Table III), $C_e$ is the ethylene coefficient ($1/\sqrt{2}$), and $\Delta E_e$ is the change in frontier orbital energy of ethylene caused by substitution (Figure 7).

**Summary.** We have derived, wherever possible from experimental data, a set of rules for the qualitative deduction of the coefficients and energies of all common 1,3 dipoles, dienes, and dipolarophiles. These last compounds are, of course, also dienophiles, enophiles, ketenophiles, sulfenophiles, etc., so that these considerations should lead not only to increased understanding of 1,3-dipolar cycloadditons[12,13] but also to an understanding of all types of cycloaddition reactions.

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# The Origin of Reactivity, Regioselectivity, and Periselectivity in 1,3-Dipolar Cycloadditions

**K. N. Houk,*[1] Joyner Sims,[2] Charles R. Watts,[3a] and L. J. Luskus[3b]**

*Contribution from the Department of Chemistry, Louisiana State University—Baton Rouge, Baton Rouge, Louisiana 70803.* *Received April 28, 1973*

**Abstract:** Perturbation theory is applied to 1,3-dipolar cycloaddition phenomena. The generalizations made in the previous paper concerning 1,3 dipole and dipolarophile frontier orbital energies and coefficients allow a specific qualitative treatment of reactivity of individual 1,3 dipoles. The explanation of regioselectivity and periselectivity phenomena also follows from this treatment. Extensions of the frontier orbital method to other cycloaddition reactions are outlined.

The previous paper derived a set of generalized frontier orbitals of 1,3 dipoles and dipolarophiles.[4] The motive of that exercise was to develop a simple, yet theoretically meaningful, explanation of perplexing regioselectivity phenomena observed in 1,3-dipolar cycloadditions. The use of these generalized frontier orbitals within the framework of qualitative perturbation molecular orbital theory will be shown here to provide a qualitative explanation for the phenomena of differential reactivity, regioselectivity, and periselectivity in 1,3-dipolar cycloadditions as well as provide additional insight into selectivity phenomena observed in Diels–Alder reactions and thermal and photochemical [2 + 2] cycloadditions.

**Applications of Perturbation Theory to Cycloadditions.** Perturbation theory has been an increasingly powerful tool for the understanding of diverse organic phenomena.[5,6] Applications of perturbation theory to cycloaddition reactions have recently been reviewed.[7] Salem has derived the following second-order perturbation expression for the change of energy which accompanies the interaction of two molecules involved in a cycloaddition reaction.[7,8]

$$\Delta E = -\sum_{\mathrm{ab}} (q_{\mathrm{a}} + q_{\mathrm{b}})\gamma_{\mathrm{ab}} S_{\mathrm{ab}} - \sum_{\mathrm{ab}} Q_{\mathrm{a}} Q_{\mathrm{b}} \frac{\Omega}{\epsilon} + 2\sum_{R}^{\mathrm{occ}} \sum_{S}^{\mathrm{unocc}} - \sum_{R}^{\mathrm{unocc}} \sum_{S}^{\mathrm{occ}} \frac{\left(\sum_{rs} c_{\mathrm{a}} c_{\mathrm{b}} \gamma_{\mathrm{ab}}\right)^2}{E_R - E_S} \qquad (1)$$

The first term is a closed-shell repulsion term, the second term is a Coulombic repulsion (or attraction) term, and the third term is called variously the delocalization, overlap, or charge-transfer stabilization. In this equation $q_{\mathrm{a}}$'s and $Q_{\mathrm{a}}$'s are orbital and total electron densities, respectively, at atomic orbital a in molecular orbital $R$, $\gamma_{\mathrm{ab}}$ is the interorbital interaction integral and $S_{\mathrm{ab}}$ is the interorbital overlap integral for atomic orbitals a and b in MO's $R$ and $S$, and $c_{\mathrm{a}}$'s are the atomic orbital coefficients at atom a in molecular orbital $R$. The last term is a quantitative expression of the qualitative statement that interaction of two orbitals results in depression of the energy of the lower energy orbital and raising of the energy of the higher energy orbital, with the extent of energy change inversely proportional to the difference in energy of the orbitals prior to interaction.[5] This is shown schematically in Figure 1 for the interaction of the HO ($E_1$) of one polyolefin with the LU ($E_2$) of a second.

Most perturbation treatments of cycloaddition reactivity have focused on the last term of eq 1 and have

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(1) Camille and Henry Dreyfus Foundation Teacher–Scholar Grant Recipient, 1972–1977.

(2) National Science Foundation Summer Faculty Research Participant, 1971. On leave from Chipola Junior College, Marianna, Fla., 1972–1973.

(3) American Chemical Society—Petroleum Research Fund Graduate Fellow: (a) 1971–1972; (b) 1970–1971.

(4) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Amer. Chem. Soc.*, **95**, 7287 (1973).

(5) E. Heilbronner and H. Bock, "Das HMO-Modell und Seine Anwendung," Verlag-Chemie, GmbH, Weinheim/Bergstr., 1968; M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969; R. Hoffmann, *Accounts Chem. Res.*, 4, 1 (1971); R. F. Hudson and G. Klopman, *Tetrahedron Lett.*, 1103 (1967); G. Klopman, *J. Amer. Chem. Soc.*, 90, 223 (1968).

(6) K. Fukui, *Fortschr. Chem. Forsch.*, **15**, 1 (1970); *Accounts Chem. Res.*, 4, 57 (1971).

(7) W. C. Herndon, *Chem. Rev.*, 72, 157 (1972).

(8) L. Salem, *J. Amer. Chem. Soc.*, 90, 543, 553 (1968).

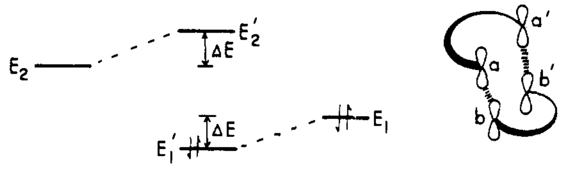

Figure 1. Schematic representation of orbital mixing.

considered only interactions between $\pi$ orbitals on both reactants.

Interactions between only the frontier orbitals (highest occupied (HO) and lowest unoccupied (LU)) of both reactants are frequently considered, since the inverse dependence of stabilization energy on orbital energy differences ensures that terms involving the frontier orbitals will be larger than others. Fukui has also argued that the frontier orbital interactions should be even more important than is implied by the inverse dependence of stabilization energy on orbital energy differences since, during the course of the reaction, the difference between energies of the frontier orbitals of the two reactants will diminish. This is called the "principle of narrowing of inter-frontier level separation."[6]

Early treatments of cycloaddition reactions by frontier orbital theory[9] resulted in the landmark orbital symmetry selection rules for concerted cycloadditions, and explanation of exo/endo phenomena,[10] as well as an explanation of the propensity for cyclopentadienones to dimerize.[11] The latter phenomenon was also treated by calculations of the full overlap stabilization including interactions of all $\pi$ orbitals,[12] and a similar approach was used to rationalize regioselectivity of Diels–Alder reactions of styrene and methyl acrylate.[13]

Woodward and Hoffmann used qualitative frontier orbital theory to rationalize exo/endo phenomena in cycloadditions,[10] while an all-$\pi$ orbital perturbation treatment was also applied to this phenomenon in Diels–Alder reactions.[14,15]

Salem treated the selection rules for concerted cycloadditions as well as regioselectivity and stereoselectivity by the more complete treatment (eq 1),[8] and later extended this to a treatment of photochemical cycloadditions.[16] Recently, a SCF perturbation treatment of cycloadditions, including all types of interactions (overlap, Coulombic, and steric), has been developed and applied to stereoselectivity in the Diels–Alder reaction of cyclopentadiene and cyclopropene,[17] as well as to ketene cycloadditions.[18]

A recent return to the frontier orbital method has resulted in rationalizations of reactivity and mechanistic phenomena observed in photochemical cycloadditions,[19] Diels–Alder and 1,3-dipolar cycloadditions,[20] and [2 + 2] cycloadditions.[21] Recently, one of us has applied frontier orbital theory to explain the phenomenon of regioselectivity in diazonium betaine cycloadditions.[22] Similar results for diazomethane have been reported by others.[23]

Eisenstein, *et al.*, have claimed complete correspondence of observed Diels–Alder regioselectivity to frontier orbital theoretical predictions using Hückel calculations.[24] Others have found that not all regioselectivity in Diels–Alder cycloadditions can be explained by the perturbation approach, particularly if Hückel MO's are used or if all interactions are considered.[16,25,26]

Although the previous treatments of Diels–Alder reactivity have depended on calculations of varying complexity, we have shown previously that it is possible to use generalized frontier orbitals[4] to qualitatively rationalize Diels–Alder regioselectivity without resorting to explicit calculations.[27,28] This treatment has the benefit of not only rationalizing (or predicting) regioselectivity in Diels–Alder reactions but also of revealing the origin of this phenomenon.[28a] This paper adopts the same approach for the rationalization of 1,3-dipolar cycloadditionr egioselectivity, reactivity, and periselectivity.

Experimental evidence for the overriding importance of frontier orbital interaction between the diene HO and dipolarophile LU in controlling reactivity in Diels–Alder reactions has been obtained from correlations between ionization potential of the diene or the electron affinity of the dienophile and the relative rates of Diels–Alder reaction,[29] while U-shaped plots for phenyl azide are also in agreement with the frontier orbital treatment of 1,3-dipolar cycloaddition reactivity.[30]

**The Frontier Orbital Model of 1,3-Dipolar Cycloadditions.** In the early stages of a cycloaddition reaction, when interaction between two addends is small, perturbation theory is particularly suited for estimating the relative energies of different geometries of approach of the addends. Since most cycloadditions have low activation energies and large heats of reaction, the relative energies of different transition states should be paralleled by the relative energies of the corresponding weakly interacting complexes. If the assumption is

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(20) (a) R. Sustmann, *Tetrahedron Lett.*, 2717 (1971); (b) 2721 (1971).

(21) N. D. Epiotis, *J. Amer. Chem. Soc.*, **94**, 1924, 1935, 1941, 1946 (1972).

(22) K. N. Houk, *ibid.*, **94**, 8953 (1972).

(23) J. Bastide, N. El Ghandour, and O. Henri-Rousseau, *Tetrahedron Lett.*, 4225 (1972).

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(25) J. Bertrán, R. Carbó, and T. Moret, *An. Quim.*, **67**, 489 (1971).

(26) T. Inukai, H. Sato, and T. Kojima, *Bull. Chem. Soc. Jap.*, **45**, 891 (1972).

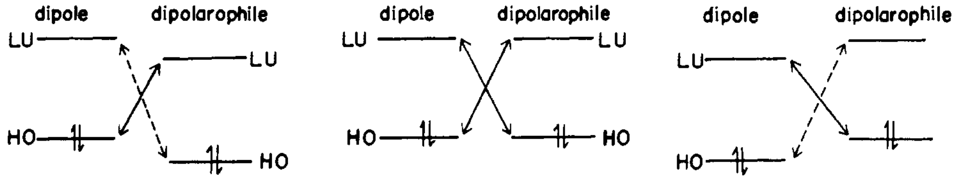
(27) K. N. Houk, *J. Amer. Chem. Soc.*, **95**, 4092 (1973).

(28) K. N. Houk and R. W. Strozier, *ibid.*, **95**, 4094 (1973).

