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CATION RADICAL CYCLOADDITIONS AND RELATED SIGMATROPIC REACTIONS

NATHAN L. BAULD
Department of Chemistry, The University of Texas, Austin, TX 78712, U.S.A.

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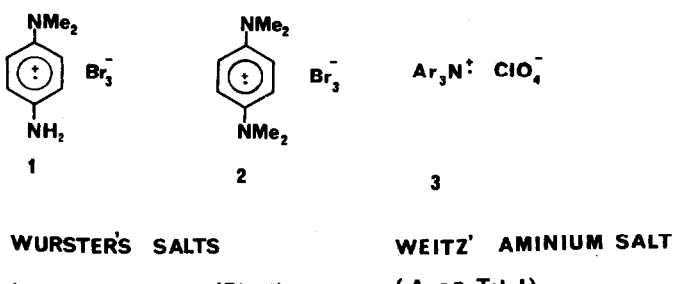
CONTENTS

1. INTRODUCTION AND HISTORICAL PRECEDENTS

1.1. *Introduction*

In a splendid, brief review of the development of cation radical chemistry, Bellville has emphasized the circumstance that cognitive cation radical chemistry has consistently lagged behind both carbocation and radical chemistry in each stage of its historical development.[1] It was Bellville's premise that not only were the concepts of 'carbocation' and 'radical' both necessary precursors in the evolution of the 'cation radical' concept but that cognition of the latter concept required a further, quite fundamental intuitive leap from both of the precursor concepts. This leap was, in fact, made extremely difficult by the primitive state of bonding theory at the time.[1,2]

Paradoxically, stable cation radical salts were isolated much earlier than analogous carbocation salts or stable free radicals. Thus, Wurster's Red and Blue salts (**1** and **2**, Scheme 1) were isolated as early as 1879,[3] whereas the trityl radical and trityl carbocation salts would not be isolated until

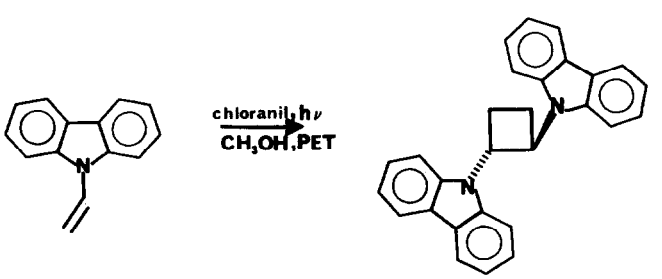


Scheme 1.

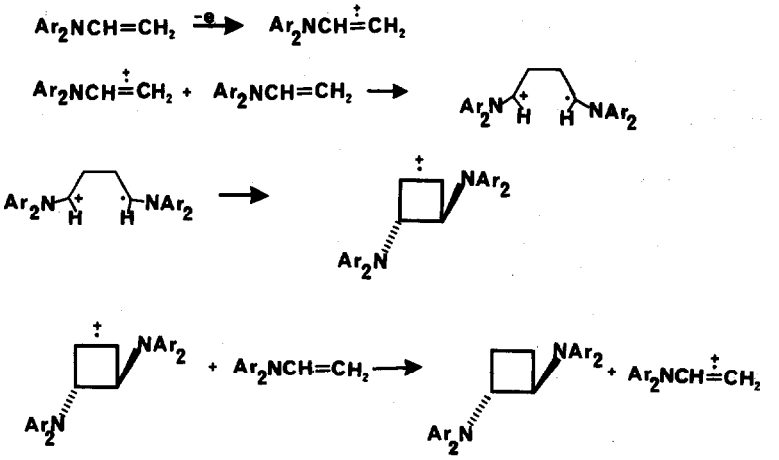
1900 (Gomberg[4]) and 1902 (von Baeyer[5]), respectively. However, the essential chemical nature of each of these latter two species was recognized virtually immediately, whereas the nature of the cation radical salts was essentially misunderstood for fifty years. As one indication of this, thirty years after the isolation of the Wurster salts, Willstatter's proposal (1908) that they were actually dimeric complexes of a dication with a neutral was apparently widely accepted.[6] Not until Weitz's seminal researches in 1926,[7] coinciding with his isolation of triarylaminium perchlorates (**3**, Scheme 1, the corresponding tribromide salts had actually been prepared first by Wieland in 1907[8]), was the true nature of these salts (**1–3**) as monomeric species possessing both an unpaired electron and a single unit of positive charge finally appreciated and decisively imputed. It was Weitz, incidentally, who also coined the terms 'cation radical' and 'aminium' ion. The history of *cognitive* cation radical chemistry may thus be dated to the time of Weitz's contribution. It remained for Michaelis (1935) to provide a resonance theoretical description of the bonding and delocalization which would stand reasonable scrutiny even today.[9] A similar chronological pattern was repeated in the historical process of recognizing transient versions of these three species as reaction intermediates [carbocations: 1922, Meerwein;[10] radicals: 1922, Paneth and Hofeditz;[11] cation radicals: 1946, Weiss[12]]. Extensive chemistries, of course, have long since developed around the carbocation and radical concepts. Again belatedly, beginning about 1963, indications have begun to emerge that a similar and perhaps equally formidable body of chemistry based upon the cation radical concept exists and awaits full development. The emerging corpus of cation radical chemistry is in fact diverse, but one general class of reactions appears to be attracting especial attention because of its major potential for impact upon organic synthesis. This class of reactions, viz. cycloadditions, is the primary subject of this review. In addition, the vinylcyclobutane and closely related sigmatropic rearrangements, which are mechanistically closely interrelated to cycloadditions, are reviewed. Cation radical cycloadditions to dioxygen have been carefully reviewed recently and are specifically excluded from the present review.[13]

1.2. *Significant historical precedents*

1.2.1. *Cyclobutanation.* Ultimately, the existence of a broad range of efficient pericyclic chemistry depends (*vide infra*) on the existence and viability of a fundamental mechanistic type, the cation radical chain mechanism, which was unknown prior to 1968. The first published proposal of and evidence for the participation of organic cation radicals in any type of chain mechanism appears to be that of Scott, Miller, and Labes, who surmised in 1963 that the polymerization of N-vinylcarbazole (NVC) in acetonitrile induced by chloranil (CA), tetracyanoethane (TCNE), or certain Wurster cation radical salts was, in fact, initiated by the NVC cation radical (NVC^{+}).[14] The following year, Ellinger published his study of the same polymerization but appeared to withhold full agreement on the mechanistic assignment.[15] Of greater importance, in the latter research, was the finding that in the presence of daylight, and in solvent methanol, the polymerization of NVC was largely diverted to cyclodimerization (Scheme 2). In retrospect, this appears to be the prototypical application of



ELLINGER, 1964
Scheme 2.

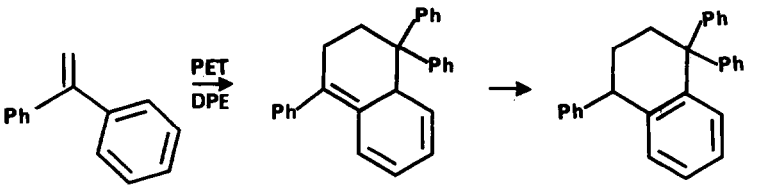


Scheme 3.

the photosensitized electron transfer (PET) method of cation radical generation and the first example of a cation radical pericyclic reaction. Unfortunately, the mechanism of the cyclodimerization was not understood, and the cyclodimer was considered to arise from some sort of radical process. Subsequently, Bawn *et al.* (1965) disclosed the efficient cyclodimerization of NVC by ferric nitrate/methanol.[16] These authors also followed suit in misassigning the reaction mechanism, attributing cyclodimerization to the formation of triplet NVC, formed by back electron transfer from NVC†. Eventually, the cation radical chain nature of the reaction was established as a result of careful studies by Crellin *et al.* (Scheme 3).[17] This fundamental mechanistic type is the basis for all subsequent cation radical chain pericyclic processes.[18]

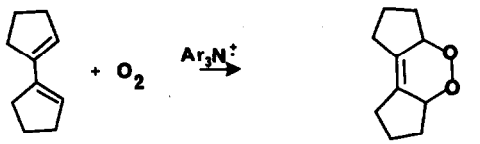
Although the identification of the cation radical chain mechanism and of cation radical chain pericyclic reactions was of undoubted mechanistic significance, the new reaction at first appeared of little value synthetically, since it apparently could not be extended even to other vinylamines.[18] Subsequent developments of the early seventies, however, extended the observation of PET induced cyclodimerizations to other electron rich alkenes such as phenylvinyl ether (PVE) and to a number of styrenes and indenes (see Section 3).

1.2.2. *Diels–Alder cycloadditions.* At about the same time (1964) as the earliest developments in the area of cation radical cyclobutanation the ^{60}Co γ-radiolysis of 1,3-cyclohexadiene (CHD) was found to produce primarily Diels–Alder cyclodimerization, but the involvement of cation radicals was apparently not suspected.[19] However, in 1969 Schutte and Freeman clearly established the cation radical chain nature of this process, just a year after the definitive clarification of the cyclobutanation mechanism.[20] Very shortly thereafter, Penner *et al.* published the results of their analogous study of the same reaction.[21] In 1973, Arnold and Neunteufel contributed the additional important observation that Diels–Alder (DA) cyclodimerization of 1,1-diphenylethene (DPE) occurs under PET conditions (Scheme 4).[22a] A most remarkable aspect of this cyclodimerization is the utilization of the styrene-type moiety of DPE as the dienic component. Even cross additions of DPE as the dienic component with isobutene and 2,3-dimethyl-2-butene were subsequently observed.[22b] Libman has also proposed the intervention of cation radical intermediates in the formation of DA cyclodimers from a conjugated diene (2,4-dimethyl-1,3-pentadiene) under PET conditions,[23] and Mizuno has observed the DA cycloaddition of indene and furan.[24]



DPE

Scheme 4.



Scheme 5.

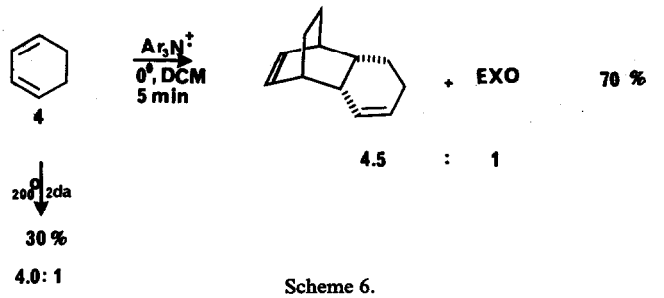
1.2.3. *Addition of triplet oxygen to dienes.* In 1975, Barton *et al.* used catalytic quantities (3–5%) of the stable cation radical salt tris(4-bromophenyl)aminium hexachlorantimonate ($Ar_3N^{+\cdot}$) to overcome the 'spin barrier' and accomplish the conjugate addition of triplet oxygen to conjugated dienes (in effect, a DA cycloaddition, Scheme 5).[25] These authors considered the reaction to occur via an assembly complex of oxygen, diene, and aminium salt, as opposed to free cation radicals, but later work established the cation radical chain nature of the reaction and the specific involvement of diene cation radicals in the propagation cycle.[26]

2. DIELS–ALDER CYCLOADDITIONS

2.1. *The aminium salt initiated cation radical Diels–Alder*

Both the scope and the synthetic utility of the cation radical DA reaction were enhanced by the observation of efficient chemical initiation of this reaction by shelf-stable triarylaminium salts under extraordinarily mild conditions.[27]

2.1.1. *The prototype: cyclodimerization of* 1,3-*cyclohexadiene* (**4**). The thermal DA cyclodimerization of **4** requires at least 20 h at 200°C to achieve the modest and apparently optimum yield of 30% of the DA cyclodimers (*endo*: *exo* = 4 : 1).[28] When 5 mol % of the stable cation radical salt tris(4-bromophenyl)aminium hexachloroantimonate[29] (5 ≡ $Ar_3N^{+\cdot}$) is used to initiate a cation radical chain process, **4** is DA cyclodimerized in 70% yield in less than 5 min (0°C, 0.1–0.4 M **4**, dichloromethane ≡ DCM, Scheme 6).[27] The *endo* stereoselectivity is very similar to but slightly higher than in the uncatalyzed thermal reaction (4.5 : 1.0). Small amounts (ca 2 %) of the *syn* and *anti* cyclobutane (CB) cyclodimers of **4** are also detected, but no other volatile products are formed. These CB cyclodimers, synthetically accessible from triplet photosensitized cyclodimerization of **4**,[28] are completely stable under the reaction conditions. Polymerization appears to be the only significant side reaction competing with cyclodimerization of **4**. Among a wide variety of solvents investigated, DCM still appears to be by far the most effective one for this and, it would appear, most other aminium salt initiated cation radical pericyclic reactions. In particular, acetonitrile, which is used so effectively for PET initiated cation radical reactions, affords rather poor yields in the aminium salt initiated reactions. Reaction temperatures as low as −45°C are available when using **5** as

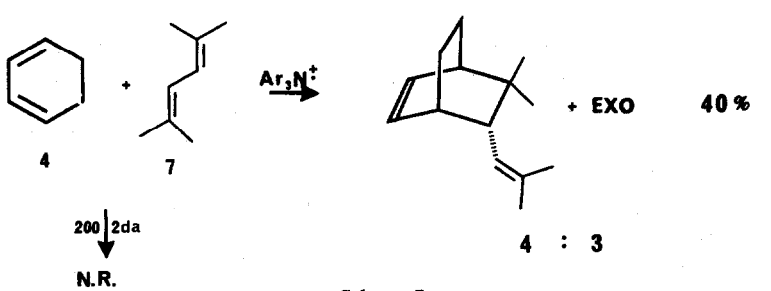


Scheme 6.

initiator, but both reaction rates and reaction efficiencies are diminished at the lower end of this temperature range as a consequence of the unfavorable temperature coefficient of the endothermic initiation step (see kinetics) and also of the low solubility of **5** in cold DCM. Both of these adverse effects are alleviated by the use of the more potent initiator tris(2,4-dibromophenyl)aminium hexachloroantimonate[30] (**6** = Ar'_3N^+), which can be employed at temperatures down to at least −78°C. Nevertheless, reaction efficiency remains somewhat below that at the apparent global optimum consisting of 0°C, Ar_3N^+ (**5**), DCM.

The low yields obtained and the forcing conditions required in the uncatalyzed DA cyclodimerization of **4**[28] are a reminder of a generic weakness of the DA reaction, viz. that DA reactions are typically not efficient unless the dienophile is substantially electron deficient.[31] Ionization to the cation radical state is an effective and direct remedy for the absence of electron deficiency in the dienic system of **4** (Umpolung).[32] An important synthetic niche for the cation radical DA reaction is thus foreseen, since the conjugated and electron rich pi systems which are most readily converted to their cation radical states are precisely those systems which are least reactive in the conventional DA reaction. The inherent preference of $\mathbf{4}^+$ for pericyclic as opposed to acyclic reaction modes (e.g. polymerization, deprotonation, coupling) is impressive and encouraging. That periselective DA cycloaddition, as opposed to cyclobutanation or formation of a 1,5-cyclooctadiene, can be characteristic of such a reactive species as $\mathbf{4}^+$ is even more astonishing.

2.1.2. *Kinetic impetus: the Diels–Alder cycloaddition of a highly hindered diene to* 1,3-*cyclohexadiene.* A second well known limitation of the uncatalyzed DA reaction is its pronounced sensitivity to steric effects. The sterically hindered diene 2,5-dimethyl-2,4-hexadiene (**7**), for example, has never been observed to participate in the DA reaction as either diene or dienophile. Under the relatively forcing conditions used to cyclodimerize **4** (>200°C, 2 da), **7** does not react with **4** at all. That the kinetic impetus of the cation radical DA is sufficient to overcome this steric effect is evident when an equimolar mixture of **4** and **7** is subjected to the previously defined standard aminium salt conditions (0°C, DCM, 5 mol % **5**). A 40% yield of DA cross adducts (*endo*: *exo* = 4:3) is obtained in addition to 20% of the cyclodimers of **4** (Scheme 7). The relatively facile installation of a



Scheme 7.

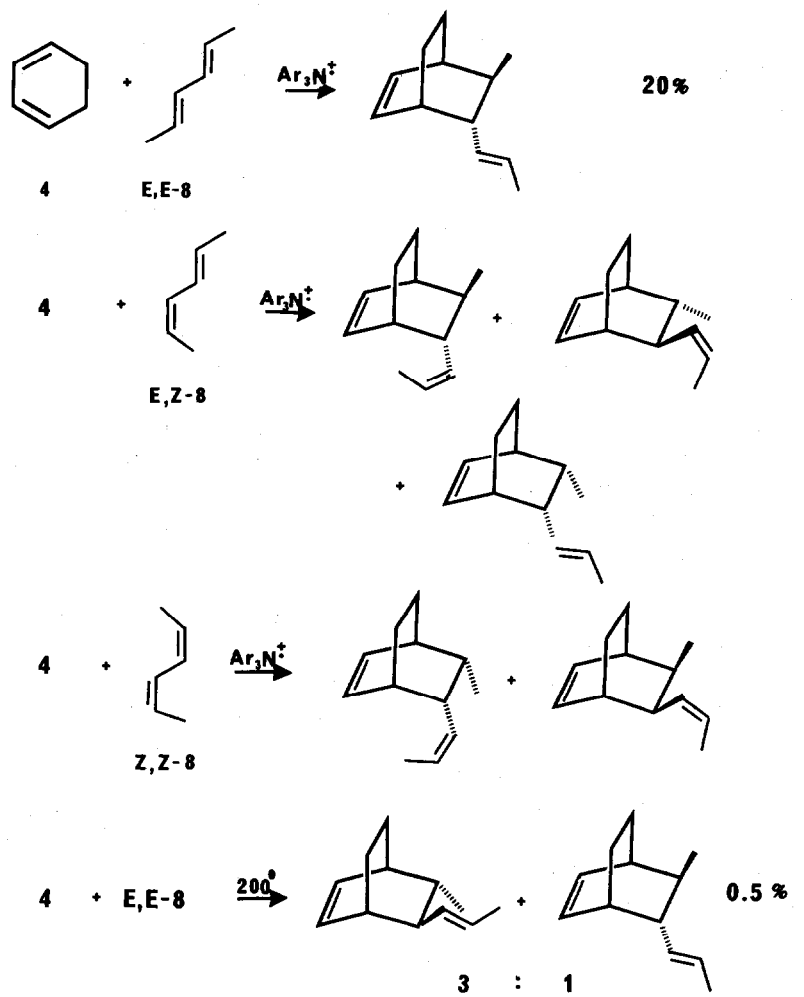
quaternary carbon is thus demonstrated. Mechanistically, the much lower oxidation potential of **7** than **4** implies that $7^{\dagger}$ should be the diene cation radical predominantly formed in this reaction. Consequently the cross adduct is presumed to arise by reaction of $7^{\dagger}$ with neutral **4** rather than the reverse circumstance ($4^{\dagger}+7$). According to this mechanistic formulation, the smaller amount of $4^{\dagger}$ which is formed is the precursor of the **4** cyclodimers. The aforementioned mechanism for the formation of cross adducts is supported not only by the greater caticogenicity (tendency to form a cation radical) of **7** than **4**, but also by the circumstance (*vide infra*) that steric effects render neutral **7** far less caticophilic (reactive toward cation radicals) than **4**. Consequently, the formulation $7^{\dagger}+4$ rather than $4^{\dagger}+7$ is favored by considerations of both caticogenicity and caticophilicity. From the structure of the cross adduct, the hindered diene is seen to execute the DA dienophilic role. Mechanistically, the reaction can then be classified as [4+1] in the Woodward–Hoffmann sense.[27,33]

2.1.3. *Reaction stereochemistry: cycloaddition of the* 2,4-*hexadienes to* 1,3-*cyclohexadiene*. Prior to the study of the title reactions, little attention had been directed toward the stereochemistry of cation radical cycloadditions generally. The pioneering mechanistic studies of the Ledwith group on the CB cyclodimerization of N-vinylcarbazole had led that group to propose a stepwise cycloaddition involving an acyclic (a type of 1,4-butanediyl cation radical) intermediate. Theoretical results had also been construed to suggest that both cation radical cyclobutanation and DA additions would be stepwise.[34] On the usual premise that under at least some conditions rotations around the appropriate sigma bonds will not consistently be at least an order of magnitude slower than cyclization of the acyclic intermediate, the expectation of such a stepwise mechanism is at least partial stereorandomization, i.e., non-stereospecific reaction. In sharp contrast, the stereochemical study of the DA cycloadditions of **4** to *E,E*-; *E,Z*-; and *Z,Z*-**8** reveal complete suprafacial stereospecificity in all three reactions (Scheme 8). These results led Bellville *et al.* to propose a concerted mechanism for the cation radical DA.[27] Incidentally, the rigorous retention of original stereochemistry in the pendant double bond of the dienophilic fragment (*E*- or *Z*-propenyl) strongly counterindicates a Brønsted acid catalyzed mechanism for these reactions (*vide infra*). It is also significant that the addition of *E,E*-**8** to **4** occurs with nearly complete (>99%) *endo* stereoselection, as does the addition of **4** to the *Z* double bond of *E,Z*-**8**. In both of these cases the pendant double bond has an *E*-propenyl substituent. This level of *endo* stereoselection can be compared with that observed in the uncatalyzed addition of **4** and *E,E*-**8** (0.5% yield, 200°C, 2 da), viz. 1:3 (*exo* prevailing; *endo* stable under these reaction conditions).[35] In every other case discussed thus far, including the cyclodimerization of **4**, the cross addition of **4** and **7**, the addition of **4** to the *E* double bond of *E,Z*-**8**, and the addition of **4** to *Z,Z*-**8**, the pendant double bond has a *Z*-alkenyl substituent and the *endo* stereoselection is reduced to a modest level (the '*cis*-propenyl' effect).[27,36] This effect is consistently observed (*vide infra*) and, in addition, exclusive *endo* stereoselection has been observed for a pendant vinyl group (*vide infra*). It was proposed that the cation radical DA inherently has an extremely high *endo* stereoselectivity as a consequence of the low reaction temperature and the powerfully electron deficient pendant group.[36] The latter provides for an unusually strong secondary orbital interaction in the transition state for *endo* addition. An exactly analogous situation exists for the Lewis acid catalyzed DA.[37] It is further proposed that *cis*-alkenyl substituents attenuate the *endo* stereoselection through steric interference in the *endo* transition state. This is best accommodated by postulating a preference for the *s-cis* conformation in the dienophilic diene moiety.

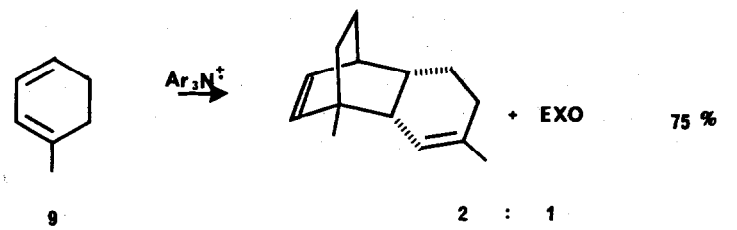
Finally, the [4+1] reaction mechanism is again considered likely for this reaction. Not only is **8** somewhat more caticogenic than **4**, but the much greater caticophilicity of **4** than **8** assures that the $4^{\dagger}$ which is also undoubtedly formed primarily reacts with neutral **4** to form the cyclodimer of **4**. The greater caticophilicity of **4** than **8** is presumably based at least in part upon the relative *s-cis* diene populations, but steric factors are also more favorable with **4**.

