Prediction of S_N2 Transition State Variation by the Use of More O'Ferrall Plots

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Abstract: The More O'Ferrall and Thornton approaches for prediction of the effects of reactant variation on transition-state structure are applied to direct displacement reactions on benzyl derivatives. Experimental measures of transition-state structure are derived from the α-deuterium isotope effects, the response to solvent ionizing power (m values), the $k_{\mathrm{OTs}}/k_{\mathrm{Cl}}$ ratio, and the $k_{\mathrm{EtOH}}/k_{\mathrm{H_2O}}$ ratio. Complications in interpretation of the leaving-group ratio resulting from steric effects are discussed, and it is shown that there is a small electronic effect on this ratio. Also, potential-energy diagrams are used to demonstrate that there are certain instances in which a change in reactivity should not be accompanied by a change in selectivity.

In the study of reaction mechanisms it is frequently helpful to be able to predict the effects of reactant variation on transition-state structure. In the present paper we derive such predictions for a series of substituted benzyl derivatives reacting by an S_N2 mechanism. Predictions of transition-state structure have long been made by applying "chemical intuition"[1] and Hammond's postulate[2] and related theories,[3-6] and more recently by applying more rigorous rules.[7-10] Hammond's postulate is presented in the two dimensions of potential energy and reaction coordinate. A significant advance resulted from Thornton's consideration of transition-state bond stretching and compression other than that along the reaction coordinate.[7a] To illustrate, examination of the three-dimensional potential energy surface for a direct displacement reaction (eq 1, Figure 1) reveals that a complete theory for changes in

$$\mathrm{N} + \mathrm{R{-}X} \rightarrow \mathrm{N^+{-}R} + \mathrm{X^-} \qquad (1)$$

transition-state structure must include not only movement of the transition state along ("parallel" to) the reaction coordinate (the path of minimum energy) but it must also include movement of the transition state away from ("perpendicular" to) the reaction coordinate. In other words, perpendicular motion involves a shift in the saddle point perpendicular to the original reaction coordinate, and parallel motion involves a shift in the saddle point along the original reaction coordinate. In this particular case, progress along the reaction coordinate involves a reduction in distance between N and R and an increase in the distance between R and X. Consequently a theory such as Hammond's,[2] which considers shifting the transition state only along the reaction coordinate, can lead to predictions of only those new transition-state structures in which bond lengths N-R and R-X are inversely related (i.e., a later transition state with N-R shorter and R-X longer, or an earlier transition state with N-R longer and R-X shorter). In fact, reactant variation can result in a perpendicular shift to give a new transition state in which both N-R and R-X bonds are shorter or longer. Thornton's theory[7] and several recent works[8-10] include consideration of such perpendicular motion.

The application of theories relating to variation in transition-state structure has been greatly simplified by the presentation of potential energy surfaces in terms of the reactive intermediates which *could* be involved in a mechanism.[7b,9,11-19] In the present paper we will for the sake of simplicity refer to such diagrams as More O'Ferrall plots,[11] although it should be noted that Ingold,[18] Jencks,[9] and Thornton[7b] have also pioneered in their use.

To illustrate the More O'Ferrall approach, nucleophilic substitution at carbon, eq 1, can be presented as in Figure 2. Along the y and x axes are presented R-X and N-R bond orders, respectively, so that progress along the x axis represents N-R bond formation and progress along the y axis represents R-X bond cleavage. Consequently, proceeding directly along the y axis would lead to the $\mathrm{R^+X^-}$ ion pair, whereas proceeding directly along the x axis would yield the unknown $\mathrm{N^+{-}R^-{-}X}$ species. Potential energy is the third dimension in this drawing, and is represented by the contour lines. Alternatively, a simpler plot can be constructed by deleting the contour lines and representing the path of minimum potential energy (the reaction coordinate) by a single solid line. Such a simple plot is given in Figure 3. This plot contains two reaction coordinates, *a* for an S_N2 mechanism and *b* for an S_N1 mechanism (two coordinates are presented for the purpose of illustration only).

