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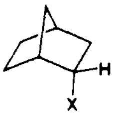
Modeling Chemical Reactivity. 1. Regioselectivity of Diels–Alder Cycloadditions of Electron-Rich Dienes with Electron-Deficient Dienophiles

S. D. Kahn, C. F. Pau, L. E. Overman, and W. J. Hehre*

Contribution from the Department of Chemistry, University of California, Irvine, California 92717. *Received March 18, 1985*

Abstract: Careful examination suggests that while arguments based on frontier molecular orbital (FMO) theory are generally capable of assigning absolute regiochemistry in Diels–Alder cycloadditions of monosubstituted dienes with electron-deficient dienophiles, they are less successful in ordering the magnitudes of observed regiochemical preferences among closely related systems. In particular, we have found that the FMO model often misassigns the observed regioproduct in cycloadditions to dienes substituted by two different groups or by the same group in different diene positions. The problem does not appear to be in the assumption of control by a single frontier interaction, i.e., in the case of the systems considered here, between the highest occupied orbital on the diene and the lowest unoccupied function on the dienophile. For cycloadditions involving a variety of electron-deficient dienophiles, the energy gap separating the diene HOMO and dienophile LUMO is calculated to be significantly (50–80 kcal mol^{-1}) smaller than that separating diene LUMO and dienophile HOMO, as long as the diene is not substituted by a strong electron-withdrawing group. Rather, the shortcomings may reside either in the assumption of additivity of substituent effects on orbital coefficients or in the underlying theoretical model, which equates differences in orbital coefficients to regiochemical preferences. Both possibilities are examined. An alternative approach to the discussion of Diels–Alder regiochemistry is proposed. It is based on the matching of complementary reactivity surfaces for diene and dienophile. For the case of addition of electron-rich dienes to electron-deficient dienophiles, this involves matching of an electrophilic surface for the diene and a nucleophilic surface for the dienophile. The reactivity modeling procedure, like the FMO analysis, appears to be successful in assigning absolute Diels–Alder regiochemistry. It also succeeds where the FMO model generally fails, in properly ordering the directing abilities of different substituents or of the same substituent attached to different diene positions.

One of the most fruitful applications of qualitative molecular orbital theory has been to explain the observed products of pericyclic reactions.[1,2] Foremost in this broad category is Diels–Alder chemistry. Since the reaction was first uncovered in 1928,[3] several explanations have been advanced to account for the formation of what often appear to be contrathermodynamic products, crowded *endo* adducts such as **1** instead of less encumbered *exo* alternatives **2** and, where both diene and dienophile are terminally substituted, *ortho* products such as **3** in preference of the corresponding *meta* adducts **4**. Observations such as these have led to the belief that, under conditions of kinetic control, Diels–Alder regio- and stereochemistry is not directed (entirely) by steric factors but rather influenced primarily by interactions between valence orbitals on diene and dienophile fragments. Furthermore, it has come to be accepted that only *frontier interactions*, i.e., those involving the highest filled and lowest empty orbitals on the diene and dienophile, are important in dictating kinetic product distributions.



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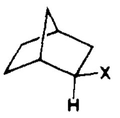

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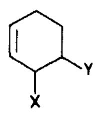

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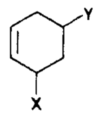

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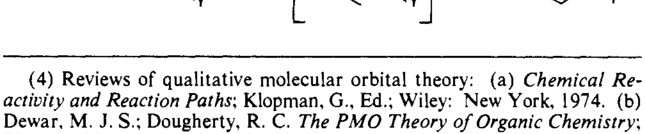
This paper addresses the question of the success of arguments based on *frontier molecular orbital* (FMO) theory[1,2,4] to properly assess the directions and magnitudes of regiochemical preferences in Diels–Alder cycloadditions. It points to serious problems in the analysis and suggests an alternative approach, which involves matching the electrophilicity of the diene and the nucleophilicity of the dienophile. This appears to succeed not only in assigning absolute regiochemistry (as frontier-orbital arguments generally do) but also in ordering the magnitudes of these preferences in a series of closely related reactions (as the FMO model generally does not do). The approach extends our work directed at the formulation of models and modeling strategies for chemical reactivity.[5]

We restrict ourselves at present to reactions involving electron-rich dienes and electron-deficient dienophiles. From a synthetic point of view, these are the most utilized class of Diels–Alder reactions. Forthcoming papers will address the performance of FMO arguments and reactivity modeling techniques to other classes of Diels–Alder cycloadditions, as well as extend this treatment to Diels–Alder-like reactions, e.g., 1,3-dipolar cycloadditions.

Both the FMO model and the approach presented here are quite distinct from reasoning based on the stability of any diradical or zwitterionic-like intermediate (or transition structure) which might lie along the pathway between reactants and products, i.e.,



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(1) For reviews, see: (a) Herndon, W. C. *Chem. Rev.* **1972**, *72*, 157. (b) Epiotis, N. D. *J. Am. Chem. Soc.* **1973**, *95*, 5621. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (d) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1975. (e) Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523. (f) Matatoshi, K. *Can. J. Chem.* **1979**, *57*, 2564. (g) Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. (h) Gleiter, R.; Bohm, M. C. *Pure Appl. Chem.* **1983**, *55*, 237.

(2) For recent studies, see: (a) Alston, P. V.; Gordon, M. D.; Ottenbrite, R. M.; Cohen, T. *J. Org. Chem.* **1983**, *48*, 5051. (b) Alston, P. O.; Ottenbrite, R. M.; Cohen, T. *Ibid.* **1978**, *43*, 1864. (c) Alston, P. V.; Ottenbrite, R. M. *Ibid.* **1975**, *40*, 1111. (d) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554.

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Table I. Frontier Orbital Energies for Monosubstituted Dienes and Energy Gaps to Acrolein[a]

position and substituent	orbital energy		energy gaps to acrolein[b]		difference
	HOMO	LUMO	HOMO → LUMO	LUMO → HOMO	
1-OCH_3	−190	87	250	337	87
1-$SCH{=}CH_2$	−178	71	239	321	82
1-SCH_3	−183	75	244	325	81
1-$NHCO_2H$	−189	78	250	327	77
1-CH_3	−197	81	257	331	74
2-OCH_3	−199	83	259	333	74
2-SCH_3	−193	75	253	325	72
2-$SCH{=}CH_2$	−187	69	248	319	71
2-CH_3	−201	78	261	332	71
1-$CH{=}CH_2$ (perp)	−196	77	256	327	71
1-$CH{=}CH_2$ (planar)	−186	61	246	311	65
2-$CH{=}CH_2$ (perp)	−202	77	262	327	65
2-$NHCO_2H$	−198	73	258	323	65
H	−204	78	264	327	63
2-$CH{=}CH_2$ (planar)	−195	67	255	317	62
1-OCHO	−203	70	263	320	57
1-OCO_2H	−205	71	266	321	55
1-F	−209	74	270	323	53
2-SiH_3	−208	70	268	320	52
2-OCHO	−210	70	270	320	50
1-Cl	−209	65	269	315	46
1-SiH_3	−208	63	268	313	45
2-F	−214	69	274	319	44
2-Cl	−214	65	274	315	41
2-CO_2H	−213	55	273	305	32
1-SOH	−215	50	276	300	24
2-CF_3	−224	58	284	308	24
1-CO_2H	−217	46	277	296	19
2-CN	−221	49	281	299	18
1-CF_3	−227	53	287	303	16
1-CN	−218	43	279	293	14
1-SO_2H	−230	43	291	292	1

[a] kcal mol^{-1}. 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for molecules incorporating second-row elements). [b] HOMO energy of acrolein, −250 kcal mol^{-1}; LUMO energy, 60 kcal mol^{-1}.

Table II. Frontier Orbital Energies for Dienophiles and Energy Gaps to 1-Methoxybutadiene[a]

dienophile	orbital energy		energy gaps to 1-methoxybutadiene[b]		difference
	HOMO	LUMO	HOMO → LUMO	LUMO → HOMO	
$CH_2{=}CHCHO/BF_3$	−288	10	200	375	175
$CH_2{=}CHNO_2$	−268	30	220	355	135
$CH_2{=}CHCHO$	−250	60	250	337	87
$CH_2{=}CHCOOH$	−252	67	257	339	82
$CH_2{=}CHCF_3$	−268	84	274	355	81
$CH_2{=}CHCN$	−249	66	256	336	80
$CH_2{=}CHSiH_3$	−240	92	282	327	45
$CH_2{=}CHCH{=}CH_2$	−204	78	268	291	23
$CH_2{=}CH_2$	−238	117	307	325	18
$CH_2{=}CHCH_3$	−227	122	314	312	2

[a] kcal mol^{-1}. 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for molecules incorporating second-row elements). [b] HOMO energy in 1-methoxybutadiene, −190 kcal mol^{-1}; LUMO energy, 87 kcal mol^{-1}.

We assume at the outset that, as a class, Diels–Alder cycloadditions of electron-rich dienes with electron-deficient dienophiles are *concerted processes*, i.e., where old bonds are broken and new bonds formed more or less continuously, and do not involve an intermediate or transition structure with significant diradical or zwitterion character.

Frontier Molecular Orbital Theory

In its usual application, frontier molecular orbital theory[1,2,4] involves a perturbation expansion of the energy arising from stabilizing interaction of the highest filled molecular orbital on one fragment and the lowest empty function on the other, and vice versa. Destabilization resulting from interaction of the highest occupied orbitals on the two fragments is generally ignored.[6] To second order in Rayleigh–Schrödinger perturbation theory,[7] the interaction energy may be written.

$$\Delta\epsilon = \frac{2(\sum_i^{A}\sum_j^{B} c_i^{A,HOMO} c_j^{B,LUMO} H_{ij}^{AB})^2}{\epsilon^{A,HOMO} - \epsilon^{B,LUMO}} + \frac{2(\sum_i^{A}\sum_j^{B} c_i^{A,LUMO} c_j^{B,HOMO} H_{ij}^{AB})^2}{\epsilon^{B,HOMO} - \epsilon^{A,LUMO}} \quad (1)$$

$c_i^{A,HOMO}$, $c_i^{A,LUMO}$ $\epsilon_i^{A,HOMO}$, and $\epsilon_i^{A,LUMO}$ are molecular orbital coefficients and orbital energies for the highest occupied and lowest unoccupied functions, respectively, on fragment A; $c_j^{B,HOMO}$, $c_j^{B,LUMO}$, $\epsilon_j^{B,HOMO}$, and $\epsilon_j^{B,LUMO}$ are the corresponding quantities associated with fragment B. The summations are carried out over all atomic orbitals, *i*, on fragment A, and *j* on fragment B. In actual applications of FMO arguments, the perturbation matrix elements, H_{ij}^{AB}

$$H_{ij}^{AB} = \int \phi_i^{A} \hat{H}^{pert} \phi_j^{B}\, d\tau \quad (2)$$

where ϕ_i^{A} and ϕ_j^{B} are atomic orbitals on fragments A and B

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[6] Neglect of the use of all of the terms of the perturbation expansion has lead several investigators to question the validity of the FMO approach; see, for example, ref 1a, 1c, and: Feuer, J.; Herndon, W. C.; Hill, L. H. *Tetrahedron* **1968**, *24*, 2575.

[7] For a discussion, see: Levine, I. N. *Quantum Chemistry*, 3rd ed.; Allyn and Bacon: Boston, 1983; p. 193ff.

Table III. HOMO Coefficients in Substituted Dienes[a]

substituent	HOMO coefficient[b] C_1	C_2	C_3	C_4	difference[c]
H	0.318	0.262	0.262	0.318	0
	1-Substituted Dienes				
OMe	0.235	0.345	0.226	0.313	0.078
F	0.266	0.292	0.260	0.319	0.053
$NHCO_2H$	0.269	0.324	0.213	0.302	0.033
OCHO	0.281	0.291	0.242	0.309	0.028
OCO_2H	0.283	0.286	0.247	0.310	0.027
SMe	0.240	0.309	0.174	0.256	0.016
$SCH{=}CH_2$	0.212	0.280	0.138	0.220	0.008
SO_2H	0.293	0.226	0.283	0.298	0.005
CH_3	0.314	0.288	0.244	0.315	0.001
$CH{=}CH_2$ (planar)	0.274	0.296	0.188	0.267	−0.007
Cl	0.303	0.269	0.240	0.296	−0.007
SiH_3	0.315	0.255	0.259	0.306	−0.009
$CH{=}CH_2$ (perp)	0.328	0.286	0.241	0.315	−0.013
SOH	0.271	0.219	0.215	0.249	−0.022
	2-Substituted Dienes				
SiH_3	0.311	0.260	0.266	0.312	0.001
$CH{=}CH_2$ (perp)	0.329	0.278	0.251	0.306	−0.023
CH_3	0.340	0.275	0.243	0.296	−0.044
CO_2H	0.279	0.261	0.291	0.326	−0.047
Cl	0.331	0.263	0.242	0.282	−0.049
F	0.356	0.232	0.241	0.291	−0.065
OCHO	0.350	0.253	0.238	0.283	−0.067
$CH{=}CH_2$ (planar)	0.343	0.262	0.187	0.225	−0.118
$NHCO_2H$	0.382	0.244	0.193	0.241	−0.142
SMe	0.399	0.226	0.201	0.250	−0.149
$SCH{=}CH_2$	0.306	0.169	0.081	0.102	−0.204
OMe	0.352	0.222	0.129	0.103	−0.249

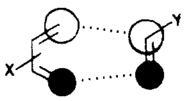
[a] 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for molecules incorporating second-row elements). [b] The coefficients listed are given in terms of absolute values for the "*outer*" component of the valence atomic orbital. The corresponding "*inner*" components show the same trends. There is a change in sign in the orbital between carbons 2 and 3. [c] Carbon 4 − carbon 1.

respectively, and $\hat{H}^{\mathrm{pert}}$ is the perturbation Hamiltonian, i.e., describing the interaction between the two fragments, are replaced by overlap elements, $S_{ij}{}^{AB}$,

$$S_{ij}{}^{AB} = \int \phi_i{}^{A}\phi_j{}^{B}\, d\tau \tag{3}$$

In addition, treatment is usually restricted to a single stabilizing interaction between that pair of occupied and empty frontier orbitals which are the closer in energy. For the case of Diels–Alder reactions involving electron-rich dienes, e.g., methoxybutadiene and electron-deficient dienophiles, e.g., acrolein and maleic anhydride, this is assumed to be between the highest occupied orbital on the diene and the lowest-vacant function on the dienophile. We examine this assumption in more detail below, and attempt to elucidate those situations where (on the basis of energy considerations) the opposite interaction (between the LUMO on the diene and the HOMO on the dienophile) will be the more important and where the two interactions will both likely play significant roles[1g].

