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RIGID CYCLOPHANES THAT ILLUSTRATE STEREOCHEMICAL PRINCIPLES

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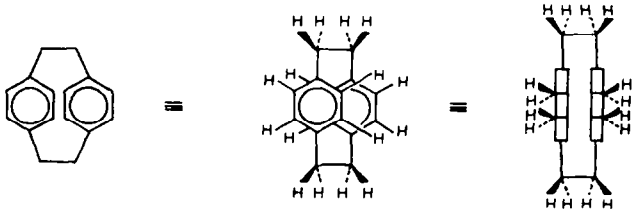
Abstract—All of the point groups common to organic chemistry except two are illustrated by known compounds that are rigid [2.2]paracyclophane derivatives. Examples are given of transannular directing effects by acetyl, nitro, and acetoxyl substituents attached to [2.2]paracyclophane. In bromination or chloromethylation, proton loss of a *sigma* complex is rate-determining, and the oxygens already in the molecule remove the proton being substituted. The synthesis of [2.2.2](1,2,4)cyclophane and [3.2.2](1,2,5)cyclophane, and their unusual chemical properties are described. Transannular hydride shifts out of methyl groups due to proximity effects are reported. Torsional racemizations and epimerizations of [2.2]paracyclophane derivatives are reviewed. The diradical intermediates formed have been intercepted by either H· donors, or by addition to substituted olefins. To account for the stereochemical course of addition and substitution reactions in the side-chains of [2.2]- and [4.2]paracyclophanes, new types of bridged carbonium ions are suggested. Conformational equilibria in the four-carbon side-chain of [4.2]paracyclophane derivatives are discussed.

Few organic compounds are as thick, rigid and symmetrical as [2.2]paracyclophane (**1**).[1] This hydrocarbon contains two benzene rings held face-to-face by two *para* attached ethylene bridges. The *pi–pi* repulsion between the benzene rings bends them into shallow boats, and slightly lengthens the benzyl–benzyl bond lengths (1·562 Å).[2] Although the resulting strain energy (31 kcal/mol)[3] makes the molecule very reactive chemically,[4] rotation about any of the 6 C–C single bonds in the molecule is restricted to a few degrees at room temperature.[2] For practical purposes, the molecule is rigid.



[2 2] Paracyclophane or 1

The hydrocarbon [2.2]paracyclophane (**1**) is interesting stereochemically for several reasons. (1) The symmetry properties of **1** have been manipulated by replacing one or more of the hydrogens with substituents. The first section describes how most of the common point groups are illustrated by known compounds derived from **1**. (2) Functional groups attached to **1** provide proximity effects for highly regiospecific reactions. The second part of this paper describes the stereochemical basis for these effects, and how they were put to synthetic use. (3) The steric strain of **1** and its derivatives results in unusual reactions. In the third section is described the use of the unusual symmetry properties of the substituted [2.2]paracyclophanes to elucidate the mechanisms of these reactions. (4) The geometry of **1** and its derived compounds results in high stereospecificity in reactions carried out in bridges between the two aryl groups. The conformational and mechanistic basis for the stereospecificity is discussed in section 4.

Illustrations of point groups with [2.2]*paracyclophane derivatives*

The symmetry properties of organic structures are described in terms of three symmetry elements,[5] the mirror plane (σ), the simple axis of rotation (C_n), and the mirror (or alternating) axis of rotation (S_n). Each organic structure belongs to one of several point groups,[5] defined in terms of their numbers and kinds of symmetry elements. The

minimum number of symmetry elements are used to uniquely define each point group.

The synthetic and stereochemical virtuosity of [2.2]paracyclophane and its derivatives is indicated by the fact that all but two of the classes of point groups common to organic compounds are illustrated with known compounds. Since [2.2]paracyclophane is essentially rigid, the molecule's symmetry elements and point groups are described without specification of conformation, or conformational equilibria. Chart 1 contains the structures of the compounds that illustrate these point groups.

The highly symmetrical parent hydrocarbon[1] (**1**) contains three σ planes that are perpendicular to one another. Their lines of intersection define the three mutually perpendicular C_2 axes, which are also S_2 axes. The point of intersection of all three σ planes is a center of symmetry, i. Thus, **1** contains three σ planes, three C_2 axes, three S_2 axes, and one i as its symmetry elements, and the molecule belongs to the D_{2h} point group.

Substitution in various patterns of the sixteen hydrogen atoms of **1** by other atoms or groups selectively destroys different symmetry elements of **1** to produce compounds of lower symmetry. Up to four aromatic hydrogens of **1** have been directly and somewhat selectively substituted by bromine with ferric bromide catalyst to produce compounds **2**, **4**, **5**, **8**, **9**, and **10**, each of which has been isolated and identified.[6-8] Treatment of **1** with N-bromosuccinimide produced derivatives in which up to four aliphatic hydrogens were substituted by bromine. Compounds **3**, **11** and **12** were isolated and identified.[9] Compound **7** was produced by the exclusively *cis*-addition of bromine to 1,2-dehydro[2.2]paracyclophane.[9,10] Treatment of **7** with lithium bromide in dimethyl formamide at 100° gave exclusively the more stable *trans*-isomer, **6**.[10]

The two other classes of point groups common to organic compounds can not be illustrated with the [2.2]paracyclophane system. The tetrahedral point group ($T_d = 4C_3 + 3C_2 + 6\sigma$) illustrated by methane or adamantane is one. The second is $D_{nd} = C_n + nC_2 + n\sigma$, which is illustrated by allene (n = 2) or by the chair form of cyclohexane (n = 3).

Of compounds **1–12**, **2–6** and **9** are chiral, as they contain only C_n symmetry elements. Whereas, **3** and **6** contain asymmetric carbon atoms, **2**, **4**, **5** and **9** owe their dissymmetry to the restricted rotation of the benzene rings (torsional dissymmetry). A future section of this paper will show how, under appropriate conditions, this restriction can be removed chemically.

