

## Rationalisation of Cycloaddition Behaviour by Use of Hückel Frontier Molecular Orbitals

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A simple method for predicting various aspects of cycloaddition reactions is tested with particular attention to reactivity and electroselectivity, but also including regioselectivity, periselectivity, and stereoselectivity (*exo/endo* in diene reactions). The method combines three techniques: (a) the Frontier Molecular Orbital approach, (b) potential energy diagrams, and (c) Hückel calculation (by computer). The computer method is easy to apply since it requires only standard parameters for atoms and bonds, and the whole technique is suitable for devising new syntheses of organic compounds.

NUMEROUS attempts have been made to explain and predict the various mechanistic aspects of cycloaddition reactions.<sup>1</sup> Particular attention has been paid to reactivity,<sup>2</sup> electroselectivity,<sup>3</sup> † regioselectivity,<sup>4</sup> and stereoselectivity.<sup>5</sup> Electroselectivity can now be predicted reliably for most systems by the elegant orbital symmetry correlation approach of Woodward and Hoffmann,<sup>3a</sup> but the other phenomena cannot be explained by that technique; instead, perturbation methods are more applicable. Early work<sup>1</sup> involving use of these latter methods met with only limited success, but in the last few years more reasonable correlations between theory and experiment have emerged from use of the Frontier Molecular Orbital (FMO) technique, a perturbation method pioneered by Fukui.<sup>3b</sup> In this treatment the dominant role in determining electroselectivity, stereoselectivity, *etc.* is believed to be played by the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO). The approach not only leads to an alternative derivation of Woodward and Hoffmann's rules for electroselectivity, but in addition is the basis for qualitative correlations between theory and reactivity,<sup>2d-g</sup> regioselectivity,<sup>4c,e,f</sup> and stereoselectivity<sup>5b,c</sup> in cycloaddition reactions. However although recent literature indicates that the FMO approach is becoming firmly established for understanding cycloadditions, like other methods it has not yet produced good quantitative predictions of reactivity.

A basic equation<sup>6</sup> for use in perturbation methods relates energy of interaction to eigenvalues and eigen-

vector coefficients of reacting orbitals. The methods for obtaining these data have included HMO, CNDO, INDO, MINDO, SCF and *ab initio* theoretical methods as well as experimental approaches to eigenvalues from ionisation potentials and electron affinities obtained from photoelectron spectra, reduction potentials, and charge transfer spectra *etc.* These latter experimental orbital energies have been preferred in several recent papers<sup>2e,f,7,8</sup> on the grounds that theoretical eigenvalues cannot yet be obtained accurately. However the experimental eigenvalues also must be treated with caution because not only are there conflicting values reported, but many of them have to be obtained by extrapolation, since very few data are available at present. Regarding comparison of the theoretical methods there is conflicting opinion as to which is best.

Since the HMO method, unlike the others, does not require knowledge of molecular geometry, it is by far the simplest to apply. The purpose of the work reported here was to establish whether the HMO method coupled with Frontier Molecular Orbital principles can be applied with sufficient success to the prediction of reactivity, electroselectivity, regioselectivity, periselectivity, and stereoselectivity (*exo/endo*) of cycloaddition reactions for complex systems to be of practical value to the synthetic organic chemist. In order that the testing should be rigorous, particular attention was directed to the less usual non-alternant hydrocarbons and heterocycles.

### EXPERIMENTAL

The standard Hückel program employing the Jacobian matrix diagonalisation procedure was used. Regarding

† Electroselectivity refers to the ability of a system to undergo cycloaddition to another system formally containing a definite number of  $\pi$ -electrons between the reaction termini. For example a compound which undergoes cycloaddition to dienes is  $4n$ -electroselective, whereas one which adds to enes is  $(4n + 2)$ -electroselective.

<sup>1</sup> W. C. Herndon, *Chem. Rev.*, 1972, **72**, 257, and references therein.

<sup>2</sup> Selected references: (a) M. G. Evans and E. Warhurst, *Trans. Faraday Soc.*, 1938, **34**, 614; (b) R. D. Brown, *J. Chem. Soc.*, 1950, 691, 2730; (c) M. J. S. Dewar and R. S. Pyron, *J. Amer. Chem. Soc.*, 1970, **92**, 3098; (d) R. Sustmann, *Tetrahedron Letters*, 1971, 2717, 2721; (e) R. Sustmann and H. Trill, *Angew. Chem. Internat. Edn.*, 1972, **11**, 838; (f) R. Sustmann and R. Schubert, *ibid.*, p. 840; (g) N. D. Epiotis, *J. Amer. Chem. Soc.*, 1972, **94**, 1924; (h) M. N. Padden-Row, *Tetrahedron Letters*, 1972, 1409.

<sup>3</sup> Selected references: (a) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, 1965, **87**, 2046; (b) K. Fukui, 'Theory of Orientation and Stereoselection,' Springer Verlag, Heidelberg, 1970.

<sup>4</sup> Selected references: (a) J. Feuer, W. C. Herndon, and L. H. Hall, *Tetrahedron*, 1968, **24**, 2575; (b) A. Devaquet and L. Salem, *J. Amer. Chem. Soc.*, 1969, **91**, 3793; (c) O. Eisenstein, J.-M. Lefour and N. T. Anh, *Chem. Comm.*, 1971, 969; (d) T. Inukai, H. Sato, and T. Kojima, *Bull. Chem. Soc. Japan*, 1972, **45**, 891; K. N. Houk, *J. Amer. Chem. Soc.*; (e) 1972, **94**, 8953; (f) 1973, **95**, 4092; (g) N. D. Epiotis, *ibid.*, 1973, **95**, 5624.

<sup>5</sup> Selected references: (a) R. B. Woodward and T. J. Katz, *Tetrahedron*, 1959, **5**, 70; (b) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, 1965, **87**, 4388; (c) L. Salem, *ibid.*, 1968, **90**, 553; (d) K. N. Houk and R. B. Woodward, *ibid.*, 1970, **92**, 4143.

<sup>6</sup> M. J. S. Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3341.

<sup>7</sup> K. N. Houk, J. Sims, R. E. Duke, jun., R. W. Strozler, and J. K. George, *J. Amer. Chem. Soc.*, 1973, **95**, 7287.

