A Theoretical Study of Substituent Effects. Analysis of Steric Repulsion by Means of Paired Interacting Orbitals

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The steric effect of substituent groups is studied by taking a simple model of the acid-catalyzed esterification
of acetic acid. By replacing the hydrogens of the acetyl group by methyl groups, the changes in activation barriers
for the nucleophilic attack are examined by means of MO calculations. The possible origin of steric repulsion
is investigated by applying the transformation of MO's into paired interacting orbitals. The transition-state
structures are located for some simple reaction models. The Cram and anti-Cram selectivities in the nucleophilic
additions to chiral C=O systems are also discussed.

Introduction

Among the factors that govern rates and selectivities of
chemical reactions, the polar effect and steric effect of
substituents have been investigated most extensively.[1]
With respect to the polar effects, there exists a very useful
and practical way of generalization, i.e., electron-with-
drawing and electron-releasing groups. This view has been
represented in a concise equation by Hammett[2] and has
been applied widely throughout the vast field of chemistry.
The usefulness of the equation and the parameters in-
volved in it have also been discussed from theoretical
viewpoints.[3,4]

An attempt to represent quantitatively steric effects of
substituent groups was made by Taft[5] by measuring the
rates of some model reactions suggested by Ingold.[6] The
steric parameters E_s were determined from average values
of log (k/k_0) for four types of related reactions, e.g., acid-
catalyzed ester hydrolysis and esterification of carboxylic
acids at 25 °C, where k_0 stands for the reaction rate for
the reference group CH_3 and k for other substituent
groups. Since then, several papers appeared to criticize
and/or attempt to improve the Taft E_s scale.[7–9] Dubois
and his collaborators proposed a revised version of steric
parameters and called them E_s'.[10] To eliminate possible
errors originating from averaging the reaction rates for
different reactions in the Taft E_s values, they have reev-
aluated the steric constant of groups for the rates of

acid-catalyzed esterification of carboxylic acids in methanol
at 40 °C. These steric parameters, however, do not seem
to indicate a complete separation of steric and polar effects.

When we carry out molecular orbital (MO) calculations,
both the steric and polar effects are included. For instance,
we may partition the energy of interaction between two
fragment species into several energy terms, e.g., the Cou-
lombic, delocalization, polarization, and exchange ener-
gies.[11–13] The delocalization interaction brings about
formation of new bonds between the reagent and reactant,
as well as transfer of an electronic charge from one frag-
ment to the other fragment.[14] This interaction, as well
as the Coulombic interaction, is closely related to the polar
effect of the substituent groups. The exchange interaction
arises from the interaction between the occupied MO's of
two fragments.[15] A bulkier group possesses a greater
number of occupied MO's having large amplitude in the
space spanned by that group and, hence, brings about a
stronger closed-shell repulsion with the occupied MO's of
an attacking reagent. The understanding of steric effects
is clearly of profound significance in organic syntheses.
Thus, we made an attempt to elucidate the steric effects
of substituents by means of theoretical calculations.

Method of Calculation

In order to discuss steric effects theoretically, we set up
first a simplified reaction model as sketched in Figure 1.[16]
A methoxy anion attacks a carboxylic acid molecule in the
presence of a proton as an acid catalyst. Acetic acid is the
reference system in the present study. One may start a
discussion of reactivities and selectivities from a com-
parison of the magnitudes of activation energy by calcu-
lating the transition-state structures for each reacting
system and for each path.[17] In this work, we try to in-

(1) See for example: (a) Ingold, C. K. *Structure and Mechanism in
Organic Chemistry*; Cornell University Press: New York, 1969. (b)
Gould, E. S. *Mechanism and Structure in Organic Chemistry*; Holt: New
York, 1959; pp 199–249.
(2) (a) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill:
New York, 1940; pp 184–199. (b) McGary, C. W.; Okamoto, Y.; Brown,
H. C. *J. Am. Chem. Soc.* 1955, *77*, 3037.
(3) Henri-Rousseau, O.; Texier, F. *J. Chem. Educ.* 1978, *55*, 437.
(4) Fujimoto, H.; Mizutani, Y.; Iwase, K. *J. Phys. Chem.* 1986, *90*,
2768.
(5) Taft, R. W. *Steric Effects in Organic Chemistry*; Newman, M. S.,
Ed.; Wiley: New York, 1956; pp 556–675.
(6) Ingold, C. K. *J. Chem. Soc.* 1932, 1032.
(7) Shorter, J. *Advances in Linear Free Energy Relationships*;
Chapmann, N. B., Shorter, J., Eds.; Plenum: London, 1972.
(8) Charton, M. *J. Am. Chem. Soc.* 1975, *97*, 1552.
(9) Hancock, C. K.; Meyers, E. A.; Yager, B. Y. *J. Am. Chem. Soc.*
1961, *83*, 4211.
(10) (a) MacPhee, J. A.; Panaye, A.; Dubois, J. E. *Tetrahedron* 1978,
34, 3553. (b) Panaye, A.; MacPhee, J. A.; Dubois, J. E. *Ibid.* 1980, *36*, 759.
(c) Dubois, J. E.; MacPhee, J. A.; Panaye, A. *Ibid.* 1980, *36*, 919. (d)
MacPhee, J. A.; Panaye, A.; Dubois, J. E. *J. Org. Chem.* 1980, *45*, 1164.