According to the qualitative FMO model, therefore, stabilization, afforded the transition state for Diels–Alder cycloaddition for a given diene/dienophile combination, may be equated simply to the square of the total overlap between the highest occupied diene function and the lowest-unoccupied orbital on the dienophile. For combinations involving both asymmetrically substituted dienes and dienophiles, the extent of overlap will depend on regiochemistry and will be larger where the diene and dienophile termini in which the respective orbitals are more heavily concentrated align, i.e.,



rather than the other way around. This follows because the magnitude of two-electron stabilization depends on the *square* of the overlap, i.e., $[\mathrm{Overlap(L,L')}]^2 + [\mathrm{Overlap(S,S')}]^2 > [\mathrm{Overlap(L,S')}]^2 + [\mathrm{Overlap(S,L')}]^2$, where L and L′ correspond to the larger diene and dienophile termini, respectively, and S and S′ to the corresponding smaller termini.[8] The preference for one regioisomer over another should depend on the difference in overlap resulting from the two possible arrangements. For a fixed dienophile, this in turn is a function of the relative sizes of the termini in the diene HOMO; for a fixed diene, it is the relative sizes of termini of the dienophile LUMO which provides the deciding factor.

The FMO model has been widely and successfully employed to rationalize both the observed regiochemistry and endo/exo

Table IV. Comparison of Observed Regiochemistry for Diels–Alder Additions to Monosubstituted Dienes with Those Suggested by FMO and Reactivity Models

experiment substituent	dienophile[a]	regiochemistry (regioselectivity)	ref[b]	theory substituent	regiochemistry FMO	reactivity model
			1-Substituted Dienes			
OMe	1	ortho	a	OMe	ortho	ortho
$NHCO_2Et$	2	ortho (>49:1)	b,c	$NHCO_2H$	ortho	ortho
CH_3	2,3	ortho (7.3:1)	d,e	CH_3	none[c]	ortho
Ph	1	ortho	f	$CH{=}CH_2$ (perp)	meta	ortho
$CH{=}CH_2$	4	ortho	g	$CH{=}CH_2$ (planar)	none[c]	meta
SPh	2,5	ortho	h,i	$SCH{=}CH_2$	none[c]	none[d]
OAc	3	ortho	j	OCHO	ortho	ortho
$SiMe_3$	2	ortho (3:1)	k	SiH_3	none[c]	ortho
			2-Substituted Dienes			
OMe	6	para	l	OMe	para	para
CH_3	2	para (2.3:1)	m	CH_3	para	para
Ph	2	para (4:1)	m	$CH{=}CH_2$ (perp)	para	meta
SPh	2	para	h	$SCH{=}CH_2$	para	para
$SiEt_3$	7	para (3.3:1)	n	SiH_3	none[c]	meta
Cl	2	para (6.7:1)	m	Cl	para	none[d]

[a] Dienophiles: 1, acrolein; 2, methyl acrylate; 3, acrylic acid; 4, hexatriene; 5, methyl vinyl ketone; 6, propynal; 7, ethyl acrylate. [b] References to experimental work: (a) Wichterle, O. *Coll Czech. Chem. Commun.* **1938**, *10*, 497. (b) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182. (c) Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. a.; Ono, R. K.; Taylor, G. F.; Jessup, P. L. *Ibid.* **1981**, *103*, 2816. (d) Bohlman, F.; Förster, H. J.; Fischer, C. H. *Liebigs Ann. Chem.* **1976**, 1487. (e) Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 869. (f) Alder, K.; Vagt, H.; Vogt, W. *Justus Leibigs Ann. Chem.* **1949**, *565*, 135. (g) Kharasch, M. S.; Sternfeld, E. *J. Am. Chem. Soc.* **1939**, *61*, 2318. (h) Cohen, T.; Mura, A. J., Jr.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. L. *J. Org. Chem.* **1976**, *41*, 3218. (i) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891. (j) Alder, K.; Schumacher, M. *Justus Leibigs Ann. Chem.* **1949**, *565*, 148. (k) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2415. (l) Petrov, A. A.; Sopov, N. P. *Zh. Obshch. Khim.* **1956**, *26*, 2452. (m) Inukai, T.; Kojima, T. *J. Org. Chem.* **1971**, *36*, 924. (m) Batt, D. G.; Ganem, B. *Tetrahedron Lett.* **1976**, 3323. [c] Coefficients at C_1 and C_4 differ by less than 0.01. [d] Average bond potentials at C_1C_2 and C_3C_4 differ by less than 0.5 kcal mol^{-1}.

stereochemistry of a wide variety of Diels–Alder[1,2] and related cycloadditions, e.g., 1,3-dipolar additions.[9] It has gained general acceptance among organic chemists and has even recently been introduced as a component of a computer-assisted synthesis program.[10] The (apparent) qualitative success of the theory is impressive. Consider, for example, the extensive compilation of calculated regioselectivities due to Anh and co-workers.[1e] These include cycloadditions of monosubstituted dienes with electron-deficient dienophiles, cyclodimerizations of α,β-unsaturated carbonyl compounds, and additions of *p*-chloronitrosobenzene (the NO bond acting as the dienophile) to various dienes. For the vast majority of reactions considered, observed and calculated regioselectivities are in agreement. In a number of cases they are not. Furthermore, both Anh[1e] and other investigators[1,2] have noted the sensitivity of the calculations to theoretical level, insofar as both the magnitude of the regiochemical preference is concerned and (in a few cases) the direction of the preference.

Results and Discussion

Selection of Dominant Orbital Interaction(s) in the FMO Treatment of Diels–Alder Reactivity. We examine here one of the basic assumptions underlying the application of qualitative molecular orbital theory to Diels–Alder reactivity, specifically the notion that one of the two frontier interactions involves orbitals which are much closer in energy than the other interaction and hence is likely to be significantly the more important. Frontier orbital energies for dienes substituted at either the 1- or 2-position by typical electron-donor or -acceptor groups are provided in Table I. These have been obtained from single-determinant wavefunctions using the 3-21G split-valence basis set[11] (3-21G$^{(*)}$ for second-row elements[12]) and are based on structures optimized at this level. Detailed structural parameters are provided in the Appendix to this paper. Only *s-cis*-diene conformations have been considered; even though these are not the lowest-energy forms for many or all of the systems considered, they are the conformations from which the dienes are presumed to react. Also tabulated are energy gaps between the diene HOMO and the LUMO of a typical electron-deficient dienophile (acrolein), as well as the corresponding LUMO(diene)/HOMO(dienophile) energy differences. These data allow classification of Diels–Alder reactions involving these dienes and electron-deficient dienophiles into three general categories: "normal", those which are likely controlled by the orbital interaction between the diene HOMO and dienophile LUMO, "inverse", those which are controlled by interaction of the diene LUMO and dienophile HOMO, and "neutral", those where, on the basis of energy considerations, both interactions will probably play important roles.[1g]

As expected, the data show that for additions to acrolein the gap between the diene HOMO and LUMO on the dienophile is smaller than that separating diene LUMO from dienophile HOMO. The differences are generally sizable (>60 kcal mol^{-1}) for dienes substituted by strong electron donors but are often quite small (<20 kcal mol^{-1}) for systems substituted by strong electron-withdrawing groups. The assumption that a single frontier interaction should exhibit controlling influence is certainly more valid for reactions involving electron-rich dienes than for those involving electron-deficient dienes. It is the former class of reactions that concerns us in this paper.

These results extend to other electron-deficient dienophiles. The data in Table II show that for reactions involving 1-methoxybutadiene, gaps between the diene HOMO and dienophile LUMO are at least 80 kcal mol^{-1} smaller than the corresponding diene LUMO, dienophile HOMO separations for all common electron-deficient dienophiles.

Table V. LUMO Coefficients in Electron-Deficient Dienophiles[a]

dienophile	LUMO coefficient[b] α	β	difference ($\beta - \alpha$)
$CH_2{=}CHSiH_3$	0.299	0.665	0.366
$CH_2{=}CHCHO/BF_3$	0.253	0.529	0.276
$CH_2{=}CHNO_2$	0.307	0.491	0.184
$CH_2{=}CHCHO$	0.404	0.581	0.177
$CH_2{=}CHCOOH$	0.461	0.631	0.170
$CH_2{=}CHCN$	0.544	0.675	0.131
$CH_2{=}CHCF_3$	0.651	0.742	0.091
$CH_2{=}CHCH_3$	0.746	0.744	−0.002

[a] 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for vinylsilane). [b] The coefficients listed are given in terms of absolute values for the "*outer*" component of the valence atomic orbital. The corresponding "*inner*" components show the same trends. There is a change in sign between the α- and β-carbons.

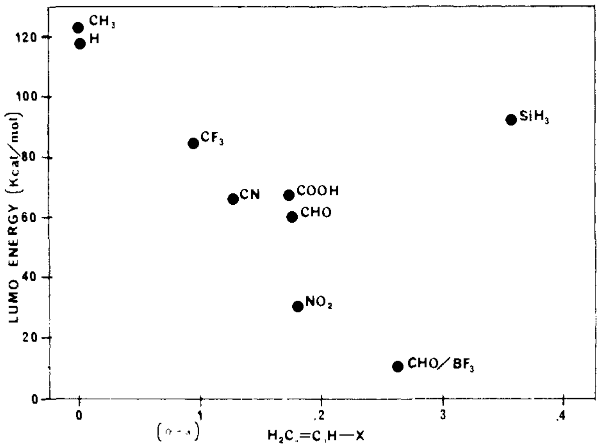


Figure 1. Energy of the lowest unoccupied molecular orbital (kcal mol^{-1}) in dienophiles vs. absolute difference in molecular orbital coefficients $c_\beta - c_\alpha$. 3-21G//3-21G.

Some experimental data are available with which to assess the performance of the theory in describing energy gaps between interacting frontier orbitals or, more importantly, differences in energy gaps between the two competing interactions. At the 3-21G level, the HOMO in *s-cis*-butadiene is separated from the LUMO in ethylene by 321 kcal mol^{-1}; the corresponding difference between the diene LUMO and alkene HOMO is nearly the same, 316 kcal mol^{-1}. Differences obtained by experimental ionization potentials and electron affinities[13] are smaller (254 and 256 kcal mol^{-1}, respectively) but like the theoretical quantities are nearly identical. Presuming the ability of the theory to describe *relative* ionization potentials and electron affinities,[14] this suggests that the data in Tables I and II probably provide a reasonable account of the relative energy separations between competing frontier orbital interactions. The success of FMO arguments in properly describing Diels–Alder regiochemistry would, therefore, provide support for the hypothesis that the dominant frontier interaction (insofar as reaction regioselectivity is concerned) is that where the component fragments are closest in energy. The failure of the simple model might, on the other hand, cast doubt on this fundamental assumption.

In conclusion, the calculations support the selection of a single frontier interaction as dominant (on the basis of energy considerations) in Diels–Alder processes involving electron-rich dienes and electron-deficient dienophiles. They also suggest that the proper treatment of additions of electron-poor dienes with electron-deficient dienophiles may need to consider more than a single frontier interaction. We defer discussion of this specific case to a future paper.

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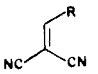
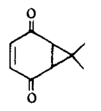
Table VI. Comparison of Observed Regiochemistry for Diels–Alder Addition to Disubstituted Dienes with That Suggested by FMO and Reactivity Models

experiment					regiochemistry	
substituent	dienophile[a]	directing[b] (regioselectivity)	ref[c]	theory substituents	FMO	reactivity
		1,4-Substituted Dienes				
1-OMe 4-CH_3	1,2	OMe (4.6:1)	a,b	1-OMe 4-CH_3	OMe	OMe
1-$NHCO_2Et$ 4-CH_3	3	$NHCO_2Et$	c	1-$NHCO_2H$ 4-CH_3	$NHCO_2H$	$NHCO_2H$
1-$NHCO_2Bz$ 4-SPh	4	$NHCO_2Bz$ (>99:1)	d	1-$NHCO_2H$ 4-$SCH{=}CH_2$	$NHCO_2H$	$NHCO_2H$
1-$NHCO_2Bz$ 4-SO_2Ph	4	$NHCO_2Bz$ (>99:1)	d	1-$NHCO_2H$ 4-SO_2H	$NHCO_2H$	$NHCO_2H$
1-$NHCO_2Bz$ 4-S(O)Ph	4	$NHCO_2Bz$ (>99:1)	d	1-$NHCO_2H$ 4-S(O)H	$NHCO_2H$	$NHCO_2H$
1-CH_3 4-Ph	5	Ph (9:1)	e	1-CH_3 4-$CH{=}CH_2$ (perp)	CH_3	$CH{=}CH_2$
1-Et 4-OAc	6	OAc (>99:1)	f	1-CH_3 4-OCHO	OCHO	OCHO
1-CH_3 4-$SiEt_3$	3	CH_3 (2:1)	g	1-CH_3 4-SiH_3	CH_3	CH_3
1-SPh 4-OAc	7	SPh (15:1)	h	1-$SCH{=}CH_2$ 4-OCHO	OCHO	OCHO
		2,3-Disubstituted Dienes				
2-CH_3 3-Ph	5,8	Ph	e	2-CH_3 3-$CH{=}CH_2$ (perp)	CH_3	CH_3
2-CH_3 3-Cl	5	Cl	e	2-CH_3 3-Cl	none[d]	CH_3
2-OMe 3-SPh	3,7,9,10	SPh (8:1 to 15:1)	i	2-OMe 3-$SCH{=}CH_2$	OMe	$SCH{=}CH_2$
2-OAc 3-SPh	5,7,9,10,11,12	SPh (9:1)	h,i	2-OCHO 3-$SCH{=}CH_2$	$SCH{=}CH_2$	$SCH{=}CH_2$
2-CH_3 3-SPh	3,9,10	SPh (13:1 to 24:1)	j	2-CH_3 3-$SCH{=}CH_2$	$SCH{=}CH_2$	$SCH{=}CH_2$
		1,2-Disubstituted Dienes				
1-CH_3 2-OEt	2,13	CH_3	b,k	1-CH_3 2-OMe	OMe	CH_3
1-Bu 2-$NHCOCl_3$	3	Bu	l	1-Me 2-$NHCO_2H$	$NHCO_2H$	CH_3
1-CH_3 2-CH_3	8,11	1-CH_3 (6:1)	e	1-CH_3 2-CH_3	2-CH_3	1-CH_3
1-CH_3 2-Ph	5	CH_3 (4:1)	e	1-CH_3 2-$CH{=}CH_2$ (perp)	$CH{=}CH_2$	CH_3
1-CH_3 2-OAc	14	CH_3	m	1-CH_3 2-OCHO	OCHO	CH_3
1-CH_3 (Et) 2-Cl	8	CH_3 (3:1)	e	1-CH_3 2-Cl	Cl	CH_3
1-Ph 2-Ph	5	1-Ph (>99:1)	e	1-$CH{=}CH_2$ (perp) 2-$CH{=}CH_2$ (perp)	2-$CH{=}CH_2$	1-$CH{=}CH_2$
1-SPh 2-OMe	10,15	SPh	n,o	1-$SCH{=}CH_2$ 2-OMe	OMe	OMe

[a] Dienophiles: 1, A; 2, 2,6-dimethylbenzoquinone; 3, methyl acrylate; 4, acrolein; 5, acrylic acid; 6, acrolein/BF_3; 7, methacrolein; 8, propiolic acid; 9, acrylonitrile; 10, methyl vinyl ketone; 11, methyl methacrylate; 12, cyclohexenone; 13, B; 14 C; 15, methyl acrylate/$MgBr_2$.



