmaier formylation results in aldehyde **201**, which reacts with methyl Grignard reagents to give **200** or with sodium borohydride to give **203**, from which **206** is obtained in a nucleophilic substitution with HCl. **206** can also be obtained from **198** by a chloromethylation with formaldehyde/hydrogen chloride. Reaction with acetic acid-d_1 causes an electrophilic substitution to result in deuteriated **202**. Treatment with dimethylamine/formaldehyde gives **204**, and the reaction with mercuric acetate in the presence of sodium chloride gives mercuration product **205** (equation 46). The rich chemistry of cyclobutadiene metal complexes has been reviewed by Efraty[148] and more recently by Seyferth[145]. Recently, Bunz published a review article about new carbon-rich organometallic architectures based on cyclobutadienecyclopentadienylcobalt and ferrocene modules[149]. Therefore, the discussion here will be restricted to the more prominent and more recent developments in the field.

Uncoordinated cyclobutadiene can be obtained from **198** by oxidative decomplexation with ceric ammonium nitrate and it can be used as a C_4 building block in cycloaddition reactions. For example, the presence of methyl propiolate during the decomplexation causes the formation of cycloadduct **208**, which presumably formed via free cyclobutadiene (**207**) (equation 47)[150]. A cycloaddition of free cyclobutadiene (**207**) with a quinone derivative played a key role in the synthesis of cubane 1,3-dicarboxylic acid[151]. Study of the stereochemistry of cycloadditions of cyclobutadiene (**207**) thus generated with dimethyl maleate or fumarate revealed cyclobutadiene to react as a singlet diene[152, 153].



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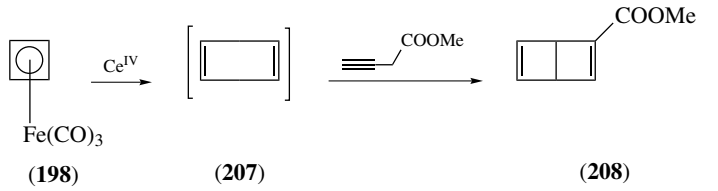
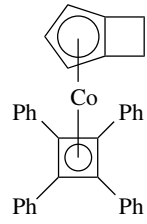


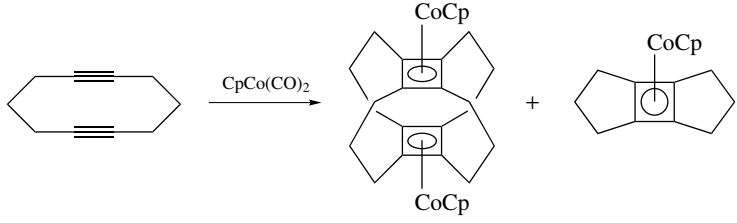
(47)

The syntheses of cyclobutadiene complexes devised by the early work in this field are still the most important ways to obtain these complexes. Thus, cyclopentadienylcobalt complexes of cyclobutadienes are often observed as side products in the alkyne cyclotrimerization catalyzed by CpCo[154]. As these complexes are extremely stable species, their formation often marks the end of the desired catalytic process[155,156]. There is evidence for a reversibility of their formation from alkynes[157]. The stability of cyclobutadiene CpCo complexes, which usually can be heated in the air up to 400 °C without decomposition, has been exploited in reactions of **209**, which require 200 °C, a temperature at which usual metal complexes decompose[158–161]. The more modern developments in the field of cyclobutadiene metal complexes include recent work by Gleiter and Merger, who used cyclodiynes such as **210** to prepare a variety of cyclobutadienosuperphane cobalt complexes like **211** in addition to tricycles **212** (equation 48). Similar complexes were constructed with unequal bridges between the cyclobutadiene moieties, with heteroatoms in the bridges or with interesting substitution patterns such as isopropylidene or spirocyclopropyl groups. Some of the cyclobutadienosuperphane complexes were characterized structurally[162].



(**209**)

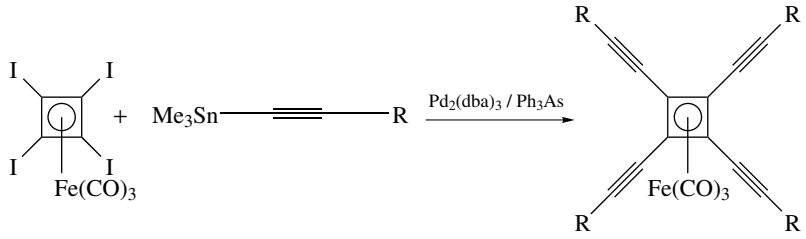
(48)



(**210**) (**211**) (**212**)

Another actual field of cyclobutadiene complex chemistry is that of planar extended systems, which is closely connected to the work of Bunz and coworkers. Here the cyclobutadiene ligand bears up to four alkynyl substituents, which themselves give rise to the formation of new cyclobutadiene complex moieties. For example, tricarbonyl(tetraiodocyclobutadiene)iron **213** couples in a palladium catalyzed coupling reaction with stannylalkynes **214** to give **215** usually in high yields (>80%), depending on the nature of R (equation 49). This chemistry is being extended to polymeric, cyclic and even three-dimensional fullerene related structures with potential importance in material science[163,164].

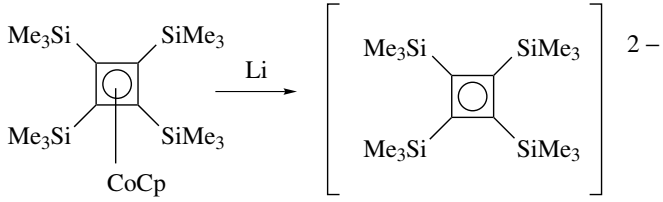
Recent work of Sekiguchi and coworkers represents some very fundamental aspects of cyclobutadiene chemistry. It was found that CpCo tetrakis(trimethylsilyl)cyclobutadiene complex **216** can be reduced with lithium to give **217**, which was characterized crystallographically and shows some evidence for aromaticity (equation 50)[165–167].



(49)

(213) **(214)** **(215)**

R = H, *t*-Bu, $SiMe_3$



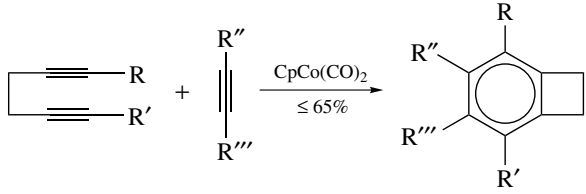
(50)

(**216**) (**217**)

V. BENZOCYCLOBUTENES AND RELATED SYSTEMS

There is a rich chemistry including both the organometallic synthesis, as well as reactions of benzocyclobutenes and related systems[155, 156, 168–170].

Among the syntheses of benzocyclobutenes the transition metal catalyzed [2 + 2 + 2] cyclization is among the most versatile methods. The reaction of 1,5-hexadiynes **218** with alkynes **219** in the presence of catalysts like dicarbonyl(cyclopentadienyl) cobalt gives benzocyclobutenes **220** (equation 51)[155, 156, 171].



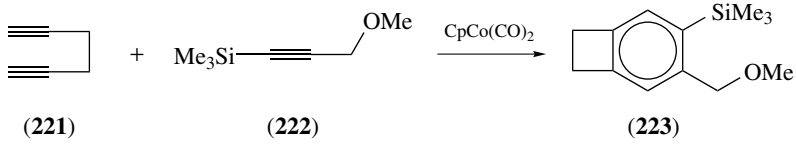
(51)

(**218**) (**219**) (**220**)

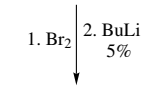
R, R′ = H, Me, CH_2OMe, $SiMe_3$

R″, R‴ = CO_2Me, Ph, H, Hex, $SiMe_3$, CH_2OMe, CH_2OH

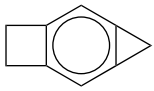
Among the more interesting benzocyclobutenes prepared by this route is **224**, which was obtained from 1,5-hexadiyne (**221**) and alkyne **222** via **223**. **224** was obtained in 5% yield (equation 52)[172]. Later, this was improved by McNichols and Stang, who used alkyne **225** to obtain **226** and subsequently **224** in 65% yield (equation 53)[173].



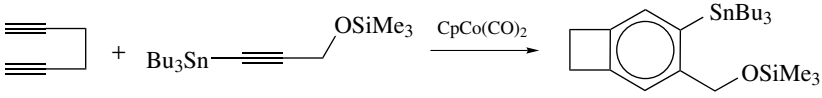
(**221**) (**222**) (**223**)



(52)

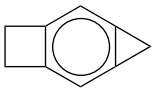


(**224**)



(**221**) (**225**) (**226**)

(53)



(**224**)

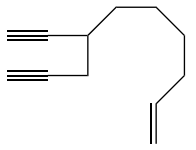
This type of reaction can be used in a way that, under reaction conditions of its formation (usually boiling xylenes), the benzocyclobutene ring opens with formation of an *ortho*-quinodimethane intermediate, which is trapped by cycloaddition with a present dienophile. This strategy allows for the synthesis of complicated polycycles without isolation of the benzocyclobutene intermediate. For example, treatment of **227** with bis(trimethylsilyl) ethyne (**228**) in the presence of $CpCo(CO)_2$ gives **229** in 80% yield (equation 54)[171].

This chemistry was applied in the syntheses of a number of natural products[155, 156]. A more spectacular example was the synthesis of steroid **231** from enediyne **230** without isolation of the intermediate benzocyclobutene, published by Funk and Vollhardt in 1977 (equation 55)[174].

Another organometallic synthesis of benzocyclobutenes was provided by Stanger and coworkers, who treated the easily available tetrabromo-*ortho*-xylene **232** with nickel complexes such as bis(tributylphosphine)(anthracene)nickel or (cyclooctadiene)bis(triphenylphosphine)nickel in 65–70% yield with predominant formation of the *trans* isomer **233** and only minor amounts of **234** (equation 56)[175]. Later, some stereocontrol of the reaction was shown for substituted systems[176].

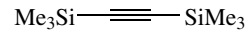
Stanger and coworkers also succeeded in the preparation of a hexabromotricyclobutabenzene **235** and hexabromohexaradialene **236** from hexakis(dibromomethyl)benzene in 24% and 16% yield, respectively, by treatment of the starting material with $(Bu_3P)_2Ni(cod)$.

Both reaction products were characterized crystallographically[177].

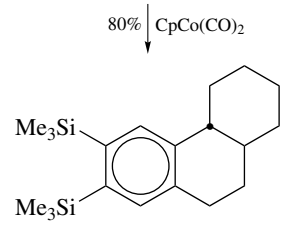


(**227**)

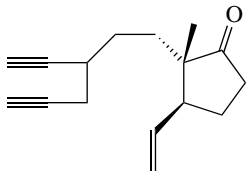
+



(**228**)



(**229**) (54)



(**230**)

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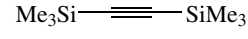
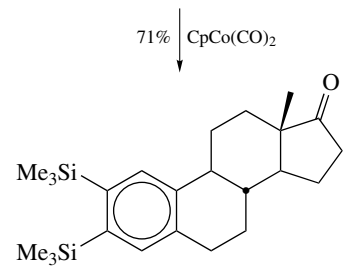
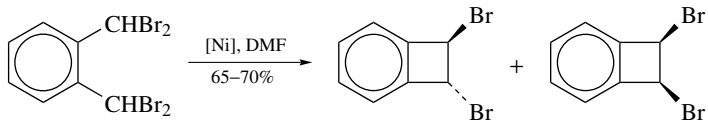


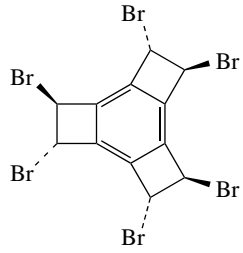
(**228**)



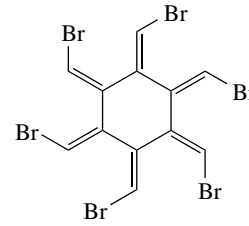
(**231**) (55)



(**232**) (**233**) (major) (**234**) (minor) (56)



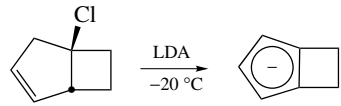
(**235**)



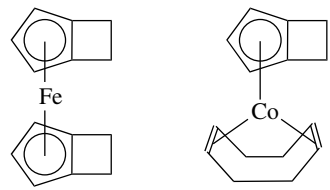
(**236**)

Barluenga and coworkers have developed an organometallic benzocyclobutenone synthesis, which has already been mentioned in the formation of **155** from carbene complex **153** via cyclobutenylcarbene complex **154**[113].

Bicyclo[3.2.0]heptadienyl complexes can be regarded as homologs of benzocyclobutene complexes. The anionic ligand system **238** can be prepared from 5-chlorobicyclo[3.2.0]hept-2-ene (**237**) by treatment with a base like LDA at low temperature (equation 57)[178]. **238** gives ferrocene **239** upon treatment with $FeCl_2$ or can be converted to cobalt complex **240** in 49% yield by treatment with chlorotris(triisopropylphosphite)cobalt(I) followed by heating with 1,5-cyclooctadiene[178, 179].



(**237**) (**238**) (57)

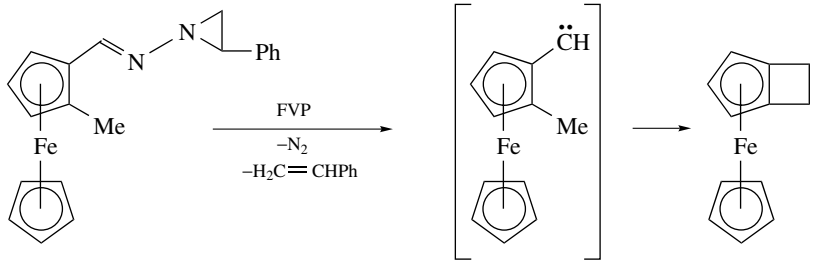


(**239**) (**240**)

A different approach to this type of complexes was published by Trahanovsky and Ferguson, who prepared hydrazone **241**, which was subjected to flash vacuum pyrolysis to afford complex **243** via carbene **242** in 30–35% yield (equation 58)[180].

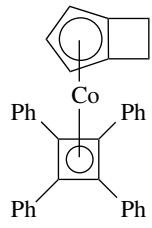
While the chemistry of **239** and **243** remained virtually unexplored up to now, some reactions of **240** were reported, the most important being the replacement of the COD ligand by tetraphenylcyclobutadiene upon treatment with diphenylethyne, affording sandwich complex **209** in 61% yield. Cobalt(I) complexes bearing a cyclopentadienyl and a cyclobutadiene ligand usually are thermally very stable and can be heated in the air up to 400 °C without decomposition. In contrast to this, DSC (DSC = differential scanning calorimetry) investigations with **209** showed this complex to react at about 200 °C. The process was identified to be a ring opening presumably affording the *ortho*-quinodimethane analog

244, which is prone to cycloaddition reactions with a variety of dienophiles. Reactions at 200 °C with dimethyl fumarate and *N*-methylmaleimide gave cycloadducts **245** (65%), and **246** (93%)[159, 161]. A corresponding cycloaddition with maleimide was reported for **243** to proceed in 13% yield[180].

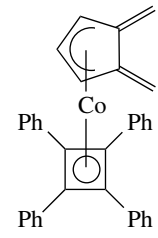


(58)

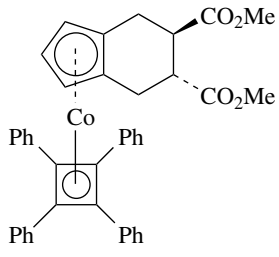
(**241**) (**242**) (**243**)



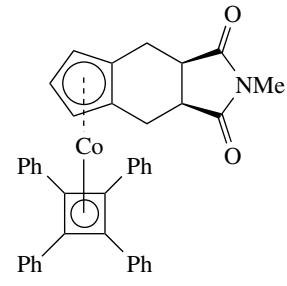
(**209**)



(**244**)



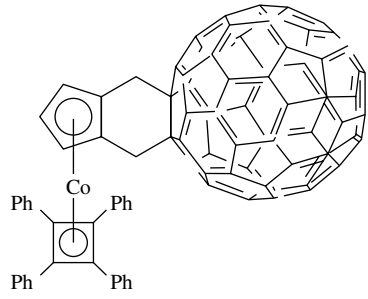
(**245**)



(**246**)

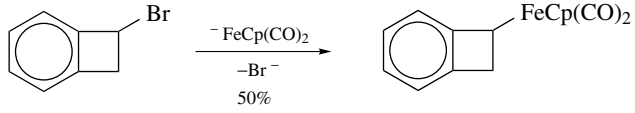
When C_{60}-fullerene was used as the dienophile, complex **247** was obtained in 28% yield in addition to diadducts as the first fullerene derivative containing cobalt[181].

While the bicyclo[3.2.0]heptadienyl ligand system is up to now known in its unsubstituted form only, this is quite different with benzocyclobutene and a variety of derivatives being known[170, 182–185]. There are two basic types of benzocyclobutene metal complexes, those with a carbon–metal σ bond at the cyclobutene ring and π complexes with the anellated benzene ring being coordinated.



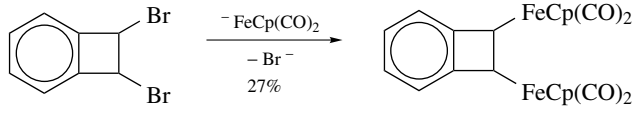
(247)

1-Bromobenzocyclobutene (**248**) and 1,2-dibromobenzocyclobutene (**250**) can undergo a nucleophilic substitution with the (cyclopentadienyl)dicarbonyliron(II) anion giving organometallic complexes **249** and **251** in 50% and 27% yield, respectively (equations 59 and 60)[186–188].



(59)

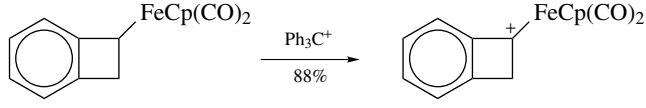
(248) **(249)**



(60)

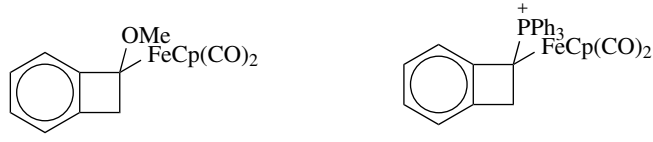
(250) **(251)**

249 releases a hydride ion from the metallated benzylic position upon treatment with the triphenylmethyl cation. The benzylic cation **252**, which is formed in up to 88% yield (equation 61), can be trapped with a variety of nucleophiles giving rise to the formation of complexes such as **253**–**255** in moderate or good yields, with the bimetallic complex **255** being converted to allyl derivative **256** in 30% yield (equation 62)[189–191].

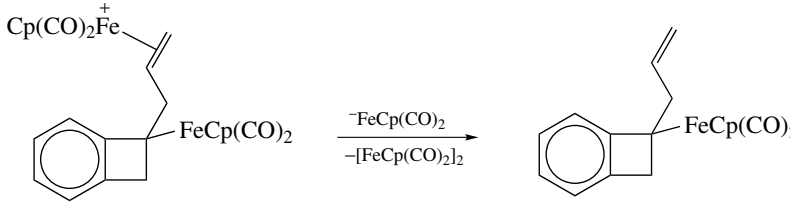


(61)

(249) **(252)**



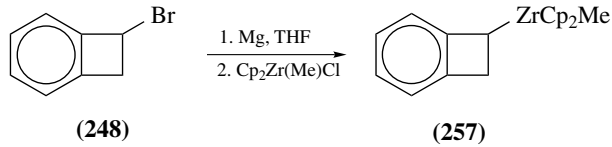
(253) 79% **(254)** 83%



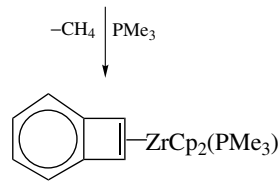
(62)

(255) 43% **(256)** 30%

Recently, Sharp and coworkers published the synthesis of zirconium complex **257** from 1-bromobenzocyclobutene (**248**) by treatment with magnesium followed by chlorodi(cyclopentadienyl)methylzirconium(IV). Interestingly, subsequent treatment with trimethylphosphine afforded benzocyclobutadiene complex **258** (equation 63), from which anellated benzocyclobutenes **259**–**262** were obtained by treatment with terminal alkynes, diphenylethyne, nitriles and *tert*-butylisocyanide, respectively, in good yields[192].

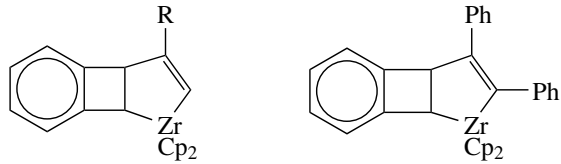


(248) **(257)**

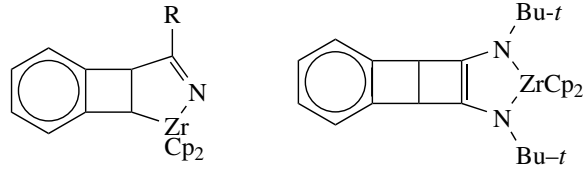


(63)

(258)

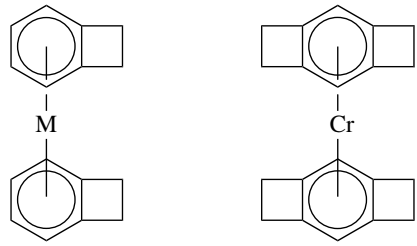


(259) R = $SiMe_3$, Ph **(260)**



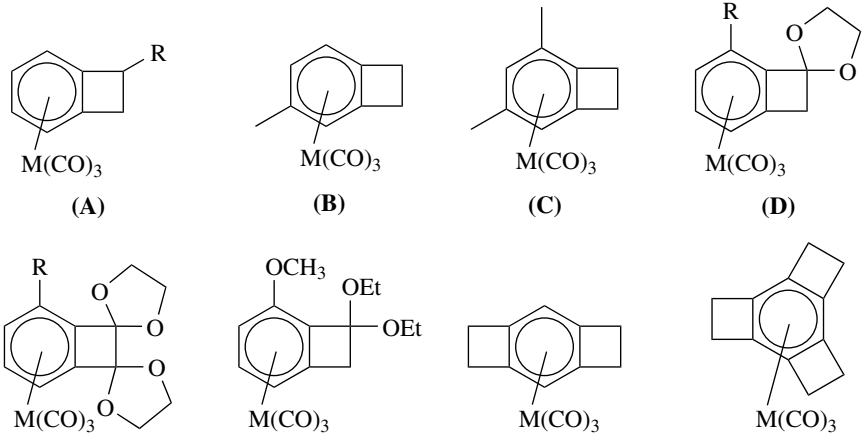
(261) R = Ph, *t*-Bu **(262)**

Homoleptic benzocyclobutene derived complexes **263** (M = Cr, Mo, W) and **264** were obtained by co-condensation of the ligands with metal vapor[193].



(263) **(264)**

Many π complexes of benzocyclobutene derivatives can be obtained by direct complexation of the stable ligands with appropriate complexation reagents, such as $Cr(CO)_6$, $Cr(CO)_3(NH_3)_3$, (benzene)$Mo(CO)_3$ or $W(NCMe)_3(CO)_3$. Ligands substituted at the benzylic position can be coordinated as *endo* or *exo* complexes, the diastereomeric ratio often reflecting the steric bulk of the substituents with preference of the *exo* diastereomer. However, there are important examples in which the substituent contains ether functions. In these cases, most likely due to pre-complexation phenomena, a significant preference for the *endo* diastereomers has been reported. Known benzocyclobutene π complexes **265**–**297** of types **A**–**H** are summarized in Table 1; a number of them were characterized crystallographically.



(A) **(B)** **(C)** **(D)**

(E) **(F)** **(G)** **(H)**

While the chemistry of the molybdenum and tungsten complexes has not been investigated further, a rich chemistry has been developed on the basis of chromium benzocyclobutene complexes. Starting from the complexes listed in Table 1 a number of related complexes were obtained.

Reduction of (benzocyclobutene)tricarbonylchromium (**265**) with lithium sand gives η^4 complex **298** as the result of a ring slippage reaction[205] as the main product, which

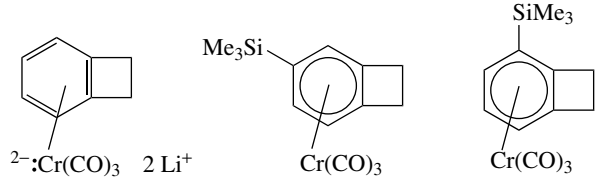
TABLE 1. Benzocyclobutene complexes by direct complexation of the ligand

System	M	R	No.	Yield	*endo/exo*	Reference
A	Cr	H	**265**	40	—	194–196
				51	—	
A	Cr	D	**266**	53	50:50	195, 196
A	Cr	OEt	**267**	70	40:60	197
A	Cr	OH	**268**	35	9:1	198
A	Cr	OAc	**269**	70	50:50	199
A	Cr	OMe	**270**	54	55:45	198
A	Cr	OMEM	**271**	58	81:19	198
A	Cr	OTHP	**272**	61	97:3	198
A	Cr	Me	**273**	62	40:60	195, 196
A	Cr	Bu	**274**	27	50:50	195, 196
A	Cr	$(CH_2)_2CH{=}CH_2$	**275**	49	50:50	195, 196
A	Cr	$SiMe_3$	**276**	64	12:88	195, 196
A	Cr	$SnMe_3$	**277**	89	24:76	195, 196
A	Mo	H	**278**	67	—	200
A	Mo	Me	**279**	70	47:53	201
A	Mo	Bu	**280**	33	50:50	201
A	Mo	$SiMe_3$	**281**	50	10:90	201
A	Mo	$SnMe_3$	**282**	68	15:85	201
A	W	H	**283**	31	—	201
A	W	$SiMe_3$	**284**	9	17:83	201
B	Cr	—	**285**	65	—	195, 196
B	Mo	—	**286**	57	—	201
C	Cr	—	**287**	60	—	195, 196
C	Mo	—	**288**	60	—	201
C	W	—	**289**	12	—	196
D	Cr	H	**290**	83	—	195, 196
D	Cr	OMe	**291**	81	—	202
D	Mo	—	**292**	34	—	201
E	Cr	H	**293**	82	—	203
E	Cr	OMe	**294**	78	—	202
F	Cr	—	**295**	69	—	202
G	Cr	—	**296**	78	—	193
H	Cr	—	**297**	21	—	204

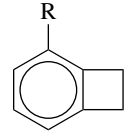
can be re-oxidized to **265** by air[206]. The predominant formation of **298** reflects the more general principle that if the system has a choice which double bonds to coordinate, the more strained ones are preferred due to the strain release upon complexation.

Deprotonation of benzocyclobutene complexes with organolithium bases preferentially takes place at the position next to the anellated ring. Deprotonation of **265** with BuLi/TMEDA followed by addition of chlorotrimethylsilane gave 10% of **299** and 31% of **300**[195, 196].

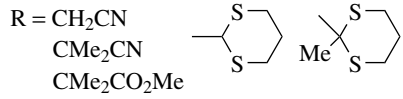
Kündig and coworkers developed a procedure for the formation of substituted benzocyclobutenes on this basis. (Benzocyclobutene)tricarbonylchromium (**265**) was treated with a lithium enolate or dithianyl lithium in THF or in THF/HMPA followed by oxidation with iodine to afford substituted benzocyclobutenes **301** in 64–96% yield[207, 208]. Kündig and coworkers reported the thermal ring opening of ethoxy substituted complex **267** at 160 °C to the *ortho*-quinodimethane complex **302**, which was trapped by [4 + 2] cycloaddition with *trans*-1,2-bis(trimethylsilyl)ethene to give cycloadduct **303** in 53% yield. **267** was used as a mixture of diastereomers, and it was shown that the *endo* and the *exo* diastereomers interconvert via intermediate **302** (equation 64)[209].

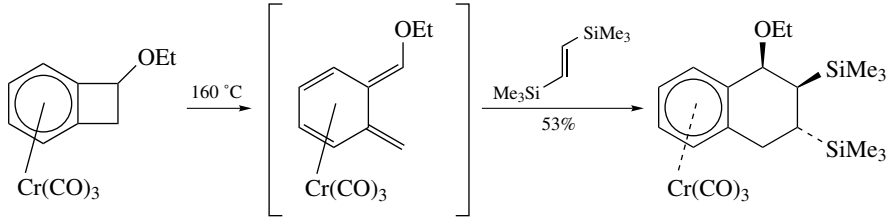


(298) **(299)** **(300)**



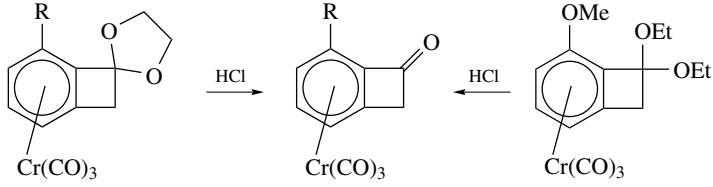
(301)





(267) **(302)** **(303)** (64)

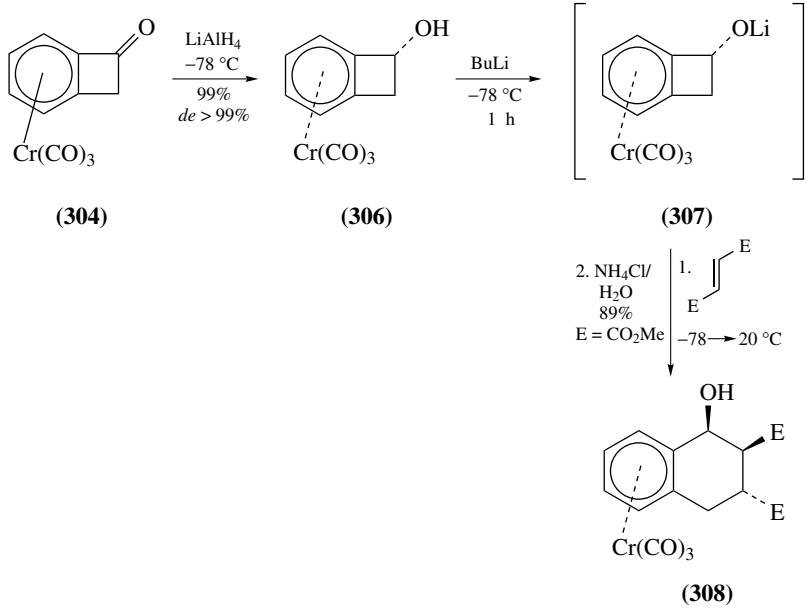
Some of the benzocyclobutene complexes listed in Table 1 serve as educts for the synthesis of other substituted benzocyclobutene complexes bearing important functionality at the four-membered ring. Thus, complexes **290, 291** and **295** are hydrolyzed giving benzocyclobutenone complexes **304** and **305** in 99%, 98% and 95% yield, respectively (equation 65). The electrophilic character of the keto functionalities in these complexes is enhanced due to the electron withdrawal of the tricarbonylchromium moiety and the rigidity of the anellated four-membered ring, which causes the carbonyl π system to be parallel to that of the aromatic system.



(65)

(**290**) R = H (**304**) R = H, 99%
(**291**) R = OMe (**305**) R = OMe, 95–98 % (**295**)

In particular, complex **304** served as a basis for a number of oxyanion accelerated reactions. The enhanced reactivity of **304** and **305** becomes evident in their reduction with $LiAlH_4$, which yields the diastereomerically pure alcohol **306** in 99% yield. Remarkably, the reduction takes place immediately at $-78\,^{\circ}C$, while the reduction of uncoordinated benzocyclobutenone has been reported to take place in boiling diethyl ether in 89% yield[210]. According to work of Choy and Yang, who investigated the uncoordinated ligand system[211], alcohol **306** was deprotonated by butyllithium. Alkoxide **307** undergoes a ring opening to the respective *ortho*-quinodimethane complex at *ca* $-30\,^{\circ}C$ and was trapped with dimethyl fumarate to give cycloadduct **308** in 89% yield (equation 66)[212,213]. The oxyanion acceleration made this reaction possible at a reaction temperature about $200\,^{\circ}C$ below that of the thermal reaction!

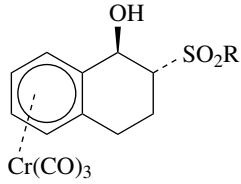


(66)

This type of reaction sequence has been carried out with a number of other dienophiles with predominant formation of the *endo* cycloadducts such as **308** via an *ortho*-quinodimethane intermediate with an *E* configurated exocyclic double bond with the alkoxide substituent as a result of a torquoselective[214] ring opening reaction[199,213].

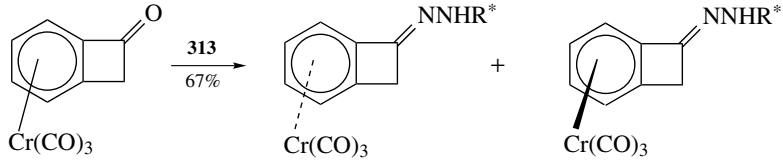
Remarkably, a reversed stereochemistry was observed in reactions involving vinyl sulfones as dienophiles. Here, products **309** and **310** with 1,2-*trans* configuration were exclusively obtained corresponding to an *exo* selective [4 + 2] cycloaddition. A control experiment using the thermal cycloaddition of uncoordinated benzocyclobutenol with methyl vinyl sulfone also resulted in an *exo* cycloaddition, indicating that the reason cannot be found in the complexation to the metal. Instead, it is thought that the *endo* transition state is by far more sterically hindered than the *exo* one, which is the result of the quasi tetrahedral environment of the sulfur atom; this is not the case with usual carbonyl substituted dienophiles, which are more planar[199,213].

A special stereochemical feature of benzocyclobutenone complexes is their planar chirality. As the oxy anion driven ring opening/cycloaddition sequences of the respective benzocyclobutenol complexes proceed with high levels of diastereoselectivity, an access

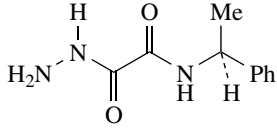


(**309**) R = Ph, 80%
(**310**) R = Me, 81%

to enantiomerically pure benzocyclobutenone complexes opens an access to the respective enantiomerically pure cycloadducts. Classic enantiomeric resolution of **304** was achieved via semioxamizides **311** and **312** using **313** as the chiral auxiliary (equation 67)[213,215,216].



(304) (6a*S*-**311**) (6a*R*-**312**) (67)



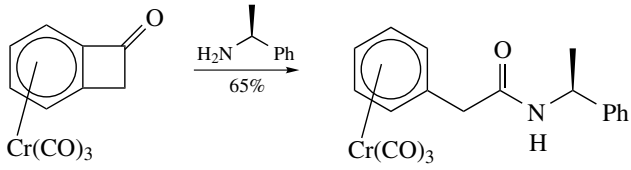
(**313**) = H_2NNHR^*

Other ways to enantiomerically pure **304** include the use of chiral HPLC[217,218] and the diastereoselective complexation[219] of the enantiomerically pure tetrahydropyranyl ether of **304** followed by hydrolysis and Swern oxidation[198]. In addition to this, Kündig and coworkers generated the enantiomerically pure alkoxide complex **307** starting from enantiopure acetoxybenzocyclobutene, which had been obtained by a kinetic resolution from the racemate. The cycloaddition showed the chirality to be transferred into the cycloadducts[220].

In addition to a hydride reduction, the keto function in **304** reacts with a number of nucleophiles. However, particularly with most N or O nucleophiles, a proximal ring opening is often observed leading to less interesting complexes of acetic acid derivatives, such as **314** (equation 68)[221].

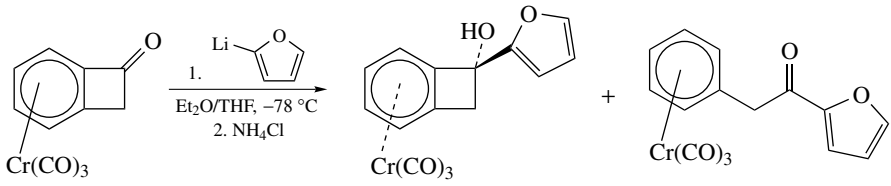
In some cases with carbon nucleophiles a proximal ring opening reaction was observed, too. Thus **304** reacts with 2-lithiofuran with formation of **316** as the main product with a reaction time of 60 min. However, when the reaction was stopped after 1 min the benzocyclobutene complex **315** was obtained as the main reaction product. There are a number of examples in which **304** is treated with organolithium or Grignard reagents

with formation of the respective adducts at the keto function. This addition always occurs with full diastereoselectivity from the face opposite to the tricarbonylchromium moiety (equation 69)[218, 221].



(68)

(**304**) (**314**)



(**304**) (**315**) (**316**)

60 min:	19%	60%
1 min:	63%	18%

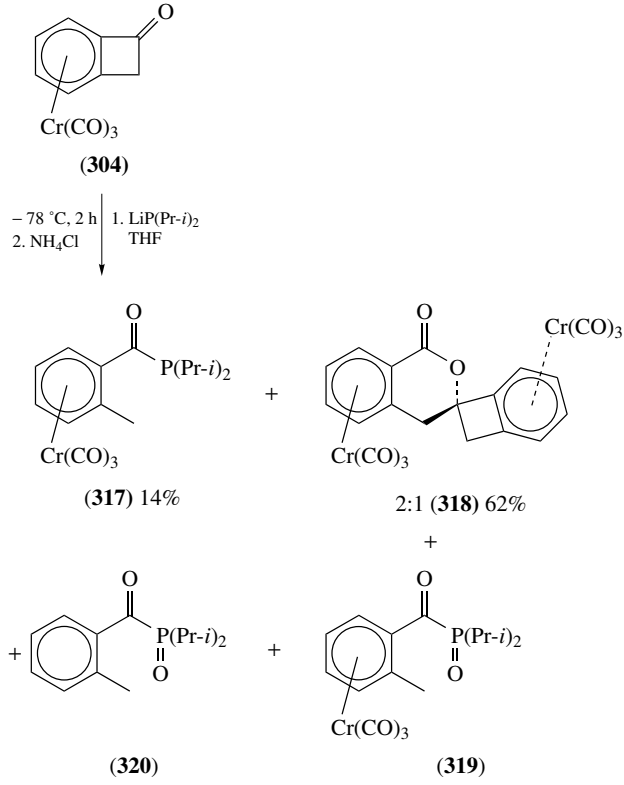
(69)

More recently, the reaction of **304** with lithium dialkylphosphides was shown to result in a distal ring opening of the cyclobutane ring. Upon treatment of **304** with lithium diisopropylphosphide (LDP) the spiro anellated isochromanone complex **318** was obtained as the main product in addition to distal ring opening product **317** and oxidized products **319** and **320** (equation 70)[222].

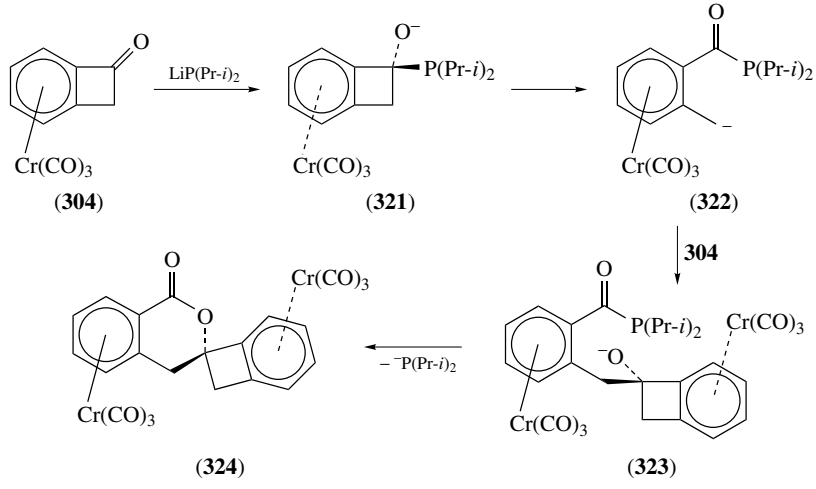
The formation of **318** is explained by a nucleophilic addition of LDP at the keto group of **304** resulting in **321** followed by an oxyanion driven distal ring opening to benzylic anion **322**, which undergoes a nucleophilic attack at a second molecule of **304** to give alkoxide **323**, which gives **324** in a subsequent ring closing reaction (equation 71)[222].

It was shown that this type of reaction also works with **304** and a different carbonyl component. Remarkably, the reaction using benzaldehyde takes place with full diastereoselectivity, giving **325**. The availability of enantiomerically pure **304** thus opens an access to enantiomerically pure 3-phenylisochromanone, which displays some antifungal activity[222–224].

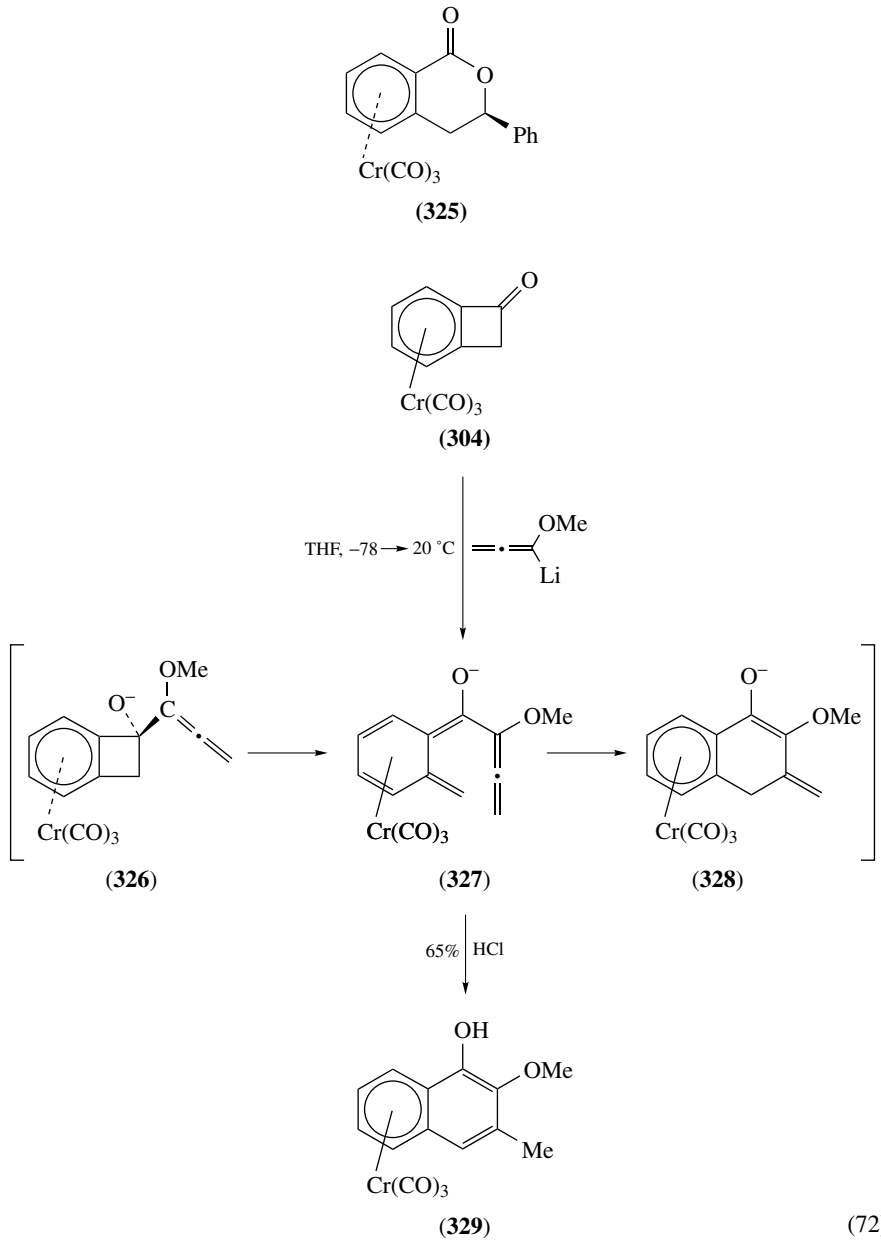
An interesting oxyanion driven ring expansion was observed upon treatment of **304** with 1-lithio-1-methoxyallene. It is presumed that adduct **326** is formed first, which undergoes an anionic ring opening to *ortho*-quinodimethane complex **327**, which cyclizes to **328** with re-aromatization to give **329** as the final product (equation 72). This reaction sequence constitutes an anionic 1-vinylcyclobutenol–cyclohexadiene rearrangement. While anionic 2-vinylcyclobutenol–cyclohexadiene rearrangements are quite common, the number of such anion driven rearrangement reactions starting from 1-vinylcyclobutenols is rather limited[225].


O
Cr(CO)3
(304)
– 78 °C, 2 h
2. NH4Cl
1. LiP(Pr-i)2
THF
P(Pr-i)2
(317) 14%
2:1 (318) 62%
(320)
(319)
18%

(70)


LiP(Pr-i)2
(304)
(321)
(322)
304
(323)
– ⁻P(Pr-i)2
(324)

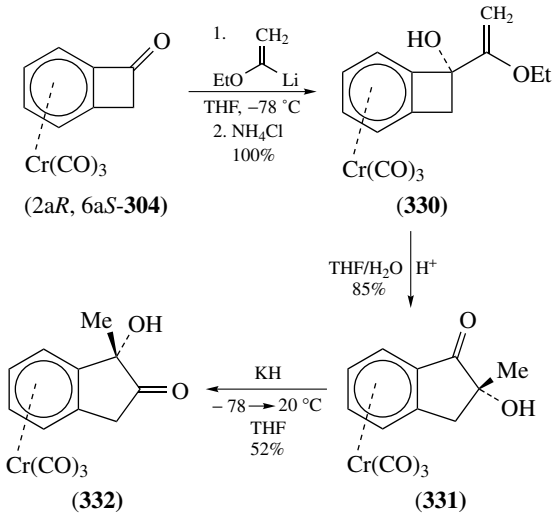
(71)



(72)

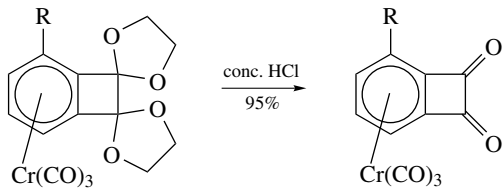
Nucleophilic addition of acyl anion equivalents such as 1-ethoxy-1-lithioethene takes place in high yield from the face opposite to the tricarbonylchromium moiety to give **330**. Hydrolysis under acidic conditions leads to ring expansion product **331**, a type of reaction which has earlier been observed by Stone and Liebeskind[226]. However, use of the

enantiomerically pure starting material **304** allowed the stereochemistry of the reaction to be investigated. It was found that in the case of 1-ethoxy-1-lithioethene the chirality of the starting material was quantitatively transferred into **330**, which was characterized crystallographically. Even more, deprotonation of **331** with potassium hydride caused an oxyanion driven α ketol rearrangement to take place, which also transferred the chirality to the product **332** in a quantitative way (equation 73). It is thought that the resonance stabilization of the enolate of **332** accounts for the ease of the reaction[218].



(73)

Next to the benzocyclobutenone complex **304** the related complex **333** of benzocyclobutenedione came out to be the basis for most interesting reactions, many of them being also oxyanion accelerated. **333** and **334** are obtained by acid hydrolysis of **293** and **294**, respectively, in high yield (equation 74). Interestingly, the X-ray structure analysis shows that the ligand system is not planar, but that the anellated cyclobutane ring is bent towards the tricarbonylchromium moiety by about 9°[202, 227, 228].



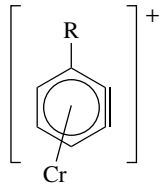
(293) R = H
(294) R = OMe

(333) R = H, 95%
(334) R = OMe, 83%

(74)

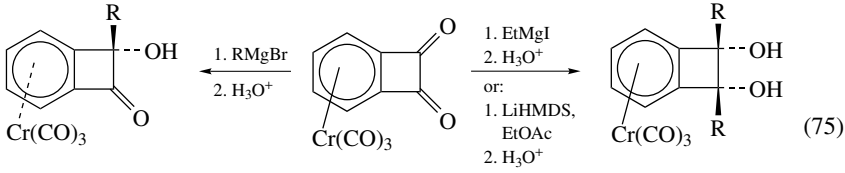
The mass spectra of **333** and **334** are remarkable in that the base peak is observed at $m/z = 128$ and at $m/z = 158$, respectively, corresponding to the loss of five CO fragments. Isotopic labelling experiments revealed that the three carbonyl ligands are lost first, followed by the two keto groups with no evidence for C_2O_2 being dissociated. An FT-ICR

study of **333** revealed that the remaining fragment is the respective benzyne chromium cation **335**. The existence of **336** was concluded from the analogous fragmentation pattern. These are remarkable, as the known benzyne complexes coordinate the benzyne ligand at the triple bond instead of the aromatic π system[229].



(**335**) R = H
(**336**) R = OMe

The chemistry of complexes **333** and **334** is dominated by nucleophilic addition reactions taking place from the face opposite of the tricarbonylchromium moiety. This is remarkable, as nucleophilic diadditions at the keto groups of uncoordinated benzocyclobutenedione usually result in decomposition. Starting from **333** a number of nucleophilic additions are possible, which lead to adducts such as **337**–**339, 340** or **341** (equation 75)[228].



(75)

(**337**) R = CH═CH$_2$, 87%
(**338**) R = C≡CH, 78%
(**339**) R = Ph, 77%

(**333**)

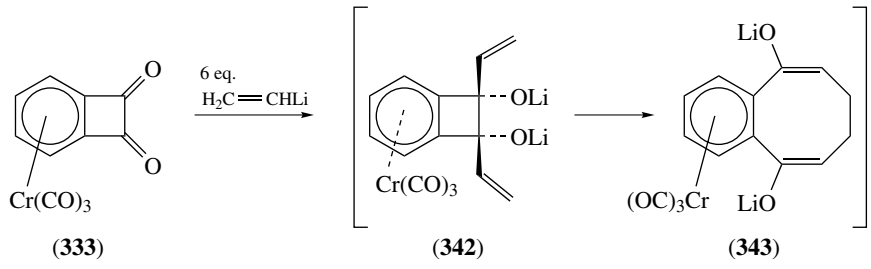
(**340**) R = Et, 60%
(**341**) R = CH_2CO_2Et, 88%

The exclusive *cis, anti* diaddition of nucleophiles to **333** sets the stage for the corresponding reaction of an excess of vinyllithium with **333**, which results in a dianionic oxy-Cope rearrangement taking place at a temperature as low as $-78\,^{\circ}C$. After diaddition leading to **342** the primary product of the rearrangement is the di(enolate) **343**, which can either be hydrolyzed to give benzocyclooctene complex **344** in 87% yield (equation 76) or be trapped as the corresponding bis(trimethylsilyl)enol ether[228].

It must be emphasized that the possibility of the dianionic oxy-Cope rearrangement to occur is a direct consequence of the stereochemistry of the diaddition at **333**, which leads to a *cis*-divinylcyclobutane moiety[230]. Interestingly, the reaction can be carried out in a sequential manner. When **337** was treated with 2-propenyllithium, **345** was obtained in >60% yield as a single diastereomer after hydrolysis.

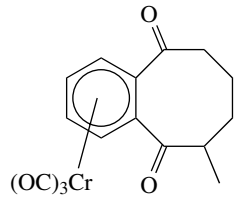
In many cases the dianionic oxy-Cope rearrangement is followed by an intramolecular aldol addition, and often the intramolecular aldol adducts are the main or even the only product of the reaction sequence. These are formed in a selective way in that the enol or the enolate attacks the keto functionality from the face opposite to the tricarbonylchromium group. Consequently, the polycycles formed are diastereomerically pure. Representative

examples for these products obtained from the benzocyclobutenedione complex in a one pot reaction sequence are **346**–**350**[228, 231].

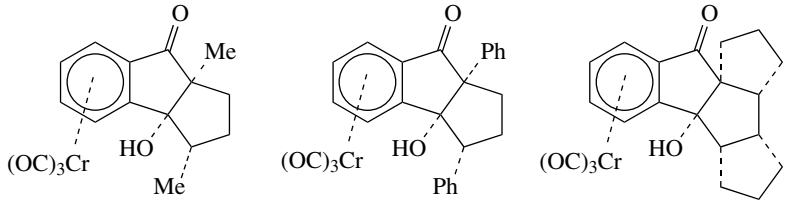


(**333**) (**342**) (**343**)

(**344**)

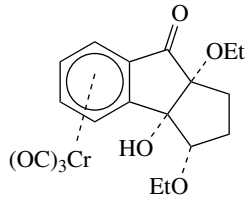


(**345**)

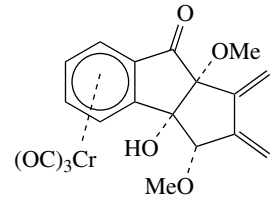


(**346**) (**347**) (**348**)

For example, **348** is the result of the reaction using 1-cyclopentenyllithium as the alkenyllithium component. The formation of **349** demonstrates the feasibility of 1-lithiated vinylalkyl ethers in this reaction. **350**, which is obtained in 60% yield, clearly shows the possibility of creating highly functionalized complex polycycles by this reaction sequence:



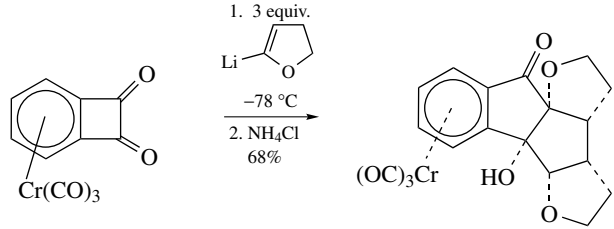
(349)



(350)

The compound has, in addition to the keto and the hydroxy functional groups, two allyl ether units and an exocyclic diene moiety, which easily undergoes Diels–Alder cycloadditions, e.g. with dimethyl butynedioate giving the respective tetracycle in 90% yield as a single diastereomer[231].

A particularly interesting question is how far would it be possible to introduce heteroatoms into the polycycles formed. When 5-lithio-2,3-dihydrofuran was used as the alkenyllithium component, tetracycle **351** was formed in 68% yield (equation 77). However, when lithiated heteroaromatics such as 2-lithio-*N*-methylpyrrole, 2-lithiothiophene or 2-lithiofuran were tried, only single adducts or ring opened products were obtained. Clearly, it was not possible to overcome the resonance energies of two heterocyclic aromatics[232].



(77)

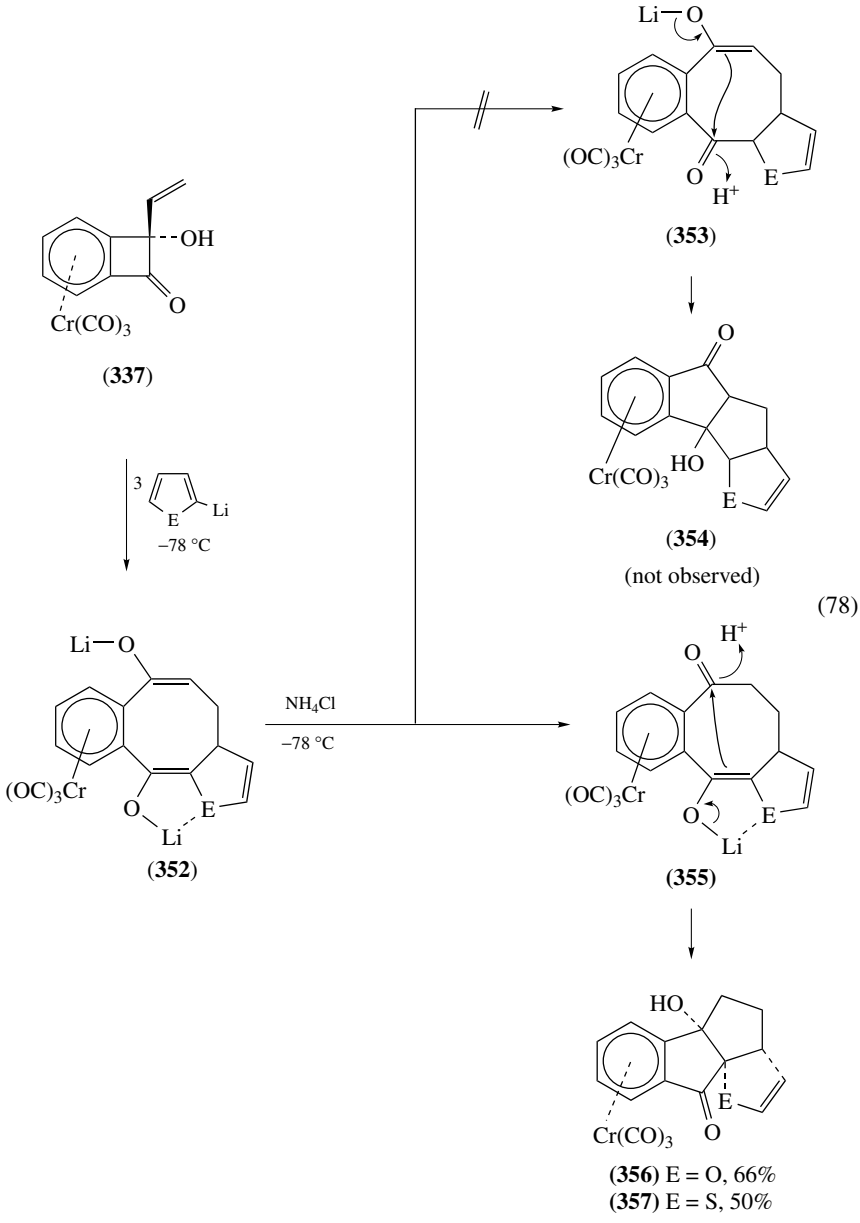
(**333**) (**351**)

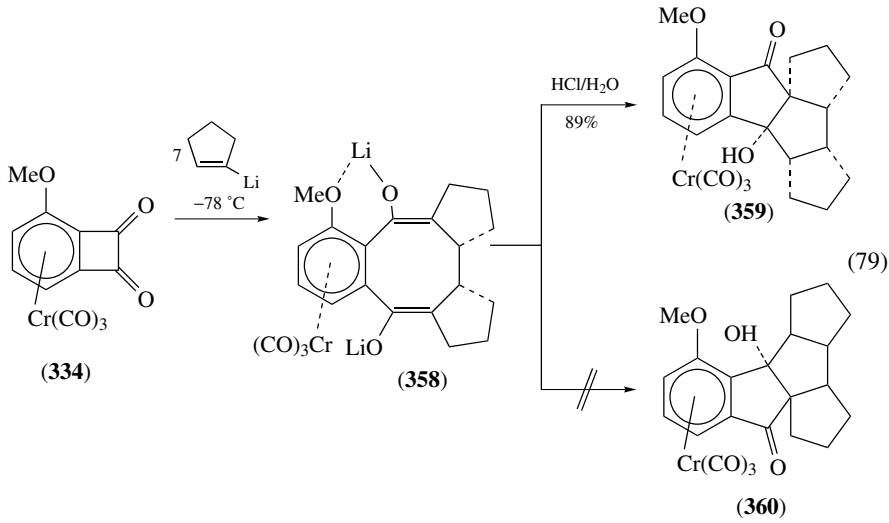
However, when vinyl adduct **337** was used as the starting material, treatment with 3 equiv. of 2-lithiofuran or 2-lithiothiophene resulted in a dianionic oxy-Cope rearrangement at low temperature. As a result the asymmetric di(enolate) **352** was formed. For the following hydrolysis/intramolecular aldol addition two consequent different reaction paths are possible.

Remarkably, the two enolate moieties in the rearrangement product **352** are fully discriminated. Keto enolate **353** (or the respective enol) and aldol adduct **354** are not formed; the exclusive reaction pathway is that via **355** to **356** or **357** (equation 78). Presumably the enolate moiety opposite to the anellated heterocyclic ring in **352** has a considerably higher kinetic basicity than that next to the heteroatom, which possibly stabilizes this enolate group by some chelation. As a result only **356** and **357** are observed; the latter was characterized crystallographically[232].

While the asymmetry of the di(enolate) **352** has its cause in the addition of two different alkenyllithium reagents to **333**, the methoxy substituted **334** is an asymmetric benzocyclobutenedione complex. From this, an asymmetric di(enolate) can be obtained by addition of two identical alkenyllithium reagents. When **334** was treated with a large excess of 1-cyclopentenyllithium, **359** was formed in high yield as the only isolated product. Among other spectroscopic techniques, the identity of **359** was confirmed by an X-ray structure

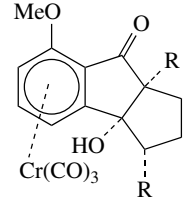
analysis. No **360** was found (equation 79). It is thought that the rearrangement product, i.e. the di(enolate) **358**, is hydrolyzed first at the enolate moiety opposite to the methoxy substituent. The second enolate moiety is apparently stabilized by some chelation, rendering it kinetically less basic[233].





(79)

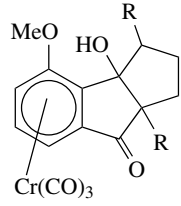
This kind of regioselective discrimination of two enolate moieties in one eight-membered ring was observed in a number of cases starting from **334**. Thus, compounds **361** and **363** were formed, but no **362** or **364** was obtained[233].



(**361**)

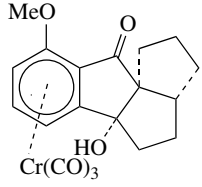
67–76%

R = H, Me, OMe, OEt



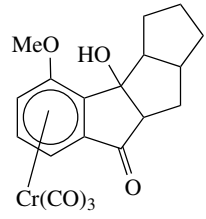
(**362**)

not observed



(**363**)

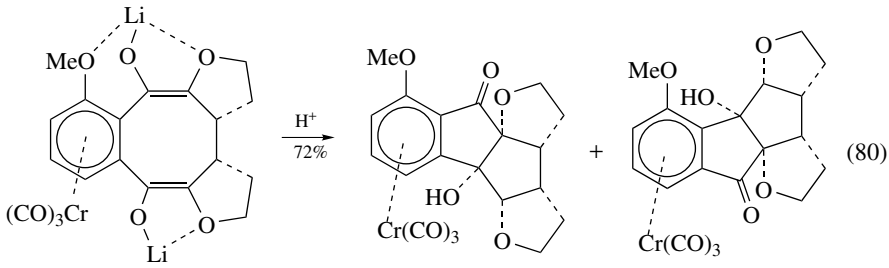
62%



(**364**)

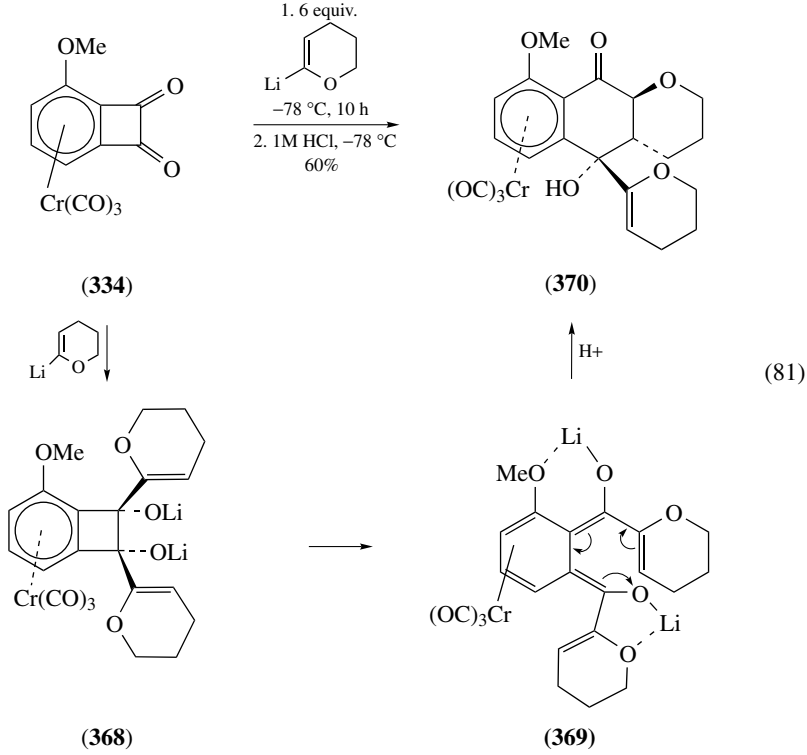
not observed

There is one case in which, in contrast to the cases discussed so far, this selectivity was not observed. When **334** was treated with 5-lithio-2,3-dihydrofuran a 1:1 mixture of **366** and **367** was obtained (equation 80). This was explained by a variety of possibilities for chelation in the rearrangement product **365** at either one of the enolate moieties[233].



(**365**) (**366**) 1:1 (**367**) (80)

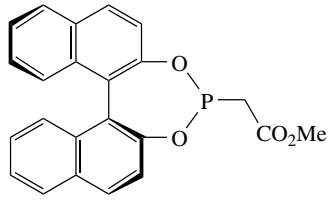
An unexpected result was obtained when **334** was treated with 6-lithio-3,4-dihydro-2-*H*-pyran. Instead of a dianionic oxy-Cope rearrangement, in this case an anionic 1-oxyvinylcyclobutene–cyclohexadienol rearrangement was observed. Presumably via intermediates **368** and **369**, product **370** was formed in 60% yield (equation 81)[233].



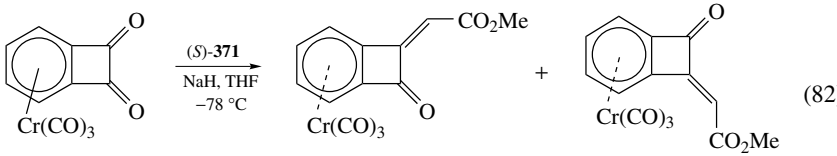
(**334**) (**370**)

(**368**) (**369**) (81)

In the symmetric benzocyclobutenedione complex **333** the keto groups are enantiotopic. Tanaka and coworkers succeeded in a discrimination of these by performing an olefination reaction using the phosphonoacetate **371**. Olefination products **372** and **373** were obtained in 61% and 29% yield with *ee* of 94% and *ca* 30%, respectively (equation 82)[234].

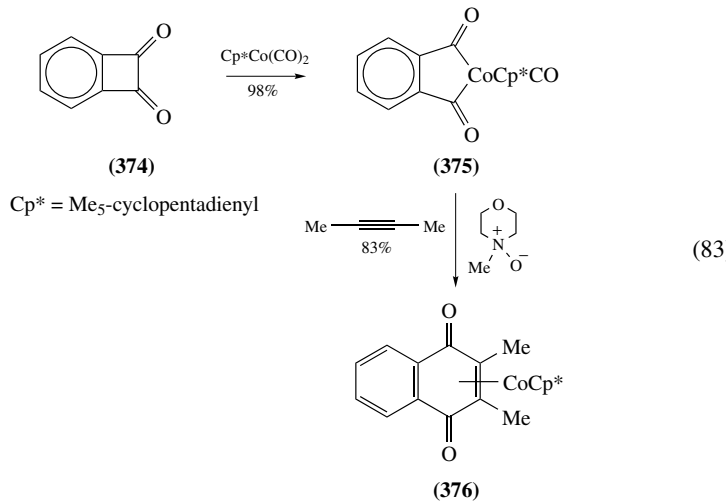


(*S*-**371**)



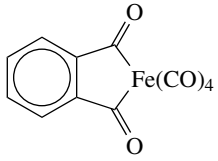
(**333**) (**372**) 61%, 94% *ee* (**373**) 29%, *ca*, 30% *ee* (82)

A completely different type of organometallic reaction of benzocyclobutenediones was found by Liebeskind and coworkers, who treated benzocyclobutenedione (**374**) with low valent metal complexes and observed the formation of phthaloyl complexes (2-metallaindan-1,3-diones) such as **375**, which form naphthoquinone complexes like **376** upon treatment with alkynes in the presence of suitable N-oxides (equation 83). Metals undergoing this type of reaction include cobalt, rhodium, iridium and iron, leading to complexes such as **377–379**[235–239].

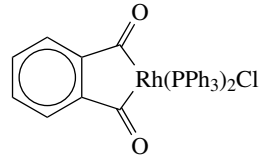


(**374**) (**375**) (**376**)

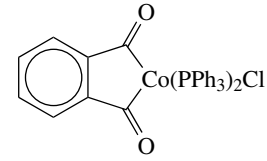
Cp* = Me_5-cyclopentadienyl (83)



(377)



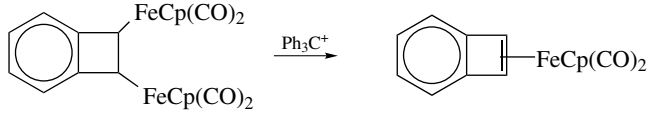
(378)



(379)

VI. BENZOCYCLOBUTADIENES

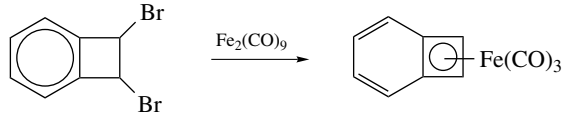
Due to its partial antiaromatic character benzocyclobutadiene is highly reactive[240–242]. However, transition metal complexes are more stable and can be obtained by different ways. Sanders and Giering reported the synthesis of η^2 benzocyclobutadiene complex **380** by treatment of **251** or similar compounds with the trityl cation (equation 84)[243]. The synthesis of the related **258** from 1-bromobenzocyclobutene (**248**) has already been mentioned.



(84)

(**251**) (**380**)

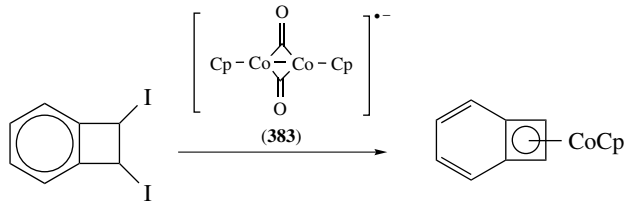
The more usual η^4 benzocyclobutadiene complexes like **381** are obtained by dehalogenation of 1,2-dihalobenzocyclobutenes, such as 1,2-dibromobenzocyclobutene **250** with low valent metal complexes, e.g. diironenneacarbonyl (equation 85)[143]. **381** has been investigated structurally and shows some anti-Mills–Nixon bond localization[244]



(85)

(**250**) (**381**)

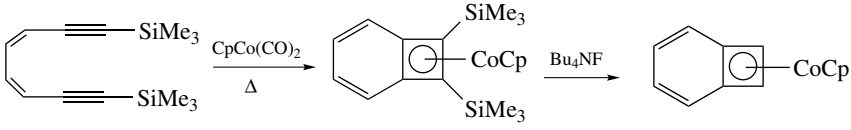
The respective cyclopentadienylcobalt complex **384** is obtained by treatment of 1,2-diiodobenzocyclobutene (**382**) with the radical anion **383**, which can be obtained from $CpCo(CO)_2$ by reduction with sodium (equation 86)[245].



(86)

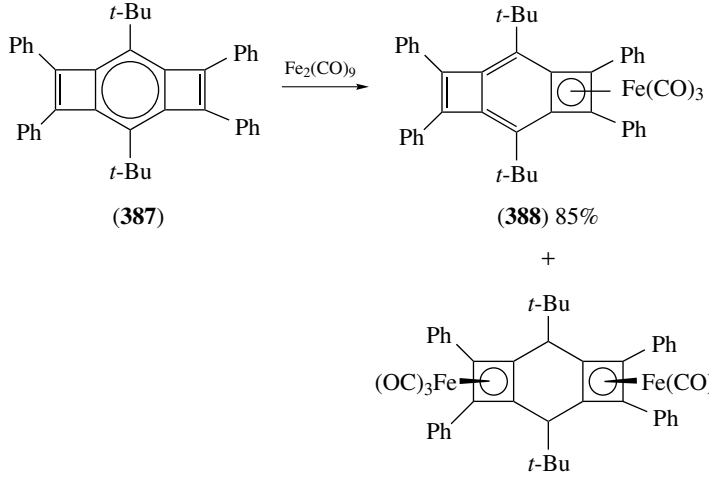
(**382**) (**384**)

Cyclopentadienylcobalt complex **384** was also obtained by an intramolecular alkyne cyclotrimerization of dienediyne **385**, which gave **386** and **384** after its desilylation with tetrabutylammonium fluoride (equation 87)[246].



(**385**) (**386**) (**384**) (87)

A particularly interesting example was reported by Butters, Toda and Winter, who performed the reaction of the tricyclic ligand **387** with $Fe_2(CO)_9$ and obtained complexes **388** and **389** in 85% and 5% yield, respectively. The configuration of **389** was established by an X-ray crystal structure analysis to be the sterically less favored *syn* isomer (equation 88), suggesting that in the course of the complexation a dinuclear iron carbonyl species attacked the ligand[247].

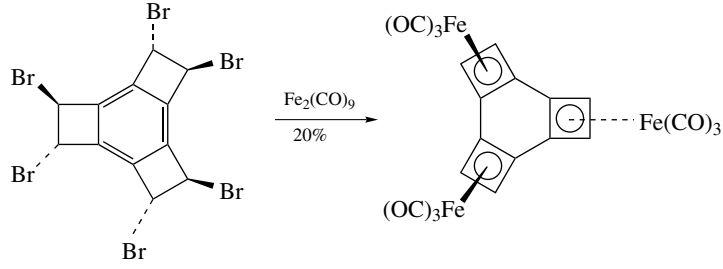


(**387**) (**388**) 85%

(88)

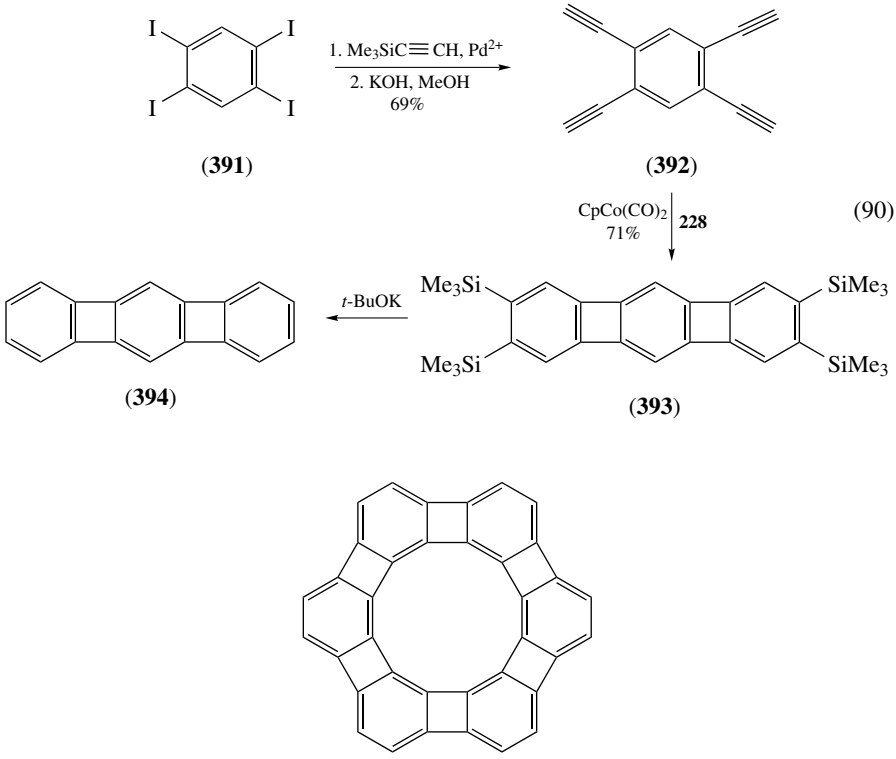
(**389**) 5%

Even more spectacular, Stanger and coworkers reported the synthesis and structural characterization of tris(tricarbonylironcyclobutadieno)benzene **390** formed by the reaction of **235** with $Fe_2(CO)_9$ (equation 89). **390** was the only diastereomer formed; the corresponding *all-cis* complex was presumably not observed for steric reasons[248].



(**235**) (**390**) (89)

A class of cyclobutane derivatives, which in principle is an extension of the benzocyclobutadienes, are the oligophenylenes. This chemistry has been developed by Vollhardt and coworkers, who use the cobalt catalyzed [2 + 2 + 2] cyclization of 1,2-dialkynylbenzenes with bis(trimethylsilyl)ethyne (**228**) to construct a variety of these compounds. A representative example is the synthesis of terphenylene (**394**) from 1,2,4,5-tetraiodobenzene (**391**) via tetrayne **392** and the silyl derivative **393** (equation 90). Now there are many linear, bent or branched oligophenylenes in the literature which are thought to be interesting compounds for applications, e.g. in molecular electronics. One target structure, which has not yet been made, is the so-called anti-kekulene **395**, which deserves interest due to fundamental questions concerning aromaticity. However, organometallic aspects in this chemistry are mainly restricted to their Co-catalyzed synthesis. For further information leading references are available[155, 156, 171, 249–259].



(**391**) (**392**) (90)

(**394**) (**393**)

(**395**)

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CHAPTER **17**

Photochemistry of cyclobutanes: Synthesis and reactivity

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I. INTRODUCTION

The photochemical paths to cyclobutanes are many and varied and since the onset of modern organic photochemistry researchers have used a variety of cycloaddition reactions to achieve the synthesis of the title compounds. Much of the earlier work was directed towards the synthesis of newly discovered naturally occurring compounds with a cyclobutane as a key structural feature. This review will focus on the synthesis of isolable cyclobutanes and will not discuss photoreactions that lead to compounds that have photo- or thermally-labile cyclobutane rings, such as the de Mayo addition reactions of 1,2- and 1,3-diketones. Since there are so many paths to cyclobutanes this review cannot be encyclopaedic. Thus, the examples chosen will provide paths to cyclobutanes that give substituted derivatives that can undergo chemical transformations. Many review sources are available for reference such as the thirty-five years of annual compendia of photochemical reactions[1]. The subject matter dealt with here has also been covered in recent handbooks[2,3].

II. CYCLOADDITION REACTIONS INVOLVING ALKENES

Dimerization of substituted alkenes has been of considerable interest for many years and Kaupp[4,5] has reviewed the application of this to the synthesis of cyclobutanes in the liquid and solid phases.

A. Alkenes and Cycloalkenes

The additions within this class of alkene are generally restricted to compounds that have chromophores that can be excited by light >200 nm. For example, the photolysis at 248 nm of *trans*-1,2-difluoro-1,2-diiodoethene brings about *trans,cis*-isomerization and dimerization to yield ultimately 1,2,3,4-tetrafluoro-1,2-diiodocyclobutene by loss of iodine[6].

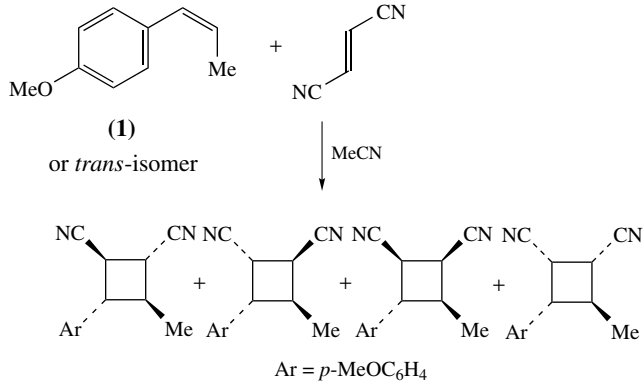
A further example is the observation by Kropp and his coworkers[7] that cyclohexene undergoes dimerization when irradiated at *ca* 200 nm in aprotic media. The mechanism for the formation of the dimers involves the isomerism of the cyclohexene to the strained *E*-isomer followed by the thermal addition of this isomer to the ground state *Z*-cyclohexene, yielding a mixture of the *trans,anti,trans, cis,trans* and *cis,anti,cis* dimers in ratios of 1.6:2.3:1. The dimerization of cyclohexene has also been studied in the triplet state using sensitization by chiral benzene carboxylates[8]. Mori and Inoue[9] have reviewed reactions of this type recently. An early study of the direct irradiation of 1-phenylcyclohexene indicated that the S_1 excited state was involved and this brings about the formation of a diastereoisomeric mixture of head-to-head cyclobutane dimers[10]. Later work demonstrated that the dimerization also took place in methanol solution, giving a mixture of three head-to-head dimers in the ratio of 55:40:5[11]. 1-Carboxymethyl cycloheptene undergoes dimerization on irradiation in pentane. Two head-to-head dimers are formed in a ratio of 86:14 with the *trans,anti,cis* isomer predominant. Again the *E*-isomer of the cycloheptene is involved[12].

Dimers (both *cis*oid and *trans*oid) are also formed on irradiation of acenaphthylene[13]. The formation of a cyclobutane derivative has also been reported following the irradiation of *N*-substituted indole derivatives in the presence of cyclopentene. This affords both the

cis- and the *trans*-cycloadducts. The yields are in a range up to 80% and better can be achieved by acetophenone sensitization[14].

B. Styrenes

Some simple styrenes undergo dimerization. For example, prolonged irradiation of *p*-acetylstyrene in the presence of styrene affords a mixture of the *cis*- and *trans*-head-to-head dimers of *p*-acetylstyrene[15]. Cycloaddition reactions are also reported, such as the addition of 1,2-dicyanoethene to the styrene (**1**). This yields the four adducts shown in Scheme 1[16]. The medium in which the reactions are carried out can have a major effect, such as the efficient dimerization of *p*-methoxystyrene in a NaY zeolite. This treatment yields a mixture of the corresponding *cis*- and *trans*-head-to-head cyclobutanes[17,18]. Cycloaddition also occurs on irradiation of 1,4-diphenyl-1-cyanobutadiene. This affords the dimer identified as 1,3-dicyano-1,3-diphenyl-2,4-distyrylcyclobutane[19].

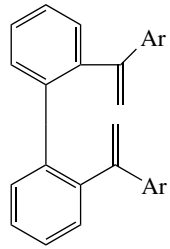


SCHEME 1

Styryl substituted systems are good electron donors with oxidation potentials low enough for electron transfer to 9,10-dicyanoanthracene (DCA) in its excited singlet state. The SET-induced cyclization (dicyanoanthracene as the electron-accepting sensitizer) of the biphenyl derivatives (**2**) results in the formation of the cyclobutane derivatives (**3**)[20]. DCA-induced cyclization has also been reported for the dienes **4** and **5** in acetonitrile. Stereoselective intramolecular (2 + 2)-cycloadditions occur yielding the *endo*- and *exo*-bicyclo[3.2.0]heptanes **6** and **7**, respectively. The *E*-isomer **4** appears to react non-stereoselectively but shorter irradiation times give better selectivity. The radical cation of the diene is involved and this cyclizes to afford the cyclic radical cation (**8**)[21]. An analogous study was reported for the parent (**9**) of this system again involving SET to DCA. This forms the radical cation (**10**) that cyclizes to the bicyclic compounds (**11**)[22,23].

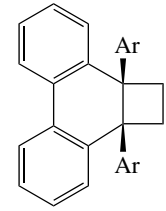
Other work has examined the influence of chain length on the yield of products in the SET-induced cyclizations of **12**. The products obtained are the bicycloalkanes (**13**) and the cycloalkenes (**14**). Again the cyclic 1,4-radical cations are the proposed intermediates[24]. There is a solvent dependency on the outcome of the reaction as can be seen from the results shown. Radical cation cyclization is also observed with the ether **15** using tetracyanoethene as the sensitizer. When this is irradiated using $\lambda > 350$ nm or >450 nm in acetonitrile it gives the product **16**[25].

The cycloaddition within styrene systems takes many forms. One of these is the cycloaddition encountered within the styrene systems tethered by silyl ethers[26,27]. The silyl



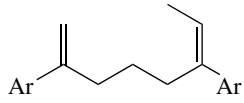
(2)

(a) Ar = C_6H_5
(b) Ar = *p*-MeC_6H_4
(c) Ar = *p*-$MeOC_6H_4$



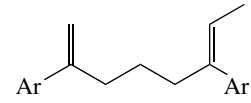
(3)

73%
68%
81%



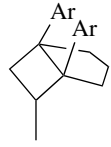
(4)

(a) Ar = *p*-$MeOC_6H_4$
(b) Ar = C_6H_5



(5)

(a) Ar = *p*-$MeOC_6H_4$
(b) Ar = C_6H_5



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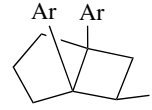

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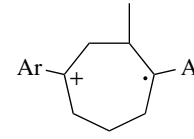
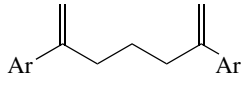


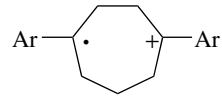
(8)

		Ratio *endo*:*exo*	
$E_{\mathbf{4a}}$	65	0	0
$E_{\mathbf{4b}}$	70	0	0
$Z_{\mathbf{4a}}$	27	45	1:1.7
$Z_{\mathbf{4b}}$	32	34	1:1.1

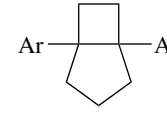


(9)

Ar = 4-$MeOC_6H_4$
Ar = 4-MeC_6H_4
Ar = Ph

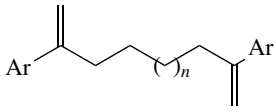


(10)

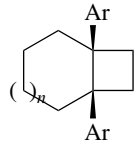


(11)

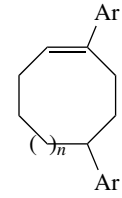
yield(%)
53
80
76



(12)



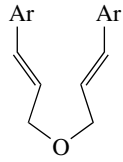
(13)



(14)

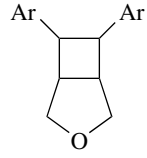
(a) Ar = 4-$MeOC_6H_4$
(b) Ar = Ph
n = 1 or 2

Solvent				yield (%)
MeCN	$n = 1$	**a**	0	86
C_6H_5		**a**	65	31
MeCN		**b**	58	24
MeCN	$n = 2$	**a**	0	9
MeCN		**b**	10	21



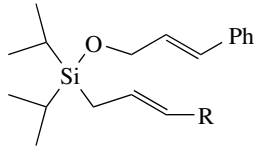
(15)

Ar = 4-$MeOC_6H_4$



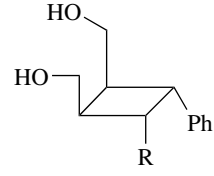
(16)

ethers (**17**) are reactive in the singlet state and direct irradiation brings about cyclization, and thereafter the silyl ethers groups are cleaved to afford cyclobutane diastereoisomers such as **18**.



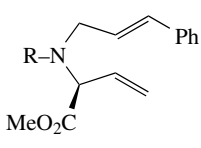
(17)

R = PhCH═CH,
R = *Z*-PhCH═CH,
R = *E*-MeCH═$CHCH_2$



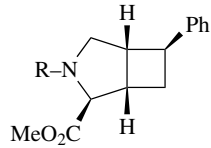
(18)

Cycloaddition also occurs on acetophenone-sensitized irradiation of non-conjugated dienes such as **19** that affords the *exo*-adduct **20** where facial selectivity is observed. Similar reactivity is observed with the diene **21** that yields adduct **22** in 77% yield. Perfect facial diastereoselection is exhibited in the more rigid diene **23**. Its irradiation under the same conditions as in the previous examples affords **24** with a selectivity of $>95:<5$[28, 29].



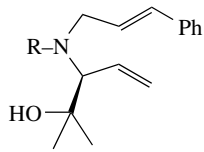
(19)

R = benzyloxycarbonyl



(20)

53%



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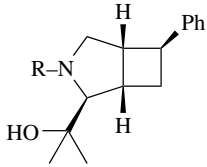

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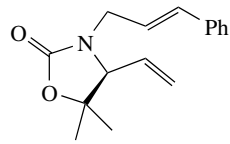

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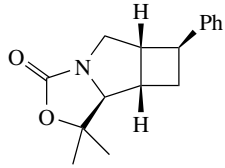
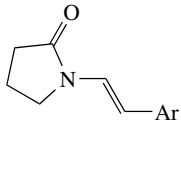


(24)

74%

Dimerization of more complex styrenes has been reported in the crystalline phase. The enamides **25** apparently crystallize with relatively short intermolecular distances between the alkene moieties and irradiation at 350 nm yield head-to-tail dimers **26** in high yield. Dimerization is also observed on irradiation of crystals of **27** that gives the dimer **28** in 89% yield[30].

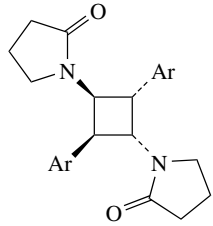


(25)

Ar = Ph

Ar = *o*-ClC_6H_4

Ar = *m*-ClC_6H_4

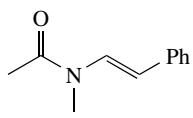


(26)

87%

92%

90%



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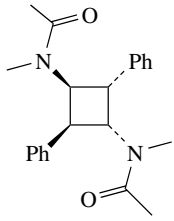
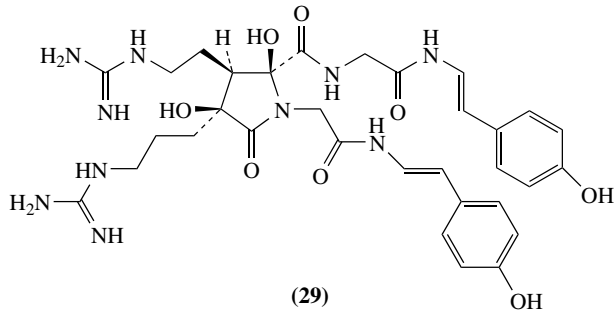


(28)

Finally in this section there is the report of an unprecedented (2 + 2)-photocycloaddition with the anchinopeptolide **29** that occurs on irradiation at 350 nm in D_2O. The cycloaddition makes use of the hydrophobic effect in water that forces the two side chains into close proximity. The product obtained was identified as **30** resulting from (2 + 2)-cycloaddition of the styryl double bonds[31].

C. Stilbenes and Related Systems

Stilbenes also undergo dimerization. The solution phase dimerization has been known for a considerable time and the overall process is exemplified by the dimerization shown



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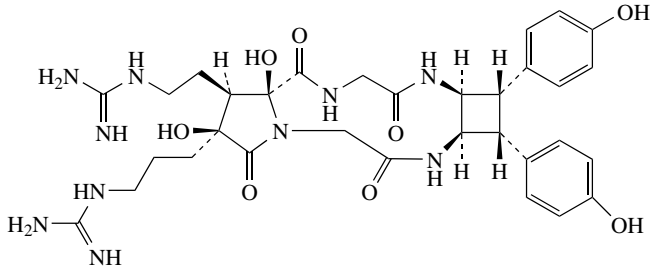

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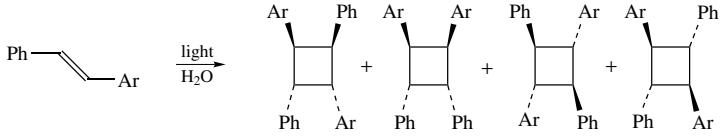


(31)

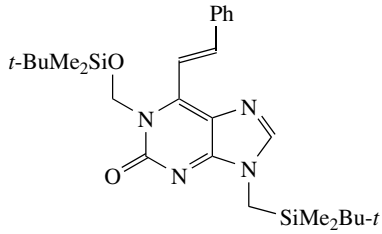
$Ar = p\text{-}NCC_6H_4$

SCHEME 2

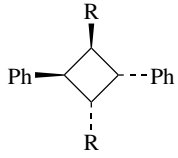
in Scheme 2 for stilbene **31**. The dimerization occurs at low concentrations in water and affords the four cyclobutane isomers in the yields shown[32].

Other stilbene analogues are also reactive in solution. Thus the daylight or UV irradiation of **32** in ethanol brings about dimerization and the formation of the cyclobutane **33**[33]. The photochemical dimerization of the *trans*-1-[2-(5-R-benzoxazolyl)]-2-(4-R′-phenyl)ethenes (R = H, Me, R′ = H, OMe) affords cyclobutane derivatives by head-to-tail dimerization[34].

In more recent times interest has developed in the control that can be exercised on the photoaddition reactions of stilbene either by irradiation in the crystalline phase or with the stilbene moiety locked into a template. Thus, irradiation of the *E*-stilbenes **34** as solid inclusion compounds within γ-cyclodextrin affords the *syn*-tetraarylcyclobutanes **35** in yields as high as 60%. As can be seen from the results shown under the appropriate structure, the effect of different aryl groups upon the reaction was also studied. The ratios of head-to-head (HH) and head-to-tail (HT) isomers that are formed were also quantified[35]. A report has recorded the results of irradiating the complex of stilbene (**34**, $R^1 = R^2 =$



(32)



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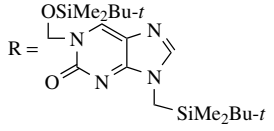

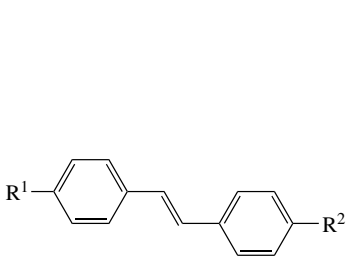

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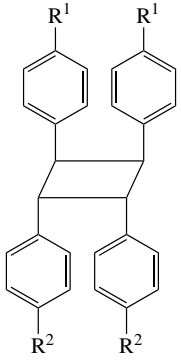
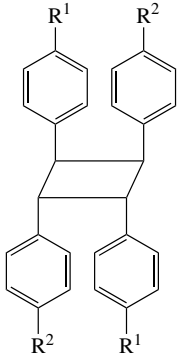


syn-HH



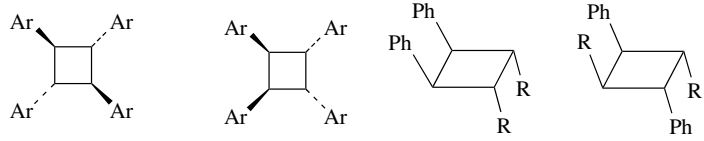
syn-HT

(35)

	R^1	R^2	Yield (%)	Ratio HT : HH
(a)	H	H	48	–
(b)	MeO	MeO	42	–
(c)	Me	H	46	57 : 43
(d)	Cl	H	52	55 : 45
(e)	MeO	H	42	60 : 40
(f)	CN	H	60	54 : 46

Me_2N^+ HC_6H_4) in γ-cyclodextrin. Rather than *cis,trans*-isomerism, dimerization occurs to afford **36** and **37** in 79% and 19% yields, respectively. These results are different from those obtained by irradiation of the stilbene in aqueous solution when the isomerization occurs as the major process and only low yields of the dimers **36** and **37** are obtained under these conditions[36]. When 2-styrylpyridine is encapsulated in γ-cyclodextrin and irradiated in the solid state little isomerism occurs (7% of the *cis*-isomer is formed) and the principal reaction is the formation of the head-to-tail *cis,anti,cis*-dimer in 50% yield[37].

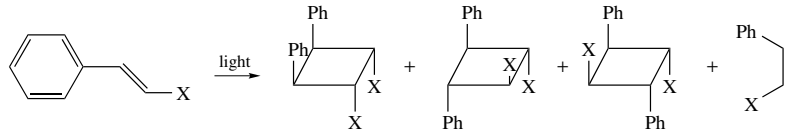
Lalitha and coworkers[38] have also demonstrated that 2-styrylpyridine undergoes dimerization at high loadings in faujasite zeolites. Again *trans,cis*-isomerism is the only result at low concentrations.



(36) **(37)** **(38)** **(39)**

R = $H_2OCC_6H_4$

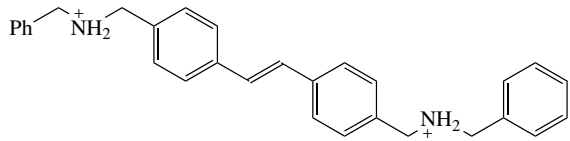
The control of photochemical reactions in the constrained environment of a hydrotalcite clay as the supporting medium has also been examined. This particular study examined the irradiation ($\lambda > 280$ nm) of a mixture of 4-benzoylbenzoic acid and 2-phenylethenylbenzoic acid in this environment. While the regioselective formation of oxetanes was observed, dimerization of the phenylethenylbenzoic acid also takes place yielding the cyclobutanes **38** and **39** in a total yield of 45%[39]. The same investigators have also demonstrated that the stereoselectivity of dimerization of 2-phenylethenylbenzoic acid in clays is dependent upon the site distances. These distances can be controlled by varying the fraction of Al^{3+} in the clay. Typical results for the selectivity observed are shown in Scheme 3[40].



X =	Site distance (Å)	Selectivity (%)			
CO_2H	5.4	67	0.8	30	0.8
	6.2	59	4.9	34	1.6
	8.2	42	11	42	3.6

SCHEME 3

The environment within single crystals can also provide a situation where dimerization is the dominant reaction. Typical of this is the irradiation of stilbene **40**, co-crystallized with bis-*p*-phenylene[34]crown-10, that yields the dimer **41** in 80% yield[41]. The co-crystals obtained from 1,8-naphthalenedicarboxylic acid and the *trans*-1,2-di(4-pyridyl)ethene **42** are arranged in such a manner that the two ethene units lie in close proximity. The arrangement is as shown in **43**, where the diacid behaves as a linear template with hydrogen bonding to the pyridine nitrogens. Irradiation at 300 nm results in 100% stereospecific conversion into the corresponding cyclobutane derivative[42]. A layered ternary solid is formed between



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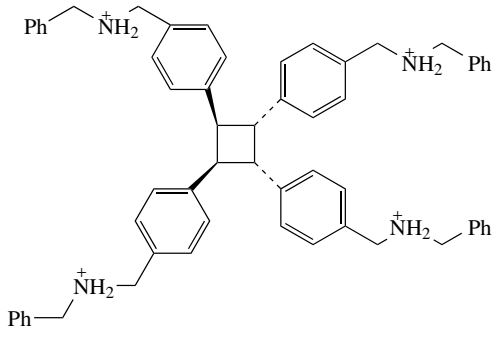
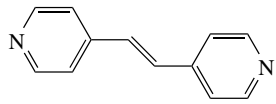
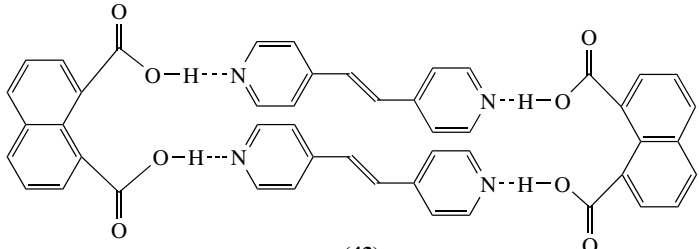


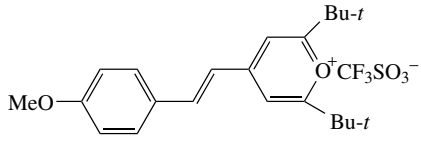
(41)



(42)



(43)



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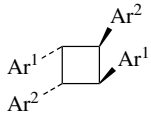
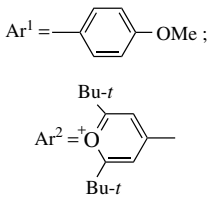


(45)

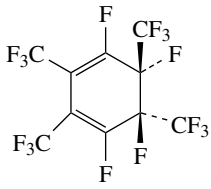


1,2-dihydroxybenzene and *trans*-1-(2-pyridyl)-2-(4-pyridyl)ethene. Within this the stilbene analogue is held in a head-to-tail arrangement. Irradiation brings about the formation of a cyclobutane identified as *rctt*-1,3-bis(2-pyridyl)-2,4-bis(4-pyridyl)cyclobutane[43]. Irradiation at 313 nm of films of liquid crystalline polymer containing the *trans*-4,4′-stilbene dicarboxylate chromophoric systems leads to the disappearance of the stilbene system. The absence of the chromophore after irradiation is attributed to the formation of (2 + 2)-cycloaddition products[44]. The dimerization of the stilbene analogue **44** to afford **45** can be brought about in the crystalline phase by irradiation at $\lambda > 570$ nm. Single crystal to single crystal dimerization and the thermal reverse has been studied for the same alkene (**44**)[45–47].

III. CYCLOADDITION REACTIONS INVOLVING DIENES AND TRIENES

A. Conjugated Dienes

The usual path for cyclization of a conjugated diene is the formation of a cyclobutene. However, sometimes as a result of terminal substitution on the diene system, cyclization results in a bicyclo[2.2.0]hexene one part of which is a cyclobutane. Typical of this is the cyclization of the perfluorocyclohexadiene **46** that affords the cyclized product **47**. The diene **46** is formed readily by photocyclization of the corresponding hexa-1,3,5-triene[48]. Other dienes are also reactive and the dimerization 1-(2′-methoxyphenyl)-4-(4′-nitrophenyl)butadiene affords cyclobutane derivatives[49].



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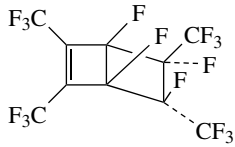
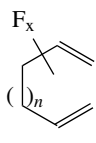
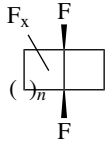


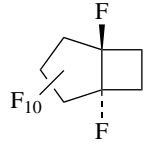
(47)

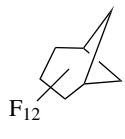
B. Non-conjugated Dienes

This area of study has been reviewed recently within this series of monographs[50]. Cycloaddition to form a cyclobutane derivative is also observed as a result of mercury-sensitized vapour-phase photolysis at 254 nm of the fluorinated diene **48**. This yields the two cyclobutane derivatives **49** and **50** as well as the cross-addition product **51** in ratios of 5.7:1.0:2.8. When the reaction system was diluted with nitrogen, the formation of the $(2 + 2)$-cycloadducts became dominant. Similar additions were observed for the diene **52**. The straight $(2 + 2)$-adduct **53** and the cross-addition product **54** are formed in a ratio of 1:4[51]. One of the double bonds can be contained within a ring as in the cycloaddition encountered in the study of cyclopropene **55** where sensitized irradiation affords the tricyclic compounds **56** by a head-to-head $(2 + 2)$-cycloaddition[52].



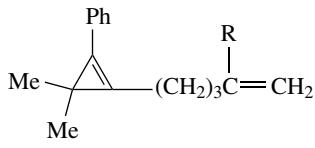






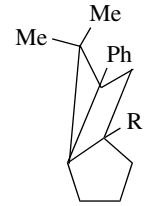
(48) $n = 2,\ x = 12$ **(49)** $n = 2,\ x = 10$ **(50)** **(51)** **(54)**
(52) $n = 1,\ x = 10$ **(53)** $n = 1,\ x = 8$

The introduction of a heteroatom does not appear to influence adversely the cycloaddition. Thus head-to-head $(2 + 2)$-cycloaddition is observed on irradiation of the diallylic amines **57** that yields the cyclobutanes **58**. The reaction is diastereoselective and detailed semi-empirical calculations support the proposed mechanism for the formation of these products[53,54]. Related to this is the reported cycloaddition of the indole derivatives **59** that provides an effective route to the synthesis of the polycyclic adducts **60**. The yields, as can be seen from those quoted, range from moderate to good. The quantum efficiencies for the cyclizations are also reasonable. Interestingly, the ester derivatives **61** are



(55)

(a) R = H
(b) R = Me



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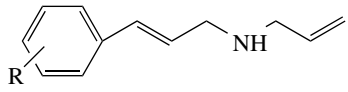
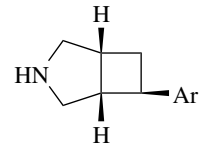


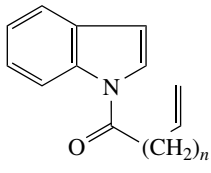
(57)

R = H, 4-F, 4-Cl, 4-NO_2, 3-Cl, 2-F



(58)

Ar = RC_6H_4



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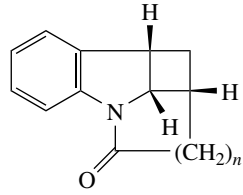
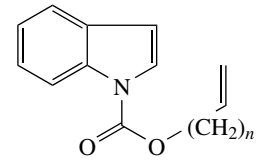


(60)

$n = 1$	29%	$\phi = 0.0078$
$n = 2$	92%	$\phi = 0.017$
$n = 3$	25%	$\phi = 0.0032$



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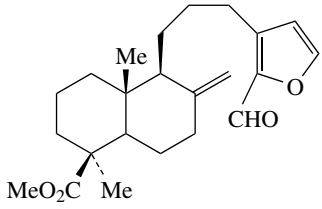
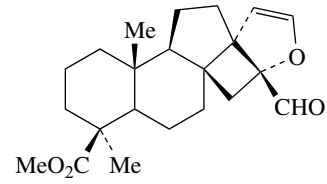


(62)



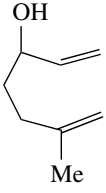
(63)

photo-unreactive[55,56]. Isolated double bonds can also undergo addition to furan moieties as in the (2 + 2)-photocycloaddition of the lambertianate derivative **62** that results in the formation of the cyclobutane adduct **63**[57].

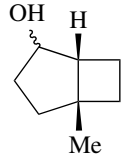
C. Copper(I) Catalysed Reactions of Non-conjugated Dienes

The use of copper(I) triflate salts as templates for the (2 + 2)-photocycloaddition reactions of non-conjugated alkenes has become a significant route for synthesis of cyclobutanes. This area has been the subject of a major recent review[58] and has been discussed in this series previously[50]. There is little doubt that this copper catalysed cycloaddition provides cyclobutanes in high yields and in a stereoselective manner. The cyclobutanes obtained can have a variety of substituent groups and thus can be used as starting materials for the synthesis of many natural products. Thus, only a few examples will be given here to provide a flavour of what can be achieved by the method.

A stereochemical synthesis of grandisol has been developed using the copper(I) catalysed cycloaddition of the dienol **64** to afford the bicycloheptenols **65**[59]. The *exo/endo* ratio in this cyclization is solvent dependent. The racemic grandisol **66** can be synthesized starting from the heptenol **65** in eight steps. A more detailed study by Langer and Mattay[60] has reported on the use of the copper triflate controlled (2 + 2)-cycloaddition of 1,6-dienes such as the (*S*)-diene **67**. This affords the two enantiomerically pure cyclobutane derivatives **68** and **69**. These can be converted into enantiomerically pure (+)-grandisol and the corresponding (−)-grandisol. The use of chiral copper catalysts was also examined, but this gave only products with enantiomeric excesses (*ee*) of below 5%. The authors[60] reason that low *ee*s are obtained due to the low reactivity of the chiral copper complexes as confirmed by CD-spectroscopic measurements. Another approach to the synthesis of grandisol involves the cyclobutane derivatives **70** that can be prepared photochemically by irradiation of the corresponding 1,6-dienes in the presence of Cu(I) triflate. The appropriately substituted product can be converted into grandisol[61].



(64)



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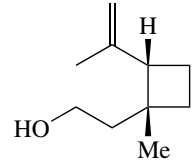

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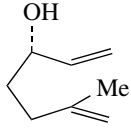

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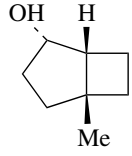

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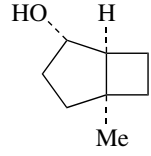

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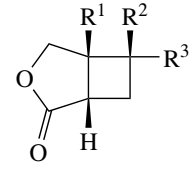
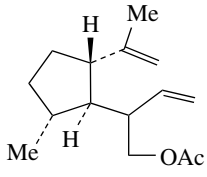


(70)

R^1	R^2	R^3
H	H	H
H	H	Me
H	Me	Me
Me	H	H

More complex structures have been synthesized by Bach and Spiegel[62]. They made use of the Cu(I) catalysed (2 + 2)-photocycloaddition of the diene **71** to afford the adduct **72** in 89% yield. This product was a key intermediate of a synthesis of kelsoene. The cycloaddition of the diene (**73**, $n = 1$), with the alkene moieties *trans* to each other, proceeds with excellent facial selectivity and affords the cycloalkane **74**, $n = 1$, in 80% yield with a *dr* of 98:2 related to this general approach. The *cis*-isomer **75** is also reactive and gives the cycloalkane **76** (77%, *dr* 75:25). The corresponding cyclohexane derivatives **73** and **75**, $n = 2$, are also reactive and yield the cycloalkanes in similar yield and diastereoselectivity[63].



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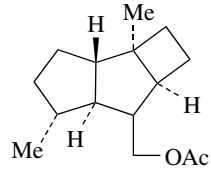

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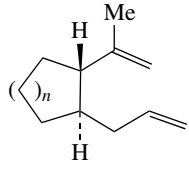

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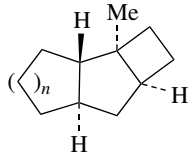
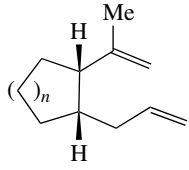


(74)



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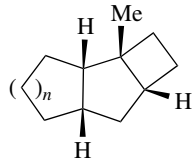
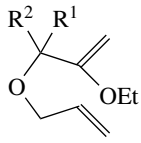
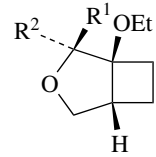


(76)

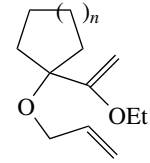
The presence of an oxygen atom in the chain linking the two alkene moieties does not appear to affect the efficiency of the cyclizations encountered. Thus, the (2 + 2)-intramolecular cycloaddition of the divinyl ether **77a** in ether solution with CuOTf affords a reasonable yield of the tetrahydrofuran derivative **79a**. The influence of substituents was studied using **77b** and **77c** and stereoselectivity in the cycloaddition was observed[64]. Copper triflate controlled cyclizations of this type are used to construct suitable key molecules for the synthesis of naturally occurring compounds. To this end the dienes **77** and **78** have been cyclized intramolecularly to yield the cyclobutanes such as **79** in moderate to good yields. Other cyclizations with different substitution have also been reported, exemplified by the conversion of **80** into **81**. The basic aim of this work was to achieve the synthesis of cyclopentanones by chemical conversion of the resulting (2 + 2)-adducts and this was demonstrated by the rearrangement of the products **81**[65,66]. These adducts are key components in an approach to the synthesis of $\Delta^{9(12)}$-capnellene. In the simplest example (**80**, R^1 = Me, R^2 = H) adducts (**81**, R^1 = Me, R^2 = H) can be converted to the cyclopentanone **82** that has been converted into the natural product β-necrodol[67,68]. The variations of the substitution around these molecules have been studied in some detail and these are exemplified for the conversion of the dienes **83** into adducts **84**[69]. The intramolecular photocycloaddition of **83e** affords a mixture of the two cycloadducts **85** and **86**[70]. Adducts like those illustrated as **79** are key intermediates in the synthesis of natural products such as cedrene (**87**)[71].



(77)

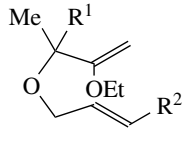


(79)

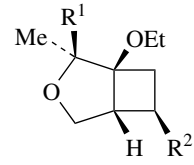


(78)

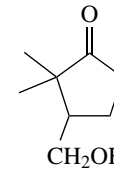
(a) $R^1 = R^2 = Et$
(b) $R^1 = CH_2CH_2Ph$, $R^2 = Me$
(c) $R^1 = Et$, $R^2 = Me$



(80)

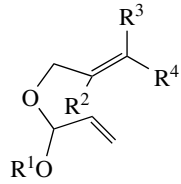


(81)

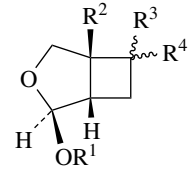


(82)

	R^1	R^2	Yield(%)	*exo*:*endo*
(a)	Me	Me	41	2:5:1
(b)	Me	Ph	53	0:100
(c)	Me	MeCH=CH	52	2.2:1
(d)	$PhCH_2$	MeCH=CH	52	3:1

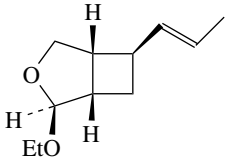


(83)

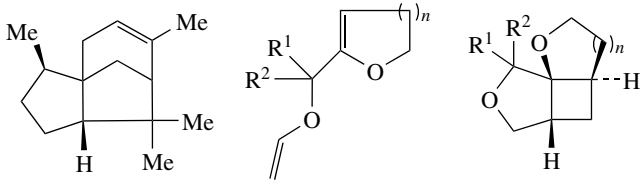


(84)

	R^1	R^2	R^3	R^4	Yield(%)
(a)	Et	H	Me	Me	50
(b)	Me	H	H	H	-
(c)	Me	Me	H	H	-
(d)	Et	H	H	Me	69
(e)	Et	H	H	CH=CHMe	70



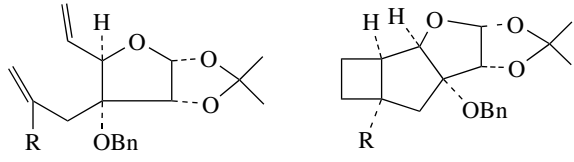
(85) **(86)**



(87) **(88)** **(89)**

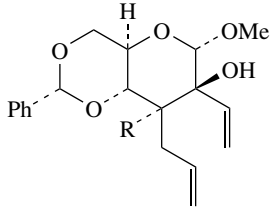
	R^1	R^2	Yield(%)	
			$n = 1$	$n = 2$
(a)	Me	Me	50	46
(b)	Me	CH_2CH_2Ph	59	45
(c)	Me	CH_2Ph	70	40
(d)	$-(CH_2)_4-$		45	58
(e)	$-(CH_2)_5-$		60	57

Approaches to polycyclic ring systems have also been developed from the cyclization of the dienes **88** under the copper(I) controlled conditions. This affords the adducts **89** that can be transformed by thermal reactions into variously substituted derivatives of cyclopentane[72]. The Cu(I) catalysed intramolecular cycloaddition of compounds such as **90** results in the formation of adducts **91**. The authors[73] suggest that the formation of this *cis,syn,cis*-adduct is unusual. A further demonstration of the use and variety of such Cu(I) controlled cycloaddition reactions is the recent application to the synthesis of carbohydrate systems. Several examples of this process were reported. Some of these are the photoconversion of **92** into **93** and **94** into **95**[74].

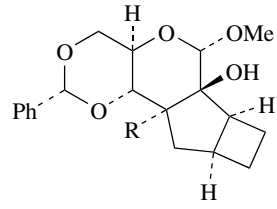


(90) **(91)**

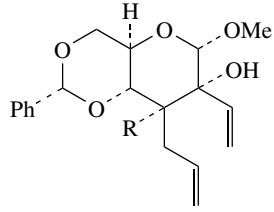
	Yield (%)
R = H	73
R = Me	72



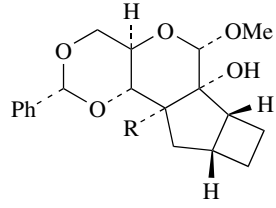
(92) R = H 86%
R = Me 18%



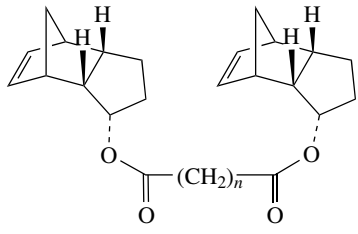
(93)



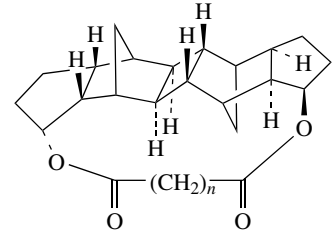
(94) R = H 86%
R = Me 89%



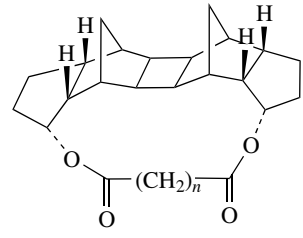
(95)



(96)

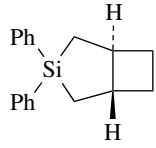


(97)

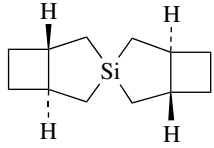


(98)

Cu(I) controlled (2 + 2)-photoadditions of some tethered alkenes have also been studied. Typically, the irradiation of **96** affords a 1:1 mixture of the adducts **97** and **98**[75,76]. Photochemical cyclization of diphenyldiallylsilane in the presence of Cu(I) salts affords the adduct **99**. Similar addition is observed with tetraallylsilane that affords the spiro product **100**.[77]



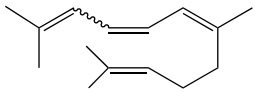
(99)



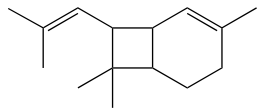
(100)

D. Trienes

Trienes are also photochemically reactive in dimerization reactions and can produce cyclobutanes on irradiation. Typical of this is the conversion of the tetraene **101** into the bicyclo[4.2.0]octene **102**[78]. This cycloaddition probably involves excitation of the triene component and it is the excited state of this that adds to the terminal alkene. It is likely that an analogous excited state is involved in the more complex system **103**. Addition within this molecule also occurs to an isolated double bond to yield the product **104**[79]. The environment in which the compounds are irradiated can also change the outcome of a process. Thus only photochemical isomerism occurs when the trienes **105** are irradiated in solution but in the solid-phase irradiation, using wavelengths >370 nm, induces (2 + 2)-cycloaddition to yield the dimers **106**, R = CHO, 16% and **106**, R = CN, 21%[80,81]. The photoreactivity of (1*E*,3*E*)-1-pentafluorophenyl-4-(4-aryl)buta-1,3-diene (aryl = phenyl, 4-methoxyphenyl and 4-methylphenyl) in the crystal has been studied. The compounds undergo double (2 + 2)-cycloadditions to yield *anti* head-to-tail adducts[82].



(101)



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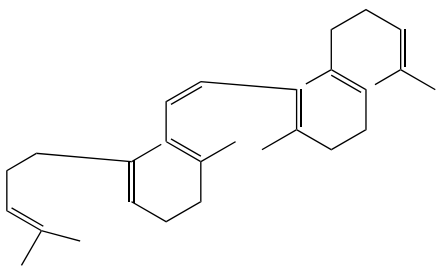
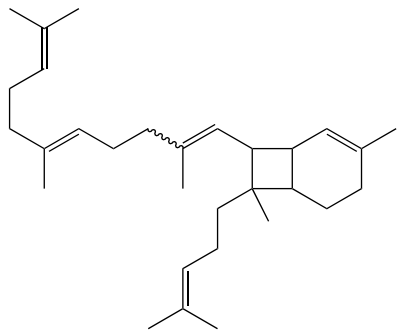


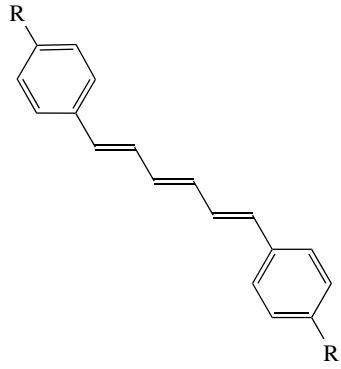
(103)



(104)

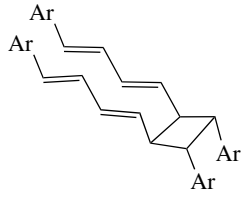
E. SET Processes

Cyclobutane derivatives **107** can be formed efficiently from the dienes **108** using SET (Single Electron Transfer) activation. This treatment yields the radical cation **109** formed



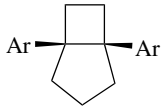
(105)

R = CHO or CN



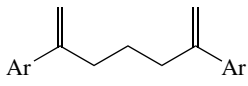
(106)

Ar = *p*-RC_6H_4



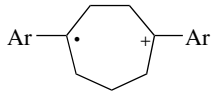
(107)

Yield (%)
53
80
76



(108)

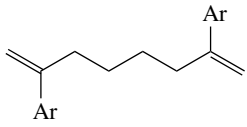
Ar = 4-$MeOC_6H_4$
Ar = 4-MeC_6H_4
Ar = Ph



(109)

from **108** using SET to DCA (9,10-dicyanoanthracene)[83]. Griesbeck and coworkers[84] have also reported on the cyclization of **108**. In addition, they have examined the reactions encountered with the dienes **110** where cyclization to the bicyclo[4.2.0]octane system (**111**) takes place via the radical cation. The cyclization within these compounds is not quite as efficient as the previous examples. The head-to-head products, the cyclooctenes (**112**), are formed in competition with the intramolecular process. Further study has examined the influence of an alkyl substituent on one of the double bonds of the dienes **113** and **114**. Stereoselective intramolecular (2 + 2)-cycloadditions occurred on DCA sensitization yielding the *endo*- and *exo*-bicyclo[3.2.0]heptanes **115** and **116**, respectively. Although the reactions with the *E*-isomer **113** appeared not to be stereoselective, this effect was found to be time-dependent and shorter irradiation times gave better selectivity[85]. The influence of solvent on such cyclizations of the type described above has also been investigated. A further study of these cyclizations has examined the conversion of **117** into the two products **118** and **119**. The mechanism proposed again utilizes the cyclic radical cation and the involvement of this intermediate has been substantiated by trapping experiments with oxygen[86].

The presence of heteroatoms within the molecule remote from the alkene double bonds does not have an adverse influence on the SET processes that occur. Thus, (2 + 2)-cyclization of this type described for **117**, for example, is also seen with the dialkenyl ether



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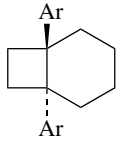
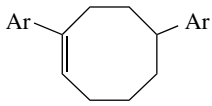
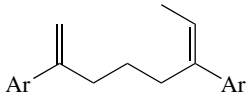


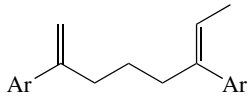
(111)



(112)

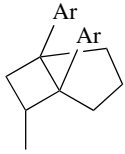
Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$

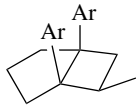




(113) **(a)** Ar = 4-$MeOC_6H_4$
(b) Ar = C_6H_5

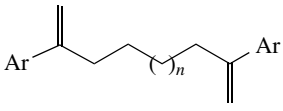
(114)

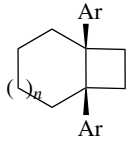


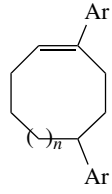


(115) **(116)**

			exo:*endo* ratio
$E_{\mathbf{113a}}$	65%	0%	0
$E_{\mathbf{113b}}$	70%	0%	0
$Z_{\mathbf{113a}}$	27%	45%	1:1.7
$Z_{\mathbf{113b}}$	32%	34%	1:1.7



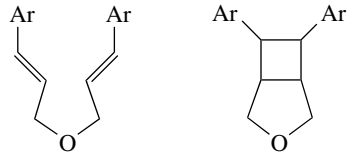




(117) **(118)** **(119)**

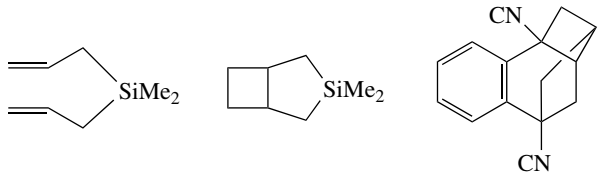
n = 1 or 2
(a) Ar = 4-$MeOC_6H_4$
(b) Ar = C_6H_5

		Yield (%)	Solvent
n = 1 **a**	0	86	MeCN
a	65	31	C_6H_6
b	58	24	MeCN
n = 1 **a**	0	9	MeCN
b	10	21	MeCN



(120) **(121)**

Ar = 4-$MeOC_6H_4$



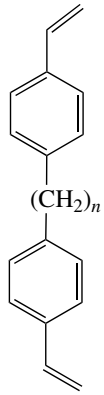
(122) **(123)** **(124)**

120. When this is irradiated using $\lambda > 350$ nm or $\lambda > 450$ nm in acetonitrile solution with tetracyanoethene as the electron-accepting sensitizer, the product **121** is obtained. Again a radical cation cyclization is proposed to account for this[87]. The diene **122** also undergoes cyclization in benzene solution with 1,4-dicyanonaphthalene (DCN) as the electron-transfer sensitizer to afford the cyclobutane **123** in 78% yield. Benzene, or an arene solvent, is vital for the success of the reaction. When acetonitrile is used, allylation of the sensitizer [akin to the photo-NOCAS (nucleophile-olefin combination aromatic substitution) reaction] results in the formation of products such as the cyclobutane **124**[88].

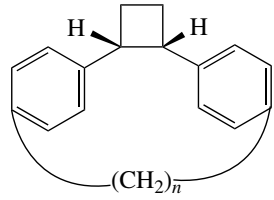
F. Cyclophanes

The synthesis of cyclophanes provides a fascinating path to a series of substituted cyclobutanes. This approach to the so-called phanes has been pioneered by Inokuma and Nishimura[89] and makes use of the dimerization of vinyl substituted arenes with the arenes linked by chains of varying length. Nishimura and coworkers[90] have also published an up-to-date review. The vinyl groups attached to the arenes can be placed *ortho, meta* or *para* to the linker, thus providing a remarkable number of these derivatives. The majority of results have been obtained with *para* substitution and it is this arrangement that is described first.

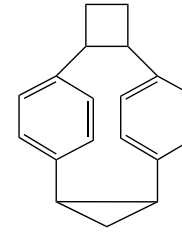
One of the earliest examples of this is the selective conversion of the arylalkenes **125** into the adducts **126**. The yield of products is dependent to some extent on the chain length separating the aryl groups and the best yield of 41% is obtained when the separation includes four methylene units (**125**, $n = 4$)[91]. Other more constrained systems have been synthesized by chemical modification of **126**, $n = 3$. This yielded the derivative **127** as a mixture of *exo*- and *endo*-isomers[92]. Heteroatom-substituted cyclophanes **128** can be obtained by irradiation of the divinyl compounds **129**[93,94]. The use of tin and germanium derivatives has also been examined[92]. A natural extension of the study has been the development of synthetic approaches to crown-ether based systems (**130**) that can be formed in high yield (up to 90%) by the irradiation using $\lambda > 280$ nm of the derivatives **131**[95,96].



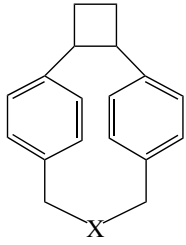
(125) $n = 3$, 4, 5 or 6



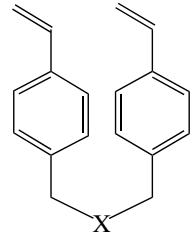
(126)



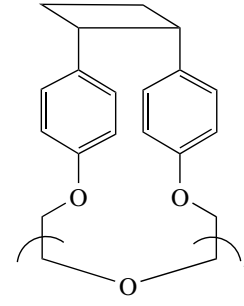
(127)



(128)

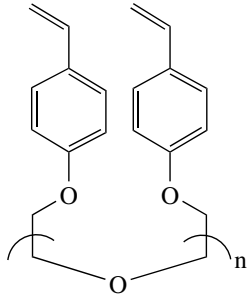


(129)

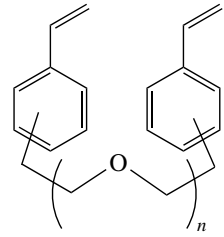


(130)

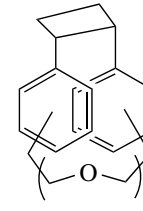
X = S, Se or $SiMe_2$



(131)



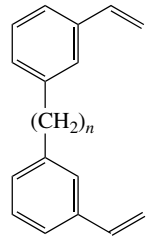
(132)



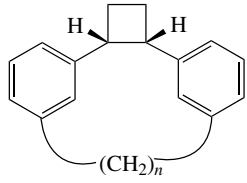
(133)

$n = 1$ *para*-attachment	85%
$n = 1$ *meta*-attachment	40%
$n = 2$ *para*-attachment	63%
$n = 2$ *meta*-attachment	26% *cis*, 6% *trans*

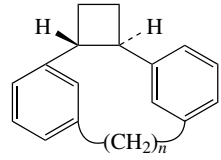
Similar intramolecular cycloadditions are encountered where an ether linkage has been incorporated into the *meta* or *para* linking groups as in **132**. In these cyclizations the better yields were obtained from the *para*-attached systems. The yields obtained are again dependent on the chain length of the separator and are indicated below the appropriate structures (**133**)[97]. Mixtures of products are formed when the *m*-isomers **134** are used and cyclization affords **135** and **136**[98,99].



(134)
$n = 2, 3, 4, 5$ or 6

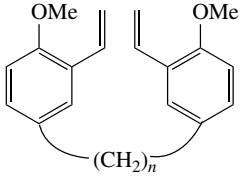


(135)

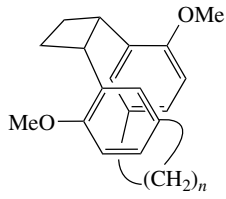


(136)

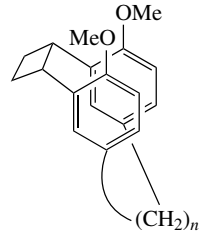
Additional substitution on the aryl rings is not detrimental to the cyclization as can be seen from the irradiation of **137** that affords the *m*-cyclophanes **138** and **139**[100]. Further study has sought to evaluate the steric effect of *o*-methoxy groups in such molecules[101]. Further examples of compounds of this type with substitution adjacent to the vinyl moieties have been synthesized by cyclization of **140**[102]. Other cyclophanes with two cyclobutane moieties have also been isolated following the irradiation of the derivative **141**. In this instance, however, the yields are not good and the three isomers **142**, **143**, and **144** are obtained only in a total yield of 20%[103].



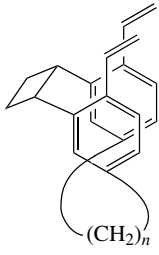
(137)



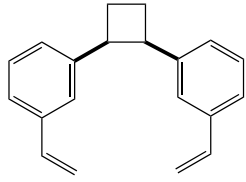
(138)
$n = 2$–6



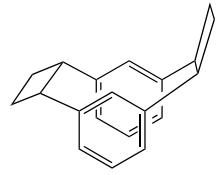
(139)



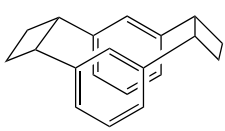
(140)



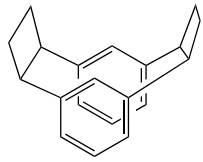
(141)



(142)

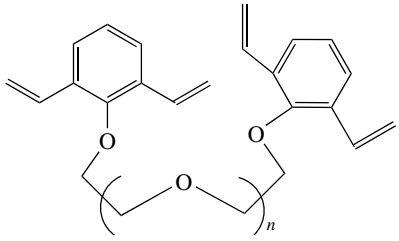


(143)

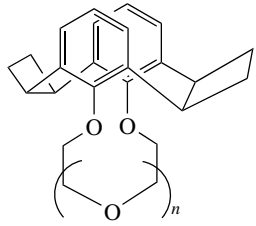


(144)

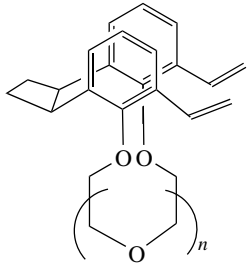
Irradiations of the vinyl arenes **145** are carried out through Pyrex and yields are best when cyclohexane is used as the solvent. The yield of adducts **146** formed by the double (2 + 2)-cycloaddition and thus with two cyclobutane moieties is excellent. These products are accompanied by small amounts of the mono cycloaddition product **147** formed by a single (2 + 2)-cycloaddition process[104].



(145)
$n = 2$
$n = 3$

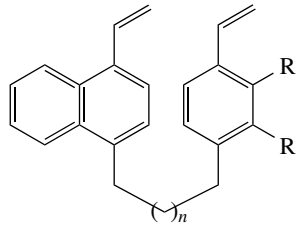


(146)
$n = 2$ 84%
$n = 3$ 92%



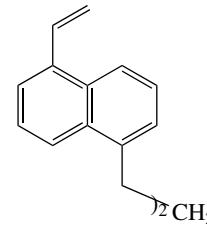
(147)
$n = 2$ or 3 6%

Naphthalenophane analogues can also be obtained in moderate yield by the photochemical cyclization of the corresponding alkenes **148** and **149**[105]. The vinyl groups of the styryl systems need not be unsubstituted, as has been illustrated for the cyclizations encountered in the synthesis of naphthalenophanes from **150**[106]. More complex naphthalene-based cyclophanes can be obtained from **151**. These undergo cyclization on irradiation through Pyrex in benzene solution. The yields of the naphthalenophanes **152a** and **152b** are 45% and 47%, respectively. Shortening the methylene chain separating the two units from four to three results in failure of the cycloaddition reaction[107].

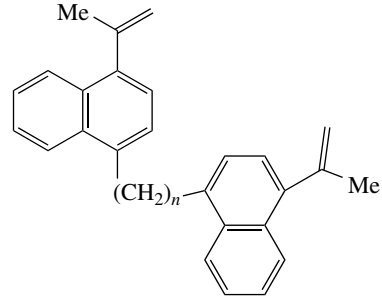


(148)

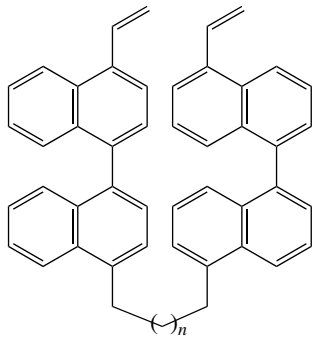
(a) $n = 1$, R = H
(b) $n = 1$, 2, or 3
RR = $(CH{=}CH)_2$



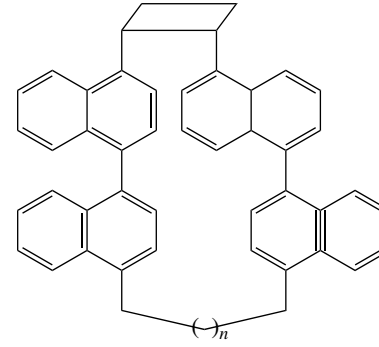
(149)



(150)
$n = 3$ or 4

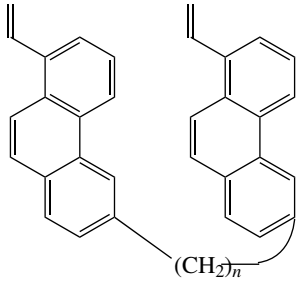


(151) **(a)** $n = 4$
(b) $n = 5$

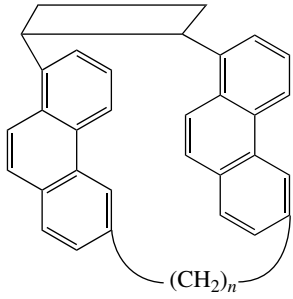


(152) **(a)** 45%
(b) 47%

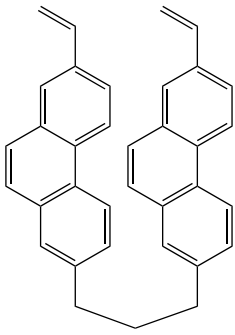
Phenanthrene-based cyclophanes can also be prepared in moderate yields by the intramolecular photocycloaddition of the vinylphenanthrene derivatives **153**. The *syn*-cyclophanes **154** are formed exclusively[108]. Other derivatives with different points of attachment of the linker are also obtained on irradiation of the 1,3-diphenanthrylpropane



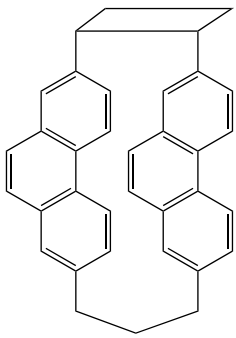
(153)



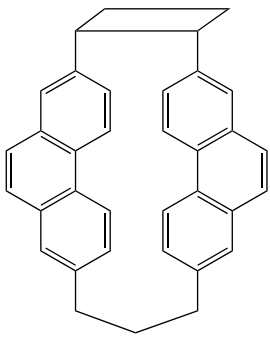
(154)
$n = 3$ 49%
$n = 4$ 38%



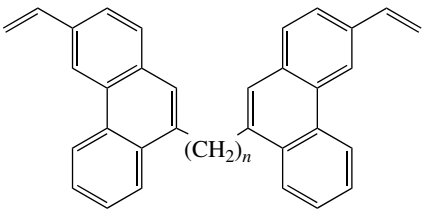
(155)



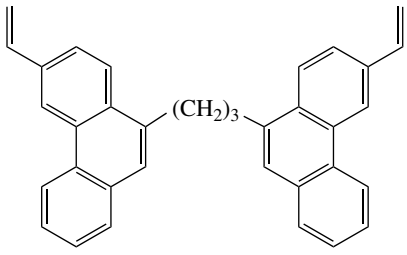
(156)



(157)

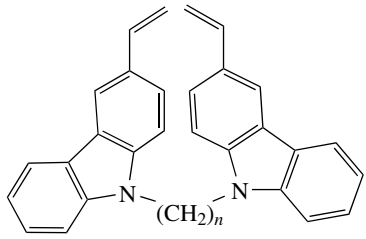


(158)
$n = 3$ or 4

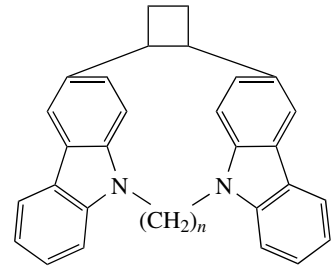


(159)

155 in benzene solution through a Pyrex filter. This treatment gives a 40% yield of a mixture of the two phenanthrenophanes *syn*-**156** and *anti*-**157** in a ratio of 1:1.3. No interconversion of these compounds takes place at ambient temperatures[109]. Linking via the 9 positions of the phenanthrene moieties and the vinyl groups on C3 occurs on irradiation of the phenanthrene derivative **158**. Two isomeric adducts are obtained from this process[110]. Two adducts are also formed in a total yield of 40% from phenanthrene **159**, with the vinyls on C6, on irradiation through Pyrex in benzene solution[111].

