$W(r,\theta=0°)\cos\theta + W(r,\theta=90°)\sin\theta$. We can evaluate eq 2 as follows

$$K_a = \int_0^{2\pi} d\phi \int_0^{\pi} \int_0^{r_c} e - \frac{W(r,\theta)}{kt} r^2\, dr \sin\theta\, d\theta$$
$$\text{and } \Delta G = -RT \ln K_a$$

With these approximations, $\Delta G = -2.0$ kcal/mol, still in very respectable agreement with the experimental $\Delta G = -2.9$ kcal/mol.

Acknowledgment. The calculations were carried out at the Pittsburgh Supercomputer Center, supported by the National Science Foundation. Research support from the NIH (GM-29072 and NSF (CHE-85-10066) to P.A.K is acknowledged, as is the use of the UCSF computer Graphics Lab, supported by RR-1081 (R. Langridge, P.I.). We thank Allison Howard for providing us coordinates of 18-crown-6, potential parameters, and many useful discussions during the course of this work.

Activation Hardness: New Index for Describing the Orientation of Electrophilic Aromatic Substitution

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Abstract: The *activation hardness* concept is defined and used to predict the orientation of electrophilic aromatic substitution. With the transition state defined much in the manner of Wheland, it is shown that the activation energy is the negative of twice the change in hardness in going from reactant to transition state (called the activation hardness). The smaller the activation hardness is the faster the reaction is; the harder the transition state is the better. Calculations presented show that the activation hardness is an excellent index for predicting orientation effects. Several new principles of maximum hardness or softness are stated and discussed.

I. Introduction

The ultimate goal of quantum chemistry is molecule design. The exploration of chemical reactions is one of the ingredients of which the path to this goal is made. As early as in the 1930's there was devised the absolute rate theory,[1] which is still considered as one of the most sophisticated theories to predict reaction rate. For most practical problems the value of sophisticated theories is limited by their tractabilities. Hence simpler model theories have been developed over the years. A simple reactivity index is attractive not only because it can be easily calculated but also because a simple index can provide general chemical insights. In this paper we define and demonstrate the utility of a new reactivity index.

The molecular orbital theory as formulated by Mulliken and Hund has been very successful in explaining and predicting chemical behaviors for an enormous number of molecules. It was Fukui who first noticed the prominent role played by the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) in governing chemical reactions.[2] The energy difference between the LUMO of an electron acceptor and the HOMO of an electron donor has long been used as a reactivity index.[3] Recent investigations have been revealing that the HOMO–LUMO gap is an important stability index for the individual species concerned.[4–7] A large HOMO–LUMO gap implies high stability. High stability of a molecule reflects its low reactivity toward chemical reactions in some sense.

There exists a semiempirical principle, the hard and soft acids and bases (HSAB) principle, that encapsulates both thermodynamic and kinetic propensities of numerous molecules.[8] The concept of hardness, first emphasized by Pearson as an index of reactivity,[8] was quantified in 1983 by Parr and Pearson.[9] The quantified "absolute hardness" concept has been shown to be useful in chemistry.[4,10–13] For example, for organic molecules the property conventionally called aromaticity has been shown to parallel hardness,[10] and an index called relative hardness has been introduced to distinguish aromatic from antiaromatic species.[11]

In the present paper we show how the hardness concept can be employed to predict the orientation of electrophilic aromatic substitution, a problem area in which there is a large literature.[2,15–25] We introduce the concept of *activation hardness*, and

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we show that it is a good index for orientation of electrophilic aromatic substitution. We also provide a proof within the HMO model for an expanded principle of maximum hardness[10,11] and identify several other extremum principles involving hardness and softness.

