Theoretical Study of Nucleophilic Substitution on Simple Alkyl Systems

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Abstract: The substitutions of H_2O on ROH_2^+ and F^- on RF (R = methyl, ethyl, and isopropyl) have been studied by the INDO molecular orbital method. All of the significant geometrical parameters were optimized at each point along the reaction path. Both reactions are predicted to be direct substitutions when R = methyl. The F^- + RF reaction path becomes complex when R = ethyl and isopropyl. Deep energy minima corresponding to hydrogen-bonded species unlikely in solution suggest that this is not an ideal model reaction. The $H_2O + ROH_2^+$ reaction is better behaved, but the reaction paths are more complex for R = ethyl and isopropyl than for R = methyl. An additional energy minimum is found for R = isopropyl, which corresponds to a possible "ion pair". On the basis of the results of these calculations a general and experimentally verifiable model is proposed for nucleophilic substitution where the "intimate" and "solvent-separated ion pairs" of uncertain geometry are replaced by "anion stabilized" and "anion–cation stabilized intermediates" of specified geometries.

Nucleophilic substitution at saturated carbon has been the subject of renewed interest, much of which has been catalyzed by Sneen's proposal that SN2 reactions can occur on intimate ion pairs.[2] There is extensive evidence for the intermediacy of ion pairs in nucleophilic substitution reactions.[3] Winstein[4] has proposed that solvolysis reactions proceed through the generalized mechanism outlined in eq 1. In this mechanism, solvolysis product may arise from solvent attack upon either the "solvent-separated" ion pair or the dissociated carbocation. This scheme has been recently elaborated by Sneen,[2] Bordwell,[5] and Schleyer.[3] The existence of at least two different ion pairs was demonstrated by the observation that addition of small amounts of $LiClO_4$ to the acetolysis of optically active *threo*-3-*p*-anisyl 2-butylbrosylate caused a dramatic increase in the titrimetric rate constant for disappearance of brosylate (special salt effect), while the change in the rate of loss of optical activity was only that expected from a normal salt effect. It was therefore proposed that two different ion-pair intermediates must exist.[4] Both of these can eventually return to starting brosylate; both can undergo aryl migration (racemization); but, only one of them (the "solvent-separated" ion pair) can be intercepted by perchlorate, thereby impeding subsequent return. Since the experimental studies do not define the geometries of these species, the definitions of "intimate" and "solvent-separated" are clearly phenomenological. In particular, there exists no compelling reason that the "solvent-separated" ion pair must have one solvent molecule sandwiched between the anion and cation, as often envisioned. Because the elucidation of the geometries of these ion pairs (particularly that of the "solvent-separated" ion pair) is a subject of substantial interest that could lead to a more complete understanding of nucleophilic substitution at saturated carbon and because direct experimental determination of these geometries is extremely difficult (especially in the absence of alternative testable models), we have undertaken to explore the potential surfaces of various nucleophilic substitution reactions in the hope of providing a verifiable model for these ion pairs. At the same time, we hope to gain whatever insight into the general mechanism for nucleophilic substitution at saturated carbon that can be provided by a semiempirical MO study of these potential surfaces.

$$\begin{tikzcd}
\mathrm{R{-}X} \arrow[r, leftrightharpoons] & \mathrm{R^+X^-} \arrow[r, leftrightharpoons] & \mathrm{R^+X^-} \arrow[r, leftrightharpoons] & \mathrm{R^+ + X^-} & (1) \\
 & \text{intimate ion pair} & \text{solvent-separated ion pair} \arrow[d, "\mathrm{HOS}"] & \text{dissociated ions} \arrow[d, "\mathrm{HOS}"] & \\
 & & \mathrm{ROS} & \mathrm{ROS} &
\end{tikzcd}$$

There have been several[5] previous MO studies on nucleophilic (SN2) substitution: most notably, those of Simonetta et al.[6], and Veillard et al.[7] Both of these groups studied the symmetrical reaction of F^- with CH_3F. Simonetta showed that although CNDO calculations predict the symmetrical "transition state" for this reaction to be more stable than the isolated reactants (or products), introduction of specific solvation interactions in the form of several water molecules leads to an activation energy for this process.[6] Veillard (who also studied $H^- + CH_4$ and the two possible $H^- + CH_3F$ processes) showed that ab initio calculations with an appropriate basis set predicts a barrier of 7.9 kcal/mol for the symmetrical reaction of F^- with CH_3F in the absence of solvent.