A



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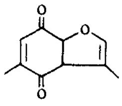


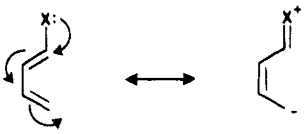
C

[b] See text for explanation. [c] References to experimental work: (a) Broekhuis, A. A.; Schreen, J. W.; Nivard, R. J. F. *Recl. Chim. Pays-Bas* **1979**, *99*, 6. (b) Schmidt, C.; Sabnis, S. D.; Schmidt, E.; Taylor, D. K. *Can. J. Chem.* **1971**, *49*, 371. (c) Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2816. (d) Overman, L. E.; Petty, C. B.; Huang, G. T. *Ibid.* **1983**, *105*, 6335. (e) Titov, Y. A. *Russ. Chem. Rev.* (*Engl. Transl.*) **1962**, 267. (f) Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. (g) Fleming, I.; Percival, A. *J. Chem. Soc., Chem. Commun.* **1978**, 178. (h) Trost, B. M.; Ippen, J.; Vladuchick, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 8116. (i) Trost, B. M.; Vladuchick, W. C.; Bridges, A. G. *J. Am. Chem. Soc.* **1980**, *102*, 3554. (j) Proteau, P. J.; Hopkins, P. B. *J. Org. Chem.* **1985**, *50*, 141. (k) Yamakama, K. T.; Satah, T.; Ohba, N.; Sakaguchi, R. *Chem. Lett.* **1979**, 763. (l) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (m) Bohlman, F.; Forster, H. J.; Fischer, C. H. *Leibigs Ann. Chem.* **1976**, 1487. (n) Cohen, T.; Mura, A. J., Jr.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *J. Org. Chem.* **1976**, *41*, 3218. (o) Cohen, T.; Kosarych, Z. *Ibid.* **1982**, *47*, 4008. [d] Coefficients at C_1 and C_4 differ by less than 0.01.

Appraisal of FMO Analysis of Regiochemistry in Diels–Alder Cycloadditions. HOMO coefficients for *s-cis*-1,3-butadiene as well as *s-cis*-dienes substituted in the 1- and 2-positions by a variety of common substituents are given in Table III. Most of the substituents considered may be classed as electron donors and, except for sulfoxide and sulfone groups, strong electron acceptors have been excluded. Experimental regiochemical data (isomer preferences and where available isomer ratios) for cycloadditions to a variety of monosubstituted dienes involving a number of the substituents dealt with in Table III (or closely related substituents) are summarized in Table IV. References to experimental data are supplied in this table and will not be cited individually in the discussion which follows. Regiochemical preferences based on frontier orbital coefficients are also provided in Table IV. No preferences are recorded in instances where coefficient differences are less than 0.01; these are considered to be insignificant.

Some of the dienes that have been investigated experimentally are too large to be treated at the theoretical levels employed here. These have been modeled by simpler systems as detailed in the tabulated comparisons that follow. Some of the substitutions are subtle, e.g., $NHCO_2H$ for $NHCO_2Bz$. Here, the theoretical results would be expected to parallel quite closely those for the actual systems were calculations able to be performed. Others are more precarious, e.g., a perpendicular vinyl group for phenyl, and may themselves lead to errors in application of the theory. For clarity, we will generally refer to the experimental system (and not to the model) in discussions that follow.

The calculations show that the HOMO in dienes substituted at the 1-position by strong π-donor groups, e.g., OMe and $NHCO_2H$, is more heavily localized on the 4-position (away from the substituent) than it is on the carbon to which the substituent is bonded. This is in accord with the general observation of *ortho* rather than *meta* products resulting from addition of electron-rich dienes to electron-poor dienophiles (see Discussion) and with simple resonance theory, which suggests the high affinity for electrophiles at the C_4 position, i.e.,



Interestingly, substitution by fluorine (a weak π donor but very strong σ acceptor) also effects significant polarization of the butadiene π system toward C_4 (to nearly as great an extent as does methoxy). Apparently *σ effects are also capable of directing regiochemistry, at least according to the simple FMO Model.*

Substitution in the 1-position by methyl (a σ- and π-electron donor) has little if any effect, contrary to the known preferences of alkyl-substituted dienes to direct ortho products.[15] Vinyl and phenylthio groups in the 1-position also do not give rise to significant regiochemical preferences according to the analysis. Experimentally, both substituents direct *ortho* products.

A perpendicular vinyl substituent at the 1-position is suggested by the frontier orbital analysis to direct *meta* products, in contrast to the experimentally observed preference for a phenyl group to yield *ortho* adducts. Note, however, that the preference suggested by the model is very weak; the disagreement with experiment could well lie in the assumption that the phenyl substituent can be adequately modeled by a perpendicular vinyl group.

The FMO model suggests that a silyl group (a σ donor and weak π acceptor) substituted in the 1-position will not give rise to any significant preference for one regioisomer over another. This is not supported by the available experimental evidence, which shows a preference for an *ortho* adduct upon addition of 1-(trimethylsilyl)-1,3-butadiene to methyl acrylate. It is not apparent whether the problem resides solely with the underlying theory or if the modeling of the trimethylsilyl group by SiH_3 is in part to blame.

The effect of π-donor substituents in the 2-position is a buildup of the HOMO at the adjacent carbon and presumably a preference for *para* as opposed to *meta* products. Again simple resonance arguments anticipate the noted polarization.

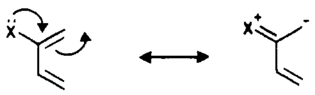


Table VII. Average Hydride Potentials for Substituted Ethylenes, $CH_2{=}CHX^a$

substituent X	average hydride potential α	average hydride potential β	difference[b]
CH_3	−0.3	0.6	−0.9
CO_2H	1.5	−0.4	1.9
SiH_3	−1.5	−2.2	0.7
CF_3	−2.3	−6.7	4.4
CHO	−3.6	−6.8	3.2
CN	−4.9	−7.3	2.4
NO_2	−7.4	−9.9	2.5
CHO/BF_3	−10.3	−14.9	4.6

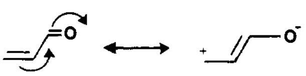
[a] kcal mol^{-1}, relative to ethylene. Absolute average hydride potential for ethylene, 4.0 kcal mol^{-1}. 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for molecules incorporating second-row elements). [b] $\epsilon_\alpha - \epsilon_\beta$.

The available experimental data (Table IV) concur.

Vinyl substituted at the 2 position (and constrained to be perpendicular to the diene skeleton) weakly polarizes the π system toward C_1, making the group a *para* director. While this is in accord with experimental regiochemical data on 2-phenylbutadiene, we again caution that the use of a perpendicular vinyl group to model phenyl may not be satisfactory.

The silyl substituent is again problematic. Experimentally, the addition of 2-(triethylsilyl)-1,3-butadiene to methacrolein results primarily in a *para* adduct, whereas the FMO model indicates no significant preference for one regioisomer over the other. The FMO analysis does properly assign the observed *para* regioproducts in additions of 2-(phenylthio)butadiene and 2-chlorobutadiene to methyl acrylate.

We pause here to examine the extent to which the nature of the dienophile affects Diels–Alder regiochemistry. According to the data given in Table V, the LUMO in olefins substituted by electron-withdrawing groups will be polarized toward the β-carbon. This is, of course, in line with simple resonance arguments, e.g.,



A plot of LUMO energy vs. difference in the corresponding molecular orbital coefficients at the β- and α-positions (Figure 1) shows a *strong parallel between reactivity and regioselectivity* (within the framework of the FMO model). Specifically, dienophiles with low LUMO energies show greater polarization toward the β-carbon than those with higher energies. Experimental data with which to confirm or refute this observation are all but lacking. Oddly enough, no similar correlation appears to exist between the HOMO energies of substituted dienes (Table I) and the extent of polarization of the π system (Table III).

Relatively little experimental data exist with which to assess the performance of the theory in ordering the regiochemical preferences of closely related systems. Some of this is summarized in Table VI. These data not only allow quantitative comparisons of the effects of different substituents on the same diene position, i.e., terminal or internal sites, but also the same substituent on different diene positions. Only 1,2-, 1,4-, and 2,3-disubstituted dienes have been dealt with; substituents placed 1,3 on butadiene generally reinforce rather than compete with one another. Therefore, regiochemical data on these systems contribute little to what has already been established by using monosubstituted dienes.

Studies on the addition of acrolein to 1,4-disubstituted dienes have established that the $NHCO_2R$ group (R = Et, Bz) is a better (*ortho*) regiodirector than are SPh, S(O)Ph, or SO_2Ph groups. HOMO coefficients for dienes substituted by closely-related substituents ($NHCO_2H$, $SCH{=}CH_2$, and SO_2H) all show polarization toward C_4, the strongest polarization being for the acylamino group. The sulfoxide group effects the opposite polarization of the diene π system, although the magnitude of the effect is also less than that noted for the acylamino group. Thus, *assuming additivity of substituent effects* (the additivity approximation in the FMO analysis of Diels–Alder regiochemistry involving disubstitued dienes is examined in the Appendix to this

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(15) Regiodirection in this case has been attributed to secondary orbital interactions.[2c]

(16) Calculations (MINDO/3,[2d] CNDO/2,[2b] Hückel[2b]) on 2-methoxy-3-(phenylthio)-1,3-butadiene suggest that the phenylthio group will exert a greater directing influence.

Table VIII. Electrostatic Potentials for Monosubstituted Dienes[a]

position and substituent	electrostatic potential							
	C_1	C_2	C_3	C_4	$\overline{C_1C_2}$[b]	$\overline{C_3C_4}$[c]	$C_4 - C_1$[d]	$\overline{C_3C_4} - \overline{C_1C_2}$[e]
2-OMe	**-20.5**	-14.6	-17.6	-15.5	**-17.6**	-16.6	-5.0	-1.0
1-OMe	-10.5	-19.1	-19.4	**-20.0**	-14.8	**-19.7**	9.5	4.9
2-CH_3	**-19.3**	-17.0	-17.4	-16.5	**-18.2**	-17.0	-2.8	-1.2
1-$NHCO_2H$	-8.6	-16.8	-18.2	**-18.8**	-12.7	**-18.5**	10.2	5.8
1-CH_3	-14.1	-19.6	-19.3	**-18.7**	-16.9	**-19.0**	4.6	2.1
1-$CH{=}CH_2$ (perp,up)	-12.1	-19.4	-19.3	**-18.5**	-15.8	**-18.9**	6.4	3.1
1-$CH{=}CH_2$ (planar)	**-17.7**	-18.0	-17.6	-16.5	**-17.9**	-17.0	-1.2	-0.9
2-$CH{=}CH_2$ (perp,up)	**-17.5**	-15.1	-17.6	-16.5	-16.3	**-17.0**	-1.0	0.7
1-$CH{=}CH_2$ (perp,down)	1.4	-15.0	-18.1	**-17.5**	-6.8	**-17.8**	18.9	11.0
1-SMe	-15.9	-16.8	-17.3	**-17.2**	-16.4	**-17.3**	1.3	0.9
-H	-16.6	-17.8	-17.8	-16.6	-17.2	-17.2	0	0
2-$CH{=}CH_2$ (planar)	**-16.4**	-19.3	-18.1	-16.1	**-17.9**	-17.1	-0.3	-0.8
2-SMe	**-16.3**	-18.4	-17.1	-14.0	**-17.0**	-15.6	-2.3	-1.8
2-$CH{=}CH_2$ (perp,down)	-15.7	-12.6	-16.3	**-16.2**	-14.1	**-16.3**	0.5	2.2
2-$NHCO_2H$	**-15.8**	-10.5	-14.0	-12.5	-13.2	**-13.3**	-3.3	0.1
2-$SCH{=}CH_2$	**-15.3**	-16.9	-15.4	-12.6	**-16.1**	-14.0	-2.7	-2.1
1-$SCH{=}CH_2$	-14.2	-16.1	-16.0	**-15.0**	-15.2	**-15.5**	0.8	0.3
2-SiH_3	-10.9	-12.0	-15.4	**-14.6**	-11.5	**-15.0**	3.7	3.5
1-S(O)H (oxygen)	**-14.4**	-5.3	-5.6	-8.3	**-9.9**	-7.1	-6.1	-2.9
2-OCHO	**-13.8**	-7.8	-11.5	-10.3	-10.8	**-10.9**	-3.5	0.1
1-OCHO	-3.9	-12.3	-13.6	**-13.3**	-8.1	**-13.4**	9.4	5.3
1-OCO_2H	-3.6	-12.2	-13.0	**-12.8**	-8.0	**-12.9**	9.2	4.9
1-SiH_3	-11.8	-12.2	-14.2	**-12.6**	-12.0	**-13.4**	0.8	1.4
2-F	**-12.2**	-6.1	-9.3	-7.5	**-9.1**	-8.4	-4.7	-0.7
1-F	-2.5	-11.1	-12.1	**-11.5**	-6.8	**-11.8**	9.0	5.0
1-Cl	-8.8	-9.0	-10.7	**-9.7**	-8.9	**-10.2**	0.9	1.3
2-Cl	**-8.9**	-10.8	-11.1	-8.6	**-9.9**	-9.8	-0.3	-0.1
1-S(O)H (lone pair)	2.0	0.9	-6.1	**-1.4**	1.5	**-3.8**	3.4	5.3
1-SO_2H	-0.7	6.8	2.1	**-1.4**	3.1	**0.4**	0.7	2.7

[a] kcal mol^{-1}. 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for molecules incorporating second-row elements). [b] Average of potentials at C_1 and C_2. [c] Average of potentials at C_3 and C_4. [d] Difference in potentials at C_4 and C_1. [e] Difference in average of potentials between C_3 and C_4 and between C_1 and C_2.

Table IX. Additivity of HOMO Coefficients and Average Electrostatic Potentials in 1,4-Disubstituted Dienes[a]

substituents	difference in HOMO coeff[b]		difference in av electrostatic potentials[c]	
	direct	additivity	direct	additivity
1-OMe 4-SMe	0.007	0.013	1.6	1.3
1-OMe 4-$NHCO_2H$	0.003	0.014	1.1	1.0
1-SMe 4-$NHCO_2H$	0.011	0.001	0.2	0.3

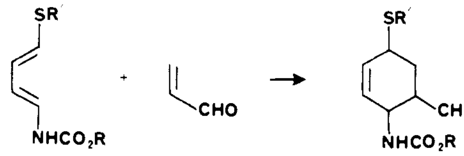
[a] STO-3G//STO-3G. [b] $C_4 - C_1$. Positive number indicates *ortho* direction by substituent in 1-position. [c] $C_3C_4 - C_1C_2$, kcal mol^{-1}. Positive number indicates *ortho* direction by substituent in 1-position.