II. Principles of Maximum Hardness or Softness

For any chemical system the electronic chemical potential μ and the absolute hardness η are the first and the second derivatives of the electronic energy E with respect to the number of electrons N, respectively.[9,26] Namely

$$\mu = (\partial E/\partial N)_v \tag{1}$$

$$\eta = (\partial^2 E/\partial N^2)_v \tag{2}$$

where v is the external potential due to the nuclei. The finite difference approximations to eqs 1 and 2 are

$$\mu = -(I + A)/2 \tag{3}$$

$$\eta = (I - A)/2 \tag{4}$$

where I is the ionization potential and A is the electron affinity. One recognizes that $-\mu = (I + A)/2$ is the Mulliken electronegativity.[27] Note that both of these formulas are independent of any molecular model. When molecular orbital theory is used, eqs 3 and 4 become

$$\mu = (\epsilon_{\text{LUMO}} + \epsilon_{\text{HOMO}})/2 \tag{5}$$

$$\eta = (\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}})/2 \tag{6}$$

as first pointed out by Pearson.[14] In this paper eqs 5 and 6 are our operational formulas. Softness is the reciprocal of hardness.

In previous papers there was proved a principle of maximum hardness.[10,11] *Relative to its positive and negative ions, a species is more stable the larger is its absolute hardness.* Here we provide a proof in HMO theory for another theorem: *Under the constraint of constant chemical potential, a species is more stable the greater is its absolute hardness.* The proof goes as follows.

The total π energy of a conjugated molecule is

$$E_\pi^{\text{HMO}} = N\alpha + \beta\sum_i x_i \tag{7}$$

where the summation is over all the occupied orbitals, and α is the Coulomb integral, β the resonance integral, and N the number of π electrons (we assume the molecule is neutral here, and there is no difficulty in extending the conclusion to other cases). By eqs 5 and 6, the chemical potential and the absolute hardness for the molecule are

$$\mu = \alpha + \beta(x_{\text{LUMO}} + x_{\text{HOMO}})/2 \tag{8}$$

and

$$\eta = \beta(x_{\text{LUMO}} - x_{\text{HOMO}})/2 \tag{9}$$

respectively. Hence

$$E_\pi^{\text{HMO}} = N\mu + G\beta \tag{10}$$

with

$$G = \sum_i x_i - N(x_{\text{LUMO}} + x_{\text{HOMO}})/2 \geq 0 \tag{11}$$

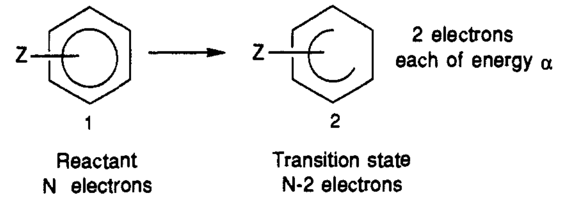

Figure 1. Diagram of reactant to transition state.

Now, given the conjugated molecule the adjacency matrix in the HMO model for the corresponding molecular graph is known. Therefore the eigenspectrum of the adjacency matrix, $\{x_i\}_{i=1}^{N}$, is fixed.[28] Hence for constant chemical potential smaller E_π^{HMO} means larger $|\beta|$ (see eqs 10 and 11). But larger $|\beta|$ implies greater η (see eq 9 and note that both $x_{\text{LUMO}} - x_{\text{HOMO}}$ and β are negative). Therefore, within the Hückel model maximum hardness is equivalent to minimum total energy if the chemical potential is kept constant. The results previously obtained about aromaticity thus constitute no surprise.

Another well-known principle that can be compactly stated in hardness–softness terms is the fundamental tenet in the simple molecular orbital theory of chemical reaction rates: Transfer of electrons from a donor D to an acceptor A is facilitated the closer in energy the HOMO of D is to the LUMO of A.[3] This is an approximation to the more basic principle that it is beneficial for reaction if the energy required to ionize D, its ionization potential I_D, is completely provided by the energy gained by giving an electron to A, its electron affinity, A_A. That is, the smaller $I_D - A_A$ is the better. But this is no more no less than the hardness of the D····A pair before any interaction occurs between D and A:

$$\eta_{\text{D}\cdots\text{A}} = (I_D - A_A)/2 \approx (-\epsilon_{\text{HOMO,D}} + \epsilon_{\text{LUMO,A}})/2 \tag{12}$$