The conceptual advance of the More O'Ferrall approach lies in the fact that the potential energy diagram includes possible intermediates, thus making it possible to translate substituent effects on intermediate stability into effects on the potential energy surface (and transition-state structure) even when the intermediate is not involved in the reaction. For example, using this approach, it is possible to determine the effect of an electron-donating substituent on an S_N2 transition state (curve A, Figure 3) by considering the obvious effect of such a substituent on the ion pair $\mathrm{R^+X^-}$. The More O'Ferrall plots can be used by applying Thornton's rules.[7,12] This is done by determining the atomic motions expected for the two perpendicular and two parallel motions from a point on the reaction coordinate, and then determining which of these will be favored by a particular substituent change. Alternatively, the More O'Ferrall plots can be used by applying three simple rules stated here in terms of stabilizing corners of the potential energy surface: (1) if species corresponding to a corner *along* the reaction coordinate (e.g., the reactant corner, N RX, of curve A, Figure 3) are stabilized, the effect will be to move the transition state along the coordinate *away* from the stabilized corner (a Hammond effect); (2) if species corresponding to a corner *perpendicular* to the reaction coordinate (e.g., N $\mathrm{R^+X^-}$ of curve A, Figure 3) are stabilized, the effect will be to move the transition state *toward* the stabilized corner; (3) if the stabilization is both along and perpendicular to the reaction coordinate (e.g., both N $\mathrm{R^+X^-}$ and N RX of curve A, Figure 3), the transition-state movement will be determined by the resultant of the vectors for the movements prescribed in rules 1 and 2. The relative amounts of perpendicular and parallel motion of the transition state for a given amount of corner stabilization will be determined by the symmetry of the energy surface at the saddle point.[7,9,10b] In the present work we make the simplifying assumption that the surface is symmetrical, so that perpendicular and parallel shifts will be of equal magnitude for the same amount of corner stabilization. Although this assumption is generally made, it is not necessarily appropriate and can lead to differences in predictions of

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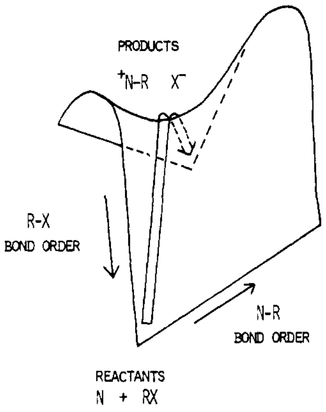

Figure 1. A potential energy surface for a direct displacement reaction. The path of minimum energy from reactants to products is indicated by the arrow.

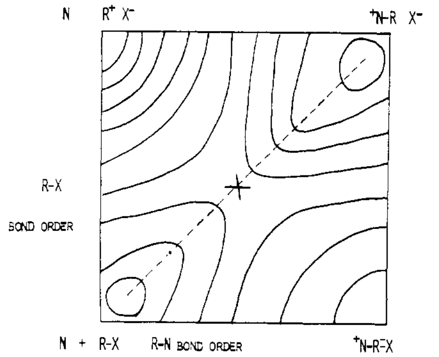

Figure 2. A contour map illustrating the potential energy surface for a direct displacement reaction, eq 2. The reaction coordinate is indicated by the dotted line, and the saddle point is indicated by the cross mark.

transition-state movement. We will return to this point later.

In the remainder of this paper we present the results of experiments designed to measure variations in transition-state structure for a series of substituted benzyl derivatives reacting by an S_N2 mechanism. The More O'Ferrall approach is used to explain the observed changes. In addition we comment on the utility of tosylate-chloride rate ratios and reactivity-selectivity relationships for measuring transition-state structure.

The Benzyl System

The benzyl system is used in the present study for several reasons. First, ring substitution permits gradual variation of reactivity without changing the steric environment of the reaction site. Second, a large body of recent work indicates that the solvolyses of these substrates, under the conditions of this study, proceed by a simple S_N2 mechanism.[20] Thus we have available a well-characterized system in which remote electronic effects can be used to vary reactivity.