<sup>8</sup> K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Amer. Chem. Soc.*, 1973, **95**, 7301.

parameters, Anh *et al.*<sup>4c</sup> found in their study of regioselectivity in the Diels-Alder reaction that the same qualitative predictions were obtained irrespective of whether they used Streitwieser's,<sup>9</sup> Herndon's,<sup>10</sup> or Julg's<sup>11</sup> parameters. In this work Streitwieser's parameters were used throughout. In addition the following parameters were chosen for the cyano- and nitro-groups: coulomb integrals: cyano C =  $\alpha + 0.05\beta$ , cyano N =  $\alpha + 0.5\beta$ , nitro N =  $\alpha + 1.5\beta$ , nitro O =  $\alpha + 1.0\beta$ ; resonance integrals: CN =  $\beta$ , nitro NO =  $0.8\beta$ . Oxygen parameters were used for the sulphur compound (15).

As a check on the HMO method, three compounds of diverse types were studied by HMO, CNDO/2, INDO/2, and *ab initio*<sup>12</sup> methods; no changes in nodal behaviour or relative magnitudes of important eigenvector coefficients were observed.

## RESULTS AND DISCUSSION

(A) *Reactivity*.—(a)  $\Delta E_{\text{FMO}}$  correlations. Based on the perturbation approach, Dewar derived a general equation for the potential energy change occurring when two molecules (A and B) react together in a cycloaddition between their reaction sites (1 and 2) as shown in Figure

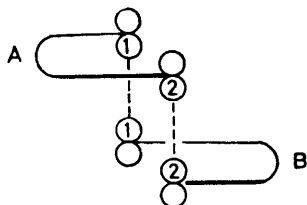


FIGURE 1

1. If this equation is simplified so that only second-order mixing of FMOs is considered, we get equation (i),

$$\Delta E_{\text{FMO}} = 2\gamma^2 \left[ \frac{(C_{A1H}C_{B1L} + C_{A2H}C_{B2L})^2}{|E_{AH} - E_{BL}|} + \frac{(C_{A1L}C_{B1H} + C_{A2L}C_{B2H})^2}{|E_{BH} - E_{AL}|} \right] \quad (\text{i})$$

where  $\Delta E_{\text{FMO}}$  is the interaction energy;  $\gamma$  is the resonance integral for the two interacting lobes at each of the reaction sites; C and E refer respectively to particular eigenvector coefficients and eigenvalues indicated by the subscripts; subscripts A and B refer respectively to the reacting molecules A and B; subscripts 1 and 2 refer respectively to the reaction sites 1 and 2; and H and L refer respectively to the HOMO and the LUMO. This equation has been advocated and used by several groups studying cycloadditions, but surprisingly, it has not been thoroughly tested experimentally.

In order to test the equation it is first necessary to relate the rate constant ( $k$ ) of a cycloaddition reaction to  $\Delta E_{\text{FMO}}$ . The Eyring equation (ii) or (iii) connects the rate constant with the energy of the transition state

\* Sustman *et al.*<sup>3d,f</sup> were conscious of this problem in their studies of substituent effects in cycloaddition reactions of tetracyanoethylene and maleic anhydride with various dienes.

<sup>9</sup> A. Streitwieser, 'M.O. Theory for Organic Chemists,' Wiley, New York, 1961, p. 135.

( $\Delta E^\ddagger$ ). The energy of the transition state may be divided into two parts: first the stabilisation energy of

$$k = Ae^{-\Delta E^\ddagger/RT} \quad (\text{ii})$$

A = constant for each combination of reactants

$$\ln k = \ln A - \Delta E^\ddagger/RT \quad (\text{iii})$$

interaction  $\Delta E_{\text{FMO}}$ , calculated by equation (i), and secondly the destabilisation energy of van der Waals repulsions of filled orbitals, designated  $\Delta E_{\text{VDW}}$ . In this work coulombic interaction is being neglected on the assumption that it is the minor term when compared with FMO interaction, as pointed out by Herndon.<sup>1</sup> Now we obtain equation (iv). In A depends on the

$$\ln k = \ln A - \Delta E_{\text{VDW}}/RT - \Delta E_{\text{FMO}}/RT \quad (\text{iv})$$

probability of a collision between reactants having favourable orientation for reaction and is sensitive to steric influence of substituents as well as any entropy effects arising from solvation. For a series of suprafacial/suprafacial cycloadditions of the types [2 + 3], [2 + 4], [3 + 3], and [3 + 4], ln A should be reasonably constant as long as the reactants carry no extremely bulky substituents or exist predominantly in unfavourable conformations. The latter point is very important for dienes\* since if the reactive cisoid conformation does not predominate, A must include the equilibrium constant for its formation from the transoid form. In A has been determined for a series of cycloadditions between cyclopentadiene and 9,10-dimethylantracene and diverse dienophiles by Sauer *et al.*<sup>13</sup> and was found to be fairly constant between the extremes of 11.19 and 15.77 for the former and 10.36 and 14.14 for the latter.  $\Delta E_{\text{VDW}}$  should be constant for a given cycloaddition type such as [2 + 4], only if the substituents are of constant size. In this work we assume that the steric effect of substituents is minimised by the interplanar distance in the transition state being large. The assumption is backed up by the values of the overlap integrals ( $\gamma$ ) calculated herein, which are found to be very low compared with the expected value for a tight transition state. Therefore, within the limitations given above and at constant temperature equation (iv) becomes equation (v). Com-

$$\ln k = C - \Delta E_{\text{FMO}}/RT \quad (\text{where } C \text{ is a constant}) \quad (\text{v})$$

bin of equations (i) and (v) leads to (vi). The only

$$\ln k = C - \frac{2\gamma^2}{RT} \left[ \frac{(C_{A1H}C_{B1L} + C_{A2H}C_{B2L})^2}{|E_{AH} - E_{BL}|} + \frac{(C_{A1L}C_{B1H} + C_{A2L}C_{B2H})^2}{|E_{BH} - E_{AL}|} \right] \quad (\text{vi})$$

remaining unknown variable is  $\gamma$ , and this can be assumed

<sup>10</sup> J. Feuer, W. C. Herndon, and L. H. Hall, *Tetrahedron*, 1968, **24**, 2575.

<sup>11</sup> A. Julg and O. Julg, 'Exercices de Chimie Quantique,' Dunod, Paris, 1967.

<sup>12</sup> M. C. Zerner, *J. Chem. Phys.*, 1975, **62**, 2788.