(28a) NOTE ADDED IN PROOF. N. D. Epiotis, *J. Amer. Chem. Soc.*, **95**, 5625 (1973), has applied a similar method to regioselectivity in [2 + 2] and Diels–Alder cycloadditions.

(29) (a) A. I. Konovalov and V. D. Kiselev, *J. Org. Chem. USSR*, **2**, 136 (1966); A. I. Konovalov, V. D. Kiselev, and O. A. Vigdorovich, *ibid.*, **3**, 2034 (1967); A. I. Konovalov, *ibid.*, **5**, 1661 (1969); (b) R. Sustmann and R. Schubert, *ibid.*, **11**, 840 (1972).

(30) R. Sustmann and H. Trill, *Angew. Chem., Int. Ed. Engl.*, **11** 838 (1972).



Type I
(HO controlled)

Type II
(HO, LU controlled)

Type III
(LU controlled)

Figure 2. Sustmann's classification of 1,3-dipolar cycloadditions.

made that entropies of activation will not differ significantly for two isomeric transition states formed from a pair of addends, then the relative energies of the isomeric transition states can be approximated from perturbation theory. Although regioselectivity is the result of very small energy differences (0.1–5 kcal/mol) between two diastereomeric transition states, the estimation of such small energy differences is the forte of perturbation theory.

Rather than use the complete perturbation expression (eq 1), we will neglect the closed-shell repulsion terms, except that it will be shown later that these terms can reinforce the arguments based on overlap interactions. The Coulombic repulsion (or dipole–dipole repulsion) terms will also be neglected, and the possible importance of these terms will be discussed later. In addition, only the overlap terms arising from interactions of frontier orbitals on the 1,3 dipole and the dipolarophile will be considered, and these only qualitatively.

Thus, our model reduces to that proposed by Sustmann[20a] who classified 1,3-dipolar cycloadditions into three types, depending on the relative disposition of 1,3 dipole and dipolarophile frontier orbitals (Figure 2). We will call these three types HO-controlled (the interaction of the dipole HO with the dipolarophile LU is greatest), HO,LU-controlled (both frontier orbital interactions are large), and LU-controlled (the interaction of the dipole LU with the dipolarophile HO is greatest). In Sustmann's terminology, these are Types I, II, and III, respectively.[20a]

Qualitatively, substituents which raise the dipole HO energy (R,X,C)[4] or lower the dipolarophile LU energy (C,Z)[4] will accelerate HO-controlled reactions and decelerate LU-controlled reactions. Conversely, substituents which lower the dipole LU energy (C,Z) or raise the dipolarophile HO (R,X,C) energy will accelerate LU-controlled reactions and decelerate HO-controlled reactions. HO, LU-controlled reactions will be accelerated by an increase of *either* frontier orbital interaction.

Once the frontier orbital model is assumed, a distance of separation between addends must be chosen. The expression for overlap stabilization depends not only on the energy difference between interacting orbitals but also on products of the type $C_aC_b\gamma_{ab}$, where $C_a$ and $C_b$ are coefficients at one site of interaction and $\gamma_{ab}$ is a resonance or bond integral for orbitals on atoms a and b. In a variety of semiempirical calculations, resonance integrals such as $\gamma_{ab}$ are often estimated from the Mulliken approximation,[31] $\gamma_{ab} = \beta_{AB}A_{ab}$ or $\gamma_{ab} = S_{ab}(\beta_a + \beta_b)/2$, where $S_{ab}$ is the overlap integral for orbitals on atoms a and b, and the $\beta$'s are constants characteristic of the identity of atoms involved. In the CNDO/2 method, the values of these empirical constants of interest are (in eV) −21, −25, and −31 for C, N, and O.[32] The overlap integrals $S_{ab}$ which appear in the expression for $\gamma_{ab}$ are different for different types of atoms and numerical values may most easily be obtained from extensive published tabulations.[33] A graphical comparison of CC, CN, and CO overlap integrals as a function of distance for 2p Slater orbitals overlapping in a $\sigma$ fashion is also available.[34] Table I shows how $\gamma_{ab}$ varies as a function of the separation of overlapping orbitals and the types of atoms involved.[35]

**Table I.** $-\gamma_{ab}$ (eV) for 2p$\sigma$, 2p$\sigma$ Overlap

| $r$, Å | $\gamma_{CC}$ | $\gamma_{CN}$ | $\gamma_{CO}$ | $\gamma_{NN}$ | $\gamma_{NO}$ | $\gamma_{OO}$ |
|---|---|---|---|---|---|---|
| 1.50 | 6.97 | 7.20 | 7.05 | 7.18 | 6.92 | 6.63 |
| 1.75 | 6.22 | 5.83 | 5.38 | 5.35 | 4.81 | 4.19 |
| 2.00 | 5.00 | 4.35 | 3.77 | 3.65 | 3.02 | 2.45 |
| 2.50 | 2.63 | 2.14 | 1.53 | 1.40 | 1.04 | 0.68 |
| 3.00 | 1.20 | 0.78 | 0.55 | 0.45 | 0.28 | 0.16 |

The main point of this table is that as the number and electronegativity of heteroatoms involved in the newly forming bond increases, the resonance integral decreases. Furthermore, although the overlap of any given type increases as the distance between overlapping atoms decreases, the differences between resonance integrals between atoms of different types diminish. Thus, the choice of distance separating the addends in our perturbation model is important. In numerical perturbation calculations, this distance has been variously set at 2.65,[35] 3.0,[18] and 3.2 Å.[12,26] Salem considered 2.5–3.5 Å a reasonable value and provided a general discussion of the behavior of $S_{CC}$ as a function of distance.[8] The large negative entropies of activation and sizable steric effects,[36] as well as the large negative activation volumes,[37] for cycloaddition reactions suggest that a rather small distance separates the addends in the transition state. We have chosen, rather

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(31) R. S. Mulliken, *J. Phys. Chem.*, **56**, 295 (1952).

(32) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970, p 72.

(33) R. S. Mulliken, C. A. Rieke, D. Orloff, and H. Orloff, *J. Chem. Phys.*, 17, 1248 (1949); E. A. Boudreaux, L. C. Cusachs, and P. Dureau, "Numerical Tables of Two-Center Overlap Integrals," W. A. Benjamin, New York, N. Y., 1970.

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(37) R. A. Grieger and C. A. Eckert, *J. Amer. Chem. Soc.*, **92**, 7149 (1970), and references therein.

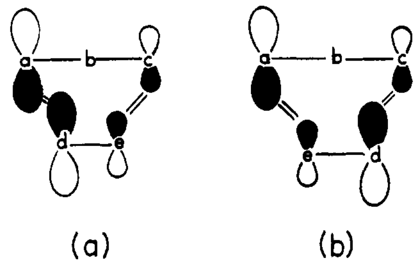
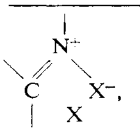
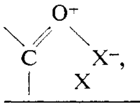


Figure 3. Schematic representation of greater stabilization of transition state (a) than (b) due to different coefficient magnitudes.

arbitrarily (and not without some bias), a distance of 1.75 Å for this separation. Although this distance is quite small, it does not appear unreasonable for at least one pair of addend termini to approach this close in the cycloaddition transition state. This is also about the distance of maximum overlap of the $(2p\sigma, 2p\sigma)_{CC}$ type.[5]

The preferred regioisomeric transition state will be that in which the larger terminal coefficients of the interacting orbitals are united, and the propensity for addition in one direction will depend on the difference in the squares of the terminal coefficients. Table II shows the squares of the products of the CNDO/2 calculated frontier orbital coefficients of 1,3 dipoles[4] and the appropriate $\gamma_{CX}$ at 1.75 Å. Qualitatively, the preferred regioisomer in a 1,3-dipolar cycloaddition will be that one in which the atoms with the larger terminal coefficients of the interacting frontier orbitals interact. This conclusion must be somewhat tempered by the fact that $\gamma_{CC} > \gamma_{CX} > \gamma_{CO}$. Figure 3 shows this schematically. Case a results in more stabilization than case b. A cycloaddition controlled by a strong interaction as in (a) would lead to unequal extents of bond formation in the transition state, bond a–d being more fully developed than bond c–e. Salem has elegantly demonstrated this more quantitatively by means of calculated bond-order diagrams.[8]

**Table II.** Values of $[(C_X\gamma_{CX})^2/15]^a$

| $HC{\equiv}N^+X^-$, | HO |  |  | NLU (π) |  |  |
|---|---|---|---|---|---|---|
| X | C | N | X | C | N | X |
| $CH_2$ | 1.07 | 0.01 | **1.50** | **0.69** | 1.09 | **0.64** |
| NH | 0.90 | 0.01 | **1.45** | **0.92** | 1.09 | 0.36 |
| O | 0.81 | 0.10 | **1.24** | **1.18** | 1.03 | 0.17 |
| $N{\equiv}N^+X^-$, X | N | N | X | N | N | X |
| $CH_2$ | 0.85 | 0.04 | **1.57** | **0.56** | 1.12 | **0.66** |
| NH | 0.72 | 0.00 | **1.55** | **0.76** | 1.14 | 0.37 |
| O | 0.67 | 0.04 | **1.33** | **0.96** | 1.09 | 0.19 |
|  X | C | N | X | C | N | X |
| $CH_2$ | **1.28** | 0 | **1.28** | **0.73** | 0.98 | **0.73** |
| NH | 1.15 | 0.01 | **1.24** | **0.87** | 1.01 | 0.49 |
| O | **1.11** | 0.05 | **1.06** | **0.98** | 1.03 | 0.32 |
|  X | C | O | X | C | O | X |
| $CH_2$ | **1.29** | 0 | **1.29** | **0.82** | 0.70 | **0.82** |
| NH | 1.04 | 0.01 | **1.34** | **1.06** | 0.73 | 0.49 |
| O | 0.82 | 0.07 | **1.25** | **1.30** | 0.72 | 0.24 |

[a] $C_X$ for parent compounds from CNDO/2;[4] $\gamma_{CX} = \frac{1}{2}(\beta_C + \beta_X)S_{CX}$ at 1.75 Å.

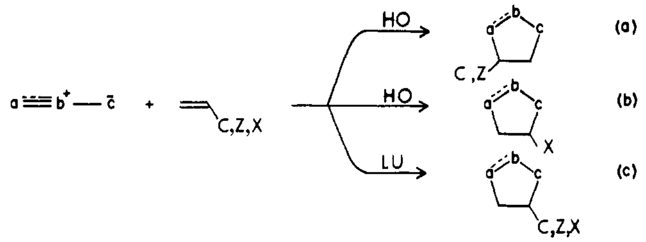


Figure 4. Regioisomer expected from HO or LU control by the dipole.

**Regioselectivity and Reactivity in 1,3-Dipolar Cycloadditions.** Table II indicates that the HO's of almost all the parent 1,3 dipoles have larger values of $(C_X\gamma_{CX})^2$ for the "anionic" terminus c than the "neutral" terminus a. The only exception other than the trivial symmetrical cases is the nitrone, which has nearly identical values of $(C_X\gamma_{CX})^2$ for both termini.