That this is the correct formula for hardness follows from the argument given some time ago,[29] that the electronegativity is the corresponding sum

$$-\mu_{\text{D}\cdots\text{A}} = (I_D + A_A)/2 \tag{13}$$

That is to say: *Transfer of electrons from D to A is faster the smaller the hardness of the D····A pair before interaction is or the greater the softness is.*

The topic of the present paper is something else still, the relation between hardness change of a reacting system as it progresses through a transition state. We consider only electrophilic aromatic substitution.

III. Activation Hardness

In transition-state theory, a stabler transition state signals an easier reaction. The stability of the transition state is measured by the activation energy $\Delta E^{\neq}$. What we wish to examine is whether there exists some hardness principle that benefits a reaction. That this is the case we here demonstrate for electrophilic aromatic substitution. *With an activation hardness suitably defined, the smaller the activation hardness is, the faster the reaction is.*

We introduce a Wheland-like transition state (see **2** in Figure 1).[22] At the transition state, two π electrons of the original π system are separate from the other π electrons. They do not conjugate with the other π electrons, and they are bound to the carbon atom where the substitution will take place. In Hückel theory, each of these two localized electrons has an energy of α; more generally we set the energy of these two electrons equal to $E(2)$, which is yet to be determined.

From density functional theory[30] we have

$$E(N + \delta) = E(N) + \mu_N\delta + \eta_N\delta^2 \tag{14}$$

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in general. For the specific case here (see Figure 1)

$$E(N) = E(N-2) + 2\mu_{N-2} + 4\eta_{N-2} \qquad (15)$$

$$E(N-2) = E(N) - 2\mu_N + 4\eta_N \qquad (16)$$

Hence

$$\begin{aligned} \Delta E^* &= E(N-2) - E(N) + E(2) \\ &= -2(\eta_{N-2} - \eta_N) - (\mu_N + \mu_{N-2}) + E(2) \qquad (17) \end{aligned}$$

Here we make an assumption about these two electrons, namely,

$$\mu_N + \mu_{N-2} = E(2) \qquad (18)$$

This results in

$$\Delta E^* = -2(\eta_{N-2} - \eta_N) = 2\Delta\eta^* \qquad (19)$$

where $\Delta\eta^*$ is the activation hardness.

Equation 18 is an assumption that partly defines the particular transition-state model we are using. Its reasonableness agrees with the idea that reactants and transition state are in equilibrium. One way to imagine the situation is that the pair of electrons with total energy $E(2)$ consists of one in equilibrium with a bath at chemical potential μ_N and another in equilibrium with a bath at chemical potential μ_{N-2}. In fact, numerical calculations show that predictivity of rate is not much affected by details in this assumption.

The second equality in eq 19 defines the activation hardness. Equation 19 can be applied to more general situations than the model transition state we have assumed here. The activation hardness can be calculated at any level of molecular orbital theory. But in the present paper we exclusively use the simplest molecular orbital theory—HMO. The HMO approximation for $\Delta\eta^*$ is

$$\begin{aligned} \Delta\eta^* &= \eta_R - \eta_T \\ &= \beta(x^R_{LUMO} - x^R_{HOMO} - x^T_{LUMO} + x^T_{HOMO})/2 \qquad (20) \end{aligned}$$

where R and T stand for reactant and transition state, respectively.

In the following, we examine the activation hardness $\Delta\eta^*$ as an orientation index for electrophilic aromatic substitution. Figure 2 shows the molecules studied.

IV. Orientation of Electrophilic Aromatic Substitution

From eq 19, minimum change in hardness, $\Delta\eta^*$, is equivalent to minimum ΔE^*. Hence reactions prefer $\Delta\eta^*$ values as small as possible. We test this prediction by calculations by the standard HMO procedure. Parameters for heteroatoms are from ref 31.