<sup>13</sup> J. Sauer, H. Wiest, and A. Mielert, *Chem. Ber.*, 1964, **97**, 3183.

to be approximately constant for a series of closely related reactions where the elements at the reaction sites are kept constant, and the substituents are not so unsymmetrically placed that the mechanism might reasonably be expected to be nonsynchronous.

We now have an equation that can at least be readily tested by taking reaction rate data from the literature and plotting  $\ln k$  against  $[(C_{A1H}C_{B1L} + C_{A2H}C_{B2L})^2/|E_{AH} - E_{BL}| + (C_{A1L}C_{B1H} + C_{A2L}C_{B2H})^2/|E_{BH} - E_{AL}|]$  calculated from HMO data. The plot should be a straight line of negative slope. Such a plot for the reaction between cyclopentadiene and a series of dienophiles exhibits widely scattered points showing that equation (vi) is not applicable. However, we find that if  $\ln k$  is plotted against  $[1/|E_{AH} - E_{BL}| + 1/|E_{BH} - E_{AL}|]$  instead, the points fall on a straight line of negative slope, and further, the correlation is improved even more by plotting  $\ln k$  against  $[1/(E_H - E_L)]$ , where  $E_H$  and  $E_L$  are the eigenvalues of the more closely lying pair of HOMOs and LUMOs (Figure 2).

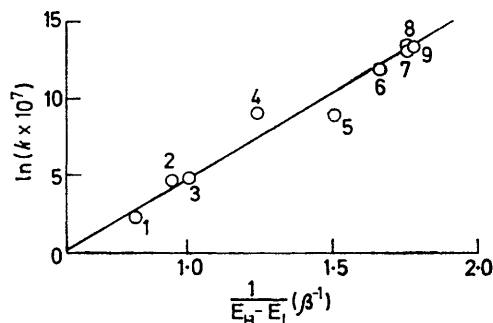


FIGURE 2 Plot of  $\ln(k \times 10^7)$  versus  $1/(E_H - E_L)$  for the cycloaddition reactions of cyclopentadiene: rate data from ref. 13; 1, cyclopentadiene; 2, acrylonitrile; 3, methyl acrylate; 4, fumaronitrile; 5, dimethyl fumarate; 6, *trans*-1,2-dibenzoyl-ethylene; 7, *N*-methylmaleimide; 8, *N*-phenylmaleimide; 9, maleic anhydride

An explanation as to why the values of the eigenvector coefficients are unimportant in correlating the rate data lies in Fukui's 'principle of growing frontier electron density along the reaction path',<sup>3b</sup> which states that the eigenvector coefficients at the reaction sites will be very much enhanced at the transition state. They should tend towards a maximum of  $\pm 0.71$  ( $1/\sqrt{2}$ ) and the numerators in equation (vi) therefore should tend towards unity. Even if the polarisation is not extreme, there should still be a levelling of the values of the coefficients so that their differences become less pronounced. A rationalisation as to why one of the terms in equation (vi) can be ignored to obtain the best correlation is found in Fukui's other 'principle of narrowing interfrontier level separation',<sup>3b</sup> which states that as the transition state is approached both  $1/|E_{AH} - E_{BL}|$  and  $1/|E_{BH} - E_{AL}|$  become larger, and the more closely lying pairs of levels will be modified the most. If this

effect is pronounced the contribution of the minor term is diminished relative to the other until a point is reached at which it is better to omit it.

Equation (vii) therefore represents the observed correlation where  $\delta$  is the ratio between the values of  $1/|E_H - E_L|$  and the contents of the square bracket in equation (vi) at the transition state. While  $\delta$  is at

$$\ln k = C + \frac{2\gamma^2\delta}{RT} \left[ \frac{1}{|E_H - E_L|} \right] \quad (\text{vii})$$

present the least studied<sup>14</sup> quantity in the FMO treatment, the results of this study imply that it is reasonably constant at least for a related group of cycloaddition reactions. Note that if the donor/acceptor behaviour is not pronounced, as in dimerisation, equation (viii) would be more appropriate.

$$\ln k = C + \frac{2\gamma^2}{RT} \left[ \frac{\delta'}{|E_{AH} - E_{BL}|} + \frac{\delta''}{|E_{BH} - E_{AL}|} \right] \quad (\text{viii})$$

In addition to the kinetic data on cyclopentadiene cycloadditions, four other sets of data from the literature, namely for cycloadditions of 9,10-dimethylantracene, diphenylnitrilimine *N*-benzylidenemethylamine *N*-oxide, and maleic anhydride, were plotted<sup>15</sup> in the same way and showed no correlation with equation (vi) but a linear correlation with equation (vii) in each case. In order to evaluate the plots quantitatively, a least-squares fit computer program for both linear and quadratic relationship between  $1/|E_H - E_L|$  and  $\ln k$  was run. Using  $Y = a + bX$  (for linear relationship) and  $Y = a' + b'X + c'X^2$  (for quadratic relationship) where  $Y = \ln k + 1/|E_H - E_L|$ , the sum of the squares of the vertical errors was found, and by means of an *F*-test (variance ratio test)<sup>16</sup> it was found that the quadratic was not significantly better (at both 5 and 1% levels of significance) than the linear relationship. It was concluded that there was a surprisingly good linear correlation between  $\ln k$  and  $1/|E_H - E_L|$  for the cycloadditions studied, despite the assumptions made.

One of the assumptions, namely that the frequency factor *A* is a constant, may be circumvented for the two sets of data in the literature by Sauer *et al.*<sup>13</sup> for cycloadditions of cyclopentadiene and 9,10-dimethylantracene, for which *A* as well as the enthalpy ( $\Delta H^\ddagger$ ) and the entropy ( $\Delta S^\ddagger$ ) of activation were determined, and a slightly improved correlation is found as expected if  $\Delta H^\ddagger$  rather than  $\Delta E^\ddagger$  is plotted against  $1/|E_H - E_L|$ . Such a plot is shown in Figure 3. Unfortunately, apart from the two cases cited, very few values of *A*,  $\Delta H^\ddagger$ , and  $\Delta S^\ddagger$  are available for cycloadditions.

(b)  $\Delta E_\pi$  correlations. It is appropriate now to compare the degree of success obtained with the FMO- $\ln k$  correlations with other methods of correlating rates of cycloadditions. The other reported method was pioneered by Brown<sup>2b</sup> and later by Dewar.<sup>2c</sup> Basically their methods assume a correlation between the rate of a

<sup>14</sup> K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Japan*, 1969, **42**, 3399.

