Theoretical Analysis of Selectivity in the Cation-Radical Diels–Alder

Dennis J. Bellville, Nathan L. Bauld,* Raul Pabon, and Steven A. Gardner

Contribution from the Department of Chemistry, The University of Texas, Austin, Texas 78712.

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Abstract: Chemo- and regioselectivities in the cation-radical Diels–Alder reaction are interpreted theoretically using a charge-denisty analysis and also PMO theory. Diene cation radicals acting as Diels–Alder dienophiles tend to react at the position of highest positive charge density, but steric effects and product character development are also significant factors. The position of highest negative charge density in the neutral diene tends to combine with the most reactive site in the dienophile cation radical. A PMO theory appropriate to cation-radical pericyclic reactions is also developed and successfully applied to the prediction of these same selectivity elements. The extremely high endo stereoselection observed in some cation-radical Diels–Alder reactions is interpreted, via PMO theory, in terms of secondary interactions.

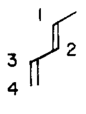
The tactic of enhancing the dienophilicity of neutral or electron-rich dienophiles by converting them, via electron transfer, to highly electron-deficient cation radicals has proved enormously successful.[1,2] The resulting cation-radical-catalyzed Diels–Alder reaction is characterized by exceptionally high reaction rates, suprafacial stereospecificity, and an impressive array of stereoselectivities which, in some instances, approaches exclusivity. Conjugated dienes, styrenes, and electron-rich alkenes, among others, can function as potent dienophiles when converted to cation radicals by triarylaminium salts or by photosensitized electron transfer. The stereospecificity of the reaction has been rationalized on the basis of orbital correlation diagrams, which reveal it to be allowed. Moreover, the cycloaddition is role selective, being allowed for the addition of an ionized dienophile to a neutral diene component, but forbidden for the addition of a neutral dienophile to an ionized diene component. The profound effect of dienophile ionization on the Diels–Alder reaction rate has been interpreted theoretically and extended to other types of cation-radical pericyclic reactions.[3] The focus of the present paper is the exceptional selectivity profile of the cation-radical Diels–Alder, which has previously been commented on only rather briefly.[2] The theoretical analysis to be presented provides the necessary basis for rationalizing and predicting the endo/exo-, regio-, and chemoselection patterns observed for the cation-radical Diels–Alder.

Chemoselectivity and Regioselectivity

Chemoselection (or, alternately, site selection), in the present context, refers to discrimination between chemically nonequivalent double bonds, particularly in an unsymmetrically substituted, conjugated diene acting in the Diels–Alder dienophilic role. Regioselection refers to the head-to-head or head-to-tail orientational choice involved when both diene and dienophile are unsymmetrically substituted, thereby offering the possibilities of (for example) "ortho" vs. "meta" substitution patterns on the cyclohexene ring of the adduct.

Chemoselection, regioselection, and endo stereoselection patterns have been reported for several cation-radical Diels–Alder reactions and are summarized in Table I. Regioselection is essentially complete in every instance, within experimental error (±1%). Chemoselection is also virtually complete in six of the eight cases, but endo stereoselection is widely variable. The reactions of all dienes except **3**, **5**, and **7** refer to addition to 1,3-cyclohexadiene. Those of **3**, **5**, and **7** are Diels–Alder dimerizations.

Direct comparison of these chemoselectivities with those of corresponding uncatalyzed Diels–Alder reactions would be relevant, but such data have not been reported and are not readily available because of the extreme inefficiency of the uncatalyzed Diels–Alder when dienes are employed as dienophiles. However, a number of indirect observations suggest that chemoselection in uncatalyzed cycloadditions can be quite substantial, even when based only on differential alkyl group substitution patterns. In the addition of a series of α-substituted fumaric acids to anthracene, for example, methyl substitution engenders a 150-fold decrease in reaction rate.[4] The [2 + 2] cycloaddition of 1,1-dichloro-2,2-difluoroethane to 1,3-pentadiene occurs with virtual exclusivity at the less substituted double bond.[5] These observations are in keeping with the tradition that the uncatalyzed Diels–Alder (and other cycloadditions) is a sterically sensitive reaction.[6] Thus, the observation that the cation-radical Diels–Alder is quite chemoselective is not astonishing per se, but is noteworthy especially in the context of the extreme rapidity of the reaction, an attribute which is usually associated with low selectivity. Moreover, the qualitative sense of chemoselection is reversed in the cation-radical Diels–Alder as illustrated particularly by the simpler dienophiles (**1–3**). In these cases, reaction occurs predominantly at the more highly substituted dienic double bond, suggesting that steric effects are less important than in the uncatalyzed Diels–Alder. Nevertheless, where the more highly substituted double bond has one terminal *gem*-dialkyl substituent and the other terminal carbon is monosubstituted (the (2,1) terminal substitution pattern), preference returns to the less substituted double bond, suggesting that steric effects are still significant in the cation-radical Diels–Alder and in these specific cases are dominant. However, the simultaneous operation of another major effect, which is dominant in all other cases, is apparent.



