diphenylethanol as a probe for chromium species in intermediate oxidation states, as indicated by the results in Table VII. The formation of oxochromium(V) could result from two consecutive one-electron reductions,[44c]

$$Cr^{VI} + S \rightarrow Cr^{V} + S^{+\cdot} \quad (19)$$

$$Cr^{VI} + S^{+\cdot} \rightarrow Cr^{V} + P \quad (20)$$

or an initial two-electron reduction followed by disproportionation.

$$Cr^{VI} + S \rightarrow Cr^{IV} + P \quad (21)$$

$$Cr^{IV} + Cr^{VI} \rightarrow 2Cr^{V} \quad (22)$$

However, the absence of oxidative cleavage of 1,2-diphenylethanol to benzaldehyde and benzyl alcohol precludes the presence of Cr(IV) species. We thus favor the sequence in eq 19-20.

The indication of the viability of oxochromium(V) as an epoxidizing agent can also be obtained from ESR studies. To a frozen solution of oxochromium(V) prepared from chromyl nitrate and acetone was added a small amount of either styrene or tetramethylethylene at -80 °C. Immediately upon addition, the signal intensity was greatly diminished, followed by a slower decay over a period of 1 h. We surmise that the epoxidation of alkenes by oxochromium(V) must be very rapid at these temperatures since the ESR signal disappeared immediately when the mixture was mixed.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for the support of this research.

Registry No. $O_2Cr(ONO_2)_2$, 16017-38-2; $O_2Cr(OAc)_2$, 4112-22-5; O_2CrCl_2, 14977-61-8; $O_2Cr(O_2CCF_3)_2$, 27184-84-5; $OCrCl_5^{2-}H_2Bpy^{2+}$, 54170-73-9; 1-octene, 111-66-0; cyclohexene, 110-83-8; norbornene, 498-66-8; 2,3-dimethyl-2-butene, 563-79-1; 2,3-dimethyl-1,3-butadiene, 513-81-5; diadamantylidene, 30541-56-1; α-methylstyrene, 98-83-9; (*E*)-β-methylstyrene, 873-66-5; (*Z*)-β-methylstyrene, 766-90-5; 1,1-diphenylethene, 530-48-3; 2-methyl-1,1-diphenylpropene, 781-33-9; (*E*)-stilbene, 103-30-0; 1,2-diphenylethanol, 614-29-9; styrene, 100-42-5; dimethylformamide, 68-12-2; tetramethylurea, 632-22-4; 1-octene oxide, 2984-50-1; cyclohexene oxide, 286-20-4; *exo*-norbornene oxide, 3146-39-2; 2,3-dimethyl-2-butene oxide, 5076-20-0; 2,3-dimethyl-1,3-butadiene monoxide, 34485-82-0; diadamantylidene oxide, 29186-07-0; styrene oxide, 96-09-3; α-methylstyrene oxide, 2085-88-3; *trans*-β-methylstyrene oxide, 23355-97-7; *cis*-β-methylstyrene oxide, 4541-87-1; 1,1-diphenyl-2-methylpropene oxide, 60227-39-6; *trans*-stilbene oxide, 1439-07-2; 1-octene glycol ketal, 79413-15-3; styrene glycol ketal, 52129-03-0; α-methylstyrene glycol ketal, 84895-18-1; 1,1-diphenylethylene glycol ketal, 84895-19-2; *trans*-cyclohexene glycol ketal, 24148-95-6; *cis*-β-methylstyrene glycol ketal, 64216-06-4; *trans*-β-methylstyrene glycol ketal, 64216-05-3.

Theory of Cation-Radical Pericyclic Reactions

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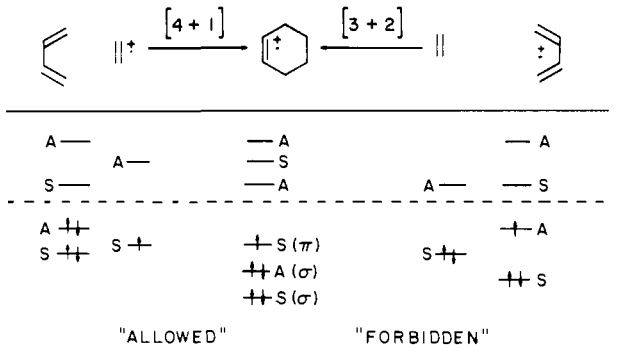
Received September 30, 1982

Abstract: Reaction paths are calculated for representative cation-radical pericyclic reactions, including the Diels-Alder, olefin cycloaddition, and the Cope reaction. Ionization to form cation radicals is found to lower the activation energy dramatically in each case, in agreement with experimental observations relative to cation-radical pericyclic reactions. The basis for this effect is analyzed theoretically and found to be consistent with a nonsynchronous, concerted mechanism for such reactions, but not with a synchronous mechanism. It is suggested that the sequence (i) ionization, (ii) pericyclic reaction, (iii) electron acceptance provides a powerful catalytic route for a wide variety of pericyclic reactions.