<sup>15</sup> K. Mok, M.Sc. Thesis, University of Guelph, 1974.

<sup>16</sup> J. E. Freund, 'Mathematical Statistics,' Prentice-Hall, New Jersey, 1962, p. 369.

cycloaddition reaction and the loss in energy in the  $\pi$ -system during reaction ( $\Delta E_\pi$ ). While Brown did not attempt quantitative correlations, Dewar *et al.* have

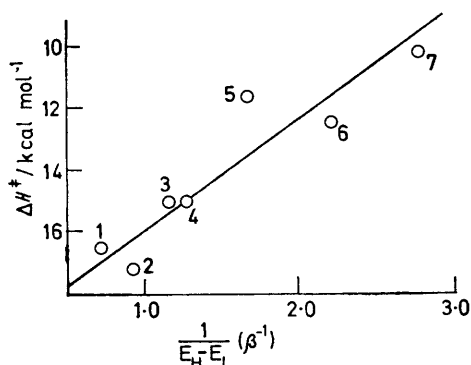


FIGURE 3 Plot of enthalpy of activation  $\Delta H^\ddagger$  versus  $1/(E_H - E_L)$  for the cycloaddition reactions of 9,10-dimethylantracene; thermochemical data from ref. 13; 1, cyclopentene; 2, styrene; 3, acrylonitrile; 4, methyl acrylate; 5, fumaronitrile; 6, dimethyl fumarate; 7, maleic anhydride

published a correlation of the rates of cycloaddition of maleic anhydride to various aromatic hydrocarbons with  $\Delta E_\pi$  and observed a linear relationship. They found that a decrease in  $\Delta E_\pi$  caused an increase in rate, which may be interpreted in terms of energy profile diagrams using a technique originally discussed by Eyring, Polanyi, and Evans *et al.*<sup>2a,17,18</sup>

In Figure 4, curve R represents the potential energy of

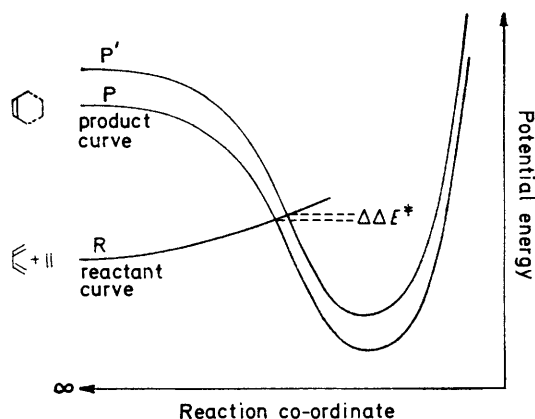


FIGURE 4

a system containing the two addends (ethylene and 1,3-butadiene in this example) in a cycloaddition reaction as the two are brought progressively closer together but without allowing rehybridisation of the carbon atoms involved. Curve P represents the potential energy of the cycloaddition product as the molecule is progressively pulled apart in a cycloreversion, also without allowing rehybridisation of the carbon atoms involved.

<sup>17</sup> A. E. Stearn and H. Eyring, *J. Chem. Phys.*, 1935, **3**, 778.

<sup>18</sup> M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, 1938, **34**, 11.

In this treatment the actual energy curve is considered to follow curve R at first and then curve P after the intersection. If conjugating substituents are placed on either of the reactants, after arbitrarily adjusting the new curve R' to superimpose on curve R, it is found that the new curve P' lies at a different level (assumed to be higher in this example) relative to curve P. The energy of activation is therefore increased from  $\Delta E^\ddagger$  to  $\Delta E'^\ddagger$ , which means that an increase in  $\Delta E_\pi$  would lead to a decrease in rate, as observed by Dewar. So at first sight the combination of  $\Delta E_\pi$  theory and the principle of intersecting potential energy surfaces satisfactorily explains the observed correlations. However, if the same principles are applied to the other series of cycloadditions studied in this paper namely those involving diphenylnitrilimine, *N*-benzylidenemethylamine *N*-oxide, dimethylantracene, and cyclopentadiene, in all these cases a reasonably linear correlation is obtained between  $\Delta E_\pi$  (obtained from HMO calculations) and  $\ln k$ , but the slopes of the lines are the opposite of what would be expected from the theory. This we feel is a strong piece of evidence against directly relating rates to  $\Delta E_\pi$  values. The observed linear correlations can be explained by noting that the absolute magnitudes of  $\Delta E_\pi$  and  $\Delta E_{\text{FMO}}$  are expected<sup>19</sup> to be interrelated on theoretical grounds. Fukui has pointed out that the parallelism will be greatest for alternant hydrocarbons, but less if heteroatoms are present. In our work, we have found that  $|\Delta E_\pi|$  and  $|\Delta E_{\text{FMO}}|$  for a wide range of systems including heteroatoms exhibit rough parallelism if all substituents in a series are either electron-withdrawing or electron-donating, but mixing of the two types of substituents leads to much poorer correlation.

(c) *Combined  $\Delta E_{\text{FMO}}$  and  $\Delta E_\pi$  correlations.* While plots of reaction rates versus  $\Delta E_\pi$  often give the wrong sign for the slope when interpreted by the energy profile method, in contrast plots of reaction rates versus  $1/(E_H - E_L)$  give correct signs for the slopes for all cycloadditions looked at, namely for cyclopentadiene, 9,10-dimethylantracene, diphenylnitrilimine, *N*-benzylidenemethylamine *N*-oxide, and maleic anhydride (using Dewar's<sup>2c</sup> data). (The energy profile diagram for the latter treatment is shown in Figure 5.) An explanation for this observation is forthcoming when the energy profile diagram treatment is used taking into account both  $\Delta E_\pi$  and  $\Delta E_{\text{FMO}}$  effects as in Figure 6. Note that the two effects may either reinforce or counteract each other. Figure 6 shows the latter, which would be the case for example for the reactions of buta-1,3-diene with ethylene and acrylaldehyde. The treatment can be made quantitative by assuming that the two sets of lines are straight and parallel in the region of intersection, in which case equations (ix) and (x) can be shown<sup>15</sup> by geometry to apply, where unprimed symbols refer to a

$$\Delta E'^\ddagger - \Delta E^\ddagger = \Delta \Delta E^\ddagger = \phi(\Delta E'_{\text{FMO}} - \Delta E_{\text{FMO}}) + (1 - \phi)(\Delta E'_\pi - \Delta E_\pi) \quad (\text{ix})$$