Four measures of transition-state structure are readily applicable to benzyl solvolyses: the Grunwald-Winstein m value (response to changes in solvent ionizing power),[21] the kinetic α-deuterium isotope effect (α-d), the selectivity for displacement by ethanol as opposed to water (k_E/k_W), and the tosylate-chloride leaving group ratio (k_{OTs}/k_{Cl}). Regarding the interpretation of these experimental probes, there is little doubt that increases in m values[22] and α-d's[23] result from the increasing looseness of S_N2 transition states. A loose S_N2 transition state is one in which there is an increase in the length of the bond to the entering nucleophile and to the leaving group, and in which there is increased localization of charge at the reactive carbon and at the leaving group, **1** (for a neutral nucleophile). Hoffmann has suggested that an increase in

$$\overset{\delta+}{\mathrm{N}}-\overset{\delta+}{\mathrm{R}}-\overset{\delta-}{\mathrm{X}}$$

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k_{OTs}/k_{Cl} (or k_{OTs}/k_{Br}) also indicates a looser transition state.[24] However, it has been shown that the data used by Hoffmann to support his theory are complicated by steric effects, since increased substitution near the reaction site results in dramatic steric enhancement of the tosylate-chloride rate ratio.[25] In the present work we show that there is an electronic effect on the tosylate-chloride ratio such that increased charge localization on the leaving group results in an increase in the ratio. This electronic effect is much smaller than the steric effect,[25] however, and is detectable in the present instance only because our substituent changes are remote from the reaction site.

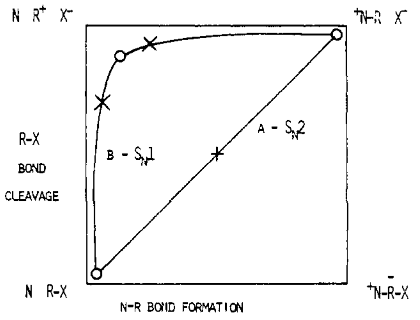


Figure 3. A More O'Ferrall plot for a nucleophilic displacement reaction, where N is the nucleophile, X is the leaving group, and minima and maxima are represented by circles and cross marks, respectively. Path A represents the reaction coordinate for an S_N2 reaction, while path B represents the reaction coordinate for an S_N1 reaction.

Serious question now exists as to the validity of the long-assumed relationship between reactivity and selectivity.[26-31] Several examples of reactions for which there is no change in selectivity despite large changes in reactivity have been carefully studied (whether such an event should be termed a "failure" of the principle is a matter of opinion; the absence of a measured change in selectivity could simply result from the change being too small to be measured with the techniques employed).[26-31] However, several selectivity studies have been made of solvolysis reactions, and *all* show adherence to the reactivity-selectivity relationship.[26,32-35] Thus, the factors which cause failure of the relationship in other reactions are apparently not present in solvolysis reactions. Of course, it is possible that adherence to the relationship for solvolysis reactions results because of some as yet undiscovered reason. In any event, it seems legitimate to assume that the reactivity-selectivity relationship will be applicable to the solvolysis of benzyl chlorides. In the present work this assumption is tested experimentally and the More O'Ferrall approach utilized to determine if it is supported theoretically.

Another parameter which is often used as a measure of transition-state structure is the Hammett ρ value. Hammett plots for benzyl reactions are usually curved or U-shaped (depending on the particular system). Young and Jencks[36] have shown that this curvature probably results from transition-state variations in (a) the balance between polar and resonance effects and (b) the relative amount of bond formation and cleavage, with the former effect being dominant. Johnson[5a] has suggested that ρ values (for linear plots) are not a measure of transition-state structure. However, McLennan[37] has shown that ρ values can be used to measure variation in transition-state structure if compensation is made for differences in the efficiency of charge transmission for different reaction series. In view of the obvious complexity involved in

Table I. Solvolysis Rates for *p*-X Substituted Benzyl Chlorides (at 100°C) and Tosylates (at 25 °C)

X	L	k, s^{-1} 60E[a]	70E[a]	80E[a]
NO_2	OTs[b]		3.09×10^{-6}	
	Cl	$4.39 (\pm 0.06) \times 10^{-5}$	$3.05 (\pm 0.02) \times 10^{-5}$	
Cl	OTs[b]		1.10×10^{-4}	
	Cl	$2.82 (\pm 0.19) \times 10^{-4}$	$1.76 (\pm 0.02) \times 10^{-4}$	
H	OTs[b]		2.09×10^{-4}	
	Cl	$4.80 (\pm 0.05) \times 10^{-4}$	$2.78 (\pm 0.07) \times 10^{-4}$	$1.58 (\pm 0.04) \times 10^{-4}$
CH_3	OTs[b]		7.24×10^{-3}	
	Cl[c]	2.94×10^{-3}	1.47×10^{-3}	6.90×10^{-4}

[a] The solvents are 60, 70, and 80% (v/v) ethanol in water; error limits are given as the standard error, i.e., standard deviation/(number of runs)$^{1/2}$. [b] G. S. Hammond, C. E. Reeder, F. T. Fang, and J. K. Kochi, *J. Am. Chem. Soc.*, **80**, 568 (1958). [c] Reference 20.

