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Models for selectivity in organic reactions

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Abstract: Factors contributing to product selection in organic reactions are analyzed using two different approaches. The first involves consideration only of electrostatic preferences upon initial encounter of reagent and substrate, that is, well in advance of the actual reaction transition state. This model, while computationally very simple and applicable to systems of considerable complexity, is capable only of providing a qualitative account of selectivity preferences. The second approach involves direct evaluation of energy differences for transition states leading to different regio- and stereoproducts, based on well designed and calibrated Hartree-Fock and correlated levels of *ab initio* molecular orbital theory. This is both generally applicable and, subject to the validity of the underlying transition state model, capable of quantitative accuracy, although it is also computationally very demanding and in practice applicable using only the very simplest molecular orbital methods and then only to very simple systems. Examples are provided, among them stereochemistry in electrophilic and nucleophilic additions and regio- and stereochemistry of Diels-Alder cycloadditions. Generalities regarding the factors which infludence product selection in simple organic reactions are discussed.

We are perhaps not far removed from the time when we shall be able to submit the bulk of chemical phenomena to calculation

Joseph Louie Gay-Lussac 1778-1850

To what extent may information from quantitative electronic structure calculations now be used to supplement (or to replace) experimental data? Are calculations now able to provide a quantitative account of product distributions in organic reactions and to assist in the development of qualitative rationale? It is on these questions which we focus at present.

INTRODUCTION: ELECTROSTATIC MODELS FOR PRODUCT SELECTION

In preface to constructing a model to account for observed regio- and stereochemistry in simple organic reactions, it is essential to know where along the reaction coordinate product selection actually occurs. The obvious answer, "at the transition state", may not in all situations, and perhaps even in the majority of situations, be correct. Computational work clearly suggests that transition states are not typically so loosely bound as to permit large scale geometrical reorganization without significant energetic price. This implies that initial product selection necessarily occurs well in advance of the actual transition state, where different stereo- and regioisomers may interconvert with little or no energy barriers.

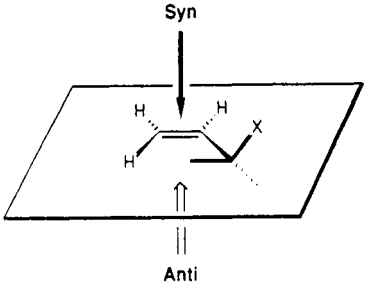
The notion that product selection may occur relatively early in the overall reaction, i.e., well in advance of the transition state and even before reactant geometries have been significantly perturbed, leads to the suggestion that electrostatic forces and not steric effects are the primary factors which influence product selection. Such an hypothesis may be rationalized by examining the form of the usual expression for the (intermolecular) potential energy, equation (1),

$$V = \sum_a \sum_b (A^{ab}/r^{12} - C^{ab}/r^6 + q^a q^b/r) \qquad (1)$$

Here, the summations are carried out over "atoms" on the individual molecules, A and C are Lennard Jones parameters and the q are atomic charges. Note, that while the terms associated with van der Waals (steric) interactions fall off very rapidly (as $1/r^{12}$ and $1/r^6$), electrostatic (Coulombic) interactions fall off at a much slower rate (as $1/r$). Thus, for separations beyond van der Waals contact distances, steric effects are of little consequence and electrostatics may be expected to dominate.

Our early attempts to rationalize the observed stereochemistry of both electrophilic and nucleophilic additions were based on computational investigations of allylic silanes, alcohols and ethers, as model compounds for electrophilic additions to asymmetric olefins (ref. 1), and of vinyl sulfoxides, as model compounds for nucleophilic additions to asymmetric olefins (ref. 2). These investigations led to a set of selection rules (Figure 1), which subsequently proved to be remarkably successful in accounting for observed product distributions in the majority of cases. Detailed analyses have already been published and full discussion is not warranted at this time. Rather, we only summarize the major conclusions. Electrophiles prefer to add from the side of oxygen in allylic alcohols and ethers and from the side away from silicon in allylic silanes. Not unexpectedly, nucleophiles show opposite preferences, avoiding electron-rich areas even at the expense of increased steric crowding.