<sup>19</sup> K. Fukui, T. Yonezawa, and C. Nagata, *J. Chem. Phys.*, 1957, **26**, 831.

reference reaction (ethylene and buta-1,3-diene throughout this paper) and primed symbols refer to the reaction in question.  $\phi$  is a weighting factor shown<sup>15</sup> to be

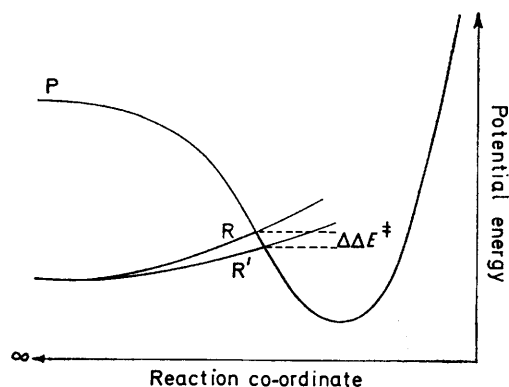


FIGURE 5

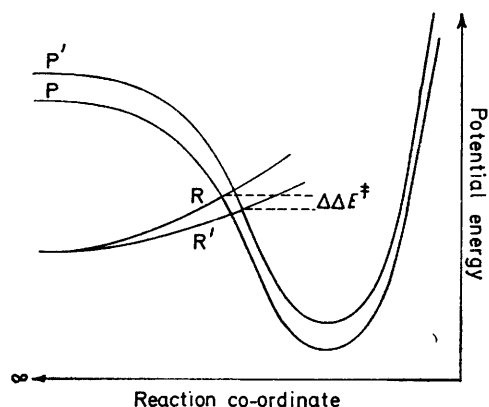


FIGURE 6

related to the slopes of the intersecting curves by equation (x). Equation (ix) is directly related to rate data *via*

$$\phi = \frac{\text{slope of P}}{\text{slope of P} + \text{slope of R}} \quad (\text{x})$$

the Eyring equation (iii). If we again assume that the  $\ln A$  term is a constant for closely related reactions, we get equation (xi). A best value for  $\phi$  may be obtained

$$RT (\ln k' - \ln k) = \Delta E^\ddagger - \Delta E'^\ddagger = \phi(\Delta E'_{\text{FMO}} - \Delta E_{\text{FMO}}) + (1 - \phi)(\Delta E'_\pi - \Delta E_\pi) = \phi\Delta\Delta E_{\text{FMO}} + (1 - \phi)\Delta\Delta E_\pi = \Delta\Delta E^\ddagger \quad (\text{xi})$$

from experimental data for a series of reactions by using a least-squares fit computer program to find out which value for  $\phi$  gives the best linear plot of  $RT \ln k'$  versus the right hand side of the equation.

The above analysis was carried out with the same data as used in section (a), and the results are given in Table 1. For each set of reactions variation of  $\phi$  gave a minimum for a combination of  $\Delta\Delta E_{\text{FMO}}$  and  $\Delta\Delta E_\pi$  rather

\* Concerning extreme reaction types, if the treatment presented here is to remain valid, then the reaction must be both synchronous and free from strong coulombic effects.

than for either uncombined, which is supporting evidence for the theory. Also the value of  $\phi$  fell around 0.9 consistently, which implies that the energy profile at the transition state retains fairly constant slopes for a series of quite varied cycloaddition reactions. In all cases the reactions are predominantly FMO-controlled, and

TABLE 1

Results of the least-squares analysis of the kinetic data for the given compounds

Compound	$\phi$	$\gamma\sqrt{\delta}$
Cyclopentadiene	0.91	7.5
9,10-Dimethylantracene	0.91	6.0
Diphenylnitrilimine	0.92	5.2
N-Benzylidenemethylamine N-oxide	0.90	6.6

this very likely is the general rule for the majority of known cycloaddition reactions. However, since the assumption that the intersecting energy profile curves are straight and parallel in the region of intersection would tend to become invalid if an extreme range of reaction types\* were treated, then it is quite possible that highly inactive reactants such as benzene and highly reactive reactants such as tetracyanoethylene (a strong electron acceptor), cyclopropene (a strained alkene), or cyclobutadiene (an antiaromatic system) might have quite different degrees of FMO control and also might not exhibit linear correlations.

Another quantity that can be roughly estimated by the above treatment is the resonance integral ( $\gamma$ ), and knowledge of this gives us information on the distance of separation of the two reactants in the transition state. The value of  $\gamma\sqrt{\delta}$  [*cf.* equation (vii)] can be calculated directly from the slopes of the graphs and it is dependent on whatever value is used for the resonance integral ( $\beta$ ) of the  $\pi$  bonds in the reactants. A value of 40 kcal mol<sup>-1</sup> for  $\beta$  yields a range of values for  $\gamma\sqrt{\delta}$  of 5–8 kcal mol<sup>-1</sup> for the systems studied (see Table 1). When this value is compared with the theoretical values for  $2p\sigma$ - $2p\sigma$  overlap available from the literature,<sup>20</sup> it is found to correspond to a bond length of at least 3.7–3.9 Å. This is the largest estimate for distance of separation of the reactants in the transition state of a cycloaddition yet suggested, and while we do not maintain that the value is anywhere near precise, particularly bearing in mind the uncertainty in the value of  $\gamma$ , perhaps its magnitude at least may be used as evidence for a transition state having a bond length on the large side of the range 2.5–3.5 Å which is usually considered.<sup>8</sup> Probably the relative differences in the values of  $\gamma\sqrt{\delta}$  in Table 1 are not significantly large enough to be trusted, but if one compares the two carbocycles dimethylantracene and cyclopentadiene it is worth noting that the transition state is nearer products in the former than in the latter as might be expected from consideration of the effect of  $\Delta E_\pi$  (see Figure 4). In using such arguments in general, however, one should take into account the different

<sup>20</sup> R. S. Mulliken, C. A. Rieke, D. Orloff, and H. Orloff, *J. Chem. Phys.*, 1949, **17**, 1248.

degree of overlap occurring when heteroatoms are involved at the reaction termini,<sup>8</sup> and also the possibility that one of the two new bonds is formed a little ahead in time of the other, in which cases there would be two values for  $\gamma$ . This complication may not be very important except for highly unsymmetrical addends.\* 1,1-Dicyanoethylene may be such a case since it reacts considerably more quickly<sup>13</sup> than expected from the Hückel/FMO method relative to the other mono-, di-, and tri-cyanoethylenes, and the rate enhancement may arise from a more favourable entropy of reaction occurring in a concerted two-step mechanism.

