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A PERTURBATIONAL MO METHOD APPLIED TO DIELS–ALDER REACTIONS WITH UNSYMMETRICAL DIENES AND DIENOPHILES

PREDICTION OF THE MAJOR PRODUCT

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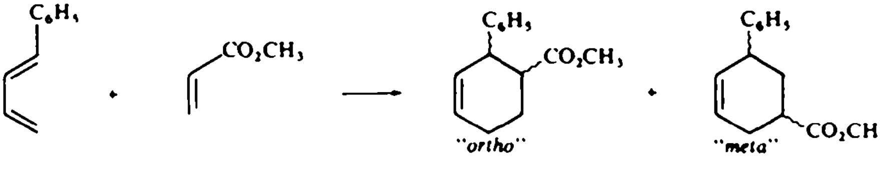
INTRODUCTION

In general, the products of Diels–Alder reactions may be predicted with reference to three rules, mainly elucidated by Alder and Stein.[2]

1. The diene in cisoid conformation combines with the dienophile to yield a 6-membered ring product.
2. The principle of *cis* addition is followed, that is, the relative orientation of groups in the dienophile is preserved in the final adduct.
3. The "*endo* addition rule" is obeyed. During a Diels–Alder synthesis the two reactants are preferentially oriented in *endo* configurations.

In this paper, we will discuss an element of stereoselectivity which is not covered by these rules. If both diene and dienophile are asymmetrically substituted, cycloaddition can lead to two structural isomers. Typical examples are the reactions of *trans*-1-phenylbutadiene and 2-phenylbutadiene with methyl acrylate.[3] The reaction is highly selective, leading to over 97% of the "*ortho*" isomer in reaction 1, and to approximately 80% of "*para*" product in reaction 2. These patterns of substitution



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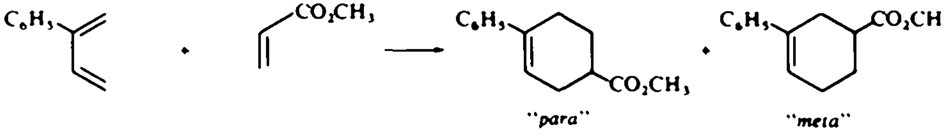

(2)

in the adducts are the general results for these types of reactions.[4,5] The conclusion that subtle electronic and steric effects are operating in these systems seems inescapable.

The resonance theory approach to this problem of positional isomerism is outlined in a review article by Ettlinger and Lewis.[6] If one is adept at the art of drawing and interpreting resonance structures, it is possible to predict the product formed in highest yield in most cases. Dewar[7] has pointed out several possible objections to a treatment of this kind. One important objection is that in the resonance theory approach, post facto manipulation of the results are possible and sometimes even necessary. The weighting of resonance structures is nearly always a matter of opinion. Another objection is that the results of resonance theory are not suitable for the quantitative correlations and predictions which are of interest in physical-organic chemistry.[*]

MO treatments of the Diels–Alder reaction have appeared sporadically over the last 30 years, but none of these are concerned with the aspect of positional selectivity. Earlier work, which is reviewed by Streitwieser,[9] includes that of Evans[10] who postulated a benzene-type model for the transition state of the Diels–Alder reaction between butadiene and ethylene, and several papers by Brown[11] who defined a MO index called the *para*-localization energy[11b] which can be used a a reactivity crierion for a diene in the Diels–Alder reaction. This localization energy is the decrease in energy calculated upon the removal of the specified 2p π orbitals from the π system. The usefulness of the general idea has been demonstrated by several workers[11–13] and the concept has even been extended to a very nice correlation of experimental data for iron and chromium tricarbonyl derivatives of unsaturated hydrocarbons.[14]

Unfortunately, the interaction between the dienophile and the diene is neglected in the localization energy treatment, so the selectivity of any specific Diels–Alder reaction is not understandable on that basis. The status of the problem is summarized by Sauer[15] in the statement that "No satisfactory explanation can be given for the orientation phenomena."