Proximity effects

The two aromatic rings of [2.2]paracyclophane are close enough so that they become mechanistically coupled in electrophilic substitution reactions in which proton loss is the rate-determining step.[11] In the ferric-bromide catalyzed bromination of **13-d** in dichloromethane, the deuterium *para* to the methyl group is substituted by bromine. With **13-h** the reaction is faster, and $k_H/k_D = 3{\cdot}7$. Thus, proton or deuteron loss from a reversibly formed *sigma* complex is rate limiting. In the substitution of **13-d**, the deuterium is transferred to the *pseudo-gem* position of the adjacent ring during the reaction course to give **14**. In the overall substitution reaction, an electrophile attacks a position on the face of one benzene ring, and the hydrogen isotope there is then transferred to the closest (*pseudo-gem*) carbon on the second ring. In the final step, the proton originally on the second ring leaves from the face of that ring. Thus both rings undergo electrophilic substitution reactions, one by an external and the other by an internal electrophile.[11]

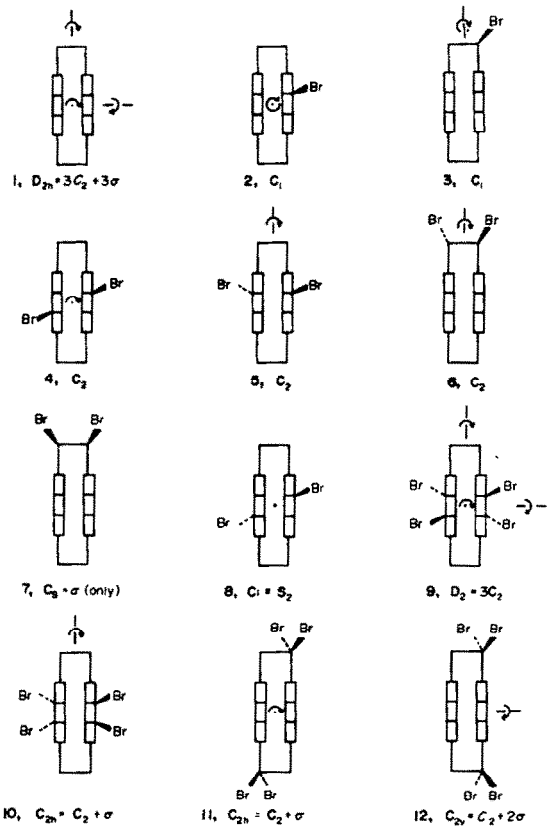
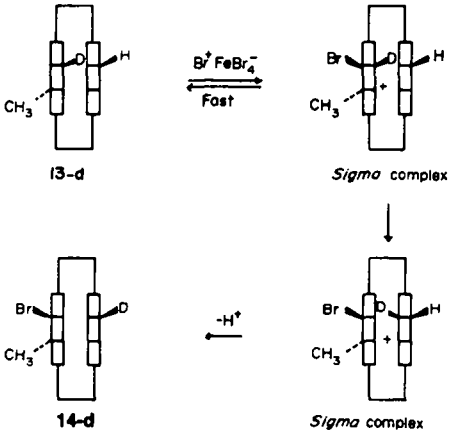


Chart 1. Point groups illustrated.

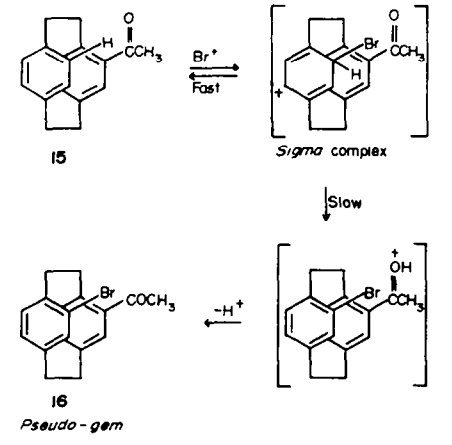
When one ring of [2.2]paracyclophane contains an acetyl, carboxyl or carbomethoxy group, bromination of the compound occurs exclusively in the position *pseudo-gem* to the original substituent.

With an original nitro group, bromination occurs predominantly (70%) in the *pseudo-gem* position. With an original cyano group, bromination occurs in all three positions of the unsubstituted ring except the *pseudo-gem*.[11] The *pseudo-gem* directing effect of the carbonyl-containing and nitro groups was attributed to the basicity and geometric availa-



bility of the oxygens of these groups. The oxygens are probably the strongest bases in the medium. In the rate- and product-controlling step, the oxygen accepts a proton from the *pseudo-gem sigma* complex, and thus produces a *pseudo-gem* disubstituted product. Although basic, the electron pair of the cyano group is held too far from the proton of the *pseudo-gem sigma* complex, so that the corresponding intermediate decomposes back to starting material whenever formed. The operation of this proximity directing effect by the acetyl group is formulated in the sequence, **15** → **16**.[11]

An examination of molecular models* of **17** indicated that the carbonyl oxygen of the acetoxyl group was located close to the hydrogen atoms in the 4- and 13-positions. Should a proximity directing effect dominate in bromination of this system, then bromine should enter only these positions. When treated with bromine in dichloromethane under various conditions of temperature (0–25°) and amounts of ferric bromide, varying amounts of isomeric dibromides **18–21** were produced.[12] When treated with base, the reaction mixture gave only **22**. Thus aromatic bromination occurred only in the positions of the benzene rings *ortho* to the substituted ring. Under the most vigorous conditions of the above brominations, 1-bromo[2.2]paracyclophane (**3**) was not brominated. Thus the aromatic bromination preceded side-chain substitution of the acetoxyl group by bromide.



These facts indicate that the acetoxyl group exerted both an activating and proximity directing effect on the aromatic bromination reaction by accepting the proton from the sigma complexes to give A and B. Since protonated acetoxyl is a good leaving group, and the bromide ion present is a good nucleophile, substitution occurred. The reactions leading to isomers **18** and **19** were simple $S_{N}2$ reactions, and went with inversion of configuration. Those leading to **20** and **21** involved neighboring aryl participation, and went with retention of configuration.[12] Neighboring aryl participation will be discussed in a future section of this paper.