2.1.4. *Regiospecificity: the cyclodimerization of* 1-*methyl*-1,3-*cyclohexadiene* (**9**). The experiments described previously show the cation radical DA to be capable of impressively high levels of stereospecificity and *endo* stereoselectivity. Another element of the selectivity profile, regiospecificity,

is at least equally impressive.[36,38] The combination of an unsymmetrical diene component with an unsymmetrical dienophile permits scrutiny of this selectivity element. The cyclodimerization of **9** under typical aminium salt conditions occurs efficiently (75% yield) to give a 2:1 (see *cis*-propenyl effect) *endo*:*exo* mixture of DA adducts with 100% regiospecificity (Scheme 9). The sense of this specificity is in accord with a conventional non-synchronous (diradicaloid) DA transition state



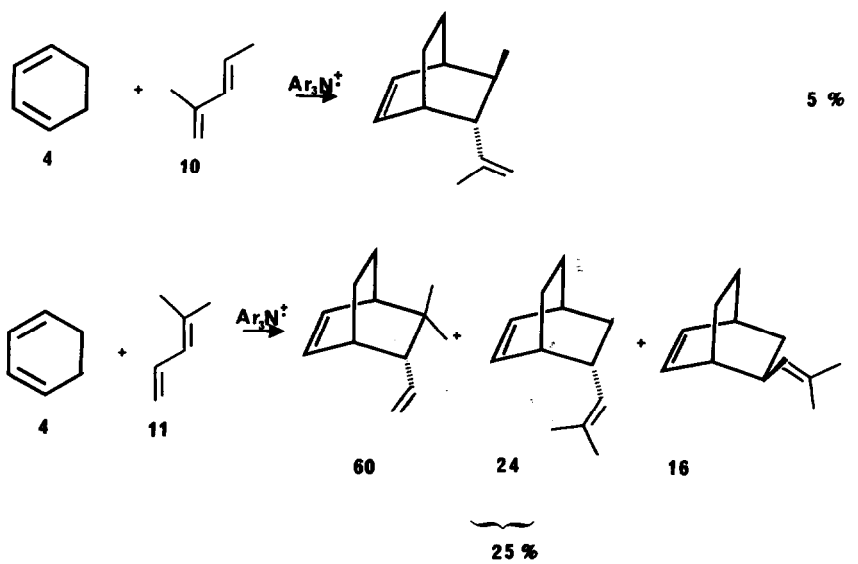
Scheme 8.



Scheme 9.

model (the more stable bisallylic cation radicaloid is preferred) and also with FMO predictions.[36] Additional examples of rigorous regiospecificity (*vide infra*) confirm the reliability and predictability of this selectivity element. The cross addition of **9** with other dienes, incidentally, is rarely efficient. Even when as much as 10–15 fold excesses of other dienes are used, cyclodimerization of **9** is overwhelmingly dominant. This follows as a consequence of the fact that **9** is both more caticogenic and more caticophilic than the great majority of dienes. As a terminally trisubstituted diene it surpasses most dienes in its ability to form cation radicals (caticogenicity). The resulting cation radicals ($\mathbf{9}^{+\cdot}$) preferentially react with neutral **9** in competition with other neutral dienes as a consequence of both the cyclic nature of **6** (large *s-cis* content) and its ability to stabilize (terminal dialkyl groups) the bisallylic cation radicaloid transition state (caticophilicity).

2.1.5. *Chemoselection.* The cyclodimerization of **9** illustrates a further element of the selectivity profile of the cation radical DA which, for lack of a better term, has been called chemoselection. This term was used to refer to the selection between chemically non-equivalent double bonds of an unsymmetrical (dienophilic) diene.[38] The dienic unit of **9** has one doubly substituted and one monosubstituted terminal carbon (the 2,1 substitution pattern), and addition is seen to occur exclusively at the monosubstituted diene terminus. This chemoselection sense is precisely that expected in the conventional DA and is readily rationalized on the basis of (i) steric effects and (ii) maximum stabilization of the bisallylic transition state by the terminal alkyl substituents. Other examples of this diene substitution pattern (*vide infra*) confirm the consistency of this chemoselection sense and, implicitly, the associated interpretation. Incidentally, results such as this clearly indicate that as formidable as is the kinetic impulse of the cation radical DA, it is nevertheless subject to steric regulation of selectivity. Other diene substitution patterns, however, reveal chemoselection senses which are atypical of the conventional DA and which suggest that an additional effect is operative and can even assert dominance over the two effects mentioned previously. The cycloadditions of **4** with 2-methyl-1,3-pentadiene (**10**) and 4-methyl-1,3-pentadiene (**11**), which represent the 1,0 and 2,0 terminal substitution patterns, respectively, illustrate this point (Scheme 10). In both cases reaction occurs predominantly at the sterically more hindered diene terminus, leading to the less stable bisallylic transition state. Apparently a charge density effect,[36] not implausibly for a

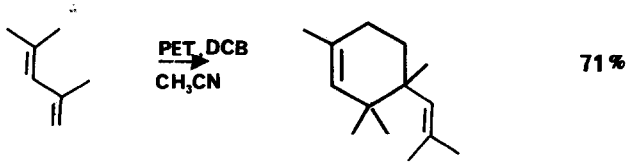


Scheme 10.

charged species, has asserted control. Indeed such control had previously been postulated for a cation radical cycloaddition.[39] Molecular orbital calculations confirm the intuitive supposition that the more highly substituted diene terminus typically bears the greater partial positive charge.[38] That charge effects should be operative in cation radical reactions appears to present no particular problem, but the circumstance that charge effects are dominant in some cases and not in others warrants comment. In the case of **10**, charge density control is not surprising, since neither terminus is disubstituted. Steric effects would conventionally be assumed to experience a sharp increase at this latter substitution level. Thus, steric differentiation in the 1,0 system is considered to be much less than in the 2,1 system. In the case of the 2,0 system (**11**), steric differentiation should be but little greater than in the 2,1 system, but charge differentiation is considerably greater in the former. The three effects (steric effects/bisallylic stabilization/charge effects) appear to provide a sufficient basis for rationalizing chemoselection senses, but predictive applications are not necessarily straightforward because the effects are apparently rather precariously balanced, and modest changes in the blend are capable of producing major effects on the preferred chemoselection sense. An intriguing illustration is the cyclodimerization of 2,4-dimethyl-1,3-pentadiene (**12**, Scheme 11), which, although it is a diene of the 2,0 substitution pattern, exclusively reacts at the less substituted terminus. This reaction, incidentally, must be carried out in the presence of a hindered pyridine base or using PET conditions in order to avoid a Brønsted acid catalyzed reaction.[40] In this system the presence of the methyl group at the 2-position constitutes an ideal substitution pattern for bisallylic stabilization when reaction occurs at C_1. Consequently, it is proposed that bisallylic stabilization effects are accentuated and now become dominant. Indeed, when electron donor substituents more powerful than alkyl are present at one diene terminus, bisallylic effects appear always to be dominant (*vide infra*).

Portions of the previous discussion of charge effects tacitly assume that the acyclic diene, which performs the dienophilic role, is the cation radical moiety in the cross cycloadditions to **4**, i.e., that these cycloadditions are also of the [4+1] type. The validity of this assumption is supported, in the case of **11**, by the greater caticogenicity (see Table 1) of **11** than **4**. More importantly, in the case of both **10** and **11**, the far greater caticophilicity (especially as a DA diene component) of **4** than **10** or **11** should assure that any $\mathbf{4}^+$ produced should predominantly lead to cyclodimerization. Incidentally, cyclodimerization of **10** and **11** is, as expected, quite minimal.

2.1.6. *Role selectivity.* It was noted in the early stages of research on the aminium salt initiated cation radical DA, that whereas the [4+1] version of the reaction is formally symmetry allowed, the role-reversed reaction, a [3+2] cycloaddition in which the *s-cis* diene cation radical reacts with a neutral dienophile, is formally symmetry forbidden.[27,33] In conjunction with this, it was noted that virtually all of the efficient radical DA cross reactions which had been observed involved systems in which the dienophile is more caticogenic than the diene, i.e., they are apparently of the [4+1] type. The concept of role selectivity was thus emphasized. As in any orbital symmetry analysis the preference for the allowed reaction mode was not considered absolute nor were reactions of the forbidden type considered difficult, since it was already known and recognized that cyclobutanation,



12

Scheme 11.

Table 1

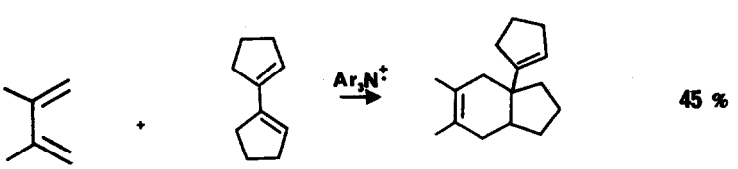
Half Wave Oxidation Potentials

(vs. S.C.E., CH_3CN, irreversible)

Compound	Potential (V)
E-anethole	1.11
1,1'-dicyclopentenyl	1.36
4-methyl-1,3-pentadiene	1.42
phenyl vinyl sulfide	1.42
4-isopropenyl-1-vinylcyclohexene (3)	1.52
1,3-cyclohexadiene (2)	1.53
N-methyl-N-vinylacetamide	1.55
E,E-2,4-hexadiene (1)	1.59
ethyl vinyl ether	1.60
phenyl vinyl ether	1.62
E-2-methyl-1,3-pentadiene	1.70
α-methylstyrene	1.72
E-1,3-pentadiene (5)	1.73
2,3-dimethyl-1,3-butadiene	1.95
2-methyl-1,3-butadiene	1.98

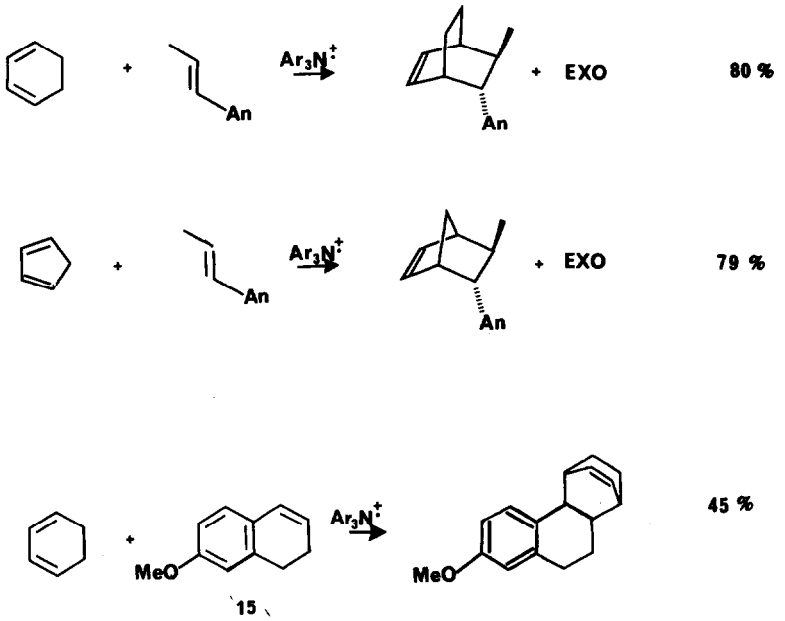
a formally symmetry-forbidden [2+1] cycloaddition, is incredibly facile. As would conventionally be the case, it was considered that, *ceteris paribus*, the allowed mode would be at least slightly preferred. This point remains difficult to establish rigorously and has been questioned.[41,42] It remains true that the vast majority of efficient cation radical DAs yet known are best classified as [4+1], but as has been emphasized in previous discussions this selection is not necessarily based on pericyclic factors correlated with orbital symmetry. Indeed, the extraordinarily high caticophilicity of cyclic dienes such as **4** is sufficient to engender this outcome by effectually blocking the [3+2] route and diverting it to cyclodimerization. Indeed, examples (not necessarily efficient) of [3+2] cycloaddition are now well established (*vide infra*). Nevertheless, reactions such as that in Scheme 12 continue to suggest that, in at least a practical sense, role selectivity can be a rather reliable predictive tool. In this latter example, 1,1'-dicyclopentenyl (**13**) is by far the more caticogenic diene (Table 1). Nevertheless, $\mathbf{13}^+$ could easily elect either the dienic or the dienophilic role, since **13** is a diene with relatively high *s-cis* conformational content. The sole product, formed (in 45% yield), corresponds to the election of the dienophilic role.[43]

2.1.7. *Acyclic diene components.* The previous example illustrates the observation that the dienic component in the cation radical DA need not be cyclic (i.e. rigidly *s-cis*). The cyclodimerization of **13** illustrates the same point. The simple acyclic dienes 2,3-dimethyl-1,3-butadiene (**14**) and 2,4-



14 **13**

Scheme 12.

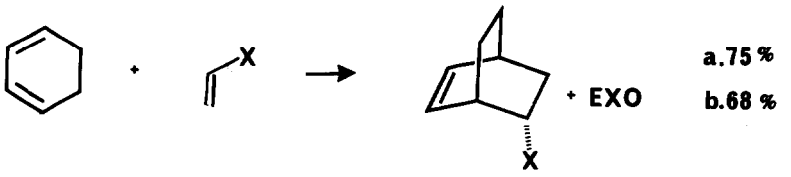


Scheme 13.

dimethyl-1,3-pentadiene (**12**) have also been utilized as diene components. It is nevertheless true that cyclodimerizations of, and cross cycloadditions to, simple acyclic diene components such as 1,3-butadiene, isoprene, piperylene, and even the 2,4-hexadienes are not efficient at all. In general, dienic components with substantial *s-cis* contents appear to be necessary for efficient reactions.

2.1.8. *Styrenes as dienophiles.* As with conjugated dienes, the conjugated systems of styrenes are often sufficiently caticogenic to participate in the cation radical DA, normally in the dienophilic role. However, it should be recalled that Arnold's group demonstrated quite early that the styrene functionality of 1,1-diphenylethene can also assume the dienic role in the cyclodimerization of the latter compound.[22] Styrene itself does not cycloadd to **4** significantly, but *E*-β-methylstyrene adds in poor yield (8%). The former is subject to rapid polymerization and both are less caticogenic than **4** (the cyclodimerization of **4** predominates). 4-Vinylanisole, a much more caticogenic substrate than **4** yields only 21% of the DA adducts (*endo*:*exo* = 2:1), but *E*-anethole (**12**) adds smoothly to both **4** (80%) and to 1,3-cyclopentadiene (74%, Scheme 13). An even more interesting example is the DA addition of the methoxydihydronaphthalene **15** to **4** (45%; *endo*:*exo* = 2:1). The failure of 4,4'-dimethooxystilbene to add to **4** suggests that the desideratum of high dienophilic caticogenicity has limits and may have the concomitant of low reactivity.

2.1.9. *Electron rich alkenes.* A third category of caticogenic substrates has been found capable of participating in the cation radical DA reaction, viz., electron rich alkenes. These substrates distinguish themselves from the conjugated dienes and styrenes in that, though they are just moderately caticogenic (see Table 1), they are extraordinarily caticophilic as a class. Presumably this quality issues from the ability of the heteroatom donor substituents to powerfully stabilize the cation radical character (and perhaps especially the carbocation aspect of this) in the bisallylic transition state. Cycloaddition of **4** with phenylvinyl ether (**16a**) and phenyl vinyl sulfide (**16b**) occurs smoothly when a large (ca 9:1) excess of **16** is used, to give predominantly the DA adducts (75% and 68% yields, respectively, Scheme 14). However, cycloaddition to acyclic dienes is predominantly cyclobutane (CB) periselective. The mechanisms of these reactions will be discussed in detail in the section on cyclobutanation.



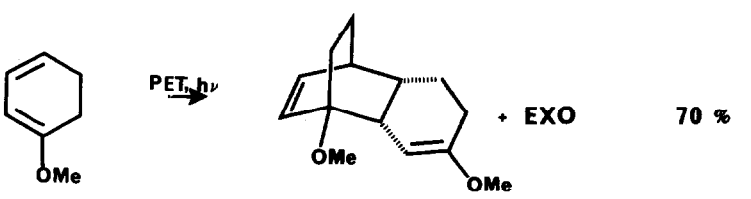
16 a. X=OPh
b. X= SPh

Scheme 14.

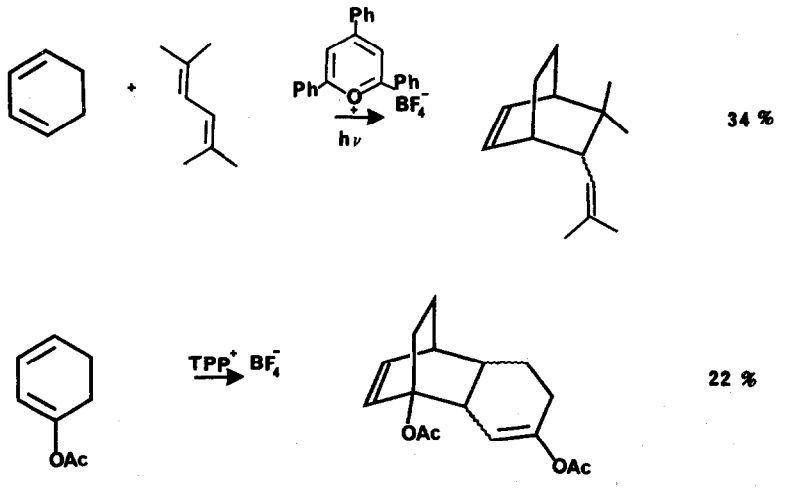
2.2. *Photosensitized electron transfer (PET) initiation*

Subsequent to the discovery of the aminium salt initiated cation radical DA reaction by this group, the cyclodimerization of **4** under PET conditions (9,10-dicyanoanthracene ≡ DCA, CH_2Cl_2, hv) was reported by Jones *et al.*[44] However, the attempt to effect cross addition of **4** and the hindered diene 2,5-dimethyl-2,4-hexadene (**7**) failed. To explain the contrast between the latter result and the rather smooth aminium salt initiated cross addition of these same addends, the authors proposed that the PET reaction intermediates may be tightly bound complexes (either exciplexes or radical ion pairs) of lower reactivity than the cation radicals involved in the aminium salt reaction. This proposal would not appear to be viable for several reasons. First, the PET results are identical in acetonitrile and DCM. The former is actually a more polar solvent than the solvent used in the aminium salt procedure (DCM). Further, the hexachloroantimonate counterion, present in the aminium salt initiated cycloadditions, would appear to be one of the more tightly ion pairing anions available. Finally, the PET results with a wide variety of other dienes (*vide infra*), closely parallel the aminium salt results. The observations suggest that the unique unreactivity of **7** in PET initiated cycloadditions is engendered not by deactivating ion pairing or incomplete electron transfer, but by the circumstance that cation radical lifetimes in radical ion pairs (PET conditions) are limited by back electron transfer, and when cycloadditions are exceptionally slow, as in the case of a sterically hindered substrate, back electron transfer can dominate.[35] Steric hindrance of the cation radical DA has, of course, been demonstrated previously. Incidentally, the formation of $7^{+\cdot}$ is undoubted, since **7** completely quenches the cyclodimerization of **4** under PET conditions.

In the same year as the work described above, a more extensive study of DA cycloadditions under PET conditions was reported and the close similarity of the results to the corresponding aminium salt initiated cycloadditions was emphasized.[45,35] The DA cyclodimerization of 1-methoxy-1,3-cyclohexadiene (**17**), which is quite inefficient under aminium salt conditions, was found to occur in 71% yield under PET conditions (DCB, CH_3CN, Scheme 15). The reaction is, as in previous examples, completely regiospecific but only mildly *endo* selective (2:1; see *cis*-propenyl effect).



Scheme 15.



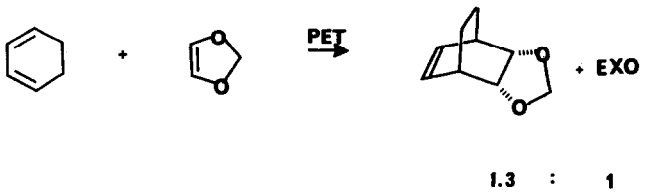
Scheme 16.

Chemoselection is apparently dominated by bisallylic transition state stabilization by the methoxy group and is exclusive. The inefficiency of the aminium salt cyclodimerization of **17** appears to be related to the instability of the enol ether product under aminium salt conditions, since this cyclodimer has been shown to be decomposed rapidly by the aminium salt. Apparently both Brønsted acid and electron transfer processes operate in these decompositions.

Thus, although the scope of the conventional PET initiated DA cycloaddition is limited by the phenomenon of back electron transfer, it is especially advantageous in the case of cycloadditions involving very sensitive functionalities. The relative mildness of the PET conditions (in this sense) also makes possible cleaner and more efficient DA cycloadditions of a number of simple hydrocarbon dienes. The cyclodimerization of 1,1′-dicyclopentenyl (**13**) occurs in 71% yield under PET conditions, as compared to a 50% yield under aminium salt conditions. In the case of 2,4-dimethyl-1,3-pentadiene (**12**), the PET initiated process produces the cation radical cyclodimer in 71% yield; the typical aminium salt procedure actually generates a different DA cyclodimer, which appears to derive from a Brønsted acid catalyzed reaction (*vide infra*).

More recently the scope of the PET procedure for effecting cation radical DA cycloadditions has been extended significantly by the observation that 2,4,6-triphenylpyrylium tetrafluoroborate (TPP^+) sensitizes the cycloaddition of 2,5-dimethyl-2,4-hexadiene (**7**) to 1,3-cyclohexadiene (**4**) in 34% yield, a reaction which fails completely under DCB photosensitized conditions (Scheme 16).[46] This observation appears to be consistent with the postulate that back electron transfer overwhelms cycloaddition in the latter case. The use of pyrylium salts, of course, circumvents anion radical formation and may be presumed to reduce the back electron transfer rate. The cyclodimerization of 1-acetoxy-1,3-cyclohexadiene, which fails under both aminium salt and conventional PET initiation conditions, also occurs to a modest extent (22%) under the pyrylium salt PET conditions.

The results of Mattay's laboratory using ketone (fluorenone, benzil)-$LiClO_4$ mixtures in acetonitrile to photosensitize the cation radical DA are also of interest.[41] The cyclodimerization of **4** is said to yield only DA adducts but the *endo*:*exo* ratio is 1:1. A triplex channel was proposed, along with differential ion pairing effects. The cycloaddition of 1,3-dioxole and **4** is especially interesting. An increase in the *endo*:*exo* ratio (from 1.3 to 2.0) with a doubling of the dioxole:diene ratio is interpreted on the basis of competing normal and role reversed cycloaddition (Scheme 17).



Scheme 17.

2.3. *Mechanistic diagnosis*

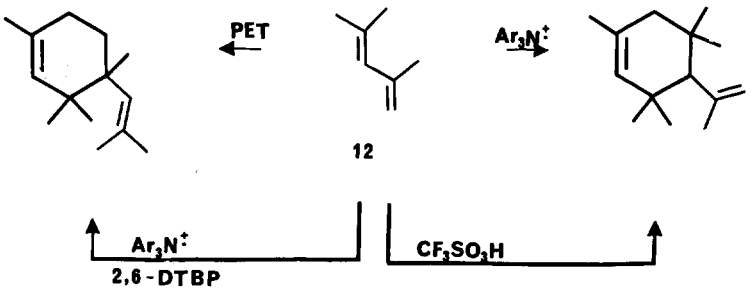
The early radiolytic studies of the cyclodimerization of **4** developed two useful criteria for the mechanistic characterization of cation radical chain reactions.[20,21] Both DA and CB cyclodimers were formed under these conditions, but the formation of DA dimers was found to be selectively quenched by ethanol or isopropanol and accelerated by electron quenchers such as carbon tetrachloride and *m*-dinitrobenzene. Quenching by added nucleophiles is consistent with the interception of chain carrying cation radicals, and acceleration by electron traps suggests interdiction of the quenching of these chain carriers by free electron or anion radicals. More specifically, these criteria would appear to identify the intermediate in the DA reaction as a positively charged species as opposed, for example, to the neutral diene triplet which engenders the CB cycloaddition and other neutral (e.g. radical) and anionic (e.g. carbanion, anion radical) species. Carbocation intermediates would not, however, necessarily be excluded.