Table X. Dependence of HOMO Coefficients and Average Electrostatic Potentials in Monosubstituted Dienes on Theoretical Level

substituent	difference in HOMO coeff[a]		difference in average electrostatic potential[b]	
	STO-3G	3-21G[c]	STO-3G	3-21G
1-OMe	0.040	0.078	4.4	4.9
1-SMe	0.027	0.016[d]	3.1	0.9[d]
1-$NHCO_2H$	0.026	0.033	3.4	5.8

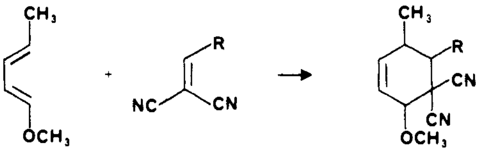
[a] $C_4 - C_1$. Positive number indicates favoring of *ortho* products. [b] $C_3C_4 - C_1C_2$, kcal mol^{-1}. Positive numbers indicate favoring of *ortho* products. [c] The coefficient differences listed are for the "*outer*" component of the valence atomic orbital. The corresponding differences in "*inner*" components are much smaller and show the same trends. [d] 3-21G$^{(*)}$//3-21G$^{(*)}$.

paper), 1,4-disubstituted systems with the $NHCO_2H$ substituent at one end and one of the sulfur containing groups on the other would all be expected (on the basis of the FMO analysis) to lead to products where the former was *ortho* to the formyl group of acrolein, i.e.,



This is in accord with the available experimental data. (Here, and in the examples which follow, only the major regioisomer has been indicated. Where available, data on actual product ratios have been provided in Table VI.)

The frontier orbital analysis suggests that, attached 1,4 to a diene, a methoxy substituent will dominate a methyl group in directing regiochemistry. The experimental evidence concurs, e.g.,



The simple frontier orbital analysis also properly orders the relative directing abilities of acetoxy and ethyl groups positioned 1,4 in a diene. It fails, however, to reproduce the fact that a phenyl substituent is a significantly better regiodirector than methyl (the FMO analysis cannot distinguish between the two). It is not clear, however, that part of the blame does not belong to the use of a perpendicular vinyl group to model phenyl. The FMO model also incorrectly assigns the regioproduct in competition between terminal phenylthio and acetoxy substituents. Experimentally, the former shows the stronger directing ability.

While the FMO model leads to the observed product in competition of methyl and trimethylsilyl substituents, i.e.,

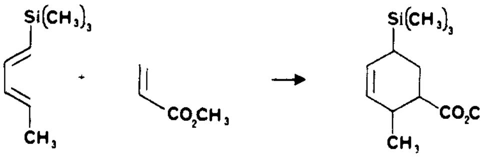


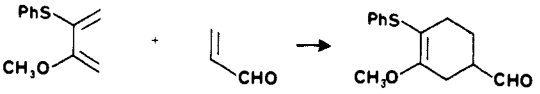
Table XI. Sum of Electrostatic and Polarization Potentials for Monosubstituted Dienes[a]

position and substituent	C_1	C_2	C_3	C_4	$\overline{C_1C_2}$[b]	$\overline{C_3C_4}$[c]	$C_4 - C_1$[d]	$\overline{C_3C_4} - \overline{C_1C_2}$[e]
1-OMe	−22.6	−30.1	−30.3	−29.9	−26.4	−30.1	7.3	3.7
1-$NHCO_2H$	−21.0	−28.1	−29.1	−28.7	−24.6	−28.9	7.7	4.3
1-SMe	−28.4	−29.2	−28.8	−27.5	−28.8	−28.2	−0.9	−0.6

[a] kcal mol^{-1}. 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for 1-(methylthio)butadiene). [b] Average of potentials at C_1 and C_2. [c] Average of potentials at C_3 and C_4. [d] Difference in potentials at C_4 and C_1. [e] Difference in average of potentials between C_3 and C_4 and between C_1 and C_2.

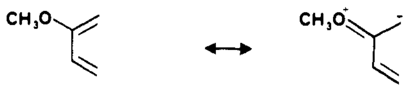
this result is fortuitous. As previously mentioned, the FMO analysis shows that neither 1-silyl nor 1-methyl substituents are effective regiodirectors; their combined effect, while above the threshold which we consider significant, is only slight.

The FMO analysis does not always provide a satisfactory account of the relative directing abilities of internal diene substituents. For example, while experimental work suggests that a phenylthio group is more effective in directing para regiochemistry than a methoxy substituent, i.e.,

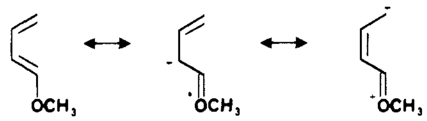


HOMO coefficients for dienes substituted at the 2-position by $SCH{=}CH_2$ and OMe groups (both of which are indicated to be strong para directors) suggest instead that the methoxy substituent will exert the stronger directing influence.[16] The model also fails to reproduce the observations that, placed internally, both phenyl and chloro substituents are better regiodirectors than methyl. In the latter instance, the simple theory shows no distinction. The FMO analysis is, however, successful in properly ordering the relative directing abilities of internal methyl, acetoxy, and phenylthio substituents; the latter is seen to exert the dominant influence in accord with experiment.

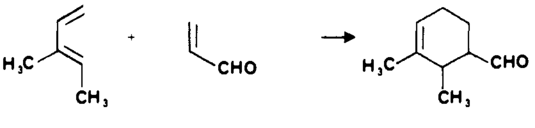
FMO theory suggests that methyl, vinyl, methoxy, fluoro, phenylthio, and vinylthio groups exert far greater influence on Diels–Alder regiochemistry when substituted in the 2-position than when attached to the diene termini (see Table III). This result is in fact anticipated by simple resonance theory. A π-donor substituent attached at the 2-position leads to buildup of negative charge *only* at the 1-position, e.g.,



while the same group attached at the 1-position results in charge buildup both on the far terminus of the diene and on an internal position.

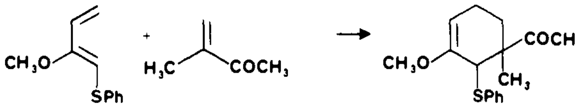


Of the substituents examined here, only SiH_3, which is indicated to be a very weak director independent of substitution, is an exception. The available experimental data are not in accord. For example, the addition of 1,2-dimethyl-1,3-butadiene to acrolein leads primarily to an *ortho* adduct.



Thus, the alkyl group in the 1-position exerts the greater control over product regiochemistry, opposite the suggestion made by the FMO model.[17] These same comments apply to competition between phenyl groups on terminal and internal diene positions. The experimental data indicate control by the terminal substituent, whereas the FMO analysis leads to the opposite conclusion.

The FMO model also fails to reproduce experimental observations that 2-ethoxy, 2-acetoxy, 2-(*N*-trichloroacetoxy), 2-phenyl, and 2-chloro substituents are dominated by the regiodirecting ability of a methyl group in the 1-position. The addition of 2-methoxy-1-(phenylthio)butadiene to methyl vinyl ketone results predominately in an adduct in which the SPh group is *ortho* to the ester, i.e.,



suggesting that a methoxy substituent at the 2-position is less effective in directing regiochemistry than a phenylthio group in the 1-position. The FMO analysis leads to the opposite conclusion.

Thus far in our discussion we have avoided commentary into the role of *secondary orbital interactions*, i.e., interactions between atoms not directly involved in the formation of new σ bonds, in determining regiochemistry in Diels–Alder cycloadditions. For the cycloadditions treated in this study, the most likely secondary interactions are those between the internal diene carbons and the electron-withdrawing group on the dienophile. These should be significant only for endo transition states.[1f,1a–c,18] While there is no direct measure of the magnitude of secondary orbital effects, the available experimental evidence suggests that while secondary interactions may contribute to overally regioselectivity, it is unlikely that these contributions will dominate the selection.[19] It appears to us, therefore, that the common practice of "adjusting" the results of the simple FMO analysis for secondary orbital interactions in order to bring them into line with observation is unfounded.

Overall, the FMO model, while generally capable of assigning absolute regiochemistry, i.e., for Diels–Alder additions to monosubstituted dienes, is much less satisfactory in judging the relative directing effects of different substituents or of the same substituent on different diene positions. The situation is particularly severe in comparisons involving terminal and internal diene substituents, where the model generally favors direction by the latter, in disagreement with experiment (see Table VI). With the advent of synthesis design based on highly functionalized dienes,[20] this shortcoming is indeed unfortunate.

Application of Reactivity Models to the Description of Regioselectivity in Diels–Alder Cycloadditions

Here we introduce an alternative to the description of the regiochemistry of interaction of two molecules of arbitrary complexity. It should be particularly appropriate for those Diels–Alder processes where one partner is electron rich and the other electron poor. The procedure is based on the matching of atomic reactivity surfaces obtained independently for each of the two molecules involved in reaction, e.g., a diene and dienophile, with chemically complementary reagents. In the case of "normal" Diels–Alder reactions, where interaction of the highest occupied molecular orbital on the diene and the lowest vacant function on the dienophile is presumed to exert the dominant influence on regiose-

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[17] Regioselectivity results for 1,2-disubstituted butadienes have been rationalized on the basis of the dominance of secondary orbital interactions.[2a,b]

(18) Alston, P. V.; Ottenbrite, R. M.; Shillady, D. D. *J. Org. Chem.* **1973**, *38*, 4075. (b) Bachler, V.; Mark, F. *Tetrahedron* **1977**, *33*, 2857. (c) Cohen, T.; Ruffner, R. J.; Shull, D. W.; Daniewski, W. M.; Ottenbrite, R. M.; Alston, P. V. *J. Org. Chem.* **1978**, *43*, 4052. (d) Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095.

(19) Fleming, I.; Michael, J. P.; Overman, L. E.; Taylor, G. F. *Tetrahedron Lett.* **1978**, 1313.

(20) For a recent review, see: Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753.

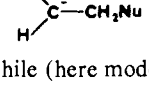
lectivity, the diene is probed with a "test" electrophile, e.g., H^+, and the dienophile with a "test" nucleophile, e.g., H^-. Reaction regiochemistry is then determined in order to effect a best match of the complementary (electrophilic and nucleophilic) reactivity surfaces. If one were to deal instead with "inverse" Diels–Alder processes, i.e., where the important interaction was between the diene LUMO and the HOMO on the dienophile, the probes would have to have been reversed and comparison of the potential of the diene toward nucleophiles and of the dienophile toward electrophiles effected. Only in those situations where neither frontier interaction provided the dominant influence would application of the matching techniques prove cumbersome. Here, as in the application of the FMO model, a balance between different (and possibly competing) interactions would need to be struck. In this paper, we focus on "normal" Diels–Alder processes, i.e., those involving additions of electron-rich dienes and electron-deficient dienophiles. We draw on the results of our previous discussion for support of the notion that here it is the nucleophilicity of the diene and the electrophilicity of the dienophile that will characterize the overall reactivity of these systems.

Nucleophilic Reactivity of Activated Olefins

Hydride surfaces for nitroethylene, acrylonitrile, 3,3,3-trifluoropropene, and acrolein, i.e., olefins substituted by strong electron-withdrawing groups, are shown in Figure 2. These images have been constructed by treating the spherical electron distribution of the nucleophile as a nondeformable "ball" which then "rolls around" on top of the electron-density surface of the substrate. For each point of contact, a potential energy of interaction is evaluated (quantum-mechanical methods are discussed in the Appendix to this paper), and this potential is then encoded as a color onto the previously shaded (to indicate three-dimensional structure) electron-density surface of the substrate *at the point of contact*. In these examples, and in others that follow, the color red, near one end of the visible spectrum, corresponds to maximum attraction between substrate and reagent (most negative interaction energy), and the color blue, near the other end of the spectrum, corresponds to maximum repulsion. (The visible spectrum extends beyond blue into the violet. However, "color" may be perceived as a closed dimension, the color violet being bordered both by the colors blue and red. To avoid confusion the color violet has not been utilized.) The "size" of hydride (defining its radius of contact with a substrate surface) is 1.547 Å, corresponding to a value of the electron density function of 0.002 electron/bohr^3 at the 3-21G level.[21]

Note that the images in Figure 2 *appear to convey* four dimensions of information, three of which are involved with the description of the size and shape of the substrate electron-density surface and the fourth with indication of the sign and magnitude of the interaction of the substrate with the external reagent.

As expected, all the olefins shown are activated toward nucleophilic attack relative to ethylene (also shown). The ordering of activation (as seen by inspection), follows the sequence $NO_2 > CN \simeq CHO \simeq CF_3 >> H$. This is qualitatively similar, but not identical, to the usual ordering of electron-withdrawing abilities: $NO_2 > CHO > CN > CF_3 >> H$, based on stabilization of negatively charged centers.[22] Average potentials for the α- and β-carbons derived from these surfaces, as well as those for a number of other substituted olefins, are presented in Table VII. (Numerical methods for averaging are discussed in the Appendix to this paper.) All activated alkenes favor hydride attack β to the substituent, leading to carbanions of the form

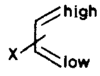


where Nu^- is the nucleophile (here modeled by H^-) and X is an electron-withdrawing group. Propene, which is weakly deactivated according to the reactivity models, favors attack onto the α-carbon.

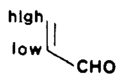
The average hydride potentials in these systems are displayed schematically in Figure 3, which provides an overview not only of the effect of substituents on the reactivity of ethylene but also of their differentiation of the two olefinic positions, i.e., regioselectivity. Recall from our earlier discussion that the LUMO energy in electron-deficient olefins was found to correlate linearly with the degree of polarization of the corresponding orbital toward the β-carbon. *The data here do not show any obvious relationship between the extent of activation of the olefinic bond by the substituent and the magnitude of the preference for β over α attack.* The acrolein/BF_3 complex (the most activated system examined) and 3,3,3-trifluoropropene show the largest site preferences. Of the highly activated olefins, nitroethylene and acrylonitrile show the smallest preferences. The unique place of acrolein as a highly activated yet selective olefin is fortunate as this molecule and closely related systems are among the most synthetically utilized dienophiles in Diels–Alder reactions.