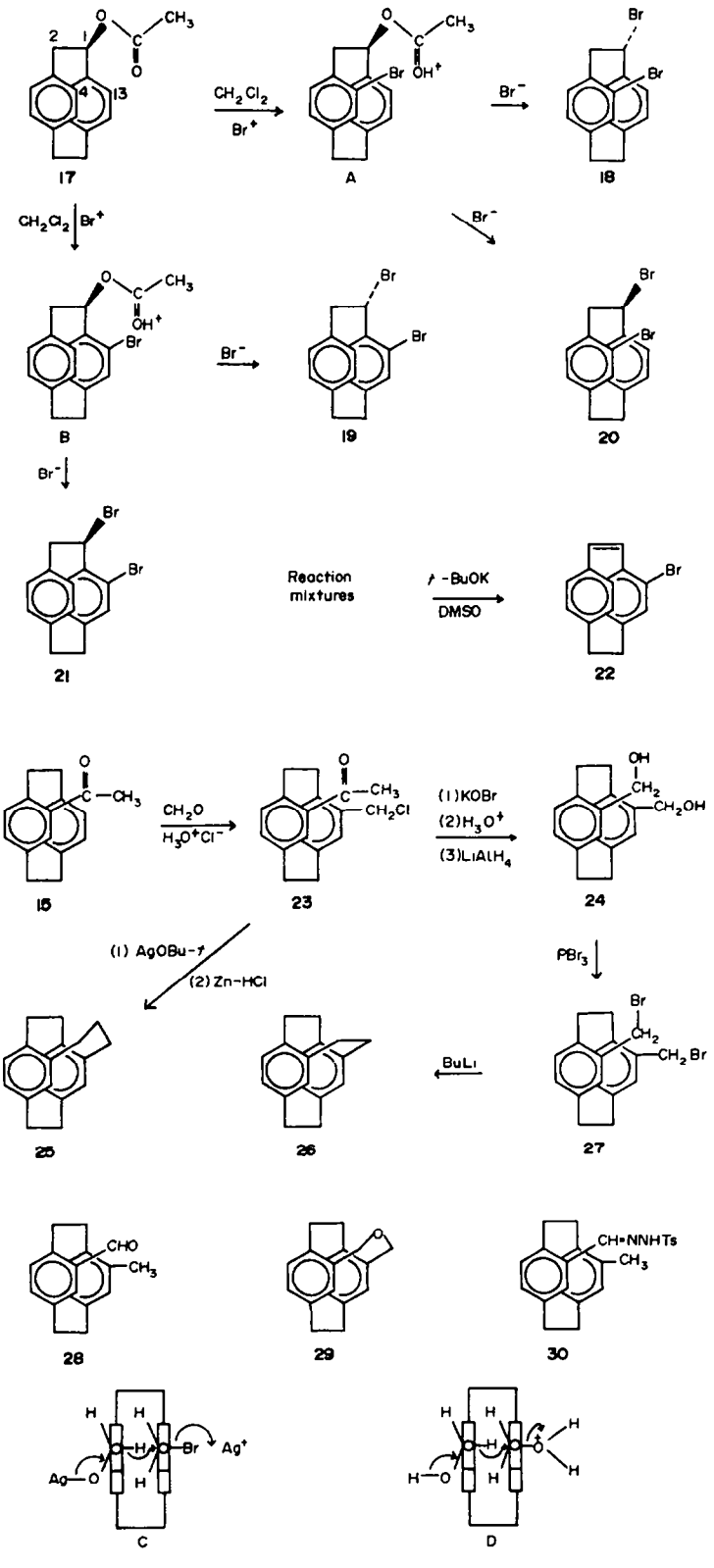
Compounds **18** and **19** were isolated, and their structures determined by mass spectrometry, NMR analysis, and conversion to **22**. Compounds **20** and **21** were characterized by the same techniques, but not as separate entities.[12]

The proximity directing effect of the acetyl group of **15** has been useful in preparing derivatives of [2.2]paracylophane with carbon side chains disposed *pseudo-gem* to one another. When treated with formaldehyde and concentrated hydrochloric acid, **15** gave **23** (55%) as the only disubstituted [2.2]paracyclophane. Compound **23** was used to construct the additional methylene bridges found in **25** and **26**. The ready occurrence of the ring-closing reactions formulated undoubtedly is associated with the close proximity of the reacting groups. The interesting chemistry of compounds **25** and **26** is discussed in the next section.

Other examples of proximity effects involve transannular hydride shifts. When dibromide **27** was treated with silver oxide at 25° in tetrahydrofuran, a mixture of aldehyde **28** (35%) and ether **29** (40%) was produced. In cyclohexane as solvent, only **28** was obtained (80%). Diol **24** gave aldehyde **28** (29%) and ether **29** (67%) when heated at 50° in acetic acid-*p*-toluenesulfonic acid. Ether **29** gave aldehyde **28** (89%) when treated with boron trifluoride etherate in dry benzene at 25°.[14]

Molecular models of the *pseudo-gem* diol (**24**) and dibromide (**27**) indicate that one hydrogen of one methylene group is pressed against the carbon of the second as in C and D. The reaction paths envisioned for these transannular pinacol rearrangements involve the stages formulated in C and D.[14] Similar reactions have been observed in the medium sized carbocyclic diols such as *cis*-1,5-dihydroxycyclooctane.[15]

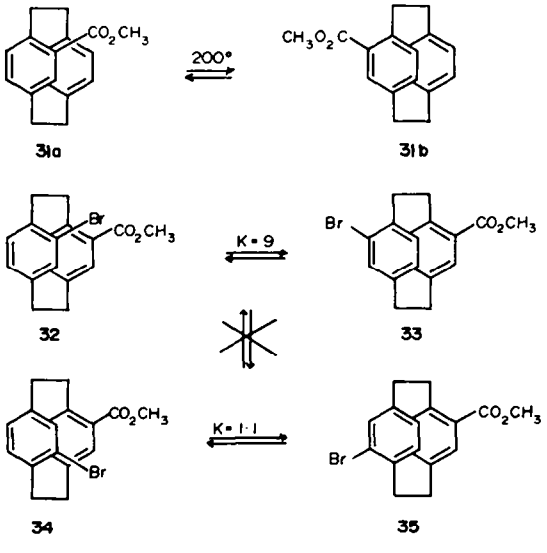
*Corey–Pauling–Koltun, with one face of each benzene ring ground down, were used here and elsewhere in this paper.