Control of regioselectivity by the dipole HO will lead to products with the substituent remote from the "anionic" terminus for monosubstituted, conjugated, and electron-deficient dipolarophiles (larger coefficients at unsubstituted carbon in the LU) and to products with the substituent near the "anionic" terminus for electron-rich dipolarophiles (larger LU coefficient at substituted carbon), as shown in Figure 4. Since, except for $CH_2N_2$, the larger terminal $C_X\gamma_{CX}$ of the dipole LU orbital is on the "neutral" atom, a, and all dipolarophiles have the largest HO coefficient on the unsubstituted carbon, LU dipole control will lead to the predominant product with the substituent near the "anionic" atom (Figure 4c). Possible complications produced by electrostatic and closed-shell repulsions as well as by the reversal of terminal coefficient magnitudes by substitution will be discussed later, but for most cases it will only be necessary to identify the controlling frontier orbital interaction in order to rationalize or predict product regiochemistry. All 1,3 dipoles will react with monosubstituted electron-rich dipolarophiles to form the product with the substituent adjacent to the "anionic" atom (Figure 4c). This is because all of these reactions will be shown to be dipole LU-controlled. However, for conjugated and electron-deficient dipolarophiles, the regiochemistry of the reaction will depend on which frontier orbital interaction is dominant (Figure 4a, c).

**Azides.** Azides add to conjugated, electron-rich, and electron-deficient dipolarophiles to give predominantly the preferred regioisomers shown.[38–40]

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(38) R. A. Firestone, *J. Org. Chem.*, 37, 2181 (1972), contains a recent survey of 1,3-dipolar regioselectivity.

(39) G. L'Abbe, *Chem. Rev.*, **69**, 345 (1969).

(40) (a) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, 100, 2494 (1967); (b) P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Amer. Chem. Soc.*, **87**, 306 (1965); (c) P. Scheiner, *Tetrahedron*, 24, 349 (1967); (d) M. E. Munk and Y. K. Kim, *J. Amer. Chem. Soc.*, **86**, 2213 (1964); (e) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965); (f) R. Huisgen and G. Szeimies, *ibid.*, **98**, 1153 (1965); (g) P. Ykman, G. L'Abbe, and G. Smets, *Tetrahedron*, 27, 845 (1971); (h) W. Kirmse and L. Horner, *Justus Liebigs Ann. Chem.*, **614**, 1 (1958); (i) J. C. Sheehan and C. A. Robinson, *J. Amer. Chem. Soc.*, 73, 1207 (1951); (j) R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.*, **91**, 849 (1961).

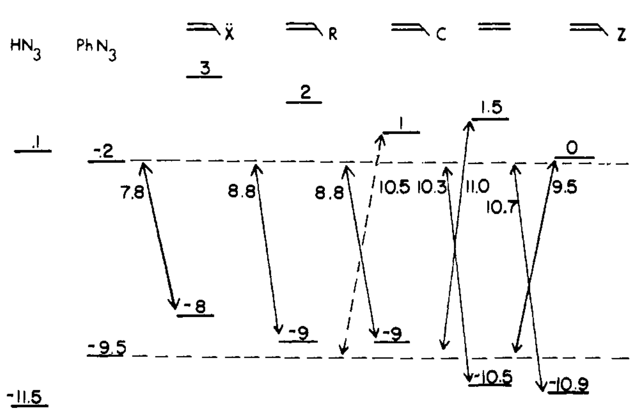
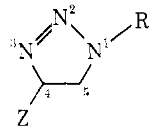
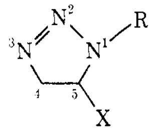


Figure 5. Frontier orbital energies for azides and dipolarophiles.





The frontier orbital energies for hydrazoic acid and the various classes of dipolarophiles deduced in the previous paper are shown on the same scale in Figure 5. Since the majority of cycloaddition studies have been performed with phenyl azide, for which frontier orbital energies are not available, these have also been estimated in the following way. Since the phenyl group is attached to the "anionic" nitrogen, the destabilization of the HO will be larger than the stabilization of the LU. Figure 5 shows the estimated energy levels derived from $\Delta E_d^s = (C_d^2/C_c^2)(\Delta E_e^s)$, as explained in the previous paper.[4]

Reactions with electron-rich dipolarophiles are LU-controlled. Since the larger terminal coefficients are on the unsubstituted nitrogen in the azide and unsubstituted terminus in the dipolarophiles, the 5-substituted $\Delta^2$-triazolines are favored, in agreement with experiment.[40] Furthermore, electron withdrawal in the azide will increase the controlling interaction and accelerate reaction. Thus, para-substituted phenyl azides give Hammett $\rho$'s of 1.88 with norbornene (IP = 8.97 eV) and +2.5 with 1-pyrrolidinocyclopentene (IP = 7.33 eV).[40a,b] No charge separation need be invoked in the transition states of these cycloadditions to explain reactivity and regioselectivity.[22] However, since bond formation in the transition state should be more advanced at the site of largest frontier orbital coefficients, the traditional[40] concept of bond formation nonsynchroneity is confirmed by these frontier orbital arguments.

Reactions with electron-deficient dipolarophiles are HO-controlled, and union of the substituted azide N with the unsubstituted dipolarophile C leads to the 4-substituted $\Delta^2$-triazoline. The dipole LU interaction, although not negligible, is of lesser regiochemical importance due to the more nearly equal magnitudes of the electron-deficient dipolarophile HO coefficients. Once again, Huisgen's "classical" charge-separated model, with more complete formation of the 1–5 bond in the transition state, is given theoretical support. Any further electron release in the azide will accelerate reaction due to raising of the azide HO energy. Electron withdrawal in the azide will have the opposite effect. Thus, para-substituted phenyl azides give a Hammett $\rho$ of $-1.1$ (electron release accelerates) in reactions with maleic anhydride.[40a]

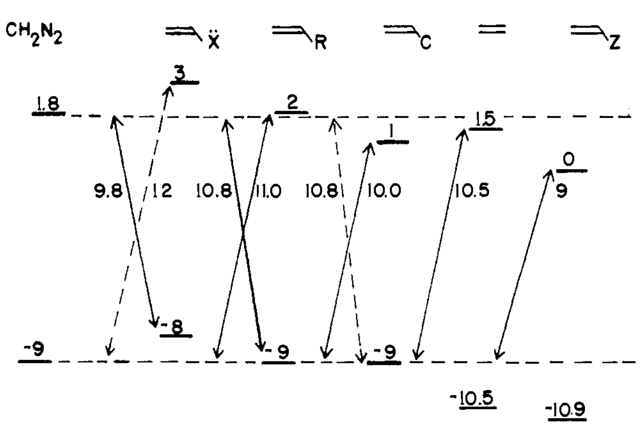


Figure 6. Frontier orbital energies for diazomethane and dipolarophiles.

Although the phenyl azide LU–conjugated dipolarophile HO separation is estimated to be smaller than the opposite frontier orbital interaction, the latter interaction will be of some importance. A slight predomminance of the 5-substituted $\Delta^2$-triazoline is expected, although regioselectivity should not be high. This is in accord with experiment.[40h]

A crucial test of the approach proposed here involves the cases where only low regioselectivity is observed. Such cases have traditionally been considered to involve a delicate competition between electronic and steric effects.[36] Azides are examples where the balance between control of regiochemistry by the dipole HO or dipole LU is delicate, and with conjugated dipolarophiles, in which the coefficients are largest at the unsubstituted carbon in both HO and LU orbitals, mixtures of adducts are expected. Thus, the reaction of phenylacetylene with phenyl azide to form approximately equal amounts of the two diphenyltriazolines is not surprising.[40h] Only in the case of electron-rich alkenes do both sets of frontier orbital interactions preferentially stabilize transition states leading to the same regioisomer.

Another effect which would tend to produce mixtures is any diminution in the difference in magnitudes of the coefficients of the two carbons in the dipolarophile frontier orbital. Thus, if conjugating or electron-withdrawing substituents are attached to both ends of a dipolarophile, the frontier orbitals may have nearly identical coefficients at both carbons. An example of this can be found in reactions of phenylpropynal with phenyl azide to produce a 40:22 ratio of the 5-phenyl and 4-phenyl adducts.[40i] Thus, a decrease in regioselectivity need not arise from steric effects.

**Diazoalkanes.** The frontier orbital energies of diazoalkanes and dipolarophiles, deduced in the previous paper,[4] are displayed in Figure 6. Since the frontier orbitals of diazoalkanes are of higher energy than those of azides, diazoalkanes are predominantly HO-controlled 1,3 dipoles. Both conjugation and electron withdrawal will accelerate reactions of dipolarophiles with diazomethane as compared to ethylene. With these dipolarophiles, the dipole HO–dipolarophile LU interaction is largest, and experimentally observed 3-substituted $\Delta^1$-pyrazolines are favored

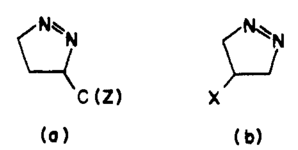


Figure 7. Preferred regiosiomers in diazomethane cycloadditions.

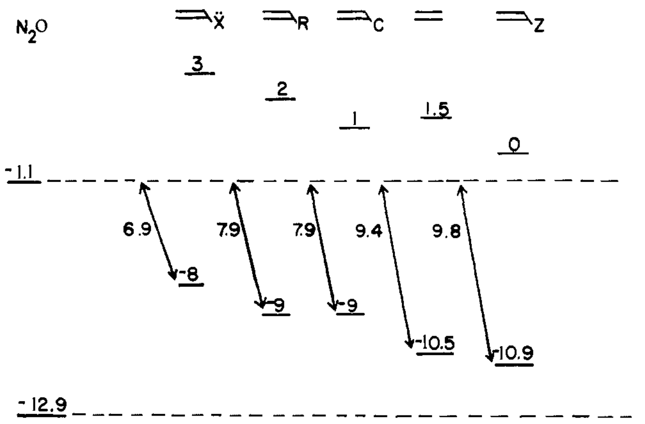


Figure 8. Frontier orbital energies for nitrous oxide and dipolarophiles.

(Figure 7), a result of union of the larger diazomethane HO coefficient on carbon with that of the larger dipolarophile LU coefficient on the unsubstituted carbon.[36,41,42] Acceleration of diazoalkane reactions by electron-withdrawing substituents on the dipolarophile is well known, as exemplified by the the Hammett $\rho$ of +0.90 in reactions of substituted styrenes with diazomethane.[42d] Electron release on the diazoalkane accelerates reaction as shown by the order of reactivity of diazoalkanes ($MeCHN_2 > CH_2N_2 \gg Ph_2CN_2 > EtO_2CCHN_2$).[41] Diphenyldiazomethane is less reactive than expected, undoubtedly due to steric hindrance.

Simple diazoalkanes and alkylethylenes are rather unreactive, while enol ethers react very slowly with diazomethane to give the 4-substituted pyrazolines (Figure 7b).[42a,b] In these cases, the difference between the two frontier orbital interactions is quite small, but the nearly equal magnitude of the terminal coefficients in the diazomethane LU ensures that the diazomethane HO will determine product regiochemistry. More powerful electron release in the dipolarophile or electron withdrawal on the diazoalkane should accelerate reaction. Thus, diazo ketones react rapidly with enamines.[42c] Reactions between very electron-rich dipolarophiles, such as polyaminoethylenes and diazoalkanes, as well as reactions between diazo ketones or diazo esters and very electron-deficient alkenes, have not been studied but should proceed with facility.