Regiochemistry of Diels–Alder Reactions

The hydride reactivity surface for *trans*-acrolein, shown in Figure 2, shows a strong preference for nucleophile addition β to the carbonyl group, as do the corresponding surfaces for other electron-deficient olefins. The preferred regiochemistry of Diels–Alder cycloadditions of acrolein and other electron-deficient dienophiles with an asymmetrically substituted diene is then one in which the diene terminus with the larger reactivity toward electrophiles aligns with the β-carbon in the dienophile, and the terminus with the smaller electrophile affinity lines up with the α-carbon. The situation, illustrated schematically below for the case of acrolein acting as the dienophile,



electrophilic reactivity



nucleophilic reactivity

is closely akin to the frontier molecular orbital approach (see previous discussion), whereby regiochemistry is specified by the pairing of the larger HOMO coefficient in the diene with the larger LUMo coefficient in the dienophile.

Average proton potentials (more commonly termed electrostatic potentials) for the four carbons in the same set of monosubstituted dienes already dealt with in our earlier discussion of the analysis of Diels–Alder regiochemistry using FMO theory are provided in Table VIII. These have been ordered according to the larger of the two potentials on the diene terminii, from most negative (most reactive toward electrophiles) to most positive (least reactive). The more reactive terminal potential is set in bold type for each entry in the table. The magnitude of the larger of the terminal electrostatic potentials corresponds to one measure of overall diene reactivity; on this basis, methoxy, methyl, vinyl, and acylamino substituents appear to enhance the reactivity of parent butadiene, methylthio has little effect, and the remaining groups retard reactivity.

It is reasonable to anticipate that HOMO energies for substituted dienes will parallel calculated electrostatic potentials. This is illustrated in Figure 4. Note that while a rough correlation does exist between HOMO energies for substituted dienes (Table I) and the more negative of the electrostatic potentials at the terminal carbons (set in bold type in Table VIII), data for a number of systems fall far from the least-squares line.

An alternative measure of reactivity is provided by choosing the larger average electrostatic potential corresponding to the terminal double bonds in the substituted diene. We define *bond averages* as the larger of the average of the electrostatic potentials at C_1 and C_2 and those at C_3 and C_4. This value has also been set in bold type for each entry in the table. While the bond averaging procedure produces a somewhat different ordering of effects from consideration of the electrostatic potentials at the terminal carbons alone, with only minor exceptions, the individual dienes considered here each fall into the same category as before,

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[21] See: Francl, M. M.; Hout, R. F., Jr.; Hehre, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 563.

[22] Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.

Table XII. Structure Data for 1-Substituted Butadienes Optimized at 3-21G and 3-21G(*)$^{a-c}$

Methoxy; Energy = −267.307 26

$A = 1.322$, $B = 1.473$, $C = 1.322$, $D = 1.073$, $E = 1.073$, $F = 1.075$, $G = 1.070$, $H = 1.072$, $I = 1.367$, $J = 125.0$, $K = 128.0$, $L = 123.1$, $M = 121.0$, $N = 113.9$, $O = 115.2$, $P = 122.7$, $Q = 127.6$, $a = 1.437$, $c = 1.077$, $d = 1.083$, $g = 119.9$, $i = 105.8$, $j = 111.0$, $m = 0.0$, $o = 180.0$, $p = 119.1$

Methylthio; Energy = −588.541 00

$A = 1.323$, $B = 1.476$, $C = 1.321$, $D = 1.073$, $E = 1.073$, $F = 1.075$, $G = 1.074$, $H = 1.072$, $I = 1.752$, $J = 125.5$, $K = 127.5$, $L = 123.0$, $M = 121.1$, $N = 114.1$, $O = 114.6$, $P = 120.5$, $Q = 128.7$, $a = 1.807$, $c = 1.082$, $d = 1.081$, $g = 103.2$, $i = 106.6$, $j = 111.1$, $m = 0.0$, $o = 180.0$, $p = 118.6$

Formylamino; Energy = −395.366 19

$A = 1.322$, $B = 1.473$, $C = 1.321$, $D = 1.073$, $E = 1.072$, $F = 1.075$, $G = 1.070$, $H = 1.075$, $I = 1.398$, $J = 125.3$, $K = 127.6$, $L = 123.0$, $M = 121.0$, $N = 114.1$, $O = 115.6$, $P = 123.2$, $Q = 124.3$, $a = 1.353$, $b = 0.998$, $c = 1.209$, $d = 1.354$, $e = 0.966$, $g = 121.5$, $h = 120.6$, $i = 126.0$, $j = 110.2$, $k = 111.5$, $m = 180.0$, $n = 180.0$, $o = 0.0$, $p = 180.0$, $q = 180.0$

Sulfone; Energy = −698.538 23

$A = 1.320$, $B = 1.473$, $C = 1.320$, $D = 1.073$, $E = 1.072$, $F = 1.073$, $G = 1.072$, $H = 1.077$, $I = 1.729$, $J = 126.6$, $K = 125.9$, $L = 123.0$, $M = 120.9$, $N = 114.9$, $O = 114.5$, $P = 123.3$, $Q = 122.8$, $a = 1.327$, $b = 1.433$, $g = 98.8$, $h = 109.7$, $m = 0.0$, $n = 113.4$

Sulfoxide; Energy = −624.089 28

$A = 1.321$, $B = 1.476$, $C = 1.320$, $D = 1.073$, $E = 1.072$, $F = 1.074$, $G = 1.073$, $H = 1.076$, $I = 1.765$, $J = 126.5$, $K = 126.3$, $L = 122.9$, $M = 121.0$, $N = 114.7$, $O = 114.5$, $P = 121.5$, $Q = 125.5$, $a = 1.341$, $b = 1.490$, $g = 92.1$, $h = 111.2$, $m = 0.0$, $n = 112.3$

Carbonate; Energy = −415.067 50

$A = 1.312$, $B = 1.473$, $C = 1.321$, $D = 1.073$, $E = 1.072$, $F = 1.074$, $G = 1.072$, $H = 1.072$, $I = 1.406$, $J = 125.5$, $K = 127.2$, $L = 123.0$, $M = 121.0$, $N = 114.2$, $O = 117.0$, $P = 127.2$, $Q = 118.7$, $a = 1.336$, $c = 1.203$, $d = 1.334$, $e = 0.966$, $g = 119.6$, $i = 125.4$, $j = 109.2$, $k = 112.0$, $m = 180.0$, $o = 0.0$, $p = 180.0$, $q = 180.0$

Formate; Energy = −340.591 22

$A = 1.323$, $B = 1.473$, $C = 1.321$, $D = 1.074$, $E = 1.072$, $F = 1.074$, $G = 1.072$, $H = 1.072$, $I = 1.390$, $J = 125.8$, $K = 127.4$, $L = 123.1$, $M = 121.0$, $N = 114.1$, $O = 117.0$, $P = 124.6$, $Q = 120.2$, $a = 1.356$, $c = 1.190$, $d = 1.082$, $g = 121.1$, $i = 122.7$, $j = 112.9$, $m = 180.0$, $o = 180.0$, $p = 180.0$

Formate; Energy = −340.600 33

$A = 1.313$, $B = 1.474$, $C = 1.321$, $D = 1.073$, $E = 1.072$, $F = 1.074$, $G = 1.072$, $H = 1.067$, $I = 1.403$, $J = 125.6$, $K = 127.2$, $L = 123.0$, $M = 121.0$, $N = 114.2$, $O = 116.9$, $P = 126.5$, $Q = 119.0$, $a = 1.353$, $c = 1.197$, $d = 1.074$, $g = 120.7$, $i = 124.6$, $j = 109.3$, $m = 180.0$, $o = 0.0$ $p = 180.0$

Formate; Energy = −340.600 21

$A = 1.316$, $B = 1.475$, $C = 1.321$, $D = 1.073$, $E = 1.072$, $F = 1.074$, $G = 1.067$, $H = 1.067$, $I = 1.401$, $J = 124.3$, $K = 127.7$, $L = 123.1$, $M = 121.0$, $N = 113.8$, $O = 116.6$, $P = 124.7$, $Q = 127.3$, $a = 1.349$, $c = 1.198$, $d = 1.075$, $g = 127.0$, $i = 126.2$, $j = 108.6$, $m = 0.0$, $o = 0.0$, $p = 180.0$

Formate; Energy = −340.566 63

$A = 1.317$, $B = 1.476$, $C = 1.320$, $D = 1.073$, $E = 1.072$, $F = 1.074$, $G = 1.067$, $H = 1.071$, $I = 1.388$, $J = 124.5$, $K = 127.6$, $L = 123.2$, $M = 120.9$, $N = 114.0$, $O = 114.6$, $P = 123.4$, $Q = 128.2$, $a = 1.358$, $c = 1.191$, $d = 1.075$, $g = 126.3$, $i = 121.6$, $j = 114.3$, $m = 0.0$, $o = 180.0$, $p = 180.0$

Carboxylic acid; Energy = −340.623 44

$A = 1.323$, $B = 1.471$, $C = 1.321$, $D = 1.073$, $E = 1.072$, $F = 1.074$, $G = 1.070$, $H = 1.072$, $I = 1.464$, $J = 126.5$, $K = 126.2$, $L = 122.7$, $M = 121.2$, $N = 114.9$, $O = 115.8$, $P = 123.5$, $Q = 122.4$, $a = 1.361$, $b = 1.206$, $c = 0.968$, $g = 113.1$, $h = 125.3$, $i = 111.4$, $m = 180.0$, $n = 180.0$, $o = 180.0$

Vinyl; Energy = −230.513 38

$A = 1.327$, $B = 1.473$, $C = 1.322$, $D = 1.073$, $E = 1.073$, $F = 1.075$, $G = 1.075$, $H = 1.075$, $I = 1.463$, $J = 126.7$, $K = 127.0$, $L = 122.8$, $M = 121.1$, $N = 114.6$, $O = 114.9$, $P = 120.4$, $Q = 123.5$, $a = 1.322$, $b = 1.076$, $c = 1.072$, $d = 1.074$, $g = 124.0$, $h = 116.2$, $i = 121.8$, $j = 121.8$, $m = 180.0$, $n = 180.0$, $o = 180.0$, $p = 180.0$

Vinyl; Energy = −230.453 73

$A = 1.327$, $B = 1.473$, $C = 1.322$, $D = 1.073$, $E = 1.073$, $F = 1.075$, $G = 1.075$, $H = 1.075$, $I = 1.463$, $J = 126.7$, $K = 127.0$, $L = 122.8$, $M = 121.1$, $N = 114.6$, $O = 114.9$, $P = 120.4$, $Q = 123.5$, $a = 1.322$, $b = 1.076$, $c = 1.072$, $d = 1.074$, $g = 124.0$, $h = 116.2$, $i = 121.8$, $j = 121.8$, $m = 90.0$, $n = 180.0$, $o = 180.0$, $p = 180.0$

Vinylthio; Energy = −626.169 28

$A = 1.322$, $B = 1.475$, $C = 1.321$, $D = 1.073$, $E = 1.073$, $F = 1.075$, $G = 1.075$, $H = 1.072$, $I = 1.764$, $J = 125.9$, $K = 127.3$, $L = 122.9$, $M = 121.1$, $N = 114.2$, $O = 115.1$, $P = 121.6$, $= 123.2$, $a = 1.770$, $c = 1.315$, $d = 1.074$, $e = 1.073$, $f = 1.073$, $g = 100.5$, $i = 123.0$, $j = 115.9$, $k = 121.0$, $l = 122.0$, $m = 180.0$, $o = 128.6$, $p = 180.0$, $q = 180.0$, $r = 180.0$

Vinylthio; Energy = −626.168 84

$A = 1.322$, $B = 1.475$, $C = 1.321$, $D = 1.073$, $E = 1.072$, $F = 1.075$, $G = 1.075$, $H = 1.072$, $I = 1.759$, $J = 125.9$, $K = 127.3$, $L = 123.0$, $M = 121.1$, $N = 114.2$, $O = 115.1$, $P = 121.3$, $Q = 123.0$, $a = 1.763$, $c = 1.316$, $d = 1.073$, $e = 1.072$, $f = 1.073$, $g = 101.7$, $i = 123.4$, $j = 115.7$, $k = 120.8$, $l = 122.5$, $m = 180.0$, $o = 180.0$, $p = 180.0$, $q = 180.0$, $r = 180.0$

Chloro; Energy = −610.876 00

$A = 1.315$, $B = 1.476$, $C = 1.320$, $D = 1.073$, $E = 1.072$, $F = 1.074$, $G = 1.073$, $H = 1.068$, $I = 1.744$, $J = 125.7$, $K = 127.0$, $L = 123.0$, $M = 121.0$, $N = 114.2$, $O = 115.7$, $P = 124.7$, $Q = 122.4$

Trifluoromethyl; Energy = −487.870 37

$A = 1.317$, $B = 1.472$, $C = 1.320$, $D = 1.073$, $E = 1.072$, $F = 1.074$, $G = 1.072$, $H = 1.070$, $I = 1.476$, $J = 126.6$, $K = 126.2$, $L = 122.9$, $M = 121.1$, $N = 114.8$, $O = 115.5$, $P = 124.0$, $Q = 121.6$, $a = 1.352$, $b = 1.355$, $g = 112.5$, $h = 111.8$, $m = 0.0$, $n = 120.7$

Cyano; Energy = −245.274 87

$A = 1.326$, $B = 1.472$, $C = 1.321$, $D = 1.073$, $E = 1.072$, $F = 1.074$, $G = 1.074$, $H = 1.072$, $I = 1.423$, $J = 126.6$, $K = 126.3$, $L = 122.9$, $M = 121.0$, $N = 114.7$, $O = 115.4$, $P = 122.1$, $Q = 122.2$, $a = 1.141$, $g = 180.0$

Table XII (Continued)

Silyl; Energy = −442.705 05

$A = 1.330, B = 1.479, C = 1.321, D = 1.073, E = 1.073, F = 1.075, G = 1.076, H = 1.080, I = 1.863, J = 127.1, K = 126.4, L = 122.6, M = 121.2, N = 114.9, O = 114.0, P = 118.7, Q = 123.6, a = 1.477, b = 1.477, g = 109.1, h = 127.5, m = 0.0, n = 126.2$

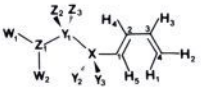
Methyl; Energy = −192.876 83

$A = 1.321, B = 1.478, C = 1.321, D = 1.073, E = 1.073, F = 1.075, G = 1.076, H = 1.076, I = 1.508, J = 126.7, K = 127.2, L = 122.8, M = 121.2, N = 114.4, O = 114.8, P = 120.1, Q = 124.3, a = 1.083, b = 1.086, g = 111.2, h = 126.8, m = 0.08\ n = 126.3$

Fluoro; Energy = −252.372 64

$A = 1.310, B = 1.472, C = 1.320, D = 1.073, E = 1.072, F = 1.074, G = 1.072, H = 1.067, I = 1.364, J = 125.8, K = 127.4, L = 123.1, M = 121.0, N = 114.3, O = 116.8, P = 126.2, Q = 121.4$

[a] Energies in hartrees. [b] Skeletal parameters. Bond lengths in angstroms: $A = C_1C_2$; $B = C_2C_3$; $C = C_3C_4$; $D = C_4H_1$; $E = C_4H_2$; $F = C_3H_3$; $G = C_2H_4$; $H = C_1H_5$; $I = C_1X$. Angles in degrees: $J = C_1C_2C_3$, $K = C_{23}C_4$; $L = C_3C_4H_1$; $M = C_3C_4H_2$; $N = C_2C_3H_3$; $O = C_3C_2H_4$; $P = C_2C_1H_5$; $Q = C_2C_1X$. [c] Substituent parameters. Bond lengths in angstroms: $a = XY_1$; $b = XY_{2(3)}$; $c = Y_1Z_1$; $d = Y_1Z_{2(3)}$; $e = Z_2W_1$; $f = Z_2W_2$. Angles in degrees: $g = C_1XY_1$; $h = C_1XY_{2(3)}$; $i = XY_1Z_1$; $j = XY_1Z_{2(3)}$; $k = Y_1Z_2W_1$; $l = Y_1Z_2W_2$. Dihedral angles in degrees: $m = C_2C_1XY_1$; $n = Y_1XC_1Y_{2(3)}$; $o = C_1XY_1Z_1$; $p = Z_1Y_1XZ_{2(3)}$); $q = XY_1Z_1W_1$; $r = W_1Z_1Y_1W_2$.