Table II. Measure of Transition-State Structure for the Solvolysis of *p*-X Substituted Benzyl Derivatives

X	m(Cl,100°C)	m(OTs,25°C)	k_{OTs}/k_{Cl}[a]	k_E/k_W[b]	α-d Cl,H_2O[c]	OBs,80E[d]
NO_2	0.31	0.48	0.10	4.30		1.005
Cl	0.39	0.69	0.62	3.13	1.030	
H	0.41	0.74	0.69	1.82	1.045	1.074
CH_3	0.56 (0.63)[e]	0.89	4.9 (3548)[e]	1.52	1.131	

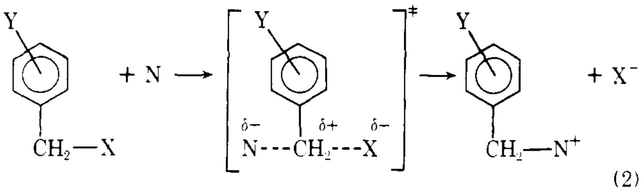
[a] In 70% (v/v) aqueous ethanol; for the tosylate at 25 °C and the chloride at 100 °C. [b] Calculated from k_E[ethanol]/k_W[water] = [ROEt]/[ROH] in 70% (v/v) aqueous ethanol at 100 °C: J. R. Moffatt, unpublished results. [c] V. J. Shiner, Jr., M. W. Rapp, and H. R. Pinnick, Jr., *J. Am. Chem. Soc.*, **92**, 232 (1970). [d] K. M. Koshy and R. M. Robertson, *ibid.*, **96**, 914 (1974). [e] At 25 °C.

interpreting ρ values, we have chosen not to use this parameter in the present study.

In Table II are presented the experimentally determined values of m, α-d, k_{OTs}/k_{Cl}, and k_E/k_W.

Application of the More O'Ferrall Approach

In this section we apply the More O'Ferrall approach and examine the predictions for the effects of variations of Y, N, and X on the S_N2 transition state, eq 2.

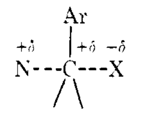


(2)

N = EtOH, H_2O X = Cl, OTs

Y = $-NO_2$, $-Cl$, $-H$, $-CH_3$

Two possible pathways for a nucleophilic substitution are presented in Figure 3: path A (S_N2) and path B (S_N1). Note that the S_N2 reaction coordinate given is that expected for a symmetrical process in which R-X bond cleavage and N-R bond formation proceed at the same rate. The transition state for this process will have equal R-X and N-R bonds lengths and no charge on carbon. Judging from the accelerating effects of electron-donating ring substituents, Table I, benzyl solvolyses proceed via transition states in which there is significant positive charge development on carbon, **2**. Such transition



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states result when R-X bond cleavage proceeds more rapidly than N-R bond formation. In this case, the reaction coordinate (as shown in Figure 4) will lie somewhere between the S_N2 and S_N1 processes represented in Figure 3. The transition state could lie anywhere, except very late, along this reaction coordinate, because a very late transition state would have essentially no positive charge development on R. The predictions which result from applying the More O'Ferrall approach depend on the placement of the transition state on the reaction coordinate. We have therefore chosen to examine three possibilities to determine which, if any, of the possible transition states leads to predictions consistent with experiment; the three placements chosen are (Figure 4) early (A), midway (B), and late (C).

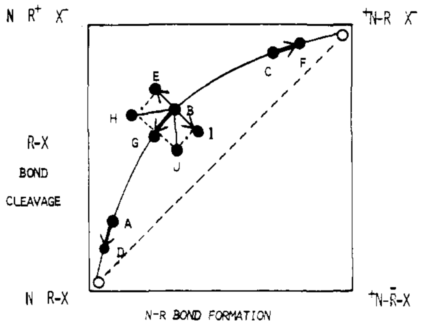

Figure 4. A More O'Ferrall plot for an S_N2 process in which RX bond cleavage precedes NR bond formation. Energy maxima and minima are represented by closed and open circles, respectively.