(11) Murrell, J. N.; Randić, M.; Williams, D. R. *Proc. R. Soc.* 1965,
A284, 566.
(12) Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* 1968, *41*, 1989.
(13) Kitaura, K.; Morokuma, K. *Int. J. Quantum Chem.* 1976, *10*, 325.
(14) Fujimoto, H.; Inagaki, S.; Fukui, K. *J. Am. Chem. Soc.* 1976, *98*,
2670.
(15) (a) Mulliken, R. S. *J. Chem. Phys.* 1955, *23*, 1841. (b) Fujimoto,
H.; Osamura, Y.; Minato, T. *J. Am. Chem. Soc.* 1978, *100*, 2954 and the
references cited therein.
(16) We assumed here tentatively that the anion attacks at the right
angle to the C=O bond (cf. Ann, N. T. *Fortschr. Chem. Forsch.* 1980, *88*,
145). The O–C bond was taken to be 1.5 Å and the standard values were
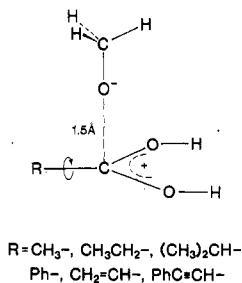taken for other bonds and bond angles.

Figure 1. A sketch of the reaction model for attack of a CH_3O^- to a protonated acetic acid molecule and its substituted systems.
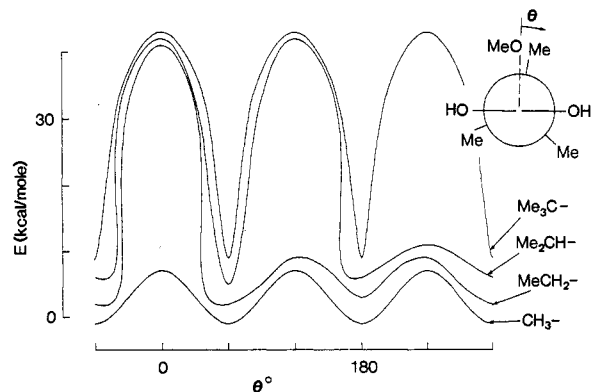

Figure 2. Changes in potential energy with rotation of alkyl groups attached to the carboxylic carbon in the models of acid-catalyzed esterification of acetic, propionic, isobutyric, and pivalic acids.

vestigate the steric effect from a somewhat different viewpoint; we compare first the width of the reactive channel that connects the reactant and the product. In order to examine the steric repulsion between the substituent groups and the attacking anion, we fixed the sp^2 planar structure of the reaction center. If we allow the rehybridization of the reaction center, another repulsive interaction will intervene between the substituent group and the C–O bonds of the carboxyl group in an eclipsed conformation. This repulsion will be discussed later. The calculations have been carried out mainly at the minimal basis STO-3G level[18] since we are dealing with sizable systems. Our main purpose here is to get an insight into the physical significance of steric effects that have been discussed empirically.[5,10]

Discussion

Origin of Steric Effects. Figure 2 illustrates the potential energy for different values of rotational angle θ in the reference system, acetic acid ($R = CH_3$), and those for the substituted systems, $R = CH_3CH_2$, $(CH_3)_2CH$, and $(CH_3)_3C$. The energy values are plotted by taking the most stable conformation of the reference system as the standard. The shape of the potential curves characterizes each reacting system. For $R = CH_3$ and $(CH_3)_3C$, the systems possess a 3-fold rotational symmetry, showing potential barriers at $\theta = 0°$, $120°$, and $240°$. The barriers are shown to be much higher in the system with $(CH_3)_3C$ than in the reference system. The other two systems are seen to be located in between.

The following points are noted with respect to the results given in Figure 2. Firstly, the reactive domain θ with the low potential energy gets narrower with an increase in the

Table I. Overlap Populations between Paired Interacting Orbitals

	R		
	CH_3	CH_3CH_2	$(CH_3)_2CH$
$\theta = 0°$	−0.273	−0.284	−0.286
$\theta = 30°$	−0.271	−0.275	−0.277
$\theta = 60°$	−0.268	−0.267	−0.269

number of methyl groups in the substituent R. This is clearly due to the steric effect of the methyl groups. Secondly, the lowest value of potential energy for the variation of the angle θ is elevated as the number of methyl group increases. This energy difference is regarded as originating primarily from the polar effect of methyl groups. It is interesting to see that the potential curves are much the same for ethyl, isopropyl and *tert*-butyl groups in the range of $\theta = -40°$ to $40°$, so far as the geometry at the reaction center is frozen.