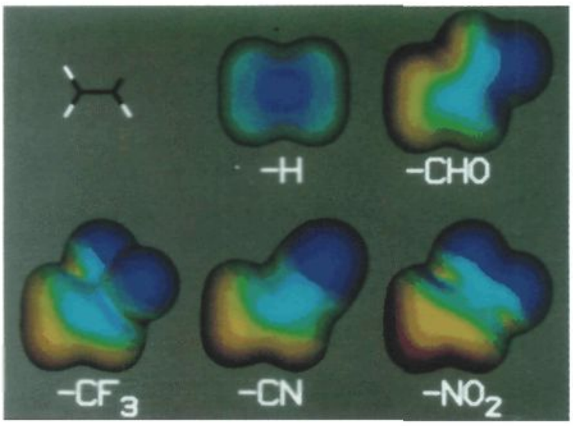


Figure 2. Skeletal framework (top, left) and hydride surfaces for ethylene (top, middle), acrolein (top, right), 3,3,3-trifluoropropene (bottom, left), acrylonitrile (bottom, middle), and nitroethylene (bottom, right). Scale: −11 kcal mol^{-1} (red) to 4 kcal mol^{-1} (blue). 3-21G//3-21G.

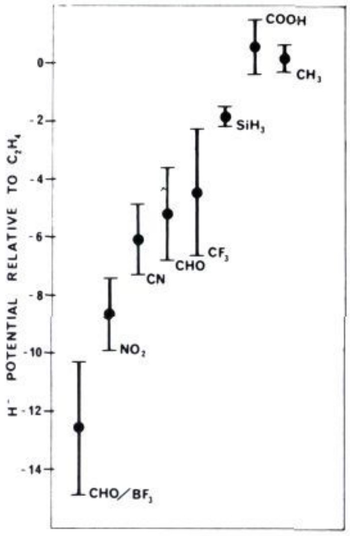


Figure 3. Range of hydride potentials in dienophiles (kcal mol^{-1}). 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for dienophiles incorporating second-row elements).

i.e., activated or deactivated relative to parent butadiene. The correlation between bond averages and diene HOMO energies (also displayed in Figure 4) is not significantly improved over that based instead on atomic electrostatic potentials.

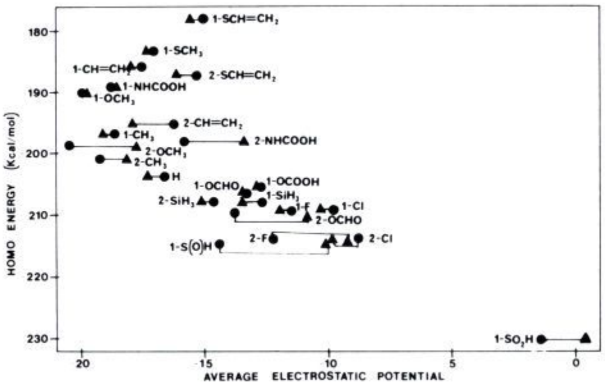


Figure 4. Energy of the highest occupied molecular orbital in monosubstituted dienes (kcal mol^{-1}) vs. maximum atomic electrostatic potential (kcal mol^{-1}) at C_1 or C_4 (●) or maximum of average of atomic electrostatic potentials (kcal mol^{-1}) at C_1 and C_2 or C_3 and C_4 (▲). 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for dienes incorporating second-row elements).

The two averaging procedures also lead to the same assignment of absolute regiochemistry for most dienes considered. There are, however, some differences both in the sizes of the regiochemical preferences and in the ordering of these preferences. These may be significant in attempts to reproduce the known regiochemistry of dienes with more than a single substituent (see discussion following) and *eventually to predict product distributions in Diels–Alder reactions involving complex dienes*. Averages based on the terminal positions alone are generally numerically larger and differences to other systems are generally greater than those which consider instead terminal "bonds". The decision as to which set of average values is probably the more suitable for modeling Diels–Alder regiochemistry requires careful examination of the total potential surfaces. Surfaces for a selection of 1-substituted dienes are provided in Figure 5. These have been constructed in an analogous manner to the hydride potentials shown in Figure 2. In this case, the test electrophile (H^+) lacks electrons and actually "contacts" the substrate surface. According to this model, dienes substituted terminally by OCH_3, $NHCO_2H$, and OCO_2H groups are strong *ortho* regiodirectors. The highly deactivating SO_2H substituent also clearly directs *ortho* but with less of a preference, while the SCH_3 group appears to exhibit only a modest preference for *ortho* regiochemistry. The ordering of directing abilities concluded from visual inspection is properly accounted for in the "bond" averages, i.e.,

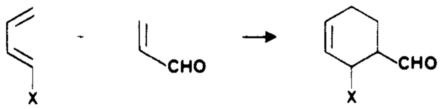
$$NHCO_2H \simeq OCH_3 \simeq OCO_2H > SO_2H > SCH_3$$

while it is not correctly reproduced in full in the tabulation of "atom" averages, i.e.,

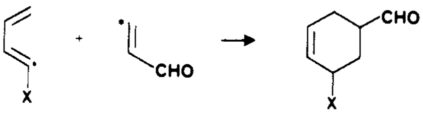
$$NHCO_2H \simeq OCH_3 \simeq OCO_2H > SCH_3 \simeq SO_2H$$

Inspection of the total images for the 2-substituted dienes (Figure 6) perhaps best reveals differences between the two averaging procedures. According to atom averages, a methoxy substituent in the 2-position effects strong regiodirection. The full visual images are better conveyed by the bond-averaged potentials which do not show this large differentiation. Instead, they suggest only a weak influence, i.e., comparable to that noted in 2-(methylthio)butadiene. We, therefore, employ bond-averaged potentials throughout in our discussion of Diels–Alder regiochemistry and, in particular, as a means to assess the ability of reactivity models to order the directing abilities of different substituents. In most cases, the same results would have been reached using potentials based on atomic averages.

The regiochemical preferences for substituted dienes follow from the "atom" or "bond" averages provided in Table VIII. The latter are displayed graphically in Figure 7. On the left are calculated preferences (in kilocalories per mole) for substituents in the 1-position. Following our previous usage, the label "*ortho*" designates greater affinity for electrophiles onto the bond away from the substituent, leading to *ortho* products upon addition with electron-deficient dienophiles,



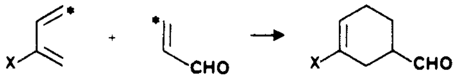
and the label "*meta*" designates a greater affinity for the bond to which the substituent is attached, leading to *meta* addition products,



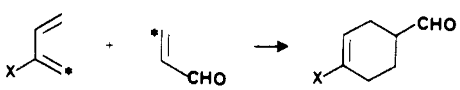
The * denotes the position (bond) of highest electrophilic reactivity in the dienophile.

Regiochemical assignments following from these data for the same set of monosubstituted dienes previously considered in our assessment of the FMO model are provided in Table IV. Except for hexatriene and 1-(phenylthio)butadiene, the reactivity models successfully assign the known *ortho* regiochemistry of all 1-substituted dienes. This includes dienes substituted by phenyl and trimethylsilyl groups, the first of which was incorrectly assigned by FMO arguments to be a *meta* regiodirector, and the second of which was suggested to exhibit no appreciable regiochemical preference. (The phenyl substituent has been modeled by a perpendicular vinyl group. The molecule no longer possesses a plane of symmetry, and average potentials for the face in which the vinyl group is above the diene skeleton (used here) are necessarily different from those in which the model substituent is below.) Dimerization of hexatriene is incorrectly indicated by the reactivity models to lead preferentially to *meta* products, while Diels–Alder additions involving (1-(phenylthio)butadiene are suggested to exhibit no significant preferences for one regioisomer over the other.

Preferences arising from substitution at the 2-position are shown on the right-hand-side of Figure 7. Here also, the label "*meta*" designates *meta* products upon addition to electron-deficient dienophiles, meaning a polarization of the electrostatic potential away from the substituent,



while the label "*para*" indicates formation of *para* products, from polarization of the diene potential toward the substituent.



The reactivity models are generally successful in assigning preferred regiochemistry in these systems where electron-donating substituents are involved. In particular, the observed *para* regiochemistry of dienes substituted in the 2-position by methoxy, methyl, and phenylthio groups is properly accounted for (as it also is in the FMO approach). Note, however, that the *para*-directing effect of phenyl, triethylsilyl, and chloro substituents at this position are not reproduced. *Meta* products are suggested for the first two, while the analysis for 2-chlorobutadiene shows no regiochemical preference.

In conclusion, the reactivity models properly account for the observed regiochemistry of Diels–Alder cycloadditions for the majority of monosubstituted dienes dealt with here. In particular, they generally succeed for dienes substituted in both 1- and 2-positions, in contrast to the performance of the FMO model, which fails to properly account for the regiochemistry in the latter class of compounds.

Assignment of the regiochemistry of disubstituted dienes from the theoretical data on monosubstituted systems requires the assumption that *substituent effects on electrostatic potentials are additive*. (This assumption is discussed further in the Appendix to this paper). This is, or course, strictly analogous to the assumption of the additivity of coefficient sizes made in the application of FMO theory to the problem. A comparison of experimental and theoretical results is provided in Table VI (for the same set of disubstituted dienes previously considered in assessment of the FMO model).

With a single exception, involving competition between phenylthio and acetoxy groups, the reactivity models properly account for the observed regiochemistry of all 1,4-disubstituted dienes examined here. This particular case was also improperly described by the FMO treatment, as was the competition between methyl and phenyl substituents which is dealt with correctly here. The series of dienes involving the $NHCO_2R$ functionality on one end are all indicated by the reactivity models to yield adducts in which the acylamino substituent is *ortho* to the electron-withdrawing group on the dienophile, consistent with experiment. The predicted ordering of regioselectivity for 4-substituted diene carbamates

$$S(O)Ph > SPh > CH_3 > SO_2Ph$$

follows from the decreasing (*ortho*) regiodirecting abilities of SO_2Ph, CH_3, and SPh substituents, and from the fact that the S(O)Ph group is indicated by the models to be a *meta* regiodirector. Thus, it enhances, rather than detracts from, the *ortho*-directing effect of the acylamino group.

Note, that the butadiene sulfoxide no longer possesses a plane of symmetry irrespective of its conformation. As indicated by the averages in Table VIII and pictorially in Figure 8, the two diene faces exhibit significantly different reactivity and in fact different regiochemical preferences. The more reactive face, with the oxygen atom above the diene plane and the sulfur lone pair behind, directs *meta* regiochemistry. The opposite face is indicated to be strongly *ortho* regiodirecting. Efforts directed at the modeling of facial stereoselectivity in Diels–Alder cycloadditions are in progress, and will be dealt with in future papers.

Only a few examples of competition involving substituents on internal diene positions have been experimentally examined. The reactivity models properly assign the directing ability of the phenylthio group to be greater than that of a methoxy substituent. As previously indicated, the FMO analysis leads to the opposite result.[16] On the other hand, the reactivity models fail to rank both internal phenyl and chloro substituents as better regiodirectors than internal methyl.

It is in the comparison of terminal and internal diene substituents that the performance of the reactivity models and FMO treatment differs most markedly. As previously commented, the simpler frontier analyses consistently favor direction by the substituent in the 2-position, while the experimental data for all systems considered here lead to the opposite conclusion. Even strong electron-donor substituents, e.g., OMe and $NHCOCCl_3$, at the 2-position are dominated by relatively "weak" groups, e.g., alkyl, at the 1-position. The reactivity models fare well and properly assign the observed regioproduct for all but one of the systems considered, i.e., involving competition between 1-SPh and 2-OMe groups. Particularly important are the competitions in-

Table XIII. Structure of Data for 2-Substituted Butadienes Optimized at 3-21G and 3-21G(*)[a-c]

Methoxy; Energy = −267.310 76

$A = 1.321$, $B = 1.478$, $C = 1.317$, $D = 1.073$, $E = 1.072$, $F = 1.072$, $G = 1.070$, $H = 1.069$, $I = 1.376$, $J = 126.1$, $K = 126.7$, $L = 123.0$, $M = 120.8$, $N = 112.7$, $O = 122.9$, $P = 120.6$, $Q = 108.8$, $a = 1.434$, $c = 1.078$, $d = 1.083$, $g = 120.1$, $i = 105.8$, $j = 111.1$, $m = 0.0$, $o = 180.0$, $p = 119.1$

Methylthio; Energy = −588.538 61

$A = 1.322$, $B = 1.489$, $C = 1.318$, $D = 1.072$, $E = 1.073$, $F = 1.075$, $G = 1.070$, $H = 1.072$, $I = 1.776$, $J = 124.5$, $K = 126.3$, $L = 123.1$, $M = 120.7$, $N = 115.0$, $O = 123.0$, $P = 121.1$, $Q = 110.6$, $a = 1.806$, $c = 1.082$, $d = 1.081$, $g = 103.6$, $i = 106.6$, $j = 111.2$, $m = 0.0$, $o = 180.0$, $p = 118.5$

Formylamino; Energy = −395.353 75

$A = 1.325$, $B = 1.486$, $C = 1.319$, $D = 1.072$, $E = 1.073$, $F = 1.064$, $G = 1.072$, $H = 1.068$, $I = 1.421$, $J = 123.3$, $K = 125.0$, $L = 123.9$, $M = 120.2$, $N = 115.4$, $O = 122.0$, $P = 121.6$, $Q = 119.5$, $a = 1.354$, $b = 1.001$, $c = 1.356$, $d = 1.211$, $e = 0.967$, $g = 135.1$, $h = 114.0$, $i = 114.9$, $j = 123.7$, $k = 110.2$, $m = 180.0$, $n = 180.0$, $o = 0.0$, $p = 180.0$, $q = 180.0$