Several recent papers have advanced ideas and methods which could be used in attacking the problem of orientation selectivity. If the number of atoms involved is not too great, one could carry out extended Hückel[16] or approximate SCF[17] calculations on several postulated transition complexes. Those of lower energy ought to correlate with observed reaction pathways. This approach was evidently used in providing confirmation of the various Woodward–Hoffman rules,[18] but the number of such studies which can be made is certainly limited by financial considerations.

Another possibility would be to use perturbational MO methods (PMO) which have been outlined and advocated by Dewar,[7,12,19–21] Fukui,[22] and Hudson and Klopman.[23] Applications of perturbational methods have already been applied to the problem of *endo-exo* isomerism in Diels–Alder reactions by Tyutyulkov and Markov,[†] and Herndon and Hall.[25,26] The latter workers also found an excellent correlation of the relative rates of several Diels–Alder reactions with calculated perturbation energies.[25] Because of the ease with which a PMO method can be

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[*] Recent papers[8] propose a semiquantitative theory of resonance. This would be very difficult to apply to the reactions considered in the present paper

[†] Papers[24] which antedate our work (Ref 25) were graciously brought to our attention by Dr Markov.

applied, and because of the success of earlier work, this is the approach which we will use in this paper.

THEORETICAL METHOD

The Diels–Alder reaction is considered to be a concerted 4 + 2 cycloaddition.[27] As the diene and dienophile approach one another in the orientation required for reaction, new bonds begin to form between certain atoms of the diene and dienophile. The transition state model we choose resembles the adduct in gross geometry, but is postulated to be more closely related in electronic distribution to the reactant molecules. This choice of transition state is not arbitrary, but is in accord with the exothermicity of the reaction,[28] the zero entropies of activation for retro reactions,[28] the very small secondary isotope effects for Diels–Alder reactions,[29] and the larger effects in retro-Diels–Alder reactions.[30]

The procedure involves first a determination of wave functions and energies for the two separated reactant molecules. These follow from a solution of the usual secular determinant.[9] The Hamiltonian for the transition state is then considered to be $H_R + P$ where H_R is the Hamiltonian for the isolated reactant molecules and P is a perturbation Hamiltonian. The perturbation involves increases in the exchange integrals between the atoms of diene and dienophile from initial values of zero (isolated reactant molecules) to values characteristic of the interacting state. The perturbation energy can be defined in terms of the basis set of atomic orbitals, ϕ_m of the diene, ϕ_n of the dienophile, as a matrix element in the secular determinant for the perturbed system. Assuming no degeneracy between occupied orbitals of one reactant and vacant orbitals of the other reactant, there is no first-order perturbation energy change and the energy change to the second-order is given by Eq. 3. The superscripts occ., vac., refer to summations over all occupied and vacant molecular orbitals.

$$\Delta E = 2\left[\sum_{m}^{\text{occ.}} \sum_{n}^{\text{vac.}} - \sum_{m}^{\text{vac.}} \sum_{n}^{\text{occ.}}\right] \left[\sum_{i,j} a_{m,i} b_{n,j} P_{mi,nj}\right]^2 / (E_m - E_n) \tag{3}$$

The coefficients of the atomic orbitals are a_{mi} (diene) and b_{nj} (dienophile). The sum subscripted i, j is over all pairs of atoms i, j through which diene interacts with dienophile in the perturbed state. $P_{mi,nj}$ is the exchange integral for the interaction between atoms, i, j. This treatment is patterned after Dewar's[19] work on the applications of perturbational MO methods to reactivity and structure. It should be noted that the effects of nuclear and electron repulsion and nuclear-electron attraction are neglected in this simple approach.