The nuclear repulsion and interatomic electron repulsion are counterbalanced by the attractions between the nuclei and electrons to yield the Coulomb interaction in bimolecular interactions.[19] Steric repulsion is regarded as another electronic effect that arises from the overlap of the occupied MO's of the reagent and reactant.[20,21] This repulsive interaction, that is called exchange repulsion or very often overlap repulsion, is roughly proportional to the square of overlap integrals[22] and, hence, is very sensitive to the separation between the two species. It causes a decrease of electron density in the intermolecular region between the reagent and reactant molecules.

We have developed a simple method of representing bimolecular interactions by pairs of fragment orbitals.[23,24] Let us try to utilize that method to reveal the origin of steric effects. For the purpose of representing the repulsion, we recombine the occupied MO's of A, ϕ_i ($i = 1$, $2, ..., m$), and the occupied MO's of B, ϕ_k ($k = 1, 2, ..., n$), simultaneously within each orbital set in such a manner that a new occupied MO ϕ'_f of A interacts only with its paired occupied MO φ'_f of B. These orbitals may be obtained by making the bond-order matrix that represents overlap repulsion between A and B show nonzero off-diagonal elements only between the paired fragment orbitals (ϕ'_f, φ'_f). Our previous calculations have shown that chemical interactions are expressed practically by one or two orbital pairs in most cases.[23,24]

Figure 3 illustrates the orbitals of the acid molecules that play the dominant role in the repulsive interaction by overlapping out-of-phase with the paired orbital of the attacking anion shown on the top. It is demonstrated that a strong repulsive interaction arises between the electron pair of the attacking anion and the π electrons of the $COOH(+H^+)$ group. This type of antibonding interaction is characteristic of nucleophilic attacks to a conjugated molecule.

The participation of the substituent groups R in the steric repulsion is shown by the left-hand tail of the acid orbitals. At $\theta = 0°$, there appears a repulsive interaction between the attacking anion and the group R. The re-

(17) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Pandon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257.

(18) Binkley, J. S.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; DeFrees, J.; Schlegel, H. B.; Topiol, S.; Kahn, L.; Pople, J. A. *QCPE* **1981**, *13*, 406.
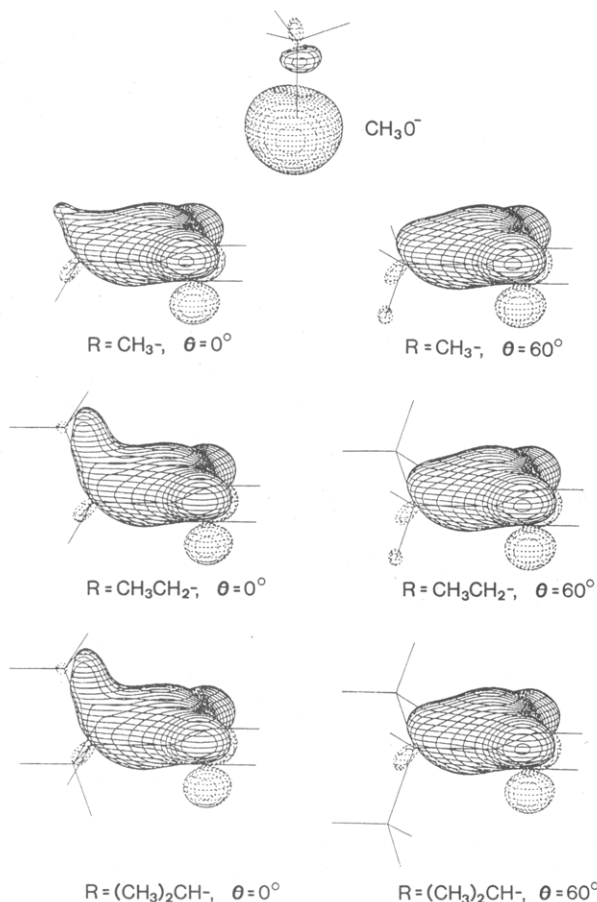
(19) Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2787.

(20) Ref 1a, p 68.

(21) Saillard, J.-Y.; Hoffmann, R. *J. Am. Chem. Soc.* **1984**, *106*, 2006.

(22) (a) Fujimoto, H.; Yamabe, S.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1566. (b) Fujimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* **1972**, *94*, 9205.

(23) (a) Fukui, K.; Koga, N.; Fujimoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 196. (b) Fujimoto, H.; Koga, N.; Hataue, I. *J. Phys. Chem.* **1984**, *88*, 3539.

(24) (a) Fujimoto, H.; Koga, N.; Fukui, K. *J. Am. Chem. Soc.* **1981**, *103*, 7452. (b) Fujimoto, H.; Yamasaki, T.; Koga, N. *Ibid.* **1985**, *107*, 6157. (c) Fujimoto, H.; Yamasaki, T. *Ibid.* **1986**, *108*, 578.

Figure 3. A representation of steric repulsion in terms of a paired interacting orbitals.

Figure 4. Relation between the theoretically estimated steric repulsion and an empirical steric parameter $-E_s'$.