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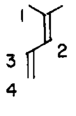

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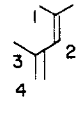

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Prior to the present work, little was known concerning site selectivity in cation-radical reactions or the factors which control or correlate with this selectivity. The mass spectrometric reaction of the fulvene cation radical with 1,3-butadiene, which was found to result in the formation of a [6 + 4]-type cycloadduct, was rationalized on the basis of the high charge densities at the C_2 and C_6 positions of the fulvene cation radical.[7] The concept that charge densities might be a major factor in determining the preferred sites of reactivity in a delocalized cation radical appears especially plausible when one considers that the preferred site(s) of reaction of delocalized carbocations (e.g., allylic, benzylic, and pentadienylic carbocations) with nucleophiles are often correlated with charge densities.[8] Theoretically, the existence of a charge

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[1] Bellville, D. J.; Wirth, D. D.; Bauld, N. L. *J. Am. Chem. Soc.* **1981**, *103*, 718.

[2] Bellville, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1982**, *104*, 2665.

[3] Bellville, D. J.; Bauld, N. L., submitted for publication.

[4] Vaughn, W. R.; Anderson, K. S. *J. Org. Chem.* **1956**, *21*, 673.

[5] Bartlett, P. D.; Montgomery, L. K.; Seidel, B. *J. Am. Chem. Soc.* **1964**, *86*, 616.

[6] Sauer, J. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 16.

[7] Russell, D. H.; Gross, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 6279.

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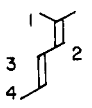
Table I. MINDO/3 Charge Densities and Stereoselection in the Cation-Radical Diels-Alder

diene	position	charge density in cation radical	chemo-selection (%)	charge density in diene	regioselection (%)	endo stereo-selection (%)
1	1	+0.233	100	–0.002	*a a*	100
	4	+0.192	0	–0.038	*a a*	*e*
2	1	+0.225	60	+0.002	*a a*	100[c]
	4	+0.204	40	–0.030	*a a*	60[d]
3	1	+0.222	100	+0.001	0	*e*
	4	+0.183	0	–0.032	100 ($C_1^{+\cdot}$-C_4°)[b]	*e*
4	1	+0.219	0		*a*	*e*
	4	+0.227	100		*a*	15
5	1	+0.183	0	–0.014	0	*e*
	4	+0.167	100	–0.020	100 ($C_4^{+\cdot}$-C_4°)	66
6	1	+0.122	0	–0.122	*a*	*e*
	4	+0.168	100	–0.079	*a*	60
7	1	+0.546[f]	0	+0.381[f]	0	*e*
	4	+0.179	100	–0.075	100 ($C_4^{+\cdot}$–C_4°)	65
8	1	+0.111[f,g]		–0.107[f]	*a*	
	2	–0.068	100	–0.033	*a*	75
	0	+0.031, 0.018		+0.002, –0.007	*a*	
	0	+0.264	0	+0.117	*a*	

[a] Not observed, cyclohexadiene used as diene component. [b] Implies C_1 of cation radical binds to C_4 of neutral diene. These are dimerizations. [c] Endo percentage in product of reaction at C_1 of cation radical. [d] Endo percentage in product of reaction at C_4 of cation radical. [e] Product not observed or not relevant. [f] Calculation employs hydroxyl in lieu of methoxy. [g] MNDO.

density–reactivity correlation is usually taken to imply a somewhat reactant-like transition state,[8] a circumstance most often associated with relatively exothermic reactions. Although it is generally less exothermic than the neutral Diels–Alder, the cation-radical Diels–Alder is apparently substantially exothermic[3] and could reasonably be assumed to have an early (relatively reactant-like) transition state. This possibility appears even more likely when the abnormally low activation energy for these reactions is considered.