**Nitrous Oxide.** The final diazonium betaine, nitrous oxide, also conforms to this frontier orbital scheme. Data in the previous paper[4] indicate a considerable lowering of the nitrous oxide frontier orbitals with respect to those of hydrazoic acid, as shown in Figure 8. The dipole LU–dipolarophile HO separation is now

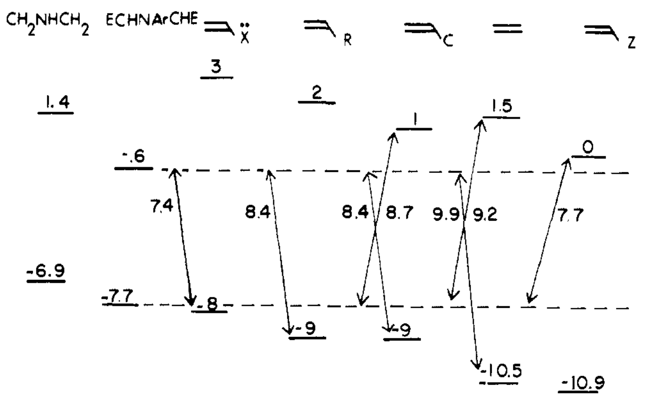
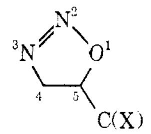


Figure 9. Frontier orbital energies for azomethine ylides and dipolarophiles (E = ester).

smallest. Electron withdrawal on the dipolarophile will result in decreased reactivity. Buckley and coworkers have investigated nitrous oxide reactions with a large number of alkenes.[43a] Nitrous oxide does not react with electron-deficient dipolarophiles, but does react with conjugated and electron-rich alkenes to give fragmentation products consistent with the intermediacy of 5-substituted 1,2,3-oxadiazolines. The structure shows preferred regioisomers in nitrous oxide cycloadditions. Although enol ether and enamine reactions have not been attempted, Figure 8 indicates that these electron-rich species should be the most reactive dipolarophiles with nitrous oxide.



**Azomethine Ylides.** The azomethine ylide system has $C_{2v}$ symmetry, so that no regioselectivity is possible. Unsymmetrically substituted azomethine ylides such as the Münchnones[43b] can form regioisomers with unsymmetrical dipolarophiles, but the regiochemistry will be caused by asymmetry in the dipole frontier orbitals caused by the substituents. It is likely that azomethine ylides will react readily with both electron-deficient and electron-rich dipolarophiles due to the narrow frontier orbital separation. Figure 9 shows the estimated frontier orbitals energies for the unknown azomethine ylide parent, as well as for the type of azomethine ylide which has been studied most extensively. For the parent azomethine ylide and simple derivatives, reactions with electron-deficient alkenes should be very rapid, while reactions with electron-rich dipolarophiles should be slow. However, for the extensively studied systems such as those formed from thermolysis of aryl-2,3-carboalkoxyaziridines,[44] Figure 9 shows that reactions with all types of dipolarophiles should be facile, with fastest reactions expected for electron-rich and electron-deficient species. Huisgen and coworkers have observed rapid reactions of azomethine ylides with electron-defi-

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(41) G. W. Cowell and A. Ledwith, *Quart. Rev.*, 24, 119 (1970).

(42) (a) S. H. Groen and J. F. Arens, *Recl. Trav. Chim.*, 80, 879 (1961); (b) I. A. D'yakonov, *J. Gen. Chem. USSR*, 17, 67 (1947); (c) F. Piozzi, A. Umani-Ronchi, and L. Merlini, *Gazz. Chim. Ital.*, 95, 814 (1965); (d) P. K. Kadaba and T. F. Colturi, *J. Heterocycl. Chem.*, 6, 829 (1969).

(43) (a) F. S. Bridson-Jones, G. D. Buckley, L. H. Cross, and A. P. Driver, *J. Chem. Soc.*, 2999 (1951); S. F. Bridson-Jones and G. D. Buckley, *ibid.*, 3009 (1951); G. D. Buckley and W. J. Levy, *ibid.*, 3016 (1951). (b) R. Huisgen, E. Funke, H. Gotthardt, and H.-L. Panke, *Chem. Ber.*, 104, 1532 (1971).

(44) R. Huisgen, W. Scheer, and H. Mäder, *Angew. Chem., Int. Ed. Engl.*, 8, 602 (1969); R. Huisgen, W. Scheer, H. Mäder, and E. Brunn, *ibid.*, 8, 603 (1969); R. Huisgen and H. Mäder, *ibid.*, 8, 603 (1969).

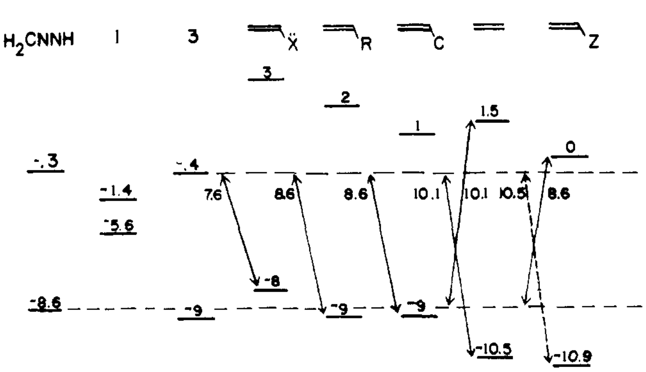
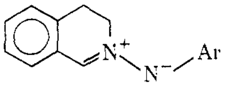


Figure 10. Frontier orbital energies for azomethine imines and dipolarophiles.

cient dipolarophiles and slower reactions with cyclic alkenes.[44] Enamines and similar electron-rich species are predicted to react rapidly.

**Azomethine Imines.** The frontier orbitals are shown in Figure 10. The unsubstituted azomethine imine is predicted to react rapidly with electron-deficient and electron-rich dipolarophiles. Substituents should be capable of changing the azomethine ylide from a HO- to a LU-controlled dipole.

For the extensively studied azomethine imine, **1**, both aryl and alkyl substitution will result in a large destabilization of the HO and a smaller stabilization of the LU. In this case, the second phenyl substitution is assumed to have a much smaller effect on energies than the first. The reaction of **1** with conjugated dipolarophiles should be influenced by both pairs of frontier orbital interactions, and mixtures are expected. Both styrene and 1,1-diphenylethylene give approximately equal amounts of the two regioisomers in reactions with **1**.[36] With acrylonitrile, dipole HO control leads to formation of **2**. For the dipole **3**, both HO and LU are lowered (Figure 10) so that reaction of **3** with styrene will be dipole LU-controlled. Experimentally, **4** is formed in 98% yield.[45] Reactions of electron-deficient alkenes with **3** experience the influence of both frontier interactions, and some of the 4-substituted isomer is formed.[45]



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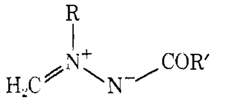

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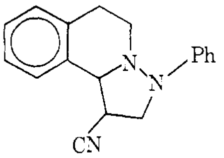

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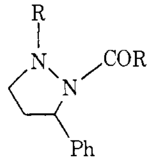


4

The sydnones **5** are another type of azomethine imine whose reactions have been studied extensively.[46] Considerations in the previous paper indicate that sydnone LU's are much lower than those of simple azomethine imines, but that the terminal LU coefficients are nearly identical.[4] Thus, although LU control of reactivity will obtain, a decrease in regioselectivity of sydnone cycloadditons with respect to that observed with simpler azomethine imines is expected. In fact, sydnones do undergo regioselective reactions, but the degree of regioselectivity appears to be smaller than is observed with simpler azomethine imines. *N*-Phenyl sydnone reacts with all three classes of dipolarophiles to give predominantly the products resulting from intermediate adducts **6**. Methyl propiolate gives a 70:22 mixture of adducts arising from **6** and the other regioisomer, respectively.[46] *N*-Phenyl *C*-methyl sydnone reacts with indene to give a 6:1 mixture of the adducts from **6** and the opposite regioisomer.[46]

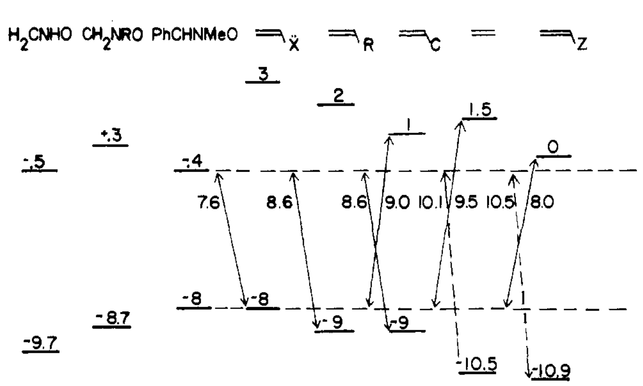
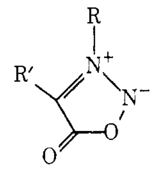


Figure 11. Frontier orbital energies for azomethine oxides and dipolarophiles.



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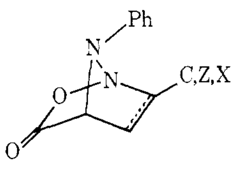

6

**Nitrones (Azomethine Oxides).** The orbital energies for the parent, an *N*-alkyl-, and *C*-phenyl-*N*-methylnitrones are shown in Figure 11. These orbital energies are based on experimental data and estimates in the previous paper.[4] Inspection of Table II indicates that the "corrected" HO coefficients are nearly identical, while the LU coefficients are quite different. Thus, for the reactions of the parent nitrone with electron-deficient dipolarophiles, the dipole HO interaction is larger but does not contribute to regioselectivity. Thus the LU, with a much larger coefficient on carbon, controls regioselectivity with moderately electron-deficient as well as all other dipolarophiles, leading to the 5-substituted isoxazolidines. Nevertheless, nitrone cycloadditions are accelerated by electron withdrawal in the dipolarophile.

The parent nitrone, a tautomer of formaldoxime, reacts with monosubstituted alkenes of various types to form the 5-substituted products,[47] as do a variety of substituted nitrones;[48] the structure below shows pre-

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[45] W. Oppolzer, *Tetrahedron Lett.*, 2199 (1970).

[46] H. Gotthardt and R. Huisgen, *Chem. Ber.*, 101, 552 (1968); R. Huisgen, H. Gotthardt, and R. Grashey, *ibid.*, **101**, 536 (1968); R. Huisgen, R. Grashey, and H. Gotthardt, *ibid.*, 101, 829 (1968); R. Huisgen and H. Gotthardt, *ibid.*, 101, 839, 1059 (1968).

[47] M. Ochiai, M. Obayashi, and K. Morita, *Tetrahedron*, 23, 2641 (1967).

[48] (a) R. Huisgen, R. Grashey, H. Hauck, and H. Seidl, *Chem. Ber.*, 101, 2548 (1968); (b) R. Huisgen, R. Grashey, H. Seidl, and H. Hauck, *ibid.*, 101, 2559 (1968); (c) H. Seidl, R. Huisgen, and R. Knorr, *ibid.*, 102, 904 (1969); (d) R. Huisgen, H. Seidl, and I. Brüning, *ibid.*, 102, 1102 (1969); (e) Y. Nomura, F. Furusaki, and Y. Takeuchi, *Bull. Chem. Soc. Jap.*, 40, 1740 (1967); nitrone review: J. Hamer and A. Macaluso, *Chem. Rev.*, 64, 473 (1964).