Figure 5. Changes in the potential energy with rotation of unsaturated groups in conjugation with the carboxyl group in the presence of an attacking methoxy anion.

pulsion is shown to be stronger in the case of R = CH_3CH_2 and $(CH_3)_2CH$ than in the reference system (R = CH_3). On the other hand, the ethyl group and isopropyl group show little difference from each other. This explains why the potential curves look similar in the region of $\theta = -40°$ to $40°$ for R = CH_3CH_2, $(CH_3)_2CH$, and $(CH_3)_3C$. When the groups are rotated to the position of $\theta = 60°$, all the groups have orbitals that bear a close resemblance with each other. The repulsive interaction does not intervene in this region, in agreement with the energy curves presented in Figure 2.

Table I shows the overlap populations of the orbital pairs. At $\theta = 60°$, the three systems give negative overlap populations that are almost the same in magnitude. They represent the repulsive interactions between the attacking anion and the π electrons of the acid molecules. At $\theta = 0°$, all three groups show stronger antibonding interaction than at $\theta = 60°$, indicating the participation of substituents in the repulsion. The antibonding interaction is stronger in the case of R = CH_3CH_2 than in the reference system, but is almost the same in magnitude in the case of R = CH_3CH_2 and R = $(CH_3)_2CH$. These results indicate that steric repulsion is not governed by the global size of substituents but controlled principally by their local conformation. The groups having similar arrangements of bonds should exhibit similar steric effects. The paired interacting orbitals allow us to see how the steric repulsion arises in chemical interactions.

The overall rate of reaction may be evaluated by integrating the rate over all the θ values. The geometry around the reaction center is frozen here with a view to seeing the repulsion between the substituent group and the attacking reagent, and, therefore, the rotational barrier in Figure 2
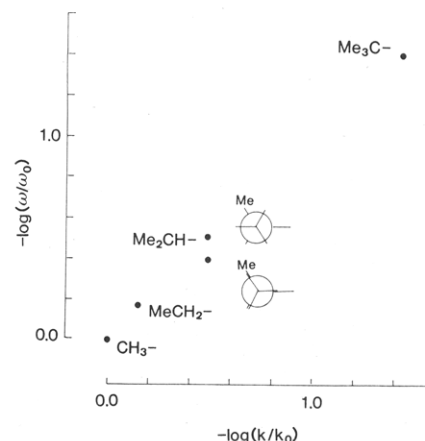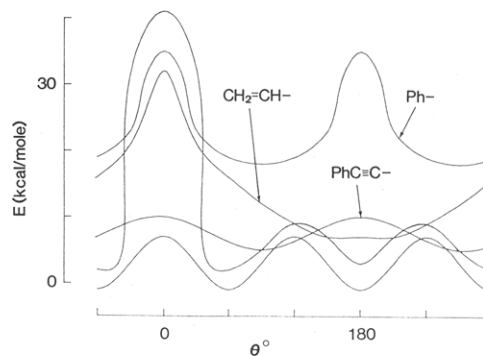
is very much exaggerated. If we assume tentatively that the reaction would take place only in the region where the potential energy is below 10 kcal/mol, the width of reactive channel ω defined in this manner is 360/360 for the reference system, 290/360 for R = CH_3CH_2, 140/360 for R = $(CH_3)_2CH$, and 14/360 for R = $(CH_3)_3C$, by fixing the methyl groups of R in the eclipsed conformation. Figure 4 illustrates the relation between log (ω/ω_0) and the $-E_s'$ value where ω_0 refers to the acetic acid. Though the apparent correlation may be fortuitous, the result obtained here is in line with the aforementioned proposition that the steric effect is determined principally by the local arrangement of bonds in the substituent groups near the reaction center. The conclusion is much the same when we take 20 kcal/mol as the threshold.

Unsaturated Substituents. Let us examine next the effects of substituent groups that are in conjugation with the carbon pπ orbital of the reaction center. The potential energies calculated for the rotation around the C–C bond are illustrated in Figure 5 with regard to phenyl, vinyl, and phenylethynyl groups. By looking at the energy changes in the region of $\theta = -40°$ to $40°$, it is suggested that the steric effect of these groups is not necessarily large in comparison with an ethyl or isopropyl group. The local arrangements of bonds are not so different from those in alkyl groups. In experiments, however, these groups have been allotted much greater $-E_s'$ values than the *tert*-butyl group.[10]