The recent discovery of the cation-radical catalyzed Diels-Alder reaction[1,2] naturally stimulates interest in the general concept of cation-radical pericyclic reactions. The observation that ionization of one of the components (specifically, the dienophile) in a Diels-Alder cycloaddition can engender enormous rate enhancements immediately evokes interest in the possibility that hole formation (ionization) may exert analogous effects on other pericyclic reactions. Using FMO, MINDO/3, MNDO, and optimized ab initio calculations, the effect of hole formation on activation energy has been studied for a variety of pericyclic reactions. The results suggest that a wealth of cation-radical pericyclic chemistry of minimal activation requirements may await discovery. The important question of the theoretical basis for the observed powerful kinetic effect has also been explored and answered, and the analysis yields valuable insights concerning the structure of the transition states of the cation-radical Diels-Alder and other cation-radical pericyclic processes.

The Cation-Radical Diels-Alder. Although not many pericyclic reactions of doublet (spin) species are symmetry allowed,[3] the cation-radical Diels-Alder is one such reaction. The orbital correlation diagrams presented in Scheme I reveal that cycloaddition of the ethene cation radical to *s-cis*-1,3-butadiene is indeed

Scheme I. Orbital Correlation Diagrams for the Cation-Radical Diels-Alder



symmetry allowed. Interestingly, the role-reversed cycloaddition of neutral ethene to the butadiene cation radical is forbidden. This preference of the cation radical for the dienophilic role has been observed experimentally and termed role selectivity.[1,2] Although orbital correlation diagrams for the corresponding Diels-Alder dimerization of a conjugated diene, such as 1,3-butadiene, cannot rigorously be constructed because of insufficient symmetry, local symmetry considerations suggest a similarly favored status for this reaction. The experimentally observed stereospecificity of the cation-radical Diels-Alder is, in fact, in excellent accord with

(1) Bauld, N. L.; Bellville, D. J.; Wirth, D. *J. Am. Chem. Soc.* **1981**, *103*, 718.
(2) Bauld, N. L.; Bellville, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 2265.
(3) Bauld, N. L.; Cessac, J *J. Am. Chem. Soc.* **1977**, *99*, 23.

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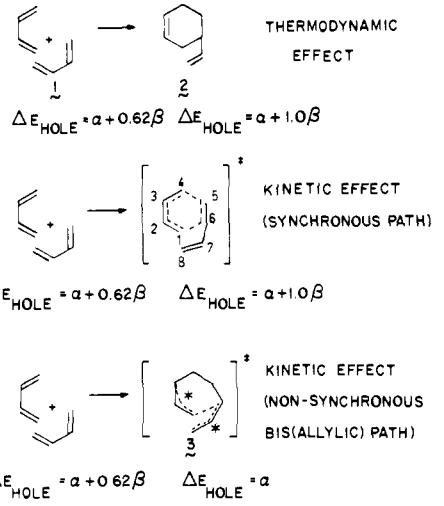
Scheme II. Effect of Hole Formation on the Cation-Radical Diels–Alder



the characterization of the reaction as allowed pericyclically.[1] One key aspect of the cation-radical Diels–Alder, viz., its powerful kinetic impetus, remains to be explained.