Since the complexity of the previous calculations made the study of larger systems with more complete geometrical optimization prohibitively expensive, we decided that a more complete semiempirical study of the general problem was warranted.

Methods

The molecular orbital calculations were performed using the INDO method.[8] This method was chosen as it is (a) well documented; therefore, the results are interpretable within the context of many other calculations reported using the same or similar (e.g., CNDO) methods; and (b) not overly parameterized; thus, although the results (as those of all MO calculations on complex molecules) should be approached with some caution, the basic molecular orbital model is reasonably well preserved.

The reaction paths were obtained by fixing a series of distances between the nucleophile and reactive carbon, then completely optimizing all the remaining geometrical parameters except those involving bonds to hydrogen, where the standard Pople[9] bond lengths and bond angles (not dihedral) were used. These bonds were not optimized to save computation and to avoid formation of hydrogen-bridged intermediates which INDO and CNDO favor.[10] Such an optimization is equivalent to complete optimization (except as noted) with the constraint that the nucleophile move only on the surfaces of a series of concentric spheres. The reaction path is determined by connecting the minimum on each sphere.

The optimization was performed using a steepest-descent minimization procedure developed by Chaillet, Dargelas, and Liotard.[11] This program uses the standard version of CNINDO to perform the MO part of the calculation. Reproducibility of energy minima (from different starting geometries) was ±0.1 kcal/mol.

The substitution of water on protonated alcohols was chosen as the model reaction, since it probably better mimics nucleophilic substitution in solution than does the more usual F^- + RF reaction. Nevertheless, the paths of the latter reactions were also calculated for

Table I. Calculated Properties for Various Stages of Nucleophilic Substitution of Water on Alcohols[a]

	ROH (alcohol)	ROH_2^+ (protonated alcohol)	$(H_2OROH_2)^+$ (symmetrical)	R^+ (carbocation)
Methyl				
r(C-O), Å	1.378	1.408	1.539	
∠(OCH), deg	108	109	90	
∠(HCH), deg	109	111	120	120
q_{C_α}	0.268	0.202	0.345	0.545
q_R	0.126	0.370	0.339	1.000
ΔE(protonation)		−261 kcal/mol		
Ethyl				
r(C-O), Å	1.383	1.425	1.550	
∠(OCC), deg	108	110	95	
∠(HCC), deg	112	115	121	124
r(C-C), Å	1.477	1.471	1.494	1.388
q_{C_α}	0.277	0.240	0.346	0.424
q_R	0.148	0.427	0.398	1.000
ΔE(protonation)		−269 kcal/mol		
Isopropyl				
r(C-O), Å	1.396	1.442	1.577	
∠(OCC)	109	109	93	
∠(CCC)	114	115	122	129
∠(HCC)	109	112	119	116
r(C-C), Å	1.484	1.480	1.492	1.419
q_{C_α}	0.262	0.250	0.324	0.397
q_R	0.167	0.464	0.434	1.000
ΔE(protonation)		−278 kcal/mol		

[a] All bond lengths and angles involving oxygen refer to the oxygen of the alcohol.

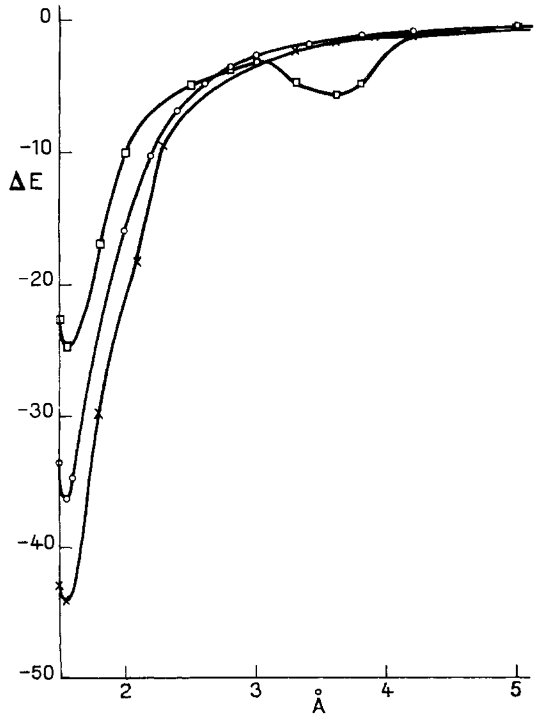


Figure 1. Stabilization of $ROH_2^+ + H_2O$ (kcal/mol) vs. C-O distance of approaching H_2O: X, R = methyl; ○, R = ethyl; □, R = isopropyl; ΔE taken as zero at 6 Å C-O distance.