Benzenoid Hydrocarbons. Calculated activation hardness values for benzenoid hydrocarbons, along with Hammett's σ^+ constants obtained from the empirical fitting of experimental data and Wheland's cation localization energies L^+, are given in Table I. Figure 3 shows the correlations of $\Delta\eta^*$ and L^+ with σ^+. We see that both $\Delta\eta^*$ and L^+ correlate very well with σ^+.

It can be seen from the $\Delta\eta^*$ values in Table I that the α-position of naphthalene is more reactive than its β-position (compare $\Delta\eta^* = 0.118(-\beta)$ for the α-position with $\Delta\eta^* = 0.255(-\beta)$ for the β-position). For anthracene, position 9 is the most reactive site in the molecule, and position 1 is more reactive than position 2. All these facts are well-known. Predictions for all other molecules except **18** agree reasonably well with experimental results. Fluoranthene (**18**) is the only nonalternant hydrocarbon included in this class because of the availability of its σ^+ values. Predictions for relative reactivity at different positions in this molecule do not agree with experiment. This discrepancy may come from the transition state assumption. According to Brown, the transition state for some reactions may occur early in the reaction.[32] It resembles the reactant. But the Wheland-like transition state here occurs late in the reaction. It resembles the intermediate.

Azulene. $\Delta\eta^*$ values for reactions at different positions in azulene are given in Table II. The predictions for reactive site agree with the experimental facts.

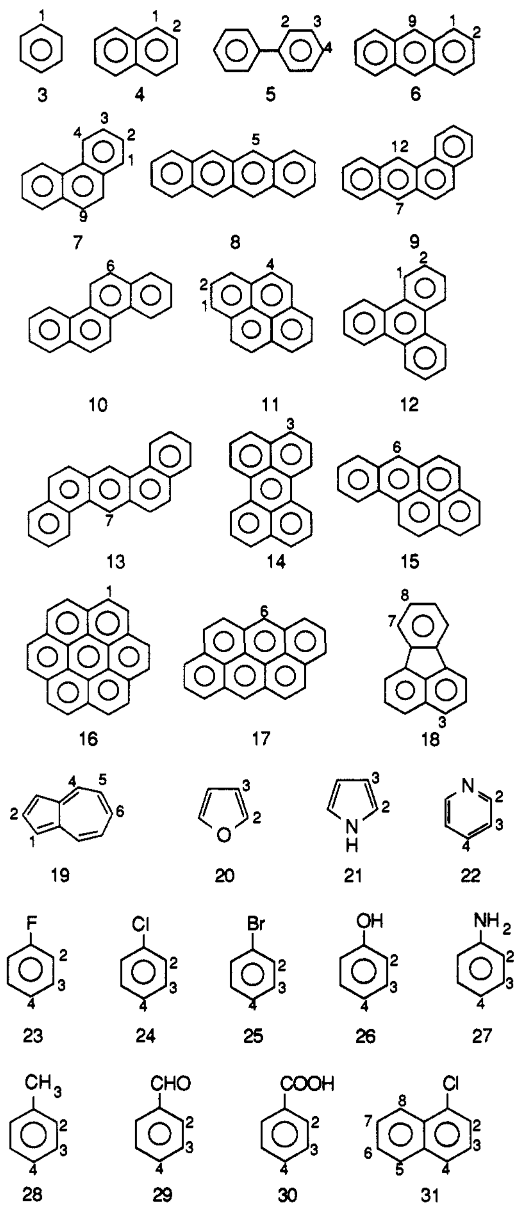

Figure 2. Molecules studied.