Rate acceleration in polar solvents (e.g. acetonitrile) or even failure of the reaction to proceed at all in nonpolar solvents (e.g. benzene) has often been used to distinguish cation radical intermediates (which require polar solvents) from exciplexes (which do not). Similarly, quenching by highly caticogenic substrates such as 1,3,5-trimethoxybenzene has often been used to characterize cation radical processes (*vide infra*).

The observation of aminium salt initiated DA cycloadditions permits development of a more specific mechanistic criterion. Generation of the cation radical of a selected substrate by different means should provide an excellent check of intrinsic cation radical behavior. This is potentially a fingerprint comparison since multiple selectivity elements (*vide supra*) are often involved in cycloadditions. An extensive mechanistic diagnosis of cation radical cycloadditions has been carried out using this criterion. In applying this criterion, the interdiction of cycloaddition by rapid back electron transfer, particularly for hindered systems, must be recalled as a specific limitation of the PET method. On the other hand, acid sensitive functional groups in either the reactant or product may engender low yields in the aminium salt process. Where both sets of conditions produce cycloadducts which are demonstrably primary products, fingerprint comparisons should be quite reliable.[35]

2.4. *Cation radical vs carbocation mechanisms*

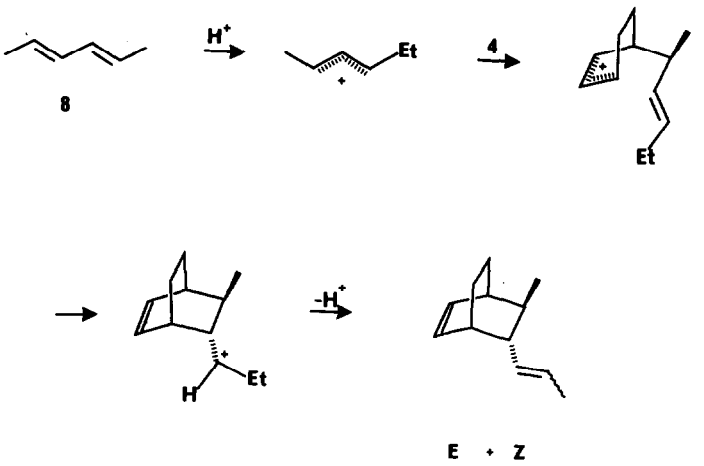
The distinction between these two particular mechanistic types is particularly challenging not only because of the charge type similarity, but also because cation radicals themselves are often strong general Brønsted acids,[47] and are capable of generating carbocations which may then mediate cycloaddition reactions. Conversely, carbocations are also hole-containing species and may be capable, in turn, of generating cation radicals by single electron acceptance from a neutral substrate. An excellent illustration of the potential mechanistic complexity is available in the cyclodimerization of 2,4-dimethyl-1,3-pentadiene (**12**, Scheme 18).[38,36,40,23] The aminium salt and PET-initiated cyclodimerizations of this diene each yield a single diastereomer in good yield, but the products are constitutional isomers. Gassman and Singleton have demonstrated that 2,6-bis(*tert*-butyl)-pyridine(2,6-DTBP), when used in molar excess over the aminium salt initiator, completely sup-



Scheme 18.

presses formation of the 'normal' aminium salt dimer and diverts the reaction to form the PET cyclodimer. The 'fingerprint' criterion suggests that the modified aminium salt and PET procedures, but not the unmodified aminium salt procedure, involve cation radical/neutral cycloaddition. The mechanism involved in the unmodified aminium salt procedure is considered to be a Brønsted acid-catalyzed process, since it is completely quenched by the hindered base. Indeed typical Brønsted acids cyclodimerize **12** efficiently to give the same dimer as obtained in the normal aminium salt procedure.[40,35] That **12** could be rather uniquely susceptible to acid catalyzed, carbocation mediated cyclodimerization appears quite plausible in view of its substitution pattern, which provides ideal stabilization of the allylic carbocation formed by protonation, as well as an unusually large *s-cis* diene conformational population. No further examples of analogous carbocation mediated cycloadditions have yet emerged in an extensive mechanistic study of *intermolecular*[48] cycloadditions of conjugated dienes. The premise of the hindered base criterion is that such bases are capable of accepting protons and neutralizing Brønsted acids but are too sterically hindered to react as nucleophiles with cation radicals. The limitation of this assumption is that cation radicals are often strong Brønsted acids and can probably react with these hindered bases by proton transfer, although the rates of proton transfer may indeed be slowed by steric effects. Further, evidence is available from kinetic studies that such hindered bases are capable of decomposing the aminium salt initiator even in the absence of a caticogenic substrate.[49] One consequence of these effects is that large amounts of initiator (50 mol %, as compared to the usual 3–5 mol % in the unmodified procedure) must be used in the modified aminium salt procedure to achieve satisfactory conversions. The specific case of the cross cycloaddition of 2,5-dimethyl-2,4-hexadiene (**7**) and 1,3-cyclodexadiene (**4**) illustrates the limitations of the hindered base criterion. This reaction is rather effectively, but *incompletely* quenched by the hindered base. Alternate criteria (e.g. the kinetic criterion discussed below) support the assignment of a cation radical mechanism to this reaction.[49,35] The hindered base criterion should therefore be employed as a mechanistic razor to exclude cation radical mechanism only with circumspection and, specifically, with insistence on complete suppression of the cycloadduct formed under unmodified conditions. Failure to observe suppression is, of course, a definitive counterindication of Brønsted acid catalysis.

An obvious criterion for establishing a Brønsted acid catalyzed mechanism is to subject the addends to *bona fide* Brønsted acid conditions. The cyclodimerization of **12**, for example, occurs efficiently under acidic conditions. No cross addition between **4** and **7**, however, is observed under acidic conditions. An especially effective medium for inducing Brønsted acid catalyzed reactions is triflic acid/DCM/0°C. At appropriate concentrations of this powerful acid, true Brønsted acid catalyzed reactions of most pi substrates can be examined and the results compared with both the aminium salt and PET results.[35] Incidentally, Brønsted acid catalyzed cyclodimerizations under PET conditions have not been reported. Presumably the anion radicals also present under these conditions neutralize any accumulating Brønsted acid.

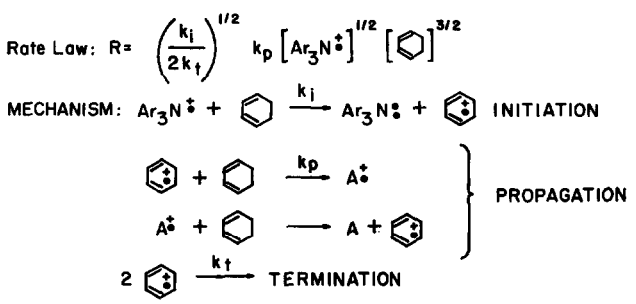


Scheme 19.

Finally, a stereochemical criterion which unequivocally distinguishes the cation radical DA from the carbocation DA has been observed. It will be recalled that the three geometric isomers of 2,4-hexadiene add to 1,3-cyclohexadiene with suprafacial stereospecificity *and* with retention of the stereochemistry of the pendant double bond. This observation excludes Brønsted acid catalysis, since protonation of the diene terminus immediately erases this stereochemical element. When, in the final step of the reaction, the proton is eliminated, the double bond must be regenerated stereorandomly (Scheme 19). In addition, it is doubtful that the intermediate allylic carbocation, which is unsymmetrical, would react exclusively at the methyl-substituted terminus in preference to the ethyl-substituted one. Finally, rigorously suprafacial stereospecificity is by no means an obvious result of the hypothetical carbocation mechanism.[35]

2.5. *Kinetic studies*

2.5.1. *Rate law and activation parameters.* Rigorous kinetic studies of the aminium salt-initiated cation radical DA cyclodimerization of 1,3-cyclohexadiene (**4**) and also of the CB cyclodimerization of *E*-anethole have recently been reported.[49] The rate law for the DA dimerization of **4** is Rate $= k_{app}[Ar_3N^{+}]^{1/2}[CHD]^{3/2}$, a typical rate law for radical chain processes (half order in the initiating system consisting of Ar_3N^{+} and CHD and first order in the monomer, **4**) which is exactly that predicted from a steady state treatment of the proposed mechanism (Scheme 20) with



Scheme 20.

$$Ar_3N^{\ddagger} + 4 \rightleftharpoons Ar_3N^{\ddagger}\cdots 4 \xrightarrow[rds]{4} Ar_3N^{\ddagger} + \text{DA dimer}$$

Scheme 21.

termination by coupling of two cyclohexadiene cation radicals. Temperature dependence studies define an apparent activation enthalpy of 7.95 kcal mol^{-1} and an apparent activation entropy of −26.9 eu. Cyclic Voltammetric measurements of the half wave oxidation potentials of Ar_3N: and CHD (1.05, 1.60 V vs S.C.E. in DCM solvent) permit estimation of the activation enthalpy for the cycloaddition step as $\Delta H_p = 1.6$ kcal mol^{-1}. These measurements clearly confirm the proposed powerful kinetic impetus of the cation radical DA and correspond to a catalytic factor CF = 10^{23} relative to the uncatalyzed diene DA cyclodimerization. They are also in excellent agreement with theoretical results (*vide infra*).

It is interesting to note that the initiation step of the reaction mechanism is rather strongly endothermic. This is, of course, not atypical of radical chain processes if one considers for example, peroxide initiated radical chain reactions. More fundamental than the endothermicity of the initiation step is the requirement, for an efficient chain reaction, of a steady, low concentration of reactive initiating species. If reactive initiating species or chain carriers are supplied in high concentrations, termination is favored. For reactions initiated thermally (as opposed to photochemically, radiolytically, etc.), endothermic initiation steps should be regarded as not only inevitable but desirable. Though such considerations do not enter into this qualitative argument, it is nevertheless relevant that initiation in the cyclodimerization of **4** depends only upon the initiator concentration to the one-half power and thus only one-half of the endothermicity of the initiation step is incorporated into the overall (apparent) activation enthalpy of the reaction.[49]

2.5.2. *The hypothetical 'complex' mechanism.* The rate law observed for the DA cyclodimerization of **4**, incidentally, decisively negates a hypothetical 'complex mechanism' (Scheme 21) wherein cation radical formation is circumvented.[49] This reaction mechanism, which assumes an equilibrium formation of an aminium salt/**4** complex, followed by rate-determining reaction of the complex with **4**, corresponds to a rate law first order in the aminium salt ($Ar_3N^{\ddagger}$) and second order in **4**. Of course, neither of these is observed. Rate-determining formation of an $Ar_3N^{\ddagger}$/**4** complex is obviously also excluded by the rate law.

2.5.3. *A kinetic criterion.* The observation of rate retardation by added neutral Ar_3N: in the cyclodimerization of **4** further excludes the complex mechanism and provides a very specific kinetic criterion for cation radical chain reactions under aminium salt conditions. When relatively small amounts of Ar_3N: are added, rates are retarded without affecting the rate law (Scheme 22). Larger

REACTION	ADDED Ar_3N, mol %	k°_{app}/k_{app}
$4^{\ddagger}$ + 4	25	2.2
$7^{\ddagger}$ + 4	100	17
$An^{\ddagger}$ + An	100	3.3

An = t-Anethole

Scheme 22.

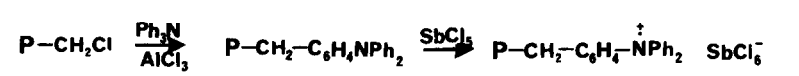
amounts completely suppress the reaction. The electron transfer between $\mathbf{4}^{+\cdot}$ and Ar_3N: is highly exothermic and undoubtedly is diffusion controlled. Chain lengths are thus shortened in the presence of the triarylamine. The aminium salt-initiated cyclodimerization of 2,4-dimethyl-1,3-pentadiene, which is actually a carbocation mediated process, is indeed unaffected by added Ar_3N:. However, the cycloaddition of **4** and **7** is strongly retarded by added free triarylamine.

2.5.4. *The triplex Diels–Alder.* The cation radical mechanism of the PET-initiated DA cyclodimerization of **4** in acetonitrile receives support from quenching studies using 1,3,5-trimethoxybenzene and 4,4′-dimethoxybiphenyl as quenchers.[50] The bimolecular rate constant for the reaction of $\mathbf{4}^{+\cdot}/\mathbf{4}$ was thereby found to be $3 \times 10^8\ M^{-1}\ s^{-1}$. This rate is only a factor of ca 60 times less than the diffusion controlled rate in acetonitrile (1.8×10^{10}). However, neither cation radical nor anion radical intermediates are detected when the solvent is benzene, and quenchers exert no effect on the already much slower reaction. Under these conditions, Schuster and Calhoun have suggested a triplex mechanism where in the excited sensitizer forms an exciplex with CHD $(S \cdots CHD)^*$ and the latter reacts with more CHD to yield a triplex $(S \cdots CHD \cdots CHD)^*$. The triplex was then presumed to collapse to the DA adduct and ground state sensitizer. A termolecular mechanism does indeed seem to be demanded by the increase in DA (as opposed to CB) selectivity at higher diene concentration. Further study of the PET cross additions of **4**, 1,3-cyclopentadiene, and furan with indene in benzene solvent confirm and extend the previous experimental observations.[51] In the more recent work, the mechanistic option of a triplex transition state, as opposed to a triplex intermediate was proposed. Thus, the exciplex might react directly with the diene in a termolecular process. Indeed this latter option appears likely to be correct. The distinction between this and the cation radical DA fades somewhat when it is realized that the exciplex undoubtedly has predominant ion radical pair character.

2.6. *Heterogeneous catalysis of the cation radical Diels–Alder*

2.6.1. *Cation radical polymers.* To facilitate, ultimately, the transfer of cation radical DA technology to an industrial context, the synthesis of insoluble polymers containing functionality readily converted to the cation radical state would be desirable. Such polymers are efficiently prepared by Friedel–Crafts alkylation of triphenylamine by cross-linked Merrifield's resins ($DCM/AlCl_3$; Scheme 23).[52] Conversion to stable, insoluble cation radical polymers is readily achieved using $SbCl_5$/DCM. Of interest is the fact that while *para* substitution of all three aryl rings is required for stability of non-polymeric triarylaminium salts, this is not required in the cation radical polymers. Suspensions of these polymers in DCM readily promote the same range of cation radical DA reactions discussed earlier. The cation radical functions can be restored to the spent polymer by treatment with $SbCl_5$/DCM.

2.6.2. *Catalysis on zeolites and clays.* The presence in zeolites, of 'hole' sites capable of generating and stabilizing aromatic cation radicals is well known. The widespread use of zeolite catalysts in the chemical industry is further incentive for exploring possible zeolite catalysis of the cation radical DA. The DA cyclodimerization of **4** is indeed observed on 13X and other zeolites, and the reaction is further accelerated by photoassistance.[53] Unfortunately, most of the other reactions discussed herein are not efficiently catalyzed on zeolites. The scope of heterogeneous cation radical DA reactions is, however, much wider on ferric ion/4-*tert*-butylphenol-doped montmorillonite clays.[54] Not only is **4** cyclodimerized smoothly, but the cross addition of 2,5-dimethyl-2,4-hexadiene (**7**) to



Scheme 23.

4 occurs moderately efficiently. Cation radical DA cycloadditions of dienes on UV irradiated semiconductor surfaces (TiO_2) have also been observed.[55]

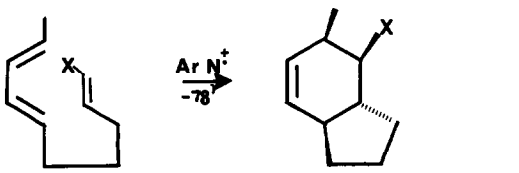
2.6.3. *Anodic initiation.* The anodic generation of cation radicals and the subsequent initiation of cation radical chain DA cycloaddition has recently been demonstrated.[42] Some of these reactions, incidentally, appear to be of the role-reversed ([3+2]) type.

2.7. *The intramolecular cation radical Diels–Alder*

The conventional intramolecular DA reaction is characterized by a special entropic driving force and by its unique capacity for the simultaneous construction of two (fused) rings. The stereochemistry of the resulting ring juncture is a feature of special urgency in synthetic applications and is controlled, for a specific stereoisomer, by the *endo* or *exo* orientation of the dienophilic moiety relative to the dienic moiety. The prospect of uniting the concept of cation radical catalysis, with its exceptional kinetic driving force and its high *endo* selectivity, with the intramolecular DA is therefore highly attractive. In two instances, thus far, construction of a hydrindane ring system with >98% *endo* stereoselection has been demonstrated (Scheme 24).[56]

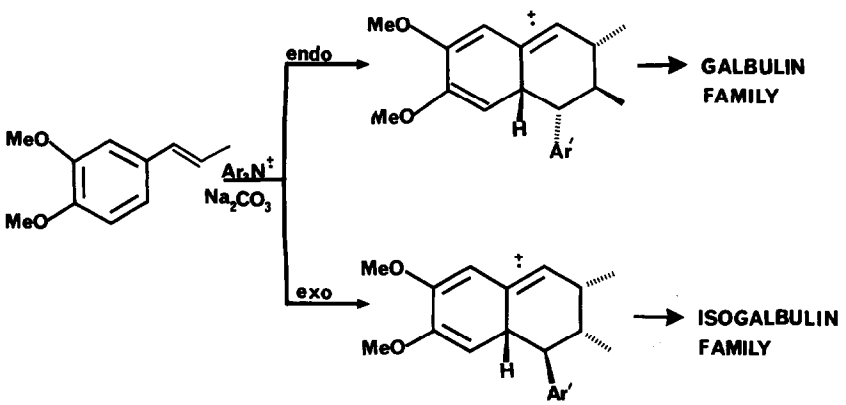
2.8. *Potential biological applications*

The potency of hole catalysis of pericyclic reactions is commensurate with enzyme catalysis, and the discovery of biological transformations which involve cation radical pericyclic chemistry is now a matter of paramount interest. In this connection a recent report[57] from Wilson's group that methylisoeugenol undergoes aminium salt initiated cation radical chain DA cyclodimerization to give intermediate aryltetralins which have the stereochemistry of the lignans galbulin (*via endo* addition) and isogalbulin (*via exo* addition) is encouraging (Scheme 25).



X = 4-MeOPh 83 % } 98-100 % stereoselective
SPh 38 % }

Scheme 24.



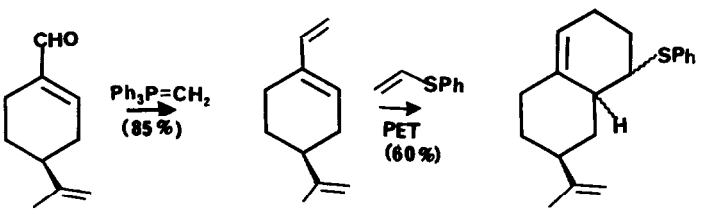
Scheme 25.

2.9. *Applications to natural products synthesis*

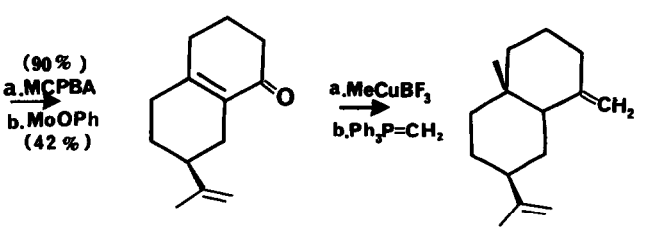
The study of hole catalyzed cycloadditions would appear to be sufficiently justified by the novel theoretical and mechanistic aspects of these reactions, *per se*. The potentiality of commercial and biological applications of this catalytic concept gives a more immediate practical significance to research in this area. Nevertheless, the practicality of hole catalyzed cycloadditions for laboratory scale organic synthesis has been especially emphasized by this research group from the inception of its studies. Synthetic utility in this sense is often demonstrated by the illustrative synthesis of natural product molecules. Whereas the breadth of the mechanistic, theoretical, and methodological studies undertaken by this laboratory necessarily slowed the development of such illustrative syntheses, a number now appear to be near at hand. A compact synthesis of the sesquiterpenoid β-selinene, a major essential oil of celery, is illustrated in Scheme 26. This synthesis illustrates the effective and selective DA cycloaddition to an electron rich alkene (PVS), and the subsequent conversion of the sulfur functionality to a ketone function—in effect, DA addition to a ketene equivalent. It is noteworthy that the oxidation reaction used is mild enough to circumvent migration of the carbon–carbon double bond (in case this is desirable). In contrast, an attempted cycloaddition of phenyl vinyl sulfone to the same triene (readily obtained from the commercially available perillaldeyde by a simple Wittig reaction) gave more than 10 adducts in comparable quantities. Many of these resulted from reaction at the isopropenyl function (presumably via ene type reactions, *inter alia*). In contrast, the vast difference in ionizability of the dienic moiety and the isopropenyl function guarantee a highly selective formation of the dienic cation radical. The overall yield in this synthesis, commencing from commercially available reactants, is 20%.

2.10. *Synthetic profile and limitations*

The cation radical DA reaction can be carried out in a synthetically convenient manner, on virtually any scale, using chemical or photochemical initiation procedures. The reactions are, of



(−)-perillaldehyde



β-Selinene

Scheme 26.

course, extremely rapid and often outstandingly stereoselective and stereospecific. The optimum chemical initiator system appears, at present, to be $Ar_3N^{+\cdot}$/DCM/0°C/5 min. A particularly convenient PET initiator system is DCB/CH_3CN/hv/pyrex/RT. The latter is a more powerfully ionizing system than the optimum chemical one and can produce higher yields, but is somewhat limited in scope by back electron transfer. In such cases, 2,4,6-triphenylpyrylium fluoroborate may be the PET sensitizer of choice.

Diene components should either be cyclic (i.e., rigidly *s-cis*) or, if acyclic, have at least moderate (say $\geqslant 10\%$) *s-cis* conformational populations. Neither the diene nor dienophile is permitted electron withdrawing groups, since these adversely affect both caticophilicity and caticogenicity.

The dienophile typically is of one of three basic structural types: conjugated diene, styrene, or electron rich alkene. Alkyl substituents placed anywhere in these systems typically enhance reaction efficiency, and multiple alkyl substitutions are especially advantageous. When unsubstituted vinyl groups are present as part of the conjugated system, polymerization is often predominant.

In general practice, the preferred synthetic strategy appears to be to utilize dienophiles which are more caticogenic than the diene component. When this condition is not met, cyclodimerization of the diene component may be prevalent. This latter reaction may or may not be susceptible of suppression by use of an excess of dienophile. The ideal preference, which normally results in excellent yields even when dienophile and diene are employed on an equimolar basis is for dichotomous addends, i.e., the circumstance in which the dienophile is much more caticogenic than the diene, and the latter is much more caticophilic than the dienophile. Caticogenicity can be quantitatively assessed on the basis of oxidation potentials or ionization potentials (Table 1). Caticophilicity, specifically in the case of the DA reaction, is considered to be affected by ability to stabilize the bisallylic cation radicaloid transition state, steric hindrance toward bond formation, *s-cis* conformation content and other factors yet to be defined. Nevertheless, many reactions which are non-dichotomous may proceed well, especially when appropriate reagent excesses are provided.