Indeed, the observed chemoselectivities in the cation-radical Diels–Alder (Table I) correlate qualitatively moderately well with MINDO/3 charge densities at the terminal diene carbons, and, in fact, very well when account is taken of the competing steric factor discussed earlier. The charge densities at the terminal diene carbons, specifically, are appropriate for two reasons. Firstly, the SOMO (singly occupied MO) eigenfunction is most heavily weighted at the termini, giving rise to greater positive charge densities at these positions. Secondly, the reaction path for the cation-radical Diels–Alder reaction has been inferred to be rather highly nonsynchronous, with extensive bond formation at the terminal carbon but with much less substantial development of the bond to the adjacent dienophile position.[3] Because of the concentration of the SOMO on the terminal carbons, electron donor groups stabilize such diene cation radicals more effectively when attached to a terminal carbon. Terminal alkyl groups, specifically, tend to draw more positive charge to the terminal carbon to which they are attached (see Table I), thus accounting for the preference of the simpler diene cation radicals to react at the more highly substituted terminus. For some reason (it is not entirely clear why) MINDO/3 predicts greater charge densities at the less substituted termini (C_4) of **4** and **6**, thereby preserving the charge-density correlation. The charge-density differential is extremely small, however, and is reversed with **5**, which nevertheless maintains the consistent pattern (in these (2,1) substituted dienes) of preferred reaction at the less substituted terminus. It appears plausible to propose that in all of these latter cases (**4**–**6**) the extremely small charge-density differential coupled with the presence of a disubstituted terminus alters the balance of steric and charge-density factors and produces a dominant steric effect. Nevertheless, charge densities correctly predict the preferred site of reactivity in every case except **5**. In the more complex diene **6**, the preference has reached virtual exclusivity.



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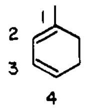

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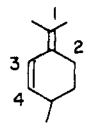

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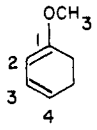

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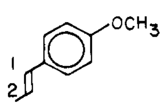

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Reaction is exclusively at the least substituted double bond in 1-methoxycyclohexadiene (**7**), in formal agreement with the combined charge-density/steric effect rationale, considering that this diene has one disubstituted and one monosubstituted terminus. However, this case demands more detailed consideration. The terminal methoxy group, being a strong π-electron-donor group, powerfully draws positive charge to the attached diene terminus. The charge differential (Table I) is now so large as to appear highly unlikely to be dominated by a modest steric effect. This assertion still appears valid even if the charge associated with the carbon–oxygen σ bond is ignored and only π charges are considered. A much more plausible explanation for the exclusive reaction at the less substituted double bond in this diene therefore takes into account the relatively unfavorable thermodynamics of the reaction at the double bond substituted by the methoxy group. When reaction occurs at this latter double bond, the methoxy group is removed from conjugation, and the resulting adduct cation radical is a simple alkene-type cation radical, of comparable thermodynamic stability to those formed in the cation-radical Diels–Alder of hydrocarbon dienes. However, the reactant diene cation radical is powerfully stabilized by the terminal methoxy group, engendering a major loss in exothermicity and quite possibly even rendering the reaction thermodynamically unfavorable. On the other hand, reaction at the double bond remote from the oxygen function can generate a cation-radical adduct having a stabilized enol-ether-type cation-radical function. Indeed, since a methoxy group should stabilize a simple alkene cation radical more than a diene cation radical, the thermodynamics of this addition should be even more favorable than in the case of hydrocarbon dienes. To state the argument simply, it is logical to assume that any transition state has at least some product character and particularly so for a demonstrably pericyclic reaction. This product character is an additional factor which must be considered, especially when the reaction, because of a loss in thermodynamic impetus, acquires greater product character. The foregoing analysis is strongly supported by studies currently being pursued, which find a similar chemoselection pattern for dienes having terminal oxygen functions but lacking the terminal disubstitution pattern.