comparison. Since solvation of the incipient anion is undoubtably an important driving force for many nucleophilic substitutions (particularly solvolyses) and it is reasonable that this solvent stabilization of the leaving group occurs early along the reaction path (protonated alcohols are generally considered to be intermediates in nucleophilic substitutions), we considered H_2O substitution on *protonated* alcohols. This model also has the computational advantage of being a symmetrical reaction. The alkyl groups used were methyl, ethyl, and isopropyl (severe SCF convergence problems were encountered for protonated *tert*-butyl alcohol + water). The alkyl groups were varied

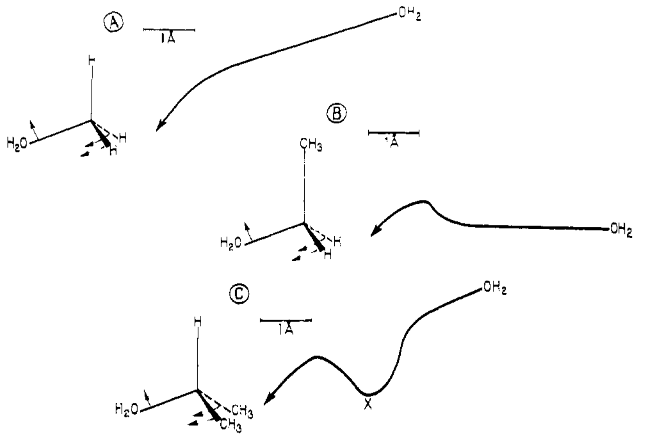


Figure 2. Optimized approaches of H_2O to protonated (A) methyl alcohol, (B) ethyl alcohol, and (C) isopropyl alcohol. The approximate geometrical changes of the protonated alcohols are indicated by the small arrows. More precise data appear in Table I. The point marked with an X in part C corresponds to the energy minimum at 3.6 Å in Figure 1.

to allow differences in reactivity to be manifest. In particular, ion-pair formation might be more likely to arise with larger alkyl groups, where more significant internal charge reorganization is possible.

Results

The significant features of the optimized alcohols, protonated alcohols, symmetrical "transition states", and corresponding carbocations are collected in Table I. It is immediately evident that the significant geometrical changes upon protonation of the alcohols are lengthening of the C–O bond and a slight broadening of the bond angles involving the substituted carbon. Both of these trends are continued upon going to the symmetrical "transition state".

The calculated energy differences as a function of approach of the nucleophile are plotted in Figure 1, while the reaction paths are indicated in Figure 2. The energy differences indicated are relative to the energy at 6-Å separation of nucleophile

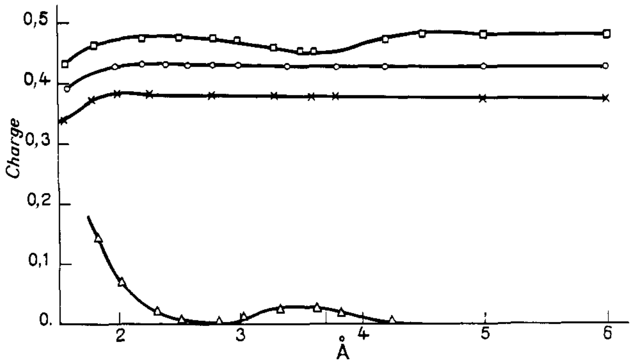


Figure 3. Variation of charge upon the approach of H_2O to ROH_2^+: X = methyl; ○ = ethyl; □ = isopropyl; and △ = H_2O (approaching protonated isopropyl alcohol).