3. CATION RADICAL CYCLOBUTANATION

3.1. *PET initiated cyclobutanation*

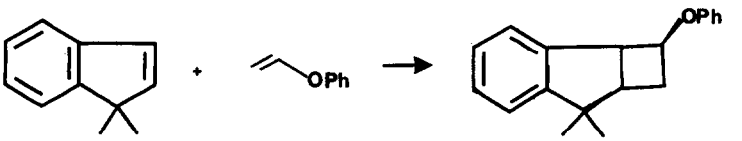
3.1.1. *Cyclodimerization.* The PET cyclodimerization of N-vinylcarbazole, a reaction discovered by Ellinger,[15] played a pivotal role in the historical development of cation radical cycloadditions. The subsequent careful mechanistic characterization of this reaction by the Ledwith group led to the discovery of a fundamental, new mechanistic type, the cation radical chain reaction.[17,18] This latter group observed sensitization by a wide variety of sensitizers (including chloranil, fluorenone, and many others) and in essentially every case quantum yields exceeded unity and ranged up to as high as 66, thus clearly documenting the chain nature of the reaction. A direct connection between cyclodimerization and the quenching of sensitizer (S) fluorescence by NVC was inferred from the fact that NVC does quench the fluorescence of these sensitizers very efficiently and that substances like DABCO, ferrocene, and iodine ion, which quench the sensitizer fluorescence even more efficiently than does NVC, selectively retard cyclodimerization. That electron transfer, giving $NVC^{+\cdot}S^{-\cdot}$ ion radical pairs, is a concomitant of fluorescence quenching was indicated by the observation that cyclodimerization rates are fastest in relatively polar solvents such as acetonitrile and acetone and quite low in nonpolar solvents. The feasibility and likelihood of complete electron transfer was further supported by applying the Weller equation, which reveals that the singlet excitation energy of each of the sensitizers which is effective in cyclodimerizing NVC exceeds the difference between the oxidation potential of NVC (1.02 V vs SCE) and the reduction potential of the ground state sensitizer (+0.02 V for chloranil, −0.29 V for fluorenone.) Moreover, involvement of triplet NVC in the cycloaddition is readily excluded. Since NVC has a much higher triplet energy (70 kcal mol^{-1}) than any of the sensitizers used, the former should not be accessible from sensitizer triplets via energy transfer. Triplet NVC formation by back electron transfer with the ion radical pair is also

strongly endothermic for most of the sensitizers and in any case should preferentially form the lower energy sensitizer triplets. Indeed, a number of the sensitizers have triplet energies too low even to effect electron transfer. In these cases the involvement of the singlet excited state of the sensitizer is unambiguously demonstrated.

An additional aspect of these mechanistic studies is of special interest, viz the powerful acceleration of the cycloaddition rate by atmospheric oxygen. This effect is observed for all sensitizers, and in some cases is so strong that oxygen appears to be an absolute requirement. Presumably, oxygen acts to interdict electron transfer from sensitizer anion radicals to the chain carrying (e.g. $NVC^{+\cdot}$) cation radicals, instead oxidizing the sensitizer anion radicals and forming dioxygen anion radicals. In this manner, chain termination by back electron transfer to the relatively long lived $NVC^{+\cdot}$ is averted or minimized.

Synthetically, the cyclodimerization reaction proved not to be extensible to vinylamines generally, and it was not until 1972 that the next significant extension of the scope of the cation radical chain cyclobutanation reaction was reported. In that year, the cyclodimerization of phenyl vinyl ether (PVE) under PET conditions was reported by Kuwata *et al.*[58] These authors considered an exciplex a possible intermediate but, surprisingly, made no explicit mention of the possibility of a cation radical chain mechanism. In 1974, detailed mechanistic studies of the reaction were reported independently by Evans *et al.*[59] and by Farid *et al.*[60] Both groups confirmed the chain nature of the reaction by observing a limiting quantum yield (at infinite concentration of PVE) of greater than unity (1.7 and 1.5, respectively). The former group observed a linear dependence of quenching of the sensitizer (9,10-dicyanoanthracene ≡ DCA) fluorescence by PVE upon solvent polarity and even detected exciplex emission at −40°C in methylcyclohexane. These results were interpreted in terms of the formation of a weakly bound exciplex between PVE and DCA* which dissociates in nonpolar solvents (to PVE and DCA*) and in polar solvents forms the ion radical pair $PVE^{+\cdot}/DCA^{-\cdot}$ by electron transfer. Dissociation of the latter then affords separated $PVE^{+\cdot}$, which initiates the chain cycloaddition. A salt effect on fluorescence quenching was also observed in DCM with added tetrabutylammonium perchlorate. Farid's studies emphasized quenching of the cation radical chain reaction by substrates (such as 1,5-dimethoxynaphthalene) more oxidizable than PVE, and established the impressive rate constant for the cycloaddition step of 6.3×10^8. In the meantime, Farid and Shealer had already described (1973) the cyclodimerizations of indene and 1,1-dimethylindene using 2,4,6-triphenylpyrylium tetrafluoroborate (TPP^+) as the PET sensitizer.[61] These reactions were also accelerated by dioxygen and quenched by caticogenic substrates. Quenching efficiencies (Φ_0/Φ) were observed to increase regularly as the oxidation potential of the quencher decreased. A mechanism entirely analogous to that of Ledwith was proposed. The involvement of cation radicals in these cyclobutanations is further supported by the observation of cyclobutadimerization of 5,6-dimethoxyindene under anodic oxidation conditions, as reported by Cedheim and Eberson.[62]

In these and all of the cation radical cyclobutanations yet studied, head to head regioselection is observed exclusively. Farid and Shealer pointed out that, in contrast, the triplet sensitized cyclodimerizations of the indene substrates involved in their study are not completely regiospecific.[61] The sense of the cation radical regiospecificity is of course that predicted by considering, as a transition state model, the most stable 1,4-butanediyl cation radicaloid. The NVC and indene cyclodimerizations are apparently rather highly *anti* stereoselective (100 and 97%), but the PVE dimerization actually yields an excess (ca 60 : 40) of the *syn* stereoisomer. Incidentally, the *syn* isomer has been shown to isomerize rather efficiently to the more stable *anti* isomer at longer irradiation times.[59] A cation radical mechanism involving an acyclic 1,4-butanediyl cation radical is believed to be involved in this isomerization. The cyclodimerization of 4-vinylanisole has also been observed under PET conditions (DCB, acetonitrile).[63,64] The reaction proceeds in 42% yield, giving exclusively head/head regioselection. The *syn* : *anti* ratio is 2 : 98. By way of interesting contrast, the direct irradiation (DCB omitted) of this same monomer in acetonitrile yields predominantly the *syn* isomer (*syn* : *anti* = 87 : 3) of the same cycloadduct. Predominant *syn* stereoselection appears characteristic



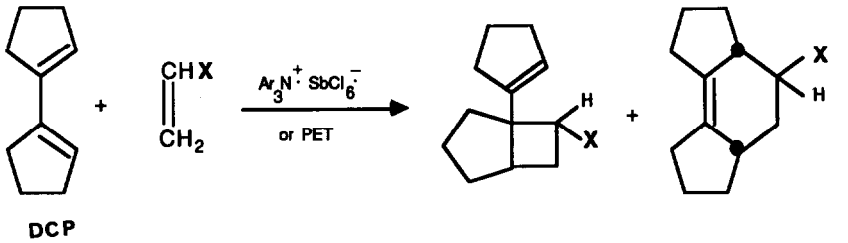
DMI PVE + anti

Scheme 27.

of excimer cyclodimerizations and exciplex cycloadditions, in contrast to the mildly *syn* to strongly *anti* stereoselection involved in cation radical/neutral cycloadditions. In the exciplex cycloadditions the two vicinal substituents (e.g. 4-anisyl) are oppositely charged and therefore exert substantial attractions toward each other. It would appear that the substituent interactions in cation radical/neutral cycloadditions vary from mildly attractive to rather strongly repulsive. The *syn/anti* stereoselectivity observed in a cyclobutanation may represent a useful mechanistic criterion for distinguishing exciplex cycloadditions from cation radical/neutral cycloaddition.

3.1.2. *Cross additions.* The scope and utility of cation radical cyclobutanation is greatly enhanced by the option of cross additions, the first of which was reported by Farid *et al.*[60] Irradiation of an equimolar mixture of PVE and 1,1-dimethylindene (DMI) in the presence of $TPP^+BF_4^-$ in acetonitrile yields predominantly (91%) cross adducts (*syn*: *anti* = 60:40) along with small amounts of the known cyclodimers of both DMI and PVE (Scheme 27). The new mechanistic question posed here is which of the two substrates is the caticogen and which performs the role of the caticophile (the neutral component). This element of mechanistic selectivity has subsequently been termed role selectivity.[38] Both DMI and PVE are, of course, easily within the range of ionizability of the sensitizer, but the former is somewhat more caticogenic than the latter (1.68 V compared to 1.75 V). Although both cation radicals must be formed initially, it is to be expected that diffusion controlled electron transfer will rapidly equilibrate DMI^+ and PVE^+, the equilibrium favoring DMI^+. Indeed, Mattes and Farid were able to decisively demonstrate the specific role sense DMI^+/PVE in this cross addition. Given the circumstance that DMI^+ is the more prevalent cation radical species, the primary products are expected to be the observed cross adduct and the DMI dimer. The strong predominance of the former is the result of the far greater caticophilicity of PVE than DMI. Indeed the rate constants for the cycloaddition of DMI^+ to PVE and DMI, respectively, are 10^8 and 10^6. It will be noted further on that electron rich alkenes generally (including PVE) tend to have more highly developed caticophilicity than caticogenicity and thus tend to participate in cation radical/neutral cycloadditions as the neutral component. The preceeding analysis suggests that, while relative caticogenicity primarily determines the role sense of cross addition, the cross adduct/dimer selectivity derives from relative caticophilicities. However, a more complete analysis of the basis of the observed role selectivity also considers the caticophilicity factor. Thus, the PVE^+ which is undoubtedly formed and sustained in significant equilibrium amounts could also engender cross adduct by reacting with neutral DMI. This reaction is, in effect, suppressed by the greater caticophilicity of PVE, which makes formation of the PVE dimer the prevalent reaction of PVE^+.

3.1.3. *Cross additions to conjugated dienes.* The scope of PET cyclobutanations is further extended, in a synthetic sense, by the observation of cross additions to conjugated dienes. Valuable mechanistic insights are also permitted in view of the potential competition between CB and DA cycloadditions. Since the time of the pioneering mechanistic proposal by the Ledwith group (1968), cyclobutanation has been considered to be a stepwise process involving an acyclic 1,4-butanediyl cation radical intermediate. To the extent this proposal is valid, addition to the *s-cis* conformation of a conjugated diene would yield an acyclic intermediate which is capable of cyclizing to both CB and DA adducts. Product development control should then actually favor the DA adduct in the competition.



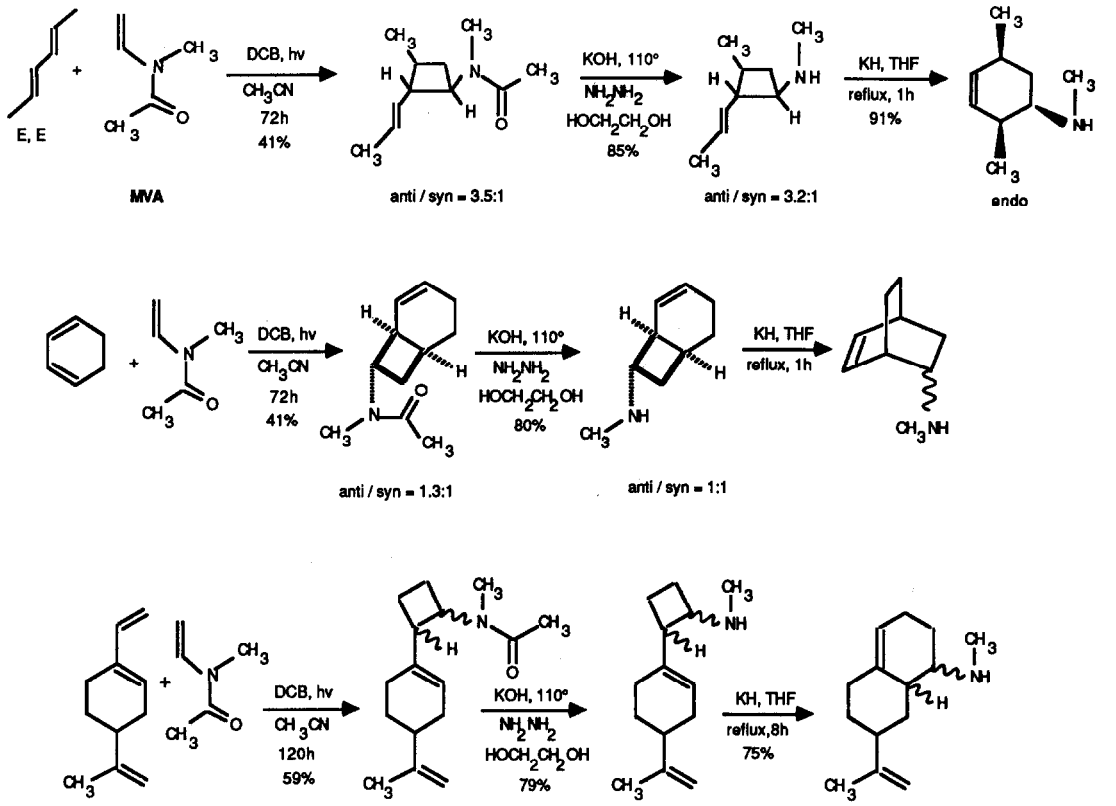
DCP

X =		
NAcMe	100	0
OEt	98	2
OCH_2CH_2Cl	97	3
OPh	82	18
SPh	69	31

Scheme 28.

Consequently, the prediction of the Ledwith mechanism for acyclic dienes which provide at least moderate *s-cis* conformational populations is that quite significant amounts of DA cycloadducts should accompany the CB adducts. The PET cycloadditions of a series of electron rich alkenes (ERA, Scheme 28) to 1,1′-dicyclopentenyl (DCP) qualitatively reflect this expectation.[65] However, the generation of such minute amounts of DA adducts, particularly in the case of ethyl vinyl ether, appears surprising and even anomalous in view of the relatively high *s-cis* content usually attributed to 1,1′-dicyclopentenyl. In terms of the gross mechanism, the role sense DCP^{+}/ERA is strongly indicated by both the relative caticogenicity (favors DCP^{+}; Table 1) and relative caticophilicity (favors the ERA). These reactions are therefore analogous, in a role sense, to the DMI/PVE reaction of Farid.[60] All of the reactions maintain the typical head to head regioselectivity and modest *syn* diastereoselectivity. The tendency for increasingly electron donating substituents to increase CB selectivity is noteworthy, but also does not appear to be in particularly straightforward accord with the acyclic mechanism. The cycloadditions of some of these same ERAs to a rigidly *cis* diene (CHD), as had been noted previously, does afford primarily DA cycloadducts, as would be expected if the Ledwith mechanism were operative here.

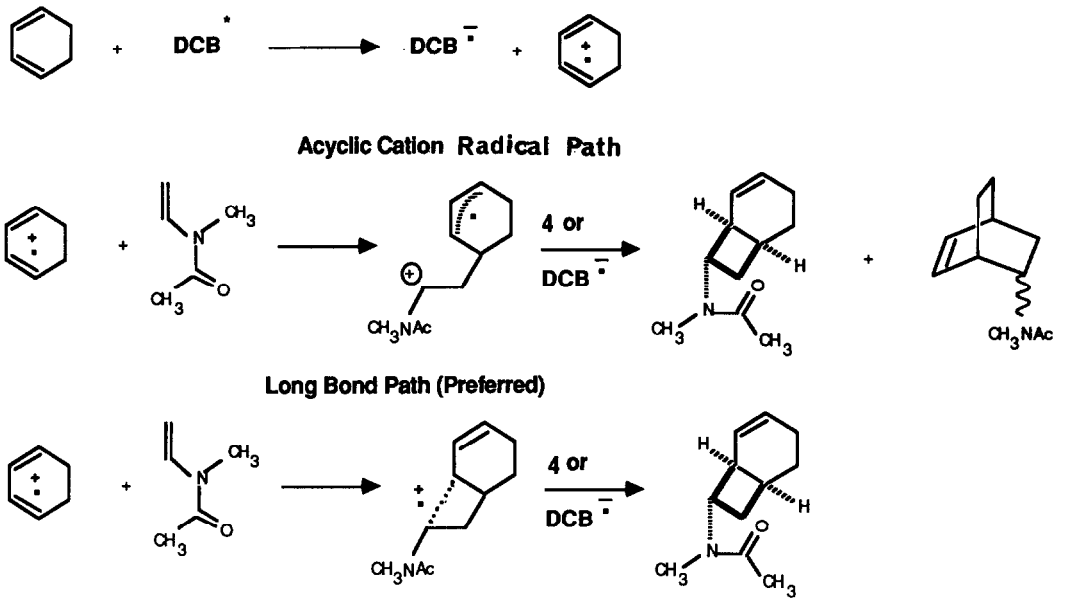
3.1.4. *Cross additions of conjugated dienes to enamides.* As was noted earlier, the efficient cyclodimerization of NVC did not emerge as a general reaction of vinylamines, and cross additions to NVC have still not been observed. In sharp contrast, cross additions to N-vinylamides (i.e., enamides) have recently been observed to be more efficient and general than those of any other subclass of ERAs studied thus far and indeed than to any other known class of cation radical CB cross addition components (Scheme 29).[66] In part, this outstanding versatility and reactivity is the result of the superior caticophilicity of enamides even among ERAs, as established in direct competition experiments. This reactivity order appears plausible in view of the powerful donor qualities of the amide substituent, which is especially effective in stabilizing an adjacent, positively charged site. However, the fact that enamides are typically less caticogenic, or at least no more caticogenic, than most conjugated dienes is equally critical. In the opposite circumstance that the enamide is more caticogenic than the diene, initially formed diene cation radicals are rapidly converted, by diffusion controlled electron transfer, to enamide cation radicals. The superior caticophilicity of the neutral enamide, in this scenario, then assures that the enamide cation radicals engender cyclodimerization rather than cross addition. In general, the circumstance that caticophilicity is relatively more highly developed than caticogenicity in ERAs is responsible for the role selectivity observed in these cycloadditions. It is of incidental interest that even when the diene is less caticogenic than the enamide, or when no diene at all is present, enamide cyclodimerization is not observed in more than



Scheme 29.

trace quantities. It appears likely, therefore, that this cyclodimer is unstable (cycloreversion?) under cation radical conditions.

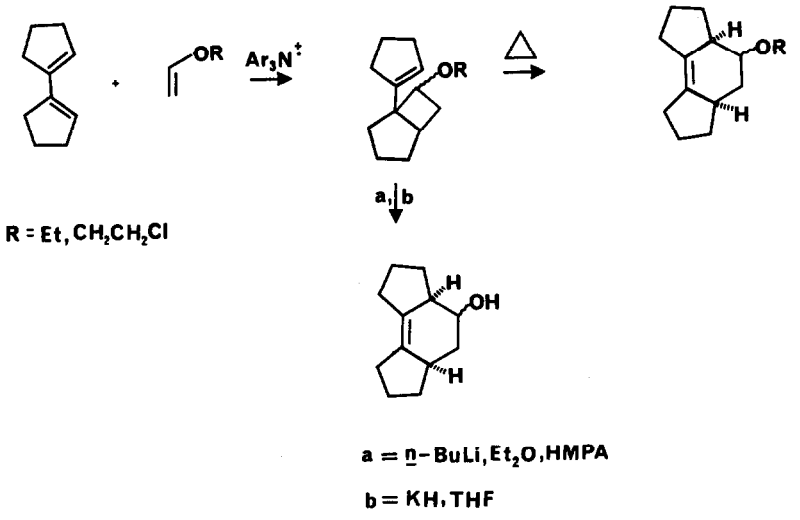
The powerful electron donating ability of the N-amido substituent is apparently also reflected in CB vs DA periselectivity. The cycloaddition of N-methyl-N-vinylacetamide (MVA) to 1,1′-dicyclopentenyl reveals essentially complete CB periselection. As was remarked previously, this is a surprising result if an acyclic 1,4-butanediyl cation radical intermediate is involved. To underscore the validity of this point, the cycloaddition of MVA to 1,3-cyclohexadiene was also investigated and found to occur with 100% cyclobutane periselectivity (Scheme 29). That these PET reactions do not involve closure of acyclic diradical, as opposed to cation radical, intermediates is strongly supported by the observation that the same (CB) products are exclusively formed in the analogous aminium salt initiated reaction. Evidently these cycloadditions are legitimately CB periselective, even where the diene is rigidly *s-cis*. The traditional concept of an acyclic 1,4-butanediyl cation radical appears decisively excluded by these results, at least in the case of these ERAs. On the other hand, all of the results appear compatible with a concerted cyclobutanation mechanism, which is in competition with a typically concerted DA cycloaddition (Scheme 30). The concerted CB addition could produce either an intact cyclobutane cation radical or a so-called 'long bond' cyclobutane cation radical, but the latter is suggested on the basis of theoretical and some experimental results. It appears important to call attention to the fact that the descriptor 'concerted', which is conventionally interpreted to imply that formation of a second bond has at least begun before the first bond is wholly formed, is applicable to the long bond mechanism even though the mechanism may be 'stepwise' (the formation of an intact cyclobutane cation radical may then follow long bond



Scheme 30.

formation). Of course, mechanistic variety is by no means precluded for cyclobutanations in other systems, which may indeed pursue the acyclic cation radical (Ledwith) path or even the concerted formation of an intact cyclobutane cation radical.

In view of the role selectivity sense attributed to these reactions, the competing DA cycloadditions, which are also assumed to be concerted, must be of the [3+2] or role-reversed type. A final aspect of these results with conjugated dienes and ERAs is the correlation between CB periselection and electron donor substituents. In a formal sense, both cyclobutanation (a [2+1] cycloaddition) and ([3+2]) DA addition are symmetry forbidden. Nevertheless, the evidence suggests that both can occur via concerted mechanisms and that both are indeed extraordinarily fast for reactions in the cycloaddition class. For reactions, like these, which are evidently affected but very minimally at most by allowedness/forbiddenness, it is not unreasonable to propose that the necessary pericyclic overlaps might, in fact, be organized more efficiently in cyclobutanation than in cyclohexenation. The addition of carbenes to (even *s-cis*) conjugated dienes, of course, yields vinylcyclopropanes to the exclusion of cyclopentenes. The bridging of a dienic system by a one or two carbon unit appears, in fact, to present significant problems for efficient, synchronized pericyclic overlap and bonding. However, in addition to the relaxation of orbital symmetry constraints and the efficiency of pericyclic overlaps, the consistent increase in CB preference observed for increasingly electron donating groups must be rationalized. The explanation which was originally proposed still appears the most reasonable. Theory strongly suggests that both CB and DA reactions, even if concerted, are highly non-synchronous. They both may therefore be presumed to have substantial allylic cation radicaloid character in their transition states. Presumably much, and in the case of the N-amido substituent most, of the positive charge resides on the carbon to which the donor substituent is attached. Both transition states will therefore be strongly stabilized by such substituents. However, the transition state of any reaction, other than an activationless one, will have at least some product character. For the CB reaction this is long bond character, and this is still highly stabilized by donor substituents. In the DA reaction, the product is a cyclohexene type cation radical, a character which is not stabilized at all by the donor substituents. In effect, the transition state model specifically



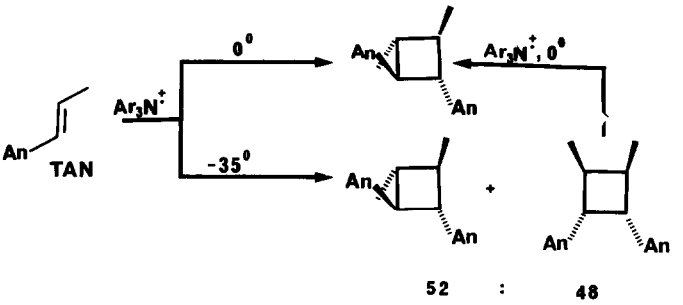
Scheme 31.

depicted above suggests that there is more carbocation character at the carbon bearing the heteroatom substituent in cyclobutanation than in DA addition. Donor substituents therefore prefer the former over the latter.