Another way of correlating rates of cycloadditions with FMO data is to use eigenvalues estimated from photoelectron spectra, charge-transfer spectra, and reduction potential and other experimental data instead of using quantities obtained from molecular orbital calculations. This was tried for the four cycloaddition series but in each case the scatter of points was worse relative to the corresponding Hückel/FMO plot. The eigenvalues used for the plot were taken from the work of Houk and his co-workers<sup>7</sup> who had to estimate some of the values by extrapolation from existing ionisation potential and electron affinity data, and it is probable that better correlations will be obtained as better experimental eigenvalues become available.

(B) *Electroselectivity*.<sup>22</sup>—According to FMO theory,<sup>3</sup> electroselectivity is governed entirely by the symmetry of the HOMO and LUMO of reactants. The HOMO and LUMO of a given compound interact favourably with the LUMO and HOMO respectively of either an ene or a diene depending on which has correct symmetry. In this way the electroselectivity of a reactant can be obtained immediately by inspection of the symmetries of the frontier orbitals and then applying Table 2. In describing an orbital as symmetric or antisymmetric the

TABLE 2

Relationship between symmetry and electroselectivity

Orbital of reactant	Symmetry	Electroselectivity
HOMO	Symmetric	$4n$
	Antisymmetric	$4n + 2$
LUMO	Symmetric	$4n + 2$
	Antisymmetric	$4n$

eigenvector coefficients are ignored and only the signs of the terminal lobes are considered (Figure 1).

Table 3 shows some of the more interesting results of the Hückel calculations. In no case was there any

\* This popular view has recently been strongly challenged by the theoretical work<sup>21</sup> of Dewar's group which indicates that even the simple symmetrical reaction of ethylene and butadiene should proceed through a highly unsymmetrical transition state.

<sup>21</sup> M. J. S. Dewar, A. C. Griffin, and S. Kirschner, *J. Amer. Chem. Soc.*, 1974, **96**, 6225.

<sup>22</sup> (a) K.-L. Mok and M. J. Nye, Abstracts of the Fourth International Congress of Heterocyclic Chemistry, Salt Lake City, U.S.A., 1973, p. 264; (b) N. Dennis, B. Ibrahim, and A. R. Katritzky, *J.C.S. Chem. Comm.*, 1974, 500; (c) K.-L. Mok and M. J. Nye, *ibid.*, p. 608.

significant conflict between theory and observation. The allyl system [(3) and (4)] is expected to show either  $4n$ -electroselectivity or  $(4n + 2)$ -electroselectivity depending on whether it contains two or four electrons respectively in its  $\pi$ -system. This is backed up by experiment for both the allyl cation<sup>23</sup> and the allyl anion<sup>24</sup> and also the whole host of  $(4n + 2)$ -electroselective 1,3-dipoles<sup>25</sup> which are isoelectronic with the allyl anion. The dual behaviour of the oxyallyl system (5) is correctly predicted, as is the behaviour of the same system with extended conjugation (6) which has been a centre of interest as an intermediate in photochemical reactions of dienes, but which has also been generated thermally. Moving to cyclic zwitterionic systems, the wide range of sydnone (7) and other related five-membered ring aromatic zwitterions are predicted to be  $(4n + 2)$ -electroselective, in accord with experiment,<sup>26</sup> as are also the systems (8)—(11). A good test for the method is the fact that the only observed examples of  $4n$ -electroselective heteroaromatic zwitterions are the systems (12)<sup>22b</sup> and (13),<sup>15,22a,c</sup> and this is in accord with prediction. Other systems predicted to be  $4n$ -electroselective are (14), which is under study in this laboratory but has proved so far to be resistant to reaction with dienes, and (15), which reacts with enes across N-1 and S as predicted but has not apparently been tried with dienes. The Hückel/FMO method was also tried on the antiaromatic compounds such as (16) and there was in general good agreement between predicted and observed products. Occasionally one of the reaction termini has a zero eigenvector coefficient in one of the FMOs. For example in considering cycloadditions of oxyallyl (5) and cyclohepta-2,4,6-trienone (17) at the sites *a* and *b*, the more reactive LUMOs have zero coefficient at oxygen and hence electroselectivities cannot be decided until the symmetries of the HOMOs are taken into account.  $4n$ -Electroselectivity is then indicated for these systems in agreement with experiment. Sometimes the symmetries of both the HOMO and LUMO are identical at the reaction sites considered. Under these circumstances the full FMO reactivity equation (i) should be invoked to predict electroselectivity. Qualitatively one would expect greatly reduced reactivity under these circumstances. An instructive example is the behaviour of the two isomeric systems (18) and (19). In (18) cycloaddition across *a* and *b* is unfavourable because of the identical symmetries in the HOMO and the LUMO, whereas  $(4n + 2)$ -electroselective cycloaddition across *a* and *c* is expected and has been observed for the electronically related system bearing a sulphur atom instead of N'. In (19) the situation is reversed;  $(4n + 2)$ -electroselective cycloaddition is both predicted and observed across *a* and *b*.

<sup>23</sup> H. M. R. Hoffmann, K. E. Clemens, and R. H. Smithers, *J. Amer. Chem. Soc.*, 1972, **94**, 3940.

<sup>24</sup> J. P. Marino and W. B. Mesbergen, *J. Amer. Chem. Soc.*, 1974, **96**, 4050.

<sup>25</sup> R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565.

<sup>26</sup> M. Ohta and H. Kato in 'Nonbenzenoid Aromatics,' ed. J. P. Snyder, Academic Press, New York, 1969, p. 117.