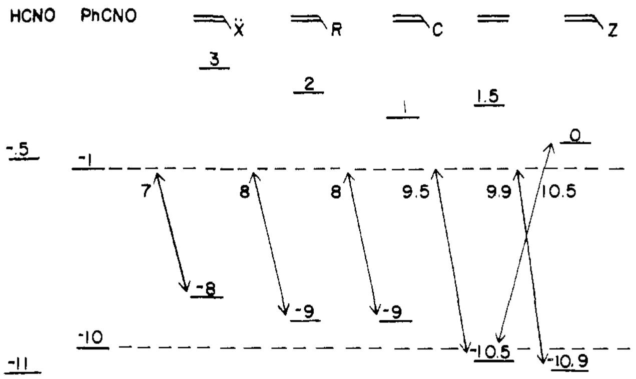
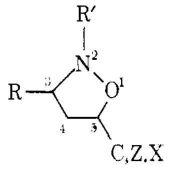


Figure 12. Frontier orbital energies for nitrile oxides and dipolarophiles.

ferred regioisomers in nitrone cycloadditions. For the most widely studied nitrone, *C*-phenyl-*N*-methylnitrone,

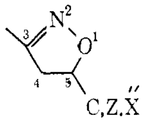


the frontier orbital energies (Figure 11) indicate a crossover from LU control for electron-rich dipolarophiles to HO control with electron-deficient dipolarophiles. The phenyl and methyl substituents will tend to decrease and increase, respectively, the HO coefficient on carbon. The phenyl group effect should predominate, leading to a larger coefficient at oxygen than carbon. In the LU, both substituents will decrease the carbon coefficient so that the difference in magnitude between the carbon and oxygen coefficients will decrease. The following predictions result. With very electron-deficient dipolarophiles, dipole HO control will eventually totally predominate, so that about 50:50 mixtures of adducts are expected in reactions of methylene nitrones (terminal HO coefficients about the same) while complete reversal of regiochemistry is expected with *C*-aryl-*N*-alkylnitrones; *i.e.*, 4-substituted isoxazolidines will be formed with very electron-deficient dipolarophiles such as vinylidene cyanide, nitroethylene, and the like.[48f]

Nitrones differ from nitrous oxide and nitrile oxides (*cf.* later) in the narrower frontier orbital separation of the nitrones. Sensitivity to substitution should be less for nitrones than for the other oxides. Furthermore, both electron-releasing and electron-withdrawing substituents on the nitrone should accelerate reaction. For example, *C*-benzoyl-*N*-phenylnitrone reacts 110 times faster than *C*,*N*-diphenylnitrone with ethyl crotonate, whereas, with the same dipolarophile, benzoyldiazomethane reacts 5400 times slower than diazomethane.[48d] In the nitrone reactions where both frontier orbital interactions are important, the benzoyl group lowers the LU, increasing the stabilization of the transition state resulting from the dipole LU–dipolarophile HO interaction. With the HO-controlled diazoalkane, the electron-withdrawing benzoyl group will lower the HO orbital, decreasing the stabilization of the transition state arising from dipole HO–dipolarophile LU interaction.

So far, steric interactions have not been mentioned. It is clear that steric effects will have an overall effect on rate even if they do not have much influence on regioselectivity.[36,48d] One example where great steric hindrance can overcome LU control has been reported, although the experiment was interpreted as showing steric control in the less hindered dipolarophile case and electronic control in the more hindered dipolarophile case.[49] Our analysis suggests the opposite explanation.

**Nitrile Oxides.** The frontier orbital energies of formonitrile oxide and benzonitrile oxide are shown in Figure 12. These energies were estimated from considerations in the previous paper.[4] For electron-rich and conjugated dipolarophiles, the dipole LU is controlling and union of the larger coefficients leads to the 5-substituted isoxazolines. Only these isomers are experimentally observed.[36,50] Furthermore, electron release on the dipolarophile accelerates reaction; the structure shows preferred regioisomers in nitrile oxide cycloadditions.



Electron-deficient dipolarophiles also react rapidly due to the influence of both dipole HO and LU orbital interactions. Furthermore, regioselectivity should decrease since the dipole LU tends to produce 5-substituted isoxazolines while the dipole HO tends to produce 4-substituted isoxazolines. Thus the formation of small amounts of the 4-substituted isomers in the reactions of methyl acrylate with acetonitrile oxide (5.1%), benzonitrile oxide (3.6%), and 2,4,6-trimethylbenzonitrile oxide (6.6%) is the result of some influence of dipole HO–dipolarophile LU control with these species, whereas formonitrile oxide, for which dipole HO control is less important (Figure 12), gives none of the 4 isomer.

A particularly dramatic and hitherto unexplained experimental observation which is compatible with the discussion of the preceding paragraphs involves the reactions of methyl propiolate with nitrile oxides. Alkynes generally have higher ionization potentials (lower HO energies) than the corresponding alkenes, while the LU energies are affected to a lesser extent.[4] Inspection of Figure 12 indicates that in the case of an electron-deficient acetylenic dipolarophile, the dipole HO–dipolarophile LU interaction will become increasingly significant. Formonitrile oxide reacts with methyl acrylate to give 100% of the 5-carbomethoxy (dipole LU-controlled) adduct, while methyl propiolate gives 84% of the 5-carbomethoxy and 16% of the 4-carbomethoxy adducts.[50–52] When the dipolarophile frontier orbital energies are lowered by incorporation in a triple bond and the dipole frontier orbital energies are raised by substitution of electron-releasing groups, di-

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[48f] Note Added in Proof. Since submission of this paper, experimental results in general accord with these predictions have been obtained: J. Sims and K. N. Houk, *J. Amer. Chem. Soc.*, **95**, 5798 (1973).

(49) Y. Nomura, F. Furusaki, and Y. Takeuchi, *Bull. Chem. Soc. Jap.*, 43, 1913 (1970).

(50) (a) K. Bast, M. Christl, R. Huisgen, W. Mack, and R. Sustmann, *Chem. Ber.*, **106**, in press; (b) Ch. Grundmann and P. Grünanger, "The Nitrile Oxides," Springer-Verlag, Heidelberg, 1971.

(51) M. Christl and R. Huisgen, *Tetrahedron Lett.*, 5209 (1968).

(52) M. Christl, Ph.D. Thesis, University of Munich, 1969.

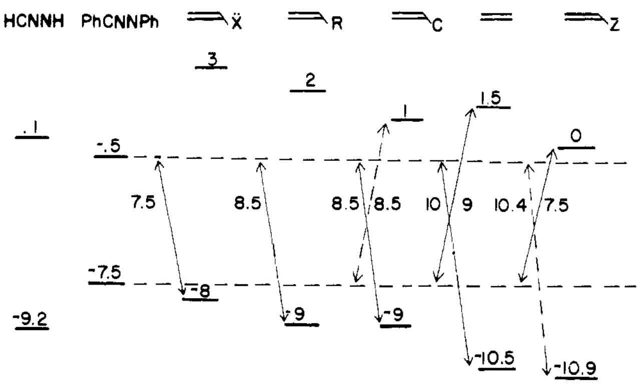


Figure 13. Frontier orbital energies of nitrile imines and dipolarophiles.

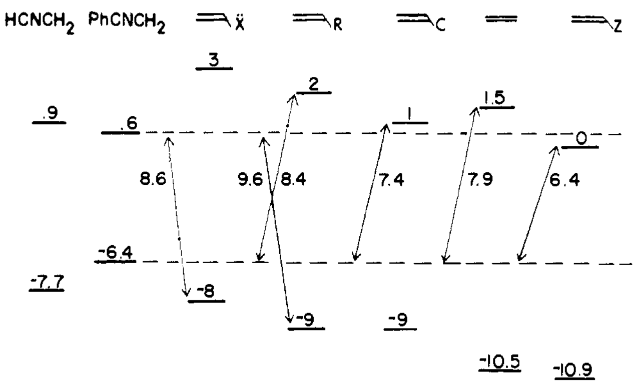
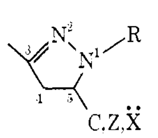


Figure 14. Frontier orbital energies of nitrile ylides and dipolarophiles.

pole HO control increases further. Thus, 2,4,6-trimethylbenzonitrile oxide reacts with methyl propiolate to produce 72% of the 4-carbomethoxy-$\Delta^2$-isoxazoline.[52] Although this appears to be one of the few examples of this effect, these considerations lead to the prediction that unsymmetrical dipolarophiles with very low-lying frontier orbitals such as 1,1-dicyanoethylene will react with benzonitrile oxides to produce predominantly 4,4-disubstituted $\Delta^2$-isoxazolines. Most of the dipolarophiles of this type which have been studied are symmetrical, so that generality of this phenomenon has not yet been discovered.

**Nitrile Imines.** The nitrile imine orbitals are similar in energy to those of nitrile oxide, except that the degeneracies of the $\pi$ orbitals in the latter are split and the orbitals of the former are moved to higher energies. Figure 13 shows the estimated energies for the unknown formonitrile imine and the thoroughly studied diphenylnitrile imine. Since the phenyl groups tend to decrease the coefficient in both the HO and LU at the site of attachment, the relative coefficient magnitudes should be similar to those in the parent.

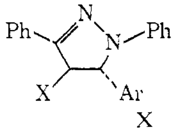
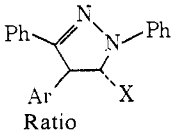
Once again, the interpretation of the reactivity and of regioselectivity of cycloadditions of diphenylnitrile imine to electron-rich dipolarophiles is straightforward; the 5-substituted $\Delta^2$-pyrazolines are favored. Preferred regioisomers in nitrile imine reactions are shown in the structure. For conjugated dipolarophiles, both



HO and LU interactions are important, but the greater difference in LU coefficient magnitudes once again leads to a preference for 5-substituted products. With electron-deficient dipolarophiles, both HO and LU interactions are important, but with weakly electron-deficient dipolarophiles, the 5-substituted product is favored. Again, methyl propiolate gives some reversal: a 78:22 mixture of the 5- and 4-substituted adducts is observed.[53] Further or complete reversal of regiochemistry is predicted for more strongly electron-deficient dipolarophiles.

Huisgen has dissected rates of diphenylnitrile imine cycloadditions into electronic and steric partial rate factors.[54] According to the interpretation given here, orientation phenomena can all be explained more or less satisfactorily by electronic effects alone. A particularly interesting case which may be rationalized by a refinement of the present theory can be found in the regioisomer ratios found in the reactions of $\beta$-substituted styrenes with diphenylnitrile imine.[54b] As shown in Table III, the trend in isomer ratios is not clearly a function of either the electron-donating or releasing ability of substituents, or of the steric requirements of the substituents. However, all substituents tend to produce an increase in the HO coefficient of the carbon remote from the substituent. Assuming dipole LU control of orientation in all cases, the relative ability of each of the substituents to increase the coefficient on the more remote carbon in the dipolarophile HO can be concluded to be MeO > Ph > *i*-Pr > Me > Br (>H). Nitro will cause the same type of change in relative magnitudes of HO coefficients, but will also lower the frontier orbital energies, further favoring the 4-phenyl product. Such an order is in qualitative agreement with calculated coefficient changes induced by substituents.[4]

**Table III.** Regioisomer Ratio from Reaction of Diphenylnitrile Imine with $\beta$-Substituted Styrenes

|  <br>X |  <br>Ratio |
|---|---|
| H | 100:0 |
| Br | 85:15 |
| Me | 72:28 |
| *i*-Pr | 69:31 |
| MeO | 35:65 |
| $NO_2$ | 31:69 |

This order also leads to correct rationalizations of the predominant isomers formed in unsymmetrical *trans*-stilbene reactions.[54b]

**Nitrile Ylides.** The previously deduced frontier orbital energies are shown in Figure 14.[4] With all dipolarophiles except the very electron-rich, nitrile

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(53) R. Huisgen, R. Sustmann, and G. Wallbillich, *Chem. Ber.*, 100, 1786 (1967).