3.1.5. *An indirect synthetic route for Diels–Alder addition to electron rich alkenes.* Intermolecular DA addition to electron rich alkenes is a potentially valuable synthetic operation which previously has been mechanistically blocked by the exceptionally low cycloaddition reactivity of such dienophiles in the conventional DA reaction. Recently, cation radical DA cycloadditions of ERAs to 1,3-cyclohexadiene have demonstrated a novel solution to this challenging methodological problem for cyclic dienes.[66] However, the CB periselectivity observed in cation radical cycloadditions of ERAs to most acyclic dienes would appear to impose serious practical limitations upon this strategy. Nevertheless, a heteroatom anion assisted vinylcyclobutane (VCB) rearrangement strategy has been found to circumvent this difficulty and to permit efficient, net DA cycloaddition to electron rich alkenes. Both oxyanion (previously precedented, Scheme 31) and aminyl anion (unprecedented) assisted VCB rearrangements have been demonstrated (Scheme 29) and both are observed to be convenient and efficient. The superior facility of cyclobutanation of enamides, however, makes the aminyl anion route especially attractive.

3.2. *Aminium salt initiated cyclobutanation*

3.2.1. *Cyclodimerization.* The observation of initiation of the cation radical DA by triarylaminium salts ($Ar_3N^{\ddagger}$) suggested that cyclobutanation might be subject to similar initiation. The cyclodimerization of *trans*-anethole was the first reported example of aminium salt initiated cyclobutanation (Scheme 32).[67] Interestingly, the PET initiated cyclodimerization of this monomer has not been reported. The cyclodimerization proceeds rapidly and moderately efficiently under the same conditions as developed for the cation radical DA and, under these conditions, yields a single stereoisomer corresponding to head to head regioselection, retention of the *trans* geometry of both anethole units, and exclusive *anti* CB stereoselection. However, at −35°C, the same initiator yields a 52:48 *anti*:*syn* diastereoisomer mixture. At 0°C, the pure *syn* isomer is smoothly converted to the *anti* with intermediate formation of *trans*-anethole. Retrocycloaddition is thus facile with the *syn* isomer at 0°C, but is frozen out at −35°C. Not even traces of *cis*-anethole are formed in this retrocycloaddition, suggesting the cycloreversion may be concerted.



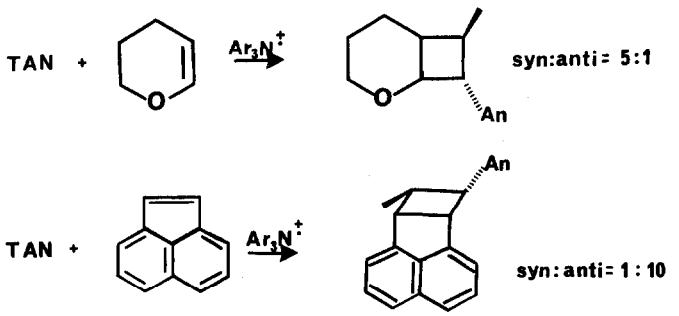
Scheme 32.

The Ledwith mechanism of cyclobutanation, involving an acyclic 1,4-butanediyl cation radical had not previously been subjected to a rigorous stereochemical test, but the aminium salt initiated cyclodimerization of *cis*- and *trans*-anethole provided an excellent opportunity to probe concert via a classic stereochemical test. The cyclodimerization of *cis*-anethole is complicated by a competing *cis*-to-*trans*-anethole isomerization which eventually yields the *trans, anti, trans* dimer derived from *trans*-anethole and also isomers derived from cross addition of *trans* and *cis*-anethole. However, careful kinetic analysis at early times, with extrapolation to zero time, established that none (0.0%) of the thermodynamically most stable *trans, anti, trans* dimer is formed from *cis*-anethole. These observations indicate that the cation radical cyclobutanation of the anethole system is stereospecific and therefore effectively concerted. It was noted that an acyclic (Ledwith type) intermediate could not be rigorously excluded but appeared unlikely in view of the high degree of stereospecificity. One might add that if the Ledwith intermediate were indeed involved, it would appear likely to be formed preferentially in the more stable extended or *s-trans* form, which should almost certainly have more than ample opportunity to undergo appropriate stereorandomizing torsional motions prior to conversion to the gauche conformer necessary for cyclization. Whether even this gauche conformer would be likely to undergo cyclization a minimum of 20 times as rapidly as torsional randomization appears questionable. Further, the selective formation of the gauche or other *s*-cisoid conformation would seem to imply at least some incipient bonding between the termini and thus to suggest a quasi cyclic structure for the intermediate. *Ab initio* SCF MO reaction path calculations (*vide infra*)[68] suggest the possibility that the intermediate may actually be a long bond cyclobutane cation radical, analogous to the long bond *cis*- and *trans*-1,2-diphenylcyclopropane cation radicals established by Roth and Mannion.[69] The long bond, in these latter cases, has been shown capable of maintaining stereochemical integrity.

These conclusions are in excellent accord with those reached on the basis of the CB periselectivity observed in the cross additions of enamides to conjugated dienes, especially 1,3-cyclohexadiene. The intervention of purely acyclic 1,4-butanediyl cation radical intermediates in different chemical systems or under different conditions (solvent, counterion, temperature,...) is not precluded nor even rendered unlikely, but the presence of a viable, concerted mechanistic path appears clearly established.

3.2.2. *Cross additions.* Aminium salt initiated cross additions of *trans*-anethole to dihydropyran and acenaphthene have also been observed (Scheme 33).[67] Further, the cycloadditions of a series of ERAs to 1,1-dicyclopentenyl and 1,3-cyclohexadiene, discussed in the previous section on PET initiated cyclobutanation (3.1) have been carried out under aminium salt conditions and closely analogous results obtained. Enamide cycloadditions to conjugated dienes have also been noted to occur in like fashion to the PET initiated reactions.

3.2.3. *Kinetic studies and mechanistic diagnosis.* A detailed kinetic study of the aminium salt initiated cyclodimerization of *trans*-anethole (TAN) has been carried out and strongly supports a



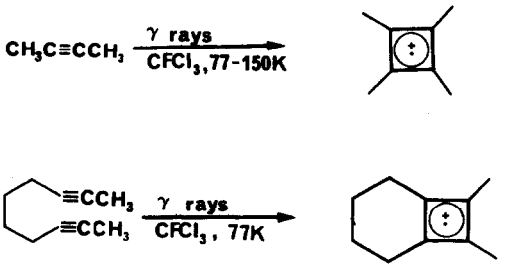
Scheme 33.

cation radical chain mechanism.[49] In this case, the rate law $R = k_{app}[TAN]^2[Ar_3N^{+\cdot}]$ requires termination by unimolecular decay of the $TAN^{+\cdot}$, presumably a deprotonation reaction. Strong rate depression by added neutral Ar_3N: again supports a free cation radical mechanism, as opposed to one involving cycloaddition of neutral TAN with an $Ar_3N^{+\cdot}$/TAN complex.[49] The yield in the reaction, as run under synthetic conditions, is enhanced from 45% under conventional aminium salt conditions, to 75% in the presence of a hindered amine (DTBP), thus eliminating a Brønsted acid catalyzed reaction mechanism.[35] Furthermore, in the presence of triflic acid in dichloromethane at 0°C, no cyclodimers of *t*-anethole are formed at any acid concentrations or reaction times.[35]

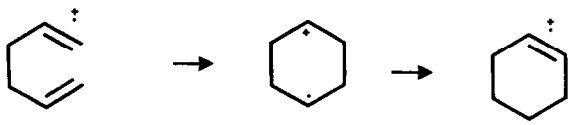
The first activation parameters for a cation radical cyclobutanation reaction were obtained in a detailed temperature dependence study of the *t*-anethole cyclodimerization.[49] The apparent activation parameters are $\Delta H^{\ddagger}_{app} = 2.14$ kcal mol^{-1} and $\Delta S^{\ddagger}_{app} = -29.85$ e.u. Using cyclic voltammetric measurements of the oxidation potentials of *t*-anethole (1.11 V) and Ar_3N(1.05 V) and assuming $\Delta H^{\ddagger} = 0$ for exothermic electron transfer steps, the activation enthalpy $\Delta H^{\ddagger}_{p} = 0.76$ kcal mol^{-1} is obtained for the cycloaddition step. Thus, even in solution, cation radical cycloadditions can (and usually do) proceed with very minimal activation energy requirements. It is especially interesting to find an activation energy of this magnitude for a formally 'forbidden' pericyclic reaction. The unusual ability of hole formation to relieve symmetry constraints is especially evident in cyclobutanation, where the activation energies for thermal (neutral) cycloaddition can be as high as 62.5 kcal mol^{-1} (dimerization of ethene).

3.3. *Mass spectrometric studies of cyclobutanation*

Cation radical/neutral cycloadditions of both the CB and DA type have been studied extensively by Gross, using tandem mass spectrometry (MS/MS) and Fourier transform mass spectrometry (FT/MS).[70,71] The addition of the styrene cation radical to neutral styrene, for example, yields an adduct which has been considered to have an acyclic, Ledwith type structure.[71] Although both *cis*- and *trans*-1,2-diphenylcyclobutane also yield this same species upon ionization (as indicated by CAD spectra), the possibility that the adduct cation radical might have an intact cyclobutane structure was considered to be ruled out by the fact that the acyclic adduct cation radical was estimated to be at least 8 kcal mol^{-1} more stable than the intact cyclobutane cation radical, using a thermochemical estimate. These results do not, however, appear to distinguish the purely acyclic cation radical from a possible long bond cyclobutane structure. In addition, the finding[71] that the styrene cycloaddition is essentially activationless is quite significant and is in excellent agreement with theory (*vide infra*). Additional examples of MS studies of cation radical/neutral cycloadditions which may involve initial cyclobutanation but which ultimately yield DA adducts are discussed in the following section on vinylcyclobutane rearrangements.



Scheme 34.



Scheme 35.

3.4. *Cyclobutanation in solid matrices*

The cyclodimerization of 2-butyne to the 1,2,3,4-tetramethyl-1,3-cyclobutadiene cation radical, an interesting example of cation radical cyclobutanation in the alkyne series, has been observed directly by ESR spectroscopy in the solid phase.[72] For example, γ-irradiation of 2-butyne in $CFCl_3$ at 77 K, followed by annealing up to 150 K produces the ESR spectrum of the indicated cation radical (Scheme 34). The 2-butyne cation radical spectrum is poorly defined, but its presence at 77 K is strongly suggested both by the typical cation radical generating reaction conditions and the subsequent facile cycloaddition at 150 K. An intramolecular version of the reaction, using 2,8-decadiyne (Scheme 34) actually proceeds at 77 K, revealing a cycloaddition of incredibly low activation energy.[72]

The cyclodimerization of simple alkenes appears more formidable than of alkynes, perhaps because the latter reaction yields a resonance-stabilized cation radical. The intramolecular reaction of the 1,5-hexadiene cation radical to give the 1,4-cyclohexanediyl cation radical (Scheme 35) has been observed recently, but ring strain in the potential cyclobutane adduct (bicyclo[2.2.0]hexane) apparently precludes cycloaddition. Instead, 1,3-hydrogen shift occurs, giving the cyclohexene cation radical.[73]

3.5. *Heterogeneous cyclobutanation*

The cyclodimerization of *trans*-anethole on zeolite surfaces has been observed and is thought to be a cation radical reaction. The monomer is refluxed in DCM solution containing 13 × (wide pore) molecular sieves for 48 h, producing a 25% yield of the familiar *trans, anti, trans* head to head cyclodimer.[53]

4. THE VINYLCYCLOBUTANE AND RELATED REARRANGEMENTS/CYCLOPROPANATION

4.1. *Introduction*

Although the primary theme of the present review is cation radical cycloadditions, a major underlying purpose is to present these reactions as viable and, in fact, highly effective procedures in a synthetic context. Accordingly, it was shown in a previous section that the heteroatom (N and O) anion assisted vinylcyclobutane rearrangement provided an efficient synthetic link between cation

radical cyclobutanation adducts of conjugated dienes/electron rich alkenes and their corresponding formal DA adducts. The result is an attractive strategy for net DA addition to electron rich alkenes (ERAs) which is based upon a cation radical cycloaddition strategy. Recent research has revealed a substantial range of highly efficient *cation radical* VCB rearrangements which provide an alternative and wholly cation radical-based synthetic strategy for accomplishing net DA addition to ERAs. These studies also reveal that the three processes, CB and DA addition and VCB rearrangement, are so intimately linked mechanistically as to make discussion of cycloaddition grossly incomplete without some simultaneous consideration of the cation radical VCB rearrangement.

4.2. *Historical precedents*

Relatively few observations of [1,3] sigmatropic shifts of carbon–carbon bonds of ground state cation radicals have been reported and apparently none of these have been considered to be true pericyclic (i.e., concerted) processes.[74] A particularly explicit example is available in the general category of what might be termed the 'phenylcyclopropane' rearrangement. The PET induced rearrangement of 3-phenylcyclopropenes to indenes (Scheme 36) was considered a stepwise process involving cleavage of the phenylcyclopropene cation radical to a carbene cation radical, followed by cyclization of the latter functionality to the *ortho* position of the phenyl ring.[75] A rather substantial number of analogous 'phenylcyclobutane' rearrangements (to hydronaphthalenes) have also been reported (Scheme 37, e.g.).[76] More recently, CIDNP studies of an actual PET induced vinylcyclobutane rearrangement have been reported (Scheme 38) and also interpreted in terms of a stepwise mechanism.[77]

Scheme 36.

Scheme 37.

Scheme 38.

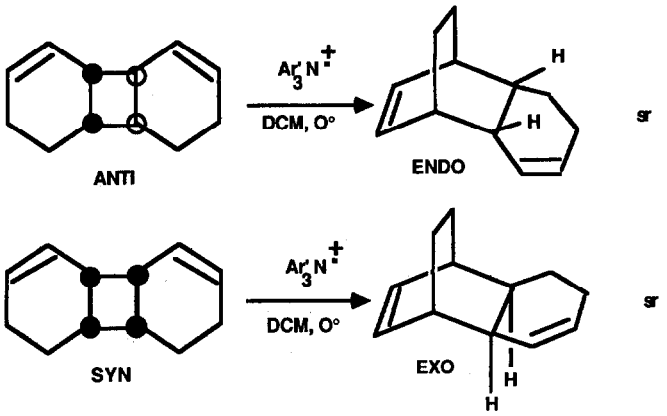
4.3. *Aminium salt initiated rearrangements of hydrocarbons*

The DA periselectivity observed in diene/diene cycloadditions (Section 2) is interesting in view of the demonstrable facility of cation radical cyclobutanation and especially of the pronounced

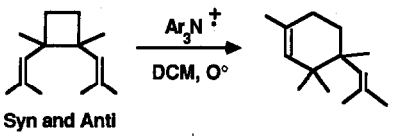
CB periselectivity observed in diene/enamide cycloadditions, even where the diene is rigidly *s-cis*. Specifically, if the cation radical VCB rearrangement is a generally facile reaction, the possibility must be considered that DA addition occurs indirectly, via a selective cyclobutanation/VCB rearrangement path. This possibility has been investigated in two ways.

The familiar (20 : 60) *syn*, *anti* mixture of the CB dimers of 1,3-cyclohexadiene was prepared by fluorenone triplet photosensitized cyclodimerization.[78] The mixture also contained 20% of the *exo* DA cyclodimer. This (predominantly CB) cyclodimer mixture was subjected to the standard aminium salt conditions. The starting cyclodimer mixture was recovered, unchanged. This experiment shows conclusively that neither of the CB dimers, once neutralized by electron capture, would be rearranged to the DA dimer under the standard aminium salt conditions. Thus, the neutral cyclobutane dimers are not intermediates in the DA cyclodimerization. The possibility that the cation radicals of the CB dimers are involved as intermediates but that these rearrange to DA adduct cation radicals more rapidly than they are neutralized by electron acceptance is more difficult to exclude. Since this electron transfer is undoubtedly diffusion controlled, the rate constant for the VCB rearrangement would have to be at least 10^{10}. Further, since no more than 2% of the CB adducts are formed in the cyclodimerization, the rate constant would necessarily be at least 5×10^{11}. Since the VCB rearrangement is intramolecular, and because cation radical processes are often so facile, it would be unwise to exclude the possibility of such a fast reaction *a priori*. An independent probe for neutral CB dimer intermediates has also been implemented, viz. examination of the cycloaddition products of 1,3-cyclohexadiene at very early times corresponding to rather minute conversions (often $<1\%$). In the aminium salt procedure, implemented at either 0°C or −30°C, the DA : CB product ratio (98 : 2) is unchanged from the very earliest time at which products are detectable by GC/MS ($\ll 1\%$ conversion) to the completion of the reaction (70% conversion). Further, the cycloadduct composition is invariant over a ten-fold range of initial diene concentrations, up to 5 M. These results not only confirm the conclusion that the neutral CB dimers are not intermediates on the path to the DA dimers, but the formation of a constant fraction of CB adducts which is independent of the extent of the reaction or the concentration of single electron donor (diene) confirms the presence of a cyclobutadimerization route which is independent of the rate of electron transfer quenching. Unless two discrete cyclobutanation pathways exist, the former observation decisively demonstrates that electron transfer quenching of CB cation radicals is faster than their VCB rearrangement under all conditions investigated and that DA addition cannot occur via this path. Similar results have been observed in the aminium salt initiated cyclodimerizations of 1,1′-dicyclopentenyl and 2,4-dimethyl-1,3-pentadiene (the latter in the presence of a hindered base). Finally, *ab initio* SCF MO reaction path calculations on the prototype VCB cation radical rearrangement (MP2/6-31G*//3-21G) reveal an activation energy of 9.5 kcal mol^{-1}, a value which appears much too large to be consistent with a process faster than exothermic electron transfer (i.e., diffusion control).[79]

The large difference in the oxidation potentials of Ar_3N: (1.05 V vs S.C.E.) and the CB adducts (believed to be >2.0 V) suggests that the failure to observe the VCB rearrangement at all in this system is perhaps the result of the inability of the aminium salt to generate the required VCB cation radicals. Indeed, when the more powerfully ionizing aminium salt *tris* (2,4-dibromophenyl)aminium hexachloroantimonate (Ar_3N^{+}; $E_{1/2} = 1.47$ vs S.C.E.) is employed, the rearrangement of the CB to DA adducts is quite smooth (0°C, 10 min, Scheme 39). Rearrangement of the *syn*-CB isomer selectively produces the *exo*-DA adduct, and the *anti*-CB adduct yields the *endo*-DA adduct, in *sr* (suprafacial/retention) stereospecific reactions.[80] The intramolecularity of the rearrangement is thus demonstrated, since retrocyclobutanation to cyclohexadiene coupled with DA addition should give the familiar 4.5 : 1 ratio of *endo* : *exo* DA adducts. The *syn* → *exo* result is thus particularly decisive. The stereochemical (*sr*) results are less informative in the present system than would normally be the case in, e.g., an acyclic system, since neither antarafaciality nor inversion are geometrically feasible in these cyclic systems. Consequently, a stepwise mechanism can not be ruled out on the



Scheme 39.



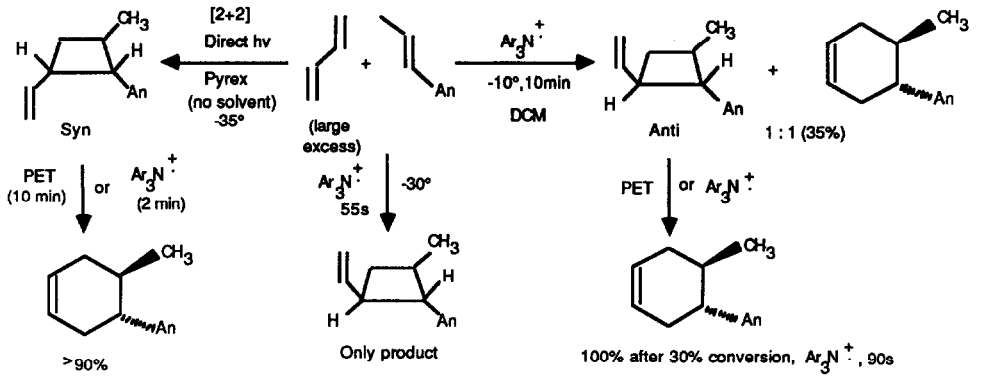
Scheme 40.

basis of the *sr* stereospecificity. The possibility of a Brønsted acid catalyzed rearrangement is, however, ruled out on the basis of the DTBP (hindered base) criterion.

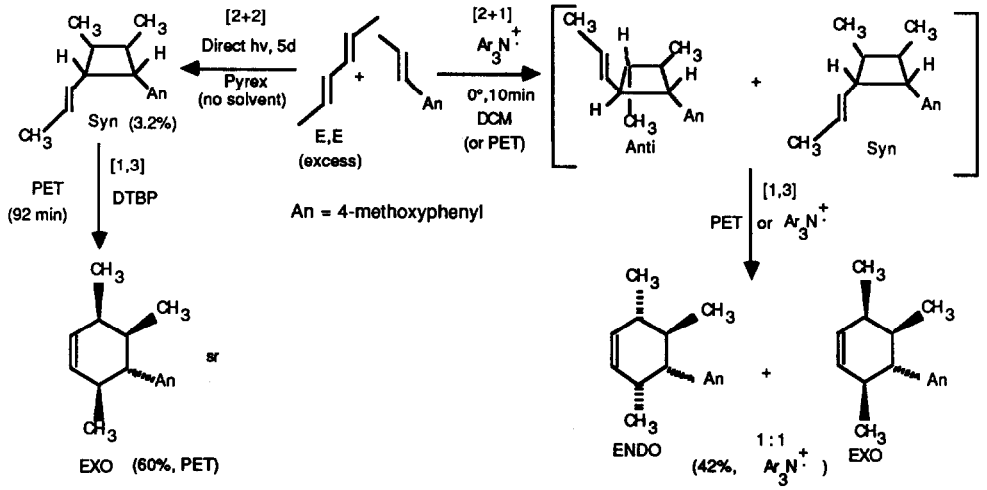
The VCB rearrangement of a pair of CB dimers of a second hydrocarbon diene, 2,4-dimethyl-1,3-pentadiene (DMP), has also been observed. The mixture of *syn*:*anti* dimers of DMP (also containing DA dimers) derived from the fluorenone sensitized photocyclodimerization of DMP (Scheme 40) rearranges essentially quantitatively (at least at low to moderate conversions) even using the milder aminium salt (Ar_3N^{+}).[80] The DA adduct formed is actually constitutionally isomeric with that formed in the aminium salt initiated cyclodimerization of DMP (earlier shown to be a Brønsted acid catalyzed reaction). Retrocyclobutanation/DA addition is therefore again excluded.