Figure 6 compares the effect of methyl, phenyl, and vinyl groups on the rotation around the C–C bond in the absence of the attacking nucleophile. The most stable conformation was taken as the standard to represent the change in the potential energy upon rotation in each system. The
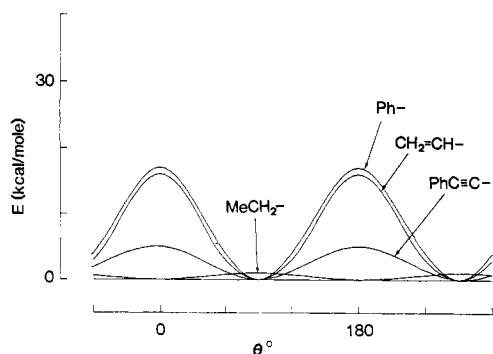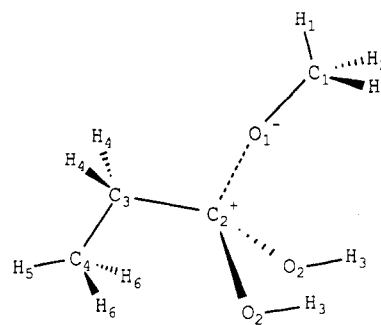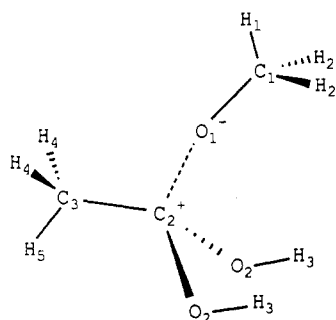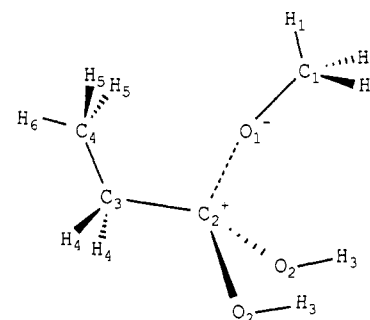
Figure 6. Destabilization due to the loss of conjugation energy in isolated acid molecules due to the rotation of the substituent groups.

C1-H1 : 1.102	C1-H2 : 1.102	C1-O1 : 1.369	C2-O1 : 1.359
C2-O2 : 1.436	C2-C3 : 1.569	O2-H3 : 0.991	C3-H4 : 1.085
C3-H5 : 1.085			
C1-O1-C2 : 178.2		O1-C2-C3 : 113.0	O2-C2-C3 : 106.6

C1-H1 : 1.102	C1-H2 : 1.102	C1-O1 : 1.369	C2-O1 : 1.358
C2-O2 : 1.435	C2-C3 : 1.560	O2-H3 : 0.991	C3-H4 : 1.085
C3-H5 : 1.085			
C1-O1-C2 : 178.3		O1-C2-C3 : 113.4	O2-C2-C3 : 106.8

C1-H1 : 1.091	C1-H2 : 1.094	C1-O1 : 1.435	C2-O1 : 1.441
C2-O2 : 1.429	C2-C3 : 1.551	O2-H3 : 0.991	C3-H4 : 1.085
C3-H5 : 1.085			
C1-O1-C2 : 114.3		O1-C2-C3 : 105.5	O2-C2-C3 : 107.3

Figure 7. A sketch of transition structures for $CH_3COOH(+H^+)$ + CH_3O^- system and its preceding ion-pair complex calculated by retaining the C_s symmetry.

planar conformation has been taken at θ = 90°. The phenyl and vinyl substitutions show much higher rotational barriers at θ = 0° and 180° than the propyl group.

C1-H1 : 1.102	C1-H2 : 1.102	C1-O1 : 1.369	C2-O1 : 1.359
C2-O2 : 1.435	C2-C3 : 1.568	O2-H3 : 0.991	C3-C4 : 1.539
C3-H4 : 1.088	C4-H5 : 1.086	C4-H6 : 1.086	
C1-O1-C2 : 178.2		O1-C2-C3 : 112.3	O2-C2-C3 : 107.1
C2-C3-C4 : 112.2			

C1-H1 : 1.101	C1-H2 : 1.102	C1-O1 : 1.369	C2-O1 : 1.358
C2-O2 : 1.436	C2-C3 : 1.578	O2-H3 : 0.991	C3-C4 : 1.538
C3-H4 : 1.088	C4-H5 : 1.086	C4-H6 : 1.086	
C1-O1-C2 : 178.6		O1-C2-C3 : 114.6	O2-C2-C3 : 106.4
C2-C3-C4 : 113.5			

Figure 8. Transition structures for $(CH_3)CH_2COOH(+H^+)$ + CH_3O^- system.

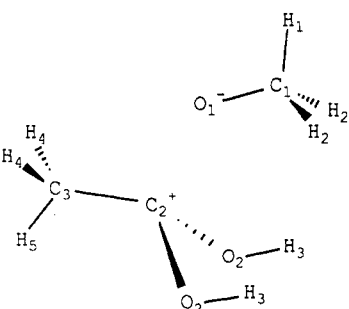This measures the magnitude of conjugation energy at the level of present calculation.

Nucleophilic attacks to a benzoic acid molecule and to an acrylic acid molecule are likely to occur at $\theta \sim 90°$. In addition to the destabilization due to the rotation of the phenyl or vinyl group at θ = 0° and 180°, the phenyl and vinyl-substituted systems are subjected to a significant elevation of the energy in the range of θ = 60–120°, compared with nucleophilic attacks to acetic acid and to propionic acid. The destabilization in this region implies that the conjugation between the substituent groups and the carbon atom is destroyed partially by the attack of a nucleophile.[25] The loss of conjugation should be a significant part of the steric parameters for phenyl, vinyl, and other unsaturated groups.