The styrene-type dienophile (*trans*-anethole, **8**) is formally similar to **7** in that addition to the aromatic ring, where highest charge densities reside, is thermodynamically unfavorable. Reaction therefore occurs exclusively at the exocyclic double bond.

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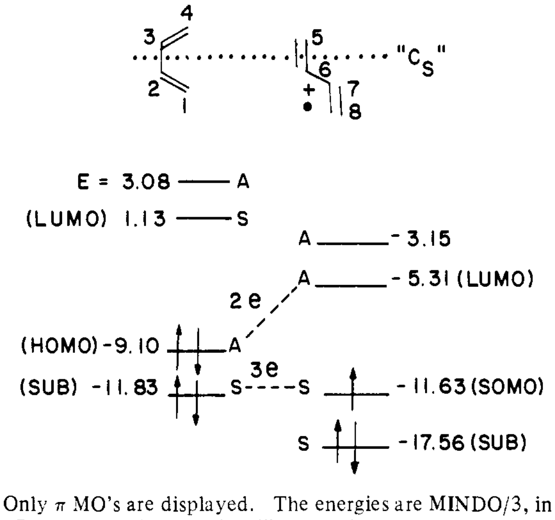
(8) Streitwiesser, A. "Molecular Orbital Theory for Organic Chemistry", Wiley: New York, 1961, pp 378–9.

Scheme I. PMO Energy-Level Diagram of Cation-Radical Diels–Alder Dimerization of 1,3-Butadiene[a]



[a] Only π MO's are displayed. The energies are MINDO/3, in eV. The C_s symmetry is only "local" or quasi-symmetry.

The charge-density theoretical framework can also be extended to provide a simple treatment of regioselection using the premise that the terminal site of highest negative charge density (Table I) in the diene component combines preferentially with the dienophile terminus of highest positive charge density. Regiochemical outcomes have been observed in the dimerizations of dienes **3**, **5**, and **7** and in each case the product structure is correctly predicted by this simple scheme (Table I). Similarly, the dimerization of **7** to a head-to-head cyclobutane structure (although not, of course, a Diels–Alder addition) is correctly anticipated.

PMO Theory of Chemo/Regioselecivity. Although it does not appear feasible to interpret the chemo/regioselectivity results without taking separate account of steric effects, it is feasible to construct a PMO theory which appears to unify the charge-density and product character aspects of the previously described charge-density theory. The strategy of the PMO (perturbation molecular orbital) theory is to adopt an abbreviated form of second-order perturbation theory (eq 1) which takes into account