Thermodynamically, the addition of the cation radical of 1,3-butadiene ($\mathbf{1}^{\cdot+}$) to *s-cis*-1,3-butadiene (Scheme II, **1**) appears actually to be less favorable than the corresponding neutral Diels–Alder reaction as a consequence of diminished delocalization in the adduct cation radical ($\mathbf{2}^{\cdot+}$), an alkene-type cation radical, relative to the delocalized diene cation-radical ($\mathbf{1}^{\cdot+}$). A simple FMO theoretical framework suffices to state the argument. The reactant diene molecule has HOMO (highest occupied MO) energy $E = \alpha + 0.62\beta$ in the HMO approximation. The adduct has HOMO energy $E = \alpha + 1.0\beta$, corresponding to an ethenic double bond in the HMO approximation. Hole formation therefore requires 0.38β more energy in the product than in the reactant. The reduction in thermodynamic driving force is confirmed by a fully optimized MINDO/3 calculation, which gives $H = -44$ kcal mol^{-1} for the neutral Diels–Alder dimerization of butadiene and -42.5 kcal mol^{-1} for the corresponding cation-radical process. In the more common case in which the dienophilic cation radical has stabilizing terminal substituents (including alkyl groups), the cation-radical process becomes still less favorable. It is therefore apparent at the outset that the special kinetic facility of the cation-radical Diels–Alder is in no way related to the development of relatively stable product character in the transition state, but rather is achieved in spite of any development of product character, which is relatively unfavorable in the cation-radical process.

The unique characteristic of the transition state of a pericyclic reaction is, of course, its cyclic conjugated system, and the facility of pericyclic reactions is often discussed in terms of the delocalization stabilization (aromaticity or antiaromaticity) of these cyclic systems. The six-electron (benzene-like) cyclic array of orbitals present in the pericyclic transition state of the neutral Diels–Alder is a classic aromatic system. The status of the five-electron (benzene cation-radical-like) system in the cation-radical transition state is less clear, but would appear almost certain to be less favorable than the six-electron system. An FMO framework can again be invoked (Scheme II) to frame the argument more precisely. Hole formation in a benzene-like cyclic system formally requires $E = \alpha + \beta$, whereas the reactant diene would required only $E = \alpha + 0.62\beta$ for ionization. Kinetically, the cation-radical process is still 0.38β less favorable than the neutral one. Only when ethene is the dienophile would the reactant hole formation energy approach that of the transition state. The kinetic effect of interest apparently also does not have its origin in an especially stable five-electron cyclic conjugated system in the pericyclic transition state.

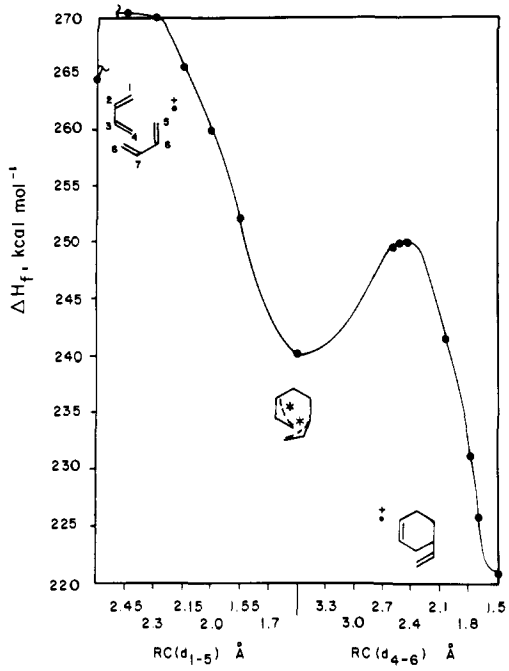
The failure of the foregoing analyses to provide a basis for the kinetic effect suggests that the structural models for the transition state examined thus far may not be wholly valid. A better model is suggested by the following argument. Although the transition state for the prototype neutral Diels–Alder (ethene and butadiene) may be approximately synchronous (i.e., involve approximately equal extents of formation of both new carbon–carbon bonds), there appears to be no doubt that, at least when unsymmetrical dienophiles are involved, the reaction path becomes quite nonsynchronous (though probably still concerted). The Diels–Alder dimerization of dienes is such a case, and it therefore is clearly preferable to adopt an unsymmetrical model (**3**, Scheme II) for the transition state for both neutral and cation-radical processes and to investigate the energy of hole formation in this kind of transition state. In its extreme form, **3** approaches the structure of a bis(allylic) system with a relatively small pericyclic perturbation (C_1–C_6). Hole formation in an allylic system is especially facile since the HOMO is nonbonding ($E = \alpha$) and is now 0.62β less difficult in the transition state than in the reactant. The highly nonsynchonous model (**3**) is therefore not only the theoretically most plausible one for both neutral and cation-radical reactions, but also uniquely explains the enormous rate enhancements observed in the cation-radical Diels–Alder.