17
A
18
B
19
20
21
Reaction mixtures
t-BuOK
DMSO
22
15
23
24
25
26
27
28
29
30
C
D

Another example of a proximity effect is found in what is formally a carbenoid insertion reaction. The tosylhydrazone **30**, prepared from **28**, when heated with sodium methoxide in diglyme gave **26** (71%). Conversion (85%) of **30** to **26** (in tetrahydrofuran–sodium methoxide) also was caused by light.[14] Several analogies for transannular proximity insertion reactions initiated by tosylhydrazone decomposition are in the literature.[16] To our knowledge, no transannular pinacol or insertion reactions have been previously observed that involve arylmethylene groups.

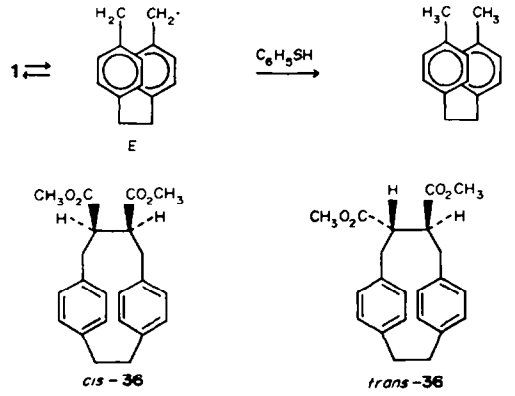
Stereochemical probes of the mechanisms of reactions caused by release of strain in the starting material

Optically pure **31a** racemized when heated to 200°.[17] More interestingly, racemic **32** and **33** equilibrated at 200° as did racemic **34** and **35**. No leakage of **32** ⇄ **33** to and from **34** ⇄ **35** was observed.[17] To determine if only one or both rings of **32** rotated during isomerization of racemic **32** to racemic **33**, optically pure **32** was prepared and partially isomerized.[14] In five runs (neat) at 201° for periods of time that gave 14 to 63% **33**, the samples of **33** produced were completely racemic, and the



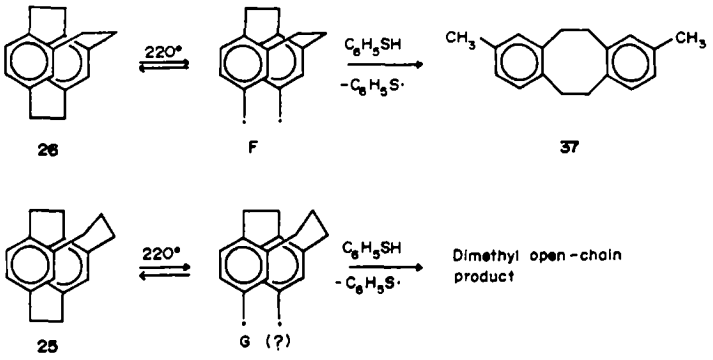
recovered **32** was 67 to 5% racemized (94–99% material was accounted for). To produce racemic **33** from optically pure **32**, one aryl had to undergo one more 180° rotation than the other. To produce (−)-**32** from (+)-**32**, each aryl had to undergo an even number of 180° rotations.[14]

That these reactions occurred through benzyl diradical intermediates such as E is indicated by the results of trapping experiments. When **1** was heated to 220° in thiophenol, *p,p'*-dimethylbibenzyl was produced (74%).[14] When **1** was heated in either dimethyl maleate or fumarate, approximately equal amounts of *cis* and *trans*-**36** (combined yield of 60%) were generated in each experiment.[17] These transformations are 1,2 to 1,12-cycloaddition reactions, and undoubtedly involved benzyl diradical E as one of their intermediates.



The interesting question arises as to the fate of the tris-bridged cyclophanes **25** and **26** when subjected to similar treatments. When **26** was heated to 220° for three days in thiophenol, an 88% yield of **37** was produced.[14] That benzyl–benzyl bond broke which led to the least strained diradical, F. When identically treated, **25** gave 81% of monomeric material, 78% of which was **25** and 22% was an unidentified ring-opened compound containing arylmethyl groups. This result suggests both that **26** opens faster than **25**, and that the activation energy for diradical F to reclose to **26** is greater than that for diradical G to reclose to give the less strained **25**. Both processes compete with the H· abstraction process from the thiol solvent.[14]

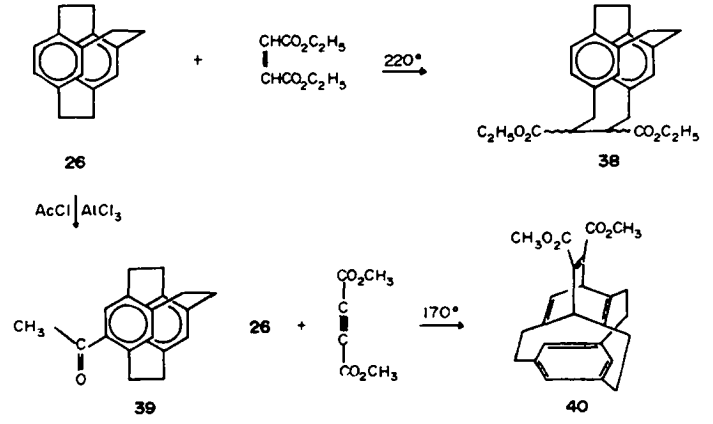
When **26** was heated in either diethyl fumarate or maleate at 220° for three days, a 1,2 to 1,12-adduct was obtained (60%) which to TLC and GLC was homogeneous, and whose two ethyl groups gave different chemical shifts. The UV spectrum of the substance was similar to that of the isomers of **36**. The PMR spectrum, coupled with the probability that F was an intermediate, suggested the compound was **38**, either the pure *trans* isomer, or a mixture of *cis* and *trans*-isomers. Repeated attempts failed to produce an adduct of the less strained hydrocarbon, **25**. Although a benzyl diradical undoubtedly forms (G ?), the additional bridge of the system probably increases the rate of reformation of the original cyclophane compared to that rate for diradical E. The rate of reclosure of diradical F is probably slower than the rates for either E or G because of the increased strain of **26**. The UV absorption spectrum of **25** was sufficiently similar to that of [2.2]paracyclophane itself to suggest that the trimethylene bridge of **25** introduced little additional strain into the molecule. The spectrum of **26**



was somewhat modified, particularly in the 230 to 260 nm region. Molecular models suggest the benzene rings of **26** are somewhat more bent than those of either **1** or **25**.[13,14]