First, we examine the effect expected from increasing the electron-donating ability of Y, eq 2, thus stabilizing R^+X^- and lowering the upper left corner of Figure 4. If the transition state lies at the midway point B, then applying the rules presented earlier results in movement of the transition state to point E. In this case the transition state will be looser, involving more R-X cleavage, less N-R formation, more positive charge development on R, and more negative charge development on X. Such a change in transition states would result in measurement of higher α-d (less crowding), higher m values (more charge development), higher k_{OTs}/k_{Cl} (more charge on X), and decreased selectivity (less N-R formation; note that the More

Table III. A Summary of Predictions for Different S_N2 Transition States as a Function of Substitution of Electron-Donating Substituents on R

parameter	prediction early (A)	midway (B)	late (C)	obsd
m	lower	higher	lower	higher
k_E/k_W	lower	lower	higher	lower
α-d	lower	higher	lower	higher
k_{OTs}/k_{Cl}	lower	higher	no change	higher

O'Ferrall approach does lead to the prediction that an increase in reactivity is accompanied by a decrease in selectivity). For the early transition state at point A, the upper left corner is essentially parallel to the reaction coordinate in this region, and lowering the upper left corner will primarily result in movement along the reaction coordinate to point D. Since the reaction coordinate at point A is not perfectly parallel to the upper left corner, there also will be some small amount of perpendicular motion, and some small shift of point D toward the y axis. The overall effect will be to give a tighter transition state, with less R-X cleavage, essentially unchanged N-R formation, and less charge development. The experimental manifestations will be a lower α-d, a lower m value, a lower k_{OTs}/k_{Cl}, and essentially unchanged k_E/k_W. Finally, the upper left corner lies essentially along the reaction coordinate at point C, the "late" transition state. Stabilizing R^+X^- will then result in movement to F to produce a tighter transition state with more N-R formation, not much change in R-X cleavage, and greater dispersal of positive charge onto N. The experimental prediction will be a lower α-d, a slightly lower m value, an essentially unchanged k_{OTs}/k_{Cl}, and an increase in selectivity. Any perpendicular motion toward the top of the plot would accentuate these effects.

The predictions for the three transition states are summarized in Table III along with the experimentally observed variations for the parameters in question. As can be seen, the predictions for the midway transition state (point B) are in agreement with experiment.

The effect on the S_N2 transition state of varying the nucleophile and leaving group will be considered shortly, but first we discuss the results obtained for the leaving-group ratios. As noted earlier, it has been observed that k_{OTs}/k_{Cl} values increase dramatically with steric crowding around the reaction site and that this effect obscures any electronic effect which might result from increased ionization in the transition state.[25] In the case of the benzyl solvolyses, however, it is important to note that the increase in k_{OTs}/k_{Cl} with the increase in electron-donating ability of Y occurs despite an apparent decrease in crowding at the transition state; the More O'Ferrall approach predicts, and the experimental probes indicate, that substitution at Y is giving a looser transition state. These results, therefore, clearly indicate that there is a small increase in k_{OTs}/k_{Cl} when there is an increase in the degree of ionization in a solvolytic transition state. However, it is also important to recall that steric effects can increase this ratio by several thousands.

It is also of interest to examine the More O'Ferrall predictions for the effect of leaving-group variation on S_N2 transition structure. Increasing the stability of the departing anion X^- will result in lowering the top edge of the potential energy surface. The transition state at point B will move to point H, which is the resultant of vectors to points E and G, caused by lowering the upper left and upper right corners, respectively. The new transition state will have less N-R formation, essentially unchanged R-X cleavage, and less dispersal of positive charge from carbon to the nucleophile. The experimental results of this change should be a higher m value, a higher α-d, and a reduction in selectivity. Reference to Table II confirms the m-value prediction. The other two predictions can be confirmed by referring to the work of others. Shiner has observed that changing the leaving group from methanesulfonate to the better leaving group trifluoromethanesulfonate results in an increase in α-d for neophyl solvolysis;[19] these substrates react by neighboring aryl assistance and thus have a transition state similar to that for an S_N2 reaction. Similarly Swain and Langsdorf have observed a reduction in selectivity for aminolysis of benzyl halides upon changing the leaving group from chloride to bromide.[38] Kirby and Varvoglis observed a similar decrease in selectivity for the aminolysis of phosphate esters.[39]