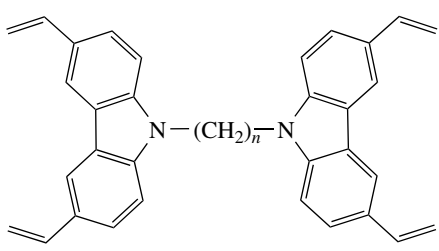


(160)
$n = 4$ or 5

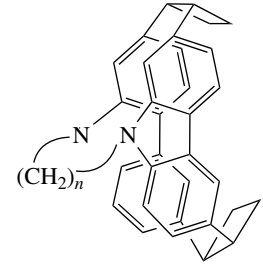


(161)

Irradiation of the vinyl carbazolylalkanes **160** brings about the formation of the carbazolophanes **161**. The cycloaddition is chain-length dependent and when the linking chain has less than four methylene units the reaction fails. This presumably is due to failure of close approach of the vinyl groups[112]. A further example has demonstrated that irradiation of **162** through Pyrex in toluene solution affords a mixture of cycloadducts such as the *endo,endo*-adduct **163**. This is formed in addition to the corresponding *exo,endo*- and *exo,exo*-adducts. These products are formed in a ratio of 9:3:1. Single addition is also reported[113].



(162)



(163)

IV. CYCLOADDITIONS OF ENONES AND RELATED COMPOUNDS

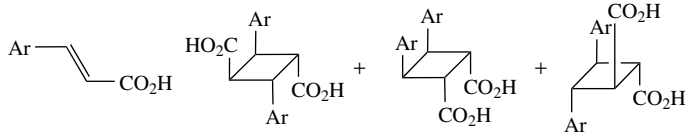
One of the largest sources of cyclobutane derivatives is the (2 + 2)-photoaddition reactions of enones and related compounds. These reactions are many and varied and can be either intra- or intermolecular. Since the literature contains many thousands of references dealing with these reactions, only a few will be illustrated to show the potential of the method.

A. Cinnamic Acid and its Derivatives

Cinnamic acid, including its derivatives, has provided a fruitful area for the synthesis of cyclobutane derivatives. The dimerization was observed nearly a century ago[114, 115] and since then there has been exploitation of this remarkable dimerization especially in the solid state. Bassani[116], in a recent review, pointed out that cinnamic acid dimerization is extremely versatile and is used in a number of industrial applications, ranging from cosmetics to polymers for photoresists and lithography. He also has drawn attention to

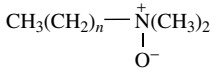
the presence of hydroxycinnamic acids in natural materials and that dimers have been isolated from plants.

The dimerization, in principle, can yield eleven different products arising from either head-to-head dimerization yielding the truxinates (six forms) or head-to-tail dimerization giving the truxillates (five forms). Dimerization in solution has not been studied in as much depth as dimerization in the solid state and most of the recent studies have examined the control that environment places on the dimerization process. The irradiation of monolayers of 4-octadecyloxy-*E*-cinnamic acid on a water surface has been studied. The cycloaddition reactions that occur reflect the packing within the monolayers. The cinnamic acid derivative yields β-truxinic acids[117]. The dimerization of cinnamic acid derivatives in micelles and vesicles has been studied. The dimerization to yield head-to-head dimers is more efficient in vesicles than in micelles[118]. Cinnamic acid has been irradiated in a bilayer with the surfactant *N*,*N*-dimethyl-*N*,*N*-dioctadecylammonium bromide. Films of this mixture were cast and irradiated at $\lambda > 280$ nm. This resulted in the formation of the *cis*-cinnamic acid, the *syn* head-to-head dimer (ω-truxinate) as the major product and a trace of the *syn*-head-to-tail dimer (*peri*-truxillate). Heating the cast film followed by irradiation brings about a decrease in the amount of the *syn* head-to-head dimer, previously the major product. This change is thought to be the result of change of molecular order within the film. The authors[119] reason that the formation of the major product arises from the fact that hydrogen bonding within the film holds the cinnamic acid units parallel to each other. A further example of control exercised by surfactants is the report[120] of the dimerization of the cinnamic acid derivatives (**164**) in the presence of surfactant vesicle *N*-oxides (**165**) in water. The dimerization affords β- and δ-truxinic and γ-truxillic acids. The yields of adducts obtained are reasonable with a preponderance of the truxillic acid type. These results are illustrated in Scheme 4. The yields of cyclodimers decrease with decreasing molar ratio of the acid to the surfactant.



(164)

Ar = Ph or *p*-$MeOC_6H_4$



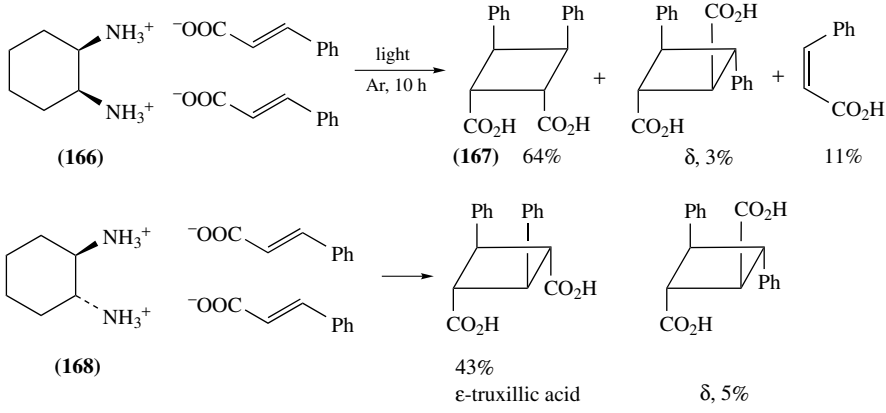
(165)

n in **165**	Yield (%) for Ar = Ph		
12	5	12	25
14	5	16	38
16	6	17	31

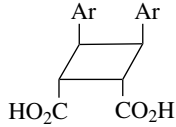
SCHEME 4

A further mode of control is the use of templates to hold the cinnamate moieties in a constrained environment. Scheffer and his coworkers[121] have examined the use of diamine salts of the acid as a means of directing the photodimerization in the solid state. Typical

examples of the success of the process are shown in Scheme 5 where the *cis*-amine salt (**166**) affords predominantly the β-truxinic dimer (**167**). This is accompanied by a low yield of the δ-acid. When the *trans*-amine salt (**168**) is used as the template, the ε-truxillic acid is the predominant dimer formed. The photochemical dimerization of other double salts (this time using ethylenediamine as the template) of variously substituted *trans*-cinnamic acids has also been studied[122]. This process affords the truxinic acids (**169**) in yields that appear to be dependent upon the aryl group.

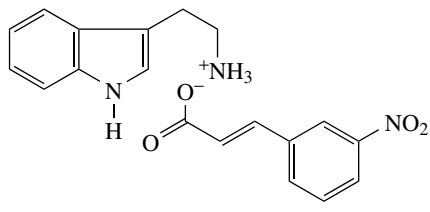


SCHEME 5

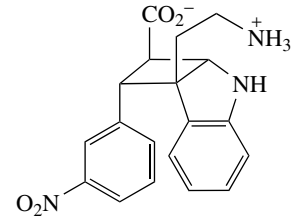


(169)

Ar	Yield(%)
o-$MeOC_6H_4$	30
o-ClC_6H_4	84
m-$O_2NC_6H_4$	70
2-thienyl	13

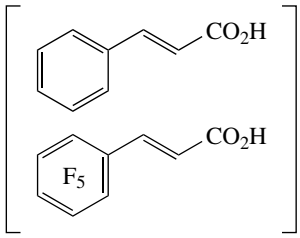


(170)

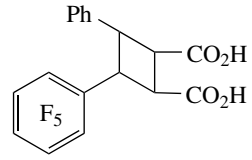


(171)

The crystalline salt **170** was irradiated through Pyrex under an atmosphere of argon. This brings about specific (2 + 2)-cycloaddition to afford **171** in 83% yield[123]. Others[124] have demonstrated the dimerization of cinnamic acid in mixed crystals composed of cinnamic acid and the pentafluoro derivative **172**. The orientation within the crystal is such that the phenyl group interacts with the pentafluorophenyl group, thus ensuring the orientation within the crystal. Irradiation for several hours affords an 87% yield of the ξ-truxinic acid **173**. Dimerization of cinnamates in the crystalline phase where hydrogen



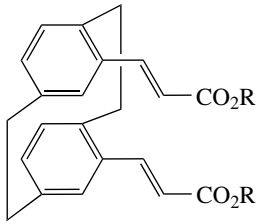
(172)



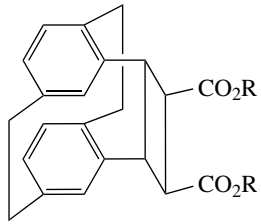
(173)

bonded systems are involved affords cyclobutanes with the α-truxillate structure[125]. A molecular dynamic study of the dimerization of 3- and 4-cyanocinnamic acids in a microcrystalline environment has been carried out[126]. The solid-state dimerization of 4-methylcinnamic acid can be brought about photochemically and the mechanism of this process has been studied using Raman spectroscopy, giving results that suggest topochemical control[127]. The (2 + 2)-photodimerization of cinnamic acid and some of its derivatives has been studied using Raman spectroscopy[128]. Photodimerization of a series of phenyl-substituted cinnamates has also been examined[129].

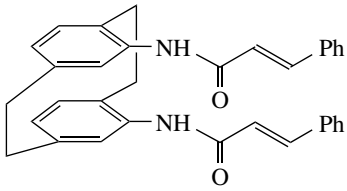
An interesting solution-phase cycloaddition reaction has made use of the cyclophane derivative **174**. Here, the two cinnamate chromophores are held in close proximity. Irradiation in methanol brings about photodimerization quantitatively to afford the β-truxinate dimer **175** with a quantum yield of 0.55[130–132]. The related cyclophane moiety shown in the derivative **176** has been suggested as a useful reaction control system. The irradiation of this cinnamate derivative affords the β-truxinic acid derivative **177** that can be uncoupled from the paracyclophane[133].



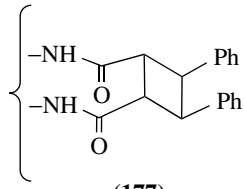
(174)
R = Me or Et



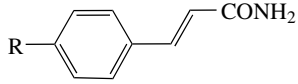
(175)



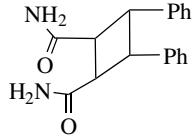
(176)



(177)



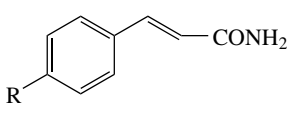
(178)
R = Me, H or Cl



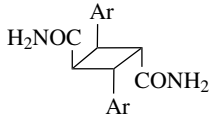
(179)

Usually, the efficient dimerization of cinnamamides occurs in the crystalline phase. An example of this is the dimerization of the *trans*-cinnamamides **178,** R = H, that results in (2 + 2)-photodimerization without destruction of the crystalline form[134]. A study of the crystals formed from phthalic acid/*trans*-cinnamamide (1:2) has shown that the double bonds lie in a criss-cross fashion. However, irradiation does afford adduct **179**, the formation of which suggests that a conformational change occurs within the crystal during the irradiation[135]. The cinnamamides **180** also undergo (2 + 2)-cycloaddition to afford the dimers **181** and **182** and the *Z*-cinnamamide. The yields vary, however, and cinnamamide **180a** itself gives only 18% of the dimer. Control over the dimerization of these cinnamamides (**180**) can be exercised using hydrogen bonding within co-crystals prepared using a variety of diacids, such as **183**. Some of these results are shown in Scheme 6[136].

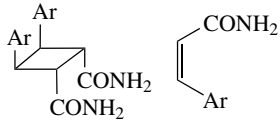
Cycloaddition between the ethylenic double bonds sometimes does not occur in the crystalline phase. An example of this occurs with the dopamide derivative **184**, where the molecules line up as shown. Irradiation of these crystals yields the (2 + 2)-cycloaddition product **185**, where addition of a cinnamamide double bond has taken place to a double bond of a benzene ring in another[137].



(180) **(a)** R = H
(b) R = Me
(c) R = Cl



(181)



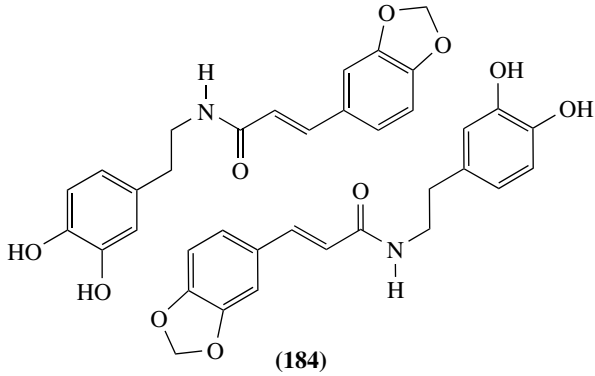
(182)

	Yield(%)		
180a/183a	6	42	8
180a/183b	44	4	2
180a/183c	3	37	5
180a	18	-	-
180b	100	-	-
180c	100	-	-

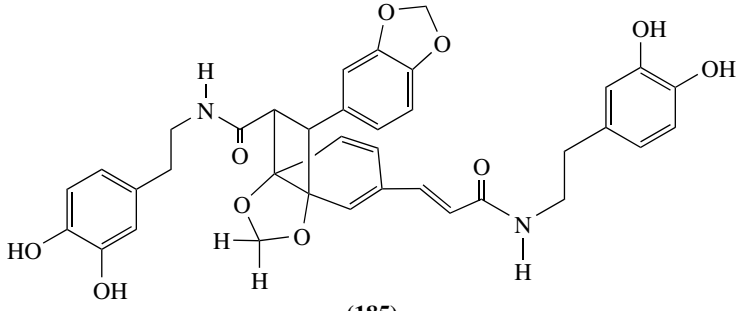
$HO_2C(CH_2)_nCO_2H$

(183) **(a)** $n = 0$
(b) $n = 2$
(c) $n = 3$

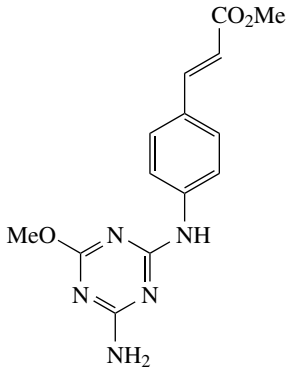
SCHEME 6



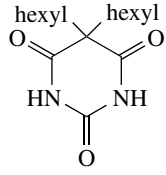
(184)



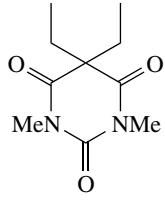
(185)



(186)

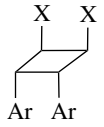
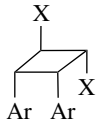
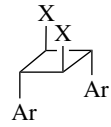


(187)



(188)

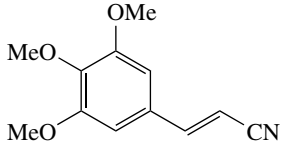
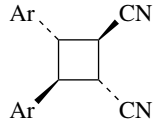
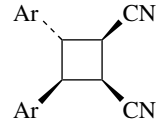
Unlike cinnamic acid, cinnamate esters are often reluctant to dimerize. However, a study was conducted of the dimerization of derivatized cinnamates **186** as an intermolecular complex with **187** or **188**. The complex places the double bonds of cinnamates in close proximity. Irradiation of **186** affords three cyclobutane derivatives [β-truxinate (**189**), neo-truxinate (**190**) and ε-truxillate (**191**)] with the quantum efficiencies shown. The results demonstrate that the dimerization and probably the complex formation is poorer with **187** than with **188**[138].

X = CO_2Me

(189) **(190)** **(191)**

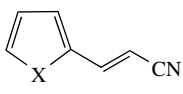
With 0.5 mol of **187**	0.7×10^{-3}	0.1×10^{-3}	$<0.1 \times 10^{-3}$
With 0.5 mol of **188**	2.3×10^{-3}	0.6×10^{-3}	0.8×10^{-3}

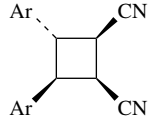
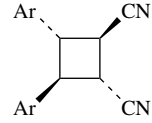
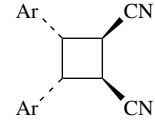
(192) **(193)** **(194)**

Ar = 3, 4, 5-$(MeO)_3C_6H_2$

Cinnamonitriles such as **192** also undergo dimerization that yields the two cyclobutane adducts μ-truxinate (**193**) and ξ-truxinate (**194**)[139]. D'Auria and Racioppi[140] have reported that the arylacrylonitriles **195** undergo facile (2 + 2)-cycloaddition when subjected to benzophenone-sensitized irradiation in acetonitrile solution. The products obtained from this treatment and their yields are shown under the appropriate structures in Scheme 7. Again a mixture of addition types is encountered in line with results obtained from the cycloaddition reactions with the cinnamic acids.



(195)

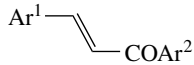
X = O	25%	38%	18%
X = S	34%	31%	24%

Ar = 2-furanyl or 2-thienyl

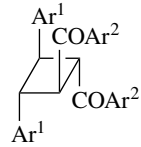
SCHEME 7

B. Chalcones and Related Systems

Chalcones such as **196** undergo photodimerization when they are irradiated in the molten state. Heating the crystalline material to 60 °C and irradiating the melt with light from a 400-watt mercury vapour lamp for 24 h results in exclusive formation of the racemic *anti*-head-to-head dimers **197**[141]. Asokan and his coworkers[142] have described a method whereby topochemical control can be exercised on the (2 + 2)-photocycloaddition reactions of cinnamoyl groups. This involves the synthesis of the alkenoylketene thioacetals **198**. The irradiation of these in benzene solution with Pyrex-filtered light brings about the formation of the cycloadducts **199**. The yields of these are moderate, as can be seen from the details below the structures. The stereochemistry of the additions was



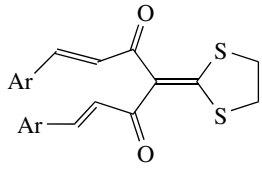
(196)



(197)

$Ar^1 = Ar^2 = Ph$

$Ar^1 = Ph$, $Ar^2 = p\text{-}MeC_6H_4$



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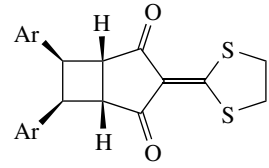
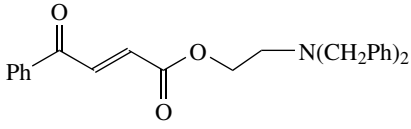


(199)

Ar	Yield (%)
Ph	50
p-$MeOC_6H_4$	55
p-$ClOC_6H_4$	57
m-$MeOC_6H_4$	62
o-$MeOC_6H_4$	55
3,4-$(MeO)_2C_6H_3$	70
Thienyl	40



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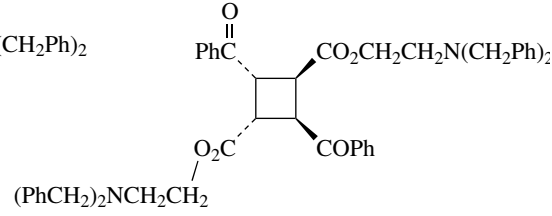
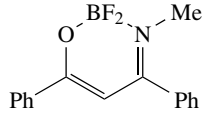


(201)

verified by X-ray crystallography. Hasegawa and coworkers[143] have reported the highly efficient dimerization of the enone **200**. This is irradiated for one hour in the crystalline phase through Pyrex and is converted quantitatively into **201**. Complexes of enaminoketonatoboron difluorides under benzophenone-sensitized conditions afford *syn*-head-to-tail and *anti*-head-to-tail dimers[144]. A specific example of this is the photocycloaddition of the enaminoketonatoboron difluoride **202** to cyclopentene that affords adduct **203**[145]. A comparison of the rate of addition of acetylacetonatoboron difluoride and acetylacetonatoboron oxalate to alkenes has shown that the oxalate addition is slightly faster[146]. A further report of the photocycloaddition of vinylogous imides has demonstrated that **204**



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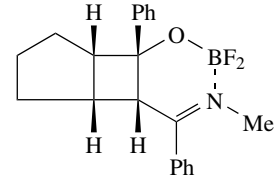

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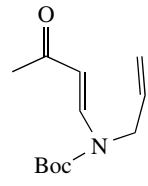

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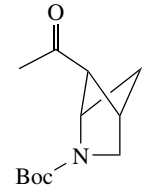
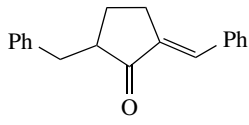


(205)

undergoes cycloaddition to yield **205** (87%) when irradiated in acetonitrile using a Pyrex filter. The rearrangement of this product provides a path to the hetisine alkaloids[147].

The photodimerization of the enone **206** has been reported. The work examined the photochemistry involving single crystal–single crystal processes. The dimer formed from this was identified as **207**[148]. Kinetic data has been obtained for the photochemical dimerization of the cyclopentanone derivative **206**[149] and further work has shown that the dimerization reaction is first order. Apparently, there is molecular movement within the crystal and migration of one enone molecule towards another prior to dimerization[150].



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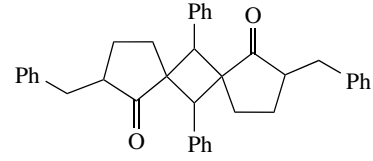
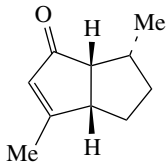


(207)

C. Cyclopentenone Cycloadditions

Additions to cyclopentenones can make use of both acyclic and cyclic alkenes. One such addition is the use of 1,2-dichloroethene as the alkene component and this affords cyclobutane adducts with the stereochemistry established as *cis,anti,cis* and *cis,syn,cis*[151]. The use of the same alkene with the enone **208** affords a mixture of the isomeric products **209** in what was described as 'a good yield'[152]. The cycloaddition affords the correct stereochemical arrangement of ring-fusion for the synthesis of naturally occurring compounds with the 4/5/5 backbone. The isomeric adducts **209** are used as precursors to a synthesis of kelsoene **210**. Photocycloaddition of *Z*- or *E*-1-phenylpropene to the enone **211a** results in the formation of the two adducts **212** and **213** in a ratio of 53:47. The outcome of this addition is different than that for the irradiation of enone **211b** in the presence of the same alkene when only **214** is formed. A detailed mechanistic examination of the reaction has sought to resolve the difference in the observed reactivities[153].



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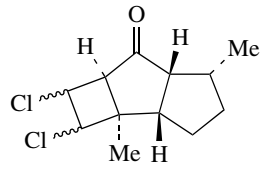

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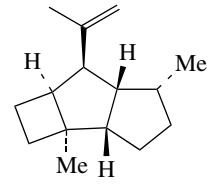

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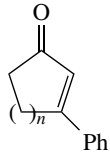

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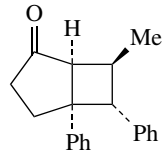

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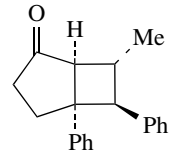

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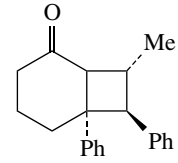
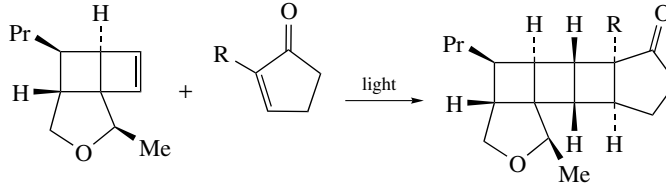


(214)

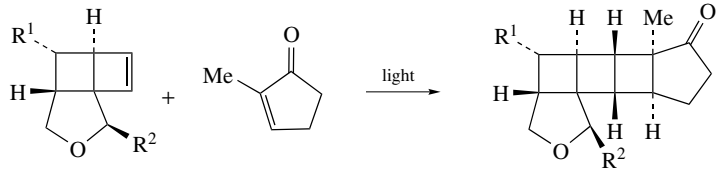
(a) $n = 1$
(b) $n = 2$

Photochemical cycloaddition[154] of cyclopentenone or 2-methylcyclopentenone to substituted cyclobutenes **215** or **216** provides a path to the pentacyclic adducts **217** or **218**, respectively. With cyclopentenone and **215**, two isomers of the product are formed in a total yield of 91%. The major isomer is shown as **217**, R = H. With 2-methylcyclopentenone, only one isomer (**217**, R = Me) is formed in 55% yield. The adducts **218**, formed from **216** and 2-methylcyclopentenone, are thermally labile and ring open readily to afford functionalized 5,8,5 ring systems **219**. Cyclopentenes are common addends for the cyclopentenone cycloaddition. This mode of reaction has been demonstrated many times and one example is the report by Lange and coworkers[155] who synthesized the (2 + 2)-photoadduct **220** by the cycloaddition of methyl cyclopentenone 3-carboxylate to cyclopentene. The photoaddition of the same enone to the alkene **221** gives adduct **222** in 47% yield. The reaction is best carried out at lower temperatures with 0 °C being the one reported. The adduct **222** was converted into the diketone **223**[156].



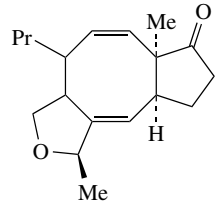
(215) **(217)**

Intramolecular additions also provide many interesting results. Cycloaddition occurs intramolecularly with the derivatives **224** that give **225** in moderate to good yields[157]. Irradiation ($\lambda > 350$ nm in THF) of the enone **226** affords a single diastereoisomer identified as **227** in 95% yield. The outcome of the reaction does not seem to be solvent dependent and the same degree of success is obtained with methylene chloride, acetonitrile



(216) **(218)**

(a) R^1 = Pr, R^2 = Me (a) 84% one isomer
(b) R^1 = CO_2Me, R^2 = HO (b) 58% one isomer



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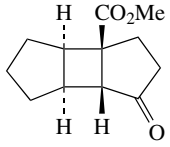
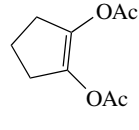


(220)



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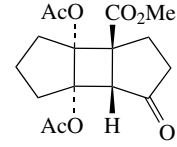

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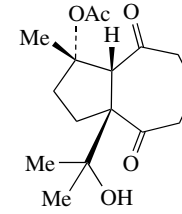

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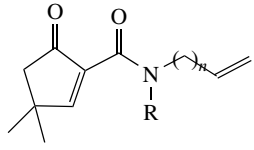
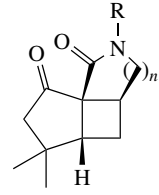


(224)

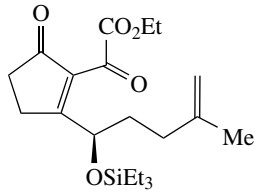


(225)

R	*n*	Yield(%)
Allyl	1	71
Me	1	36
t-Bu	1	50
Me	2	28
Me	3	39

or methanol as solvents. The corresponding amide also cyclizes efficiently[158]. Crimmins and his coworkers[159] have demonstrated that irradiation ($\lambda > 350$ nm) of the enone **228** results in cycloaddition and the formation of the diastereoisomeric adducts **229** and **230** in a ratio of 83:17. A single product **231** is obtained on irradiation of the related enone **232**. These adducts are key intermediates in a synthesis of some spirovetivanes.

Irradiation of the cyclopentenone derivative **233** brings about intramolecular (2 + 2)-cycloaddition with the formation of **234**. Subsequent thermal transformation by cleavage of the lactone system followed by a Cope rearrangement affords an appropriately substituted



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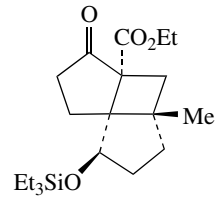

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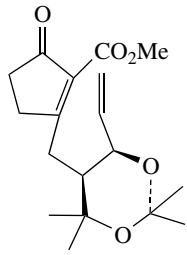

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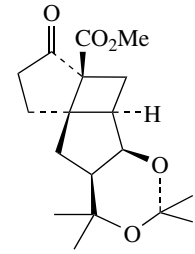

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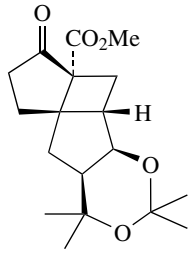

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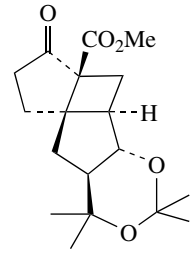

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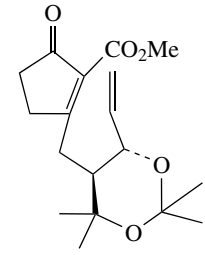

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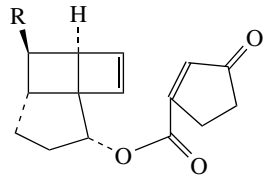

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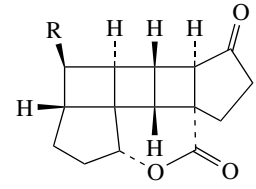
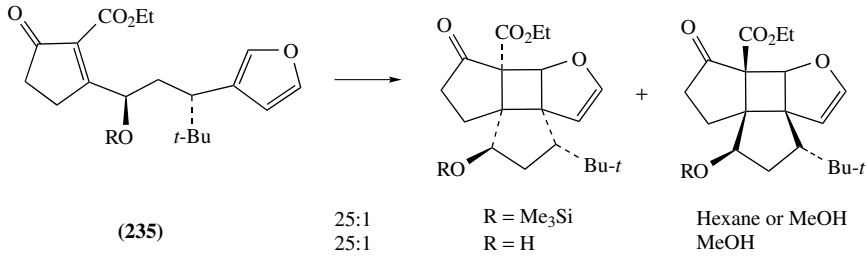


(234)

R = Me or Et

cyclooctadiene derivative[160]. The photochemical intramolecular cycloadditions within the enones **235**–**237** have been used as the synthetic approach to key intermediates in the synthesis of antagonist Ginkolide B. Several examples of this cycloaddition and the

specificity occurring within the reaction were reported. Some of these are illustrated in Scheme 8[161,162]. The foregoing reactions are examples of typical head-to-head additions to an enone. Crossed cycloadditions are also known that afford highly strained cyclobutanes. An example of this comes from a recent study where **238** is formed by intramolecular addition of enone **239**. The reaction occurs with high regioselectivity and **238** is formed in preference to the head-to-head adduct **240** in a ratio of 94:6[163].



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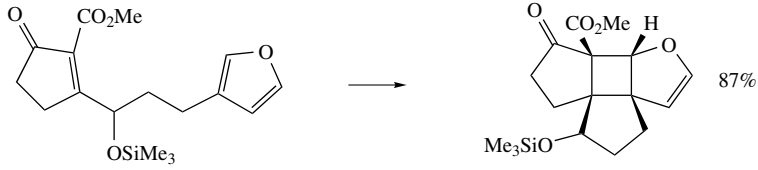
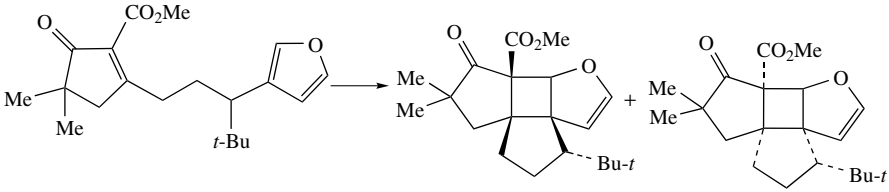
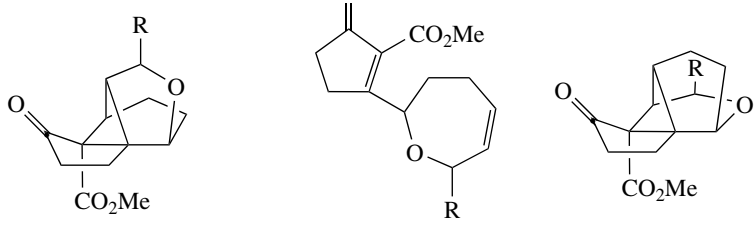


(236)



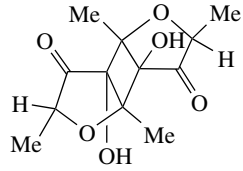
(237)

SCHEME 8



(238) R = H or EtO **(239)** **(240)**

Much interest has been shown over the years in the photochemical addition reactions of 2(5*H*)-furanones that have become useful building blocks for complex systems. This area has been the subject of a review[164]. Like the cyclopentenone compounds, these furanones undergo cycloaddition reactions with the formation of cyclobutanes. This is exemplified by the (2 + 2)-photocycloaddition between 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone and chloroethenes[165]. Dimerization is also an option and the *anti* head-to-head dimer **241** is formed exclusively when crystals of 4-hydroxy-3(2*H*)furanone are irradiated[166]. A series of (2 + 2)-photocycloaddition reactions have been carried out using (5*R*)-5-menthyloxy-2(5*H*)-furanone (**242**) as the substrate to which the additions take place. Photoaddition of cyclopentenone to this substrate gives the four products **243**–**246**. There is some level of regioselectivity but no facial selectivity. Interestingly, cyclohexenone, cycloheptenone and cyclooctenone fail to undergo the mixed addition[167]. Other studies have focused on the photocycloaddition of vinylene carbonate to the homochiral furanones **247**. The cycloadditions give reasonable yields of adducts such as **248** and **249**. More importantly, the diastereoselectivity (*de*) of the processes rises from 40% *de* with **247a** to almost 92% *de* for **247b**[168]. These adducts have been chemically developed as synthetic precursors to some carbohydrate derivatives[169]. Bis-butenolides (**250**) can also undergo addition of ethene as the addend. This particular work was aimed at an attempt to establish the influence of the ether-protecting groups of the diol system. Generally, only two adducts are formed, as can be seen from the results shown below the appropriate structures. The most effective ether-protecting group is the trimethylsilyl function in **250c** and here the facial selectivity yields predominantly the *anti,anti* adduct **251** accompanied by a small



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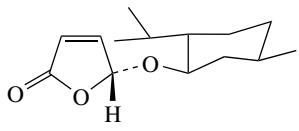

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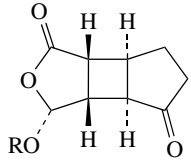

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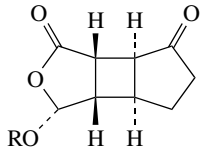

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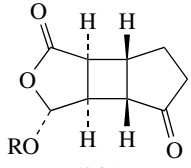

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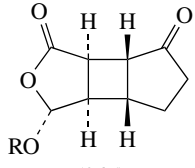

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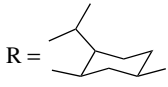

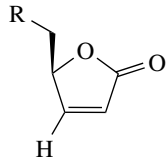

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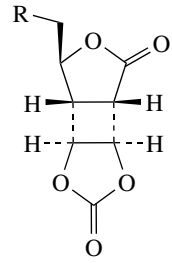
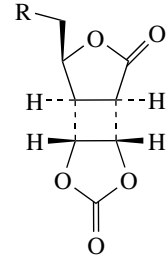
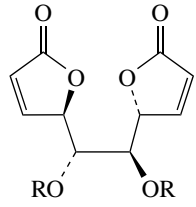


(248)

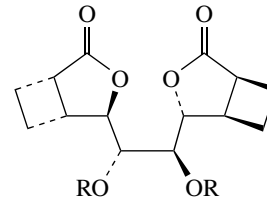


(249)

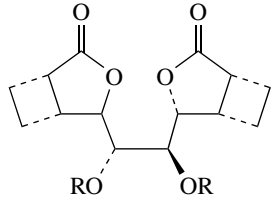
(a) R = H
(b) R = OAc
(c) R = OCOBu-*t*
(d) R = $OSiPh_2Bu$-*t*
(e) R = OCOPh



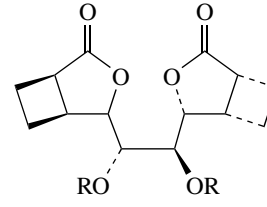
(250)



(251)



(252)

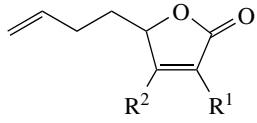


(253)

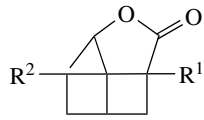
		Yield (%)		
	R	**(251)**	**(252)**	**(253)**
(a)	Et	30	10	–
(b)	$PhCH_2$	5	–	–
(c)	TMS	83	2	–
(d)	H	44	38	8

amount of **252**. With unprotected ethers as in **250d**, R = H, there is virtually no selectivity and in this case three adducts (**251–253**) are formed[170]. A synthesis of (+)-grandisol has been devised utilizing the (2 + 2)-photoaddition of ethene to bis(α,β-butenolide) as the key step[171].

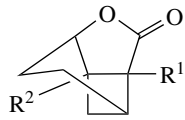
The intramolecular cycloaddition within the butenolides **254** affords the two products **255** and **256**. The products arise by two different cycloaddition modes and the outcome is dependent upon the substitution pattern and on the stability of the intermediate biradicals formed during the addition. Thus, biradical **257** yields **255** while **258** affords **256**. These suggestions have been substantiated by some simple theoretical calculations[172]. Interestingly, the addition encountered with the enone **259** when irradiated through a quartz filter affords adducts **260a** and **260b**. This type of product is similar to **255** formed from **254**. The biradical suggested for the formation of **260** is shown as **261**, different from **257** and **258** discussed above. This intermediate is formed by addition at the β carbon of the enone moiety and affords the more stable biradical[173]. Bach and coworkers[174] have also examined (2 + 2)-intramolecular addition in furanones. Irradiation at 350 nm results in the conversion of **262** into the expected bicyclooctane **263**. Lengthening the side chain changes the regioselectivity of the reaction and both **264a** and **264b** afforded the bicyclononanes **265a** and **265b** in the yields shown. Photoaddition reactions have also been



(254)

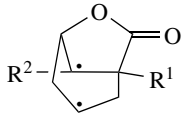


(255)



(256)

R^1	R^2	**255:256**
H	H	3:1
H	Me	7:1
Me	H	1.6:1



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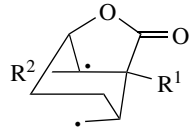

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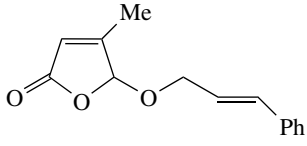

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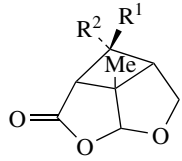
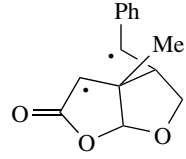


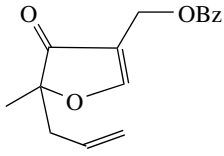
(260)



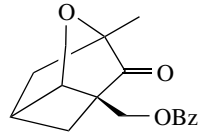
(261)

(a) R^1 = Ph, R^2 = H

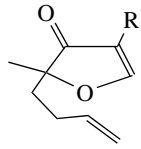
(b) R^1 = H, R^2 = Ph



(262)



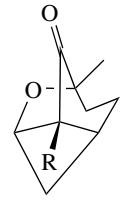
(263) 87%



(264)

(a) R = CH_2OBz

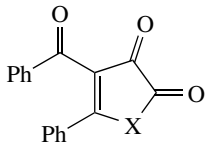
(b) R = H



(265)

(a) 92%

(b) 90%

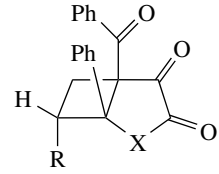


(266)

X = O, S, NH or NMe

(267)

R = OAc, Ph or OEt

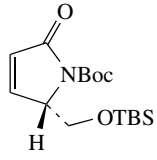


(268)

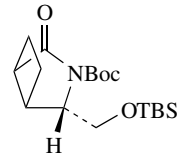
described using **266** as the substrate. (2 + 2)-Photocycloaddition of simple alkenes **267** to the enones results in the formation of the adducts **268**[175].

Lactams such as **269** can also undergo photochemical addition of ethene under acetone-sensitized irradiation at 0 °C. The two products formed were identified as a mixture of the 1*R*,5*S*-adduct **270** and the 1*S*,5*R*-isomer in a ratio of 11:1. Compound **270** was used as a starting material in a synthesis of *L*-2-(2-carboxycyclobutyl)glycine derivatives. Addition also occurs to the bicyclic lactam **271**, where the two products isolated were identified as **272** and **273** in a ratio of 3:1[176]. Intramolecular addition can also take place as demonstrated by the photoreactivity of the diastereoisomeric compounds **274** and **275**. The irradiation of the individual compounds, using perdeuteriated acetone as the sensitizer, results in the conversion into the cycloadducts **276** and **277**, respectively. Direct irradiation of **275**, however, affords a mixture of the two cycloadducts while direct irradiation of **274** affords only the cycloadduct **276**. The authors[177] suggest that fission to yield the radical pair **278** must be involved in the direct irradiation.

The triplet state of maleimide is produced on irradiation in various solvents. In hydrogen-donating solvents, however, the radical **279** is formed. This adds to ground state maleimide to afford a 1,4-biradical that ring closes to yield the dimer **280**[178]. Intramolecular addition



(269)



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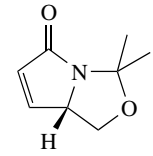

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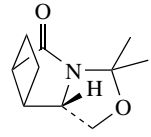
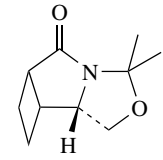


(272)



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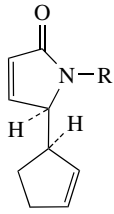

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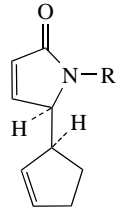
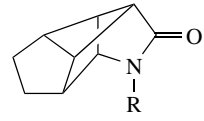


(275)



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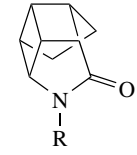
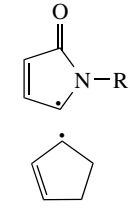
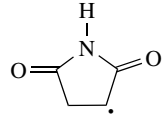


(277)



(278)

R = COOBu-*t*



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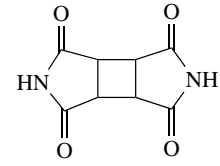

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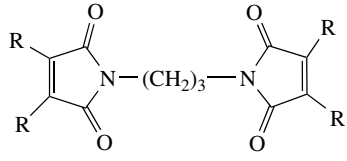
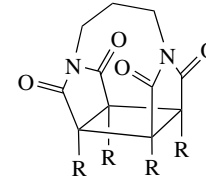


(281)

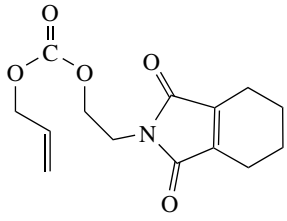
R = Me or RR = $-(CH_2)_4-$



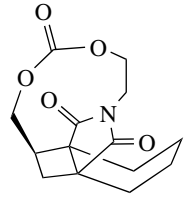
(282)

R = Me, 65%; RR = $-(CH_2)_4-$, 8%

of **281** in acetone/acetonitrile has provided a route to the cyclobutane derivatives **282**. The outcome of the reactions is variable and with **281**, R = Me, the product **282**, R = Me, is obtained in 65% yield while only 8% of **282**, RR = $[CH_2]_4$, is obtained from **281**, RR = $[CH_2]_4$[179]. The tetrahydrophthalimide derivative **283**, on irradiation in acetonitrile solution using Pyrex-filtered light, undergoes cycloaddition and gives reasonable yields of **284**. The silicon-tethered alkenes **285** afford the diastereoisomeric diols **286** and **287** after work-up[180].



(283)



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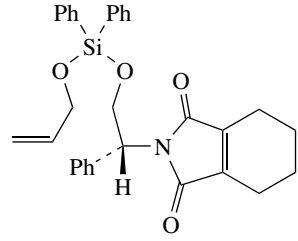

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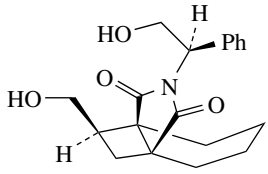

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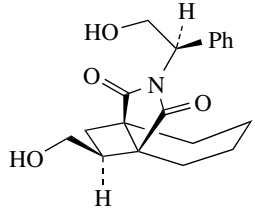
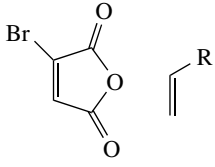


(287)

Anhydrides also provide a substrate that can undergo (2 + 2)-cycloaddition reactions and the formation of a cyclobutane derivative. Thus, the sensitized irradiation (benzophenone in acetonitrile) of the anhydride **288** with a variety of 1-alkenes (**289**) affords the adducts **290**. Chemical treatment readily converts these into the cyclobutenes **291** that can undergo cycloaddition to yield the dimers **292**[181]. The adduct **290**, R = Pr, can be transformed into the bis-anhydride **293**. Irradiation of this affords the two adducts **294** and **295**. These adducts can then undergo thermal ring-opening and further chemical transformation ultimately affords byssochlamic acid (**296**)[182]. The maleic anhydride derivatives (**297**) add photochemically to the anhydrides **298** to afford adducts **299**[183].



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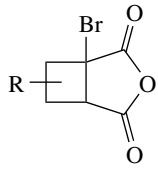

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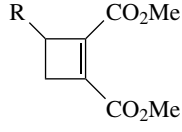

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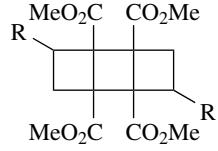
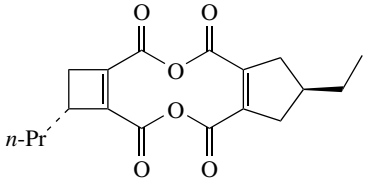


(292)

R = Pr, C_6H_{13}, *i*-Pr, CHMePr, *t*-Bu, CH_2CH_2Br, CH_2OAc, CH_2CH_2OAc, CH_2SiMe_3



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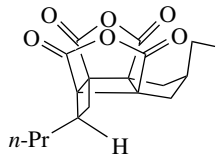

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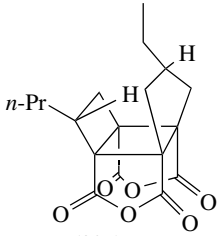

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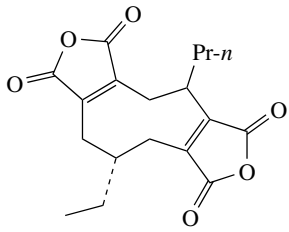

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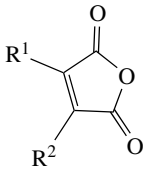

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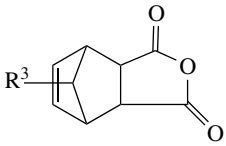

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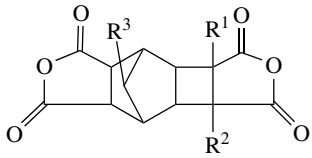
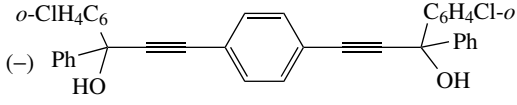


(299)

D. Cyclohexenone Cycloadditions

Madhavan and Pitchumani[184] have reported the dimerization of 2-cyclohexenone confined in clay interlayers (cation-exchanged bentonite). The reaction is remarkably regioselective and affords the head-to-head dimer almost exclusively. Enantioselective (2 + 2)-photodimerization of cyclohexenone has also been described. This used an inclusion complex formed between cyclohexenone and **300**. The head-to-head dimer **301** was obtained with an *ee* of 58%[185]. The dimerization of **302** as an inclusion complex with **303** affords the head-to-head dimer **304**[186]. The thio-analogues **305** of **302** also undergo dimerization. The derivative **305a** yields only the *cis*-head-to-head dimer **306** while **305b** in the crystalline state affords a 4:5 mixture of the dimers **306**, R = CF_3 and **307**[187]. Brett and coworkers[188, 189] have determined the packing of 7-methyl and 7-hydroxycoumarin in β-cyclodextrin. The irradiation of the complexes led to the *anti*-head-to-tail dimers as a result of the way in which the coumarins pack within the complexes. Photodimerization of 4-methyl-7-fluorocoumarin affords the *cis,anti,cis*-head-to-tail dimer while irradiation of 4-methyl-6-fluorocoumarin yields the *cis,syn,cis* head-to-head dimer[190]. Other studies have examined the influence of 6- or 7-fluoro substituents on the dimerization of the 4-substituted coumarins[191]. Photodimerization of isophorone (3,5,5-trimethylcyclohex-2-enone) takes place in solution and the influence of solvent and of the concentration of the enone was examined. Some of the results and the yields of dimers obtained are shown in Scheme 9. From this detailed



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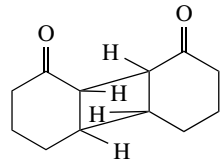

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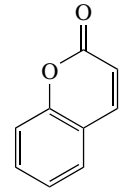

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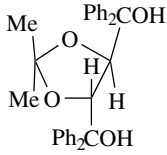

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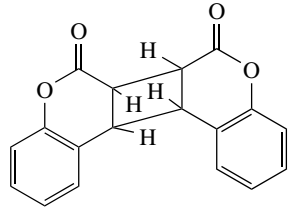

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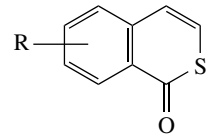
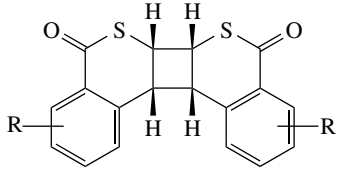


(a) R = 7-Me
(b) R = 5-CF_3

(305)



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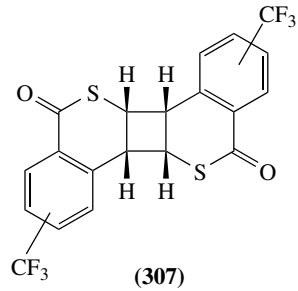

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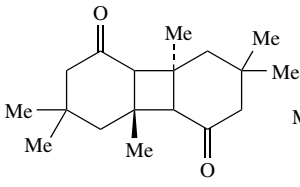
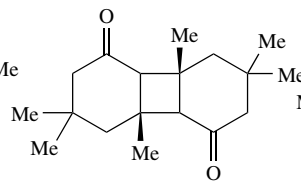
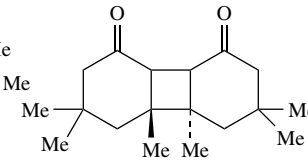




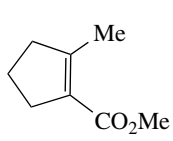


Solvent	[M]	Dimers (%)	Conversion (%)	HH:HT
Cyclohexane	0.1	25	40	30:70
n-Butanol	0.1	70	5	70:30
H_2O	0.02	90	95	95: 5
H_2O	0.06	85	90	90:10
H_2O (under argon)	0..02	100	100	99: 1

SCHEME 9

study the authors[192] suggest that supramolecular structures are involved in the dimerization. These apparently take part even at low concentrations of enone.

By far the most studied cycloaddition path is the addition of alkenes to cyclohexenones and related compounds. The mechanistic aspects of the addition have been reviewed recently[193]. The scope is vast and only a few examples will be supplied here. Thus, the irradiation in methanol solution of 3-methylcyclohexenone in the presence of the ester **308** results in the synthesis in moderate yields of adduct **309**. This product was used as the starting material for an approach to the synthesis of trichodiene[194]. Others have shown that addition of alkenes can take place to 2-acyl-6,6-dimethylcyclohexen-2-ones[195] and also to 2-cyano-6,6-dimethylcyclohexen-2-one to afford cycloadducts[196].



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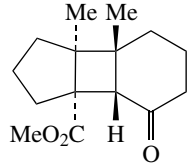
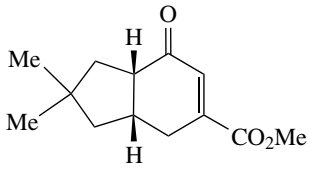


(309)

The efficient photoaddition of *trans*-1,2-dichloroethene to the enone **310** affords adduct **311** in 95% yield. This compound was a key molecule in the development of a new route to the sesquiterpene, sterpurene[197]. Lange and coworkers[198] have investigated photoadditions to the chiral 2,5-cyclohexadienone synthons (**312**). The addition to cyclopentene affords **313** as the major product in the yields shown. Pyrones also are a source of cyclobutanes as demonstrated by Somekawa and coworkers[199–201]. These authors have demonstrated that irradiation of ground-up mixtures of the pyrones **314** and maleimide can be photochemically reactive. However, of the derivatives **314**, only **314b** is reactive and affords the single product identified as **315**. Interestingly, all the simpler derivatives (**316**) are reactive and afford adducts of the type represented by **315**. The reactions are not always as regioselective and on occasion the isomeric adducts **317** are obtained from **316**, R = Me[202, 203]. Dihydropyrones such as quinic acid are also effective substrates for cycloaddition, as demonstrated by the addition of ethene to afford adduct **318**. This was used as precursor to grandisol (**319**)[204]. The cyclic alkene **320** undergoes photochemical addition to unsaturated ester derivatives to afford adducts **321** and **322** in the yields shown[205]. Bach and coworkers[206] have demonstrated the use of enantioselective intermolecular additions mediated by the chiral lactam hosts (**323**) in the synthesis of cyclobutanes. Examples of this are the additions to the quinolone **324** to alkenes **325** at $-60\,^{\circ}C$ in toluene as solvent. These processes gave the (2 + 2)-adducts **326** and **327**. High yields were obtained from the additions with *ee*s in the range of 81–98%.



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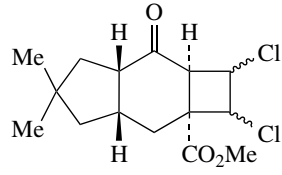

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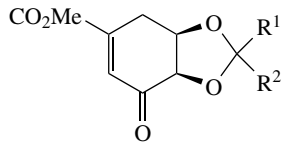
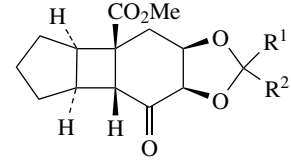


(312)

$R^1R^2 = -(CH_2)_5-$	74%
$R^1 = R^2 = Me$	70%
$R^1 = R^2 = Et$	82%



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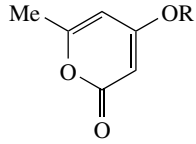
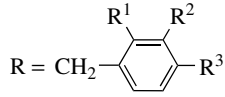
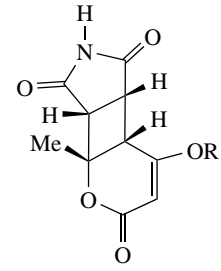


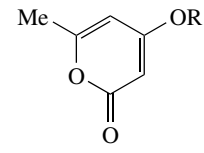


	R^1	R^2	R^3
(a)	Me	H	H
(b)	H	Me	H
(c)	H	H	Cl
(d)	Ph	H	H
(e)	H	H	CH_2Cl

(314)

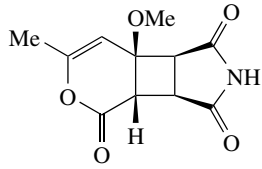


(315) (R = Me)

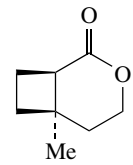


R = Me, $(CH_2)_nPh$, $n = 1, 3$
p-$MeOC_6H_4CH_2$

(316)



(317)



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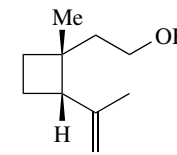
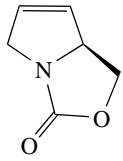


(319)

As mentioned earlier, the mechanistic details of (2 + 2)-cycloadditions of alkenes to enones have been reviewed recently[192]. There is no doubt that there is still interest in the minutiae of the mechanism of cycloaddition. A variety of methods have been used and one has involved the intramolecular cycloaddition of the enone **328**. Apparently both C_α



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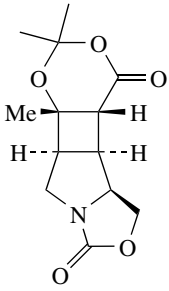
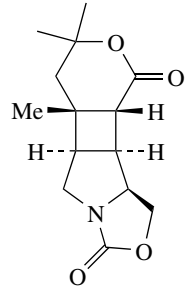


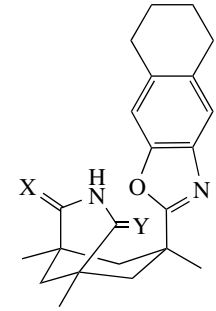
(321)

38%

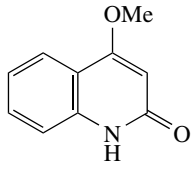


(322)

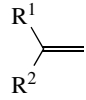
43%



(323) **(a)** X = O, Y = H_2
(b) X = H_2, Y = O



(324)



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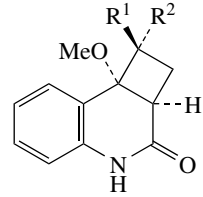
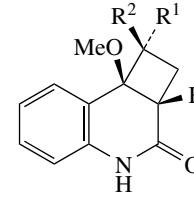
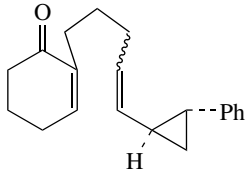


(326)

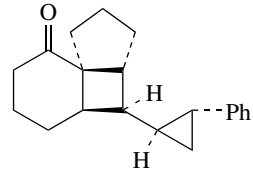


(327)

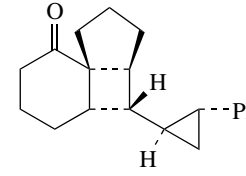
R^1	R^2
H	$CH_2CH_2CH_2OH$
H	CH_2OAc
H	OAc
H	Ph
H	CO_2Me
Et	Et



(328)



(329)

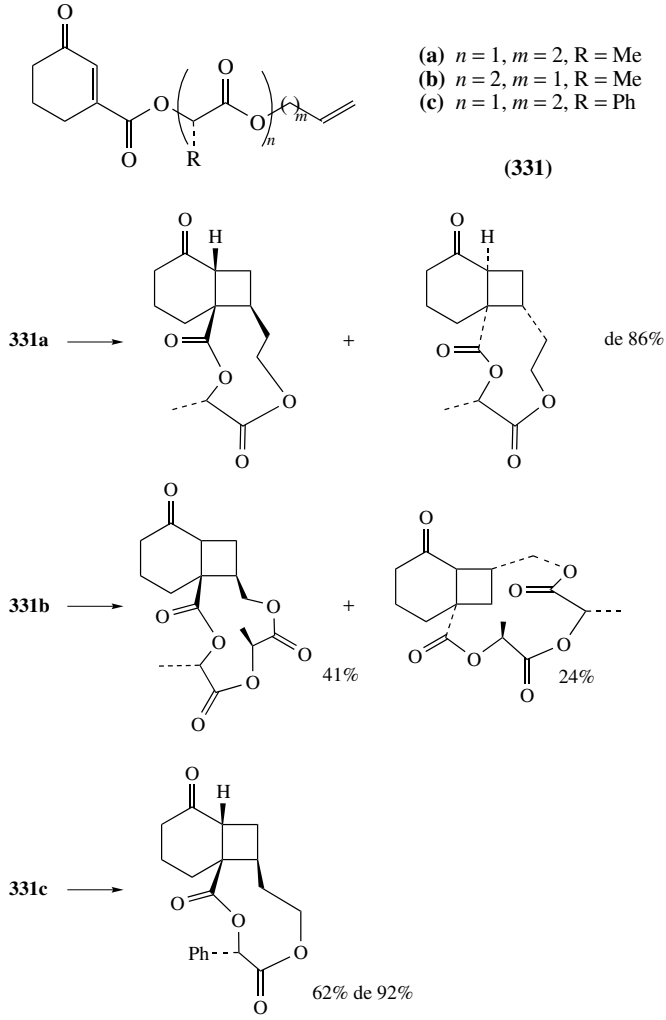


(330)

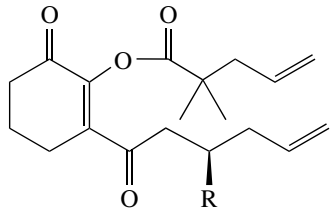
and C_β bond formation can occur as the first step. The principal cycloadducts formed from the reaction are **329** and **330**[207]. Others have also examined the different bonding paths when the enones are confined within zeolites[208, 209].

A detailed investigation of the intramolecular cycloaddition reactions within the enones **331** (only a few of those reported are described here) has been carried out. The derivatives (**331a–c)** all undergo the intramolecular addition with the formation of the products shown

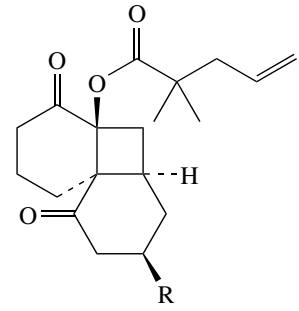
in Scheme 10. The cycloadditions are diastereoselective, as can be seen from the *de* values reported[210]. The same authors have reported earlier on these additions[211–213]. Others have also studied intramolecular additions such as the cycloaddition of **332** to yield adduct **333** in yields of around 58%[214]. In these, the 2-position of the enone is substituted with an acyl group. Further study by the same group of authors[215] has suggested that from the irradiation of (**334a–d**), bond formation can either arise by 2,7 or 1,8 closure. Good yields of products are obtained. It is interesting to note that with the irradiation of **334c** and **334d** only one product is formed in each case. The exclusive formation of the products **335c** and **335d** must arise by a path involving diastereoisomeric transition states. Changes in the substitution pattern close to the alkene moiety have an adverse effect on the yield of product. Thus, the irradiation of **336** yields **335e** but only in 50% yield.



SCHEME 10

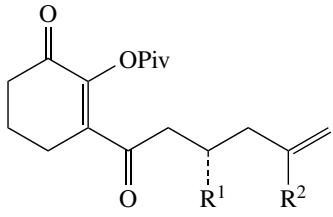


(332)

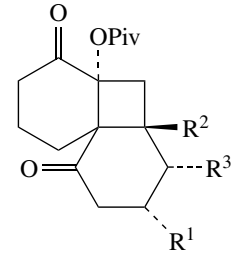


R = H or Me

(333)



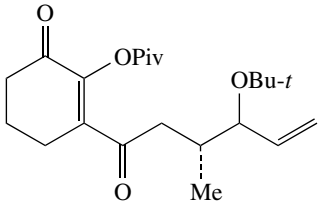
(334)



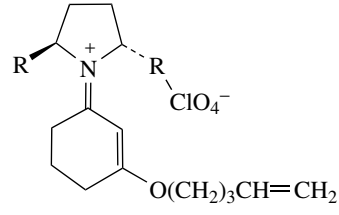
(335)

(a) $R^1 = R^2 = H$
(b) $R^1 = H$, $R^2 = Me$
(c) $R^1 = Me$, $R^2 = H$
(d) $R^1 = OSi\,Ph_2Bu\text{-}t$, $R^2 = H$

(a) 65% $R^1 = R^2 = R^3 = H$
(b) 78% $R^1 = R^3 = H$, $R^2 = Me$
(c) 70% $R^1 = Me$, $R^2 = R^3 = H$
(d) 75% $R^1 = OSi\,Ph_2Bu\text{-}t$, $R^2 = R^3 = H$
(e) 50% $R^1 = Me$, $R^2 = H$, $R^3 = OBu\text{-}t$

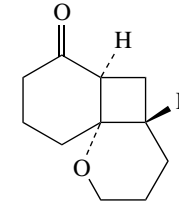


(336)



(337)

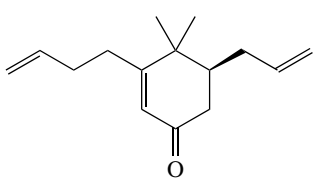
R = $MeOCH_2$ or Me



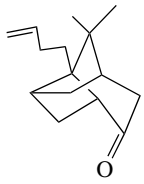
(338)

Mariano and his coworkers[216,217] have demonstrated that the photocyclizations of derivatives of enones, the perchlorate salts **337**, to yield **338** provide a useful strategy for stereochemical control in the formation of the (2 + 2)-cycloadducts. The reactions do show some selectivity dependence on the nature of the R groups in **337**. Thus with R = $MeOCH_2$ a 61% yield of adduct can be obtained with an *ee* of 82%. When R = Me, the yield from the reaction is poorer and the adduct is formed with an *ee* of only 37%.

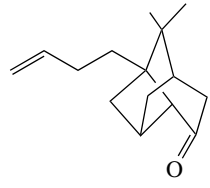
Some highly strained cyclobutanes can also be synthesized by the intramolecular mode. Thus, irradiation of the (+)-enone **339** yields the (+)-adduct **340**, by a 1,5-cyclization mode, and the (−)-adduct **341**, by the 1,6-mode, in 45% and 15% yield, respectively[218]. The unsaturated δ-lactone **342** undergoes intramolecular photochemical (2 + 2)-cycloaddition to afford the product **343**[219] and a further strained cyclobutane is reported by irradiation of **344** that yields adduct **345**[220].



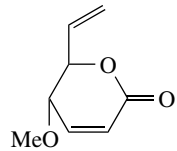
(339)



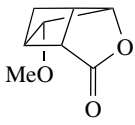
(340)



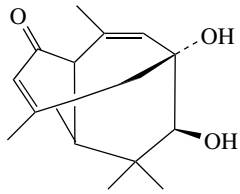
(341)



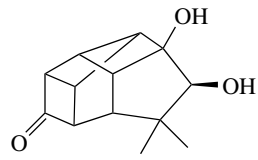
(342)



(343) 42%



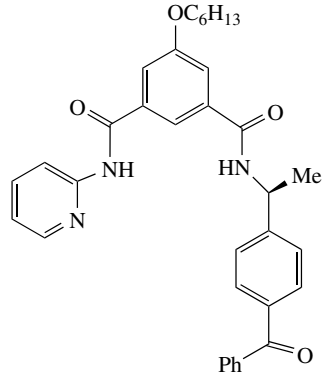
(344)



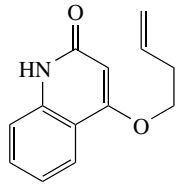
(345)

Examples of intramolecular cycloadditions have been reported that can be carried out enantioselectively in the presence of the complexing agent **346**. This is illustrated for enone **347** that forms the mixture of cyclobutanes **348** and **349** in a total yield of 21%[221]. Others[222] have reported the cyclization of the same prochiral quinolone **347** to yield the diastereoisomeric products **350** and **351** using the chiral substrates **352–354**. The reactions are temperature-dependent with the best enantiomeric excesses being obtained at −60 °C.

The scope of the intramolecular (2 + 2)-photoadditions within the derivatives of dioxenones has been assessed[223,224]. The irradiation at 300 nm of **355** in acetonitrile/acetone (9:1) affords the cycloadduct **356** as a 1:1 mixture of diastereoisomers. This mixture can be converted into compound **357** in two steps in a yield of 52%. Intramolecular photoaddition also occurs on irradiation of enones **358** and **359**[225] and dioxenones **360**[226]. The irradiation of the last of these affords adducts **361** and **362** in the ratios shown. The adducts can be opened by thermal means to provide routes to tetrahydrofuran-3-ones and tetrahydropyran-4-ones. Haddad and coworkers[227] have demonstrated that enone **363** undergoes benzophenone-sensitized cyclization at 0 °C in acetonitrile to give the single adduct **364** in 90% yield after only 35 min irradiation. Recent work in this area has been directed towards the synthesis of naturally



(346)



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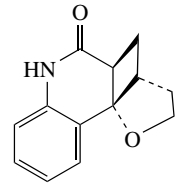

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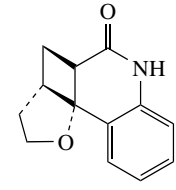

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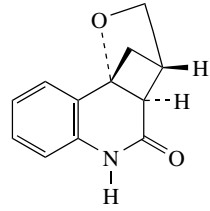

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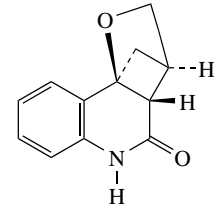

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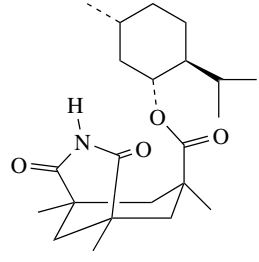
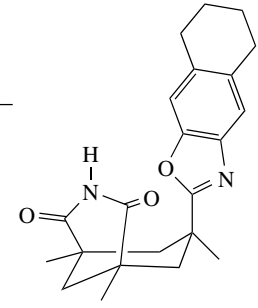
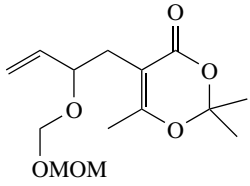


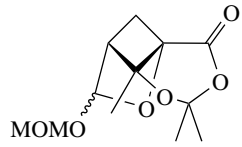
(−)-**(352)**



(−)-**(353)**
(+)-**(354)**



(355)



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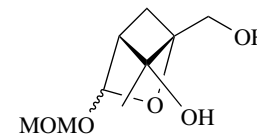

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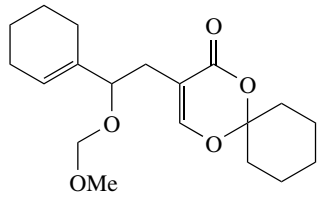

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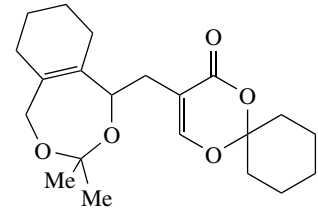

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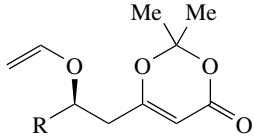
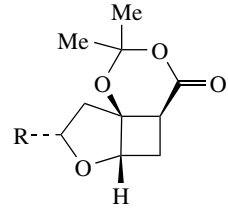
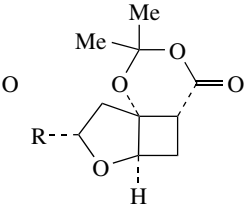


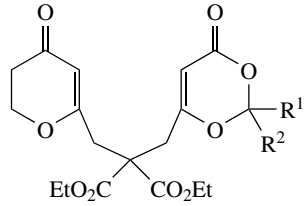
(360) R = Ph
R = $PhCH_2CH_2$



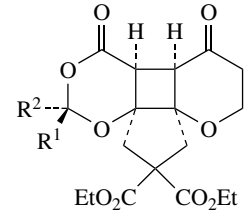
(361) 77:23
73:27



(362)

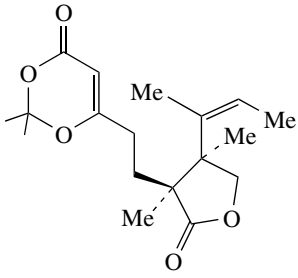


(363) $R^1 = R^2 = Me$



(364)

occurring compounds. Thus, intramolecular cycloaddition within dioxenone **365** affords a diastereoisomeric mixture of **366** and **367** in a ratio of 2.5:1. These compounds are important in an approach to the total synthesis of saudin[228]. Irradiation of dioxenone derivative **368** in acetonitrile/acetone at 0 °C affords the adduct **369** in 60% yield. This compound was a key intermediate in the first total synthesis of racemic ingenol[229]. A further study has shown that the enone **370** also undergoes cycloaddition on irradiation



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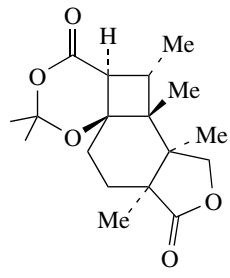

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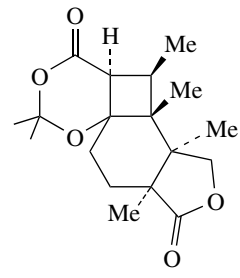
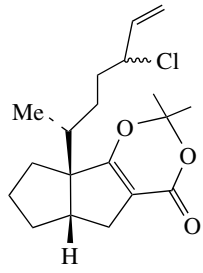


(367)



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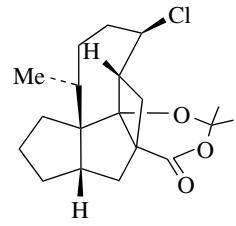

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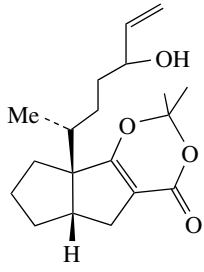

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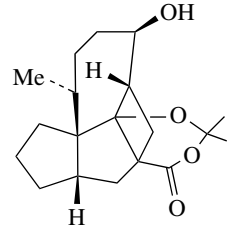
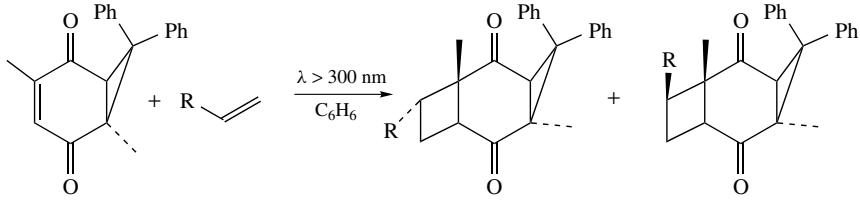


(371) 16%

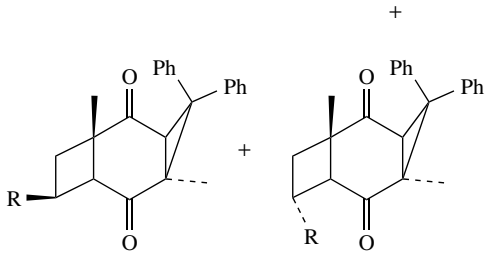
under the same conditions. This process yields adduct **371** similar to **369**. Other products are also formed arising from failure of the intermediate 1,4-biradical to ring close to **371**[230].

Homoquinones have also proved an interesting substrate that undergo (2 + 2)-cycloaddition reactions. Kokubo and Oshima[231] have reviewed this area in recent times. Typical reactions are those of addition of a variety of alkenes to dienone **372** to yield the photoadducts **373**–**376** quantitatively. The regiochemistry is dictated by the stability of the 1,4-biradicals that are the key intermediates in the cyclization. Radical trapping experiments were carried out to justify the involvement of such species. The results obtained and the yields of products are shown in Scheme 11[232, 233]. Quinones also undergo addition to alkenes as demonstrated by the addition of 1,1-diarylethenes **377** to *p*-chloranil.

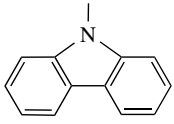
Several products are formed from all the ethenes used. For example, the formation of the cyclobutane derivatives **378** arises from the triplet excited state and involves a biradical intermediate. Substitution products are also formed, but this involves a SET process between the triplet quinone and the donor alkene[234].



(372) **(373)** **(374)**

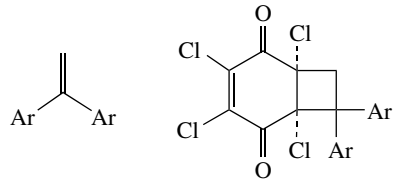


(376) **(375)**

R	**373**	**374**	**375**	**376**
Pho	62	9	19	6
Eto	69	11	14	6
CN	71	16	9 (total)	
Aco	53	34	6	3
4-$MeOC_6H_4$	12	69	10	8
4-ClC_6H_4	12	71	8	9
	4	57	16	22
t-Bu	–	90	–	–

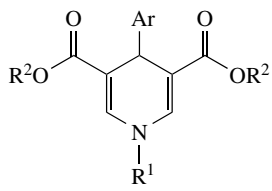
SCHEME 11

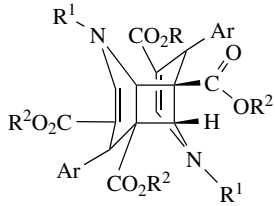
Dihydropyridine derivatives are also photochemically reactive and can undergo dimerization to afford cyclobutane derivatives. An example of this is the reactivity of **379** in the solid phase that affords the (2 + 2)-cycloaddition product **380** in the first step. Secondary irradiation of this then gives cage compounds in yields >90%[235]. Others have also



(377) **(378)**

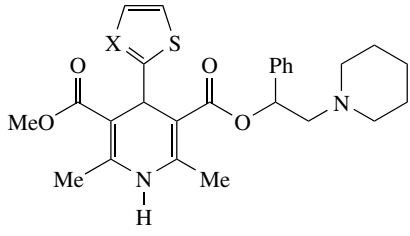
Ar = *p*-FC_6H_4, *p*-ClC_6H_4, *p*-MeC_6H_4





(379) **(380)**

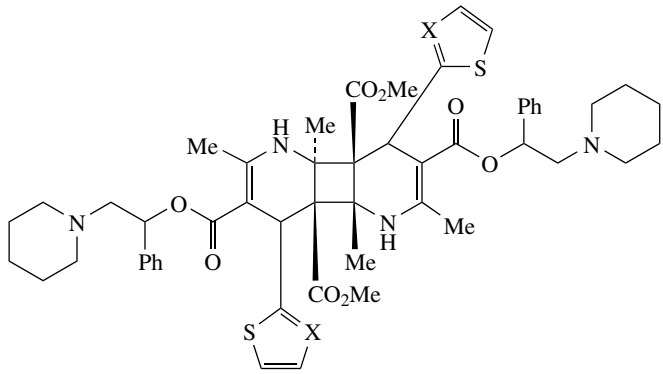
R^1	R^2	Ar	Yield (%)
H	Me	*p*-$MeOC_6H_4$	65
H	Et		40
CH_2Ph	Et		60
Me	Me		60
Me	Et		52



(381) X = CH or N

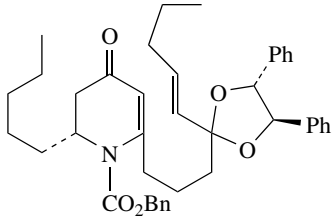
demonstrated the solid-state dimerization of three polymorphic forms of **381**. From the irradiations the dimer **382** is obtained in 58% yield when light in the range 320–400 nm is used[236]. In solution, irradiation of **381** brings about aromatization quantitatively[237].

On acetone-sensitized irradiation the pyridone **383** readily undergoes (2 + 2) head-to-head photochemical addition. The reaction appears to be very facile and requires only 16 min irradiation at 5 °C to give a 79% yield of the adduct **384**. This was used as the starting material in a total synthesis of (−)-perhydrohistrionicotoxin[238]. Simpler derivatives of



(382)

pyridones, such as **385**, undergo (2 + 2)-photocycloaddition[239] and cycloaddition of **386** occurs on acetone-sensitized irradiation to yield a *cis,syn,cis*-cyclobutane derivative[240]. Only direct irradiation is effective in bringing about the photochemical addition of pyridones **387** to the pentadienoate **388**. This reaction yields at least eight cyclobutane adducts by a variety of head-to-head or head-to-tail additions at either of the two double bonds in the pyridone[241]. Sieburth and Zhang[242] have described the intramolecular addition of a diene group within pyridone **389** that results in the formation of the (2 + 2)-cycloadduct **390**. This is not the primary photochemical product. The route to **390** is thought to involve (4 + 4)-photocycloaddition to yield adduct **391**. This adduct is thermally unstable and undergoes a facile Cope rearrangement to yield the isolated product.



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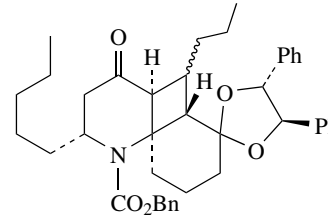

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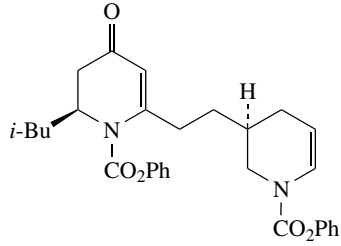

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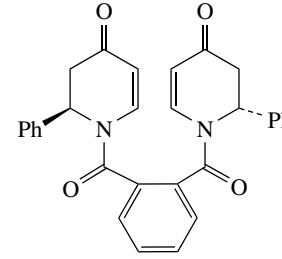

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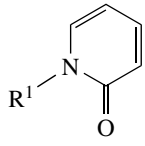
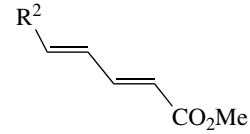
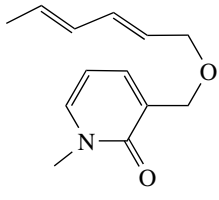


(387) R^1 = H or Me



(388) R^2 = H or Me



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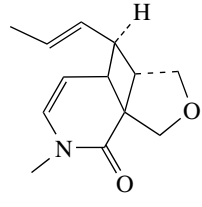
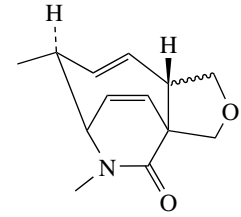
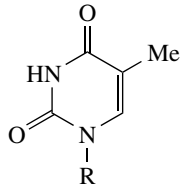


(390)



(391)

Single crystals of thymine derivatives with long alkyl-chain substituents are photochemically reactive. Irradiation of these brings about photodimerization with the formation of only one (2 + 2)-cycloadduct. The single adduct obtained from irradiation in the crystalline phase was identified as the *trans*, *-anti* dimer[243]. Such dimerization and the reversible nature of the process have been reviewed recently by Inaki[244]. In solution, however, cycloaddition affords the usual four cycloadducts, the *cis,syn, cis,anti, trans,syn* and *trans,anti*. In another study two crystalline modifications, plates and needles, were obtained from the thymine **392**. Only the needle modification was reactive and this affords *cis,anti* (**393**), *trans,syn* (**394**) and *trans,anti* (**395**)[245,246]. Cycloaddition between two thymine units can also take place intramolecularly when they are held together within a complex as in the pyrophosphate complex **396**[247]. Irradiation of this brings about *syn*-(2 + 2)-cycloaddition of the thymine units. Irradiation of the bis-thymine PNA dimer **397** brings about intramolecular cycloaddition and gives adduct **398** in 50% yield[248]. The thymidyl system **399** is also reactive in this (2 + 2)-cycloaddition mode[249]. Dimerization also occurs between the thymine units on irradiation at 280 nm of the modified cyclodextrin (CD) (**400**). The kinetic details of the forward and back reactions were analysed[250]. Other cycloadditions, such as the intramolecular cyclization of the dinucleotide model **401**, have been investigated. The reaction affords the cycloadduct **402** by irradiation using wavelengths >300 nm[251].



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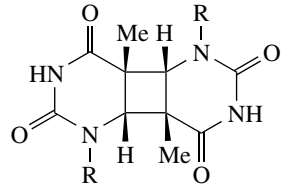
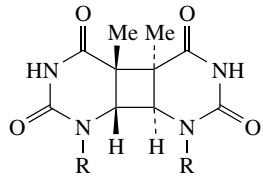


(393)

$R = (CH_2)_1Me$



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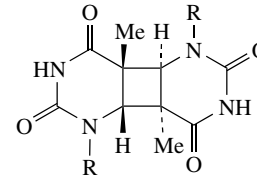

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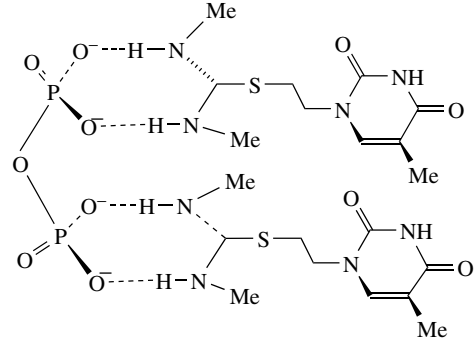

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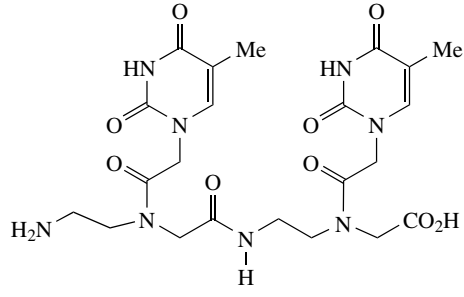

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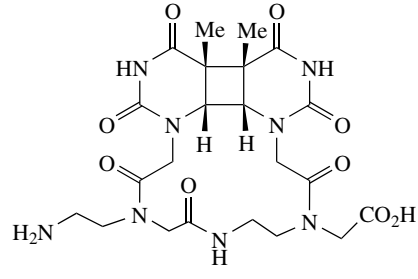

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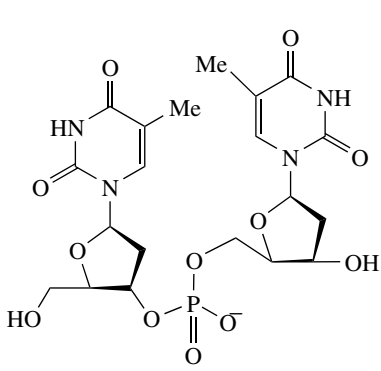

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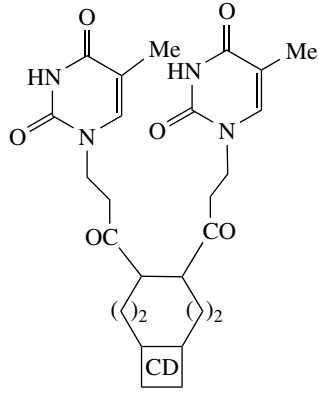

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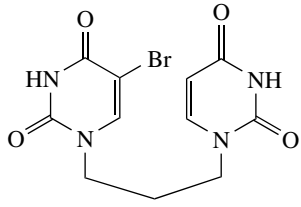

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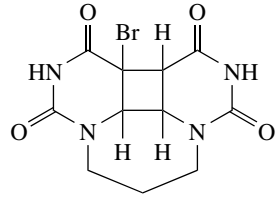
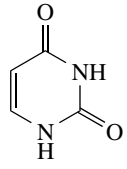


(402)

Additions of alkenes to thymines and related compounds are also common. Acetone-sensitized irradiation of uracil (**403**) with ethene affords adduct **404** in 75% yield. This compound can be transformed into the cyclobutane derivative **405** in an overall yield of 52%[252]. The addition of **406** and the vinyldeoxyuridine **407** yields the cycloadduct **408**[253, 254].



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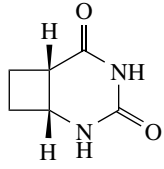

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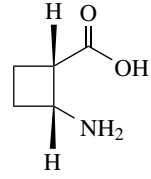
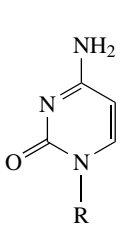


(405)

V. PHOTOCHEMISTRY OF KETONES

A. Norrish Type II Processes

The formation of cyclobutanols by irradiation of ketones and abstraction of a γ-hydrogen is perhaps the most studied reaction in modern-day organic photochemistry and often is referred to as the Yang photocyclization. Wagner[255], one of the most prolific



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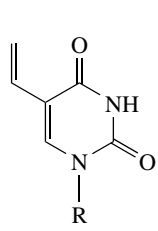

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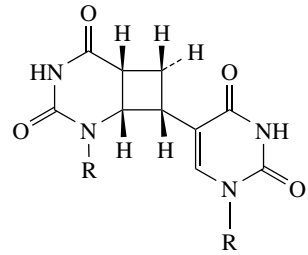

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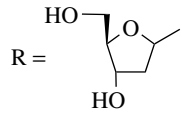
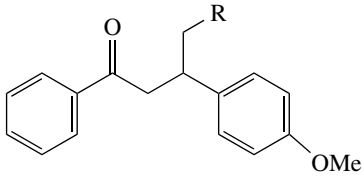


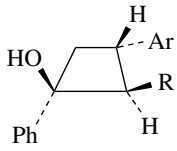
authors in the area, has reviewed this recently and details of the reaction are spelled out there. Other reviews have discussed the Norrish Type II process[256], the influence of environment[257], the regioselectivity[258] and the solid-state control of the process[259]. Hasegawa[260] has also reviewed the influence of environment on such reactions. Since the cover in these reviews is quite comprehensive, only a few reaction types will be illustrated here to illustrate the scope.

A typical example of such reactivity is the irradiation of valerophenone in aqueous solution that yields acetophenone and cyclobutanols[261]. The reaction follows the same path to that in hydrocarbon solution and arises from the triplet state. Interestingly, the formation of the cyclobutanols (*cis:trans* ratio is 2.4:1) is more efficient in the aqueous system than in hydrocarbons. Moorthy and Mal[262] have reported that irradiation of the ketones **409** results in photochemical conversion to the mixture of cyclobutanes **410** and **411**. The yields are in the 31–43% range and, as can be seen from the ratios of products, there is a good degree of selectivity when the reactions are carried out in non-polar solvents. The ratios change when polar solvents are used. This change is more dramatic with the ketones (**409**, R = Ph) where the selectivity is reversed from non-polar to polar solvents. Griesbeck and his coworkers[263,264] have studied the outcome of the formation of 1,4-biradicals formed on hydrogen abstraction within the amido ketones **412**. The results for the irradiation of **412a** exhibit the competition between cyclization and fission within the biradicals with $\phi_{\text{cycl.}} = 0.11$ and $\phi_{\text{frag.}} = 0.08$. The cyclization affords the cyclobutanol **413a** in 45% yield as a single diastereoisomer. Cyclization is also observed with the other derivatives **412b–d** affording the cyclobutanes **413b–d**. The results obtained can be explained either as selective γ-hydrogen abstraction or by selection of the reaction path at the 1,4-biradical stage. The biradical dynamics are claimed to be the controlling feature with the (2*R*,3*S*)-derivative **414**. This cyclizes efficiently to yield **415** with a *ds* of 96%. The diketone **416** also undergoes Norrish type II cyclization to afford the cyclobutanol **417**[265]. This product, however, is thermally labile and transforms further into 2,5-diphenylfuran.

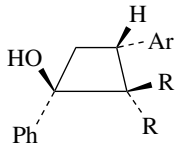
Two reports have given details of the photochemical reactivity of the large ring diketones **418**[266,267]. In solution, the irradiation brings about conventional γ-hydrogen abstraction in every case except with the cyclo-C_{10} diketone. As can be seen from the yields cited in Table 1, the products formed are dependent on ring size. Fission products also



(409) R = Me or Ph



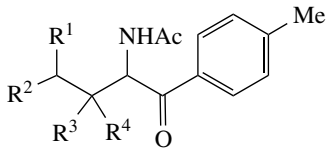
(410)



(411)

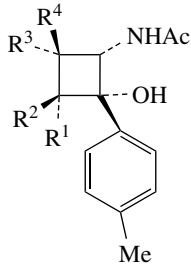
Ar = *p*-$MeOC_6H_4$

		ratio
c-C_6H_{12}	R = Me	80 : 20
C_6H_6	R = Me	82 : 18
EtOAc	R = Me	56 : 44
CH_3OH	R = Me	57 : 43
CH_3CN	R = Me	60 : 40
C_6H_6	R = Ph	85 : 15
CH_3CN	R = Ph	44 : 56

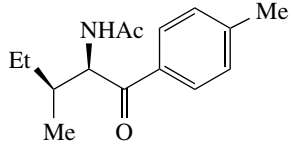


(412)

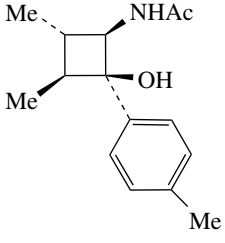
	R^1	R^2	R^3	R^4
(a)	H	H	Me	Me
(b)	Me	Me	H	H
(c)	H	H	H	Me
(d)	H	Et	H	H



(413)



(414)



(415)

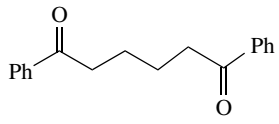
result on irradiation. Similar reactivity or lack of it is exhibited in the solid state and these yields are shown in parentheses. It is interesting to note that the outcome of the irradiation of the cyclo-C_{26} ketone is dependent on the type of crystal. Thus the needle

TABLE 1. Yields of products **419**–**421** obtained from the irradiation of ketones **418**[a]

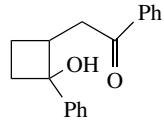
Ring size **418**	*m*	*n*	*cis*-Product **419** (%)	*trans*-Product **420** (%)	Open chain **421** (%)
12	4	2	84 (99)	0 (0)	16 (1)
14	5	3	65 (58)	25 (27)	10 (13)
16	6	4	22 (89)	35 (10)	43 (1)
18	7	5	17 (3)	42 (84)	41 (13)
20	8	6	10 (90)	23 (4)	67 (6)
22	9	7	10 (4)	34 (91)	56 (5)
24	10	8	15 (98)	27 (1)	58 (1)
26[b]	11	9	14 (9)	33 (91)	53 (0)
26[c]	11	9	14 (97)	33 (3)	53 (0)

[a] Yields in parentheses relate to solid-state reactions.
[b] Needle crystals of compound.
[c] Plate crystals of compound.

crystals yield 91% of **420** while the plates yield 97% of **419**. A detailed X-ray analysis of all the crystalline compounds was carried out.



(416)



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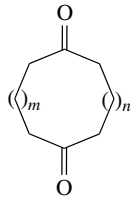

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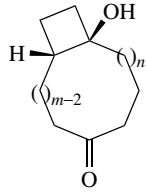
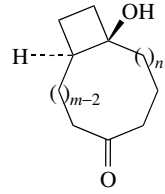
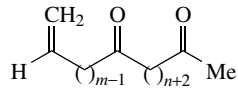


(419)



(420)

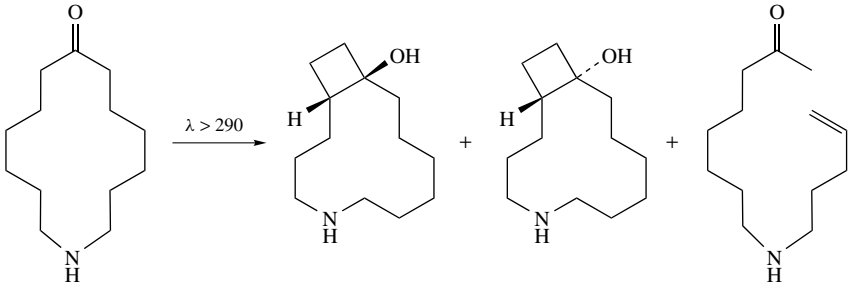
m	*n*
4	2
5	3
6	4
7	5
8	6
9	7
10	8
11	9



(421)

The irradiation ($\lambda > 290$ nm) of the crystalline salts formed between the large-ring cyclic amino ketones **422** and enantiomerically pure carboxylates [using (*S*)-(−)-malic acid, (*R*)-(+)-malic acid and (2*R*,3*R*)-(+)-tartaric acid, for example] has provided examples of

selectivity in the formation of the *cis*-cyclobutanol **423a**. The selectivity is the result of hindered motion within the crystalline environment. Some of the many results obtained are shown in Scheme 12. The principal reaction in all of the examples is a Norrish Type II hydrogen abstraction and the formation of a 1,4-biradical. This leads mainly to **423a** by bond formation or to the keto alkene **424** by fission within the biradical. A very minor path is cyclization to the *trans*-cyclobutanol **423b** that is followed only in the malate example[268].

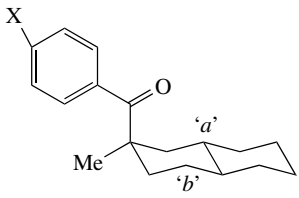


(422) **(423a)** **(423b)** **(424)**

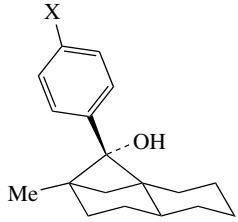
Yield (%)	**423a**	**423b**	**424**	% Conversion
(*S*)-(−)-Malic	24	2	32	60
(*R*)-(+)-Malic	45	0	24	69
(2*R*,3*R*)-(+)-Tartaric	24	0	0	24

SCHEME 12

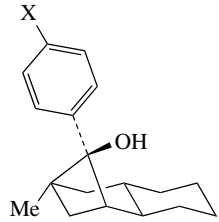
There is little doubt that control over reactions when the compounds are held in a constrained environment is one of the major areas undergoing development. The regioselectivity of the Norrish–Yang hydrogen abstraction process of the ketone **425** in the crystalline phase provides evidence for hydrogen abstraction from both positions 'a' and 'b' in the cyclohexane ring. Abstraction from 'a' affords **426** while **427** arises from the biradical afforded by abstraction from 'b'. The selectivity observed depends on the nature of substituents on the aryl ring[269]. A different attachment point on the decalin skeleton provides a different result and irradiation of **428** in the crystalline state affords the cyclopropyl derivative **429**, exclusively. The authors[270] suggest that the biradical formed by abstraction of the hydrogen at C10 in **428** is slow to cyclize in solution but cyclization becomes the dominant process in the crystal. The attachment of chiral auxiliaries to the molecules is also an important area of study. Thus, for the ketoester **430a** irradiation in the crystal affords the cyclobutane with a *de* of 96%. The results are less encouraging with **430b** where only 18% *de* is obtained in the crystal[270]. Earlier work had also been reported using auxiliaries to control the reactivity in cyclohexyl ketones[271]. Confinement of the ketones within chirally modified zeolites [using known amounts of (−)-ephedrine] also controls the photochemical reactivity of ketones such as **431** and **432** that are known to undergo the Norrish Type II hydrogen abstraction process. Irradiation of the ketones in the zeolites brought about some enantiomeric enhancement. However, the various zeolites studied behaved differently and the NaX zeolite favoured the (+)-**433** from **431** while the NaY zeolite favoured the (−)-isomer. The other ketone **432** showed only low enantiomeric



(425)

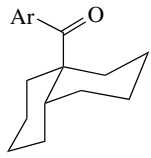


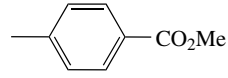
(426)

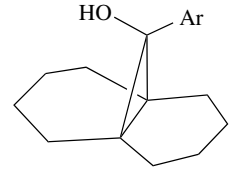


(427)

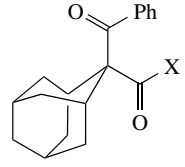
X = COOMe, COOH, COOAd-1, $CO_2^-H_3N^+CH(Ph)Me$



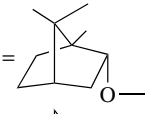
(428) Ar = 

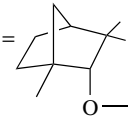


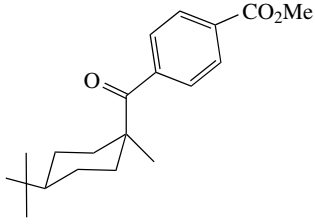
(429)



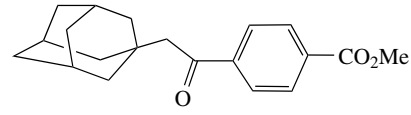
(430)

(a) X = 

(b) X = 

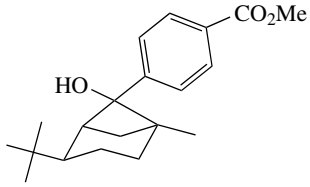


(431)



(432)

enhancement and gave both the *cis*- and the *trans*- cyclobutanols **434** and **435** in a ratio of 4:1[272]. A further study with the adamantyl ketones **436** under similar conditions shows that only *endo*-products **437** are formed and the best *ee*s for both derivatives are obtained with (−)-pseudoephedrine as the chiral auxiliary[273].



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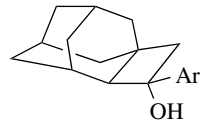
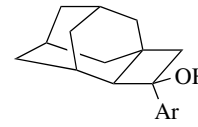
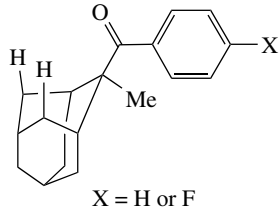


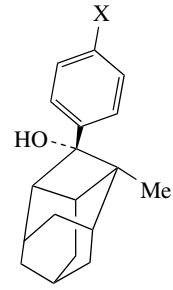


Ar = *p*-$MeO_2CC_6H_4$

(434) **(435)**



X = H or F



(436) **(437)**

B. Decarbonylation

Some examples of decarbonylation of substituted cyclopentanone derivatives can also provide a route to cyclobutanes. Thus irradiation of *trans*-3,4-dimethylcyclopentanone in the gas phase affords 1,2-dimethylcyclobutane among other products[274]. A more recent study has examined the effect of irradiating 1-phenylcyclopentanone with a Na/YAG laser emitting at 266 nm. Under these conditions α-fission affords the usual biradical. However, there is no evidence for the formation of the aldehydes by a hydrogen abstraction path and instead, decarbonylation is followed by ring closure to give phenylcyclobutane[275].

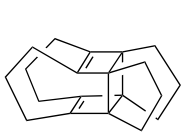
VI. CAGE COMPOUNDS

Intramolecular (2 + 2)-photocycloaddition has proved to be an excellent route to the synthesis of cage compounds. This area was reviewed earlier in this series[276]. Ideally, this route utilizes substrates where the alkene moieties are held face-to-face within a preformed structure. The irradiation brings about excitation and coupling of the two groups to afford a cyclobutane ring. Such compounds are of use in the study of ring strain and also in synthetic approaches to starting materials for more complex systems. Several

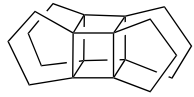
review articles have highlighted this[277]. The ring systems within these cage compounds are generally quite complex and the previous simple nomenclature is used here to illustrate the synthetic paths available to these heavily substituted cyclobutane derivatives.

A. Cubanes

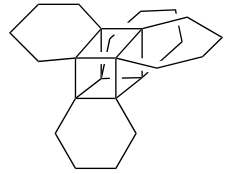
The diene **438** photochemically converts on irradiation in pentane solution at 254 nm to a photostationary mixture of the cubane **439** and a diene isomeric with the starting material[278]. The synthesis of cubane **440**, referred to as a propellaprismane, can be effected by irradiation of the diene **441**[279].



(438)



(439)



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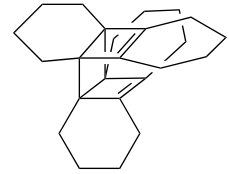
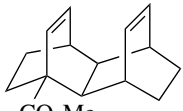


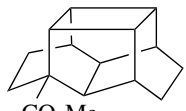
(441)

B. Hexacyclotetradecane Systems

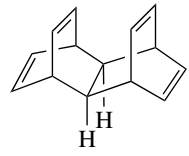
Normal (2 + 2)-photocycloaddition takes place on the acetone-sensitized irradiation of the per-ester **442a** to yield the cage compound **443** in 76%[280]. Analogously, the tetraene **442b** undergoes photochemical cage formation yielding **444**[281]. Other cyclizations are also of interest, such as the formation of the cage compound **445** (90%) from direct irradiation of a benzene solution of the diene **446**[282]. The presence of hetero atoms does not seem to affect the cyclization adversely and the irradiation of **447** results in a quantitative (2 + 2)-cycloaddition yielding **448**[283].



(442a)



(443)



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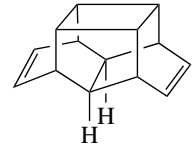
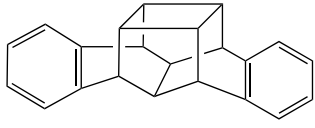


(444)



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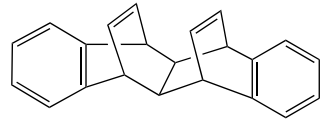

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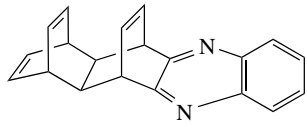

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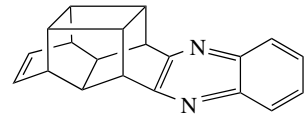
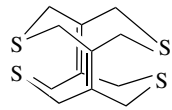


(448)

C. Pagodanes and Related Compounds

It seems from the examples cited above that, provided the alkene moieties are held in a rigid framework, then addition is often highly efficient. This is demonstrated again in the irradiation of **449** that readily affords the cyclobutane derivative **450**[284]. A further good example is the conversion of **451** into the pagodanes **452** by either direct irradiation in ether with a quartz filter or by acetone-sensitization through Pyrex[285]. A benzene ring can also be one of the components of the reaction system as demonstrated by the photo-ring closure of **453a** and **453b** into **454a** and **454b**, respectively. In the addition with **453a,** the resultant diene **454a** was trapped by a Diels–Alder addition[286].



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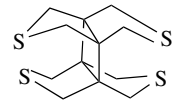

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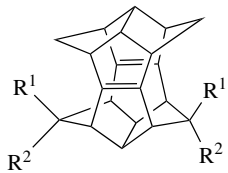

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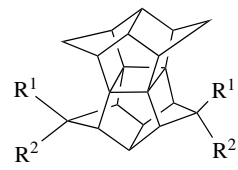
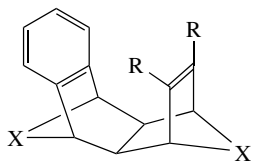
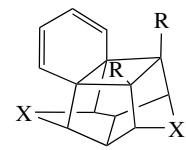


(452)
$R^1 = R^2 = H$
$R^1 = CO_2Me$, $R^2 = H$
$R^1R^2 = O$



(453) **(a)** $X = CH_2$ or  , $R = H$

(b) $X = CH_2$, $RR = (CH{=}CH)_2$

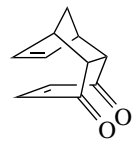


(454a)

(454b)

D. Peristylanes and Related Systems

Syntheses of complicated structures such as the peristylane system and related compounds can also be approached by (2 + 2)-photocycloadditions, such as the photoconversion of **455** into the cage compound **456**[287]. Thus irradiation of the compound **457** affords the cage compound **458** when acetone-sensitization is employed[288]. Triplet-sensitized irradiation (350 nm) in acetone of the triene **459** affords the cage compound **460** in 32% yield[289].



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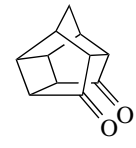

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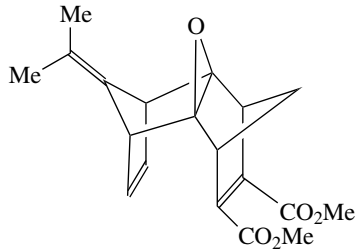

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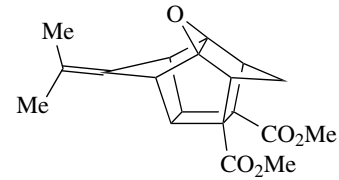

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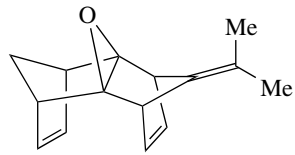
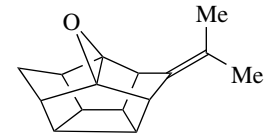


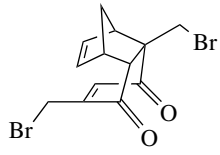
(459)



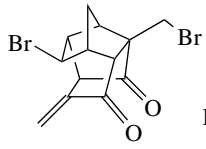
(460)

E. Other Cycloadditions

Sunlight irradiation of **461** in ethyl acetate brings about its conversion into the two products **462** (63%) and **463** (18%). It is clear that the cycloaddition occurs via a biradical **464**. Within this, abstraction of the bromine yields **462** while CC bond formation gives **463**[290]. The enones **465** fail to undergo (2 + 2)-cycloaddition when irradiated. The only photochemical reaction encountered is reduction of the remote double bond. The authors[291] suggest that the failure of the cyclization is a result of nitrogen lone pair/double bond interaction. When such an interaction is minimized by the acylation of the nitrogen, normal (2 + 2)-cycloaddition becomes efficient giving high yields of the cage compounds **466** (R = COMe, CO_2Me or $COCH_2Ph$).



(461)



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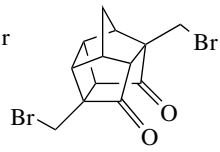
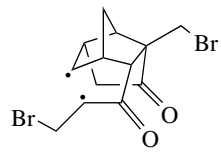


(463)



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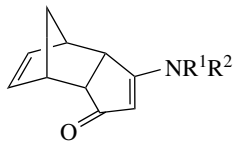
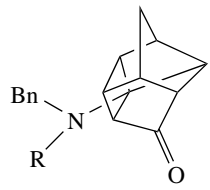


(465)



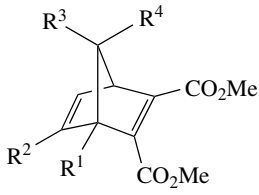
(466)

		Yield (%)
R^1 = H, R^2 = cyclohexyl	R = COMe	99
R^1 = H, R^2 = benzyl	R = CO_2Me	67
R^1 = R^2 = morpholino	R = $COCH_2Ph$	81

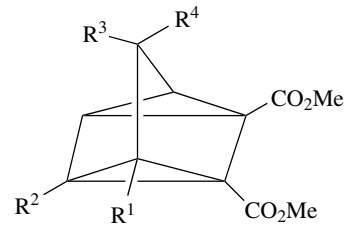
F. Norbornadiene–Quadricyclane

One of the areas that has been studied in considerable detail is that of cyclization of norbornadiene to quadricyclane that can be brought about either by direct or by sensitized irradiation. The subject has been reviewed extensively in a recent article[292] and was also discussed in an earlier book in this series[293]. This reaction was first reported almost fifty years ago by Cristol and Snell[294] and soon became an area of interest to many others. Much of the earlier work has appeared in most textbooks devoted to photochemistry and, in addition, most of the standard textbooks and monographs on the subject now have details of these reactions. Since this is the case, this section will highlight what has been achieved in the last decade or so.

The reaction is best exemplified by the simple systems such as **467**, which readily undergo cyclization to the quadricyclanes (**468**) in good yield[295]. The principal reason for the study of these systems was an attempt to obtained energy storage molecules. If the use of the norbornadiene/quadricyclane as energy storage systems is to be exploited, systems have to be devised that can be cyclized using sunlight. This is the case with the water-soluble norbornadiene (**469**) that is efficiently converted into the corresponding quadricyclane on irradiation with sunlight[296]. Other norbornadienes with carboxylic acid functional groups (e.g. **470**) also undergo efficient cyclization to **471**[297], as does **472** into **473** in a yield of 75%[298]. The photochemical formation of the quadricyclanes (**474**) by acetophenone-sensitized irradiation of **475** has been reported. The quadricyclanes obtained were used as substrates in an approach to the synthesis of 1,5-dehydroquadricyclane[299].

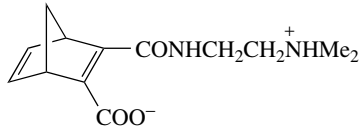


(467)

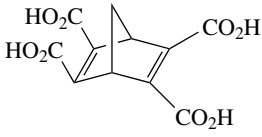


(468)

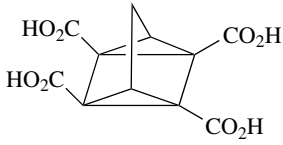
$R^1 = R^2 = R^3 = R^4 = H$
$R^1 = Me, R^2 = R^3 = R^4 = H$
$R^2 = Me, R^1 = R^3 = R^4 = H$
$R^3 = Me, R^1 = R^2 = R^4 = H$
$R^4 = Me, R^1 = R^2 = R^3 = H$
$R^1 = R^2 = H,\ R^3 = R^4 = Me$



(469)



(470)



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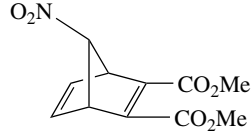
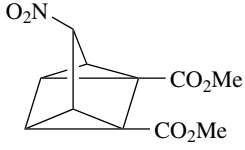
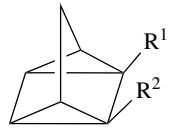


(472)



(473)



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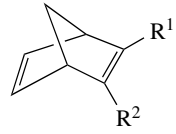
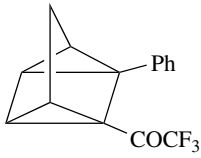


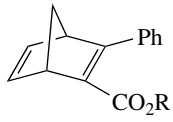
(475)



(476)

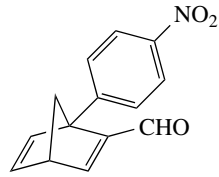
$R^1 = Br, R^2 = Br$ or Cl

Other substituted derivatives have also been studied, such as the formation of the quadricyclane **476** on irradiation of the corresponding norbornadiene[300]. Others have demonstrated that the related norbornadiene **477** undergoes cyclization with a quantum yield in the range of 0.18 to 0.36. The authors[301] suggest that the results are in agreement

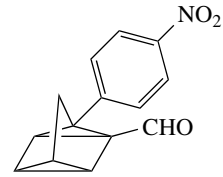


(477)

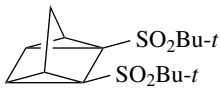
R = H, $PhCH_2$, *p*-$MeOC_6H_4$



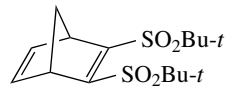
(478)



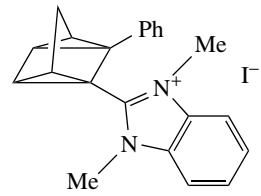
(479)



(480)

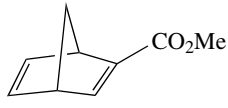


(481)

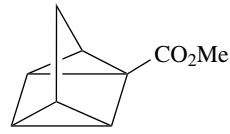


(482)

with the involvement of a radical cation mechanism for the cyclization. Dubonosov and coworkers report the conversion of the diene **478** and derivatives thereof into the quadricyclane **479** by irradiation[302] while Gleiter and Ohlbach[303] report that the quadricyclane **480** is readily prepared by irradiation of the norbornadiene derivative **481**. The polar derivative **482** has also been described[304]. In recent times, studies with circularly polarized light have demonstrated that it is possible to obtain enantiomeric enrichment. Thus the irradiation of the chiral norbornadiene ester **483** affords the corresponding chiral quadricyclane derivative **484**[305, 306].

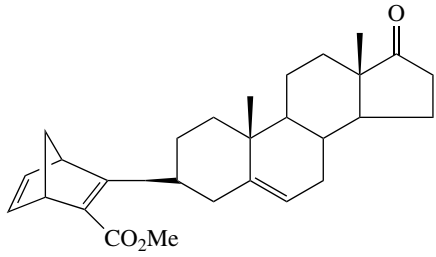


(483)

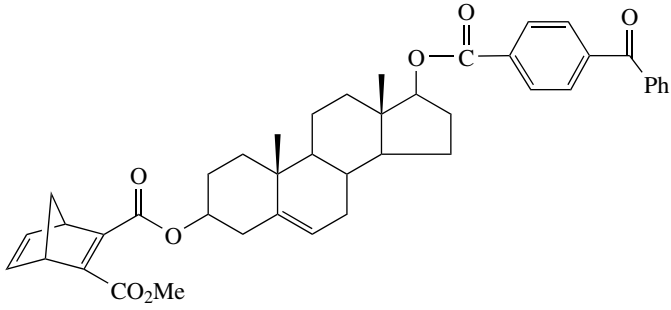


(484)

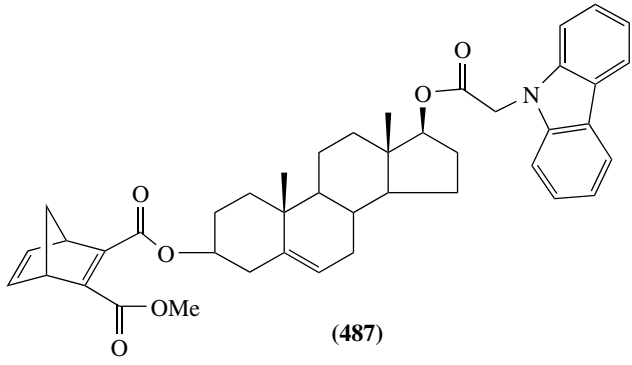
Some studies have focused on energy transfer within bichromophoric systems based on norbornadiene. Thus, irradiation ($\lambda > 300$ nm) of the norbornadiene derivative **485** results in excitation of the androstene carbonyl group and affords the triplet excited state that transfers triplet energy by a through-bond mechanism to the norbornadiene. This undergoes cyclization to the corresponding quadricyclane. The energy transfer occurs with 18.6% efficiency[307]. Cao and coworkers[308] have demonstrated that intramolecular triplet energy transfer from the benzophenone moiety to the norbornadiene unit in **486** takes place with a rate constant of 6.1×10^4 s^{-1}. Studies have also demonstrated that energy transfer from a benzidine moiety to the norbornadiene can occur with 12% efficiency[309]. Further work on such systems has shown that intramolecular triplet energy transfer from the carbazole to norbornadiene moiety also occurs in the molecule **487**.[310]



(485)



(486)



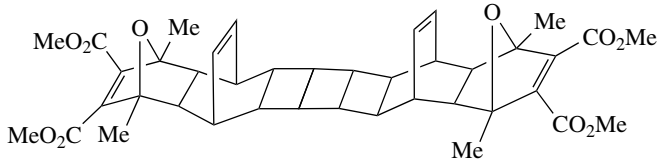
(487)

VII. CYCLOBUTANE RING OPENING REACTIONS

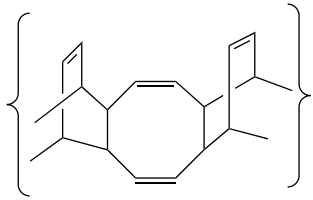
The behaviour of small rings in confined environments has been reviewed recently[311]. It is obvious that simple cyclobutanes do not absorb in the readily accessible wavelengths in the UV. They can, however, be induced to undergo fission by irradiation at 254 nm in bromine-doped xenon matrices or in xenon matrices at 248 nm. The fission usually affords the corresponding ethene and but-1-ene[312]. Such cleavage into fragments is common in the processes undergone by cyclobutane derivatives under a variety of conditions. For example, an account describes the fission of 1,2,3,4-tetraphenylbutane into *trans*-stilbene on either γ irradiation or pulse radiolysis[313,314]. Solvated electrons bring

about reactions of this type. Other work has demonstrated that similar behaviour could be observed with *trans*-methyl cinnamate (μ-dimethyl truxinate), dimethyl α-truxillate and dimethyl β-truxinate in 2-methyltetrahydrofuran[315] when methyl cinnamate was obtained. Photolytic cycloreversion of cyclobutane derivatives such as cinnamic acid dimers and their diamides[316] have also been studied. The X-ray irradiation of the derivative **488** in the crystalline state brings about conversion to the cycloocta-1,5-diene (**489**) without destruction of the crystal[317].

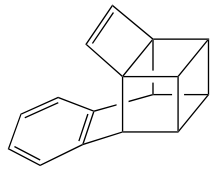
For ring fission to occur the cyclobutane needs to be substituted by a suitable chromophore. This is observed in the reversible ring opening and ring closing of the dissymmetric cage compounds (Scheme 13) formed from substituted cyclopentadienones[318]. The synthesis of cage compounds related to this and others has been reviewed[319]. Irradiation of adducts **490** and **491** at 260 nm, where the benzenoid moiety absorbs, results in efficient (ϕ can be as high as 0.5) conversion to the corresponding naphthalene derivatives[320]. Fission has also been reported following 254 nm irradiation, in both argon and N_2 matrices, of the pentalene dimer **492**[321]. Irradiation at this wavelength affords the biradical **493** that can be cleaved further to yield pentalene by irradiation at 313 nm. Photochemical monomerization of the cyclobutane dimers (**494**) can be brought about effectively using tetra-O-acylriboflavins as the sensitizer. The reaction is efficient when carried out in aqueous solution with surfactants such as sodium dodecyl sulphate and sodium hexadecyl sulphate[322]. Others[242] have also commented upon the monomerization of thymine dimers and have reviewed the area recently[323]. 1-*n*-Alkylthymines dimerize readily. Irradiation brings about photosplitting and the driving force for this is steric repulsion of the methyl groups at C5 of the thymine. When the C5 methyl is absent as in uracil the photosplitting is not observed.



(488)

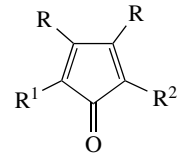


(489)

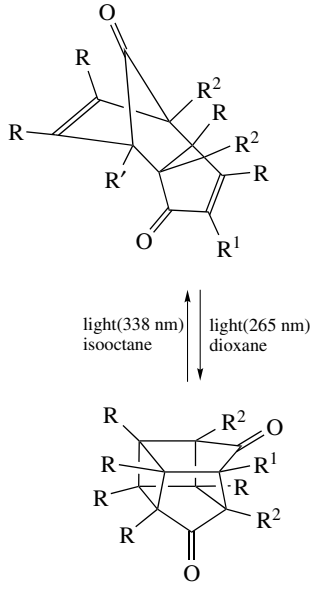


(490)

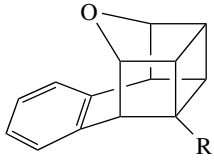
Considerable research has been devoted to the electron-transfer-induced reactions (SET) of cyclobutane derivatives. An example of this is provided by Miranda and his coworkers[324] who have studied the cycloreversion of the cyclobutanes **495** and **496** using pyrylium salts (**497**) as electron-accepting sensitizers. The reactions are brought about by irradiation at wavelengths >340 nm and arise from the triplet state of the sensitizers. The ring opening involves an electron transfer and the best sensitizer is the thiapyrylium salt for ring opening of **495**. The quantum yields for the ring splitting using the three sensitizers are shown in Table 2.



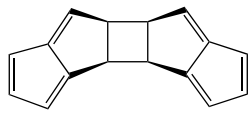
	a	b	c	d	e
R	H	Ph	Ph	Ph	*p*-Tol
R^1	H	Me	Et	Pr	Me
R^2	H	Me	Me	Me	Me



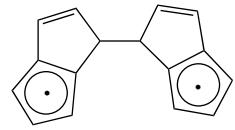
SCHEME 13



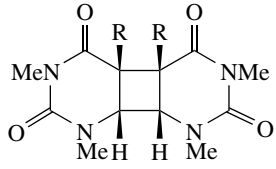
(491) R = H or CN



(492)



(493)



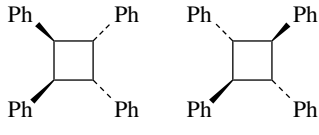
(494) R = Me or H

Suitably substituted bicyclohexanes are also readily ring opened by SET. Thus, **498** and **499** undergo SET to dicyanobenzene (DCB) or tricyanobenzene (TCB) and this affords the diene **500** as the principal product. The formation of this implies that the radical cation involved has the boat conformation (**501**) that ring opens to the final product[325]. Differently substituted derivatives also undergo such reactions and the bicyclohexane **502** affords at low conversion a mixture of the dienes **503** and *E*,*E*-**504** in ratios that are independent of temperature[326,327].

The photo-NOCAS reaction path pioneered by Arnold and coworkers and reviewed by Mangion and Arnold[328] has also been applied to the ring opening of cyclobutane

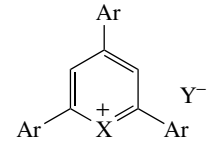
TABLE 2. Quantum yields for ring splitting of 1,2,3,4-tetraphenylcyclobutane isomers

Compound	Sensitizer	Quantum yield
495	**497a**	0.1
495	**497b**	0.5
495	**497c**	0.4
496	**497a**	0.02
496	**497b**	0.09
496	**497c**	0.13



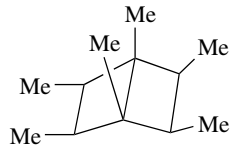
(495)

(496)

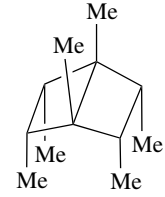


(497)

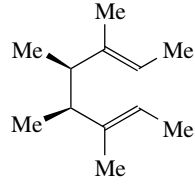
	X	Y	Ar
(a)	0	BF_4	Ph
(b)	S	ClO_4	Ph
(c)	0	BF_4	*p*-BrC_6H_4



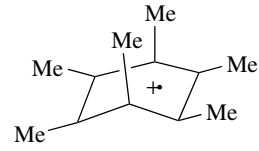
(498)



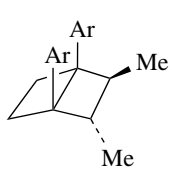
(499)



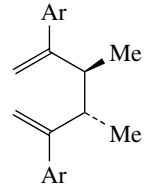
(500)



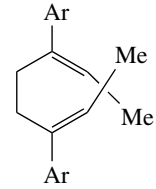
(501)



(502)



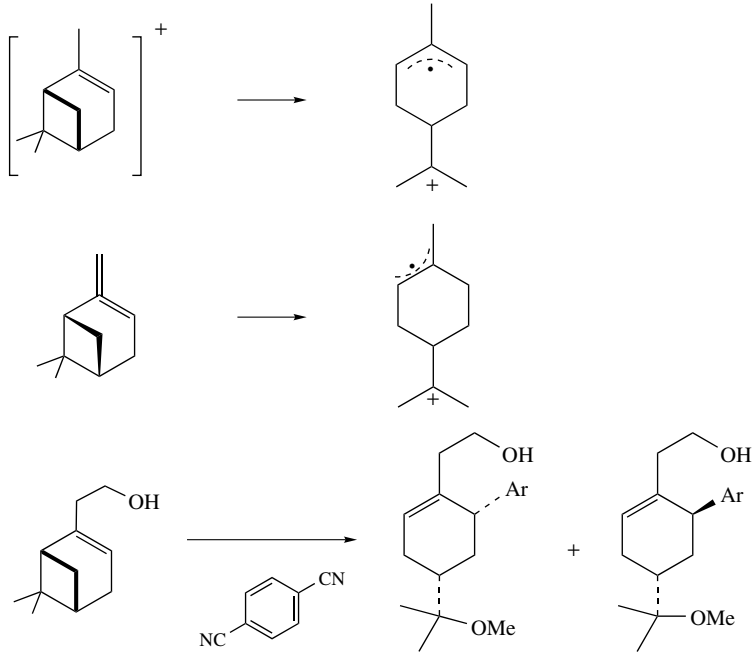
(503)



(504)

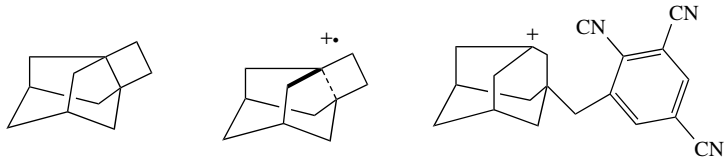
Ar = *p*-$MeOC_6H_4$

containing molecules such as α- and β-pinene and nopol (**505**)[329]. The use of DCB(1,4-dicyanobenzene) as the electron-accepting sensitizer converts the two pinenes into the cation radicals shown in Scheme 14. These undergo irreversible ring opening to afford the distonic radical cations that react as tertiary alkyl cations and allylic radicals. Nopol (**505**) behaves similarly and the products obtained from this are shown in Scheme 14. Similar products are obtained from the pinenes. The photo-NOCAS procedure has also been carried out on the adamantane derivative **506** illustrated in Scheme 15[330]. Here again the radical cation **507** is formed and ring opening followed by trapping by the tetracyanobenzene affords the cation **508**.



(505) 32% 22%

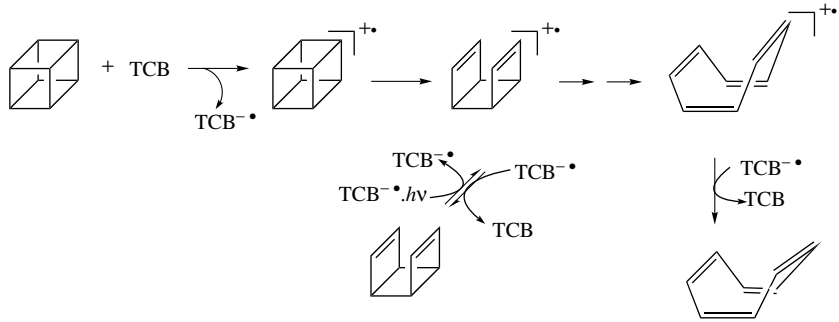
SCHEME 14



(506) **(507)** **(508)**

SCHEME 15

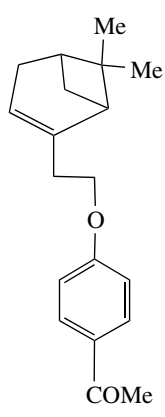
Other more complex systems such as cubane have also been examined under such conditions. This time tetracyanobenzene is the electron-accepting sensitizer and irradiation brings about the formation of the cubane radical cation that undergoes a series of bond breaking processes to ultimately yield cyclooctatetraene (COT) and the bicyclic diene **509** as illustrated in Scheme 16[331]. It should also be noted that the product **509** could be converted to COT. Albini and Fagnoni have reviewed SET-induced ring-opening and alkylation reactions[332]. Ring opening is also observed in the pinene derivative **510**. This rearrangement occurs on irradiation in benzene or methanol and excitation results in triplet energy transfer from the benzene moiety to the pinene. The ring opening affords the *cis*-isomer **511** of the ocimene derivative but continued irradiation affords a ratio of *trans:cis* of 52:48[333].



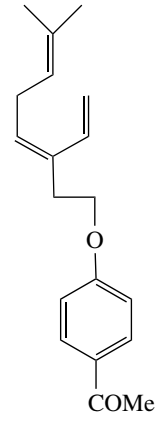
(509)

SCHEME 16

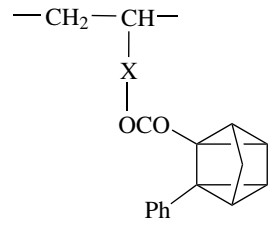
The norbornadiene/quadricyclane system is perhaps the most intensively studied area involving the ring opening of the cyclobutane ring in quadricyclane on the reversal to norbornadiene. The details of the mechanism for this reversal have been the subject of a review[334] as has the field of norbornadiene photochemistry[335]. The use of the quadricyclane systems for energy storage has also been reviewed[336]. Most of the quadricyclanes can be transformed to norbornadiene by thermal or catalytic methods. There are, however, some that revert on irradiation, such as the polymeric films based on **512** that can also undergo ring opening on irradiation[337]. Other routes to ring opening involve the radical cation of quadricyclane that can be formed readily by using dibenzoylmethanatoboron difluoride as the electron-accepting sensitizer. Yang and coworkers[338] have demonstrated that this treatment converts quadricyclane into norbornadiene. Through-bond transfer has



(510)

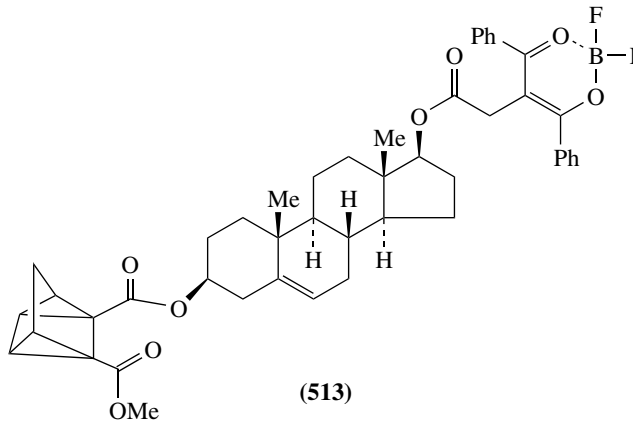


(511)

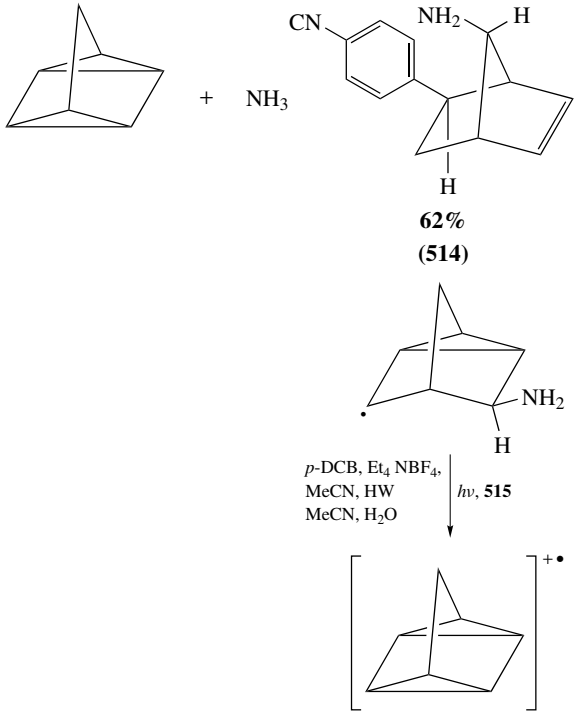


X = –O(CH$_2$)$_2$–, – C$_6$H$_4$CH$_2$–

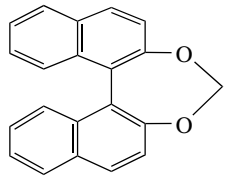
(512)



(513)



SCHEME 17



(515)

also demonstrated that intramolecular electron transfer is involved in ring opening of the quadricyclane derivative to the corresponding norbornadiene. The study has indicated that electron transfer occurs from the quadricyclane moiety to the BF_2 chromophore in **513**[339]. Electron transfer is also involved in the conversion of quadricyclane to the aminated derivatives **514**. These reactions are sensitized by the binaphthalene derivative **515**. The outcome of the process, involving the radical cation of quadricyclane, is shown in Scheme 17[340].