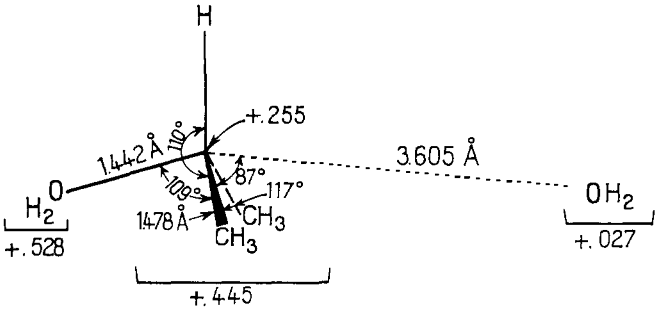


Figure 4. The geometry and charge distribution for the anion-cation stabilized intermediate in the H_2O displacement on protonated isopropyl alcohol. This geometry corresponds to the minimum at 3.6 Å in Figure 1 and the point marked by an X in Figure 2C.

and substrate. The sums of the energies for the isolated species were not used, since, as observed by Daudey and Malrieu, they overestimate the stability of the combined system due to an increase in the basis set for each part.[12] The maximum distance studied was 6 Å, since it is unlikely the species considered could be nearest neighbors in solution at greater separation.

Several characteristics are immediately apparent. First, the symmetric "transition states" are all calculated to be more stable than the reactants (or products). While this may be partially due to the tendency of INDO (or CNDO) to overestimate certain bonding interactions, it may also be due to our neglect of specific solvations and the fact that *protonated* alcohols are already fairly active species. Second, the net positive charges on the alkyl groups increases in the order methyl < ethyl < isopropyl, while the net charges on C_α decreases, indicating increasing charge delocalization. Third, while the energy decreases monotonically with approach of the nucleophile for methyl and ethyl, there is an additional minimum (at ~3.6 Å) for the isopropyl substitution. A similar minimum is evident for the charge on isopropyl (coupled with a maximum for the approaching water) in Figure 3. These extrema correspond with the geometry indicated with an (x) in Figure 2C. An exploration of the surface near this point showed it to be rather flat. Changes in the $C-O_2$ distance of 0.1 Å and changes in the OCC angle of 5° caused energy changes of only 0.2 kcal/mol close to the experimental error of the minimization. This geometry corresponds to a probable intermediate, likely to be an "ion pair". Its geometry (indicated in Figure 4) is similar to that of protonated isopropyl alcohol with the C-C-C and H-C-C bond angles slightly broadened. The C-O bond length remains unchanged. The central carbon is still far from assuming the trigonal sp^2 geometry.

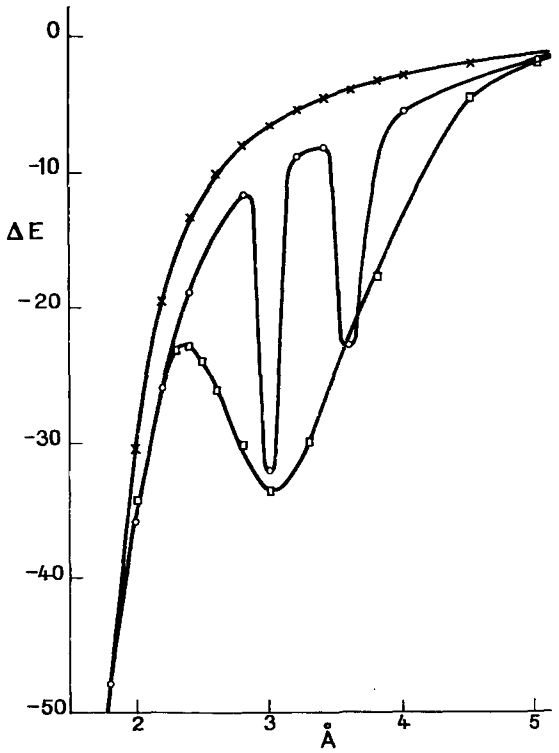


Figure 5. Stabilization of $F^- + RF$ (kcal/mol) vs. C_α-F distance: X: R = methyl; ○: R = ethyl; □: R = isopropyl; ΔE taken as zero at 6 Å C-F^- distance. All three minima correspond to specific interactions between F^- and hydrogens on the alkyl groups.

Table II. Calculated Properties for Alkyl Fluorides and Symmetrical Substitution "Transition States"

	RF (alkyl fluoride)	F-R-F (symmetrical)
Methyl		
r(C-F), Å	1.351	1.463
∠(FCH)	109	90
∠(HCH)	110	120
q_{C_α}	0.327	0.604
q_R	0.231	0.134
Ethyl		
r(C-F), Å	1.363	1.474
∠(FCC)	111	93
∠(HCC)	114	120
r(C-C), Å	1.474	1.499
q_{C_α}	0.332	0.563
q_R	0.257	0.147
Isopropyl		
r(C-F), Å	1.374	1.488
∠(FCC)	109	92
∠(CCC)	115	120
∠(HCC)	110	120
r(C-C), Å	1.479	1.501
q_{C_α}	0.322	0.518
q_R	0.277	0.171