Predictions regarding the effects of nucleophile variation can also be made. In this case, an increase in nucleophilicity means that N will better bear a positive charge and the right edge of the More O'Ferrall diagram, Figure 4, will be lowered. Lowering the lower right corner will give the perpendicular vector from B to I, while lowering the upper right corner will give a parallel vector from B to G. The new transition state will, therefore, lie at J, the resultant of these two vectors, and will be characterized by a reduction in R-X cleavage, essentially no change in N-R formation, and a decrease in charge development on R and X. Support for this prediction can again be taken from the study by Kirby and Varvoglis[39] of phosphate aminolysis and from the study of Swain and Langsdorf[38] of benzyl halide aminolysis. In both cases, these workers found that an increase in nucleophilicity was accompanied by a decrease in leaving-group ratio consistent with a decrease in R-X bond cleavage in the transition state.

Related Work

In their treatment of curved Hammett plots for nucleophilic substitution on benzyl derivatives, Young and Jencks[36] have applied the More O'Ferrall approach to predict substituent effects on transition-state structure. Similarly, Shiner applied Thornton's rules to predict perpendicluar effects on α-d's for benzyl solvolyses.[23] Shiner and his co-workers also have used the More O'Ferrall approach to explain some particularly confusing trends in α-d's for neophyl solvolysis, including the effects of leaving-group variation.[19] They were able to rationalize the observed effects by assuming a late transition state (approximately at point C, Figure 4). As we discussed above, leaving-group effects can also be explained by assuming a "midway" transition state at point B, Figure 4.

Harris and Kurz[10a] have also examined the effects of reactant variation on S_N2 transition state structure. Their work is essentially a critical examination and attempt at extension of Thornton's rules.[7] The present application of the More O'Ferrall approach successfully predicts the results of one experiment that the Harris-Kurz approach does not. The experiment is again one of Swain and Langsdorf;[38] these workers observed that, in the aminolysis of benzyl chlorides, the substitution of electron-withdrawing substituents in the benzyl derivative resulted in a decrease in leaving-group ratio. Referring to Figure 4, this substituent change would destabilize R^+X^- and move the transition state to I. Such a movement would give a transition state with reduced R-X bond cleavage, and would result in a reduced sensitivity to leaving-group effects. Harris and Kurz[10a] found that applying their modification of Thornton's rules led to the prediction, counter to experiment, of increased R-X cleavage and increased sensitivity toward leaving-group effects.

Failure of the Reactivity-Selectivity Relationship

As noted earlier, we have used the reactivity-selectivity relationship as one of our probes of variation in transition-state structure despite there being several instances in which the relationship has been observed to fail. This failure can possibly be explained on the basis of solvent effects,[26] or on the basis of highly reactive reagents having early transition states which reflect little of the difference in product energies.[5] However, the More O'Ferrall approach can also be used to identify instances in which a change in reactivity would not be expected to result in a change in selectivity. In our discussion above concerning the position of the S_N2 transition state on the reaction coordinate, we noted that for an early transition state (point A, Figure 4) an increase in reactivity (by stabilizing the upper left corner) would result in a new transition state in which there would be little or no change in N–R bond length and thus little or no change in selectivity. This result provides an example of what must be a general principle, which is that a transition state may move on a potential energy surface, but there need not be any movement along one of the bond-order coordinates. Thus, the failure of the reactivity–selectivity relationship may be exactly what is expected for certain variations in transition-state structure.