(54) (a) R. Huisgen, H. Knupfer, R. Sustmann, G. Wallbillich, and V. Weberndorfer, *Chem. Ber.*, 100, 1580 (1967); (b) J. S. Clovis, A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, and V. Weberndörfer, *ibid.*, 100, 1593 (1967).

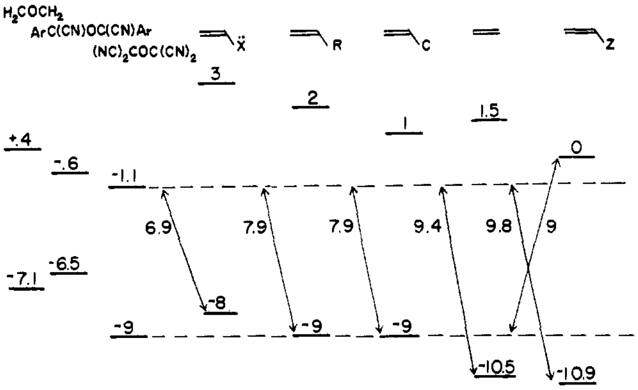
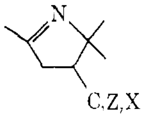
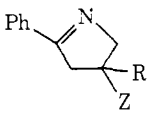


Figure 15. Frontier orbital energies of carbonyl ylides and dipolarophiles.

ylide reactions are HO-controlled. In fact, reactions of nitrile ylides with electron-rich dipolarophiles have not been observed, indicating that the dipole LU–dipolarophile HO interaction is never large. Only very strong electron donation on the dipolarophile is predicted to lead to reactivity, as with the diazoalkanes.

Conjugated and electron-deficient dipolarophiles react readily with nitrile ylides,[55,56] in agreement with Figure 14, and electron withdrawal on the dipolarophile clearly accelerates reaction.[55,56] The HO coefficients calculated in the previous paper[4] or the values in Table II are larger at the "anionic" carbon (trivalent) than at the "neutral" carbon (divalent). These coefficients lead to the wrong prediction for the regioisomer formed. That is, experimentally, acrylonitrile and methyl acrylate react with various nitrile ylides to give only the 4-substituted regioisomers, **7**;[55,56] preferred regioisomers are shown in the structure. This case can only be rationalized by assuming that the calculations give the wrong result; that is, the larger coefficient must be on the "neutral" carbon. As shown in the previous paper, the relative magnitudes of the HO and LU coefficients are reversed in the CNDO/2 calculations upon alteration of the relative lengths of the two CN bonds. Assuming the larger HO coefficient is, in fact, on the "neutral" carbon, all the regiochemical observations become understandable.[56a] Thus, benzonitrile ylide reacts with both $\alpha$-methylacrylonitrile and methyl methacrylate to give adducts of type **7** and **8** in a 60:40 ratio.[56] The ylide HO controls regioselectivity, and, whereas the cyano or ester group enhances the LU coefficient at the unsubstituted carbon, the methyl group has the opposite effect. Thus, the terminal coefficients in the LU of $\alpha$-methylacrylonitrile and methyl methacrylate are more nearly the same than for the nonmethylated analogs, so that regioselectivity decreases. A similar effect is not found for diazomethane, apparently due to the larger difference in HO terminal coefficients in diazoalkanes than in nitrile ylides.





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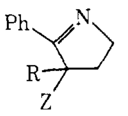

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Nitrile ylides react with methyl propiolate to give only the 4-substituted pyrrolines, compatible with HO control and the larger nitrile ylide HO terminal coefficient on the "neutral" carbon. Similarly, heterodipolarophiles react with nitrile ylides to give regioselectivity compatible only with the experimentally deduced HO coefficient magnitudes (see later).

**Carbonyl Ylides.** The estimated frontier orbital energies for the parent carbonyl ylide shown in Figure 15 indicate that this species should be a typical HO-controlled dipole. The tetracyano compound has considerably lowered frontier orbitals, and reacts most readily with electron-rich or conjugated dipolarophiles and less readily or not at all with electron-deficient dipolarophiles.[57]

The less electron-deficient carbonyl ylide formed from 2,3-dicyano-2,3-diphenyloxirane is reactive with both electron-deficient and electron-rich dipolarophiles,[58] compatible with the estimated frontier orbital energies in Figure 15. Since a large number of substituents are present, only a crude approximation of orbital energies is made here. Carbonyl oxides substituted only with alkyl and conjugating substituents will be HO-controlled, reacting readily with electron-deficient dipolarophiles, less readily with conjugated dipolarophiles, and slowly or not at all with electron-rich dipolarophiles. The conclusions are compatible with the qualitative data currently available for such species.[59]

**Thiocarbonyl Ylides.** Although our discussion of 1,3 dipoles has been confined to those containing second-row elements, some recent results with thiocarbonyl ylides are relevant here. Simple thiocarbonyl ylides are expected to have frontier orbitals displaced to higher energies relative to carbonyl ylides. Thus di-*tert*-butylthiocarbonyl ylide reacts only with electron-deficient dipolarophiles and is unreactive with electron-rich or conjugated dipolarophiles;[60] strong dipole HO control is indicated.

**Carbonyl Imines.** These appear to be unknown species, but should be reactive with electron-rich species, forming the 3-substituted isoxazolidines, and less reactive with electron-deficient dipolarophiles, forming the 4-substituted isoxazolidines (Figure 16). Substituent effects will parallel those for carbonyl ylides.

**Carbonyl Oxides.** These species have frontier orbital energies depicted in Figure 17. The carbonyl oxide reactions are LU-controlled, and reactions should be facile only with electron-rich species. The role of these species as intermediates in the conversion of molozon-

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(55) K. Bunge, R. Huisgen, R. Raab, and H. J. Sturm, *Chem. Ber.*, **105**, 1307 (1972).

(56) A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Amer. Chem. Soc.*, **95**, 1945 (1973).

(56a) NOTE ADDED IN PROOF. Recent experimental determinations of the site of attack of electrophiles on nitrile ylides are compatible with this contention: A. Padwa and J. Smolanoff, *J. Chem. Soc., Chem. Commun.*, 342 (1973).

(57) W. J. Linn and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3657 (1965); P. Brown and R. C. Cookson, *Tetrahedron*, **24**, 2551 (1968).

(58) H. Hamburger and R. Huisgen, *J. Chem. Soc., Chem. Commun.*, 1190 (1971).

(59) D. R. Arnold and L. A. Karnischky, *J. Amer. Chem. Soc.*, **92**, 1404 (1970); J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **49**, 3443 (1971).

(60) J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, **37**, 4045 (1972).

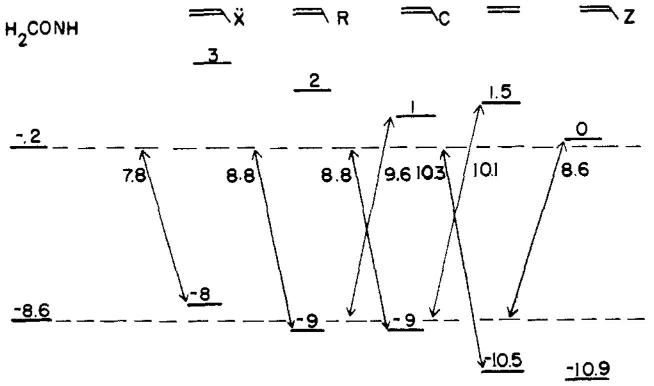


Figure 16. Frontier orbital energies of carbonyl imines and dipolarophiles.

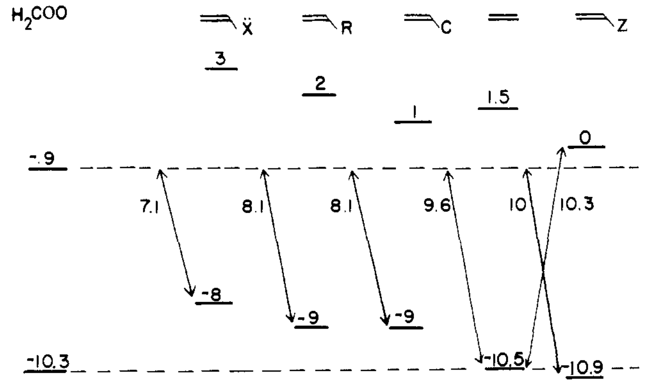


Figure 17. Frontier orbital energies of carbonyl oxides and dipolarophiles.

ides to ozonides in the ozonolysis reaction has been extensively discussed.[61]

**Ozone.** The ozone frontier orbital energies are displayed in Figure 18. Ozone LU control predominates, compatible with acceleration of ozone reactions by electron release in the alkene. Furthermore, alkynes, which have lower HO's than the corresponding alkenes, react more slowly with ozone.[61]

**Heterodipolarophiles.** This discussion has been limited to reactions of substituted alkenes. However, similar considerations may be readily applied to heterodipolarophiles such as ketones, nitriles, imines, thioketones, Wittig reagents, and nitrosoalkanes. The HO and LU orbitals of the first three types of heterodipolarophiles are shown in Figure 19, where X represents an oxygen or nitrogen. These orbitals will be, in general, located at energies similar to those of electron-deficient dipolarophiles. With the exception of the nitrile ylides and symmetrical species, all 1,3 dipoles have the larger coefficient at the anionic terminus in the HO and at the neutral terminus in the LU. Both of these interactions as well as the better overlap of carbon with carbon than with oxygen or nitrogen (Table I) lead to preferential formation of products **9**.[36] As shown later, Coulombic and closed-shell repulsion effects will also favor the formation of **9**. Exceptions to these generalizations arise with nitrile ylides, which react with ketones and imines in the sense opposite to that in **9**,[55,56] but we have already concluded that these HO-controlled dipoles

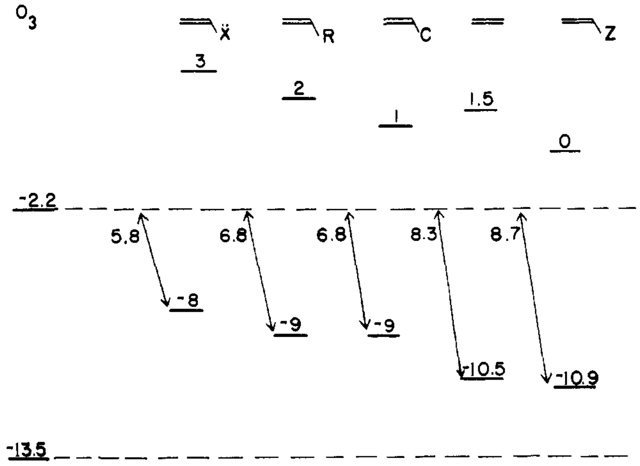
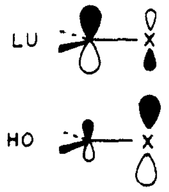
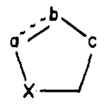


Figure 18. Frontier orbital energies of ozone and dipolarophiles.





**9**

Figure 19. Frontier orbitals of heterodipolarophiles.

have the largest HO coefficient on the "neutral" carbon so that the product is that expected on this basis. Since S and C have nearly equal electronegativities, thiocarbonyls should have more nearly equal coefficients than those shown in Figure 19. When several strongly electron-withdrawing groups are attached to a carbonyl group, reversals in regiochemistry from that shown in **9** are found.[55] It is quite likely, however, that carbonyl compounds of that type have the relative magnitudes of the LU coefficients reversed.