Acetylation of **26** gave **39**, (72%), thus **26** exhibits aromatic behavior. When heated at 170° for 1 h in dimethyl acetylenedicarboxylate, **26** behaved like a triene and underwent a Diels–Alder reaction (61%) to give the bridged barrelene adduct, **40**.[13] Repeated attempts to induce **1** to react similarly failed, although it does react with "super" dieneophiles.[18] Thus **26** appears more strained than **1**.

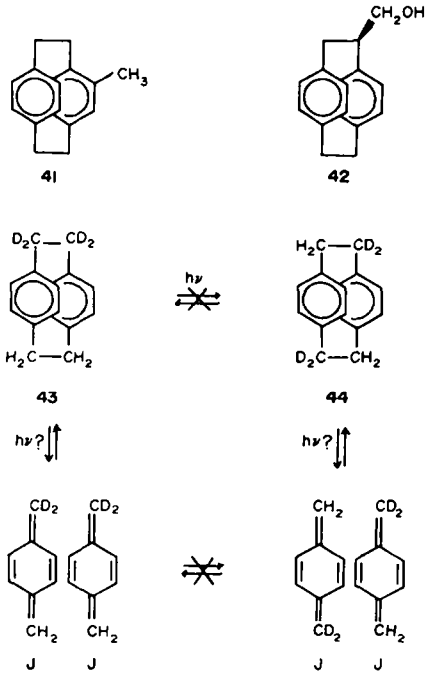
ization of compounds such as **41** and **42** in solvents such as cyclohexane, benzene, acetone or acetophenone.[20] A possible mechanism involved cleavage of each system into its *p*-xylylene fragments, these tetraenes rotating relatively to one another, and their recombining to produce racemic product. To see if such *p*-xylylene intermediates, if formed, rotated about their shorter axes with respect to one another, systems **43** and **44** were prepared. Their tricarbonylchromium derivatives exhibited PMR spectra distinctly different from one another. When either **43** or **44** was submitted to the



The *pi*-basicity of many of the cyclophanes have been measured by the positions in their UV spectra of the charge transfer bands of their *pi*-salts with tetracyanoethylene in dichloromethane.[19] The band observed for the salt of **26** was at $\lambda_{max} = 541$ nm ($\epsilon = 56$). However, within 25 minutes the red-purple color faded to a pale pink, and the extinction coefficient of the 541 nm band decreased to $\epsilon = 25$. Although cycloaddition appeared to be occurring reversibly, the adduct could not be isolated. The charge transfer band of the *pi*-salt of **25** occurred at $\lambda_{max} = 563$ nm ($\epsilon = 75$). Thus the less strained *tris*-bridged cyclophane is the stronger *pi*-base.[14]

Another use of symmetry properties as a probe of reaction mechanism involved the photoracemphotolytic conditions that racemized **41** or **42**, they were not interconverted.[14] Thus if *p*-xylylene fragments J intervened in the photolyses of **43** or **44**, they must have rotated *only* around their longer axes with respect to one another before recombining.[14]

When [2.2]paracyclophane (**1**) was heated in a vacuum to about 550° in the gas phase, *p*-xylylene was formed, which when condensed on cold surfaces produced a film of linear polyparaxylylene (**45**).[21] If *tris*-bridged cyclophanes **25** or **26** behaved similarly, highly cross-linked polymer might be produced. Possibly pyrolysis and condensation of appropriate mixtures of **25** and **1** might give a film such as **46**, cross-linked to a desired degree, much



as the addition of *p*-divinylbenzene to styrene provides cross-linked polystyrene.

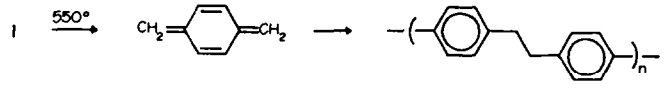
Pyrolysis of **1** and condensation of the product at − 15° at 20 μ pressure gave a slightly opaque film which was soft and elastic. Samples of **25** and **26** treated similarly gave only oils, whose PMR spectra indicated the material contained no cyclophane. A ten-to-one mixture of **1** and **25** then was pyrolyzed and the products similarly condensed. At the mouth of the condenser, a film of soft white polymer was deposited which was only slightly elastic. In the condenser was a clear and nearly colorless film which appeared somewhat more sturdy and less elastic than the polymer obtained from **1** alone. These facts suggest that copolymer **46** was formed to a small extent.[14]

Stereochemistry of bridge-substituted cyclophanes

Acetolysis of **48** goes with complete retention of configuration as shown by completion of the reaction cycle, **47** → **48** → **49** ← **47**.[22] Methanolysis and trifluoroacetolysis of **48** followed the same stereochemical path.[22] Olefin **50** underwent solely *cis*-addition of bromine and DBr to give **7** and **51**, respectively. Acetolysis of the *cis*- and *trans*-dibromides **7** and **6** gave diacetates **52** and **53**, respectively, with complete retention of configuration. The stereospecificity and stereochemical direction of these reactions were explained by the formation of highly strained phenonium ions, K, as intermediates in these substitution and addition reactions.[10] In the substitution reactions, phenonium ion formation should go with inversion of configuration, as would its opening to give overall retention of configuration.[23] In the mechanism for the addition reactions, the electrophile (H^+ or Br^+) adds from one side of the double bond at the same time that one of the aryls in effect adds to the other. The resulting phenonium ion is opened by the nucleophile with inversion of configuration to give overall *cis* addition.