Similar data for the reaction of $F^- + RF$ are collected in Table II and Figure 5. Unlike the case of $H_2O + ROH_2^+$, deep energy minima (particularly evident in the ethyl substitution at 3.0 and 3.6 Å) are observed which correspond to strong hydrogen-bonding interactions between the methyl hydrogens and F^-. It is extremely unlikely that these minima could exist in solution, where hydrogen bonding to the solvent must be more advantageous. Nevertheless, the $F^- + CH_3F$ reaction (where the hydrogens are *negative*) is well behaved, following a reaction path essentially equivalent to that drawn for $H_2O + CH_3OH_2^+$ (Figure 2A). This result agrees well with that reported by Simonetta[6] in the absence of solvation.

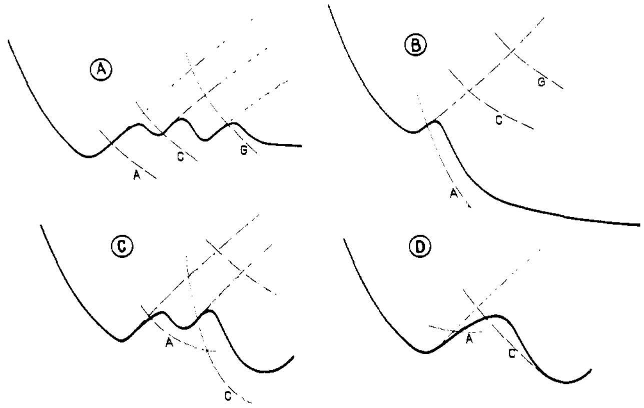


Figure 6. Energy (vertical) vs. reaction-path (horizontal) diagrams for various possible types of nucleophilic substitution obtained by adding anion stabilization (A), cation stabilization (C), and general solvation (G) to an arbitrary reaction coordinate for heterolytic R–X bond cleavage. Broken lines indicate individual contributions, while solid lines indicate the sum in each case. See text for discussion.

Discussion

Several of the calculated differences upon changing R in the $H_2O + ROH_2^+$ substitutions reflect the increasing carbocation character of R upon changing from methyl to ethyl to isopropyl. Thus, the C–O distance and the charge on R increase both for ROH_2^+ and the symmetrical "transition state"; the charge on C_α in the "transition state" approaches that of the free carbocation; and, the stabilization gleaned from the addition of H_2O to ROH_2^+ decreases. Nevertheless, there remain several important trends that emphasize the difference between the "transition states" and the corresponding carbocations. In particular, the charge on the alkyl group does not approach unity; the charge is much more localized on C_α in the "transition state" than in the carbocation; and the C–C bond distances (for ethyl and isopropyl) increase upon going from ROH to the "transition state", but decrease upon going to the free carbocation. These data suggest that even in a simple SN2 reaction of H_2O on ROH_2^+, the R group assumes increasing cation character as R changes from methyl to ethyl to isopropyl, but that R does not tend toward the structure of the free carbonium ion. Thus, we might anticipate that changes in the system (i.e., electron-donating substituents) that stabilize the positive charge on R ought to facilitate the reaction, but we should not expect too close a parallel with carbonium-ion stabilization by the same substituents. One should note, however, that in the series $F^- + RF$, C_α becomes more positive, but R becomes more *negative* in the "transition state". Evidently, the change in the charge on R and C_α depend upon both the nucleophile/leaving group and R. It is, therefore, difficult to define the charge distribution, and consequently, to predict substituent effects for the general case of an SN2 reaction.

The reaction paths for the $H_2O + ROH_2^+$ reactions (Figure 2) indicate that the direct colinear approach and displacement used in previous calculations[6,7] is a good approximation when R = methyl, worse for ethyl, and quite poor for isopropyl. One should note, however, that for C–O distances of less than 2 Å, all three reaction paths become quite similar.