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CHAPTER **18**

Solvent-free photosynthesis of cyclobutanes: Photodimerization of crystalline olefins

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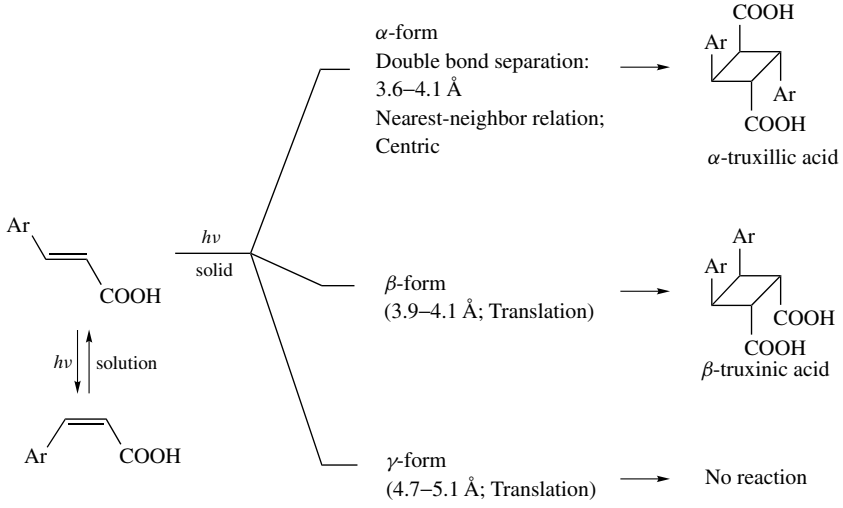
I. INTRODUCTION

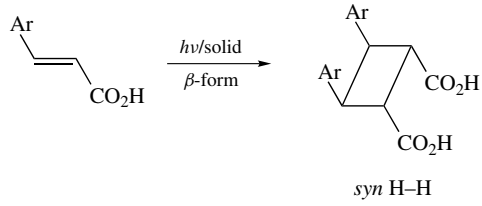
As early as 1889, Liebermann observed the photodimerization of olefins to yield cyclobutanes in crystals[1]. In 1918, Kohlschutter proposed that the nature and properties of the products of solid state reactions are governed by the fact that they take place within or on the surface of the solid[2]. Bernstein and Quimby in 1943 interpreted the formation of α-truxillic and β-truxinic acids from two types of cinnamic acid crystals as a crystal lattice-controlled reaction[3]. From crystallographic investigations, pioneered by Schmidt and his coworkers during the early 1960s, of a large number of cinnamic acids (which exhibit a rich variety of polymorphic forms and photochemical reactivity patterns) emerged the important set of 'topochemical postulates' connecting the configuration of the product and the crystal structure of the reactant[4–6]. In this chapter we provide a brief summary of bimolecular photodimerization leading to cyclobutanes in crystals[7–22]. Photoreactions of two component crystals (mixed dimerizations) are not covered. Our emphasis in this chapter is toward conceptual developments. Toward the end of the chapter we have listed most (maybe not all) one-component crystals that have been investigated in the solid state from the perspective of dimerization. We hope that the listing would serve readers to investigate some of these systems in depth to better understand the mechanism of solid state dimerizations.

II. PHOTODIMERIZATION OF CINNAMIC ACIDS: EMERGENCE OF TOPOCHEMICAL POSTULATES

The reactions of cinnamic acids are examples of [2 + 2] photodimerization that have been investigated extensively. Some of these acids, on photolysis of the crystal, react to give dimeric products (Scheme 1) while in solution *trans–cis* isomerization occurs but there is no dimerization. The acids are observed to crystallize in three polymorphic forms, namely α, β and γ, and show photochemical behavior, which is determined by this structure type. In all three modifications, cinnamic acid molecules pack in one-dimensional stacks,



SCHEME 1



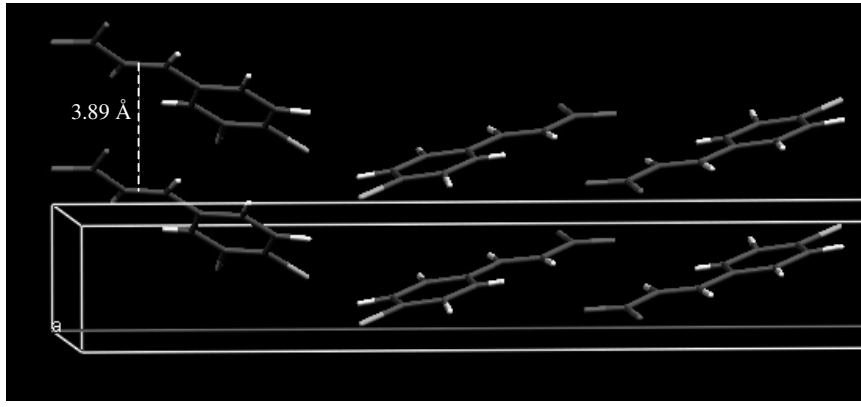


FIGURE 1. Packing arrangement of *para*-chlorocinnamic acid (β-packing)

adjacent stacks being paired by hydrogen bonding across centers of symmetry. Within the stacks the molecules lie parallel with the normal distance between molecular planes being of the order of *ca* 3.5 Å. The three structural types differ in the angle that the stack axis makes with the normals to the molecular planes. This is equivalent to a difference in the distance between equivalent points on the molecules, which is the crystallographic repeat distance, '*d*'. In the β-type structure the molecules are separated by a short repeat distance of 3.7–4.1 Å, thus neighboring molecules up the stack are translationally equivalent and show considerable face-to-face overlap. The β-type packing arrangement in the case of a substituted (e.g. *p*-chloro) cinnamic acid is shown in Figure 1. All cinnamic acids, which crystallize in this structure, react photochemically to give products of the same stereochemistry (mirror symmetric dimers). In the γ-type structure, adjacent molecules are offset so that the reactive double bonds do not overlap, and furthermore the distance between them is large (4.7–5.1 Å). Crystals of this type are photostable. In the α-type, the double bond of a molecule in one stack overlaps with that of a centrosymmetrically related molecule in an adjacent stack. The distance between the equivalent double bonds is greater than 5.5 Å, but that between the overlapping double bonds is *ca* 4.1 Å. This type of crystal upon irradiation produces centrosymmetric dimers. The α-type packing arrangement in the case of cinnamic acid is shown in Figure 2.

In Table 1, a list of most cinnamic acids whose behavior has been investigated in the solid state till 2003 is provided[3, 5, 6, 18, 23–48]. The important results obtained by analyzing the solid state behavior of these are the following:

1. The product formed is governed by the environment rather than by the intrinsic reactivity of the reactive bonds in the crystalline state.

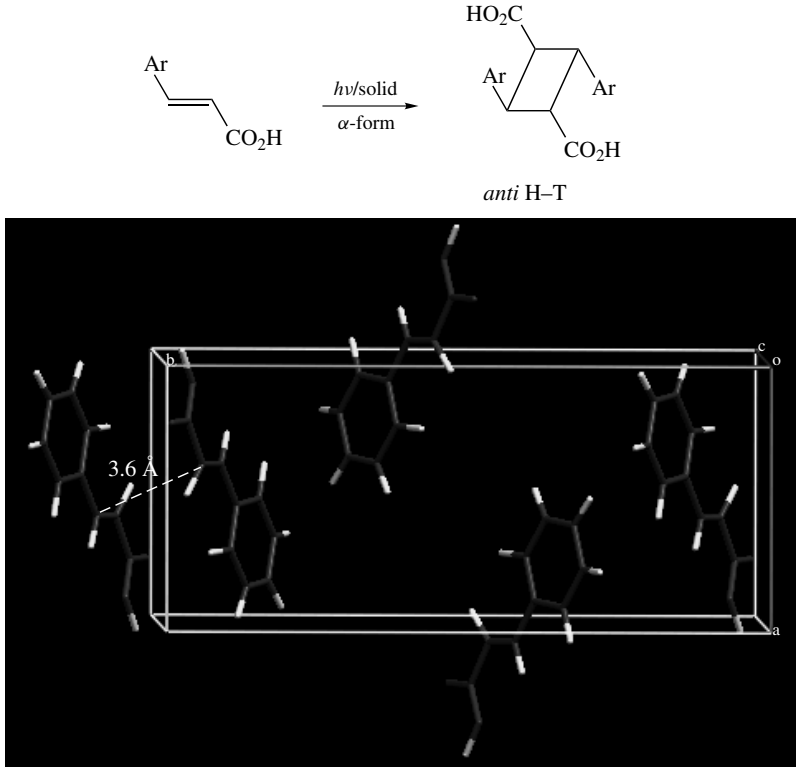


FIGURE 2. Packing arrangement of cinnamic acid (α-packing)

2. The proximity and degree of parallelism of the reacting centers are crucial for the dimerization.
3. There is a one-to-one relationship between the configuration and symmetry of the product with the symmetry between the reactants in the crystal.

Although there had been sporadic reports relating to solid state photodimerization earlier, it must be said that the systematic and thorough studies by Schmidt and coworkers on cinnamic acids laid the foundation for the flowering of this field (Scheme 1).

Schmidt has drawn attention to the fact that not only must the double bonds of the reacting monomers of cinnamic acid be within *ca* 4.2 Å, but they must also be aligned parallel for cycloaddition to occur. A reaction that behaves in this way is said to be 'topochemically controlled'. Schmidt has drawn the geometrical criteria for dimerization only with the view of inferring how precisely the π electron system of the reacting double bonds must be aligned in the crystal lattice for reaction to occur. These topochemical postulates are landmarks in organic solid state photochemistry and are used as rules, as they are able to provide an understanding of a large number of [2 + 2] photodimerization reactions of widely varying structures (see examples in Section XI). However, recent results discussed below suggest that these concepts should be considered as guidelines rather than strict rules.

TABLE 1. Photodimerization of *trans*-cinnamic acids in the crystalline state (see Scheme 1)

Cinnamic acids	Nature of packing	% Yield	Nature of dimer
Cinnamic acid (CA) [a]	α	74	*anti* H−T
	β	80	*syn* H−H
ortho-Hydroxy CA [a]	α	90	*anti* H−T
meta-Hydroxy CA [a]	α	76	*anti* H−T
para-Hydroxy CA [a]	α	78	*anti* H−T
ortho-Methoxy CA [a]	α	83	*anti* H−T
ortho-Ethoxy CA [a]	α	93	*anti* H−T
	β	90	*syn* H−H
ortho-Propoxy CA [a]	α	94	*anti* H−T
ortho-Isopropoxy CA [a]	α	97	*anti* H−T
ortho-Allylloxy CA [a]	α	93	*anti* H−T
ortho-Methyl CA [a]	α	—	None
para-Methyl CA [a]	α	95	*anti* H−T
ortho-Nitro CA [a]	β	27	*syn* H−H
meta-Nitro CA [a]	β	60	*syn* H−H
para-Nitro CA [a]	β	70	*syn* H−H
ortho-Chloro CA [a]	β	85	*syn* H−H
meta-Chloro CA [a]	β	70	*syn* H−H
para-Chloro CA [a]	β	71	*syn* H−H
ortho-Bromo CA [a]	β	82	*syn* H−H
meta-Bromo CA [a]	β	91	*syn* H−H
para-Bromo CA [a]	β	90	*syn* H−H
5-Bromo-2-hydroxy CA [a]	β	30	*syn* H−H
5-Chloro-2-methoxy CA [a]	β	85	*syn* H−H
5-Bromo-2-methoxy CA [a]	β	50	*syn* H−H
2,4-Dichloro CA [a]	β	78	*syn* H−H
2,6-Dichloro CA [a]	β	70	*syn* H−H
3,4-Dichloro CA [a]	β	60	*syn* H−H
3,4-Methylenedioxy CA [b]	β	74	*syn* H−H
3,4-Dimethoxy CA [b]	α	—	*anti* H−T
α-Acetylamino CA [c]	α	—	*anti* H−T
para-Formyl CA [d]	β	—	*syn* H−H
6-Chloro-3,4-methylenedioxy CA [e]	β	—	*syn* H−H
para-Cyano CA [e]	β	94	*syn* H−H
meta-Cyano CA [e]	β	80	*syn* H−H

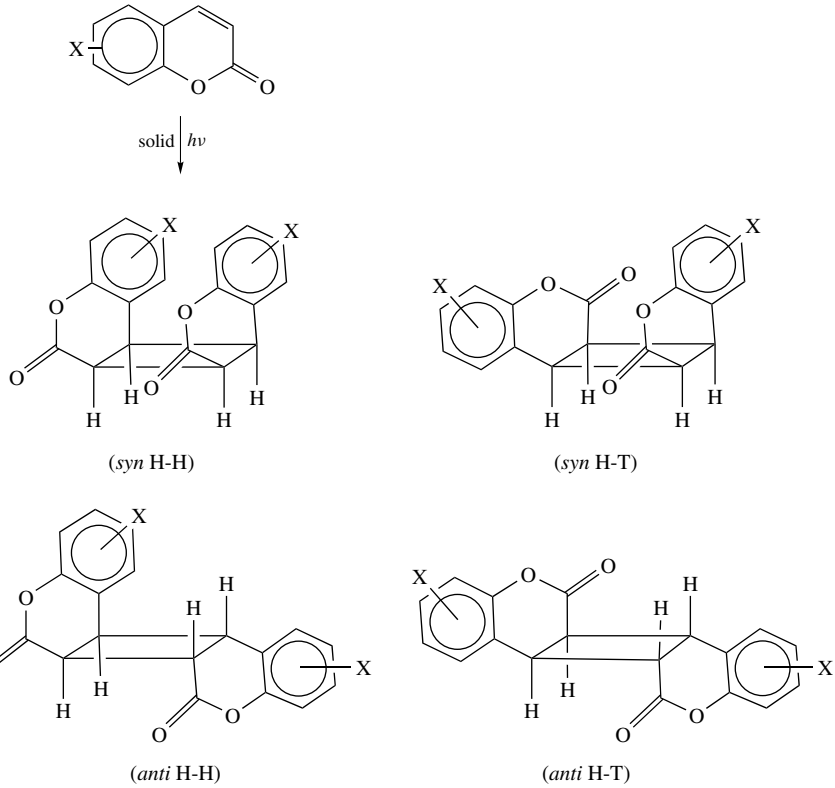
[a] Reference 4.
[b] References 5 and 6.
[c] Reference 30.
[d] Reference 48.
[e] Reference 39.

III. PHOTODIMERIZATION OF COUMARINS, STYRYLCOUMARINS AND BENZYLIDENECYCLOPENTANONES

Following the pioneering studies of cinnamic acids by Schmidt, systematic investigations on the photodimerization of coumarins, styrylcoumarins and benzylidenecyclopentanones (Schemes 2–4) have been carried out during the last two decades[10,22,49–85]. A summary of the systems investigated and the photochemical results are presented in Tables 2–4. Most observations support the original topochemical postulate of Schmidt. α and β packing arrangements of coumarins and styrylcoumarins are shown in Figures 3 and 4[53]. In the majority of examples, the structure of the dimer could be predicted based on the packing arrangement obtained through X-ray crystallographic investigations.

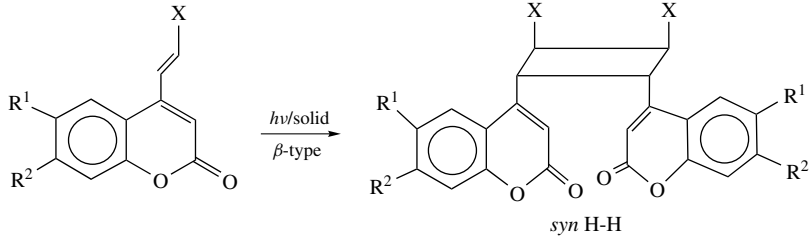
IV. REACTION CAVITY CONCEPT: ROLE OF EMPTY SPACE AND IMMEDIATE NEIGHBORS

The topochemical postulate states that *reaction in the solid state is preferred and occurs with a minimum amount of atomic or molecular movement.* This implies that a certain

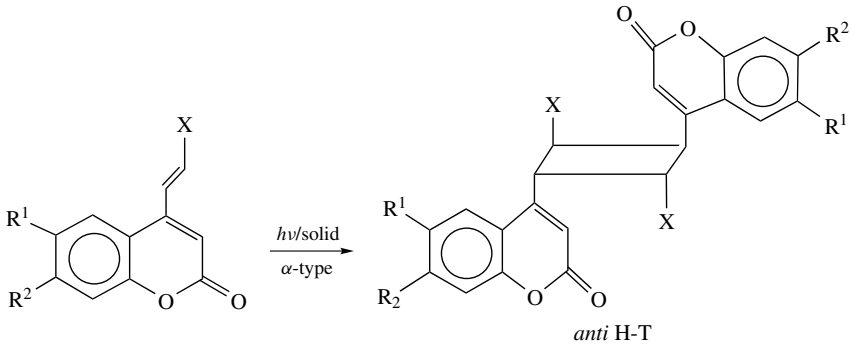


H-H : Head-Head
H-T : Head-Tail

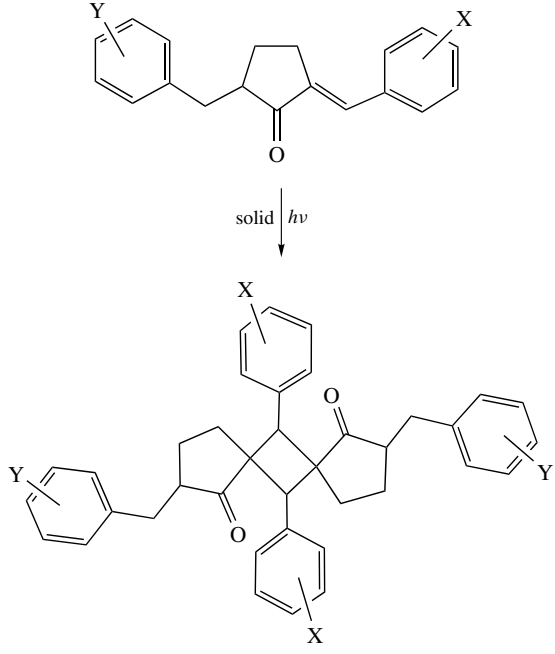
SCHEME 2



SCHEME 3



SCHEME 3. (*continued*)



SCHEME 4

amount of motion of various atoms in the crystal lattice is tolerable. Based on this, one could assume that for the formation of a cyclobutane ring with C−C bond length of 1.56 Å, the double bonds can undergo a total displacement of about 2.64 Å toward each other from the original maximum distance of 4.2 Å. Even under ideal conditions, movement of double bonds toward each other is essential for dimerization to take place. The criterion of less than 4.2 Å separation implicitly assumes that such a motion would be accommodated by the molecules surrounding the reactant pair in the crystal. Thus,

TABLE 2. Photodimerization of coumarins in the crystalline state (see Scheme 2)

Coumarins	Nature of packing	% Yield	Nature of dimer
Coumarin [a]	γ	20	Three dimers
6-Chlorocoumarin [a]	β	100	*syn* H−H
7-Chlorocoumarin [a]	β	70	*syn* H−H
4-Methyl-6-chlorocoumarin [a]	β	50	*syn* H−H
4-Methyl-7-chlorocoumarin [a]	β	80	*syn* H−H
4-Chlorocoumarin [a]	NT[f]	25	*anti* H−H and *syn* H−T
7-Methylcoumarin [a]	NT[f]	65	*syn* H−H
6-Methoxycoumarin [a]	β	60	*syn* H−H
7-Methoxycoumarin [a]	β	90	*syn* H−T
8-Methoxycoumarin [a]	α	50	*anti* H−T
6-Acetoxycoumarin [a]	β	70	*syn* H−H
7-Acetoxycoumarin [a]	β	90	*syn* H−H
4-Methyl-7-acetoxycoumarin [a]	β	80	*syn* H−H
6-Fluorocoumarin [c]	β	100	*syn* H−H
7-Fluorocoumarin [c]	β	100	*syn* H−H
7-Fluoro-4-methylcoumarin [d]	β	25	*syn* H−H
6-Fluoro-4-methylcoumarin [d]	NT[f]	30	*anti* H−T
6-Bromocoumarin [b,e]	β	90	*syn* H−H
7-Bromocoumarin [b,e]	β	100	*syn* H−H
6-Iodocoumarin [e]	β	40	*syn* H−H

[a] Reference 85.
[b] P. Venugopalan, T. Bharathi Rao and K. Venkatesan, *J. Chem. Soc., Perkin Trans. 2*, 981 (1991).
[c] V. Amerendra Kumar, Noor Shahina Begum and K. Venkatesan, *J. Chem. Soc., Perkin Trans. 2*, 463 (1993).
[d] Reference 10.
[e] G. R. Desiraju, *Crystal Engineering; The Design of Organic Solids*, Elsevier, Amsterdam, 1989.
[f] NT: Non-topochemical or defect initiated.

although the topochemical postulate focuses its attention essentially on the geometrical relationship of the reacting pairs, it seems to indirectly take into account the role of the surrounding molecules.

Once a compound has been crystallized, the template, either for good or otherwise, has been cast for the reaction. The topochemical postulate derives from this point. However, the postulate lacks precision in the following details: (1) Do the immediate neighbors of the reacting partners have any role to play? (2) Does the postulate consider the changes in the molecular geometry upon excitation? In order to take these into account at the phenomenological level, Cohen proposed the idea of the reaction cavity[86]. The cavity or cage is the space in the crystal occupied by the reacting partners. The reaction cavity by definition includes the space occupied by the reacting molecules and the void space surrounding them. The reaction cavity wall is made up of molecules adjacent to the reacting molecules. The atomic movements during a reaction would exert pressures on the cavity wall, which becomes distorted. However, the close packing works against large-scale changes in shape, so that only minimal change can occur (Figure 5). This concept has been of help in qualitatively understanding the course of a variety of solid state reactions.

The usefulness of the reaction cavity concept is readily apparent when applied to photostable crystals that would be expected to be otherwise on the basis of topochemical postulates. Based on the topochemical distance criterion, compounds **1**–**5** in Scheme 5

TABLE 3. Photodimerization of styrylcoumarins in the crystalline state (see Scheme 3)

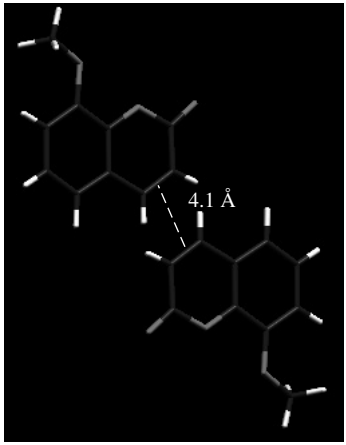
Styrylcoumarins	Nature of packing	% Yield	Nature of dimer
R^1=R^2=H, X=Ph [b]	α	46–48	*anti* H–T
R^1=F, R^2=H, X=Ph [c]	α	50	*anti* H–T
R^1=R^2=H, X=3-FC_6H_4 [c]	α	78	*anti* H–T
R^1=R^2=H, X=3-FC_6H_4 [c,f]	β	70	*syn* H–H
R^1=R^2=H, X=2-FC_6H_4 [b]	β	80	*syn* H–H
R^1=R^2=H, X=4-FC_6H_4 [b]	β	82	*syn* H–H
R^1=H, R^2=F, X=Ph [c]	γ	—	—
	β [d]	78–80	*syn* H–H
R^1=F, R^2=H, X=4-FC_6H_4 [e]	β	80	*syn* H–H
R^1=F, R^2=H, X=2-FC_6H_4 [e]	β	81	*syn* H–H
R^1=R^2=H, X=2,6-$F_2C_6H_3$ [e]	γ	—	—
R^1=F, R^2=H, X=2,6-$F_2C_6H_3$ [e]	β	85	*syn* H–H
R^1=H, R^2=F, X=2,6-$F_2C_6H_3$ [e]	β	78	*syn* H–H
R^1=H, R^2=OH, X=Ph [a]	α	100	*anti* H–T
R^1=H, R^2=OMe, X=Ph [a]	α	—	—
R^1=H, R^2=Cl, X=Ph [a]	α	70–80	*anti* H–T
R^1=R^2=H, X=2-ClC_6H_4 [a]	α	70–80	*anti* H–T
R^2=OH, R^1=H, X=3-ClC_6H_4 [a]	α	70–80	*anti* H–T
R^1=R^2=H, X=$COCH_3$ [a]	α	70–80	*anti* H–T
R^1=H, R^2=Cl, X=$COCH_3$ [a]	α	70–80	*anti* H–T
R^1=R^2=H, X=$CSCH_3$ [a]	α	70–80	*anti* H–T
R^1=H, R^2=H, X=4-ClC_6H_4 [a]	α	70–80	*anti* H–T

[a] Reference 54.
[b] K. Vishnumurthy, T. N. Guru Row and K. Venkatesan, *J. Chem. Soc., Perkin Trans. 2*, 1475 (1996).
[c] K. Vishnumurthy, T. N. Guru Row and K. Venkatesan, *J. Chem. Soc., Perkin Trans. 2*, 615 (1997).
[d] Reference 63.
[e] Reference 10.
[f] Coumarin was added as an additive during crystallization.

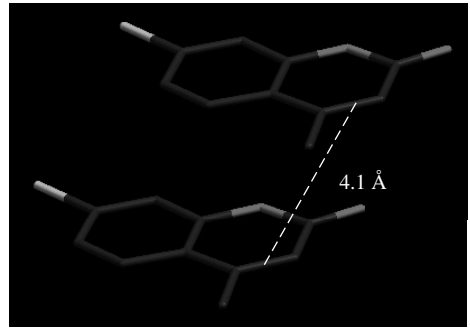
TABLE 4. Photodimerization of benzylidenecyclopentanones in the crystalline state (see Scheme 4)

Compound	Reactivity (distance between reactive double bonds)	Nature of dimer
X=Y=H [a]	Yes (4.2 Å)	*anti* H–T
X=*p*-Br, Y=H [a]	Yes (3.8 Å)	*anti* H–T
X=H, Y=*p*-Cl [a,b]	Yes (4.0 Å)	*anti* H–T
X=*p*-Br, Y=*p*-Me [a,b]	Yes (3.92 Å)	*anti* H–T
X=H, Y=*p*-Br [a]	Yes	*anti* H–T
X=H, Y=*p*-Me [a,b]	Yes	*anti* H–T
X=*p*-Cl, Y=H [a,b]	No (5.03 Å) [c]	—
X=*p*-Br, Y=*p*-Cl [a,b]	No (4.7 Å) [c]	—
X=*m*-Br, Y=H [a,b]	No [c]	—
X=*o*-Br, Y=H [a,b]	No [c]	—
X=*o*-Cl, Y=H [a,b]	No [c]	—
X=*p*-Me, Y=H [a,b]	No [c]	—
X=*m*-Me, Y=H [a,b]	No [c]	—

[a] References 22 and 77.
[b] Reference 67.
[c] Photostability arises from increased separation (>4.3 Å) of the reactive double bonds.

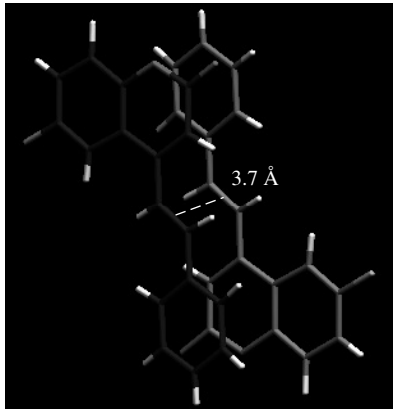


α-packing
(A)

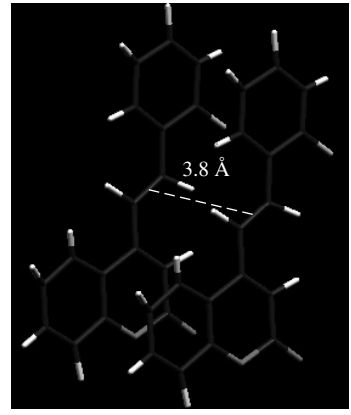


β-packing
(B)

FIGURE 3. (A) Packing arrangement of 8-methoxycoumarin (α-packing). (B) Packing arrangement of 4-methyl-7-chlorocoumarin (β-packing)



α-packing
(A)



β-packing
(B)

FIGURE 4. (A) Packing arrangement of styryl 6-fluorocoumarin (α-packing). (B) Packing arrangement of 2-fluorostyrylcoumarin (β-packing)

and Table 2 are not expected to react. In spite of the large distance of separation, they dimerize in the solid state. In compounds **6**–**12** listed in Scheme 5 and Table 5, the separation distances between reactive double bonds are less than 4.2 Å, yet they do not undergo dimerization upon photolysis[49, 50, 52, 73, 87]. The exceptional situations in all these cases can be understood qualitatively by invoking the 'reaction cavity' concept.

Analysis of the systems listed in Table 5 and Scheme 5 highlights the role of the surrounding molecules in controlling the reactivity of olefins in crystals. One of the polymorphs of distyrylpyrazine (**6**)[88], where the potentially reactive double bonds are separated by 4.19 Å, is photostable. The photostability of this compound has been

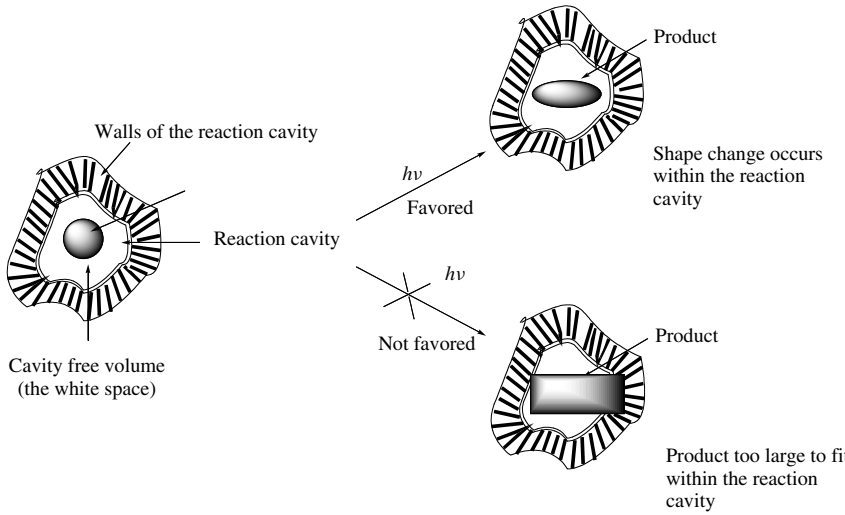
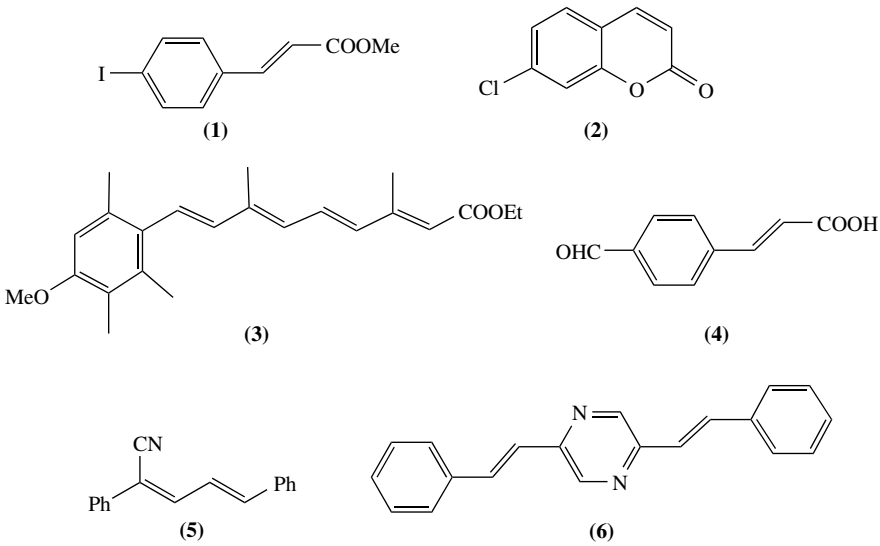
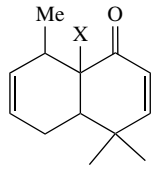


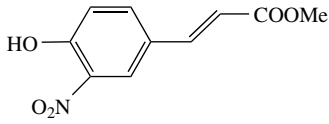
FIGURE 5. Concept of reaction cavity illustrated. Reaction cavity by definition includes the space occupied by the reactants and the empty space surrounding them



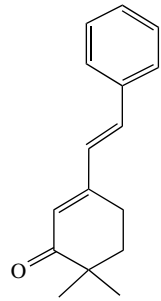
SCHEME 5



X= COOMe
(7)



(8)



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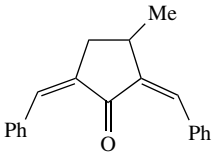

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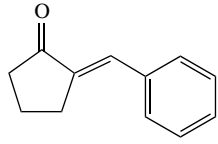

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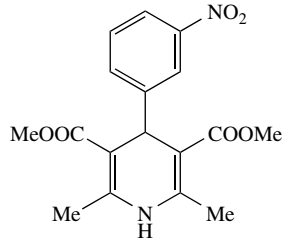


(12)

SCHEME 5. (*continued*)

TABLE 5. Examples of exceptions to original topochemical principles regarding distance (see Scheme 5)

Compound	Distance between reactive double bonds	Reactivity	Nature of dimer
Methyl *p*-iodocinnamate (**1**)	β-type, 4.3 Å	Yes	mirror symmetric
7-Chlorocoumarin (**2**)	β-type, 4.45 Å	Yes	*syn* head-head
Eteretinate (**3**)	4.4 Å	Yes	—
p-Formylcinnamic acid (**4**)	β-type, 4.825 Å	Yes	mirror symmetric
(1*Z*,3*E*)-1-Cyano-1,4-diphenylbutadiene (**5**)	5.04 Å	Yes	—
2,5-Distyrylpyrazine (**6**)	<4.19 Å	No	—
Enone (**7**)	3.79 Å	No	—
Methyl 4-hydroxy-3-nitrocinnamate (**8**)	3.78 Å	No	—
Benzylidene-*dl*-piperitone (**9**)	<4.0 Å	No	—
(+)-2,5-Dibenzylidene-3-methyl cyclopentanone (**10**)	3.87 Å	No	—
2-Benzylidenecyclopentanone (**11**)	4.14 Å	No	—
4-*m*-Nitrophenyl-2,6-dimethyldihydroPyridine-3,5-dicarboxylate (**12**)	3.73 Å	No	—

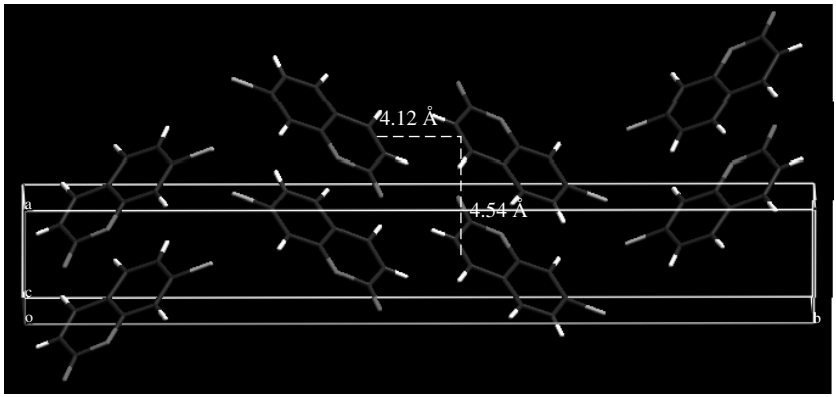


FIGURE 6. Packing arrangement of 7-chlorocoumarin. Note that one molecule is closer to two adjacent molecules, one α-packing and the other β-packing

ascribed to the layered structure which suppresses the molecular deformation necessary for the cycloaddition reaction. Another example, where the molecular packing satisfies the topochemical criteria but yet is photostable, is enone **7**[89]. The potentially reactive double bonds are parallel with a center-to-center distance of 3.79 Å. Nevertheless, **7** is photochemically inert when irradiated in the solid state. The attributed reason for the lack of solid state reactivity of this enone is the steric compression experienced by the reacting molecules at the initial stages of photocycloaddition. In the crystal of methyl-4-hydroxy-3-nitrocinnamate (**8**)[90], the neighboring molecules are related by a translation of 3.78 Å. But it has been observed that this compound is photostable in the solid state. In the crystal structure the molecules are linked by hydrogen bonds to form a sheet-like structure close to the (102) plane. It is likely that the extensive intermolecular hydrogen bond network and C−H−O type interactions involving the ethylenic carbon atom do not permit the easy spatial movement of the atoms of the double bond in the lattice for the reaction to proceed. It has been reported that benzylidene-*dl*-piperitone (**9**)[91] is photostable in spite of the fact that there are two pairs of centrosymmetrically related double bonds which are parallel and at a distance of 3.92 and 3.98 Å, respectively. Crystalline (+)-2,5-dibenzylidene-3-methylcyclopentanone (**10**)[65] and 2-benzylidenecyclopentanone (**11**)[73] are photostable while closely related molecules possessing similar packing arrangements undergo dimerization readily in the solid state. The distance between the centers of the olefinic bonds of the inversion related pairs in the former and in the latter are 3.87 and 4.14 Å, respectively. The photostability is attributed to the reduced overlap between potentially reactive C=C bonds. Analyses of the above examples reveal that it is important to consider the arrangement of surrounding molecules with respect to the reacting pairs in addition to the relative orientation of the reacting molecules. As discussed below, the absence of photoreactivity in many of these cases can be understood by performing lattice energy calculations.

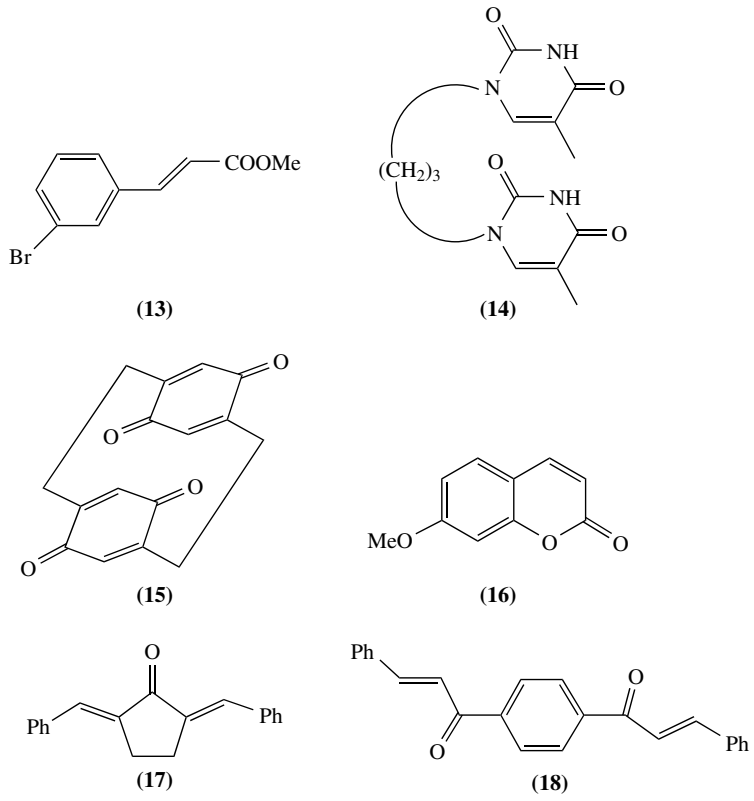
We discuss below the lattice energy calculations performed on one of these systems, 7-chlorocoumarin (**2**)[49]. These calculations were performed using the computer program WMIN developed by Busing on a large number of photodimerizable olefins. It should be stressed that in these calculations only the relative values within a series are meaningful in view of the many approximations made. Although the calculations have been carried out using the ground state geometry with the dispersion constants appropriate to the ground

state, the results provide some insight. Irradiation of crystalline 7-chlorocoumarin yields a single dimer (*syn* head-to-head)[85]. The packing arrangement shown in Figure 6 reveals that there are two potentially reactive pairs of 7-chlorocoumarin molecules in a unit cell. One pair, being translationally related, has a center-to-center distance of 4.45 Å (favored to yield the *syn* head-to-head dimer). The other pair, being centrosymmetrically related, has a center-to-center distance of 4.12 Å (favored to yield the *anti* head-to-tail dimer). Despite the favorable arrangement of the centrosymmetric pair, the dimer is obtained only from the translationally related pair. It has been calculated that the rise in the lattice energy to achieve the ideal geometry for the translated pair (separated by 4.45 Å) is 177 kcal mol^{-1}, whereas for the centrosymmetric pair (separated by 4.12 Å) the energy increase is as large as 18,083 kcal mol^{-1}. This shows that the reaction pathway leading to the experimentally observed *syn* head–head dimer is energetically more favorable than the *anti* head–head isomer. In other words, the free volume around the translationally related pair is much larger than that near the centrosymmetrically related pair whose double bonds are initially closer. Lack of free volume in the most topochemically favored pair leads to no reaction while the presence of sufficient free volume allows dimerization of the less favored pair. The above example emphasizes the importance of void space around the reacting partners, the size of which may vary from system to system. Thus the crystal reactivity requires the availability of free space around the reaction site.

V. FINE TUNING OF TOPOCHEMICAL POSTULATES

According to the original topochemical postulates, the photodimerization in the solid state is likely to occur when separation between the reacting C=C π-bonds is less than 4.2 Å and the two C=C bonds are parallel to one another. These criteria were set based on extensive studies on cinnamic acids. These rules are still followed by a large number of molecules listed in Tables 2–4 and listed in Schemes (24–27) in Section XI. With the exception of methyl *p*-iodocinnamate (**1**), all the cinnamic acid derivatives which have adjacent double bonds separated by a distance of more than 4.2 Å in the crystalline phase are photostable. In the case of methyl *p*-iodocinnamate, the molecules are arranged in a β-type packing with an inter-double bond distance of 4.3 Å and yet react to yield the expected photodimer[49]. One should note that the upper limit of the critical distance for photodimerization in the solid state was set in the absence of experimental data in the range 4.2–4.7 Å, above which photodimerization does not occur.

Five examples in which photodimerization does occur, even when the separation between reacting C=C bonds is more than 4.2 Å, are presented in Table 5. Irradiation of crystalline 7-chlorocoumarin (**2**) yielded a single (*syn* head–head) dimer. The packing arrangement reveals that the two reactive 7-chlorocoumarin molecules are separated by 4.45 Å (Figure 6). Since the only dimer obtained corresponds to *syn* head–head, it is clear that the reaction is between the pairs translated along the *a*-axis. It is noteworthy that the distance of 4.45 Å lies beyond the so far accepted limit of 3.5–4.2 Å for photodimerization in the solid state. Photodimerization of etretinate (**3**)[87] in the solid state yield two dimers. The center-to-center distance for the two sets of dimerizable bonds are 3.8 and 4.4 Å, the latter being outside the presently accepted limit. The most unusual case reported so far is *p*-formylcinnamic acid (**4**)[33,48]. This crystal, possessing a *b*-axis of 4.825 Å, dimerizes in the solid state to yield a mirror symmetric dimer. The above examples point out the need for a closer examination and modification of the distance criteria for photodimerization. These suggest that if the surrounding molecules can tolerate motions of the reacting pair, the reacting C=C bonds need not be within the initially stipulated distance of 4.2 Å.



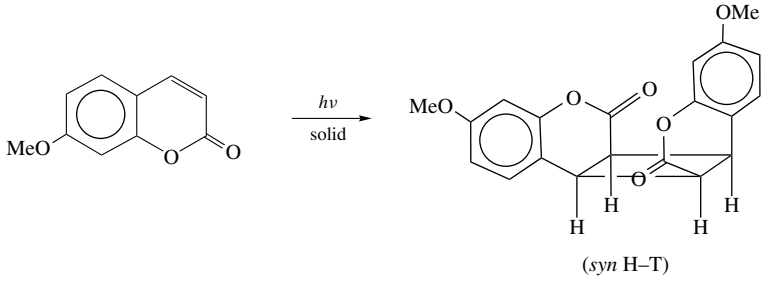
SCHEME 6

TABLE 6. Examples of exceptions to original topochemical principles regarding parallelism of double bonds (see Scheme 6)

Compound	Rotational angle of one bond with respect to the other (deg)	Reactivity–dimerization
Methyl *m*-bromocinnamate (**13**)	28	No
1,1′-Trimethylene-bis-thymine (**14**)	6	Yes
[2,2](2,5)-Benzoquinophane (**15**)	3	Yes
7-Methoxycoumarin (**16**)	65	Yes
2,5-Dibenzylidenecyclopentanone (**17**)	56	Yes
1,4-Dicinnamoylbenzene (**18**)	6	Yes

Apparently, a reacting pair can move much more than 2.64 Å, originally envisioned by Schmidt. Note that motion is along a plane perpendicular to the molecular plane.

A few cases (**13**–**18** in Scheme 6 and Table 6) have also been reported where exact parallelism between reactant double bonds has not been adhered to and yet



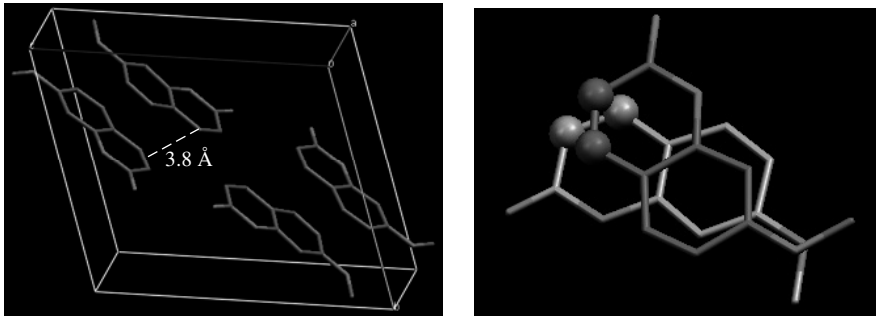
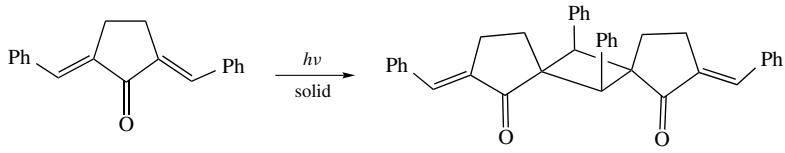
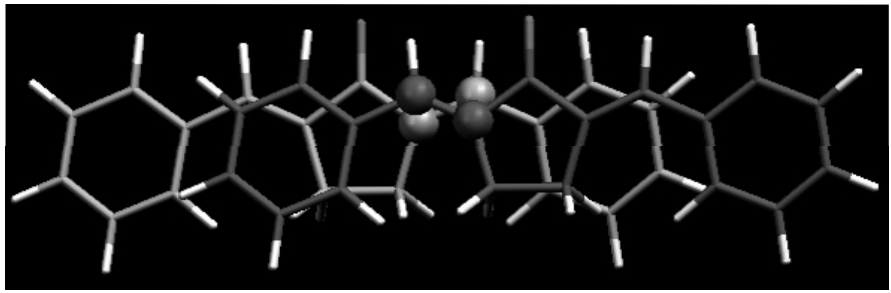


FIGURE 7. Packing arrangement of 7-methoxycoumarin. Note that the two reactive double bonds are not parallel to one another

photodimerization occurs[49,92]. Two most glaring examples are 7-methoxycoumarin (**16**)[50] and 2,5-dibenzylidenecyclopentanone (**17**)[65,66,76,77,80–84]. In these two molecules the reacting C=C pairs are criss-crossed (Figures 7 and 8). In the crystals of 7-methoxycoumarin, the reactive double bonds are rotated by about 65° with respect to each other, the center-to-center distance between the double bonds being 3.83 Å. In spite of this 'unfavorable' arrangement, photodimerization occurs giving *syn* head–tail dimer as the only product in quantitative yield. 2,5-Dibenzylidenecyclopentanone **17** is analogous in its behavior and packing to 7-methoxycoumarin. When **17** is irradiated by UV light in the crystalline state, the principal product is formed by a [2 + 2] dimerization. The cyclopentanone **17** molecules are arranged such that the mean distance separating the potentially reactive centers is *ca* 3.7 Å, the angle between the two bonds being 56°. Although this is not the geometry considered conducive for a topochemical reaction, dimerization does indeed take place in the solid state. It is remarkable that although the relevant olefinic π orbitals are not overlapping in their ground state geometry, both are photoreactive. These cases in which the nonparallel alignment of the π orbitals does not inhibit photoreactivity indicate that there must be enough freedom for the reactive molecules to undergo the necessary movements to reorganize in their respective crystal lattices to allow dimerization to occur. In these two examples the motion required to bring the two reactive C=C bonds one over the other is translation along the molecular plane.

At this stage one obvious question is: if 7-methoxycoumarin and 2,5-dibenzylidenecyclopentanone which are not aligned properly react, why not methyl *m*-bromocinnamate (**13**)[93] in which the two reactive C=C bonds make an angle of 28°





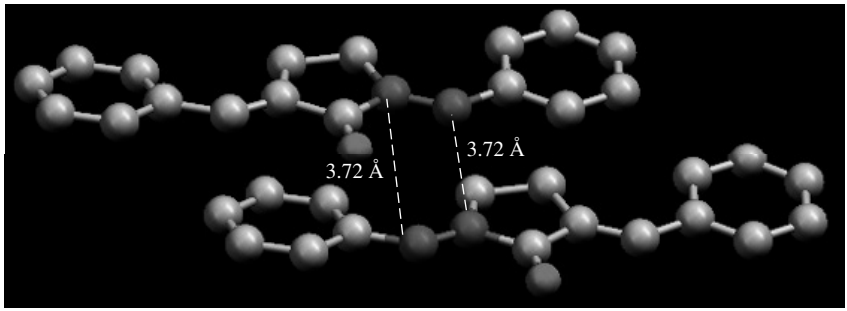
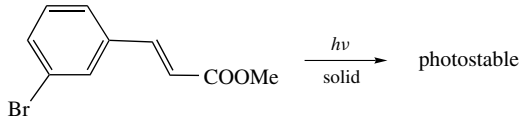


FIGURE 8. Packing arrangement of 2,5-dibenzylidenecyclopentanone. Note that the two reactive double bonds are not parallel to one another

(Figure 9)? Recognition of the possible differences in the nature of reaction cavities in 7-methoxycoumarin, 2,5-dibenzylidenecyclopentanone and methyl *m*-bromocinnamate leads to a better understanding. In methyl *m*-bromocinnamate, similarly to 7-methoxycoumarin, the double bonds are not ideally oriented for topochemical dimerization. Although the distance between the centers of adjacent double bonds is 3.93 Å, the double bonds are not parallel. They make an angle of 28° when projected down the line joining the centers of the bonds. The energy increase needed to bring the two reactant molecules together to obtain the right isomer in 7-methoxycoumarin is about 200 kcal mol^{-1}, roughly the same order of magnitude as for many photoreactive crystals with favorably oriented pairs. On the other hand, in the case of methyl *m*-bromocinnamate, the energy increase to align the molecules parallel to each other in a geometry suitable for dimerization is enormous (6726 kcal mol^{-1}). Such a large increase in the lattice energy probably does not favor reorientation of the molecule to result in photodimerization.



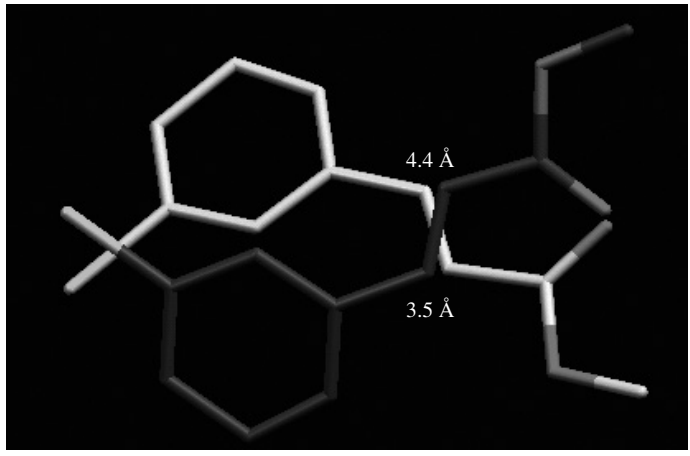


FIGURE 9. Packing arrangement of methyl *m*-bromocinnamate. Note that the two reactive double bonds are not parallel to one another

All these examples, which appear anomalous in the light of topochemical postulates, can be understood on a unified conceptual basis if one incorporates the reaction cavity concept of Cohen within the topochemical postulates due to Schmidt. Dimerization may be considered as taking place in a 'nano-cavity' within the bulk crystal, the latter being the host and the reactive pair the guest. The size and shape of the cavity and the interactions between the 'guest reactants' and the host lattice will determine whether the nontopochemically arranged molecules would be permitted to undergo the motion necessary to reach a topochemical arrangement. Before assigning the reactivity of these anomalous pairs to bulk crystals, it is important to rule out defects being responsible for reactivity of these unusually placed pairs. In this chapter we do not discuss defect centered photodimerizations in the solid state.

It is clear that in addition to relative atomic positions, relative orientation of the reactive π orbitals must be monitored to assess the feasibility of dimerization in the solid state. Less than ideal atomic and orbital orientations can still give rise to dimerization if the surrounding lattice can tolerate motions that would steer the molecules to proper mutual orientation.

VI. IMPACT OF EXCITATION ON MOLECULAR GEOMETRY AND INTERMOLECULAR ARRANGEMENT

The static concept of preorganization does not correspond to reality inasmuch as it does not take into account the changes caused by molecular excitation. Excitation of molecules to higher electronic levels brings about changes, among other things, in the geometry and

polarizability of molecules. For example, it is well known that formaldehyde undergoes pyramidalization upon excitation with a corresponding change in dipole moment. For olefins, the preferred minimum energy configuration in the excited state is the perpendicular (orthogonal π orbitals) rather than planar form. It is also established that for some aromatics, dimeric complexes, i.e. excimers, are stabilized with respect to monomers in the excited state. Such differences in geometry and polarizability between the ground and the reactive excited state is expected to have subtle consequences on the topochemical postulates based on ground state properties. It is important to note that predictions concerning excited state reactivity are made based on accurate ground state geometries and packing arrangements obtained crystallographically. Accurate predictions are possible only if the difference in geometry between the ground and the reactive excited states is taken into account. In this context, it is of interest to note that work on obtaining X-ray crystal structures of molecules in excited states has already begun.

In the ground state, the crystal is expected to be homogeneous and the forces operating between molecules in the crystals are expected to be uniform. However, upon excitation the crystal will contain two types of molecules, most in the ground state and a few in the excited state. The forces operating between an excited molecule and its neighbors differ from those operating between a ground state molecule and its surroundings. The change in polarizability upon excitation increases the attractive part of the intermolecular force, while the repulsive part remains, initially, unchanged. *The localized excitation produces a particular type of local instability of the lattice configuration that may lead to large molecular displacements*. The displacements may favor the formation of excimers and photodimers in crystals.

Craig and coworkers[94–96] have carried out an incisive theoretical investigation of this problem and have shown that a short-term lattice instability created upon excitation has the effect of driving one molecule close to a neighbor, thus promoting excimer or exciplex formation. The calculation for 9-cyanoanthracene showed that, for a short period after excitation, an excited molecule can be displaced away from its equilibrium crystal lattice position into an unsymmetrical local structure, with the excited molecule closer to one neighbor in the stack of molecules than to the other. In such a model there is a transient preformation of an excimer not evident in the equilibrium local structure. The important message of the investigations by Craig and coworkers is that it is of the utmost importance to consider the dynamic properties of lattices (caused by photoexcitation) in order to understand the processes involved in photochemical reactions in crystals. This also implies that the dimerization may occur within a reaction cavity under conditions where the molecules are less than ideally oriented. The driving force to bring the pair into proper orientation will be provided by electronic excitation energy and the increased attractive interaction energy in the excited state.

Two recent examples provided in Figures 10 and 11 further highlight the role of excitation and flexibility of reactant molecules in the crystalline state. In these two examples, interaction between an amine (or an amide) and an acid is used to steer the olefinic chromophores within the reacting distance. In the example provided in Figure 10[97,98], the hydrogen bonded complex between *trans*-cinnamamide and phthalic acid upon irradiation yields the β-truxinamide. However, the packing is not suitable for such a dimer formation. As seen in Figure 10, the two olefinic bonds are not parallel and the two ends are separated by 3.8 and 4.8 Å. Based on the dimer (β-truxinamide) formed, it is speculated that one of the olefins performs a pedal-like motion prior to dimerization. A similar motion must also be involved during the irradiation of the salt between diaminocyclohexane and 2,4-dichlorocinnamic acid (Figure 11)[99]. Once again, the two olefinic bonds

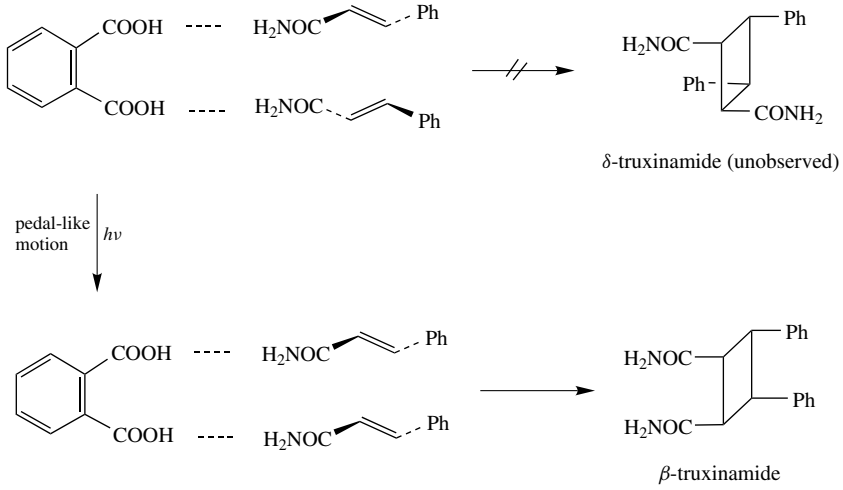


FIGURE 10. Packing arrangement in hydrogen bonded co-crystals of phthalic acid and *trans*-cinnamamide. Note that the two double bonds are not aligned properly for dimerization. As shown in the scheme, pedal-like motion brings the two double bonds parallel and leads to β-dimer

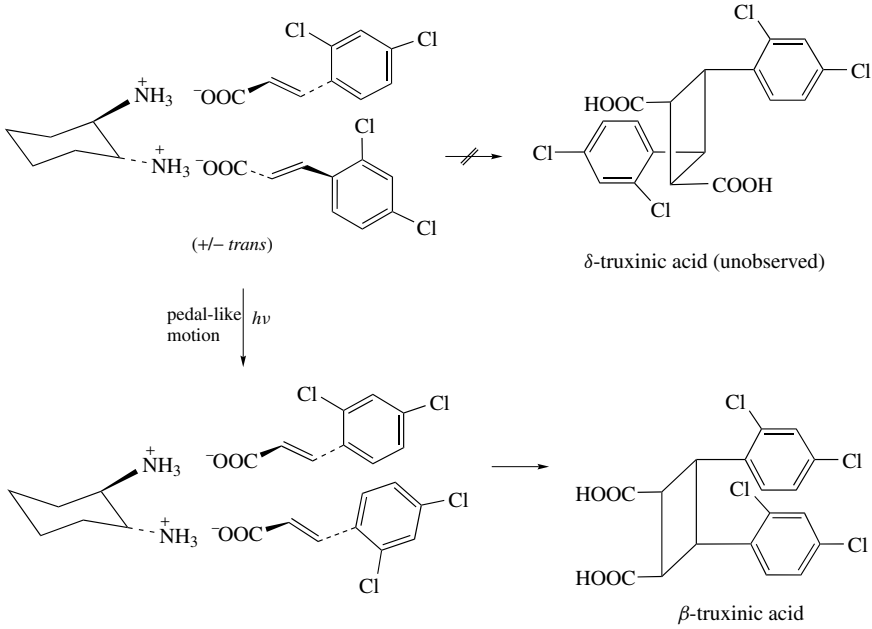


FIGURE 11. Packing arrangement in crystals of the double salt of 1*R*,2*R*-diaminocyclohexane and 2,4-dichlorocinnamic acid. Note that the two double bonds are not aligned properly for dimerization. As shown in the scheme, pedal-like motion brings the two double bonds parallel and leads to β-dimer

are not parallel and the two end distances are not equal (3.39 and 4.55 Å). A pedal-like motion prompted by excitation energy is likely to bring the pairs of double bonds parallel and allow the dimerization to occur.

The examples provided above illustrate that one of the two reacting olefins could exert substantial motion (move perpendicular to or along the molecular plane or undergo rotation around C−C bonds). The driving force to bring the pair into proper orientation is provided by electronic excitation energy and the increased attractive interaction energy in the excited state.

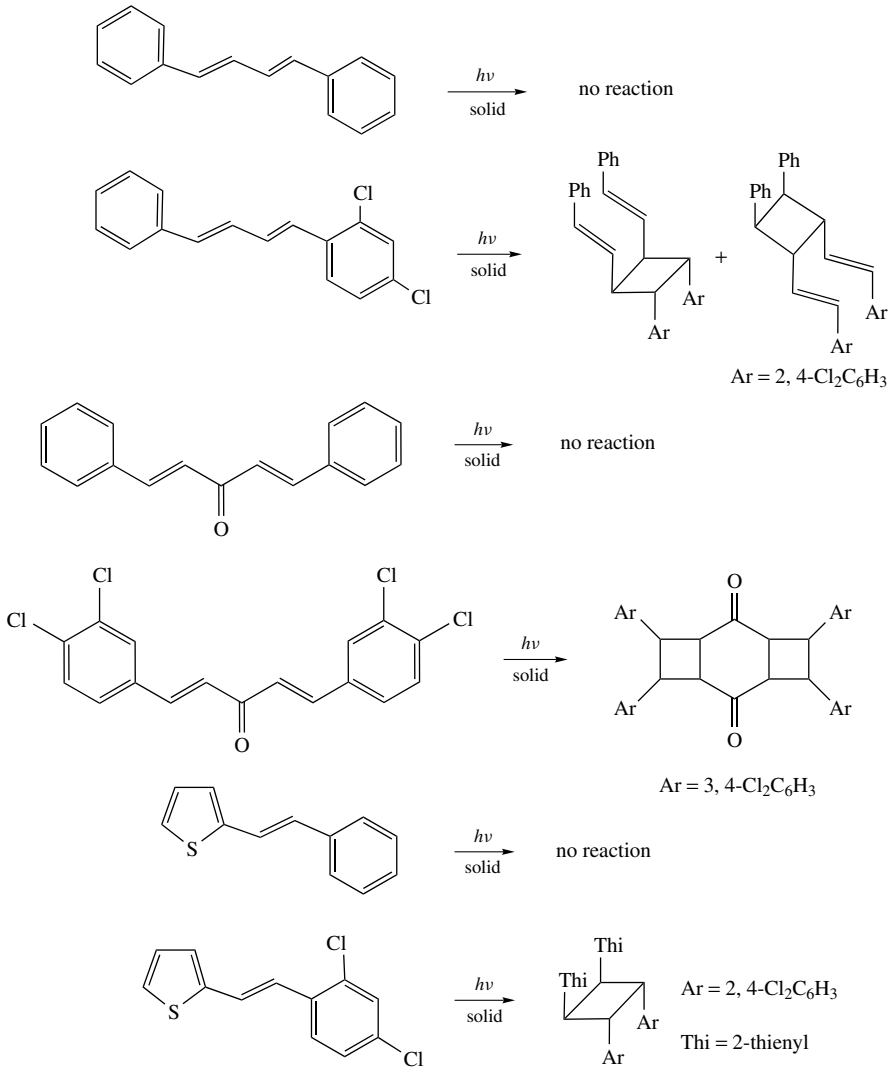
VII. CRYSTAL ENGINEERING

Based on topochemical postulates discussed above, it is clear that in order for a reaction to occur in the crystalline state one has to have the molecules preorganized in the desired pattern in the crystals. However, some amount of tolerance in terms of distance (4.2 Å) and parallel arrangement of C=C bonds is expected. Most of the current efforts in this area are devoted to establishing reliable strategies that would steer molecules so as to obtain an organic crystal structure of a predetermined form. Schmidt has termed this operation 'crystal engineering'[37]. One of the major problems encountered here is lack of complete understanding of the intra- and intermolecular interactions leading to the observed crystal packing. If one had a complete understanding of the ways in which inter- and intramolecular interactions control packing of molecules in crystals, it would be feasible to design template groups, perhaps of temporary attachment, to the functional molecules to guide photochemically reactive groups into appropriate juxtaposition in crystals. In order to bring the reactive molecules into proper orientations, several distinct strategies have been employed: (a) Intramolecular substitution, (b) templation with host structures, (c) mixed-crystal formation, (d) generation of polymorphic forms, (e) steering crystallization through donor–acceptor and hydrogen-bonding strategies and (f) structural isomorphism through groups of equivalent size. We briefly discuss the first two that have proven to be more general and reliable than the last four.

A. Substitution of Halogens

Schmidt and coworkers recognized quite early that monochloro substitution and especially dichloro substitution in aromatic molecules tend to steer molecules in crystal lattices with a short axis of *ca* 4 Å, the so-called β-structure. A few examples are provided in Scheme 7[37,51,100–106]. It is remarkable to note in Scheme 7 that while the parent alkene or enone in each case fails to photodimerize in the solid state, the dicholoro substitution leads to mirror symmetric dimers. The packing arrangement shown for (1*E*,3*E*)-1-phenyl-4-(2′,6′-dichlorophenyl)-1,3-butadiene in Figure 12 reveals that the attractive Cl−Cl interaction steers the molecule in the correct orientation for dimerization. Chloro substitution has been successfully employed during dimerization of coumarins and 2-benzyl-5-benzylidenecyclopentanones (Tables 2 and 4)[75–78,80,84]. It has been observed that coumarin undergoes photodimerization nontopochemically, yielding three dimers. However, all of the five chlorocoumarins investigated underwent clean dimerization in the solid state. The *syn* head–head dimers were obtained in 6-chloro-, 7-chloro-, 4-methyl-6-chloro- and 4-methyl-7-chlorocoumarins as a direct consequence of their β-packing structure[50,58,59].

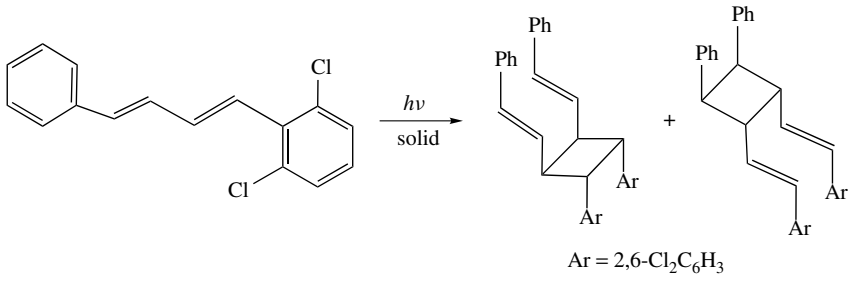
There have been several theoretical studies reported on the nature of Cl···Cl interactions. From the crystal structure data for Cl_2, Br_2 and I_2, it has been observed that the intermolecular contacts Cl···Cl, Br···Br and I···I are much shorter than the sum of



SCHEME 7

the van der Waals radii, indicating the presence of specific attractive interactions. This has been confirmed from the Cambridge Data Base statistical analyses of the packing arrangement of a large number of chloro-substituted organic molecules[51]. It appears from the experimental data available so far that chlorine is a good steering group, although there are a few failures.

In addition to chloro substitution, fluoro substitution has been effectively used to steer molecules in the correct orientation for dimerization[64, 107–111]. Although monofluoro



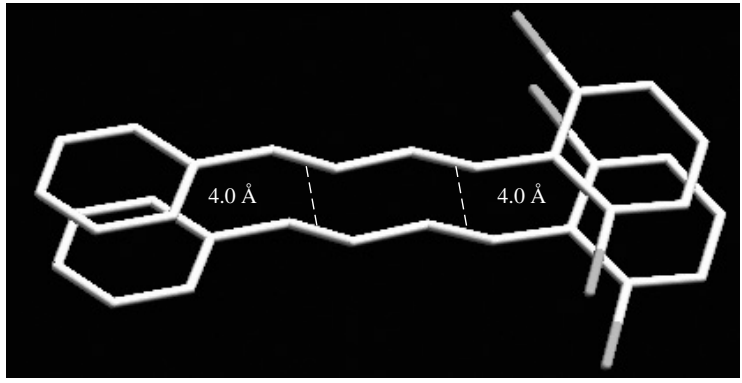


FIGURE 12. Packing arrangement in the crystals of (1*E*,3*E*)-1-phenyl-4-(2′,6′-dichlorophenyl)-1,3-buta-diene. The dichloro substitution brings the two molecules within reactive distance and keeps them parallel

substitution has been successfully used to steer coumarins into β-packing (Table 2), the origin of such an influence is unclear. Its use in other systems is yet to be established. The most reliable and predictable approach has been the use of pentafluoro derivatives. Several examples are provided in Figures 13 and 14 and Schemes 8 and 9[109, 112]. In all these cases the interaction between parent and fluoro substituted aryl groups drives the packing. The packing arrangements shown in Figures 13 and 14 bring out this feature. The nature of interaction may be of donor–acceptor or quadrupolar–quadrupolar type interaction between electron-rich phenyl and electron-deficient pentafluorophenyl groups. This strategy works well even during photodimerization between two different olefins (Scheme 9).

B. Use of Templates: Aligning Reactants Through Hydrogen Bonding and Ionic Interactions

In this strategy, a template molecule is chosen such that the packing of the template/host molecules in the crystalline state will enable the potentially reactive guest molecules to pack in a manner that will facilitate photodimerization. In most examples thus far explored, hydrogen bonding between the template and the reactant molecules aligns the reacting pair.

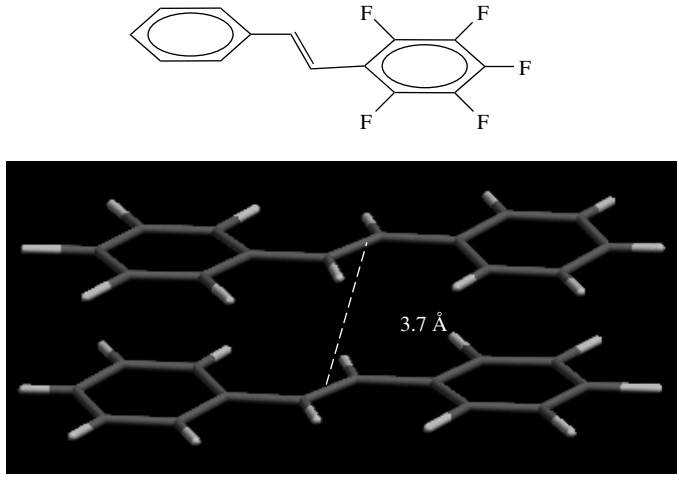


FIGURE 13. Packing arrangement in the crystals of *trans*-2,3,4,5,6-pentafluorostilbene

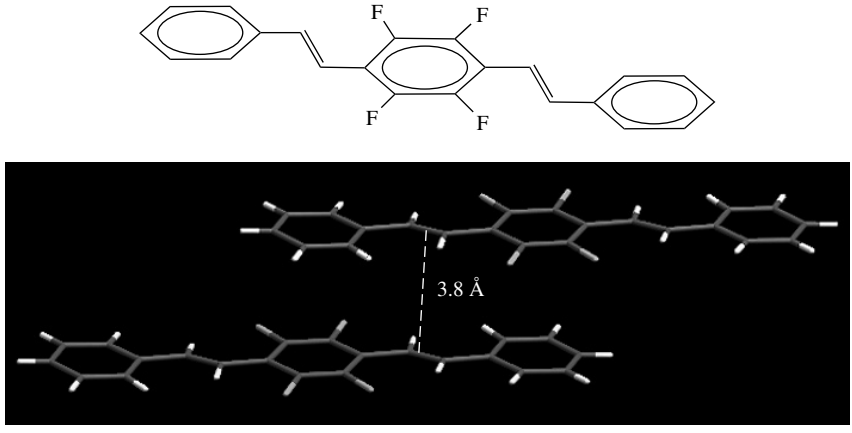
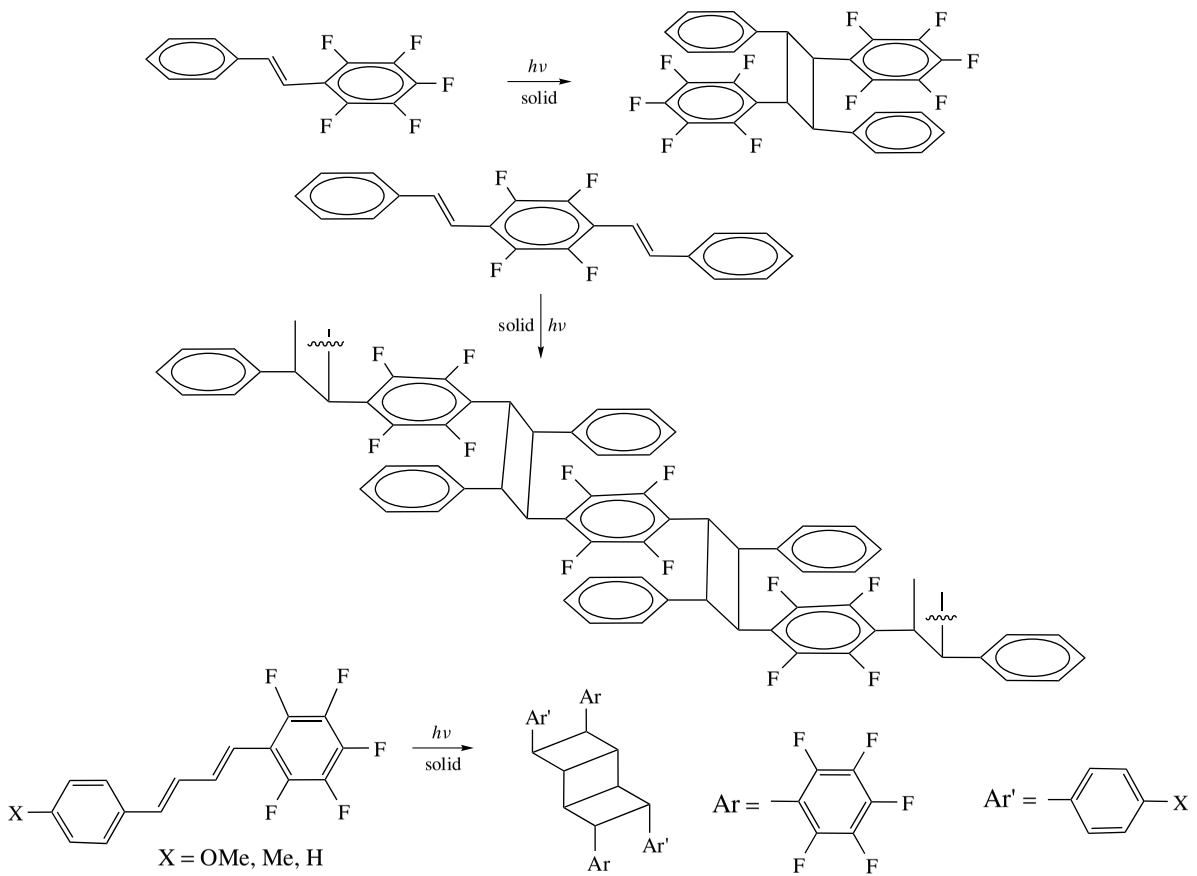


FIGURE 14. Packing arrangement in the crystals of *trans, trans*-1,4-bis(2-phenylethenyl)-2,3,5,6-tetrafluorobenzene

One of the early examples involved the use of a diacetylene diol as a templating agent. Irradiation of powdered complexes of benzylidene acetophenone (chalcone) with the achiral diacetylene diol **19** gave a single photoproduct (>80% yield), which has been characterized as a *syn* head–tail dimer (Scheme 10)[113–120]. It is important to note that benzylidene acetophenone in the absence of template crystallizes in two polymorphic modifications and the center-to-center distances between the double bonds are 5.2 and 4.8 Å in the two polymorphs. A remarkable effect of diacetylene diol **19** template is to bring the two reactive molecules closer. The molecules of the guest are packed in parallel

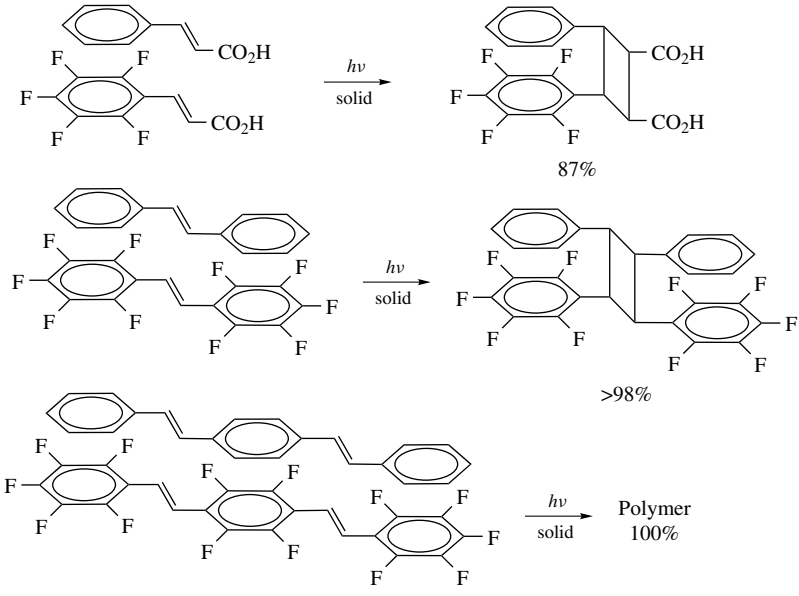


SCHEME 8

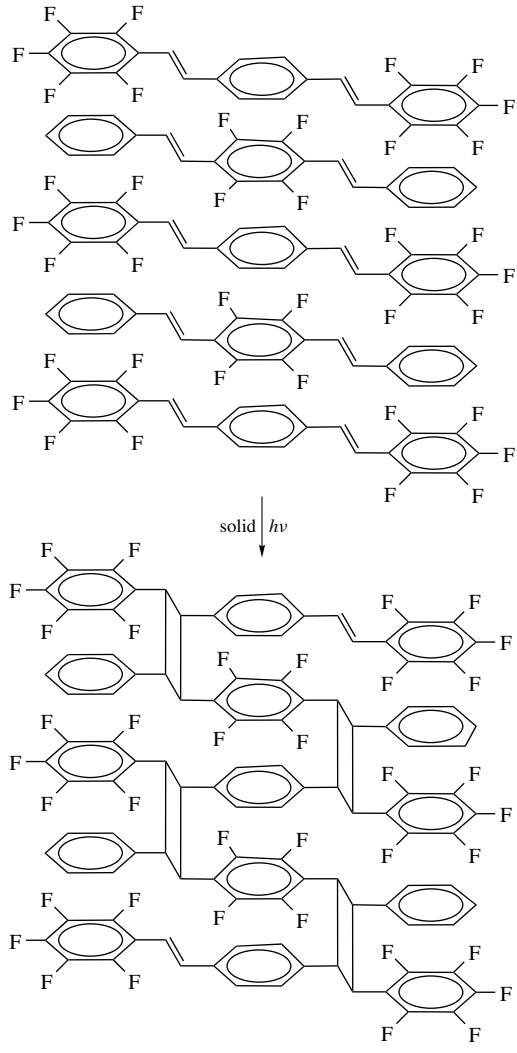
pairs related by an inversion center. As a result, the planes of the double bonds are parallel and the center-to-center distance is 3.8 Å (Figure 15)[121–123]. This arrangement enables the photodimerization to give the *syn* head–tail dimer. A number of coumarins have been successfully dimerized to *syn* head-head dimers with the help of a chiral diacetylene diol **20** template (Scheme 10).

Although generality of the use of diacetylene diol templates is yet to be established, striking examples of template strategy using 1,3-dihydroxybenzene as a template have recently been provided (Schemes 11 and 12)[113–120]. *Trans*-1,2-bis(4-pyridyl)ethylene upon irradiation in solution, not surprisingly, undergoes *cis–trans* isomerization. Irradiation of crystals of *trans*-1,2-bis(4-pyridyl)ethylene does not give any products. Scrutiny of the crystal structure reveals that *trans*-1,2-bis(4-pyridyl)ethylene molecules crystallize in a layered structure in which olefins of neighboring molecules are separated by more than 5.7 Å (Figure 16)[114]. Such a large distance does not allow dimerization. This molecule can be engineered to dimerize in the crystalline state if it is co-crystallized in the presence of 1,3-dihydroxybenzene (resorcinol). Irradiation of a mixture of 1,3-dihydroxybenzene and *trans*-1,2-bis(4-pyridyl)ethylene in solution resulted only in geometric isomerization. On the other hand, in the crystalline state a single photodimer was obtained in quantitative yield. In this case hydrogen bonding between 1,3-dihydroxybenzene and *trans*-1,2-bis(4-pyridyl)ethylene keeps the olefins parallel to each other and within 3.65 Å, thus facilitating the dimerization process (Figure 16). As illustrated in Scheme 11, this approach has been extended to dienes and trienes. The key realization in these studies is that 1,3-disubstituted benzenes and 1,8-disubstituted naphthalenes can organize stacking of olefins at a distance of 4 Å. The main interaction used to organize is the hydrogen bonding.

Double salt formation between diamines and acids has been used to align reactive C=C bonds within 4.2 Å. In these examples, if the amine is chosen properly, the two olefinic



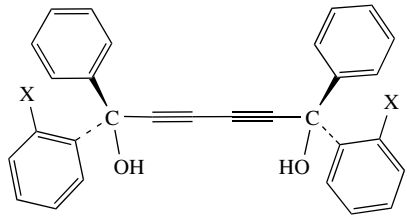
SCHEME 9



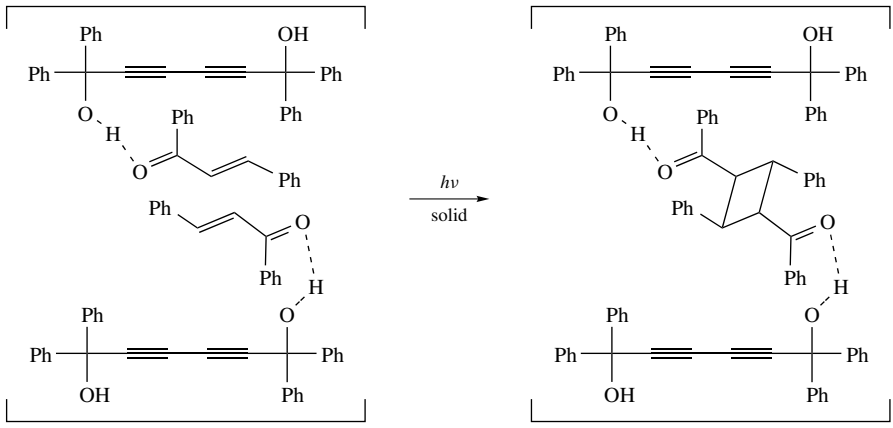
SCHEME 9. (*continued*)

chromophores will stay within the reactive distance. The main force that holds the system together is the ionic interaction between the template and the olefin. Successful examples of this strategy are provided in Schemes 13 and 14[97,98,124–128]. One of the problems of this approach is that in a number of cases the *cis* isomer (due to *trans–cis* isomerization) accompanies the dimer. This suggests that the packing must be loose enough to allow a large rotational motion of the reacting olefin.

While impressive examples to support the usefulness of the template strategy have been provided, there is likely to be an equal number of examples that have not worked. The



(19) X = H
(20) X = Cl



SCHEME 10

key to success is the choice of the template. One has to recognize that a given template may not work well for all systems.

VIII. DOES DIMERIZATION PRECEDE GEOMETRIC ISOMERIZATION?

From the above discussion it is clear that a crystal lattice could tolerate some amount of molecular motion. If this was true, the occurrence of a volume demanding geometric isomerization along with the dimerization should not come as a surprise. In Schemes 15 and 16 we have listed a few olefins that isomerize in the crystalline state[129–139]. One of the earliest observations on geometric isomerization in the crystalline state comes from the laboratory of Schmidt[129, 130]. Several crystalline *cis*-cinnamic acid derivatives upon irradiation yielded the corresponding *trans*-isomers (Scheme 17)[130]. Based on their study on cinnamic acids, Schmidt and coworkers suggested that the isomerization occurs through a mechanism that involves a metastable cyclobutane intermediate (Scheme 18)[130]. Formation of such an intermediate requires an interaction of an excited olefin with a nearest-neighbor C=C bond. This would suggest that the isomerization takes place only when two olefin units are within 4.2 Å. However, in several examples listed in Schemes 15 and 16 the olefinic units are not within 4.2 Å and also are not suitably disposed to form a cyclobutane[87, 131–136]. Therefore,

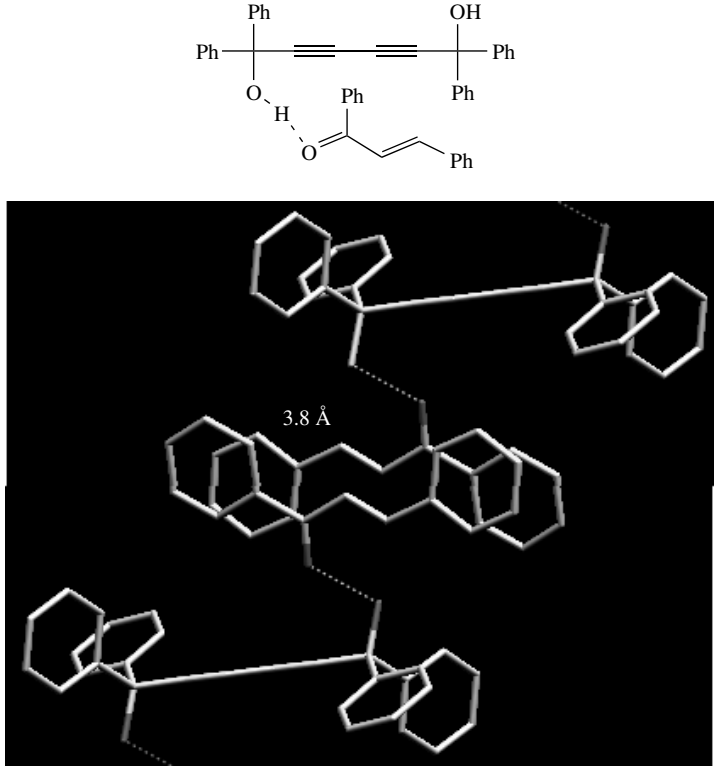
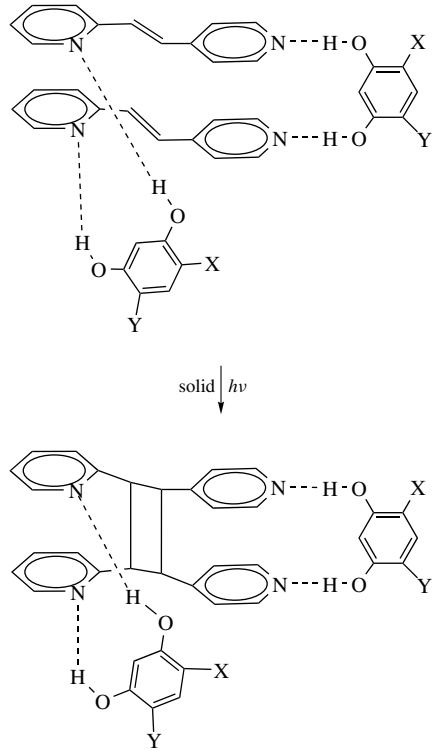


FIGURE 15. Packing arrangement in the crystals of the host–guest complex between 1,1,6,6-tetraphenyl-2,4-diyne-1,6-diol and chalcone

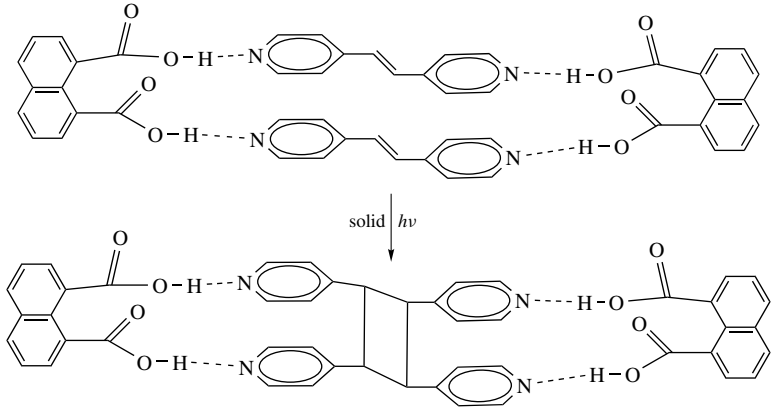
Scheme 18 may not represent a general mechanism of isomerization. But then, how does the large volume demanding isomerization occur within a crystal lattice?

The conventional model of photochemical geometric isomerization is torsional relaxation of the double bond which involves a one-bond-flip (OBF) process, i.e. turning over one-half of the molecule (Scheme 19)[137–139]. This is a three-dimensional process requiring the presence of a large free volume within a reaction cavity. In the absence of a large globular (three dimensional) free volume this process would be prevented by the walls of the reaction cavity. An alternative new mechanism known as 'hula-twist' is being currently discussed in the literature[137–139]. The 'hula-twist' (HT) process, unlike the conventional one-bond process, requires less volume change during *cis* to *trans* conversion (Scheme 19). The hula twist is more of a two-dimensional rather than a three-dimensional process. The difference between a conventional one-bond flip and the hula twist is illustrated in Scheme 20 with 5-*cis*-decapentaene as an example. During the *cis*-to-*trans* conversion via the one-bond-flip mechanism, one-half of the molecule undergoes a 180° flip, i.e. half of the molecule rises from the molecular plane and sweeps a 180° motion before it rests on the same plane in a different geometry. On the other hand, a

SCHEME 11



(a) X = Y = H
(b) X = Cl, Y = H
(c) X = Y = Cl



SCHEME 12

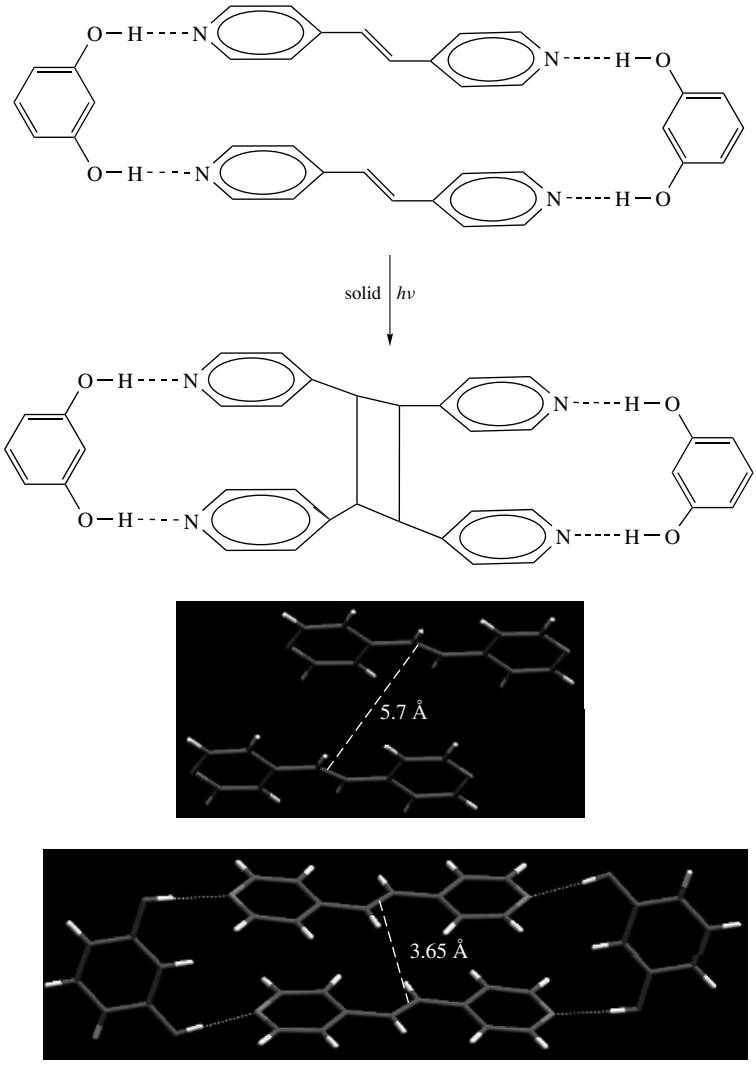
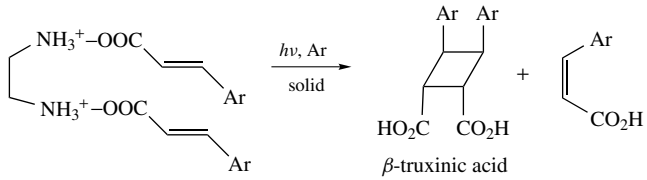
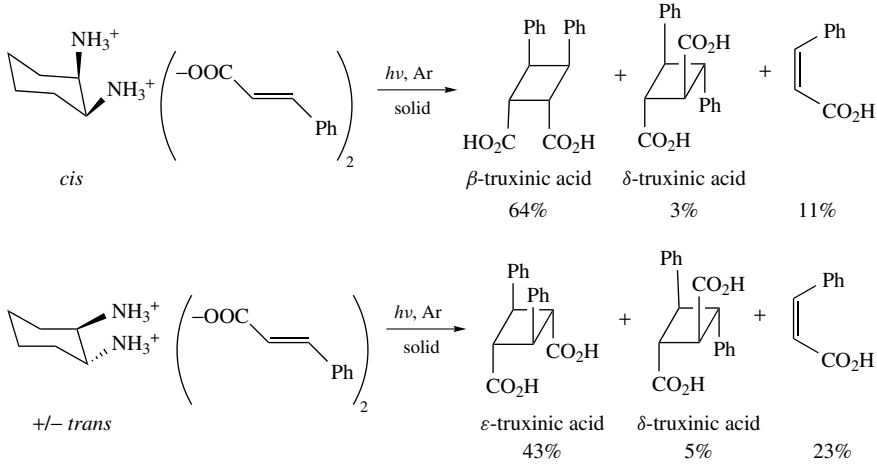


FIGURE 16. Packing arrangement in the crystals of *trans*-1,2-bis(4-pyridyl) ethylene (top). The two reactive double bonds are far apart. Packing arrangement in the co-crystals of *trans*-1,2-bis(4-pyridyl) ethylene and resorcinol (bottom). The two bonds are brought closer

hula-twist process which involves simultaneous rotation of two adjacent bonds (a single and a double bond) or 180° translocation of one C−H unit results in *cis*-to-*trans* isomerization. This process as shown in Scheme 20 results in simultaneous configurational (*cis* to *trans*) and conformational changes (*transoid* to *cisoid*). In the hula-twist process, only one C−H unit of the molecule rises above the molecular plane during *cis*-to-*trans*



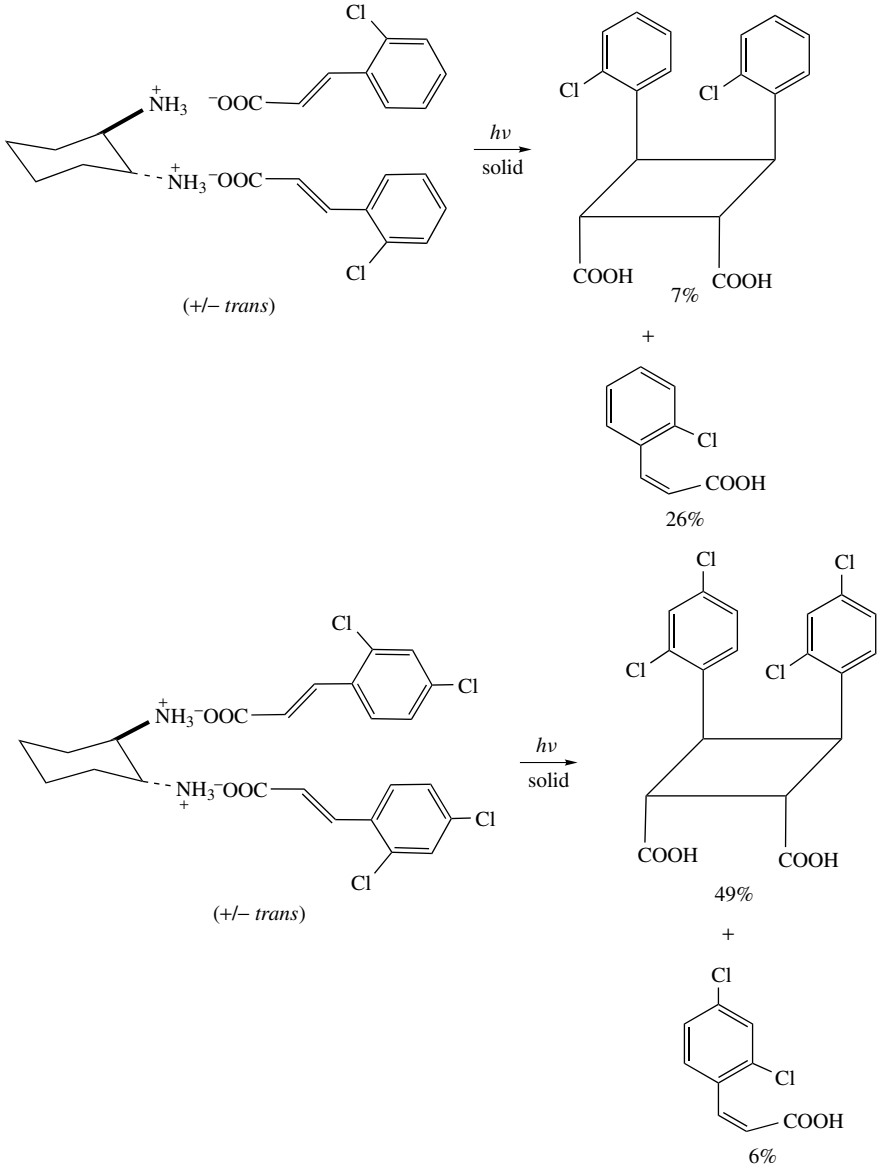
Ar = *o*-MeO-Ph	30%	23%
Ar = *o*-Cl-Ph	84	9
Ar = *m*-NO_2Ph	70	4
Ar = 2-thienyl	13	0



SCHEME 13

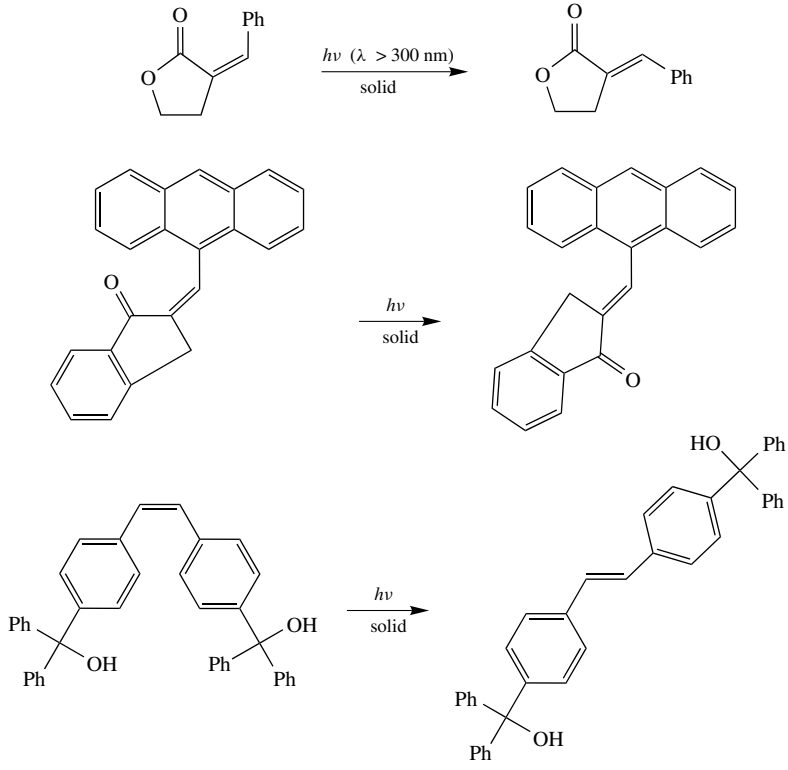
conversion. Therefore, the volume demand on this process is much less than that during the one-bond flip. In the hula-twist process, only the central atom moves in a sweeping semicircular manner (in and out of the plane of the molecule) while the two terminal atoms translate sideways in the original plane of the molecule. The point to be noted is that between the one-bond flip and the hula twist, the latter would be preferred under conditions where the reaction cavity has only a limited free volume. Although it is likely that the geometric isomerization within a crystal may occur via a hula-twist process, concrete evidence in favor of this is still lacking.

A number of organic salts investigated in the solid state have been reported to yield products of geometric isomerization. A few such examples are collected in Schemes 21 and 22[140–144]. A very interesting observation relates to the isomerization of Z,Z diene salts to the E,E isomers (Scheme 21). Neither the reverse isomerization (E,E to Z,Z) occurred nor was the product of one-bond isomerization isolated. In solution, two-bond isomerization from the excited singlet state is not common. The mechanism of this unusual phenomenon in the solid state remains unclear. In all these cases the distance between the reactive double bonds was more than 4.2 Å, suggesting that the dimerization may not precede the geometric isomerization process.



SCHEME 14

The final example in this category relates to the salts of cinnamic acids (Schemes 13, 14 and 22)[99, 125, 126, 141]. Several salts listed in Schemes 13 and 14, upon excitation, yield both dimers and the corresponding *cis* isomers. As seen in the scheme, the relative yields of the dimer vs. the *cis* isomer vary with the substitution on the cinnamic acid and with

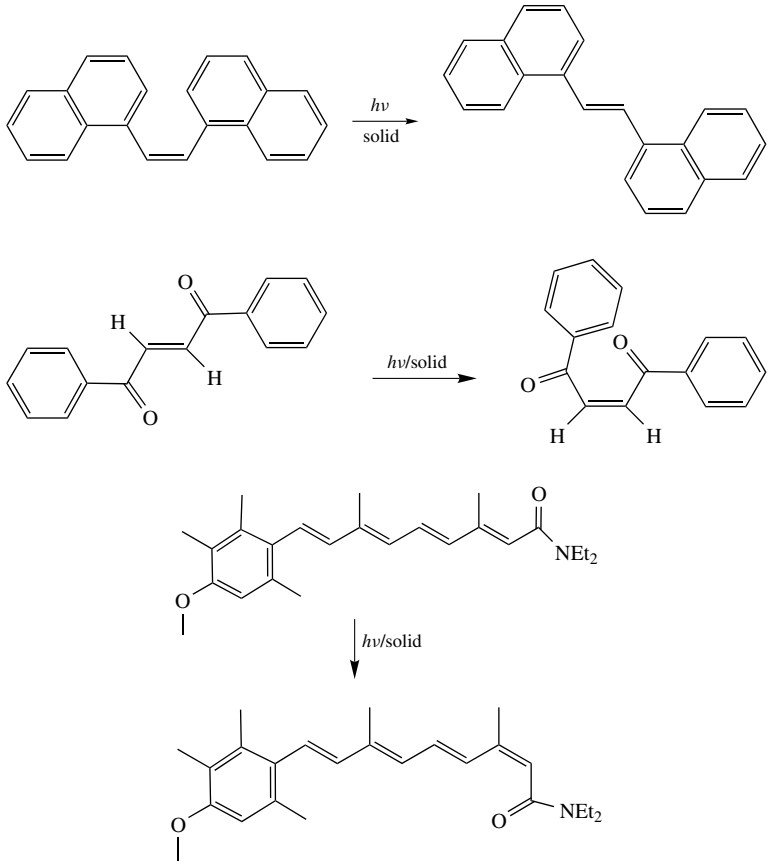


SCHEME 15

the nature of the amine used to form the salt. Temperature-dependent study in the case of 2,4-dichlorocinnamic acid and 2-chlorocinnamic acid–1,2-diaminocyclohexane salts showed that the isomerization and dimerization are independent processes. As seen in Figure 17, the ratio of the two varies with the temperature. Had the formation of metastable cyclobutane intermediate been the rate-determining step, one would expect the ratio to be independent of the temperature. The mechanism of the geometric isomerization in the crystalline state is yet to be resolved.

IX. SINGLE CRYSTAL TO SINGLE CRYSTAL PHOTODIMERIZATION OF OLEFINS

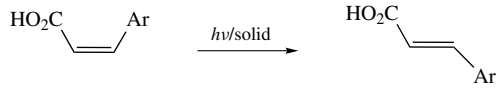
The overall phototransformation of olefins into cyclobutanes in the solid state can proceed by two pathways: single crystal to polycrystalline and single crystal to single crystal (SCSC). In the first case, the product phase goes into solid solution in the lattice of the monomer and then, as the dimer concentration rises, the solubility limit is exceeded, and the new phase precipitates. Most of the dimerization examples presented in this chapter belong to this class. For example, X-ray powder diagrams in the case of coumarins show a gradual and complete loss of long-range order and an eventual appearance of an ordered product phase. There is no evidence yet as to whether the product phase separates out



SCHEME 16

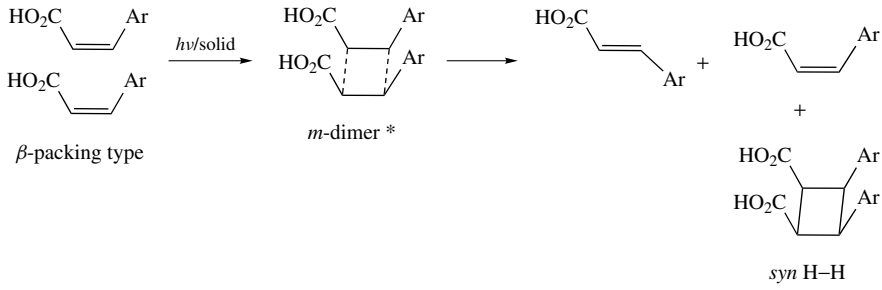
of the parent phase at specific or at random sites. Once the original monomer crystal breaks down due to contamination by the product dimer, the photodimerization may no longer be controlled by the initial packing. Since the solubility limit of the dimer in the monomer phase will vary with the reactant molecule, one might expect the maximum yield of topochemical dimer also to vary with the reactant molecule.

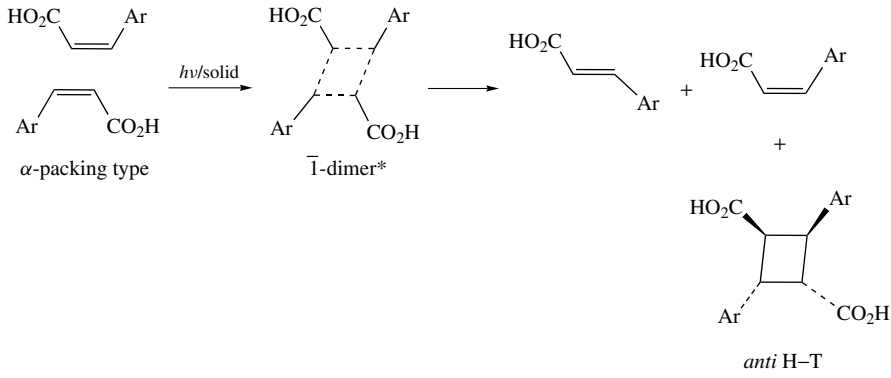
The second type of photoreactions, namely single crystal to single crystal transformation, continues to be rare. There are at least three examples of photodimerization of olefins known to belong to this category (Figures 18–20)[27, 70, 80–83, 145, 146]. The chances of achieving single crystal to single crystal transformation are much higher when the irradiation is conducted at the tail edge of the absorption of the olefin. This allows the molecules present at the surface as well as at the interior of the crystal to be uniformly excited. In these examples, the dimerization proceeds through a series of solid solutions of varying composition and is under topochemical control throughout. In these examples there is a topotactic relationship between these solid solution phases. Structure–photodimerization



cis-Cinnamic acid	Nature of packing	*Trans* CA
p-Methoxycinnamic acid	α	78
o-Ethoxycinnamic acid	α	46
α-Bromocinnamic acid	α	100
α-Bromo-o-methoxycinnamic acid	β	80
α-Bromo-m-methoxycinnamic acid	α	100
α-Bromo-p-methoxycinnamic acid	β	80
β-Methylcinnamic acid	β	—

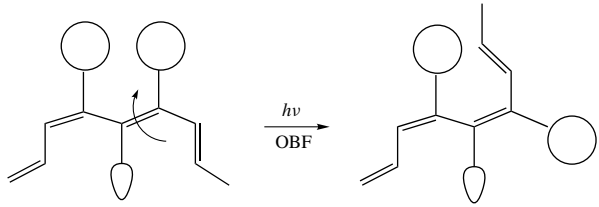
SCHEME 17



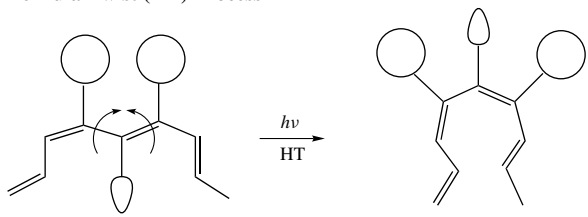


SCHEME 18

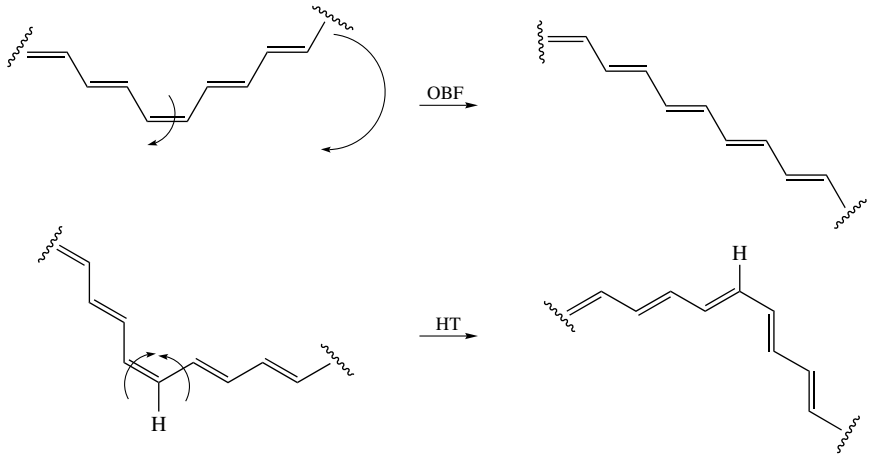
Conventional One-Bond-Flip (OBF) Process



The Hula-Twist (HT) Process



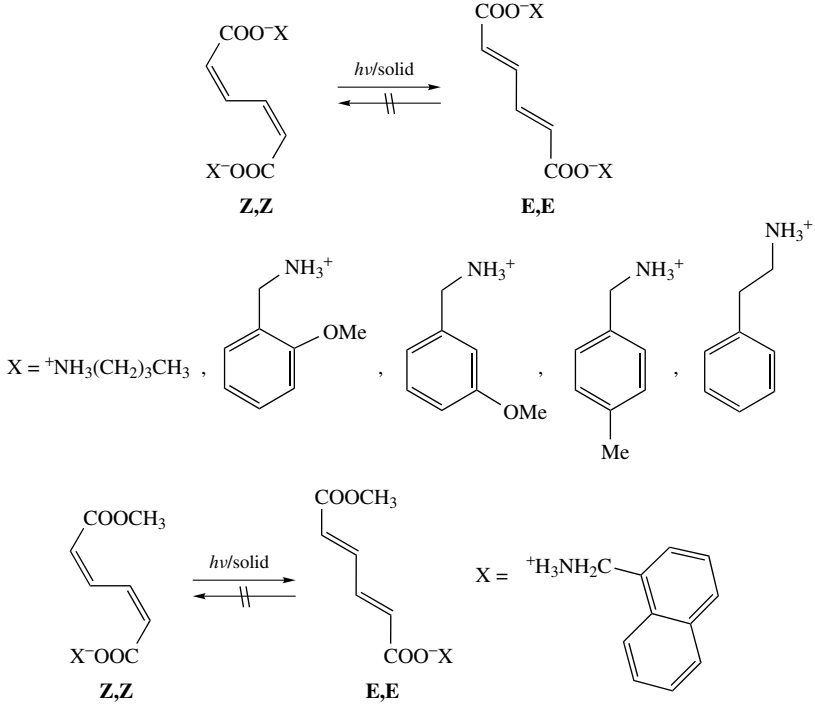
SCHEME 19



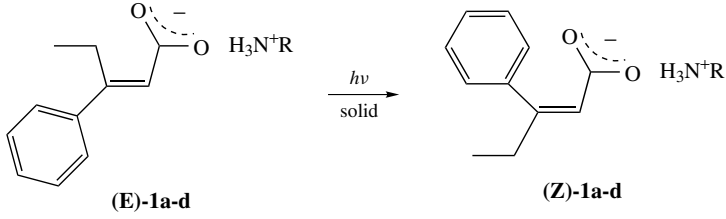
SCHEME 20

correlation studies on 2-benzyl-5-benzylidenecyclopentanone (Figure 18)[70,80–83] reveal that it undergoes single crystal to single crystal dimerization. Other examples include the photodimerization of cinnamic acid (Figure 19)[27] and styrylpyrylium salt (Figure 20)[146]. Crystal cell parameters of the reactant prior to and after irradiation are provided in the figures. There are only small changes in cell parameters even after total conversion of the reactant to the product, suggesting that the phototransformation has occurred with very little changes in the atomic positions of the reactant molecule. We discuss one example below and the other two follow the same trend.

In the crystals of 2-benzyl-5-benzylidenecyclopentanone, the neighboring molecules are related by a center of symmetry with the reactive double bonds separated by 4.1 Å in the monomer. Photolysis of crystals yields single-crystals of its dimer (Figure 18)[70, 147]. The fact that the product is crystalline indicates that there is a definite crystallographic



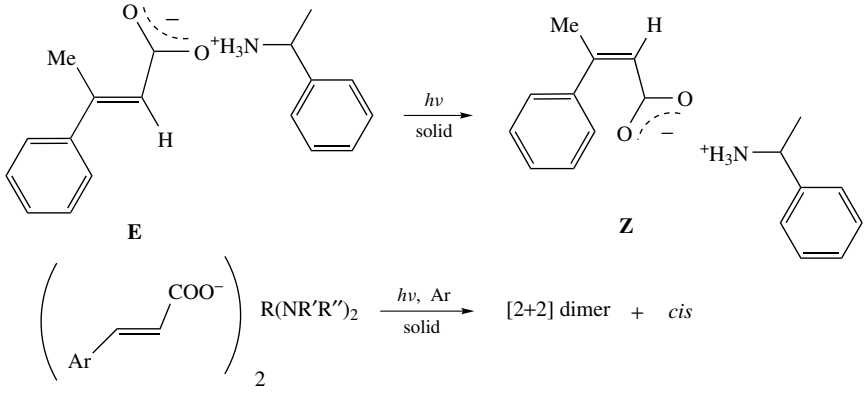
SCHEME 21



Amines used:

R = PhCHMe, *t*-Bu, 1-Ad, Ph_2CH

SCHEME 22

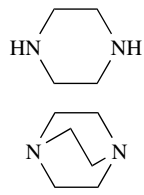


Amines used:

$R(NR'R'')_2$: $R = (CH_2)_3$, $R' = R'' = H$

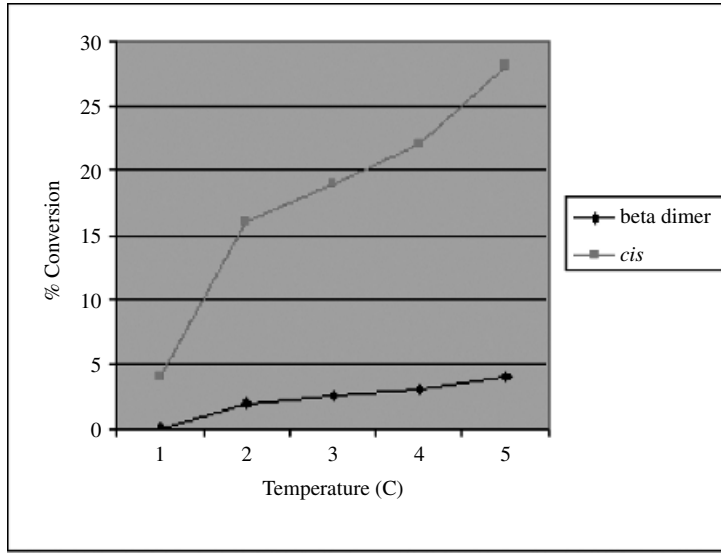
$R = (CH_2)_2N(CH_2)_2$, $R' = R'' = H$

$R = (CH_2)_2$, $R' = H$, $R'' = Me$



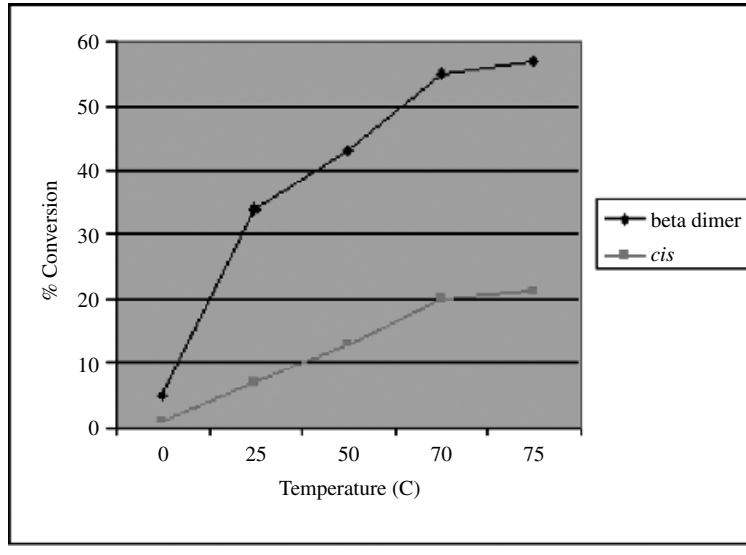
SCHEME 22. (*continued*)

relationship between the parent and the daughter phases. Indeed, the maximum change in unit cell parameters between the monomer and the dimer is only about 0.7%. By careful control of the rate at which dimerization takes place it was possible to retain a homogeneous single crystal–single crystal dimerization reaction. 'Why the single crystal to single crystal photodimerization is rare' is an important question to be addressed. One of the basic conditions for single crystal to single crystal transformation is that the formation of the dimer should not introduce too much strain in the monomer crystals. Further, there should not be strong intermolecular forces (such as hydrogen bonding) in the crystal. All these conditions are met in 2-benzyl-5-benzylidenecyclopentanone. In this case, the reactive double bond is essentially at the central part of the molecular framework. During the course of the dimerization, it is this part of the molecule that undergoes a large movement with the peripheral part of the molecule remaining essentially at the same position. In rigid molecular systems such as coumarins one cannot hope to achieve this condition. Dimerization of the double bond in such rigid systems would result in large changes in the atomic positions of the peripheral atoms leading to disruption of the crystal. In the case of cinnamic acids and similar molecules, the presence of strong hydrogen bonding in the crystal would not allow sufficient relaxation of the dimer within the monomer crystals. This would result in disruption of the crystal packing and formation of amorphous product. This is the case in 99+% of dimerization examples reported in this chapter.



Double salt of *trans*-(1*R*,2*R*)diaminocyclohexane with 2-chlorocinnamic acid

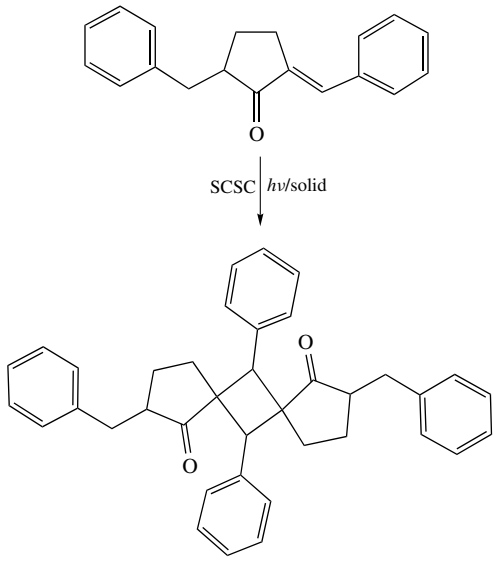
(A)



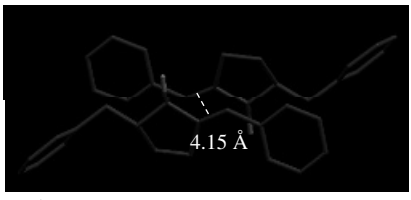
Double salt of *trans*-(1*R*,2*R*)diaminocyclohexane with 2,4-chlorocinnamic acid

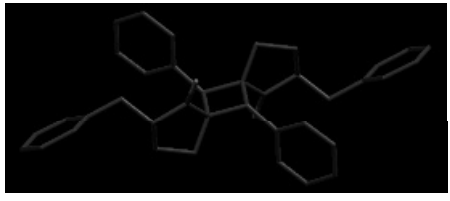
(B)

FIGURE 17. Temperature dependence of *cis–trans* isomerization and cyclobutane formation for: (A) 2-chlorocinnamic acid and (B) 2,4-dichlorocinnamic acid double salts with *trans*-(1*R*, 2*R*) diaminocyclohexane



anti H–T dimer



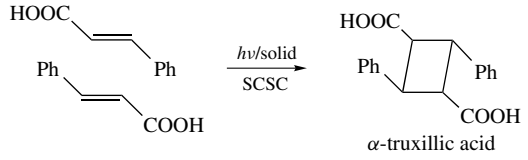


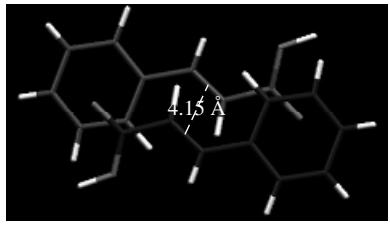
a (Å)	31.10	31.32
b (Å)	10.78	10.81
c (Å)	8.69	8.63
Z	8	8
Space group	P_{bca}	P_{bca}
Unit cell volume (Å^3)	2932	2922

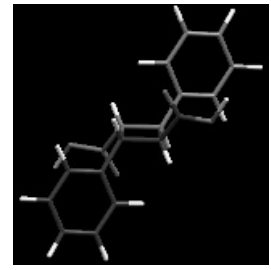
FIGURE 18. Single crystal to single crystal transformation of 2-benzyl-5-benzylidenecyclopentanone. Packing arrangements and cell parameters in the reactant and product crystals are provided

X. CONCLUDING REMARKS

Photodimerization of olefins in the solid state has been subjected to extensive and systematic study by several groups. Numerous examples supporting the original topochemical postulates have been provided. Still, mechanistic studies are not that many and this problem needs more attention. Recent progress in solving crystal structures of molecules present in the excited state should allow us to gain a deeper understanding of the progress of photoreactions in the crystalline state. In spite of the active efforts put forth by







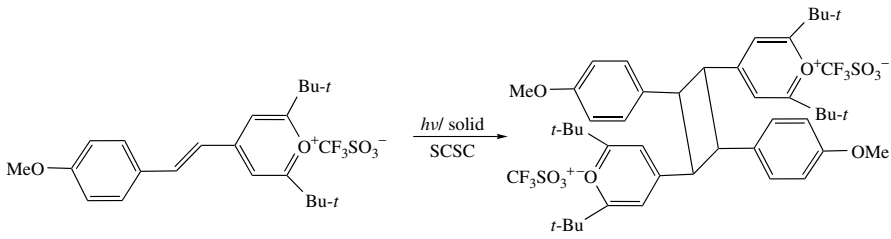
a (Å)	7.7163	7.668
b (Å)	17.6101	18.231
c (Å)	5.5655	5.595
Z	4	4
Space group	$P2_1/n$	$P2_1/n$
Unit cell volume (Å^3)	751.6	750.9

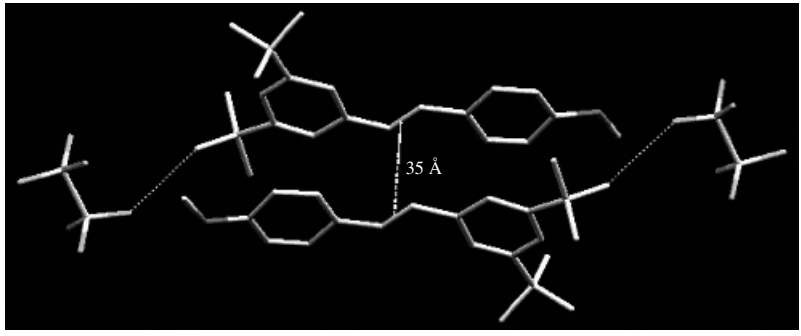
FIGURE 19. Single crystal to single crystal transformation of *trans*-cinnamic acid. Packing arrangements and cell parameters in the reactant and product crystals are provided

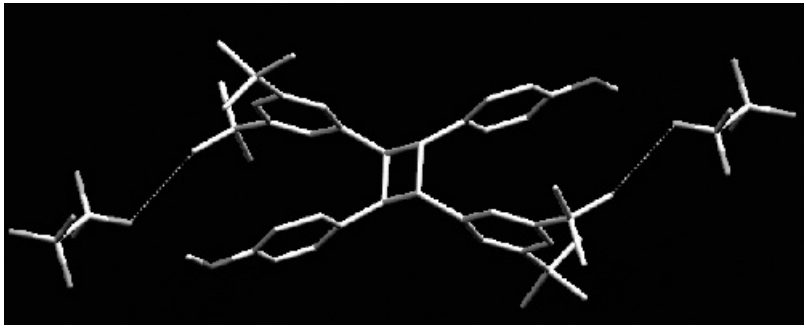
several groups and some significant developments in solid state photochemistry, it must be conceded that this area has not yet attracted the attention of mainstream organic chemists. This is mainly owing to the fact that the principal problem, namely to be able to preorganize the molecules in the lattice the way one would like to have, has not been fully surmounted. In this context the Cambridge Database, which contains a wealth of structural information, is of enormous value. Analyses of the Database have already started yielding results in terms of potential steering groups. Given the current emphasis in green chemistry, solvent free synthesis using organic crystals has a great deal of untapped potential. I hope that this potential is tapped by those who read this article.

XI. APPENDIX: MORE EXAMPLES OF SOLID STATE PHOTODIMERIZATION OF OLEFINS

Since the in-depth studies on cinnamic acids by Schmidt and coworkers, several groups have explored photodimerization of olefins in the solid state. These studies have repeatedly shown that the stereochemistry of dimer obtained in solid state is different from that in solution. These examples emphasize the importance of product selectivity in the solid state. In the majority of examples, no attempt has been made to relate the product cyclobutane structure with the packing arrangement of olefins in the reactant crystal. Such investigations require collaboration between an organic chemist and a crystallographer. For the sake of completeness we have listed the majority of the examples (not all) on solid state photodimer-



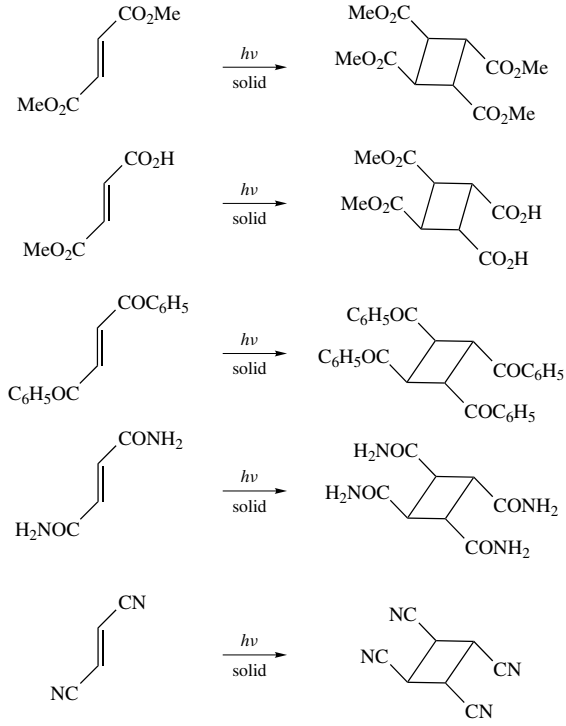




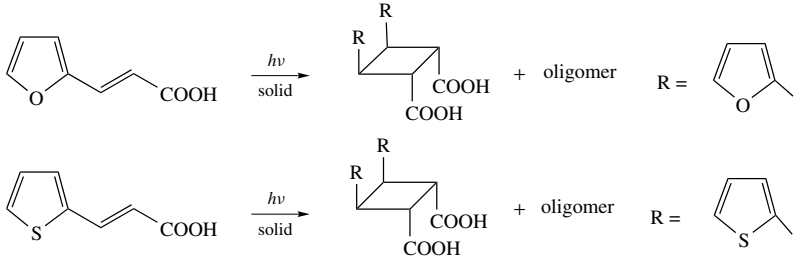
	Monomer	Dimer
a (Å)	10.3873	10.8603
b (Å)	14.7855	14.1449
c (Å)	16.4929	16.4046
Z	4	4
Space group	$P2_1/c$	$P2_1/c$
Unit cell volume (Å^3)	2466.5	2418.5

FIGURE 20. Single crystal to single crystal transformation of styrylpyrylium salt. Packing arrangements and cell parameters in the reactant and product crystals are provided

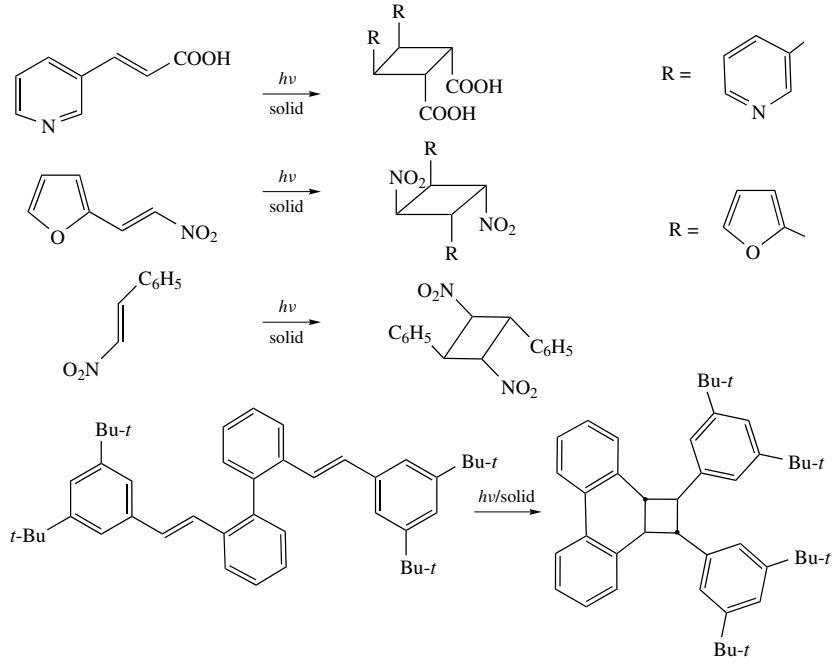
ization: Scheme 23[148–150], Scheme 24[44–46,151–154], Scheme 25[155–160], Scheme 26[161–164], Scheme 27[165–167], Scheme 28[168–173], Scheme 29[58,100,110,174–177], Scheme 30[178–183], Scheme 31[184–189], Scheme 32[190], Scheme 33[60,61,191,192], Scheme 34[193–196], Scheme 35[37,188,197–200], Scheme 36[198,201–203], Scheme 37[204–207], Scheme 38[207–209], Scheme 39[204–207,210–216], Scheme 40[37,217–223], Scheme 41[218,219,224–233] and Scheme 42[225,230,232,233]. No examples of two-component crystal dimerizations and polymerizations are included. Those who wish to explore solid state photodimerizations should first examine the literature carefully before embarking on a new system.