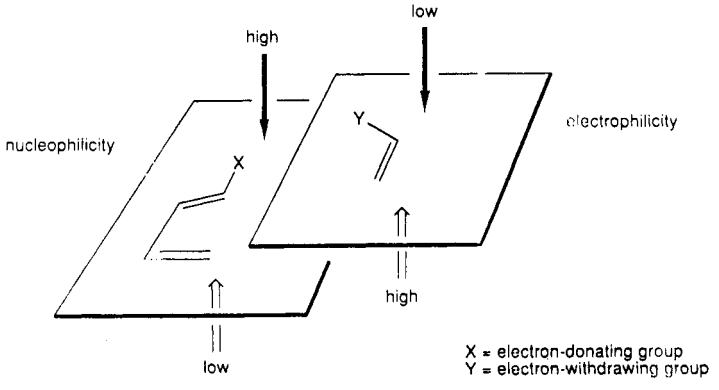
Among the electrophilic processes investigated, two series of reactions which do not appear to be properly described by the electrostatic model are osmium tetraoxide (ref. 3) and permanganate (ref. 4) additions. These common reagents consistently result in products of opposite stereochemistry than those typical of other "electrophiles", for situations both in which the asymmetry in the substrate is due to electron poor and electron rich functionality, e.g.,



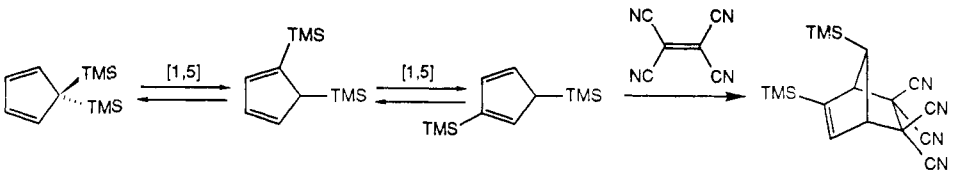
	ELECTROPHILE	NUCLEOPHILE
X=electron rich	syn	anti
X=electron poor	anti	syn

These are perhaps not exceptions. Closer examination suggests that they are consistent with the notion that product selection in this class of reactions is accomplished at a very early stage. At large separations, reagents such as osmium tetraoxide and permanganate do not appear to the substrate as electrophiles but rather as nucleophiles, i.e., they appear as an exposed "ball" of negatively charged oxygens encapsulating a metal of high positive charge. This being the case, the stereochemistry of additions involving osmium tetraoxide and permanganate would be expected on the basis of electrostatics (alone) and is exactly the opposite of that for other "electrophilic reagents". This is exactly what is observed. Of course, other explanations, e.g., differences in steric demands between the substrate faces, may be the true cause of selection in these systems.

The electrostatic selection rules may easily be applied to the elucidation of stereochemistry of more complex processes, i.e., those which may be described as a combination of simple electrophilic or nucleophilic additions. An important example relates to the determination of diastereofacial selectivity in Diels-Alder cycloadditions (refs. 5,6). Within the framework of the simple electrostatic model, the preferred stereoproduct is that in which the more nucleophilic face of an electron-rich diene "adds" to the more electrophilic face of an electron poor dienophile, i.e.,

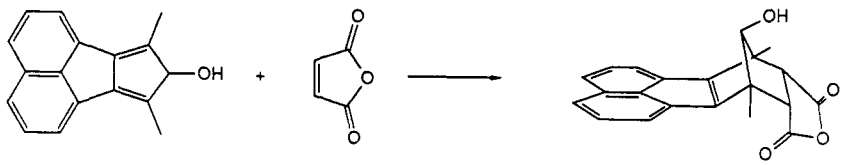


This simple picture is remarkably successful in accounting for the observed facial selectivity in a large variety of Diels-Alder cycloadditions involving both asymmetric dienes and asymmetric dienophiles. While in some cases, electrostatic preferences are identical to those which would have been expected on purely steric grounds, e.g.,



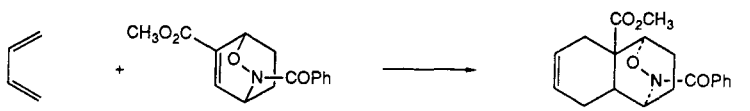
(ref. 7)

in other situations, the simple electrostatic picture properly assigns the dominant stereoproduct as the one which would be expected to be the sterically more crowded, e.g.,



(ref. 8)

There do, however, appear to be important exceptions, and these can aid us in the development of more quantitative models. One particular class are reactions where the product which appears to be favored on purely electrostatic grounds necessarily proceeds through a hindered transition state. For example, cycloaddition of butadiene with methyl N-benzoyl-3-aza-2-oxabicyclo-[2.2.2]oct-5-ene-6-carboxylate proceeds stereoselectively *syn* to the NO bridge (ref. 9),



apparently contrary to electrostatic dictates, but consistent with addition onto the less crowded face of the dienophile. What is clear here is that any successful attempt at quantitative descriptions of actual product distributions will require explicit account of steric effects in addition to electrostatic interactions. Transition state models based on application of quantitative molecular orbital theory provide such an avenue.