Huisgen has rationalized the selective formation of adducts like **9** with nitrile imines, nitrile oxides, azomethine imines, and nitrones by the principle of maximum gain of $\sigma$ bonding energy.[36] Perturbation arguments provide an alternative, but related, explanation.

**General Reactivity Considerations.** Although the preceding treatment gives a satisfactory accounting for the regioselectivity of all 1,3-dipolar cycloadditions and properly accounts for the relative reactivities of each individual dipole with a series of dipolarophiles, the perturbation treatment often performs poorly in the comparison of relative reactivities of quite widely different 1,3 dipoles. For example, the low reactivity of nitrous oxide in an absolute sense is not predicted, while the relative rates of reactions of different types of dipolarophiles with nitrous oxide are.

These difficulties may be attributed in part to the crudeness of the frontier orbital energy estimates, as well as to the neglect of electrostatic interactions, closed-shell repulsions, and steric effects. An additional factor which must be taken into account is the stability of products and reactants. For example, benzene, which has an ionization potential of 9.25 eV, would be expected to behave like a conjugated alkene with LU-controlled dipoles if only frontier orbital separation were considered. However, such a reaction would normally

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[61] R. Criegee, *Rec. Chem. Progr.*, **18**, 111 (1957); P. S. Bailey, *Chem. Rev.*, **58**, 926 (1958).

be endothermic and not observable. Other common difficulties with this frontier orbital treatment are discussed below.

**Coulombic Effects.** Although terms of the type $-\Sigma_{ab}Q_aQ_b(\Omega/\epsilon)$ in the second-order perturbation expression have been neglected in the discussion of regioselectivity, they will have some influence on the relative rates of cycloadditions of different 1,3 dipoles. The "anionic" terminus of the 1,3 dipole always has a larger negative charge ($-0.10$ to $-0.37$) than the "neutral" dipole terminus ($+0.06$ to $-0.21$).[4] However, charge separation is slight for conjugated and moderately electron-deficient dipolarophiles, so that little difference in Coulombic terms is expected for two regioisomeric transition states. For dipolarophiles with strongly electron-withdrawing substituents, ground-state polarization in the sense $(\delta^+)CH_2CH(\delta^-)Z$ results in Coulombic terms favoring the formation of products with substituent Z on the carbon remote from the "anionic" atom. This orientation is only observed with diazoalkanes, which have the smallest differences in charges between terminal atoms of all the unsymmetrical 1,3 dipoles. We have, however, predicted that the latter orientation will be observed for the reactions of very electron-deficient dipolarophiles with nitrile oxides, nitrones, and some of the imines.[48f] Coulombic forces will also favor this reversal. In the case of electron-releasing groups, polarization in the sense $(\delta^-)CH_2$-$CH(\delta^+)\ddot{X}$ will lead to a Coulombic term favoring the product with the dipolarophile substituent adjacent to the "anionic" atom. Thus, in these cases, the Coulombic term does increase the energetic preference for formation of the same regioisomer favored by overlap effects.

Firestone has noted that as a dipole approaches a dipolarophile a considerable repulsion or attraction between the dipole moments of the two addends may develop.[38] As with the Coulombic terms, consideration of the more favorable dipole alignment leads to prediction of the wrong regioisomer with electron-deficient dipolarophiles. Firestone suggests that this proves that the reaction mechanism is not concerted unless some factor "not yet identified" stabilizes the dipole–dipole disfavored transition state. In the preceding discussion this factor has been identified.

Although Coulombic effects apparently have a negligible effect on regioselectivity, the overall effect on rate is undoubtedly nonnegligible. All dipoles have excess negative charges on the terminal atoms. Thus, there will be an overall acceleration of rate of formation of both regioisomers as the double-bonded carbons of the dipolarophile are made less negative or more positive. That is, in addition to the effects of frontier orbital separations on rate, there will be a constant superimposed preference for reaction of 1,3 dipole with electron-deficient dipolarophiles. This may partially account for the fact that the frontier orbital diagrams in this paper usually indicate that the separation of dipole HO–electron-deficient dipolarophile LU is larger than the dipole LU–electron-rich dipolarophile HO separation for two reactions which proceed at the same rate.

**Closed-Shell Repulsions.** Another neglected factor appears in the terms $-\Sigma_{ab}(q_a + q_b)\gamma_{ab}S_{ab}$, which represent closed-shell repulsion resulting from mixing of filled orbitals on the two reactants. If only the interaction of HO orbital charge densities on the two addends is considered, then closed-shell repulsions lead to an additional explanation of the seemingly unreasonably large influence of dipole LU control in reactions with electron-deficient and conjugated dipolarophiles.

Since the HO coefficients are generally larger for the "anionic" terminus of the dipole and the unsubstituted terminus of the dipolarophile, closed-shell repulsion effects will favor formation of adducts in which these positions are not united. This is, the adducts with the substituted carbons joined to the "anionic" dipole terminus will be favored by closed-shell repulsion effects. In other words, for conjugated and electron-deficient dipolarophiles, closed-shell repulsion effects between HO orbitals will reinforce the preference for formation of those adducts favored by LU control.

**Charge Transfer and Synchroneity in 1,3-Dipolar Cycloaddition Transition States.** It has recently been proposed that charge transfer is of importance in stabilizing the transition states of cycloadditions.[21] This is simply a restatement of the overlap effect which has been treated in a qualitative way here. That is, for a cycloaddition in which the interaction of the HO of one addend with the LU of the second addend dominates, there will be net charge transfer from the HO of the first to the LU of the second.[6] The stabilization resulting from the "charge transfer" is calculated from the second-order perturbation expression given in the beginning of this paper. The effects of configuration interaction on the stabilization of cycloaddition transition states have also been considered recently,[62] but such effects are not of importance in thermally allowed cycloadditions for which the ground state energy surface is well separated from doubly excited configurations.

Identification of the dominant orbital interaction immediately provides information on the direction of charge transfer in the transition state and also provides insight into the extent and direction of nonsynchroneity in the cycloaddition. The degree of nonsynchroneity in the concerted cycloadditions will depend both on the inherent asymmetry of the dipole (oxides > imines > ylides) and on which frontier orbital interaction is controlling. Several examples suffice to show the type of information obtainable. With nitrous oxide, bond formation at the nitrogen terminus is more advanced than that at oxygen in the transition state, while with diazomethane, bond formation at carbon is more advanced than that at nitrogen. With azides, bond formation at the unsubstituted nitrogen is more advanced for electron-rich dipolarophiles, is nearly symmetrical for conjugated dipolarophiles, and is more advanced at the substituted nitrogen for electron-deficient dipolarophiles. This nonsynchroneity makes reasonable the assumption that separations of as little as 1.75 Å occur for that pair of termini for which bonding is most advanced in the transition state.

In extremes of nonsynchroneity, it might be argued that dipolar or diradical intermediates might intervene in 1,3-dipolar cycloadditions. In fact, the application of perturbation theory to such reactions would follow

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[62] J. E. Baldwin, A. H. Andrist, and R. K. Pinschmidt, Jr., *Accounts Chem. Res.*, **5**, 402 (1972); N. D. Epiotis, *J. Amer. Chem. Soc.*, **95**, 1191 (1973).

exactly the lines followed here. Nevertheless, no experimental evidence whatsoever has been obtained to indicate formation of any type of intermediate in a 1,3-dipolar cycloaddition.[36b] Firestone attempted to explain the phenomenon of regioselectivity in 1,3-dipolar cycloadditions by considerations of the relative energies of alternate polarized diradical intermediates. Ignoring for the moment the fact that Huisgen has provided a permanent and devastating demolition of Firestone's arguments,[63] the diradical hypothesis and the explanation proposed here differ in two significant respects. The diradical hypothesis provides no explanation for the relative reactivities of different 1,3 dipoles with a series of dipolarophiles, and the direction of addition of dipoles to monosubstituted alkenes is predicted to be the same regardless of the nature of the substituent. The latter prediction is in disagreement with the facts, and the treatment used here indicates that numerous contradictions of the predictions based on the diradical hypothesis will be revealed by proper experimental tests.[48f]

**Secondary Orbital Interactions.** In the discussion of reactivity and regioselectivity in the preceding sections, the influence of orbitals other than the HO and LU (or NLU) $\pi$ orbitals was largely neglected. Even if the in-plane LU orbital interaction were appreciable, this would only strengthen the regioselectivity arguments made. Although no direct evidence for the geometry of the transition state is available, it is of interest to consider what effect the "in-plane" orbitals might exert. For the unsubstituted nitrilium and diazonium ylides and imines, the in-plane vacant orbital (LU) is of lower energy than the vacant $\pi$ orbital (NLU).[4] The stabilization of the transition states for dipole LU-controlled cycloadditions can be enhanced by interaction of this in-plane orbital with the dipolarophile HO orbital. In order to accomplish this, some contortion away from the strictly parallel planes approach of the dipole and dipolarophile would necessarily occur. Thus the transition state in Figure 20 for the reaction of a nitrilium or diazonium betaine with a dipolarophile could involve appreciable interaction of both the in-plane and out-of-plane $\pi$ unoccupied orbitals of the dipole with the dipolarophile-filled orbitals. Such a skewed transition state may be necessary to explain the secondary stereoselectivity observed in some 1,3-dipolar cycloadditions. For example, 1,3-diarylnitrile ylides react with methyl acrylate and acrylonitrile to give predominantly the syn epimers.[55,56] In a transition state such as that shown in Figure 20, the hydrogen of the nitrile ylide will prefer to be near the hydrogen of the dipolarophile rather than the substituent, in order to minimize van der Waals' repulsions in the transition state. Completion of bond formation leads to formation of the syn adduct. Alternatively, direct through-space secondary orbital interactions between extending conjugating substituents may be invoked, but in the case under discussion these interactions are repulsive rather than attractive.

In spite of these speculations about transition state geometries, no compelling evidence exists for the transition state geometries of reactions involving $C_s$ or $C_{2v}$ 1,3 dipoles. Huisgen's contention that all 1,3-dipole cycloadditions involve the "parallel-planes approach" of addends[36] remains the most logical view, since cyclic 1,3 dipoles such as sydnones behave normally in 1,3-dipolar cycloadditions.

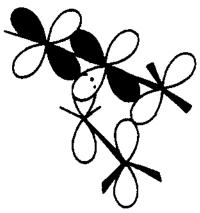

Figure 20. A hypothetical twisted transition state for a 1,3-dipolar cycloaddition.

Another secondary effect which has been overlooked up to now is the influence of the coefficient at the central atom in the dipole LU orbital. For dipole HO-controlled reaction (ylides and some imines), no secondary orbital interactions are expected since the central atom has a node or a near-node. However, for 1,3-dipolar cycloadditions in which the dipole LU–dipolarophile HO orbital interactions are important in the transition state, the central atom, whose coefficient in the LU is large and opposite in sign to those of the terminal atoms, will introduce a destabilizing interaction in the transition state which can be relieved by bending of the dipole. This bending will simultaneously increase the mutual overlap of the orbitals on the terminal atoms of the two addends.

The possibility of bending of this type leads to interesting predictions about exo/endo phenomena in 1,3-dipolar cycloadditions to dipolarophiles with extended conjugation. The interaction of the LU orbital of a "bent" 1,3 dipole with the HO orbital of a cisoid conjugated diene can lead to stabilizing "secondary orbital interactions" between the central atom of the dipole LU and the double bond of the diene at which bonds are not formed. The preference for the endo transition state will only be large in those cycloadditions where the dipole LU–dipolarophile HO interaction is important. One example of this type, for which endo stereochemistry is preferred, has been noted.[64] In a specific search for such a phenomenon diazoalkanes were used,[65] but since these reactions are HO-controlled the considerations here led to an explanation of why no effect was observed.