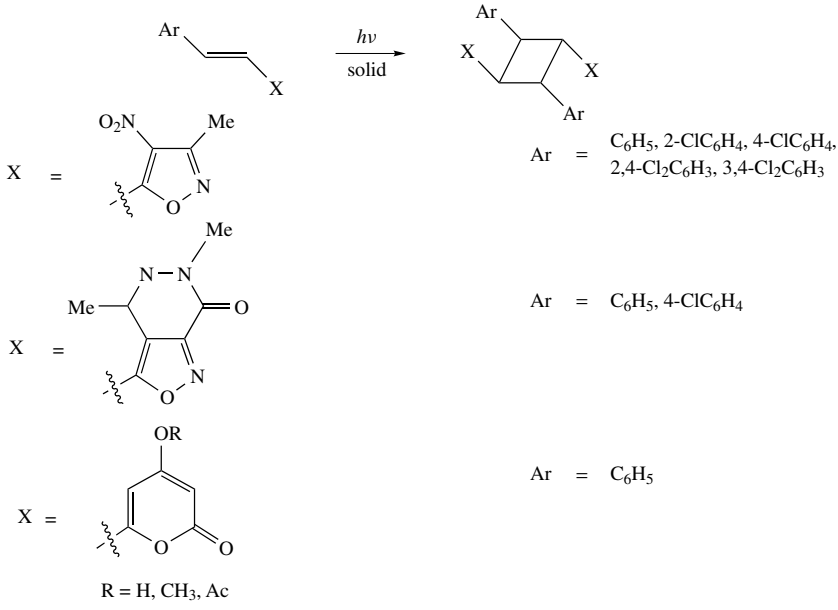
SCHEME 23. Photodimerization of nonaromatic olefins



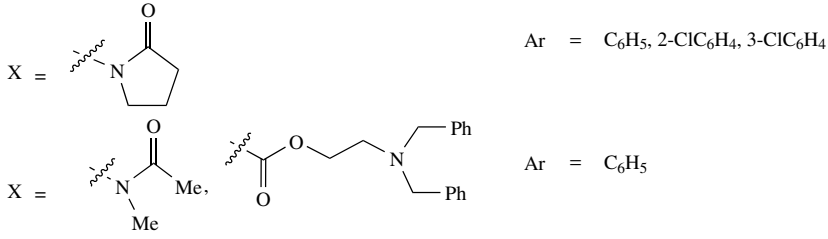
SCHEME 24. Photodimerization of aromatic olefins



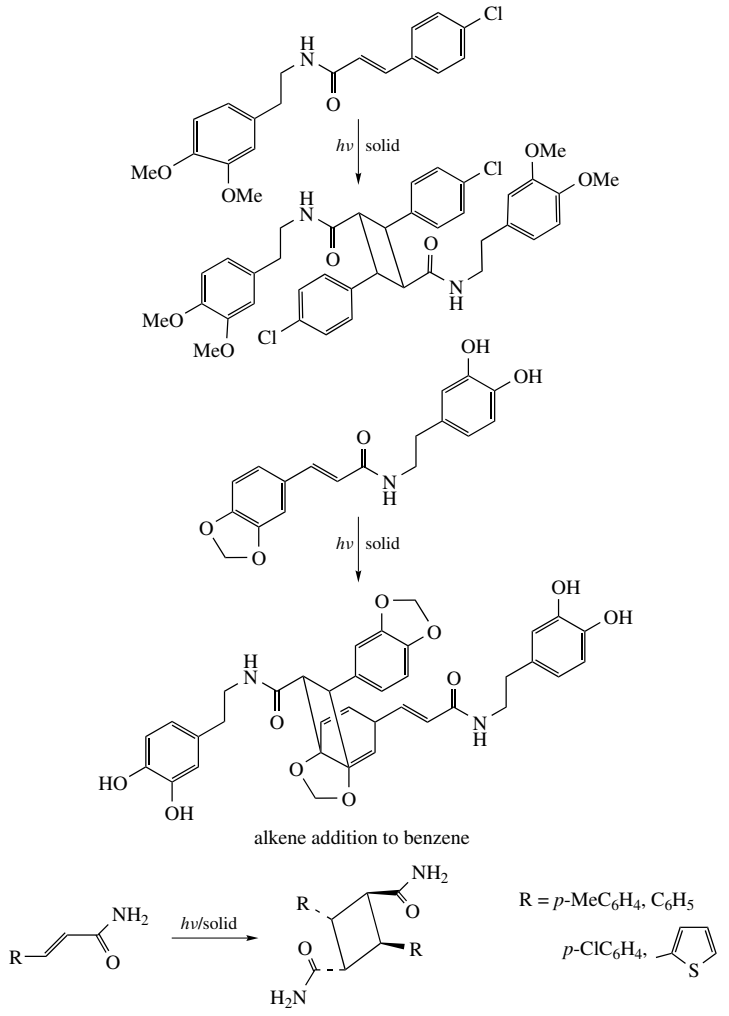
SCHEME 24. (*continued*)



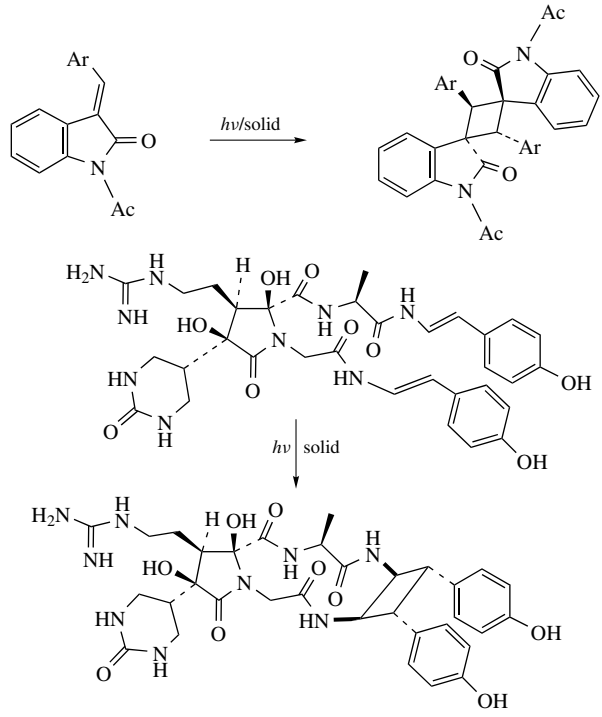
SCHEME 25. Photodimerization of aryl olefins



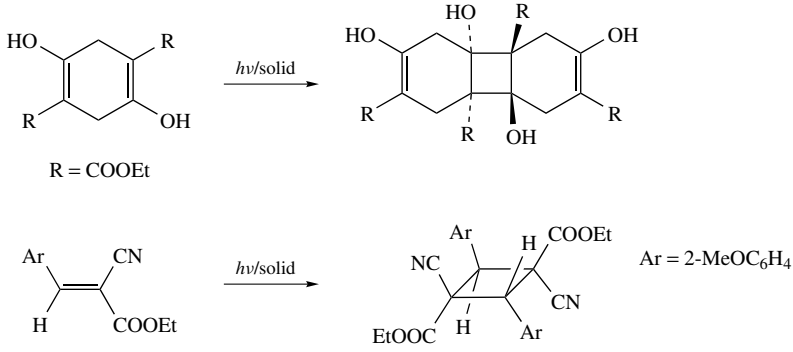
SCHEME 25. (*continued*)



SCHEME 26. Photodimerization of amide derivatives



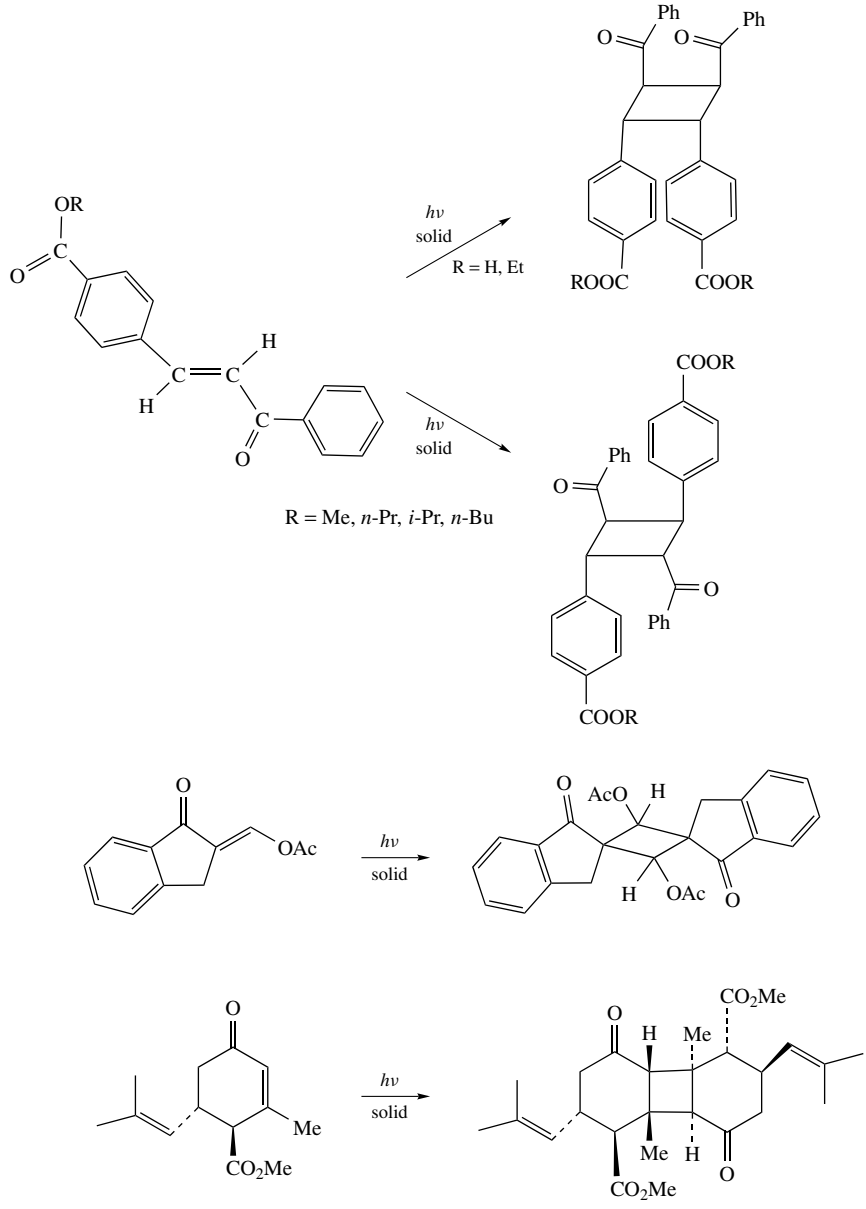
SCHEME 26. (*continued*)



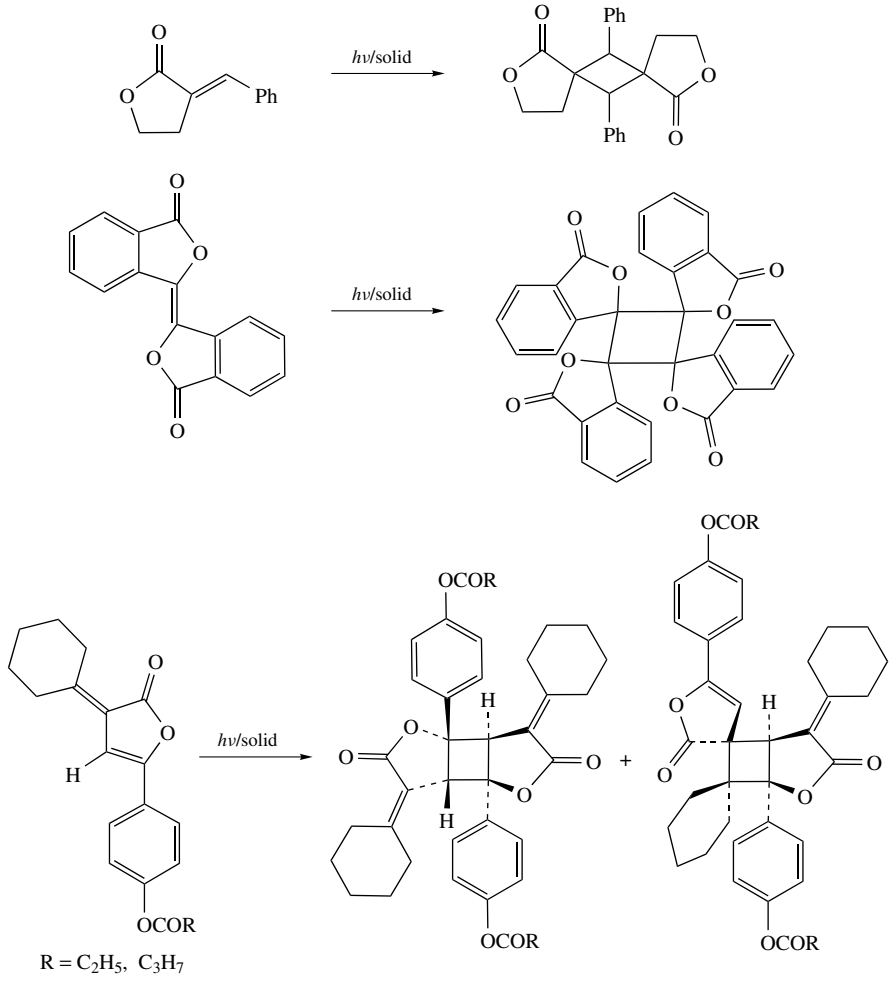
SCHEME 27. Photodimerization of olefins

XII. ACKNOWLEDGMENT

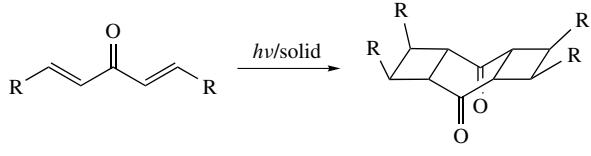
VR thanks the National Science Foundation (CHE-9904187 and CHE-0212042) for support of the work presented from our laboratory in this chapter.



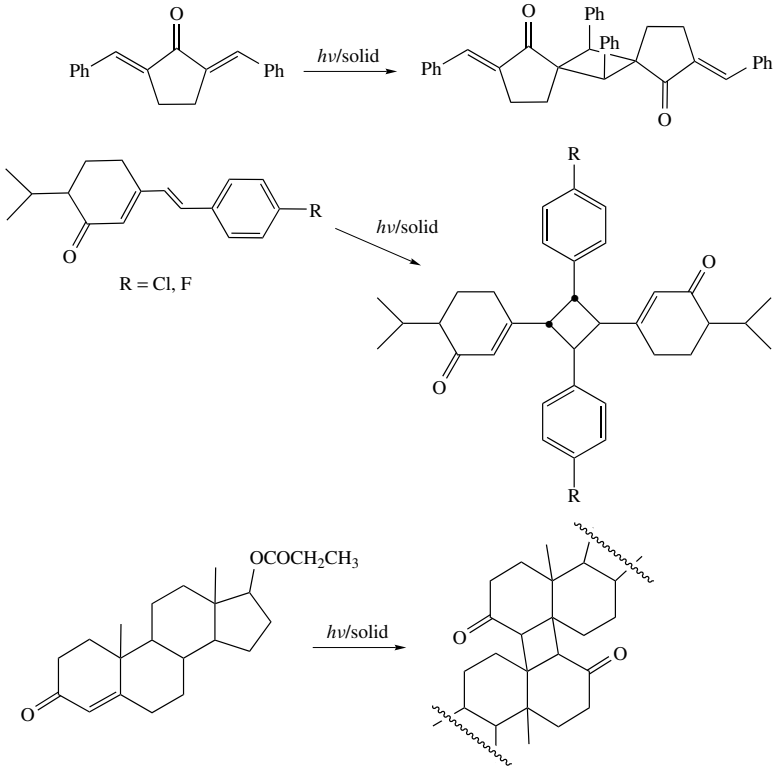
SCHEME 28. Photodimerization of enones



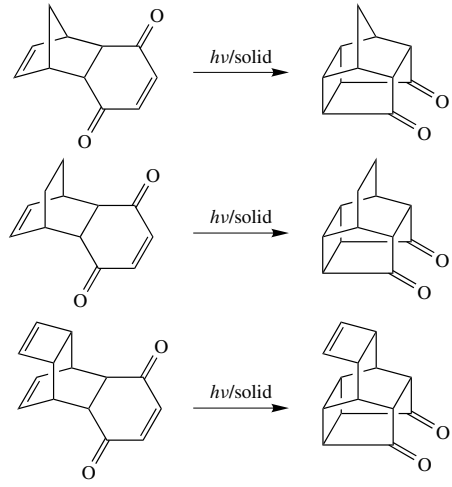
SCHEME 29. Photodimerization of lactones



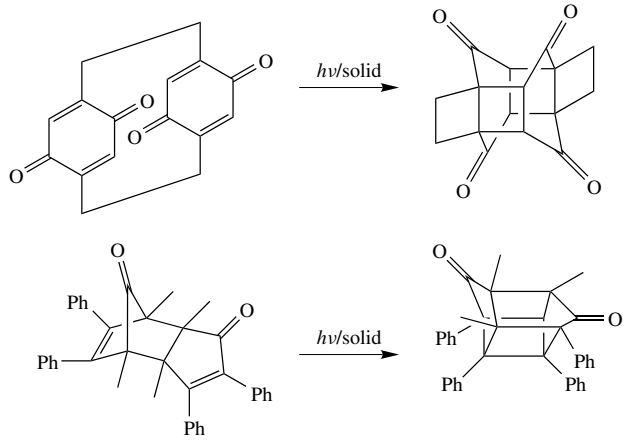
SCHEME 30. Photodimerization of enones and dienones



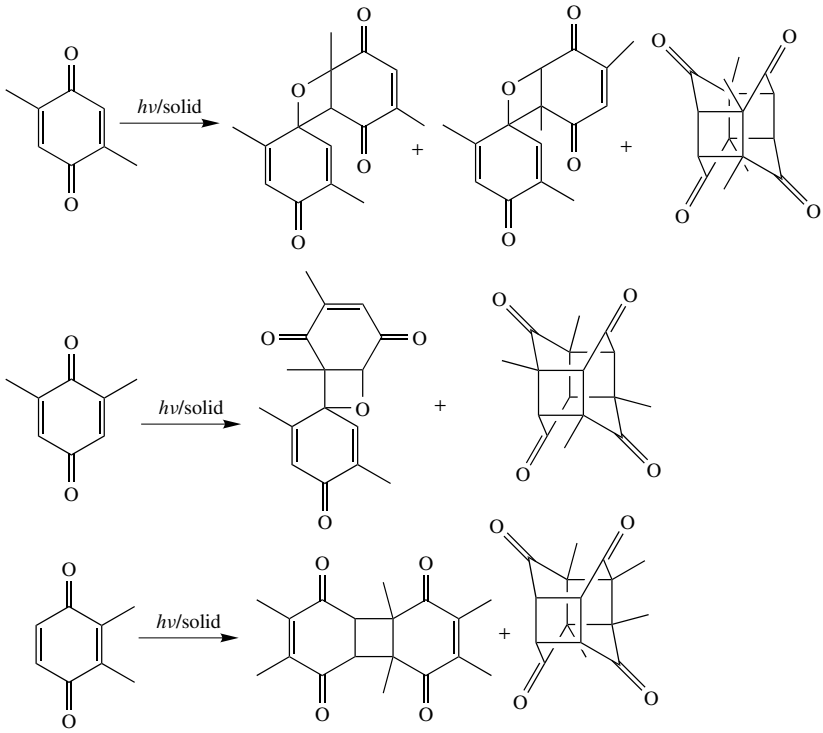
SCHEME 30. (*continued*)



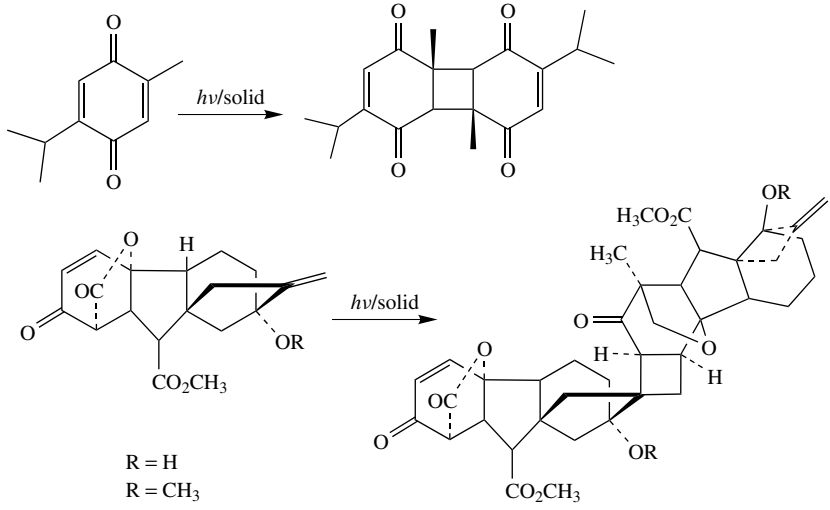
SCHEME 31. Intramolecular photodimerization of enones



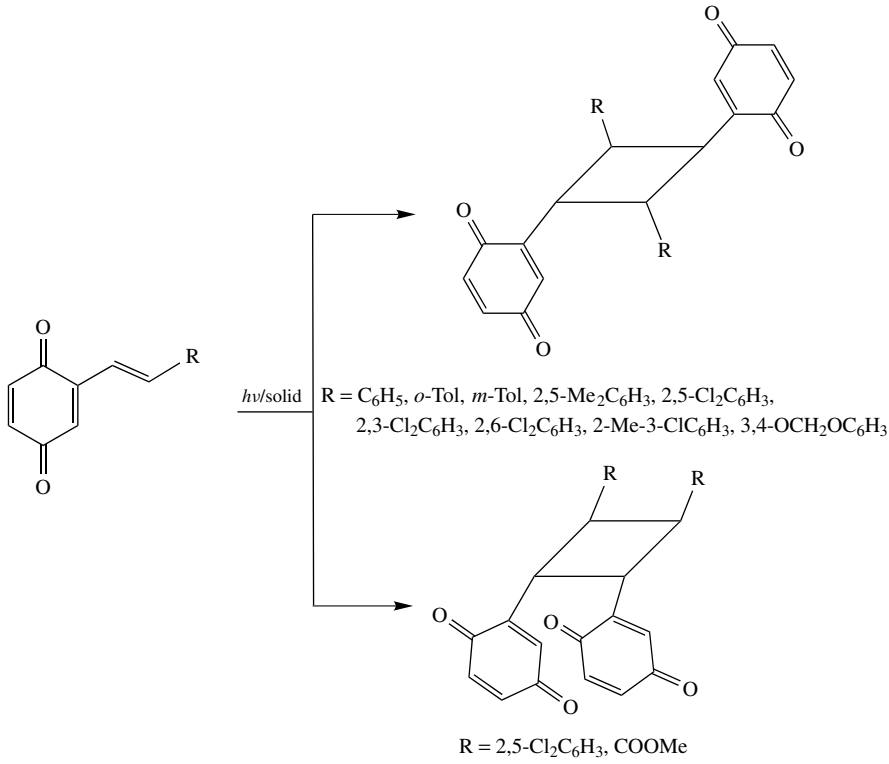
SCHEME 31. (*continued*)



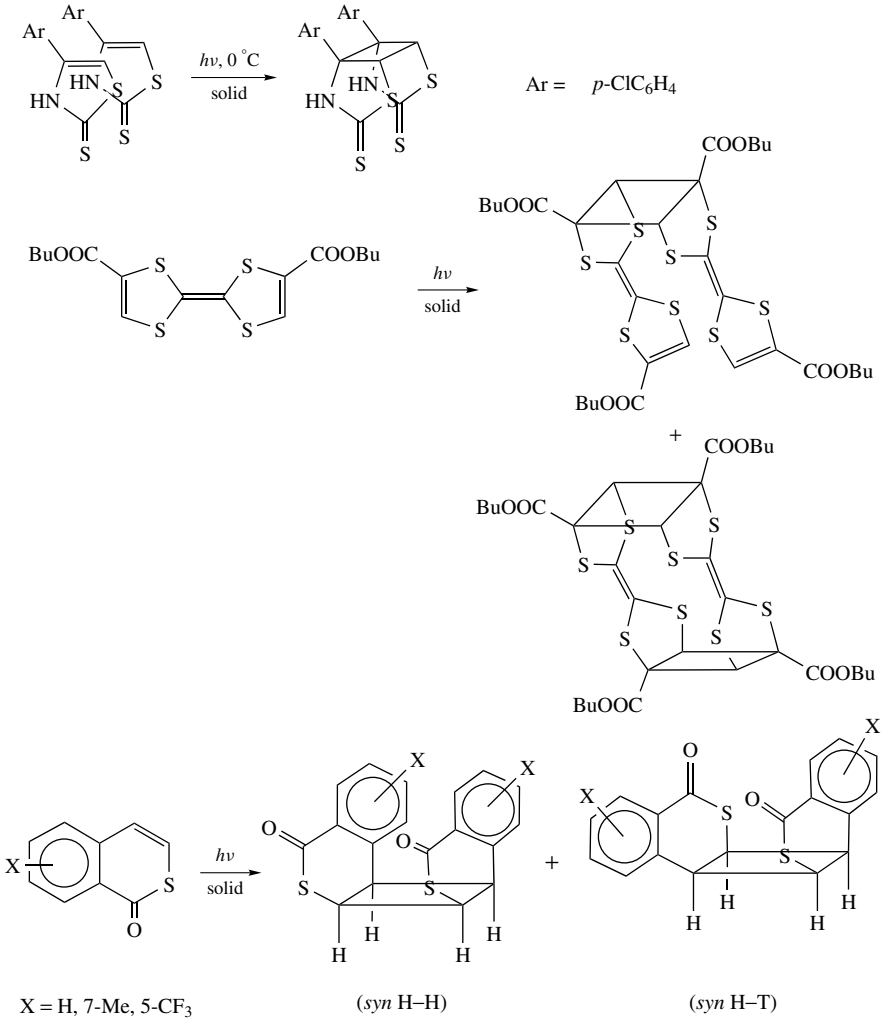
SCHEME 32. Photocycloaddition of enones and dienones



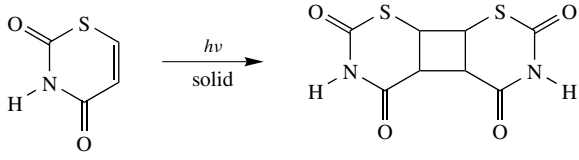
SCHEME 32. (*continued*)



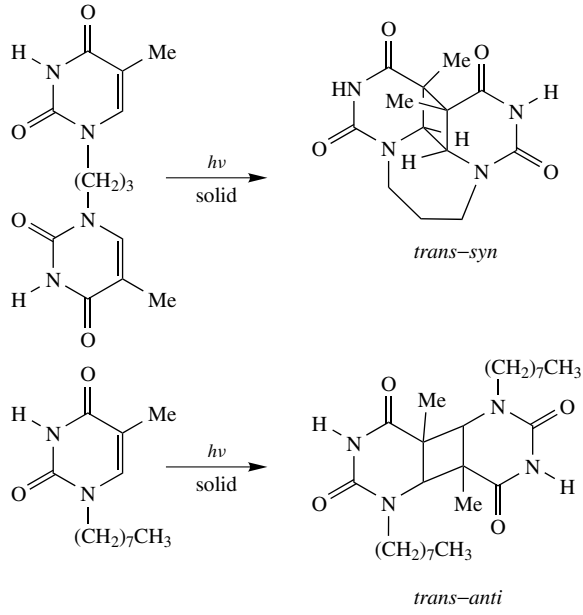
SCHEME 33. Photodimerization of vinylquinones



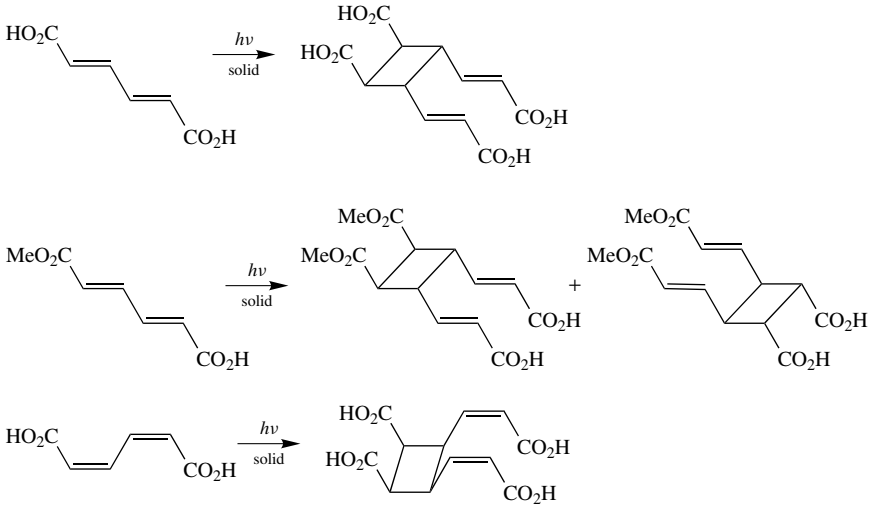
SCHEME 34. Photodimerization of miscellaneous olefins



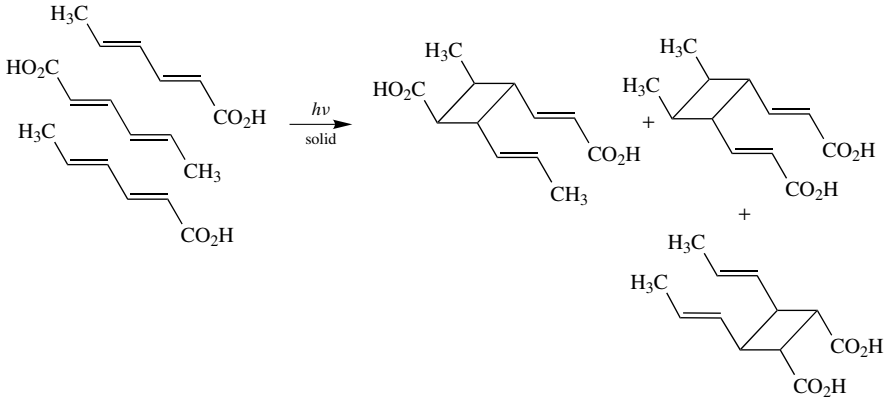
SCHEME 35. Photodimerization of enones



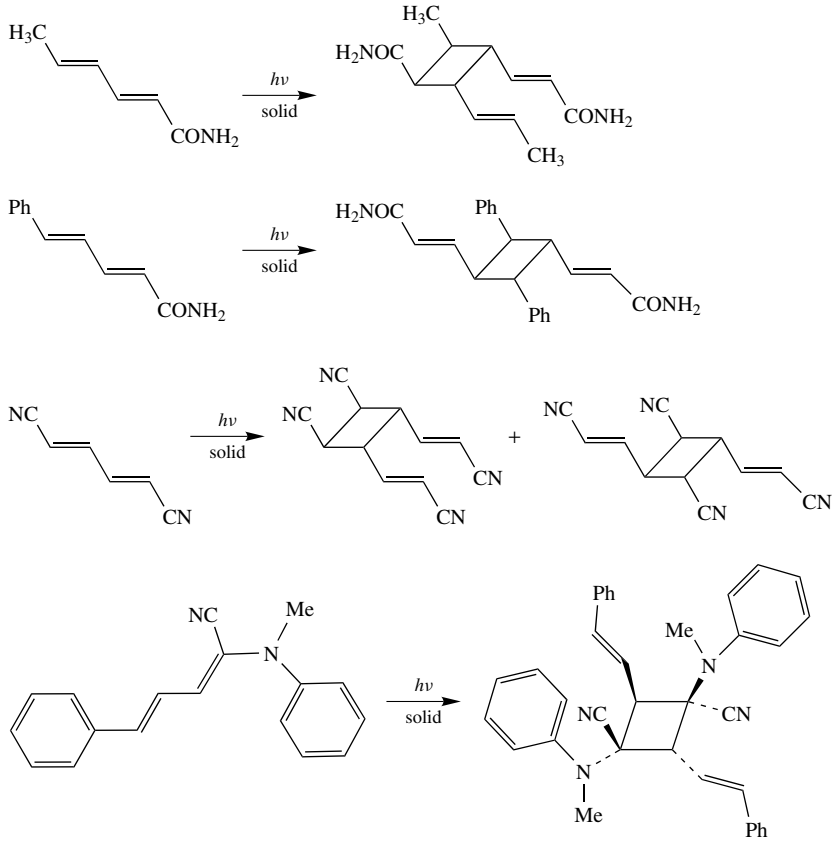
SCHEME 35. (*continued*)



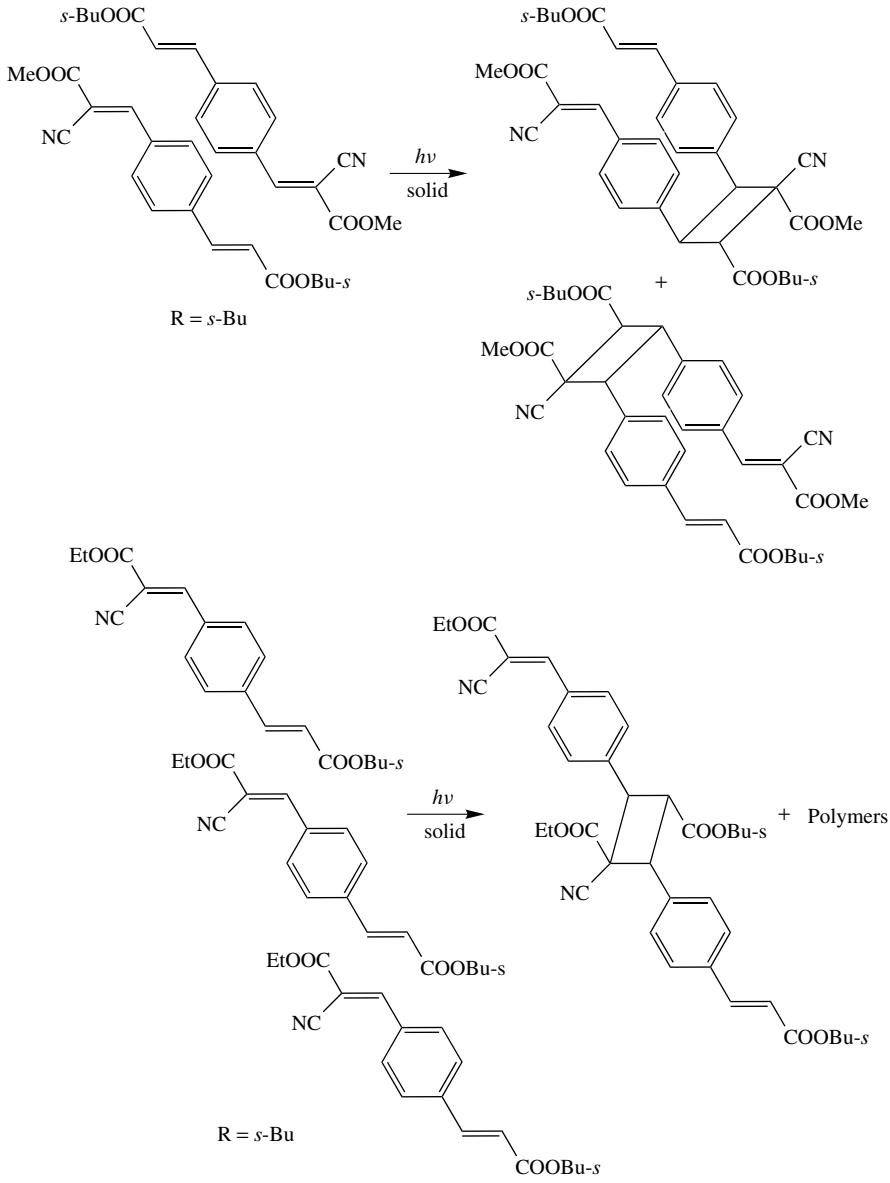
SCHEME 36. Photodimerization of diene carboxylic acids



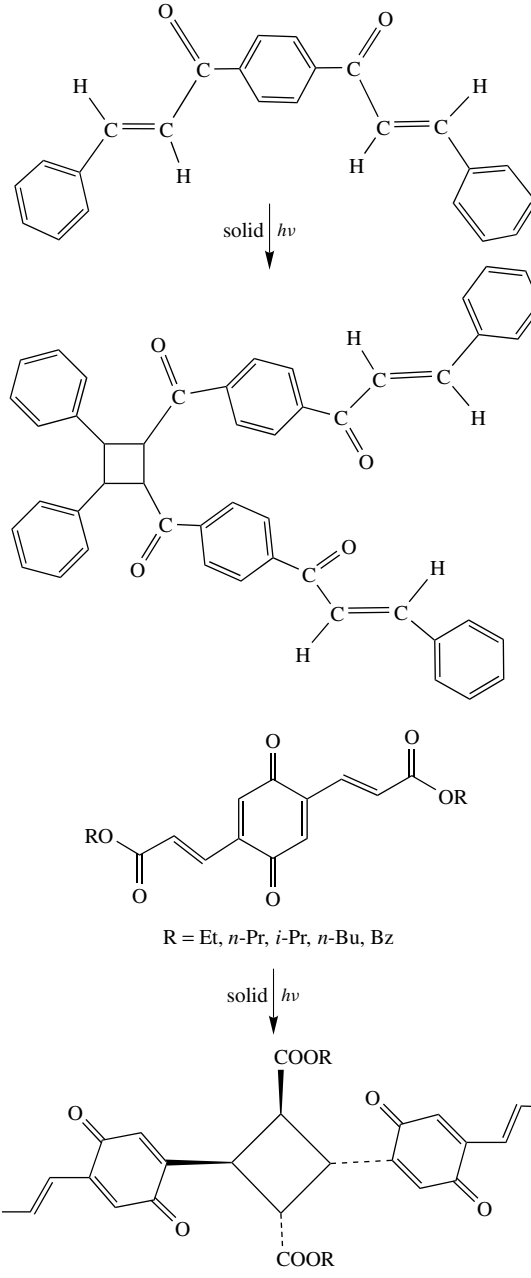
SCHEME 36. (*continued*)



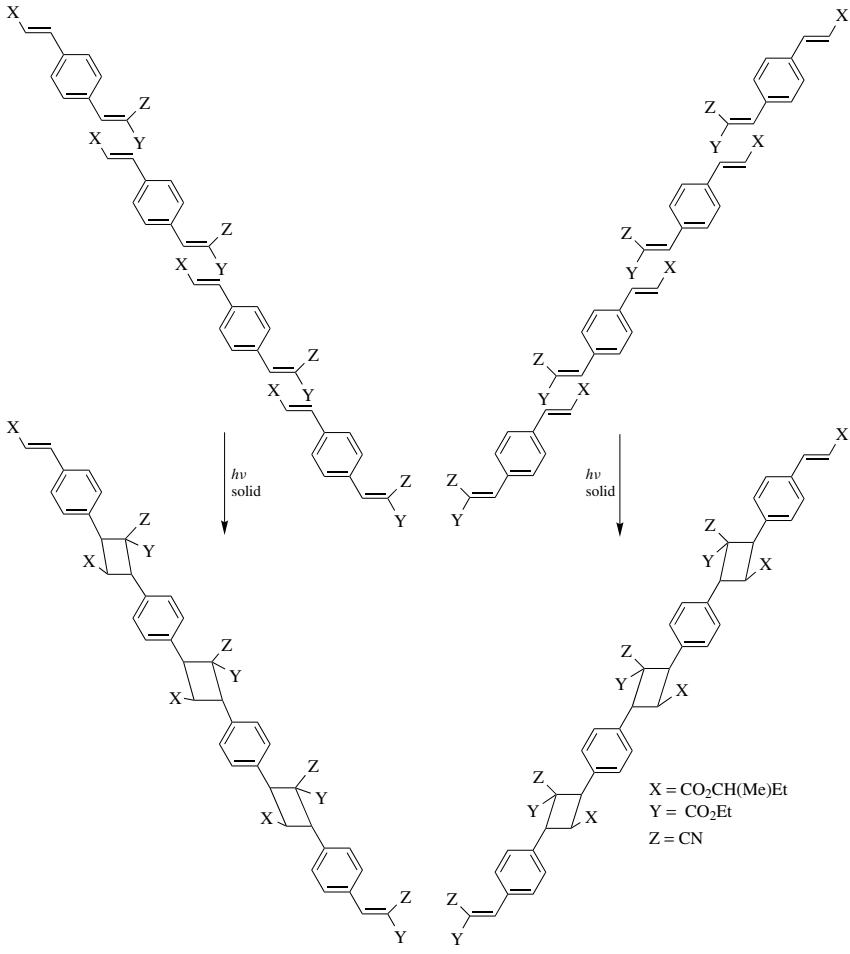
SCHEME 37. Photodimerization of diene amides and diene nitriles



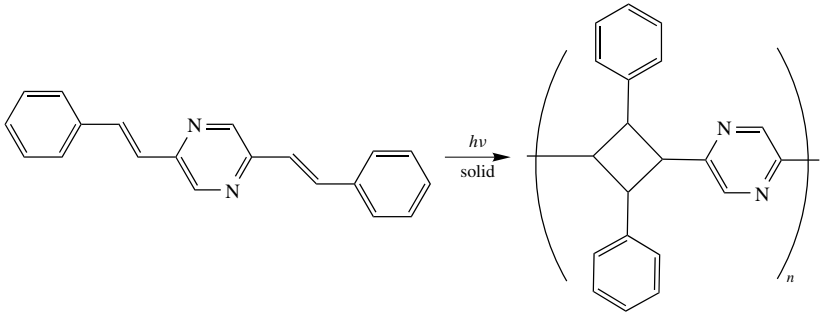
SCHEME 38. Photodimerization of *para*-phenylenes



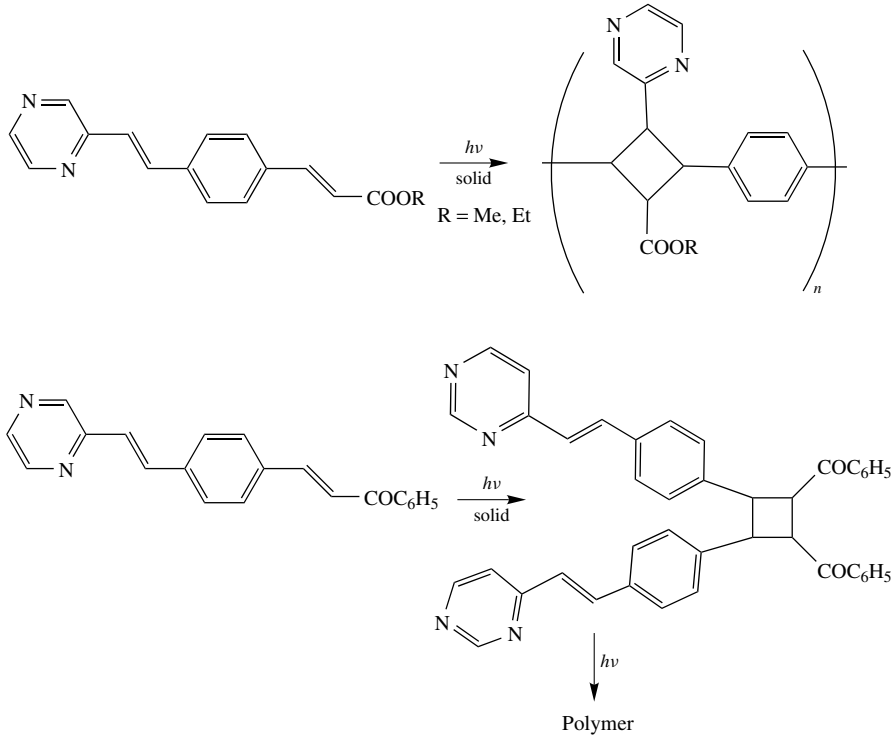
SCHEME 39. Photochemistry of dienones



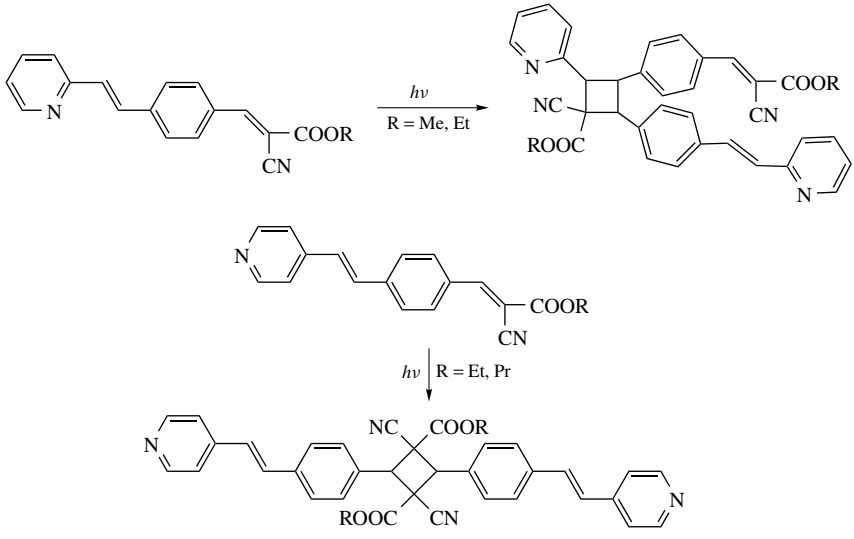
SCHEME 40. Asymmetric photopolymerization of *para*-phenylenes



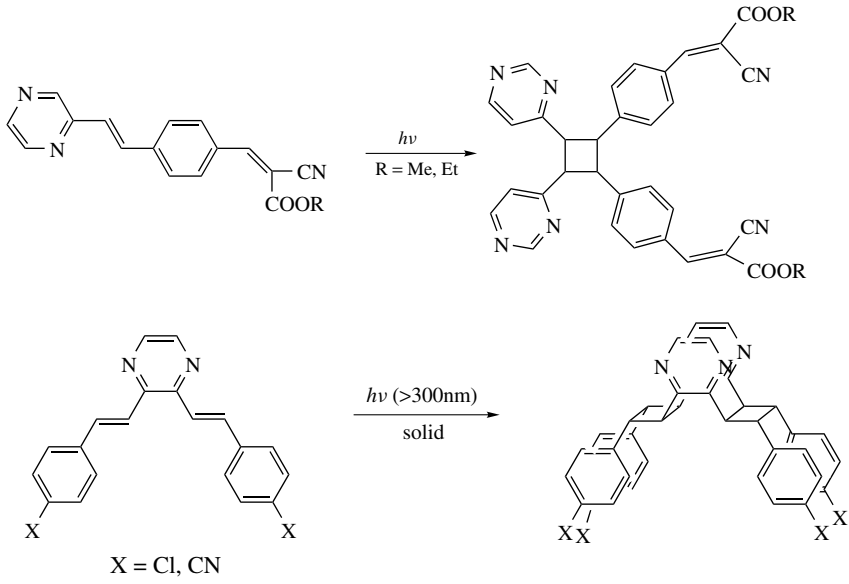
SCHEME 41. Photodimerization and polymerization of 1,4-diolefins



SCHEME 41. (*continued*)



SCHEME 42. Photodimerization of 1,4- and 1,2-diolefins



SCHEME 42. (*continued*)

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CHAPTER **19**

Chemistry of cubane and other prismanes

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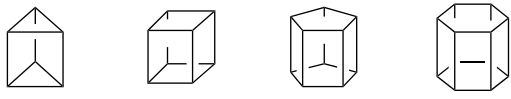
I. INTRODUCTION

The name prismane is given to a group of columnar compounds in which two regular polygonal rings are surrounded symmetrically by four-membered rings[1]. So far, the first three prismanes, **1** (triprismane), **2** (tetraprismane) and **3** (pentaprismane), have been successfully synthesized through respective unique and elegant methodologies.



(1) **(2)** **(3)** **(4)**

Among these three highly strained carbocyclic cage compounds, the so-called 'cubane' **2** first appeared on the scientific research stage after painstaking experimentation and was conclusively synthesized by Eaton and Cole in 1964[2]. In the meantime, triprismane **1** (commonly called prismane), originally introduced as one of the valence isomers for benzene by Ladenburg in 1869 (thus, sometimes called 'Ladenburg benzene')[3], was synthesized as the parent compound by Katz and Acton in 1973 after more than a century had passed since 'Ladenburg benzene'[4]. Finally, the most recent one, pentaprismane **3**, temporarily named 'housane' as well from the viewpoint of its geometrical shape[1,5], was again synthesized by Eaton and coworkers in 1981[6].

Ever since the glorious breakthrough, especially in the synthesis of cubane, the chemistries of **1**–**3** and their related compounds have been developed vastly in various directions including their physical properties[7], chemical reactivities[8], functionalization[9], theoretical investigations[10], biological activities[11] and applications[12].

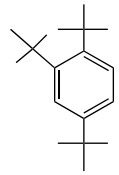
The above-mentioned three prismanes were unveiled in three consecutive decades, though not in increasing order of their size. From such a historical viewpoint, the next higher homolog, hexaprismane **4**, seems to have arrived considerably late. In the next section, the chemistries of prismanes **1, 2** and **3** will be surveyed first in this order and then the challenging projects for the synthesis of **4** will be described.

II. SYNTHESIS OF PRISMANES

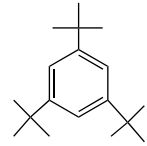
A. Triprismane (Prismane)

The first synthetic report of a triprismane system was made by Wilzbach and Kaplan in 1965, describing photo-interconversion of 1,2,4- (**5**) and 1,3,5-tri-*t*-butylbenzenes (**6**) via a benzvalene intermediate to the tri-*t*-butylprismane derivative **7**[13]. The isolation of **7**, however, was unsuccessful due to the difficulty of separation from the other products including the Dewar benzene **8**. Therefore, the full characterizations of a triprismane was never performed until the parent compound was prepared.

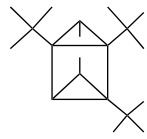
Prismane **1** was successfully synthesized by reformation of the framework of benzvalene **9**[14a], utilizing the powerful dienophile 4-phenyltriazolinedione **10** as a reagent (Scheme 1).



(5)



(6)



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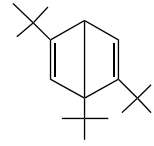

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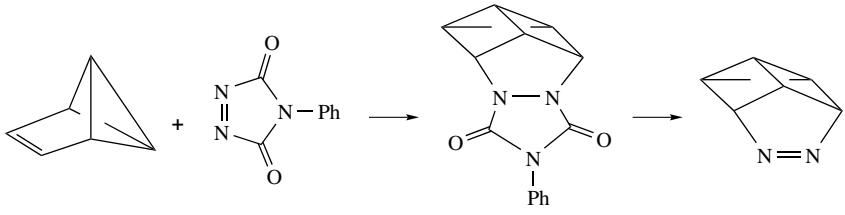


(9) **(10)** **(11)** **(12)**

SCHEME 1

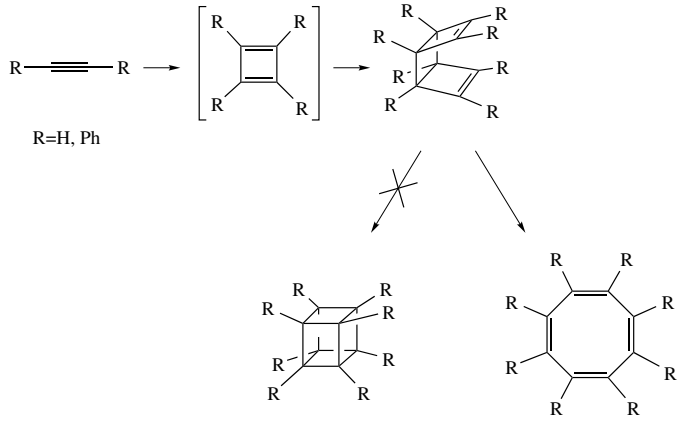
In this conclusive synthesis, the success of converting of benzvalene **9** to **1** could be ascribed to an extremely high reactivity of the two cyclopropane rings in the bicyclo [1.1.0] system of **9**. The 1:1 adduct **11** was treated tandem with KOH and acidic $CuCl_2$, to form a cuprous chloride derivative, which readily underwent alkaline hydrolysis to yield the azo compound **12**[15]. Photolysis of **12** under the conditions developed by Trost and Cory (through Pyrex, at 35 °C in isobutane in a sealed tube)[16] was tried and afforded **1** as an explosive colorless liquid[14b]. However, the isolated yield of **1** by photo-extrusion of molecular nitrogen from **12** was only 1.8%.

B. Tetraprismane (Cubane)

Cubane **2**, pentacyclo[4.2.0.$0^{2,5}$.$0^{2,8}$.$0^{4,7}$] octane, the most exotic member of the family of 20 possible $(CH)_8$ species, was originally thought impossible to synthesize[17].

Indeed, earlier approaches to the syntheses of cubanes by tetramerization of acetylenes were unsuccessful and all attempts resulted in a ring opening rather than in closure of the very strained ring (Scheme 2)[18].

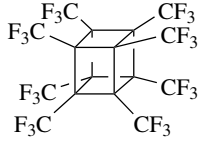
Reasons suggested for the failure include a symmetry-forbidden [2+2] process, a large non-bonded distance (3.05 Å) between two double bonds and an excessive strain build-up



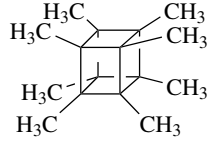
SCHEME 2

(>70 kcal mol^{-1}) upon the ring closures in the final intramolecular photocyclization stage.[19]

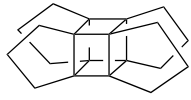
Nevertheless, a few substituted cubanes such as octakis(trifluoromethyl) cubane **13**[20], octamethylcubane **14**[21], the bridged cubane (propellaprismane) **15**[22] and the heterocyclic phosphacubane **16**[23] have been obtained from the photocyclization of the corresponding acetylenes.



(**13**)



(**14**)



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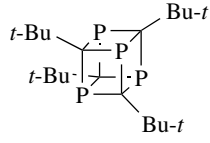
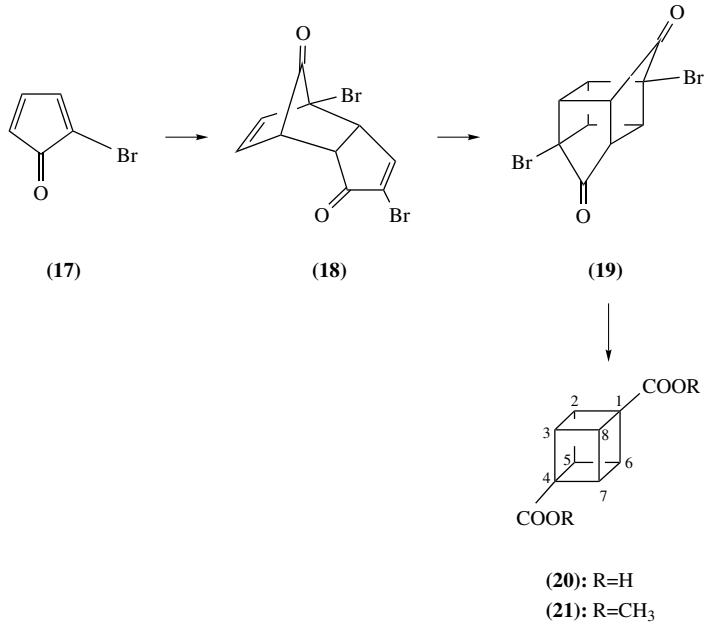


(**16**)

The first successful synthesis of cubane was achieved by Eaton and Cole at the University of Chicago[2a]. Diels–Alder reaction of bromocyclopentadienone **17** occurred spontaneously to afford the dimer **18** which, under ultraviolet irradiation in methanol containing hydrogen chloride, readily undergoes intramolecular [2+2] cycloaddition to form the diketone **19**. Originally, the ring contraction of **19** bearing the skeleton of 1,3-bishomocubane to the cubane system was carried out by applying a Favorskii reaction,

formulated as a benzilic acid-type rearrangement, to give 1,4-cubane dicarboxylic acid **20** as a first example of the cubane system (Scheme 3).



(17) **(18)** **(19)**

(20): R=H
(21): R=CH_3

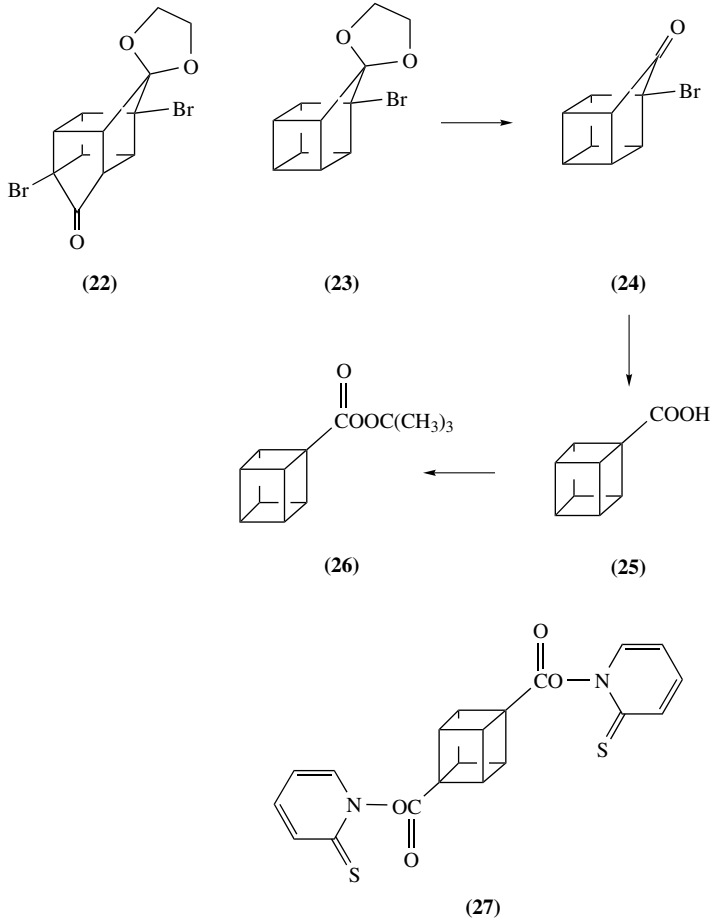
SCHEME 3

Each reaction took place smoothly and thus, for example, the over-all yield of the methyl ester **21** (itself obtained by the methanolysis of the diacid **20**) from **18** attained up to *ca* 30%.

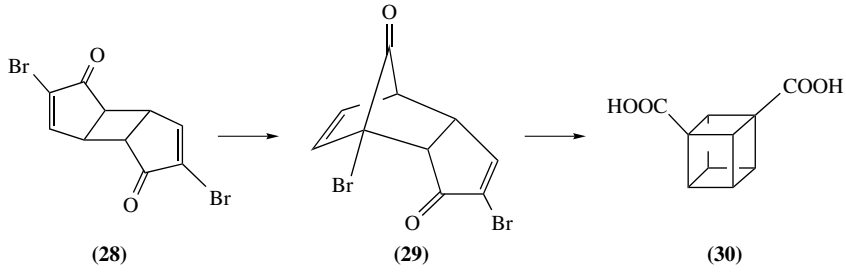
Afterwards, in the same year of 1964, the conclusive synthesis of **2** was performed via **22**, the analog of **19**, in which one of the two carbonyl groups was protected (Scheme 4)[2b].

In this route, a more sophisticated tactic for construction of the cubane system **25** was applied starting from **22**, via **23**, **24** and **25**, following the idea that well-established reactions crowd the bond- and ring-strains step by step into molecular skeletons which simultaneously raise the molecular symmetry. Finally, decarboxylation was carried out adroitly by converting the carboxylic acid to the corresponding peracid ester **26** which, by heating in diisopropylbenzene at 150 °C, gives rise to radical fragmentation to yield the parent cubane **2** (mp 130–131 °C). The radical-induced decomposition of the ester **27** is also useful for preparation of the hydrocarbon on a 10-gram scale[24]. Since then, improved and/or modified syntheses of the cubane system have been demonstrated on occasion. Irradiation of the 4,9-dibromo compound **28** afforded the isomer **29** of the ketone **18**, which is a useful synthon for cubane-1,3-dicarboxylic acid **30** (Scheme 5)[25].

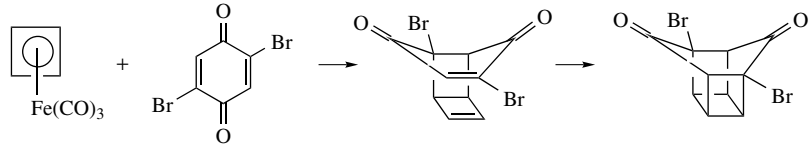
Oxidative decomposition of (cyclobutadiene)iron tricarbonyl **31** in the presence of 2,5-dibromobenzoquinone **32** afforded the endo Diels–Alder product **33** which, under irradiation in benzene, readily affords [2+2] cycloadduct **34**, a new synthon for **30** (Scheme 6)[26].



SCHEME 4



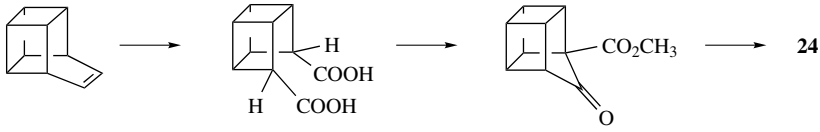
SCHEME 5



(31) (32) (33) (34)

SCHEME 6

Oxidative cleavage of the C=C double bond in basketene **35** afforded the secocubanedicarboxylic acid **36**[27]. After esterification of **36**, Dieckmann condensation led to the formation of α-substituted homocubanone **37**, which was followed by Hunsdiecker reaction to form the important intermediate **24** (Scheme 7).

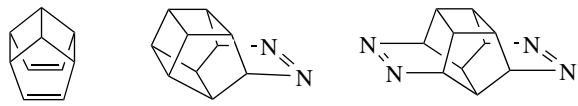


(35) (36) (37)

SCHEME 7

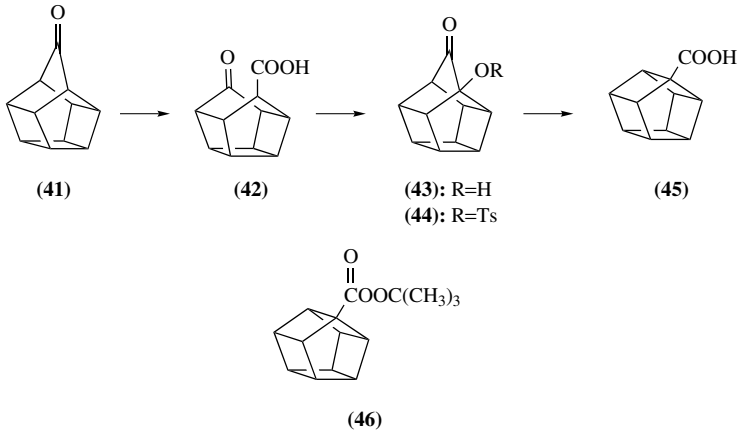
C. Pentaprismane

Synthesis of pentaprismane **3** was also outstandingly tough, so that hopeful attempts by photoclosure of hypostrophene **38**[28] and photo/thermal extrusion of molecular nitrogen from diaza compounds **39**[29a] and **40**[29b] all met with failure. Then, Eaton and coauthors[6] focused on an α-functionalization of homopentaprismanone **41** prepared by Ward and Pettit[30], in order to apply their successful methodology for preparing the cubane system from an intermediate such as **43** (Scheme 8).



(38) (39) (40)

One of the highlights is an adventurous series of cleavage-recoupling reactions from **41** via **42** to **43**, that for α-functionalization once breaks down the cage structure of **41** and again recovers the original frameworks of **43** under fairly severe conditions. Beyond expectation, all the reactions occurred very smoothly, giving excellent yields of at least 80% for each step. In the course of the α-functionalization of homopentaprismanone **41**, a hydroxyl group rather than halogen was introduced at the bridgehead. This modification was introduced in order to avoid a competing reaction to the Favorskii contraction, arising from the fact that Haller–Bauer cleavage of nonenolizable ketones is favored by the presence of electronegative groups[31]. As illustrated in the final reaction sequence, heating the tosylate of **44,** formed from **43**, with strong aqueous base effected successful



(41) **(42)** **(43):** R=H **(44):** R=Ts **(45)** **(46)**

SCHEME 8

contraction to **45**, the first derivative of the pentaprismane system. The contraction yield was as high and reproducible as that for the formation of the cubane system from homo- and bishomocubanes and reached up to 60–65%. Then, similarly to the formation of the parent cubane, decarboxylation via thermolysis of the *t*-butyl perester **46** of acid **45** gave pentaprismane in 42% yield.

III. PHYSICAL AND STRUCTURAL PROPERTIES OF PRISMANES

It is exciting to compare the physical properties of non-natural products, especially those possessing high symmetric carbocyclic cage compounds. Heats of formation (ΔH_f) were calculated by means of *ab initio* STO 6-31G* (RMP2) to give 136.4, 148.5 and 119.6 kcal mol^{-1} for **1, 2** and **3**, respectively. Also, strain energies (SE) were estimated to be 148.7, 164.9 and 140.1 kcal mol^{-1} corresponding to 24.8, 20.6 and 14.0 kcal mol^{-1} (per carbon), respectively[32]. Since then, another calculation of ΔH_f and SE performed for **2** gave higher values by 15 kcal mol^{-1} [33a]. The most recent measurement of the enthalpy of sublimation of cubane gave a value of 13.2 kcal mol^{-1} at 298.15 K[33b].

Such strained molecular skeletons are also reflected in their other spectral behaviors. Mass spectra had identified *m/z* 78 for **1**[4], *m/z* 104 for **2**[2] and *m/z* 130 for **3**[6] as the parent peaks. In the IR spectra three strong absorptions appear at similar regions, at 3066, 1233 and 798 cm^{-1} for **1**, 2992, 1235 and 852 cm^{-1} for **2** and 2973, 1231 and 875 cm^{-1} for **3**. In ^{1}H NMR spectra, the prismanes displayed chemical shifts as one singlet for each compound at 2.28 ppm for **1**, 4.40 ppm for **2** and 3.48 ppm for **3**. Similarly, the ^{13}C NMR resonances are at 30.6 ppm for **1**, 47.3 ppm for **2** and 48.6 ppm for **3**. Based on the ^{13}C–H coupling constants J_{C-H} of 180 Hz for **1**, 155 Hz for **2** and 148 Hz for **3**, the *s* characters of the C–H bond of prismanes were estimated to be 36%, 31% and 30%, respectively, revealing that the C–C bond of each prismane possesses a double bond character almost comparable to the vinylic C–C bond[6]. The crystal and molecular structures of **2** and **45** were successfully determined by means of X-ray and/or electron diffraction analyses. The X-ray result for cubane **2**, in which all the C–C bonds should ideally be identical, showed

the carbon atoms vibrating almost isotropically to afford the mean C−C bond length of 1.551 Å[34], while electron diffraction showed a somewhat longer C−C bond length of 1.5727 Å[35]. It is interesting that this distance is not much different from the C−C bond length in a simple cyclobutane[36]. The C−C−C and C−C−H angles are 90° and 126° respectively, far from the normal tetrahedral angle of 109.5° most often found in ordinary aliphatics[2]. The crystal density of cubane **2** is 1.29 $g\,cm^{-3}$, 40% higher than that of its isomer cyclooctatetraene **47** ($d = 0.93\ g\,cm^{-3}$)[34].

The skeleton of the derivative **45** is only slightly distorted by the carboxylic acid substituent and exhibits an almost D_{5h} symmetry, and thus it must be very similar to that of pentaprismane **3**, which exhibited two kinds of mean C−C bonds: 1.548 Å for the C−C bond in the five-membered rings and 1.565 Å for the C−C bond connecting the two five-membered rings[37].

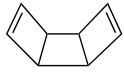
Other spectral investigations such as photoelectron spectra[38], vibrational spectra[39], Raman spectra[40] and so forth are of importance as well for understanding the electronic properties of such highly strained C−C bonds, though they are not discussed here due to the space limitations. In conclusion, in contrast to naïve expectations, prismanes are apparently fairly stable, both kinetically and thermodynamically. When recalling their physical properties, the reader should note the versatile reactivities of prismanes in the following sections.

IV. CHEMICAL REACTIVITIES OF PRISMANES

A. Valence Isomerization of Prismanes

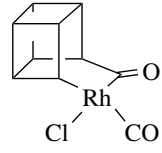
Prismanes make round walls with consecutive cyclobutane rings, so that the enormously large ring and skeletal strains would cause their characteristic behavior. Triprismane **1** is fairly stable at room temperature and gradually isomerizes to benzene (half-life: 11 h) at 90 °C in toluene[4]. Though cubane **2** is also stable enough to sublime and to show a clear melting point[2b], it is sensitive to a number of transition metals which, by serving as Lewis acids, lead to various strain-releasing reactions. Cubane **2** rapidly isomerizes quantitatively to cuneane **47** in benzene with a catalytic amount of $AgClO_4$ and with a catalytic amount of $[Rh(norbornadiene)Cl]_2$ in chloroform[41] to *syn*-tricyclo[4.2.0.0]octa-3,7-diene **48**, which in turn readily converted at 50–60 °C into cyclooctatetraene **49**[42]. In the latter case, use of a stoichiometric amount of $[Rh(CO)_2Cl]_2$ induces an oxidative insertion reaction of carbon monoxide into a C−C bond to afford compound **51** from the stable acylrhodium product **50**[42].

(47)

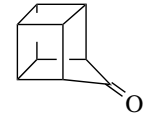


(48)

(49)



(50)

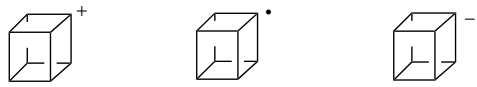


(51)

As compared with such a high reactivity of cubane, pentaprismane **3** is very stable towards Ag(I) ion even under much more drastic conditions[43]. Treatment of **3** with a Rh(I) complex, however, opens the rings to afford hypostrophene **38**[6b].

V. PROPERTIES OF CATION, RADICAL AND ANION SPECIES OF CUBANE

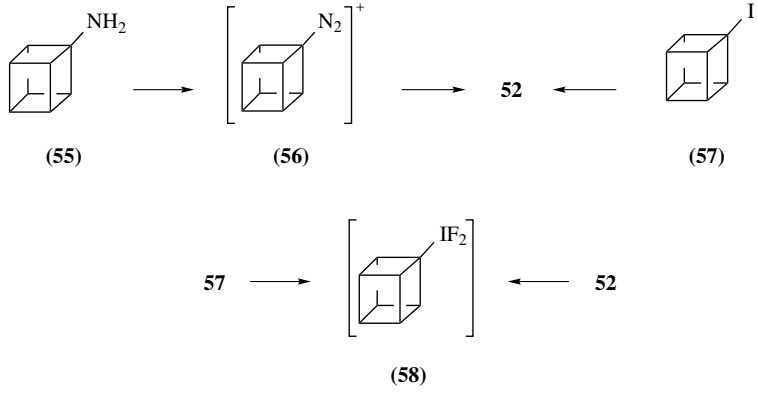
Much effort has been expended in understanding the properties of reactive species in the different oxidation states derived from **2**, which include cubyl cation **52**[44], cubyl radical **53**[45] and cubyl anion **54**[46].



(52) **(53)** **(54)**

Experimental and theoretical results revealed that all these species are kinetically stable enough to undergo substitution reactions on the cubane ring without C−C bond cleavage. In particular, the cation species **52**, which contains a trigonal carbon in the cubyl skeleton, was expected to be too unstable to exist. In this unusual intermediate, the geometry of the carbocation is very far from being flat, and C−H hyperconjugation requires a contribution from a high-energy cubene-like structure. *Ab initio* calculations (6-31G*) place the cubyl cation about 20 kcal mol^{-1} higher in energy than *t*-butyl cation and about 5 kcal mol^{-1} above 1-norbornyl cation[44f].

Nevertheless, numerous reactions which should proceed via cationic species have been observed under various conditions. Decomposition of cubyl diazonium salts **56** formed from cubyl amine **55**[44d], photo-Ritter reaction of iodocubanes **57**[44c] and decomposition of hypervalent derivatives **58**[44a, b] are striking examples (Scheme 9).



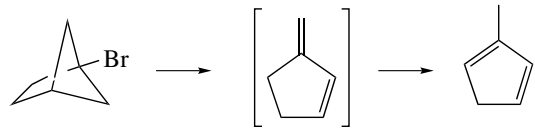
(55) **(56)** **(57)** **(58)**

SCHEME 9

In contrast, 1-bromobicyclo [2.1.1] hexane **59** is well known to solvolyze very rapidly, but with complete ring opening and concomitant relief of strain to afford the product **60** (equation 1)[47].

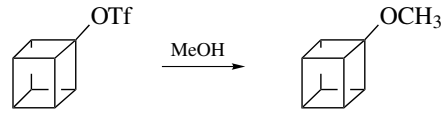
Delocalization of the positive charge in the cubyl cation might occur via interaction with the strained cubane C−C bonds, resulting in a lower activation energy and a faster formation of the cubyl cation[48]. In another manifestation of the stability of **52**, it was shown that solvolysis of cubyl triflate **61** in pure dry methanol is facile and very clean,

and no rearrangement is observed. The only significant product is cubyl methyl ether **62** (equation 2)[44e,g].



(1)

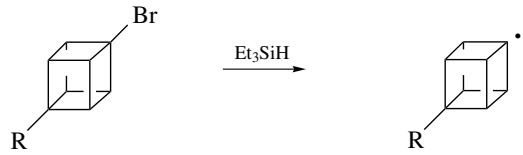
(59) **(60)**



(2)

(61) **(62)**

Cubyl radicals, such as **53**, R=H, were successfully generated from the corresponding bromo derivatives **63** in the temperature range 170–240 K, in cyclopropane or *t*-butylbenzene, with triethylsilane as an initiator (equation 3)[45a].



(3)

(**63**) (**53**)

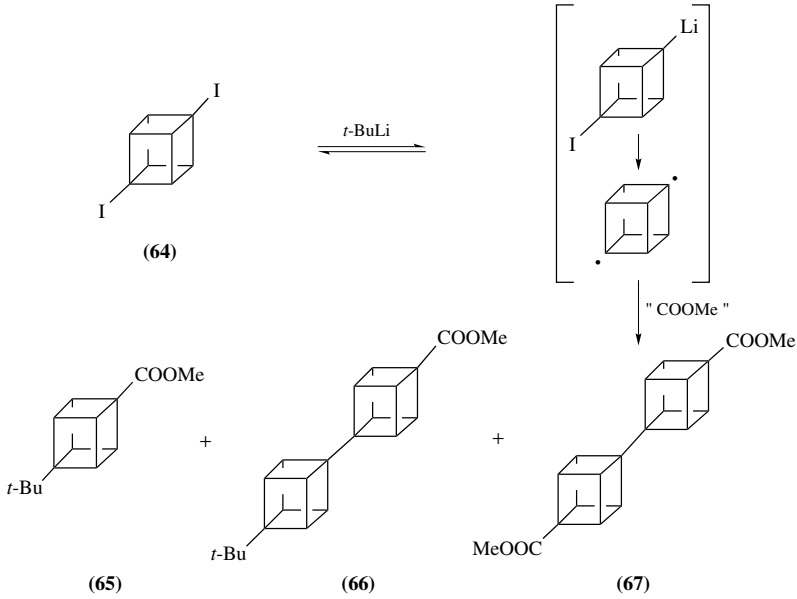
R = H, F R = H

Later on, it was also reported that a *t*-butoxyl radical directly substitutes the cubane skeleton by initial cleavage of the carbon–hydrogen bond at 150 K[49]. Based on these investigations of the cubyl radical, the studies on cubane-1,4-diyl, a very versatile and extraordinary intermediate, have been expanded to view a possibility of body-diagonal bond in the cubane system[39]. The diiodide **64** was used to generate the nonisolable intermediate cubane-1,4-diyl, on reaction with organolithiums (Scheme 10)[50].

Carbomethoxylation of the reaction mixture gave carbomethoxycubane **65** and bicubyls **66** and **67**. A notable challenge to explore the limits of bonding is to prepare cubene (dehydrocubane) **69**[51], the most highly pyramidalized olefin yet made with a calculated pyramidalized angle of 84°. It was speculated that this enormously high reactive species is generated from lithiation of 1,2-diiodocubane **68** with *t*-butyllithium, but to be instantly trapped as adducts with lithium reagents in the reaction medium with a consequent formation of bicubyl **70** and *t*-butylcubane **71** (Scheme 11)[51].

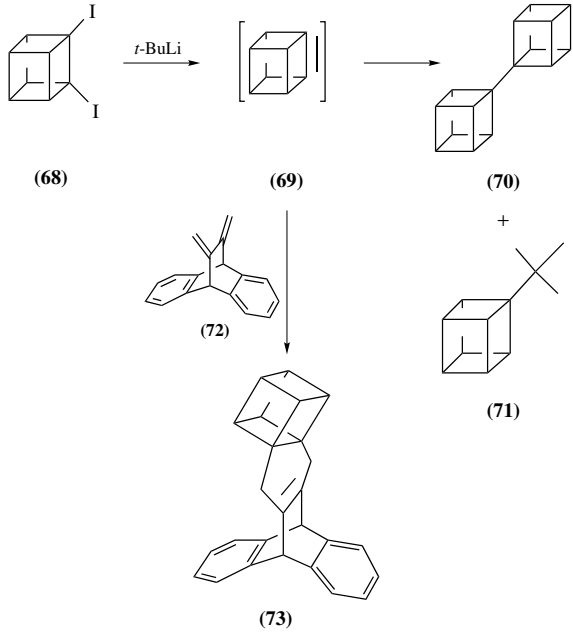
Also, cubene **69** was found to react as a dienophile and with the diene **72** to afford the Diels–Alder cycloadduct **73**[52].

The cubyl anion **54** was prepared in the gas phase by reacting trimethylsilylcubane **74** with fluoride ion in an FTMS spectrometer (equation 4)[53].



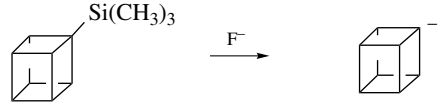
(64) **(65)** **(66)** **(67)**

SCHEME 10



(68) **(69)** **(70)**

SCHEME 11



(74) (54)

m/z 103 (4)

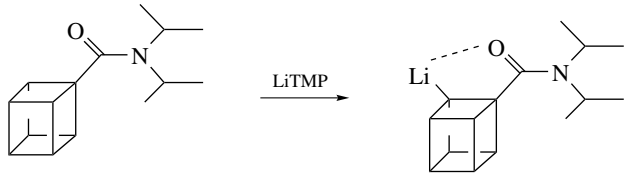
The acidity of cubane was measured by deuterium transfer experiments from ammonia-d_3 to the cubyl anion and proved to be comparable to that of ammonia (pK_a *ca* 33).

VI. FUNCTIONALIZATION OF CUBANES

A. Anionic Reactions

The exocyclic C−H bonds in cubane have 31% s character, being therefore much more acidic than saturated strain-free hydrocarbons. The most recent measurement by application of ^{3}H NMR spectroscopy puts the kinetic acidity of cubane as 6.6×10^{-4} times less than that of benzene and very close to the acidity of cyclopropane[54].

It is conceivable that the introduction of a diisopropylamido group as an *ortho* directing group will enhance the activity of the *ortho* hydrogens toward metalation. Reaction of diisopropylamidocubane **75** with an excess of lithium tetramethylpiperidide (LiTMP), however, gave only a very small amount of the lithiated product (equation 5)[55].



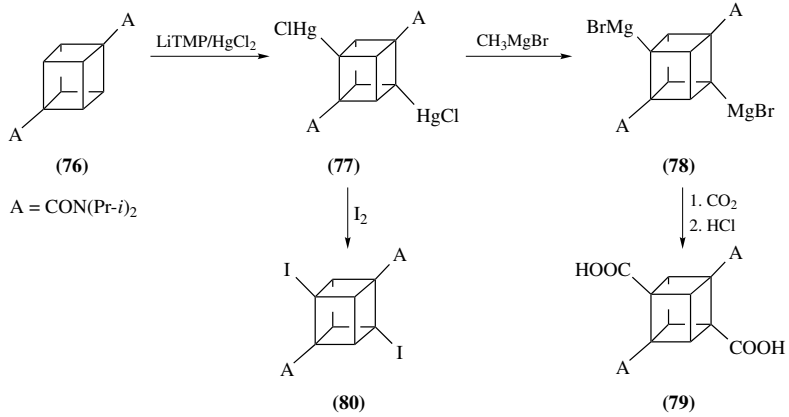
(75) ~ 3% (5)

Following this observation, Eaton and Castaldi applied a reverse transmetalation procedure to replace the acidic hydrogens of cubane[55]. For example, cubane diamide **76** reacts with an excess of LiTMP and mercuric chloride to give compound **77**, which upon reverse transmetalation with CH_3MgBr yields cubane diGrignard reagent **78**. Carboxylation of the intermediate **78** gives 1,4-diamidocubane-2,7-dicarboxylic acid **79** in >75% yield. The isolable compound **77** reacts with iodine to give diamido diiodocubane **80** (Scheme 12).

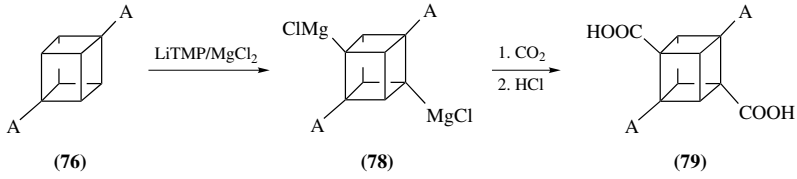
This pioneering work, however, has only a few synthetic applications. The high toxicity and limited reactivity of the organomercury intermediate **77** were some of the problems associated with this approach. Therefore, an alternate procedure was pursued in order to avoid the use of toxic mercury compounds.

One could expect that $MgBr_2$ would be a good choice as a replacement for $HgCl_2$ since it should give **78** directly. Indeed, reaction of **76** with an excess of LiTMP/$MgBr_2$ in THF, followed by quenching the reaction with CO_2 and then HCl, gave **79** in >90% yield (Scheme 13)[56].

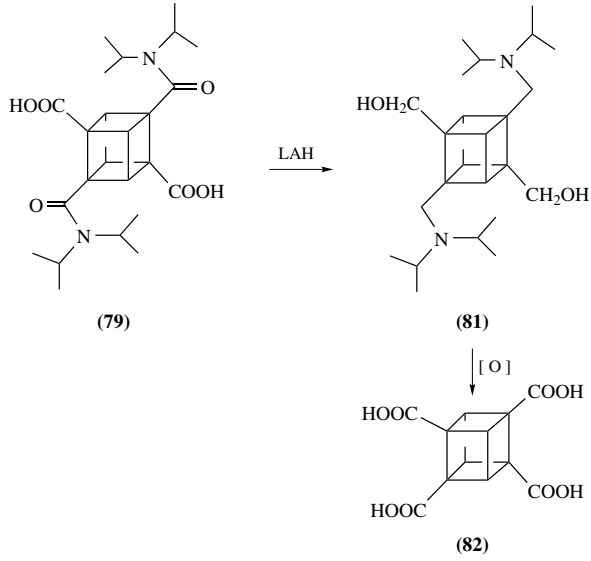
Compound **79**, a precursor to 1,2,4,7-cubanetetracarboxylic acid **82**, can be obtained in one pot and a very high yield on a multi-gram scale. A two-step process was developed to convert the diisopropylamido groups (A) of **79** to carboxy groups. Reaction of **79** with $LiAlH_4$ giving **81**, followed by oxidation with dimethyldioxirane or $KMnO_4$, gave 1,2,4,7-cubanetetracarboxylic acid **82** in good yield (Scheme 14)[56].



SCHEME 12

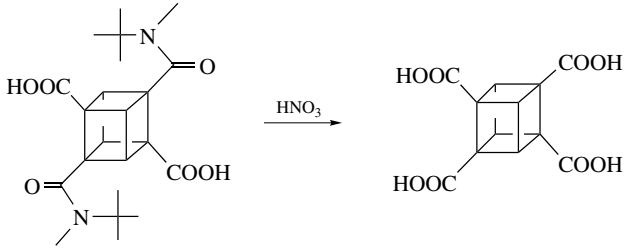


SCHEME 13



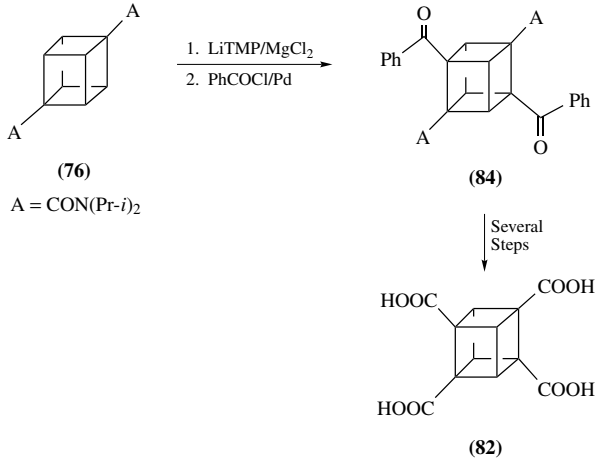
SCHEME 14

An alternative process was developed using concentrated nitric acid to convert amido groups on cubane to the corresponding cubane carboxylic acids in one step. However, this reaction is applicable if only methyl (or ethyl) *t*-butyl amide **83** is employed (equation 6)[57].



(83) **(82)** (6)

The original synthesis of the tetraacid **82** was accomplished in a multi-step process from **76** via intermediate **84** (Scheme 15)[58].



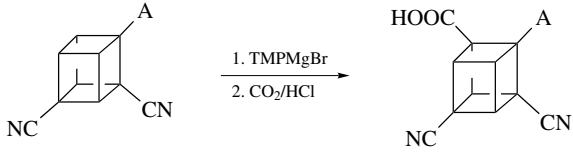
(76)
A = CON(Pr-*i*)$_2$

(84)

(82)

SCHEME 15

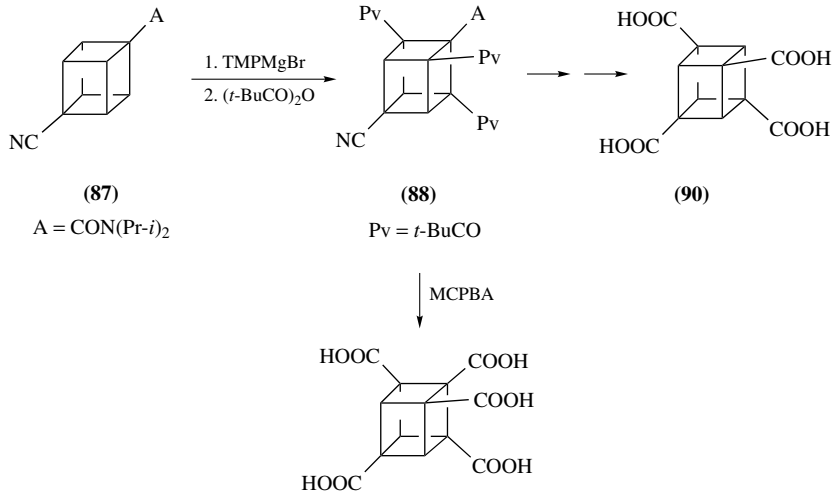
In the presence of two different electron-withdrawing groups, such as cyano and amido groups, functionalization takes place on the lesser acidic side but on the stronger directing group site. For example, selective functionalization of amido 2,4-dicyanocubane **85**, using TMPMgBr and/or (TMP)$_2$Mg, occurs next to the amido group rather than the cyano groups giving **86** (equation 7)[59].



(85)
A = CON(Pr-*i*)$_2$

(86) (7)

An important application of the *ortho*-magnesiation method was the functionalization of 4-cyanoamidocubane **87** in a synthesis of 1,3,5,7-cubane tetracarboxylic acid **90**. By using TMPMgBr and *t*-butyl pivalate *in situ*, three pivaloyl groups were introduced in one pot at the three *ortho* positions to the amide group, to give compound **88**. Baeyer–Villiger oxidation of the pivaloyl groups gave cubane pentacarboxylic acid **89** (Scheme 16)[60].



(87) **(88)** **(90)**

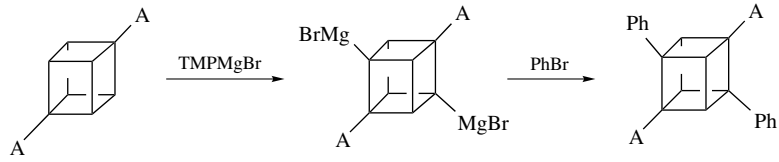
A = CON(Pr-*i*)$_2$ Pv = *t*-BuCO

(89)

SCHEME 16

Application of the LiTMP/$MgBr_2$ procedure also led to the synthesis of phenylcubanes[56] which had been the target of intensive studies for some time[18]. It was earlier reported that the tetramerization of diphenylacetylene gave octaphenylcubane; however, based on the X-ray diffraction, the structure of the product was proven to be octaphenylcyclooctatetraene (Scheme 2).

The first synthesis of a phenylcubane derivative was achieved by the reaction of cubane diamide **76** with an excess of LiTMP/$MgBr_2$, followed by reaction with bromobenzene to provide diphenylcubane diamide **91** (Scheme 17)[56].

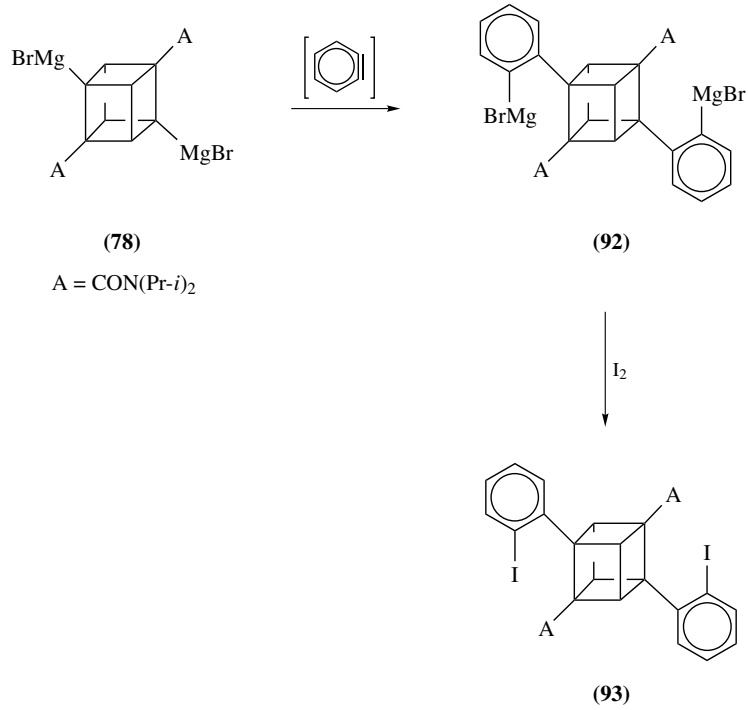


(76) **(78)** **(91)**

A = CON(Pr-*i*)$_2$

SCHEME 17

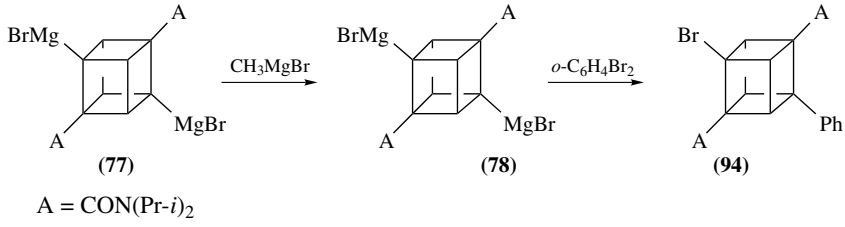
An intermediate benzyne is formed in this reaction from the reaction of excess LiTMP with bromobenzene which reacts subsequently with the diGrignard reagent **78** to give



SCHEME 18

intermediate **92**. Compound **93** was obtained upon quenching the reaction mixture with I_2 (Scheme 18).

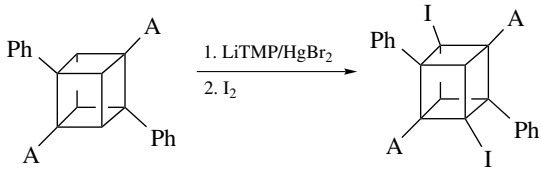
Similarly, **78** was prepared *in situ* from the reaction of **77** and CH_3MgBr. Reaction of the intermediate **78** with *ortho*-dibromobenzene gave bromophenylcubane diamide **94** (Scheme 19).



SCHEME 19

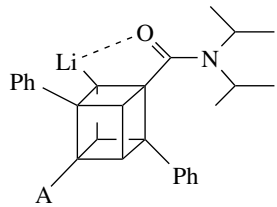
In a competitive site selectivity, between cubane and phenyl groups, metalation of **91** with LiTMP/$HgCl_2$ occurs on the cubane skeleton and not on the phenyl groups. The increased acidity of the cubane protons and their proximity to the amide carbonyl as well as formation of a stable five-membered ring in the transition state (**95′**) might contribute

to the site selectivity. Quenching the reaction mixture with I_2 gives compound **95**, a hexasubstituted cubane with three different substituents (equation 8)[56b].



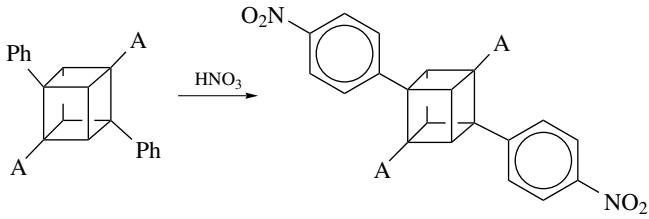
(91) **(95)**

(8)



(95')

Reaction of **91** with a 90% nitric acid in CH_2Cl_2 at room temperature gave 2,7-bis (*p*-nitrophenyl)cubane-1,4-diamide **96** in 93% yield (equation 9)[60].

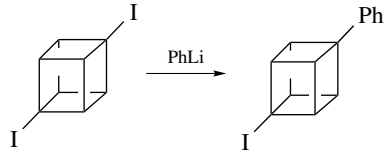


(91) **(96)**

A = CON(Pr-*i*)$_2$

(9)

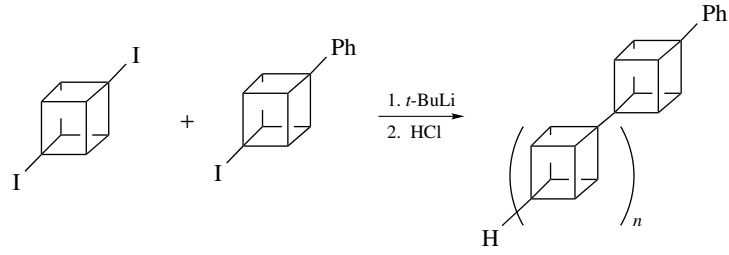
Iodophenylcubane **98** was also prepared from the reaction of phenyllithium with halocubanes **97** via a halogen–metal exchange mechanism (equation 10)[45d, 61].



(97) **(98)**

(10)

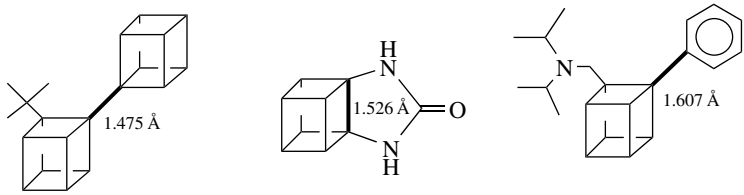
Application of this reaction was extended to the formation of the cubyl–cubyl bond, and ultimately to the synthesis of rigid, rod-shaped polymeric cubanes **99** (equation 11)[62].



(11)

(97) **(98)** **(99)**

The molecular structure of cubylcubane **100** shows a short bond (1.475 Å) between the two cubyl moieties which is much shorter than a normal single carbon–carbon bond (1.542 Å)[51]. It is interesting to note that while 1,2-cubylurea **101** has one of the shortest cubane carbon–carbon bonds (1.526 Å vs. 1.551 Å for cubane)[63], cubane **102** has one of the longest carbon–carbon bonds to a cubane ring (1.607 Å)[56b].

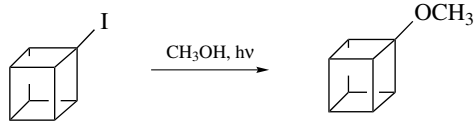


(100) **(101)** **(102)**

B. Cationic Reactions

Unlike anionic reactions, only a very limited number of cationic reactions of cubane are known. Although the cubyl cation has not been observed directly at low temperatures, it was more easily obtained than originally expected.

Irradiation of iodocubane **57** in methanol gives methoxycubane **62** via a photo-Ritter reaction, in which formation of an intermediate non-classical cationic center is most probable (equation 12)[44c].

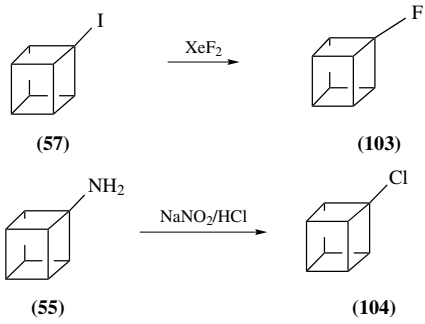


(12)

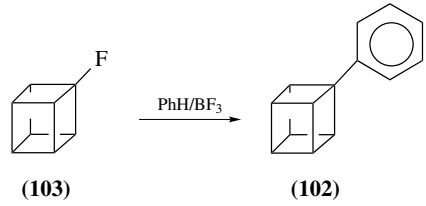
(57) **(62)**

Other examples of cubyl cation intermediates in reaction giving fluoro (**103**) and chloro (**104**) cubane are given in Scheme 20[44].

Using **103**, another synthesis of phenylcubane **102** was achieved by its Friedel–Crafts reaction with benzene in the presence of boron trifluoride (equation 13)[64].



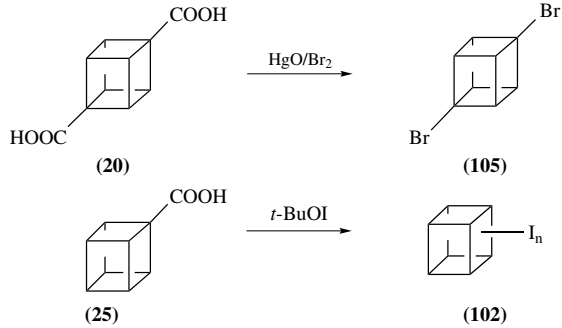
SCHEME 20



(13)

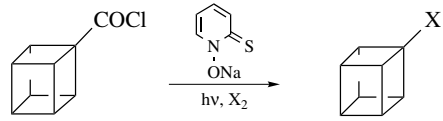
C. Radical Reactions

The cubyl radical has been generated at high temperatures without rearrangement. Synthesis of dibromocubane **105** from the corresponding dicarboxylic acids by the Hunsdiecker reaction[65] or by polyiodination of cubane carboxylic acid with *t*-butyl hypoiodite[49] are examples of reactions proceeding via radical intermediates (Scheme 21).



SCHEME 21

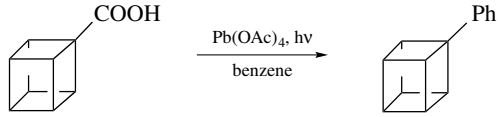
Barton's method has been used effectively for the synthesis of halogenated and reduced cubanes via a radical process (equation 14)[24].



(14)

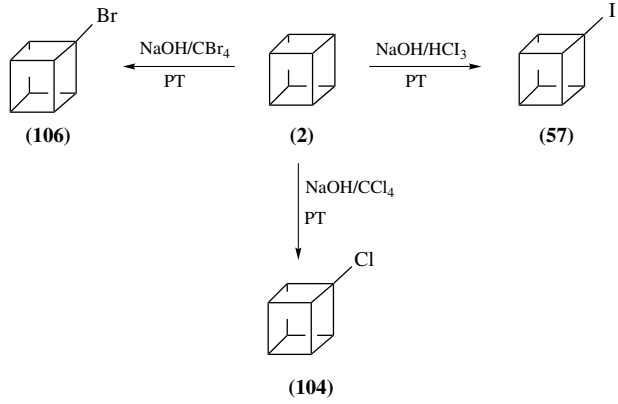
X = H, halogen

The synthesis of phenylcubane **102** was also achieved by the reaction of cubanecarboxylic acid **25** with lead tetraacetate in benzene under ultraviolet light (equation 15)[66].



(25) **(102)** (15)

It has been reported that free-radical halogenation of cubane causes skeleton fragmentation[67]. However, under phase transfer [PT, 10 mol% (n-Bu)$_4$NBr)] conditions, halogenation of cubane to give **57**, **104** or **106** has been achieved (Scheme 22)[68].

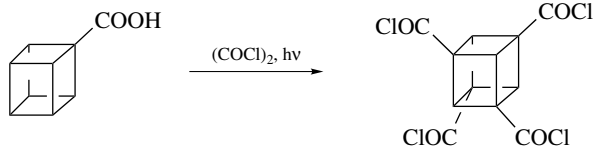


(106) **(2)** **(57)** **(104)**

SCHEME 22

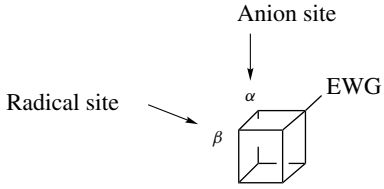
1. Photochemical chlorocarbonylation

The history of photochemical chlorocarbonylation of hydrocarbons goes back to the earlier work of Kharasch and Brown at the University of Chicago some sixty years ago[69]. In their pioneering work, the photochemical chlorocarbonylation of cyclohexane with oxalyl chloride in carbon tetrachloride, followed by hydrolysis, gave cyclohexanecarboxylic acid. At ARDEC, Picatinny Arsenal, the regioselectivity of the photochemical chlorocarbonylation reaction was recognized and applied to molecules such as adamantane[70] and cubane to obtain multi-substituted cage compounds with unique substitution patterns[71]. For example, photochemical reaction of cubane carboxylic acid **25** and oxalyl chloride gave in a one pot reaction 1,3,5,7-tetra(chlorocarbonyl)cubane **107**, where the substituents are on alternate corners of the cube (equation 16). The original synthesis of **107** required more than twenty synthetic steps[72].



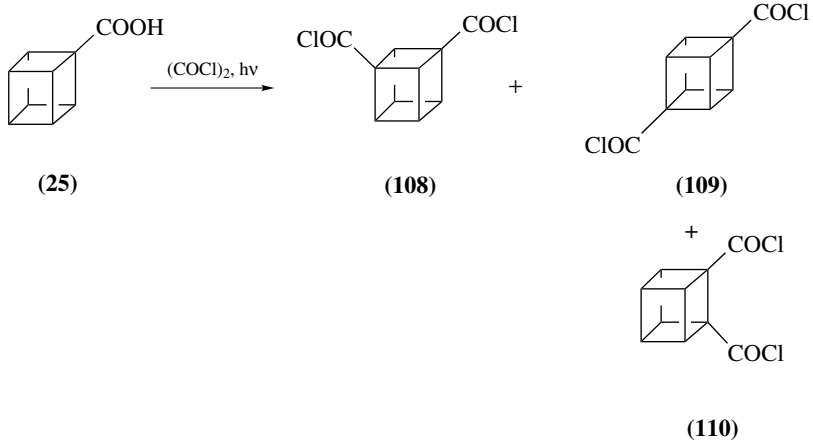
(25) **(107)** (16)

The regioselectivity of the photochemical chlorocarbonylation was explained in terms of an electron-withdrawing field effect of the carboxyl group. This effect would result in a retarded cleavage of the α C−H bonds, leading to predominant chlorocarbonylation at the β positions[73].



EWG = Electron Withdrawing Group

In one experiment, a solution of cubanecarboxylic acid **25** and oxalyl chloride was irradiated in a Rayonet photochemical reactor at 254 nm. The starting material was consumed after 30 min and *meta*-, *para*- and *ortho*-disubstituted cubanes **108, 109** and **110** were formed in an approximate ratio of 3:1:1, respectively (equation 17).



(25) **(108)** **(109)** (17)

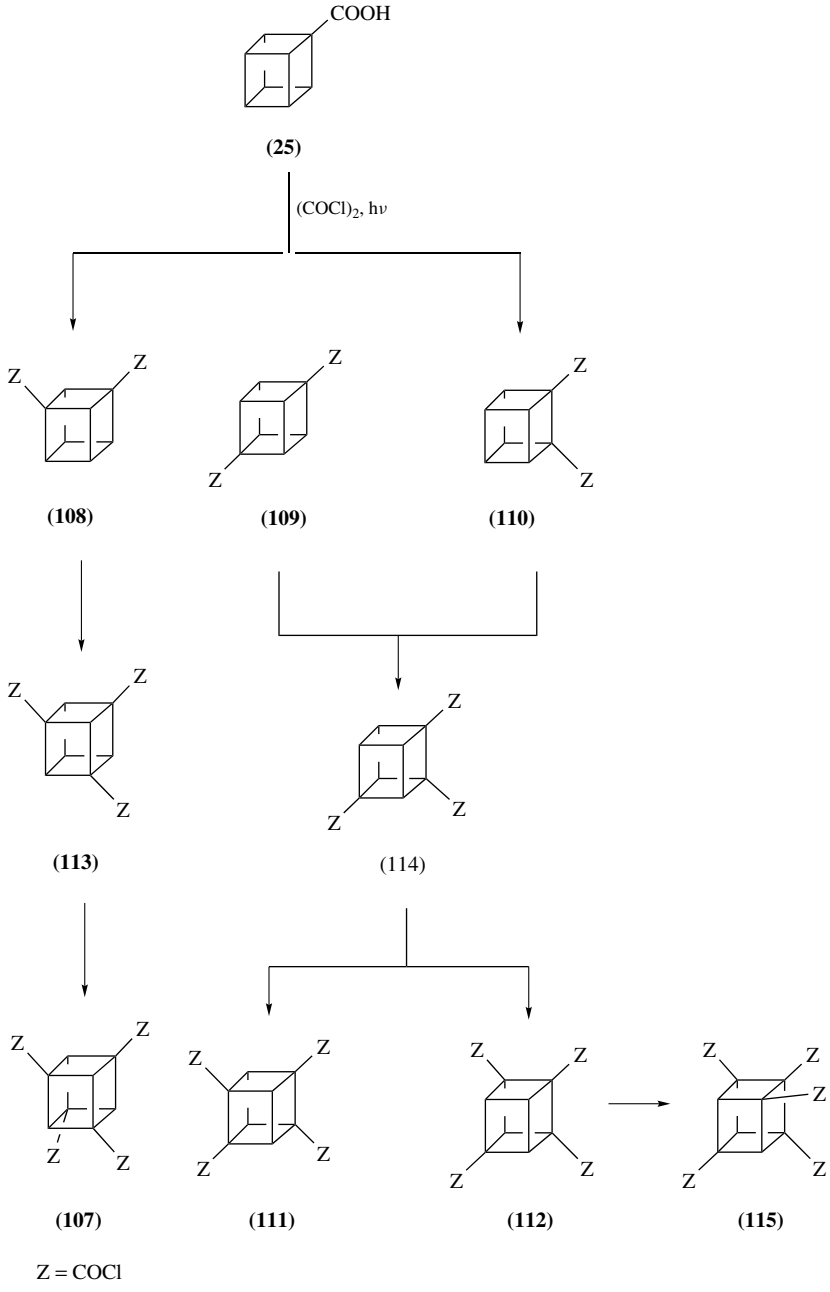
(110)

Statistical factors (three *ortho*, three *meta* and one *para* position) as well as polar effects can explain the higher ratio of the *meta* substituted cubane **108**. The electrophilic chlorocarbonyl or chlorine radicals preferentially abstract a hydrogen from the least electron-deficient carbon atom distant from the electron-withdrawing groups.

Further chlorocarbonylation of disubstituted cubanes led to the tri- and higher substituted cubanes. The progress of the reaction was followed by ^{1}H NMR spectroscopy and after 8 h the spectra showed a mixture consistent with tetrasubstituted cubanes **107, 111** and **112** in an approximate 55:10:35 ratio, respectively (Scheme 23). The trisubstituted intermediates are **113** and **114**, and the pentasubstituted system **115** is formed from **112**.

There are twenty-one possible cubanecarboxylic acids and more than half can be made by the chlorocarbonylation method.

The tetrahedrally substituted compound **107** was the major product and was easily separated from other isomers by triturating the reaction mixture with ether. The rate of the substitution decreases as the reaction progresses.

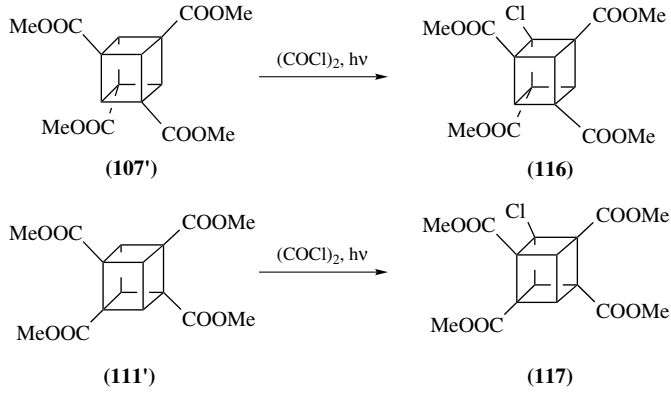


SCHEME 23

The pentasubstituted cubane **115** along with trace amounts of hexa- and heptasubstituted cubanes were obtained after 48 h of irradiation.

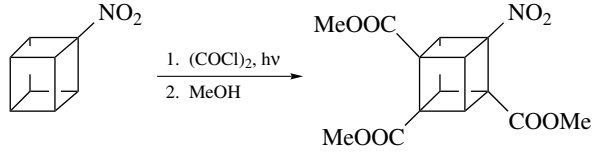
It should be noted that compounds **113b** (Z = COOMe) and **114b** can be obtained in much improved yields from the photochemical reaction of commercially available 1,4-dicarbomethoxycubane **21** and oxalyl chloride, followed by esterification with methanol.

The photochemical reaction of the tetra(carbomethoxy) analogs of **107** and **113**, i.e. **107′** and **111′** with oxalyl chloride at higher temperatures and for longer reaction time, gave only the chlorinated products **116** and **117** (Scheme 24).



SCHEME 24

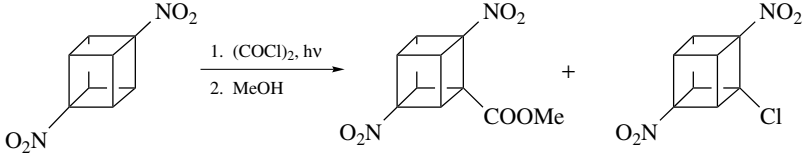
Chlorocarbonylation methodology also provided an interesting approach to functionalization of nitrocubanes. Chlorocarbonylation of nitrocubane **118** gave a very high yield (>90%) of 1-nitro-3,5,7-tricarbomethoxycubane **119** after methanolysis (equation 18)[74].



(18)

(118) **(119)**

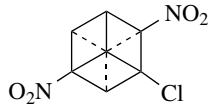
Irradiation of 1,4-dinitrocubane **120** with oxalyl chloride produced, after esterification with methanol, 2-carbomethoxy-1,4-dinitrocubane **121** and 2-chloro-1,4-dinitrocubane **122**, in 84% and 16% yields, respectively (equation 19)[75].



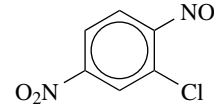
(19)

(120) **(121)** **(122)**

Interestingly, the structure of 2-chloro-1,4-dinitrocubane (shown as **122a)** resembles the structure of 2-chloro-1,4-dinitrobenzene **123**, a potential biologically active, anti-AIDS drug[76].



(122a)

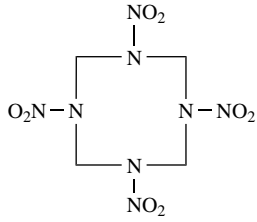


(123)

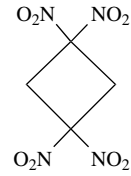
However, attempts at photochemical chlorocarbonylation of 1,3,5,7-tetranitrocubane under various reaction conditions failed, and the starting material was recovered. Two factors, an increased C−H bond strength and a large polar effect arising from four nitro groups, might have contributed to the lack of reactivity.

VII. NITROCUBANES

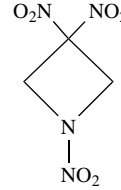
The idea of using nitrocubanes as explosives and propellants was conceived by the late E. E. Gilbert at ARDEC, New Jersey, in the early 1970s and reported later[77]. Nitrocubanes are predicted to be more powerful than HMX **124**, the Military's benchmark energetic material, as well as tetranitrocyclobutane (TNCB) **125**[78] and trinitroazetidine (TNAZ) **126**[79]. Both TNAZ and TNCB derive their power from their strain energy (SE = *ca* 27 kcal mol^{-1}) contained in the four-membered rings[80].



(124)

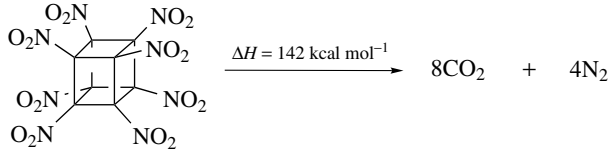


(125)



(126)

The cubane cage is a polycyclic molecule with six cyclobutane rings that are fused together in a closed structure. Theoretical calculations predicted a crystal density of 2.0–2.1 g cm^{-3} for octanitrocubane **127**[77a], and heat of formation of 142 kcal mol^{-1}. Octanitrocubane has a perfect oxygen balance and converts completely to CO_2 and nitrogen (equation 20)[77b].

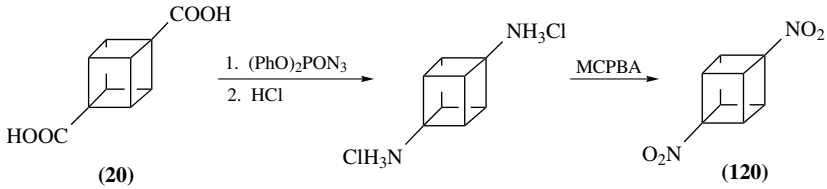


(20)

(127)

The sp^2–sp^2 nature of the C−C bonds prevents direct nitration of the cubane skeleton. Earlier attempts at direct nitration of the cubane hydrocarbon resulted in its complete destruction and in a violent explosion.

The first synthesis of 1,4-dinitrocubane **120** was achieved by Eaton and coworkers in 1984[81] by converting the carboxylic acid groups of 1,4-cubane dicarboxylic acid



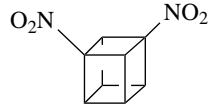
(20) **(120)**

SCHEME 25

to the amino groups using diphenylphosphoryl azide, followed by oxidation with *m*-chloroperbenzoic acid (MCPBA) to the nitro groups (Scheme 25).

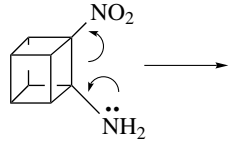
Although the synthesis of dinitrocubane has been improved over the years[81], it is still far from being a practical process for multi-pound production.

1,3-Dinitrocubane **128** was prepared from 1,3-cubane dicarboxylic acid **30** in only a few milligrams by Griffin and coworkers[82].



(128)

Although the synthesis of 1,4- or 1,3-dinitrocubanes is relatively straightforward, the synthesis of 1,2-dinitrocubane from 1,2-cubane dicarboxylic acid has not been successful. A push–pull mechanism in the intermediate 1-amino-2-nitrocubane is responsible for the cleavage of the highly strained cubane bond between the two substituents (equation 21).



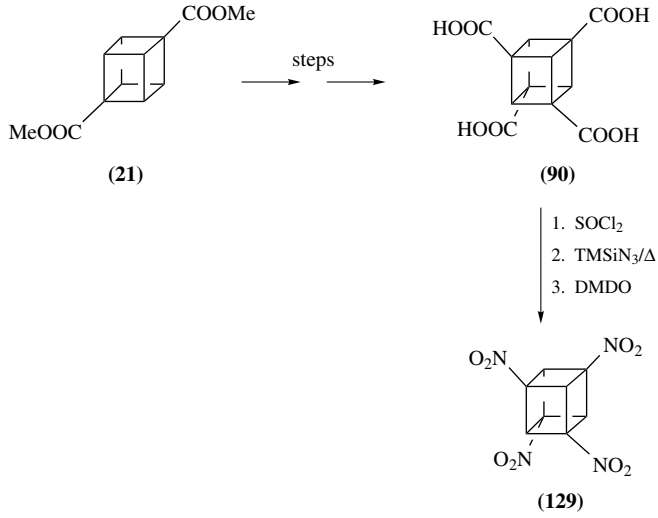
(21)

The first synthesis of 1,3,5,7-tetranitrocubane **129** from 1,3,5,7-cubane tetracarboxylic acid **90** was achieved in 1993 by Eaton and coworkers[72] in more than twenty-eight steps, starting from 1,4-dicarbomethoxycubane **21** (Scheme 26).

The DSC exotherm for **129** is 278 °C, the highest among the nitrocubyl derivatives[12]. Apparently, the strongly electron withdrawing nitro groups on the tetrahedral positions kinetically stabilize the cubane system.

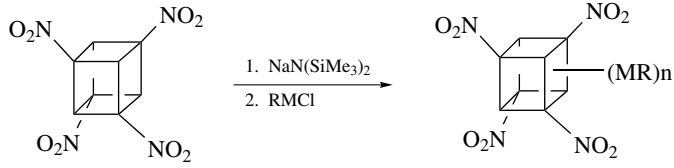
The crystal density of **129** is 1.814 $g\,cm^{-1}$, very high for a nitrohydrocarbon. The cubane skeleton displays some flexibility in its internal bond angles. For example, the X-ray structure of **129** shows that the average angle between cube-edge bonds is 91.7° at corners bearing a nitro group, and only 88.3° at corners substituted by hydrogen atoms[46c].

The pK_a value of **129** is in the range of 20.5–22.5 and it should be deprotonated under mild conditions. A successful metalation of tetranitrocubane was achieved and corresponding lead, tin, silyl and mercury derivatives were prepared (equation 22)[83].



(21) **(90)** **(129)**

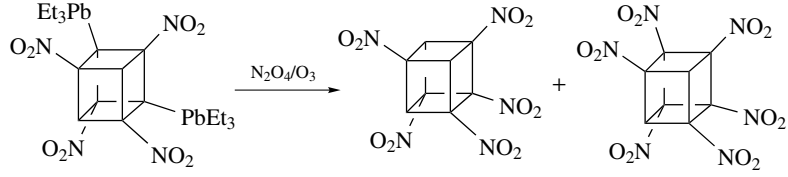
SCHEME 26



(22)

(129) RM = Et_3Pb, Me_3Sn, Me_3Si, EtHg

Pentanitrocubane **131** and hexanitrocubane **132** were synthesized from the reaction of bis(trialkyl) lead compound **130** with N_2O_4 followed by ozonolysis (equation 23)[83].

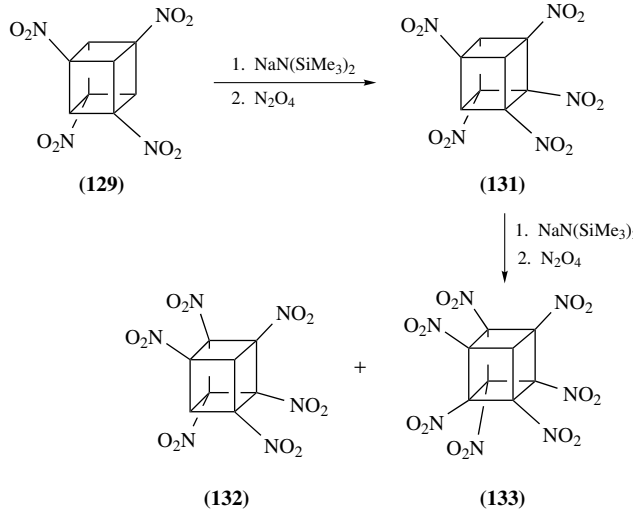


(23)

(130) **(131)** **(132)**

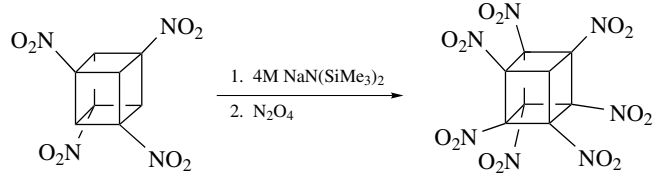
Direct nitration of the sodium salts of 1,3,5,7-tetranitrocubane **129** and 1,2,3,5,7-pentanitrocubane **131** with dinitrogen tetroxide in THF at very low temperature (−115 °C) gave hexanitrocubane **132** and heptanitrocubane **133**, respectively (Scheme 27). In this reaction, the nitration occurs at the melting interface of THF/N_2O_4[83].

Heptanitrocubane **133** was obtained directly from tetranitrocubane **129** in a very high yield by using excess (4.0 equivalent) of the base (equation 24). The X-ray crystal density of **133** was determined to be 2.028 g cm^{-3}, the highest density among polynitrocubanes[83].



(129) (131) (132) (133)

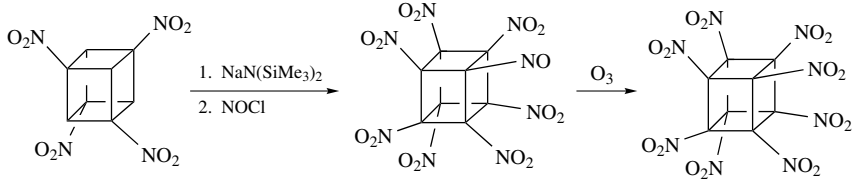
SCHEME 27



(24)

(129) (133)

The synthesis of octanitrocubane **127**, the milestone, was achieved in two steps[84]. Addition of excess nitrosyl chloride (NOCl) to a solution of the lithium salt of heptanitrocubane **133** in dichloromethane followed by ozonation of the nitroso compound **134** at −78 °C gave octanitrocubane **127** in *ca* 50% yield (Scheme 28)[84].



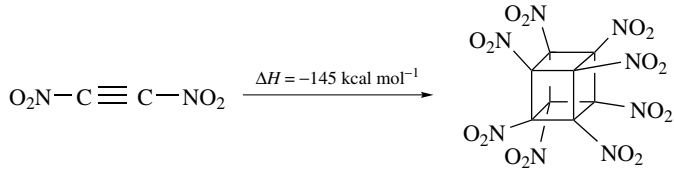
(129) (134) (127)

SCHEME 28

Direct nitration of the heptanitrocubane salt with usual nitrating reagents (N_2O_4, NO_2BF_4, NO_2Cl, N_2O_5 etc.) failed to give octanitrocubane. This might be due to the higher stability of the anion of heptanitrocubane toward reaction with N_2O_4 or NO_2Cl. Therefore, a more powerful oxidant, nitrosyl chloride, was required.

Octanitrocubane is a stable white solid with a density of 1.979 g cm^{-3} [84].

So far, only a few milligrams of octanitrocubane have been obtained, albeit by a very lengthy process. Consequently, a more realistic method for the large-scale synthesis of octanitrocubane **127** is needed. For example, the tetramerization of the unknown dinitroacetylene **135** to **127** should be a much more practical approach. This cyclooligomerization has been predicted to be a feasible process, both kinetically and thermodynamically (equation 25)[19].

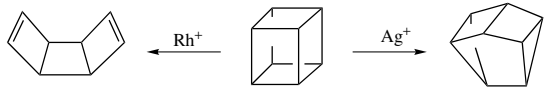


(25)

(127)

VIII. TRANSFORMATION OF CUBANES TO OTHER CAGE SYSTEMS

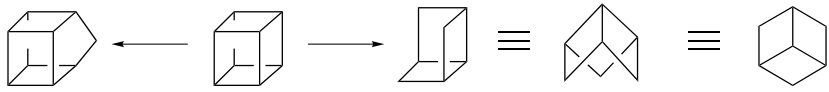
Several cage systems can be obtained from cubane which otherwise are difficult to prepare by regular synthetic methods. As mentioned earlier, in the presence of metal catalysts such as Ag^+ or Rh^+, the cubane skeleton rearranges to cuneane **47** and to *syn*-tricyclooctadiene **48**, respectively in almost quantitative yields (Scheme 29)[41–43].



(48) **(2)** **(47)**

SCHEME 29

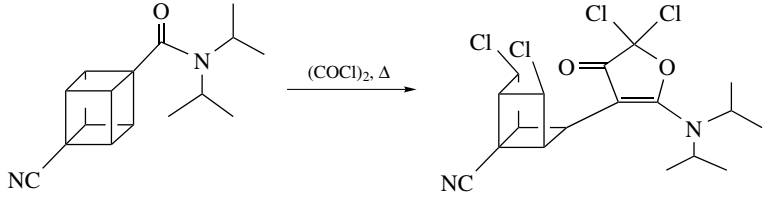
In a series of some interesting and unexpected transformations, the cubane skeleton went through ring-expansion and ring-contraction processes. For example, reaction of amidocubanes or acetylcubanes with oxalyl chloride gave norcubane **136** (also called tricycloheptane, trisnoradamantane) and homocubane **137**, respectively (Scheme 30).



(137) **(2)** **(136)**

SCHEME 30

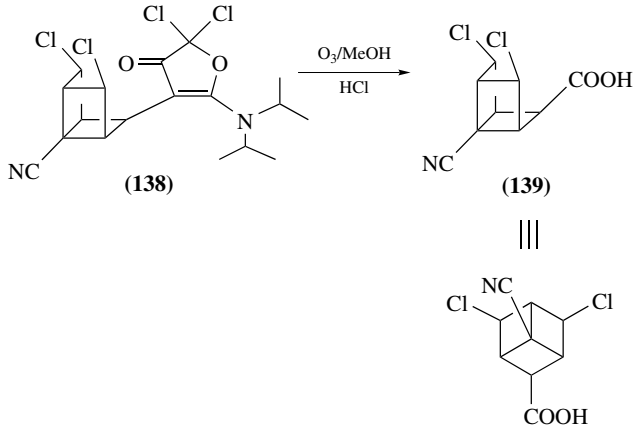
A tetrahedrally substituted tricycloheptane **138** was obtained in >90% yield from the reaction of amidocyanocubane **87** with oxalyl chloride at room temperature (equation 26)[85].



(26)

(87) **(138)**

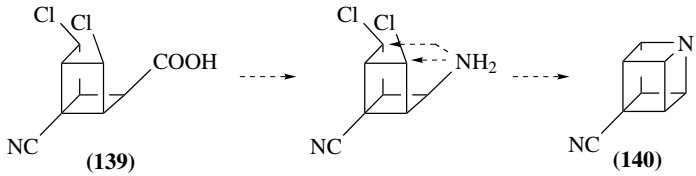
Ozonolysis of the dichlorofuranone ring in methanol followed by hydrolysis gave carboxylic acid **139** (equation 27).



(27)

Interestingly, reaction of oxalyl chloride with 1,4-diamidocubane **76** proceeded rather slowly and complete conversion occurred within one hour. In this reaction, both bond cleavages of the cubane skeleton occur simultaneously at one amido site without participation of the other amido substituent.

Single crystal X-ray diffraction of compound **139** shows two chlorine atoms occupying *exo* positions relative to the tricycloheptane skeleton. Of particular interest is that the distances from carbon atoms bearing chlorines to C_8 are 3.10 Å and 3.13 Å, i.e. shorter than the non-bonded van der Waals contact distance, which usually ranges from 3.20 Å to 3.40 Å. This close proximity might lead to the construction of very desirable molecules, such as azacubane **140** (Scheme 31)[86].

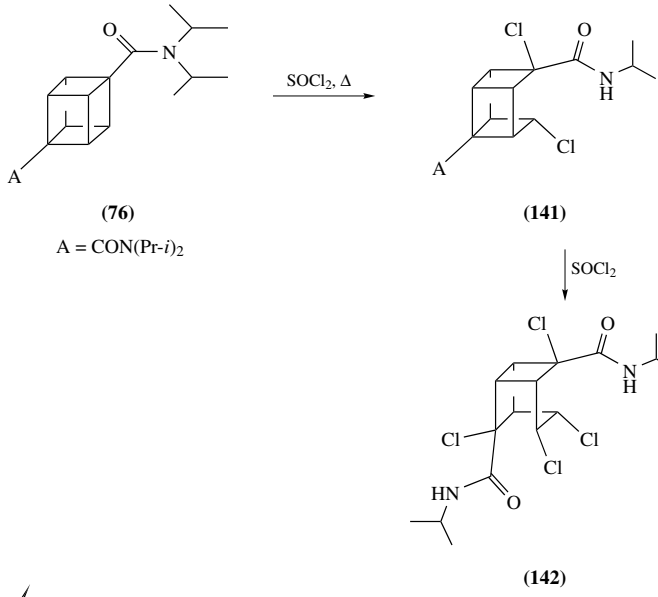


SCHEME 31

The rearrangement of cubane diamide with oxalyl chloride is the first example in which adjacent cubane carbon–carbon bonds are broken to give a substituted tricycloheptane ring system. In similar cases, usually, and preferably, two non-neighboring bonds are cleaved. For example, reaction of 1,4-diamidocubane **76** with thionyl chloride results in formation of the more stable product, substituted nortwistbrendane **142** via the secocubane structure **141**[87]. Starting from **143**, nortwistbrendane **144** is favored over the more symmetric configuration, diasterane **144a**, by 34 kcal mol^{-1} (Scheme 32)[88].

A similar reaction was observed when 1,4-cubane dicarboxylic acid **20** was reacted with HBr, to give dibromonortwistbrendane dicarboxylic acid **146** through a bromosecocubane dicarboxylic acid intermediate **145** (Scheme 33)[89].

While reaction of oxalyl chloride with carbomethoxycubane did not cause any ring opening, acetylcubane **147** reacted with oxalyl chloride via a totally different transformation to give methylhomocubanol **148** as the major product (46% yield). In this case, a

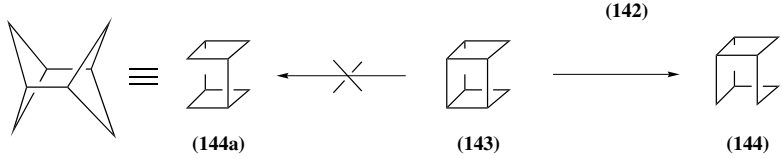


(76)

A = CON(Pr-*i*)$_2$

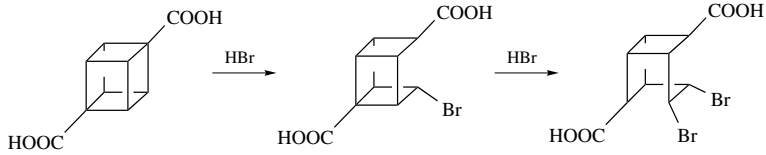
(141)

(142)



(144a) **(143)** **(144)**

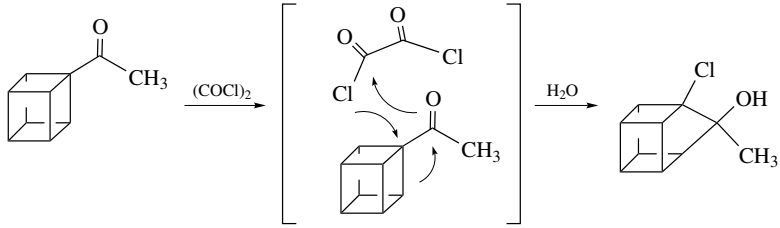
SCHEME 32



(20) **(145)** **(146)**

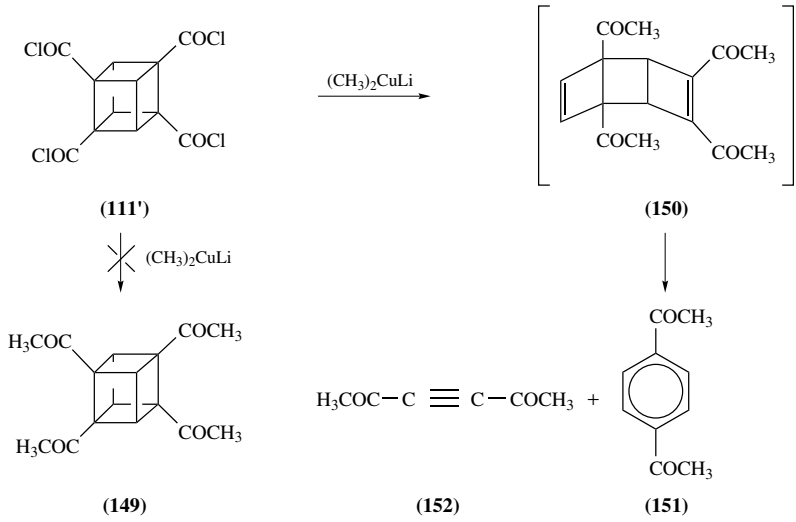
SCHEME 33

Wagner–Meerwein 1,2 shift of the cubane bond to the carbonyl carbon is preferred over exocyclic double-bond formation (equation 28)[90].



(147) **(148)** (28)

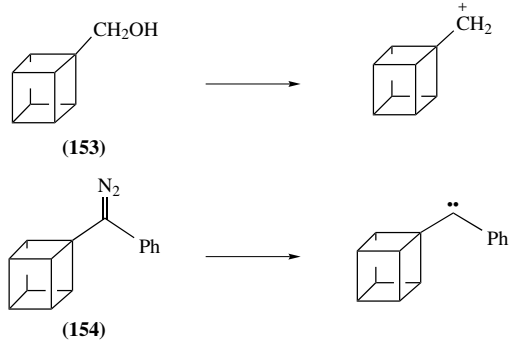
Surprisingly, attempts to synthesize 1,2,4,7-tetraacetylcubane **149** from the reaction of 1,2,4,7-tetra(chlorocarboxy)cubane **113** with $(CH_3)_2CuLi$ gave quantitatively 1,4-diacetylbenzene **151** and diacetylacetylene **152,** most probably through a tricyclooctadiene intermediate **150** (Scheme 34)[91].



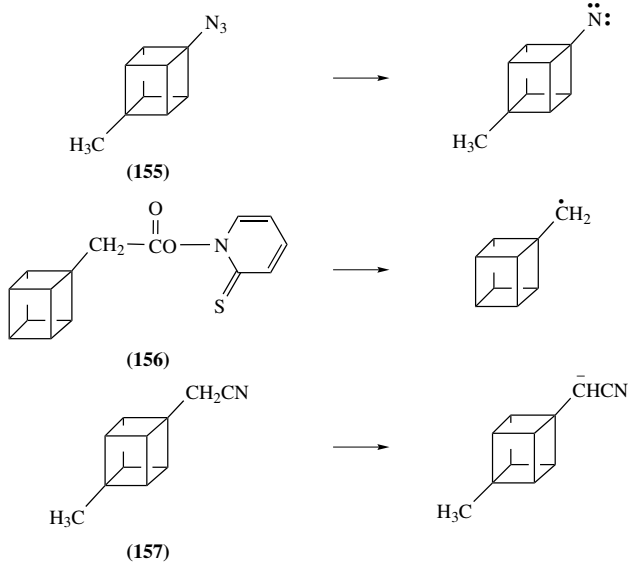
SCHEME 34

Cubylmethyl derivatives **153**[92], **154**[93], **155**[94], **156**[95] and **157**[96] are expected to generate the corresponding carbenium, carbene, nitrene, radical and anion at the α-carbon of the cubane skeleton, respectively (Scheme 35).

Each species spontaneously undergoes cage fragmentation or ring enlargement reaction to transform it into a unique strain-relieved ring system (*vide infra*). Similarly, the strained carbinol derivatives of homocubane **158** readily undergo ring expansion to bishomocubane via a Wagner–Meerwein 1,2-shift in acidic media, because the framework of homocubane is less strained by only 20 kcal mol^{-1} than that of cubane **2**[92c, 97].

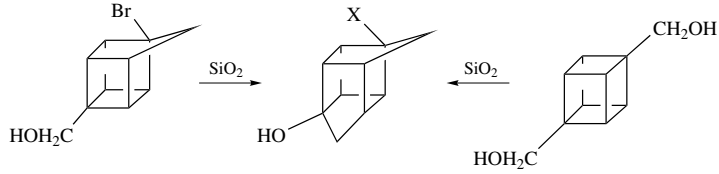


SCHEME 35



SCHEME 35. (*continued*)

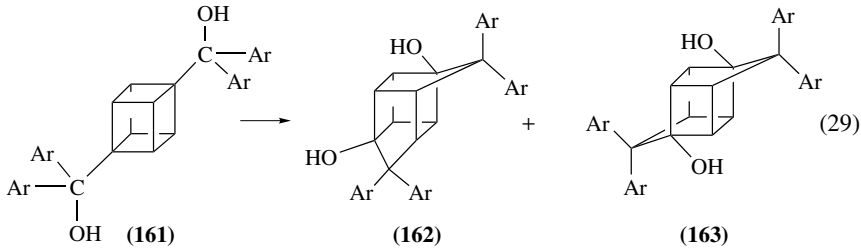
With respect to the ring expansion product, the Wagner–Meerwein rearrangement of homocubylcarbinol **158** preferably proceeds via kinetically controlled processes to afford exclusively 1,3-bishomocubanes **159**, which is the same system formed from cubane-1,4-bis(carbinol) **160** (Scheme 36)[97,98].



X = Br or OH

SCHEME 36

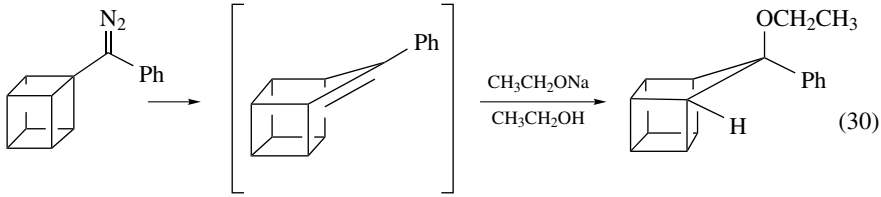
Ring expansion of the stabilized diarylcubylmethyl carbenium ion formed from the bis(carbinol)s **161**, however, was found to form not only 1,3-bishomocubanes **162** but also the kinetically less stable 1,4-bishomocubanes **163** (equation 29)[99].



(29)

This result suggests that an interaction between the two carbenium centers through the cubane skeleton has a critical role in lowering the activation energy for the C−C bond cleavage.

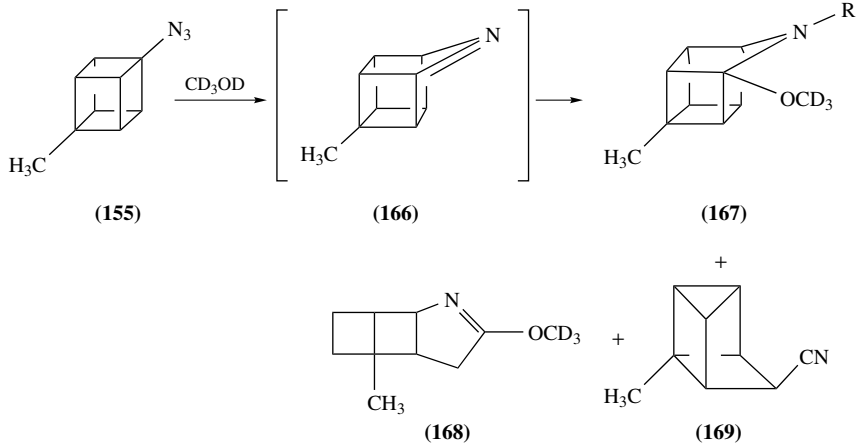
On photolysis or thermolysis, the diazomethane derivative **154** was converted to the homocubane derivative **165** via intermediate **164**, which contains an extremely twisted C=C double bond (equation 30)[93].



(30)

(154) **(164)** **(165)**

Similarly, the solvolysis of cubylazide derivative **155** affords the cubane cleavage products **167, 168** and **169,** presumably via azahomocubene **166**, with the extremely twisted C=N bond. However, as yet there has been no evidence for the intermediacy of the anti-Bredt imine (Scheme 37)[94].