TRANSITION STATE MODELS FOR PRODUCT SELECTION

The central hypothesis underlying the use of simple electrostatic models in accounting for product distributions is that the most favorable long-range orientation of reagent and substrate maintains as the reaction proceeds through the transition state. This will certainly not be true in cases with severe steric constraints close to the actual transition state. Here, a more appropriate description of product selectivity involves the use of quantitative levels of molecular orbital theory, in particular, non-empirical or *ab initio* molecular orbital theory. This offers the advantage of generality as well as a complete lack of bias; no preconceived notions about molecular structure and energetics have been incorporated into the formulation of the method. The *ab initio* method has two major disadvantages. For one, *ab initio* procedures are computationally very demanding, although rapid advances both in hardware and software continue to make applications evermore routine. Secondly, interpretation of the results of the quantitative calculations is necessarily more difficult than those of such simple models as described above.

While *ab initio* electronic structure methods are very well documented insofar as their ability to reproduce known structures and relative energies of a wide variety of stable organic molecules (ref. 10), far less experience exists with regard to the properties of reaction transition structures. In part, this is due to a complete lack of experimental data on transition state geometries; calculations must stand entirely on their own here. Another factor contributing to the lack of experience is the accurate perception that transition states are inherently more difficult to locate than are equilibrium structures or stable molecules. For the most part, this is due more to "not knowing what transition states look like" than it is to any technical difficulties.

Lacking experimental data for direct comparison with theory, the best way to provide a level of confidence in the calculations is to seek convergence of results, that is to say, to establish that further improvements either in basis set or in level of treatment of electron correlation would not lead to significant changes. While for systems of the size dealt with here, i.e., transition states for very simple organic reactions, it is not yet practical to closely approach the actual limits of either basis set or electron correlation models, it is perhaps possible to go far enough to permit at least a crude

Table 1. Effect of level of calculation on the absolute activation energy (in kcal/mol) of Diels-Alder cycloaddition of *cis* 1-fluorobutadiene with *trans* acrolein leading to an *endo, ortho* adduct.

HF/3-21G//	HF/6-31G*//3-21G	MP2/6-31G*//
30.2	39.8	8.4

Table 2. Effect of level of calculation on relative activation energies (in kcal/mol) for Diels-Alder cycloaddition of *cis* 1-fluorobutadiene with *trans* acrolein.

stereochemistry of addition	regiochemistry of addition	HF/3-21G//	HF/6-31G*//3-21G	MP2/6-31G*//
endo	*meta*	0.0	0.0	0.0
endo	*ortho*	1.2	1.0	0.2
exo	*meta*	1.0	1.1	1.0
exo	*ortho*	2.3	2.0	1.5

assessment of the effect of further improvements. As seen by the data in Tables 1 and 2, the result of this assessment depends to great extent on the exact quantity of interest. The calculated absolute activation energy for a reaction as simple as the Diels-Alder cycloaddition of *cis* 1-fluorobutadiene with *trans* acrolein leading to a product with *endo* stereochemistry and *ortho* regiochemistry varies widely with level of theory (Table 1). Extension of the basis set from a split-valence to a polarization representation leads to a significant increase in activation energy, while introduction of electron correlation using the MP2 model causes a drastic reduction in activation energy. Certainly, little if any confidence can be placed in even the best of these theoretical models. Fortunately, convergence of energy differences as a function of both stereochemistry and regiochemistry of the transition state for this same reaction appears to be far better (Table 2). Indeed, even the lowest level (Hartree Fock with the split valence 3-21G basis set) calculations reproduce the ordering of stabilities obtained from the highest level calculations (MP2 treatment of electron correlation with the 6-31G* polarization basis set). Note the insensitivity of these relative energy data to basis set. Note also, that introduction of electron correlation has the effect of reducing the range of relative energies. Both of these trends have been observed in numerous other systems which we have examined.