Young and Jencks[36] have also noted that a change in reactivity may not produce a movement of the transition state if the curvatures at the saddle point are sufficiently steep. This point can be illustrated by reference to the recent work of Arnett and Reich.[30] These workers found a constant selectivity despite variation in reactivity for the quaternization of substituted pyridines with methyl and ethyl sulfonates and iodides. Application of the More O'Ferrall approach to this reaction can be done by using Figure 4 with the understanding that R–X is a methyl or ethyl derivative and N is a substituted pyridine. Reactivity will increase for this reaction upon substitution of ethyl for methyl. This substitution will stabilize the upper left corner of Figure 4, and, if we assume that the transition state is at point B, it will result in movement of the transition state to point E. The transition state at point E will have less N–R bond formation and thus would be expected to be less selective. Contrary to this prediction, the change from methyl to ethyl is not accompanied by a change in selectivity, yet this same sort of prediction *is* consistent with the experimental results observed for similar substitutions in the benzyl series (above). An explanation for this dichotomy can be derived from the proposal of Young and Jencks:[36] the curvature at the saddle point would be expected to be much steeper for the simple methyl and ethyl compounds (the upper left corner is much "higher") than for the benzyl compounds, so that the predicted perpendicular movement simply does not occur or is much less important for the species less able to support a positive charge.

Another possible explanation for constant selectivities has been presented by Thornton,[40] and is based on a construction of energy profiles from crossing Morse-type curves for reactant and product. Using this approach it can be shown that the proportionality between changes in free energy of activation and free energy of reaction as a function of reactant change is determined by the slopes of the Morse-type curves at their points of intersection. Since the slopes along a significant portion of the sides of the Morse curves are essentially constant, this proportionality constant can be invariant, and an invariance of ρ values, β values, and selectivity can be expected over rather wide ranges of reactivity. Another way of phrasing this concept is to say that the More O'Ferrall approach is correct in predicting that transition-state geometry will change as a result of an increase in reactivity, but that this geometry change need not lead to a change in selectivity if the potential energy surfaces have certain characteristics.

In summary, we have pointed out several reasons for failure of the reactivity–selectivity relationship (or selectivity changes too small to measure) which permit us to retain the fundamental concepts embodied in the More O'Ferrall approach for predicting transition-state structure. However, it seems obvious that the reactivity–selectivity relationship is not a basic principle of chemistry. A major task of physical organic chemistry is to gain an understanding of these various possible explanations for failure of the reactivity–selectivity relationship, and to determine when a relationship between reactivity and selectivity can be expected to exist.

Experimental Section

Rates were determined conductimetrically and solvents prepared as described previously.[41] The benzyl chlorides were commercially available and were distilled before use, except for the *p*-nitro derivative, which was recrystallized from 95% ethanol.

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References and Notes

(1) For example, a better leaving group might be expected to give a heterolysis transition state in which cleavage of the bond to the leaving group is more advanced.

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Heavy-Atom Isotope Effects on the Alkaline Hydrolysis and Hydrazinolysis of Methyl Benzoate

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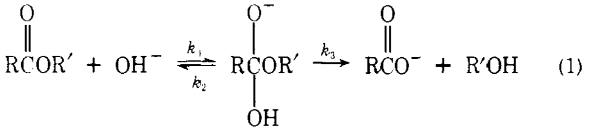
Abstract: A double-labeling procedure has been devised for use in measurement of heavy-atom isotope effects. This method is of particular value for measurement of isotope effects at sites which are not easily amenable to study by standard isotope-ratio techniques. Substrate is synthesized which is highly labeled at two positions—one the position of interest in the isotope effect experiment and the other a position whose isotope effect is easily measured by standard isotope-ratio methods. This labeled substrate is mixed with unlabeled substrate, and the "isotope effect" is measured for the measurable site. This apparent isotope effect is actually the product of the isotope effect at the measurable site and that at the site of interest. Separate measurement of the former isotope effect then permits calculation of the isotope effect at the site of interest. Heavy-atom isotope effects on the hydrolysis and hydrazinolysis of methyl benzoate at 25 °C in aqueous solution have been measured by this procedure, using the methyl carbon atom as the measurable site. In the alkaline hydrolysis the carbonyl oxygen isotope effect is $k^{16}/k^{18} = 1.0046 \pm 0.0020$; the carbonyl carbon isotope effect is $k^{12}k^{13} = 1.0426 \pm 0.0026$; the ether oxygen isotope effect is $k^{16}/k^{18} = 1.0062 \pm 0.0006$; the methyl carbon isotope effect is $k^{12}/k^{13} = 1.0004 \pm 0.0005$. For the hydrazinolysis at pH 7.9 the values are carbonyl oxygen, 1.0184 ± 0.0014; carbonyl carbon, 1.0410 ± 0.0022; ether oxygen, 1.0413 ± 0.0028; methyl carbon, 1.0022 ± 0.0004. These isotope effects indicate that the rate-determining step in the alkaline hydrolysis is the formation of the tetrahedral intermediate. The small magnitudes of the oxygen isotope effects require that the transition state in this step be relatively reactant-like. The isotope effects on the hydrazinolysis indicate that the decomposition of the tetrahedral intermediate is rate determining and that the transition state for this step is relatively product-like.