$$\Delta E_m = \sum_{n \neq m} \frac{P_{mn}^2}{E_m - E_n} \qquad (1)$$

$$P_{mn} \approx a_{1m}a_{6n}\beta_{1,6} + a_{4m}a_{5n}\beta_{4,5} \qquad (2)$$

only the strongest (usually filled-vacant, symmetry-allowed) interactions.[9] An extreme form of the PMO theory is the FMO (frontier molecular orbital) approach, in which only the two HOMO–LUMO interactions, or even just the leading one of these, is considered.[10,11] It will be apparent that the development of a simple PMO theory of cation-radical pericyclic reactions is not merely a routine exercise in FMO theory since the significance of frontier orbitals is blurred in the context of a species with an unpaired electron. Moreover, a unique new element, the SOMO (singly occupied MO) is introduced. The analysis derived here begins with the second-order perturbation expression (eq 1) and uses the simplyfing assumption that charge transfer is unilateral, proceeding only from the diene component to the cation radical, since the latter species is unlikely to be an effective donor. Consequently, interactions between the SOMO or any of the filled MO's of the diene cation radical (Scheme I) and a vacant diene MO are ignored as negligible. Of the remaining interactions, which involve filled diene MO's interacting with vacant cation-radical MO's or with the SOMO, two stand out as most significant based upon the energy gaps between the interacting MO's (denominator in eq 1). It will be noted that the diene cation-radical MO's are all powerfully stabilized, relative to the corresponding orbitals of the neutral diene, as a result of decreased electron repulsions. Consequently, the energy of the SOMO approaches that of the diene subjacent MO (the lowest energy π MO) unusually closely ($\Delta E = 0.21$ eV). The subjacent-SOMO interaction (hereinafter labeled the SUB-SOMO interaction for brevity) must therefore receive careful attention in any PMO analysis of the cation-radical Diels–Alder. The second most favorable symmetry-allowed interaction, from the standpoint of the energy gap, involves the interaction of the diene HOMO with the vacant cation-radical orbital immediately above the SOMO. Since the later orbital would correspond to the LUMO of a neutral diene molecule, this interaction is referred to as the HOMO-LUMO interaction. Though considerably disfavored relative to the SUB-SOMO interaction by the much larger energy gap (3.79 eV), the HOMO-LUMO interaction possesses two marked advantages. Firstly, it is a filled-vacant (two-electron) interaction, which allows the stabilized HOMO to be doubly occupied without populating the correspondingly destabilized LUMO. The three-electron SUB-SOMO interaction, in contrast, requires the population of the destabilized MO by one electron, thus greatly diminishing the net stabilization. In the Hückel approximation, and with neglect of overlap, the stabilization of the subjacent MO is equal to the destabilization of the SOMO, yielding a net stabilization of exactly one-half that in the two-electron case. Inclusion of overlap is known to engender a destabilization which is greater than the stabilization and hence to further diminish the net bonding in the three-electron case. The effects of including electron repulsion and correlation energy are presently uncertain, and it is therefore difficult to compare the efficacy of the two kinds of interaction quantitatively. Moreover, a second factor also favors the HOMO-LUMO interaction. The coefficients of the terminal diene carbons in the diene HOMO (0.561) are substantially larger than those in the diene subjacent MO (0.429). These coefficients affect the magnitude of the integral P_{mn} (which occurs squared) in the second-order perturbation expression. The relationship between the coefficients and the integral is expressed in eq 2. If one proceeds with the MINDO/3 energy gaps and coefficients and employs eq 1 and 2, assuming a three-electron interaction one-half as efficient as the two-electron interaction, the SUB-SOMO interaction emerges as dominant by a factor of 3.4. This calculation very probably underestimates the relative contribution of the HOMO-LUMO interaction both because of the inherent weakness of the three-electron interaction, as discussed above, and because the SUB-SOMO interaction relies exclusively, for its apparent dominance, on an energy gap which is so small as to be subject to considerable calculational uncertainty. In order to rationalize the full spectrum of selectivities observed in the cation-radical Diels–Alder, it will ultimately prove essential (vide infra) to include both interactions, and to consider them of comparable importance energetically, but with the HOMO-LUMO interaction actually somewhat surpassing the SUB-SOMO in magnitude.

Even though both interactions mentioned above must apparently be important energetic contributors, it is easily seen (Scheme II) that the SUB-SOMO interaction alone controls regioselection. This simple circumstance ensues as a result of the much greater differences between the two diene terminal carbon coefficients in the diene subjacent MO than in the diene HOMO. This disparity, which fundamentally controls regioselection, tends to be quite miniscule in the HOMO, but is very substantial in the subjacent MO. Consequently, only the SUB-SOMO interaction need be considered in predicting regioselection. Chemoselection is governed by the relative magnitudes of not only the terminal (C_1, C_4) but also the internal (C_2, C_3) coefficients of the diene cation radical. It does not appear to be true that the two competing double bonds are more highly differentiated in the SOMO than in the LUMO of the cation radical, but fortunately the trends of the coefficients in these MO's are parallel for at least the hydrocarbon dienes, and they both generate the same predictions in regard to chemoselection. Consequently, only the SUB-SOMO interaction need be considered for the purposes of predicting chemo/regioselection. Two illustrations are provided in Scheme

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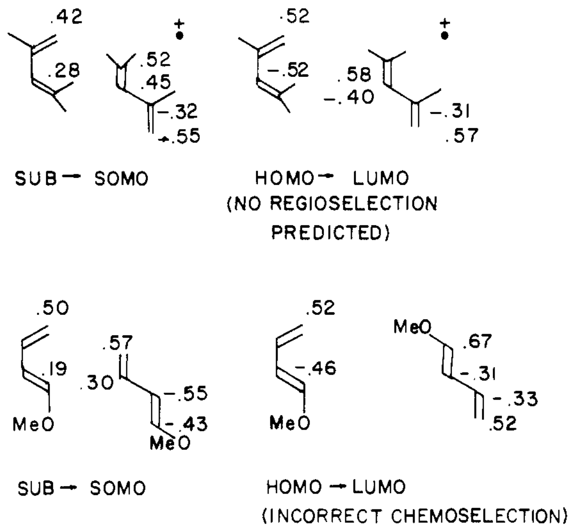
(9) Dewar, M. J. S. "The Molecular Orbital Theory of Organic Chemistry"; McGraw-Hill: New York, 1969; pp 47–53.