4.4. *VCB rearrangements of 2-anisylvinylcyclobutanes*

As might be expected, the presence of a *p*-anisyl group at the 2-position of a VCB greatly facilitates ionization to the VCB cation radical and makes feasible initiation via the milder aminium salt conditions and by PET. The *syn* and *anti* isomers of Scheme 41 were prepared by two distinct routes, involving direct photoaddition of 1,3-butadiene and *E*-anethole via the exciplex (*syn*) and cation radical cycloaddition (aminium salt initiation; *anti*) of these same two components.[81] Rearrangement of both isomers to the same DA adduct does indeed occur smoothly under either PET or aminium salt conditions. Added 2,6-DTBP has no effect on the results, but added *E*-anethole strongly suppresses the reaction rate. The yield of DA adducts under PET conditions is quantitative (GC) up to at least 70% conversion, which is attained in only 10 minutes of irradiation. Quantum yields have not been measured, but the extremely short irradiation time strongly suggests a rather efficient chain process. The mechanistic possibility of retrocyclobutanation/DA addition was investigated once more by trapping experiments involving the inclusion of a large (800 mol %) excess of 2,3-dimethyl-1,3-butadiene (DMB) in the reaction mixture. The VCB rearrangement occurs normally and, despite the considerably greater reactivity of the trapping diene than 1,3-butadiene



Scheme 41.



Scheme 42.

toward the *E*-anethole cation radical (at least 3 : 1), only slight traces of the *E*-anethole/DMB cycloadducts are formed. Even these minute amounts appear to derive from traces of *E*-anethole present in the VCB substrates (cf. method of preparation).

As has been noted previously, the traditional viewpoint concerning cation radical pericyclic reactions has regarded them as stepwise processes. Early work on [1,3] shifts has not departed from this tradition. In order to probe the stereochemistry of a cation radical VCB rearrangement, the *syn* CB cycloadduct of *E*-anethole and *E,E*-2,4-hexadiene (Scheme 42) was synthesized via direct (exciplex) photoaddition. The rearrangement of this VCB under PET conditions is also extremely efficient; the yield is quantitative up to 85% conversion, which is achieved in only 30 minutes of irradiation. The intramolecular character of the rearrangement is again decisively demonstrated by *in situ* trapping experiments. In this case the dienic trap of choice is *E*-1,3-pentadiene, which is 13 times as reactive as *E,E*-2,4-hexadiene toward the *E*-anethole cation radical. The cation radical nature of the reaction is demonstrated by the failure of hindered base to quench the reaction and by the strong rate retardation of the rearrangement by added *E*-anethole. The selective production of the '*exo*' DA adduct again reveals an *sr* stereochemical course, but this time in a system where

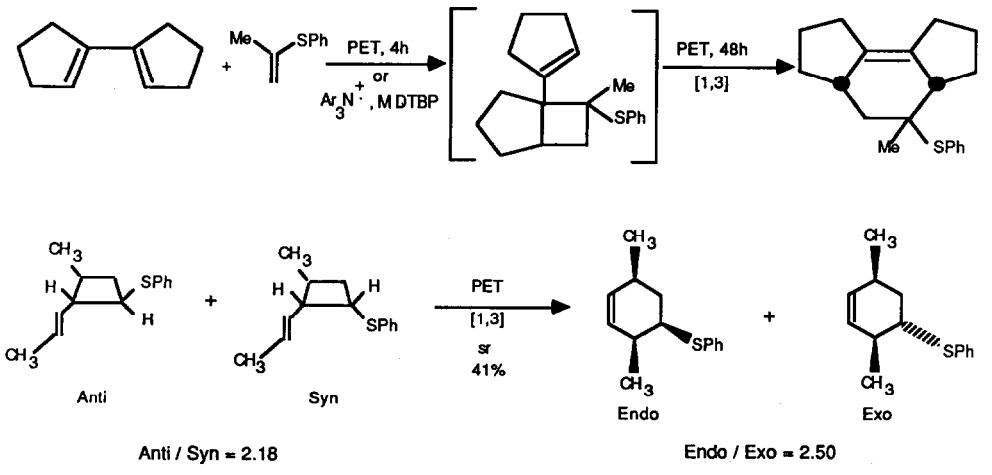
the intervention of a purely acyclic cation radical intermediate could potentially permit realization of all four stereochemical modes (*sr*, *si*, *ar*, *ai*) at least to some degree. None of the products corresponding to reaction modes other than *sr* are found in significant amounts. Consequently, the reaction appears to be best characterized as concerted (*sr*).

The corresponding anti-VCB would ordinarily be accessed synthetically via the cation radical cycloaddition route, but it proved inaccessible in this instance because of an incredibly rapid VCB rearrangement under the cation radical conditions. Thus, in either the PET or aminium salt catalyzed cross cycloadditions of *E*-anethole and *E,E*-2,4-hexadiene (Scheme 42), GC/MS investigation of the product composition at very short times (on a synthetic time scale) reveals that the DA adducts ultimately isolated (*endo*:*exo* = 1:1) are not the initial products, but that they result from VCB rearrangement of the *syn* and *anti*-VCB isomers discussed previously. Since, the *syn*-VCB isomer is known to yield exclusively the *exo*-DA adduct, it is apparent that the *anti*-VCB must certainly yield at least primarily the *endo* adduct. The reactions are thus stereospecifically *sr*. It is again important to note that a purely acyclic intermediate should be able to cyclize to give a variety of DA stereoisomers in addition to these two (*endo* and *exo*) DA adducts. Consequently, it again appears warranted to classify these reactions as concerted.

4.5. *VCB rearrangement of 2-phenylthiocyclobutanes*

Second only to the *p*-anisyl group in promoting the cation radical VCB rearrangements observed thus far is the phenylthio substituent. In the addition of phenyl propenyl sulfide to 1,1′-dicyclopentenyl (Scheme 43), CB adducts are again detected as the sole primary products at very short reaction times and low conversions. Very quickly, these primary products give way to the DA adducts, which are eventually the only products detectable or isolable. The extreme rapidity of the rearrangement, however, again precludes isolation of the CB adducts; thus, independent study of their VCB rearrangement was not feasible.

The CB adducts of phenyl vinyl sulfide (PVS) and *E,E*-2,4-hexadiene are, however, readily available from cation radical cycloaddition (PET). Rearrangement of the 2.5:1 *anti*, *syn* mixture occurs smoothly under PET conditions (78% conversion in 20 min), producing a 2.3:1 *endo*:*exo* DA adduct mixture (Scheme 43). While not wholly conclusive, these results are at least consistent with a preferred *sr* VCB rearrangement of the predominant (*anti*) isomer. Again, intramolecularity and a cation radical mechanism are established by appropriate control experiments.



Scheme 43.

4.6. *VCB rearrangement of 2-phenoxyvinylcyclobutanes*

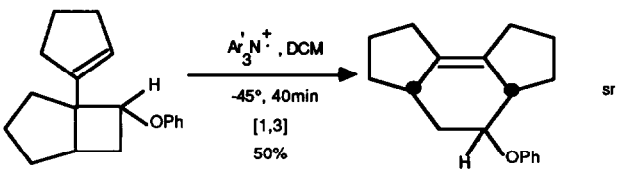
The cation radical cycloaddition of 1,1′-dicyclopentenyl and phenyl vinyl ether (PVE) has previously been shown to yield mainly (82%) CB adducts, with the *syn* CB predominating (2:1). The cation radical VCB rearrangement of these CBs apparently requires $Ar'_3N^+/-45°C$ to achieve efficient conversion (69% yield) to the DA adduct, which is predominantly (2:1) the '*exo*' adduct (Scheme 44). Although this result *per se* does not rigorously establish *sr* stereospecificity, the combination of the *syn* → *endo* preference observed in this reaction and the *anti* → *endo* preference observed in the case of the PVS/*E*,*E*-2,4-hexadiene CB adduct system mounts a more compelling argument for at least modest *sr* stereoselectivity for at least the major isomer in each of these systems. Thus, stereochemical results for six different molecules in four systems uniformly exhibit *sr* stereoselectivity, and in two of these systems (cyclohexadiene; *E*-anethole/*E*,*E*-2,4-hexadiene) stereospecificity is found. In no case has evidence for a purely acyclic cation radical emerged. In all cases save one (the last case discussed) appropriate trapping experiments establish the intramolecularity of the VCB rearrangements.

All of the aforementioned VCB rearrangements are strongly quenched by the addition of the more ionizable addend (e.g. *E*-anethole, PVS, or 1,1′-dicyclopentenyl), thus further affirming the cation radical nature of the transformation and also clarifying the circumstance that they occur under essentially the same conditions (PET or aminium salt) used to synthesize some of these vinylcyclobutanes. Isolation and purification of the latter is thus usually an essential prerequisite for successful VCB rearrangement. Two pertinent exceptions have been noted, however, where the VCB rearrangements are so facile that not only is isolation of the VCB not required for rearrangement, but such isolation becomes extremely difficult because of the rapidity of the rearrangement. The phenomenal ability of the *p*-anisyl group to promote the VCB rearrangement warrants further study.

Attempted VCB rearrangements in systems where the electron donor group is an N-amido or ethoxy substituent have not proved successful. The implication appears to be that anisyl, phenylthio, and phenoxy groups provide suitably ionizable sites, but that, not unexpectedly, N-amido and ethoxy are insufficiently caticogenic to support the reaction.

4.7. *Stereochemistry of the VCB rearrangement*

Using a straightforward application of Woodward and Hoffman's 'HOMO RULE', it has been predicted that [1,3]sigmatropic shifts of ground state cation radicals (if concerted) should occur preferentially with *si* (suprafacial/inversion) or *ar* (antarafacial/retention) stereochemistry.[82] Orbital correlation diagram analysis of sigmatropic shifts is, of course, precluded by the failure of (even a simplified model of) the reactant and product to share a common symmetry element. However, a modified aromaticity/antiaromaticity approach to evaluating relative transition state stability is available.[83] Thus, the *sr* and *ai* transition states both have a pericyclic array in the transition state which is modeled by a Huckel cyclobutadiene cation radical. The *si* and *ar* transition states are both modeled by a Mobius cyclobutadiene cation radical. Neither transition state model is aromatic, but

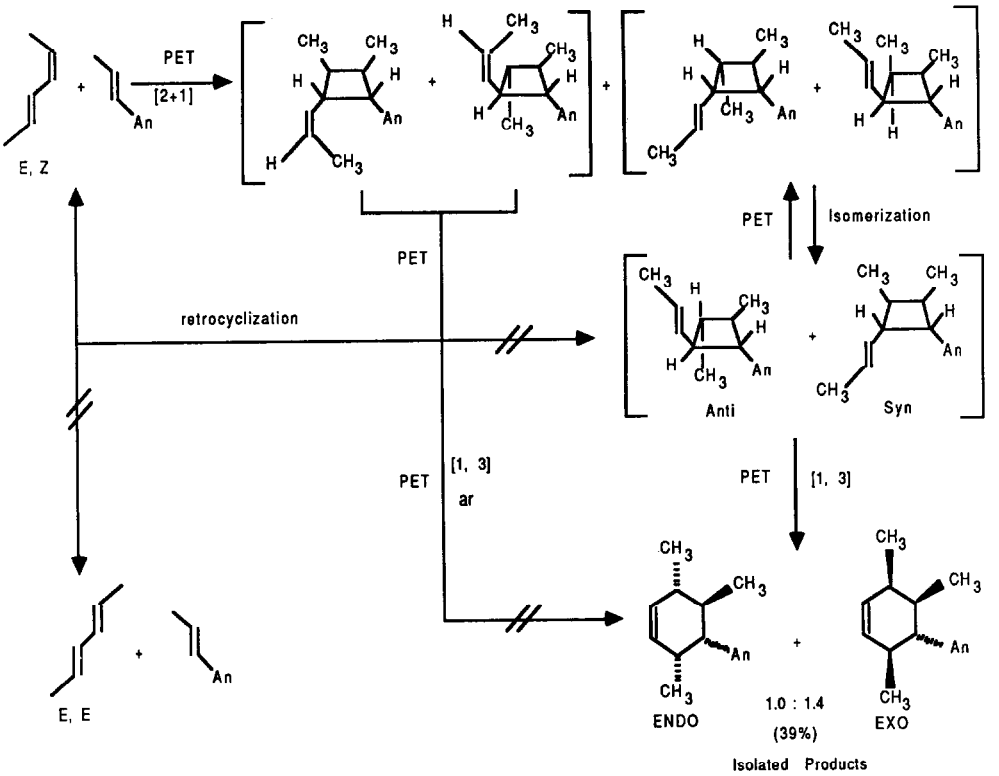


Scheme 44.

the Mobius model is 0.28β more stable than the Huckel model, in the HMO approximation. In the 'Idealized Pericyclic Array' model just considered, the *si/ar* modes should be slightly favored over the *sr/ai* modes. The predicted preference is considered very slight because the energy difference between the two model pericyclic arrays is just about an order of magnitude less than that found in typical neutral systems where aromaticity/antiaromaticity distinctions are sharply drawn. Indeed, even in such neutral systems [1,3] shifts do not display a strong preference for the aromatic pericyclic array. An excellent analogue for the cation radical VCB rearrangement is available in the [2+1] cation radical cyclobutanation reaction. The idealized pericyclic arrays for this reaction are again the Huckel and Mobius versions of the cyclobutadiene cation radical, and the Mobius version (*sa* cycloaddition) should be slightly preferred. However, exactly as in the VCB rearrangement case, the *ss* mode is actually observed. The inevitable conclusion appears to be that idealized pericyclic arrays in cation radical transition states are rarely sufficiently distinguished in terms of energy to be the dominant factor in determining reaction stereochemistry. It appears logical to assume that, rather, it is the quantitative efficiency of overlap in the pericyclic array, as determined by orbital overlap, rather than the qualitative nature of the cyclic array, which is the primary determinant of reaction stereochemistry. In essence, if incorporating an antarafacial (or invertive) element in the context of the actual geometry of the transition state diminishes overlap efficiency, this negative factor may prevail over the gain in inherent stability of the idealized pericyclic array. Steric factors may also exert a dominant effect in some instances (*vide infra*).

4.8. *A transition state model for the VCB rearrangement*

The cycloaddition of *E*-anethole to *E,E*-2,4-hexadiene occurs with *ss* (doubly suprafacial) stereochemistry, and the ensuing VCB rearrangement occurs with an *sr* stereochemical outcome. Consequently, the net (indirect) Diels–Alder addition occurs with the same net stereochemical outcome (*ss*) as would be expected for the direct DA addition of these two components and as has been observed experimentally in an authentic, direct cation radical DA addition. The possibility that the transition state for the cation radical VCB rearrangement may be similar to that in the DA cycloaddition in more respects than just stereochemistry is an intriguing one. A further group of observations suggests that the proposal to use DA transition states as a model for VCB transition states has at least some validity. The analogous cycloaddition of *E*-anethole to *E,Z*-2,4-hexadiene is also found to proceed via CB adducts (Scheme 45). Ultimately, however, DA products are once more produced, and these are the same *endo* isomer as produced from *E,E*-2,4-hexadiene and its corresponding *exo* epimer. Thus the net DA cycloaddition has an overall $[\pi 4_a + \pi 2_s]$ outcome, in contrast to all of the earlier results. Closer scrutiny of the CB adducts at early times, however, reveals, in addition to a unique set of CB adducts produced from *E,Z*-2,4-hexadiene, the two CB adducts derived from *E,E*-2,4-hexadiene. Apparently, these latter isomers are formed from the primary CB adducts by *cis* → *trans* isomerization. The two DA adducts are by no means the most thermodynamically stable DA stereoisomers of the system, and it therefore appears highly unlikely that a common, purely acyclic cation radical could selectively produce these two adducts. Furthermore, the *syn* → *exo* and *anti* → *endo* stereochemical outcome of the VCB rearrangement of the *E*-anethole/*E,E*-2,4-hexadiene adducts suggests a concerted path for those rearrangements. It is therefore concluded that the primary CB adducts produced from the *E,Z* diene have difficulty undergoing the VCB rearrangement and instead establish an equilibrium with the two adducts derived from the *E,E* diene, which then undergo the VCB rearrangement very rapidly. This postulate is nicely consistent with the transition state model proposed above for the VCB rearrangement. It is well known that direct DA addition to an *E,Z* diene is extremely slow. Although cyclobutanation of such a diene is feasible on either double bond, a subsequent VCB rearrangement will experience the same steric repulsion in its transition state as are present in the DA transition state. In the case of addition to the E double bond, the troublesome element is the *Z*-methyl substituent on the propenyl group, which is analogous to a *Z* terminal group on an *E,Z* diene in the direct DA (Scheme 46). In

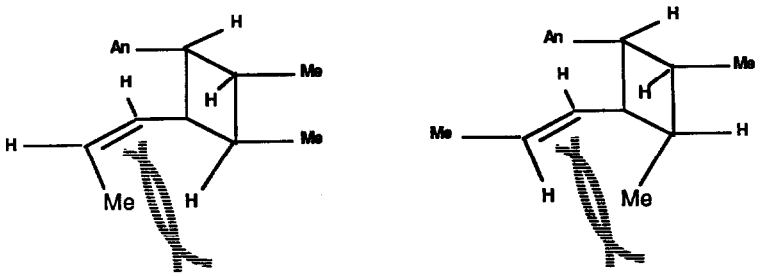


Scheme 45.

the case of addition to the *Z*-double bond, the troublesome element is the methyl group on the cyclobutane ring and *cis* to the propenyl function. Though less obvious, this structural feature also becomes analogous, in the VCB rearrangement transition state, to a *Z*-terminal group on the diene in the direct DA (Scheme 46). It is noted that rearrangement of the *E,Z* diene to the *E,E* diene does not occur during the reaction.

4.9. *The indirect cation radical Diels–Alder*

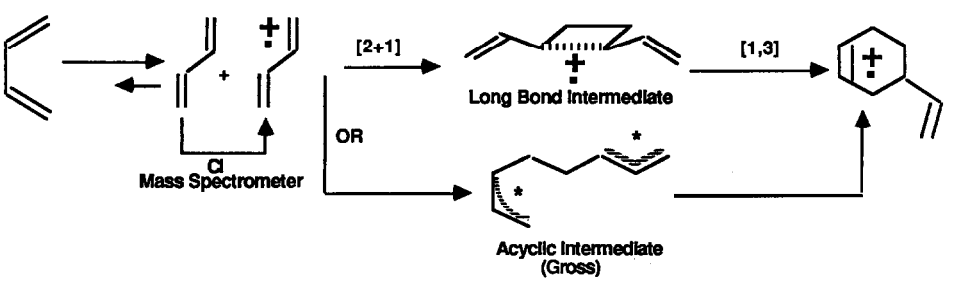
As noted previously, the tremendous facility of many VCB rearrangements naturally raises the question of whether some cation radical reactions which are DA cycloadditions in a synthetic sense



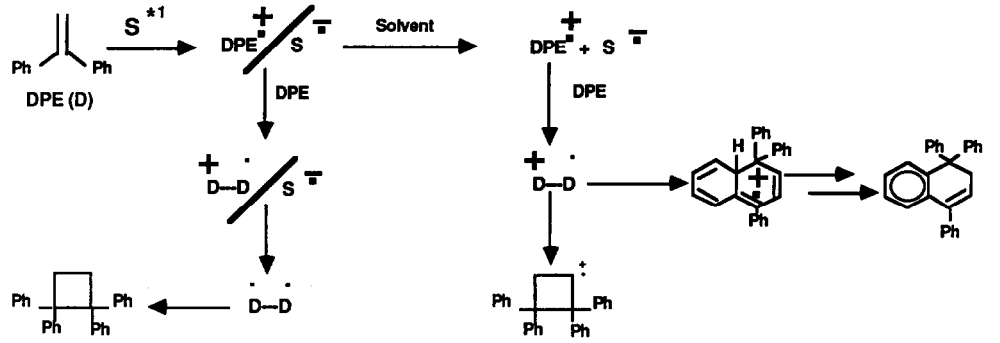
Scheme 46.

may occur via a cyclobutanation/VCB rearrangement route mechanistically. Examples of such indirect DA cycloadditions from the author's work has already been discussed in this section. Two additional classic examples of apparent cation radical DA cycloadditions which could, subject to definitive mechanistic test, be mechanistically indirect are discussed in this section.

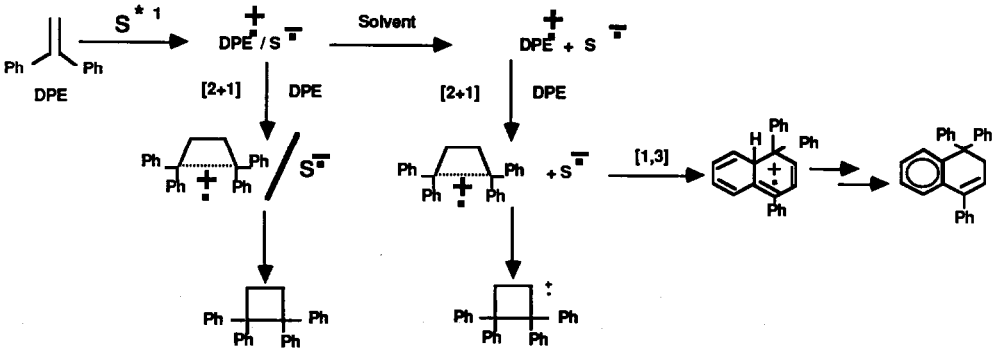
Classic vapor phase studies of cation radical/neutral cycloadditions have been carried out by Gross and collaborators, using MS/MS techniques. The cyclodimerization of styrene has already been discussed in Section 3. This basic cyclobutanation study and analogous studies on the cation radical DA cycloaddition confirm the inherent tendency of cation radicals to undergo cycloaddition to neutrals, and they also establish vanishingly low activation energies for these reactions. In the DA addition of the 1,3-butadiene cation radical to methyl vinyl ethers, it was also observed that, when butadiene is the ionized component, electron transfer from the more caticogenic enol ether to the diene cation radical occurs prior to cycloaddition.[84] The subsequent reaction of the methyl vinyl ether cation radical with neutral 1,3-butadiene gives the DA adduct (4-methoxycyclohexene) cation radical. Similarly, the reaction of the 1,3-butadiene cation radical with neutral 1,3-butadiene yields the 4-vinylcyclohexene cation radical.[85] The mechanism of both of these reactions was investigated by the expedient of collisional stabilization of intermediates and study of their collisionally activated decomposition (CAD) spectra. In both cases intermediates were detected, the CAD spectra of which were clearly distinguished from those of the respective DA adducts. The intermediates were considered, on the basis of model studies, to be acyclic and the conclusion was drawn that these cation radical DA cycloadditions are not concerted, as had earlier been suggested, but stepwise. In fact, both of these reactions are viewed here as indirect DA additions, from which circumstance they draw their stepwise nature. This conclusion follows from the fact that 1,3-butadiene exists principally (probably >98%) in the *s-trans* conformation, and the conformation must be the direct precursor of the great preponderance of the molecular ions. Diene cation radicals are known to have rather large barriers to rotation around C_2–C_3, so that equilibration with the *s-cis* diene cation radical is readily excluded.[86] Cycloadditions of cation radicals to neutrals (both CB and DA) are known to have extremely low activation barriers (a fact also confirmed in the works being discussed), so that unselective reaction with the preponderantly *s-trans* diene population is expected. Therefore, since direct DA addition to an *s-trans* diene component is geometrically precluded, the initial cycloaddition must almost certainly be a cyclobutanation (or a linear addition, *vide infra*). The ultimate formation of the 4-vinylcyclohexene cation radical is then construed as strong indication of a subsequent facile VCB rearrangement. It would not appear plausible for a purely acyclic intermediate with bis(*trans*-allylic) character to cyclize to a DA adduct, so that a VCB cation radical would appear to be an obligatory intermediate which is capable of being transformed smoothly to the DA adduct (Scheme 47). That the VCB rearrangement can be prevented by collisional deactivation can also be taken as evidence that this VCB rearrangement has at least some minimal activation requirement.



Scheme 47.



Scheme 48.