Let us look at the experimental parameters from this point of view, taking an isopropyl group $(-E_s' = 0.48)$ and a phenyl group $(-E_s' = 2.31)$.[10] The difference in $-E_s'$ values of these two groups is 1.83. By replacing a hydrogen atom by a methyl group, one finds $-E_s' = 1.00$ for CH_3-$(C_2H_5)CH$ and $-E_s' = 2.81$ for the o-tolyl group.[10] The difference is 1.81. Thus, this amount of difference should be attributed to the conjugation effect.

Structures. We assumed above a common planar structure of the reaction center for the molecules with different conformations and with different numbers of methyl groups with a view to seeing the repulsion between the attacking nucleophile and the substituent group in the

(25) The attack of CH_3O^- retaining the planar structure destabilizes acids, the destabilization being ~ 7 kcal/mol greater in acrylic acid than in propionic acid at the present level of calculation. A complete breaking of the π conjugation is estimated to cost about twice by comparing the energy difference between the protonated acid molecule and the sp³ rehybridized adduct, $RC(OH)_2OCH_3$, for R = ethyl and vinyl.

C1-H1 : 1.102	C1-H2 : 1.102	C1-O1 : 1.369	C2-O1 : 1.359
C2-O2 : 1.435	C2-C3 : 1.575	O2-H3 : 0.991	C3-C4 : 1.543
C3-H4 : 1.090	C4-H5 : 1.086	C4-H6 : 1.086	C4-H7 : 1.085
C1-O1-C2 : 178.5	O1-C2-C3 : 113.5		O2-C2-C3 : 106.7
C2-C3-C4 : 110.5			

C1-H1 : 1.103	C1-H2 : 1.102	C1-O1 : 1.369	C2-O1 : 1.362
C2-O2 : 1.435	C2-C3 : 1.592	O2-H3 : 0.991	C3-C4 : 1.545
C3-H4 : 1.090	C4-H5 : 1.086	C4-H6 : 1.085	C4-H7 : 1.085
C1-O1-C2 : 178.3	O1-C2-C3 : 111.8		O2-C2-C3 : 108.4
C2-C3-C4 : 112.0			
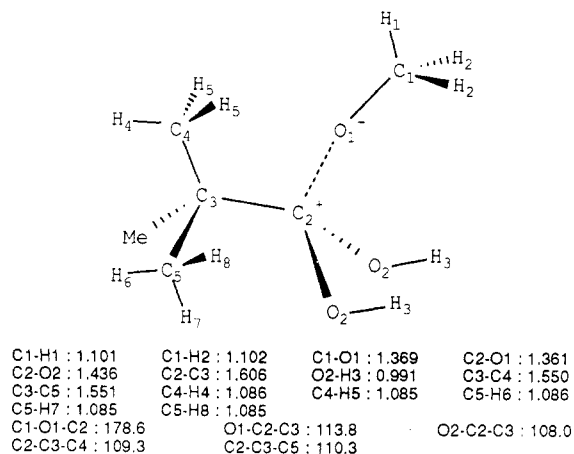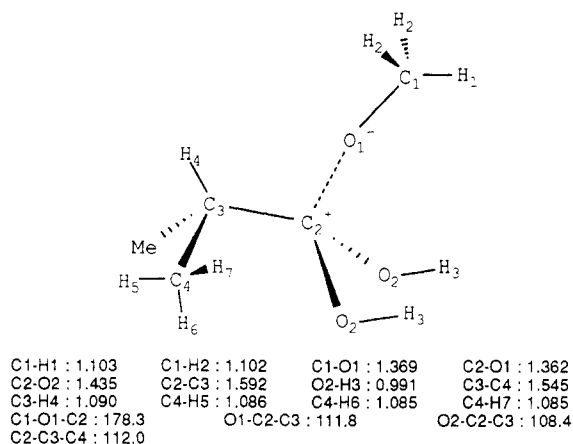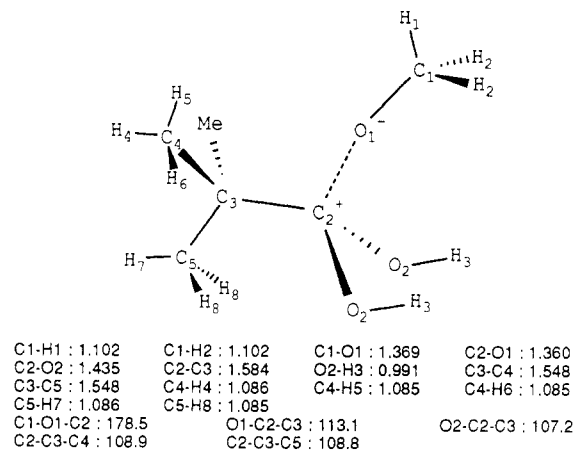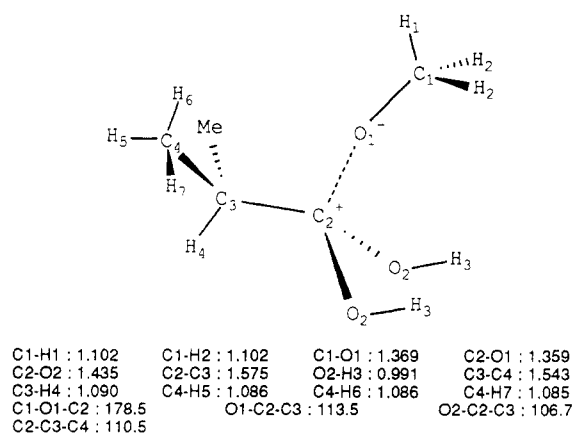
Figure 9. Transition structures for $(CH_3)_2CHCOOH(+H^+) + CH_3O^-$ system.