In our previous work[25] we used extended Hückel wave functions as devised by Hoffmann[16] and considered all possible interactions. The exchange integrals were thus evaluated from a knowledge of the postulated geometry for the transition state using the Wolfsberg–Helmholz approximation.[31]

The simplest possible variant would be to use ordinary Hückel molecular orbitals, and to consider only interactions at the points where bonds are actually made. This procedure will be adopted in this work. A further simplification would be to consider only the highest filled MO of diene and the lowest vacant MO of dienophile. Many of the Woodward–Hoffmann rules are predicated on this basis,[18] and we will also consider this point here. After these assumptions the perturbation energy is given by the following formula:

$$\Delta E = 2\left[\sum_{m}^{\text{occ.}} \sum_{n}^{\text{vac.}} - \sum_{m}^{\text{occ.}} \sum_{n}^{\text{vac.}}\right] (a_{mr}b_{ns} + a_{mu}b_{nv})^2 \, \gamma^2/(E_m - E_n) \tag{4}$$

Here subscripts r, s and u, v refer to the two pairs of atoms in diene and dienophile at which bonds are formed, and γ is the interaction integral which can be left undefined or given an empirical value, based on experimental results. The units of the orbital energies would be β, the usual Hückel exchange integral. Perturbation energies are therefore determined in terms of γ^2/β.

Computer programs were written to solve the secular determinant for each reactant molecule and to compute the perturbation energies. The Hückel heteroparameters were those compiled by Streitwieser[9] and Liberles,[32] although it should be noted that the results given in the next section are not too sensitive to the chosen parameters. The resonance integrals were chosen roughly proportional to overlap integrals. The values are given in Table 1.

TABLE 1. HÜCKEL PARAMETERS FOR MO CALCULATIONS

α (C)	α
α (O-one electron)	$\alpha + \frac{3}{2}\beta$
α (O-two electrons)	$\alpha + \frac{3}{2}\beta$
α (N-one electron)	$\alpha + \frac{1}{2}\beta$
α (saturated C-hetero atom model)	$\alpha + 2\beta$
β (C—O, ester linkage)	$0{\cdot}64\beta$
β (C—O, carbonyl)	$0{\cdot}88\beta$
β (C N, nitrile)	$1{\cdot}20\beta$
β (C to saturated C)	$0{\cdot}70\beta$

Finally, it is necessary to translate the perturbation energies for various pairs of reactant molecules into differences in reactivity. We must assume that the major contribution to the difference in free energy of activation for two different reactions is the π energy change calculated by the perturbation treatment. The justification for such an assumption has been discussed by several authors,[11,14e,f,i,23,33] but especially relies upon some theoretical work of Evans and Polanyi.[34]

In a specific application to the relative yields of products in the reaction of 2-phenylbutadiene with methyl acrylate, application of transition state theory then gives Eq. 5. Thus, the relative yields

$$\ln(k_m/k_o) = (\Delta E_o - \Delta E_m)/RT \tag{5}$$

of products can be correlated with the calculated perturbation energies. Subscripts m and o refer to "*meta*" and "*ortho*" product respectively and the other symbols have their usual or previously defined meanings.

RESULTS

Hückel MO calculations were carried out for Me and Ph substituted butadienes and for four asymmetric dienophiles, acrylonitrile, methyl acrylate, acrolein, and styrene. This group of compounds constitutes the only extensive series which has been studied quantitatively, and in which product ratios are known.[3] Table 2 presents the perturbation stabilization energies for the 16 possible pairs of reactants calculated according to Eq. 4. Table 2 also gives the stabilization energy which is calculated considering only the highest occupied MO (HOMO) of the diene and the lowest vacant MO (LVMO) of the dienophile. The third number for each substituent and dienophile in the tables is that calculated from back donation of HOMO of dienophile and LVMO of diene.

In the Ph-substituted dienes there are a number of points at which 1,4-addition can take place. For example, in 1-phenylbutadiene there are four possible positions of attack. We carried out calculations for every possible 1,4-addition for each of the dienes, and in each case the butadiene system was confirmed as the calculated most reactive position.