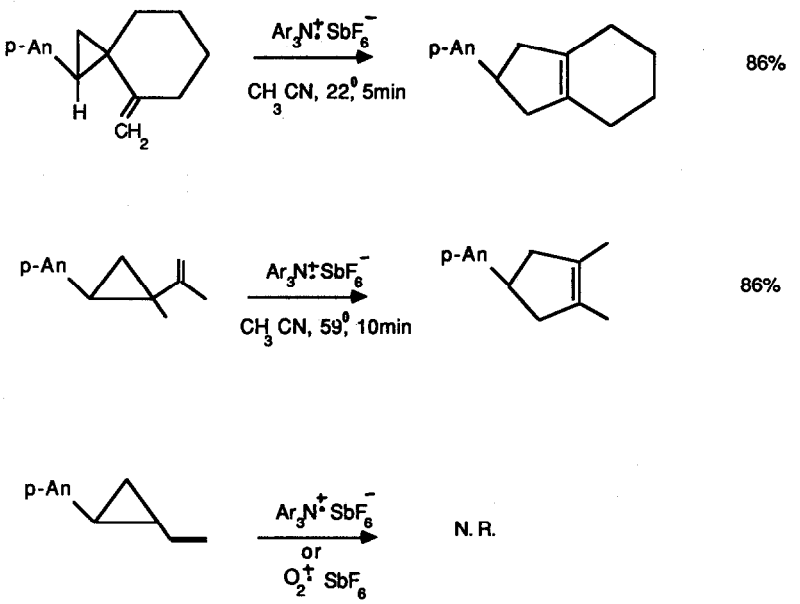


Scheme 49.

Still more recently, a classic study of the cyclodimerization of 1,1-diphenylethene (DPE) under PET conditions has revealed that a mixture of CB and DA adducts are formed and, importantly, that the latter is formed exclusively from the separated DPE^{+}, while the former derives primarily from the geminate ion radical pair (DPE^{+}/S^{-}).[87] The mechanism proposed (Scheme 48) invokes competition between, on the one hand, diffusional separation of the geminate ion pair to the separated ions which then react with DPE to yield separated acyclic dimer cation radicals (D_2^{+}) and, on the other hand, bimolecular reaction of DPE^{+}/S^{-} with DPE to yield dimer cation radical geminate pairs (D_2^{+}/S^{-}). The separated dimer cation radicals then cyclize predominantly to the DA adduct, but the geminate ion pairs undergo rapid back electron transfer to give an acyclic dimer diradical, which then cyclizes exclusively to the CB adduct. These important results could also be construed, without loss of kinetic rigor, in terms of a long bond (or ion dipole stabilized quasi-cyclic) cyclobutane cation radical and its competitive quenching and VCB rearrangement (Scheme 49).

4.10. *The vinylcyclopropane rearrangement*

The recent observation of aminium salt initiated vinylcyclopropane (VCP) rearrangements (Scheme 50) is especially gratifying in that all carbocyclic systems from C_3–C_6 are now synthetically available via hole catalyzed routes.[88] Apparently these reactions are less facile than the corresponding VCB rearrangements, since neither *cis*- nor *trans*-1-*p*-anisyl-2-vinylcyclopropane undergo the rearrangement. The corresponding cyclobutanes, of course, rearrange with great facility. Such results would seem to support the concertedness of both the VCP and VCB rearrangements.

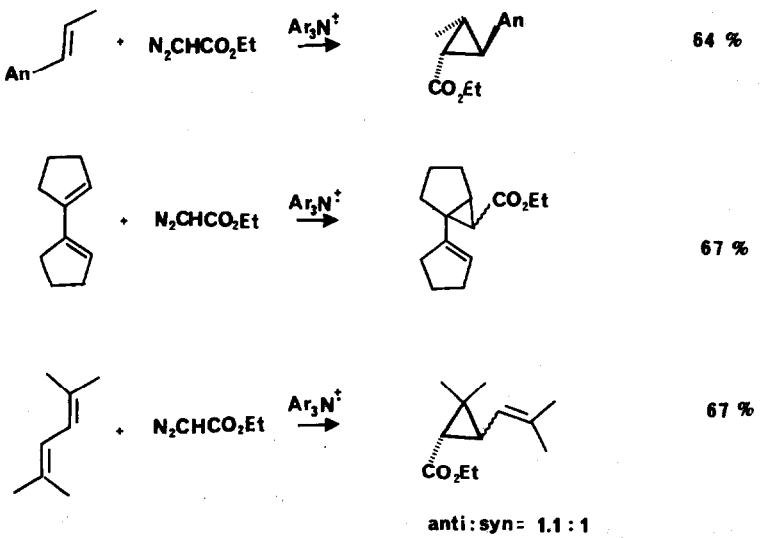


Scheme 50.

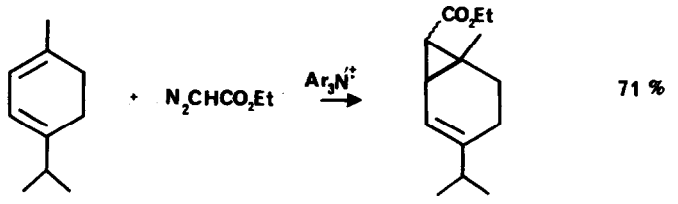
4.11. *Cyclopropanation*

The scope of cation radical cycloadditions is broadened still further by the recent discovery of cation radical cyclopropanation.[89] A varied selection of conjugated dienes, styrene derivatives and even certain unconjugated alkenes (as caticogenic substrates) have been cyclopropanated by ethyl diazoacetate under typical aminium salt conditions.

Such caticogenic substrates as *E*-anethole, 1,1′-dicyclopentenyl, and 2,5-dimethyl-2,4-hexadiene are cyclopropanated in ca 65% yield (Scheme 51). A mixture of *syn* and *anti* isomers is typically



Scheme 51.



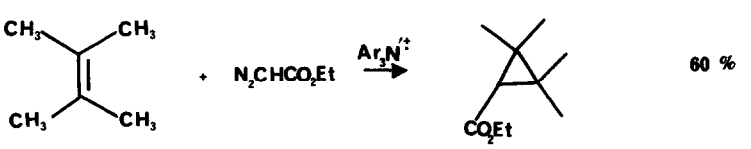
Scheme 52.

found. Analogous cyclopropanations can, of course, be effected by transition metal catalysis, but cation radical cyclopropanation has several potential advantages. In comparison to $Rh_2(OAc)_4$ catalyzed cyclopropanation, which appears to be the most efficient of the transition metal catalyzed versions of the cyclopropanation reaction, the aminium salt catalyzed cyclopropanation products are formed much more cleanly. The coupling of ethyl diazoacetate, which produces relatively large quantities of diethyl maleate and fumarate in the transition metal catalyzed reaction, is not observed at all in the aminium salt procedure. Consequently, the use of a large excess of the pi substrate to be cyclopropanated, which is an inconvenient requirement of the transition metal catalyzed procedure, can be completely avoided in the aminium salt procedure. For substrates which are especially susceptible to cation radical cyclodimerization, a modest excess of ethyl diazoacetate is recommended. This reactant is, however, readily and economically available and is volatile enough to be removed by rotary evaporation.

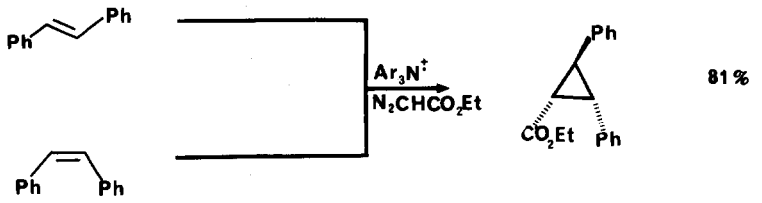
The use of the more powerful aminium salt ($Ar'_3N^+SbCl_6^-$) as initiator permits these cyclopropanation reactions to be carried out at $-78°C$, with expected concomitant dividends in selectivity (Scheme 52). Moreover, the use of this latter initiator permits efficient cyclopropanation of an unconjugated, tetraalkyl-substituted, alkene (Scheme 53).

The same reactions are observed to occur, albeit with diminished efficiency, in the presence of 2,6-bis(*tert*-butyl)pyridine and are strongly suppressed by added neutral triarylamine (cf. the Kinetic Criterion). Several of the reactions have also been observed to occur under PET conditions and also using zeolites. The chain lengths in the aminium salt reaction appear to be roughly the same as in other aminium salt initiated cation radical cycloadditions (ca 20–30), since ca 5–10 mol % of the aminium salt initiator appears to be required for optimum efficiency in both reactions.

The specific role selection sense postulated for these reactions is that involving reaction of the pi substrate cation radical with neutral ethyl diazoacetate. One indication of this role sense is the observation that less caticogenic substrates (e.g. 2,3-dimethyl-2-butene) require the more potent aminium salt. Further, ethyl diazoacetate is relatively stable in the presence of $Ar_3N^+SbCl_6^-$ at 0°C for the very short time interval of the cyclopropanation reaction, whereas many of the substrates are efficiently cyclodimerized under these conditions in the absence of ethyl diazoacetate. Modest quantities of these cyclodimers are also formed under the normal cyclopropanation conditions, particularly when ethyl diazoacetate is not used in excess. The presence of these cation radical



Scheme 53.

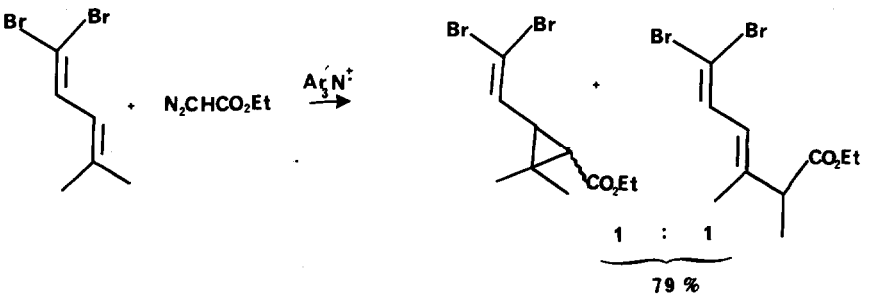


Scheme 54.

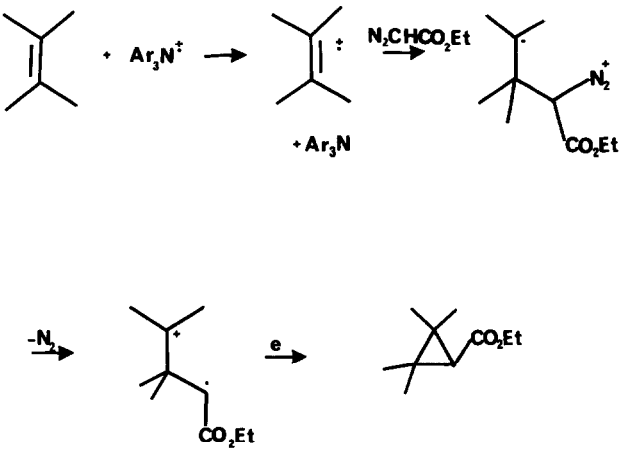
cyclodimers is construed as reliable evidence for the intermediate formation of the corresponding monomer cation radicals. It is considered likely that the presence of the strongly electron withdrawing carbethoxy substituent is important in limiting the ionization of the diazo component.

Reaction stereochemistry has been investigated in the stilbene system. Both *E*- and *Z*-stilbene are cyclopropanated efficiently and both yield the same adduct, ethyl *trans*-2,3-diphenylcyclopropanecarboxylate, as the sole cyclopropanation product (Scheme 54). Such results could be considered as evidence for a non-stereospecific two-step reaction involving an acyclic (1,3-propanediyl) cation radical intermediate. However, prior isomerization of initially formed *Z*-stilbene cation radical to the more stable *E*-stilbene cation radical is an alternative explanation for non-stereospecificity. The recovered stilbene after partial cyclopropanation of *Z*-stilbene reveals that no *Z* to *E* isomerization of the neutral substrate has occurred. The possibility nevertheless remains that the *E*-stilbene cation radical formed by isomerization of the *Z*-stilbene cation radical is not neutralized by electron transfer (from neutral *Z*-stilbene) prior to cycloaddition. This possibility actually appears quite plausible since the required electron transfer would, in fact, be quite endothermic. Further studies therefore appear necessary to define the stereochemistry of the cycloaddition reaction step *per se*.

Neither cation radical nor transition metal catalyzed cyclopropanation is outstanding with regard to *syn*/*anti* selectivity. Transition metal catalyzed cyclopropanation, moreover, is also characterized by very modest site selectivity in instances where non-equivalent double bonds compete for cyclopropanation. In contrast, site selectivity in cation radical cyclopropanation is expected to be at a level far more appropriate for synthetic applications. In the competition between isolated, non-equivalent sites, selectivity should be controlled by site caticogenicity, which should provide extremely sharp differentiation between most pi functionalities. In the alternative circumstance where the non-equivalent sites exist in a conjugated relationship, selectivity should be based (at least in part), upon a combination of differential charge densities, steric effects, and product development control. The latter should still be capable of providing adequate selectivity distinctions. An interesting instance of highly developed site selectivity of the second type is illustrated in Scheme 55. The



Scheme 55.



Scheme 56.

cyclopropane product of this reaction is of interest in connection with pyrethroid insecticides. The observation of rearranged by-products in this reaction can be construed as evidence for an acyclic propanediyl cation radical intermediate, but the required rearrangement could also be rationalized using a long bond cyclopropane cation radical intermediate. The direct formation of an adduct cation radical with an intact cyclopropane ring would, however, appear to be inconsistent with the observed rearrangement.

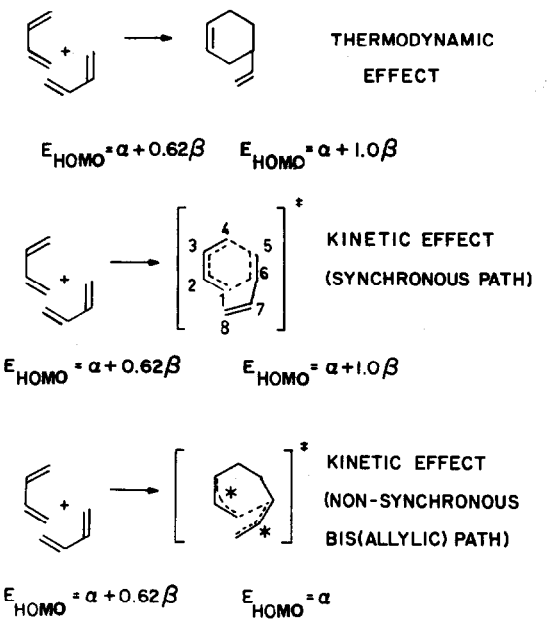
Evidence for a neutral 1-pyrazoline could not be accrued, even when reactions were run at −78°C. The intermediacy of an intact 1-pyrazoline cation radical has not yet been rigorously excluded, but the acyclic (or long bond cyclic) form of this cation radical would appear to be a more stable and therefore a more likely choice for a nitrogen containing cation radical intermediates, if one exists. The fact that cyclopropanation of conjugated dienes is cyclopropane periselective (to the exclusion of cyclopentenes) suggests that the nitrogen free intermediate is most probably a long bond cyclopropane cation radical, as opposed to an acyclic cation radical. The mechanism tentatively proposed is essentially a concerted carbene transfer to a substrate cation radical, giving a long bond cyclopropane cation radical (Scheme 56).[90]

5. THEORETICAL STUDIES

5.1. *The cation radical Diels–Alder*

The extraordinary kinetic impulse of DA and CB cation radical cycloadditions has been quantitatively characterized, experimentally, and its generality amply illustrated. The basis for this singularly powerful effect is of fundamental significance to chemistry, especially since activation barriers to cycloadditions, both allowed and forbidden, are not merely strongly diminished but virtually expunged by the effect. The theoretical studies by Bauld and Bellville were the first to address this issue. These studies also developed theoretical insights into important details of the reaction path, such as the concerted vs stepwise nature of the reaction and the preferred reaction stereochemistry.

5.1.1. *FMO studies.* The simplest theoretical approach applied by Bauld and Bellville, that of FMO analysis, yields disproportionately rich insights into the nature of the reaction path.[33] *A priori*, it was possible that the kinetic impetus ($\Delta E_a^{\ddagger} - \Delta E_a^0$) for cation radical cycloaddition has a simple, quasi-thermodynamic basis. That is, if the cation radical DA reaction is typically more exothermic than its corresponding neutral counterpart, product character in the transition state could account



Scheme 57.

for substantial acceleration of the cation radical process. In fact, a simple FMO argument (which is backed by MINDO/3 and other calculations) shows that the cation radical DA is typically *less* thermodynamically favorable than the neutral DA. Consider a prototype DA reaction between *s-cis*-1,3-butadiene and ethene (Scheme 57). In the HMO approximation, the energy change ($\Delta E^{\ddagger}$) associated with the cation radical version of the reaction is related to that in the neutral reaction (ΔE^{0}) as in eqn (1):

$$\Delta E^{\ddagger} - \Delta E^{0} = IP(P) - IP(R) \tag{1}$$

$$\Delta E^{0} - \Delta E^{\ddagger} = IP(R) - IP(P) \tag{2}$$

where IP(P) and IP(R) are the first ionization potentials of the cycloadduct product and of the reactant ensemble, respectively. The product, being a cycloalkene, has $IP = -E(HOMO) = -(\alpha+\beta)$(Huckel energies), whereas the dienic component of the reaction ensemble has $IP = -E(HOMO) = -(\alpha+0.618\beta)$. It is easily seen that the product of a cycloaddition reaction is typically less readily ionizable than the reactant, so that quite generally the cation radical DA can be expected to have less thermodynamic driving force than the corresponding neutral DA reaction. Consequently, whatever the basis may be for the kinetic impetus of the cation radical DA, an unfavorable quasi-thermodynamic effect must also be overcome.

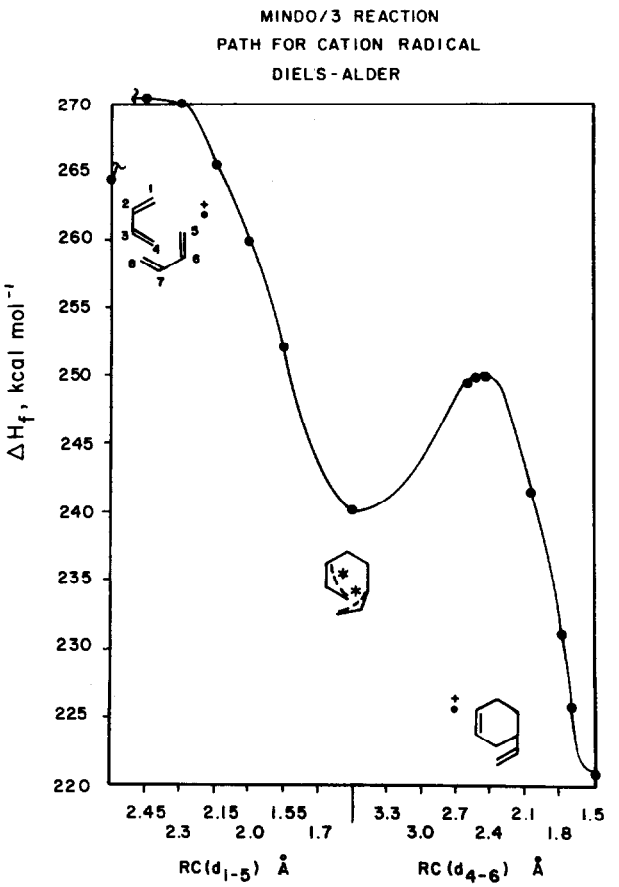
The qualitative nature of the basis factor was sought in similar FMO analyses of various transition state models. By analogy to eqn (2), the kinetic impetus for the cation radical DA ($\Delta E_a^0 - \Delta E_a^{\ddagger}$) is given by eqn (3):

$$\Delta E_a^0 - \Delta E_a^{\ddagger} = IP(R) - IP(\neq) \tag{3}$$

where IP($\neq$) is the first ionization potential of the (neutral) transition state. Positive kinetic impetus ($\Delta E_a^0 - \Delta E_a^{\ddagger} > 0$) is thus expected only if the transition state is more ionizable (more caticogenic) than the reactant ensemble. Since the reactant ensemble always contains a diene unit, we must require IP($\neq$) less than that of a conjugated diene. If one adopts, first, a synchronous transition

state model, the pericyclic conjugated system is benzenoid [IP = $-(\alpha+\beta)$] and unsuitable for positive kinetic impulse. However, a highly non-synchronous, or acyclic, transition state, which has allylic and alkyl radical sites, nicely fulfils the requirement of enhanced transition state caticogenicity (IP = $-\alpha$). The FMO analysis therefore suggests, as one possible basis for kinetic impulse in cation radical cycloadditions, the enhanced caticogenicity of highly non-synchronous transition states (or of stepwise reactions). Since most DA reactions, even of neutrals, are now usually considered to proceed non-synchronously, the even stronger preference for such paths in the cation radical DA addition is not surprising.

5.1.2. *Semi-empirical MO reaction path calculations.* Fully optimized MINDO/3 reaction path studies of the cation radical DA cycloadditions of butadiene/ethene and butadiene/butadiene were also carried out by Bauld and Bellville, and the results are in excellent accord with the simple predictions of FMO theory.[33] The reaction path, depicted in Scheme 58, is indeed found to be highly non-synchronous and in fact stepwise. The activation energy predicted for the *s-cis*-1,3-butadiene cation radical cyclodimerization is only 7.9 kcal mol^{-1}. More detailed studies revealed that, even in a synchronous path, the cation radical DA reaction is somewhat accelerated relative to the corresponding synchronous neutral DA, suggesting that some factor, in addition to synchroneity, contributes to the kinetic impetus for cation radical DA cycloaddition. The factor was postulated



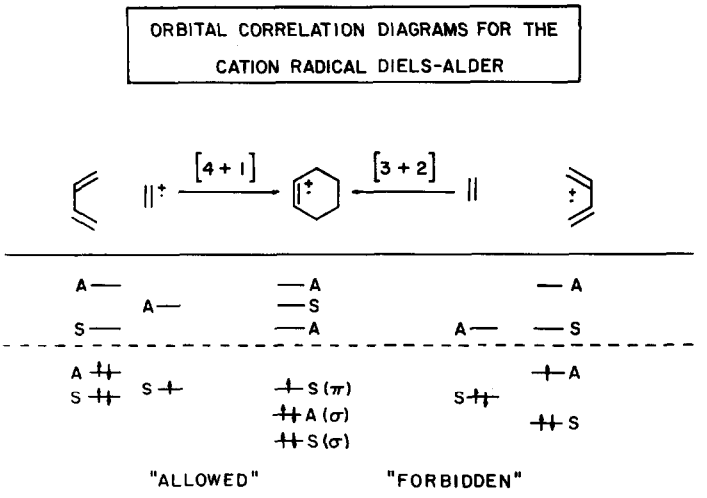
Scheme 58.

to be the strongly decreased non-bonded repulsions encountered in the formation of a carbon–carbon bond when one of the carbons is neutral and the other positively charged.

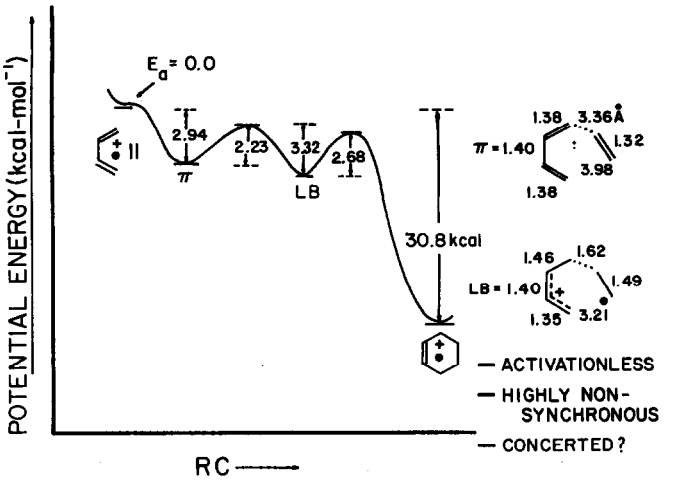
More recently, Pancir and Turecek have used the topological MO(TMO-CI)-method to study the same cation radical cyclodimerization.[91] Their results confirm the MINDO/3 prediction of a stepwise path involving an acyclic bisallylic cation radical and derive an activation energy of 14 kcal mol^{-1} for the DA addition.