(155) **(166)** **(167)**

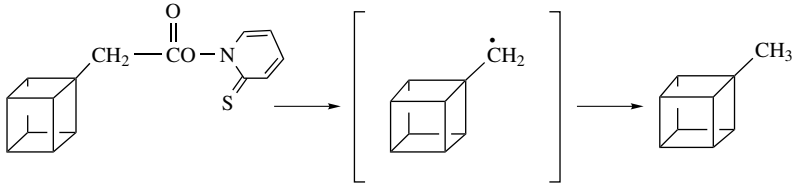
(168) **(169)**

SCHEME 37

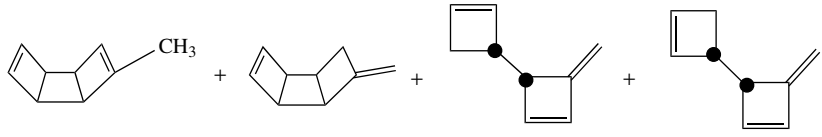
The cubylmethyl radical **170** was generated on photoirradiation of the *N*-hydroxy pyridinethione ester **156** under various conditions[95,100]. As expected, the radical intermediate ($\tau_{1/2}$ 35 ps) swiftly undergoes ($k = 2.7 \times 10^{10}$ s^{-1}) opening of the polycyclic rings to rearrange into olefinic products **172**–**175**, except for one example of methylcubane **171** formation in the presence of high concentrations of PhSeH (Scheme 38).

The treatment of **157** with an excess of LDA generates the cubylmethyl carbanion **176**, which instantly undergoes homoallylic rearrangements to afford a mixture of two ring-opened alkenes **177** and **178**, respectively (Scheme 39)[96b].

It is notable in this reaction that the homoallylic rearrangements, the ring opening of the anionic species and the successive cyclobutane C−C bond cleavage all proceed via base-promoted, regiospecific processes.

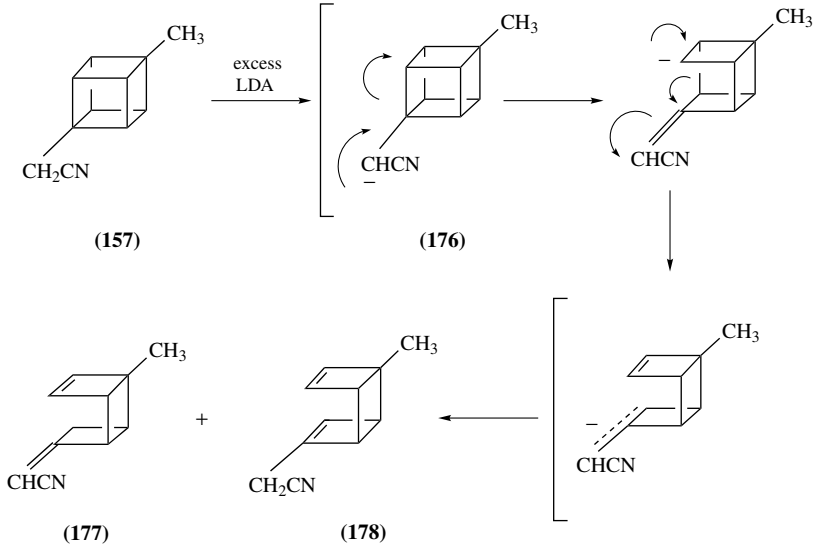


(156) **(170)** **(171)**



(172) **(173)** **(174)** **(175)**

SCHEME 38



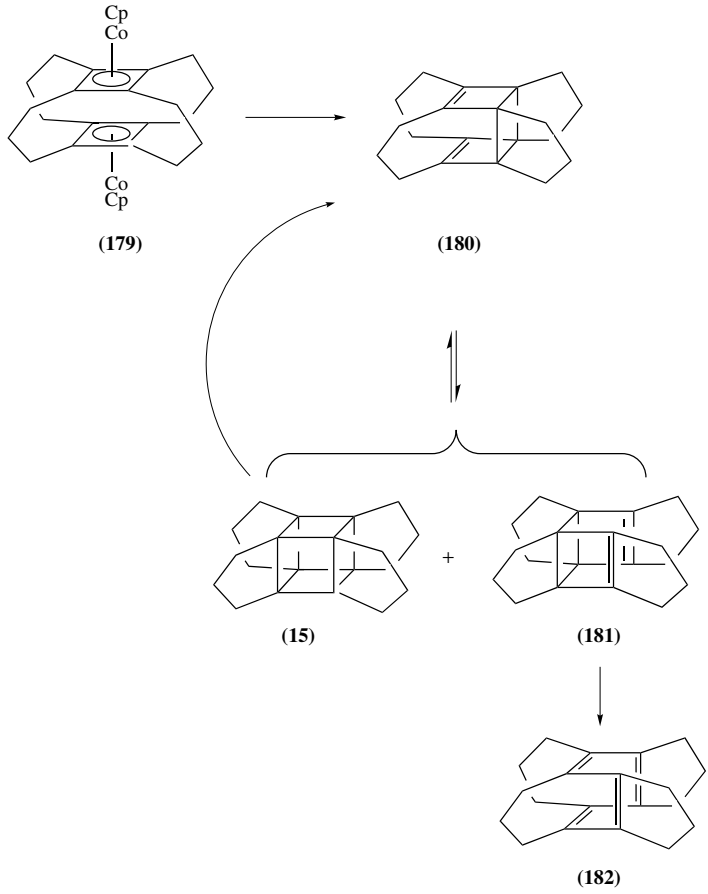
(157) **(176)** **(177)** **(178)**

SCHEME 39

IX. PROPERTIES OF PROPELLAPRISMANES

The chemistry of propellaprismanes has been constructing their unique field, which is based on their structural features of a propellane as well as those of a prismane. Oxidation of superphane **179** gave heptacyclodiene **180** whose irradiation in pentane at room temperature afforded propella[3_4]prismane **15** together with unreacted **180** and its isomer **181** (Scheme 40)[101].

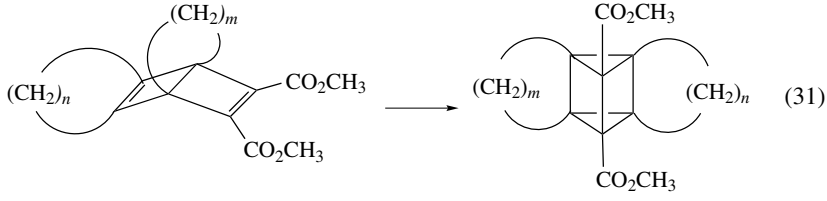
Irradiation of the isolated mixture of **180** and **15** results in an equilibrium mixture of **180, 15** and **181** in a ratio of 10:1:4. Similarly, propellaprismane **15** itself reverts to **180** both in acidic media and under thermal conditions by the valence isomerism.



SCHEME 40

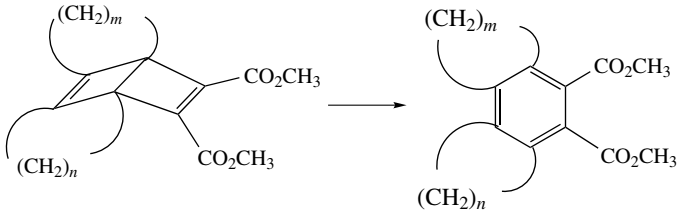
On the other hand, the isomeric diene **181** undergoes a valence isomerization to afford the cyclooctatetraene derivative **182** through column chromatography on alumina with *n*-pentane at 28 °C.

Doubly bridged Dewar benzenes of type **183** and **185** also exhibit curious behavior, depending on the chain length, the nature of two other functional groups and the irradiation energies[102]. The isomers **183** with bridges spanning the 1,4- and 2,3-positions reacted to form the corresponding prismanes **184** (equation 31).

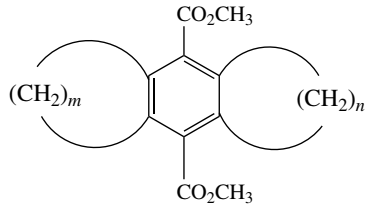


(31)

On the other hand, their isomers **185** with bridges spanning the 1,2- and 3,4-positions revealed a more complex photochemistry, via various intermediates formed from competition reactions, including phthalic/terephthalic ester rearrangement to afford the benzene derivatives **186** and **187** (equation 32).



+ (32)



Photochemistry of bridged Dewar benzenes revealed that the electronic effect induced by the ester groups is responsible for the prismane stability, and the steric factors control the prismane formation. Thus, in the case where the particular course of the reaction for a propellaprismane can be technically controlled in the bridged compounds, the research of this process would be very useful as one of the synthetic methodologies for the synthesis of higher prismanes including the yet unknown hexaprismane carbon framework (*vide infra*).

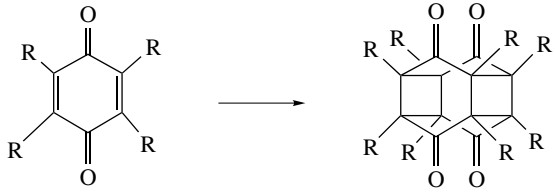
X. TOWARD HEXAPRISMANE

Hexaprismane **4** is one of the compounds on which intensive theoretical studies have been performed prior to the advent of their syntheses. MM2 calculation indicates that hexaprismane has D_{6h} symmetry, and is formally regarded as a face-to-face dimer of benzene, in which each six- and four-membered face is planar[103]. Thus, the flat six-membered rings, a very rare and strained structural shape, would have C−C−C angles of 120°, significantly above the normal tetrahedral angle. To compensate for the unusual skeletal strain of this molecule, the C−C bonds between the six-membered rings are predicted to be even longer (1.571 Å) than those of the five-membered rings of pentaprismane **3**. Contrarily, the C−C bonds within the six-membered rings are exceptionally short at 1.532 Å. These results are mainly attributed to the reduced stretch–bend interaction of the C−C−H bonds at the calculated 112.9°, due to which H···H interactions on each of the six-membered ring face increase much further, as compared with those on the corresponding four and five-membered ring faces of **2** and **3** C−C−H bond angles of 125.3° and 116.6°. Furthermore, calculations predict that among **1**–**4**, hexaprismane **4** possesses the largest ΔH_f° and SE values of 153.1 kcal mol^{-1} and 177.7 kcal mol^{-1}, respectively, which are higher by 4.6 kcal mol^{-1} and 12.8 kcal mol^{-1} than those of cubane **2**[104]. Apparently, these increased

strained features of **4** must result in extreme difficulty during construction of its molecular skeleton. Nevertheless, since prismanes **1**–**3** with the respective steric energies of 319.6, 171.5 and 143.6 kcal mol^{-1} could have been successfully synthesized, the steric energy of 164.4 kcal mol^{-1} predicted for hexaprismane **4** might show some methodological tip-off for its synthesis[105].

A. Synthetic Attempts at Hexaprismane

Attempts at the synthesis of **4** so far must be classified into two types of approaches[106]. One is based on the ring contractions from related homologous systems to its framework, the other is based on the [2+2] photocycloadditions of the pre-assembled diolefins leading to two or more cyclobutane rings which directly give the hexaprismane framework. Musso and coworkers synthesized face-to-face bis-seco-[6]prismane tetranones **189** by dimerizations of the corresponding *p*-benzoquinone derivatives **188** (equation 33)[107].

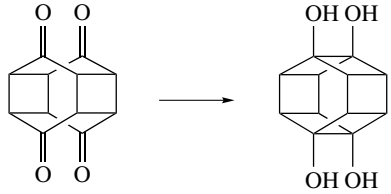


(188) **(189)**

R = CH_3 or H

(33)

In principle, those quinone dimers could be converted to the [6]prismane frameworks **191** through pinacolic coupling or related reactions starting from **190** (equation 34).



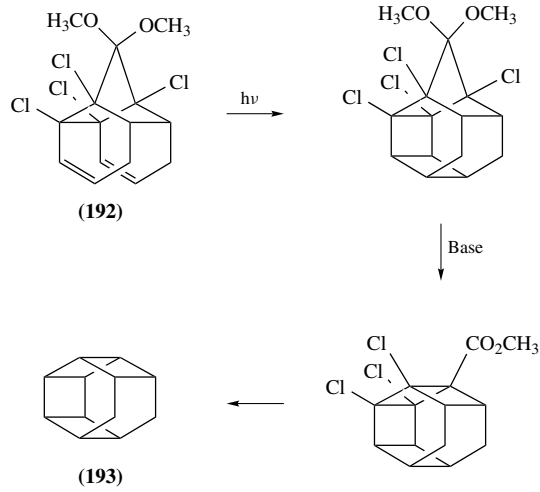
(190) **(191)**

(34)

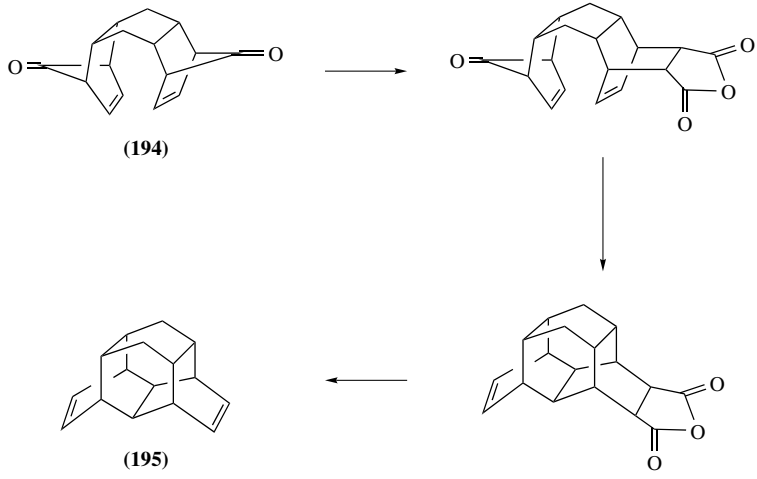
Such possibilities, however, have not succeeded due to stereoelectronically unfavorable alignment of the carbonyl groups. Secohexaprismane **193**, one of the closest precursors for **4**, has been successfully derived from the tetracyclic diene **192** by Mehta and coworkers, through the successive steps of photoclosure, Favorskii ring contraction and defunctionalization (Scheme 41)[108].

However, attempts at the final dehydrogenative C–C bond formation required to convert **193** to **4** were not successful.

A successful synthesis of hexacyclohexadecadiene **195** from pentacyclic bis-enone **194** was reported by Chou and coworkers, in relation to the carbon skeleton of secohexaprismane **193** (Scheme 42)[109]. This compound as well as the asterane-like derivative **196** prepared by Boekelheide and Hollins[110] and the 1,4-bishomo[6]prismane **197** (named 'garudane') synthesized by Mehta[111] and coworkers seem to be promising precursors for **4**.



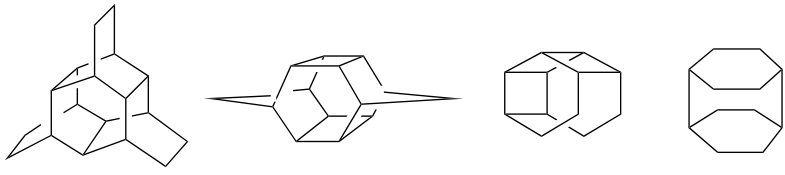
SCHEME 41



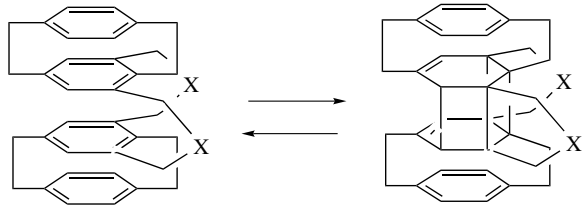
SCHEME 42

With these closely related homologous systems, further elaborations by functionalization of bridges and ring contractions toward the hexaprismane frameworks have been continued. Although Eaton and Chakraborty were successful in synthesizing pentacyclododecane **198** and octahydro[0.0]paracyclophane **199** via an elegant reaction sequence, their conversion to **4** has not been reported so far[112].

In the approach using [2+2] photocycloaddition, the most direct way to **4** would be through the union of two face-to-face benzene nuclei. In 1982, Misumi and coworkers synthesized the quadruple-layered dithia [3.3] metacyclophane derivative **200**, in which the inner benzene rings readily react on irradiation with a high pressure Hg lamp to afford the highly strained cage compound **203** (Scheme 43)[113].



(196) **(197)** **(198)** **(199)**



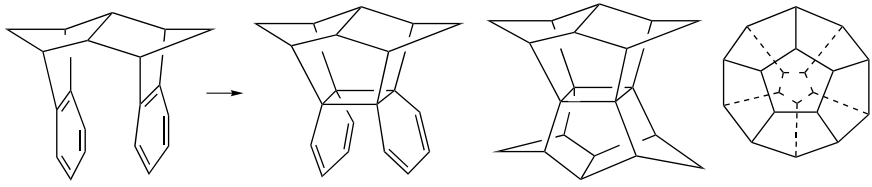
(200) X = S
(201) X = O
(202) X = Se

(203) X = S
(204) X = O
(205) X = Se

SCHEME 43

The photoisomer **203** was found to contain three consecutive cyclobutane rings with the remaining two faced double bonds, suggesting that the product was brought through double [2+2] or a combination of [4+4] and [2+2] cycloaddition processes. This reaction was reported to be the first example of photodimerization of benzene nuclei. The corresponding dioxa- (**201**) and diselena[3.3]metacyclophanes (**202**) also exhibit the same reactivity and gave **204** and **205**, respectively. All the photoisomers **203**–**205** efficiently revert back to the starting cyclophanes[114].

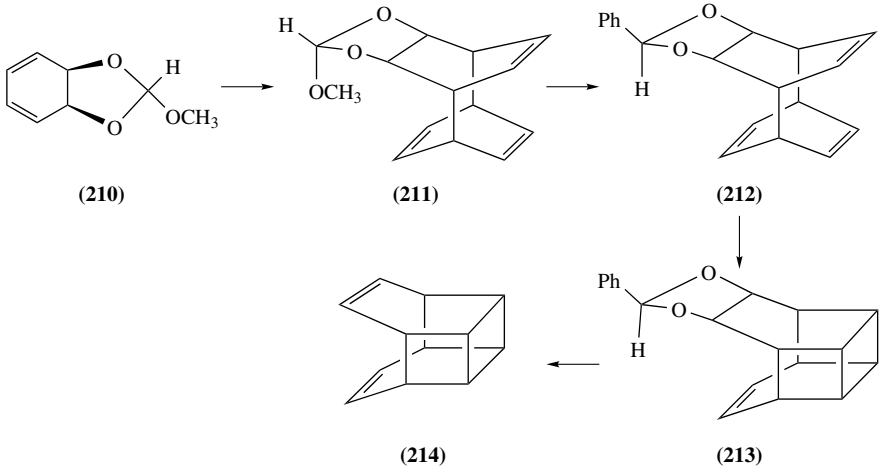
Later on, Prinzbach and coworkers also reported an example of the photodimerization of benzene nuclei (Scheme 44).



(206) **(207)** **(208)** **(209)**

SCHEME 44

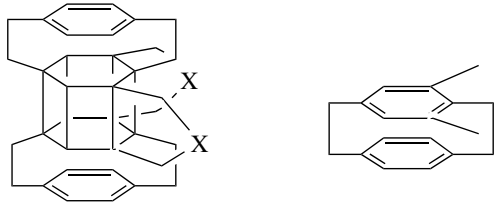
Irradiation of **206** cyclizes intramolecularly the faced benzene rings to afford the corresponding cage compound **207**, which is an important precursor of pagodane **208**[115] leading to dodecahedrane **209**[116]. On the other hand, Yang and Horner united two benzene rings stepwise through a *p*, *p*′-benzene dimer equivalent starting from the substituted cyclohexadiene **210** to construct the pentacyclic dimer of benzene **214** via **211**–**213** (Scheme 45)[117].



(210) **(211)** **(212)** **(214)** **(213)**

SCHEME 45

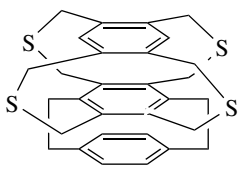
Both **203**–**205** and **214** seem to be the most promising precursors for hexaprismane frameworks, in case that the final [2+2] photocycloadditions between the remaining face-to-face double bonds can be attained. However, photocyclization of **203** under various conditions, including variation in the light sources, temperatures and solvents, afforded none of the desired hexaprismane derivative **215**, only forming a small amount of dimethyl[2.2]-paracyclophane **216** as an isolated substance[114].



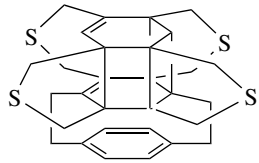
(215) **(216)**

A large increment of strain energy in the product, a too far distance between the two faced double bonds to form the two C−C bonds and a forbidden MO correlation between the starting material and the product are plausibly proposed for this unsuccessful result. Although related experimentations referring to **214** have been made[118], the attempted conversion to **4** has not been reported so far. Taking these facts into consideration, Osawa and coworkers predicted[119], based on the Paddon–Row theory[120], that the bridging of the faced double bonds with three-atomic chains effects the cycloaddition between them. In fact, it is apparent that the photocycloadditions of the faced double bonds or the benzene nuclei in **200**–**202** and **206** belong to the category of Osawa's prediction, and this also applies to **180** as a precursor for propellaprismanes[101]. Accordingly, as a first case, the compound **217**, which is related to **200**, was synthesized by Misumi and coworkers[121]. However, unexpectedly, the photoisomerization of **217** to the corresponding cage com-

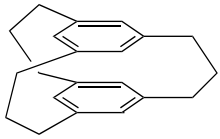
pound **218** did not take place[114]. In this connection, Shinmyozu and coworkers have also been energetically studying the photolyses of multi-bridged [3*n*]cyclophanes **219**–**223** in order to investigate the reaction intermediates bearing the corresponding hexaprismane frameworks[122].



(217)



(218)



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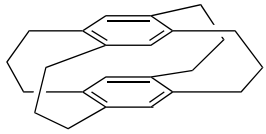

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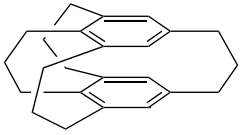

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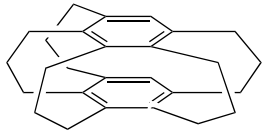

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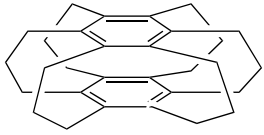

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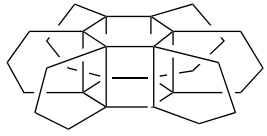


(224)

Successful isolation and characterization of the hexaprismane derivative **224**, however, has not yet been accomplished. As is usually the case, an epoch-making discovery in the methodologies including propellaprismane chemistry might be awaited for a successful synthetic of **4**.

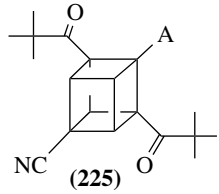
XI. SUMMARY

By far, the chemistry of cubane has outpaced and outperformed the chemistry of other prismanes. The commercial availability of dimethyl 1,4-cubanedicarboxylate by Aldrich chemicals, the surprising thermal stabilities of polynitrocubanes as energetic molecules and the recognition that some cubane derivatives have potential application as pharmaceuticals and materials have contributed to the popularity of cubane.

Although most of the efforts in the last twenty years have been directed toward the synthesis of nitrocubanes as explosives and propellants, new sources of civilian use, such

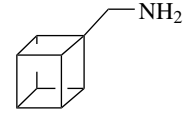
as gas generating material for a vehicle occupant protection apparatus (Air Bag), have emerged[123]. Other use of cubane has been in the area of combinatorial chemistry. For example, a cubane with multi-substituted chlorocarbonyl groups reacts combinatorially with a mixture of amino acids to generate thousands of molecules[11c].

Several cubane derivatives have shown biological activities[11]. In a preliminary test by NIH, dipivaloylcubane **225** shows moderate anti-HIV activity without affecting healthy cells[11d, 124]. In an interesting study, (aminomethyl)cubane **226** was used to probe the mechanism of monoamine oxidase (MAO), a brain enzyme involved in Parkinson's disease and other menaces[11a].



(225)

A = CON(Pr-*i*)$_2$



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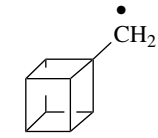
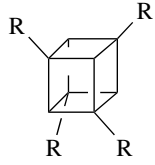
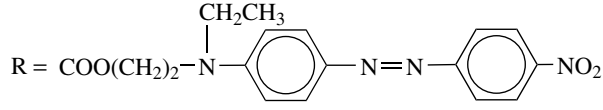


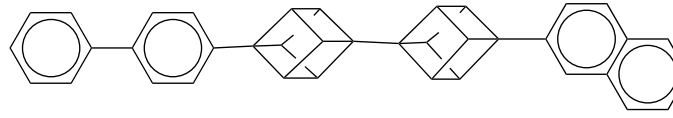
(170)

The cubylcarbinyl radical **170** rearranges with a rate constant of 2.9×10^{10} s^{-1} at 25 °C, which ranks it as one of the fastest known radical rearrangements. It was suggested as a 'molecular clock' for measuring relative rates of extremely rapid reactions in solution and as a mechanistic probe for radical forming reactions of enzymes[95].

Some tetrahedrally substituted cubanes have been used for the construction of star polymers. Star polymers have higher thermal stabilities, higher T_gs and higher solubilities than linear (two arm) polymers. The rigid cubane skeleton plays an important role in the characteristics of the glass-forming liquid crystals. Cubane with four pendant DR1 groups turned out to be a smectic ($S_{A)}$ glass[125].



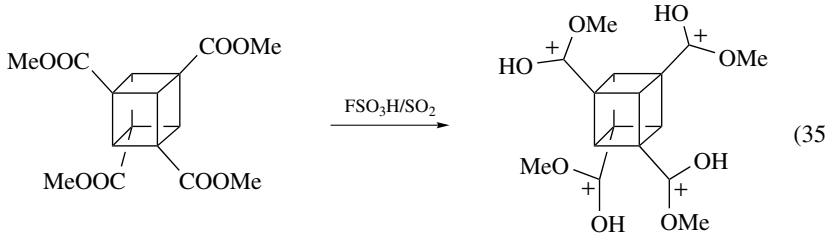




(227)

Rodlike molecules with cubyl spacers such as **227** have been synthesized and their long-distance intramolecular electron-transfer (ET) reactions have been studied[62].

Protonation of cubane tetraester **112** by FSO_3H (SO_2, −60 °C) gave a relatively stable tetracarboxonium ion of cubane **228,** a potential core molecule for building some unique polymers and dendritic macromolecules[126] (equation 35).



(35)

(112) **(228)**

The journey for the syntheses of prismanes has been rough but exciting. Octanitrocubane, the most commercially promising product of prismanes, took more than twenty years to make. Needless to say, the chemistry of prismanes in general, and cubane in particular, has contributed a lot to an understanding of the nature of strain and hybridization in organic molecules. Many methodologies which have developed for the functionalization of cubane have found general applications in other areas of chemistry as well. Despite genuine efforts for commercialization of cubane derivatives in various fields, however, these materials are very expensive and out of reach. The discovery of new approaches for building these beautiful molecules would be a great contribution to chemistry and science.

XII. ACKNOWLEDGMENT

We sincerely thank Professor Phil Eaton for teaching us cubane chemistry some twenty years ago.

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CHAPTER **20**

Bicyclo[2.1.0]pentanes and bicyclo[2.2.0]hexanes

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I. INTRODUCTION

The defining characteristic shared by these two structural motifs is the strain—i.e. suboptimal geometry for covalent σ bond formation—that arises when two small alkane rings

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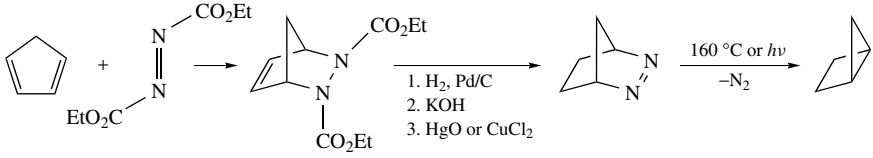
are required to share an edge. In the bicyclopentanes it is a cyclopropane and a cyclobutane that are fused so as to share a C−C bond, while in the bicyclohexanes the conjoined twins are cyclobutanes. In purely mechanical terms, one could say that since the strain of both fused rings is largely relieved by breaking their shared bond, this bond is unusually weak and reactive. Equivalently, one can recognize that the constraints of the bicyclic geometries cause the electron density associated with the shared bond to be centered quite far from the internuclear axis, and hence to exhibit strength and reactivity characteristics somewhere between those of a π bond and a σ bond. The only known examples of either class have a *cis* fusion between the shared rings, although some attempts have been made to synthesize the even more strained *trans*-bicyclo[2.2.0]hexane[1,2]. MM4 molecular mechanics calculations[3] suggest that the *trans* isomer should be 31.8 kcal mol^{-1} more strained than the *cis*, while CBS-QB3 *ab initio* calculations[4] put the value at 38.0 kcal mol^{-1}.

This chapter will review the preparation, physical properties and chemistry of the title hydrocarbons and of selected unsaturated and substituted derivatives.

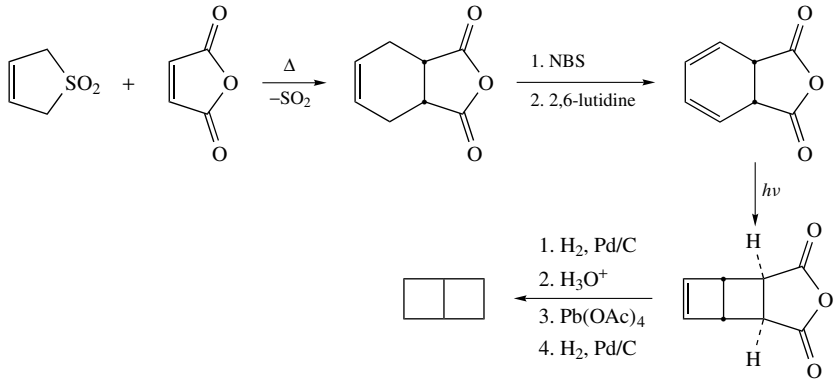
II. SYNTHESIS

For bicyclo[2.1.0]pentane and its simple alkyl derivatives, the principal synthetic procedure involves thermal or photochemical N_2 extrusion from the corresponding 2,3-diazabicyclo[2.2.1]hept-2-ene, which in turn is synthesized by Diels–Alder addition of a 1,2-diazene derivative to a 1,3-cyclopentadiene[5,6]. The sequence is illustrated for the parent hydrocarbon in Scheme 1.



SCHEME 1. Typical synthetic procedure for bicyclo[2.1.0]pentane

The corresponding approach cannot be used for the synthesis of bicyclo[2.2.0]hexane because thermal deazetization of 2,3-diazabicyclo[2.2.2]oct-2-ene affords 1,5-hexadiene as the principal hydrocarbon product[7], while photolysis has a very low quantum yield for product formation[8].



SCHEME 2. Synthesis of bicyclo[2.2.0]hexane

The first preparation of bicyclo[2.2.0]hexane was by photochemical decarbonylation of bicyclo[3.2.0]heptan-3-one[9], but this procedure has been little used subsequently, presumably because the ketone itself is quite tedious to prepare. Instead, bicyclo[2.2.0]hexane has generally been prepared by the sequence shown in Scheme 2, or some variant. This procedure is obviously easily adapted to make deuterium-labeled derivatives[10].

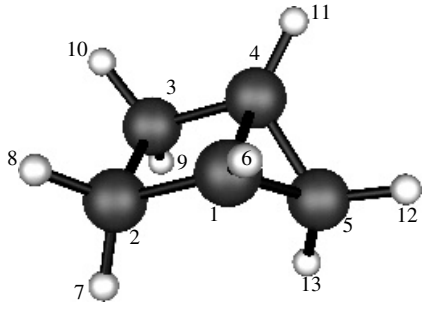
Routes exist to bicyclo[2.1.0]pentanes and bicyclo[2.2.0]hexanes by respectively cyclopropanation[11–14] and 2+2 cycloaddition[15–19] to the corresponding cyclobutene. However, since cyclobutenes themselves are often not easy to prepare, these synthetic approaches have typically been employed only when the nature or location of the substituents required in the final product precluded alternative methods.

III. PHYSICAL PROPERTIES

A. Molecular Structure

The first experimental effort to determine the geometry of bicyclo[2.1.0]pentane used gas-phase electron diffraction[20]. This study led to the surprising conclusion that the C1–C4 bond had a length of 1.439 Å while C2–C3 was 1.622 Å. However, subsequent microwave studies suggested that the interpretation of the electron-diffraction data had been erroneous[21,22]. The currently accepted values for the key structural parameters are shown in Table 1. Also included are the results of various *ab initio* and density functional

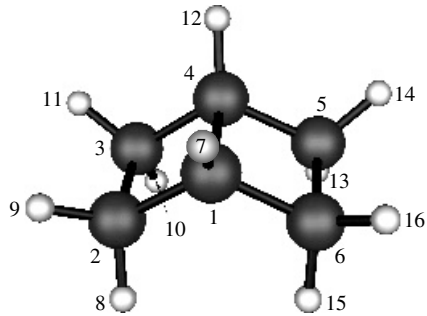
TABLE 1. Experimental and theoretical structural parameters for bicyclo[2.1.0]pentane. The distances are in Å. The parameter α is the dihedral angle, in degrees, between the planes of the cyclobutane and cyclopropane rings



Geometrical parameter	Experimental value	RHF/ 6-31G(d)	MP2/ 6-31G(d)	B3LYP/ 6-31+G(d,p)
C1–C2	1.528	1.528	1.527	1.534
C1–C4	1.536	1.513	1.528	1.535
C1–C5	1.507	1.493	1.499	1.506
C2–C3	1.565	1.558	1.560	1.567
C1–H6	1.082	1.075	1.086	1.086
C2–H7	1.097	1.086	1.096	1.097
C2–H8	1.085	1.083	1.093	1.094
C5–H12	1.088	1.077	1.086	1.087
C5–H13	1.090	1.080	1.090	1.091
α	112.7	112.9	112.8	113.3
ΔH_f° (kcal mol^{-1})[a]	37.7	39.7	37.4	35.2

[a] See Section III.B for discussion of the heat of formation data.

TABLE 2. Experimental and theoretical structural parameters for bicyclo[2.2.0]hexane. The distances are in Å. The parameter α is the dihedral angle, in degrees, defining the pucker of each cyclobutane ring



Geometrical parameter	Experimental value	RHF/ 6-31G(d)	MP2/ 6-31G(d)	B3LYP/ 6-31+G(d,p)
C1−C2	1.557 (11)	1.541	1.535	1.551
C1−C4	1.577 (17)	1.558	1.564	1.574
C2−C3	1.542 (20)	1.552	1.551	1.561
C1−H7	–	1.083	1.094	1.094
C2−H8	–	1.085	1.096	1.096
C2−H9	–	1.085	1.095	1.095
Average C−H	1.113 (4)	1.085	1.095	1.095
C2−C1−C6	113.5 (1.1)	115.0	114.5	115.2
α	11.5 (1.8)	4.7	12.4	2.4
ΔH_f° (kcal mol^{-1})[a]	29.8	32.2	30.7	27.8

[a] See Section III.B for discussion of the heat of formation data.

theory (DFT) calculations, for which a strained molecule of this kind constitutes quite a rigorous test.

Apparently there has been only one experimental effort to determine the structure of bicyclo[2.2.0]hexane[23]. It also relied on gas-phase electron diffraction, but in this case the fit to the data yielded nothing unusual, and one sees in Table 2 that the deduced molecular geometry is in reasonable agreement with the results of electronic-structure calculations. Apparently there is a small energetic preference for a puckering of each of the cyclobutane rings, giving the molecule a C_2 equilibrium geometry, and making the C_{2V} structure a transition state for interconversion of the enantiomers. A similar distortion is apparent in the X-ray diffraction structure[24] of *N*-(4-bromophenyl)bicyclo[2.2.0]hexane-1-carboxamide, although it is hard to know how much influence the substituent and the crystal-packing forces may have in that case.

B. Heat of Formation and Strain Energy

Experimental heats of formation for both bicyclo[2.1.0]pentane and bicyclo[2.2.0]hexane were determined by Roth and coworkers[25] from calorimetric measurements on the hydrogenolysis of the strained C−C bond shared between the rings in each molecule. The values found by this method, 37.7 and 29.8 kcal mol^{-1}, respectively, can be turned into strain enthalpies by comparing them with group additivity estimates[26] that omit the strain contribution. These values, respectively −18.6 and −23.5 kcal mol^{-1}, lead to

strain enthalpies of 56.3 kcal mol^{-1} for bicyclo[2.1.0]pentane and 53.3 kcal mol^{-1} for bicyclo[2.2.0]hexane. Perhaps surprisingly, the strain estimates imply that there is little energy penalty arising from the fusion of the two small rings, since the values are only slightly higher (2.5 kcal mol^{-1} and 0.9 kcal mol^{-1}, respectively) than the sums of the strain enthalpies for the individual rings[26]. This contrasts with the situation in bicyclo[1.1.0]butane, whose strain energy is about 10 kcal mol^{-1} greater than the sum of the strain for two cyclopropanes[27].

As shown in Tables 1 and 2, electronic structure calculations that include some correction for electron correlation do quite well in reproducing the observed heats of formation. The values were computed by calculating the enthalpy changes for the isodesmic reactions bicyclo[2.1.0]pentane + $2CH_4$ → cyclopentane + C_2H_6 and bicyclo[2.2.0]hexane + $2CH_4$ → cyclohexane + C_2H_6, and then combining the ΔH° values with the known heats of formation for methane, ethane, cyclopentane and cyclohexane to deduce the heats of formation of the bicyclic hydrocarbons.

For the purposes of analyzing the reactivities of bicyclo[2.1.0]pentane and bicyclo[2.2.0] hexane, whose discussion will constitute the bulk of this chapter, it would be useful to know the effect of the strain on the dissociation enthalpies of the shared C−C bonds in each molecule. However, the provision of exact values for these dissociation enthalpies is hampered by a number of complications. First, there is a definitional problem; for simple bond fission in an acyclic molecule the dissociation enthalpy is reasonably well defined since the fragments, at infinite separation, constitute a pair of doublet-state free radicals whose recombination is usually barrierless. However, when the bond being broken is in a ring, the product of its scission is a biradical for which the lowest singlet and triplet electronic states may not be degenerate. Should one pick the lower enthalpy state regardless of spin multiplicity, or always the singlet state in order to make the bond scission spin-allowed? Furthermore, there may be a barrier to reclosure of the biradical. If there is, should one define the dissociation enthalpy as the activation enthalpy for the bond breaking, or the overall enthalpy of reaction? In addition to these problems of definition, one commonly faces the practical difficulty that experimental heats of formation for biradicals are very hard to come by. Fortunately, for the case of C1−C4 scission in bicyclo[2.1.0]pentane, most of these difficulties can be circumvented, although not without the introduction of some results from *ab initio* electronic-structure theory. First, the choice between singlet and triplet biradical products is almost moot, since theory of several kinds[28–31] suggests that the two states are very nearly degenerate, with the triplet being calculated to be only about 1 kcal mol^{-1} below the singlet. Second, the heat of formation of the triplet biradical has been determined to be 71.5 kcal mol^{-1} by photoacoustic calorimetry[32]. Third, and most important, the activation enthalpy for breaking the C1−C4 bond has been directly determined to be 36.9 kcal mol^{-1} by studying stereochemical inversion in a deuterium-labeled bicyclo[2.1.0]pentane (see Section IV.A.1)[33]. Together, the experimental data and theoretical estimate of the singlet–triplet gap suggest a barrier of 2 kcal mol^{-1} to reclosure of singlet cyclopentane-1,3-diyl, although the experimental uncertainty in this number is about equal to its magnitude. This result is in good accord with the direct theoretical estimate of 1.2 kcal mol^{-1} for the reclosure barrier[34]. In summary, the C1−C4 bond of bicyclo[2.1.0]pentane has a directly determined kinetic dissociation enthalpy of 36.9 kcal mol^{-1} and a thermodynamic dissociation enthalpy of 33.8 kcal mol^{-1} to give the ground-state triplet cyclopentane-1,3-diyl. When compared with the 85.5 kcal mol^{-1} C2−C3 bond dissociation enthalpy in 2,3-dimethylbutane, these figures imply that roughly 90% of the strain energy in bicyclo[2.1.0]pentane is released when the C1−C4 bond is broken. The question of the effect of strain on bond dissociation enthalpies becomes particularly interesting for the 5-alkylidene derivatives of bicyclo[2.1.0]pentane, because the substituent not only increases the strain of the closed-shell

hydrocarbon, it also provides considerable stabilization to the triplet state of the biradical generated by breaking the C1−C4 bond. Together these factors lead a *negative* dissociation enthalpy for the C1−C4 bond, at least if the thermodynamic definition of that quantity is adopted[35]. The chemistry associated with these interesting molecules is described in detail in Section IV.A.2.

For bicyclo[2.2.0]hexane, there is less experimental evidence on which to base an estimate of the C1−C4 bond dissociation enthalpy. No experimental determination of the heat of formation of cyclohexane-1,4-diyl, singlet or triplet, exists. Furthermore, theory suggests that there may be several conformational stationary points on the potential energy surface for this biradical[36]. There is consequently no good way at present to specify a thermodynamic dissociation enthalpy for the bond in question. However, there has been an experimental determination of the kinetic barrier to bond scission[10], using a stereochemical inversion technique akin to that used for bicyclo[2.1.0]pentane. This experiment afforded a value of 34.4 kcal mol^{-1}—slightly lower than that for the smaller ring system, but not by much more than the experimental uncertainty. The value suggests that $\geqslant$95% of the strain energy in bicyclo[2.2.0]hexane is released upon breaking the C1−C4 bond.

C. Ionization and Oxidation Potentials

The first report of the determination of an ionization potential for bicyclo[2.1.0]pentane appears to be that of Taylor[37] who assigned values of 8.60 eV to the adiabatic IP and 9.49 eV to the vertical IP. Subsequently, Bieri and coworkers[38] measured UV photoelectron spectra of a very large number of hydrocarbons, including bicyclo[2.1.0]pentane, and reported a vertical IP of 9.5 eV and a band onset (which they did not assign to the adiabatic IP) at 8.7 eV. In that extensive study, Bieri and coworkers also determined a vertical IP of 9.6 eV for bicyclo[2.2.0]hexane, with a band onset at 9.0 eV.

Gassman and coworkers studied the electrochemistry of bicyclo[2.1.0]pentane, as well as a number of other strained, saturated hydrocarbons, and obtained an oxidation potential of 1.91 V vs. the saturated calomel electrode[39,40]. They showed that there was a good linear correlation between the oxidation potential and the adiabatic IP (using Taylor's value for bicyclo[2.1.0]pentane), suggesting that the electrochemical oxidation could be thought of as removing an electron from the highest-occupied molecular orbital (HOMO). That may seem like a trivial conclusion, but it is known that electrode-surface and solvation effects can cause solution-phase electrochemical oxidations to follow different paths from gas-phase photoionizations[41]. Since the HOMO is generally associated with the strained, shared C−C bond, one might expect that oxidation would be accompanied by facile ring opening. As described in Section IV.B.4, that appears to be the case, although there is some evidence for at least transient existence of ring-closed radical cations.

IV. CHEMICAL REACTIONS

A. Unimolecular Reactions

1. Bicyclo[2.1.0]pentane

Not surprisingly, the unimolecular thermal reactions of bicyclo[2.1.0]pentane all begin with the breaking of the weakest bond—the C1−C4 bond. As described in Section III.B, this step has an experimental activation enthalpy of 36.9 kcal mol^{-1} [33], determined by studying the kinetics for approach to equilibrium of the *exo* and *endo* stereoisomers of bicyclo[2.1.0]pentane-*cis*-2,3-d_2. This stereomutation had first been discovered by Chesick[42], who studied the interconversion of *exo*- and *endo*-2-methylbicyclo[2.1.0]pentane.

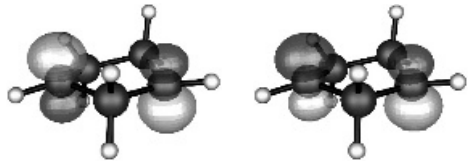
Criegee and Rimmelin, in their paper on the first preparation of bicyclo[2.1.0]pentane, reported that at high temperatures it would isomerize to cyclopentene[5]. Halberstadt

and Chesick subsequently determined the activation enthalpy for this reaction to be 45.6 kcal mol^{-1} [43]. In an independent investigation, Steel and coworkers[44] determined the activation enthalpy for the isomerization to cyclopentene to be 44.5 kcal mol^{-1}, and also discovered a yet higher-temperature reaction giving 1,4-pentadiene, with an activation enthalpy of 51.2 kcal mol^{-1}.

The isomerization of bicyclo[2.1.0]pentane to cyclopentene appears to be analogous to the isomerization of cyclopropane to propene, with one important kinetic difference. The stereomutation of cyclopropane and its isomerization to propene differ in activation enthalpy by $\leqslant$3.7 kcal mol^{-1} [45], whereas the corresponding reactions of bicyclo[2.1.0]pentane differ in activation enthalpy by about 8 kcal mol^{-1}. This observation raises the possibility that the apparent similarity between the reactions of cyclopropane and bicyclo[2.1.0]pentane is only superficial, and that the mechanisms are in reality different. Baldwin and Andrews recognized this possibility, in particular noting that the conversion of bicyclo[2.1.0]pentane to cyclopentene could be a thermally allowed $_\sigma 2_s + _\sigma 2_a$ reaction between the C1−C2 and C4−C5 bonds of the reactant. However, their experiments with bicyclo[2.1.0]pentane-5,5-d_2 ruled out this mechanism and supported a pathway analogous to the cyclopropane → propene reaction[46]. Recent CASPT2-g3 calculations[47] have offered an explanation for the higher barrier to hydrogen migration in cyclopentane-1,3-diyl. During the reaction, the erstwhile *p*-type orbitals on the 'radical' carbons of cyclopentane-1,3-diyl and of trimethylene suffer an antibonding, through-space interaction. In trimethylene this can be relieved by expanding the CCC angle (to as much as 128°, according to the calculations). However, the five-membered ring prevents a corresponding expansion for cyclopentane-1,3-diyl, and so the transition state suffers an unavoidable destabilization.

In 1970 Berson and coworkers reported a study of the stereochemistry of cleavage of the C1−C4 and C2−C3 bonds of bicyclo[2.1.0]pentane, using all three diastereomers of the 2,3-dimethyl derivative. They concluded that the C2−C3 scission occurred with about a 10:1 preference for conrotation over disrotation[48]. Such an outcome is superficially consistent with the expectations for a concerted cleavage of C1−C4 and C2−C3, which should occur in a $_\sigma 2_s + _\sigma 2_a$ manner. However, experiments and *ab initio* calculations conducted long after Berson's study have shown that the conversion of cyclobutane to two ethylenes almost certainly has no concerted component[49–55]. It is hard to imagine that the reaction would be purely stepwise when the two C−C bonds to be broken have identical properties by symmetry, as they do in cyclobutane, but largely concerted when the bonds have very different strengths, as they do in bicyclo[2.1.0]pentane. The obvious alternative mechanism, also recognized by Berson and coworkers, is that the reaction begins with the cleavage of the C1−C4 bond. However, this proposal has its own interpretive difficulties. To the extent that the cleavage of the C2−C3 bond in the biradical is controlled by orbital-symmetry effects, one should be able to relate the preferred stereochemistry to the energetic ordering of the two symmetry-adapted linear combinations of the radical *p*-type orbitals. The calculations of Sherrill and coworkers suggested that the parent singlet-state cyclopentane-1,3-diyl should have a C_2 equilibrium geometry[30]. In this point group, the two *p*-type basis orbitals form *a*- and *b*-symmetry linear combinations (Figure 1).

If the *a* orbital were significantly lower in energy than the *b* orbital, then the preferred mode of C2−C3 cleavage would be disrotatory. If *b* were far below *a*, then a conrotatory cleavage would be preferred. In trimethylene—the biradical created by homolysis of one C−C bond of cyclopropane—calculations suggest that interaction of the *p*-type orbitals with the C−H orbitals of the central methylene causes the *a* combination to be lower in energy. The same effect should be in evidence for cyclopentane-1,3-diyl. However, the distance between the radical sites is a little smaller for cyclopentane-1,3-diyl than for trimethylene. The smaller distance strengthens the through-space interaction of the *p*-type basis orbitals, which lowers the energy of the *b* combination[29]. According to the



a *b*

FIGURE 1. The *a*- and *b*-symmetry combinations of radical *p*-type orbitals in C_2 cyclopentane-1,3-diyl

calculations of Conrad and coworkers these contributing factors almost perfectly cancel, so that in a two-configuration wavefunction—the minimum necessary to describe a singlet biradical—the a^2 and b^2 configurations have almost identical weights[28]. If that prediction were correct, there should be no orbital-symmetry-derived preference for disrotatory or conrotatory cleavage of the C2−C3 bond. Again, recent CASPT2-g3 calculations[47] have suggested a solution to this conundrum. The explanation begins with a recognition of the similarity between the stereochemistries for the C1−C4 + C2−C3 cleavages in bicyclo[2.1.0]pentane and bicyclo[2.2.0]hexane. The latter reaction is described in detail in Section IV.A.3. For the present purposes it is sufficient to note that in that reaction too the C2−C3 bond breaks with a strong preference for conrotation[10]. The accepted explanation, backed by CASPT2 calculations[36], is that C2−C3 scission occurs most readily from a chair-like conformation of cyclohexane-1,4-diyl, formed by homolyzing the C1−C4 bond of the reactant. It is the change from the original boat conformation of bicyclo[2.2.0]hexane to the chair-like conformation of the biradical that determines the overall stereochemistry of the C2−C3 bond cleavage. The calculations suggest that there does also exist a transition state for C2−C3 scission that has a boat-like conformation. However, it is found to be higher in energy than the chair-like TS. The reason is presumably closely related to the preference for the chair over the boat transition states of the Cope rearrangement. That preference was explained long ago by Hoffmann and Woodward as being due to an antibonding interaction between the *p*-type orbitals on C1 and C4 in the boat conformation[56]. The relevance of this analysis becomes clear when one recognizes that the chair and boat transition structures for the Cope rearrangement can be hypothetically transformed into the conrotatory and disrotatory transition structures for ring opening of cyclopentane-1,3-diyl by pushing the C5 and C6 methylenes together symmetrically until they become one (see Figure 2).

Such a transformation leaves the *p*-type orbitals on C1 and C4 largely unaffected, and so the antibonding interaction that destabilizes the boat Cope TS should also destabilize the TS for disrotatory ring opening of cyclopentane-1,3-diyl. CASPT2-g3 calculations show that that is indeed the case. They predict a preference of 10.7 kcal mol^{-1} for the conrotatory stereochemistry. It is interesting to note that the same antibonding interaction between the *p*-type orbitals on C1 and C4 apparently causes both the high barrier to hydrogen migration and the preferred conrotatory ring opening of cyclopentane-1,3-diyl.

Substituent effects on the various unimolecular reactions of bicyclo[2.1.0]pentane are reported to be unusual. Tufariello and coworkers found that 5-cyano and 5-carbomethoxy substituents had very modest effects on the rate of epimerization of bicyclo[2.1.0]pentane. However, the *exo*-5-*p*-nitrobenzoate and *exo*-5-tosylate appeared to undergo the reaction some 200−6000 times faster than the parent hydrocarbon[57,58]. The authors attributed the substituent effect to the π-donor properties of the oxygen bound to C5. Earlier theoretical analysis by Hoffmann[59] and by Günther[60] had led to the conclusion that attachment of a π donor to cyclopropane should weaken the unsubstituted C−C bond by electron donation

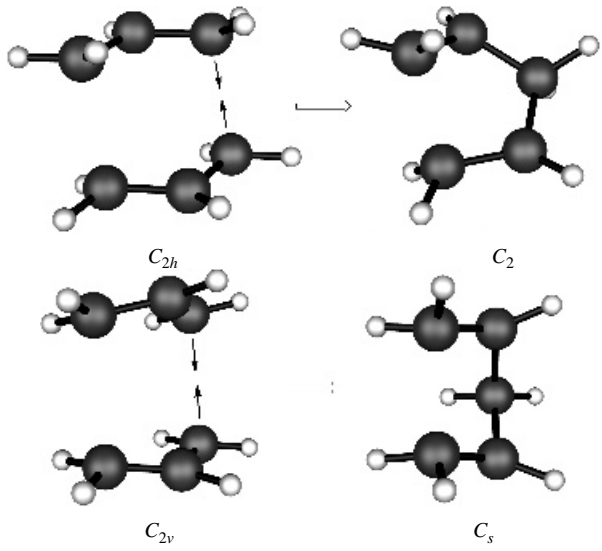


FIGURE 2. Relationships between the chair transition state for the Cope rearrangement (C_{2h}) and the conrotatory ring-opening TS for cyclopentane-1,3-diyl (C_2), and between the boat transition state for the Cope rearrangement (C_{2v}) and the disrotatory ring-opening TS for cyclopentane-1,3-diyl (C_S)

into an antibonding Walsh orbital. This analysis, when applied to bicyclo[2.1.0]pentane, suggests that a π-donor substituent on C5 should weaken the C1−C4 bond whose cleavage leads to epimerization. However, there are several reasons to be cautious about this interpretation. First, Hoffmann's analysis[59] suggested that there should be a larger effect of π-acceptors in strengthening this bond than of π-donors in weakening it, and yet Tufariello's experiments showed almost no effect from π-acceptor substituents on C5. Second, an amino substituent on C5 apparently had a smaller effect on the epimerization rate than either a *p*-nitrobenzoate or tosylate[57], despite the fact that the nitrogen should be a much better π-donor. Finally, one should note that the thermal reactions of the *p*-nitrobenzoate and tosylate derivatives were mostly carried out in aqueous acetone, and that the products were 1,3-cyclopentadiene and 3-cyclopentenol derivatives, not the *endo* epimer of the bicyclo[2.1.0]pentane. Tufariello and coworkers had shown that bicyclo[2.1.0]pentane derivatives with a leaving group in the 5-*endo* position were very susceptible to solvolysis, and so the failure to isolate such compounds was not surprising. On the other hand, the lack of direct detection of the supposed primary products of a reaction must make conclusions about its mechanism less secure. In the present case, the authors favored a mechanism involving rate-limiting epimerization of the *5-exo* derivatives to *5-endo* over one involving direct solvolysis of the *5-exo* epimer because the reactions showed unusually low sensitivity to solvent polarity[57].

More recent results on a quite different problem suggest an alternative explanation for the results of Tufariello and coworkers. Experimental and computational results indicate that the UV photolysis of iodocyclopropane leads to allyl radical and an iodine atom by a mechanism that, at least in part, occurs without the intermediacy of the cyclopropyl radical. This mechanism apparently begins on a $^1(n,\sigma^*)$ excited-state surface but crosses over temporarily to an ion-pair surface as the C−I bond begins to break[61]. CASSCF calculations located two different conical intersections between radical-pair and ion-pair

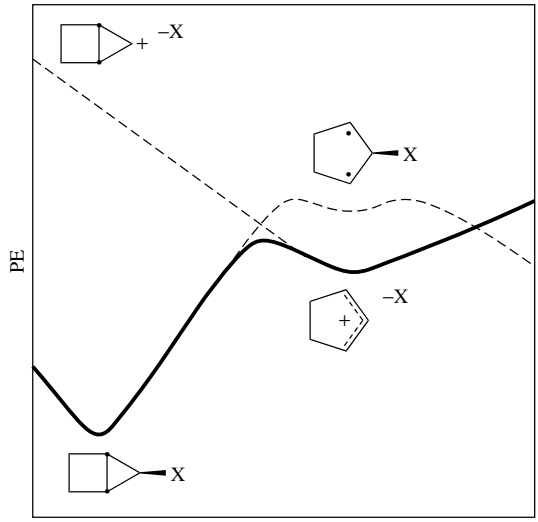


FIGURE 3. A surface-crossing explanation for the observations of Tufariello and coworkers[57]

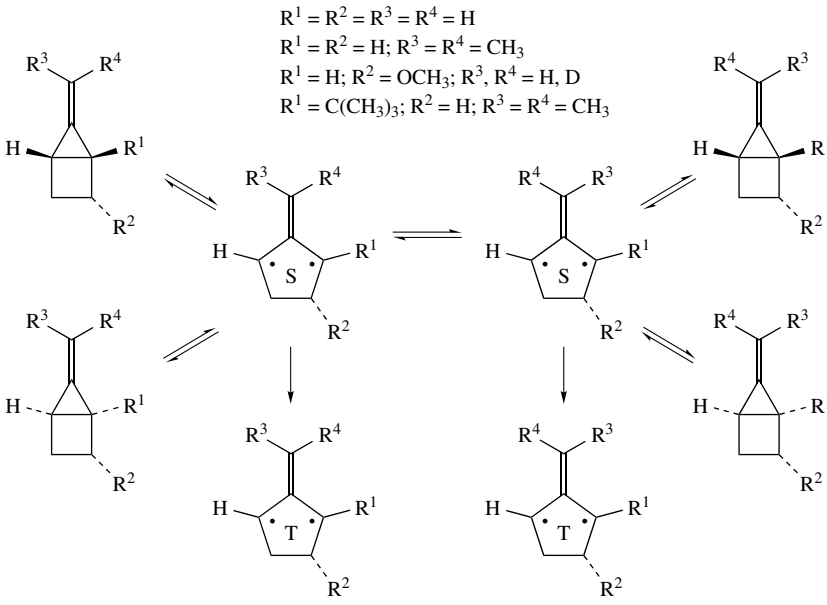
surfaces, differing principally in the degree of C2−C3 bond cleavage. The existence of these conical intersections suggests that on the ground-state adiabatic surface of a cyclopropyl−X solvolysis, there could be an avoided crossing between radical-pair and ion-pair surfaces.

Usually, this avoided crossing would be approached by breaking the C−X bond, but in an *exo*-5-X-bicyclo[2.1.0]pentane, it could be approached by starting to break the C1−C4 bond. The proposal is illustrated schematically in Figure 3. The reaction starts along the C1−C4 cleavage path, as suggested by Tufariello, but before formation of the cyclopentane-1,3-diyl is complete, the system encounters an avoided crossing with the ion-pair surface, which drops rapidly in energy as the C1−C4 bond lengthens. The avoided crossing would explain the two principal observations of Tufariello and coworkers: first, it reduces the magnitude of the barrier with respect to that for a 'normal' epimerization leading to a cyclopentane-1,3-diyl. Second, because the transition state created by the avoided crossing has both homolytic and heterolytic character, it would presumably be less sensitive to solvent polarity than that for a standard solvolysis. Obviously, the clear prediction of this mechanism is that π-donor substituents that are not good leaving groups should have no very large effect on the activation energy for the epimerization of bicyclo[2.1.0]pentane.

2. 5-Alkylidenebicyclo[2.1.0]pentanes

In the late 1970s through mid-1980s Berson's group prepared and studied a series of 5-alkylidenebicyclo[2.1.0]pentane derivatives[35,62–70]. The compounds and the unimolecular reactions that they underwent are summarized in Scheme 3.

The 5-alkylidene substituent greatly stabilizes the triplet state of the biradical that is generated by homolysis of the C1−C4 bond. In fact, as pointed out in Section III.B, the stabilization is such that, if one adopts the thermodynamic definition, the dissociation enthalpy of the C1−C4 bond is probably near zero or even negative[35].



SCHEME 3. 5-Alkylidenebicyclo[2.1.0]pentanes and their unimolecular reactions, as studied by Berson and coworkers[35,62–70]. Both singlet (**S**) and triplet (**T**) electronic states of the biradicals are implicated in the thermal chemistry

The 5-alkylidenebicyclo[2.1.0]pentanes were prepared either by the low-temperature addition of an alkylidene carbenoid to a cyclobutene, or by photolysis of the corresponding 7-alkylidene-2,3-diazabicyclo[2.2.1]hept-2-ene at −78 °C. In either case, warming of the hydrocarbon product to about −30 °C resulted in its dimerization[67]. Two things were striking about this reaction. The first was that it followed *first*-order kinetics, showing that the rate-determining step must be unimolecular. The second was that the Arrhenius A factor was $<10^{10}$, which is about 3–4 orders of magnitude smaller than one observes for most unimolecular reactions. These observations were explained by a mechanism in which the reactant underwent irreversible ring opening to the triplet ground state of the 2-alkylidenecyclopentane-1,3-diyl, which then dimerized. Whether the ring opening was a direct, spin-forbidden process, or whether it occurred by fast, reversible formation of the singlet-state biradical, followed by rate-limiting intersystem crossing, could not be determined. In either case the spin-forbidden nature of the rate-determining step would explain the very low A factor.

That a singlet biradical could be formed by the ring opening was demonstrated by the rapid *exo/endo* isomerism of a 2-methoxy derivative of 5-methylenebicyclo[2.1.0]pentane[62]. This reaction was found to occur more rapidly than the dimerization. Stereospecific cycloaddition to electron-deficient alkenes under conditions where direct reaction with the ring-closed hydrocarbon could be kinetically ruled out also signaled the involvement of the singlet biradical[66]. Another, perhaps more surprising, reaction apparently mediated by the singlet biradical is *E*/*Z* isomerism about the exocyclic double bond. That is a reaction for which one might have anticipated a substantial barrier. However, for singlet trimethylenemethanes, which is the class of biradicals to which the first formed intermediate belongs, theory suggests that a structure with a 90° dihedral angle about one of the C−C bonds is close

in energy, or may even be below the fully planar structure[71–75]. In the particular example studied by Berson's group it appears that the orthogonal structure is slightly higher in energy than the planar one, since *E*/*Z* isomerization occurred at a higher temperature than *exo/endo* interconversion[65].

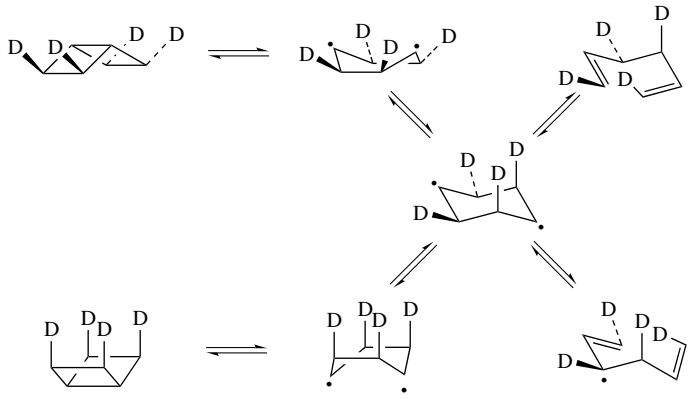
3. Bicyclo[2.2.0]hexane

The first unimolecular reaction of bicyclo[2.2.0]hexane to be identified was its conversion to 1,5-hexadiene. Steel and coworkers[44] found an activation enthalpy of 35.1 kcal mol^{-1} for the reaction. Strikingly, this value is 16.1 kcal mol^{-1} lower than that for the formally analogous conversion of bicyclo[2.1.0]pentane to 1,4-pentadiene (see Section IV.A.1). If the mechanisms of the two reactions were similar one might not have expected much of an activation enthalpy difference, and certainly not in this direction, since the strain energies in bicyclo[2.2.0]hexane and bicyclo[2.1.0]pentane are estimated to be 53.3 and 56.3 kcal mol^{-1}, respectively (see Section III.B). This issue will be addressed below, where the mechanism of the bicyclo[2.2.0]hexane ring opening is discussed.

The first stereochemical study of this reaction to be reported was that carried out by Paquette and Schwartz[76], who used 2,3-dicarbomethoxy derivatives of the hydrocarbon. They found that the ring cleavage occurred with a preference for the stereochemistry that would be classified as ${}_{\sigma}2_{s} + {}_{\sigma}2_{a}$ if it were concerted.

The second unimolecular reaction of bicyclo[2.2.0]hexane to be discovered was its degenerate ring inversion, revealed only when the molecule was deuterium labeled. Goldstein and Benzon[10] prepared bicyclo[2.2.0]hexane-2,3,5,6-d_4 with all of the labels in the *exo* sites. On heating the compound, they discovered that it would isomerize to the all-*endo* isomer with an activation enthalpy of 34.4 kcal mol^{-1}. This was slightly lower than the value obtained for the cleavage to 1,5-hexadiene-1,3,4,6-d_4, for which a value of 36.0 kcal mol^{-1} was found. The experiment also permitted the stereochemistry of the ring cleavage to be determined in a sterically unencumbered system. Since the diene product was found to consist of only the 1*Z*,3*R*,4*S*,6*E* and 1*Z*,3*S*,4*R*,6*E* isomers, it could be deduced that the ring opening occurred exclusively with the ${}_{\sigma}2_{s} + {}_{\sigma}2_{a}$ stereochemistry that had been identified as preferred in the Paquette and Schwartz study. The minor contributions from other stereochemical paths detected by the latter researchers could therefore be attributed to the substituents.

These results have considerable importance for another reaction that has been the subject of extensive study and speculation—the Cope rearrangement of 1,5-hexadiene. The connection point is the cyclohexane-1,4-diyl biradical, which seems to be an obligatory intermediate for the ring inversion discovered by Goldstein and Benzon, but had also been raised as a potential intermediate in the Cope rearrangement by Doering and coworkers[77]. At first sight, the stereochemical results from the deuterium-labeled bicyclo[2.2.0]hexane and those showing a preferred chair-like stereochemistry for the Cope rearrangement[78] seem to be economically accommodated by a mechanism in which a chair conformation of cyclohexane-1,4-diyl does indeed represent a common intermediate (Scheme 4). However, as Gajewski and Conrad have pointed out[79], the thermochemistry of the species involved rules out such a mechanistic linkage. Their argument is reproduced here using updated thermochemical values. The heat of formation of 1,5-hexadiene is 20.4 kcal mol^{-1} [80]. The activation enthalpy of 33.5 kcal mol^{-1} for the Cope rearrangement[77] therefore gives the transition state of that reaction a heat of formation of 53.9 kcal mol^{-1}. Bicyclo[2.2.0]hexane has a heat of formation of 29.8 kcal mol^{-1} [25]. Goldstein and Benzon's activation enthalpy of 34.4 kcal mol^{-1} for the ring inversion consequently assigns a heat of formation of 64.2 kcal mol^{-1} to the transition state for that process. If the mechanism of Scheme 4 were correct, the only way to explain how the

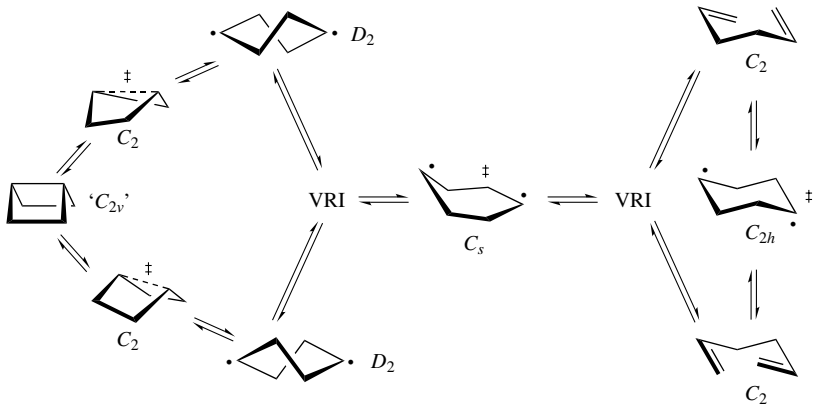


SCHEME 4. A mechanism that seems to fit the known stereochemistry of bicyclo[2.2.0]hexane ring opening and of the Cope rearrangement. However, thermochemical analysis shows that it cannot be correct

ring cleavage of bicyclo[2.2.0]hexane could have an activation enthalpy 1.6 kcal mol^{-1} higher than that for ring inversion would be to give the rate-determining transition state for the former process a heat of formation of 65.8 kcal mol^{-1}, and to place it between chair cyclohexane-1,4-diyl and 1,5-hexadiene. But then it would also be the transition state for the Cope rearrangement, for which the direct determination of the transition-state heat of formation gave a value almost 15 kcal mol^{-1} lower. This discrepancy far exceeds any plausible experimental error, and so one has to conclude that the chair conformation of cyclohexane-1,4-diyl cannot be a common intermediate for the bicyclo[2.2.0]hexane reactions and the Cope rearrangement.

CASPT2//CASSCF calculations by Hrovat and Borden[36] have served to clarify the situation. They show that the ring opening of bicyclo[2.2.0]hexane leads to a twist-boat conformation of cyclohexane-1,4-diyl, which has D_2 symmetry in the absence of any isotopic labels. In this conformation, the *p*-type 'radical' orbitals on C1 and C4 have poor overlap with the C2−C3 and C5−C6 bonds, and so ring cleavage would presumably face a high barrier. A lower energy pathway can be found by undertaking a conformational change from the twist-boat towards a chair conformation, via a half-chair transition state. Although they were not explicitly located in the calculations, one can be sure from the symmetries of the species involved that there must exist valley-ridge inflection (VRI) points[81] on either side of the half-chair transition state. The connectivity between the stationary points on the bicyclo[2.2.0]hexane and 1,5-hexadiene potential energy surface is illustrated in Scheme 5.

The point group of bicyclo[2.2.0]hexane in Scheme 5 is called 'C_{2v}' because, as described in Section III.A, computational studies on the molecule suggest that it actually has a C_2 equilibrium geometry. However, the calculations of Hrovat and Borden show that the potential energy difference between the C_2 minimum and the C_{2v} transition state for racemization is less than the difference in their zero-point energies, and so for all practical purposes the molecule has C_{2v} symmetry. Ring opening is accompanied by one of two enantiomeric C_2 twists, leading to one of two enantiomers of the twist-boat cyclohexane-1,4-diyl. Although not shown in Scheme 5, reclosure to bicyclo[2.2.0]hexane from the twist-boat intermediate provides a pathway for the *exo/endo* isomerization of the labeled hydrocarbon. There presumably exists a transition state for racemization of the twist-boat biradical, although this was not located in Hrovat and Borden's calculations



SCHEME 5. A mechanistic scheme for bicyclo[2.2.0]hexane ring cleavage and for the Cope rearrangement that is consistent with the known stereochemistry and thermochemistry, and with the CASPT2 calculations of Hrovat and Borden

and is not depicted in Scheme 5. A higher-energy pathway (by 1.6 kcal mol^{-1}, according to Goldstein and Benzon's experiments) takes one over the C_S-symmetry half-chair transition state towards the chair conformation of cyclohexane-1,4-diyl. However, before the chair is reached, the system encounters a VRI and breaks symmetry to choose one of the two paths to the 1,5-hexadiene products. Chair cyclohexane-1,4-diyl is itself a transition state—for the Cope rearrangement. Hrovat and Borden's calculations show that there are additional higher-energy pathways for several of these reactions, involving ring cleavages from boat conformations, but these are not included in Scheme 5.

This mechanism provides the following explanation for the 16 kcal mol^{-1} difference in activation enthalpy for the ring cleavages of bicyclo[2.1.0]pentane and bicyclo[2.2.0]hexane, mentioned at the beginning of this section. Both reactions begin with homolysis of the C1−C4 bond. The activation enthalpies for that event are similar (36.9 and 34.4 kcal mol^{-1}, respectively). In neither case is the C1−C4 scission rate-limiting. For bicyclo[2.2.0]hexane, the rate-determining step is a conformational change via the half-chair transition state. Once the system begins to approach the chair conformation, cleavage of the C2−C3 or C5−C6 bond can occur without a barrier. This is because the chair conformation provides near-perfect overlap of the *p*-type 'radical' orbitals on C1 and C4 with the C2−C3 and C5−C6 bonds. However, in cyclopentane-1,3-diyl—the biradical generated from bicyclo[2.1.0]pentane—there is no easily accessible conformation that provides such good overlap. For that biradical, the rate-determining step is therefore not a conformational change but instead is the actual C2−C3 bond cleavage.

Aside from Paquette and Schwartz's study on the dicarbomethoxy derivative of bicyclo[2.2.0]hexane, mentioned above, there has been relatively little investigation of the chemistry of substituted analogs. Sinnema and coworkers[82,83] have studied various hexamethyl stereoisomers, and have shown that they undergo similar ring inversion and ring cleavage reactions to those already described. The ring cleavage has also been detected in the 1,4-dimethyl-[84] and 1,4-dicyano-[15] derivatives, although in those cases the substituent pattern did not permit any information about possible ring inversions to be acquired. The same is true for the spirocyclopropyl derivatives studied by Kaufmann and De Meijere[85].

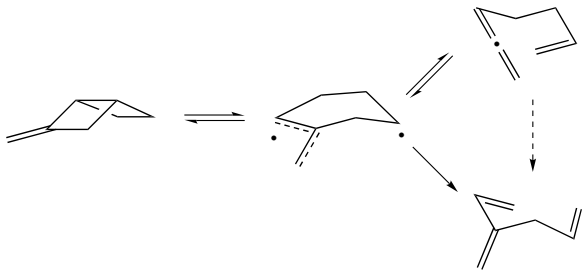
A striking change in reactivity upon perfluorination was found by Correa and coworkers[86]. At 250 °C perfluorobicyclo[2.2.0]hexane and perfluoro-1,5-hexadiene were found to reach a near 1:1 equilibrium. At higher temperatures irreversible conversion

to perfluorobicyclo[2.1.1]hexane occurred. In the parent hydrocarbons, the experimental heats of formation show the open-chain diene to be favored over the bicyclo[2.2.0]hexane by 9.4 kcal mol^{-1} (*vide supra*). No experimental heat of formation for bicyclo[2.1.1] hexane seems to exist, but CBS-QB3 calculations[4] place it 17.9 kcal mol^{-1} lower in enthalpy than bicyclo[2.2.0]hexane. Thus, while the bicyclo[2.1.1]hexane skeleton seems to be the thermodynamically most stable in both the hydrocarbon and fluorocarbon series, the fluorines selectively destabilize the open-chain diene with respect to the bicyclic isomers[87].

4. Methylene derivatives of bicyclo[2.2.0]hexane

The 2-methylene and 2,3-dimethylene derivatives of bicyclo[2.2.0]hexane have been prepared and studied in some detail, as described below. There appears to have been no experimental work on the 2,5-dimethylene, 2,6-dimethylene or trimethylene derivatives. The potentially interesting tetramethylene derivative probably does not exist as such (although a 1,4-bridged derivative has been made[88]). After some controversy[89–93], it appears that the biradical that would be generated by homolysis of the C1−C4 bond of tetramethylenebicyclo[2.2.0]hexane has a singlet ground state, is more stable than the bicyclic structure and is formed from it without an activation barrier. This differentiates the system from 5-methylenebicyclo[2.1.0]pentane which is kinetically protected from ring opening because its cognate biradical has a triplet ground state, and the singlet state of the biradical is higher in energy than the ring-closed hydrocarbon.

The ring opening of 2-methylenebicyclo[2.2.0]hexane presumably generates a singlet biradical that, once again, could play a role in the [3,3] sigmatropic interconversion of the open-chain hydrocarbon isomers in this series (Scheme 6).

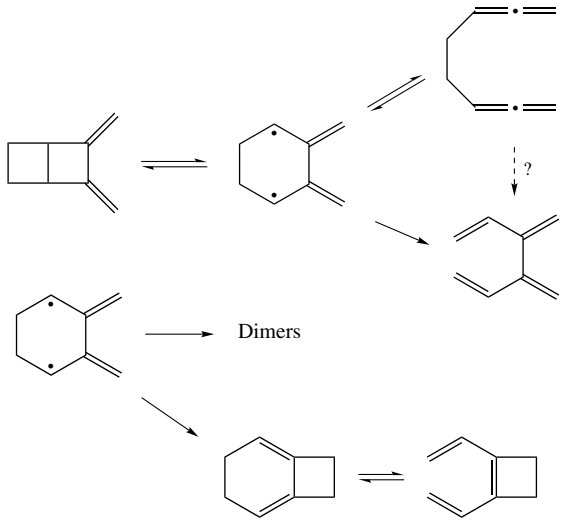


SCHEME 6. The formal connection of the ring opening of 2-methylenebicyclo[2.2.0]hexane to the [3,3]-sigmatropic interconversion of its acyclic products

The connection between these reactions has been investigated by Roth and coworkers[94]. Through trapping studies with O_2 and SO_2, they deduced that singlet 2-methylenecyclohexane-1,4-diyl is indeed a common intermediate in the ring-opening and sigmatropic reactions. They could even determine the barriers to its reactions. Ring closure to 2-methylenebicyclo[2.2.0]hexane was found to have an activation enthalpy of 7.6 kcal mol^{-1}, while ring opening to 1,2,6-heptatriene and to 3-methylene-1,5-hexadiene had barriers of respectively 10.3 and 6.8 kcal mol^{-1}. The first and the third of these numbers are sufficiently close in magnitude that one might expect to be able to detect ring inversion of 2-methylenebicyclo[2.2.0]hexane in competition with its ring opening—an expectation that was verified by preparation and thermolysis of 2-methylenebicyclo[2.2.0]hexane-*exo,exo*-5,6-d_2[94]. This relatively simple and consistent depiction of the enthalpy surface conceals an interesting complication that was revealed when Roth and coworkers studied the pressure

dependence in their O_2 trapping experiments. They found that extrapolation of their data to infinite O_2 pressure led to the prediction that roughly half of the [3,3]-sigmatropic rearrangement would occur *without* an interceptible biradical. They consequently postulated that the sigmatropic shift must take place by competitive stepwise and concerted mechanisms[94]. However, CASPT2 and DFT calculations by Hrovat, Duncan and Borden found no evidence for a concerted, pericyclic transition state[95]. This apparent discrepancy between theory and experiment was reconciled when quasiclassical trajectory calculations were run on the reaction[96]. These simulations revealed that the reaction was susceptible to nonstatistical dynamical effects. Specifically, two paths down from the transition state for formation of the biradical were found: the steepest-descent path led to the biradical, but a non-steepest-descent path (dashed arrow in Scheme 6) led directly over the second transition state. In addition, it was discovered that some of the biradicals proceeded on to the final product much faster than would have been predicted by Transition State Theory or RRKM Theory, again because of nonstatistical dynamical effects.

As summarized in Scheme 7, 2,3-dimethylenebicyclo[2.2.0]hexane could in principle be linked to the Cope rearrangement of 1,2,6,7-octatetraene via a common biradical in the same way that 2-methylenebicyclo[2.2.0]hexane is linked to the Cope rearrangement of 1,2,6-heptatriene (Scheme 6). However, the dimethylene system has two additional complications. The 2,3-dimethylenecyclohexane-1,4-diyl biradical has the ability to ring close to [4.2.0]bicycloocta-1,5-diene, which at temperatures above about 150 °C can also equilibrate with 1,2-divinylcyclobutene. In addition, the larger barriers to unimolecular reaction of the biradical (*vide infra*) can make dimerization reactions competitive in solution-phase reactions. The preparation of 2,3-dimethylenebicyclo[2.2.0]hexane was first reported by Chang and Bauld[97]. They found that, at 60 °C in solution, it dimerized, with *first*-order kinetics, and with activation parameters of $\Delta H^{\ddagger} = 17.5 \pm 1$ kcal mol^{-1} and $\Delta S^{\ddagger} = -22.7 \pm 3$ cal mol^{-1} K^{-1}. The first-order kinetics and large negative activation



SCHEME 7. The formal connection of the ring opening of 2,3-dimethylenebicyclo[2.2.0]hexane to the [3,3]-sigmatropic interconversion of its acyclic products. Additional products apparently formed from the biradical intermediate are also shown

entropy are reminiscent of the dimerization of 5-alkylidenebicyclo[2.1.0]pentanes (Section IV.A.2), and could derive from a similar mechanism—rate-determining intersystem crossing to a triplet biradical. However, it should be noted that the activation parameters could be determined only over a very narrow temperature range; under such circumstances, the covariance of errors between the enthalpy and entropy terms can lead to misleading estimates of the uncertainties in these quantities. The gas-phase rearrangement of 2,3-dimethylenebicyclo[2.2.0]hexane was subsequently reported by Roth and Erker[98]. They found that it underwent rearrangement to bicyclo[4.2.0]octa-1,5-diene and 3,4-dimethylene-1,5-hexadiene in about a 2:1 ratio at 110 °C. Roth and coworkers[99] and Grimme and Rother[100] investigated the linkage of these reactions to the Cope rearrangement of 1,2,6,7-octatetraene. They found that the bicyclic ring opening and the Cope rearrangement do lead to a common intermediate. However, Roth and coworkers were once again driven to propose a competing concerted mechanism for the Cope rearrangement by their O_2 trapping studies. Although this system has not been examined computationally, it seems plausible that the dynamical explanation offered for the similar behavior of the Cope rearrangement of 1,2,6-heptatriene has application here too.

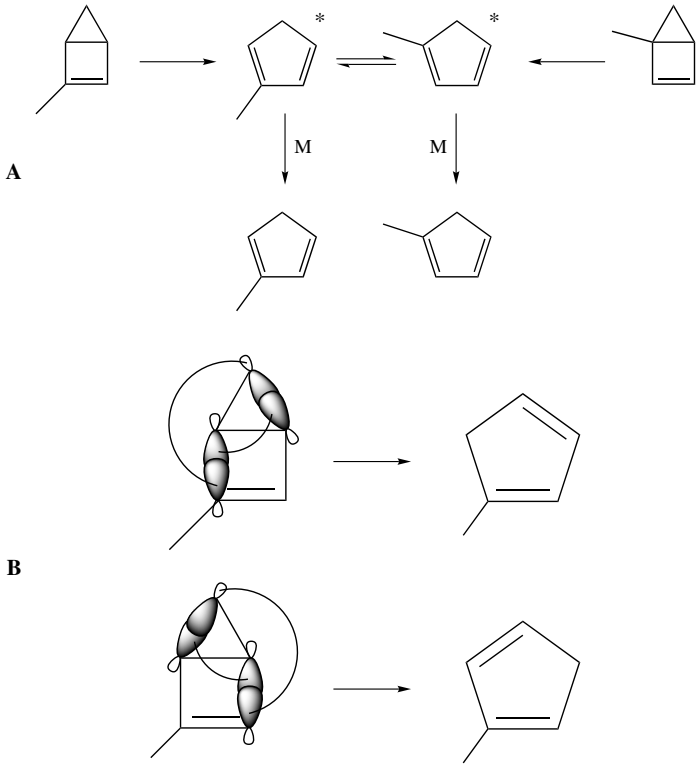
The two possible ring openings of 2,3-dimethylenecyclohexane-1,4-diyl have been estimated by Roth and coworkers[94] to have barriers of 16 kcal mol^{-1} (to 3,4-dimethylene-1,5-hexadiene) and 31 kcal mol^{-1} (to 1,2,6,7-octatetraene)—much larger than the barriers for the analogous reactions of 2-methylenecyclohexane-1,4-diyl (*vide supra*). The difference presumably reflects both the greater allylic stabilization of the biradical in the dimethylene case and, for its conversion to 1,2,6,7-octatetraene, the greater strength of the C−C bond between two sp^2-hybridized carbons.

5. *Bicyclo[2.1.0]pent-2-ene*

The only known unimolecular reaction of the parent hydrocarbon is its ring opening to 1,3-cyclopentadiene[101], although the degenerate 'ring-walk' reaction has been the subject of some theoretical investigation[102, 103], and is known to be competitive with the ring opening for certain substituted derivatives[104].

The ring-opening reaction attracted early interest because the bicyclic skeleton presumably constrains it to occur in a disrotatory fashion, which corresponds to the thermally 'forbidden' mode according to the Woodward–Hoffmann rules[101]. These initial investigations revealed an unanticipated feature of the reaction that went on to become the source of much greater interest and controversy. Specifically, studies with methyl-substituted bicyclo[2.1.0]pentenes found that the methyl group in the 1,3-cyclopentadiene product was not located solely at the site predicted by a simple ring-opening mechanism. Of course, 1,3-cyclopentadienes are subject to facile [1,5]-sigmatropic hydrogen migrations that can serve to interconvert 1-, 2- and 5-substituted derivatives, but it could be shown that the rate of such a reaction was far too low to be able to explain the amounts of the products observed. After some initial controversy about just what the product composition was[105, 106], the researchers involved in the study came to agreement that 1-methyl- and 2-methylbicyclo[2.1.0]pent-2-ene each afford *both* 1-methyl- and 2-methyl-1,3-cyclopentadiene. Little or no 5-methylcyclopentadiene was observed, but this isomer is the least favored at equilibrium among the three methylcyclopentadiene isomers.

Two explanations were offered for the formation of the unexpected products (Scheme 8). One was that the highly exothermic nature of the ring opening (roughly 60 kcal mol^{-1} from the transition state to the product) caused the cyclopentadiene product to be formed in a chemically activated state[107]. This vibrationally hot cyclopentadiene could undergo the [1,5]-hydrogen migration much faster than would be expected for a cyclopentadiene



SCHEME 8. The two mechanisms proposed for formation of both 1-methyl- and 2-methyl-1,3-cyclopentadienes from the ring opening of 2-methylbicyclo[2.1.0]pent-2-ene. In mechanism **A**, it is proposed that the initially formed cyclopentadiene is chemically activated and can isomerize by [1,5]-hydrogen migration in competition with being collisionally cooled. In mechanism **B**, the cyclopentadienes are formed by ${}_{\sigma}2_{s} + {}_{\sigma}2_{a}$ reactions involving the C1−C2 and C4−C5 (or C1−C5 and C3−C4) bonds of the reactant

at the nominal reaction temperature. The second explanation was that the ring opening occurred exclusively or partially by a ${}_{\sigma}2_{s} + {}_{\sigma}2_{a}$ mechanism involving the C1−C2 and C4−C5 bonds[108]. Supporting the chemical-activation explanation was the observation that the amount of cyclopentadiene isomerization was much greater in the gas phase than in solution[109]. In the gas phase there was some evidence for decreased isomerization at higher pressures of bath gas, and when polyatomic bath gases such as pentane were used in place of diatomic ones such as N_2[110]. However, the effects were small and only barely outside of experimental error. On the other hand the fact that about 10% of the isomerized product *was* still formed in solution seemed initially to be inconsistent with a purely chemical-activation explanation, since no other examples of 'hot-molecule' effects in solution were known. Farneth and coworkers[111] carried out RRKM calculations and concluded that the solution-phase isomerization could not be explained if one used a 'strong-collider' assumption in which a single collision would be enough to completely deactivate a vibrationally hot cyclopentadiene, but that a mechanism in which each collision removed only about 20% of the excess energy might permit the extent of isomerization observed experimentally.

Eventually, double ^{13}C-labeling studies by Andrews and Baldwin[112] definitively ruled out any significant contribution from the ${}_{\sigma}2_{s} + {}_{\sigma}2_{a}$ mechanism, and so the chemical-activation mechanism remains as the best explanation to date for the observations.

6. Bicyclo[2.2.0]hex-2-ene and bicyclo[2.2.0]hex-1(4)-ene

The ring opening of bicyclo[2.2.0]hex-2-ene to 1,3-cyclohexadiene was studied independently by Martin and Hekman[113], who obtained an activation energy of 31.7 kcal mol^{-1} in solution, and by Goldstein and coworkers[114], who found $E_a = 33.0$ kcal mol^{-1} in the gas phase. The Goldstein group used deuterium labeling to rule out all mechanisms other than ones involving cleavage of the C1−C4 bond, but they could not distinguish a single-step, 'forbidden' ring opening, occurring by disrotation, from an 'allowed' conrotatory process leading to *trans,cis*-1,3-cyclohexadiene as an unobserved intermediate. Roth and coworkers[115] calculated that the biradical generated by 90° internal rotation of one of the double bonds of 1,3-cyclohexadiene should have a heat of formation that was within 1 kcal mol^{-1} of the experimental heat of formation for the ring-opening transition state. They consequently favored an asynchronous ring-opening mechanism in which the C1−C4 cleavage occurred by uncoupled internal rotations about the C1−C2 and C3−C4 bonds. Interestingly, B3LYP/6-31+G(d,p) calculations do find a transition structure with a geometry like that proposed by Roth and coworkers (Figure 4). It has an enthalpy 32.3 kcal mol^{-1} higher than that of the reactant, in excellent agreement with the experimental $\Delta H^{\ddagger}$ of 32.1 kcal mol^{-1}. However, this TS does not have significant biradical character, as revealed by the fact that a restricted wavefunction derived from the B3LYP density is stable with respect to unrestricted symmetry-breaking. Furthermore, an intrinsic reaction coordinate study shows that this TS leads to *trans,cis*-1,3-cyclohexadiene, which is calculated to be a stable intermediate of 21.6 kcal mol^{-1} higher enthalpy than the reactant.

Whether the *trans,cis*-1,3-cyclohexadiene isomerizes to the observed *cis,cis*-stereoisomer by simple internal rotation about the *trans* double bond or by [1,5] hydrogen migration

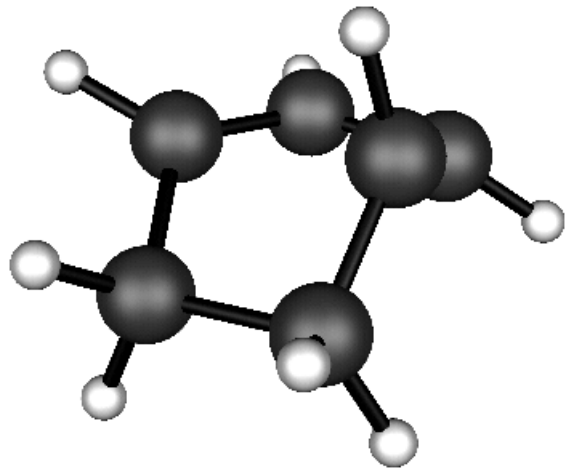
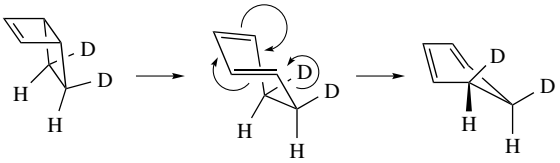


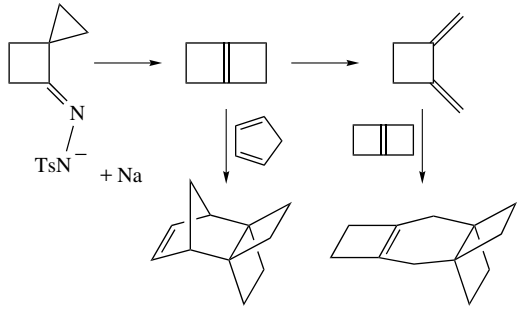
FIGURE 4. Geometry of the ring-opening transition structure for bicyclo[2.2.0]hex-2-ene from B3LYP/6-31+G(d,p) calculations. This transition structure connects the reactant to *trans,cis*-1,3-cyclohexadiene

is not known. Even Goldstein's deuterium-labeling study does not serve to distinguish between the two because the deuterium labels were in the *exo* sites on C5 and C6 of the original bicyclo[2.2.0]hex-2-ene, and those are the positions from which any [1,5] shift would occur (see Scheme 9).



SCHEME 9. A mechanism for conrotatory ring opening of bicyclo[2.2.0]hexene, followed by [1,5] hydrogen migration in the resulting *trans,cis*-1,3-cyclohexadiene. As shown, this mechanism would be consistent with the deuterium-labeling studies of Goldstein and coworkers

The first evidence for the generation of bicyclo[2.2.0]hex-1(4)-ene was reported by Wiberg and coworkers[116], who pyrolyzed the tosylhydrazone sodium salt shown in Scheme 10. In the absence of a trap, they obtained a Diels–Alder adduct of bicyclo[2.2.0]hex-1(4)-ene and its ring-opening product, 1,2-dimethylenecyclobutane. However, when the pyrolysis was conducted in the presence of cyclopentadiene, it served as a trap for the bicyclo[2.2.0]hex-1(4)-ene. A few years later, Wiberg's group reported that the hydrocarbon could be prepared at lower temperature by electrochemical reduction of 1-chloro-4-bromobicyclo[2.2.0]hexane[117]. Under these conditions the alkene could be isolated and characterized, although it was very susceptible to polymerization[118]. A good summary of the methods of preparation, physical properties and chemical reactions of bicyclo[2.2.0]hex-1(4)-ene can be found in a review article from Wiberg's group[119].



SCHEME 10. Generation and Diels–Alder trapping of bicyclo[2.2.0]hex-1(4)-ene

7. Bicyclo[2.2.0]hexa-2,5-diene (Dewar benzene)

Since it is a valence isomer of benzene—often called Dewar benzene—much interest has attended the chemistry of bicyclo[2.2.0]hexa-2,5-diene and its derivatives. A review of the very extensive literature on this topic would be outside the scope of the present chapter, and so here the focus will be restricted to the parent hydrocarbon, which was first prepared by van Tamelen and Pappas[120, 121]. They photocyclized and then oxidatively decarboxylated 1,2-dihydrophthalic anhydride. That sequence is still the method of choice for preparing the unsubstituted hydrocarbon. Microwave[122] and UV photoelectron[123] spectra have been obtained on the hydrocarbon, but, somewhat surprisingly, there appears

to have been no experimental determination of its heat of formation. Using isodesmic reactions at the G2 level of *ab initio* theory, Cheung and coworkers found its ring opening to benzene to have $\Delta H^\circ = -75.3$ kcal mol^{-1} [124]. Direct comparison of the computed enthalpies at the CBS-QB3 level[4] affords a value of -77.9 kcal mol^{-1}.

Perhaps the most interesting aspect of the ring opening of bicyclo[2.2.0]hexa-2,5-diene was first reported by Lechkten and coworkers[125], who presented evidence for formation of triplet benzene. Thermal generation of electronic excited states is quite rare, and so this report attracted a good deal of attention. If one accepts the theoretical estimates for the overall exothermicity of the ring opening, then the experimental activation enthalpy of 23.0 kcal mol^{-1} places the transition state about 98–100 kcal mol^{-1} above the benzene S_0 state. The T_1 state of benzene is only about 85 kcal mol^{-1} above S_0, and so one clearly has sufficient energy to access the excited state. However, while suitable exothermicity is obviously a necessary condition for this or any nonadiabatic reaction, it is not a sufficient one, as demonstrated by the ring opening of prismane, which is almost certainly much more exothermic than the Dewar-benzene reaction (that assertion is known to be true for the hexamethyl derivatives[126, 127]) and yet does not lead to any triplet benzene production. Explanations for this phenomenon have been presented by Turro and Devaquet[128], who also offer insight into the low efficiency with which triplet benzene is produced from bicyclo[2.2.0]hexa-2,5-diene.

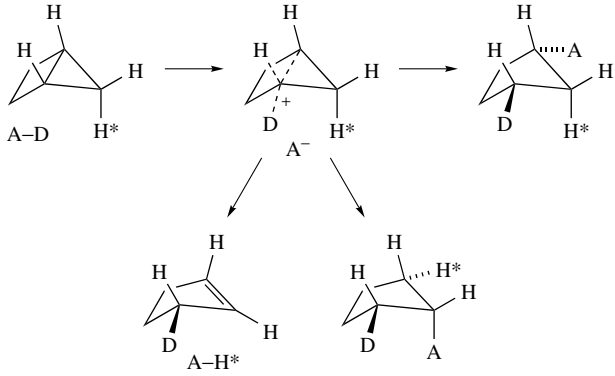
As with the calculations showing conrotatory ring opening of bicyclo[2.2.0]hex-2-ene (*vide supra*), CASSCF and MRCI calculations by Havenith and coworkers[129] suggest that the ring opening of Dewar benzene begins on a conrotatory path. However, the formal product of such a reaction—*trans,cis,cis*-1,3,5-cyclohexatriene—apparently has no barrier to isomerization to benzene. The net result, according to the calculations, is that the ring opening is a single-step reaction but not a disrotatory electrocyclic process.

B. Bimolecular Reactions

1. Reactions with Brønsted acids

Brønsted acid addition to bicyclo[2.1.0]pentane was one of the first reactions of that hydrocarbon to be reported[130]. LaLonde and Forney discovered that, in contrast to the analogous reactions of bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane, the acid-induced ring cleavage occurred exclusively by scission of the shared C–C bond. LaLonde and Ding subsequently investigated the regiochemistry of this reaction by using a D_2SO_4 catalyst in AcOD solvent. They discovered that about 35% of the resulting AcOD addition was accompanied by 1,2-hydrogen migration from C5 of the bicyclo[2.1.0]pentane[131]. In their experimental design, 1,2-hydrogen migration from C2 or C3 would not have been detectable. This initial discovery was followed by a much more extensive mechanistic investigation from Wiberg and coworkers[14, 132, 133]. Their early studies used catalytic *p*-toluenesulfonic acid (TsOH) in acetic acid, and seemed to indicate an unusually slow reaction of bicyclo[2.1.0]pentane compared to larger [*n*.1.0]bicycloalkanes. However, it was subsequently discovered that the catalyst was largely consumed by formation of cyclopentyl tosylate and was only slowly regenerated when that compound solvolyzed. Consequently, the later studies used stoichiometric TsOH in acetic acid solvent. The painstaking kinetic and isotopic labeling studies of the Wiberg group led to a mechanistic proposal whose principal steps are summarized in Scheme 11.

Notably, none of the observations required the intermediacy of a cyclopentyl cation. Minor products could be explained by initial protonation with retention at C1 and by hydrogen loss from C3 and the *exo* position of C5. Interestingly, protonation of 5,5-dimethylbicyclo[2.1.0]pentane was shown to occur by exclusive cleavage of the C1–C5 bond, indicating that the relative cation stability had a greater influence than relative strain

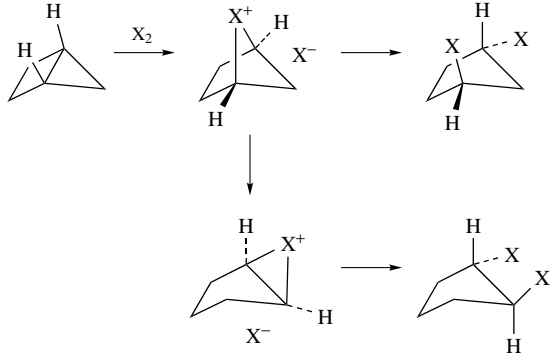


SCHEME 11. Summary of the principal mechanistic steps deduced by Wiberg and coworkers for the addition of Brønsted acids to bicyclo[2.1.0]pentane. When A = TsO, the 1,2 migration of the *endo* hydrogen on C5 occurs faster than ion-pair collapse, whereas when A = AcO the reverse is true

relief on the reaction course. No studies on Brønsted acid addition to bicyclo[2.2.0]hexane or its derivatives appear to have been reported.

2. Reactions with electrophiles

The addition of halogens to bicyclo[2.1.0]pentane was reported by LaLonde[134]. Like the Brønsted-acid addition, the halogenation is accompanied by extensive hydrogen migration. However, unlike the acid addition, the products of halogen addition are predominantly *trans* stereoisomers. LaLonde explained this by proposing an electrophilic addition occurring predominantly with retention of configuration, to make a 1,3-halonium ion, which then underwent competitive rearrangement and trapping with halide (Scheme 12).



SCHEME 12. LaLonde's mechanism for formation of the principal products in halogen (X = Cl, Br) addition to bicyclo[2.1.0]pentane. For X = Br, rearrangement of the initial 1,3-halonium ion would have to be faster than its trapping by bromide ion, since no 1,3-dibromocyclopentane was detected. For X = Cl, both 1,2 and 1,3 adducts were found

If this mechanism is correct, the preferred stereochemistries of proton addition and halogen addition to the hydrocarbon are different. Possibly that could be explained by

the easier formation of a 1,3-bridged intermediate with the larger halogen electrophiles. The identity of the hydrogen that migrates in the proposed 1,3- to 1,2-halonium ion rearrangement could not be determined from LaLonde's experiments, but Wiberg's studies on protonation of bicyclo[2.1.0]pentane (*vide supra*) might suggest that the *endo* hydrogen on C5 would be a likely candidate.

Seemingly at odds with the halogenation of bicyclo[2.1.0]pentane is the report by Bloodworth and coworkers[135,136] on its reaction with mercuric acetate and *tert*-butyl hydroperoxide. The product, formed after acetate-for-bromide exchange with KBr, was exclusively *cis*-1-bromomercuri-3-*tert*-butylperoxycyclopentane. The reaction could be catalyzed with perchloric acid, but the product was then contaminated by a 1,2-adduct, apparently derived from cyclopentene. The preferred *trans* addition of halogens but *cis* peroxymercuration is difficult to rationalize. The mercury surely ought to be large enough to make a 1,3-bridged mercurinium ion, analogous to the first-formed 1,3-halonium ions postulated by LaLonde, and yet the involvement of such an intermediate would lead one to expect overall *trans* addition of the mercury and peroxide.

Again, no electrophilic additions to bicyclo[2.2.0]hexane or its derivatives appear to have been reported.

3. Reactions with radicals

Two kinds of reaction with radicals might be expected for these strained hydrocarbons—addition and hydrogen atom abstraction—and both are known. For both bicyclo[2.1.0]pentane and bicyclo[2.2.0]hexane, the earliest studies of radical reactions involved photochemical chlorination. Boikess and Mackay[137] found that the vapor-phase photochlorination of bicyclo[2.1.0]pentane gave cyclopentene and a mixture of chlorocyclopentane and *cis*- and *trans*-1,2- and 1,3-dichlorocyclopentanes. The products seemed to implicate direct Cl-atom addition to the C1−C4 bond—generating 3-chlorocyclopentyl radical and thence the mono- and 1,3-dichlorocyclopentanes—as well as hydrogen atom abstraction—leading first to the 3-cyclopentenyl radical, then to cyclopentene and from there to the 1,2-dichlorocyclopentanes. In addition to these steps, the authors postulated that the HCl generated by hydrogen-atom abstraction could add back to the starting hydrocarbon to provide another route to chlorocyclopentane. In subsequent studies they showed that such a reaction was possible[138].

Srinivasan and Sonntag[139] studied a similar gas-phase photochlorination of bicyclo[2.2.0]hexane, but found rather different results. Unlike the reaction of bicyclo[2.1.0]pentane, the photochlorination of bicyclo[2.2.0]hexane afforded significant quantities of 1- and *exo*-2-chlorobicyclo[2.2.0]hexanes. The presence of the latter compound suggested to the authors that the bicyclo[2.2.0]hex-2-yl radical must have a half-life of several seconds. As discussed below, experimental evidence indicates that the nominally analogous bicyclo[2.1.0]pent-2-yl radical is much shorter-lived. However, Srinivasan and Sonntag deduced that the bicyclo[2.2.0]hex-2-yl radical must undergo some ring opening in competition with its reaction with Cl_2, since they also found 4-chlorocyclohexene and 1,5-hexadiene in the product mixture. The presence of dichlorocyclohexanes among the products suggested that the Cl atoms reacted with bicyclo[2.2.0]hexane by addition as well as H-atom abstraction, but in the absence of detailed regio- and stereochemical analysis of the products, no detailed mechanism for the addition could be proposed.

The rapid ring opening of the bicyclo[2.1.0]pent-2-yl radical was explicitly mentioned by Jamieson and coworkers[140] and then Roberts and Walton[141] in their studies of the reaction of bicyclo[2.1.0]pentane with Br_2, $BrCCl_3$, *N*-bromosuccinimide and *tert*-butylhypochlorite under photochemical conditions. In each case, products ascribable to addition across the C1−C4 bond could be found, along with products from

C2 hydrogen-atom abstraction. However, none of the latter class retained the bicyclic structure. Furthermore, photolysis of bicyclo[2.1.0]pentane with di-*tert*-butyl peroxide in an ESR spectrometer gave a spectrum only of the 3-cyclopentenyl radical, even at temperatures as low as −160 °C. Because these results suggested that bicyclo[2.1.0]pent-2-yl might be a useful radical 'clock', a more quantitative investigation of its ring-opening kinetics was undertaken[142–145]. This work led to the conclusion that the reaction has an Arrhenius activation energy of only 5.2 kcal mol^{-1}. These studies, in turn, have contributed to the controversy surrounding the mechanisms of oxidation of alkanes by cytochrome P450, and by dioxiranes (*vide infra*).

4. Oxidation

As described in Section III.C, the strain in the bicyclo[2.1.0]pentane and bicyclo[2.2.0]hexane skeletons raises the energies of the highest-occupied molecular orbitals and consequently lowers their ionization potentials and oxidation potentials with respect to those for unstrained alkanes[39]. This, in turn, makes the generation of the corresponding radical cations relatively straightforward. Not surprisingly, the radical cations are very susceptible to rearrangement, as illustrated by the γ radiolysis of bicyclo[2.1.0]pentane. Ushida and coworkers first reported that γ irradiation of this hydrocarbon at low temperatures in Freon matrices afforded only the cyclopentene radical cation[146]. Subsequently, Williams and coworkers discovered that the cyclopentane-1,3-diyl radical cation could be detected by ESR as an intermediate in the rearrangement[147]. A theoretical analysis of the bicyclo[2.1.0]pentane radical cation has suggested a complex situation in which a ring-closed structure, and a conical intersection between potential energy surfaces play important roles in its isomerization[148], but a full discussion of this work would be beyond the scope of the present chapter.

For bicyclo[2.2.0]hexane, the situation is rather different. ESR studies on the radical cation generated by γ radiolysis of stereospecifically deuterium-labeled bicyclo[2.2.0]hexane and 1,5-hexadiene in haloethane matrices have shown that both precursors afford the same intermediate, and that its spectrum is best fit to a chair conformation of cyclohexane-1,4-diyl radical cation. On warming, this intermediate affords cyclohexene radical cation[149,150]. In surprising contrast to this result is the work of Tsuji and coworkers[151,152], who studied the photochemical oxidation of 1,4-dimethyl- and 1,2,3,4,5,6-hexamethylbicyclo[2.2.0]hexanes and concluded that the ring-cleaved products were best rationalized by invoking a bicyclic radical cation that could give the diene radical cation directly. It is unclear whether the difference from the results obtained with the parent hydrocarbon was due to the methyl substituents or to the method of oxidation. That the latter played at least some role is indicated by the fact that the product ratio was found to be dependent on the nature of the electron acceptor in the photochemical studies[151,152].

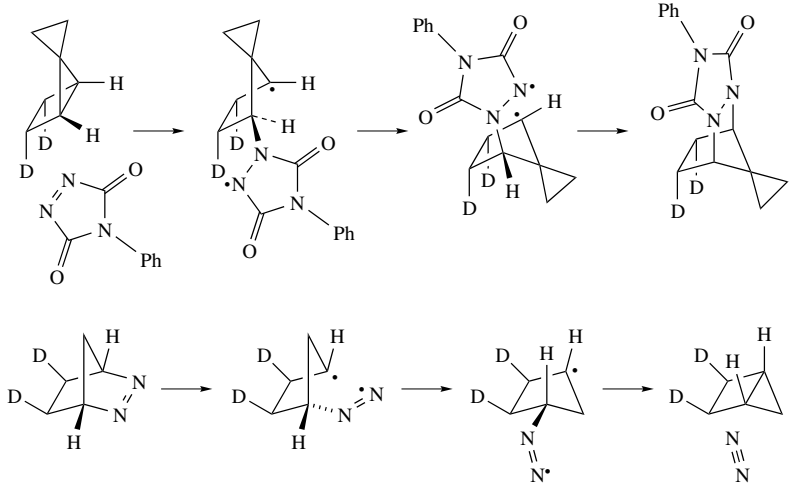
The chemical oxidation by dioxiranes and biochemical oxidation by cytochrome P450 of bicyclo[2.1.0]pentane have been investigated as components of larger studies that have involved mechanistic controversy. In each case, the principal question was whether the oxidation of alkanes by these agents occurred primarily by a free-radical mechanism or by some sort of direct 'oxene' insertion. Bicyclo[2.1.0]pentane was selected as one of a number of substrates whose corresponding free radicals were known to undergo rapid isomerizations that would lead to different products from those expected for direct insertion of oxygen into a C−H bond. Curci and coworkers[153] have reported that both dimethyldioxirane and methyltrifluoromethyldioxirane give only ring-closed alcohols and diols from bicyclo[2.1.0]pentane, and hence favor the direct-insertion mechanism. More rigorously, one could say that the known rate constant for ring opening of the bicyclo[2.1.0]pent-2-yl

radical, combined with these experimental results, require that any putative radical pair would have to collapse to products with a rate constant $\gg 10^9$ s^{-1}. In the cytochrome P450 studies[143, 144, 154–156], both ring-closed and ring-opened alcohols have been detected. If the results were interpreted in the context of a single radical-pair mechanism, the product ratio would imply a value of around 2×10^{10} s^{-1} for the rate constant of C−O bond formation. However, studies on other substrates, as well as theoretical work, have suggested that there may be more than one pathway involved in alkane oxidations by cytochrome P450, and so the validity of this calculation is open to question.

5. Cycloadditions

There appear to be no reports of cycloadditions to bicyclo[2.2.0]hexane or its derivatives. Whether this is because such reactions do not occur or because they have never been tried is unclear. By contrast, the literature on cycloadditions to bicyclo[2.1.0]pentane is extensive.

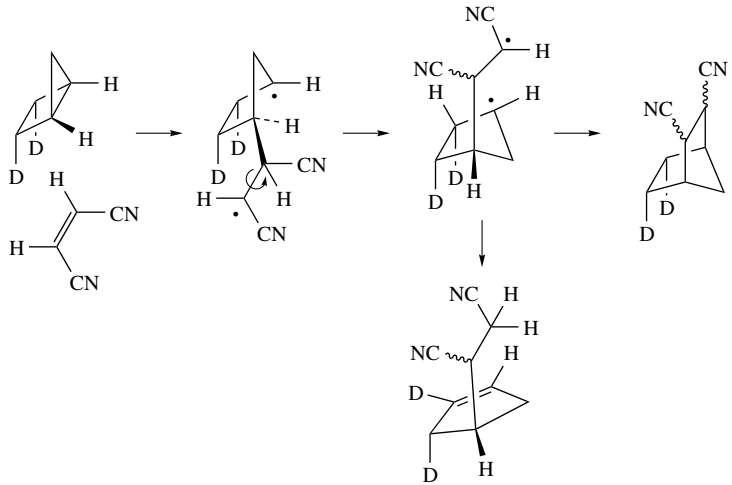
The first report of a cycloaddition to the bicyclo[2.1.0]pentane skeleton was by Roth and Martin[157], who made an observation and conceptual connection that became the subjects of lively research and discussion for decades afterwards. The cycloaddition that they studied was of *N*-phenyltriazolinedione to spiro[bicyclo[2.1.0]pentane-5,1′-cyclopropane-2,3-d_2] as a 79:21 *exo,exo*: *endo,endo* mixture of label isomers (see Scheme 13). They discovered that the adduct, derived from formal N=N cycloaddition across the C1−C4 bond of the hydrocarbon, was also a 79:21 *exo,exo*: *endo,endo* mixture of label isomers, indicating that the reaction must have occurred with inversion of configuration at both C1 and C4. They postulated a stepwise addition mechanism in which the reactants formed one C−N bond with inversion at C1, in concert with C1−C4 bond scission. The resulting biradical would then have no choice but to make the second C−N bond (to C4) also with inversion. Since Roth and Martin had earlier reported that 2,3-diaza[2.2.1]bicyclohept-2-ene-*exo,exo*-5,6-d_2 underwent thermal extrusion of nitrogen with a 3:1 preference for



SCHEME 13. The related mechanisms proposed by Roth and Martin to explain the observed preference for double inversion in cycloaddition to [2.1.0]bicyclopentanes and in N_2 extrusion from 2,3-diaza[2.2.1]bicyclohept-2-ene

double inversion[158] (subsequently shown to be closer to 5:1 once product interconversion was factored out[159]), they suggested that this reaction probably occurred by the nominal microscopic reverse of their proposed cycloaddition mechanism[157]. This suggestion is discussed in greater detail below.

In the following years, cycloadditions to the parent bicyclo[2.1.0]pentane were extensively studied by Gassman's group. With electron deficient alkenes and alkynes the reaction was found to occur readily, and was shown by deuterium labeling to follow the same stereochemical course that Roth and Martin had discovered in the reaction of the spirocyclopropyl analog[160]. Since the reactions with maleonitrile and fumaronitrile both led to the same mixture of stereoisomeric adducts, and since the cycloaddition was accompanied by products from a formal ene reaction, Gassman and coworkers postulated a stepwise addition essentially identical to Roth and Martin's mechanism. The intermediate biradical would be able to rotate about the bond between the two nitrile-bearing carbons—explaining the lack of stereoselectivity—and would be able to abstract a hydrogen atom in competition with forming the second C–C bond—explaining the formation of both cycloadducts and ene products[161,162] (Scheme 14).



SCHEME 14. The mechanism proposed by Gassman and coworkers to explain the products formed from addition of maleonitrile to bicyclo[2.1.0]pentane

Recent *ab initio* electronic-structure calculations have supported this mechanism[47]. However, they have challenged the conceptually neat analogy with the nitrogen-extrusion reaction proposed by Roth and Martin[157]. CASPT2 calculations have shown that the preferred mechanism for nitrogen extrusion from 2,3-diaza[2.2.1]-bicyclohept-2-ene involves concerted cleavage of the two C–N bonds to generate cyclopentane-1,3-diyl[34]. Because it bypasses a diazenyl biradical intermediate, this mechanism does not permit the conformational change that is responsible for the inversion of stereochemistry in the Roth and Martin proposal. Instead, the inversion appears to be due to nonstatistical dynamical effects[34].

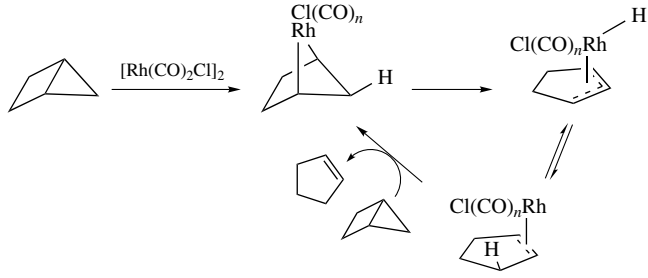
Two groups have independently studied the cycloaddition of chlorosulfonylisocyanate to bicyclo[2.1.0]pentane[163–165]. The reaction forms a cycloadduct and an ene product that are the direct analogs of those seen in the alkene and alkyne additions. Paquette and

coworkers invoked a zwitterionic rather than a biradical intermediate, but in C_1 symmetry there is not a sensible distinction between the two, since the lowest electronic state of the intermediate would undoubtedly have both biradical and zwitterionic contributing configurations. No information is available about the stereochemistry of the cycloaddition at C1 and C4, but it seems reasonable to expect that it would be double inversion, as in the other cycloadditions.

6. Reactions with transition metal complexes

The quest for transition-metal catalysts that can facilitate the cleavage of C−C bonds has led several groups to investigate the organometallic chemistry of strained-ring hydrocarbons such as bicyclo[2.1.0]pentane and bicyclo[2.2.0]hexane. These studies have shown that there do indeed exist catalysts that will promote reactions similar to some of the thermal chemistry of these hydrocarbons, but at lower temperatures and, as it turns out, by entirely different mechanisms.

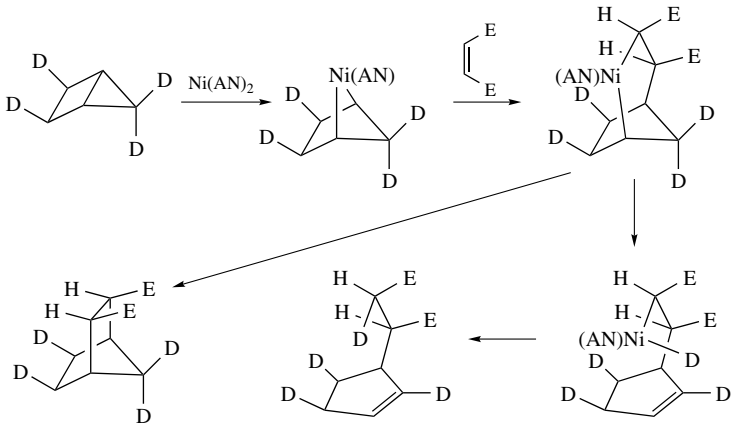
One of the earliest such reports was from Gassman and coworkers[166] who discovered that $[Rh(CO)_2Cl]_2$ would catalyze the isomerization of bicyclo[2.1.0]pentane to cyclopentene at room temperature. A subsequent study by Wiberg and Bishop[167] revealed that the same catalyst would promote the formation of various methylcyclopentenes from all of the possible regio- and stereoisomers of methylbicyclo[2.1.0]pentane, save one—the *exo*-5-methyl derivative. It was completely resistant to catalyzed rearrangement. This observation led to the proposal of a mechanism involving initial oxidative addition of the C1−C4 bond to the catalyst, followed by migration of the *exo* hydrogen on C5 to the metal (Scheme 15). Studies using deuterium-labeled substrates or deuteriated solvents have also indicated that the η^3-allyl intermediate is probably capable of multiple reductive eliminations and oxidative additions of C−H bonds before the cyclopentene is released[166, 167].



SCHEME 15. Mechanism for the Rh(I)-catalyzed isomerization of bicyclo[2.1.0]pentane to cyclopentene

A particularly striking example of transition metal catalysis was reported by Noyori and coworkers[168, 169], who discovered that bis(acrylonitrile)nickel would catalyze the addition of electron-deficient alkenes across the C1−C4 bond of bicyclo[2.1.0]pentane. The products were norbornane cycloadducts and cyclopentene products from a formal ene reaction, superficially just as one sees in the thermal, uncatalyzed reaction. However, the nickel-catalyzed process differed in that the cycloadducts retained the stereochemical relationship of the substituents on the alkene. Furthermore, when deuterium-labeled bicyclopentanes were used, it was discovered that the cycloadducts were formed with *retention* of configuration at C1 and C4, instead of the inversion seen in the uncatalyzed reaction. The nominal ene product was found to be formed by abstraction of a hydrogen from C5 of

the reactant. The mechanism proposed by Noyori and coworkers to explain these results is shown in Scheme 16. It again starts with oxidative addition of the C1−C4 bond across the nickel atom.



SCHEME 16. Mechanism for the Ni(0)-catalyzed addition of alkenes to bicyclo[2.1.0]pentane. AN = acrylonitrile; E = CO_2CH_3. A cycloadduct with both ester substituents *endo* is also formed, but the *cis* relationship between the ester groups is retained

The proposed *exo* oxidative addition step invoked for both the rhodium- and nickel-catalyzed reactions has been directly verified for Fe(0) by Aumann and Averbeck[170], who were able to isolate and characterize the product of oxidative addition and migratory CO insertion from photochemical reaction of $Fe(CO)_5$ with a tricyclic analog of bicyclo[2.1.0]pentane.

A similar mechanism has been invoked by McKinney and Chou for the Zn(II)-catalyzed isomerization of 1-phenylbicyclo[2.1.0]pentane to 3-phenylcyclopentene[12]. However, no direct test of stereochemistry was conducted in that case, and it perhaps seems more likely that Zn(II) would behave like Hg(II) and cleave the C1−C4 bond with inversion[135], since the oxidative addition would require the formation of an intermediate with a formal Zn(IV) oxidation state.

In the case of bicyclo[2.2.0]hexane, the only report of reaction with transition metals is the work of Sohn and coworkers[171] using the norbornadiene or dicarbonyl Rh(I) chloride dimers. With the norbornadiene complex, catalyzed rearrangement to cyclohexene was observed. Use of bicyclo[2.2.0]hexane-2,3,5,6-d_4 (all labels *exo*) showed that the reaction occurred by rate-determining oxidative addition to the C1−C4 bond from the *exo* face. With the dicarbonyl dimer a metallocycle derived from oxidative addition and migratory insertion of CO could be isolated—much as Aumann and Averbeck had seen in the reaction of $Fe(CO)_5$ with bicyclo[2.1.0]pentane.

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CHAPTER **21**

Fluorinated cyclobutanes and their derivatives

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The chemistry of cyclobutanes
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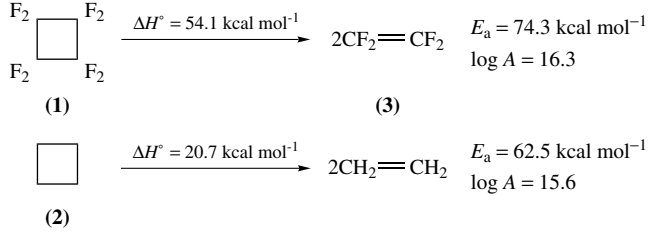
I. CYCLOBUTANES

A. Energetic Considerations

Four-membered rings play a prominent role in organofluorine chemistry. This is true in part because of the ease with which they are formed. It has been generally believed that fluorine substitution decreases ring strain in cyclobutanes, in particular that octafluorocyclobutane (**1**) experiences roughly 10 kcal mol^{-1} less strain energy than the parent hydrocarbon (**2**)[1]. While this conclusion was based on sound reasoning, there was and still remains a problem in identifying a strainless fluorinated reference system for which accurate thermochemical data are available. Recent density functional calculations, based on the (debatable) assumption that perfluorocyclohexane is strainless, place the octafluorocyclobutane strain energy 5.9 kcal mol^{-1} below that of the parent molecule[2].

Whatever its ring strain may be, octafluorocyclobutane is far more robust than cyclobutane (**2**). Its heat of fragmentation into two tetrafluoroethylene molecules is *ca* 33 kcal mol^{-1} more endothermic than the corresponding reaction of **2**[3,4], and the activation energy is *ca* 12 kcal mol^{-1} higher (Scheme 1)[3,5]. The contrast is attributable in large part to Bent's Rule, which states that p character tends to concentrate in orbitals directed toward electronegative substituents[6]. Thus fluorine, generally accepted as the most electronegative of elements, prefers sp^3 over sp^2 carbon. Another factor contributing to the stability of fluorinated cyclobutane rings relative to their unsubstituted counterparts is the enhanced strength of σ bonds between fluorinated carbons. The C−C bond in hexafluoroethane, for example, is 7 kcal mol^{-1} stronger than that in ethane[7].



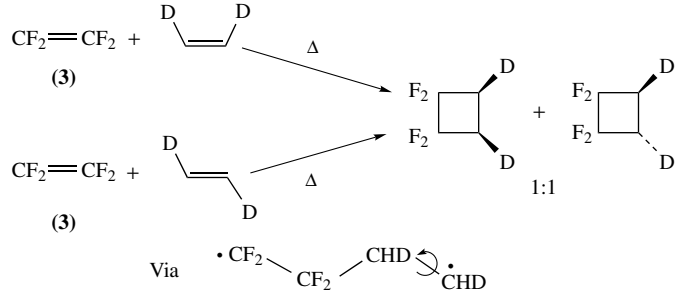
SCHEME 1

B. [2 + 2] Cycloadditions

1. Intermolecular

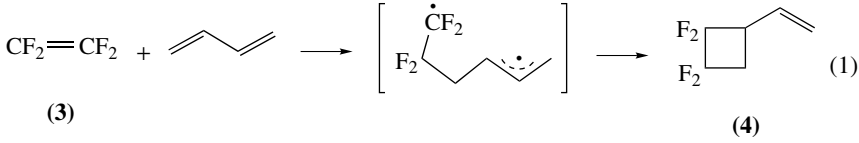
The most important source of fluorinated cyclobutanes is [2 + 2] cycloaddition, the energetically favorable reverse of the reactions in Scheme 1. Because this subject has been extensively reviewed[8], only a few selected aspects will be discussed here. *gem*-Difluoro

and more highly fluorinated alkenes dimerize and add thermally to a broad spectrum of alkenes to form cyclobutanes. As orbital-topology-forbidden processes, these reactions proceed stepwise, generally via biradical intermediates. Cycloaddition of tetrafluoroethylene (**3**) to *cis*- and *trans*-dideuterioethylene provided an elegant proof of a stepwise pathway. Both deuteriated ethylenes gave a roughly 1:1 mixture of *cis*- and *trans*-1,2-dideuterio-3,3,4,4-tetrafluorocyclobutane (Scheme 2)[9]. The respective intermediate 1,4-biradicals clearly lived sufficiently long to equilibrate by bond rotation before ring closure occurred. Biradical formation is favored by the presence of the four fluorines, as both carbons of **3** become approximately sp^3 hybridized. In addition to the influence of Bent's Rule, pyramidalization of the fluorinated radical center is driven by mixing of the SOMO with a C−F σ^* orbital[10]. Fluorines also confer extra strength on the newly formed C−C bond[11].



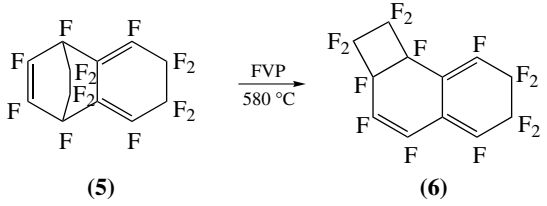
SCHEME 2

The same factors help to explain why a number of *gem*-difluoro and polyfluorinated alkenes add to dienes stepwise in [2 + 2] fashion in preference to undergoing Diels–Alder reaction, e.g. reaction of **3** with butadiene to give vinylcyclobutane **4** (equation 1)[12]. Whereas *anti* pyramidalization of the two carbons requires much less energy for **3** than for ethylene, *syn* pyramidalization, as in a Diels–Alder transition state, is actually easier for ethylene[11].



(1)

Consistent with the stepwise reaction of **3** with dienes is the finding that flash vacuum pyrolysis of **5** at 580 °C yields **6**, together with secondary reaction products (equation 2)[13]. [1,3] Sigmatropic rearrangement, presumably via a biradical, occurs instead of extrusion of **3** in a *retro*-Diels–Alder reaction.

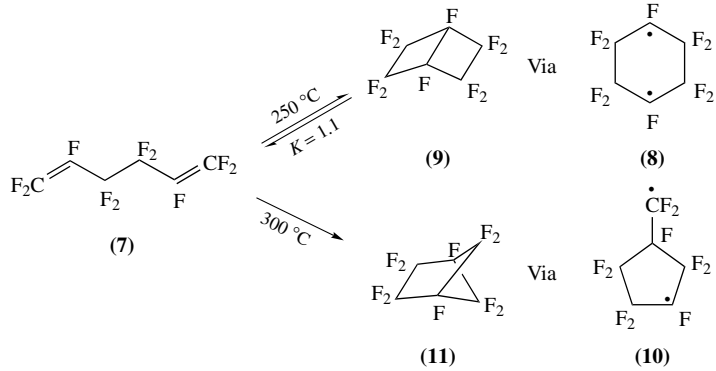


+ others (2)

The '*gem*-difluoro effect' helps to explain why geminal fluorines on an alkene are far more effective than vicinal in promoting cyclobutane formation[14]. Geminal fluorines on a *saturated* carbon strengthen each other's bonds, as illustrated by comparison of the generally accepted C−F bond dissociation energies of methyl fluoride (109.9 ± 1 kcal mol^{-1}) and tetrafluoromethane (130.5 ± 3 kcal mol^{-1})[15]. Calculations indicate that successive substitution of fluorine for hydrogen in methane results in progressively greater positive charge on the carbon while negative charges on fluorine remain similar throughout the series[16]. Thus, the coulombic attraction of carbon for fluorine increases monotonically with the number of fluorines. Negative hyperconjugation involving fluorine lone pair donation into C−F σ^* orbitals may also contribute to the mutual bond-strengthening[15].

2. Intramolecular

Perfluoro-1,5-hexadiene (**7**) cyclizes reversibly at 250 °C via biradical **8**, resulting in a closely balanced equilibrium with perfluorobicyclo[2.2.0]hexane (**9**). At 300 °C, **7** is transformed irreversibly via **10** into perfluorobicyclo[2.1.1]hexane (**11**) (Scheme 3)[17]. The hydrocarbon parents of **10** and **11** both revert to 1,5-hexadiene at 300 °C, highlighting again the driving force in the perfluoro system toward sp^3 hybridization and strong new C−C bonds[18,19]. Cyclization of **7** can also be accomplished by mercury-sensitized photolysis at 254 nm in the gas phase, which proceeds via triplet energy transfer to the diene from mercury atoms. Again bicyclohexanes **9** and **11** are the products, now in the ratio 1:3–4.



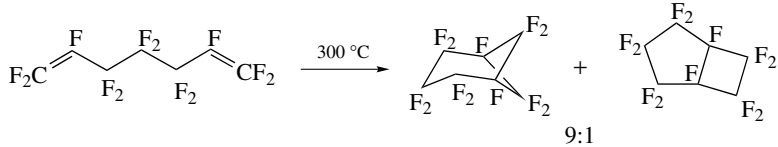
SCHEME 3

The homologous diene perfluoro-1,6-heptadiene (**12**) cyclizes at 300 °C, yielding perfluorobicyclo[3.1.1]heptane (**13**) and its [3.2.0] isomer (**14**) in the ratio 9:1 (equation 3). In the mercury-sensitized reaction the same compounds are formed, but **14** is the dominant product and some of its *trans* isomer is also obtained. Underlying these results is a consistent pattern, shown in Table 1[20]. In the thermal reactions, formation of a 6-membered is

TABLE 1. Preferred modes of internal cycloaddition for perfluorodienes

Reaction type	1,5-Diene	1,6-Diene	Intermediate ring
Thermal	Parallel	Crosswise	6-Membered
Photochemical	Crosswise	Parallel	5-Membered

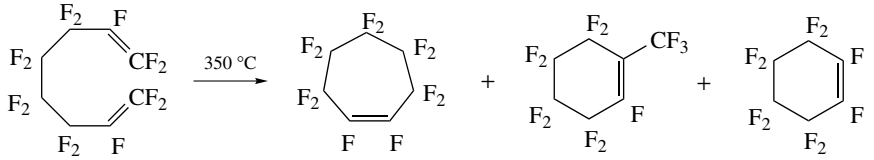
favored over a 5-membered ring biradical because of lesser ring strain. Because biradical formation is highly endothermic, transition states come late and therefore reflect well the relative energies of the two biradicals. In the photoreactions, the cyclic biradicals arise from triplet states, which can be regarded as high energy biradicals with much more than enough energy needed for cyclization[21]. Transition states therefore come early, and reflect the fact that intramolecular radical attack on a double bond strongly prefers 5- over 6-membered ring formation[22,23].



(3)

(12) **(13)** **(14)**

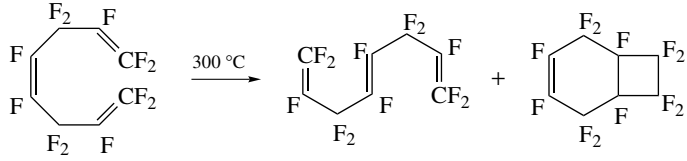
The next higher homologue, perfluoro-1,7-octadiene (**15**), behaves in radically different fashion. Unreactive at 300 °C, it cyclizes at 350 °C to give a mixture of perfluorocycloheptene (**16**), perfluoro-1-methylcyclohexene (**17**) and perfluorocyclohexene (**18**) (equation 4)[24]. The mechanism of this process remains unknown in detail, but it apparently involves extrusion of :CF_2, twice in the case of **18**.



(15) **(16)** **(17)** **(18)**

(4)

Incorporation of a *cis* double bond into the center of the diene chain restores conventional reactivity. At 300 °C *cis*-perfluoroocta-1,4,7-triene (**19**) isomerizes to its much less reactive *trans* isomer (**20**) and cyclizes to a 1:1.6 mixture of *cis*- and *trans*-perfluorobicyclo [4.2.0]oct-3-ene (**21**) (equation 5)[24].

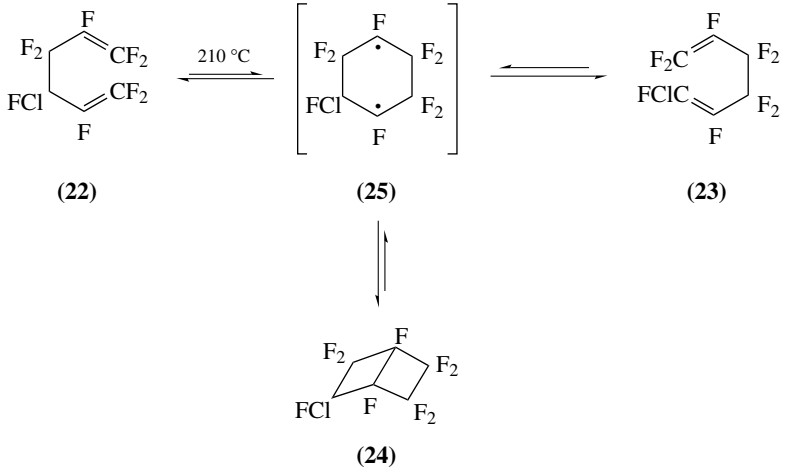


(5)

(19) **(20)** *cis*- and *trans*-(**21**)

The most characteristic reaction of 1,5-dienes is the Cope rearrangement, which was not detectable with **7** because it was degenerate. Thus, a labeled derivative of **7**, 3-chloroperfluoro-1,5-hexadiene (**22**), was heated in search of the Cope rearrangement product, the 1-chloro isomer (**23**). It was found that bicyclohexane **24** was formed much faster than **23**, and that heating **23** also gave **24** (equation 6)[25]. Since **24** must arise from biradical **25**, the Cope rearrangement must also proceed via that intermediate. The contrast with hydrocarbon analogues, which undergo concerted Cope rearrangement[26,27], is

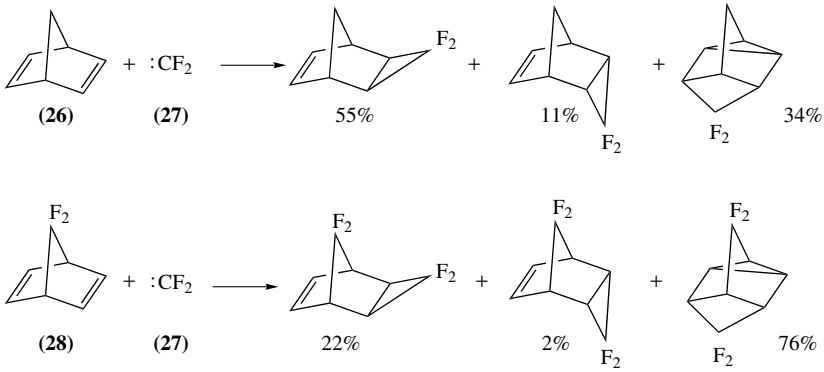
understandable in terms of Bent's Rule, as the transition states flanking biradical **25** have more p character in C−F bonds than the transition state for a concerted reaction.



(22) **(25)** **(23)** **(24)** (6)

C. Other Syntheses

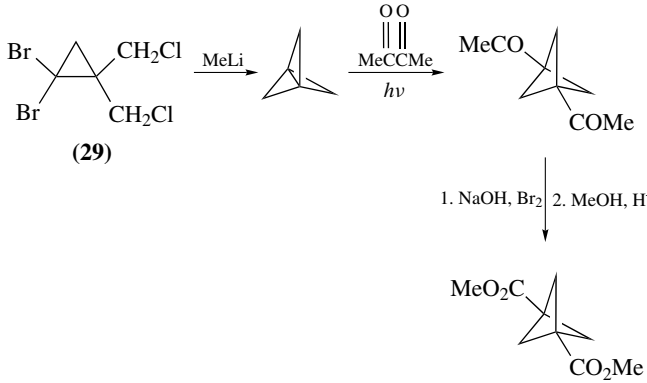
In its reactions with dihalocarbenes, norbornadiene (**26**) has the rare ability to allow homo-1,4-addition to compete with the usual 1,2-addition, thus creating a new 4-membered ring. Difluorocarbene (**27**) is regarded as an electrophilic carbene[28], and the dominant orbital interaction in its addition to an alkene is between the carbene LUMO and alkene HOMO. The carbene HOMO–diene LUMO interaction cannot be ignored, however, in the reaction with norbornadienes. Because of overlap considerations, this interaction is relatively more important in the homo-1,4- than in the 1,2-addition. Adjustment of the HOMO and LUMO energies of norbornadiene should therefore influence the ratio of 1,4- to 1,2-addition. This ratio was found to increase from 0.52 with norbornadiene to 3.2 with 7,7-difluoronorbornadiene (**28**), the FOs of which are each ~0.45 eV lower (Scheme 4)[29].