(10) Fukui, K.; Yonezawa, T.; Shingu, H. *J. Chem. Phys.* **1952**, *20*, 722.

(11) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

Scheme II. PMO Treatment of Chemo/Regioselection in 2,4-Dimethylpentadiene and 1-Methoxybutadiene[a]

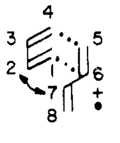


[a] Using MINDO/3 coefficients, but 1-hydroxybutadiene was used to simulate 1-methoxybutadiene.

II, but all of the reactions studied, including the oxygenated diene (but excluding the sterically controlled diene **5**), are correctly treated in regard to both chemo- and regioselection. Only the preferred relative orientations are illustrated in Scheme II, and it is easily verified from the coefficients provided and using eq 2 that these are, in fact, the preferred combinations. Use of the HOMO-LUMO coefficients to predict regioselection generates erroneous predictions in virtually every case.

Endo Stereoselectivity. In uncatalyzed Diels–Alder reactions which form bridged bicyclic adducts, preferred formation of the endo stereoisomer is traditional.[12] This preference can be exclusive for rather highly electron-deficient dienophiles such as maleic anhydride,[6] but more frequently it is modest, even when moderately electron-deficient dienophiles such as methyl acrylate (3:1) and acrylonitrile (60:40) are involved.[13] In a number of instances, including several involving dienophiles as simple as methyl methacrylate, outright violation of the endo rule is observed.[14] Somewhat curiously, cyclopentene and cyclopropene are also claimed to give mainly the endo product.[15,16] In any event, the normal selectivities are not impressively high, but can be improved greatly with Lewis acid catalysis[17] and modestly by use of polar solvents.[14] The overwhelming bulk of the endo stereoselectivity information refers to the formation of bicyclo[2.2.1]heptane ring systems from cyclopentadienes as diene components, but qualitatively similar trends have been suggested for reactions with cyclohexa-1,3-diene.[18] The latter is, in fact, a surprisingly sluggish Diels–Alder diene component, undergoing dimerization only slowly and inefficiently at temperatures above 200 °C, in contrast to the dimerization of cyclopentadiene at ambient temperatures. Consequently, many dienophiles are wholly or largely polymerized or otherwise decomposed before the temperatures requisite to Diels–Alder addition to cyclohexadiene are reached. To provide an additional and more direct comparison for the *endo* stereoselection data now available for the cation-radical Diels–Alder reactions, many of which involve additions of dienes to cyclohexadiene, the uncatalyzed Diels–Alder addition of *t,t*-2,4-hexadiene to 1,3-cyclohexadiene was studied. Although, as expected, the yield was less than 1.0% after reaction at 200 °C for 48 h, the endo and exo, trans adducts were nevertheless obtained, in an apparently stereospecific reaction. The exo isomer was found to predominate (2:1) in sharp contrast to the corresponding cation-radical addition, which leads to 99% of the endo isomer.

The fact that highly electron-deficient dienophiles tend to give the highest endo stereoselection and, further, that Lewis-acid catalysts increase the degree of endo stereoselection is consistent with the observation that the cation-radical Diels–Alder reaction, which involves a very highly electron-deficient dienophile, is capable of extremely high endo stereoselection. In each of the cases in which high endo stereoselection is observed,[2] the double bond of the dienophile which will eventually constitute the exocyclic double bond in the adduct lacks a cis substituent; i.e., it is either unsubstituted or has a trans substituent. In every case in which this exocyclic double bond has a cis substituent, the endo stereoselection is attenuated to a much more modest level or even reversed. The "*cis*-propenyl effect" is illustrated by 1,3-cyclohexadiene, which, in its dimerization, yields an endo:exo mixture of adducts in the ratio 5:1 and by *cis,cis*-2,4-hexadiene in its addition to cyclohexadiene, which yields endo and exo adducts in the ratio 2:1. Perhaps the most striking example of the *cis*-propenyl effect is the addition of *c,t*-2,4-hexadiene to cyclohexadiene. Addition to the cis double bond (generating a trans exocyclic propenyl group) gives the endo isomer exclusively, but addition to the trans double bond (generating an exocyclic *cis*-propenyl group) gives both isomers (endo:exo = 1:2). In the domain of endo:exo selectivity, therefore, two extraordinary features of the cation-radical Diels–Alder warrant theoretical attenuation, viz., the extremely high inherent endo stereoselection observed with simpler dienes as dienophiles and the attenuation of this effect by cis substituents.