Table I. Reactivity Indices for Selected Hydrocarbons

compd	position	$\Delta\eta^{*a}$	σ^{+b}	compd	position	$\Delta\eta^{*a}$	σ^{+b}
3	1	0.500	−7.8	**9**	7	0.095	6.6
4	1	0.118	0.0		12	0.126	6.6
	2	0.255	−3.4	**10**	6	0.128	2.6
5	2	0.310	−1.7	**11**	1	0.070	6.1
	3	0.342			2	0.223	
	4	0.205	−1.7		4	0.127	
6	1	0.090	1.1	**12**	1	0.342	−0.8
	2	0.139	0.0		2	0.342	−2.3
	9	−0.086	8.1	**13**	7	0.164	6.5
7	1	0.255	−0.2	**14**	3	0.022	8.4
	2	0.302	−2.5	**15**	6	−0.019	11.1
	3	0.223	−0.5	**16**	1	0.270	1.7
	4	0.281	−2.7	**17**	6	−0.019	10.0
	9	0.226	0.5	**18**	3	0.208	1.8
8	5	−0.032	9.8		7	0.128	0.3
					8	0.169	1.0

[a] In units of $-\beta$ (a positive number). [b] Values are from ref 16.

Heterocycles. Results for three heterocycles are given in Table III. Also given in Table III are the most reactive sites for the molecules. For these molecules the predicted sites are the observed ones.

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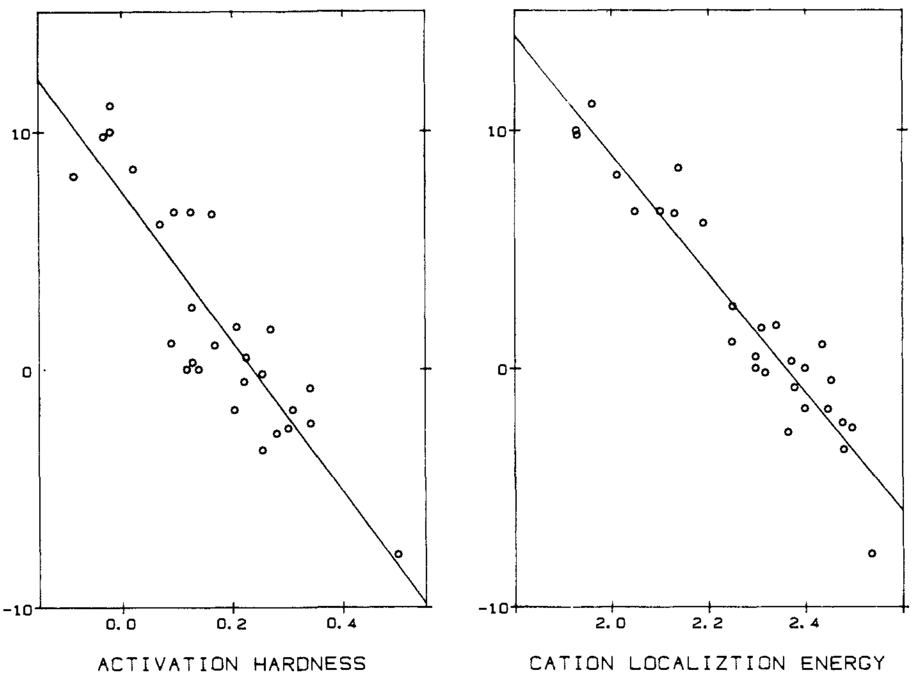

Figure 3. Correlations of activation hardness and Wheland's cation localization energy with Hammett's σ^+ constant.

Table II. Reactivity Indices for Azulene

position	1	2	4	5	6
$\Delta\eta^{\ddagger}$ [a]	−0.134	0.200	0.285	0.057	0.386

predicted reactive site: 1 and 3
observed reactive site: 1 and 3[b]

[a] In units of $-\beta$. [b] Friedel-Crafts acetylation: ref 17d, pp 825–826.