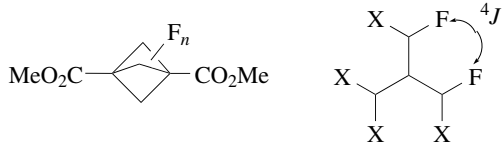
Yields are normalized to 100%

SCHEME 4

Fluorinated cyclobutane rings can also be obtained by treatment of hydrocarbon precursors with elemental fluorine. An interesting example is the fluorination of dimethyl bicyclo[1.1.1]pentane-1,3-dicarboxylate (**30**). This diester was synthesized from 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (**29**) via [1.1.1]propellane (equation 7)[30,31]. In a thorough and elegant study, the bridges of the diester were directly fluorinated, and 15 of the 16 possible fluoro derivatives (**31**) were characterized[31]. Since fluorination occurred on the methyls as well, fluorination products were saponified and reesterified with diazomethane before analysis. Polyfluorination introduces considerable strain arising from nonbonded repulsion among the fluorine and hydrogen atoms on the bridges. For the hexafluoro derivative, the increase in strain was calculated to be 33–35 kcal mol^{-1}. The ^{1}H, ^{19}F and ^{13}C NMR spectra were assigned and the chemical shifts were accurately reproduced with GIAO-HF/6-31G* calculations. Good agreement between measured and calculated values was also obtained for many coupling constants. An inverse linear correlation with a slope of −320 Hz/Å was found between the large (50–100 Hz) $^{4}J_{FF}$ values for proximal fluorines (**32**) and their calculated separation distance.



(29) **(30)** (7)



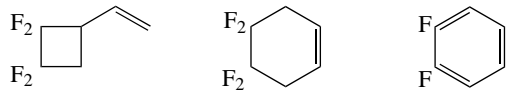
n = 1–6 **(31)** X = H, F **(32)**

D. Reactions of Cyclobutanes

1. A selection of syntheses

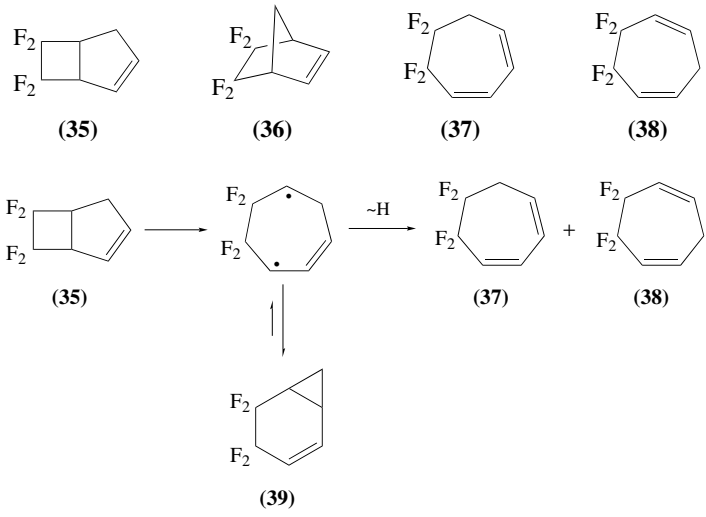
Passed through a hot tube at 500 °C, vinylcyclobutane (**4**) rearranges to cyclohexene **33**. If the pyrolysis is carried out at ⩾600 °C, the intermediate **33** undergoes dehydrofluorination to give *o*-difluorobenzene (**34**). The benzene is also obtained directly from tetrafluoroethylene (**3**) and butadiene via **4** and **33** by copyrolysis at 600 °C[32,33].

At 190 °C, **3** cycloadds to cyclopentadiene to give a mixture of [2 + 2] and [2 + 4] adducts, **35** and **36**, respectively. The same biradical intermediate may give rise to both



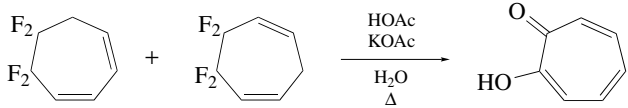
(4) **(33)** **(34)**

products. Pyrolysis of this mixture in a nickel tube at 700–750 °C gave cycloheptadienes **37** and **38**, nearly all of which arose from **35**. The reaction apparently proceeds as shown in Scheme 5, with the primary product norcarene **39** present in low steady state concentration[32, 34]. Hydrolysis of the mixture of **37** and **38** completes the best route to tropolone (**40**) (equation 8).



(35) **(36)** **(37)** **(38)** **(39)**

SCHEME 5

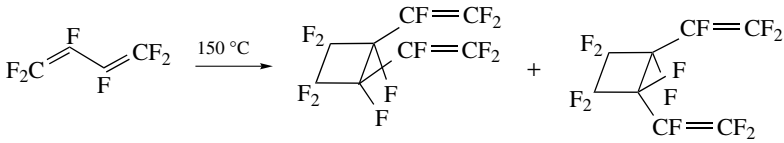


(37) **(38)** **(40)** (8)

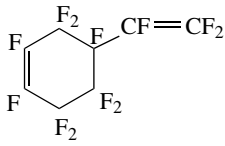
The thermal chemistry of hexafluorobutadiene (**41**) is very complex, but the primary products that arise when it is heated at 150 °C are the [2 + 2] dimers **42** and **43** plus a lesser amount of the [2 + 4] adduct **44** (equation 9)[35]. The last, which is probably formed via biradical(s) like the others, is not detected directly, as it reacts further with **41** to yield trimers via [2 + 2] and [2 + 4] cycloaddition.

At 150 °C dimer **42** slowly rearranges into **45, 46**[36, 37] and **47**, plus polymer derived from **47** (equation 10). Tricyclooctane **45** was shown to give **46, 47** and polymer under the reaction conditions. Dimer **43** is more robust thermally than **42**, but at 200 °C it is transformed during 50 h into an 11:1 mixture of **46** and **44**. Like **44**, but more slowly, dimers **42** and **43** also react with another equivalent of **41** in [2 + 2] and [2 + 4] fashion to afford an array of trimers[38]. Not surprisingly, the thermal chemistry of the parent butadiene

and of its dimers differs sharply from that of their perfluorinated counterparts[39].

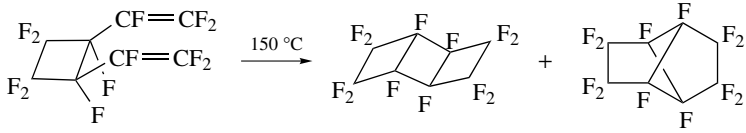


(41) **(42)** **(43)**

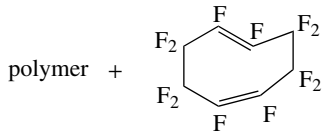


(44)

(9)



(42) **(45)** **(46)**



(47)

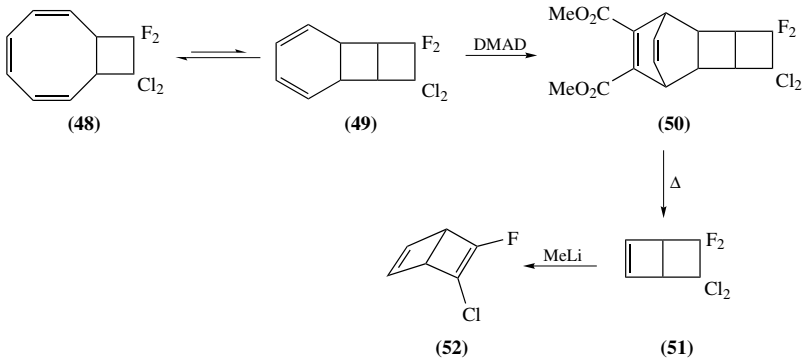
(10)

Cycloadduct **48** of 1,1-dichlorodifluoroethylene with cyclooctatetraene underwent Diels–Alder reaction with dimethyl acetylenedicarboxylate (DMAD) via valence isomer **49** (Scheme 6). Alder–Rickert reaction of the adduct **50** gave dimethyl phthalate and bicyclohexene **51**. Reductive dehalogenation of **51** with methyllithium yielded Dewar benzene **52**. This shock-sensitive liquid explodes on warming and has a half-life for aromatization to *o*-chlorofluorobenzene of 3 weeks at 20 °C[40].

The cycloadduct **53** of chlorotrifluoroethylene and cyclooctatetraene was transformed by methyllithium into red, crystalline bicyclodecapentaene **54** (18% yield)[41]. One possible pathway is shown in equation 11. Like azulene and naphthalene, **54** is a bridged [10]annulene, and pyrolysis at *ca* 600 °C isomerizes it cleanly to 1,2-dimethylazulene (**55**) (equation 12).

2. [2.2.2]Propellane chemistry

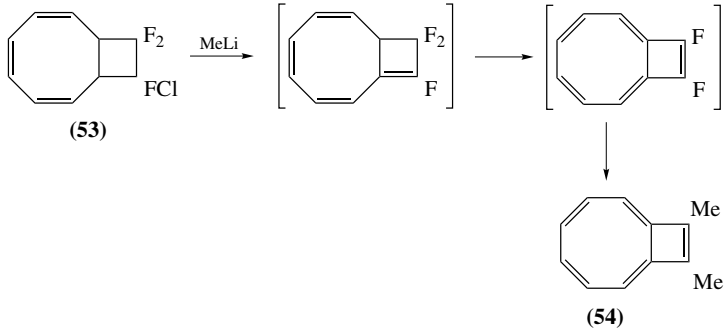
The calculated strain energy of the parent [2.2.2]propellane is 97 kcal mol^{-1} [42]. Though this molecule remains unknown, carboxamido derivative **56** was synthesized in 1973[43]. It spontaneously ring opened to dimethylenecyclohexanes **57** and **58** with a half-life of



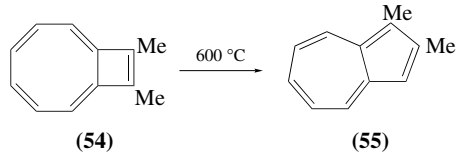
(48) (49) (50) (51) (52)

SCHEME 6

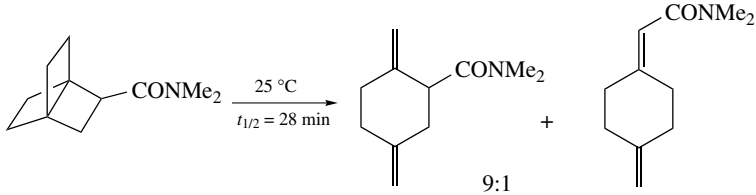
28 min at 25 °C (equation 13). Concerted cleavage of any of the 4-membered rings of **56** is of course orbital topology-forbidden, and the reaction is presumed to begin by stretching the highly strained central bond. The initially formed symmetric biradical crosses over to an antisymmetric biradical as stretching weakens through-space coupling of the radical centers and enhances through-bond interaction (bond stretch isomerization). Cleavage of an external C−C bond to complete the reaction is now an allowed event[44].



(53) (54) (11)

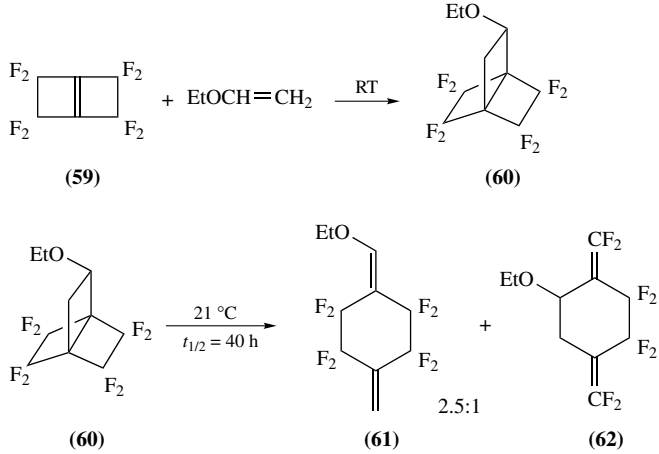


(54) (55) (12)

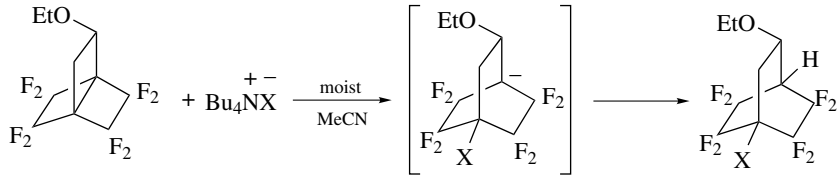


(56) (57) (58) (13)

The only other [2.2.2]propellanes known to date have been synthesized by [2 + 2] cycloaddition to perfluorobicyclo[2.2.0]hex-1(4)-ene (**59**)[45]. Ethyl vinyl ether added to **59** to give **60**, which was more stable thermally than the original [2.2.2]propellane. It ring opened to a 2.5:1 mixture of dimethylenecyclohexanes **61** and **62** with a half-life of 40 hours at 21 °C (Scheme 7). Whereas propellane **56** reacted instantly with bromine at −70 °C with cleavage of the central bond and formation of a bridgehead dibromide[43], **60** failed to react with either bromine or concentrated sulfuric acid/acetonitrile, both at RT. The powerful electron withdrawal by the fluorines that protected the molecule against electrophilic attack rendered it susceptible to nucleophilic attack, however. All four of the tetrabutylammonium halides reacted readily with **60** in moist acetonitrile, breaking the central bond in S_N2 fashion to yield a bridgehead HX adduct **64** (equation 14). The reaction proceeded with exclusive formation of the more stable bridgehead anion (**63**), the one with the charge proximal to the electron-withdrawing oxygen[46,47].

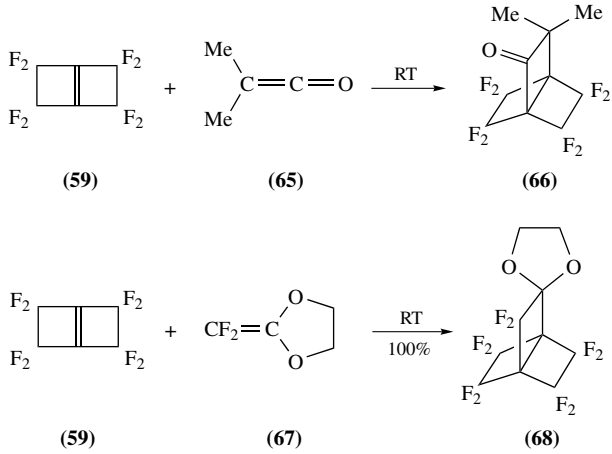


SCHEME 7



X = F, Cl, Br, I (14)

Dimethylketene (**65**) also proved capable of [2 + 2] cycloaddition to strained alkene **59**, giving **66**, the first crystalline [2.2.2]propellane (Scheme 8). This compound was unchanged after months in solution at RT. The finding that **66** was much more robust thermally than **60** supported the notion that increasing electron withdrawal from the propellane skeleton further stabilizes the molecule. The fully fluorinated [2.2.2]propellane would

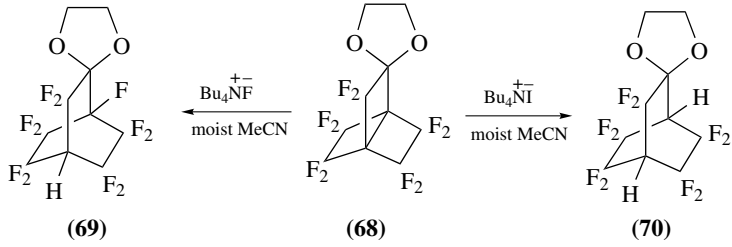


SCHEME 8

provide an excellent test of this surmise, but it is still unknown because tetrafluoroethylene is too electron deficient to cycloadd to alkene **59** even at high temperatures[47].

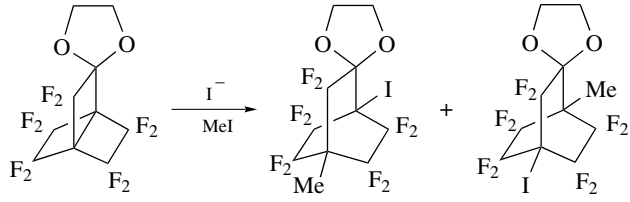
On the other hand, ketene acetal **67** adds rapidly and quantitatively to **59** at room temperature with the help of the π donor ability of the oxygens, giving propellane **68**[48] (Scheme 8). Since oxygen's σ-electron-withdrawing ability is second only to fluorine's, the skeleton of **68** is certainly very electron deficient. After at least 10 hours at 100 °C, **68** shows no signs of decomposition. Perhaps this remarkable stability can be understood in terms of the Wolfsberg–Helmholtz approximation, which assumes that the resonance integral for a bond between two atoms is proportional to the average of their coulomb integrals[49]. Electron withdrawal from the bridgehead carbons of **68** should enhance their coulomb integrals and thus the bond integral of the bridgehead bond. The increased strength of C–C σ bonds in fluorinated systems discussed earlier in this chapter may be attributable, at least in part, to the same effect.

Fluoride ion reacted with **68** in moist acetonitrile to give an HF adduct (**69**), as was the case with **60**. However, iodide ion under these conditions rapidly reduced **68** to the dihydro compound **70**, preferring electron transfer to nucleophilic attack on this extremely electron-poor propellane (equation 15). Chloride and bromide displayed intermediate behavior, giving both HX adducts and **70**, but reduction was the dominant process (3.7:1) even with chloride ion. Nucleophilic attack occurred at the ketal end of the molecule so as to place negative charge at the bridgehead with six β fluorines, though with fluoride ion the regioselectivity was only *ca* 90%[48].



(15)

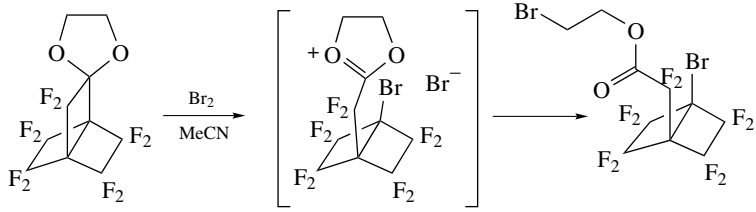
Iodide ion catalyzed addition of methyl iodide to **68** yield **71** and **72** (equation 16). Adduct **71** was formed via a radical anion chain reaction, but **72** arose via a radical chain pathway, and conditions were found to make either process virtually exclusive of the other.



(16)

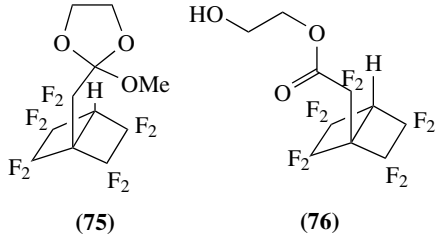
(68) **(71)** **(72)**

While all of the above reactions of **68** took place rapidly at room temperature, electrophilic attack was very slow and left the strained central bond intact. Bromine gave dibromoester **74** via **73** (equation 17), and solvolyses in methanol and aqueous acetonitrile produced **75** and **76**, respectively[48].



(17)

(68) **(73)** **(74)**



(75) **(76)**

Clearly, fluorination alters the character of [2.2.2]propellane fundamentally, transforming a molecule that is highly susceptible to electrophilic attack into a very resistant one, but one that is extremely vulnerable to assault by nucleophiles and reducing agents.

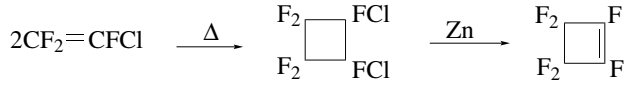
II. CYCLOBUTENES

A. Monocyclic

1. Equilibration with dienes

These cyclobutenes are typically made by [2 + 2] cycloaddition followed by dehydrohalogenation or reductive dehalogenation of the resulting cyclobutane, as illustrated with the synthesis of perfluorocyclobutene (**79**) via **78** from chlorotrifluoroethylene (**77**)

(equation 18)[50]. At elevated temperatures cyclobutenes equilibrate with dienes in an electrocyclic reaction that occurs in conrotatory fashion (in the absence of stringent geometric constraints)[51]. Because ring strain outweighs the energy difference between a C−C π bond and σ bond, the equilibrium lies far on the diene side in the unsubstituted system. Perfluorination makes a striking difference, as cyclobutene **79** is more stable than perfluorobutadiene by far, with a difference between the equilibria for the parent and fluorinated systems of $\Delta\Delta H^\circ = 19.7$ kcal mol^{-1} (Table 2). Partially fluorinated cyclobutenes **80** and **81** fall between these extremes, but it is not easy to rationalize the energetics of these four systems in detail[15]. Suffice it to say that Bent's Rule is in evidence, shifting the equilibrium for the parent system toward the cyclobutene when fluorines are introduced.



(77) **(78)** **(79)** (18)

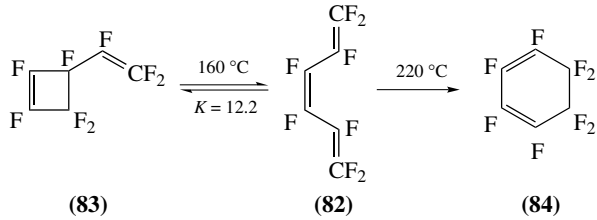
cis-Perfluoro-1,3,5-hexatriene (**82**) cyclizes reversibly to give vinylcyclobutene **83** at 160 °C, but at higher temperatures cyclohexadiene **84** is formed irreversibly (equation 19)[52,53]. Cyclobutene **83** ring opens cleanly to **82**; that is, the reaction is highly torquoselective, with the trifluorovinyl group rotating inward and the fluorine geminal to it rotating outward. π Donor substituents such as fluorine stabilize the transition state for outward rotation and destabilize that for inward rotation[54,55]. This explains why *trans*-perfluoro-1,3,5-hexatriene (**85**) cyclizes to **83** much more slowly than **82** does, for the reaction must take place via that higher energy transition state[52].

cis-Perfluoro-1,3,6-heptatriene (**86**) cyclizes at 130 °C to allylcyclobutene **87**, and quantitatively at 250 °C to bicyclo[3.1.1]hept-2-ene **88**[56]. Mercury-sensitized vapor phase photolysis of **86** affords in low yield the highly strained isomers perfluorotricyclo[2.2.1.0^{2,5}]

TABLE 2. Ring opening of cyclobutenes[13]

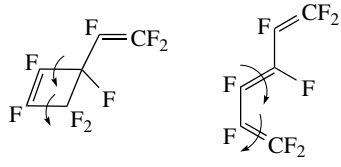
Cyclobutene $\rightleftharpoons$ Diene	ΔH°	ΔS°	K_{eq}(315 °C)
 	−8	4.5	9×10^3
 **(79)**  **(41)**	11.7	9.6	5.6×10^{-3}
 **(80)** 	2.5	6.65	3.3
 **(81)** 	—	—	77.5

heptane (**89**) and perfluorotricyclo[3.1.1.$0^{3,6}$]heptane (**90**), having C_2 and C_{3v} symmetry, respectively.

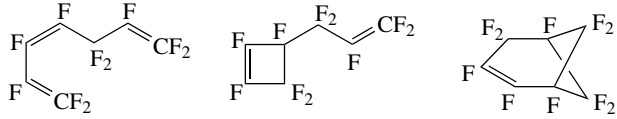


(19)

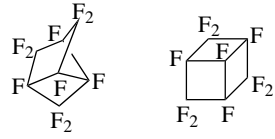
(83) **(82)** **(84)**



(83) **(85)**



(86) **(87)** **(88)**



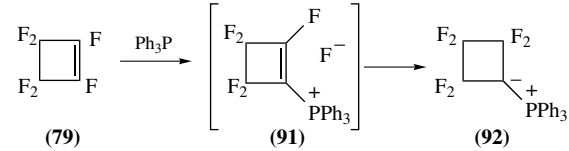
(89) **(90)**

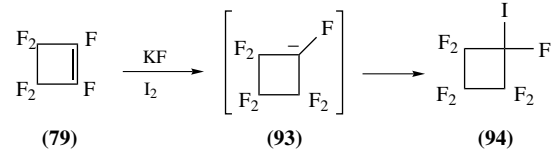
2. Reactions of hexafluorocyclobutene

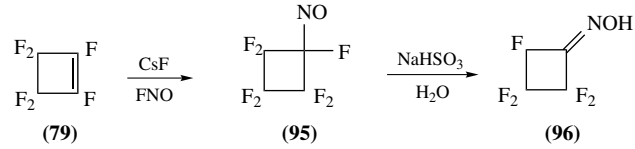
A sampling is presented in Scheme 9. In the first example, nucleophilic attack by triphenylphosphine on hexafluorocyclobutene (**79**) could result either in S_N2' reaction or addition–elimination, but the latter mechanism prevails, giving **91**. The *gem*-difluoro effect inhibits loss of fluoride from the 3-position of **79**. Subsequent formation of a stable ylid (**92**) reflects the ability of β-fluorines to stabilize negative charge[57]. The next reaction is initiated by fluoride ion attack to give anion **93**, which is trapped by iodine to afford **94**[58]. Nitroso derivative **95** is formed analogously[59,60], and is reduced to the oxime (**96**) by aqueous bisulfite[61].

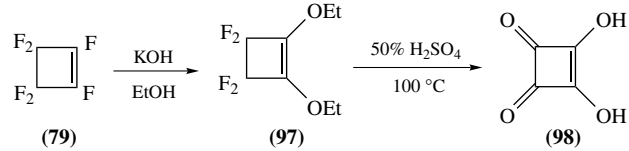
Squaric acid (**98**) was originally prepared by ethoxide attack on **79**, yielding diether **97**, followed by acid hydrolysis[62,63]. Reaction with the bifunctional nucleophile catechol in the presence of base follows a different path, as 5-membered ring formation, and thus S_N2' reaction, is favored stereoelectronically in intermediate **99**, giving spiroketal **100**.

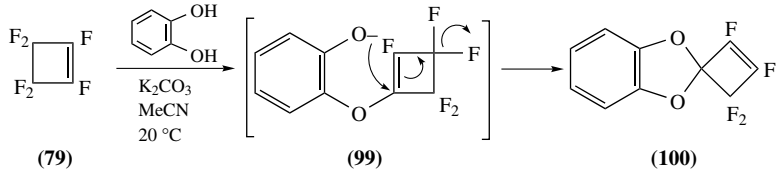
Via nucleophilic attack

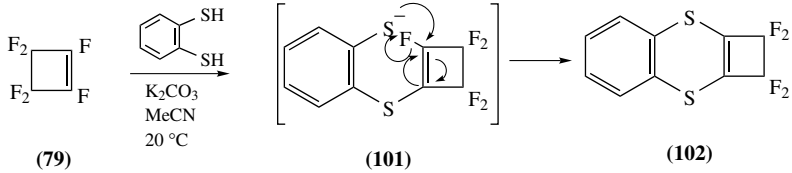


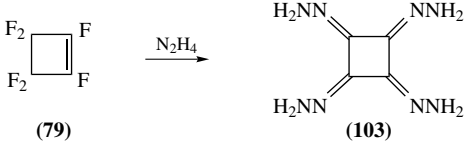




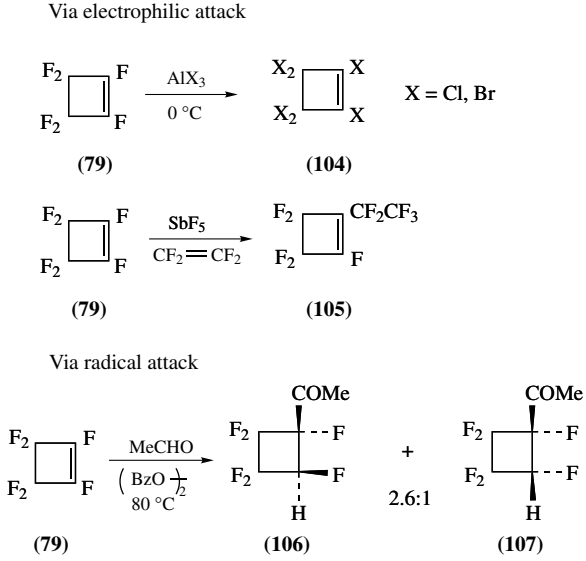








SCHEME 9



SCHEME 9. (*continued*)

Interestingly, dithiocatechol forms a 6-membered ring compound **102** under the same conditions. The thiolate ion in intermediate **101** attacks so as to develop negative charge where it can enjoy some stabilization by sulfur[64]. Treatment of **79** with a large excess of hydrazine gives tetrahydrazone **103**[65]. Whereas squaric acid formation preserves the oxidation state of cyclobutene **79**, the ring in **103** has undergone a 2-electron oxidation. Normally a reducing agent, hydrazine serves here as an oxidant in close analogy to the role of phenylhydrazine in osazone formation[66].

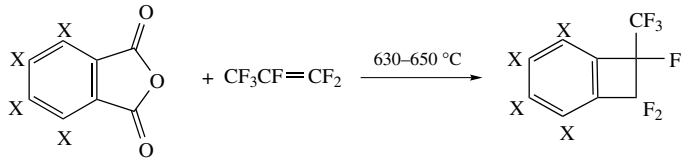
Perfluorocyclobutene (**79**) is also susceptible to attack by Lewis acids. Both aluminum chloride and bromide replace all of the fluorines of **79** to give hexahalides **104** under mild conditions[67], presumably by repetitive ionization of allylic fluorine and quenching of the resulting allylic cation with tetrahaloaluminate ion. The reaction is driven by the exceptional strength of the aluminum–fluorine bond[68]. Antimony pentafluoride effects perfluoroalkylation of **79** with tetrafluoroethylene, yielding **105**[69].

Fluorinated cyclobutenes are also susceptible to free radical addition reactions, as exemplified by the addition of acetaldehyde to **79** initiated by benzoyl peroxide or γ-radiation. A stereoisomeric mixture of ketones **106** and **107** is produced[70,71]. Other reactions of monocyclic cyclobutenes will appear in subsequent sections.

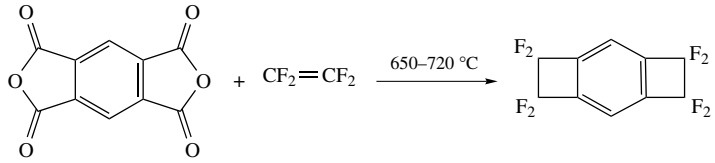
B. Benzocyclobutenes

High temperature pyrolysis of phthalic anhydrides in the presence of fluoroalkenes produces fluorinated benzocyclobutenes, presumably via benzynes. For example, anhydrides **108** (X = H, F) react with hexafluoropropene (**109**) to give benzocyclobutenes **110** (X = H, F) (Scheme 10)[72]. The reaction also works with pyromellitic anhydride (**111**) and tetrafluoroethylene, yielding the doubly annellated product **112**[73]. Treatment of perfluorobenzocyclobutene (**113**) with antimony pentafluoride generated benzylic cation **114**, which was characterized by its ^{19}F NMR spectrum. Quenching with water gave the cyclobutanone **115**, and reaction with tetrafluoroethylene afforded the perfluoroalkylation

product **116** (equation 20)[74]. When **113** was allowed to react with both antimony pentafluoride and bromine, ring opening resulted, giving **117**. A likely pathway is shown in equation 21[75]. Subjection of **110** (X = F) to the action of antimony pentafluoride at 95 °C yielded perfluoroindane (**118**). The authors favor the mechanism given in equation 22[76].

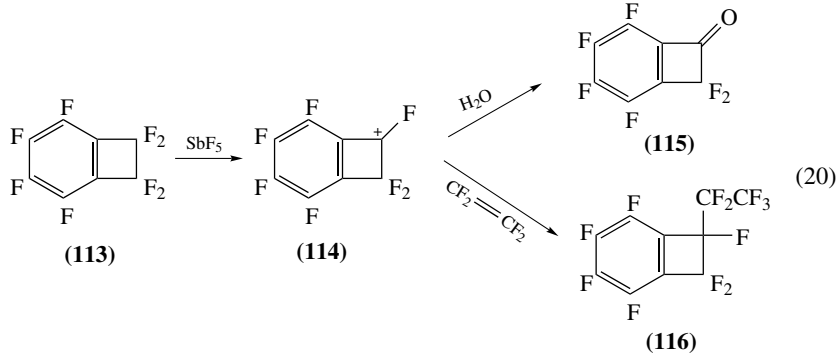


(108) X = H, F **(109)** **(110)** X = H, F

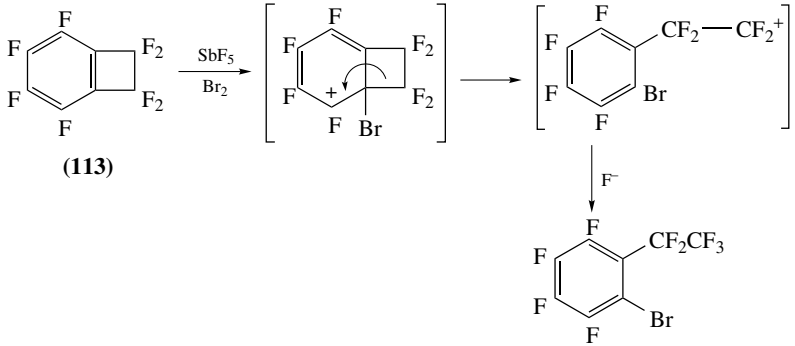


(111) **(112)**

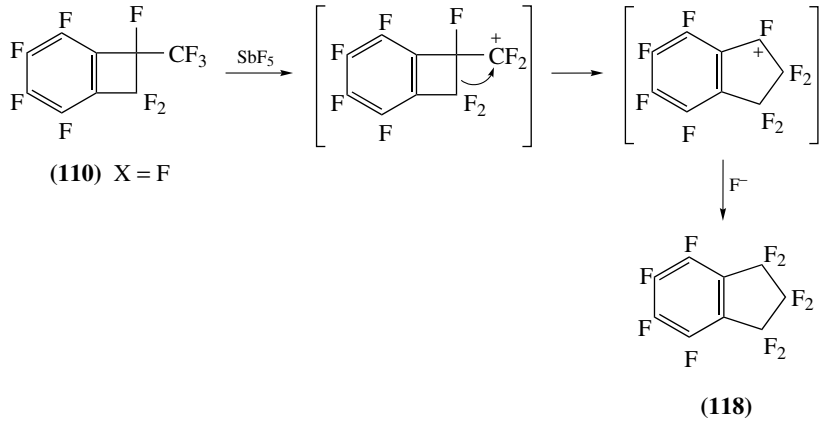
SCHEME 10



(113) **(114)** **(115)** **(116)** (20)



(113) **(117)** (21)



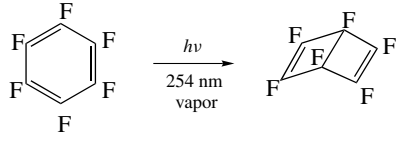
(110) X = F

(118)

(22)

C. Dewar Benzenes

Irradiation of certain benzenes results in cyclization to their Dewar isomers, and fluoro substituents promote this transformation. Several polyfluoro Dewar benzenes have been prepared and the kinetics of their thermal rearomatization have been investigated[77–80]. By far the most thoroughly studied example is hexafluoro Dewar benzene (**120**), which can be obtained in excellent yield by vapor phase irradiation of the benzene (**119**) at 254 nm (equation 23)[81,82]. Its half-life for reversion to **119** at 80 °C is 79 min[83]. Some representative reactions of **120** are shown in Scheme 11. In the photoinduced addition of HBr, bromine atom attack is cleanly *exo*, presumably for steric reasons, but the subsequent hydrogen abstraction reaction takes place on both faces of the molecule to give **121** and **122**. Bromine adds to **120** spontaneously, again yielding a mixture of *exo,exo* and *exo,endo* adducts (**123**). Light-induced addition of a second equivalent of bromine occurs exclusively with *exo,exo* stereochemistry, giving **124**, because of the hindrance on the *endo* face resulting from the initial addition[84]. Like other nucleophiles, methyllithium undergoes addition–elimination reactions with **120**, producing **125** and **126**. Aluminum chloride selectively replaces the bridgehead fluorines with chlorines to give **127**, apparently via somewhat distorted pentadienyl cations[85]. Dewar benzene **120** is a reasonably good dienophile, as illustrated by pyrrole's first Diels–Alder reaction[86]. The 1:1 adduct **128** reacts slowly with pyrrole at RT to afford 2:1 adduct **129**. Diene **120** also undergoes 1,3-dipolar cycloadditions, as exemplified by its reaction under mild conditions with phenyl azide to yield **130**. Photolysis of **130** affords aziridine **131**, and the 2:1 adduct of the azide with **120** reacts analogously[87].

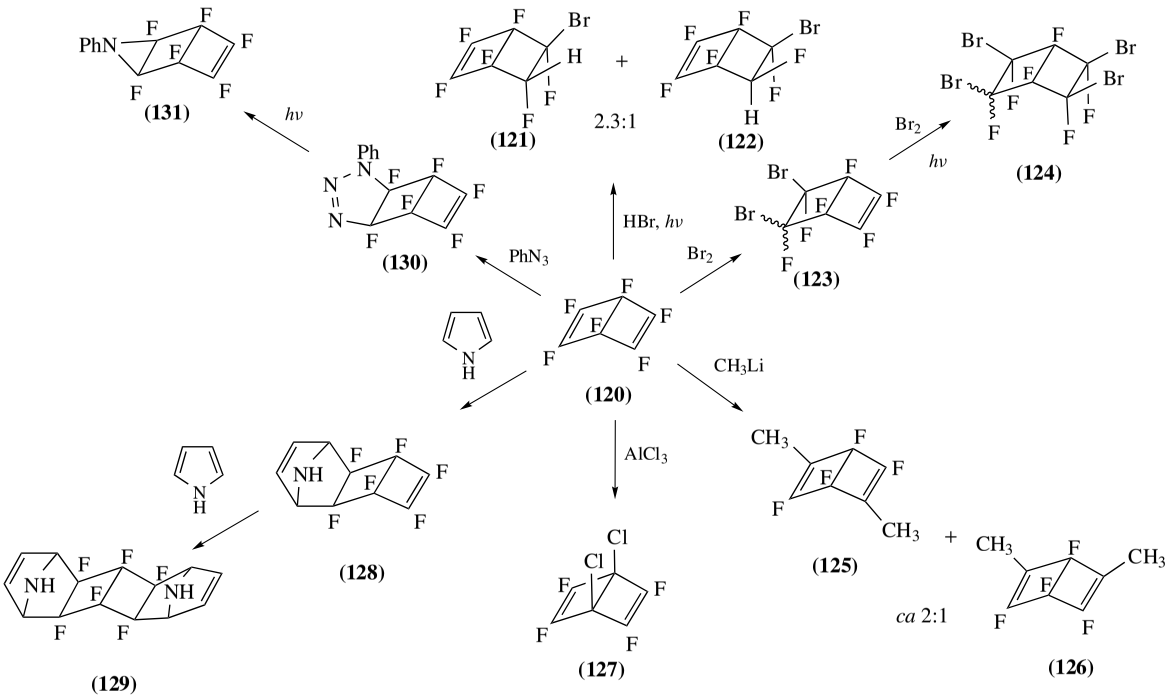


(119) **(120)**

90%

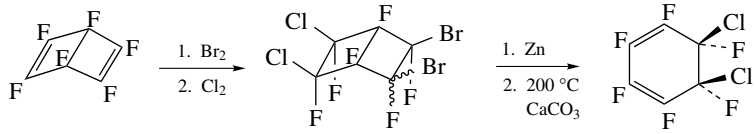
(23)

Though vulnerable to assault by strong nucleophiles and reducing agents, hexafluorobenzene (**119**) is quite inert to electrophiles and oxidants. For this reason, a synthon


(131)
hv
(121)
+
2.3:1
(122)
Br2
hv
(124)
(130)
PhN3
HBr, hv
Br2
(123)
(120)
CH3Li
AlCl3
(128)
(129)
(127)
(125)
+
ca 2:1
(126)

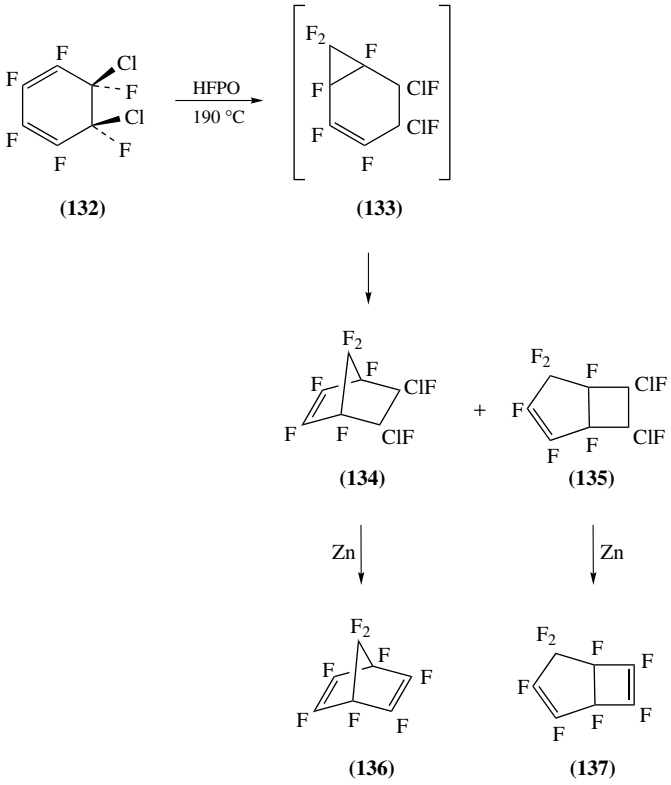
SCHEME 11

was developed for the benzene which was far more reactive. This synthon, *cis*-5,6-dichlorohexafluorocyclohexa-1,3-diene (**132**), was synthesized from **119** in five steps via **120** with an overall yield of 65% (equation 24)[88,89]. Bromination of **120** served to protect one of the double bonds and for steric reasons to force the subsequent chlorination to proceed cleanly in *cis,exo* fashion, as described above. Deprotection followed by thermal ring opening gave **132**.



(120) (132) (24)

When **132** was heated with hexafluoropropylene oxide (HFPO), a high temperature source of difluorocarbene, cyclopropanation occurred giving **133**, but this adduct suffered vinylcyclopropane rearrangement in two ways under the reaction conditions (Scheme 12). Cleavage of the allylic cyclopropane bond proximal to the geminal fluorines led to norbornene **134**, while cleavage of the distal bond gave bicyclo[3.2.0]heptene **135**. Their

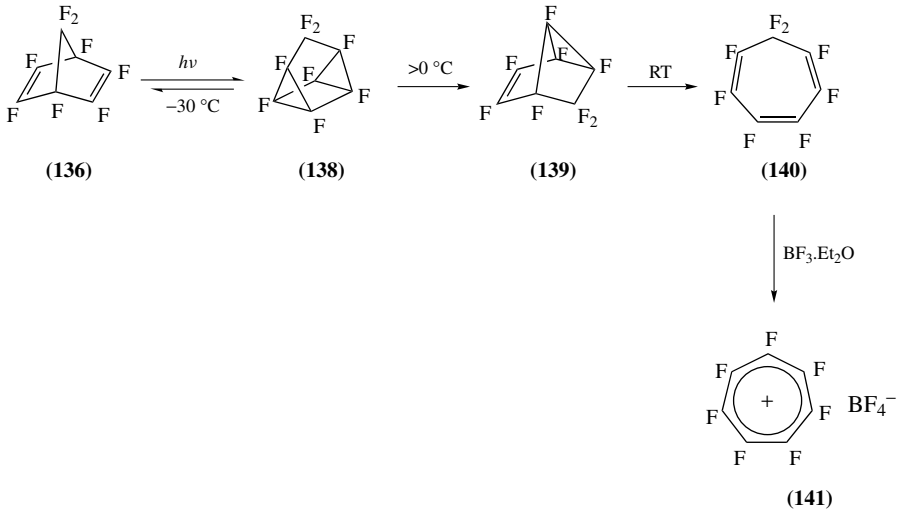


(132) (133) (134) (135) (136) (137)

SCHEME 12

formation in equal amount represents a standoff between two influences: better overlap of the proximal bond with the π orbital, and selective weakening of the distal bond[90] by the geminal fluorines. Reduction with zinc afforded dienes **136** and **137**[91].

Ultraviolet irradiation of the norbornadiene **136** at $-30\,^{\circ}C$ produced a photostationary composition rich in quadricyclane **138**, but at temperatures above $0\,^{\circ}C$ **138** rearranged spontaneously in the dark to perfluorotricyclo[3.2.0.0^{2,7}]hept-3-ene (**139**) (Scheme 13). Warmed to RT, **139** ring opened to perfluorotropilidene (**140**)[92,93]. Brief treatment of this triene with boron trifluoride etherate extracted a fluoride ion, yielding the perfluorotropylium ion (**141**). The surprising lability of **138** and **139** reflects the great strain energy of fluorinated cyclopropanes[1]. In addition to making ion **141** available, synthon **132** opened the way to perfluorobarrelene[94] and provided a superior route to perfluorotropone[89].



(136) **(138)** **(139)** **(140)** **(141)**

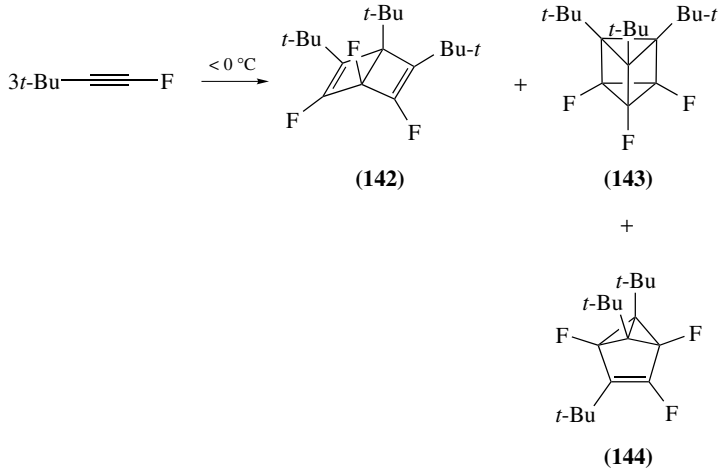
SCHEME 13

A novel synthesis of benzene valence isomers was discovered when *t*-butylfluoroacetylene spontaneously trimerized below $0\,^{\circ}C$, yielding the highly strained compounds **142–144** (equation 25)[95]. Their formation reflects the driving force for increased p character in C–F bonds (Bent's rule[6]) and perhaps also repulsion between fluorine lone pairs and the π orbitals of the acetylene[68].

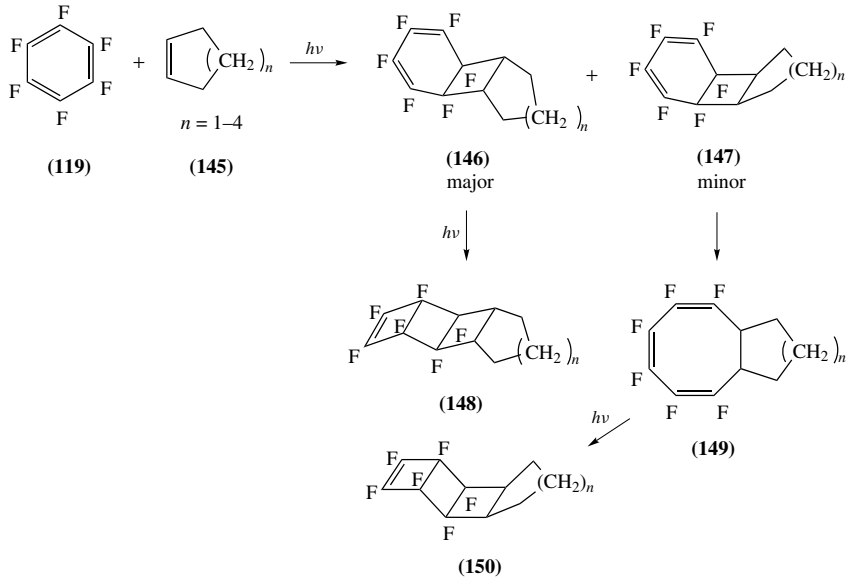
D. Hexafluorobenzene–Alkene Cycloadducts

Photocycloaddition of hexafluorobenzene (**119**) to cycloalkenes **145** in cyclohexane solution gives *anti* (**146**) and *syn* (**147**) [2 + 2] adducts (Scheme 14)[96]. The former are thermally stable compounds that photocyclize to **148** upon further irradiation. *Syn* adducts **147** spontaneously ring open at RT to cyclooctatrienes **149**, probably assisted by relief of

nonbonded repulsion between the outer rings. Irradiation of the trienes results in stereoselective cyclization to give tetracycles **150**, a surprising result.



(25)

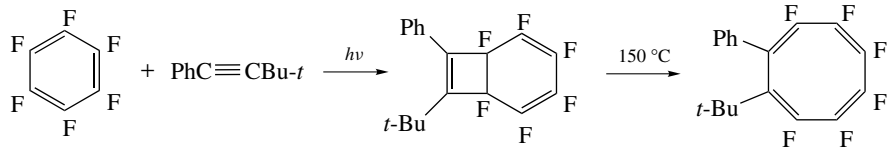


SCHEME 14

1,3-Photocycloaddition to **119** can also occur with cycloalkenes and can even predominate over 1,2-photocycloaddition, for example with cyclooctene[97]. Since this reaction

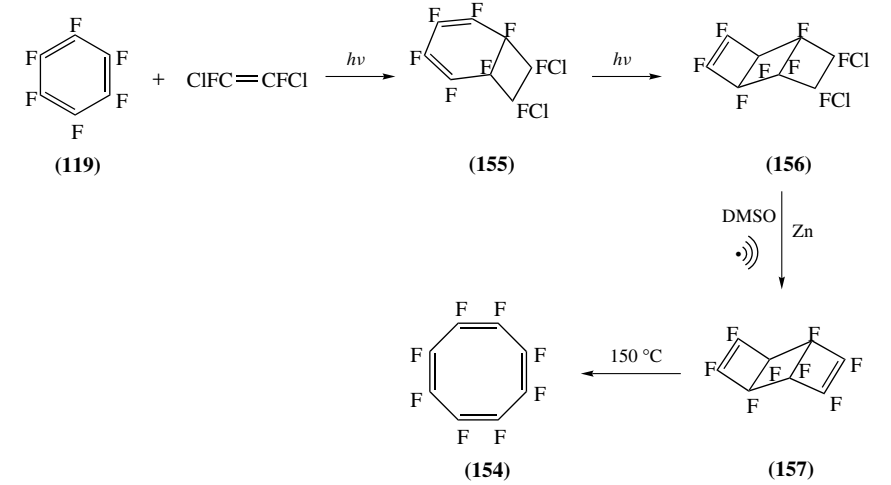
mode is favored by absence of solvent and by high alkene:benzene ratios, it may proceed via ground-state complexation of alkene with the benzene.

Alkynes, too, are capable of photocycloaddition to **119**, as illustrated with *tert*-butylphenylacetylene (**151**) in equation 26[98]. Upon heating, bicyclooctatriene **152** ring opens to a cyclooctatetraene that, for steric reasons, undergoes bond-shift isomerization to give **153**.



(119) **(151)** **(152)** **(153)** (26)

A variety of haloalkenes cycloadd to **119** under UV irradiation[99,100], and a good route to octafluorocyclooctatetraene (**154**) is based on this reaction (Scheme 15)[82,101]. The initially formed adducts **155** photocyclize under the reaction conditions to yield a stereoisomeric mixture of *anti*-tricyclo[4.2.0.0^{2,5}]oct-3-enes **156**. Ultrasound-assisted reductive dechlorination yields *anti*-tricyclo[4.2.0.0^{2,5}]octa-3,7-diene **157**, which opens cleanly upon heating to the tetraene **154**.

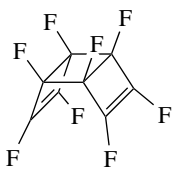


(119) **(155)** **(156)** **(157)** **(154)**

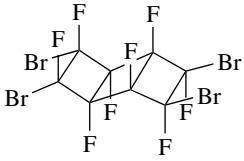
SCHEME 15

Irradiation of **154** regenerates **157** together with 5% of its *syn* isomer **158**. The two are easily distinguished by treatment with bromine, as **157** readily forms tetrabromide **159** while **158** gives **160** and refuses to react with a second equivalent. If bromine were to add to **160**, severe nonbonded repulsion would result on the *endo* face of the molecule. Steric interactions also explain the exclusive *exo,cis* stereochemistry of both bromides **159** and **160**[102].

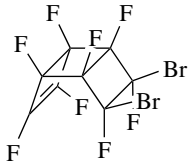
Dibromide **161** opened at 160 °C to an *endo,cis/exo,cis* mixture of dienes **162**. Debromination at 0 °C and 0.05 Torr gave in a cold trap the very labile perfluorobicyclo[4.2.0]octa-2,4,7-triene (**163**) (equation 27). This triene opened to tetraene **154** at 0 °C with a half-life



(158)

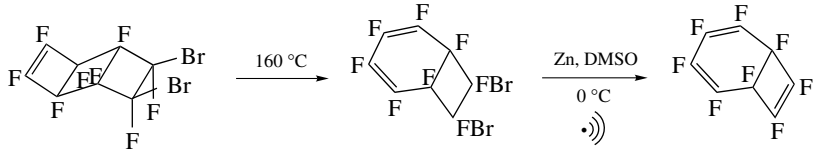


(159)



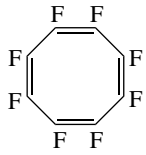
(160)

of 14 min ($E_a = 18.9 \pm 0.6$ kcal mol^{-1}, $A = 1.1 \times 10^{12}$)[103], behavior essentially indistinguishable from that of the parent hydrocarbon[104]. At 20 °C there is 0.3% of **163** in equilibrium with **154**[99] as compared with 0.01% at 100 °C for the parent bicyclo[4.2.0]octa-2,4,7-triene[105].



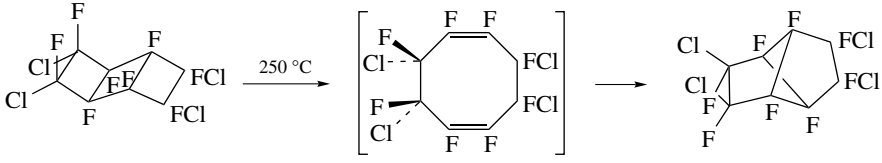
(161) **(162)** **(163)**

(27)



(154)

Chlorination of **156** yielded tetrachloride **164**, which rearranged at 250 °C via cyclooctadiene **165** to the twisted tricyclo[3.3.0.0^{2,5}]octane **166** (equation 28)[106]. This transformation is reminiscent of the thermal isomerization of **45**, the perfluorinated analogue of **164**, to tricyclo[3.3.0.0^{2,5}]octane **46**. The hydrocarbon parent of **166** ring opens thermally to 1,5-cyclooctadiene, just the reverse of the **165** → **166** cyclization[107].

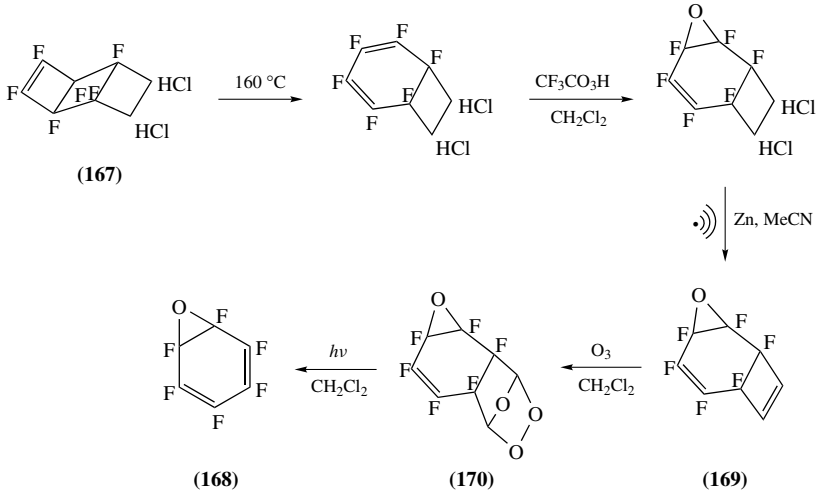


(164) **(165)** **(166)**

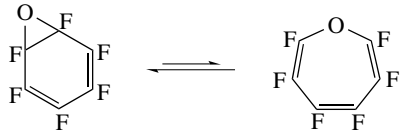
(28)

Cycloadduct **167** of 1,2-dichloroethylene with hexafluorobenzene (**119**) has made available hexafluorobenzene oxide (**168**) (Scheme 16)[108]. Thermal ring opening of the stereoisomeric mixture **167**, epoxidation and dechlorination gave diene **169**. Selective ozonation of

the more electron-rich double bond of **169** followed by photolysis of *exo/endo* ozonides **170** yielded perfluorobenzene oxide (**168**). Variable temperature ^{19}F NMR behavior revealed that **168** exists in dynamic equilibrium with its oxepin valence isomer **171**, but the oxepin was not directly detected and the equilibrium favors **168** very heavily (equation 29). For comparison, the parent benzene oxide–oxepin equilibrium is quite evenly balanced[109, 110].



SCHEME 16

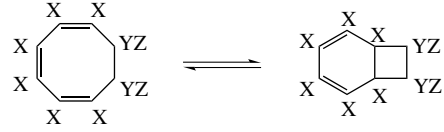


(29)

Photocycloaddition of alkenes to hexafluorobenzene has led to other cyclooctatrienes and -tetraenes, and their electrocyclic equilibria with bicyclic valence isomers have been studied. Table 3 shows that substitution of fluorines for the hydrogens on the triene moiety of 1,3,5-cyclooctatriene has little effect on the isomerization equilibrium, but that fluorine substitution at the 7- and 8-positions shifts the equilibrium strongly toward the bicyclooctadiene form[111].

Replacement of a fluorine in octafluorocyclooctatetraene (**154**) with an alkoxy group has a striking effect on its equilibrium with the bicyclooctatriene[112, 113]. As noted above, K_{eq} for the perfluoro system is 0.003 at 20 °C (acetone-d_6), but Table 4 shows much larger values for some alkoxy derivatives and the values increase with both the electron density at oxygen and solvent polarity. In principle, cyclization of the tetraene **172** could place the alkoxy group at any position in the bicyclic form, thus giving four isomers, but only 7-substituted derivatives **173** are observed. Introduction of a second methoxy group vicinal to the first gave the 7,8-dimethoxybicyclooctatriene, and none of the monocyclic isomer was detected. Vinylogous negative hyperconjugation, in which an oxygen lone pair interacts via the 7,8-π bond with a bridgehead C–F σ^* orbital, may be responsible in part for the effect of alkoxy substitution, but the phenomenon is not fully understood.

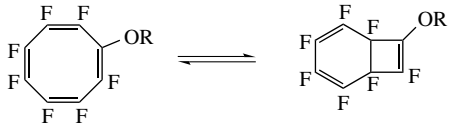
TABLE 3. Equilibrium constants for 1,3,5-cyclooctatriene-2,4-bicyclo[4.2.0]octadiene systems



System	K_{eq} (100 °C)
X = Y = Z = H[a]	0.14
X = F, Y = Z = H[b]	0.043 ± 0.002
X = F, Y = H, Z = F (*cis*)[b]	1.23 ± 0.02
X = F, Y = Z = F[c]	180 ± 5

[a] R. Huisgen, G. Boche, A. Dahmen and W. Hechtl, *Tetrahedron Lett.*, 5215 (1968).
[b] Measured in 4:1 *o*-dichlorobenzene/dodecane-d_{26}.
[c] Neat liquid.

TABLE 4. Equilibrium constants for alkoxy-substituted cyclooctatetraene-bicyclo[4.2.0]octa-2,4,7-triene systems



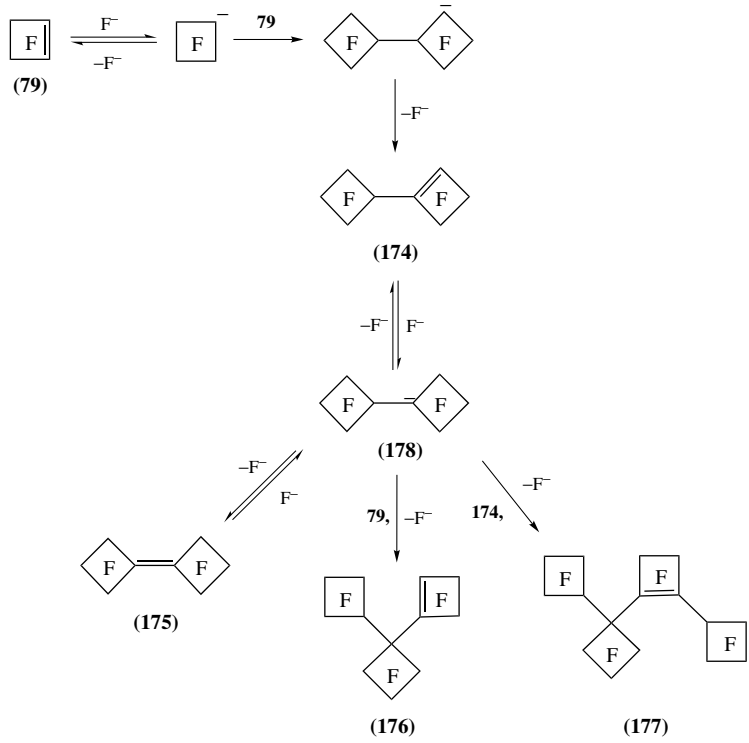
(172) **(173)**

R	K_{eq} (20 °C)	
	CCl_4	DMSO
$CH(CF_3)_2$	small	0.08
CH_2CF_3	0.14	0.35
$CHMe_2$	0.94	2.86
Me[a]	1.0	

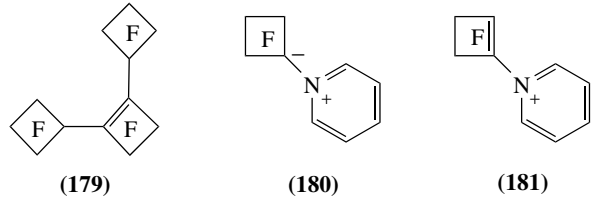
[a] In $CDCl_3$.

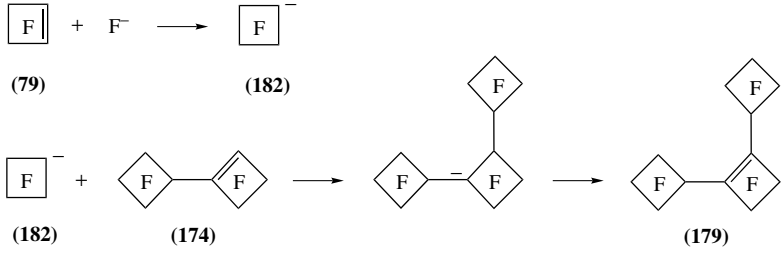
E. Hexafluorocyclobutene Oligomers

Treatment of hexafluorocyclobutene (**79**) with cesium fluoride in DMF at RT results in the formation of a trimer (**176**, 67%), a mixture of two dimers (**174, 175**, 21%) and a tetramer (**177**, 8%) (Scheme 17)[114]. Intermediate tertiary carbanion **178** is observable and quite stable[115]. When **79** is allowed to react with pyridine at RT, dimers **174** and **175** are again obtained, but this time accompanied by a new trimer **179**. The authors attribute the difference in reaction course to substitution of ylid **180** for fluoride ion as nucleophile in the reaction cascade, but the mechanism for elimination of pyridine from intermediate species might be regarded as problematic. A possible alternative explanation is that the ylid is insufficiently nucleophilic to react, that fluoride ion resulting from attack of pyridine on **79** is again the nucleophile, that the **178** → **176** step in Scheme 17 fails to occur for steric reasons because tertiary carbanion **178** exists as a tight ion pair with a very bulky counterion **181**, and that **179** is formed from **182** and **174** as shown in Scheme 18.



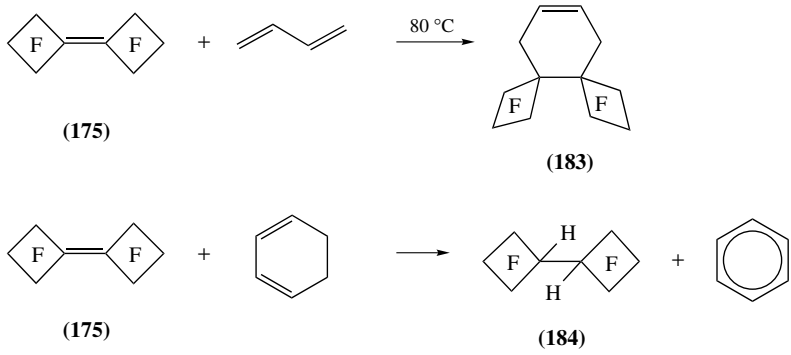
SCHEME 17





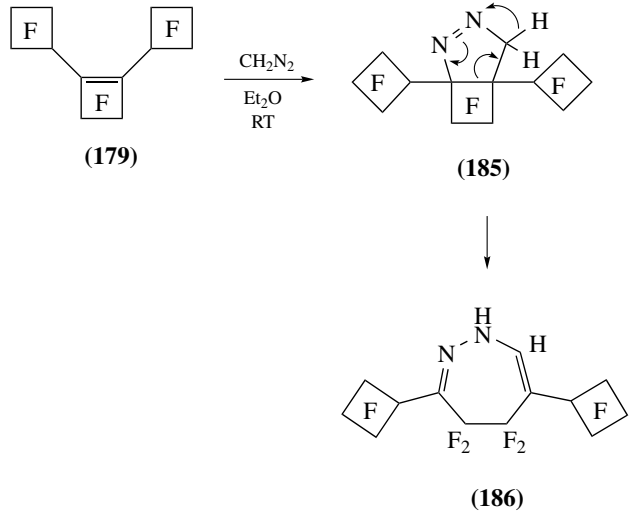
SCHEME 18

As a result of its ring strain, and perhaps for steric reasons as well, dimer **175** is far more reactive than other tetrasubstituted perfluoroalkenes. Diels–Alder addition to butadiene takes place at 80 °C to give **183**, but with 1,3-cyclohexadiene diatropic rearrangement occurs, yielding benzene and dihydro compound **184** (Scheme 19)[116].



SCHEME 19

Diazomethane undergoes 1,3-dipolar cycloaddition to trimer **179** at RT, and the adduct **185** spontaneously rearranges to diazacycloheptadiene **186** (equation 30)[117].

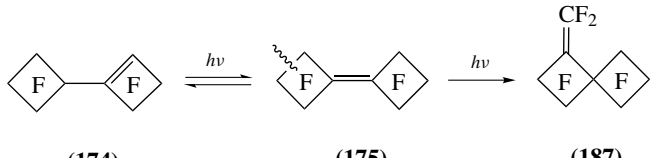


(30)

Photolysis of dimer **174** results in a reversible [1,3] sigmatropic shift of fluorine to give **175**. While fluoride shifts are generally mediated by fluoride ion, that possibility was ruled out here. Dimer **175** then suffered photorearrangement to spiroalkene **187** (equation 31)[118].

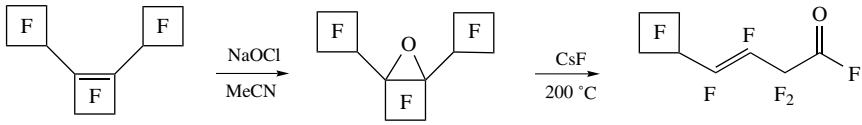
Trimer **179** was epoxidized with sodium hypochlorite to afford **188**, which fragmented upon treatment with cesium fluoride at 200 °C into acyl fluoride **189** and cyclobutene **79**. A suggested mechanism for the latter step is given in Scheme 20[119].

Treatment of a mixture of dimers **174** and **175** with sodium amalgam produces diene **190**. Fluoride ion dimerizes **190** at RT, giving the conjugated triene **191** (Scheme 21). Diene **190** also forms an isolable ylid with pyridine (**192**) and undergoes a series of addition–elimination reactions, e.g. with pyrrole to yield **193** (Scheme 22)[120].



(31)

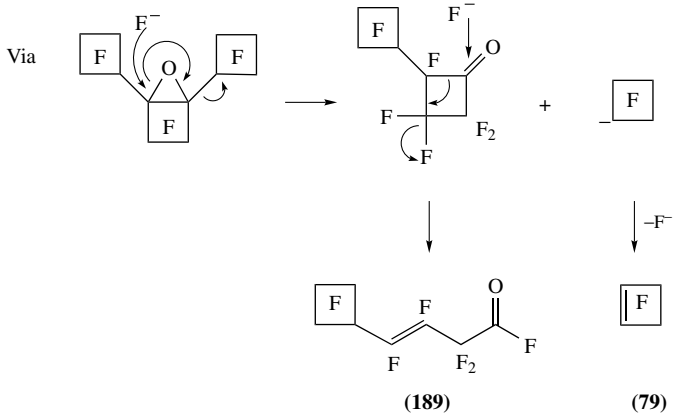
(174) **(175)** **(187)**



(179) **(188)** **(189)**

\+

(79)

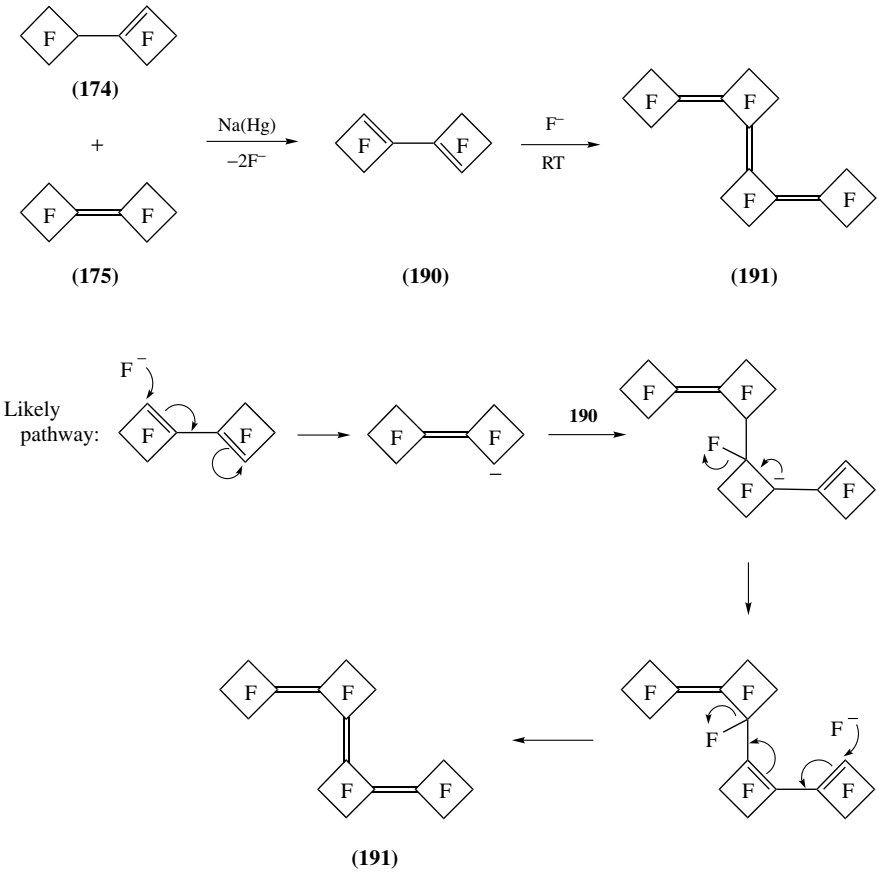


(189) **(79)**

SCHEME 20

F. 'Tetrafluorocyclobutyne Oligomers'

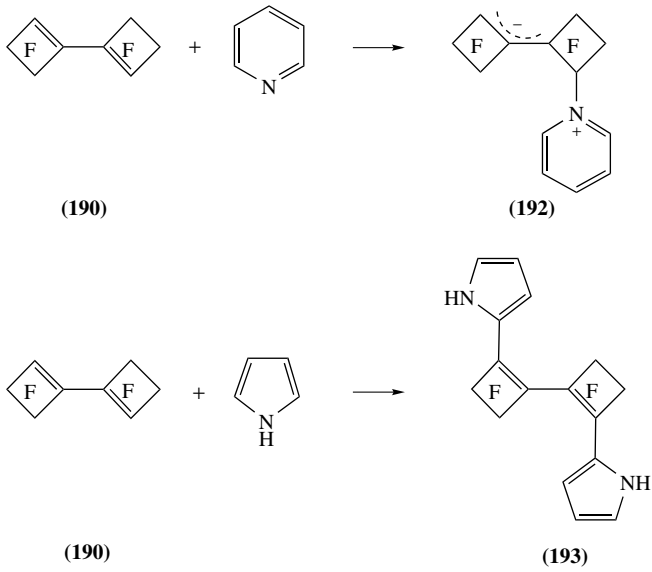
1,2-Diiodotetrafluorocyclobutene (**194**) undergoes a remarkable reductive oligomerization reaction when heated with copper, producing both the colorless benzene **195** and



SCHEME 21

deep red cyclooctatetraene **196** (equation 32)[121]. Although these products are formally oligomers of the extremely strained tetrafluorocyclobutyne (discussed below), that species is surely not an intermediate in the reaction. The benzene ring of the trimer **195** has bond lengths and angles virtually indistinguishable from those of benzene itself[122]. In contrast to the tub-shaped parent hydrocarbon, **196** is a planar molecule, both in the crystalline state[123] and apparently also in the gas phase[124]. As a consequence of the presence of many fluorines, the first ionization energies of both **195** and **196** are much higher than those of benzene and cyclooctatetraene, respectively[124]. Calculations reveal that despite strong bond alternation ($\Delta r = 8$ pm) there is a robust paramagnetic ring current in the 8-membered ring of **196**, as befits an antiaromatic species[125].

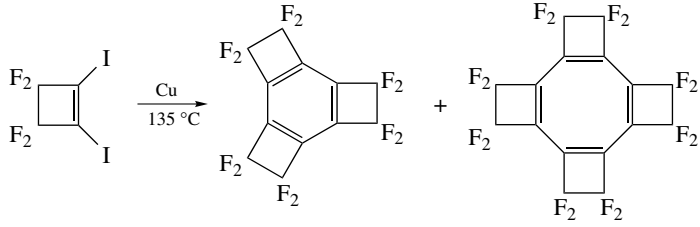
Tetraene **196** is a powerful oxidant as indicated by its two reversible reduction potentials at 0.79 and 0.14 V vs SCE, the first of which is >2.3 V positive of that of cyclooctatetraene (COT). The rate constant for electron transfer in that step is also more than an



(190) **(192)** **(190)** **(193)**

SCHEME 22

order of magnitude faster than that for COT, a reflection of the fact that COT must flatten prior to transfer[126]. Just contact of a DMF solution of the tetraene with mercury suffices to produce a stable radical anion which persists in air. Together with the electrochemical data, spectra of charge-transfer complexes it forms with a series of methylated benzenes and naphthalenes led to an estimate of the electron affinity of **196**: 3.4 ± 0.2 eV, one of the highest values known for a neutral organic molecule[127].



(32)

(194) **(195)** **(196)**

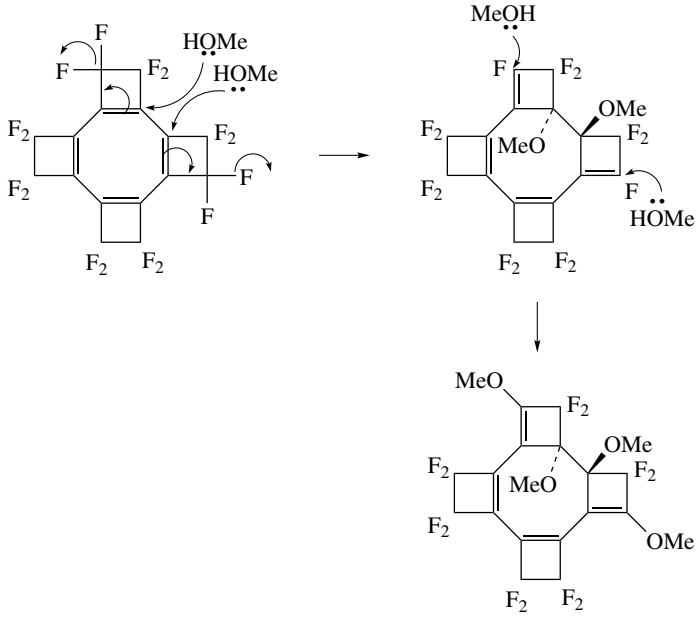
When dissolved at RT in excess methanol, **196** forms an intensely blue charge-transfer complex which quickly fades to a yellow-brown solution. Evaporation of the solvent and sublimation of the residue gives bright yellow crystals of tetramethoxy derivative **197** (equation 33)[121].

G. Octafluorobicyclo[2.2.0]hex-1(4)-ene

1. Synthesis

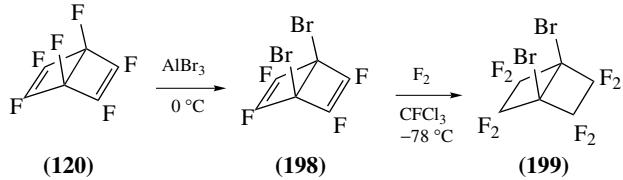
Aluminum bromide transforms hexafluoro Dewar benzene (**120**) into bridgehead dibromide **198**, and low temperature fluorination saturates the double bonds to yield **199**, a direct

precursor for the highly strained alkene **59** (equation 34). Although the corresponding diiodide **200** cannot be synthesized analogously to **199**, it can be obtained from that dibromide via a 'photo-Finkelstein' reaction[45,46]. Upon irradiation iodide ion undergoes a CTTS (charge transfer to solvent) transition, and the solvated electrons effect C−Br bond cleavage, thus allowing the formation of C−I bonds.

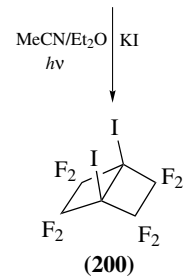


(33)

(197)



(120) **(198)** **(199)**

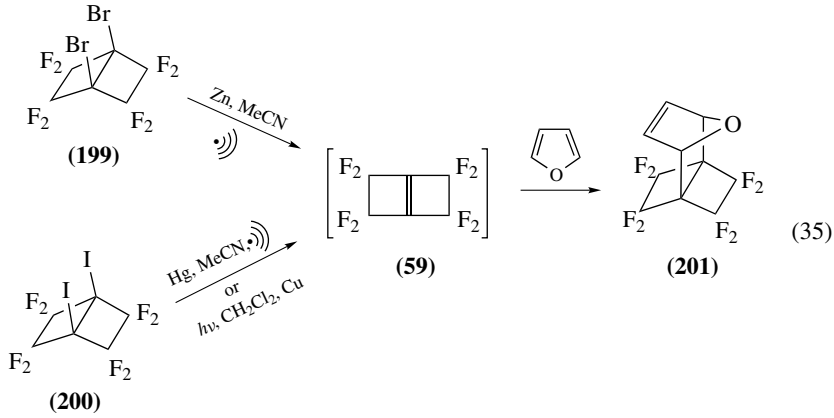


(34)

(200)

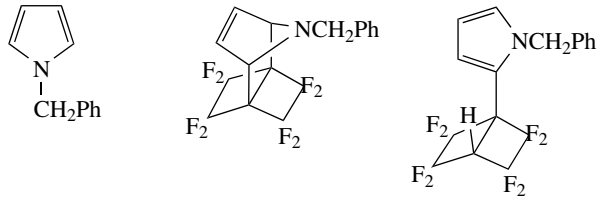
Treatment of dibromide **199** with zinc in acetonitrile at RT with the assistance of ultrasound generates alkene **59** efficiently, as indicated by high yields of trapping products

such as the Diels–Alder adduct with furan (**201**). The alkene can be produced under gentler conditions from the diiodide; simply layering an acetonitrile solution of **200** over a pool of mercury in an ultrasonic bath results in smooth generation of **59**. Ultraviolet irradiation of the diiodide in the presence of copper as an iodine scavenger is also effective, and this method led to the first direct observation of the alkene (equation 35)[128].



(35)

The method of choice for preparing **59** is via *retro*-Diels–Alder reaction of its adduct (**203**) with *N*-benzylpyrrole (**202**). As an electron-rich diene, **202** traps the alkene very efficiently, its aromaticity facilitates the *retro*-reaction and its lack of volatility makes separation from the alkene easy. The cycloelimination occurred readily in solution at *ca* 140 °C, but the principal product was the rearranged adduct **204**. This compound had to arise either via intramolecular rearrangement or via *retro*-Diels–Alder reaction followed by electrophilic substitution of the alkene on the pyrrole.

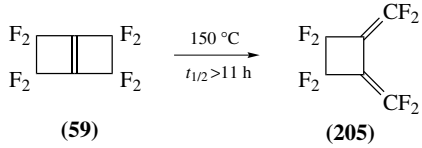


To distinguish between these alternatives, the reaction was run in the presence of a large excess of furan, and the result was a high yield of furan adduct **201** unaccompanied by any **204**. Therefore, **204** had formed via the intermolecular (*retro*-Diels–Alder) pathway despite every effort to remove the volatile alkene **59** from the reaction mixture as it was generated in an evacuated system. Flash vacuum pyrolysis (FVP) provided the solution to this problem by keeping the reaction products apart. FVP of adduct **203** was carried out at 275 °C, the pyrrole was caught in a 0 °C trap and the alkene was collected in a −196 °C trap. Essentially pure alkene was obtained in 85% yield[128]. The molecule

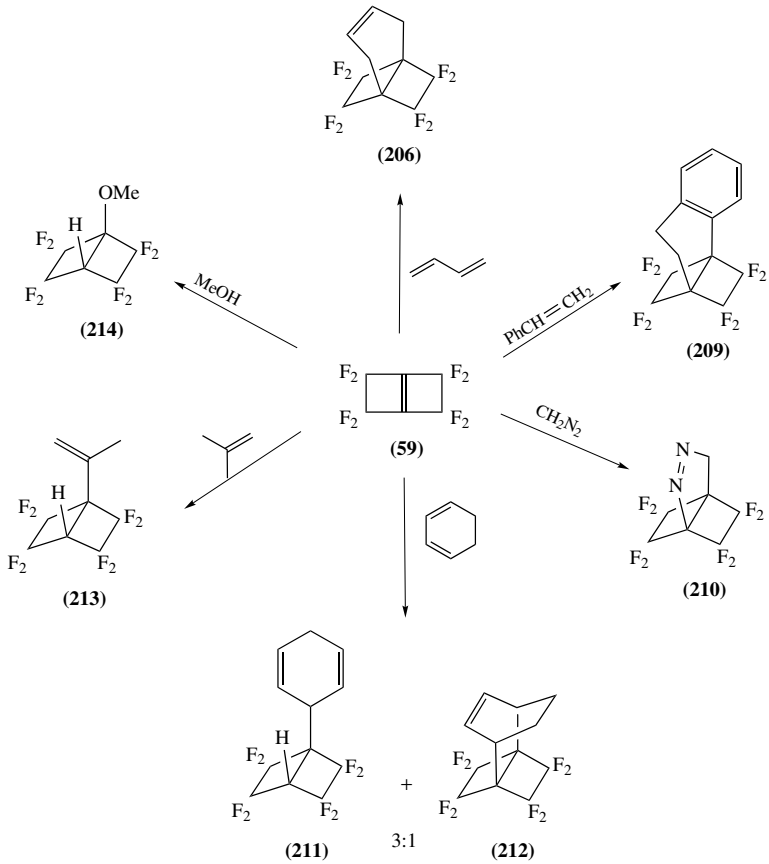
is planar with D_{2h} symmetry, as shown by an electron diffraction study and density functional calculations[129].

2. Reactions

The hydrocarbon parent of alkene **59** is an extremely labile compound that dimerizes and polymerizes readily below 0 °C[130]. In contrast, **59** is remarkably robust despite its great ring strain. It undergoes electrocyclic ring opening to diene **205**, the tetrafluoroallene dimer, but the half-life for the reaction at 150 °C exceeds 11 h (equation 36)[47].

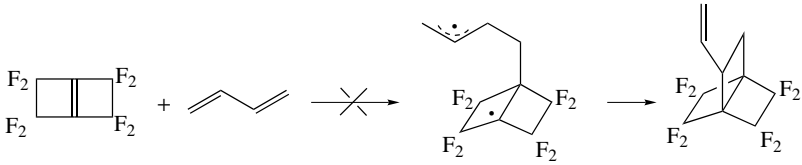


(36)



SCHEME 23

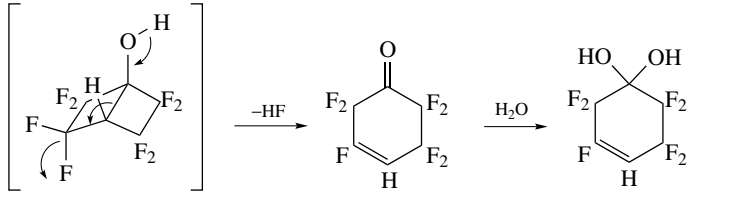
Cycloaddition reactions of alkene **59** leading to [2.2.2]propellanes were discussed in Section I.D.2. A further sampling of the chemistry of **59**, all carried out at RT, is presented in Scheme 23[128]. Among its many Diels–Alder reactions, that with butadiene is particularly significant mechanistically because formation of the adduct **206** strongly implies a concerted pathway. Since butadiene exists almost entirely in the s-*trans* conformation, stepwise reaction would proceed predominantly via biradical **207**, which should yield the unobserved [2 + 2] adduct **208** (equation 37).



(59) **(207)** **(208)** (37)

Obtaining styrene adduct **209** at RT indicated that **59** is an excellent dienophile, as the first step in its formation required loss of the benzene conjugation. Facile 1,3-dipolar cycloaddition of diazomethane to **59** afforded pyrazoline **210**. 1,3-Cyclohexadiene gave a Diels–Alder adduct (**212**), but the principal reaction course was ene addition, giving diene **211**. Isobutene underwent smooth ene reaction with **59**, yielding **213**, and methanol added in nucleophilic fashion to give **214**.

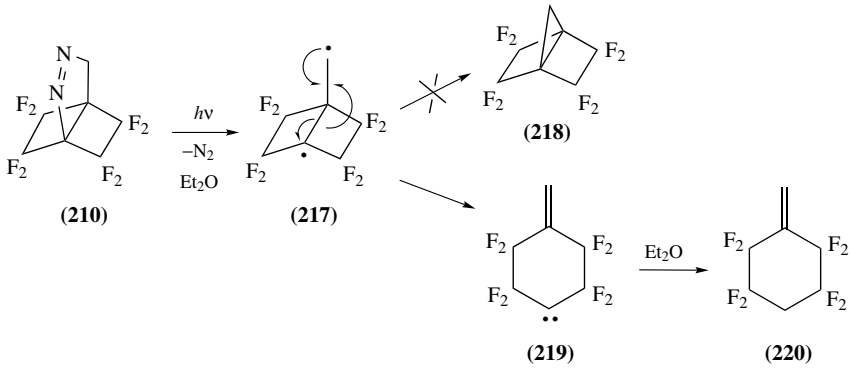
Water adds analogously to methanol, but the initial adduct **215** is not observed because it spontaneously ring opens, affording ultimately cyclohexenone hydrate **216** (equation 38)[45]. Pyrazoline **210** was photolyzed in the hope of obtaining, at least transiently, the exceedingly strained [2.2.1]propellane **218**. The putative intermediate 1,3-biradical **217** chose a more prosaic reaction course, however, cleaving open to carbene **219**, which abstracted hydrogen atoms from the ether solvent to give methylenecyclohexane **220** (Scheme 24).



(215) **(216)** (38)

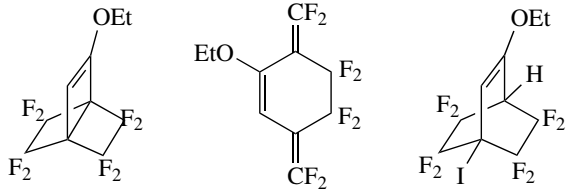
Ethoxyacetylene added in [2 + 2] fashion to **59** to give the first [2.2.2]propellene (**221**). Unlike the surprisingly stable [2.2.2]propellanes described earlier, **221** polymerized rapidly at RT, presumably via triene **222**. Nonetheless, the structure of **221** was established by its ^{19}F NMR spectrum and by trapping it at subambient temperatures as bridgehead HI adduct **223** with tetrabutylammonium iodide in moist acetonitrile[128].

With the exception of its pyrolysis, all of the transformations of **59** described above were performed at RT. The full power of the alkene as a dienophile is manifested in its Diels–Alder reactions with aromatics at elevated temperatures. At 120 °C, **59** reacts smoothly with naphthalene to give **224**, and with durene to give **225** and **226** in the ratio 2.1:1[131]. The predominance of C_2 adduct **225** over the C_{2v} **226** was unanticipated



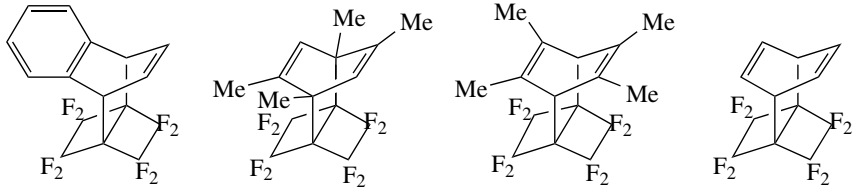
(210) (217) (218) (219) (220)

SCHEME 24



(221) (222) (223)

because Diels–Alder reactions of durene as diene normally occur at the unsubstituted positions[132–135], but nonbonded repulsions between fluorines and methyls is probably greater in the transition state leading to the C_{2v} adduct. Alkene **59** even adds to benzene, affording **227** in 65% yield after 6 h at 120 °C. As the first alkene to form a Diels–Alder adduct with benzene, **59** is clearly one of the most potent dienophiles known.



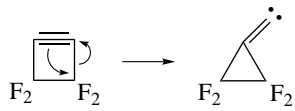
(224) (225) (226) (227)

III. OTHER UNSATURATED CYCLOBUTANES

A. Tetrafluorocyclobutyne

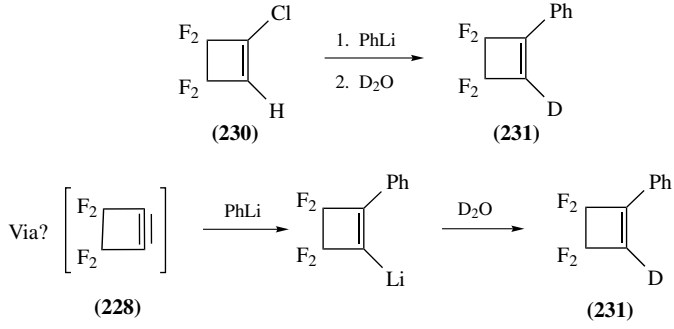
The fearfully strained fluorocarbon tetrafluorocyclobutyne (**228**) is still unknown, and high level *ab initio* calculations indicate that there may be no barrier separating it from the

much more stable tetrafluorocyclopropylidenecarbene (**229**) (equation 39)[136]. Surprisingly, the latter species is calculated to have a strongly bent C_s instead of the expected C_{2v} structure. Addition of an equivalent of hydrogen to the cyclobutyne is calculated to be *ca* 70 kcal mol^{-1} more exothermic than hydrogenation of acetylene to ethylene.



(228) **(229)** (39)

There is some evidence that **228** can exist transiently in solution, however. When chlorocyclobutene **230** was treated with phenyllithium, the chlorine was replaced by phenyl, and workup of the reaction in D_2O yielded **231**[137]. Since treatment of unlabeled **231** with phenyllithium followed by D_2O failed to incorporate deuterium, it is difficult to avoid postulating dehydrohalogenation of **230** to cyclobutyne **228** as the first step of the transformation (Scheme 25).

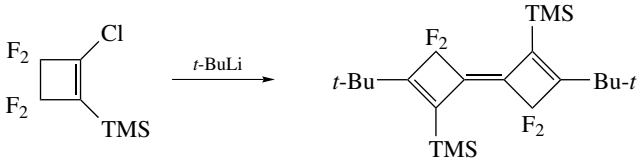


(230) **(231)**

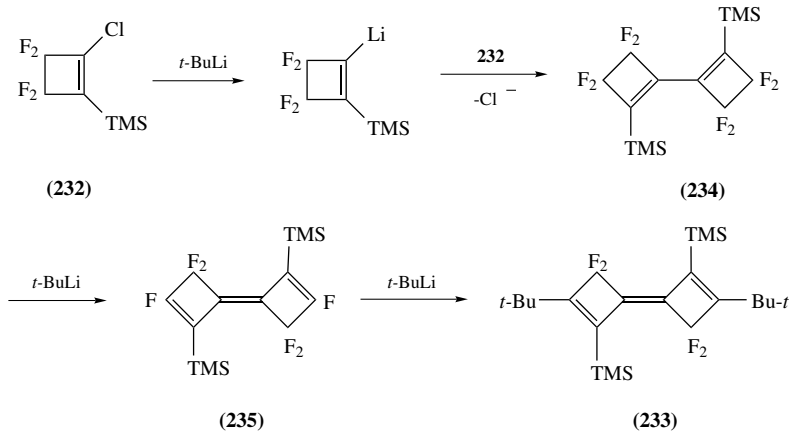
(228) **(231)**

SCHEME 25

An attempt was made to introduce a second TMS group into **232**, as the bis(trimethylsilyl) compound would be a potential precursor for the tetrafluorocyclobutyne radical anion. The result was a good yield of triene **233**, whether or not trimethylsilyl chloride was added (equation 40). The authors propose that this interesting transformation occurred via the pathway shown in Scheme 26. Lithiation of **232** followed by an addition–elimination reaction with starting material yielded diene **234**. Defluorination of the electron-deficient diene by *t*-BuLi, presumably via electron transfer, gave triene **235**. A twofold addition–elimination sequence completed the formation of **233**.



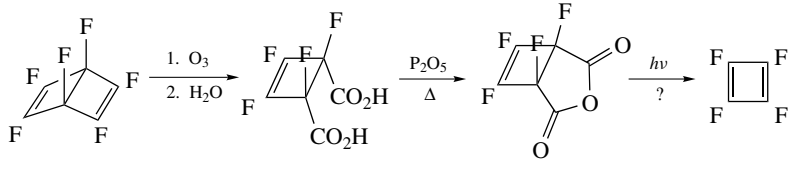
(232) **(233)** (40)



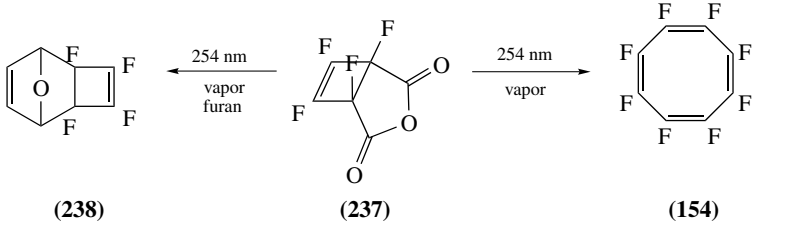
SCHEME 26

B. Tetrafluorocyclobutadiene

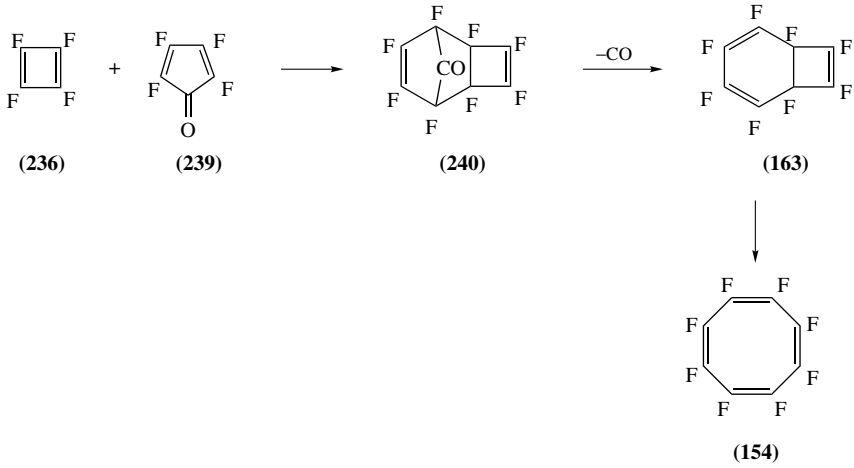
Anhydride **237** was synthesized from hexafluoro Dewar benzene (**120**) as a potential photoprecursor for the labile tetrafluorocyclobutadiene (**236**) (equation 41)[82, 138]. Photolysis of **237** in the vapor phase in the presence of furan yielded **238**, a Diels–Alder adduct that revealed that the cyclobutadiene had been formed (equation 42). In the absence of furan, photolysis at low pressure yielded octafluorocyclooctatetraene (**154**), but it was shown that **154** did not arise by ring opening of cyclobutadiene dimers **157** or **158**[139]. Apparently **154** was produced via cross-dimerization of the cyclobutadiene (**236**) and cyclopentadienone **239** (Scheme 27). Formation of both diene and dienone has been observed in the photolysis of other cyclobutenedicarboxylic anhydrides[140]. Thermal or photochemical decarbonylation of adduct **240** gave the labile triene **163**, which rapidly ring opened to tetraene **154**, as described earlier.



(41)

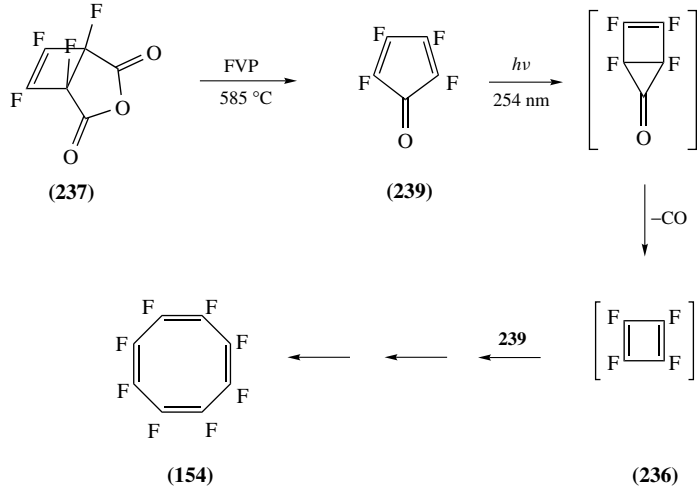


(42)



SCHEME 27

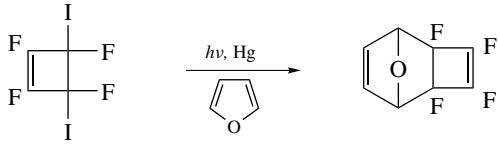
Support for this hypothesis was forthcoming when the reactive orange dienone **239** was prepared by flash vacuum pyrolysis of anhydride **237** and found to yield tetraene **154** when photolyzed in the vapor phase[141]. Presumably the dienone undergoes photodecarbonylation to the cyclobutadiene, and the events depicted in Scheme 27 ensue (Scheme 28).



SCHEME 28

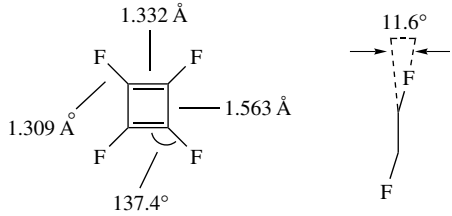
Another source of cyclobutadiene **236** became available when it was found that mercury-sensitized vapor-phase photolysis of tetrafluoro-3,4-diiodocyclobutene (**241**) in the presence of furan afforded Diels–Alder adduct **238** (equation 43)[142]. The cyclobutadiene has been generated from both **237** and **241** in an argon matrix at *ca* 10 K, and both its normal and polarized IR spectra have been measured[143]. Close agreement between the spectra

and calculations at the B3LYP/cc-pVDZ level of theory has established the structure of the diene. Surprisingly, the molecule is nonplanar, with C_{2h} symmetry. The two fluorines on one double bond lie above the plane of the ring and the other two lie below (Figure 1). The unprecedented nonplanarity of a cyclobutadiene lacking bulky substituents is probably attributable to the combination of Bent's Rule[6] and antiaromaticity, both of which would favor pyramidalization of the carbons.



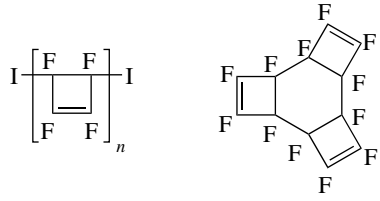
(241) (238) (43)

Photolysis of diiodide **241** in solution with mercury as an iodine scavenger had earlier been found to produce a polymer with the structure **242**[144] and a crystalline compound **243**[145], formally a polymer and cyclic trimer of tetrafluorocyclobutadiene (**236**). Pyrolysis of **241** at 250 °C yields octafluorocyclooctatetraene (**154**), perhaps via diene **236**[146].



(236)

FIGURE 1. Calculated structure of tetrafluorocyclobutadiene (**236**)



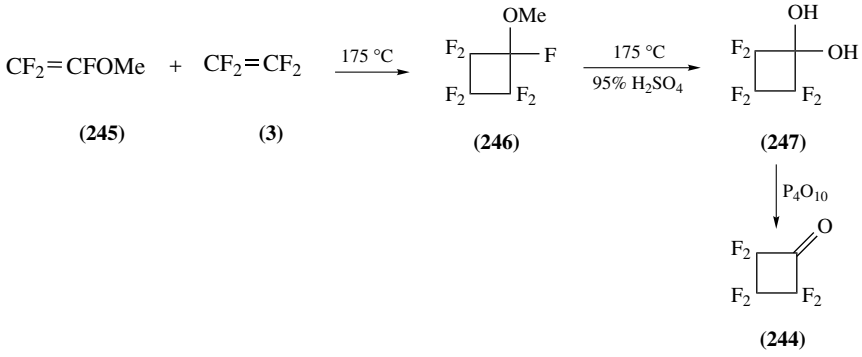
(242) **(243)**

C. Carbonyl Derivatives

1. Hexafluorocyclobutanone

This ketone (**244**) was synthesized as shown in Scheme 29[147]. Cycloaddition of methyl trifluorovinyl ether (**245**) to tetrafluoroethylene (**3**) gave **246**. The fluoroether was hydrolyzed at 175 °C with 95% sulfuric acid to *gem*-diol **247**, and P_4O_{10} freed the ketone from its hydrate.

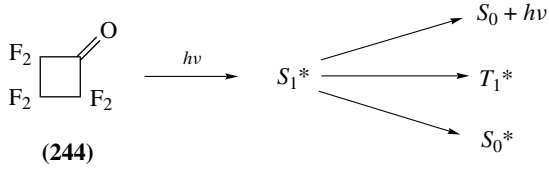
Electron-deprived ketone **244** has a very high frequency carbonyl stretching band (1850 cm^{-1})[147], and the first band in its photoelectron spectrum lies 1.6 eV higher in



SCHEME 29

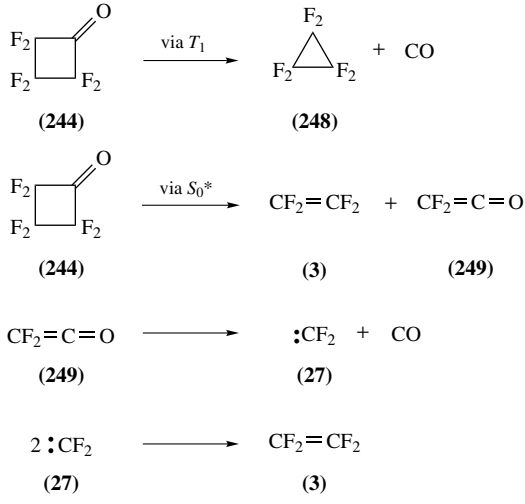
energy than that of the parent cyclobutanone. The longest wavelength band in the electronic spectrum of the pale yellow **244** is shifted *ca* 5000 cm^{-1} to the red from that of cyclobutanone[148]. That shift in the n $\rightarrow \pi^*$ transition is reasonable when one considers the differential effect of fluorine substitution on the HOMO and LUMO. While the HOMO is essentially a p orbital on the oxygen, the LUMO is concentrated on the carbonyl carbon, and therefore experiences a greater lowering of its energy as a consequence of electron withdrawal by the neighboring fluorines.

Photoexcitation of the n $\rightarrow \pi^*$ transition in **244** produces the $S_1{}^*$ state, and this vibrationally excited singlet can fluoresce or undergo either intersystem crossing to $T_1{}^*$ or internal conversion to the hot ground state ($S_0{}^*$) (equation 44)[149]. Fluorescence is a very minor pathway, but the quantum yield for photodecomposition at low pressure in the gas phase is close to unity. In the T_1 state, the ketone fragments mainly into hexafluorocyclopropane (**248**) and CO, but in the vibrationally excited ground state the molecule decomposes into tetrafluoroethylene (**3**) and CO (Scheme 30). Initially formed difluoroketene (**249**) is extremely labile[150], and the difluorocarbene (**27**) produced as it fragments is a source of additional **3**. At long wavelengths (*ca* 400 nm) the intersystem crossing yield is very high and the yield of **248** maximal. Internal conversion to $S_0{}^*$ increases in importance at progressively shorter wavelengths, and **3** becomes the dominant product.



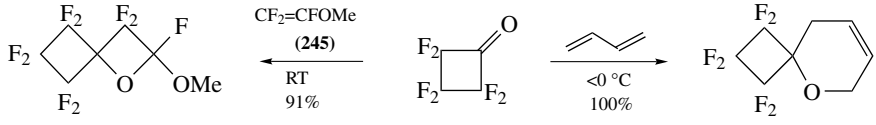
(44)

Electron deficiency and ring strain combine to confer on ketone **244** extraordinary reactivity. Both factors provide driving force for the carbonyl carbon to become tetrahedral. Cycloadditions, both [2 + 2] and [4 + 2], occur very readily, as illustrated by reactions with methyl trifluorovinyl ether (**245**) at RT to give spiroketal **250** and with butadiene below 0 °C to afford spiroether **251** (equation 45)[147]. A further selection of additions to the carbonyl group of **244** appears in Scheme 31. The ketone undergoes the ene reaction very readily, as indicated by the fact that even allene adds in this fashion at 90 °C, yielding **252**[147,151]. Hydrazoic acid adds in the cold to give **253**, the first α-azido alcohol and a stable compound[147]. Nitrosyl fluoride affords a moisture-sensitive but stable α-fluoro



SCHEME 30

nitrite (**254**)[152]. All four of the hydrogen halides form distillable adducts (**255**) in high yield, and all but the HI adduct are fairly stable upon storage[153]. Boron trichloride undergoes threefold addition to **244** at RT to give **256**[154]. Difluorocarbene (**27**), generated from hexafluoropropylene oxide at 180 °C, reacts with the ketone to form spiroepoxide **257**[155].

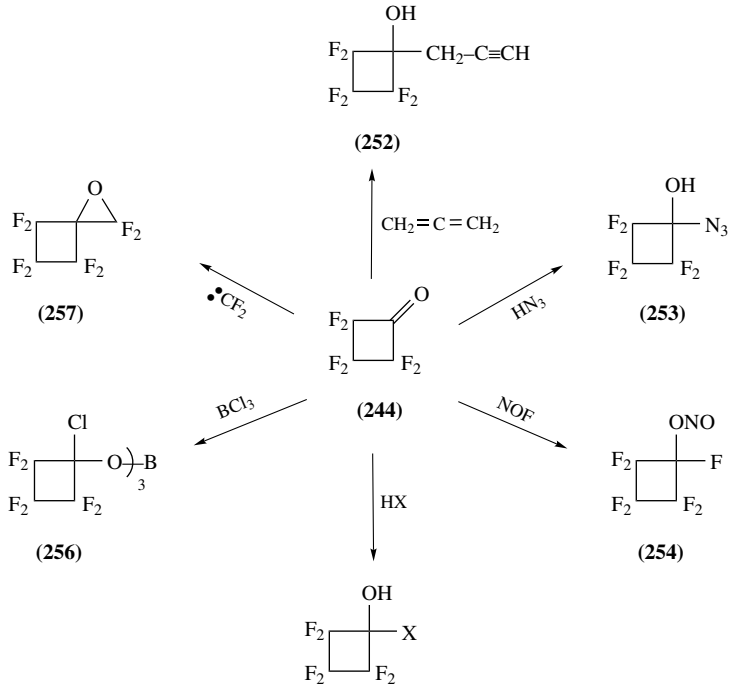


(45)

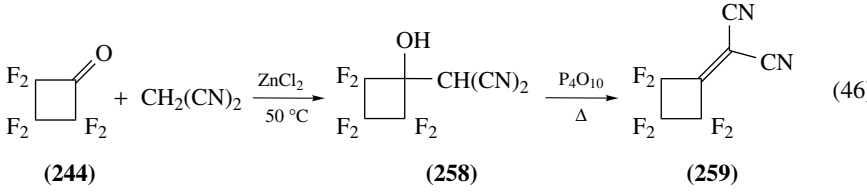
With zinc chloride catalysis, ketone **244** adds malononitrile readily, and dehydration of the adduct **258** yields the highly electron deficient alkene **259** (equation 46)[156]. As a dienophile, **259** is roughly equivalent to tetracyanoethylene. It reacts with anthracene to give a quantitative yield of Diels–Alder adduct **260** in 3 min at RT (equation 47). Alkene **259** forms intensely colored charge-transfer complexes with a variety of aromatic compounds, gives [2 + 2] adducts with electron-rich alkenes and undergoes ene reaction with alkenes having allylic hydrogens.

2. Other ketones

Tetrafluorocyclobutan-1,2-dione (**261**), a volatile blue liquid, was synthesized analogously to the monoketone **244**, i.e. by thermal dimerization of methyl trifluorovinyl ether (**245**) followed by sulfuric acid hydrolysis of the resulting 1,2-dimethoxyperfluorocyclobutane[147]. Shifts in the photoelectron and electronic spectra relative to the unsubstituted molecule are also similar to those for **244**, i.e. 1.5 eV to higher energy for the first PES band and *ca* 5000 cm^{-1} to longer wavelengths for the first electronic transition[148].



SCHEME 31



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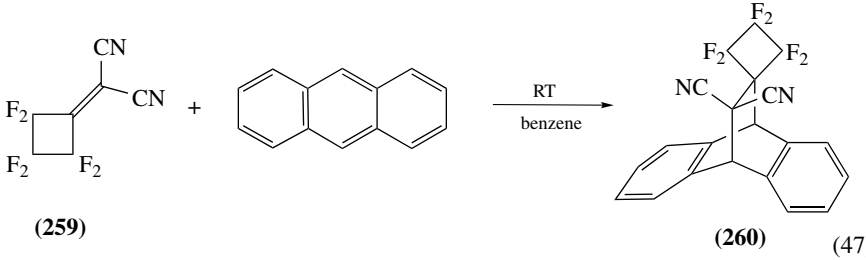

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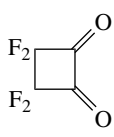

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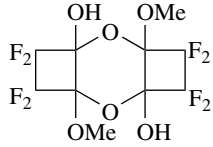

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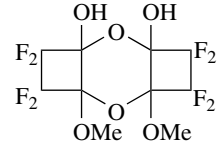
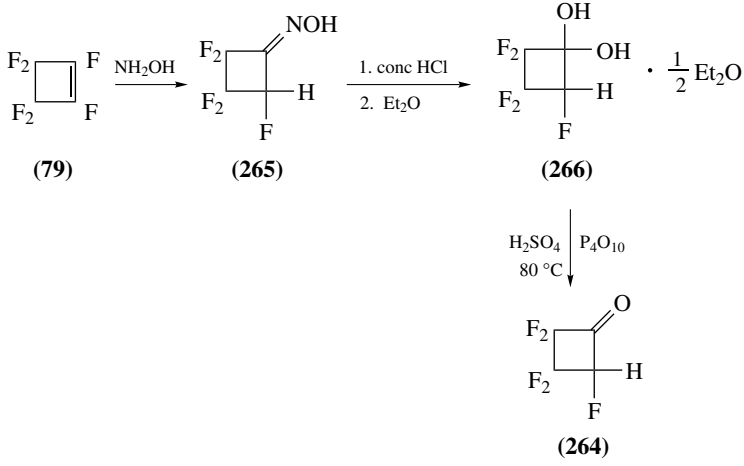


(263)

Though easily polymerized, the diketone is stable when stored over P_4O_{10}. With methanol it gives a bis(hemiketal) and a minor amount of dioxane **262** or **263**. Its reactivity parallels that of **244**, as it forms mono- or diadducts with many of the same reagents, and in some cases dioxane structures analogous to **262** or **263**[147].

2*H*-perfluorocyclobutanone (**264**) was synthesized as shown in equation 48[157, 158]. Eliminating HF, hydroxylamine transformed cyclobutene **79** into oxime **265**. Hydrolysis with concentrated hydrochloric acid followed by workup with ether gave *gem*-diol **266** as a stable ether complex, and the diol was dehydrated under strongly acidic conditions to give the desired ketone **264**.

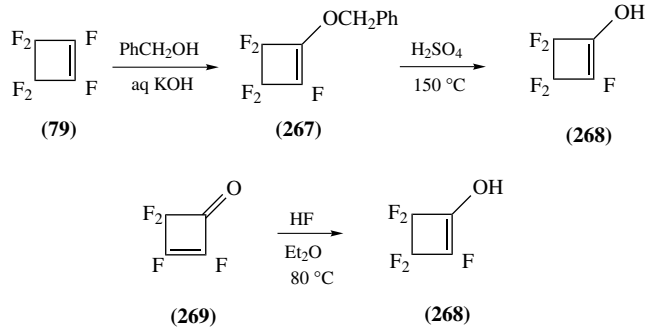


(79) **(265)** **(266)** **(264)**

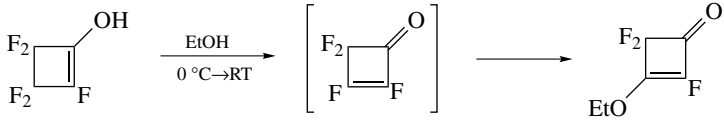
(48)

The enol of **264** was independently synthesized from **79** (Scheme 32)[159]. Treatment with benzyl alcohol and base yielded enol ether **267**, which suffered hydrolysis with sulfuric acid at 150 °C to give the enol (**268**). Alternatively, the enol was prepared via addition of hydrogen fluoride to α,β-unsaturated ketone **269**[160]. A basic solvent such as ether was required for this conjugate addition, consistent with the attack on **269** being nucleophilic in nature. Enol **268** formed a distillable etherate, a reflection of the potent hydrogen-bonding ability of perfluoroenols. It reacted with ethanol via dehydrofluorination to **269** followed by conjugate addition and elimination to give **270** (equation 49), and both water and diethylamine gave analogous products[159].

As implied by their independent creation in strong acid, both ketone **264** and its enol **268** displayed amazing inertness to powerful acids even at elevated temperatures: no equilibration of the two forms was observed. Both compounds were very sensitive to bases, which brought about dehydrofluorination to **269** or gave products resulting from further degradation. The researchers reached the remarkable conclusion that the keto and enol forms could not be interconverted either thermally or catalytically[157].

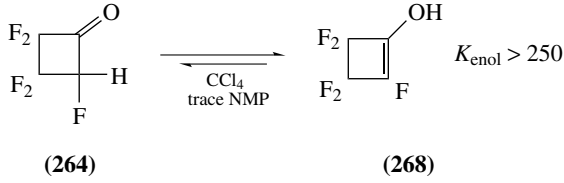


SCHEME 32



(49)

Much later it was discovered that ketone **264** and its enol **268** can be equilibrated without decomposition through the agency of an extremely weak base, *N*-methylpyrrolidone (NMP)[161–163]. The surprising finding was that **268** is significantly more stable than **264** (equation 50). This was the first example of an unhindered, unconjugated enol that was stable relative to the corresponding ketone, regardless of solvent[162, 164].



(50)

Apparently a reliable value of K_{enol} is not available for the parent cyclobutanone, but it is certainly a very small number as judged from the fact that the values for the C_5 to C_7 alicyclic ketones fall in the range 4.2×10^{-7} to 1.0×10^{-8} [165]. Support for the conclusion that many orders of magnitude separate the equilibrium constant for enolization of **264** from that of its parent is provided by a closely related system; the difference between K_{enol} for cyclopentanone **271** (in CCl_4) (equation 51) and that of its parent ketone (in H_2O) is 1×10^{10} [163].

(51)

TABLE 5. Enolization constants for ketone **272** as a function of solvent

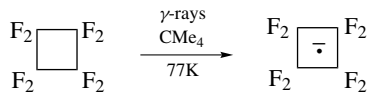
(272) **(273)**

Solvent	K_{enol}
CCl_4	0.07 ± 0.1
1.6% MeCN/CCl_4	1.94 ± 0.1
MeCN	very large

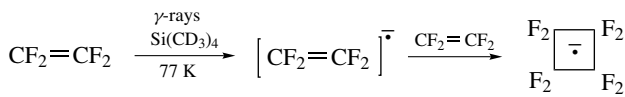
In Lewis basic solvents such as ether, THF and acetonitrile, K_{enol} values for highly fluorinated ketones are much larger than in CCl_4. This effect is easy to observe with bicyclic ketone **272**, synthesized from hexafluoro Dewar benzene (**120**), since little of its enol (**273**) is present at equilibrium in CCl_4. With less than 2% acetonitrile in CCl_4, enol is already the dominant species, and at higher concentrations the ketone soon becomes undetectable (Table 5)[161]. This dramatic shift in the equilibrium constant is further testimony to the powerful hydrogen-bonding ability of perfluoroenols.

D. Some Ionic Species

γ-Irradiation of octafluorocyclobutane (**1**) in a neopentane matrix at 77 K produced the radical anion **274**, which gave an isotropic ESR spectrum at 130 K with $a = 148$ G for each of the 8 equivalent fluorines (equation 52)[166]. The stable existence of this ion serves as a reminder that fluorocarbons have low lying σ^* (and σ) orbitals[167, 168]. When tetrafluoroethylene (**3**) was irradiated similarly at 77 K in tetramethylsilane-d_{12}, the ESR spectrum at 120 K showed the presence of **274** in addition to the radical anion from **3** (**275**)[169]. The formation of **274** was ascribed to orbital topology-allowed cycloaddition of **275** to **3** (equation 53).



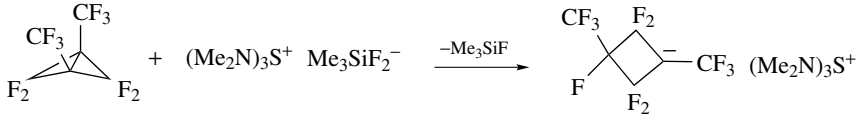
(1) **(274)** (52)



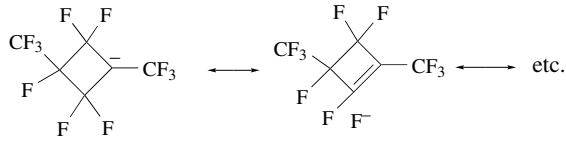
(3) **(275)** **(274)** (53)

Treatment of bicyclobutane **276** with $(Me_2N)_3S^+$ $Me_3SiF_2^-$ (TASF) yields carbanion salt **277** in a fluoride ion-promoted C−C cleavage reaction (equation 54)[170]. The X-ray crystal structure of **277** reveals strong evidence for negative hyperconjugation. The C−C ring bonds emanating from the carbanion center are nearly 0.1 Å shorter than the other ring bonds, and the C−F bonds of the CF_2 groups are 0.06–0.07 Å longer than those in

octafluorocyclobutane (**1**). In a calculated structure that agrees well with the experimental one, the CF_2 fluorines have the greatest negative charge. These data all attest to charge donation into C−F σ^* orbitals, represented below in valence bond terms.

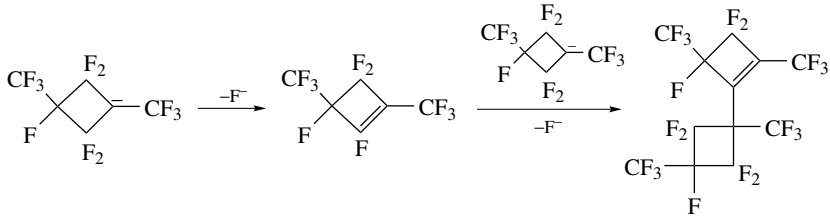


(276) **(277)** (54)



(277)

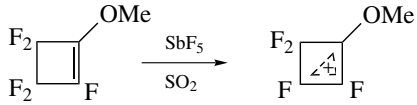
Addition of 1 mol% of the salt **277** to bicyclobutane **276** results in a quantitative yield of the dimer **279**. In this catalytic process the carbanion both loses fluoride ion to give alkene **278** and attacks **278** in an addition–elimination reaction to afford the dimer (equation 55). Quantitative reversion to the salt (**277**) takes place if the dimer is treated with 2 equiv of TASF.



(277) **(278)** **(279)** (55)

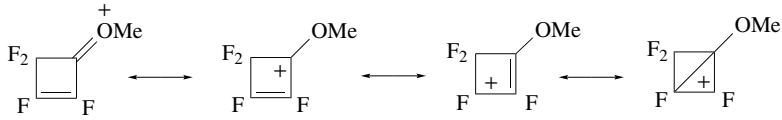
Hexafluorocyclobutene (**79**) is inert to SbF_5-SO_2ClF at −10 °C, but 1-methoxypentafluorocyclobutene (**280**) reacted with SbF_5 in SO_2 at low temperatures to yield cation **281** (equation 56)[171]. The hexafluoroantimonate salt of **281** was an isolable solid stable at RT. ^{19}F and ^{1}H NMR spectra showed the presence of two species in solutions of **281**, rotamers about the C−OMe bond separated by a substantial barrier: $\Delta G^{\ddagger}$ equals *ca* 16 kcal mol^{-1} at RT. Thus, π bonding by oxygen is important for stabilization of the ion. An acyclic analogue of **280**, 2-methoxyheptafluoro-2-butene, fails to react with SbF_5 under the conditions for preparing **281**, suggesting that C1−C3 overlap in this cyclic cation contributes to its stability. Its ^{19}F NMR spectrum confirms the presence of the 1,3-interaction and therefore the importance of resonance form **281a**. Upon ionization of **280**, the signal for the fluorine at C2 shifts downfield by *ca* 44 ppm, whereas the corresponding fluorine in the acyclic allylic cation **283** is shifted upfield by 6 ppm relative to its precursor **282** (equation 57). Cation **281** is a potent alkyling agent, as indicated by its facile reaction

with benzene in SO_2 to give **284** after hydrolysis (equation 58).

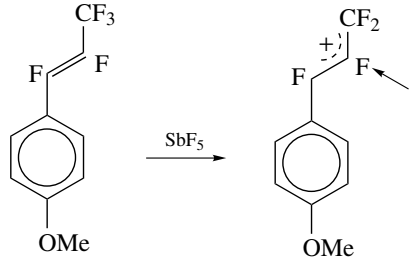


(56)

(280) **(281)**

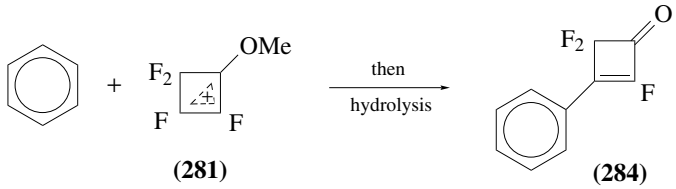


(281a)



(57)

(282) **(283)**

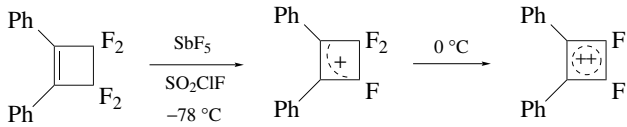


(58)

(281) **(284)**

As 2π-electron cyclically conjugated species, cyclobutadiene dications are potentially aromatic, but charge repulsion counteracts stabilization by aromaticity. Nonetheless, the difluorodiphenylcyclobutadienyl dication **285** was successfully prepared by subjecting cyclobutene **286** to the action of SbF_5. Abstraction of fluoride by the Lewis acid at $-78\,^{\circ}C$ in SO_2ClF gave cyclobutenyl cation **287**, and when the solution was warmed to $0\,^{\circ}C$, quantitative and irreversible loss of a second fluoride occurred to yield the dication **285** (equation 59)[172]. ^{19}F and ^{13}C NMR chemical shifts for **285** appear at low field, revealing substantial charge delocalization into the phenyl rings. In support of this finding, the *ortho* carbons are inequivalent, showing that the π bond order between ring and *ipso*-phenyl carbons is great enough to prevent bond rotation from occurring on the NMR timescale. The fluorine chemical shift for **285**, $\delta - 27$ ppm, is >100 ppm downfield from that of the vinyl fluorines in hexafluorocyclobutene (**79**), and the large $^1J_{CF}$, 396 Hz, is consistent

with significant fluorine lone pair donation into the π system.



(286) **(287)** **(285)** (59)

IV. PERFLUOROALKYL-SUBSTITUTED SYSTEMS

A. Valence Isomers of Aromatics

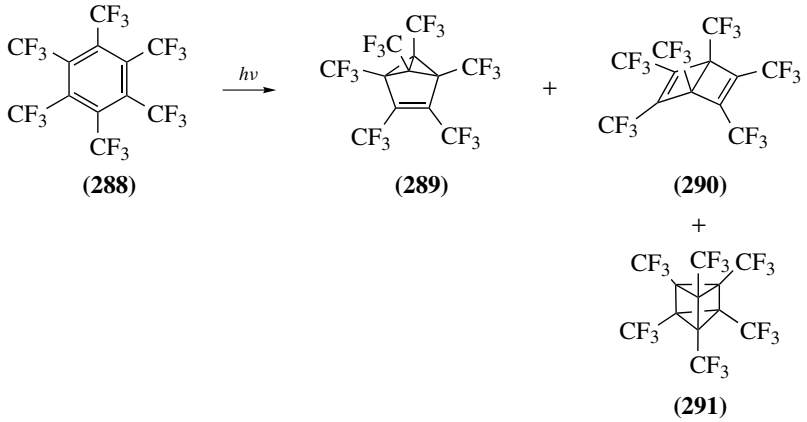
Because the subject of perfluoroalkyl-substituted valence isomers of aromatic compounds has been thoroughly reviewed[173–175], only selected aspects are discussed here. The 'perfluoroalkyl effect', i.e. the stabilizing influence that perfluoroalkyl groups exert on strained carbon skeletons[176], is evident in many structures that incorporate cyclobutane rings bearing perfluoroalkyl substituents. This stabilization, which can be both kinetic and thermodynamic, apparently results from the strengthening of carbon–carbon bonds by perfluoroalkyl substituents and in many cases from steric interactions as well[16]. Steric effects can both shield a molecule from external attack and inhibit intramolecular pathways that entail an increase in nonbonded repulsion.

The benzvalene (**289**), Dewar benzene (**290**) and prismane (**291**) valence isomers of perfluorohexamethylbenzene (**288**), prepared by UV irradiation of the benzene (equation 60)[177, 178], nicely illustrate these ideas. Thermal isomerization of prismane **291** to the Dewar benzene **290** takes place with $t_{1/2} = 29$ h at 170 °C[179], while the parent prismane ring opens with $t_{1/2} = 11$ h at 90 °C[180]. The enhanced stability of **291** presumably reflects greater strength of its skeletal bonds, as steric effects should not come into play in this reaction. On the other hand, thermal isomerization of Dewar benzene **290** to **288** results in strong nonbonded repulsions among the CF_3 groups that doubtless contribute to the high barrier to aromatization (equation 61). At 170 °C, **290** has $t_{1/2} = 135$ h[179], as compared to $t_{1/2} = 65$ min at 61 °C for Dewar benzene itself[181].

Ring opening of a Dewar benzene is generally a highly exothermic process, as it both relieves a large amount of ring strain and creates an aromatic system. For the isomerization of hexamethyl Dewar benzene (**292**) to the benzene (**293**), for example, $\Delta H = -59.5$ kcal mol^{-1} [182]. In remarkable contrast, the reaction can be driven in the opposite direction in the case of the perfluorohexaethyl analogues. When benzene **294** is passed through a hot tube at 400 °C, Dewar benzene **295** is formed in good yield (Scheme 33). For this reaction, $\Delta H^\circ = 9.00$ kcal mol^{-1} and $\Delta S^\circ = 16.3$ cal mol^{-1} deg^{-1}; thus $K_{eq} = 4.4$ at 400 °C[183]. That the enthalpy change is 50 kcal mol^{-1} smaller than in the hexamethyl system reflects relief of severe repulsion among the C_2F_5 groups in the benzene, and the rather large positive entropy change signifies the gain in degrees of freedom as those groups acquire freedom of motion. [At 140 °C, **295** slowly reverts almost entirely to the benzene (**294**).]

Dewar benzenes can also be synthesized by Diels–Alder reaction with a cyclobutadiene. Thermolysis of diazocyclopropene **296** results in rearrangement to diene **299**, which can be intercepted with hexafluoro-2-butyne (**297**) to give Dewar benzene **298** (Scheme 34).

Irradiation in pyrex of **298** causes ring opening to benzene **300**, which recyclizes photochemically to the less strained Dewar benzene **301**. The latter slowly photocyclizes to yield the prismane **302**[184, 185].



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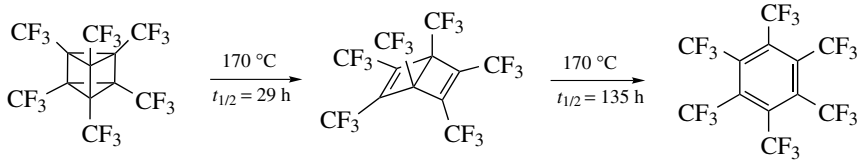
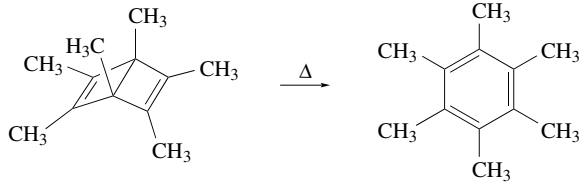
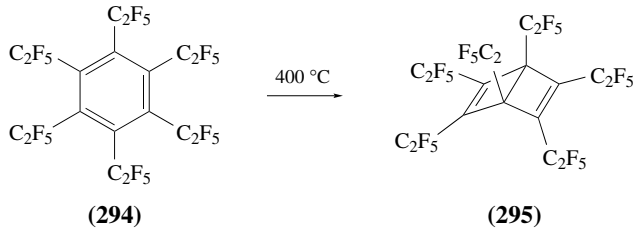
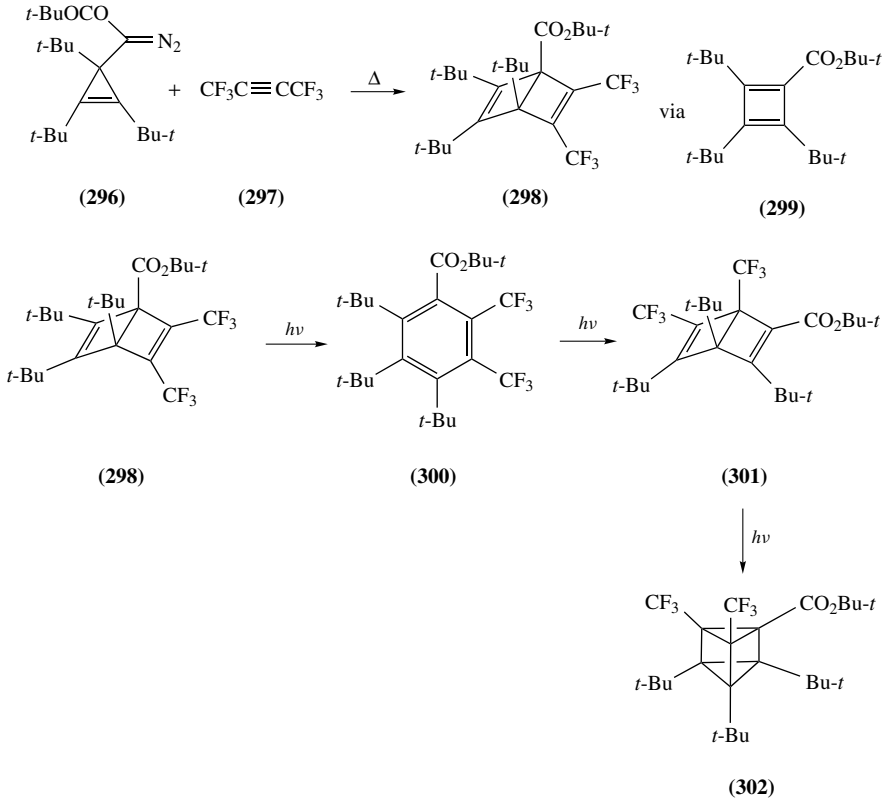


(61)



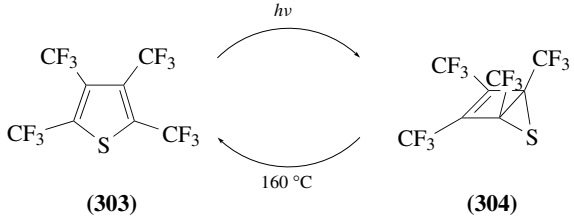


SCHEME 33

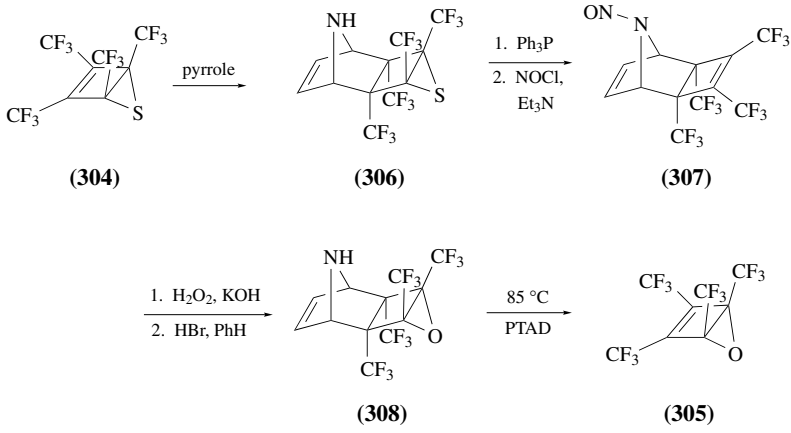


SCHEME 34

Returning to the perfluoroalkyl effect, one finds striking examples among Dewar heterocycles. UV irradiation of perfluorotetramethylthiophene (**303**) yields the Dewar isomer (**304**), which enjoys a half-life of 5.1 h at 160 °C for reversion to the aromatic isomer (equation 62)[186]. For comparison, the labile parent Dewar thiophene has been observed only in matrices at very low temperatures[187]. Perfluorotetramethyl Dewar furan (**305**) is not formed upon photolysis of the furan, but it has been synthesized from **304** by the circuitous route shown in Scheme 35[188]. It was necessary at the outset to protect the



(303) (304) (62)

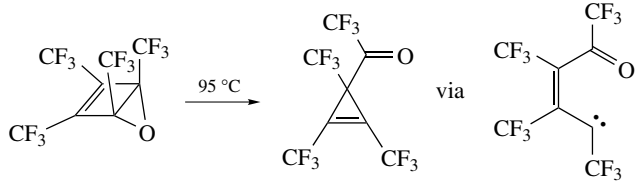


(304) **(306)** **(307)**

(308) **(305)**

SCHEME 35

double bond of **304** by Diels–Alder addition, giving **306**, and later the amino group by nitrosation, producing **307**. Thermal *retro*-Diels–Alder reaction of **308** was carried out in the presence of 4-phenyltriazoline-3,5-dione (PTAD) to consume the pyrrole byproduct, thereby facilitating isolation of the volatile Dewar furan **305**. The Dewar furan is an extremely reactive dienophile. It rearranges at 95 °C to cyclopropenyl ketone **309**, presumably via carbene **310**, with a half-life of *ca* 20 min (equation 63), but the parent Dewar furan gave the analogous product even at −80 °C[189].