5.1.3. *The transition state aromaticity/antiaromaticity model.* An excellent qualitative means of assessing allowedness/forbiddenness in pericyclic reactions is the transition state aromaticity/antiaromaticity (TSA/A) approach originated by Evans and advocated by Dewar. The benzene-like pericyclic array in the transition state of a doubly suprafacial, concerted DA reaction is considered to constitute an aromatic transition state, which is preferred over a corresponding (acyclic) stepwise path or either $s+a$ path. Concerted cycloadditions involving antiaromatic transition states, e.g. the doubly suprafacial cyclodimerization of ethene, are often considered less favorable than the alternate stepwise path. Pericyclic arrays in cation radical transition states are neither strongly aromatic nor strongly antiaromatic, but often have greater delocalization energy than the corresponding acyclic system and in this valid sense they can be considered mildly aromatic. The benzene cation radical, a model for the concerted cation radical DA, has been found by Yamaguchi, in a very sophisticated pi electron calculation, to have a greater delocalization energy than the 1,3,5-hexatriene cation radical.[34] Whether or not the term aromatic is invoked, it can be seen that the cyclic transition state has a greater delocalization energy than the acyclic one, and this was appropriately construed as representing a factor which tends to favor concerted cycloaddition (either synchronous or non-synchronous). The key question, of course, is whether the additional non-bonded repulsions incurred in joining the second bond will overwhelm this small delocalization effect. Yamaguchi considered that non-bonded repulsions, not taken into account in his calculations, were likely to dominate and thus to favor stepwise addition.

5.1.4. *Orbital correlation diagrams.* As was noted previously, two distinct role senses exist for the cation radical DA.[27,33] The mechanism involving the cation radical component in the dienophilic role is classified as a [4+1] cycloaddition and is formally symmetry allowed (Scheme 59). The alternate mode involving action of the cation radical in the dienic role, classified as a [3+2] cycloaddition, is formally symmetry forbidden. However, orbital correlation diagrams would have



Scheme 59.

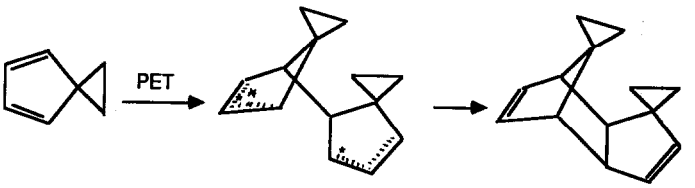


Scheme 60.

no significance for a stepwise mechanism and perhaps only marginal importance in a highly non-synchronous reaction. In any case, both types of DA cycloaddition, normal (i.e. [4+1]) and role-reversed (i.e. [3+2]) have been identified and both are extremely rapid.

5.1.5. Ab initio *SCF MO reaction path calculations.* A fully optimized SCF MO reaction path calculation at the 3-21G (extended) basis set level has been carried out for the cycloaddition of the *s-cis*-1,3-butadiene cation radical with ethene, formally a [3+2] cycloaddition.[92] Static (i.e., unoptimized) calculations were then carried out for the key points on this reaction path using the progressively more accurate basis sets 6-31G, 6-31G*, MP2/6-31G*, and MP3/6-31G*. The reaction path at the 6-31G/3-21G level is illustrated in Scheme 60. The reaction is precisely *activationless* and proceeds via a highly non-synchronous path. In full agreement with the semi-empirical paths, an intermediate is found which, however, has only a 2.7 kcal mol^{-1} barrier to closure. More importantly, this shallow minimum is completely eliminated in all of the calculations with still better basis sets (6-31G*, MP2/6-31G*, and MP3/6-31G*).[93] The cycloaddition is therefore concerted, as well as non-synchronous, as originally predicted.

All criteria, both experimental and theoretical, are therefore in perfect accord with the fact that cation radical cycloadditions are not merely strongly accelerated kinetically, but that they are often either precisely or approximately activationless either in the gas phase or in solution. The theoretical basis for this astonishing effect is less certain, but is considered to be a combination of two factors, viz. the enhanced caticogenicity inherent in a highly non-synchronous transition state and the greatly reduced level of non-bonded repulsions encountered when bond formation occurs between a neutral atom and a positively charged atom. The non-synchronous nature of the reaction path is unanimously upheld by all theoretical methods. Concertedness is compellingly supported by the *ab initio* reaction path calculation and by the experimental observation of stereospecificity. Two additional experimental observations tend to implicate concerted reaction paths. Both of these are based upon sharply contrasting behavior in DA cycloadditions as contrasted to CB cycloadditions. It has been observed that site selectivity in the cation radical DA is often dominated by charge density, as opposed to steric effects (see Scheme 12). For example, reaction of 1,3-cyclohexadiene with 4-methyl-1,3-pentadiene occurs preferentially at the terminally disubstituted center in competition with a sterically unhindered, unsubstituted terminal center. This kind of site selectivity is apparently never observed in the CB cycloadditions, which virtually always proceed through the more stable bisallylic cation radical. Indeed, cation radical cyclobutanation of a terminally disubstituted carbon



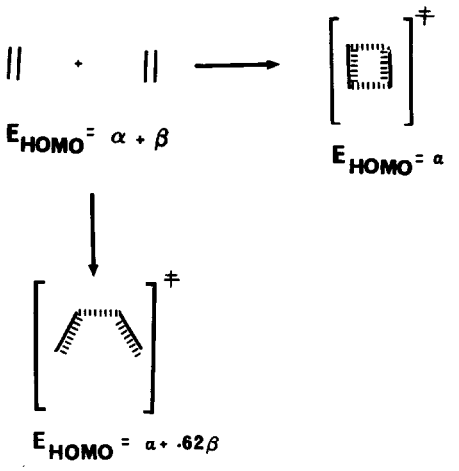
* = 1/2 $\overset{+}{\cdot}$

Scheme 61.

has not been observed at all in this laboratory. The greatly diminished sensitivity of the DA cycloaddition to steric effects at the site of the primary carbon–carbon formation is well understood on the basis of concert. Specifically, the reaction path for a concerted cycloaddition, in cooperatively developing the second carbon–carbon bond, should be less critically dependent on the ease of formation of the first (primary) bond. Similarly, the fact that in competitions between DA and CB addition to an *s-cis*-diene, the absence of substituents which strongly stabilize a carbocation site tends to favor DA cycloaddition appears to suggest that DA addition is concerted and is therefore less dependent on carbocation stabilization than cyclobutanation. Extensive mass spectrometric studies of the retro cation radical DA have also identified a large number of concerted reaction paths, but others are considered to be stepwise.[91] Roth has provided compelling CIDNP evidence for the intermediate formation of a singly linked (i.e., acyclic) dimer cation radical in the PET induced DA cyclodimerization of spiro [2.4] heptadiene (Scheme 61).[94a] This same group has also observed the formation of an analogous singly linked dimer cation radical in the PET induced ionization of the 1,3-cyclopentadiene DA dimers.[94b] Consequently, even in the DA reaction, it appears that mechanistic diversity exists. Indeed the authors clearly state that while their results establish the presence of a reaction channel in the spiro [2.4] heptadiene dimerization which involves an acyclic intermediate, the operation of a competing concerted path is by no means excluded. Unfortunately, it appears extremely difficult to quantitate the relative contributions of the two potential channels. Whether solvent polarity has any effect on the mechanistic preference is not yet known, but the solvent (DCM) used in aminium salt catalyzed DA cyclodimerizations is substantially less polar than that (CH_3CN) used in the PET induced reactions. Qualitatively, increased solvent polarity could be expected to favor the mechanism in which the charge is more localized in the transition state (the acyclic cation radical mechanism). Finally, the CIDNP data are presumably unable to distinguish a purely acyclic cation radical from a long bond, quasi cyclic structure of either the CB or DA type.

5.2. *Cation radical cyclobutanation*

The kinetic impulse for cation radical cyclobutanation is, if anything, more impressive than that for cation radical DA addition. Although the ultimate result appears to be essentially the same, viz. the virtual elimination of the entire activation barrier, the magnitude of the barrier which must be overcome (for the neutral reaction) is much greater in the case of cyclobutanation (62.5 kcal mol^{-1}) than in DA addition (34.3 kcal mol^{-1}). Thus, while both symmetry forbidden and symmetry allowed (neutral) reactions can be efficiently accomplished, almost without prejudice, in the domain of cation radicals, the capacity to effect forbidden reactions is actually more unique and requires greater kinetic impulse. The source of this kinetic impulse can be assumed to be essentially the same as in cation radical DA addition. In addition to the matter of kinetic impulse, the question of the details of the reaction path again arises. Since the earliest mechanistic proposal by the Ledwith group,



Scheme 62.

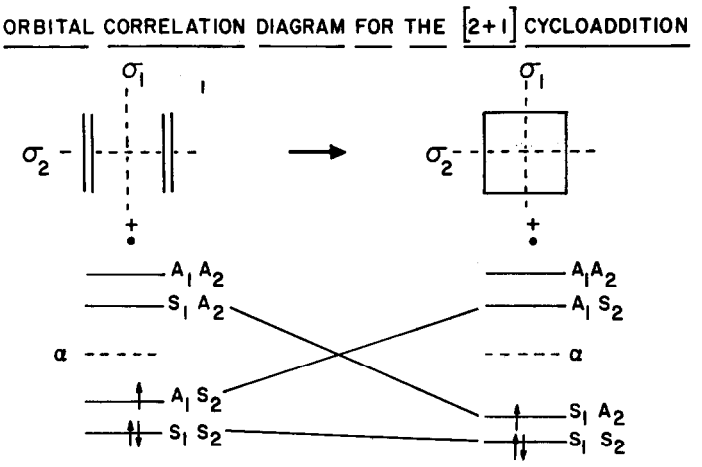
cation radical cyclobutanation has been assumed to be a stepwise reaction involving a 1,4-butanediyl cation radical intermediate. However, recent stereochemical and theoretical studies have introduced the concept of stepwise reaction involving a quasi cyclic, long bond cyclobutane cation radical intermediate.

5.2.1. *FMO analysis.* The FMO analysis of the cation radical DA reaction led to the development of the concept of enhanced transition state caticogenicity as a possible basis for the kinetic impulse of this reaction.[33] This concept, in turn, suggested a strong preference for highly non-synchronous or even stepwise reaction paths. A similar analysis of the cyclobutanation reaction (Scheme 62), reveals enhanced transition state caticogenicity for either non-synchronous or synchronous paths.[33] The idealized model for the synchronous [2+2] cycloaddition of two neutral ethene units is the cyclobutadiene pi system which, unlike the benzene pi model of the DA reaction, has a very high caticogenicity (IP = $-$E(HOMO) = $-\alpha$). Consequently, kinetic impulse is predicted in both cases, and the synchronous and non-synchronous paths are not distinguished by this simple FMO analysis.

5.2.2. *Orbital correlation diagram.* The cycloaddition of ethene cation radical to ethene, a [2+1] cycloaddition, is formally forbidden (Scheme 63).[33] Since cyclobutanation is, in reality, essentially devoid of an energetic activation requirement, it would appear more logical to assume that the synchronous path assumed in the orbital correlation diagram is probably not the actual path. The FMO analysis and orbital correlation diagram, taken together, therefore support a non-synchronous or stepwise process.

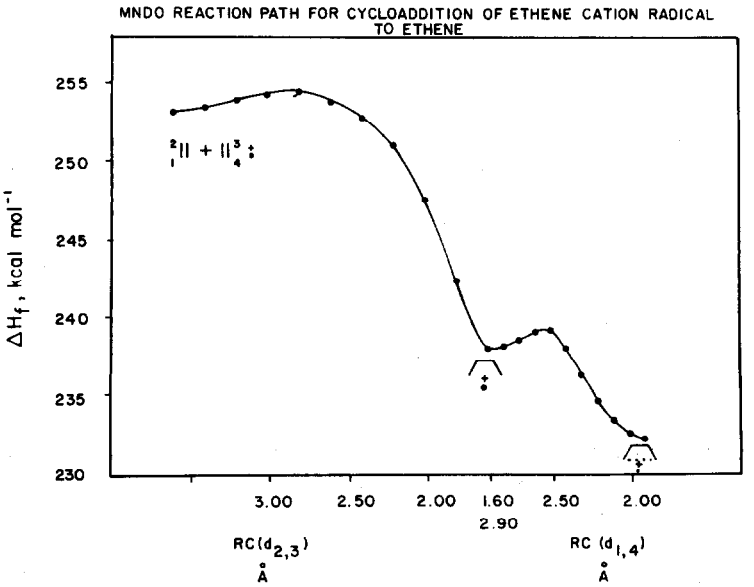
5.2.3. *Semi-empirical reaction path calculations.* An MNDO reaction path calculation for the [2+1] cycloaddition of ethene cation radical to ethene is in full accord with the foregoing quantitative arguments.[33] The activation energy is found to be a mere 1.3 kcal mol^{-1} and a stepwise path is foreseen. The intermediate acyclic cation radical, however, has an activation barrier of only 1.0 kcal mol^{-1} for cyclization. This latter cyclization does not, however, afford the intact cyclobutane cation radical, but a long bond cyclobutane cation radical (Scheme 64).

5.2.4. Ab initio *reaction path.* The *ab initio* reaction path for the prototype [2+1] cycloaddition of ethene to the ethene cation radical was calculated using a 3-21G (extended) basis set.[68] The optimized geometries were then used in static 6-31G* calculations. These paths (3-21G and 6-31G*//3-21G) are quite similar to each other (Scheme 65) and to the MNDO path, but do not reveal an acyclic 1,4-butanediyl cation radical, as MNDO does. However, both the *ab initio* and semi-empirical calculations agree on a highly non-synchronous addition. The reaction is found to be *activationless* in both basis sets in the *ab initio* treatment, in excellent agreement with MNDO.

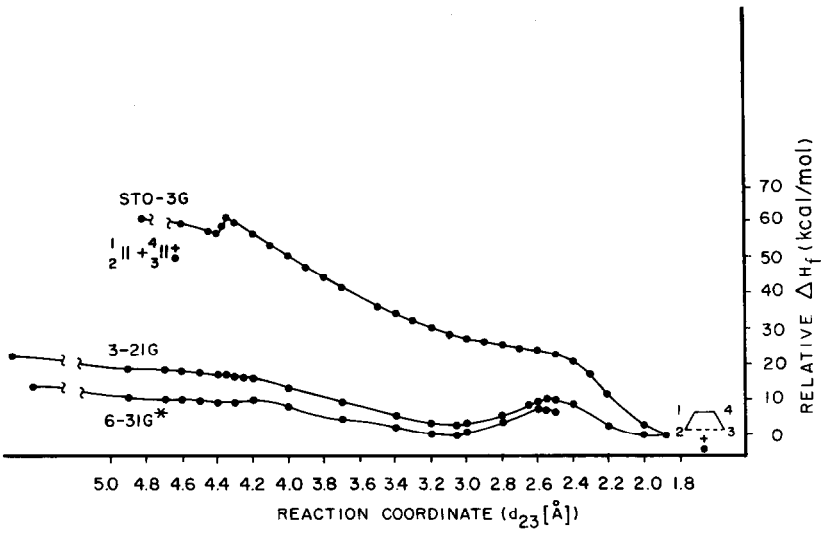


Scheme 63.

Instead of the acyclic 1,4-butanediyl intermediate found in the MNDO path, the *ab initio* path envisions an intermediate in which no sigma bonds have fully formed but in which both the closeness of approach (2.0 Å) and the binding energy (12.6 kcal mol^{-1}) surpass that normally associated with pi complexes. Nevertheless, the ethene units retain sp^2 hybridization and very strong pi bond character (1.38 Å), while the positive charge and spin density are delocalized equally over both ethene units, which assume a trapezoidal geometry. The pi long bond found in this complex has been likened to the sigma long bond of the ethane cation radical suggested by a similar calculation



Scheme 64.

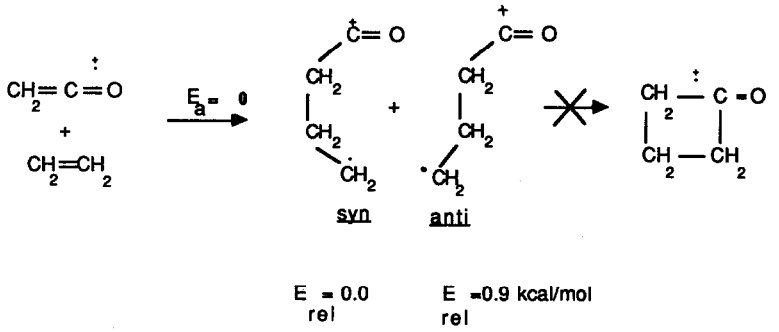


Scheme 65.

(2.02 Å). An activation energy of 7.1 kcal mol^{-1} is required to convert this pi long bond complex to the long bond cyclobutane cation radical. The transition state for this reaction is still >5 kcal mol^{-1} more stable than the original reactants, so that the overall reaction is activationless. The long bond (2.0 Å) of the long bond cyclobutane cation radical is considered to be strong enough to maintain stereochemical integrity and thus account for stereospecific addition, as observed experimentally. This suggestion is, in fact, supported by the observation that the *cis*- and *trans*-1,2-diphenylcyclopropane cation radicals exist in the long bond structure and are configurationally stable.[69] Similarly, the extensive pi character of the long bond pi complex intermediate appears sufficient to preclude stereorandomization at that stage of the reaction.

Subsequent to the execution of the previous reaction path, a detailed theoretical study of the parent cyclobutane cation radical at the fully optimized 6-31G* level (6-31G*//6-31G*) and beyond was reported.[95] These results indicate that the ground state of the parent CB cation radical actually has an intact CB ring, instead of the long bond structure. This indicates that at least in the prototype system, the long bond 'intermediate' is circumvented, and that closure may occur directly to an intact cyclobutane cation radical. This possibility appears quite plausible and would represent another possible basis for rationalizing stereospecific addition. It should be noted, however, that in practice, most [2+1] cycloadditions occur with electron rich alkenes, styrenes, or dienes in which substituents are available which should preferentially stabilize the long bond structure relative to an intact CB cation radical.[96]

An unusually thorough and definitive (MP2/6-31G**//6-31G* plus zero point vibrational energy) theoretical study of the ketene cation radical/ethene reaction path has recently been completed[97] and has important implications for the mechanisms of cation radical cyclobutanation. As has consistently been found for cation radical cycloadditions, the reaction is activationless and highly non-synchronous and leads to the formation of *syn* and *anti* acyclic adduct cation radicals ($\cdot CH_2CH_2CH_2CO^+$; Scheme 66). Interestingly, the *syn* adduct is 0.9 kcal mol^{-1} more stable than the *anti*. Since there is no energy minimum for an intact cyclobutanone cation radical, cyclization of these adducts does not occur. In solution, however, electron transfer to the acyclic adducts could produce diradicals which should cyclize readily, as proposed by Farid for the cyclobutadimerization of DPE. Such a reaction mechanism would appear clearly to have the stereochemical concomitant



Heinrich, Koch, Morrow, Schwarz : 1988

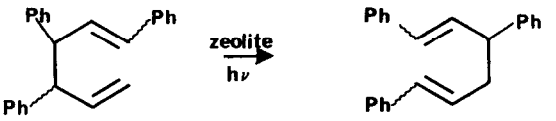
Scheme 66.

of stereorandomization (i.e. non-stereospecificity). Consequently, the observation of stereospecific cyclobutanation in a particular reaction would, as asserted earlier, appear to be a decisive counter-indication of such an acyclic mechanism. The circumstance that the *syn* ketene cation radical/ethene adduct has an unsymmetrical, acyclic structure with dominant acyclium ion/alkyl radical character rather than a quasi cyclic, long bond structure, is perhaps not surprising in view of the earlier prediction that long bonds should be especially favored in relatively symmetrical cation radicals in which both long bond locii are of comparable carbocation stabilizing ability. Moreover, the carbonyl group contributes additional strain to the intact or long bond cyclobutane structure. Indeed, the slightly greater stability of the *syn* than the *anti* adduct cation radical contrasts with expectation for a linear C_4 system and may even suggest an incipient long bond. However, this degree of bonding would appear to be insufficient to maintain stereochemical integrity. Finally, reaction of CH_2CO^+ with ethene to produce $\cdot CH_2CH_2CH_2CO^+$ rather than to give $CH_2COCH_2CH_2^+$ or its long bond version was observed to be consistent with reaction at the site of highest positive charge density (which, in CH_2CO^+, is the methylene group) and FMO considerations, and, we may additionally note, with product development control ($\cdot CH_2COCH_2CH_2^+$ is much higher in energy than $\cdot CH_2CH_2CH_2CO^+$).

As in the case of the cation radical DA, mechanistic diversity should be anticipated in cyclobutanation. It is now clear that mechanisms of at least three types must be considered for CB cycloadditions, viz. (i) concerted, (ii) long bond and (iii) stepwise. The stereospecific cyclodimerization of *E*-anethole and the periselective cyclobutanation of 1,3-cyclohexadiene by N-methyl-N-vinylacetamide appears to demand (ii).

5.3. *Vinylcycloalkane and related sigmatropic rearrangements*

The [1,3] sigmatropic shifts of H, OH, CH_3, and C_6H_5 across a propenyl system were studied by Hopilliard and Bouchoux using MINDO/3.[98] The migratory aptitudes were found to stand in the order HO < H < Ph < CH_3. The activation energy for hydrogen migration was calculated to be 21.8 kcal mol^{-1} and that for methyl migration 41.1 kcal mol^{-1}. A very recent 6-31G*//6-31G calculation of the reaction path for the [1,3] hydrogen shift in the propene cation radical gives an activation energy of 29.6 kcal mol^{-1} for the suprafacial shift.[99] The point seems clear that, while nearly all cation radical pericyclic reactions experience at least some kinetic impetus, not all have the overwhelming impetus which appears to generally characterize the cycloadditions. The same point has previously been made in relation to the retroelectrocyclic reaction of the cyclobutene cation radical.[100] However, the first stage of the [3,3] sigmatropic shift of the 1,5-hexadiene cation



Scheme 67.

radical has been calculated to have negligible activation energy (1.4 kcal mol^{-1}) by MINDO/3,[33] and this reaction has recently been observed by Williams and Guo.[73] Essentially, this reaction is an intramolecular cycloaddition. When appropriate substituents are present at C_3 and/or C_4 to make the second stage of the Cope rearrangement thermodynamically favorable, the full cation radical Cope rearrangement can, in fact, be observed (Scheme 67).[101]

It may legitimately be asked whether, given the high order of reactivity of cation radicals, efficient reactions having activation energies of approximately 30 kcal mol^{-1} are likely for this species. Certainly, they should be incapable of being constituted as chain processes in solution. It appears likely that even stoichiometric (non-chain) reactions having this kind of activation requirement would require both the reactant and product cation radicals to be extraordinarily stable.

Fortunately, the vinylcyclobutane rearrangement appears to be drastically different from the generic [1,3] alkyl shift in this respect. A MP2/6-31G*//3-21G calculation near completion in this laboratory on the prototype VCB cation radical rearrangement reveals an activation energy of only ca 9.5 kcal mol^{-1}. The preferred path is doubly suprafacial and concerted. The VCB cation radical has a long bond structure (1.96 Å).

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