C1-H1 : 1.102	C1-H2 : 1.102	C1-O1 : 1.369	C2-O1 : 1.360
C2-O2 : 1.435	C2-C3 : 1.584	O2-H3 : 0.991	C3-C4 : 1.548
C3-C5 : 1.548	C4-H4 : 1.086	C4-H5 : 1.085	C4-H6 : 1.085
C5-H7 : 1.086	C5-H8 : 1.085		
C1-O1-C2 : 178.5	O1-C2-C3 : 113.1		O2-C2-C3 : 107.2
C2-C3-C4 : 108.9	C2-C3-C5 : 108.8		

C1-H1 : 1.101	C1-H2 : 1.102	C1-O1 : 1.369	C2-O1 : 1.361
C2-O2 : 1.436	C2-C3 : 1.606	O2-H3 : 0.991	C3-C4 : 1.550
C3-C5 : 1.551	C4-H4 : 1.086	C4-H5 : 1.085	C5-H6 : 1.086
C5-H7 : 1.085	C5-H8 : 1.085		
C1-O1-C2 : 178.6	O1-C2-C3 : 113.8		O2-C2-C3 : 108.0
C2-C3-C4 : 109.3	C2-C3-C5 : 110.3		

Figure 10. Transition structures for $(CH_3)_3CCOOH(+H^+) + CH_3O^-$ system.

substrate molecule. Figures 7–10 illustrate the transition-state structures for several model systems retaining the C_s symmetry which have been determined by gradient optimization at the STO-3G level. The energy difference between the eclipsed and staggered conformations obtained above is 1.84 (STO-3G), 3.61 (4-31G), and 3.89 (4-31G/MP2) kcal/mol for R = CH_3; 2.21 (STO-3G), 3.96 (4-31G), and 3.72 (4-31G/MP2) kcal/mol for R = CH_3CH_2; 4.36 (STO-3G) and 7.39 (4-31G) kcal/mol for R = $(CH_3)_2CH$; and 5.68 (STO-3G) and 8.92 (4-31G) kcal/mol for R = $(CH_3)_3C$.

The following should be noted here. In comparison with the calculation with the rigid framework, the repulsion between the incoming methoxy anion and substituent R has been reduced by the distortion of the reaction center to make them away from each other. The repulsion is approximately proportional to the square of overlap integrals as mentioned above. In the eclipsed conformation, the distortion brings about a strong repulsive interactions between the methyl group(s) and the C–O bond(s) of COOH(+H⁺) group within the substrate molecule. The increase in energy difference between the two conformers on going from R = CH_3 to $(CH_3)_2CH$ and from CH_3CH_2 to $(CH_3)_3C$ is due to this repulsion. The repulsion between the methyl groups and the C–O bonds in the eclipsed conformation of R = $(CH_3)_3C$ is strong enough to tilt the substituent R in such a way as to shorten the distance between the oxygen of the incoming anion and the nearest hydrogen H_5 in the other methyl group by 0.109 Å upon the replacement of R = CH_3CH_2 by a $(CH_3)_3C$ group. The apparent energy difference allowing the structural changes around the reaction site includes several effects, and, therefore, it is difficult to see the steric repulsion between the reagent and reactant.

Since we attached a naked proton to the substrate molecule as an acid catalyst and used a naked methoxy anion as the attacking nucleophile, a stabilized ionic complex was formed before coming up to the transition state. The adduct is shown in Figure 7 with respect to the reference system. The activation energy of this hypothetical process was estimated to be 19.7 kcal/mol at the 4-31G level. We are studying more realistic systems by replacing the proton by a solvated cation and by lifting the C_s symmetry.

Nucleophilic Additions to Chiral Carbonyl Systems. Asymmetric inductions by means of the addition of achiral nucleophiles to chiral carbonyl bonds have been studied extensively by Cram[26] and by Karabatsos.[27] They tried to explain the stereochemistry on the basis of stable conformation of ketones deduced from the steric repulsion between substituents at the reaction center and the carbonyl oxygen in the isolated reactant molecule. On the other hand, Felkin and his collaborators stressed the importance of the repulsion between the substituents and the attacking nucleophile.[28]

Figure 11 compares the potential energies for the addition of methyllithium to a C=O bond.[29] The substit-

(26) (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (c) Cram, D. J.; Wilson, D. R. *Ibid.* **1963**, *85*, 1245 and the references cited therein.