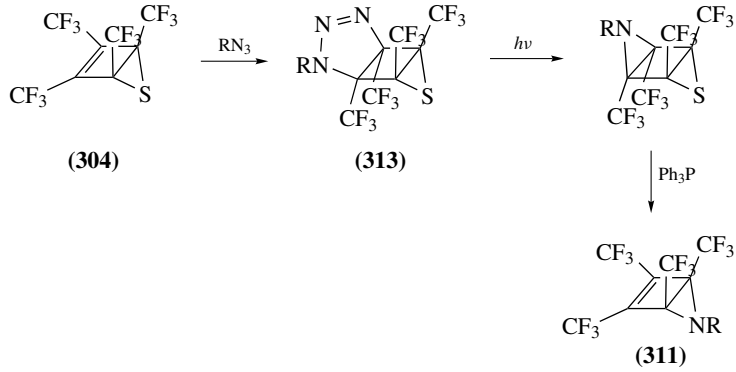


(305) **(309)** **(310)** (63)

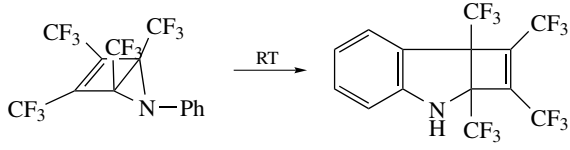
Perfluorotetramethyl Dewar pyrrole (**311**, R = H) and N-substituted analogues were also synthesized from **304**, but more directly than **305** (equation 64)[190]. The N-phenyl derivative isomerizes spontaneously via a Cope rearrangement to an indoline (**312**) (equation 65), but the other Dewar pyrroles are stable at RT and aromatize to pyrroles upon heating. Comparison of their stability with that of the parent Dewar pyrrole is not possible, as that molecule remains unknown.

In addition to providing routes to other Dewar heterocycles, Dewar thiophene makes possible the synthesis of a diverse array of interesting structures. Thermolysis of azide adducts **313** results in 1,3-dipolar cycloelimination to give diazoiminothiiranes **314**, nitrogen loss from which leads to iminothietes **315** (Scheme 36)[191]. In the case of R = Ph, the intermediate thiirane was isolated. Release of ring strain in the four-membered ring undoubtedly contributes to the driving force for the cycloelimination reaction. When adducts **313** were desulfurized and then thermolyzed, diazoimines **316** were obtained.

Thermal extrusion of nitrogen from **316** resulted in cyclization to cyclopropenylimines **317**, pyrroles **318** or both, depending upon R.



(64)



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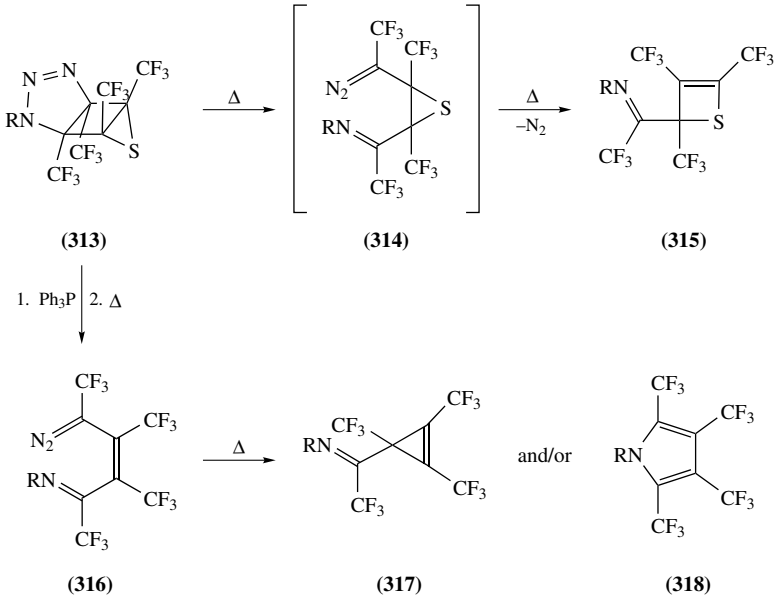
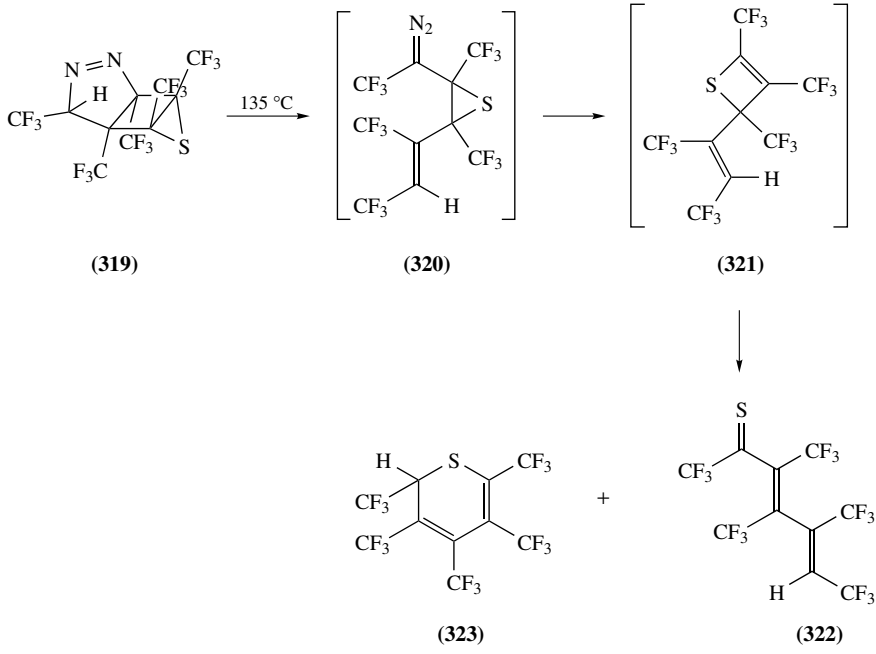


SCHEME 36

Cycloadduct **319** of Dewar thiophene **304** with 2,2,2-trifluorodiazoethane ring opened and lost nitrogen upon thermolysis, giving sky-blue **322** and a minor amount of **323**, to which **322** cyclized upon further heating (Scheme 37)[192]. The decomposition of **319** presumably proceeded analogously to that of **312**, affording first diazothiirane **320** then thiete **321**.

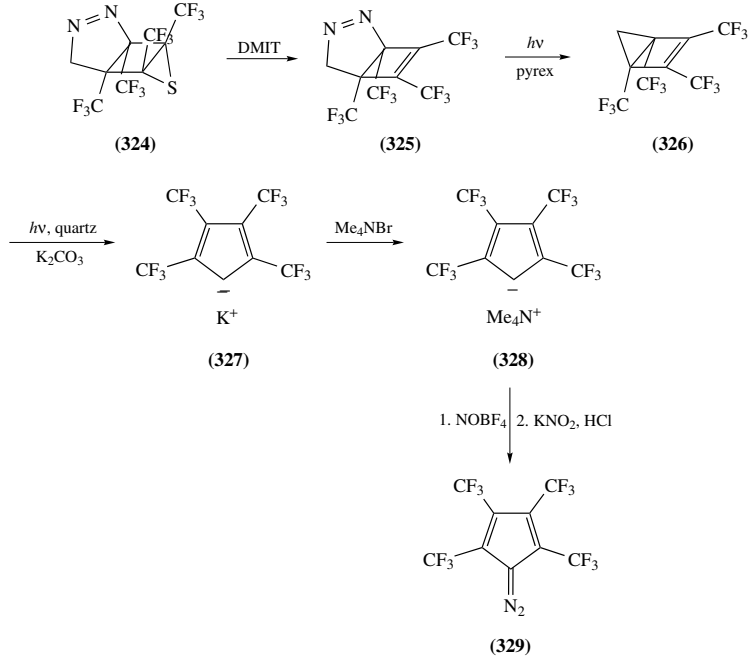


SCHEME 37

Pyrazoline **324**, from Dewar thiophene **304** and diazomethane, was desulfurized with 1,3-dimethylimidazole-2-thione (DMIT), yielding **325** (Scheme 38)[193]. This reagent was chosen because it did not cause concurrent azo → hydrazone tautomerization, to which both **324** and **325** were extremely susceptible. Photolysis of **325** in pyrex eliminated nitrogen to give bicyclopentene **326**, which upon further photolysis in quartz in the presence of potassium carbonate afforded potassium cyclopentadienide **327**. Isolated as its stable tetramethylammonium salt **328**, the anion was diazotized in two steps, giving perfluorodiazotetramethylcyclopentadiene (**329**).

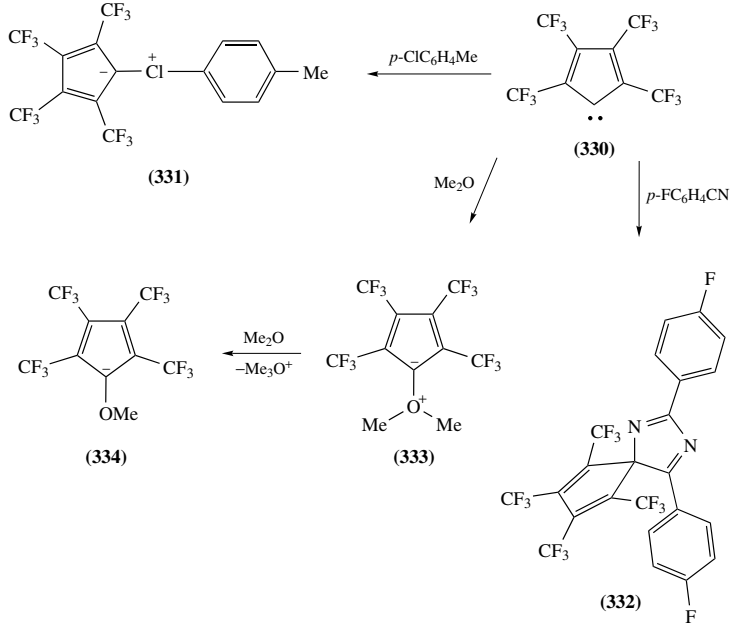
Photolysis of **329** produced the highly electron-deficient and voraciously reactive carbene **330**[193]. In addition to cyclopropanation, the carbene underwent, *inter alia*, the reactions shown in Scheme 39. *p*-Chlorotoluene gave a chloronium ylid (**331**), and *p*-fluorobenzonitrile afforded imidazole **332** via an intermediate 1,3-dipolar species. Dimethyl ether trapped the carbene, yielding methoxycyclopentadienide **334** via oxonium ylid **333**.

Oxidation of Dewar thiophene **304** with peroxytrifluoroacetic acid produced sulfoxide **335**, the ^{19}F NMR spectrum of which was simply a sharp singlet[194]. Investigation revealed that the molecule was undergoing a 'walk-rearrangement', better described in this case as a 'sprint rearrangement', in which the sulfur migrates around the cyclobutene ring undergoing inversion of configuration at each step (equation 66). Activation parameter values are $\Delta H^{\ddagger} = 6.6 \pm 0.2$ kcal mol^{-1} and $\Delta S^{\ddagger} = -0.5 \pm 0.6$ cal mol^{-1} deg^{-1}, and



(324) (325) (326) (327) (328) (329)

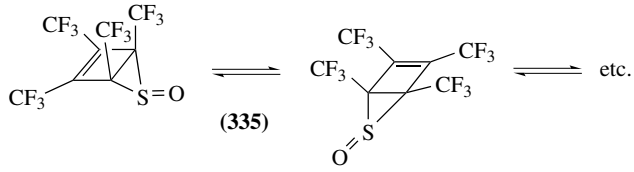
SCHEME 38



(330) (331) (332) (333) (334)

SCHEME 39

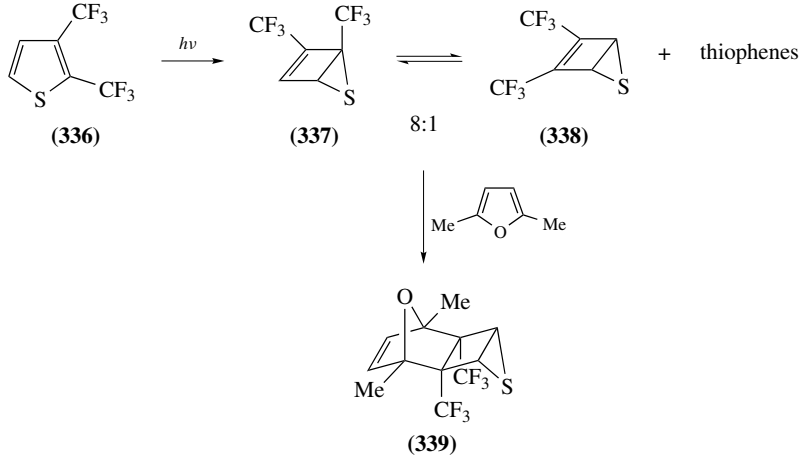
the rate constant extrapolated to 25 °C is $k = 2.3 \times 10^5$ s^{-1} [195]. The mechanism of this automerization is controversial, but its remarkable facility led to the useful concept of pseudopericyclic reactions[194–197].



(66)

Discovery of the rearrangement of sulfoxide **335** raised the question whether the Dewar thiophene itself (**304**) also automerizes. Examination of its ^{19}F NMR spectrum at high temperatures revealed that it does, but with a much higher barrier: $\Delta H^{\ddagger} = 18.8 \pm 0.3$ kcal mol^{-1} and $\Delta S^{\ddagger} = -7.7 \pm 0.8$ cal mol^{-1} deg^{-1}. Thus, sulfoxide **335** undergoes degenerate rearrangement 3×10^{10} faster than **304** at 25 °C.

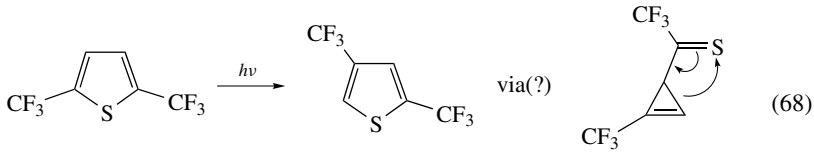
Irradiation of 2,3-bis(trifluoromethyl)thiophene (**336**) yields an 8:1 mixture of Dewar isomers **337** and **338**, together with all four (2,3-, 2,4-, 2,5- and 3,4-) bis(trifluoromethyl) thiophenes (equation 67)[198]. Consistent with the behavior of **304**, the pair of Dewar isomers interconverted at room temperature. When furan was added, Diels–Alder addition occurred with both **337** and **338**, but the ratio of adducts differed from that of the Dewar thiophenes. With 2,5-dimethylfuran the only adduct obtained was **339**, derived from the more reactive minor Dewar isomer that was continuously formed by a shift in the equilibrium.



(67)

Upon irradiation, 2,5-bis(trifluoromethyl)thiophene (**340**) is transformed into 2,4-bis (trifluoromethyl)thiophene (**341**) (equation 68)[198]. This rearrangement cannot be explained on the basis of Dewar thiophene intermediates; apparently a different valence isomer such

as cyclopropenylthione **342** is formed.



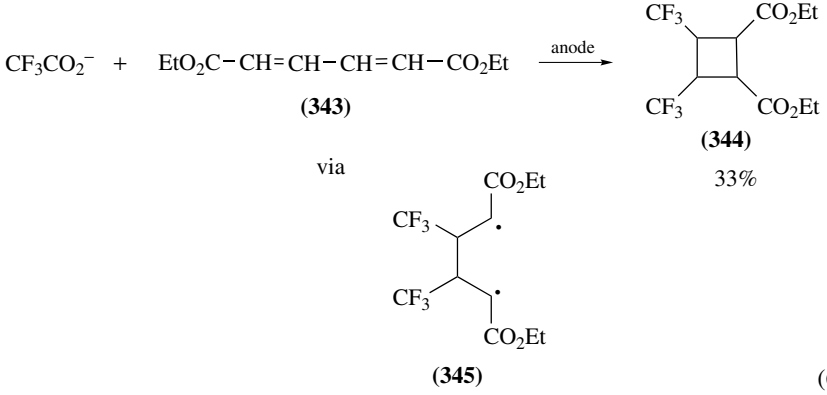
(68)

(340) **(341)** **(342)**

B. Other Systems

1. Cyclobutanes

The cyclobutane diester **344** was prepared in novel fashion by anodic oxidation of trifluoroacetate ion in the presence of diene **343** (equation 69)[199]. The authors postulate that **343** is attacked successively by two trifluoromethyl radicals to give the diradical **345**, followed by ring closure.



(343) **(344)**

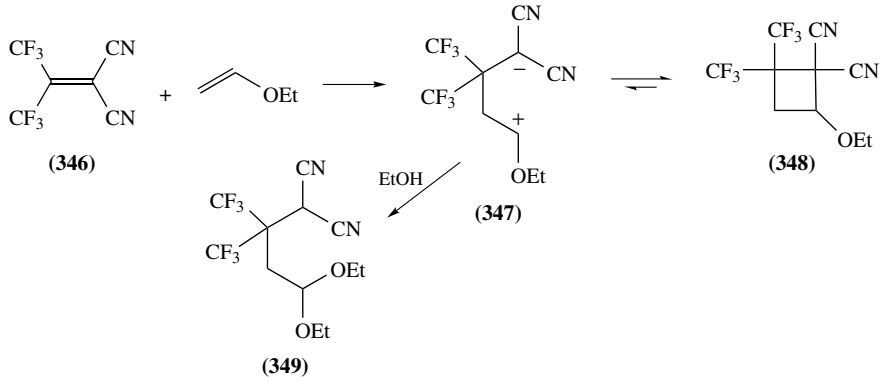
via 33%

(345)

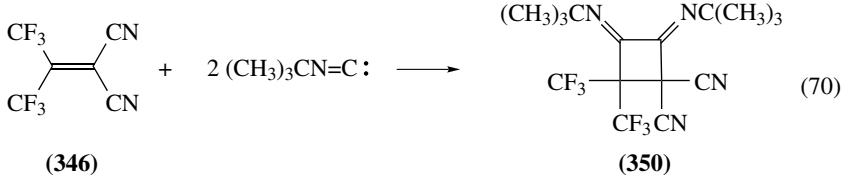
(69)

The extremely electron-deficient, highly reactive alkene 2,2-bis(trifluoromethyl)-1,1-dicyanoethylene (BTF, **346**) has been a rich source of trifluoromethyl-substituted cyclobutanes via [2 + 2] cycloadditions[156]. It reacts with ethyl vinyl ether rapidly at −78 °C, yielding cyclobutane **348** by way of zwitterion **347** (Scheme 40)[200, 201]. The product exists in equilibrium with a small amount of the zwitterion, which is quenched upon addition of ethanol to give **349**. BTF reacts analogously with vinyl sulfides, affording stable cyclobutanes at rates up to 8,200 times faster than tetracyanoethylene[202]. With *t*-butyl isocyanide BTF forms a 1:2 adduct, **350** (equation 70)[156]. 6,6-Dimethylfulvene (**351**) reacts reversibly in Diels–Alder fashion with BTF to yield **352**, which rearranges to the bicyclo[3.2.0] isomer **353** in polar solvents, on silica gel or alumina, and even in the solid state (Scheme 41)[203]. The rearrangement has been interpreted as proceeding via zwitterion **354**. Similarly, styrene undergoes Diels–Alder reaction with BTF under conditions of kinetic control, giving **355**, but affords the cyclobutane **356** via zwitterion **357** when the reaction is thermodynamically controlled (Scheme 42)[204]. Electron-rich styrenes such as the *p*-methoxy derivative give [2 + 2] adducts with BTF by way of more stable zwitterions, and yield no observable [4 + 2] adducts. For this reason, the authors

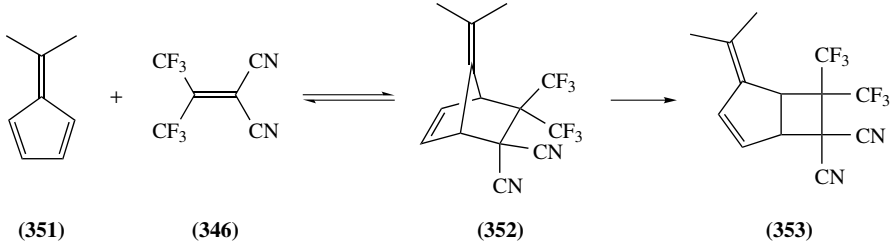
believe that zwitterion **357** is not an intermediate en route to the [4 + 2] adduct **355**. *trans*-1,3-Pentadiene (**358**) yields a Diels–Alder adduct (**359**) with BTF, but the more hindered 4-methyl-1,3-pentadiene (**360**) forms the [2 + 2] adduct **361** via zwitterion **362** (Scheme 43)[205].



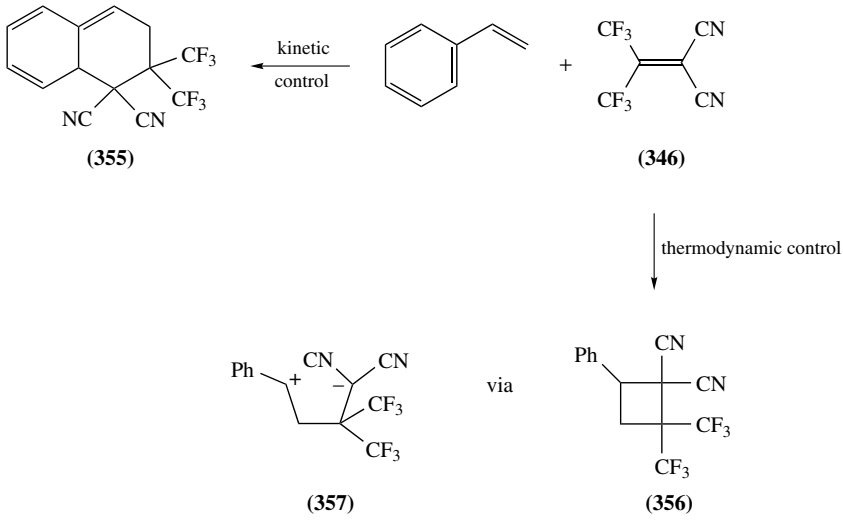
SCHEME 40



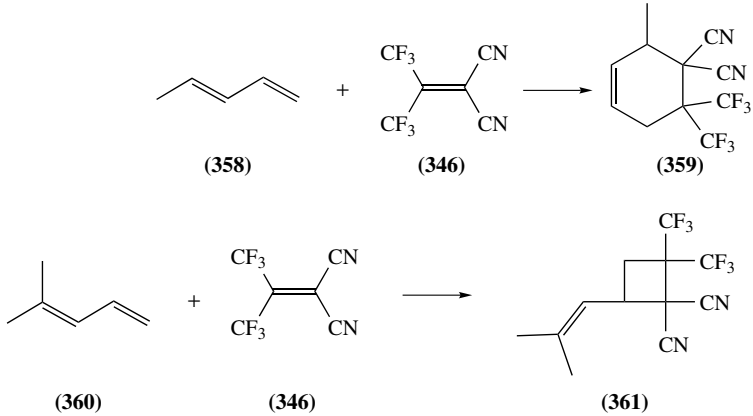
(70)



SCHEME 41



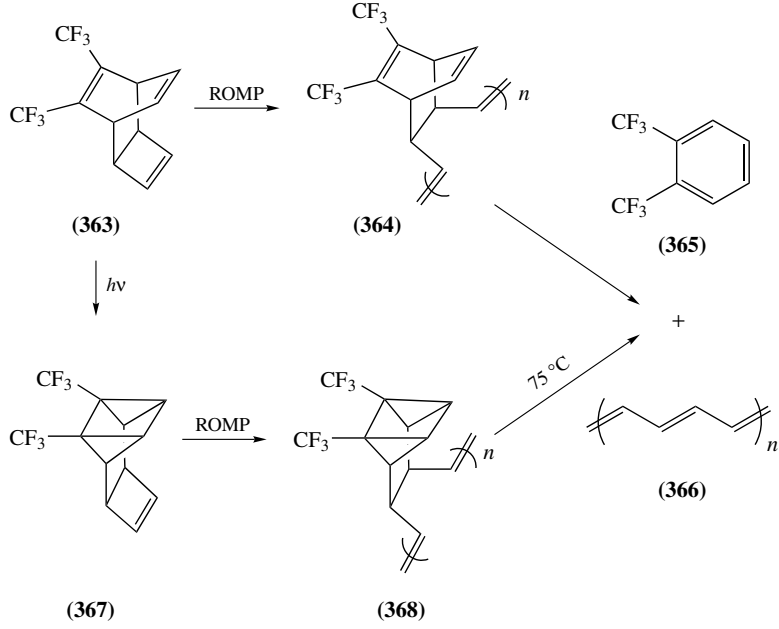
SCHEME 42



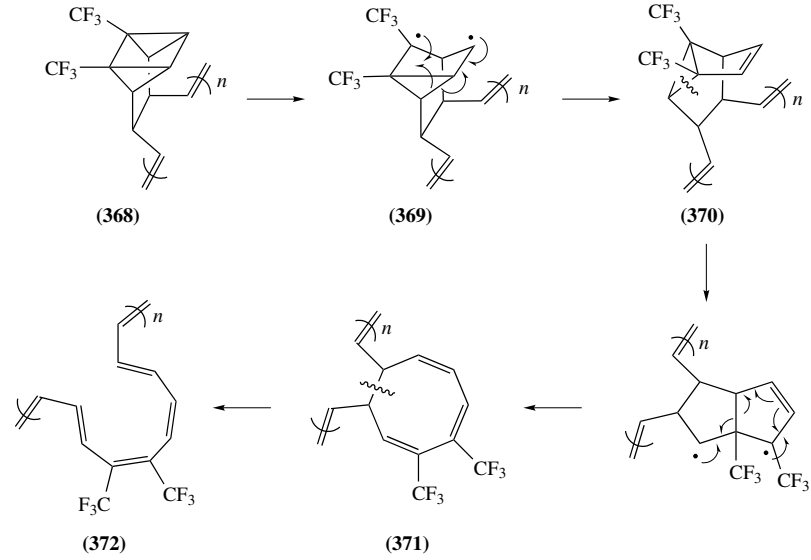
SCHEME 43

A clever route to polyacetylene was devised based on the Diels–Alder adduct **363** of hexafluoro-2-butyne with cyclooctatetraene. Ring opening metathesis polymerization (ROMP) of **363** gave precursor polymer **364**, which unlike the intractable target polymer could be processed in solution. Thermal Alder–Rickert reaction with loss of 1,2-bis(trifluoromethyl)benzene (**365**) and double bond isomerization then yielded polyacetylene (**366**) (Scheme 44)[206]. Unfortunately, the polymer **364** was somewhat unstable, as the symmetry-allowed Alder–Rickert reaction occurred slowly even at RT. To forestall this problem, adduct **363** was photolyzed to its pentacyclic isomer **367**[207, 208]. Like **364**, the derived precursor polymer **368** gives polyacetylene upon thermolysis, but it is much more stable than **364**. While it reacts smoothly when heated as a thin film, the reaction is so exothermic that the material can explode if heated in bulk. Insofar as the decomposition of **368** begins with symmetry-forbidden reversion to **364**, it should yield the same polymer obtained by the original route. It was found, however, that some fluorine was retained in the polymer obtained from **368**. The authors rationalized this in terms of fragmentation of some of the tetracyclic units in **368** in such a way as to retain all of the carbons as part of a fully conjugated structure. Scheme 45 presents another possible mechanism for this fragmentation which avoids the 'nearly simultaneous breaking of three bonds' required by the proposed pathways. Formation of diradical **369** and its rearrangement to **370** find precedent in the photochemical di-π-methane rearrangement[209]. The entire reaction sequence from **368** to **371** parallels the transformation of perfluoroquadricyclane (**138**) via perfluorotricyclo[3.2.0.0^{2,7}]hept-3-ene (**139**) into perfluorotropilidene (**140**). Ring opening of **371** would generate fully conjugated system **372**, in which *cis* → *trans* double bond isomerization would be facile.

UV irradiation of *anti*-tricyclo[4.2.0.0^{2,5}]octa-3,7-diene **373**, prepared from hexafluoro-2-butyne, transformed it into cubane **374** and cuneane **375** (Scheme 46)[210]. During the

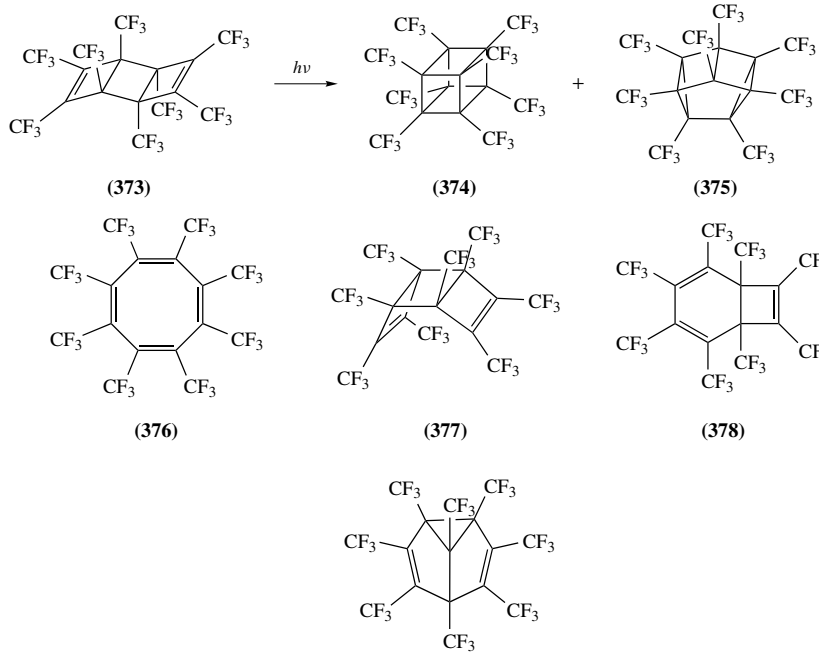


SCHEME 44



(368) **(369)** **(370)** **(372)** **(371)**

SCHEME 45



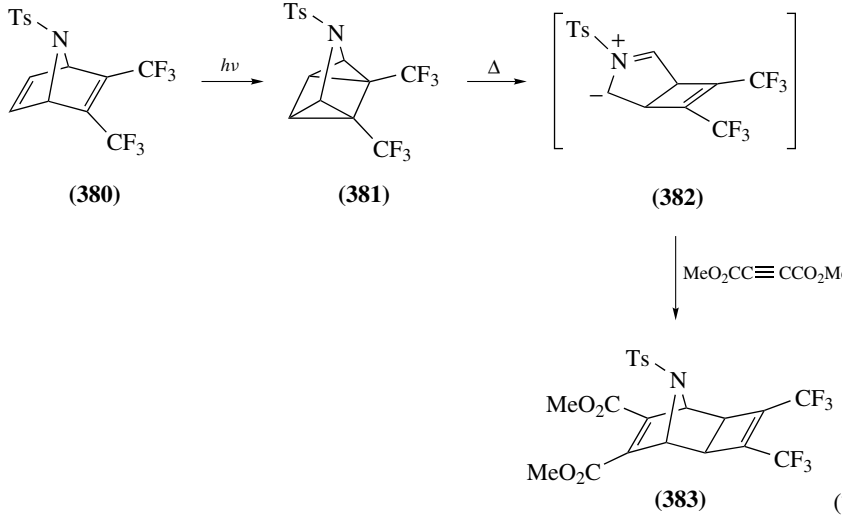
(373) **(374)** **(375)** **(376)** **(377)** **(378)** **(379)**

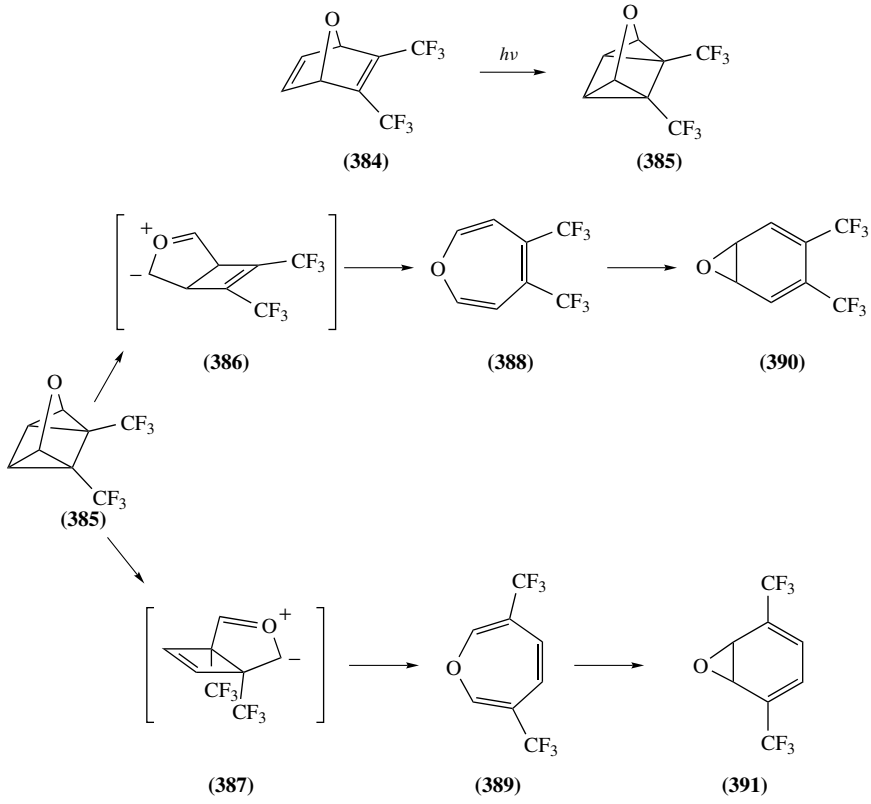
SCHEME 46

photolysis cyclooctatetraene **376** and *syn*-tricyclooctadiene **377** were formed, and evidence was obtained that bicyclooctatriene **378** and semibullvalene **379** were also intermediates in the complex reaction sequence. When heated, isomers **373**, **374**, **375** and **377** all rearranged quantitatively to tetraene **376**. The cubane was the most stable thermally; *ca* 70% survived after 4 h at 300 °C.

2. Cyclobutenes and cyclobutadienes

Photolysis of **380**, the Diels–Alder adduct of hexafluoro-2-butyne with *N*-tosylpyrrole, yielded azaquadricyclane **381** (equation 71)[211]. Upon heating, **381** underwent internal 1,3-dipolar cycloreversion to **382**, which was trapped with dimethyl acetylenedicarboxylate to afford adduct **383**. Similarly, irradiation of the adduct of hexafluoro-2-butyne with furan (**384**) gave oxaquadricyclane **385** (Scheme 47)[212]. Heating **385** resulted in both possible 1,3-dipolar cycloreversions, giving **386** and **387** as intermediates en route to oxepins **388** and **389**. The oxepins were unstable with respect to their benzene oxide valence isomers **390** and **391**, which were formed in the ratio 1:5. When the reaction was carried out at 100 °C in the presence of excess dimethyl acetylenedicarboxylate, 1,3-dipolar species **386** was trapped, but not the more hindered **387**. Thus, the product comprised adduct **392** and benzene oxide **391** in the ratio 1:5 (equation 72).



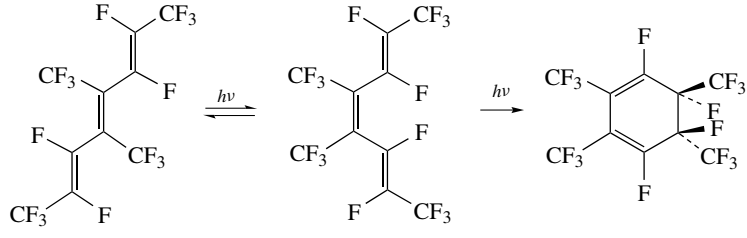


SCHEME 47

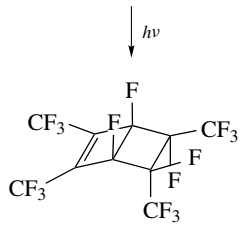
Irradiation at 254 nm of the mixture of triene isomers (*E*,*E*,*E*)- and (*E*,*Z*,*E*)-**393** interconverted them and cyclized the latter in conrotatory fashion to hexadiene **394** (equation 73)[213]. Bicyclohexene **395** gradually appeared after long photolysis times, and was formed quantitatively when pure **394** was photolyzed through either pyrex or quartz.

Treatment of cyclopropenyl ketone **309** with titanium tetrachloride at −78 °C followed by trifluoroacetamidine afforded diazatricycloheptene **396** (equation 74)[214]. The authors propose that imine **397** forms and then undergoes a novel electrocyclization to give **396**. Though **396** is quite stable thermally, it rearranges rapidly in acetone or methanol to cyclobutene derivative **398**. A plausible mechanism entails ring opening of the conjugate base **399** followed by bond migration (equation 75)[215]. The **396** → **398** transformation was also accomplished by photolysis at 254 nm, and further irradiation resulted in fragmentation of **398** into hexafluoro-2-butyne and imidazole **400** (equation 76).

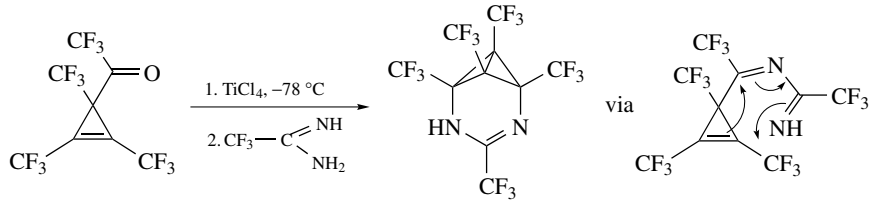
Perfluorohexamethylbenzvalene (**289**) added in Diels–Alder fashion to butadiene, giving **401** (Scheme 48)[216]. Bromination, then dehydrobromination transformed **401** into the diene **402**. Photolysis of **402** resulted in cyclization to stereoisomeric cyclobutanes **403** and **404** instead of the hoped-for fragmentation to 1,2-bis(trifluoromethyl)benzene (**365**) and perfluorotetramethyltetrahedrane (**405**). Flash pyrolysis effected cleavage in the desired



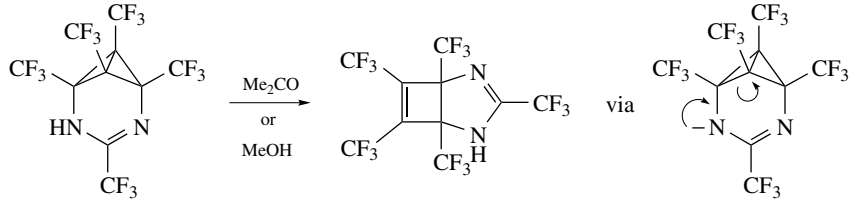
(*E*,*E*,*E*)-(**393**) (*E*,*Z*,*E*)-(**393**) (**394**)



(**395**) (73)

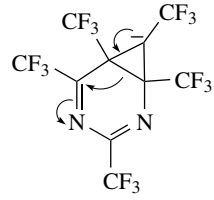


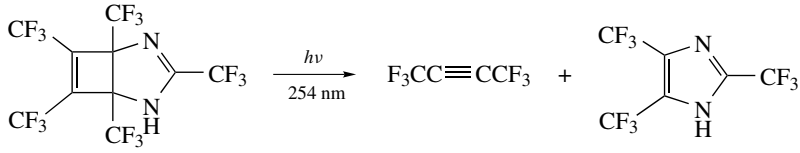
(**309**) (**396**) (**397**) (74)



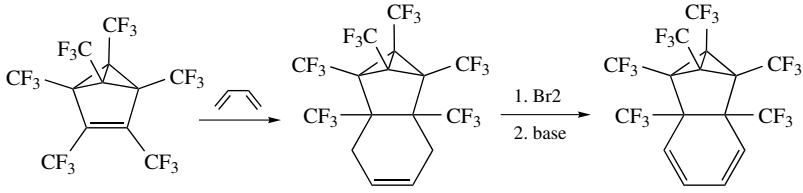
(**396**) (**398**) (**399**)

(75)

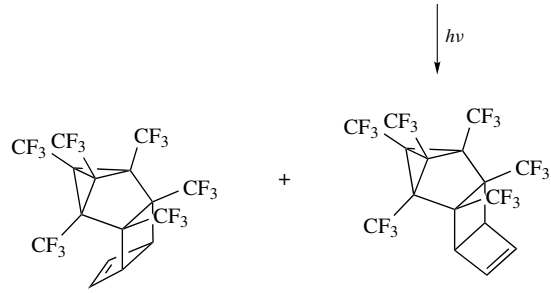




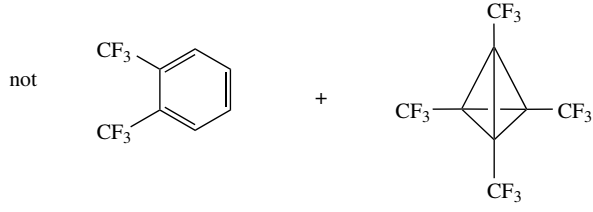
(398) (400) (76)



(289) (401) (402)



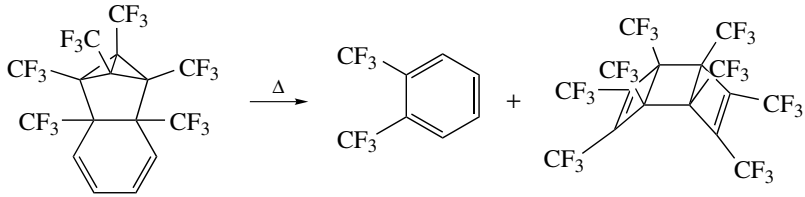
(404) (403)



(365) (405)

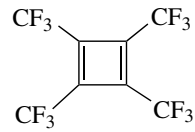
SCHEME 48

sense, but the product consisted of the benzene plus the *syn* dimer **377** formed from perfluorotetramethylcyclobutadiene (**406**) (equation 77).



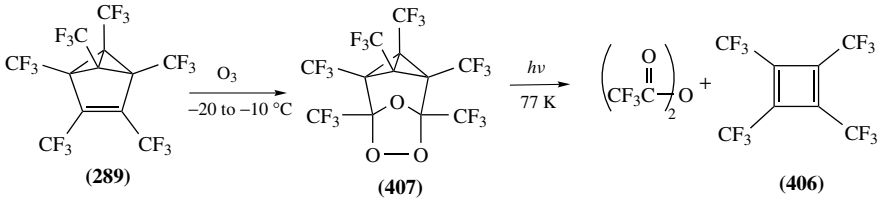
(402) **(365)** **(377)** (77)

via

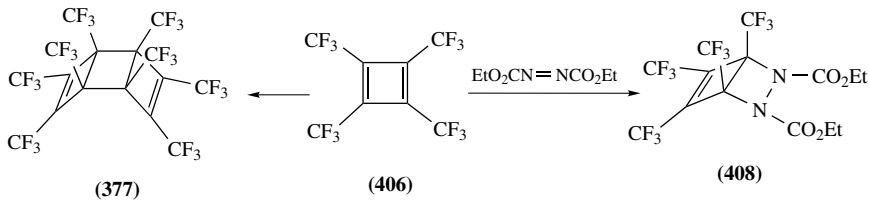


(406)

Ozonation of the benzvalene (**289**) yielded stable ozonide **407** (Scheme 49)[217]. Photolyzed at 77 K in a 3-methylpentane glass, the ozonide fragmented into trifluoroacetic anhydride and the yellow cyclobutadiene **406**. Upon thawing, the glass lost its color and crystals of the dimer **377** deposited. When diethyl azodicarboxylate was present during the photolysis Diels–Alder adduct **408** was subsequently isolated. A later study revealed that the cyclobutadiene dimerizes only slowly at 145 K, and its UV, IR and ^{19}F NMR spectra were obtained in solution at slightly lower temperatures[218]. In the hope of obtaining tetrahedrane **405**, ozonide **407** was photolyzed at 4–10 K. Though a small amount of an unidentified, labile compound was generated, the principal product ($\geqslant$90%) was again the cyclobutadiene.



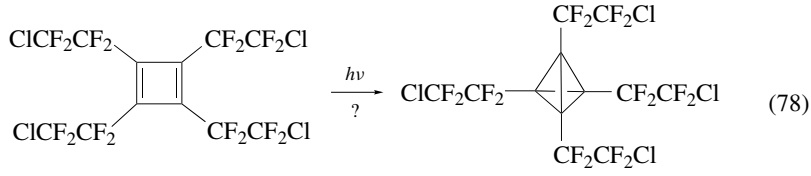
(289) **(407)** **(406)**



(377) **(406)** **(408)**

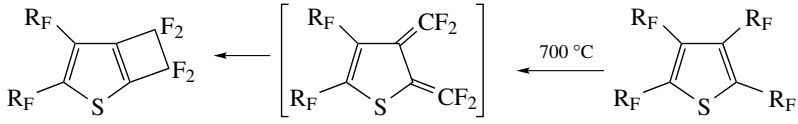
SCHEME 49

The finding that photolysis of tetra-*t*-butylcyclobutadiene yielded the corresponding tetrahedrane[219] suggested the possibility that a cyclobutadiene bearing sufficiently bulky perfluoroalkyl groups would cyclize analogously to give the first electron-deficient tetrahedrane, as illustrated with the hypothetical transformation **409** → **410** (equation 78). With this in mind, thiophene **411** was subjected to flash vacuum pyrolysis on the chance that it was hindered enough to cyclize thermally to its Dewar isomer (**412**) in analogy to perfluorohexaethylbenzene (**294**)[220]. That did not occur, but at 700 °C **411** was converted into cyclobutenothiophene **414**, presumably via thiophenoquinone dimethide **413** (equation 79). Irradiation of the thiophene at 254 nm in the vapor phase gave the desired Dewar isomer **412**, paralleling the photoisomerization of perfluorotetramethylthiophene (**303**).



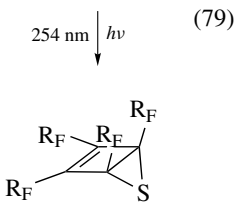
(78)

(409) **(410)**



(414) **(413)** **(411)**

$R_F = CF_2CF_2Cl$

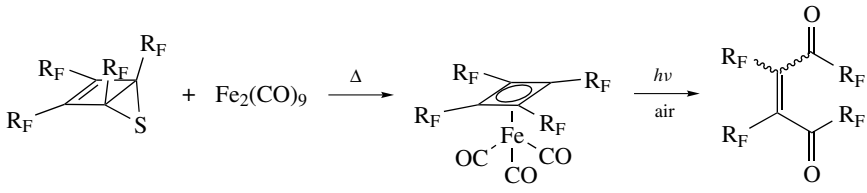


(79)

(412)

Attempts by several methods to transform **412** into cyclobutadiene **409** were unavailing, but treatment with diiron nonacarbonyl yielded cyclobutadieneiron complex **415** (equation 80). Photolysis of **415** with visible light in degassed hexane afforded an unidentified compound that reverted to starting material in the dark, but photolysis with air present yielded enedione **416**. Cyclobutadiene itself reacts with oxygen analogously, giving malealdehyde[221], but it appears that free diene **409** was not generated in the photolysis because irradiation of **415** in the presence of furan did not produce a furan–diene adduct. Mild oxidation suffices to release the ligand from typical cyclobutadiene–iron complexes[222], but **415** resisted attack by a variety of strong oxidizing agents, including

ozone. Thus, cyclobutadiene **409** remains elusive, and the question mark in equation 78 persists.



(412) **(415)** **(416)**

$R_F = CF_2CF_2Cl$ (80)

V. AFTERWORD

Clearly, four-membered rings have played a major role in the development of organofluorine chemistry, and have enriched its literature with a wealth of interesting and diverse transformations. This chapter is hardly comprehensive, but the authors hope that by conveying a sense of what has been accomplished in the chemistry of fluorinated cyclobutane derivatives, it will serve as a stimulus for exciting advances in the future.

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CHAPTER **22**

Cyclobutane pyrimidine dimers as UV-induced DNA lesions

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I. INTRODUCTION

UV irradiation of cells is one of the most dangerous exogenous events, leading to the formation of a variety of DNA modifications[1–3] such as cyclobutane pyrimidine dimers (CPD), (6-4) photoproducts and spore photoproducts depicted in Scheme 1. Many of the formed photoproducts in DNA are involved in the development of skin cancer[4–8]. The most prominent UV lesions are cyclobutane pyrimidine dimers (CPD lesions such as TT *cis-syn*). These lesions form in a photochemically allowed $[2\pi_s + 2\pi_s]$ cycloaddition reaction between two adjacent pyrimidine bases (thymine [T] and cytosine [C]) in DNA. The reaction proceeds out of the excited triplet state of the corresponding bases. Because thymine has the energetically lowest lying triplet state of all DNA bases, most CPD lesions are formed between neighboring thymines. The cycloaddition to give CPD lesions can in principle yield four different isomers (*cis-syn, trans-syn, cis-anti* and *trans-anti*). However, due to the connectivity of the bases and the constraints imposed by the double helix environment the major photoproduct formed in double helical DNA is the *cis-syn* dimer[9–11].

The high biological relevance of the *cis-syn* CPD lesion for UV induced carcinogenesis[7,8] has spurred the interest to synthesize model compounds and also the lesion itself in order to investigate the lesion formation reactions and the lesion repair processes by DNA repair enzymes such as the light-dependent repair protein DNA photolyase[12,13]. A second major goal was the synthesis of CPD phosphoramidite building blocks for the preparation of DNA strands containing a CPD lesion at a defined site for structural and biochemical analysis. The performed synthesis and research results obtained by studying the model compounds will be covered in this review.

II. SYNTHESIS OF URACIL AND THYMINE CPDS AS THE BASIS FOR THE DEVELOPMENT OF MODEL COMPOUNDS

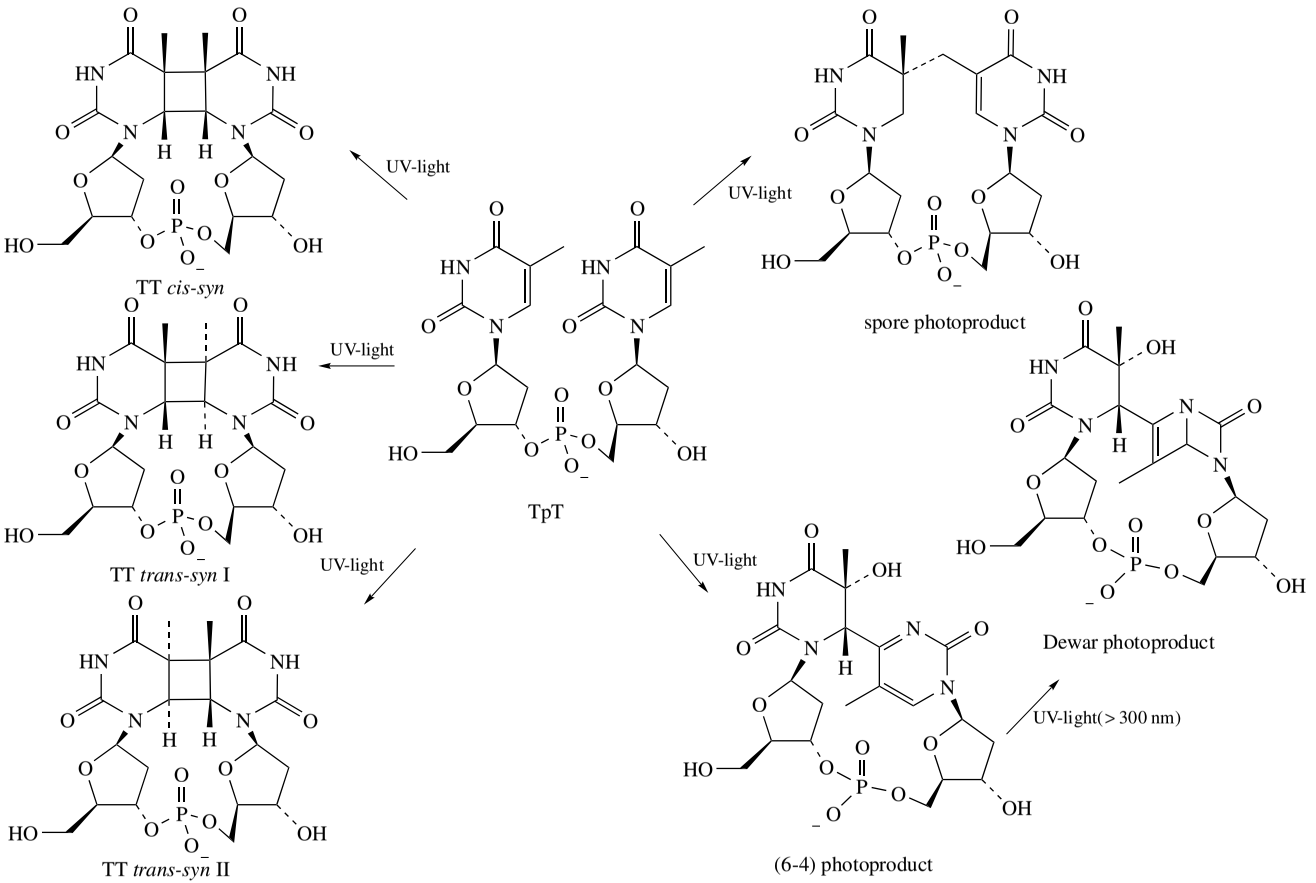
A. Irradiation of Non-covalently Linked Thymine and Uracil

1. Irradiation of thymine, uracil, dimethylthymine and dimethyluracil

The first synthesis of cyclobutane pyrimidine dimer goes back to the late 1950s and early 1960s when Beukers, Berends and coworkers discovered the formation of CPD lesions after UV irradiation of nucleobases[14–17] and DNA[18]. At the beginning the standard procedure for the preparation of photodimers was consequently based on the direct irradiation of frozen solutions of uracil **1** and thymine **2** or of derivatives thereof (Scheme 2). These experiments unequivocally established the formation of various CPD lesions (*cis-syn* **3** and **4**, *trans-syn* **7** and **8**, *cis-anti* **5** and **6**, *trans-anti* **9** and **10**) after UV irradiation of pyrimidine bases[19,20]. Several groups established independently that also the irradiation of solutions containing thymine and uracil or their *N*-methylated derivatives give CPD photoproducts in significant quantities, particularly after addition of triplet sensitizers such as acetone, acetophenone or benzophenone[21–28]. Already a few years later these triplet sensitized methods were employed for the preparation of CPD lesions in DNA as well[29,30].

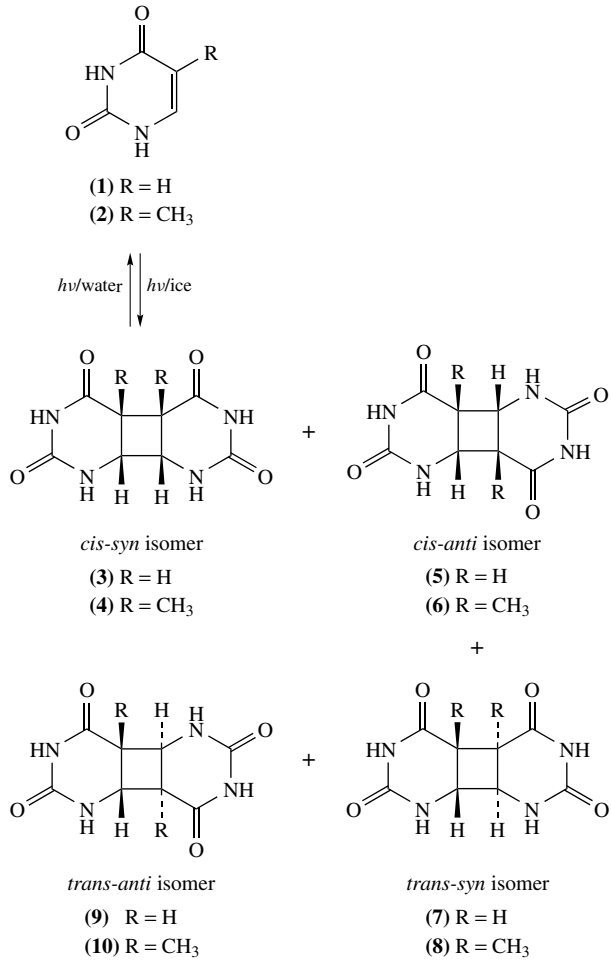
The material isolated after irradiation of frozen solutions allowed one to establish the structures of the CPD photoproducts by NMR spectroscopy[31–33], IR spectroscopy[34], chemical degradation[35–39] and X-ray crystallography[40–45]. The ability to prepare larger quantities of CPDs by triplet-sensitized irradiation enabled the preparation of the first model compounds and established that the reaction proceeds out of the triplet states of the involved molecules[46–49].

Further proof for the postulated molecular structures was gained through a total synthesis of all lesions by Fahr[39].



SCHEME 1. Various DNA lesions formed upon UV-irradiation of a TpT sequence

An important feature of the dimer formation process is the reversibility of the reaction. All dimers can be converted back into the monomers upon irradiation with light absorbed by the corresponding dimer species, which is in principle light of $\lambda < 300$ nm (Scheme 2).



SCHEME 2. Direct irradiation of uracil **1** and thymine **2** gives rise to cyclobutane pyrimidine dimers with different configuration of the cyclobutane moiety

B. Irradiation of Linked Thymine and Uracil Derivatives

The direct irradiation of pyrimidines yields, as depicted in Scheme 2, in general a mixture of all four possible isomers (**3**–**10**). Isolation of a single diastereoisomer requires inconvenient and low yielding chromatographic methods. The need to prepare larger quantities of the precious CPD material, e.g. for the synthesis of model compounds such as those developed by the groups of Rose[50–53], Begley[54] and Walsh[55], spurred the need to prepare CPD dimers as single isomers in larger quantities. These groups irradiated linked

pyrimidine derivatives, in which the linker forced the two pyrimidines to react exclusively to give the biologically most relevant *cis-syn* dimers.

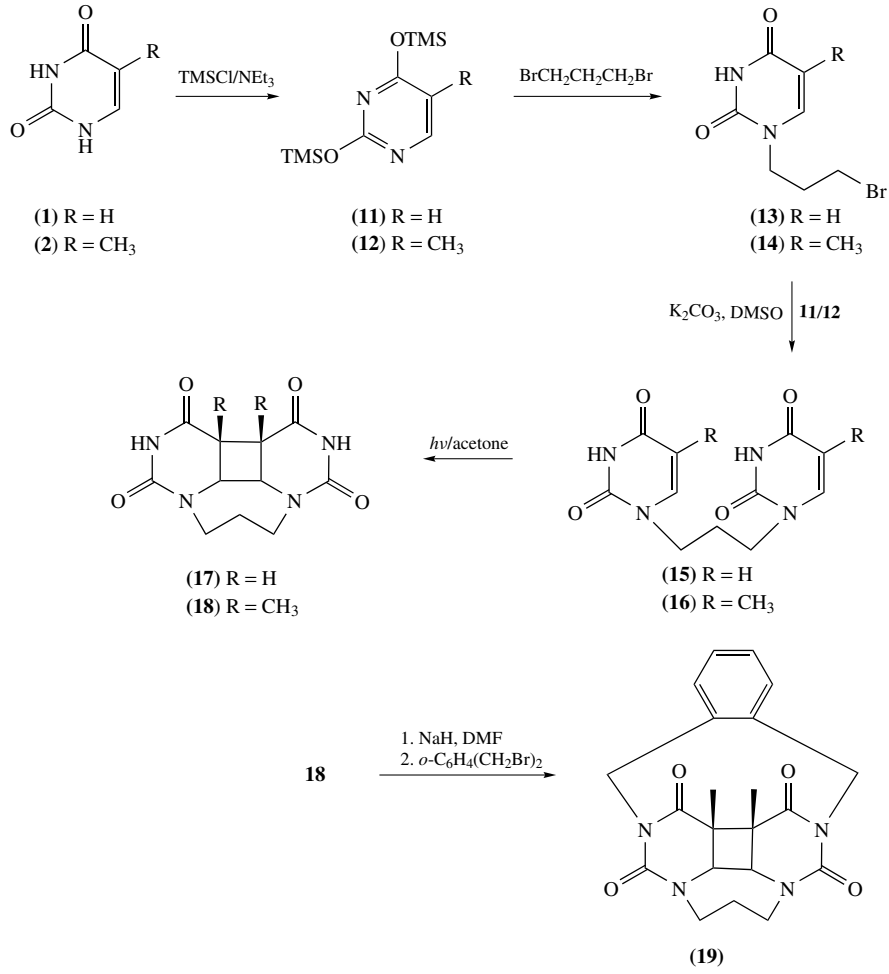
1. Non-cleavable N(1), N(1′)- and N(3), N(3′)-linked CPDs

The synthesis of C_3-linked pyrimidines was for the first time performed by Leonard and coworkers[56] from the natural nucleobases uracil **1** and thymine **2** in 1968 in order to study the intermolecular interactions of pyrimidines in the absence of the natural phosphodiester linkage (Scheme 3). Starting from bis(trimethylsilyl)uracil **11** or bis(trimethylsilyl)thymine **12** they prepared the $N(1),N(1')$ linked pyrimidines **15** and **16** in just two steps by coupling of two pyrimidines with 1,3-dibromopropane via the mono-alkylamide products **13** and **14**. Irradiation of the $N(1),N(1')$-linked bis-pyrimidines **15** and **16** with light of $\lambda = 300$ nm in aqueous solution (with or without a triplet sensitizer) furnished selectively only one of the four possible photodimers per pyrimidine (**17** and **18**). Due to the linker, only the formation of the *cis-syn* and *trans-syn* isomer is theoretically possible. Reaction of the resulting product of the thymine reaction with *o*-(dibromomethyl)benzene gave **19**[57], which established that the *cis-syn* isomer **18** was formed in this reaction as the only product (in the solid state also the formation of the *trans-syn* isomer was observed). Later, this procedure was also used to prepare the CPDs of cytosine such as the CC- and the CT-dimers by Falvey and coworkers[58] (Scheme 4). The reaction sequence started in this case with compound **15**, which was first converted into the dithione **20**. Reaction of **20** with dimethylamine furnished **21** which, upon irradiation, allowed synthesis of CC-CPD derivative **22**.

The synthesis of the alternative $N(3),N(3')$-linked photodimers depicted in Scheme 5 was also achieved[59]. Here, thymidine was the starting material. Thymidine was first reacted with 1,3-dibromopropane to give the dinucleotide **23** followed by hydrolysis of the glycosidic bond using AcOH/HCl (2:1) to cleave the glycosidic bonds to give **24**. Irradiation of the $N(3),N(3')$-linked bis-thymine **24** furnished exclusively the desired *cis-syn* photodimer **25** (Scheme 5). The special length of the C_3-linker again forced the thymine to react selectively to the *cis-syn* dimers. However, the reactivity of the $N(3),N(3')$ linked starting material under UV-light, which splits the dimers back into the monomers, was found to be strongly reduced in comparison to the $N(1),N(1')$-linked systems. Under triplet sensitization conditions (10% acetone in water) both types of compounds showed a comparable back-reactivity[59].

Although the linkage approach allowed synthesis of the biologically relevant *cis-syn* dimers in large quantities, the unusual back-reactivity questions how well these linked dimers mimic the natural CPD lesions found in DNA. Here, a major criterion is how will these dimers open upon single electron reduction. DNA-photolyases are repair enzymes, which inject a single electron into CPD lesions[12, 13]. This induces a rapid and spontaneous cycloreversion of the dimer, which in the genome of human organisms leads to the repair of UV-damaged sites.

Photo-CIDNP studies showed that in $N(1),N(1')$-trimethylene-bridged dimers the initial cleavage of the C(5)−C(5′) bond after electron injection is, in contrast to unbridged dimers, reversible[60, 61]. The X-ray crystal structure of the $N(3),N(3')$-trimethylene bridged dimer reveals in addition an almost planar cyclobutane ring, in contrast to the natural unbridged dimers which feature a pronounced cyclobutane ring twist of approximately -28° (CB^- pucker)[62]. This twist is believed to be an important factor influencing the reactivity of the dimer after single electron reduction[63–65] (the SOMO of the carbonyl group overlaps with the σ^*-orbital of the C(5)−C(5′) bond). This observation is another warning sign that the linked CPD dimer models may have limitations in their ability to mimic the physico-chemical properties of the natural CPD lesions.



(**1**) R = H
(**2**) R = CH_3

(**11**) R = H
(**12**) R = CH_3

(**13**) R = H
(**14**) R = CH_3

(**15**) R = H
(**16**) R = CH_3

(**17**) R = H
(**18**) R = CH_3

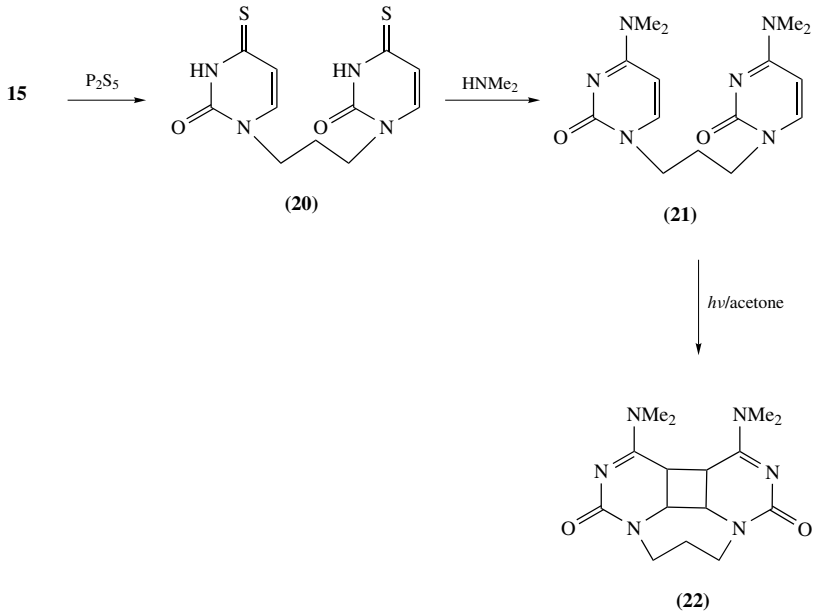
(**19**)

SCHEME 3. Irradiation of C_3-linked bis-pyrimidines to give exclusively the desired *cis-syn* CPD compounds

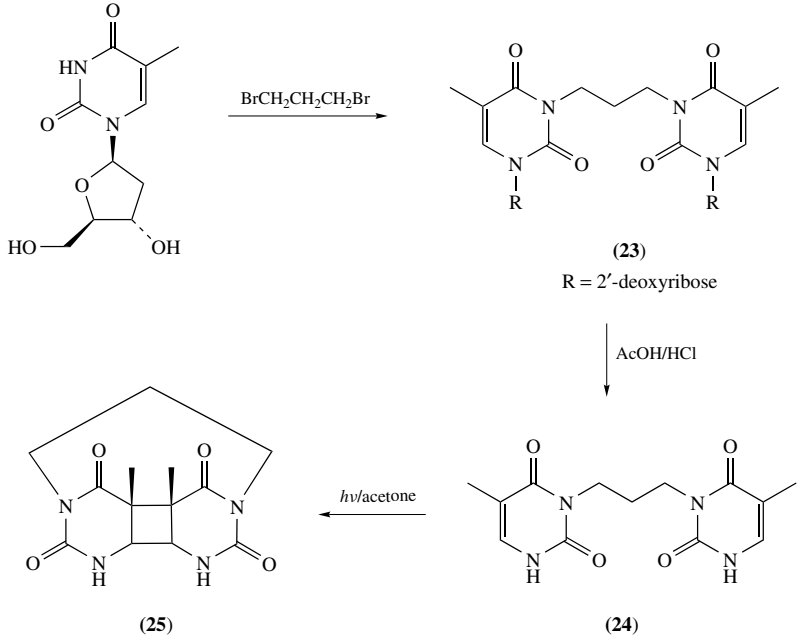
For the construction of suitable model compounds it was therefore desirable to prepare unbridged but functionalized *cis-syn* thymine dimers in large quantities.

2. Development of cleavable linkers

Begley and coworkers devised a short linker, which was designed to be cleaved after the photochemical reaction[66] (Scheme 6a). First, *N*(1)-methyl thymine **26** was linked with 1,4-dichloro-*cis*-2-butene to give first **27** and then the bis-thymine derivative **28**. Reaction of this compound after irradiation with light of $\lambda = 300$ nm in the presence of acetone as the triplet sensitizer furnished exclusively the *cis-syn* dimer **29**. In order to cleave the linker, the *cis-syn* compound was treated with pyridinium bromide perbromide in dichloromethane, which gives a 1:1 mixture of the *cis-syn/cis*- and *cis-syn/trans*-dibromide



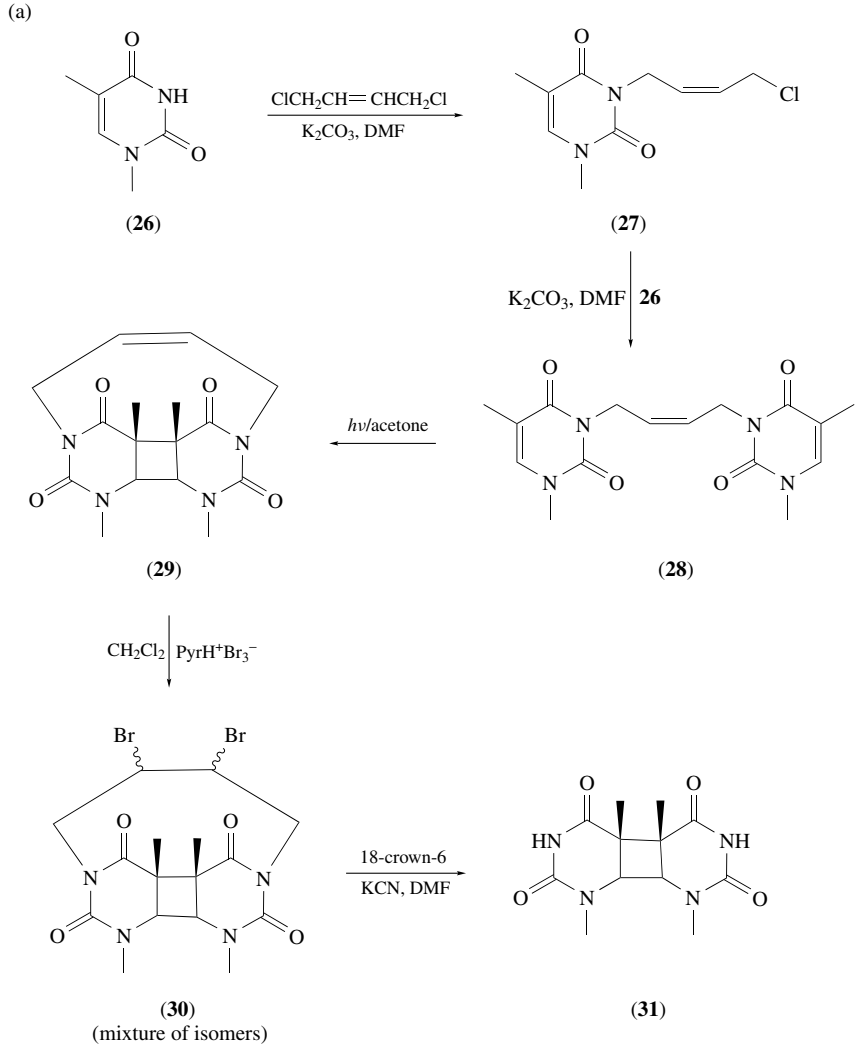
SCHEME 4. Synthesis of C_3-linked cytosine CPD compounds



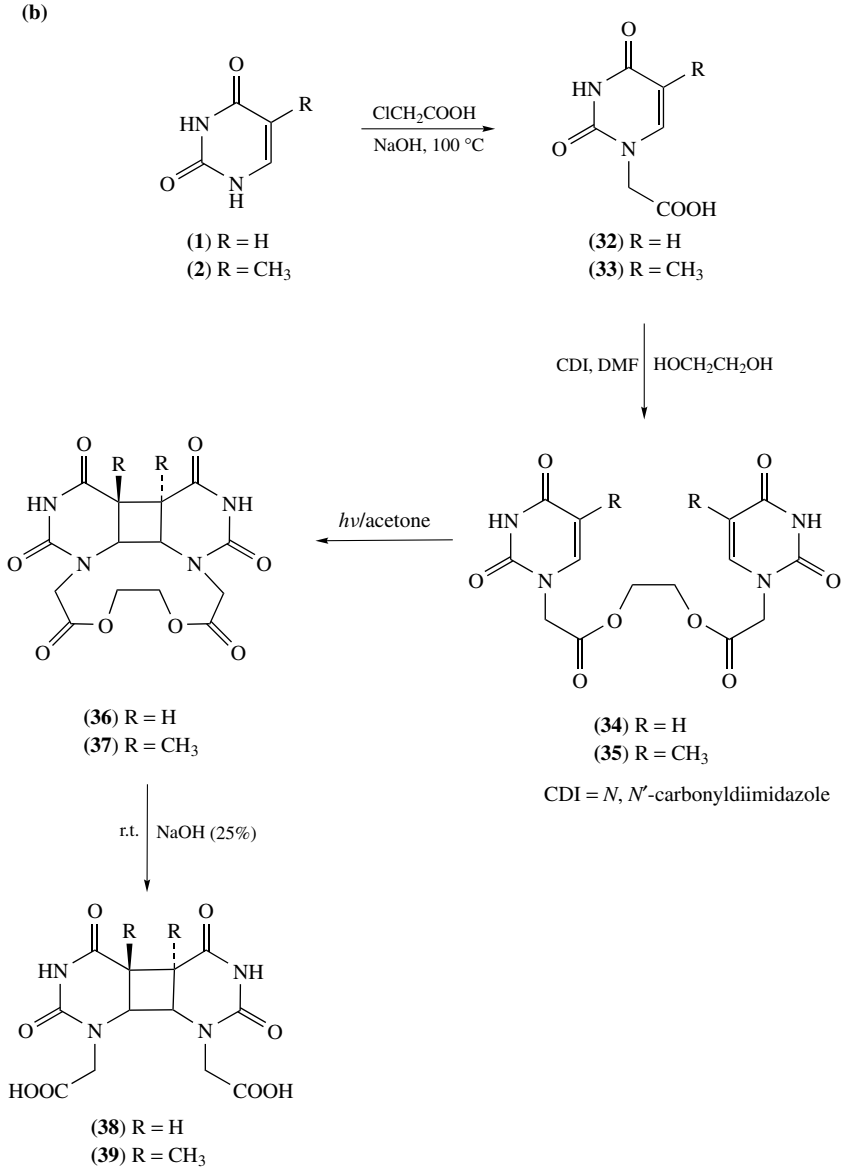
SCHEME 5. Synthesis of $N(3),N(3')$-linked CPD dimers

30. This mixture was reacted with 18-crown-6 and KCN in DMF in order to cleave the linker to give **31**. Although this enabled selective synthesis of the unlinked *cis-syn* dimer, the cleavage yield was with just 30% finally too low to allow broad application of the method for the synthesis of *cis-syn* dimers.

This problem was seemingly solved when Schultz and colleagues introduced ethylene glycol linked carboxymethylthymine as the starting material for the synthesis of *cis-syn* dimers[67,68] (Scheme 6b). The material is readily available by first reaction of thymine or uracil with chloroacetic acid to give **32** and **33** and reaction of the resulting carboxymethylpyrimidines with ethylene glycol to give **34** and **35**. Irradiation of the linked



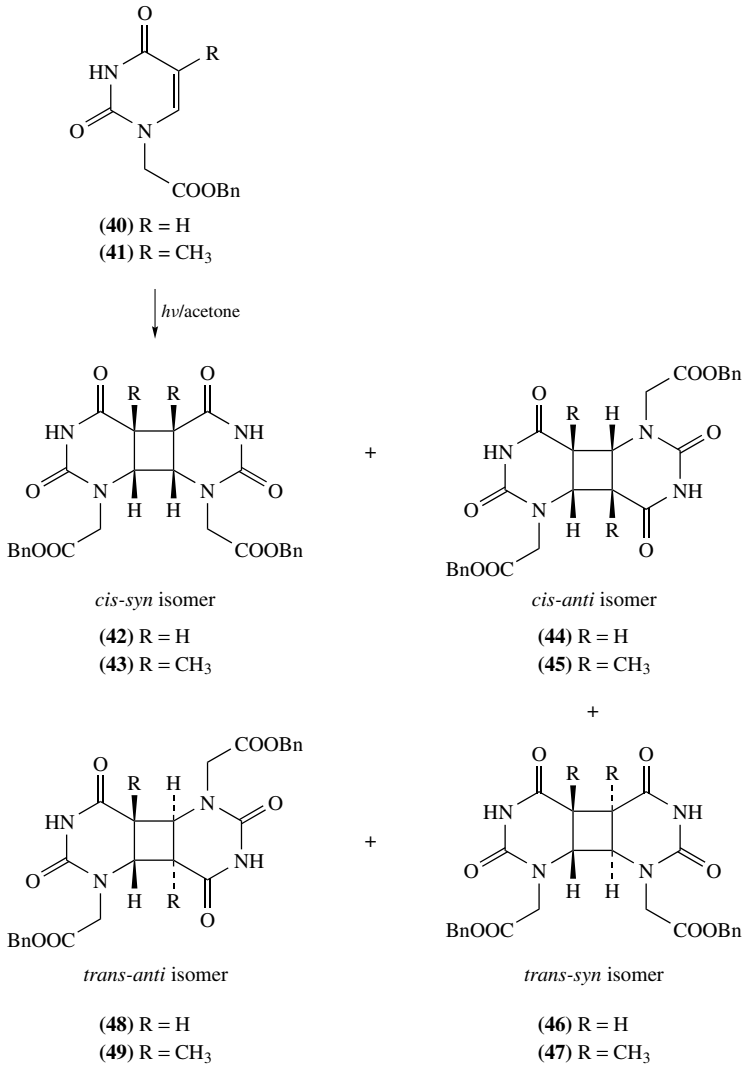
SCHEME 6. Synthesis of CPD lesions using cleavable linkers by Begley[66] (a) and Schultz[68] (b)



SCHEME 6. (*continued*)

bis-thymine and bis-uracil compounds **34** and **35** was long believed to produce exclusively the *cis-syn* dimer in high yields. Final saponification of the ester bonds was then believed to give *cis-syn* cyclobutane pyrimidine dimers with the ability for further derivatization. Antibodies were raised against these dimers[67] and synthetic receptors were reported, which were supposed to recognize the *cis-syn* dimer compound[68]. Later, however, it was

found that the original stereochemical assignment was wrong. The ethylene glycol linked pyrimidines give upon irradiation exclusively the *trans-syn* compounds **36** and **37**, which furnish after cleavage of the linker unit the *trans-syn* dimers **38** and **39**. The observation that longer linkers favor formation of *trans-syn* compounds is also supported by a study of Ganesh and coworkers, who obtained exclusively *trans-syn*-configured cyclobutane photodimers upon irradiation of various $N(1),N(1')$-polyoxyethylene-linked bis-thymine and bis-uracil compounds[69].

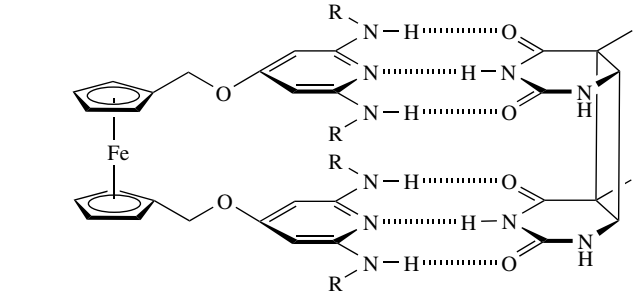


SCHEME 7. Carell synthesis of all possible CPD dimer diastereoisomers of thymine and uracil[70]

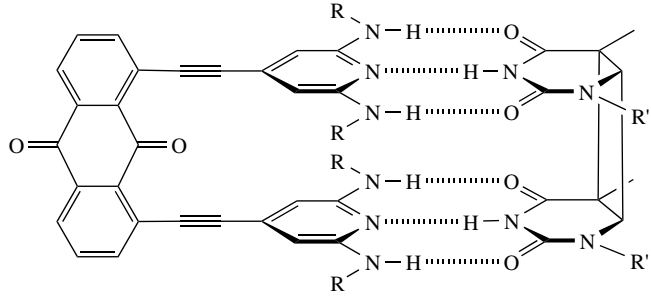
C. Irradiation of *N*(1)-Carboxymethylthymine and *N*(1)-Carboxymethyluracil

Carell and coworkers irradiated the benzyloxycarbonylmethyl uracil **40** and thymine **41** in order to obtain functionalized *cis-syn* cyclobutane pyrimidine dimers[70,71] in high yields as depicted in Scheme 7. These compounds were irradiated in the presence of acetone as a triplet sensitizer giving of course all four possible stereoisomers **42**–**49** for both types of compounds. If the benzyl esters were chosen as the starting material for irradiation, then all four diastereoisomers of uracil and thymine can be readily separated by a combination of selective precipitation, chromatography and recrystallization. X-ray crystal structure analyzes of the *cis-syn*- and the *trans-syn*-configured uracil dimers **42** and **46** as well as of all four thymine dimers **43**, **45**, **47**, **49** in combination with NMR-spectroscopic investigations allowed the unambiguous assignment of all four uracil and thymine dimer structures. The cleavage of the benzyl ester protecting groups was readily achieved using catalytic hydrogenation. This now allows synthesis of all, and in particular of the *cis-syn* dimers of uracil and thymine dimer dicarboxylic acids, in gram quantities as required for the preparation of model compounds.

Very recently this dimer synthesis was used to prepare *cis-syn* CPD compounds to study the recognition of such compounds by new synthetic receptors prepared by Inouye and coworkers[72] and Wiest and coworkers[73] (Figure 1).



R = Ac *cis-syn* dimer



R = $COCH_3$ *cis-syn* dimer
R = COBu-*n* R' = CH_2CO_2Bn

FIGURE 1. *Cis-syn* dimer recognizing receptors

III. CPD CLEAVAGE INVESTIGATIONS

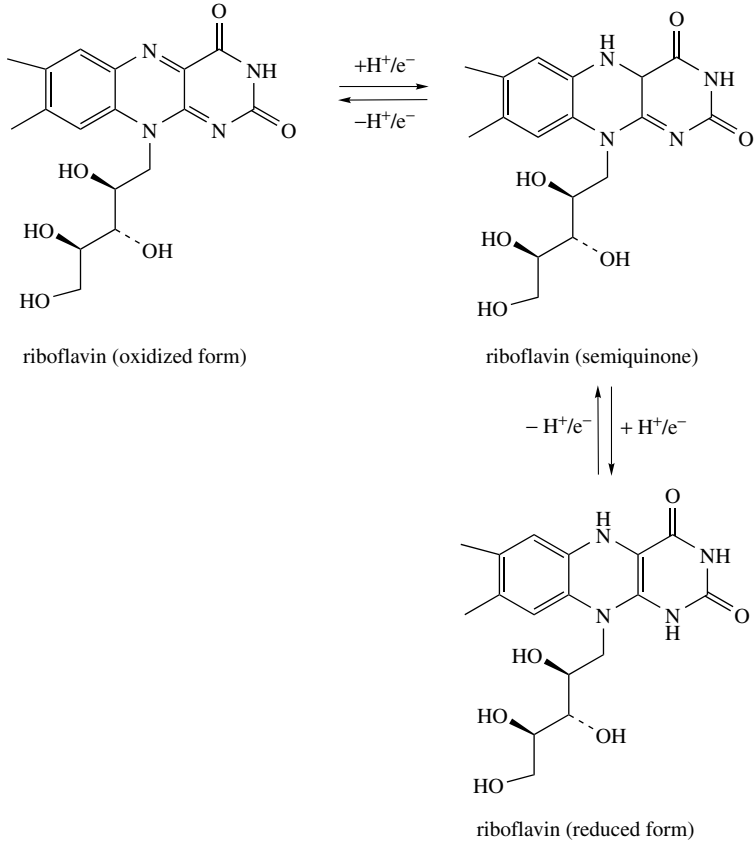
DNA photolyases are repair proteins, which inject a single electron into CPD lesions in order to split the dimers back into the monomers[12,13]. These DNA repair proteins utilize a reduced, deprotonated and light-excited flavin to inject the genome-repairing electron. Much of our knowledge about the flavin-induced reductive cleavage of pyrimidine photodimers has come in the past from model studies, which involve the analysis of compounds in which cyclobutane pyrimidine dimers are covalently connected to flavins.

Early studies showed that cyclobutane pyrimidine dimers can be split either reductively as their radical anions in the presence of electron-donating photosensitizers such as 2-methylindole or 1,4-dimethoxybenzene derivatives or reduced flavins[53,74], or oxidatively as their radical cation. The latter case requires the presence of strong oxidizing photosensitizers such as anthraquinone sulfonate, 9,10-dicyanoanthracene, *p*-chloranil, 1,4-dicyanobenzene, oxidized flavins or nitrate radicals[51,63,75–77].

A. Oxidative Cleavage of CPD Dimers

The observation that dimers can be repaired either by electron donation or electron abstraction initially raised the question, which of the two possible mechanisms photolyases would employ for the genome-repair process. One of the first experiments with flavin photosensitizers were performed by Lamola[78], who observed that oxidized flavins are unable to cleave photodimers at neutral pH. A systematic investigation by Rokita and Walsh with a variety of flavins and 5-deazaflavins revealed, however, that an inefficient light-induced cleavage of pyrimidine dimers with flavins as photosensitizers (riboflavin in the reduced and oxidized redox state is shown below) is possible but requires very high pH values (pH > 10)[79]. Under these conditions, significant deprotonation of the dimer unit seems to occur ($pK_a = 10.7$)[80]. Results of this study led initially to the proposal that electron transfer from the deprotonated dimer to the oxidized, light-excited flavin could be the initial step of the cleavage reaction. Irradiation of the covalently linked flavin dimer model compound, prepared by Hartman and Rose (Figure 2), showed that flavins are able to photosplit dimers under very acidic conditions as well[51]. Addition of perchloric acid to the model compound solution is strictly required for the light-induced dimer cleavage. Since perchloric acid may readily protonate the oxidized flavin chromophore ($pK_a = 0$)[81], the dimer cleavage was explained by the potential ability of the light-excited, protonated flavin (FlH^{+*}) to abstract an electron from the dimer, which then may split as the radical cation ($Dimer^{+\bullet}$). Similar observations were also reported by Pac and coworkers, who showed that the irradiation of solutions containing 1,3-dimethylthymine dimer and tetraacetylflavin in the presence of perchloric acid yields rapid photosplitting[82]. The presence of molecular oxygen was observed to accelerate the photo-induced cleavage[83]. The same authors reported that perchloric acid can be replaced by magnesium perchlorate[84]. In this case the (flavin)magnesium complex present is assumed to be the photo-active cleavage agent. The authors argue that the electron-deficient (flavin) magnesium complex might, in a light-induced process, abstract an electron from the dimer unit, which would then cleave as its dimer radical cation ($Dimer^{+\bullet}$).

The general oxidative cleavage mechanism is believed to involve first electron abstraction from the dimer followed by cleavage of the C(6)−C(6′) bond of the cyclobutane ring[54]. Cleavage of the C(5)−C(5′) bond is believed to proceed thereafter so that the whole process does not follow a concerted mechanism. A trapping experiment performed by Burdi and Begley allowed them to catch an intermediate[85] and also indirect methods such as isotope effects[86] and photo-CIDNAP studies[60,87] support the postulated stepwise opening mechanism. Further support comes from calculation, which predicts no barrier



for the cleavage of the C(6)−C(6′) bond after electron transfer of the radical cation and an activation barrier for the cleavage of the C(5)−C(5′) bond of about 59 kJ mol^{-1} [88].

B. Reductive Cleavage of CPD Dimers

Cyclobutane pyrimidine dimer radical anions form after electron transfer from photo-excited indoles[51,74], dimethoxybenzene[53,89], catalytic antibodies[67,68] (here it is likely a photo-excited tryptophane), photo-excited and reduced flavins[90–92] or photo-excited dimethylaniline[89,93]. The cleavage of the dimer proceeds likely with a rate of $k_{\text{cleavage}} = 1.8 \times 10^6$ s^{-1} [93]. Our mechanistic understanding of the cleavage process is so far rudimentary and various different scenarios can be envisioned[54]. The cleavage process can proceed stepwise by first cleavage of the C(5)−C(5′) bond and then of the C(6)−C(6′) bond. The cleavage can alternatively be non-synchronous but concerted. Another point of debate is the question at which point the extra electron is donated back to the sensitizer. Does this happen after the dimer is completely split, from a thymine radical anion, or is the electron transferred back from an intermediate with an opened C(6)−C(6′) bond? Photo-CIDNAP studies offered insight into these questions[61] and today it is clear that the

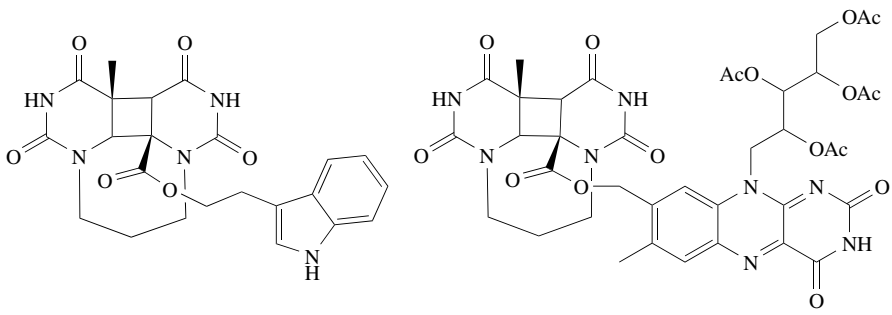


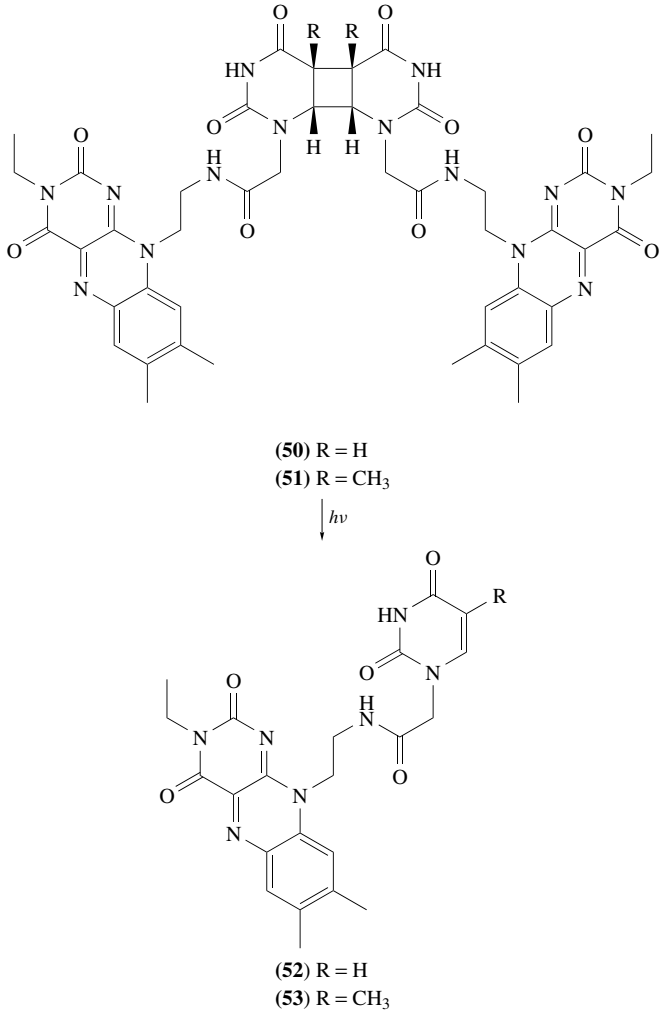
FIGURE 2. Early covalent model compounds synthesized and investigated by the Rose group[50,51]

thymine radical anion is an intermediate on the pathway to complete dimer splitting at least in solution. The extra electron has the highest probability at C(4) and C(6). EPR studies show that the radical anion of a *cis-syn* cyclobutane thymine dimer cleaves rapidly above 77 K[94]. All these studies suggest that the back electron transfer proceeds after complete dimer splitting. In order to clarify whether the dimer cleavage is stepwise or concerted, Begley and coworkers[95] as well as Fenick and Falvey[96] attempted to trap the 'one-bond-cleaved' intermediates. These experiments however failed, indicating that even in a stepwise mechanism C(6)−C(6′) and C(5)−C(5′) bond scission rapidly follows each other. Isotope studies revealed also a mixed picture[65,68,86]. Calculation predicts an almost concerted, slightly non-synchronous cleavage of the dimer unit: first of the C(5)−C(5′) bond followed by the C(6)−C(6′) bond[65,88]. The activation energy was calculated to be about 20 kJ mol^{-1} for the first bond scission and 22 kJ mol^{-1} for the cleavage of the second bond.

In nature it is today clear that photolyases utilize the reductive mode to repair thymine dimers. Strongest support for this statement stems again from model compound studies with flavins. Jorns[90] was the first who could show that, upon illumination of solutions containing a thymine dimer and various oxidized and reduced flavins and deazaflavins, rapid dimer cleavage was observable by a reduced tetraacetylflavin. The authors report the necessity to perform the cleavage reaction at rather basic conditions (pH $\geqslant$ 9). A more detailed investigation of the reductive cleavage reaction and its pH dependence with reduced flavins as photosensitizers was later reported by Hartman and Rose[92] with solutions of flavins and dimers and covalent model compounds (Figure 2). Irradiation of a solution containing reduced tetraacetylriboflavin, and dimethylthymine dimer, showed that the reduced flavin can initiate a cleavage chain reaction, giving rise to high quantum yields (up to $\phi = 1.3$). This high quantum efficiency allowed the group to obtain a pH profile of the chain reaction. This study revealed half maximum dimer cleavage at pH $\approx$ 7.5 and maximum splitting efficiency at pH $\approx$ 8.5. Although both values are not in agreement with the pK_a value of the reduced flavin (p$K_a = 6.5$)[81], this investigation provided the first chemical evidence that the efficient dimer cleavage might require the *reduced flavin species* in its *deprotonated form*[53].

IV. INVESTIGATIONS WITH COVALENTLY LINKED MODEL COMPOUNDS

From the studies above it became apparent that further insight into the flavin-induced cleavage of cyclobutane pyrimidine dimers would only be possible with covalently linked model compounds, which are able to mimic the splitting reaction more efficiently. To this end the Carell group prepared a series of flavin thymine dimer and flavin uracil dimer



SCHEME 8. Covalent flavin-CPD model compounds for the DNA photolyase DNA repair enzyme prepared by the Carell group[91,97]

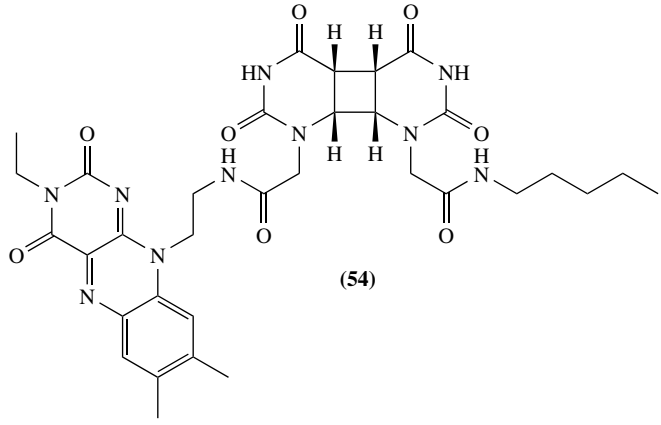
model compounds such as **50** and **51** shown in Scheme 8[71,91,97]. Initial light-induced cleavage experiments clarified the ability of these model compounds to mimic the enzymatic cleavage (repair) reaction. For the cleavage experiments the model compound such as **50** was dissolved in various solvents in standard UV cuvettes. The solutions were intensively deoxygenated and the flavins were reduced, e.g. by addition of dithionite (no reaction with the CPD was established by control measurements). Photoreduction or catalytic hydrogenation could also be employed[98]. The reduced samples were irradiated with monochromatic light. After certain time intervals, small aliquots were removed from the solution and analyzed by reversed-phase HPLC. These studies confirmed that only the reaction of the model compound containing a fully reduced flavin (FlH^-) gives a clear

and efficient splitting of the dimer to **52** and **53**. The quantum yield for the reaction was determined to be $\phi = 10\%$[91]. The observation that the irradiation of a solution containing just a CPD dimer such as **42** or **43** yielded no photoproduct under the same reaction conditions proves the strict intramolecularity of the splitting process. No photocleavage was observed in the absence of a reduced flavin or without prior reduction of the flavin chromophore, which proved the strict requirement for a covalently attached, reduced flavin moiety. The clean light-induced conversion into the photosplit products and the negligibility of the background reaction made these models ideal candidates for the intended systematic investigation of the dependencies of the flavin-induced cleavage reaction.

A. Investigation of the pH Dependency of the Cleavage Reaction[91]

Investigation of the pH dependency of the splitting process was required in order to clarify how the deprotonation of the reduced flavin chromophore affects the cleavage reaction. The monoflavin–monopentylamide model compound **54** was chosen for these experiments due to the superior solubility in organic and aqueous solvents. Figure 3 shows the quantum yields obtained for the photocleavage of **54** at $\lambda = 366$ nm in water, buffered at various pH values. Very low cleavage activity is observed below pH = 6 and maximal splitting rates were measured above pH = 7. Intermediate rates were obtained between pH = 6 and 7. These data are in full agreement with the pK_a value of the reduced flavin ($pK_a = 6.5$)[81] and therefore support the assumption that the deprotonation of the reduced flavin is absolutely required for the efficient photo-induced splitting[92]. Further measurements in organic solvents (acetonitrile, ethanol and dioxane) support this result. As depicted in Table 1, no cleavage is observed in the absence of base. Addition of triethylamine, however, caused upon irradiation the immediate cleavage of **54**. The results can be interpreted as follows: Deprotonation of the reduced flavin species FlH_2 to FlH^- first increases the electron-donating capabilities of the flavin cofactor. If we, however, consider that the photocleavage can be initiated by various arylamine donors or indole derivatives, we believe that the absolute requirement to deprotonate the flavin is not readily explained by the need to increase the electron density. One of the factors which may influence the cleavage efficiency is the lifetime of the dimer radical anion$^{-\bullet}$[99,100]. Model flash photolysis investigations by Yeh and Falvey[93] with dimethylaniline as the electron donor showed that the dimer cleavage proceeds on the microsecond time scale ($k \approx 10^6$ s^{-1}). Electron transfer from a neutral electron donor, such as a reduced flavin (FlH_2), to the dimer would give a zwitterionic intermediate Donor$^{+\bullet}$-Dimer$^{-\bullet}$[101], which may possess a high driving force for charge recombination and therefore may yield a very short-lived intermediate. Photo-CIDNP studies, performed by Rustandi and Fischer, with a dimethylthymine dimer solution in acetonitrile, revealed that the dimer cleavage, if induced by a neutral donor (2-methoxyindole), is indeed not able to efficiently compete with the back electron transfer[74]. Electron transfer from a negatively charged electron donor, such as a reduced and deprotonated flavin (FlH^-), however, would yield a non-zwitterionic (charge-shift) intermediate FlH$^\bullet$-Dimer$^{-\bullet}$. Such a negatively charged intermediate may possess a much longer lifetime. In addition, the formed neutral flavin radical intermediate FlH$^\bullet$ possesses a significant stability, which can be further increased if it is bound as an FADH$^\bullet$ to the photolyase apoenzyme. In fact, most of the isolated DNA photolyases contain the FAD unit in the blue radical form[13,102]. A reasonable explanation for the need to deprotonate the reduced flavin could therefore be to avoid a zwitterionic intermediate!

Based on the available experimental data, in addition we cannot exclude that the intermediate FlH$^\bullet$-Dimer$^{-\bullet}$ undergoes further protonation and deprotonation reactions in order to gain an even better stabilized intermediate. Begley[103] suggested that the flavin radical might become deprotonated after the initial electron transfer due to its rather



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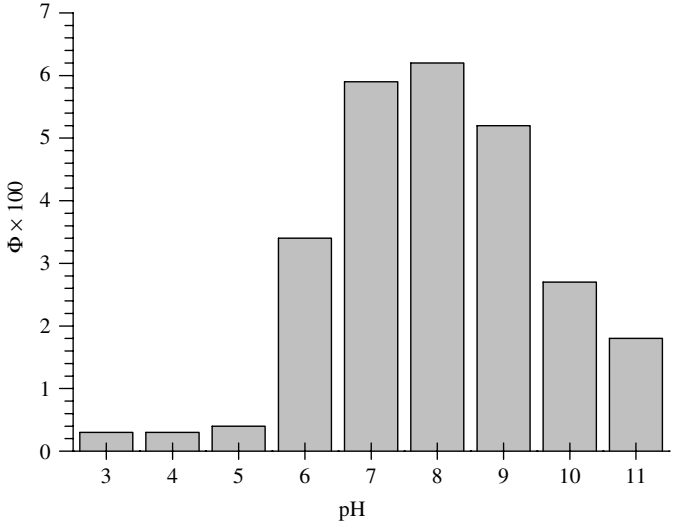


FIGURE 3. pH dependence of the splitting reaction of **54**

TABLE 1. Measurement of the quantum yield for the splitting reaction of model compound **54** in various solvents in the presence and absence of base

	$\Phi \times 100$ (no base)	$\Phi \times 100$ (50 μL NEt_3)
CH_3CN	n.d.[a]	4.6
EtOH	0.6	4.4
Dioxane	n.d.[a]	1.6

[a] Not detectable.

low pK_a ($pK_a = 6.5$)[81]. This would generate a double negatively charged $Fl^{-\bullet}$-Dimer$^{-\bullet}$ intermediate, which can undergo further dimer protonation to give an $Fl^{-\bullet}$-DimerH$^{\bullet}$ intermediate. All these intermediates could have significantly enhanced lifetimes.

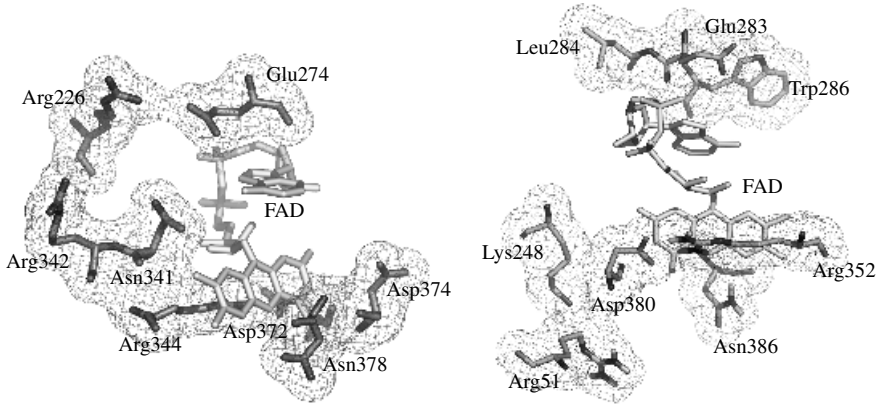
B. Investigation of the Solvent Dependency of the Cleavage Reaction

In order to gain support for a non-zwitterionic intermediate, solvent-dependent measurements were performed with the monoflavin–monopentylamide model compound **54**. Previous studies performed by Rose and coworkers[52,53,104] with donor-dimer model systems revealed a rather strong solvent dependence of the cleavage rate with high quantum yields ($\phi = 0.3$) obtained in the least polar solvent mixtures of 99:1 isopentane/dioxane[105].

Two sets of experiments were performed in order to clarify the solvent effect with the covalently linked flavin-containing model compounds. In the first set, the splitting rates were measured in water/ethanol and water/ethylene glycol mixtures. The most efficient cleavage was measured in pure water. Addition of ethanol or ethylene glycol reduced the cleavage efficiencies by a factor of not more than 2 to a quantum yield of about $\phi = 0.03$. A second set of experiments included measurements in various organic solvents (Table 1), using the catalytic reduction methodology.

Both sets of experiments showed increased splitting efficiencies in polar environments combined with a rather low total solvent dependence. The data are in full agreement with non-zwitterionic reaction intermediate(s) and therefore support the postulated charge shift process[91].

A close inspection of the FAD-binding pockets in type-I photolyases from *E. coli* and type-II photolyases from *A. nidulans*, a cyanobacteria, leads to the interesting observation that both enzymes bind the FAD cofactor in a highly conserved, rather polar environment (Figure 4a and b)[106–108]. In the *E. coli* enzyme, the flavin is positioned in van der Waals contact to a salt bridge formed by Arg344 and Asp372. The FAD is involved in hydrogen bonding via $O(2)$ to Glu274 (water-mediated) and via $O(4)$ to the backbone amide of Asp374. The $N(5)$ of the FAD is in close proximity to the side-chain oxygen atom of Asn378. In the reduced cofactor status, the N(5)H $\cdots$ O contact might contribute to the stability of the FADH$^{\bullet}$ radical and could be one of the essential features of the binding



(a) *E. coli* (b) *A. nidulans*

FIGURE 4. View of the flavin binding sites of DNA photolyases from *E. coli*[106] (a) and *A. nidulans*[107] (b)

pocket required for the stabilization of the $FADH^{\bullet}$ radical intermediate[109,110]. The $N(1)$ of the FAD is hydrogen-bonded to its own 3′-OH group, which was suggested to stabilize the negative charge of the $FADH^{-}$ [106]. Many polar amino acid side-chains like those of Arg226, Asn341 and Arg342 surround the FAD and contribute to the polarity of the binding pocket. Furthermore, the FAD is solvent-accessible through a hole in the protein, which is the putative dimer lesion binding side. All these interactions are highly conserved. The *A. nidulans* FAD-binding pocket (Figure 4b) contains also a salt bridge (Arg352 Asp380) in van der Waals contact to the flavin and features an identical set of amino acid side-chains around the FAD, with the $N(1)$ of the FAD hydrogen-bonded to the 3′-OH group and the $N(5)$ in close proximity to the Asn386.

V. SYNTHESIS OF URACIL AND THYMINE CPD PHOSPHORAMIDITE BUILDING BLOCKS[111]

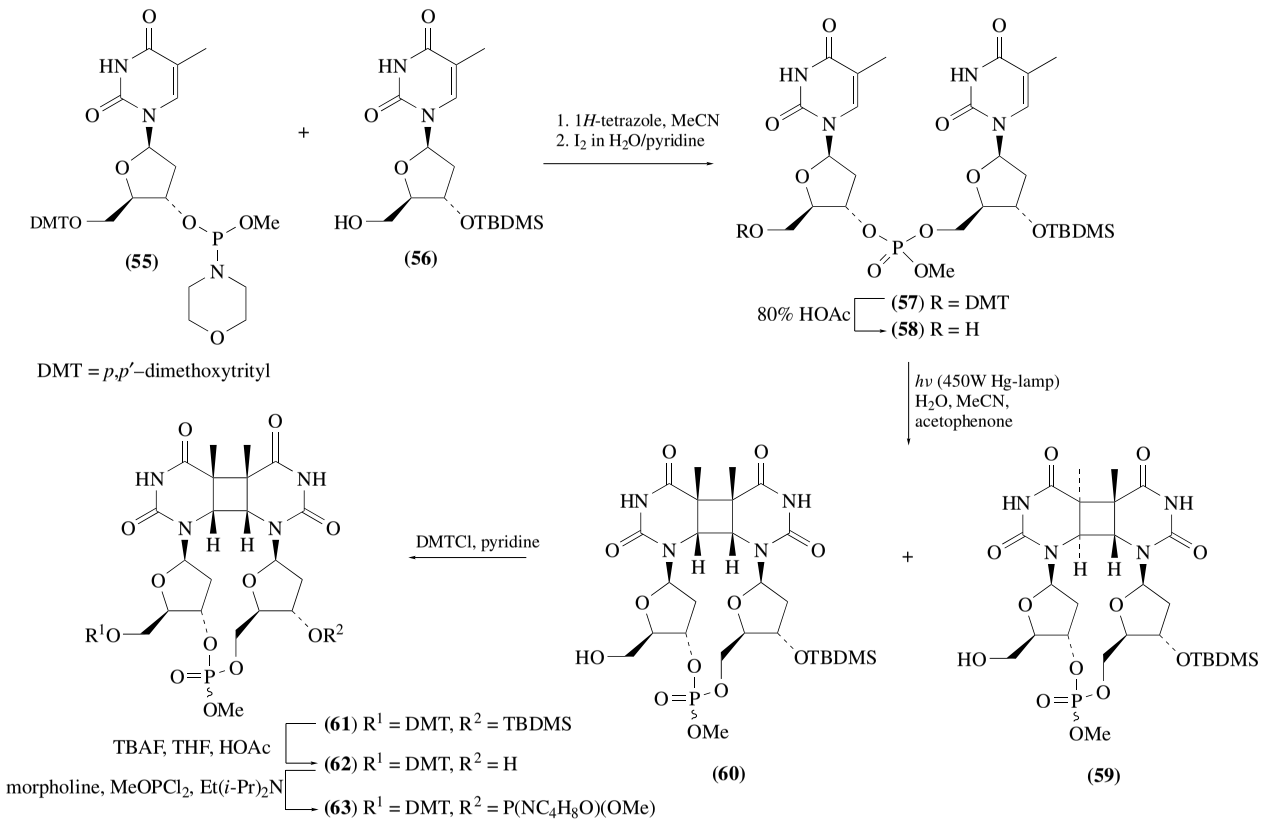
The major DNA degradation product formed after UV-irradiation are the *cis-syn* cyclobutane pyrimidine dimers. In single stranded DNA and DNA areas, which possess an unusual double helix conformation *trans-syn* dimer may form as well. In order to study how these lesions influence the structure and dynamics of the DNA double strands and how they are processed by the replication and repair machinery, short DNA strands (oligos) containing such a lesion site specifically incorporated are highly desirable. The first attempt to prepare CPD-building blocks that enable to incorporate CPD lesions into DNA using solid phase DNA synthesis were reported by Taylor and coworkers[112].

A. The Taylor CPD Phosphoramidite Building Block

In 1987 Taylor and coworkers reported the synthesis of the *cis-syn*-cyclobutane thymidine dimer lesion building block, which was incorporated into oligonucleotides using phosphoramidite chemistry[112] (Scheme 9). The starting point for the synthesis was the thymidine phosphoramidite **55**[113,114] and the 3′-*O*-(*tert*-butyldimethylsilyl)-protected (TBDMS) thymidine **56**[115]. Activation of the phosphoramidite **55** with tetrazole and coupling with **56**, followed by oxidation of the resulting phosphite with iodine afforded the dinucleotide **57**[116]. Cleavage of the dimethoxytrityl group gave **58**. Triplet-sensitized irradiation afforded two photoproducts **59** and **60** as a mixture of diastereoisomers. Isolation of both *cis-syn*-configured diastereoisomers of **60** was achieved by HPLC. Protection of the primary OH group with dimethoxytrityl chloride (DMTCl) to **61** and cleavage of the 3′-*O*-TBDMS group to **62** furnished, after reaction with chloro(methoxy)(morpholinyl)phosphine, the phosphoramidite building block **63**, which was incorporated into oligonucleotides using machine-assisted DNA synthesis. The cleavage of the synthesized oligonucleotide from the solid support as well as the removal of all protection groups required a two-step protocol. Although earlier reports described a strong base sensitivity of the cyclobutane-type photoproducts (cleavage of the $C(4)-N(3)$ bond was seemingly observed)[37,39], the building block was found to be stable even in concentrated NH_4OH. This allowed cleavage of the methoxy group at the phosphorous with thiophenol (20%), triethylamine (40%) in THF and then cleavage of the oligonucleotide from the solid support with concentrated NH_4OH (1 h, room temperature). A similar approach allowed incorporation of the *trans-syn*-I lesion by Taylor and Brockie[117]. Later, Taylor and Nadji reported improved methods which give access to larger quantities of CPD lesion containing DNA[118].

B. The Ohtsuka CPD Phosphoramidite Building Block

In order to avoid the two-step deprotection protocol, Ohtsuka and coworkers developed a cyanoethyl–levulinyl-based protection group strategy for the synthesis of a variety of CPD



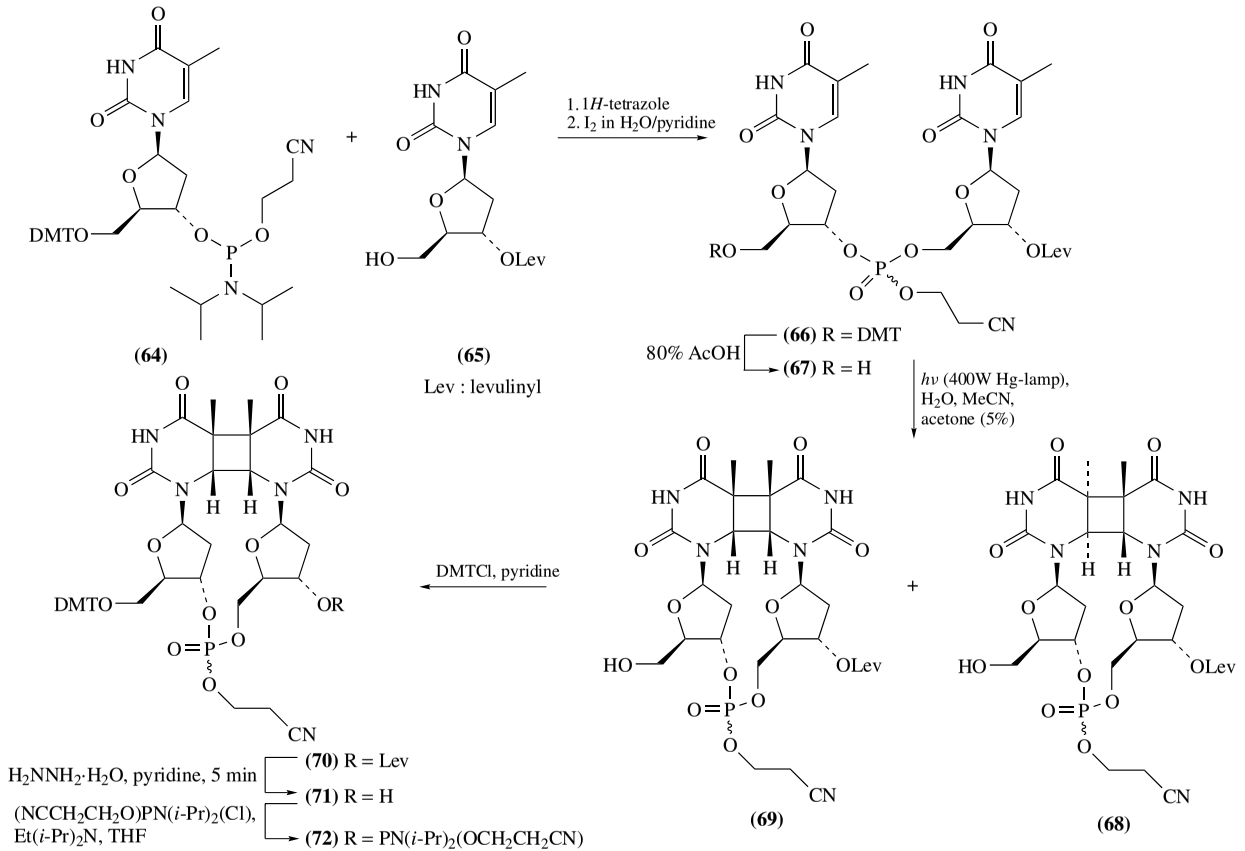
SCHEME 9. Taylor synthesis of the first cyclobutane pyrimidine dimer phosphoramidite building block used for the preparation of CPD dimer containing DNA[112]

phosphoramidite building blocks[119] (Scheme 10). Coupling of the cyanoethyl-protected phosphoramidite **64** with 3′-*O*-levulinyl-protected thymidine **65** followed by oxidation with iodine furnished the levulinyl–cyanoethyl-protected dinucleotide **66**. DMT deprotection to **67** and irradiation of **67** using a mercury arc lamp in a pyrex vessel afforded the dimers **68** and **69**. The *cis-syn*-cyclobutane pyrimidine dimer **69** was obtained in an excellent yield of about 40%, again as a mixture of two diastereoisomers. They were, however, not separated. DMT protection of the mixture **69** afforded **70**. Treatment with hydrazine allowed selective cleavage of the levulinyl group to give **71**, even in the presence of the base labile cyanoethyl group. Subsequent transformation of **71** into the phosphoramidite **72** allowed the incorporation of the photolesion into oligonucleotides. If cyanoethyl-protected phosphoramidites are used for the DNA synthesis, only a single treatment of the assembled oligonucleotide with concentrated NH_4OH was needed to achieve full deprotection and cleavage from the solid support.

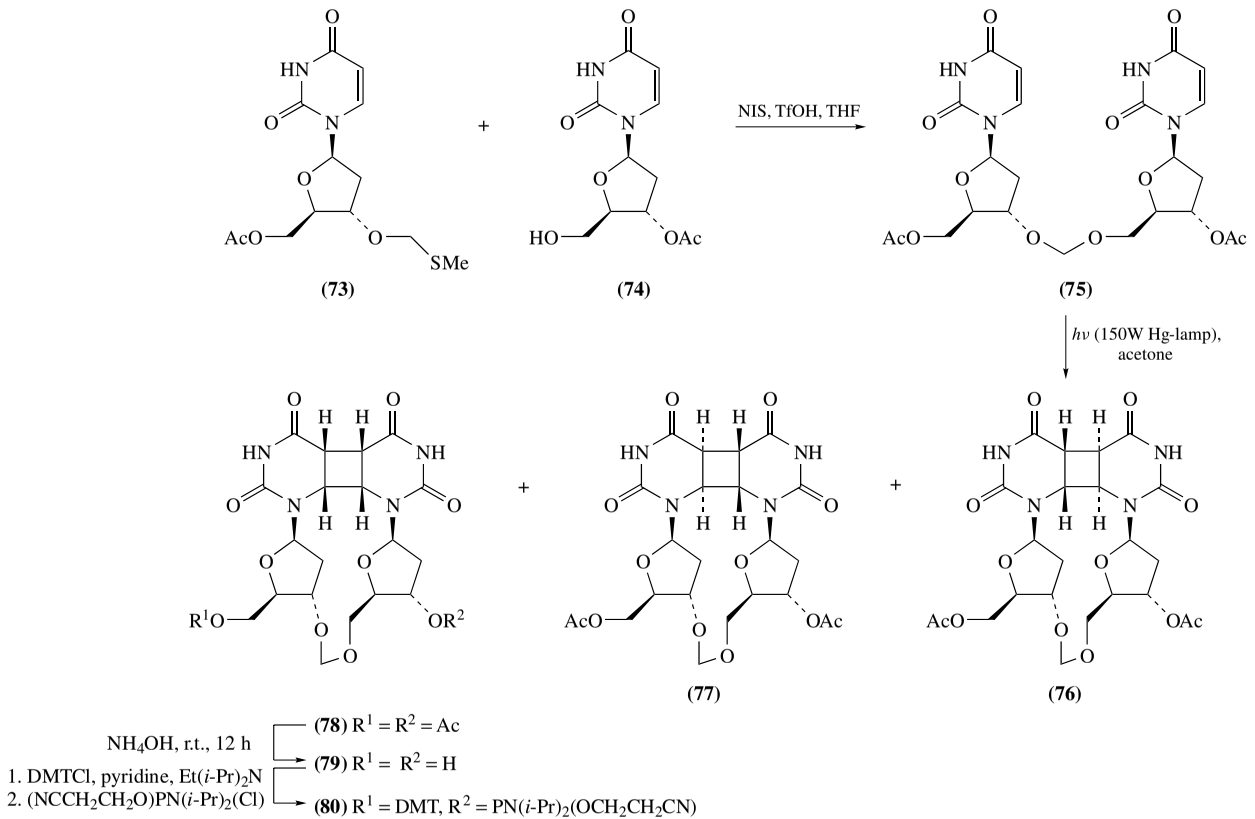
The ability to cleave the levulinyl group in the presence of a cyanoethyl-protected phosphate has also enabled the preparation of a *cis-syn*-thymine dimer dithioate building block. This modification was needed to investigate how the dimer specific repair enzyme T4-endoV achieves the recognition of the dimer lesion[120]. It was found that the negatively charged phosphodiester is important for the lesion recognition process. The co-crystal structure later allowed the rationalization of the result. In the complex of T4-endoV with a dimer-containing DNA duplex, the adenosine base opposite the 5′-thymidine in the *cis-syn* dimer is flipped out of the helix and bound in a special enzyme cavity[120]. The thymidine dimer remains inside the double helix and is firmly bound by the enzyme through charged H-bonding interactions with the central phosphodiester.

C. The Carell CPD Phosphoramidite Building Block

The observation that T4-endoV flips the base (here adenosine) opposite the lesion and not the damaged dimer itself out of the double helix is surprising, because all other repair proteins seem to turn the damaged base itself into an extrahelical position[121]. Crystal structural data from the dimer specific DNA photolyase repair enzymes suggests that this dimer repair protein favors such a lesion flipping process[106, 107, 122]. Experimental proof for this flipping process requires one to solve a co-crystal structure of a DNA photolyase in complex with a CPD-containing DNA double strand. For this, very large quantities of a CPD phosphoramidite building block are required, which are not readily available using the synthetic routes by Ohtsuka and Taylor. To solve this problem, Carell and coworkers[123] prepared a formacetal-linked[124, 125] *cis-syn*-uridine dimer building block and the corresponding thymidine dimer. Both compounds are isosteric DNA lesions[123, 126] which possess, in contrast to the phosphoramidite linkage, an achiral formacetal bridge[123], which eases the chromatographic purification of the CPDs after the irradiation step. This modification avoids one of the largest bottlenecks in the synthesis of CPD lesion phosphoramidite building blocks. The synthesis of the uridine compound is outlined in Scheme 11. It involves coupling of the 5′-*O*-acetyl-3′-*O*(methylthiomethyl)-protected uridine **73** with **74** to give the formacetal-linked dinucleotide **75**. Subsequent irradiation with a medium pressure mercury lamp afforded for the first time all three possible (*cis-syn, trans-syn-I* and *trans-syn-II*) photoproducts **76**–**78** in a 2:1:1 ratio as single (!) diastereoisomers. Separation by simple flash chromatography allowed the isolation of all three compounds in gram quantities. Only the *cis-syn* compound **78** has so far been further processed and incorporated into DNA. Cleavage of the acetyl groups and conversion of the product **79** into the 5′-*O*-DMT protected phosphoramidite **80** allowed the incorporation of this uridine dimer compound and of the similarly prepared *cis-syn*-thymidine dimer building block into oligonucleotides using standard phosphoramidite



SCHEME 10. Ohtsuka's synthesis of CPD lesion phosphoramidites for the preparation of CPD lesion containing DNA[119]



(73) (74) (75) (77) (76)

SCHEME 11. Carell's synthesis of formacetal linked isosteric CPD lesion analogs for the preparation of CPD-containing DNA in very large quantities[126]

chemistry. The introduction of the *cis-syn* uridine dimer required special care. Whereas the machine-assisted oligonucleotide assembly worked in high yields, the deprotection step has been problematic. During the treatment with concentrated NH_4OH a major side reaction was found to be the opening of the $C(4)-N(3)$ bond and the formation of a urea-type reaction product. Deprotection of the oligonucleotides with ammonia-saturated anhydrous methanol, however, proceeded cleanly and allowed the preparation of the first *cis-syn* uridine dimer containing oligonucleotides in excellent yields[126].

Investigation of the repair efficiency of these formacetal linked dimers with various DNA photolyases showed that the formacetal bridge is accepted by these enzymes[126]. The results indicate that photolyases ignore the central unit. This is in perfect agreement with DNA-footprinting studies, which show that methylation or ethylation of the central phosphate does not affect the photolyase binding step[127, 128]. The results now allow synthesis of CPD-containing DNA in sufficient quantity for co-crystallization studies[129, 130].

VI. CPD LESIONS EMBEDDED IN DNA

The ability to prepare DNA strands containing site specifically incorporated CPD lesion has enabled numerous chemical, biochemical and biophysical studies clarifying how these lesions influence the helix structure and stability and how they are processed by polymerases and repaired by repair enzymes. The studies are much too diverse for this review to cover the topic. For the chemist, however, one of the major challenges is to investigate how a CPD lesion influences directly the structure of a typical DNA double strand. Here, recent years brought true breakthroughs, which we want to discuss briefly. Taylor and coworkers[131] recently obtained a crystal structure of a DNA duplex containing a CPD lesion. The structure is shown in Figure 5 (left) in comparison to the undamaged double strand (Figure 5, right). This crystal structure in a sense highlights the fact that only

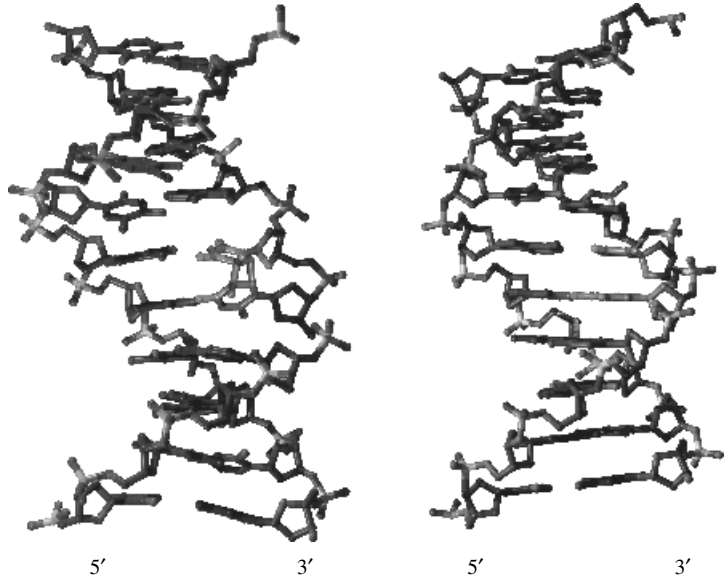


FIGURE 5. X-ray structure of a DNA duplex containing a central CPD by Taylor and coworkers[131] (left) and of the undamaged reference strand (right)

the achievements associated with the chemical synthesis of CPDs in the past made this breakthrough possible. The structural comparison shows that the DNA is bent in response to the dimer (left side) by about 30°. Both grooves are extended at the 3′- and 5′-end of the photolesion. The crystal structure supports biochemical data and shows that the 3′-T of the T=T dimer remains well paired in the double strand whereas almost no pairing occurs at the 5′-side of the DNA lesion.

Another spectacular structure is a co-crystal structure of a CPD lesion containing DNA in complex with a DNA polymerase η by Yang and coworkers[132] (Figure 6). This polymerase is used by nature to copy CPD lesion containing DNA with high precision. The structure shows again the 3′-T of the T=T dimer paired in the Watson–Crick model with the incoming dATP, and the 5′-T of the T=T dimer is engaged with a dATP in the Hoogsteen pairing modus. This T features a *syn*-conformation around the glycosidic bond.

It is a curiosity that despite the better pairing of the 3′-T part of a CPD lesions, this site shows the higher mutagenicity[133]. It is the 3′-T which gives rise to a large fraction of the observed T→C transition and T→A transversion mutation associated with a CPD lesion[4–6]. The crystal structure opens a tempting avenue for speculation. The close contact

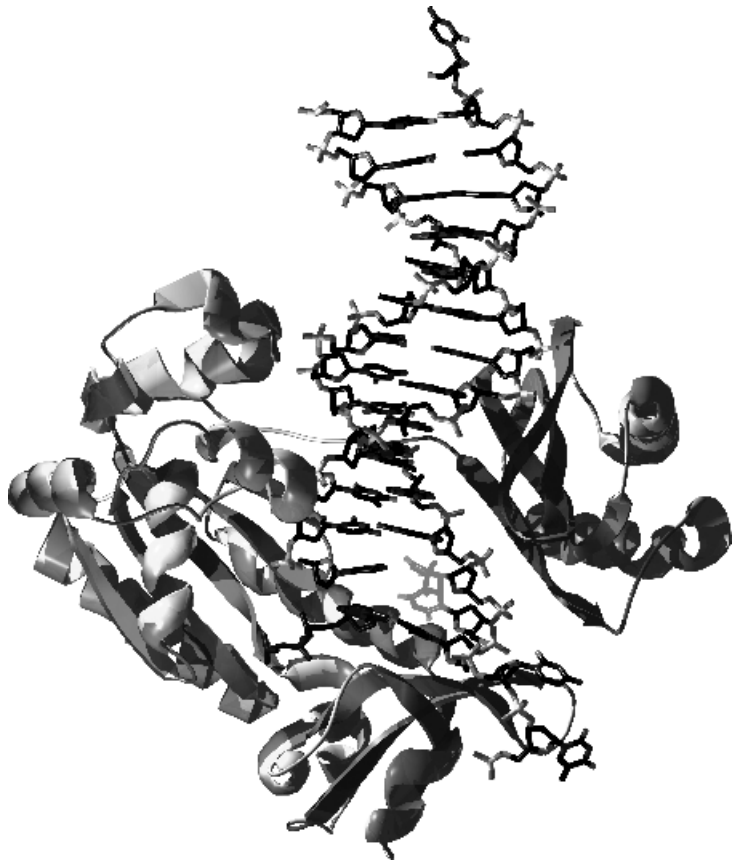


FIGURE 6. X-ray structure of the polymerase η in complex with CPD-containing duplex[132]

between the 3′-T as the template and the incoming base forces the 5′-T in close contact to the polymerase, which shift the dimer by about 3 Å in the direction of the major groove. This gives the 3′-T more space, which may facilitate wobble-base pairing with either T or G.

Overall, a single T=T dimer destabilizes a DNA duplex approximately like a single mismatch. Interestingly, the destabilization of a DNA:RNA double strand by a *cis-syn* dimer, which exists in the A-conformation, is much less pronounced[126, 129]. The destabilization effect of *trans-syn* dimers is significantly stronger due to larger structural distortions[134]. None of the two *trans-syn* dimers fits into a DNA double helix.

The amount of destabilization caused by a lesion is of paramount importance. All DNA lesions have to be removed from the genome in order to avoid cell death and mutagenesis. This is performed by series of repair proteins and repair factors[135]. Some recognize DNA lesions based on their destabilization effect[136, 137]. The UV-lesions are generally repaired by the nucleotide excision repair pathway (NER), where a small piece of DNA around the lesion is excised[135]. It is well known that this repair system recognizes DNA lesions predominantly due to their disturbing effect on the duplex structure. Based on our knowledge of how lesions destabilize the duplex, it can now be rationalized why repair of the *cis-syn* cyclobutane thymidine dimer is in general so sluggish and in certain sequence contexts almost not measurable[138]. These lesions cause only a small destabilization, which is readily overlooked by the nucleotide excision repair system. The large destabilization induced by the *trans-syn* dimers makes them, in contrast, excellent substrates for the nucleotide excision repair machinery.

The ability to now create DNA containing site specifically CPD lesions by chemists may allow one in the future to obtain co-crystal structures of CPD-containing DNA in complex with repair proteins involved in NER. We all hope that such structures will be available soon. Results from these studies will clearly deepen our understanding of the mutagenic effect of one of the most prevalent DNA lesions known today, the cyclobutane pyrimidine dimers!

VII. ACKNOWLEDGMENT

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CHAPTER **23**

Cubanes, fenestranes, ladderanes, prismanes, staffanes and other oligocyclobutanoids

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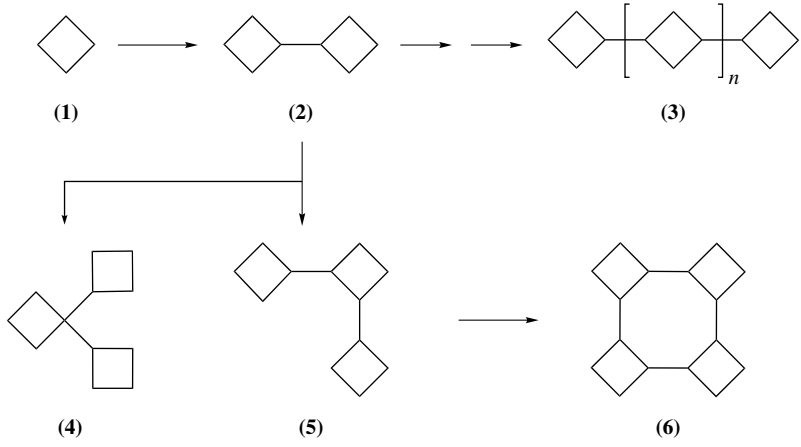
I. INTRODUCTION

The cyclobutane ring system, readily available by numerous ring-formation processes[1], is, as the present chapter shows, an interesting, versatile and unique building unit for the construction of complex organic molecules. (The effects of cyclobutyl groups on molecular properties are discussed by Charton in chapter 10 of this volume). Depending on the type of conjoining the four-membered rings organic compounds of vastly different structural properties, shapes and functions may be constructed. Provided that these reactions can be extended to the preparation of oligomeric or even polymeric derivatives, we anticipate that these will possess very interesting physical properties; whereas, for example, some representatives will be very flexible, other will be very rigid organic materials.

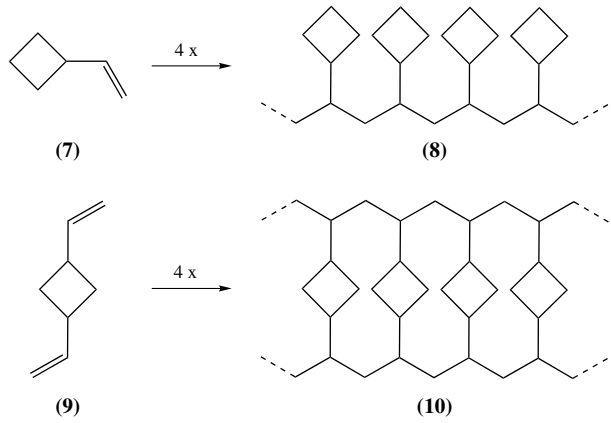
As shown in Scheme 1, one of the simplest ways to connect cyclobutane rings is by way of a single bond, i.e. the two ring units have no carbon atom in common.

Beginning the *aufbau* with cyclobutane (**1**) via bicyclobutyl (**2**), the linear structures **3** are obtained. Of course, the third cyclobutyl ring must not be bonded opposite to the first cyclobutyl unit (in 3-position), but can also be connected at the geminal or vicinal position, giving rise to 1,1- (**4**) or 1,2-dicyclobutylcyclobutane (**5**), i.e. to angular oligocyclobutyls. It is easily seen that by this set of simple building rules an endless number of structures can be obtained—including cyclic ones such as **6** or branched (dendritic) structures—even if one makes use of only a small number of distinct cyclobutyl 'tiles'. (cis- and trans-Substitution should be distinguished. Stereochemical and spectroscopic aspects of this are discussed in chapters 3 and 6 by Berg, and Seidl and Diaz, respectively, in this volume.)

Of course, in principle the number of other atoms or bonds between the cyclobutane rings can be selected freely, again generating a huge (largely so far not realized) structural variety. For example, if vinylcyclobutane (**7**) is polymerized, the cyclobutyl substituted polyethylene **8** (see below, Section III.B) is obtained (Scheme 2).