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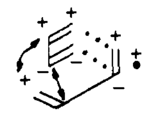

(HOMO-LUMO)

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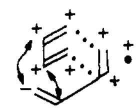

(SUB-SOMO)

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Endo stereoselection in the Diels–Alder reaction has been interpreted theoretically in terms of "secondary interactions", i.e., remote orbital interactions, in the Diels–Alder transition state (**9**).[19] Specifically, C_7 of the dienophile and C_2 of the diene are potentially proximate enough to interact significantly in the endo but not the exo transition state, and this interaction appears, in an FMO analysis, to be bonding. Whether this undoubted stabilizing effect is large enough to overcome the electron and nuclear repulsions which are likewise concomitants of the closer approach of C_2 and C_7 is perhaps uncertain. The superior endo stereoselection and the attenuating *cis*-propenyl effect which characterize the cation-radical Diels–Alder therefore represent a unique opportunity to probe the viability of the FMO secondary effect theoretical framework in a distinctly new context. The PMO analysis developed earlier can be directly applied to secondary effects. As will be recalled, it appeared desirable, in cation-radical pericyclic reactions, to retain two primary interactions from the full array of second-order perturbations, viz., the two-electron HOMO-LUMO interaction and the three-electron SUB-SOMO interaction. The coefficients for the pairs of interacting MO's are displayed in **10** and **11**, where it is evident that the C_2–C_7 interaction is bonding in the HOMO-LUMO but antibonding in the SUB-SOMO interaction. The HOMO-LUMO interaction is, incidentally, the same one which is considered to engender endo stereoselection in the uncatalyzed Diels–Alder. As was alluded to earlier, it is therefore necessary to assume that the HOMO-LUMO interaction remains the leading source of stabilization in the cation-radical Diels–Alder, dominating the SUB-SOMO in-

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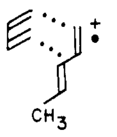
teraction. Indeed, the HOMO-LUMO interaction is expected to be greatly enhanced in the cation-radical version because of the stabilization of the cation-radical LUMO, mentioned earlier. A MINDO/3 calculation yields a HOMO/LUMO energy gap of 1.1339 - (-9.0995) = 10.23 eV for the uncatalyzed reaction and only -5.3067 - (-9.0995) = 3.79 eV for the cation-radical version. Although it may now seem curious, superficially, that the SUB-SOMO interaction, though energetically less important, should control chemo/regioselection, the appropriate basis for this was prepared earlier and related to the miniscule differentiation of the diene terminal carbons in the diene HOMO.

The simple PMO approach therefore appears to provide a potentially plausible basis for enhanced endo stereoselection in the cation-radical Diels-Alder as a consequence of the decreased energy gap, although one might legitimately wonder to what extent the SUB-SOMO effect, with its secondary antibonding interaction, may diminish the HOMO-LUMO stabilization. The *cis*-propenyl effect, fortunately, provides further insights to guide the evolution of the theory of endo stereoselection. In particular, it appears highly unlikely that a methyl group on the terminal (exocyclic) dienophile carbon could significantly affect the choice of endo vs. exo transition states for a dienophile in an s-trans conformation (**12**). In contradistinction, a cis terminal alkyl group in an s-cis dienophile would be expected to encounter very appreciable steric repulsions (**13**). The proposal of an s-cis diene cation-radical conformation, at least for those dienes which exhibit high endo stereoselection, is also plausible in terms of PMO theory. In this conformation a new interaction (C_3–C_8) is potentially incurred in the transition state, and FMO theory (**10**) reveals this also to be bonding in the HOMO-LUMO interaction. In fact, since the LUMO coefficient at C_8 is considerably larger than at C_7, the new interaction could be expected to augment the familiar C_2–C_7 interaction in a major way, and thus provides a further and probably more important reason for the enhanced stereoselection in the cation-radical Diels-Alder.