TABLE 3

## Results of Hückel calculations

Compound	HOMO Eigenvalue ( $\beta$ ) Eigenvectors	LUMO Eigenvalue ( $\beta$ ) Eigenvectors	Electroselectivity across positions indicated	Ref.
$\rightarrow\text{CH}_2=\text{CH}_2\leftarrow$	-1.00 0.71  0.71	1.00 0.71  -0.71		$4n$
	-0.61 0.37  -0.37 0.60  -0.60	0.61 -0.37  -0.37 0.60  -0.60		$4n + 2$
	-1.41 0.50  0.50	0.60 0.71  -0.71		$4n$
	-0.00 0.71  -0.71	1.41 0.50  0.50		$4n + 2$
	-0.62 -0.43  -0.43	0.00 -0.70  0.70	<i>ab</i> <i>bc</i>	$4n$
	-0.54 -0.32  0.29 0.55  0.29	0.00 -0.57  -0.57		$4n$
	-0.52 0.55  -0.12	0.25 0.34  -0.25 0.32		$4n + 2$
	-0.03 -0.50 -0.51	-0.45 0.07 -0.44		$4n + 2$
	0.43 -0.21 0.23 -0.07 -0.09 0.10 0.30 -0.30	0.41 -0.15 0.31 -0.22 -0.25 0.40 0.11 -0.32		$4n + 2$
	-0.46 -0.14 -0.18	0.26 -0.03 0.11		$4n + 2$
	-0.37 0.14 -0.41 -0.55	0.47 -0.02 -0.17 0.39		$4n + 2$
	-0.31 0.11 0.37	0.06 -0.08 -0.47	<i>ab</i> <i>bc</i>	$4n$ $4n + 2$
	-0.51 -0.25 -0.50	0.25 -0.17 -0.39		$4n$
	-0.41 0.19	0.61 -0.35		$4n$
	-0.69 -0.41 0.21	0.03 0.56 -0.42		$4n + 2$
	-0.06 -0.39 -0.34 0.36	0.40 0.51 -0.24 -0.41	<i>ab</i> <i>bc</i>	$4n$ $4n + 2$
	-0.71 -0.38 -0.09 0.32	0.44 0.52 -0.23 -0.41		$4n$
	-0.07 0.50 -0.07	0.54 0.43 -0.43	<i>ac</i>	$4n + 2$
	0.50 -0.50	0.71 0.40	<i>ab</i>	$4n + 2$

<sup>a</sup> Ref. 23. <sup>b</sup> Ref. 24. <sup>c</sup> A. W. Fort, *J. Amer. Chem. Soc.*, 1962, **84**, 4979. <sup>d</sup> N. J. Turro, S. S. Edelson, J. R. Wil-

It should be stressed that there are a few well known examples of cases where the Woodward-Hoffmann rules break down, particularly certain reactions of halogenated alkenes, acetylene- and azo-dicarboxylic esters, tetracyanoethylene, and ketens. These reactions also violate the FMO predictions. However, much has been published offering explanations for these rare anomalies, such as a two-step mechanism or an antarafacial process. Particularly interesting is Epiotis's suggestion<sup>20</sup> that there is a continuous spectrum of behaviour lying between the extreme cases of [2 + 2] and [2 + 4] cycloadditions. In this work, reagents known commonly to violate Woodward-Hoffmann rules have not been considered, and the treatment is not intended to cover them.

(C) *Regioselectivity*.—While we have shown that the values of the eigenvector coefficients do not have a marked effect on the rates of cycloaddition reactions and have suggested that this may arise from Fukui's 'principle of growing frontier electron density along the reaction path', nevertheless their values have been successfully invoked to explain regioselectivity in a range of cycloaddition reactions.<sup>4</sup> This is not unreasonable since although the coefficients will approach  $1/\sqrt{2}$  in the transition state, any residual deviation from this value should reflect the original values in the reactants. Alternatively one may argue that the reactants become oriented correctly because they are guided up valleys of correct orientation in the potential energy surface before reaching the transition state. On the basis of these arguments we would expect to be able qualitatively to predict regioselectivity by applying equation (i), and the predominant regioisomer should be the one for which  $\Delta E_{\text{FMO}}$  is greater. For reactions in which there is definite donor/acceptor behaviour, this means that the magnitude of  $(C_{\text{A1H}}C_{\text{B1L}} + C_{\text{A2H}}C_{\text{B2L}})$  is the controlling influence. Such an approach has been applied successfully, particularly by Anh and his co-workers,<sup>4c</sup> to predict the regioisomers observed for the bulk of experimental examples in the literature, and extension of the work to further compounds in this laboratory has revealed no definite anomalies.

One problem with predicting ratios of regioisomers is that since the differences in frontier energy may be often quite small, other effects such as steric, coulombic, and secondary orbital interactions may acquire greater

## References to Table 3—continued:

- liams, T. R. Darling, and W. B. Hammond, *J. Amer. Chem. Soc.*, 1969, **91**, 2283. <sup>e</sup> O. L. Chapman, J. C. Clardy, T. L. McDowell, and H. E. Wright, *J. Amer. Chem. Soc.*, 1973, **95**, 5086. <sup>f</sup> Ref. 26. <sup>g</sup> J. W. Lown and K. Matsumoto, *J. Org. Chem.*, 1971, **36**, 1405. <sup>h</sup> O. Tsuge and H. Samura, *Tetrahedron Letters*, 1973, 597. <sup>i</sup> C. W. Rees, R. W. Stephenson, and R. C. Storr, *J.C.S. Chem. Comm.*, 1972, 1281. <sup>j</sup> Ref. 22b. <sup>k</sup> Ref. 22c. <sup>l</sup> P. Rajagopalan and P. Penev, *Chem. Comm.*, 1971, 490. <sup>m</sup> L. A. Paquette and J. H. Barrett, *J. Amer. Chem. Soc.*, 1966, **88**, 2590. <sup>n</sup> R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Comm.*, 1966, 15. <sup>o</sup> M. P. Cava and M. A. Sprecker, *J. Amer. Chem. Soc.*, 1972, **94**, 6214. <sup>p</sup> V. Boekelheide and N. A. Fedoruk, *Proc. Nat. Acad. Sci., U.S.A.*, 1966, **55**, 1385.

relative importance and ought now to be taken into account. For example, the observed regioisomer in the dimerisation of acrylaldehyde is only correctly predicted when coulombic interactions are considered.<sup>4b</sup> The problem of regioselectivity is further complicated by the fact that highly regioselective reactions might be better considered as concerted two-step reactions in which one of the  $\sigma$ -bonds is formed slightly ahead of the other, in which case several of the assumptions made in the FMO statement in this paper become less valid.