Verification of these conclusions was sought via a MINDO/3 reaction path study of the cycloaddition of the 1,3-butadiene cation radical to *s-cis*-1,3-butadiene and (approximately) of the corresponding neutral cycloaddition. For further comparison, the corresponding reactions of ethene and its cation radical with butadiene were also studied. The diene dimerizations, incidentally, involve systems of eight carbon atoms and are quite time consuming even with an efficient method like MINDO/3. It is well known that MINDO/3 often tends to describe as stepwise, reactions which are symmetry allowed and in all probability concerted (pericyclic). The MINDO/3 mechanistic description of the Diels–Alder therefore includes an intermediate diradical, the existence of which is highly doubtful.[4] Nevertheless, the method appears to give activation energies that are consistently good. The reaction path points in this study were generated by optimizing all geometric variables except the reaction coordinate, values for which are varied in small increments between the extremes appropriate to reactant and product. In each case the reaction coordinate selection was the length of one of the newly forming carbon–carbon σ bonds (C_4–C_5). Since MINDO/3 envisions a diradical intermediate, the overall reaction path consists of two discrete paths, in each of which a different one of the new carbon–carbon bonds is the appropriate reaction coordinate. As found by the Dewar group for the prototype neutral Diels–Alder, it is actually more efficient to begin with the cyclized Diels–Alder adduct and deal with the reverse reaction.[4]

The MINDO/3 reaction path for the cation-radical Diels–Alder dimerization of 1,3-butadiene is illustrated in Scheme III. The path assumes an s-cis conformation for the dienophilic moiety, but the results differ minimally for the s-trans form. The 7.88 and 9.34 kcal mol^{-1} activation energies for the two steps are in qualitative accord with the expected large kinetic effect. The cation-radical Diels–Alder addition of ethene to butadiene was also studied and found to occur with relatively small MINDO/3 activation energies (16.06, 7.32 kcal mol^{-1}). For comparison, the neutral Diels–Alder has a MINDO/3 activation energy of 41.6 kcal. The activation energy for the neutral dimerization of butadiene was not calculated exactly because of computer time exigencies, but an estimate of ca. 36 kcal mol^{-1} was obtained by adopting the reaction coordinate value found for the cation-radical transition state optimizing all other parameters. The calculated effect of hole formation in both Diels–Alder reactions is thus to lower the activation energy by 25–30 kcal mol^{-1}. Although the true transition state in the cation-radical Diels–Alder appears to differ from the MINDO/3 transition state by having at least some pericyclic character, the MINDO/3 transition state still appears to be a fairly reasonable calculational model for the correct transition state. To gain additional credence for this conclusion,

(4) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650.

Scheme III. MINDO/3 Reaction Path for Cation-Radical Diels–Alder

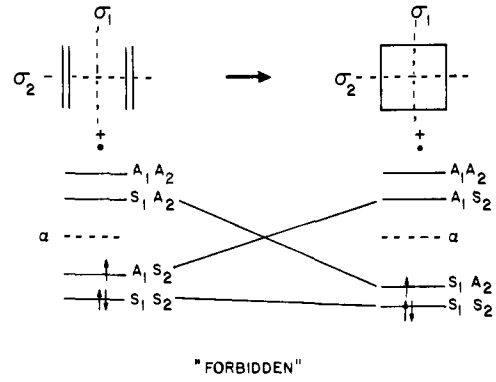


the symmetric pericyclic reaction path for the cation-radical dimerization of butadiene was studied by imposing the symmetry condition of equal pericyclic bond lengths. The complete path was calculated and the "transition state" located at the pericyclic carbon–carbon distance of 2.29 Å, with activation energy 36.7 kcal mol^{-1}. Comparing this with the estimated activation energy for the neutral dimerizations (36 kcal), there appears to be no kinetic impetus available to the cation-radical dimerization in a symmetric transition state. However, it is probably more relevant to compare the two reactions in analogous, symmetric modes. The activation energy for the neutral dimerization of butadiene via a symmetric path was again estimated by using the calculated cation-radical reaction coordinate value (2.29 Å) for the neutral transition state and optimizing all other parameters, yielding an activation energy of ca. 50 kcal. Hole formation is then seen to confer a modest kinetic advantage even in the synchronous path, but not the overwhelming stabilization associated with the nonsynchronous path. The smaller effect predicted for the synchronous path, if real, may possibly arise from long-range effects (particularly 1,3 interactions) which are known to be less repulsive in cationic species.[5]