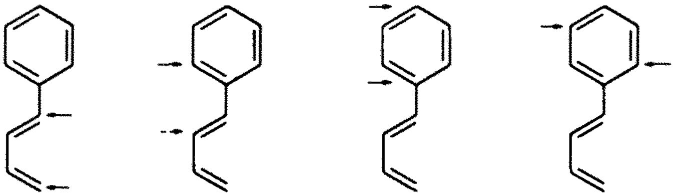

TABLE 2. PERTURBATION ENERGIES (UNITS OF γ^2/β) FOR DIELS–ALDER REACTIONS OF SUBSTITUTED BUTADIENES WITH UNSYMMETRICAL DIENOPHILES[a,b]

Dienophile / Diene substituent	Acrylonitrile		Methyl acrylate		Acrolein		Styrene	
	o or *p*	*m*	*o* or *p*	*m*	*o* or *p*	*m*	*o* or *p*	*m*
1-Methyl	1·736	1·706	1·772	1·689	1·742	1·696	1·781	1·710
	0·630	0·588	0·653	0·571	0·571	0·513	0·551	0·524
	0·605	0·613	0·596	0·592	0·469	0·475	0·515	0·525
1-Phenyl	1·650	1·633	1·670	1·616	1·662	1·622	1·660	1·636
	0·489	0·442	0·521	0·492	0·449	0·387	0·424	0·396
	0·476	0·464	0·441	0·415	0·374	0·358	0·424	0·396
2-Methyl	1·768	1·743	1·802	1·729	1·773	1·734	1·751	1·746
	0·681	0·618	0·702	0·581	0·615	0·531	0·595	0·556
	0·609	0·617	0·597	0·589	0·469	0·479	0·514	0·534
2-Phenyl	1·751	1·732	1·759	1·718	1·752	1·723	1·751	1·735
	0·601	0·514	0·641	0·357	0·553	0·436	0·520	0·465
	0·581	0·557	0·534	0·472	0·457	0·427	0·520	0·465

[a] The first number in each column for each substitutent is the perturbation energy stabilization calculated according to Eq. 4. The second number is the contribution to the energy considering only highest occupied orbital of diene and lowest vacant orbital of dienophile. The third number corresponds to highest occupied of dienophile and lowest vacant of diene.

[b] *o*, *p* and *m* refer to the orientation of the two substituent groups on the cyclohexene Diels–Alder adduct. For 1-substituted butadienes *o* and *m* are possible. For 2-substituted butadienes *p* and *m* are possible.

DISCUSSION

The results of the PMO calculations given in Table 2 should be compared with experimental data which are summarized in Table 3. The calculated values are in qualitative agreement with the experimental results. The preferred orientation of addition is predicted correctly in every case. Either the full perturbation calculation or more simply the interaction of HOMO of diene and LVMO of dienophile seems to be sufficient as a qualitative criterion for the direction of addition. The results are therefore in accord with the Woodward Hoffmann rules which have been derived for 4 + 2 addition.[18]

TABLE 3. EXPERIMENTAL RESULTS FOR THE DIELS ALDER REACTIONS OF SUBSTITUTED BUTADIENES AND VARIOUS UNSYMMETRICAL DIENOPHILES