A similar and possibly more satisfactory explanation is to substitute bridged ion L for K. Ion L represents a merging of a phenonium ion, two benzyl ions, and a cyclobutonium ion.[24] By partially breaking the benzyl–benzyl bond remote from the leaving group, not only is some of the strain relieved, but the positive charge is much more delocalized.

The ring expansion of [2.2]paracyclophane (**1**) to 2,3-dicarbomethoxy[4.2]paracyclophane (**36**)[17] provided a route to compounds useful for mechanistic studies in the 4-atom bridge of this unusual system. The *cis*-*trans* mixture of **36** upon equilibration gave >99% of the *trans*-ester which was hydrolyzed to **54**.[17] Decarboxylative elimination of **54** gave *trans*-olefin, **55** (70%)[25,26] which when photoequilibrated with its *cis*-isomer (**56**) in benzene gave a *cis*/*trans* ratio of 1·5.[26] Attempts to thermally or chemically equilibrate **55** and **56** failed.[26]



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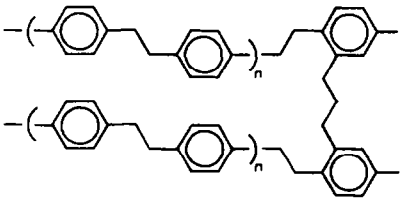

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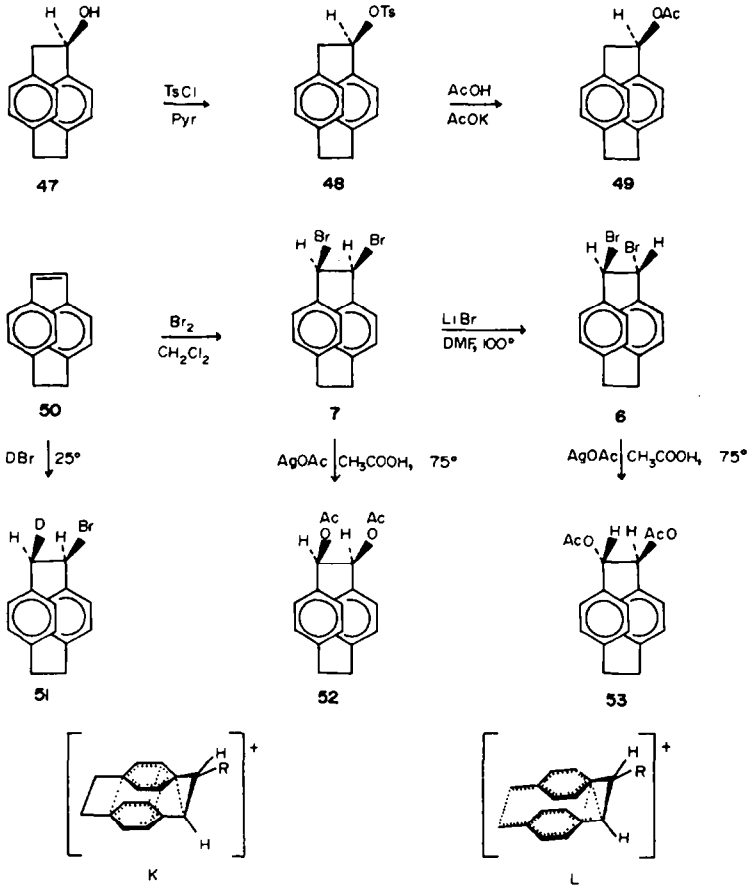
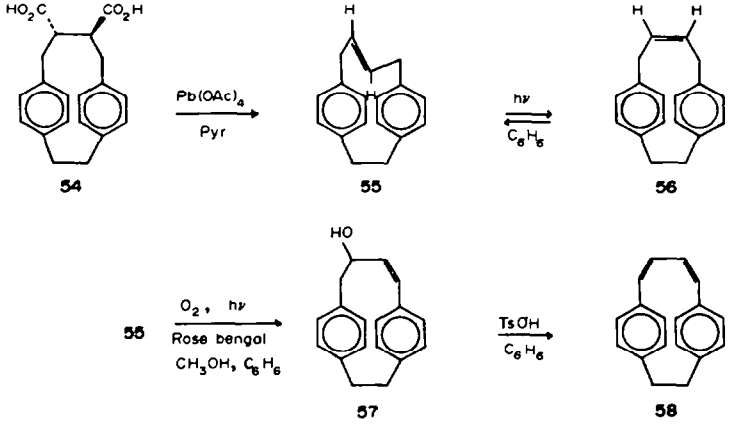
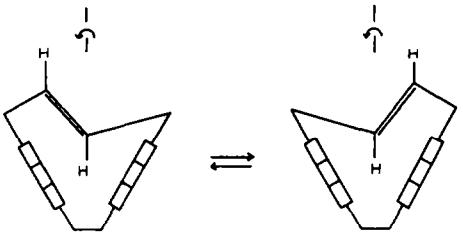


Olefin **55** was photooxygenated to give **57** (61%), which upon treatment with acid gave the slightly yellow diene, **58** (75%).[27] The structures of these compounds were assigned from their widely different PMR, IR and UV spectra.[26]

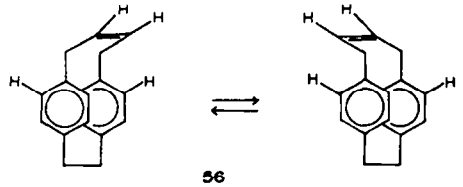
Examination of molecular models of **55**, **56** and **58** suggested that each compound was an equilibrating mixture of the two conformers formulated below. Those of **55** and of **58** each possess a C_2 axis as their only symmetry element, and, taken in pairs, compose racemates. The conformers of **56** each possess a σ plane as their only symmetry element. The PMR spectra of **55**, **56** and **58** are consistent only with each being a rapidly equilibrating mixture of their two conformations even at $-80°$.[26,27]