(27) (a) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367. (b) Karabatsos, G. J.; Hsi, N. *Ibid.* **1965**, *87*, 2864.

(28) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Cherest, M.; Felkin, H.; Tacheau, P.; Jacques, J.; Varec, D. *J. Chem. Soc., Chem. Commun.* **1977**, 372.
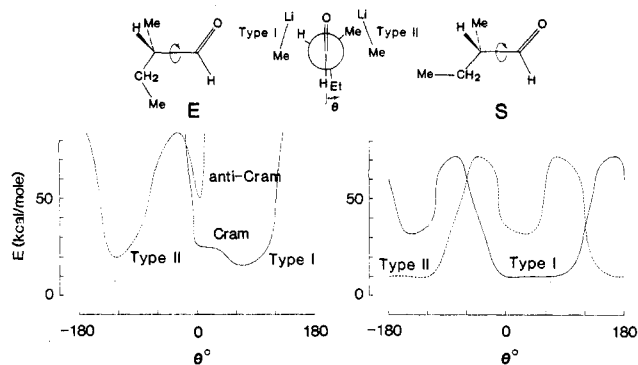
(29) As for experiments, see, for example: ref 26c.

Figure 11. Changes in potential energy in a model of Cram type and anti-Cram type addition of methyllithium to an aldehyde molecule. The geometry of the reaction center was taken after a calculation on the addition of methyllithium to formaldehyde[32] and fixed during the rotation.

uents of different sizes are represented by an ethyl (R_L), a methyl (R_M), and a hydrogen (R_S). When the ethyl group is retained in the conformation denoted by S in Figure 11, the ethyl group should provide a steric effect that is much the same as that of a methyl group. The calculation shows actually no difference between the two faces of the C=O bond; the type I curve is approximately the mirror image of the type II curve. Effects of larger substituent groups in actual experiments may be represented virtually by allowing the ethyl group to come in the conformation denoted by E in our simplified reaction model.

In the E conformation of the ethyl substituent, there exists a clearcut difference between the two faces. The lowest energy point in the path leading to the Cram-type selectivity in type I is found at $\theta \sim 90°$, which is located somewhat lower than the lowest point in the path leading to the anti-Cram selectivity in type II at $\theta \sim 0°$. Here, it is important to note that the shapes of the potential curve look different from each other. The potential energy remains low for a wider range of θ in the path leading to the Cram selectivity relative to the path that leads to the anti-Cram selectivity.

The calculation has shown that the more stable conformation S should prevail at low temperature, and, therefore, high stereoselectivity will not be observed. In experiments, the largest substituent group R_L is often a phenyl group or a cyclohexyl group.[30] These groups have

the bond arrangements that are closer to that in the E form of ethyl group. The selectivity of the reaction is likely to be controlled by the steric repulsion, which seems to be related not only with the height of barrier but also with the width of reactive channels of low potential energy. A broader range of θ should be available for nucleophilic reagents when they attack the C=O bond from the side that favors the Cram-type diastereomer.[28,31]

Conclusion

By applying a pair of orbital transformations, we attempted to visualize the parts of the reagent and reactant molecules that should take part dominantly in the repulsive interaction. The local arrangements of bonds in the groups have been shown to have a decisive effect in determining the magnitude of steric repulsion, so far as the atoms involved are of the same kind. The global size and structure of substituent groups are less important. It is obvious, however, that the steric repulsion is governed also by the electron density of substituent groups. For example, a group with a negative charge will show a greater repulsion than the same group with a neutral or positive charge. The transition structures of the systems having many degrees of freedom may not be so rigid particularly in solution. The shape of potential surfaces as well as the transition states should be of significance in understanding the selectivity of reactions.

(30) (a) Cram, D. J.; Knight, J. D. *J. Am. Chem. Soc.* **1952**, *74*, 5835. (b) Cram, D. J.; Elfahez, F. A. A.; Weingartner, H. *Ibid.* **1953**, *75*, 2293. (c) Cram, D. J.; Greene, F. D. *Ibid.* **1953**, *75*, 6005. (d) Cram, D. J.; Elfahez, F. A. A.; Nyquist, H. L. *Ibid.* **1954**, *76*, 22. (e) Cram, D. J.; Allinger, J. *Ibid.* **1954**, *76*, 4516. (f) Cram, D. J.; McCarty, J. E. *Ibid.* **1954**, *76*, 5740. (g) Gault, Y.; Felkin, H. *Bull. Soc. Chim. Fr.* **1960**, 1342.
(31) Addition of a methoxy anion onto the carbonyl carbon at an angle of 105° yields similar potential curves. As for the direction of the nucleophilic attack, see ref 16.
(32) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560.