Introduction

The alkaline hydrolysis of simple esters such as methyl benzoate is widely accepted to occur by a two-step mechanism involving a tetrahedral intermediate[1] (eq 1), although such intermediates have been infrequently observed. The principal evidence favoring their existence is the small amount of oxygen exchange between the carbonyl oxygen and the solvent that sometimes accompanies the hydrolysis.[2] Formation of the tetrahedral intermediate is presumably rate determining, and the small amount of exchange reflects the fact that the intermediate usually goes on to products, rather than returning to starting materials.



$$\mathrm{R\overset{\overset{O}{\|}}{C}OR' + OH^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R\underset{\underset{OH}{|}}{\overset{\overset{O^-}{|}}{C}}OR' \xrightarrow{k_3} R\overset{\overset{O}{\|}}{C}O^- + R'OH} \qquad (1)$$

Isotopes have played an important role in the elucidation of the mechanism of ester hydrolysis. The pioneering work of Polanyi and Szabo[3] demonstrated that the alkaline hydrolysis of *n*-amyl acetate occurs with acyl-oxygen fission. Similar studies have been conducted with a variety of other esters.[4] Bender[2a] was the first to demonstrate that oxygen exchange between the solvent and the carbonyl oxygen accompanies the hydrolysis of benzoate esters. This phenomenon has subsequently been investigated in detail by Bender and collaborators[2b-d] and by Shain and Kirsch.[2e] The amount of exchange is always small; for example, in aqueous solution the alkaline hydrolysis of methyl benzoate is faster than oxygen exchange[2e] by a factor of about 28 at 25 °C. The measured hydrolysis to exchange ratios are all rendered rather uncertain by the small amount of exchange and by the difficulty of measuring isotopic compositions with the necessary precision.

The extent of oxygen exchange is generally taken to reflect the rate constant ratio k_3/k_2 in eq 1. However, as first pointed out by Bender,[2b] it is also possible that the small amount of exchange reflects a lack of protonic equilibria within the tetrahedral intermediate. More recently, a stereochemical rationalization for the small amount of exchange has been presented.[5]

Kinetic isotope effects have also played a role in the elucidation of the mechanism of ester hydrolysis. Carbonyl carbon isotope effects in the range $k^{12}/k^{14} = 1.06$–1.08 have been measured for the alkaline hydrolysis of a number of ethyl benzoates.[6a] These isotope effects indicate that extensive changes in bonding occur on going from ground state to transition state. Solvent isotope effects on the alkaline hydrolysis of a number of benzoate esters[6b] are in the range $k^{\mathrm{H_2O}}/k^{\mathrm{D_2O}} = 0.3$–$0.5$. Small oxygen isotope effects have been observed for the ether oxygen in the alkaline hydrolysis of acetyl tryptophan methyl ester[7] (1.007) and methyl formate[8] (1.0091). These isotope effects suggest that extensive carbon-oxygen bond breaking has not occurred in the transition states for these reactions. Carbonyl oxygen isotope effects on the methanolysis of phenyl benzoates have been shown by direct kinetic comparison[9] to be about $k^{16}/k^{18} = 1.02$, consistent with the idea that the carbonyl carbon-oxygen bond is somewhat weakened at the transition state.

The alkaline hydrolysis of methyl formate has been studied in detail by Sawyer and Kirsch.[8] The hydrolysis shows an ether oxygen isotope effect $k^{16}/k^{18} = 1.009$ at 25 °C and a formyl hydrogen isotope effect $k^{\mathrm{H}}/k^{\mathrm{D}} = 0.95$. These results suggest that the transition state in this reaction is relatively early, resembling the starting materials rather than the tetrahedral intermediate.

The aminolysis of esters is more complex than the alkaline

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