The stereochemical course of acetolysis of the





55 (C_2)



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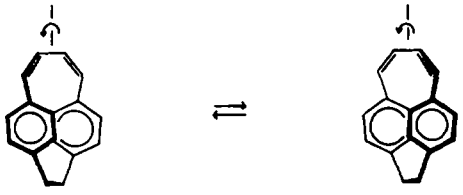
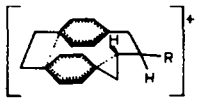


58 (C_2)

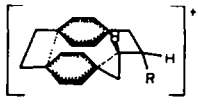
tosylate **60** was studied.[26] This substance was prepared from optically pure alcohol **59**, which was resolved through its camphanic ester. Racemic **59** was obtained (70%) by the hydroboration–oxidation procedure from *trans*-oelfin, **55**. Acetolysis at 50° in dry unbuffered glacial acetic acid of the tosylate of optically pure (−)-**59** gave optically pure acetate, (−)-**61**, in 91% overall yield based on (−)-**59**. No other products could be detected by TLC or NMR analysis of the crude reaction mixture. Acetylation of optically pure (−)-**59** also gave optically pure (−)-**61**. Thus the stereochemical reaction cycle, (−)-**59** → (−)-**60** → (−)-**61** ← (−)-**59**, was completed. Since the tosylation and acetylation reactions did not involve breaking any bonds to the asymmetric center, these reactions went with retention of configuration. Thus the acetolysis also went with retention of configuration.[26]

The first order rate constants for acetolysis of **60** were measured in 0·0133 M sodium acetate solution, and were found to be, $k^{25°} = 1{\cdot}27 \pm 0{\cdot}08 \times 10^{-6}$ sec^{-1}, and $k^{50°} = 2{\cdot}24 \pm 0{\cdot}34 \times 10^{-5}$ sec^{-1}, which provided $\Delta H^{\ddagger} = 21{\cdot}7 \pm 1{\cdot}1$ kcal/mole and $\Delta S^{\ddagger} = -10{\cdot}9 \pm 3{\cdot}7$ eu (25°). At 50°, the rate of acetolysis of **60** exceeded that of 1-phenyl-2-propyl tosylate[28] by a factor of 350. In acetic acid, this open-chain tosylate went to acetate with 65% inversion and 35% retention of configuration.[28]

Both the stereochemical and kinetic behavior of **60** indicate that the β-aryl assists in the ionization of the tosylate to produce phenonium ion, M, which is formed with inversion of configuration at the chiral center. This bridged ion is then opened by solvent with inversion of configuration, to give the overall retention of configuration observed in the solvolysis.[26]



M

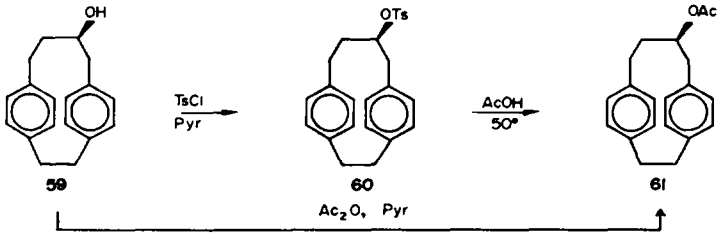


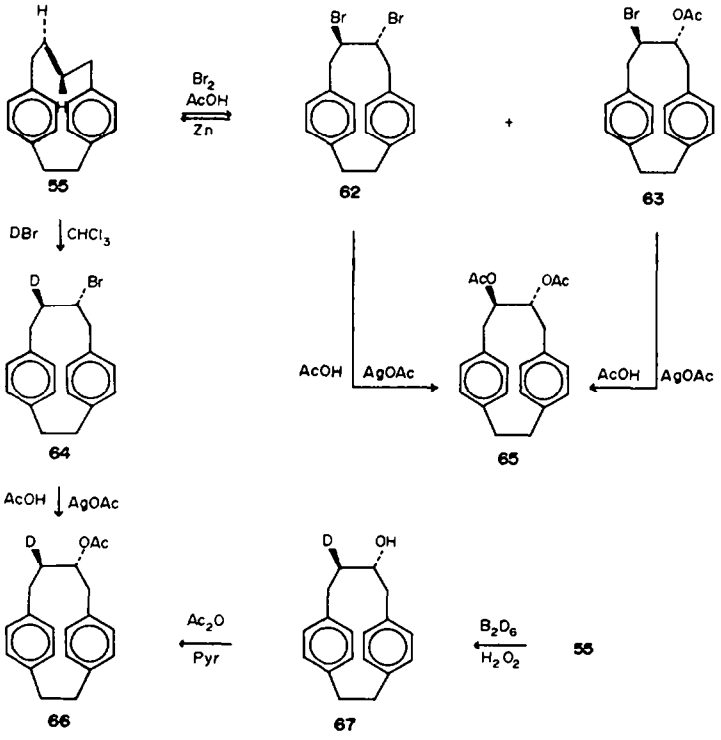
N

The *trans*-olefin, **55**, underwent exclusively *cis*-addition of bromine in carbon tetrachloride at 25° to give (74%) *trans*-dibromide **62**. In dry acetic acid, the bromination followed the same course, but a mixture of *trans*-dibromide **62** (57%) and *trans*-acetoxybromide **63** (30%) was produced. Acetolysis of **62** gave *trans*-diacetate (99%). Similar treatment of **63** gave a similar result. In acetic acid at 100° in the presence of zinc dust, *trans*-olefin **55** was regenerated (87%) from **62** in a *cis*-elimination reaction. At 148° in hexamethylphosphoramide containing brucine, *trans*-dibromide (**62**) was partially destroyed. The 20% recovered dibromide was optically active, a fact that demonstrated its *trans*-configuration.[26]