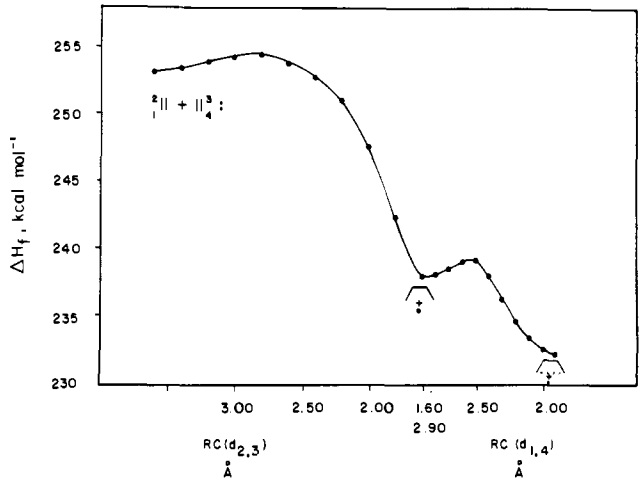
Cation-Radical Olefin Cyclodimerization. The cyclodimerization of *N*-vinylcarbazole to *trans*-1,2-bis(*N*-carbazolyl)cyclobutane via a cation-radical chain mechanism, reported by Ledwith in 1969, is one of the pioneering observations in the field of cation-radical pericyclic chemistry.[6] Since that time, a number of cation-radical cyclodimerizations of electron-rich alkenes and styrenes have been reported.[7,8] It is clear that, mechanistically, the reactions involve a [2 + 1] cycloaddition in which an alkene-type cation radical is the one-electron component and a neutral alkene molecule the two-electron component. Like the cation-radical Diels–Alder reaction, then, the cation-radical olefin cyclodimerization is known to be feasible and indeed often facile. However, no theoretical treatment of the reaction has been reported.

In contrast to the cation-radical Diels–Alder, it will be noted in Scheme IV that the [2 + 1] addition of ethene to the ethene cation radical is symmetry "forbidden". Though both reactions are obviously feasible, the experimental results are in accord with

Scheme IV. Orbital Correlation Diagram for the [2 + 1] Cycloaddition



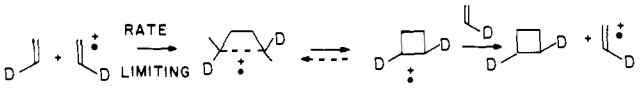
Scheme V. MNDO Reaction Path for Cycloaddition of Ethene Cation Radical to Ethene



at least a modest advantage for the cation-radical Diels–Alder process relative to the cyclodimerization. Thus, the cation radicals of conjugated dienes normally yield only Diels–Alder-type adducts in their additions to neutral dienes. Even so, the [2 + 1] cycloaddition is enormously more facile than the corresponding neutral olefin cyclodimerization. In this instance, the cyclic conjugated system in the pericyclic transition state can account for at least part of the kinetic effect, whether the reaction path is assumed to be synchronous or nonsynchronous. In the synchronous path, the transition state for the neutral cycloaddition is of cyclobutadiene character. Hole formation therefore requires only $E = \alpha$ in the transition state, compared to $E = \alpha + \beta$ in the alkene reactant. Similarly, in the nonsynchronous path, hole formation in a transition state resembling a 1,4-butanediyl diradical (with only a minimal pericyclic interaction) requires only $E = \alpha$. In both instances, an impressive kinetic effect would be foreseen relative to the neutral reaction. The reaction path was studied by both MINDO/3 and later MNDO when it became apparent from other work in progress[9-11] that the latter has an apreciable advantage in treating cation-radical reactions. The redundant intermediates are again a part of the calculated reaction path (the MNDO path is illustrated in Scheme V), but ignoring this systematic error, the results are extremely interesting. The activation energy for the first (and presumably rate-determining) step is a mere 1.3 kcal mol^{-1}. This is at least 60 kcal mol^{-1} less than that calculated or observed for the corresponding neutral reaction.[12] The second MNDO step has an even smaller activation energy (1.0 kcal mol^{-1}). The prototype [2 + 1] cycloaddition clearly has, as expected, minimal activation requirements. Almost equally

(5) Bauld, N. L.; Cessac, J. *J. Am. Chem. Soc.* **1977**, *99*, 8140.
(6) Ledwith, A. *Acc. Chem. Res.* **1972**, *58* 133.
(7) Farid. S; Shealer, S. E. *J. Chem. Soc., Chem. Commun.* **1973**, 677.
(8) Kuwata, S.; Shigemitsu, Y.; Odaira, Y. *J. Chem. Soc., Chem. Commun.* **1972**, 2.
(9) Bellville, D. J. Bauld, N. L.; *J. Am. Chem. Soc.* **1982**, **104**, 5700.
(10) Bellville, D. J. Bauld, N. L.; *J. Am. Chem. Soc.* **1982**, *104*, 294.
(11) Bellville, D. J.; Chelsky, R.; Bauld, N. L. *J. Comput. Chem.*, in press.
(12) Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1974**, *96*, 5246.