Table III. Reactivity Indices for Selected Heterocycles

compd	position	$\Delta\eta^{\ddagger}$ [a]	reactive site: predicted	reactive site: observed
20	2	0.147	2	2[b]
	3	0.279		
21	2	0.203	2	2[b,c]
	3	0.310		
22	2	0.411	3	3[b,c]
	3	0.310		
	4	0.440		

[a] In units of $-\beta$. [b] Reference 17d, pp 988–991. [c] Mazzara, G.; Borgo, A. *Gazz. Chim. Ital.* **1905**, *35I*, 477–486; *35II*, 19–27. Den Hertog, H. J.; Wibaut, J. P. *Recl. Trav. Chim.* **1932**, *51*, 382, 940. Schorigin, P.; Toptschiew, A. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 1874–1877. Fischer, O. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 62–64.

Table IV. Reactivity Indices for Substituted Benzene

			observed product,[d] % per site			
compd	position	$\Delta\eta^{\ddagger}$ [c]	nitration	chloronation	bromination	sulfonation
23	2	0.462	6			
	3	0.492	0.5			
	4	0.435	87			
24	2	0.480	15	19.5	5.6	0
	3	0.494	0	3	0.8	0
	4	0.462	70	55	87.2	100
25	2	0.483	19	22.6	6.6	0
	3	0.494	0	1.2	0.9	0
	4	0.463	62	52.5	85.1	100
26	2	0.421	20	24.9	4.9	
	3	0.486	0	0	0	
	4	0.363	60	50.2	90.2	
27	2	0.391				
	3	0.484				
	4	0.307				
28[a]	2	0.392	28.5		19.9	16
	3	0.485	1.5		0	3
	4	0.339	40		60.3	62
28[b]	2	0.439	28.5		19.9	16
	3	0.488	1.5		0	3
	4	0.392	40		60.3	62
29	2	0.269	9.5			
	3	0.139	36			
	4	0.276	9			
30	2	0.322	9.3			
	3	0.222	40.1			
	4	0.325	1.3			

[a] Inductive model. [b] Heteroatom model. [c] In units of $-\beta$. [d] Reference 15, Chapter VI.

Table V. Reactivity Indices for 1-Chloronaphthalene

position	2	3	4	5	6	7	8
$\Delta\eta^{\ddagger}$ [a]	0.233	0.260	0.099	0.132	0.262	0.252	0.136

predicted reactive site: 4
observed reactive site: 4[b]

[a] In units of $-\beta$. [b] Chlorination: Armstrong, H. E. *Chem. News* **1892**, *66*, 189. Bromination: Glaser, C. *Ann. Chem.* **1865**, *135*, 40–49. Nitration: Atterberg, A. *Ber. Dtsch. Chem. Ges.* **1876**, *9*, 926–928. Silfonation: Armstrong, H. E.; Wynne, W. P. *Chem. News* **1890**, *61*, 285–286.

Substituted Benzene. Table IV contains $\Delta\eta^{\ddagger}$ values and the isomer percentage for electrophilic substitution of substituted benzene. Since substituents F, Cl, Br, OH, NH_2, and CH_3 are ortho-para directing, $\Delta\eta^{\ddagger}$ for molecules **23**–**28** should have a larger value at the meta position (position 3) than at the ortho and para positions (position 2 and 4). This is what we see in Table IV. CHO and COOH are meta directing, so larger $\Delta\eta^{\ddagger}$ values for molecules **29** and **30** should occur at the ortho and para positions. Our results agree with this empirical rule. If we examine the numbers in Table IV we see that the ortho/para ratio also agrees with the magnitude of the $\Delta\eta^{\ddagger}$ values.

1-Chloronaphthalene. Table V gives results for 1-chloronaphthalene. That position 4 is the most reactive site is predicted by our $\Delta\eta^{\ddagger}$ values and experimentally observed. Note that position 4 is an α-position in the parent naphthalene and a para position in the benzene ring, which contains the Cl atom. Substitution at this position benefits from both these factors.