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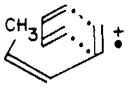

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These considerations and conclusions arouse curiosity concerning the questions of whether s-cis dienophile conformations are important in the uncatalyzed Diels-Alder and, if not, why they are uniquely important in the cation-radical version. Although the first question is not easily answered at present, some useful insights are available apropos of the second. Evidence is available that anion radicals of α-diketones and dienes often prefer the s-cis conformation, especially in less polar solvents, as a consequence of chelate-like ion pairing.[20] A similar effect should be capable of stabilizing diene cation radicals, and methylene chloride is a solvent in which ion pairing would reasonably be anticipated. It is, of course, unnecessary to assume that the diene cation radical exist exclusively in the s-cis conformation, but if they do not, the s-cis conformation must be assumed to be more reactive. Specifically, this enhanced reactivity could emanate from the stabilizing secondary interactions. In accord with these conclusions, the endo:exo ratio in the addition of *t,t*-2,4-hexadiene to cyclohexadiene is decreased to 8:1 in acetonitrile, a solvent in which ion pairing should be attenuated. In contrast, the endo selectivity in the cation-radical dimerization of cyclohexadiene (a rigidly s-cis diene) is increased to 8:1 in acetonitrile (from 5:1).

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Registry No. 1, 504-60-9; **2**, 926-56-7; **3**, 1000-86-8; **4**, 28823-41-8; **5**, 4313-57-9; **6**, 586-63-0; **7**, 2161-90-2; **8**, 104-46-1; 1,3-cyclohexadiene, 592-57-4.

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12-s-Cis Conformationally Locked 11-*cis*-Retinoids: A Delineation of the Thermal Requirements for [1,5]-Sigmatropic Shifts and Electrocyclizations in the Vitamin A Series and Novel Spectral Properties[1]

Roshantha A. S. Chandraratna, Ann L. Bayerque, and William H. Okamura*

Contribution from the Department of Chemistry, University of California, Riverside, California 92521. *Received November 19, 1982*

Abstract: The thermally induced [1,5]-sigmatropic rearrangement (69 °C, 4 h) of the six-membered ring fused vinylallenol **5b**, a process specific for preparing 11-*cis*-retinoids, afforded **24** (12%) and the 12-s-cis-locked retinols 11-*cis*-**7a** (14%), 11-*cis*,13-*cis*-**8a** (33%), and 9-*cis*,11-*cis*,13-*cis*-**9a** (23%). The formation of the tetracyclic compound **24** is rationalized on the basis of further electrocyclizations of the putative 9-cis,11-cis-isomer **25**. In the corresponding seven-membered ring fused vinylallenol **6b**, the thermal threshold (room temperature) for [1,5]-sigmatropic hydrogen shift was sufficiently lowered to enable the isolation of all four possible geometrically isomeric 11-*cis*-retinols **10a**, **12a**, **13a** and the previously elusive 9-cis,11-cis-isomer **11a**. In a separate experiment, the latter (**11a**) was shown to isomerize to the tetracyclic compound **29** analogous to the putative transformation of **25** to **24** in the six-membered ring fused series. Oxidation of the retinol analogues **7a**–**13a** yielded the corresponding retinals **7b**–**13b**. Unlike in most previously reported retinals, which exhibit prominent ultraviolet α bands and weak β bands, in these 12-s-cis-locked retinals, there is a dramatic reversal in the intensity of these bands. In fact, the 12-s-cis-locked aldehydes exhibit their main maximum (~288–300 nm) slightly to lower wavelengths than the corresponding alcohols (~298–309 nm).

Introduction

A multitude of findings in recent years has clearly established the position of retinoids (vitamin A) as ubiquitous substances of importance in biological systems. Retinoids of interest include 11-*cis*- and 9-*cis*-retinal in vision,[2] 13-*cis*- and *all-trans*-retinal in energy transduction,[3] 13-*cis*-retinoic acid in acne therapy,[4]

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