Scheme VI. Proposed Mechanism for [2 + 1] Cycloaddition of Electron-Rich Alkenes



significantly, from a mechanistic viewpoint, the "cyclobutane cation radical" exists preferentially in an unsymmetric structure (**4**, Scheme VI), which has one long (1.92 Å), one-electron carbon–carbon σ bond. This structure, and the transition state leading to it, closely resembles the unsymmetrical transition state of the nonsynchronous, but concerted, path proposed for the cation-radical Diels–Alder. The corresponding MINDO/3 activation energies are 2.5 and 8.7 kcal mol^{-1}, respectively, but the sole cyclbutane cation-radical structural minimum was located at a more or less traditional (but rhomboid) closed cyclobutane geometry. Although MNDO has proved superior to MINDO/3 in virtually every cation-radical application explored in this laboratory, it was thought desirable to further test the MNDO structural prediction via optimized ab initio SCF MO calculations. The Gaussian 76 package with an STO-3G basis set was employed. Beginning with either a square or rhomboid cyclobutane, the same optimum cyclobutane cation-radical structure was located. The geometry closely resembles the MNDO geometry, having a long bond distance of 1.85 Å (see **5**). Recent optimized, extended basis set ab initio SCF MO studies have strongly supported long-bond structures for alkane σ cation radicals generally,[9] and CIDNP studies specifically point to nonequilibrating long-bond structures for the *cis*- and *trans*-1,2-diphenylcyclopropane cation radicals.[13] Moreover, the possibility of an open, diradical-type intermediate in the [2 + 1] cycloaddition is virtually ruled out by the recent finding that the [2 + 1] cation-radical cycloadditions of *cis*- and *trans*-anethole are stereospecific.[14] On the other hand, this latter result is in excellent accord with the long-bond mechanism, assuming only that cis/trans isomerization in the long-bond cyclobutane is slow relative to closure. This constraint would be expected to be fulfilled in view of the CIDNP results cited above and the finding that the dissociation energy for the one-electron bond of the ethane cation radical is 38 kcal mol^{-1}.[9]

Final cyclization to a normal cyclobutane-type structure appears feasible only when readily ionizable substituents such as π substituents are present, preferably at the termini of the one-electron bond. In such cases, the hole can be readily transferred to the substituent and then filled by electron transfer. Although the possibility of hole filling at the long-bond stage, followed by rapid cyclization of the diradical, cannot, perhaps, be confidently eliminated, the stereochemical results do not appear consistent with this mechanism.[14] A concerted process, consisting of simultaneous hole filling and cyclization would, however, be compatible with these results, and would provide a means for cyclization of even simple alkenes lacking ionizable substituents. At present, no evidence exists to distinguish the concerted as opposed to the two-step final cyclization process.

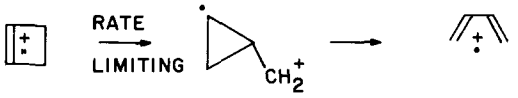
The theoretical results thus provide an excellent basis for understanding the extraordinary facility of the [2 + 1] cycloaddition, in spite of the fact that the reaction is symmetry forbidden. The detailed mechanism suggested by both the theoretical and experimental results is quite exceptional and is reproduced in Scheme VI for electron-donor-substituted alkenes.

Cation-Radical Cope Reaction. Two examples of the cycloaddition subclass of pericyclic reactions have now been discussed,

(13) Roth, H. J.; Mannion, M. *J. Am. Chem. Soc.* **1981**, *103*, 7210.
(14) Bauld, N. L.; Pabon, R. *J. Am. Chem. Soc.*, submitted for publication.