V. Concluding Remarks

Activation hardness could be calculated to any desired level of approximation. The transition state for calculation of $\Delta\eta^{\ddagger}$ could be defined so as to include the two σ-bonds, the one to be formed and the one to be broken, if we wished to use more sophisticated molecular orbital theory. The assumption in eq 18 above is natural

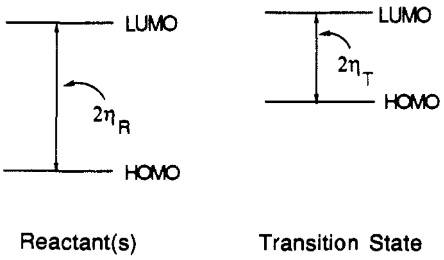

Figure 4. Typical hardness behavior for a chemical reaction: the harder the reactant(s), the more stable it is (they are), and the smaller the reactivity; the harder the transition state, the more stable it is, and the greater the reactivity. Hence the smaller the quantity $\eta_R - \eta_T$ is, the faster the reaction is.

but nontrivial and one that should be investigated further.

Activation hardness as an index of orientation of electrophilic aromatic substitution as here defined considers only the electronic effects. No efforts have been made to include the steric effects that sometimes dictate the amounts of different isomers. But for the molecules we have considered here the electronic effects appear to prevail. Also, we did not consider the effects of the electrophiles. This neglect has been rationalized previously.[33]

A transition state with a large HOMO-LUMO gap, or hardness, is more stable than one with a small gap, and therefore energetically easier to reach. In general, the HOMO-LUMO gap changes as little as possible along the reaction coordinate, as shown in Figure 4. The model theory described in section III and the results given in section IV corroborate these statements.

Activation hardness appears to be an excellent index for predicting the orientation of electrophilic aromatic substitution. *Other things being equal, the softer the reactant is the better, and the harder the transition state is the better.*

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[33] Reference 2, page 323.

A Theoretical Investigation of the Structures and Properties of Peroxyl Radicals

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Abstract: As part of a study of the mechanism of the 1,3-migration in allylperoxyl radicals, the equilibrium geometries, dipole moments, charge distributions, spin density distributions, and C-O bond dissociation energies of a variety of peroxyl radicals have been calculated with extended basis sets. It is shown that the effects of electron correlation on the structures of the peroxyl radicals are smaller than in the corresponding peroxides and that electron correlation accounts for about one-half of the C-O bond dissociation energy. The peroxyl radicals are shown to be π-radicals with large dipole moments in the 2.3-2.6 D range. The majority of the negative charge resides on the inner oxygen, while the spin density is higher on the terminal oxygen. The C-O bond dissociation energy decreases with the degree of saturation of the carbon adjacent to the peroxyl group and also when the hydrocarbon radical product is resonance stabilized.

Introduction

Peroxyl radicals are known to form via a variety of chemical processes, including the rapid reaction of oxygen with carbon radicals[1]

$$R^\bullet + O_2 \xrightarrow{k\,=\,10^9\,M^{-1}\,s^{-1}} RO_2^\bullet \qquad (1)$$

Some properties of peroxyls are known. They can be observed directly in solution by ESR, and the unpaired electron in alkyl peroxyls is located in a π-orbital.[2-4] The lifetime of peroxyl radicals may be as long as several seconds at 37 °C,[5] sufficient time for them to diffuse quite freely in solution (and presumably when formed in biological systems). On the other hand, they are sufficiently reactive to abstract hydrogen atoms from C-H bonds and thus are well-known to play a role in the initiation and propagation of free-radical autoxidation of organic substrates.[6-8]

There is renewed interest in oxygen radicals because their attack on lipid biomembranes is related to many important pathological events in biological systems (for typical reviews see references[9-13]). Intrinsic physical properties of peroxyl radicals can affect their behavior in heterogeneous lipid/aqueous systems. For example, a remarkably high polarity has been observed for the benzylperoxyl radical,[14] μ = 2.6 D. It has been suggested that this is due to a significant contribution of dipolar structure **2**.[15] It is argued that

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