In chloroform at 25°, DBr added rapidly (1 h) to **55** in 97% yield to give **64**. This substance was solvolyzed with dry acetic acid-silver acetate to give (88%) acetate **66**. Hydroboration of **55** with B_2D_6 followed by oxidation of the product gave alcohol **67** (70%). Acetylation of this material also gave acetate **66**. The PMR spectra of **64**, **66** and **67** indicate that at least 95% of the isomer is present with the deuterium *trans* to the oxygen or bromine.[26]

These results demonstrate that olefin **55** undergoes *cis*-addition reactions, and that the mono and

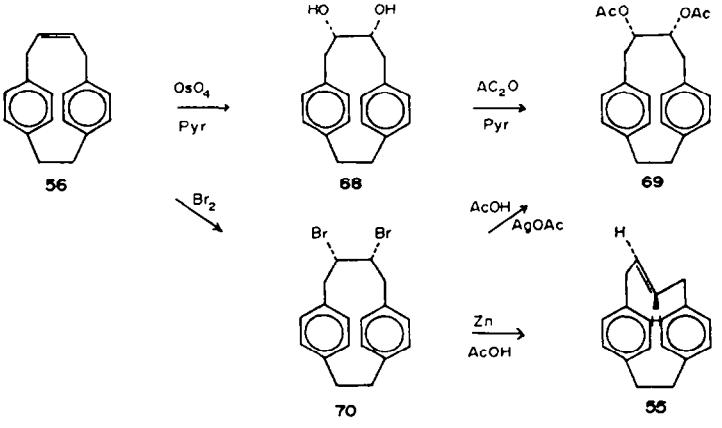




dibromides undergo acetolysis with only retention of configuration. All of these results are explained on the basis of substituted phenonium ions M as intermediates. The double bond of **55** is located just above the two benzene rings, and its *pi* system and those of each benzene are close and orthogonal to one another. A minimum of reorganization of the system is needed to form the phenonium ion.[26]

With bromine in carbon tetrachloride at 25°, *cis*-olefin **56** underwent *cis*-addition to give *cis*-dibromide **70** (88%). Dry acetolysis of **70** at 75° gave (96%) *cis*-diacetate, **69**. Treatment of **70** with zinc dust in acetic acid at 100° gave (81%) *trans*-olefin, **55**. Hydroxylation (*cis*) of *cis*-olefin (**56**) gave (96%) *cis*-diol **68**, acetylation of which also gave (86%) *cis*-diacetate **69**.[26]

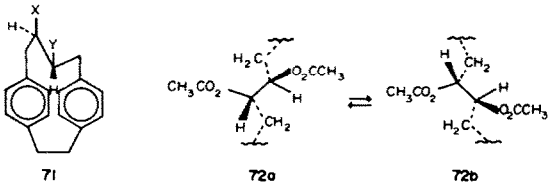
The *cis*-addition of bromine to *cis*-olefin **56**, and the retention of configuration observed for the acetolysis are both explained on the basis of phenonium ions such as N as intermediates in the sequences. In the addition reaction, the electrophile (Br^+) adds to one face of the double bond and the aryl to the other to give N. This ion in a second stage reacts with the nucleophile (Br^-), a reaction that occurs with inversion. In the acetolyses, neighboring aryl participates in the removal of Br^- to give N, which in turn reacts with acetate ion. Each of these two stages goes with inversion to give



overall retention as the stereochemical pathway. Phenonium ions N and M are diastereomerically related.[26]

The control by the aryl groups of the course of the addition and substitution reactions in the bridges of the paracyclophanes is much greater than is observed in open-chain systems of similar structure. At least three factors probably are responsible. (1) The face-to-face arrangement of the aryl rings provides conformations favorable to phenonium ion formation. (2) The *pi–pi* repulsion between the two aryl rings is decreased in the phenonium ions by distributing a positive charge on one and possibly both of them. (3) The usual involvement of solvent and ions as nucleophiles and bases in the first stage of these reactions is blocked from one side of the chain by the enforced presence of the aryls, whose *pi*-systems and *ortho* hydrogens inhibit "back side" participation by medium.

The PMR spectra of the *trans*-disubstituted [4.2]paracyclophanes are essentially invariant from − 80 to 100°, which suggests the substances possess essentially single structures. The protons of the substituted bridge form a simple ABX system. In those systems where $X \neq Y$, the H_x and H_y protons show maximum coupling, which indicates their dihedral angle is close to 180°.[29] These facts suggest that the *trans*-2,3-disubstituted[4.2]paracyclophanes approach conformation **71**, which places X and Y *anti* to the aryl groups.[26]



71 72a 72b

The *cis*-2,3-disubstituted[4.2]paracyclophanes exhibit temperature dependent PMR spectra. For example, the methyl groups of the *cis*-diacetate **69** in $CDCl_3$ exhibit a singlet at 25°, which broadens at − 10° and becomes two sharp singlets at − 30°. These results suggest that at room temperature, conformations **72a** and **72b** are equilibrating rapidly on the PMR time scale, but are frozen out at − 30°.[25]

The zinc-acetic acid-caused elimination reaction of the *cis*- and *trans*-dibromides (**70** and **62**, respectively) both gave *trans*-olefin **55**. In **70**, the two bromine atoms are nearly eclipsed (see **71**), and a five center mechanism with zinc as the fifth atom accounts for the result. In **62**, if the conformation resembles that of **72**, the two bromines are more distant, and drawing them together forces the methylene groups into an eclipsed conformation, and draws the benzene rings together, which also generates strain. As a result, a multistage, *trans*-elimination mechanism dominates. In other words, the *trans*-dibromide possesses a structure which conformationally resembles that of the *trans*-olefin, which it produces. However, the *cis*-dibromide possesses a conformation much less like that of *cis*-olefin, and a reaction path involving less reorganization is employed.[26]

The chemistry of this paper illustrates a number of homely generalizations. In rigid molecules, the courses of reactions are governed more by ground state structure than in conformationally flexible molecules. In rigid molecules, proximity effects frequently provide unusual reactions. High compression, bond angle deformation, and stretched bonds in compounds provide a driving force for reactions unobservable in relaxed molecules. For chemists who are pleased by manipulation of symmetry properties, the cyclophanes provide an art form.

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