SCHEME 1

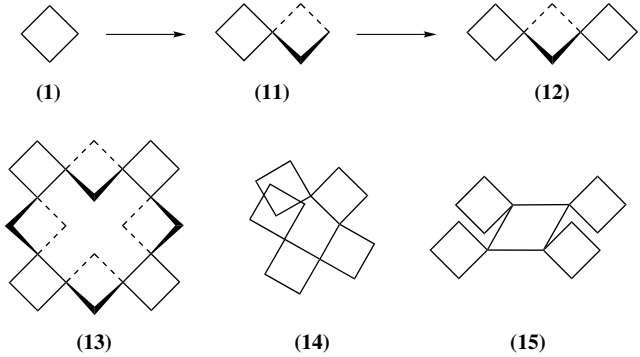


(7) **(8)** **(9)** **(10)**

SCHEME 2

When bifunctional monomers such as 1,3-divinylcyclobutane (**9**) are employed as a substrate, this could lead to cross-linked polymers such as **10**. Again, the monomeric building unit and the connectivity of the polymeric products can be made much more complex.

When the two four-membered rings share one carbon atom, spiro structures result, in the simplest case spiro[3.3]heptane (**11**). And again the building process can be carried out in many different directions: linearly as in **12**, cyclically as in **13** or in **14**, the former combination making use either of two neighboring carbon atoms as spiro centers or having these also in a 1,3-arrangement. One would expect smaller members of this series to be highly strained and, when substituents are introduced, many stereoisomers can be produced. A sterically interesting situation is illustrated by structure **14** (Scheme 3) in which a molecular helix is generated by the cyclobutane rings. And structure **15** illustrates the building of a rotane molecule, as a special case of a polyspiro compound from five cyclobutane subunits.

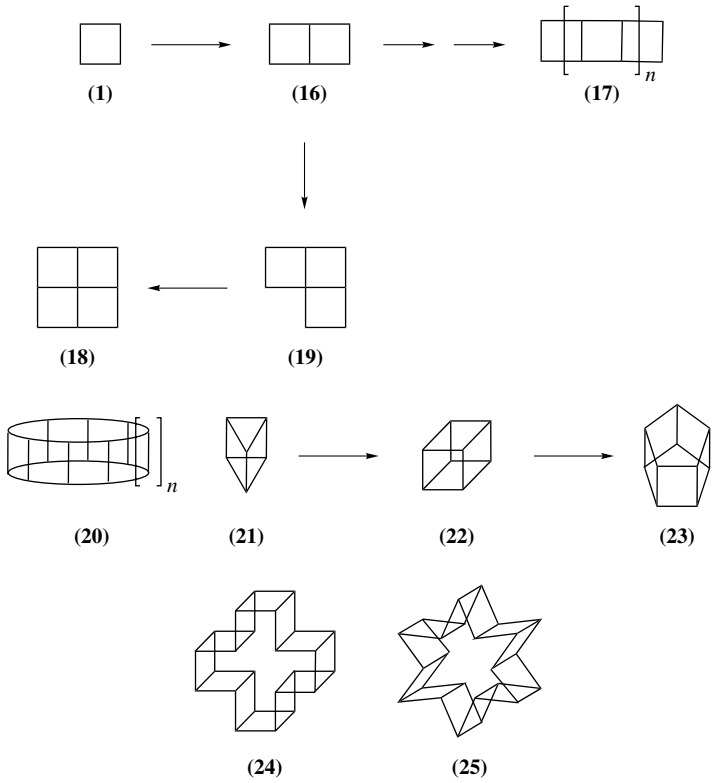


(1) **(11)** **(12)** **(13)** **(14)** **(15)**

SCHEME 3

Fusing two cyclobutane rings with one bond (sharing of two cyclobutane carbon atoms) leads to bicyclo[2.2.0]hexane (**16**), from which—again—branching in different directions can occur. Proceeding with linear annelation leads to the ladderanes, **17**, and continuing

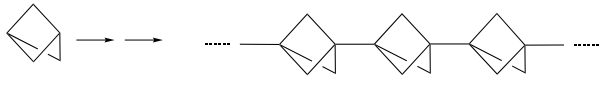
in angular or circular fashion provides fenestranes, **18** and **19**. In fact, these cases are not so simple, as illustrated in Scheme 4, since the stereochemical situation at the common bonds has been neglected (see below).



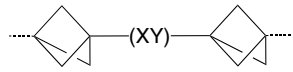
SCHEME 4

Ladderane annulation leads to interesting results when extended to cyclic derivatives, which can be represented in symbolic general form by structure **20**. In this category the simplest representative is [3]prismane (**21**), followed by the higher homologs [4]prismane (**22**, cubane), [5]prismane (**23**), all the way up to oligomers such as the isomeric dodecaprismanes **24** and **25**, which have also been called helvetane and israelane for obvious reasons, both hydrocarbons so far having been suggested as target molecules in a spoof paper only[2]. It should be noted that the prismanes themselves could also be used as building blocks for more complex polycyclobutane structures again. If these are conjoined by their faces, rod-like structures result (which are novel, highly strained forms of carbon if extend 'to infinity'); if, on the other hand, they are connected via their edges, various branched structures can be designed (see Section II.E).

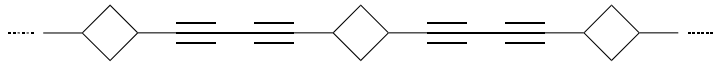
A hydrocarbon in which two four-membered rings share three carbon atoms is bicyclo[1.1.1]pentane (**26**). When this is used as a monomer and connected to other bicyclo[1.1.1]units by single bonds, the so-called staffanes, **27**, result (Scheme 5). As we shall see in Section II.E, **26** and its derivatives are obtained from an even more strained hydrocarbon, [1.1.1]propellane.



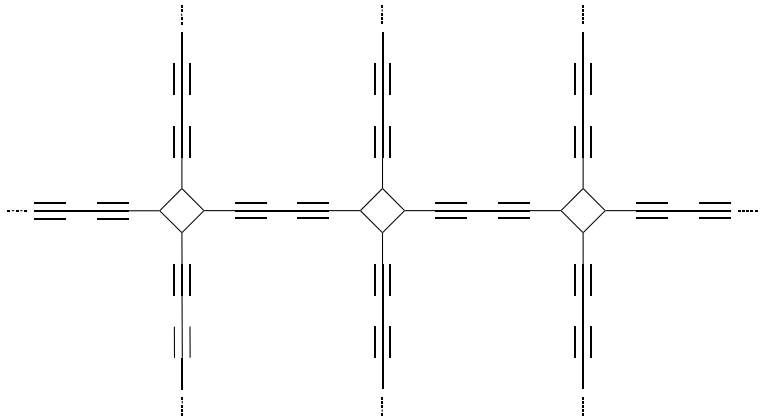
(26) **(27)**



(28)



(29)



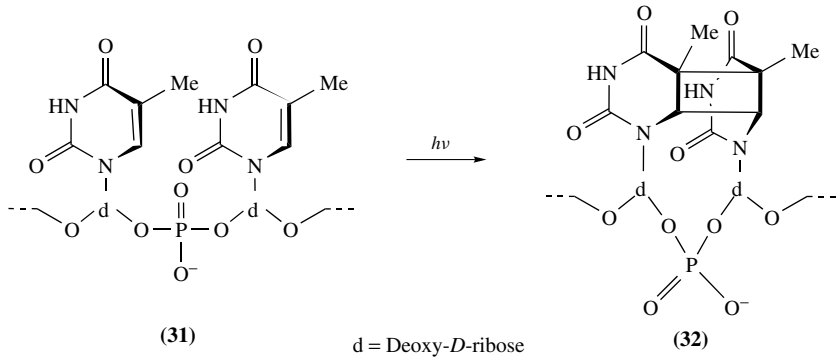
(30)

SCHEME 5

Again, the connected units (spacers XY in **28**) may by saturated—polymethylene chains, for example, or consist of functional groups—producing staffanes (which may also be cyclic, see Section II.E)—of different rigidity and chemical reactivity. In modern aromatic chemistry as well as for the preparation of substructures of novel carbon allotropes, the acetylene group has often been used, since it can be introduced readily and can be dimerized or cyclooligomerized by various metal-mediated reactions[3]. Applying this approach to cyclobutanes could yield linear structures such as **29** or sheet-like oligomers such as **30**, keeping in mind again that in both designs the stereochemical situation of the cyclobutane ring has not been considered.

A completely different polycyclobutanoid situation arises when the thymine units of DNA photodimerize, as shown in highly abbreviated form in Scheme 6[4]. For a more complete discussion see chapter 22 by Friedel, Gierlich and Carell in this volume.

In principle, the [2 + 2]photoaddition **31** → **32** can take place numerous times in a DNA double helix, giving rise to an oligo or polycyclobutanoid system whose four-membered rings are separated by highly functionalized heteroorganic spacer units. In



(31) **(32)**

SCHEME 6

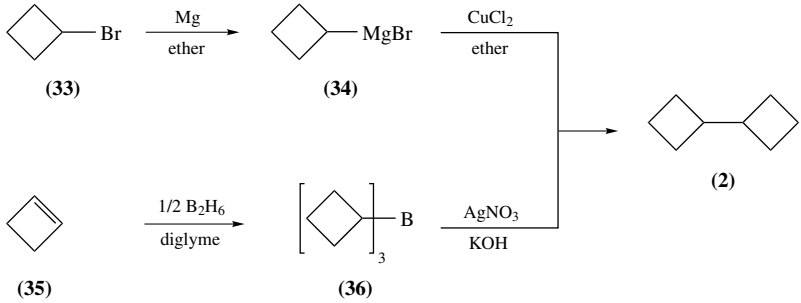
fact, derivatives such as **32** are not the only polycyclobutane derivatives that occur in nature, several ladderane fatty acids having been isolated and characterized recently (see Section II.E). In passing, we note that photodimerized DNA is detrimental to the organism's health while the ladderane fatty acids are seemingly essential to its health.

Before beginning to describe the synthesis of oligomeric cyclobutane systems, some general remarks on the preparation of four-membered rings are in order. (While our discussions that follow deal almost exclusively with the hydrocarbon derivatives, functionalized species are discussed in more detail in chapters 8 and 9 by Lee-Ruff, and Fu, Chen and Wong, respectively, in this volume.) Probably by far the most often used method to prepare four-memberd rings is the photochemical [2 + 2]cycloaddition of olefins[5]. (For a more complete discussion of photochemical aspects of cyclobutane chemistry see chapters 17 and 18 by Horspool, and Natarajan and Ramamurthy, respectively, in this volume). However, at least one of the olefinic precursors can be replaced by other substrates providing two carbon atoms (and often appropriate functional groups) to the future cyclobutane ring, ketenes and acetylenes being used most often. In the latter case a hydrogenation step has to follow, of course, if saturated rings are the target. If both double bond precursors are replaced by alkynes, the [2 + 2]cycloaddition formally leads to a 1,3-cyclobutadiene[6], and the very high reactivity of such an intermediate can also be exploited for the preparation of polycyclobutane derivatives (see Section II.E for further discussion of these derivatives. The reader should also note that "1,3" is not superfluous — 1,2-cyclobutadiene and other highly unsaturated species are discussed by Johnson in chapter 14 of this volume). Other popular routes to cyclobutanes use various ring-contraction methods and 1,4-cyclization reactions. These different approaches will be discussed in detail for the specific examples mentioned below. If a cyclobutane ring has neighboring functional groups, in principle, intramolecular reactions can take place between them. A particular important example in the context of the present chapter is the readily occurring (thermal) ring-opening of *cis*-divinylcyclobutanes by Cope rearrangements leading to eight-membered-ring systems. Since this side reaction is to be avoided here, the appropriate three-dimensional orientation of these functional groups should also be avoided if one is interested in building extended polycyclobutanoid compounds. The inherent strain of the cyclobutane ring (E_s *ca* 27 kcal mol^{-1})[7] is usually no reason for a particular instability. (For a discussion of strain energy and thermochemical and physical chemical considerations of cyclobutanes see chapters 1 and 4 by Wiberg, and Liebman and Slayden, respectively, in this volume. For related discussions of aromaticity and antiaromaticity see chapters 2 and 15 by Maksic and Maksic, and Stanger, respectively, in this volume).

II. PREPARATION OF OLIGOCYCLOBUTANOID SYSTEMS

A. Cyclobutane Rings Connected by Single Bonds

One of the simplest hydrocarbons containing more than one cyclobutane ring is bicyclobutyl (**2**); it was first prepared by either $CuCl_2$-mediated dimerization of cyclobutyl magnesium bromide (**34**), itself obtained as usual from cyclobutyl bromide (**33**) or from cyclobutene (**35**) via oxidation of the organoborane **36**. In the former case, **2** is produced as a component (43% GC-yield) in a hydrocarbon mixture; the second approach yields the pure product in 22% yield (Scheme 7)[8,9].

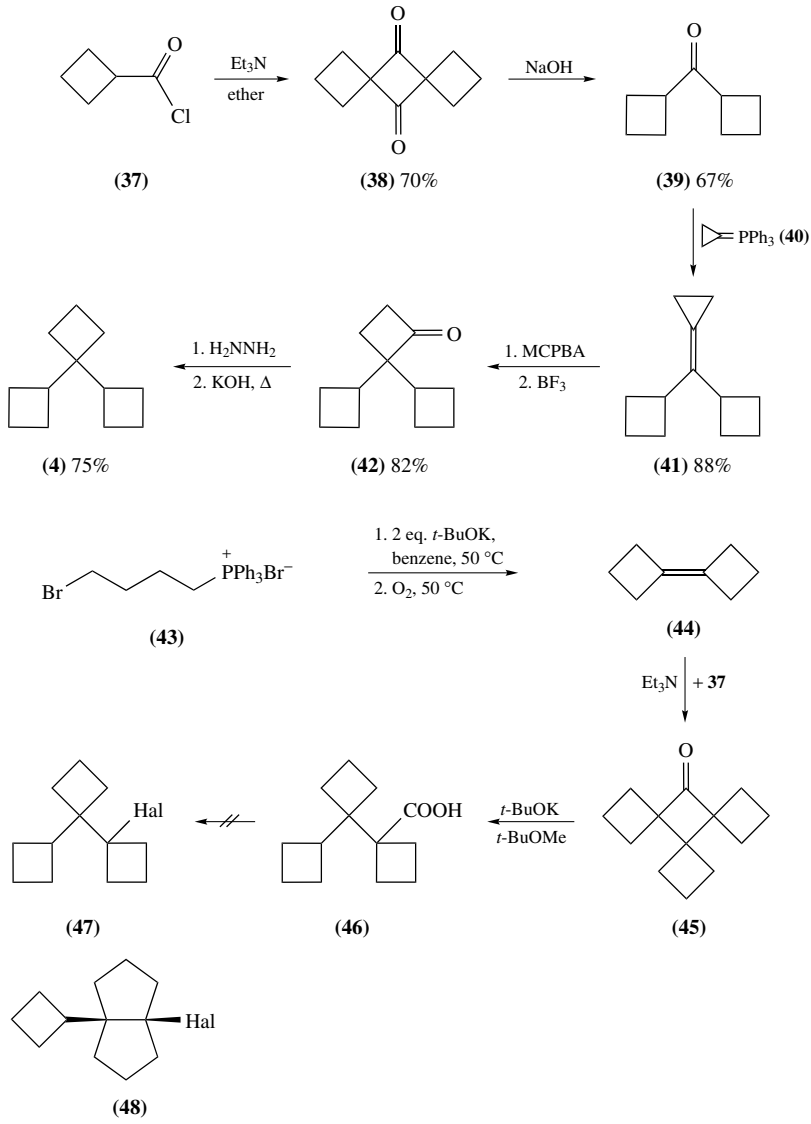


SCHEME 7

Whereas neither 1,3- (**3**, $n = 1$) or 1,2-dicyclobutylcyclobutane (**5**) seem to be known, their isomer, 1,1-dicyclobutylcyclobutane (**4**), was obtained by the route summarized in Scheme 8[10]. Treatment of the acid chloride **37** with triethylamine in ether caused dehydrochlorination and *in situ* dimerization of the generated ketene to the tricyclic diketone **38**, itself an oligocyclobutane (of the spiro type to be discussed below in Section II.C). When this is subjected to base treatment, the central ring is cleaved and the resulting intermediate decarboxylated to provide dicyclobutyl ketone (**39**) in good yield. Wittig olefination with the ylid **40** leads to the alkene **41** that, on epoxidation with *meta*-chloroperbenzoic acid (MCPBA), furnishes the expected spirocyclic oxirane. Ring-enlargement/rearrangement of the latter yields the ketone **42**, that by Wolff–Kishner reduction finally gives the desired tercyclobutane **4** (Scheme 8). (Rearrangements figure prominently in cyclobutane chemistry as discussed in chapters 11 and 12 by Tanko and Siehl, respectively, in this volume.)

To prepare various analogues of **4**, different routes were investigated. For example, the Grignard coupling used for the preparation of **2** could in principle also be applied here, provided suitable precursors such as the halides **47** would be available (Scheme 8). Although its precursor carboxylic acid **46** could be prepared readily from the phosphonium salt **43** via the intermediate **44** (itself a hydrocarbon containing two cyclobutane rings) and produced from **43** by Wittig reaction between cyclobutanone and the non-oxidized cyclic ylid generated from **43**[9,11] and the ketene adduct **45**, all methods (*inter alia* Hunsdiecker degradation, Barton bromodecarboxylation) failed to yield **47**. Instead, in all these experiments ring-expanded compounds of the general structure **48** and products derived therefrom were isolated. If, alternatively, the triketone **49** is cleaved by barium hydroxide treatment, the resulting diketone **50** could not be transformed to the diolefin **51** by the Wittig reaction with **40**. Rather, the degradation product **41** was obtained (Scheme 9).

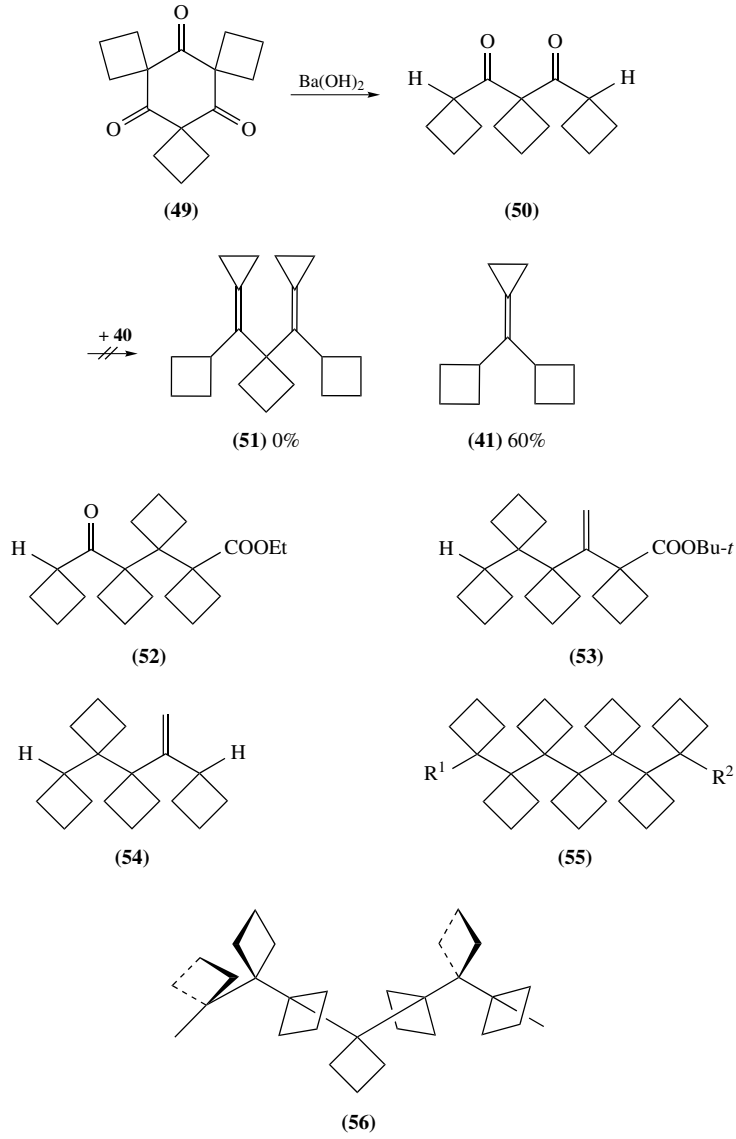
Still, several promising precursors *en route* to quinquecyclobutane, such as **52, 53** and **54**, were obtained in the course of these investigations. According to MM3(92) calculations of the septicyclobutane **55** ($R^1 = R^2 = CH_3$), these oligomers adopt a helical conformation as shown in **56** as the thermodynamically most stable conformation[10].



SCHEME 8

B. Cyclobutane Rings Connected by a Common Carbon Atom — The Spiro Oligocyclobutanes

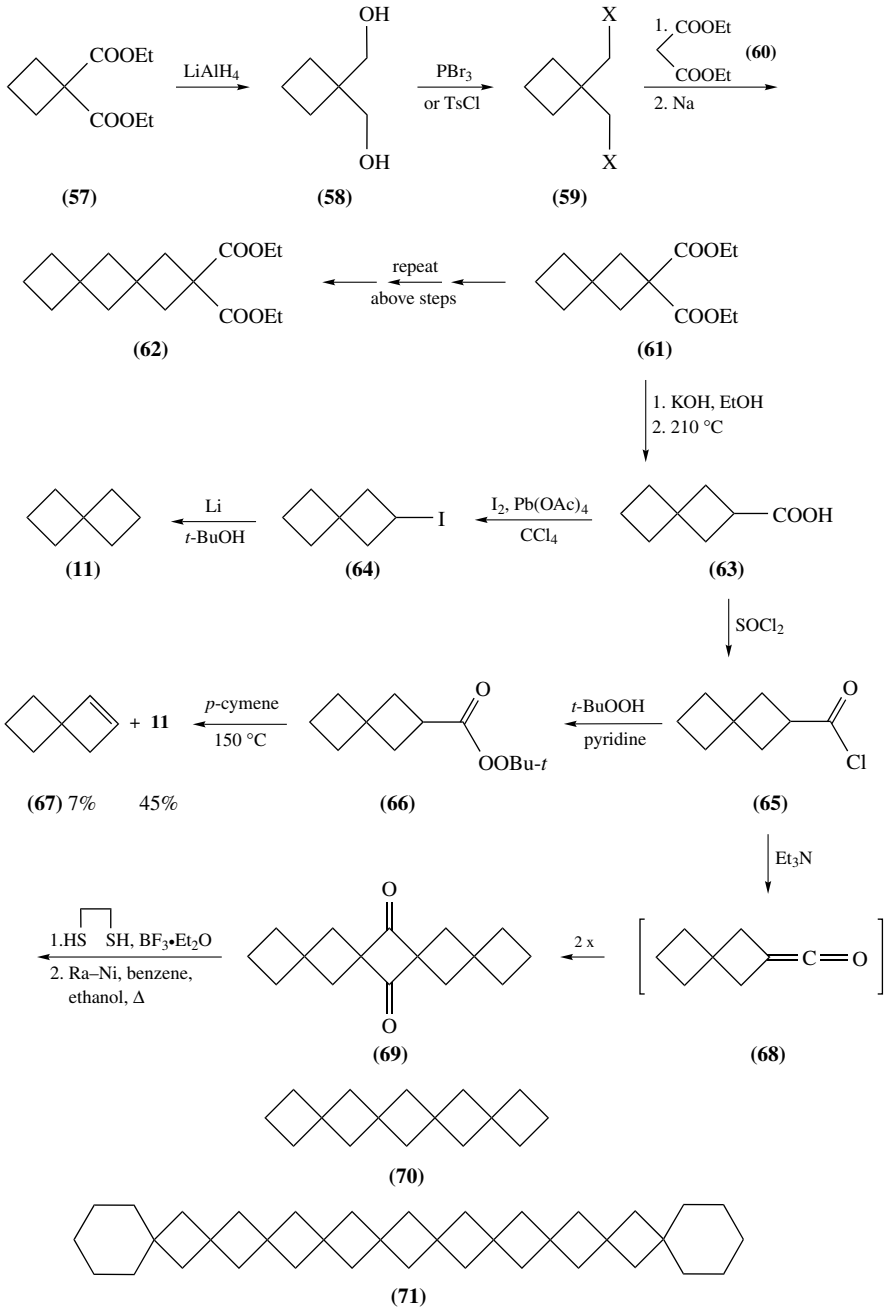
The synthesis of linear structures in which the cyclobutane units are connected by spiro centers makes use of the oldest reaction in small-ring chemistry and the first cyclobutane derivative ever to be prepared: Perkin's 1,1-diethoxycarbonylcyclobutane (**57**, Scheme 10)[12].



SCHEME 9

When **57** is reduced with lithium aluminum hydride, the diol **58** is obtained which can either be converted into the dibromide **59** (X = Br) or the ditosylate **59** (X = OTs). Both alkylating reagents react as expected with diethyl malonate (**60**) under basic condition and provide the spiro diester **61**, ready to be subjected to the same sequence of steps again[13].

Whereas **62** was indeed synthesized by the 'Perkin route', for the preparation of the higher oligomers of **11** and **13** a more efficient approach was developed (see below).


COOEt
COOEt
LiAlH4
OH
OH
PBr3
or TsCl
X
X
1. COOEt
COOEt
(60)
2. Na
(57)
(58)
(59)
COOEt
COOEt
repeat
above steps
COOEt
COOEt
(62)
(61)
1. KOH, EtOH
2. 210 °C
Li
t-BuOH
I
I2, Pb(OAc)4
CCl4
COOH
(11)
(64)
(63)
SOCl2
+ 11
p-cymene
150 °C
O
OOBu-t
t-BuOOH
pyridine
O
Cl
(67) 7%
45%
(66)
(65)
Et3N
1.HS SH, BF3•Et2O
2. Ra–Ni, benzene,
ethanol, Δ
O
O
2 x
C O
(69)
(68)
(70)
(71)

SCHEME 10

To reduce **61** to the parent hydrocarbon spiro[3.3]heptane (**11**), **61** was first saponified and decarboxylated to the monocarboxylic acid **63**[13]. Iododecarboxylation to the iodide **64** and reduction of the latter with lithium in *tert*-butanol then afforded the target hydrocarbon[14]. Later workers found the decarboxylation via the acid chloride **65** and the perester **66** preparatively more rewarding, although it also led to a small amount of the monoolefin **67**, this route also being superior to an alternative employing Hunsdiecker degradation of **63** and subsequent reduction of the resulting bromide with tri-*n*-butyltin hydride[15].

Treatment of **65** with triethylamine causes dehydrochlorination to a ketene intermediate (**68**) again, which dimerizes to the 1,3-cyclobutandione **69**. After converting this to the corresponding bis-thioketal, Raney nickel induced desulfurization in benzene/ethanol readily provided tetraspiro[3.1.1.1.3.1.1.1]hexadecane (**70**)[16]. Since in the first step of the whole sequence other α,ω-dibromoalkanes can be used for the bis-alkylation of **60**, other terminal rings can be introduced into these oligomeric cyclobutanes. Thus the decaspirane **71**, the so-far longest spiro compound of this type, was prepared from 1,1-diethoxycarbonylcyclohexane[16]. Clearly, this truly general route deserves further attention, especially as far as the preparation of chiral representatives of this structural type is concerned, and these materials also have not been investigated from the material science viewpoint either.

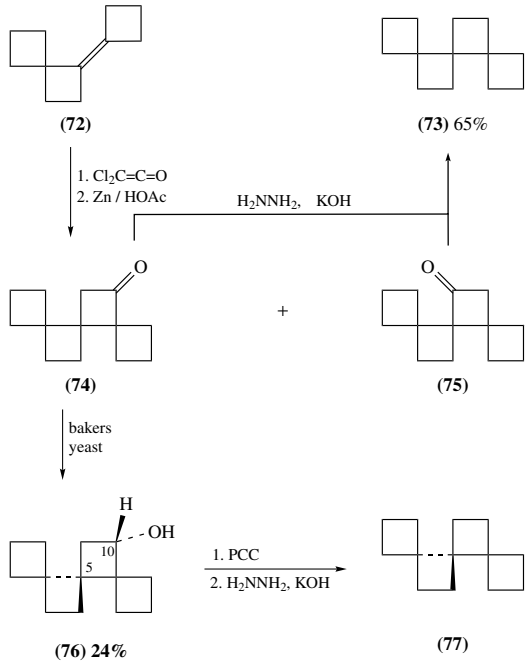
Dispiro[3.1.3.1]decane (**12**), incidentally, was obtained from diketone **38** by converting it to the bis-thioketal and reducing this to the hydrocarbon, as described for the conversion of **69** into **70**[17].

Interestingly, often chiral hydrocarbon structures arise when the spiroannulation process is not continued in linear but in angular fashion, dispiro[3.2.3.0]decane, with its two cyclobutane rings in vicinal position at a four-membered ring being the parent compound. A case in point is provided by trispiro[3.0.0.3.2.2]tridecane (**73**), recently prepared from the readily available[18] bicyclobutylidene **72** as shown in Scheme 11[19].

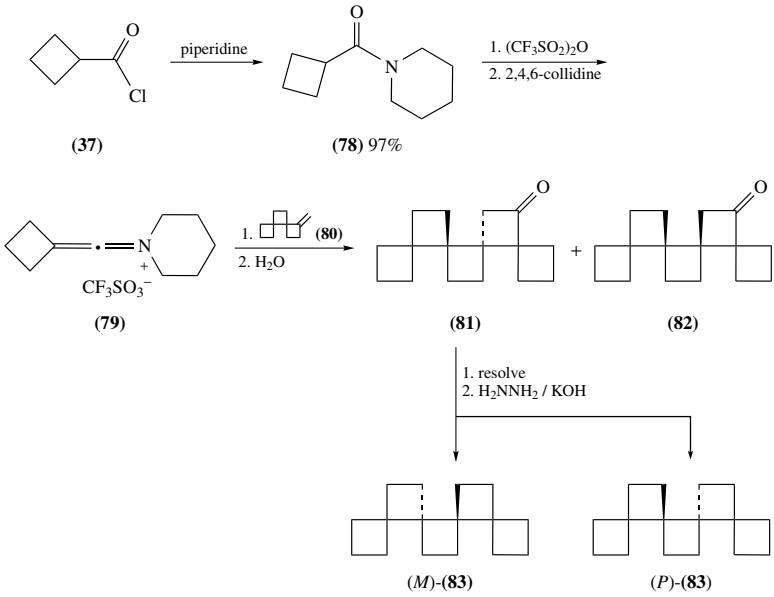
Addition of dichloroketene to **72** followed by dechlorination furnished a 2:1 mixture of the two ketones **74** and **75** in very good yield (89%). When this was subjected to Wolff–Kishner reduction, the racemic trispiro hydrocarbon **73** was obtained readily. This hydrocarbon is chiral and its (*M*)-enantiomer, **77**, the first hydrocarbon with a helical primary structure of four-membered rings, was prepared by reducing the cyclobutanone **74** with bakers yeast. The generated (5*S*,10*S*)-alcohol **76** was subsequently reoxidized with PCC and the optically active ketone deoxygenated by a Wolff–Kishner reduction again. Compared to the analogous hydrocarbon consisting of three-membered rings only[20], (*M*)-trispiro[2.0.0.2.1.1]nonane, the specific rotation of **77** is significantly smaller (about a third of the cyclopropane system). According to molecular mechanics calculations, this could be caused by the greater flexibility of **77** plus the fact that the cyclobutane-composed hydrocarbon describes a distinctly shorter section of a helix than its three-membered-ring relative.

In a later synthesis, the preparation of derivatives such as **74** and **76** could not only be improved significantly by a novel cyclobutane-ring forming reaction, but this methodology could also be used to prepare the next higher homolog of **77**, tetraspiro[3.0.0.0.3.2.2.2.2] hexadecane (**83**), as summarized in Scheme 12[21].

In the crucial step of this evidently general approach, the four-membered-ring system is produced by the addition of a keteniminium salt to a double bond. These salts, compound **79** being an example, are conveniently obtained when carboxylic acid amides such as **78**, itself prepared from the acid chloride **37** and piperidine, are treated with trifluoromethanesulfonic acid anhydride followed by 2,4,6-collidine[22]. Cycloaddition of **79** to the dispiro olefin **80**, followed by hydrolysis, lead to a mixture of diastereomeric cyclobutanones **81** and **82** in 30% yield in which the former predominated by far (product ratio 92:8). After



SCHEME 11



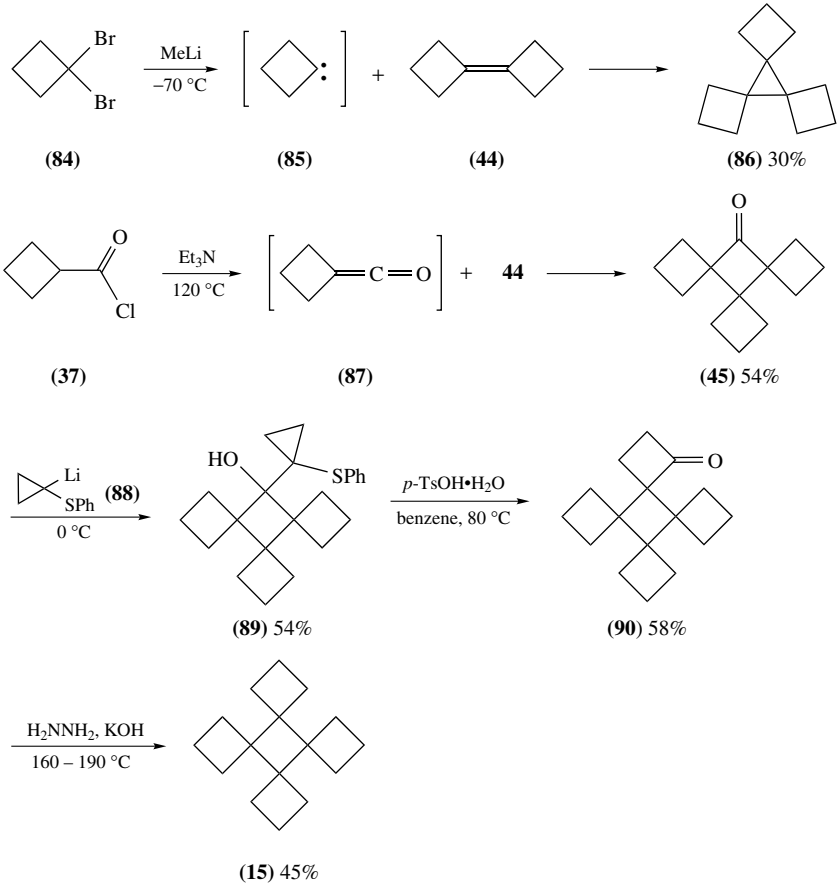
SCHEME 12

resolution of **81**, the two enantiomeric ketones were Wolff–Kishner reduced to the pure (*M*)- and (*P*)-configurated hydrocarbons **83**.

Connecting the spiro carbon atoms not in a linear fashion as above but in a cyclic array leads to a new rotane family, the [*n*.4]rotanes[23], the first analogues of which having recently been prepared. According to this nomenclature cyclobutane **15** (Scheme 3) would be [4.4]rotane[24].

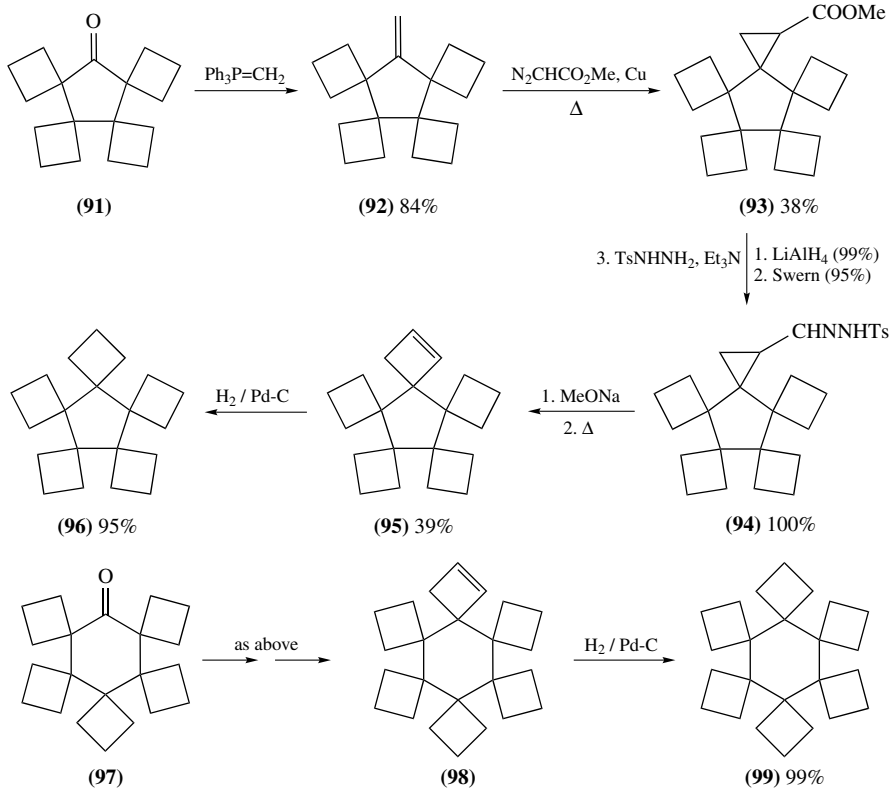
All syntheses are based on bicyclobutylidene (**44**), again demonstrating the overwhelming importance of this olefin in this area of hydrocarbon chemistry. To prepare the first member of the series, cyclobutylidene (**85**) was generated from 1,1-dibromocyclobutane (**84**) by treatment with methyl lithium in ether at low temperatures. Addition of the carbene to **44** furnished [3.4]rotane (**86**) directly (Scheme 13)[23].

To prepare the next higher 'cyclobutanolog' **15**, ketene **87** was generated from the acid chloride **37** as described above and intercepted by **44** to yield the trispiroketone **45**. Its spiroalkylation with 1-lithio cyclopropyl phenyl thioether (**88**) provided the tertiary alcohol **89**, which by acid-catalyzed isomerization/elimination gave the expected ketone **90**. This, finally, was reduced to **15** by Wolff–Kishner reduction[23].



SCHEME 13

The syntheses of [5.4]- (**96**) and [6.4]rotane (**99**) followed practically identical paths. Homologization of **45** via a β-hydroxyselenide intermediate made the ring-expanded ketone **91** available, the ketone function of which was transformed into the missing (fifth) cyclobutane ring by the following protocol. The first of the still lacking carbon atoms was introduced by Wittig olefination. The resulting semicyclic alkene **92** underwent addition of the carbene produced by copper-catalyzed decomposition of methyl diazoacetate, yielding the cyclopropane ester **93** in moderate yield (Scheme 14; the yield is even lower in the six-membered-ring case—see below—indicating the poor accessibility of the double bond in both cases)[23].



SCHEME 14

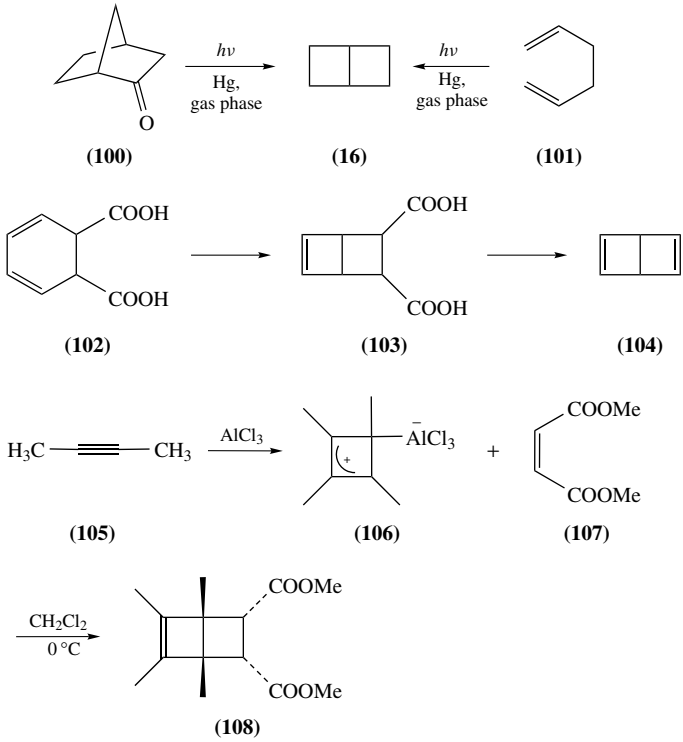
By reduction, reoxidation and reaction with tosylhydrazine, **93** was converted into the tosylhydrazone **94**. After salt formation with sodium methoxide, a cyclopropylcarbene–cyclobutene rearrangement was initiated providing the cyclobutene derivative **95** which, by catalytic hydrogenation, was cleanly transformed to [5.4]rotane (**96**). Starting with the higher homolog of **91**, the ketone **97**, and submitting it to the same sequence of steps, furnished the rotane **99** with six consecutive spiroannelated cyclobutane rings passing the cyclobutene **98** *en route*. With the exception of **86**, for all these new rotanes low-temperature X-ray structural investigations provided insights into the detailed geometric features of these interesting polycyclic hydrocarbons. Furthermore, with the help of

axially labeled [1-^{13}C]-**99**, temperature-dependent NMR studies allowed the determination of the free energy of activation for the chair-to-chair interconversion of this unusual cyclohexane derivative. With $\Delta G^{\ddagger}_{487} = 37.5$ kcal mol^{-1}, this is the highest inversion barrier ever reported for a cyclohexane derivative[23].

C. Cyclobutanes Sharing Two and More Carbon Atoms — The Ladderanes and Fenestranes

The simplest hydrocarbon in which two cyclobutane units share two carbon atoms, i.e. are conjoined by a single common bond, is bicyclo[2.2.0]hexane (**16**), the parent system of the ladderanes (**17**, Scheme 4). It was originally prepared either from norbornan-2-one (**100**)[25] or from 1,5-hexadiene (**101**)[26] as shown in Scheme 15. (For a more complete discussion of bicyclopentanes and hexanes see chapter 20 by Carpenter in this volume.)

Today, many other approaches are known, most of them involving [2 + 2]cycloaddition steps (see below)[27]. Formally, **16** is the bis-hydrogenation product of another classic hydrocarbon, Dewar benzene (**104**, bicyclo[2.2.0]hexa-2,5-diene). To arrive at this valence isomer of benzene, phthalic acid was Birch-reduced to the cyclohexadiene diacid **102**, which was photoisomerized to the bicyclic intermediate **103**. Decarboxylation of the latter with lead tetraacetate or electrolytically finally provided the target compound **104** (Scheme 15)[28].

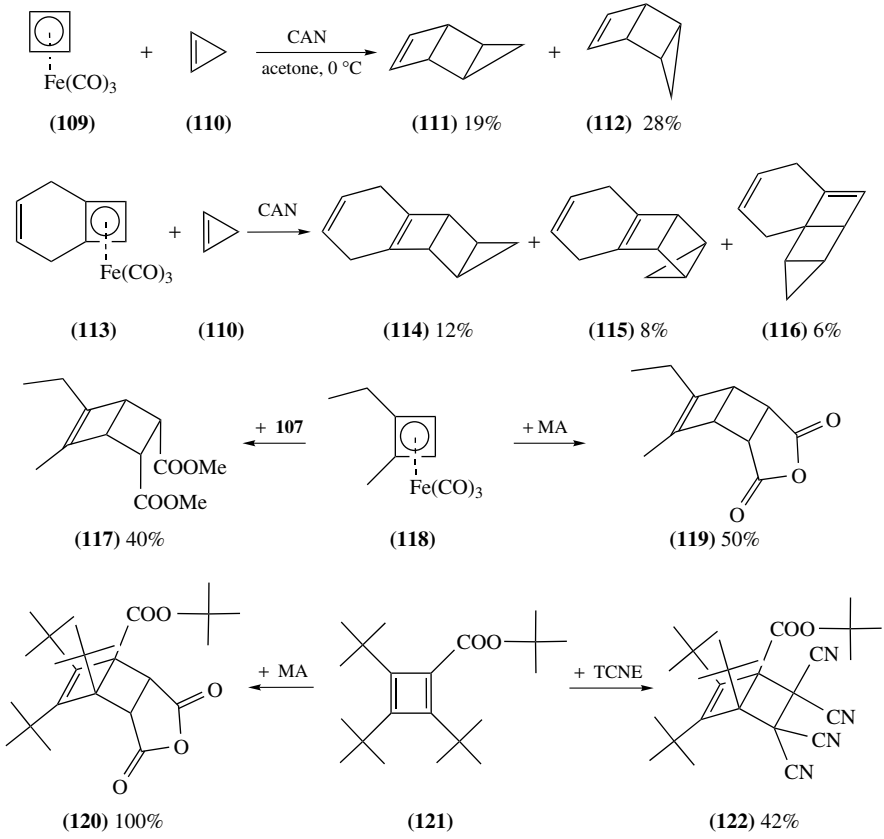


SCHEME 15

In the meantime, numerous derivatives of **16, 104** and bicyclo[2.2.0]hex-2-ene, the monoolefin corresponding to **16** (or **104**), have been prepared, usually following either of two routes.

In the first one, cyclobutenylaluminate salts, **106**, stable intermediates (Lewis acid and Lewis base complexes) produced by aluminum trichloride-catalyzed dimerization of acetylenes such as 2-butyne (**105**), are trapped with reactive olefins such as dimethyl maleate (**107**, Scheme 15) at low temperature: the resulting adducts **108** are produced in fair yields (35%) but high stereochemical integrity, dimethyl fumarate yielding the *trans*-isomer of **108**[29]. (Aspects of Bronsted acid and base chemistry of cyclobutane derivatives is discussed at greater length by Quintanilla, Davalos, Abboud and Alkorta in chapter 5 of this volume.)

Other cyclobutadiene equivalents such as various cyclobutadiene tricarbonyliron complexes lead to comparable results. For example, liberating cyclobutadiene from metal complex **109** by oxidation with ceric(IV) ammonium nitrate (CAN) in acetone at 0 °C and trapping this highly reactive intermediate with the strain-activated cyclopropene (**110**) furnished the two cyclo adducts **111** and **112**, with the *endo*-isomer **112** slightly predominating (Scheme 16)[30]. (For a more complete discussion of organometallic chemistry see chapter 16 by Butenschön in this volume.)



SCHEME 16

Analogously, the cyclobutadiene generated from **113** furnished the three cycloadducts **114**–**116** with **110**[31]. Only the *endo*-adducts **117** and **119** were obtained on oxidation of **118** in the presence of **107** or maleic anhydride (MA), respectively[32], a stereochemical outcome attributed to secondary orbital interactions. That, after these observations, isolable cyclobutadiene derivatives such as **121** can also be used in such cycloaddition experiments to form **120** and **122** is not surprising (Scheme 16)[33].

That cyclobutadienes are also excellent precursors for ladderanes really deserving this name has been known for many years. When 1,3-cyclobutadiene (**126**) is generated by treating *cis*-3,4-dichlorocyclobutene (**123**) with sodium amalgam, a reaction taking place via the metalated intermediate **124**, it dimerizes to the *syn*-diolefin **128**, a hydrocarbon readily hydrogenated to the saturated *syn*-[3]ladderane **130** (Scheme 17)[34].

Alternatively, the *trans*-isomers **129** and **131** are obtained via **125** and **127**, which, in turn, are generated by subjecting **123** to lithium amalgam treatment[34]. Note that in both isomers the ring-junctions are *cis*-configurated. Although this would produce very high strain, *trans*-fusion is also possible in principle.

To prepare the next higher analogue of **129**, the bisanhydride **132** was prepared by photoaddition of maleic anhydride to acetylene, and its anhydride rings were converted to tetrahydrothiophene units of **133**, by the steps summarized in Scheme 18[35].

Chlorination and oxidation of **133** subsequently yielded the bissulfones **134**, which by a Ramberg–Bäcklund ring contraction furnished the hydrocarbon **135**, already containing four annelated four-membered rings. To prepare derivatives of this parent hydrocarbon, an abbreviated synthesis beginning with metal complex **109** was developed[36]. Cyclobutadiene (**126**) set free from it by Ce(IV)-oxidation again (CAN) was trapped with various acetylenes **136** (R = CH_3, C_6H_5, $COOCH_3$) to yield the 2:1 adducts **137**, called pterodactyladienes because of their resemblance to the extinct flying reptiles *Pterodactyla*; that these olefins yield the [4]ladderanes **138** on catalytic hydrogenation was to be expected (Scheme 18).

Considering the high reactivity of cyclobutadiene and its derivatives and the dimerization of **126** to [3]ladderanes (see above), it should in principle be possible to obtain still higher ladderanes by letting cyclobutadienes react with themselves. Indeed, when the dimethyl ester **139** is oxidized with CAN at low temperatures, a product mixture is obtained in 55% yield containing the ladderane derivatives **140**–**142** in 3:2:1 ratio (Scheme 19)[37].

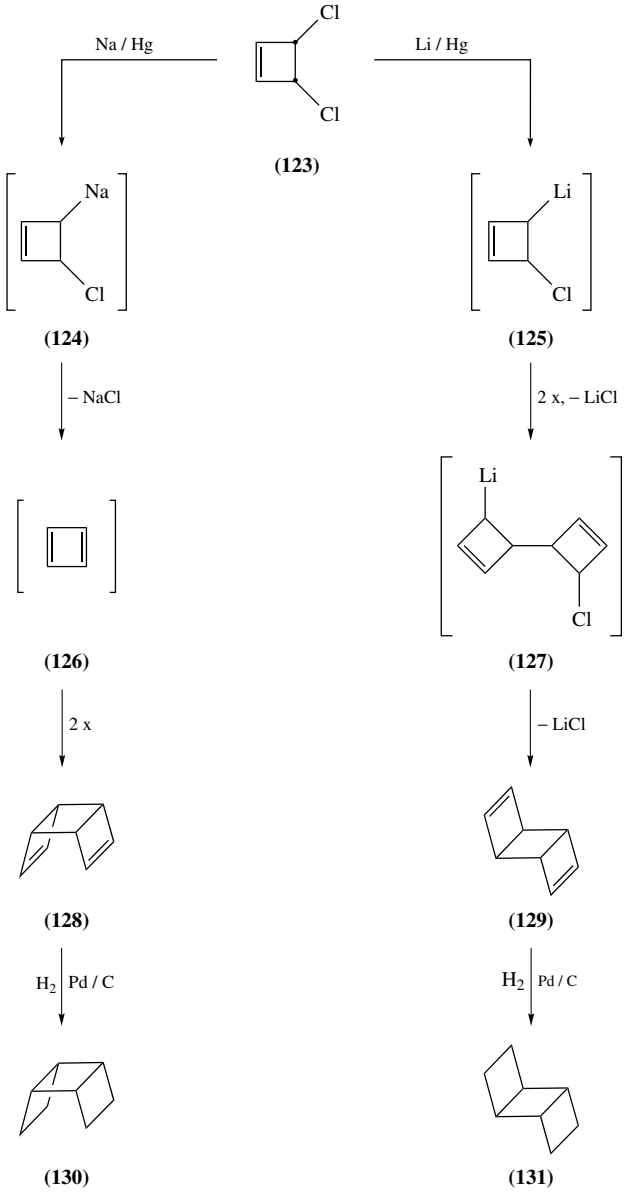
Later, this approach was extended to the preparation of [9]- (**143**) to [13]ladderanes (**144**) carrying different ester substituents[38,39]. A related tandem cycloaddition approach is exemplified in Scheme 20[40].

The norbornane-fused cyclobutene-3,4-diester **145** is reacted at 0 °C with cyclobutadiene (**126**), generated *in situ* by CAN oxidation of the iron tricarbonyl complex **109**. This cycloaddition yields adduct **146** as the major isomer, which on treatment with excess dimethyl acetylenedicarboxylate (DMAD) in the presence of a Ru(0) catalyst at 50 °C in benzene furnishes the [2 + 2]cycloadduct **147** in 52% yield. Repetition of these steps first led to the [6]ladderane derivative **148** and finally to the [9]ladderane hexaester **149** (Scheme 20). The shown *exo*-stereochemistry was proven by X-ray structure analysis of selected intermediates and reference compounds.

In a remarkable recent discovery, the tetramethylcyclobutadiene aluminium trichloride complex **106** was treated with iron pentacarbonyl in the hope that this *in situ* exchange reaction would open up a new route to the known iron tricarbonyl complex of tetramethylcyclobutadiene (see above). Actually, the desired iron complex, if formed, undergoes rapid decomposition to yield a mixture of hydrocarbons (Scheme 21).

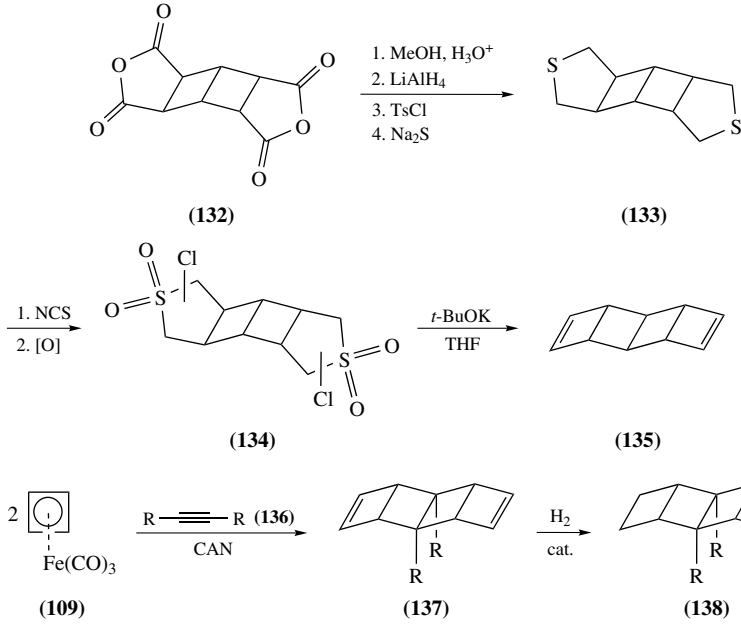
According to spectroscopic analysis this mixture consists of various ladderanes, the so far longest, the [13]ladderane derivative **150**, being constructed of 14 2-butyne units[41].

Since the most general route to cyclobutanes consists in the photodimerization of alkenes[5,42], the question may be asked whether ladderanes could not be prepared by



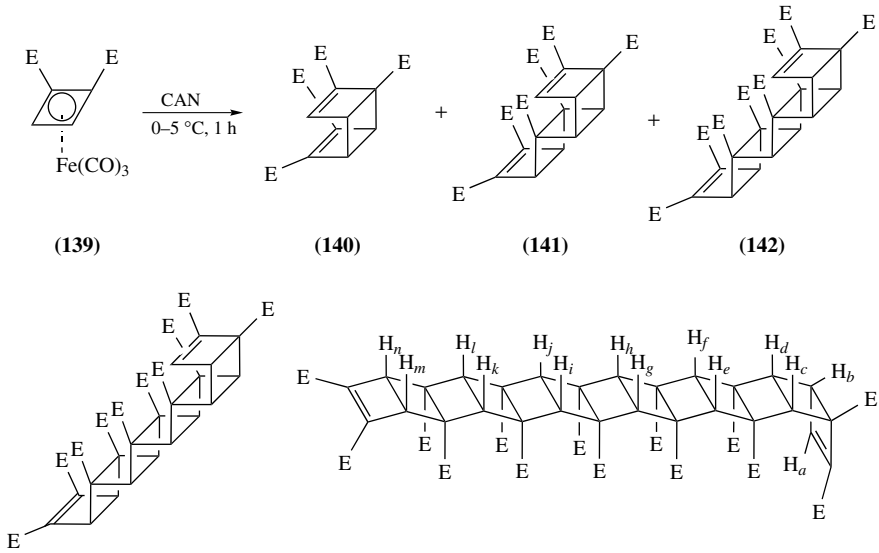
SCHEME 17

multiple [2 + 2]photoadditions between the double bonds of a di- or oligoene. Usually, these systems find other more favorable reaction channels on photoexcitation (*cis/trans*-isomerization, cyclization, photo-Diels–Alder addition etc. depending on chain length and substitution pattern)[43]. However, provided that the oligomers units are fixed with respect



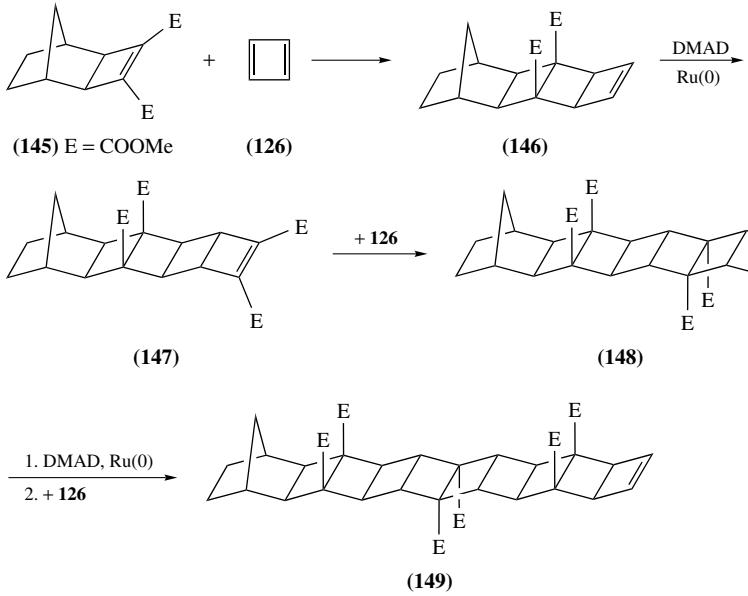
(109) **(132)** **(133)** **(134)** **(135)** **(137)** **(138)**

SCHEME 18

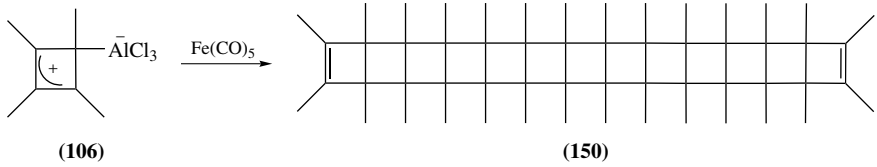


(139) **(140)** **(141)** **(142)** **(143)** **(144)**

SCHEME 19



SCHEME 20



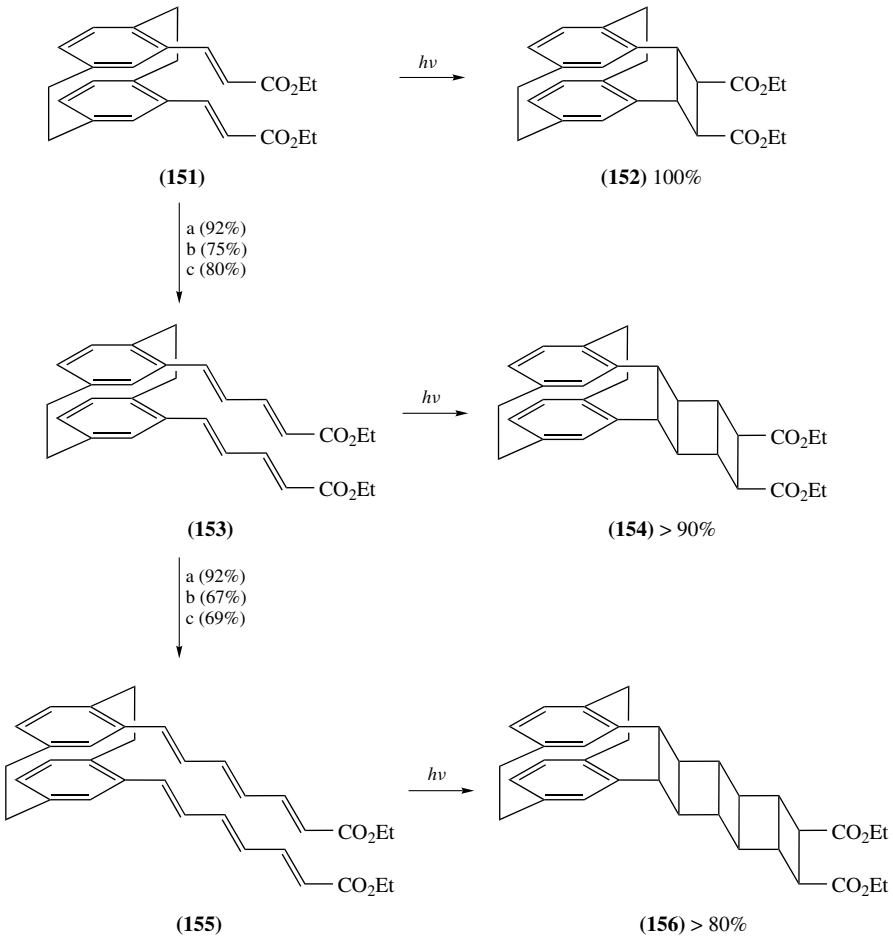
SCHEME 21

to each other and held in parallel arrangement by a suitably constructed spacer unit, multiple [2 + 2] photoaddition can indeed be performed and ladderanes be obtained by this approach.

Such a spacer is provided by the [2.2]paracyclophane system, which is not only sufficiently rigid but also displays an inter-ring distance of only 3.1 Å, short enough to allow close approach between two parallel double bond systems for [2 + 2] photoaddition to take place[44]. As shown in Scheme 22, intramolecular addition takes place when the diester **151** is irradiated, yielding the cyclobutane derivative **152** not only in quantitative chemical yield but also with the highest quantum yield (*ca* 0.8) ever observed for a *trans*-cinnamic ester photodimerization (Scheme 22)[45].

Extension of the chromophore by standard methodology converts **151** into its higher vinylogs **153** and **155**. When these diesters are irradiated, the intended multiple cycloadditions in fact take place and provide the [3]- and [5]ladderanes **154** and **156**, respectively[46]. Only from four consecutive double bonds on, the stereochemistry controlling influence of the [2.2]paracyclophane unit begins to break down and the irradiation of the corresponding diester does not yield a ladderane anymore[47].

Recently, this polyene → ladderane approach has not only been extended to other cyclophane spacers which hold the polyolefinic substituents in proper orientation[48], but



a) DIBAL-H, Et_2O, N_2, –80⟶ 0 °C; b) MnO_2, CH_2Cl_2, N_2, room temp.; c) NaH, $(EtO)_2P(O)CH_2COOEt$, THF, N_2, room temp.

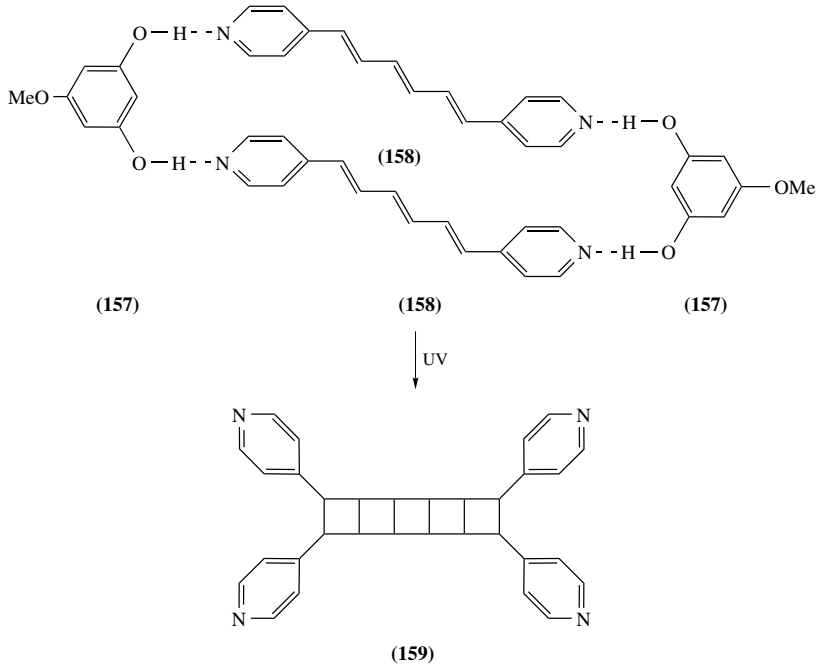
SCHEME 22

also to preorganized systems that owe the required parallel orientation of the reacting double bonds to supramolecular bonding effects.

Thus when *trans*-bis(4-pyridyl)polyenes (**158**) are co-crystallized with 5-methoxyresorcinol (**157**), a template is produced in which the two polyene molecules are fixed in parallel orientation by hydrogen-bonding interactions (Scheme 23)[49].

When powdered samples of the templated polyenes are irradiated with UV light, ladderanes such as **159** are produced[49].

Remembering that cyclobutane has a strain energy of 27.4 kcal mol^{-1} [7], the ladderanes must be highly strained organic compounds and one might assume that they are available under laboratory conditions only. Surprisingly, this is not the case, ladderanes having been discovered recently as the dominant membrane lipids of two anaerobic



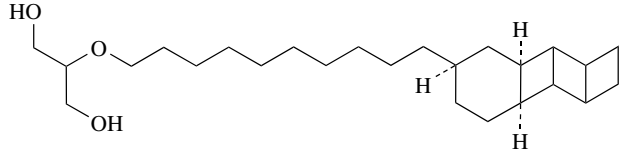
(157) **(158)** **(157)**

(159)

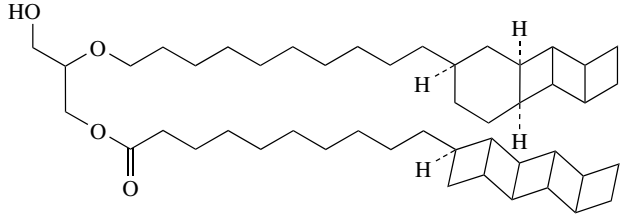
SCHEME 23

ammonium-oxidizing bacteria[50]. These ladderane lipids with structures such as **160** and **161** generate an exceptionally dense membrane, helping to contain toxic intermediates such as hydrazine and hydroxylamine; their biosynthesis is so far unknown.

In a recent theoretical development, [*n*]ladderanes have been suggested as starting materials for so-called 'shiftamers'[51]. Assuming that the ladderane **162** could undergo

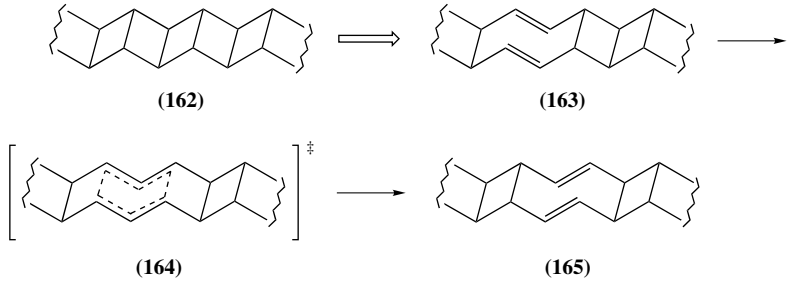


(160)



(161)

a [2 + 2]cycloreversion, this would lead to a structure with a local 'defect' consisting of two parallel double bonds, **163**. This diene could isomerize via the boatlike transition state **164** to **165**, which for the parent system would be equivalent to **163** (Scheme 24). If this process could be continued along the parallel chains, it would lead to a pair of double bonds shifting along the polymer chains, hence shiftamers. According to B3LYP/6-31G(d) calculations, the activation barrier for the Cope rearrangement is low enough to make the shiftamers **163** fluxional at room temperature. Provided the four-membered rings in ladderanes are all-*cis*-fused—as is the case in the prismanes discussed in Section II.E—polycyclic hydrocarbons would result in which appropriate double bonds could move around the perimeter in circles.



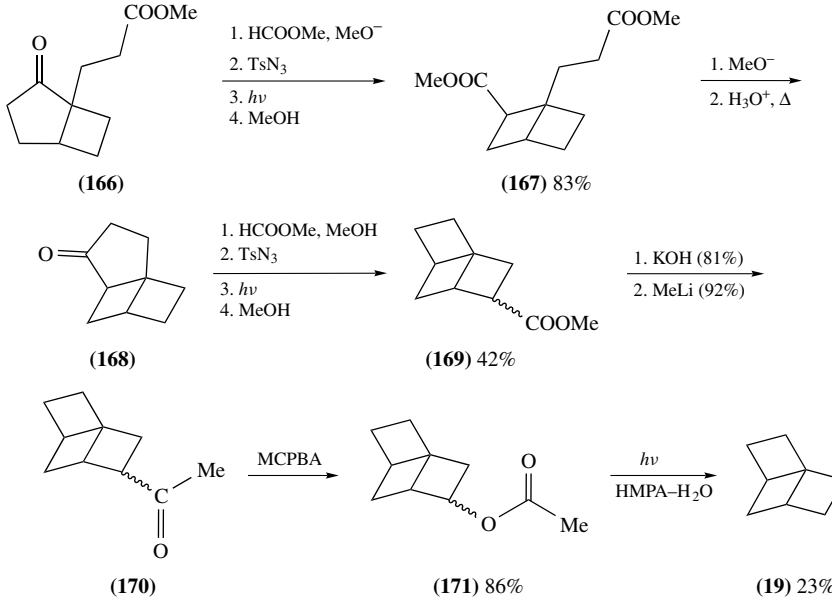
SCHEME 24

As already mentioned above (Scheme 4), the annelation of the cyclobutane rings must not necessarily continue linearly but can also take place in an angular fashion. In this latter case, tricyclo[4.2.0.$0^{1,4}$]octane (**19**) would be the first representative from which the building process could continue in different reactions. By adding a methylene group between the first and the third ring, for example, the fenestrane molecule **18** can be constructed. Although this hydrocarbon so far is unknown (see below), its immediate formal precursor **19** has been prepared as described in Scheme 25[52].

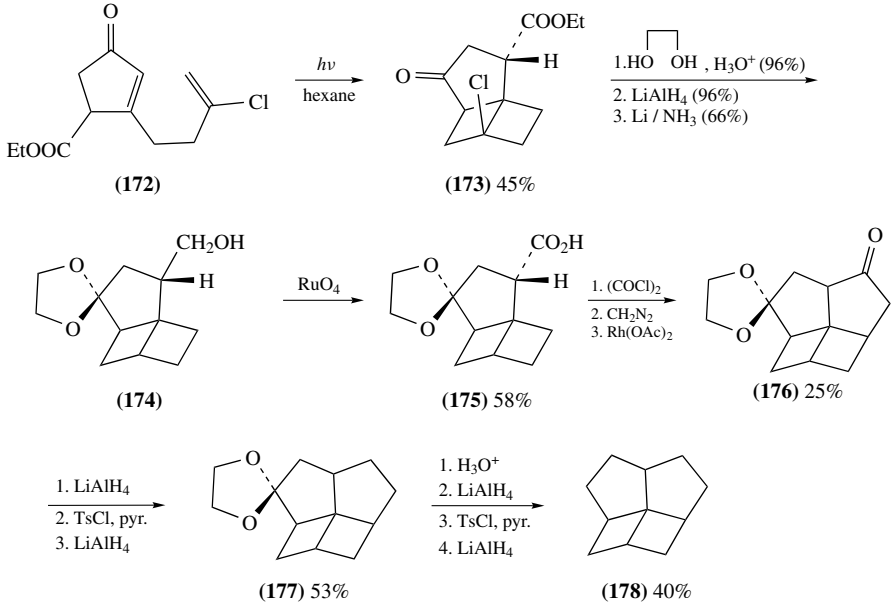
Starting with the bicyclic ketoester **166**, obtained by photoaddition of ethylene to the appropriate cyclopentenone, a contraction of its five-membered ring was first carried out by employing the often used and well established sequence of ketone activation by formylation → diazo group transfer → photolytic Wolff rearrangement → ester formation by ketene trapping with methanol. The resulting diester **167** readily underwent Dieckmann cyclization and the produced ketoester after saponification decarboxylated to the tricyclic ketone **168**, as expected. When this was subjected to another ring-contraction protocol, the ester derivative **169** of the target molecule was obtained as a mixture of isomers. Saponification and treatment of the resulting isomeric acids with methyl lithium yielded the methyl ketone **170**, which in a Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid was converted to the acetate **171**. When this was photochemically reduced by irradiation with 254 nm light in aqueous hexamethyl phosphorous triamide (HMPTA), the hydrocarbon **19** was obtained in fair yield.

Among the 'unbroken' fenestranes, the smallest parent system to be prepared so far is the [4.4.5.5]species, tetracyclo[4.4.1.$0^{3,11}$.$0^{9,11}$]undecane (**178**), and since it contains two annelated cyclobutane rings, i.e. is a derivative of '[2]ladderane' (**16**), its synthesis will also be discussed here (Scheme 26)[53].

The bicyclo[2.2.0]hexane core of the desired [4.4.5.5]fenesterane is produced early in the synthesis by a [2 + 2] photoaddition again, this time, however, by an intramolecular one, by which **173** is generated from the cyclopentenone **172**. After the keto group has been protected as a dioxolane, reduction with lithium aluminum hydride subsequently



SCHEME 25



SCHEME 26

provides a hydroxymethyl function and lithium treatment in ammonia removes the chlorine substituent. To construct the second five-membered ring, **174** is first oxidized to the acid **175**, which is then chain-extended by treatment with oxalyl chloride. Reaction of the resulting acid chloride with diazomethane gives the diazoketone, which in the presence of rhodium(II) acetate provides a ketocarbene intermediate set up to insert in a proximal C,H-bond, thus providing **176** containing the complete carbon skeleton of **178**. This hydrocarbon was finally obtained by two reduction sequences involving LAH treatment, conversion of the resulting alcohol to a tosylate and its reduction by a second LAH-attack, with the protective group having been removed after the ketal **177** had been reached from **176** as an intermediate[54].

Hydrocarbons such as **18** and **19** are of interest with respect to the problem of creating a planar tetravalent carbon atom. In the absence of stabilizing substituents, planar methane has been calculated to be *ca* 150 kcal mol^{-1} less stable than tetrahedral methane[55]. On the basis of models and molecular mechanics calculations, the $C_1-C_8-C_5$ angle in **18** should be about 130° and the strain energy on the order of 180 kcal mol^{-1}. For **19**, this angle has been estimated to be around 125° and the strain energy to be *ca* 90 kcal mol^{-1}. The introduction of the fourth methylene group hence causes a drastic increase in strain[52].

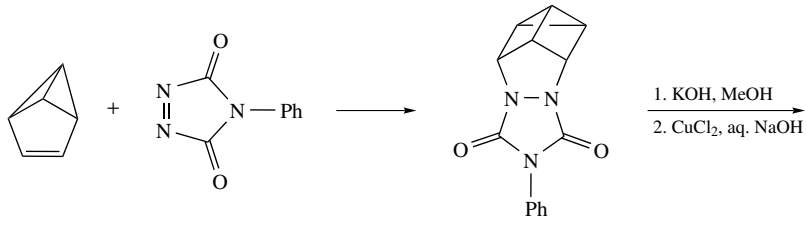
D. Cyclic Hydrocarbons Consisting of *cis*-Fused Cyclobutane Rings Only — The [*n*]Prismanes

The preparation of the prismanes [3]- (**21**) to [5]prismane (**23**) has been described and reviewed many times[56], (most notably by Bashir-Hashemi and Higuchi in chapter 19 of this volume) a brief summary in this Chapter is hence sufficient in our view.

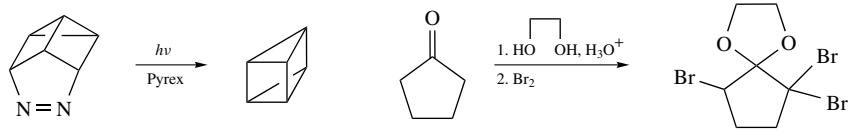
Thus beginning with [3]prismane (**21**), this archetypical prismane, also known as Ladenburg benzene, was prepared from one of its (and benzene's) $(CH)_6$-valence isomers, benzvalene (**179**, Scheme 27)[57].

The 'isomerization' of **179** to **21** is initiated by the cycloaddition of *N*-phenyltriazolindione (**180**, NPTD) to **179**. This causes a deep-seated reshuffling of the carbon atoms and provides the 1:1 adduct **181** in 50–60% yield, a process most likely taking place via polar intermediates. To close the last cyclobutane ring, **181** was first hydrolyzed and the resulting diacid oxidized to the azo compound **182**, the yield being acceptable again. When this intermediate is irradiated with ultraviolet light, nitrogen is split off and a complex photolysate is produced from which small amounts of [3]prismane (**21**) could be isolated (percentage range).

The synthesis of the next higher prismane, cubane (**22**), which is considerably less strained than **21**, has been improved several times through its long history, but the basic idea—building precursors by cycloaddition and rearrangement reactions having *more* carbon atoms than the target molecule and then 'chiseling' these atoms away after they have fulfilled their purpose—has remained the same, since cubane was first synthesized forty years ago[58]. Thus as illustrated by the optimized cubane synthesis in Scheme 27, the 1,4-dicarboxylic acid **188** can be prepared from cyclopentanone (**183**) in just five steps in about 25% over-all yield, allowing the preparation of cubanes in multi-kilogram batches. After ketalization of **183** followed by a bromination step, the tribromide **184** is obtained, which on base-treatment loses two equivalents of hydrogen bromide and provides the ethylene ketal of 2-bromocyclopentadienone, **185**, as a reactive intermediate. This undergoes spontaneous dimerization to the Diels–Alder adduct **186**, in which the two double bonds are so close that they can participate in an intramolecular $[2+2]$ photoaddition to a product that, on acid treatment, loses its protective group and furnishes the bishomocubanedione **187**. Ring contraction is subsequently readily accomplished by two Favorskii rearrangement steps and the resulting diacid **186** is best decarboxylated via

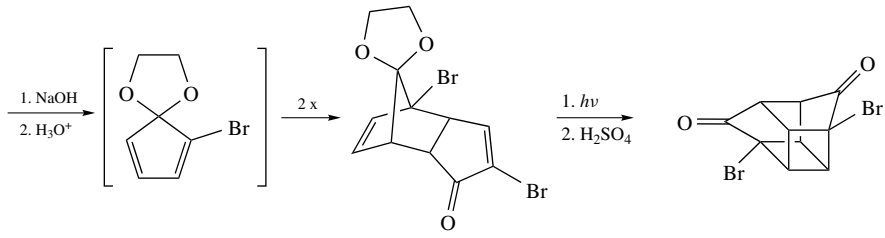


(179) **(180)** **(181)** 60%

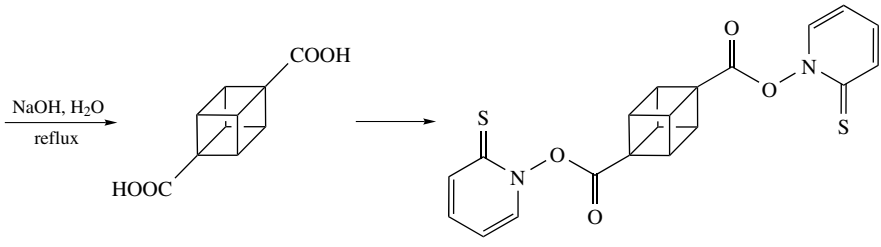


(182) 65% **(21)** **(183)** **(184)**

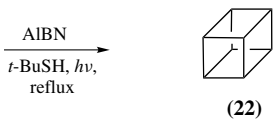
(E_S = 320 kcal mol^{-1})



(185) **(186)** **(187)**



(188) **(189)**



(22)

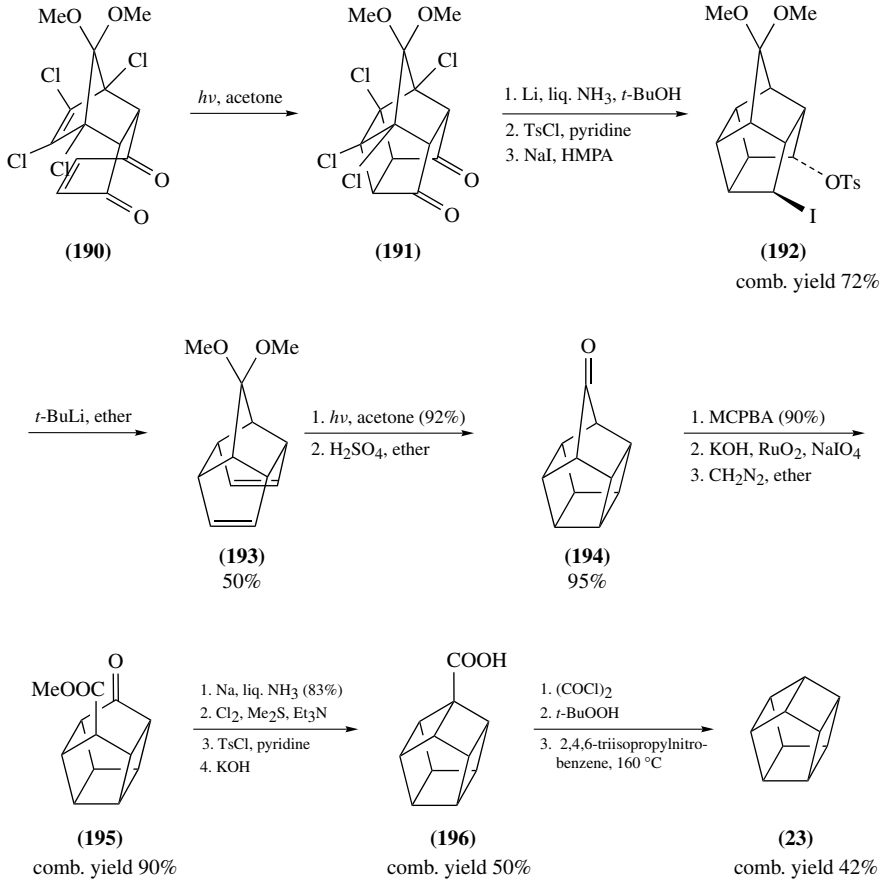
(E_S = 172 kcal mol^{-1})

SCHEME 27

189 to the parent hydrocarbon by photolysis in the presence of AIBN and the hydrogen atom donor *tert*-butyl mercaptan[59].

For the synthesis of [5]prismane (**23**), the least strained of all prismanes known to date, several of the concepts used successfully for the preparation of cubane were exploited again (Scheme 28) where the hydrogen atom donor is 2,4,6-triisopropylbenzene[60].

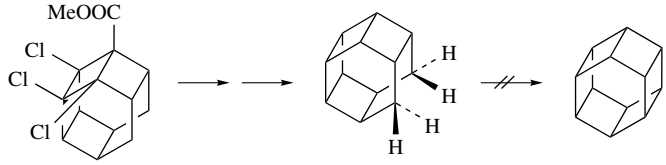
Beginning with the [2 + 4]cycloadduct between benzoquinone and the ketal of perchlorocyclopentadienone, **190**, a first photoaddition yielded the saturated diketone **191**. This was dechlorinated and reduced by treatment with lithium in liquid ammonia, and from the resulting diol the iodo tosylate **192** was prepared. When this was reacted with base, rather than the intended bridge formation between the functionalized secondary carbon atoms, a ring-opening to the hypostrophene derivative **193** took place. Photochemical recyclization quickly returned three cyclobutane rings, and after removal of the protective group, the ketone **194**, formally already very close to the target prismane, was at hand. Still, to remove the bridging carbonyl group required nine further steps, i.e. involved more than half of the whole synthesis, the main reason being that a direct functionalization of



SCHEME 28

a bridgehead—prerequisite of, e.g., a ring contraction step—is very difficult because of the 'protection' of these positions by Bredt's rule. Therefore, **194** was Baeyer–Villiger oxidized, followed by another oxidation step with ruthenium dioxide/sodium periodate to yield a keto acid which was esterified with diazomethane to **195**. Bridge closure could then be effected by an acyloin condensation and, when the resulting diol was oxidized, a homopentaprismane derivative was available with a functional group at a bridgehead, a hydroxyl group. Converting this to a tosylate set the stage for a Favorskii ring contraction which lead to **196**, with all five cyclobutane rings completed. Decarboxylation via a perester pyrolysis in a hydrogen-donating solvent finally gave [5]prismane (**23**).

Although 'in principle' there is no reason why the methodology used so successfully for the preparation of **22** and **23** should not be extended to [6]prismane (**199**), all experiments have met with failure so far. A particularly disappointing one is an approach which lead—via the intermediate **197**—to seco[6]prismane (**198**, Scheme 29). Unfortunately, all attempts to dehydrogenate/oxidize this to **199**, the face-to-face dimer of benzene, failed[61].



(197) **(198)** **(199)**

SCHEME 29

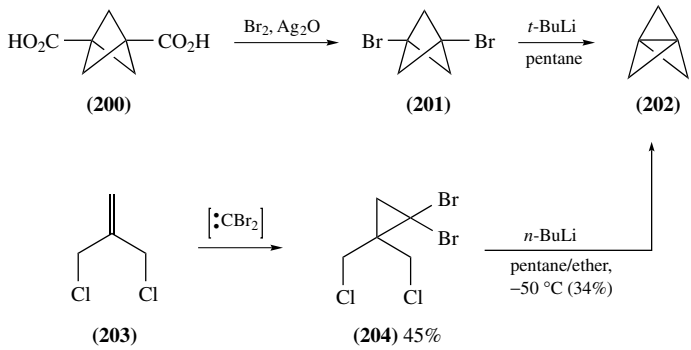
The value of n in a prismane represents the order of the hydrocarbon, and can in principle be between 3 and ∞. According to molecular mechanics and MO calculations, only the prismanes with up to 12 cyclobutane rings have been predicted to be planar with a D_{nh} symmetry. Higher members of the series should possess puckered structures displaying reduced angle strain and less-pronounced nonbonded hydrogen interactions[62].

E. Building with Oligocyclobutanoid Precursors — The [*n*]Staffanes and the Oligo[*n*]cubyls

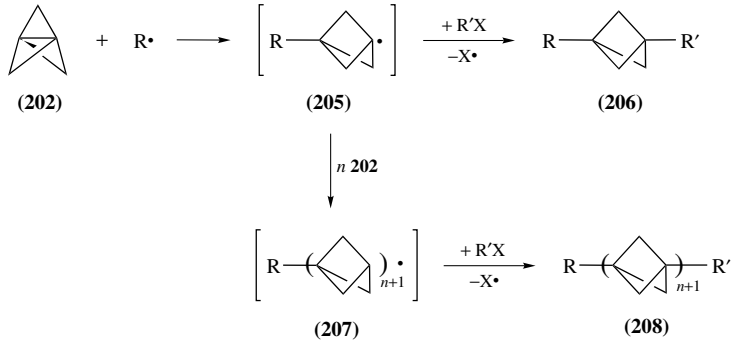
Hydrocarbons containing already several cyclobutane rings or those constructed from cyclobutane units completely are interesting building blocks for the creation of higher polycyclobutanoid oligomers. To be used for this purpose they have to be available in sufficient amounts, i.e. by straightforward and efficient synthetic protocols. Two particularly well studied cases in this context are bicyclo[1.1.1]pentane (**26**) and cubane (**22**), the monomers of the [*n*]staffanes and the oligo[*n*]cubyls.

Since all [*n*]staffanes can ultimately be traced back to [1.1.1]propellane (**202**, tricyclo-[1.1.1.$0^{1,3}$]pentane), a brief description of its synthesis appears to be justified (Scheme 30).

In the original synthesis[63], the dicarboxylic acid **200** was first converted into the dibromide **201** by Hunsdiecker degradation. When this intermediate was debrominated with *tert*-butyllithium in pentane, the propellane **202** was generated as the sole hydrocarbon. Since **200** is a rare chemical, the development of the chemistry of **202** had to await the discovery of an efficient synthesis for this smallest possible propellane. The breakthrough was accomplished by addition of dibromocarbene to the commercial product **203** which furnished the tetrahalide **204** in acceptable amounts. When this is dehalogenated with *n*-butyllithium in ether/pentane, **202** is produced in such amounts as to make the preparation of gram quantities easy[64].



SCHEME 30



SCHEME 31

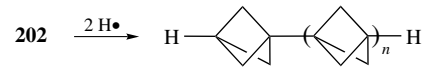
Staffane synthesis from **202** usually starts with the addition of a radical R· to the central (most reactive) bond of **202**, yielding the bicyclo[1.1.1]pentyl radical **205** (Scheme 31).

This can either react with an R′X system (which may also be a bicyclo[1.1.1]pentane derivative) to furnish the derivative **206** in a controlled fashion, or initiate the oligomerization of **202** leading to the staffyl radical **207**. In a last step the latter then stabilizes itself by insertion into another R′−X bond. Of course, this oligomerization route leads to mixtures of staffanes that have to be separated if the pure target compounds are desired. Since, however, today a wide variety of bicyclo[1.1.1]pentanes—usually obtained from **202**—is known[65], coupling reactions of these precursors provide a third, controlled entry to the staffanes (see below).

To prepare the parent systems, a mixture of argon and hydrogen or ammonia was passed through a microwave discharge and subsequently over a stirred solution of **202** in pentane at −110 °C for 10 h. After **202** had been consumed, distillation and gradient sublimation yielded the homologous series of staffanes with *n* up to 6 (Scheme 32).

The hydrocarbons **209** were characterized by their spectroscopic and analytical data and several of them also by X-ray structure analysis, which confirmed the anticipated linear molecular shape and staggered conformations[66]. Besides these oligomers, 14% of nonvolatile polymers insoluble in the common organic solvents was also produced.

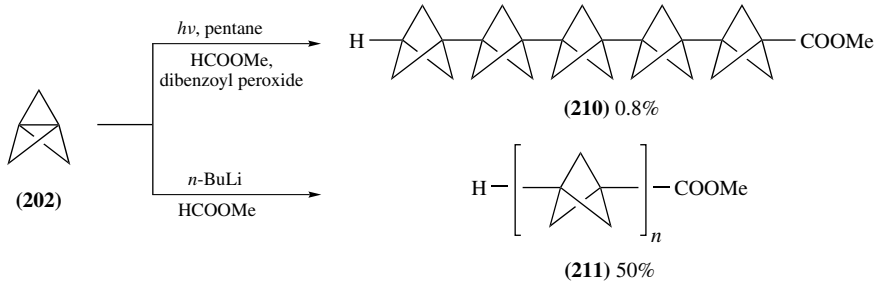
Functionalized staffanes, such as the ester **210**, were prepared by irradiation of a mixture of **202** and methyl formate in pentane using dibenzoyl peroxide as the free radical initiator (Scheme 33).



(209)

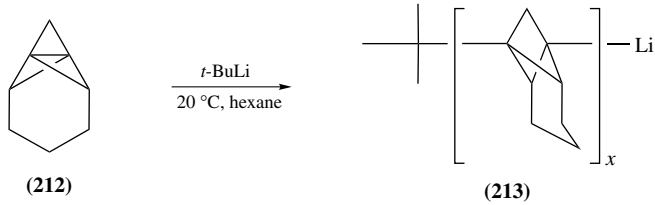
n	1	2	3	4	5
yield, %	13	9	6	2	0.3

SCHEME 32



(210) 0.8%

(211) 50%



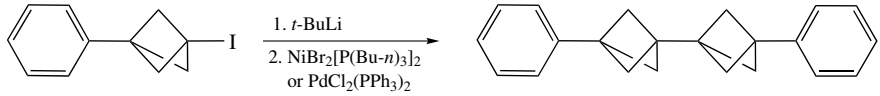
(214)

SCHEME 33

The oligomerization also takes place under ionic conditions, as shown by the conversion of **202** to the oligomeric esters **211** in the presence of *n*-butyllithium[67].

The propellane nucleus can also be a part of a more complex framework, as demonstrated by the oligomerization of **212** to **214** via the lithiated intermediate **213**[68].

A typical bridgehead-to-bridgehead coupling process takes place when 1-iodo-3-phenylbicyclo[1.1.1]pentane (**215**), itself obtained by photochemical insertion of **202** into iodobenzene[69], is first metalated with *tert*-butyllithium and the resulting metal organic intermediate subsequently subjected to metal-mediated dimerization to the diphenyl derivative **216** (Scheme 34).

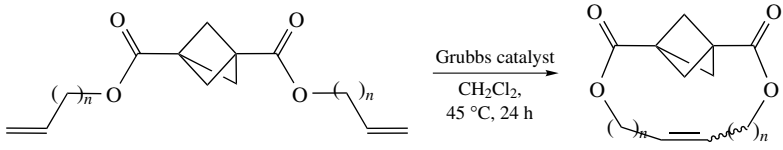


(215) **(216)**

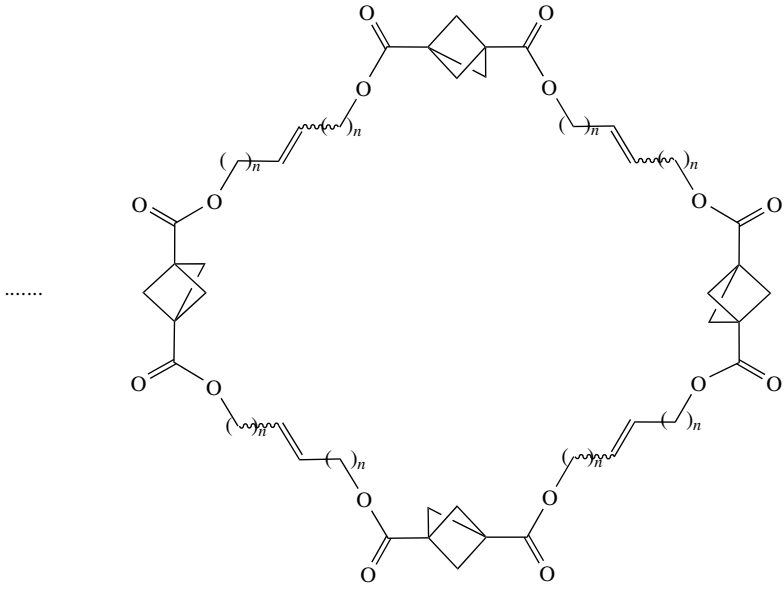
SCHEME 34

Today, staffanes constitute a widely investigated class of cyclobutane ring containing rod-like molecules, that are, *inter alia*, of interest for the preparation of novel liquid crystalline materials or the investigation of electron and energy transfer processes across the saturated spacer[70].

Incidentally, the bicyclo[1.1.1]pentane core has also been incorporated as a spacer unit in a completely different class of compounds. Thus the homologous series of bicyclo[1.1.1]-pentane-1,3-dicarboxylate esters **217** featuring ω-alkenols of differing chain length undergo ring-closing metathesis with Grubbs catalyst to provide various paddlanes with monomeric, **218**, to tetrameric structures **219** (Scheme 35)[71].



(217) $n = 4 - 8$ **(218)**

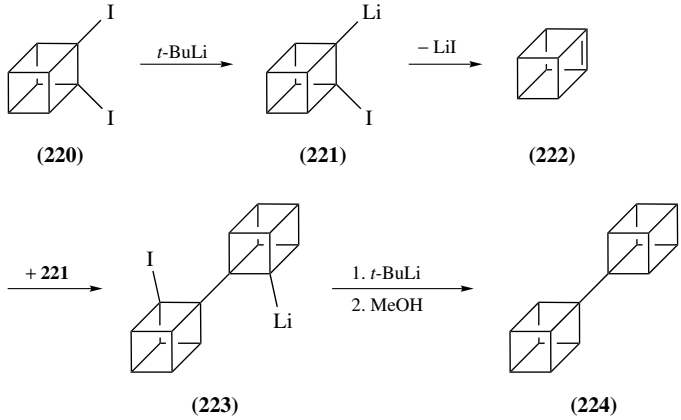


(219)

SCHEME 35

Just as propellane **202** is the central starting material in staffane synthesis, the [*n*]oligocubyls can all be traced back to two diiodocubanes: 1,2- (**220**) and 1,4-diiodocubane (**225**, see below), respectively, both readily available by the various methods for preparing functionalized cubanes developed over the years by Eaton and coworkers[58b].

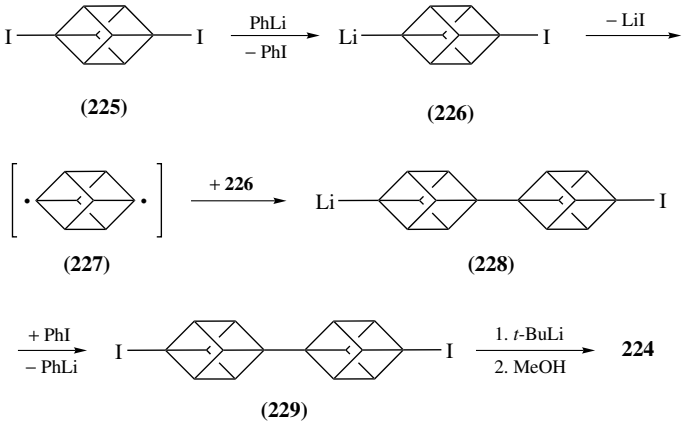
When **220** is treated with *tert*-butyllithium, deiodination takes place and dehydrocubane **222** is generated as a highly reactive (though trappable) intermediate via the organolithio compound **221** (Scheme 36).



SCHEME 36

The pyramidalized olefin reacts with a further molecule of **221** to provide the lithiated dimeric iodide **223**, which—after further metalation and quenching with methanol—yields cubylcubane (**224**) as the simplest oligocubyl.

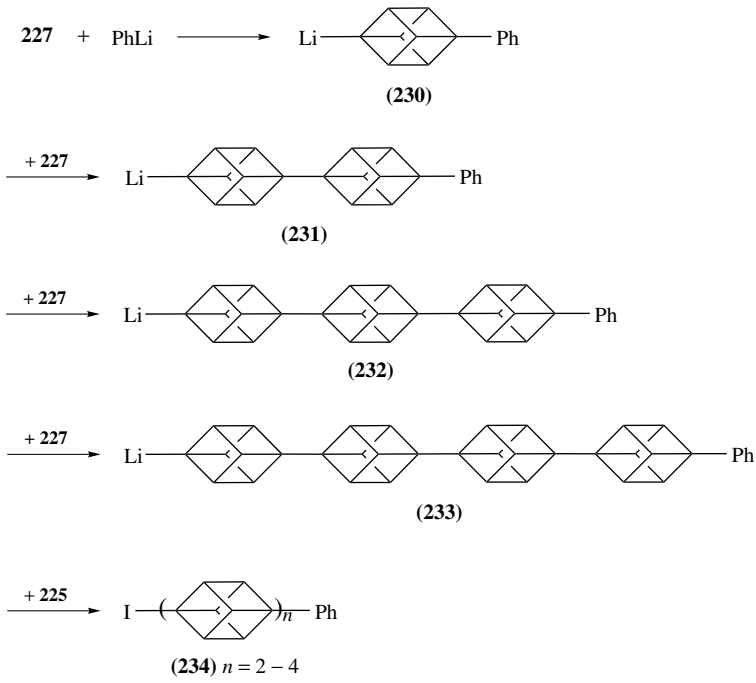
More effective routes to **224** and its derivatives involve another highly reactive intermediate generated from the isomer of **220**, 1,4-diiodocubane (**225**) by phenyllithium treatment: 1,4-dehydrocubane or cubane-1,4-diyl (**227**, Scheme 37)[72].



SCHEME 37

Reaction of **227**, the structure of which was determined by matrix isolation infrared spectroscopy[73], with intermediate **226** provides the lithio derivative **228** as a precursor for the bisiodide **229** (reaction with iodobenzene). From **229**, the hydrocarbon **224** could again be prepared by metalation/methanol quench.

With phenyllithium, **227** couples to 4-phenylcubyllithium (**230**), a most useful intermediate on the way to *p*-[*n*]cubyl oligomers, as illustrated in Scheme 38[74].



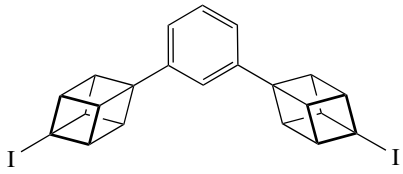
SCHEME 38

Intermediate **230** initiates a 'living polymerization' leading to the series of intermediates **231**–**233** which, by trapping with the 1,4-diiodide **225**, furnishes the *p*-[*n*]cubyls **234** ($n = 2$–4). These are not only useful precursors for the preparation of numerous other derivatives but can also be converted to the parent hydrocarbons.

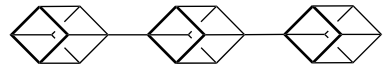
Since other aryl lithium reagents can take the role of the phenyl lithium in these transformations—or can be exchanged altogether for Grignard reagents—numerous oligocubyl systems have been synthesized, as illustrated by several representative examples, **235**–**238**.

As expected, the solubility of the [*n*]cubylcubanes decreases rapidly with growing degree of oligomerization. By introducing solubilizing alkyl groups, this drawback can be overcome and truly polymeric molecular rods may be obtained. Thus when 7,7-di-*n*-hexyl-1,4-diiodocubane (**239**) is subjected to the above coupling conditions, a polymer **240** with a molecular weight of *ca* 10,000 is isolated, corresponding to a polycubyl rod containing *ca* 40 cubane building blocks (Scheme 39)[75].

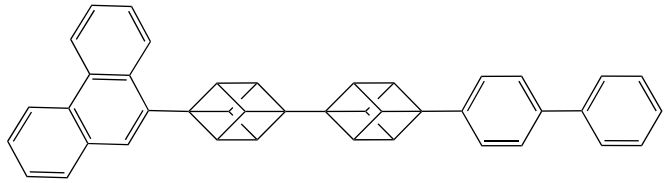
In all the above examples, the connections between the cubane blocks are established by single bonds. Other modes of sticking these cubes together are conceivable, though. By introducing additional single bonds as shown for the cubylcubane **224** and its higher



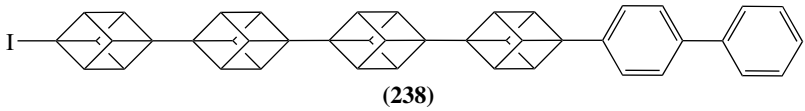
(235)



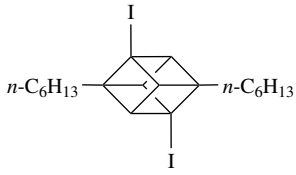
(236)



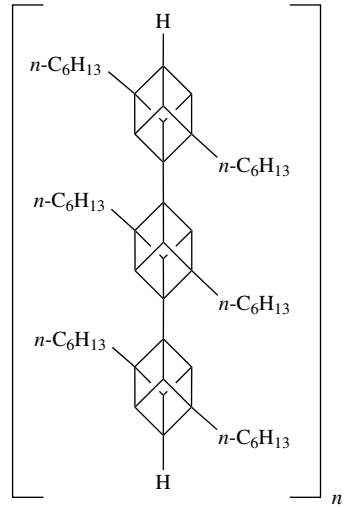
(237)



(238)



(239)

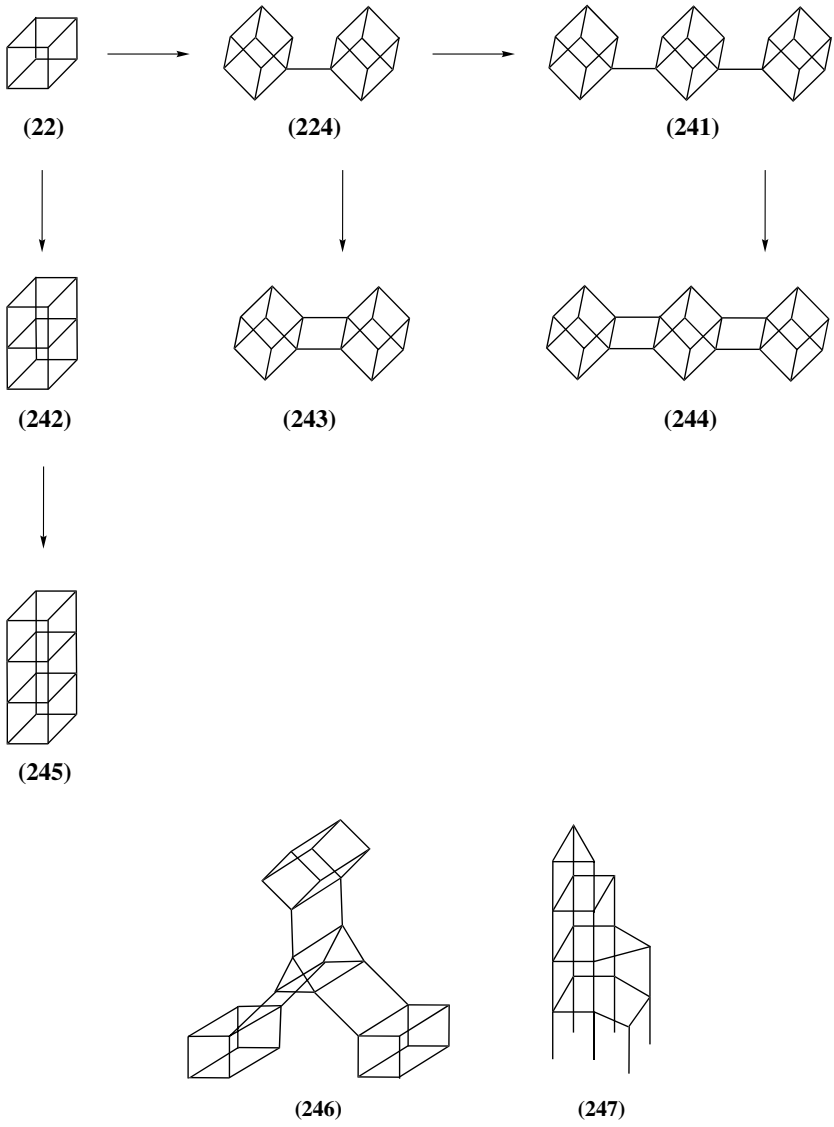


(240)

SCHEME 39

'cubylog' **241** in Scheme 40, edge-fused oligocubyls such as **243** and **244** may be generated. And when the cubane monomer units **22** are fused at their faces, columnar structures such as **242** and **245** result (Scheme 40).

Of course, hybrid types containing different prismanes—as shown for [3]prismane and [4]prismane in structure **246**—can also be imagined, and when the ring size is



SCHEME 40

not restricted to a particular size, skyscraper structures such as **247** result. None of the molecules **242**–**247** has been prepared so far, but at least DFT calculations on several of the poly[*n*]prismanes—such as **242** and **245**—have appeared recently[76]. Although these structures must contain highly distorted tetracoordinated carbon atoms, the calculations suggest relative stable D_{nh}-structures for the poly[*n*]prismanes. The main factor for the stability of these hydrocarbons is the $\pi_\sigma - \pi_\sigma$ orbital interaction between the parallel rings.

III. FROM RIGID TO FLEXIBLE OLIGO- AND POLYMERIC CYCLOBUTANES

Nearly all of the oligocyclobutanoid compounds described so far are characterized by their more or less pronounced rigidity. And for their synthesis, usually a stepwise approach has been employed, i.e. one involving the addition of one cyclobutane ring(s) containing subunit after the other. We now turn to 'real' cyclobutane-derived polymers and it is not surprising that for their preparation, classical cationic, anionic and radical chain-polymerization techniques have been widely applied. We will divide these polymers into three categories: In the first one, both the monomers and the polymeric products contain four-membered rings. In the second one, the polymers no longer contain a cyclobutane ring although the starting material is a cyclobutyl derivative. And, finally, the third category will present transformations in which cyclobutane rings are generated in the polymer although the monomers have none.

A. From Cyclobutyl Monomers to Polymers Containing Cyclobutane Rings

It is not unexpected that traditional alkene additions and condensations of carboxylic acid derivatives comprise two principal modes of polymerization of cyclobutane-containing monomers to cyclobutane polymers.

Probably the most traditional approach to polymers in this category is ester and amide condensation polymerization of cyclobutane-containing bifunctional monomers. An appreciable variety of cyclobutane polymers has been prepared by this means. As a precursor to multiple bifunctional monomers, the dicyanocyclobutane dimer of acrylonitrile (**248**) is an exceedingly versatile core synthon[77]. The dimerization produces principally the 1,2-compound as a mixture of *cis*- and *trans*-isomers, but both hydrolysis and reduction proceed to the *trans*-diacid **249** and the *trans*-diamine **252**, respectively. Polyamides prepared as melts directly from **249** and *n*-methylenediamines are isomerized unevenly back to the *cis*-form, but the milder conditions of interfacial polymerization with the diacid chloride **250** and the same diamines yielded more uniform crystalline polyamides **251** as shown in Scheme 41.

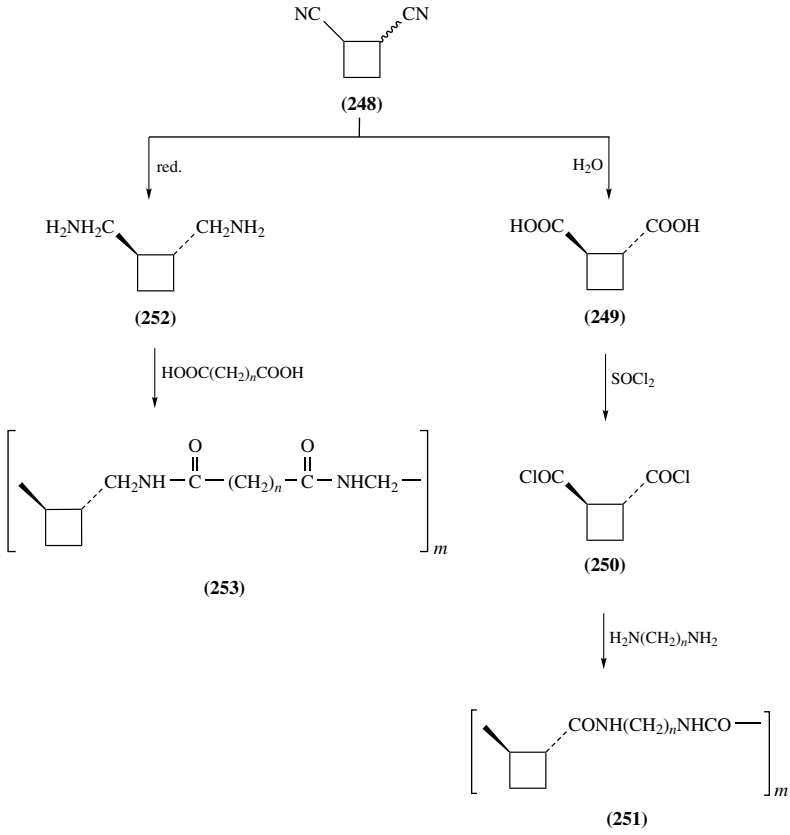
Polyamides of **252** and adipic acid and sebacic acid, the polymers **253**, can be prepared by melt methods without isomerization, as also shown in Scheme 41.

The diphenyl ester prepared from **250** yields several polyesters with diols such as bisphenol A, and the ester and amide permutations of bifunctional cyclobutanes are completed by lithium aluminum hydride reduction of **250** to *trans*-1,2-bis(hydroxymethyl) cyclobutane (**254**) and subsequent polymerization with diacids exemplified by terephthalic acid (**255**) to provide the polyesters **256** (Scheme 42).

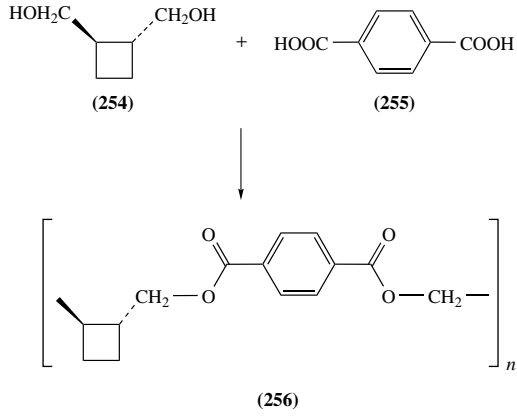
A more highly functionalized cyclobutane-containing copolyamide has been synthesized that contains both cyclobutane ring and conjugated double bond in the main chain[78]. The prototype reaction—yielding the complex polymer **260**—is shown in Scheme 43 for bis(*p*-nitrophenyl) β-truxinate (**257**) reacting with di(*p*-nitrophenyl) *p*-phenylenebis(acrylate) (**258**) and 1,3-di(4-piperidyl)propane (**259**).

Another elaborate cyclobutane-containing polyamide, poly[*p*-phenylene-*trans*-3,*cis*-4-bis(2-hydroxyphenyl)-1,*trans*-2-cyclobutane dicarboxamide] (**262**), can be made by ring-opening condensation polymerization of *p*-phenylenediamine with the *anti*-cyclobutane coumarin dimer **261** (Scheme 44)[79]. A spare cyclobutane-free poly(*p*-phenylenefumaramide) polymer **263** results from nearly quantitative asymmetric photolytic extrusion of *trans*-2-hydroxy-2′-hydroxystilbene from the cyclobutane precursor **262**[79].

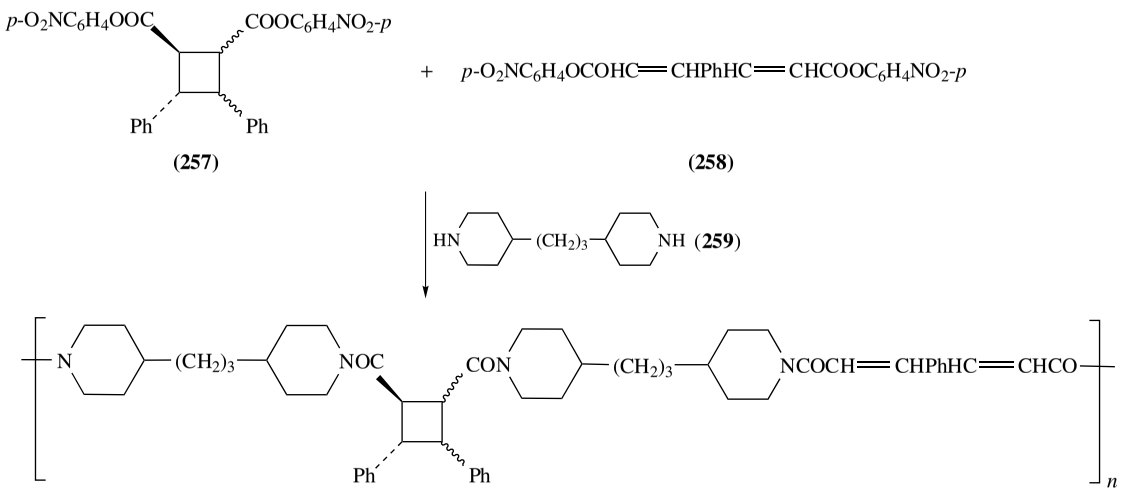
Maleic anhydride is photodimerized to 1,2,3,4-cyclobutanetetracarboxylic dianhydride (**264**) which is shown to have a *cis,trans,cis*-configuration by X-ray crystallography. The dianhydride can be condensed with various aromatic diamines, such as *p*,*p*′-diaminodiphenyl ether, to prepare polyimides such as **265**, as shown in Scheme 45[80].



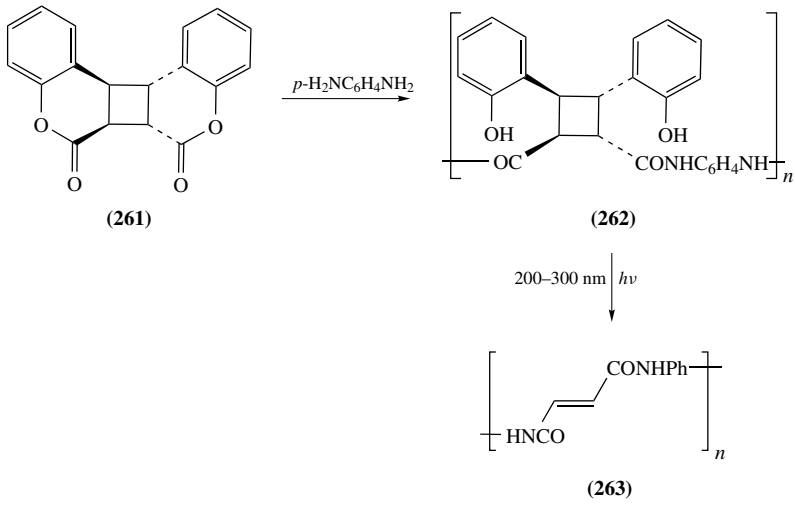
SCHEME 41



SCHEME 42

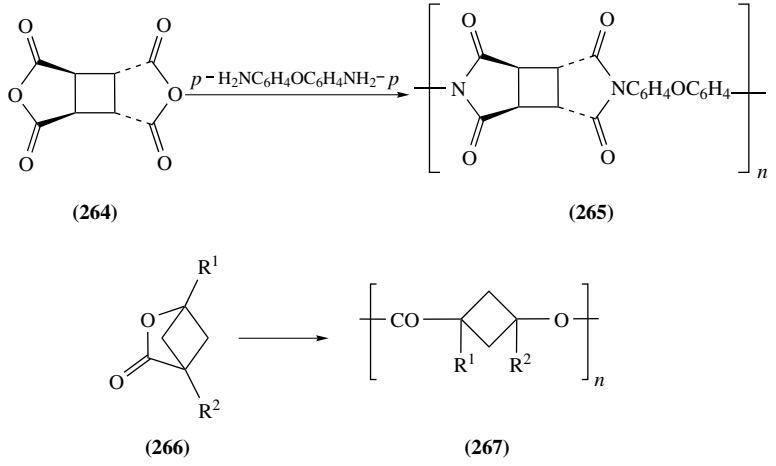

p-O2NC6H4OOC
COOC6H4NO2-p
Ph
Ph
(257)
+
p-O2NC6H4OCOHC═CHPhHC═CHCOOC6H4NO2-p
(258)
HN
(CH2)3
NH (259)
N
(CH2)3
NOC
CON
(CH2)3
NCOCH═CHPhHC═CHCO
Ph
Ph
n
(260)

SCHEME 43



(261) **(262)** **(263)**

SCHEME 44



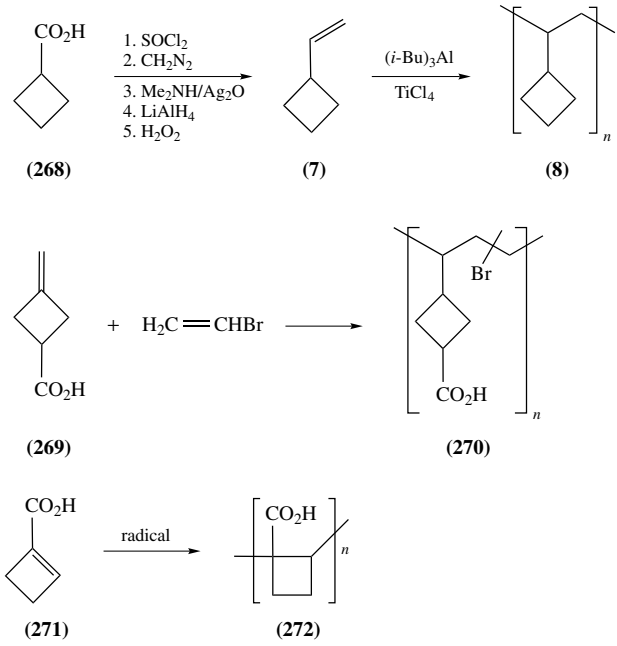
(264) **(265)** **(266)** **(267)**

SCHEME 45

Five-substituted 2-oxabicyclo[2.1.1]hexan-3-ones (**266**, $R^1 = H$, CH_3, $R^2 = H$, CH_3 and $R^1 = CH_3$, $R^2 = H$, CF_3) were synthesized from the corresponding 3-chlorocyclobutanecarboxylates obtained by addition of hydrochloric acid to the cycloadduct of allene to acrylonitrile or methacrylonitrile[81]. These bicyclic lactones resemble β-lactones in acid- or base-catalyzed polymerizations to high-molecular-weight and high-melting **267** polyesters (Scheme 45).

Another conspicuously straightforward approach to cyclobutane polymers is through conventional alkene addition polymerizations. Polymers have been prepared from cyclobutane-containing monomers with an olefin as a pendant vinyl group, *exo* to the ring or as cyclobutene. Thus, vinylcyclobutane (**7**) was prepared by the synthesis shown in

Scheme 46 from cyclobutanecarboxylic acid (**268**)[82]. A highly crystalline polymeric material as identified by crystallographic d-spacings, compound **8**, was obtained after initiation with triisobutyl aluminum and titanium tetrachloride (Scheme 46).



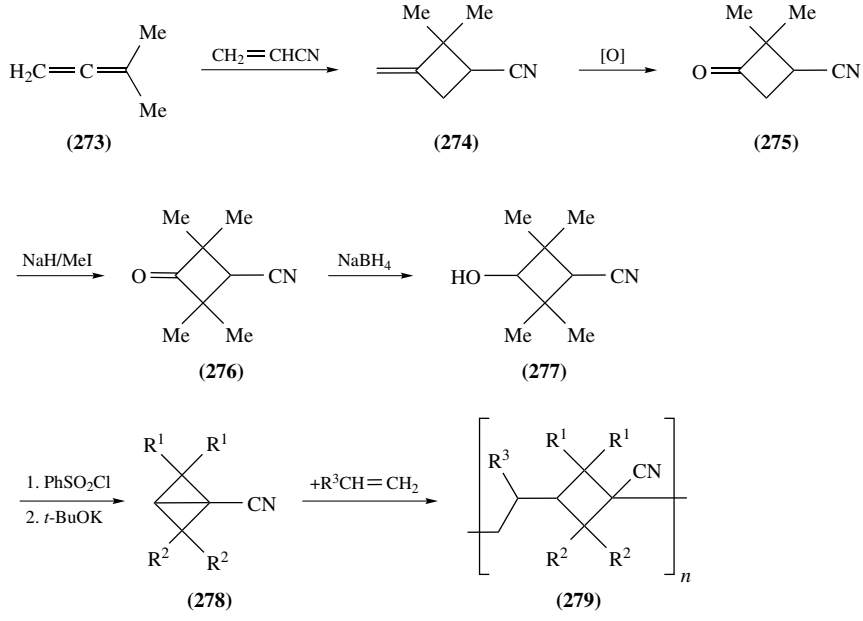
SCHEME 46

Now consider the olefin moiety contracted closer to the cyclobutane ring in the methylene-cyclobutane **269** made from allene and various acrylates en route to the bicyclic lactones **266** described above. Free-radical-initiated homopolymerization with azobisisobutyrylnitrile failed for methylenecyclobutane and all 3-substituted cyano, carboxylic acid, methyl, and phenyl derivative and the 3-methyl-3-methoxycarbonyl analogue[83]. However, the same methylene-cyclobutanes could be made to copolymerize with acrylonitrile, methyl methacrylate, vinyl acetate, vinyl bromide and styrene to furnish polymers such as **270**. In Scheme 46 a process is illustrated in which the mole percent ratios of methylenecyclobutane and vinyl bromide in the starting monomer mixture and in the final polymer are approximately equal.

As the double bond is positioned closer to the cyclobutane ring in this subcategory of alkene additions, we finally arrive at the polymerization of cyclobutenes. Spontaneous polymerization of 1-cyclobutenecarboxylic acid **271** was first observed during an attempt to purify the compound[84]. It had been prepared by dehydrohalogenation of 1-bromo-1-cyclobutane carboxylic acid obtained by free-radical bromination of 1-cyclobutanecarboxylic acid (**268**). Polymerization could be deliberately induced by UV irradiation in the presence of 2,2-dimethoxy-2-phenylacetophenone. ^{13}C NMR spectroscopy confirmed the absence of ester carbon atoms that would result from possible polymerization by Michael addition and the absence of alkene carbon that would result from possible ring-opening polymerization. The polymer **272** is a noteworthy member of a small population of 1,2-di-, tri- and tetra-substituted alkene homopolymers that

presumably issues in this case from relief of cyclobutene ring strain as well as the protection against radical termination afforded by three substituents on the olefin.

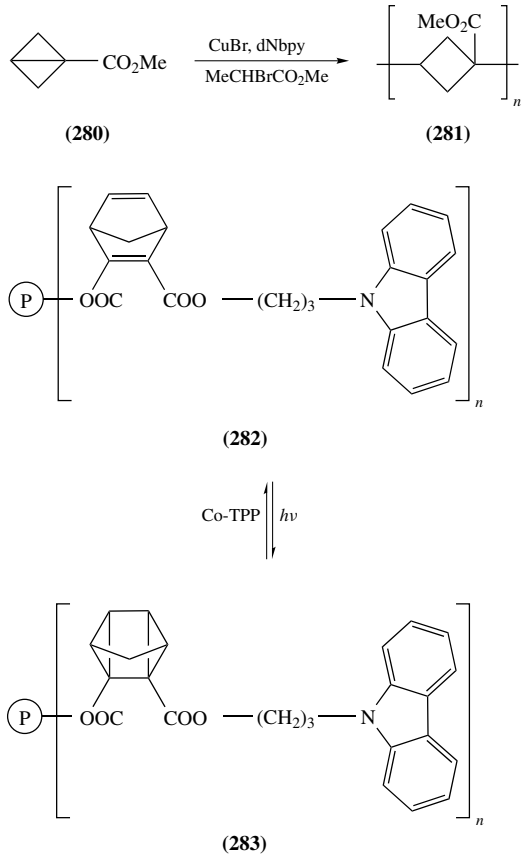
A unique polymerization route in this category is radical polymerization of bicyclobutane derivatives. There are many examples of free-radical homopolymerization of bicyclobutanes bearing bridgehead electron-withdrawing groups and copolymerization with vinyl monomers. 1-Bicyclobutanecarbonitrile and C-2 and C-4 methyl substituted 1-bicyclobutanecarbonitriles (**278**) ($R^1 = R^2 = H$; $R^1 = H$, $R^2 = CH_3$; $R^1 = R^2 = CH_3$) readily polymerized by radical and anionic initiation. Copolymers, e.g. **279**, of a great variety of the 1-bicyclobutanecarbonitriles with each other and with standard vinyl monomers were also realized (Scheme 47)[85].



SCHEME 47

2,2,4,4-Tetramethyl-1-bicyclobutanecarbonitrile (**278,** $R^1 = R^2 = CH_3$) was synthesized as shown in Scheme 47 starting from 1,1-dimethylallene (**273**) and acrylonitrile. The initially obtained [2 + 2]cycloadduct **274** was transformed to the target systems **278** via intermediates **275**–**277** following the protocol summarized in Scheme 47. Other 1-bicyclobutanecarbonitriles were synthesized similarly[86].

A more controlled and improved radical polymerization route, atom transfer radical polymerization (with CuBr, methyl 2-bromopropanoate and 4, 4′-dinonyl-2, 2′-bipyridyl (dNbyp)), has recently been applied to methyl 1-bicyclobutanecarboxylate (**280**) as shown in Scheme 48[87]. Stereochemistry of the polymer **281** is 66% *trans*-configuration of the methyl ester group to the cyclobutane polymer chain. The monomer **280** is prepared by treatment of methyl 3-chloro-1-cyclobutanecarboxylate with sodium hydride. The controlled step-growth atom transfer radical polymerization method is conveniently extended to the synthesis of block copolymers of methyl 1-bicyclobutanecarboxylate with styrene. The same investigators have also reported atom transfer radical homo- and block copolymerization of methyl 1-cyclobutenecarboxylate and methyl 1-bicyclobutanecarboxylate[88].



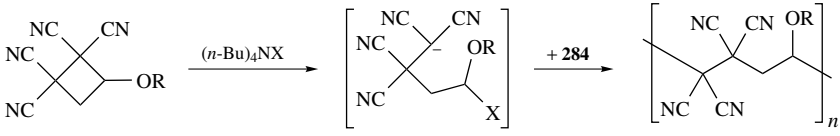
SCHEME 48

Functional polyester, polyamide and polyisoprene polymers with transient cyclobutane formation induced by irradiation have been reported by many investigators[89]. Scheme 48 depicts a norbornadiene incorporated into the polymer chain along with a carbazole sensitizer in a donor–acceptor combination, **282**. Later photoisomerization of the norbornadiene unit to a metastable quadricyclane, **283**, qualifies the polymer as one comprising a cyclobutane system. The energy stored in the quadricyclane can be released in the presence of catalytic amounts of (5,10,15,20-tetraphenyl-21*H*,23*H*-porphyrinato)-cobalt(II) (Co-TPP) and makes the combination polymer an attractive scheme for storage of radiation energy.

B. From Monomers Containing Cyclobutane Rings to Polymers Without Cyclobutane Units

Just as the strained 1,3-bridge bond of bicyclobutanes invites a radical dissociation accompanied by polymerization (see also the examples discussed above with propellanes), a strained cyclobutane itself can be exploited for polymerization by ring opening, although not necessarily through a radical route.

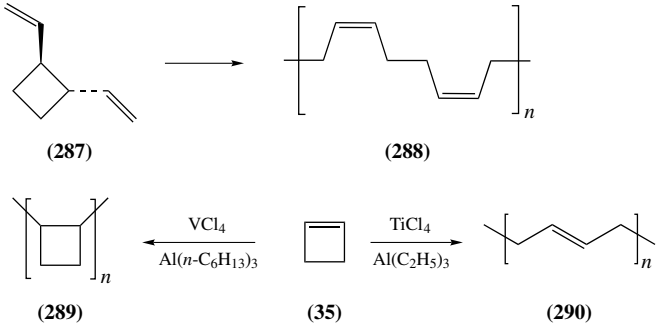
Cyclobutane adducts **284** of tetracyanoethylene and ethyl, butyl, isobutyl vinyl ethers and 2,3-dihydrofuranyl and 3,4-dihydro-2*H*-pyranyl vinyl ethers are readily polymerized anionically via intermediate **285** with tetrabutylammonium iodide as shown in Scheme 49[90]. The authors present convincing evidence that the polymerization process to **286** includes, in addition to the stepwise mechanism of Scheme 49, a linking of individually growing chains by nucleophilic substitution for halide of one chain by the anion of another chain. Other anionic initiators, Lewis acids and tertiary amines have also been reported to polymerize **284**.



(284) **(285)** **(286)**

SCHEME 49

In contrast to the radical vinyl-type polymerizations described above, anionic coordination catalysts are shown to promote ring-opening polymerization of *trans*-1,2-divinylcyclobutane (**287**) and cyclobutene (**35**). Scheme 50 shows that **287** is opened to a linear polymer, **288**[91].



(287) **(288)** **(289)** **(35)** **(290)**

SCHEME 50

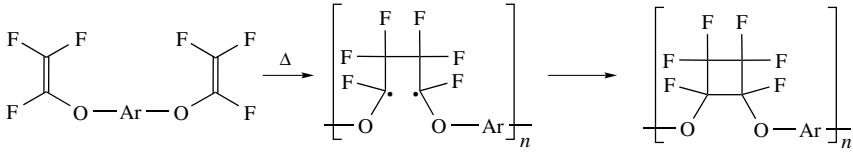
Anionic-coordinated polymerization of cyclobutene (**35**) proceeds to macromolecules of a polycyclobutane structure, **289**, similar to the 1-cyclobutenecarboxylic acid polymers (**272**) above or to macromolecules with the structure of 1,4-polybutadienes **290**, depending on the catalyst[92]. Choosing VCl_4 and trihexylaluminum yields the polycyclobutane **289**, while $TiCl_4$ and $Al(C_2H_5)_3$ as the catalyst gave pure samples of the latter 1,4-polybutadienes **290** (Scheme 50), all in heptane as solvent. A final gratifying manipulation—in the presence of δ-$TiCl_3$ (solid solution of $TiCl_3$, $AlCl_3$ and $Al(C_2H_5)_3$ in heptane—produced a simultaneous crystallization of distinct *trans*-1,4-polybutadiene and polycyclobutyl polymers but apparently no copolymer containing both-$CH_2CH{=}CHCH_2$- and 1,2-cyclo[$(CH)_2(CH_2)_2$] subunits.

C. From Monomers Without Cyclobutane Rings to Polymers Containing Cyclobutanes

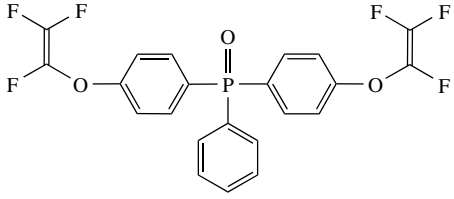
Highly fluorinated cyclobutanes show unique chemistry (see chapter 21 by Lemal and Chen in this volume). Polymeric derivatives demonstrate features of this uniqueness. For

example, perfluorocyclobutyl polymers **293** are prepared by free-radical mediated thermal cyclodimerization reactions of aryl trifluorovinyl ethers **291** as shown in Scheme 51, the process presumably involving diradical intermediates of type **292**[93]. A recent modification employs a phenylphosphine oxide group of two varieties as the ether backbone, **294**.

A unique cation radical chain cycloaddition mechanism accounts for new polymer structures from bifunctional propenyl (**295**, drawn in abbreviated form as **296**) or vinyl monomers[94]. The reaction is initiated by catalytic amounts of a stable cation radical salt, tris(4-bromophenyl)aminium hexachloroantimonate. The mechanism, involving the intermediate formation of the radical cations **297** and **298**, is shown in Scheme 52 for the

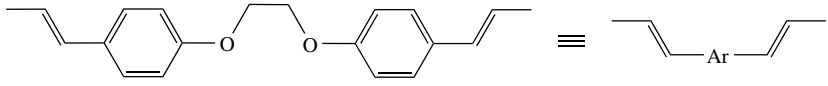


(291) **(292)** **(293)**

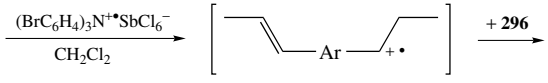


(294)

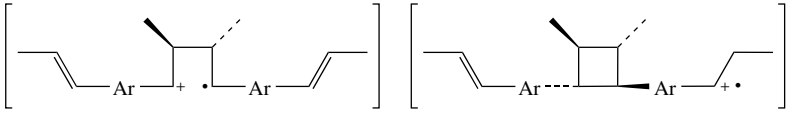
SCHEME 51



295 **296**



297

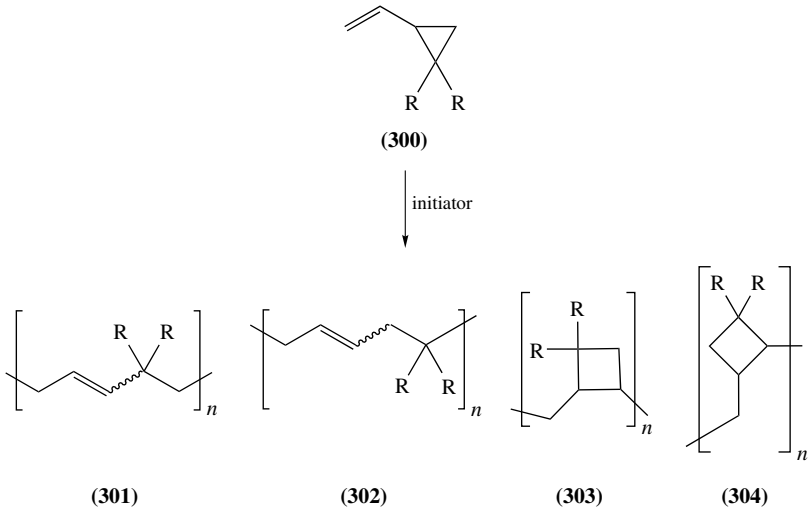


(298) **(299)**

SCHEME 52

prototypical bifunctional bis-1,2-[4-(1-propenyl)phenoxy]ethane **295/296**, which produces *trans,anti,trans*-cyclobutane units along the polymer backbone, **299**. A crucial attribute of the monomer is efficient electron transfer from the cyclobutane radical cation cycloadduct **299** to the remote end of the formed oligomer for continued chain growth. (For a more complete discussion of cyclobutane ion chemistry see chapters 7 and 13 by Kuck and Bauld, respectively, in this volume).

Traditional alkene polymerizations discussed above in Section III.A are again seen in the radical polymerizations of 1,1-disubstituted 2-vinylcyclopropanes (**300**, R = Cl, EtO_2C, CN). Although the expected 1,5-ring-opened products **301/302** comprised the bulk of the polymeric material, cyclobutane products (**303/304**) are strongly suggested as well (Scheme 53)[95].



(300) **(301)** **(302)** **(303)** **(304)**

SCHEME 53

IV. REFERENCES AND NOTES

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Author Index

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