Formate; Energy = −340.603 33

$A = 1.316$, $B = 1.475$, $C = 1.318$, $D = 1.073$, $E = 1.072$, $F = 1.072$, $G = 1.065$, $H = 1.070$, $I = 1.409$, $J = 127.7$, $K = 126.2$, $L = 123.0$, $M = 120.8$, $N = 113.3$, $O = 122.2$, $P = 119.5$, $Q = 107.8$, $a = 1.349$, $c = 1.198$, $d = 1.075$, $g = 127.8$, $i = 126.6$, $j = 108.5$, $m = 0.0$, $o = 0.0$, $p = 180.0$

Carboxylic Acid; Energy = −340.623 25

$A = 1.322$, $B = 1.478$, $C = 1.318$, $D = 1.073$, $E = 1.072$, $F = 1.072$, $G = 1.069$, $H = 1.072$, $I = 1.484$, $J = 126.5$, $K = 126.2$, $L = 123.2$, $M = 120.8$, $N = 114.0$, $O = 120.9$, $P = 121.7$, $Q = 113.7$, $a = 1.356$, $b = 1.206$, $c = 0.968$, $g = 113.3$, $h = 125.1$, $i = 111.5$, $m = 0.0$, $n = 180.0$, $o = 180.0$

Vinyl; Energy = −230.506 68

$A = 1.327$, $B = 1.487$, $C = 1.320$, $D = 1.072$, $E = 1.073$, $F = 1.071$, $G = 1.073$, $H = 1.071$, $I = 1.483$, $J = 123.1$, $K = 126.5$, $L = 123.2$, $M = 120.9$, $N = 115.6$, $O = 121.2$, $P = 122.8$, $Q = 118.5$, $a = 1.320$, $b = 1.075$, $c = 1.073$, $d = 1.071$, $g = 127.9$, $h = 113.8$, $i = 120.6$, $j = 123.7$, $m = 180.0$, $n = 180.0$, $o = 180.0$, $p = 180.0$

Vinyl; Energy = −230.505 83

$A = 1.324$, $B = 1.488$, $C = 1.319$, $D = 1.073$, $E = 1.073$, $F = 1.075$, $G = 1.072$, $H = 1.072$, $I = 1.488$, $J = 124.3$, $K = 126.9$, $L = 122.9$, $M = 121.0$, $N = 114.5$, $O = 121.1$, $P = 122.4$, $Q = 114.4$, $a = 1.318$, $b = 1.077$, $c = 1.073$, $d = 1.074$, $g = 124.9$, $h = 115.3$, $i = 121.7$, $j = 121.6$, $m = 44.7$, $n = 180.0$, $o = 180.0$, $p = 180.0$

Vinyl; Energy = −230.500 92

$A = 1.327$, $B = 1.487$, $C = 1.320$, $D = 1.072$, $E = 1.073$, $F = 1.071$, $G = 1.073$, $H = 1.071$, $I = 1.483$, $J = 123.1$, $K = 126.5$, $L = 123.2$, $M = 120.9$, $N = 115.6$, $O = 121.2$, $P = 122.8$, Q 118.5, $a = 1.320$, $b = 1.075$, $c = 1.073$, $d = 1.071$, $g = 127.9$, $h = 113.8$, $i = 120.6$, $j = 123.7$, $m = 90.0$, $n = 180.0$, $o = 180.0$, $p = 180.0$

Vinylthio; Energy = −626.167 90

$A = 1.320$, $B = 1.487$, $C = 1.318$, $D = 1.072$, $E = 1.072$, $F = 1.075$, $G = 1.070$, $H = 1.072$, $I = 1.783$, $J = 124.8$, $K = 126.3$, $L = 123.0$, $M = 120.8$, $N = 115.0$, $O = 122.5$, $P = 121.1$, $Q = 110.7$, $a = 1.769$, $c = 1.316$, $d = 1.074$, $e = 1.074$, $f = 1.073$, $g = 103.0$, $i = 122.6$, $j = 116.3$, $k = 121.1$, $l = 121.8$, $m = 180.0$, $o = 110.2$, $p = 180.0$, $q = 180.0$, $r = 180.0$

Vinylthio; Energy = −626.164 29

$A = 1.320$, $B = 1.490$, $C = 1.318$, $D = 1.072$, $E = 1.072$, $F = 1.075$, $G = 1.069$, $H = 1.072$, $I = 1.781$, $J = 124.0$, $K = 126.3$, $L = 123.2$, $M = 120.7$, $N = 115.0$, $O = 123.8$, $P = 120.7$, $Q = 109.2$, $a = 1.760$, $c = 1.317$, $d = 1.069$, $e = 1.072$, $f = 1.074$, $g = 106.5$, $i = 122.3$, $j = 117.4$, $k = 120.7$, $l = 122.6$, $m = 180.0$, $o = 180.0$, $p = 180.0$, $q = 180.0$, $r = 180.0$

Chloro; Energy = −610.876 29

$A = 1.315$, $B = 1.477$, $C = 1.319$, $D = 1.073$, $E = 1.072$, $F = 1.072$, $G = 1.070$, $H = 1.072$, $I = 1.765$, $J = 127.6$, $K = 125.5$, $L = 123.1$, $M = 120.7$, $N = 114.8$, $O = 121.9$, $P = 120.8$, $Q = 113.4$

Trifluoromethyl; Energy = −487.869 98

$A = 1.317$, $B = 1.476$, $C = 1.317$, $D = 1.073$, $E = 1.072$, $F = 1.073$, $G = 1.070$, $H = 1.071$, $I = 1.490$, $J = 127.3$, $K = 126.1$, $L = 123.1$, $M = 120.8$, $N = 114.8$, $O = 121.2$, $P = 121.8$, $Q = 113.1$, $a = 1.348$, $b = 1.354$, $g = 113.0$, $h = 111.3$, $m = 0.0$, $n = 121.1$

Cyano; Energy = −245.271 17

$A = 1.325$, $B = 1.486$, $C = 1.318$, $D = 1.073$, $E = 1.072$, $F = 1.073$, $G = 1.071$, $H = 1.071$, $I = 1.436$, $J = 126.0$, $K = 125.9$, $L = 123.2$, $M = 120.8$, $N = 114.6$, $O = 115.0$, $P = 121.7$, $Q = 121.4$, $a = 1.140$, $g = 180.0$

Silyl; Energy = −442.700 73

$A = 1.329$, $B = 1.494$, $C = 1.320$, $D = 1.073$, $E = 1.073$, $F = 1.077$, $G = 1.074$, $H = 1.075$, $I = 1.877$, $J = 123.2$, $K = 127.0$, $L = 122.9$, $M = 121.1$, $N = 115.1$, $O = 117.0$, $P = 122.9$, $Q = 121.9$, $a = 1.475$, $b = 1.477$, $g = 109.2$, $h = 126.6$, $m = 0.0$, $n = 126.2$

Methyl; Energy = −192.875 72

$A = 1.321$, $B = 1.487$, $C = 1.319$, $D = 1.073$, $E = 1.073$, $F = 1.076$, $G = 1.073$, $H = 1.073$, $I = 1.518$, $J = 124.1$, $K = 127.1$, $L = 122.8$, $M = 121.1$, $N = 114.5$, $O = 114.3$, $P = 122.6$, $Q = 121.4$, $a = 1.082$, $b = 1.086$, $g = 111.3$, $h = 126.3$, $m = 0.0$, $n = 126.1$

Fluoro; Energy = −252.379 54

$A = 1.310$, $B = 1.466$, $C = 1.317$, $D = 1.073$, $E = 1.072$, $F = 1.072$, $G = 1.070$, $H = 1.068$, $I = 1.368$, $J = 129.2$, $K = 126.2$, $L = 122.8$, $M = 121.0$, $N = 113.4$, $O = 111.3$, $P = 121.1$, $Q = 120.6$

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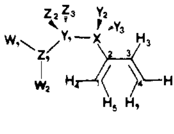
[a] Energies in hartrees. [b] Skeletal parameters. Bond lengths in angstroms: $A = C_1C_2$; $B = C_2C_3$; $C = C_3C_4$; $D = C_4H_1$; $E = C_4H_2$; $F = C_3H_3$; $G = C_1H_4$; $H = C_1H_5$; $I = C_2X$. Angles in degrees: $J = C_1C_2C_3$; $K = C_2C_3C_4$; $L = C_3C_4H_1$; $M = C_3C_4H_2$; $N = C_2C_3H_3$; $O = C_2C_1H_4$; $P = C_2C_1H_5$; $Q = C_3C_2X$. [c] Substituent parameters. Bond lengths in angstroms: $a = XY_1$; $b = XY_{2(3)}$; $c = Y_1Z_1$; $d = Y_1Z_{2(3)}$; $e = Z_2W_1$; $f = Z_2W_2$. Angles in $l = Y_1Z_2W_2$. Dihedral angles in degrees: $m = C_1C_2XY_1$; $n = Y_1XC_2Y_{2(3)}$; $o = C_2XY_1Z_1$; $p = Z_1Y_1XZ_{2(3)}$; q v $XY_1Z_1W_1$; $r = W_1Z_1Y_1W_2$.



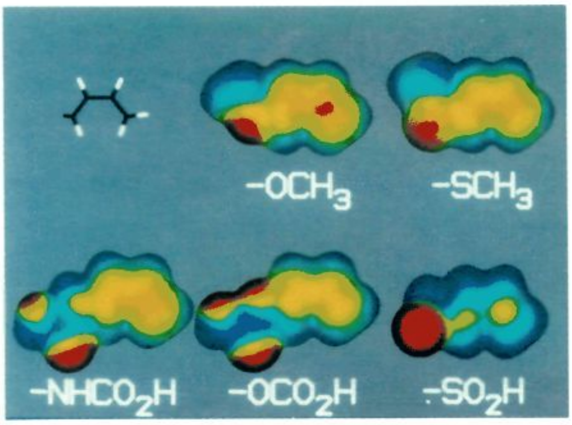


Figure 5. Skeletal framework (top, left) and electrostatic potentials for *cis*-1,3-butadiene substituted in the 1-position by OCH_3 (top, middle), SCH_3 (top, right), $NHCO_2H$ (bottom, left), OCO_2H (bottom, middle), and SO_2H (bottom, right) groups. Scale: -25 kcal mol^{-1} (red) to 20 kcal mol^{-1} (blue). 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for dienes incorporating second-row elements).

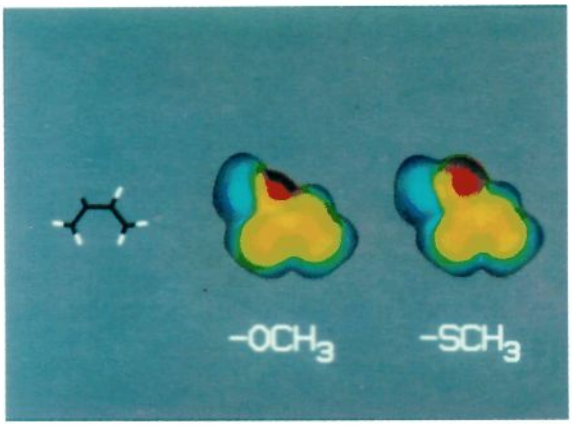


Figure 6. Skeletal framework (left) and electrostatic potentials for 2-methoxybutadiene (middle) and 2-(methylthio)butadiene (right). Scale: -25 kcal mol^{-1} (red) to 20 kcal mol^{-1} (blue). 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for 2-(methylthio)butadiene).

volving the same substituent at different diene positions; the reactivity models properly reproduce the experimental observation that both methyl and phenyl substituents on terminal diene positions are more effective regiodirectors than the same groups substituted internally. As previously indicated, the FMO analysis reaches the incorrect result in both cases. Perhaps most impressive is the case of cycloaddition to 2-ethoxy-1-methylbutadiene, where both experiment and the reactivity models show the directing effect of the methyl group on a terminal position to overide that of an internal ethoxy substituent. The analysis also properly accounts for the fact that a methyl group substituted terminally is a better regiodirector than either chlorine or phenyl substituted internally. Here too, the FMO model leads to the opposite conclusions.

Conclusion

The results presented in this paper point to deficiencies in frontier molecular orbital analysis as a means of assigning regiochemistry in Diels–Alder cycloadditions. In particular, they point to the inability of the FMO model to reliably order the relative directing abilities of closely related substituents or of the same substituent at different diene positions. An alternative approach, involving the matching of surfaces representing the attraction of model electrophiles to dienes and those describing attraction of model nucleophiles to dienophiles (for the case of "normal" Diels–Alder cycloadditions), is proposed. Such a procedure, albeit based on the same underlying theoretical principals, is much more successful than the simple frontier molecular orbital approach in reproducing subtle differences between the directing abilities of similar substituents. In particular, the models appear to succeed in two areas where FMO analyses fail, in ordering substituent effects on regiochemistry and in elucidating relative directing effects as a function of position (terminal or internal) of substitution.

A number of other important issues remain for future study. These include the investigation of the regiochemistry of Diels–Alder cycloadditions of electron-deficient dienes to electron-rich

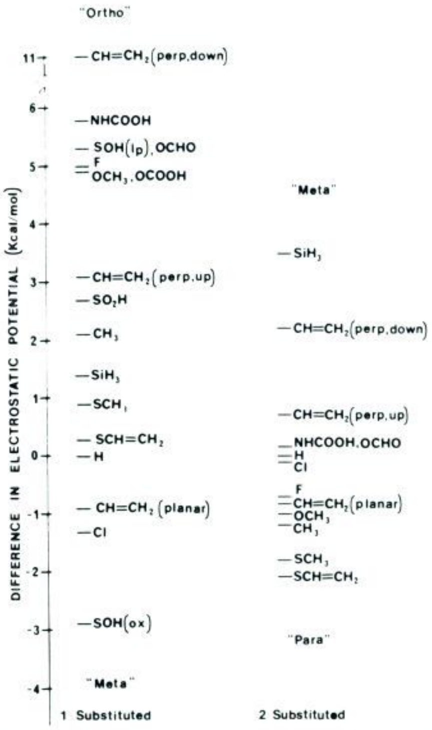


Figure 7. Differences in electrostatic potentials for terminal "bonds" in monosubstituted butadienes. 1-Substituted butadienes (left) where the label *ortho* designates a more negative potential away from the substituent and *meta* a more negative potential toward the substituent. 2-Substituted dienes (right) where the label *meta* designates a more negative potential away from the substituent and *para* a more negative potential toward the substituent. Labels lp and ox indicate electrostatic potentials from the side of the sulfur lone pair and oxygen, respectively. 3-21G//3-21G (3-21G$^{(*)}$//3-21G$^{(*)}$ for dienes incorporating second-row elements).