Scheme VII. Proposed Mechanism of Cation-Radical Cope Reaction

Scheme VIII. Nonelectrocyclic Mechanism for Cleavage of the Cyclobutene Cation Radical



one of them (the Diels–Alder) being of the symmetry-allowed and the other (olefin cycloaddition) of the symmetry-forbidden variety. To further broaden the investigation, an important member of the sigmatropic subclass, viz., the cation-radical Cope reaction, was also studied. This reaction path was studied prior to the switch to MNDO and hence uses MINDO/3. The reaction coordinate adopted was the C_1–C_6 distance in the 1,5-hexadiene cation radical. Depending upon the specific conformation assumed for the starting diene cation radical, paths of approximate (but not constrained) C_s or C_2 symmetry could be developed, corresponding roughly to boat- and chair-like conformations of the transition state, respectively. The C_s path was studied in greatest detail and has the phenomenally low activation energy of 1.4 kcal mol^{-1}. The C_2 path also had an activation energy less than 2 kcal mol^{-1}. In view of the inability of MINDO/3 to detect long-bond intermediates, it is assumed that the proper intermediate (if indeed one exists in reality) is the long-bond form illustrated in Scheme VII, rather than the open (1,4) diradical-type structure calculated by MINDO/3. Given the inability of both MINDO/3 and MNDO to properly describe the concerted nature of allowed pericyclic processes such as the Diels–Alder and Cope reactions, it is considered possible that the cation-radical Cope, like the neutral Cope, is actually concerted.

The second stage of the Cope reaction is, of course, merely the reverse of the first, with bond cleavage at C_3–C_4. Thus, it is clear that this stage must also have minimal excess activation requirements. There is, however, a thermodynamic obstacle to realization of the second stage of the cation-radical Cope reaction in the prototype (1,5-hexadiene) system. This reaction is calculated by MINDO/3 to be 34 kcal mol^{-1} endothermic. Although the actual "thermodynamic barrier" may be considerably less than that calculated, there appears little doubt that hole formation does greatly favor the cyclized diradical-type intermediate relative to the diene cation radical. Nevertheless, it should be easily possible for electron-donor substituents at C_3 and/or C_4 to overturn this effect and render the cation-radical Cope reaction a viable and potentially facile process.

Electrocyclic Reactions. The retroelectrocyclic cleavage of the cyclobutene cation radical to the 1,3-butadiene cation radical has already been the subject of a detailed theoretical report, but the results are highly pertinent to the theme of this paper. Both MINDO/3 and MNDO reaction path studies find values for the activation energy of the preferred conrotatory ring opening (constrained to C_2 symmetry) which are amazingly high in comparison with the other cation-radical pericyclic processes reported here (34 and 31 kcal mol^{-1}, respectively). However, in agreement with the principles developed earlier in this paper, the true (lowest energy) reaction path connecting the two species mentioned is a far less symmetrical one, which is not even considered an electrocyclic path. This path involves ring contraction to a cyclopropylcarbinyl type structure (Scheme VIII), followed by cleavage to the conjugated diene cation radical. This path has a MINDO/3 activation energy of only 21 kcal mol^{-1}. The existence of the intermediate in this case is confirmed by extended basis set optimized ab initio SCF MO calculations. The calculated ab initio activation energy (20 kcal mol^{-1}) agrees extremely well with the

MINDO/3 value. The cyclobutene cation radical electrocyclic reaction thus ideally illustrates the point that cation-radical pericyclic reactions are only modestly faster than the neutral variety where highly synchronous paths are involved.

Summary

Hole formation (ionization) is predicted to accelerate a variety of pericyclic reactions, especially those in which highly nonsynchronous transition states are readily accessible. The cation-radical Diels–Alder reaction path is characterized as concerted and highly nonsynchronous. The reaction path for the [2 + 1] cycloaddition emerges as a two-step sequence. An intermediate long-bond cyclobutane cation radical is formed via a nonsynchronous process, but the one-electron bonding in this usual intermediate is capable of maintaining stereochemical relationships. Reaction paths for the cation-radical Cope reaction and for the retroelectrocyclic cleavage of the cyclobutene cation radical are also discussed.