While the "predicted" product of cycloaddition of 1-fluorobutadiene and acrolein has the expected *endo* stereochemistry, it exhibits *meta* rather than *ortho* regiochemistry. Even though "experience" suggests instead a preference for an *ortho* adduct, this result is probably correct. One reason for this is the highly unfavorable dipolar interaction between the *cis* diene and the assumed *trans* conformer of acrolein present in the transition state leading to the *ortho* adduct, and the absence of such an interaction in the transition state leading to the *meta* adduct. Note, that the same arguments suggest that the situation should reverse if the dienophile were to be allowed to react from the higher energy *cis* conformer; here an *ortho* regioproduct would be expected to be preferred. Quantitative (3-21G level) molecular orbital calculations (Table 3) confirm these expectations. Experimental confirmation of the predicted reversal in regiochemistry should be straightforward. Reactions with acrolein should proceed via a *cis* conformer and lead to *ortho* products, while cycloadditions involving instead a dienophile such as cyclopentenone, which is necessarily locked into a *trans* conformation, should result in *meta* products.

There is an important lesson to be learned from this example. It is the inherent complexity of even the simplest chemical transformations, and the need to account explicitly for the possibility that reaction may occur from other than ground state conformations. Implicit is that multiple pathways leading to the same product but through different transition states may need to be considered.

Relative energies for transition states of Diels-Alder cycloadditions of *trans* acrolein with unsubstituted butadiene, as well as with both *cis* 1-methylbutadiene and *cis* 2-methylbutadiene are provided in Table 4. These reactions are devoid of complications encountered previously for cycloadditions involving 1-fluorobutadiene. All reactions proceed preferentially to *endo* stereoproducts in accord with observations on closely-related systems. Note that the relative energies of *endo* and *exo* transition states are similar in all systems (the *exo* transition state is higher in energy than the *endo* by approximately 1 kcal/mol), independent of

Table 3. Relative energies (in kcal/mol) of transition states for Diels-Alder cycloaddition of *cis* 1-fluoro-butadeine with acrolein.[a]

conformation of acrolein	stereochemistry of addition	regiochemistry of addition	relative energy
cis	*exo*	*ortho*	0.0
cis	*endo*	*ortho*	0.3
cis	*exo*	*meta*	1.0
cis	*endo*	*meta*	1.4
trans	*endo*	*meta*	3.3
trans	*exo*	*meta*	4.3
trans	*endo*	*ortho*	4.5
trans	*exo*	*ortho*	5.7

a) 3-21G//3-21G.

Table 4. Relative energies (in kcal/mol) of transition states for Diels-Alder cycloadditions of *cis* 1-methylbutadiene and *cis* 2-methylbutadiene with *trans* acrolein.[a]

diene	stereochemistry of addition	regiochemistry of addition	relative energy
butadiene	*endo*	---	0.0
	exo	---	1.0
1-methylbutadi	*endo*	*ortho*	0.0
	exo	*ortho*	0.5
	endo	*meta*	2.7
	exo	*meta*	3.6
2-methylbutadi	*endo*	*para*	0.0
	endo	*meta*	0.5
	exo	*para*	0.9
	exo	*meta*	1.5

a) 3-21G//3-21G.

regioproduct. This suggests that, whatever its origin, the *endo* preference is insensitive to the details of the diene. Also in agreement with experimental data, cycloaddition of 1-methylbutadiene and acrolein preferentially gives rise to the *ortho* regioproduct, while reaction of 2-methylbutadiene leads to the *para* regioproduct. Finally note, that a terminal methyl substituent is shown by the calculations to be a more effective regiodirector than an internal methyl group. This tendency is also seen in calculations for Diels-Alder reactions involving a variety of other substituents, and is in general accord with experimental experience. Overall then, the *ab initio* calculations do appear to be capable of providing a quantitative, or at least semi quantitative, account of product distributions in very simple Diels-Alder cycloaddition processes. This lends credence to the ability of the theory to properly account for product distributions in those cases where experimental data are incomplete or are lacking altogether.

We conclude our treatment of transition state models by returning to our earlier discussion of assignment and interpretation of diastereofacial selectivity in Diels-Alder cycloadditions. Relative energies for transition states corresponding to *syn* and *anti* adducts of a variety of 5-substituted cyclopentadienes (C_5H_5X, X = CH_3, F, Cl, Br, I, OH, SH, SeH, SiH_3) with ethylene, acrylonitrile and *cis* 1,2-dicyanoethylene, as examples of very weak, moderate and very strong dienophiles, respectively, are provided in Table 5. Only *endo* additions have been considered.