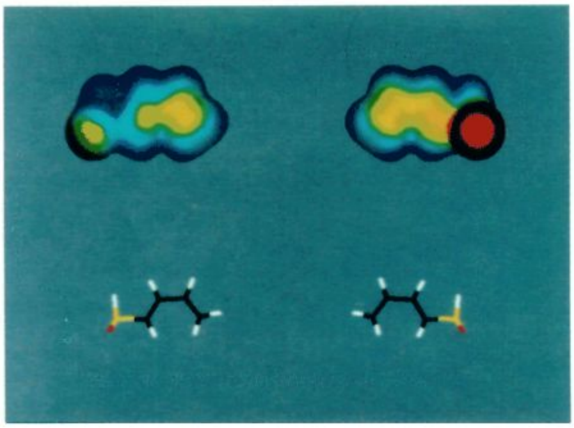


Figure 8. Electrostatic potentials for diastereotopic faces of *cis*-1,3-butadiene substituted in the 1-position by an SOH group. Oxygen "down" (left) and oxygen "up" (right). Skeletal frameworks are underneath. Scale -20 kcal mol^{-1} (red) to 20 kcal mol^{-1} (blue). 3-21G$^{(*)}$//3-21G$^{(*)}$.

dienophiles, of reactions where both diene and dienophile are electron rich or electron poor, and more generally of the regiochemistry of Diels–Alder-like processes, e.g., 1,3-dipolar cycloadditions. Also of interest will be the further scrutiny of the effects of conformation on regiochemistry and the application of modeling procedures to the stereochemistry of Diels–Alder and related cycloadditions, including both facial stereoselectivity (as illustrated in this paper for cycloaddition to butadiene sulfoxide) and to *endo*/*exo* stereoselectivity.

Acknowledgment. This research was supported in part by a grant from the National Science Foundation (CHE-8203366).

Appendix

Theoretical Methods. Quantum-mechanical calculations reported in this paper are at the single-determinant (Hartree–Fock) level, using the 3-21G split-valence basis set for first-row elements[11] and the supplemented 3-21G$^{(*)}$ representation for second-row elements.[12] Optimum equilibrium geometries have been employed and are provided. The GAUSSIAN 85 program system[23] has been utilized.

Electrostatic and hydride potentials have been superimposed onto calculated electron-density surfaces corresponding to ψ^2 = 0.002 electron/bohr^3.[21] The electrostatic energy comprises a repulsive component, E^{nn}, describing the interaction between the nuclei on the reagent and substrate, and an attractive term, E^{en}, accounting for interaction of the substrate electron distribution with the reagent nucleus.

$$E = E^{\mathrm{nn}} + E^{\mathrm{en}} \tag{4}$$

$$E^{\mathrm{nn}} = \sum_{\mathrm{A}}^{\mathrm{substrate}} \frac{Z_{\mathrm{A}}}{R_{\mathrm{AX}}} \tag{5}$$

$$E^{\mathrm{nn}} = \sum_{\mu<}^{\mathrm{substrate}} \sum_{\nu} P_{\mu\nu} \int \phi_{\mu}^{*}(1) \left[\frac{1}{r_{1\mathrm{x}}} \right] \phi_{\nu}(1)\, \mathrm{d}\tau_1 \tag{6}$$

Here, the summation which makes up E^{nn} is carried out over all nuclei A in the sustrate molecule. Z_{A} are the atomic charges (atomic numbers) of the nuclei and R_{AX} are the distances between these nuclei and the test reagent, X. The latter is assumed to be a proton, i.e., $Z_{\mathrm{X}} = 1$. The double summation which makes up E^{en} is over the N atomic orbitals, ϕ, which comprise the basis set describing the substrate. $P_{\mu\nu}{}^{\mathrm{substrate}}$ are elements on the one-electron density matrix,

$$P_{\mu\nu}{}^{\mathrm{substrate}} = 2\sum_{i}^{\mathrm{occ}} c_{\mu i} c_{\nu i} \tag{7}$$

where the summation is carried out over all occupied molecular orbitals, ψ_i.

$$\psi_i = \sum_{\mu}^{N} c_{\mu i} \phi_{\mu} \tag{8}$$

The multiplicative factor of 2 indicates double occupancy of molecular orbitals.

The integrals in eq 6 are over the coordinates of a single electron (labeled 1), and the quantity $r_{1\mathrm{x}}$ is the distance between this electron and the nucleus of the reagent.

Evaluation of the energy of interaction of hydride anion (the test nucleophile) or any other atomic reagent aside from proton with a substrate charge distribution is complicated by terms describing interaction of reagent's electron distribution with the nuclei and electrons of the substrate, E^{ne} and E^{ee}, respectively, in addition to those involving the reagent nucleus.

$$E = E^{\mathrm{nn}} + E^{\mathrm{en}} + E^{\mathrm{ne}} + E^{\mathrm{ee}} \tag{9}$$

$$E^{\mathrm{ne}} = \sum_{\lambda<}^{\mathrm{reagent}} \sum_{\sigma} P_{\lambda\sigma}{}^{\mathrm{reagent}} \int \phi^{*}{}_{\lambda}(1) \left[\sum_{\mathrm{A}}^{\mathrm{substrate}} \frac{Z_{\mathrm{A}}}{r_{1\mathrm{A}}} \right] \phi_{\sigma}(1)\, \mathrm{d}\tau_1 \tag{10}$$

$$E^{\mathrm{ee}} = \sum_{\mu<}^{\mathrm{substrate}} \sum_{\nu} \sum_{\lambda<}^{\mathrm{reagent}} \sum_{\sigma} P_{\mu\nu}{}^{\mathrm{substrate}} P_{\lambda\sigma}{}^{\mathrm{reagent}}$$

$$\int\int \phi^{*}{}_{\mu}(1)\phi_{\nu}(1) \left[\frac{1}{r_{12}} \right] \phi^{*}{}_{\lambda}(2)\phi_{\sigma}(2)\, \mathrm{d}\tau_1\, \mathrm{d}\tau_2 \tag{11}$$

The summations λ,σ are over atomic orbitals on the reagent and the density matrix elements, $P_{\lambda\sigma}{}^{\mathrm{reagent}}$, are defined analogously to those for the substrate. The integrals in eq 10 are over the coordinates of a single electron associated with the reagent; the incorporated operator involves summation over all nuclei on the substrate, and the distances $r_{1\mathrm{A}}$ separate these nuclei from the electron positions on the reagent. The integrals in eq 11 involve simultaneously the coordinates of electron 1 (associated with the substrate charge distribution) and electron 2 (associated with the reagent charge distribution); r_{12} is the distance separating the two electrons.

Because of the need to explicitly consider electron–electron repulsion, evaluation of the energy for interaction of hydride with a substrate is significantly more costly computationally than calculation of the corresponding energy for proton as a reagent.

Atomic averages, constructed from the overall potential surfaces, are based on a sampling of only a limited region around each nucleus, specifically that inside a circle of radius 0.5 Å projected onto the density surface. The individual energies comprising the average are weighted according to the cosine of the angle between the surface normal and the vieweing direction (directly onto the plane of the olefin or diene). Thus, surface regions which are directly "in front" of an approaching reagent contribute more to the average than those which are to the side.

Additivity Hypothesis in Application of FMO and Reactivity Models to the Analysis of Regiochemistry. The usual application of FMO theory to the evaluation of the relative directing abilities of different substituents (and hence the description of regioselectivity in Diels–Alder additions involving complex dienes) involves the assumption that orbital coefficients in polyfunctionalized dienes (or dienophiles) follow additively from data on the corresponding monosubstituted systems.[24] A test of this hypothesis is provided in Table IX. The results are not encouraging. While calculations (STO-3G level[25]) on the disubstituted system indicate an equal directing effect for methoxy and acylamino groups attached 1,4 in butadiene, a strong preference (in favor of methoxy) follows from additivity. The situation is the opposite for competition between methylthio and acylamino groups attached 1,4 in butadiene. The HOMO coefficients in the disubstituted system clearly show the former group to be in control of regiochemistry, while additivity suggests instead that they exert comparable influence. Only for one of the three disubstituted systems tabulated, involving competition between methoxy and methylthio groups, are the results obtained from additivity in qualitative accord with those from direct calculation. The apparent lack of additivity of molecular orbital coefficients may be due in part to the low level of theory employed here to test the hypothesis. While the magnitudes of frontier coefficient differences are sensitive to theoretical level (see appendix following), it is not clear what effects, if any, improvements in the basis set would have.

On the other hand, the data in Table IX show that average electrostatic potentials in these same systems are approximately additive. Neither the direction nor the ordering of regiochemical preferences among the three systems is affected.

In summary, while the assumption of additivity of orbital coefficients does not appear to be valid in all cases (making

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(23) Hout, R. F., Jr.; Francl, M. M.; Kahn, S. D.; Dobbs, K. D.; Blurock, E. S.; Pietro, W. J.; DeFrees, D. J.; Pollack, S. K.; Levi, B. A.; Steckler, R.; Hehre, W. J. *Quantum Chemistry Program Exchange*, Indiana University, Bloomington, IN, to be submitted.

(24) This assumption is the basis for a computer synthesis program.[9] However, several investigators[2] have performed calculations on polysubstituted dienes.

(25) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657. (b) Hehre, W. J.; Ditchfield, R.; Stewart, R. F.; Pople, J. A. *Ibid.* **1970**, *52*, 2769.

application of the FMO model to polyfunctionalized dienes tedious), electrostatic potentials do appear to behave in an additive manner, greatly facilitating their application to complex systems.

Dependence of FMO and Reactivity Models on Theoretical Level. As commented previously, the FMO model is known to be sensitive to theoretical level. An example, provided in Table X, compares HOMO coefficients for dienes substituted in the 1-position by strong electron-donating groups, obtained from STO-3G[25] and 3-21G[11] (3-21G$^{(*)}$[12]) calculations. Comparison with STO-3G is particularly appropriate; all semiempirical molecular orbital methods in common use, e.g., CNDO, INDO, and MINDO, are developed around Slater-type minimal basis sets.

Note from the data that, while the underlying polarization of the diene HOMO toward C_4 maintains, irrespective of level, both the absolute size of the effect and the ordering among the different substituents is altered significantly in going from the minimal basis set (STO-3G) to split-valence (3-21G) calculations. Unfortunately, higher level treatments, i.e., involving polarization basis sets, are not yet practical in our laboratory for systems of this size, and it is not possible to say with certainty that the results at the 3-21G level represent the limiting behavior of the Hartree–Fock model.

The data in Table X also clearly show that differences in average electrostatic potentials are sensitive to theoretical level. Again, both the magnitudes of the potentials for a given system and the ordering of potentials among related systems are affected. Indeed, the ordering of directing abilities of methoxy and acylamino substituents reverses in going from STO-3G to 3-21G level calculations, while the methylthio group moves from a close to a distant third place, insofar as its directing ability is concerned. While higher level data on these systems are presently unavailable, experience with simpler molecules[5] suggests that average electrostatic and hydride potentials evaluated at the 3-21G level are quite close to those obtained from calculations using the much larger 6-31G* polarization basis set.[26]

Improved Calculation of Proton–Substrate Interaction Energies. The Influence of the Polarization Potential on the Electrostatic Potential. The *electrostatic potential*[27] can be shown to correspond to the first-order correction to the energy of a molecular system perturbed by a point positive charge, i.e.,

$$E^{(1)} = E^{\text{electrostatic}} = \langle \Psi_0 | \hat{H}' | \Psi_0 \rangle \qquad (12)$$

where the Hamiltonian $\hat{H}'$ describes the Coulombic interactions between the test charge and the substrate. The second-order correction to the energy is termed the *polarization potential*[28] and involves contributions from all singly substituted determinants, Ψ_a, where a single electron has been promoted from an occupied molecular orbital in the ground-state (Hartree–Fock) function, Ψ_0, into a virtual orbital.

$$E^{(2)} = E^{\text{polarization}} = \sum_{a \neq 0}^{\text{determinants}} \frac{\langle \Psi_a | \hat{H}' | \Psi_0 \rangle \langle \Psi_0 | \hat{H}' | \Psi_a \rangle}{E_0 - E_a} \qquad (13)$$

The polarization correction to the electrostatic energy allows for redistribution of charge on the substrate. Its consideration presumably provides a more accurate account of the interaction of proton and substrate than available from the electrostatic potential alone.

Results for 1-methoxy-, 1-(acylamino)-, and 1-(methylthio)butadiene (in the form of sums of electrostatic and polarization potentials) are provided in Table XI. Compared to the electrostatic potentials for the same compounds (Table VIII), these data show that the effect of the polarization correction is to direct electrophilic attack toward the position of attachment of the substituent. The overall effect is small and nearly the same for the three systems. For 1-methoxybutadiene, it reduces the preference for electrophilic addition onto the C_3C_4 bond (relative to the C_1C_2 linkage) from 4.9 to 3.7 kcal mol^{-1}; a comparable reduction from 5.8 to 4.3 kcal mol^{-1} is noted for 1-(acylamino)butadiene. The favored site of attack in 1-(methylthio)butadiene is actually reversed (from C_3C_4 to C_1C_2), although results obtained from both electrostatic and the composite potentials show the preference to be very weak.

Calculated Equilibrium Structures for 1- and 2-Substituted *cis*-1,3-Butadiene. Equilibrium structures for dienes substituted at the 1-position are shown in Table XII. These have been obtained at the 3-21G level (3-21G$^{(*)}$ for molecules incorporating second-row elements). Data for 2-substituted dienes are provided in Table XIII.

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(26) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217. (b) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A.; *J. Chem. Phys.* **1982**, *77*, 3654.

(27) For a recent reviews, see: (a) Scrocco, E.; Tomasi, J. *Adv. Quantum Chem.* **1978**, *11*, 115. (b) *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum Press: New York, 1981.

(28) For recent discussions, see: (a) Douglass, C. H.; Weil, D. A.; Charlier, P. A.; Eades, R. A.; Truhlar, D. G.; Dixon, D. A. In *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum Press: New York, 1981. (b) Haymet, A. D. J.; Oxtoby, D. W. *J. Chem. Phys.* **1982**, *77*, 2466.

Communications to the Editor

Modeling Chemical Reactivity. 2. Stereochemistry of Electrophilic Additions to Chiral Allylic Double Bonds

S. D. Kahn, C. F. Pau, and W. J. Hehre*

Department of Chemistry, University of California
Irvine, California 92717

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Electrophilic additions to carbon–carbon double bonds are among the most utilized reactions in modern synthetic chemistry. The control of their stereochemistry is of fundamental concern to rational synthesis design. The stereochemical preferences of compounds incorporating allylic double bonds has attracted considerable interest in the recent literature, and numerous reports of diastereofacial selectivity have appeared.[1]

Here we communicate an approach to the description of the stereochemistry of electrophilic addition in allylic systems,[2] based on a comparison of the relative affinities of the diastereotopic olefin faces toward a test electrophile, in our case a proton. Application follows in three stages: In the first, a surface of constant electron

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