(D) *Periselectivity*.<sup>27</sup>—This phenomenon occurs when an addend has more than one pair of sites at which the other addend is thermally allowed to attack. For example a conjugated polyene might be expected to form several 1 : 1 adducts on reaction with maleic anhydride, but one isomer might predominate owing to a periselectivity effect. The factors which govern periselectivity should be exactly analogous to those which govern regioselectivity and so need not be repeated here. Houk and his co-workers<sup>8</sup> have briefly discussed the phenomenon in these terms and find no contradiction between experimental data and theory.

(E) *Stereoselectivity*.—The application of FMO principles to stereoselectivity (*i.e.* *exo* : *endo* ratio in diene reactions) was introduced by Woodward and Hoffmann<sup>5b</sup> in their pioneering series of communications on cycloaddition rules. Again the phenomenon is a manifestation of equation (i), but this time the interactions at the four reaction sites are equal and other secondary interactions between neighbouring atoms have to be considered. The method appears to work for qualitatively predicting *exo* : *endo* ratios, provided steric repulsions are allowed for in addition to secondary frontier orbital interactions. In this laboratory the method using HMOs has been employed to explain the predominant occurrence of an *exo*-adduct in an unusual reaction of (13) with dienes.<sup>22c</sup> Much more testing is required in this area.

*Conclusions*.—The following conclusions may now be stated as long as one takes into account the precautions already mentioned.

1. It is reasonable to treat the transition state as the point of intersection of two potential energy curves (Figure 6): curve R for the approach of reactants without change of geometry, and curve P for dissociation of the product without change of geometry.

2. The energy of the transition state is then dependent on two factors: first the FMO interaction which effects curve R, and secondly the stability of the product which effects curve P.

3. The net effect on the energy of the transition state is governed by equations (ix) and (x), which take into account the slopes of the intersecting curves.

4. For the cycloadditions studied the net FMO effect is greater than the net product stability effect.

5. Relative activity in a cycloaddition reaction series

can be explained by using equation (vii) where the eigenvalues ( $E_H$  and  $E_L$ ) are calculated by the Huckel method.

6. Electrosensitivity, regioselectivity, and periselectivity may be qualitatively predicted by inspection of the eigenvector coefficients of the HOMO and LUMO.

7. Stereoselectivity (*exo/endo* for diene reactions) can be qualitatively explained by allowing for secondary orbital effects and steric effects.

8. The transition state for cycloadditions is indicated as occurring soon along the reaction co-ordinate.

Certain additional limitations to the FMO technique should be mentioned. First, the method can only be applied if the products are formed by kinetic rather than thermodynamic control, and commonly data are reported

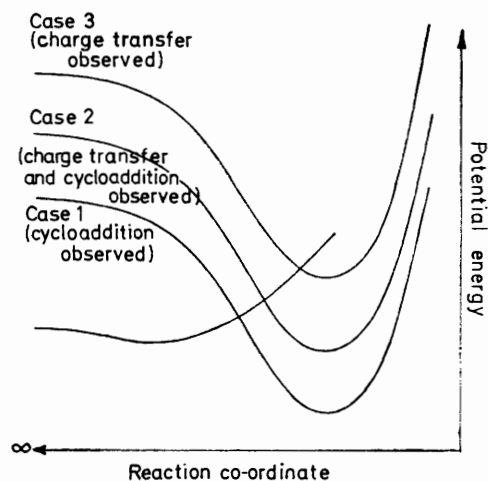


FIGURE 7

in the literature without the mode of control established. Secondly, if the transition state involves highly charged atoms it is possible that the FMO controlling effect could be overpowered by the coulombic effect which was included in more comprehensive treatments, but which was found to be unnecessary for systems treated in this paper (even the 1,3-dipolar systems). Thirdly, a more sophisticated correlation of rate data should take into account steric effects of substituents which have been blatantly ignored in this work but which are undoubtedly very important. Fourthly, the Hückel MO method tends to give exaggerated prediction of eigenvalues and eigenvector coefficients and the discrepancy is most marked for the powerfully electron-withdrawing groups such as nitro and cyano. Also these two groups are problematical with regard to the selection of coulomb and resonance integral parameters. Therefore application of the technique reported in this paper to cyano- and nitro-compounds should be handled with caution.

The relationship between charge-transfer complexation and cycloaddition reactions has been discussed in the

<sup>27</sup> K. N. Houk, L. J. Luskus, and N. S. Bhacca, *J. Amer. Chem. Soc.*, 1970, **92**, 6392.



literature.<sup>20,8,28</sup> While the two phenomena have been shown to correlate approximately, opinion differs as to whether charge-transfer complexation occurs along the reaction co-ordinate for cycloaddition or whether it is not directly involved. The treatment in this paper uncompromisingly corresponds to the former. It is of interest that while both charge transfer and cycloaddition behaviours are thought to depend on FMO effects, only the latter is considered to be dependent on product stability as treated in this paper. Since it may be this difference in treatment that leads to much of the observed deviation from linear correlations between cycloaddition rate constants and equilibrium constants of charge-transfer complexes, it would be worthwhile to reconsider the problem in the light of this work. The relationship between the two phenomena is perhaps clarified in Figure 7, which shows the intersecting energy curves for three extreme types of behaviour between two reactants. For simplicity the FMO interaction and hence the stability of the charge transfer complex is shown as constant, but the product stability is varied. Note that while the charge-transfer complex is now

shown as a slight minimum, its neglect in earlier diagrams does not alter the previous conclusions. Case 1 represents a typical cycloaddition in which the product is stable and the energy barrier for its formation from the charge-transfer complex is low, and therefore the existence of the complex cannot be detected; case 3 would occur for compounds which form observable complexes but not cycloaddition products; and case 2 represents intermediate conditions when it might be possible both to detect a complex and to isolate a cycloadduct.

We thank the National Research Council of Canada for financial assistance, and Drs. Boyd, Fyfe, Goldman, and Zerner of this Department for discussions.

[4/2431 Received, 21st November, 1974]

<sup>28</sup> A. K. Colter and M. J. Dack, 'Molecular Complexes,' vol. 2, ed. R. Foster, Paul Elek Ltd., London, 1974 and references therein; (b) R. Foster, 'Organic Charge-Transfer Complexes,' Academic Press, London, 1969; (c) A. I. Konovalov and V. D. Kiselev, *J. Org. Chem. (U.S.S.R.)*, 1966, **2**, 136; (d) A. I. Konovalov, V. D. Kiselev, and O. A. Vigdorovich, *ibid.*, 1967, **3**, 2034.