The noted preference for *syn* adducts in reactions of halogen substituted dienes with a given dienophile parallels both the electronegativity of the halogen, F>Cl>Br>I, in accord with electrostatics, and its size, I>Br>Cl>F, in accord with steric dictates. The calculations show a reversal in facial preference; additions of 5-fluorocyclopentadiene and 5-chlorocyclopentadiene are predicted to yield preferentially *syn* adducts, while reactions involving the analogous bromo and iodo compounds are shown to favor *anti* adducts. While there are no experimental data on these particular systems, Kato, Aoyama and Ishida (ref. 11) have observed *anti* facial selectivities in reactions of sulfur and selenium substituted cyclopentadienes (C_5H_5X, X=SPh, SePh) with maleic

Table 5. Relative energies (in kcal/mol) of transition states for Diels-Alder cycloadditions of 5-substituted cyclopentadienes with ethylene, acrylonitrile and *cis* 1,2-dicyanoethylene.[a]

substituent on cyclopentadiene	dienophile		
	ethylene	acrylonitrile	*cis* 1,2-dicyanoethylene
F	8.7	10.6	12.4
Cl	-0.3	1.1	2.2
Br	-1.2	0.3	1.6
I	-5.1	-4.0	-3.1
OH	2.9	5.4	7.7
SH	-3.0	-1.0	-0.3
SeH	-4.8	-2.0	-1.5
CH_3	-2.5	-2.5	-2.5
SiH_3	-7.3	-7.6	-7.8

a) 3-21G//3-21G (3-21G(*)//3-21G(*) for molecules incorporating second-row on heavier main-group elements). Positive quantities indicate preference for *syn* addition.

anhydride, in contrast to the *syn* selectivities seen in additions of the corresponding oxygen systems. Similarly, Fallis and Macaulay (ref. 12) have observed a reversal in preferred stereochemistry of Diels-Alder cycloaddition in going from sulfur substituted pentamethylcyclopentadienes (C_5Me_5X, X=SMe, SOMe) to the corresponding oxygen analogues. Calculations on closely related model reactions (Table 5) show the same pattern; cycloaddition of 5-hydroxycyclopentadiene with acrylonitrile greatly favors formation of a *syn* adduct, whereas reactions of the sulfur and selenium analogues yield preferentially *anti* products.

The key to interpretation of facial selectivities as due either to steric or electrostatic effects (or more reasonably, some combination of the two) lies in establishing the dependence of the selectivity on the strength of the dienophile. It is reasonable to expect that any change in dienophile strength (electrophilicity) will affect only electrostatic demands and not steric requirements. Support for such a notion follows from examination of reactions involving 5-methylcyclopentadiene. Note first, that addition with acrylonitrile occurs preferentially to form an *anti* product consistent with the obvious steric bias, and further that analogous additions involving both weaker and stronger dienophiles (ethylene and *cis* 1,2-dicyanoethylene, respectively) show equal preference for *anti* products. The independence of product distribution on the electrophilicity of the dienophile in this case suggests that steric effects rather than electronic interactions are the cause of the preference. On the other hand, changes in dienophile strength greatly affect the direction and magnitude of the stereoselectivity for additions involving the 5-halocyclopentadienes as well as those involving 5-hydroxycyclopentadiene and its sulfur and selenium analogues. In all cases, increasing the electrophilicity of the dienophile increases the preference for the *syn* adduct. The magnitude of the changes is largest for the most electronegative substituents (F and OH, consistent with the notion that electrostatics play a major role in product selection in these systems. For example, while only 5-fluorocyclopentadiene favors a *syn* adduct in additions involving the very weak dienophile, ethylene, only 5-iodocyclopentadiene is predicted to yield an excess of the sterically favored *anti* stereoisomer for reactions involving the much stronger dienophile, *cis* 1,2-dicyanoethylene.

A very small increase in preference for *anti* products in cycloadditions involving 5-silylcyclopentadiene is noted in going from ethylene to *cis* 1,2-dicyanoethylene. While the direction of the effect here indicates some involvement of electrostatics (favoring the *anti* product), both the small magnitude of the change (0.5 kcal/mol vs. a range of 1.5 to 3.7 kcal/mol for cycloadditions involving the halocyclopentadienes) and the large magnitude of the *anti* preference itself, leads us to believe that the major driving force behind product selection in these systems is steric. Certainly, replacement of the model silyl group by an actual trialkylsilyl substituent would further shift the balance in favor of sterics over electrostatics.

CONCLUDING REMARKS

It is evident that product selection even in very simple organic reactions is influenced both by steric and electrostatic factors. While models designed to take into account one or the other, but not both, influences are likely to prove useful only within a very limited range, they can provide insight needed to develop more quantitative treatments.

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