Diene substituent	Dienophile	Reaction temp °C	Adduct yield %	*ortho/meta* or *para/meta*^{a}	Predicted ratio of products
1-Methyl	Acrylonitrile	100	56	7·3/1^{b}	3·1/1
1-Methyl	Acrylonitrile	100	30	10/1^{c}	3·1/1
1-Methyl	Methyl acrylate	230	82	5·2/1^{c}	10·3/1
1-Methyl	Methyl acrylate	200	85	6·8/1^{d}	12/1
1-Methyl	Styrene	200	40	6/1^{c}	1·3/1
1-Phenyl	Methyl acrylate	150	61	39/1^{e}	6·1/1
1-Phenyl	Styrene	150	33	8·1/1^{e}	2·2/1
2-Methyl	Acrylonitrile	200	89	2·2/1^{f}	2·1/1
2-Methyl	Methyl acrylate	100	70	7·3/1^{c}	15·9/1
2-Methyl	Methyl acrylate	130	73	4·7/1^{g}	12·9/1
2-Methyl	Methyl acrylate	200	84	2/1^{f}	8·9/1
2-Methyl	Acrolein	200	88	1·8/1^{f}	3·3/1
2-Methyl	Styrene	200	31	3·5/1^{h}	1·2/1
2-Phenyl	Acrylonitirle	80	33	4/1^{i}	2·1/1
2-Phenyl	Methyl acrylate	150	73	4·5/1^{e}	3·9/1

[a] See footnote *b*, Table 2.
[b] R. L. Frank, R. D. Emmick and R. S. Johnson, *J. Am. Chem. Soc.* **69**, 2312 (1947).
[c] I. N. Nazarov, A. I. Kuznetsova and N. V. Kuznetsova, *Zh. Obsch. Khim.* **25**, 88 (1955).
[d] I. N. Nazarov, Yu. A. Titov and A. I. Kuznetsova, *Izv. Adak. Nauk. SSSR, Otd. Khim. Nauk* 887 (1960).
[e] *Ibid.* 1270 (1959).
[f] *Ibid.* 1412 (1959).
[g] K. Alder and W. Vogt, *Liebigs Ann.* **564**, 109 (1949).
[h] Yu. A. Titov and A. I. Kuznetsova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 1297 (1960).
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One notes, however, that the interaction HOMO (diene)-LVMO (dienophile) is a quite variable percentage of the full perturbation stabilization energy. We have previously advanced the opinion[25] that any quantitative correlations of reactivity from PMO calculations should rest upon a full calculation rather than just the highest occupied and lowest vacant orbitals of the reactants. All of the work which Fukui has reported[22] has continued to stress the importance of only the so-called "frontier orbitals" and is therefore in some disagreement with our opinion. Also, we find that the interaction HOMO (dienophile)-LVMO (diene) is in many cases calculated to be larger than the interaction HOMO (diene)-LVMO (dienophile) which again indicates a need for consideration of the full PMO calculation.

The calculations of Table 2 and the experimental results in Table 3 should allow us to make a comparison of the importance of the frontier orbitals in predicting reactivity. The relative yields of products can be compared to the energies calculated in Table 2 by means of Eq. 5. Of course, we have to assume that the relative product yields given in Table 3 are the result of kinetic control, and that the relative rate constants are proportional to the relative yields. This may not be a good assumption; many of the experimental data were obtained from experiments in which the reactants were simply heated together for a long period of time. However, at the present time, these are the only data available, and, unfortunately, neither of the calculated perturbation energies correlates precisely with the experimental product ratios. Values of γ^2/β calculated from Eq. 5 vary from 10 kcal/mole to 80 kcal/mole with the average about 28 kcal/mole. Interactions with styrene as the dienophile and 1-phenyl substituents in the diene are especially anomalous. This may be an indication of stabilization of the transition state by secondary interactions of the Ph ring which of course were not included in the calculations.

Using a value of 28 kcal/mole for the interaction integral, the ratios of products formed in the reaction of Table 3 can be roughly correlated. Perhaps this is all we can expect in a treatment in which steric hindrance and secondary attractive forces are completely ignored. The relative rate of two similar reactions is a very sensitive test to apply to any theory, and the methods presented here are simplified a great deal from our earlier work.[25] However, the fact that we can predict the favored orientation of Diels–Alder addition in all of the cases studied here, and obtain rough agreement in predicted yields of products, must be considered as support for the PMO method.

We are presently obtaining experimental data for relative rates in these systems and several related series of compounds, and we hope to have precise data for comparison with the PMO calculations in the near future.

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