**Periselectivity in 1,3-Dipolar Cycloadditions.** Another test of the generalizations made here can be found in the studies of 1,3-dipolar cycloaddition periselectivity carried out in our laboratories. In the reaction of a 1,3 dipole with a polyene, several types of thermally allowed adducts are possible. For example, with fulvenes, four [4 + 2] adducts (two pairs of regioisomers) and two regioisomeric [6 + 4] adducts are possible. Several years ago, the word "periselectivity" was coined to denote the phenomenon of selectivity in formation of one of the thermally allowed pericyclic reaction products.[66] Simple fulvenes are especially useful compounds for periselectivity studies, since they have only slightly differing steric requirements for different modes of reaction but, at the same

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(63) R. Huisgen, in press.

(64) R. Greé and R. Carrié, *Tetrahedron Lett.*, 4117 (1971).

(65) W. C. Agosta and A. B. Smith, III, *J. Org. Chem.*, **35**, 3856 (1970).

(66) Periselectivity is the selective formation of one of the thermally allowed pericyclic reaction products: K. N. Houk, L. J. Luskus, and N. S. Bhacca, *J. Amer. Chem. Soc.*, **92**, 6392 (1970).

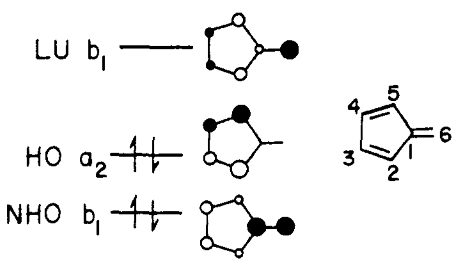
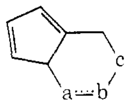


Figure 21. Frontier orbitals of fulvene.

time, have an electronic structure which is rather highly perturbed for an unsaturated hydrocarbon.

The frontier π orbitals of fulvene are represented schematically in Figure 21. This order is found in the parent system by a variety of methods of calculation,[67] but the "NHO" π orbital ($b_1$ in the $C_{2v}$ parent) is destabilized appreciably by substituents at the 6 position and becomes the highest occupied orbital in 6-dimethylaminofulvene and perhaps also in 6,6-diphenylfulvene.[68] The energies of the HO and NHO orbitals of fulvene are similar to the energy of the HO orbital of conjugated dipolarophiles. The energy of the LU orbital of fulvene and 6-conjugated fulvenes is similar to that of an electron-deficient dipolarophile, while the energy of the LU orbital of 6-alkyl and 6-aminofulvenes is similar to that of ethylene.[67] Using the generalization arrived at earlier about dipole frontier control, placing the frontier orbitals of fulvenes at energies near those of electron-deficient dipolarophiles in the figures, and using the coefficients shown schematically in Figure 21, the following predictions can be made. For strongly HO-controlled dipoles (ylides) as well as some particularly electron-rich imines, the [6 + 4] adduct **10** should be favored, except for benzonitrile ylides, where **11** will be favored. That is, since regioselectivity and periselectivity should be controlled by the same interactions, and the fulvene LU has the largest coefficient at the 6 position, the 6 position should become bonded to the dipole terminus with the higher coefficient in the dipole HO.

$a\equiv b^{+}—c^{-}$



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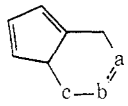

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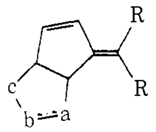

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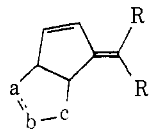

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Of the ylide dipoles, only the reactions of diazoalkanes with fulvenes have been reported. Diazomethane reacts with methylfulvene, dimethylfulvene, and phenylfulvene to give products arising from the [6 + 4] adducts **10**.[69] In 6,6-disubstituted fulvenes, CNDO/2 calculations indicate that the LU coefficients at atoms 2 and 3 are nearly identical (*e.g.*, 0.35 and −0.33, respectively for dimethylfulvene). Thus, if steric hindrance prevents formation of the [6 + 4] adduct, both regioisomeric [4 + 2] adducts formed by attack at carbons 2 and 3 should be formed. Dimethyldiazomethane and dimethylfulvene give the two [4 + 2] adducts in approximately equal amounts.[70]

With simple fulvenes, LU-controlled dipoles should give only [4 + 2] adducts, since the fulvene HO orbital has a node through C-6. Furthermore, with fulvene, methylfulvene, and other monoalkylfulvenes, the orbital energy order is that shown in Figure 21 and the fulvene HO orbital has the largest coefficients at C-2 and C-5. There, the regioisomer **12** is expected to predominate in reactions of LU-controlled dipoles (most imines and all oxides) with simple fulvenes. Preliminary results in these laboratories with nitrile imines, nitrile oxides, sydnones, and nitrones confirm these expectations.[70]

An increase in energy of the NHO of fulvene induced by alkyl or aryl substitution will increase the proportion of regioisomer **13** at the expense of **12**. Examples of this behavior are known for aryl nitrile oxides and fulvenes.[70,71] Finally, substitution of an amino group at fulvene C-6 causes a crossover ("$b_1$" is the HO) and [6 + 4] periselectivity should return. Known examples of this type have been discovered with 6,6-dimethylaminofulvene and aryl nitrile oxides.[70,71] Periselectivity studies with tropone and 1,3 dipoles are currently under investigation and indicate similar success of frontier orbital predictions.[69,70,72]

**Other Cycloadditions.** The treatment proposed here is applicable to all types of cycloadditions. For example, the relative rates and regioselectivity of Diels–Alder reactions,[27,28] as well as periselectivity in polyene cycloadditions, may be made using the generalizations in the previous paper.[4]

Although a semiquantitative perturbation treatment of ketene cycloadditions has appeared,[18] a simple model provides similar insight.[73] The LU of ketenes is a low-lying in-plane π* orbital. The largest coefficient in this orbital is on the central carbon. Ketenes will react readily with conjugated and electron-rich ketenophiles, and, since the largest coefficient is on the unsubstituted carbon of these species, 3-substituted cyclobutanones will be favored. The simultaneous $[{}_{\pi}2_{a} + {}_{\pi}2_{s}]$ interaction can lead to a concerted cycloaddition. Electron release on the ketenophile or electron withdrawal on the ketene will accelerate the reaction. According to this reasoning, very electron-deficient ketenophiles should also react with ketene, but since the interaction will now be strongest between the ketene HO and ketenophile LU, $[{}_{\pi}4_{s} + {}_{\pi}2_{s}]$ cycloadditions will now be favored if the electron-deficient ketenophile is a diene. In a similar fashion, the reactions of carbenes are dominated by the interaction of alkene HO with the LU's of these species. The regioselectivity of photochemical cycloadditions is also predicted using the frontier orbitals in the previous paper,[4] with the difference that these reactions will involve HO–HO and LU–LU

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(67) K. N. Houk, J. K. George, and R. E. Duke, Jr., submitted for publication.

(68) Photoelectron spectra of fulvene (E. Heilbronner, R. Gleiter, H. Hopf, V. Hornung, and A. de Meijere, *Helv. Chim. Acta*, 54, 783 (1971)) and 6-substituted fulvenes (E. Heilbronner, private communication; K. N. Houk, unpublished results) confirm the presence of two relatively high energy occupied π orbitals (8.55 and 9.54 eV) and also confirm the differential raising of energies of these two orbitals by 6-substitution. See, however, F. Brogli, P. A. Clark, E. Heilbronner, and M. Nevenschwander, *Angew. Chem. Int. Ed. Engl.*, 12, 122 (1973).

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interactions rather than the HO–LU interactions which govern thermal cycloadditions.[6,19]

### Summary and Conclusions

A powerful method has been developed for the rationalization and prediction of substituent effects on rates, regioselectivity, and periselectivity of 1,3-dipolar cycloadditions. Although numerous refinements in the model proposed here are desirable and will undoubtedly develop, the rationalization of a massive body of experimental data on regioselectivity in 1,3-dipolar cycloadditions using a concerted transition state model provides a conceptual framework for the solution of "the biggest *unsolved* problem in the field"[36] of cycloadditions. The treatment presented here should lay to rest previous beliefs that "the nature of the orientation . . . is not adequately predicted by either concerted or biradical mechanisms,"[41] "the whole question of orientation or regiospecificity is still shrouded with uncertainty,"[56] and "orientation phenomena are still far from being understood."[50b]

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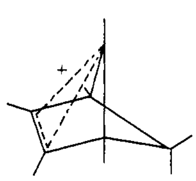
# Electronic Structure of 1,2,3,4,5,6-Hexamethylbicyclo[2.1.1]hexenyl Cations and the Mechanism of Their Reaction with Nucleophiles

**H. Hogeveen* and P. W. Kwant**

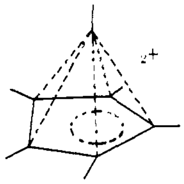
*Contribution from the Department of Chemistry, The University, Zernikelaan, Groningen, The Netherlands. Received April 23, 1973*

**Abstract:** Pmr and cmr data of various 5-substituted 1,2,3,4,5,6-hexamethylbicyclo[2.1.1]hexenyl cations are reported. From these data it is concluded that the positive charge resides mainly at carbon atoms 2 and 3. This is in agreement with the view that nucleophilic attacks at these positions, yielding tricyclic products, are kinetically controlled reactions, which occur at the site of the lowest electron density.

Numerous papers have dealt with the reaction of hexamethyldewarbenzene with acids. In strong acid[1,2] as well as in a hydrogen chloride–methylene chloride mixture[3a] a 1:3 equilibrium mixture of *exo*- and *endo*-methyl-1,2,3,4,5,6-hexamethylbicyclo[2.1.1]hexenyl cations (**1** and **2**) is obtained when the reaction is carried out at low temperature with excess acid. Recently reports have appeared concerning 5-substituted ions of this type, which are important as precursors of the stable dication **6**.[3b] The *endo*-5-chloro ion **3**[4,5] and the *endo*-5-bromo ion **4**[6] were prepared from hexamethyldewarbenzene by low temperature electrophilic addition of "$Cl^+$" and "$Br^+$," respectively. The *exo*-5-hydroxy ion **5** was prepared either from diol **7**[7] or from hexamethyldewarbenzene epoxide[7a] by reaction with a mixture of hydrogen chloride and methylene chloride at low temperature.[5] The ions **1–5** were shown to react with nucleophiles at C-2(C-3) or at C-6, the former mode of attack yielding tricyclic products and the latter one bicyclic products. Preliminary results showed the reactions that yield tricyclic products to be kinetically controlled. In this paper we report on the pmr and cmr spectra of the ions **1–5** and draw conclusions on the electronic structure, which forms the basis of the mechanism advanced for the reaction with nucleophiles.



**1–5**



**6**

— = $CH_3$

### Results

The pmr[1-6] and cmr chemical shifts of the ions **1–5** at −70° are given in Table I and the pmr and cmr data of compounds **7**,[7] **8**,[8] and **9**[8] are listed in Table II for comparison purposes. The pmr[1,2] and cmr chemical shifts of the ions **1** and **2** do not differ essentially from those in strong acid. Ion **3** was reported[4] previously with $AuCl_4^-$ as gegenion, also with essentially the same pmr chemical shifts. This indicates that ions **1–5**

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