Hydrolysis of Imidazole-Containing Amide Acetals

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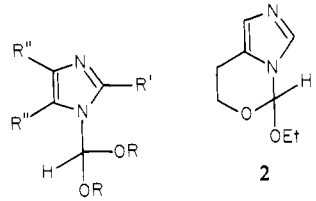
Abstract: *N*-(Dialkoxymethyl)imidazoles (amide acetals **1a–c**) are shown to hydrolyze by a common mechanism between pH 1 and pH 11 that involves preequilibrium protonation of the imidazole distal N, followed by rate-limiting C–N cleavage. The Brønsted plot of the log C–N cleavage rate vs. pK_a of the parent imidazole has a slope of −1.0 and suggests a transition state in which (+) is nearly completely transferred to the departing dialkoxymethyl group. Throughout the pH range studied, C–N cleavage is the dominant process. The bicyclic amide acetal **2** formed from 4(5)-(hydroxyethyl)imidazole and triethyl orthoformate behaves similarly to the acyclic cases at pHs >5 except that the observed rate of C–N cleavage for the former is depressed by (1–2) × 10^2-fold. This apparent reduction of C–N cleavage rate is analyzed in terms of reversibility of the ring opening. Such reversal is demonstrated by the ability of good nucleophiles such as N_3^- or H_2NOH to trap the open ion, preventing reversal and hence increasing the apparent rate of loss of **2**. From pH 0 to pH 5, an additional sigmoidal event in the pH/log k_{obsd} profile for **2** is observed, which is analyzed as a protonation of the imidazole of the open ion. Such a protonation prevents the reversible reclosure and concomitantly increases the k_{obsd}. Bicyclic **2** can be taken as a model for the tetrahedral intermediate formed during intramolecular alcoholysis of an *N*-acylimidazole or intramolecular attack of an imidazole on an ester.

Some time ago we reported[2] what proved to be an easily introduced and removed protecting group for the imidazole N. An *N*-dialkoxymethyl group can be easily introduced by heating the parent imidazole and trimethyl or triethyl orthoformate in the presence of a catalytic amount of H^+ and removing the corresponding alcohol as it is formed. Isolated yields of protected products are generally high (>80%),[3a] and a variety of electrophiles can be introduced at C-2 of the imidazole following lithiation of it at −40 °C by using *n*-BuLi.[3b,c]

An additional virtue of this protecting group is its ease of removal that can be effected by stirring with aqueous or methanolic acid or, if the final product is H^+ labile, under essentially neutral conditions with aqueous acetone. Mechanistically, an understanding of the deprotection process is desirable not only for determining the optimum conditions for effecting it but also because the amide acetal unit in **1** closely resembles the tetrahedral intermediate resulting from imidazole attack on an ester or alcoholysis of an *N*-acylimidazole. Similarly, that same unit in **2** could be taken as a model for the intermediate formed during intramolecular imidazole attack on an ester or alcohol attack on an *N*-acylimidazole, the latter two processes being of direct relevance to a number of biological processes involving the serine proteases.[4]



1a, R′ = R″ = H
b, R′ = CH_3, R″ = H
c, R′ = R″ = CH_3

2

Although some excellent and informative studies of the decomposition of amide acetals have been reported,[5] none of those has incorporated an imidazole as the N-bearing substituent. This simple structural change will be seen to significantly perturb the pH/rate constant profiles relative to those observed for secondary amine[5a] or anilide[5b] amide acetals. In the following we report a kinetic study of the hydrolyses of **1a–c** and **2** in aqueous media.

Experimental Section

Routine NMR, IR, and mass spectra were determined by using Bruker WP-80, Nicolet FTIR, and AEI-MS50 spectrometers. Compounds **1a–c** were prepared as previously reported.[2,3c] Bicyclic **2** was prepared in 26% overall yield from 1,4-dihydroxy-2-butanone[6a] (converted to 4(5)-(hydroxyethyl)imidazole by the method of Schunack.[6b] This product was extracted from an aqueous solution of the crude reaction mixture[6b] with several portions of *n*-butyl alcohol,[6c] which were

(1) Alberta Heritage Medical Research Foundation Summer Student, 1982.

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(3) (a) We have also explored the possibility of introducing dialkoxyethyl groups to the imidazole N by treatment with triethyl or trimethyl orthoacetate under the same conditions. This reaction is only successful for imidazole itself and fails when methyl substituents occupy the 2- and/or 4- and 5-positions, the only isolable products being the corresponding *N*-ethyl- or *N*-methylimidazoles in variable yield. (b) Brown, R. S.; Curtis, N. J.; Huguet, J. *J. Am. Chem. Soc.* **1981**, *103*, 6953–6959. (c) Brown, R. S.; Salmon, D.; Curtis, N. J.; Kusuma, S. *Ibid.* **1982**, *104*, 3188–3194.

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