The most evident difference between the reaction paths for isopropyl and the others is the existence of an energy minimum at a C–OH_2 distance of 3.6 Å (Figure 1), which corresponds to a deviation from a direct approach of H_2O (Figure 2C). This minimum appears to result partly from an electrostatic attraction of the water oxygen to the centroid of the delocalized charge on the protonated isopropyl alcohol. The small amount of charge transfer from the H_2O to the ROH_2^+ evident from Figure 3 suggests that there may also be some weak direct bonding between these species. Further approach of the water must ultimately lead to a strong direct bond with C_α of the protonated alcohol. Consequently, the reaction path continues by moving away from this position towards C_α. The methyl and ethyl groups apparently do not delocalize the positive charge enough to render the optimum geometry for electrostatic interactions sufficiently different from the direct approach. Thus their reaction paths do not show similar minima. However, the approach of H_2O to protonated ethanol does indicate slight attraction toward the methyl group rather than the H's.

We suggest that the intermediate corresponding to the extra minimum on the isopropyl reaction path might represent one of the "ion-pair" intermediates originally suggested by Winstein.[4] It is of interest to note here that virtually all of the experimental evidence for ion-pair intermediates in solvolysis reactions comes from studies of systems with alkyl groups that are more complex than ethyl.

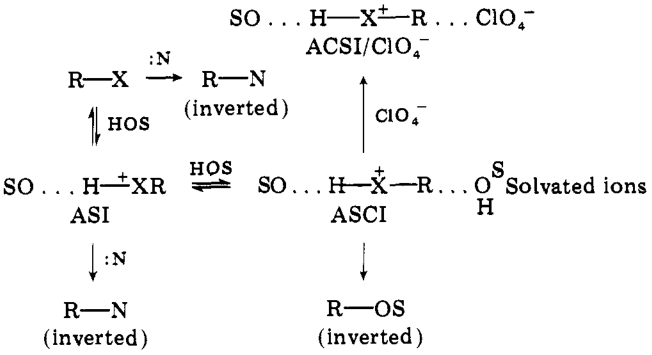
We must now decide which ion pair the structure (Figure 4) corresponds to: "intimate" or "solvent-separated". We suggest that this is actually Winstein's "solvent-separated" ion pair for the reasons outlined below.

Solvolysis reactions occur virtually exclusively in acidic media and all normal leaving groups have atoms with lone pairs. Furthermore, the "ionizing power" of the solvent is related to its acidity (among other factors). It seems reasonable that the first step in a solvolysis reaction should be protonation of the leaving group (or more exactly, transfer of a hydrogen-bonded proton from solvent to leaving group). Only at this point should there exist a driving force for stabilization of the (now positive) reactant by solvent from the other side. If these two processes occur sequentially, there could be two minima on the potential surface which correspond to the end of each process. Thus, the "intimate ion pair" could be nothing more than a protonated substrate, stabilized by solvent from the back side. Another way of describing these two species could be anion-stabilized intermediate (ASI) for the "intimate ion pair", and anion–cation stabilized intermediate (ACSI) for the "solvent-separated ion pair". We prefer to call these species intermediates as they may not, strictly speaking, be ion pairs.

Whether either or both intermediates exist in any specific reaction will depend upon the relative anion and cation stabilizing powers of the medium and the requirements of the substrate. Let us consider an arbitrary reaction profile for the heterolytic cleavage of the R–X bond of a hypothetical substrate in the absence of solvent or nucleophile. We, then, use this as an approximate reaction path to illustrate the effects of anion and cation stabilization. If anion and cation stabilization are properly balanced (Figure 6A), minima corresponding to both the ASI and the ACSI are indicated. If, however, the solvent is a very strong anion stabilizer (i.e., antimony pentafluoride, fluorosulfuric acid, etc.), the R–X bond breaks immediately upon anion stabilization, producing solvated ions without the intermediacy of either the ASI or the ACSI (Figure 6B). If the solvent is a moderate anion stabilizer, but a strong cation stabilizer, the ASI is indicated, but the product is formed directly, without the intermediacy of the ACSI (Figure 6C). The cation stabilizer need not be solvent if a better nucleophile (i.e., azide) is present. Such a case is equivalent to the Sneen hypothesis of SN2 attack on an "intimate ion pair". Finally, reaction of a good nucleophile in a solvent that is a poor anion stabilizer (i.e., aprotic) could go directly to product without the prior formation of either the ASI or the ACSI (Figure 6D). This corresponds to a classical SN2 reaction. Since any chirality extant in R–X is preserved in both the ASI and the ACSI, all product formed by backside attack on the ASI or by collapse of the ACSI to form a bond with the cation stabilizer should have inverted configuration.

The special salt effect is explained by displacement of the cation-stabilizing solvent molecule by the anion of the special salt (i.e., ClO_4^-) from the same side. This is plausible, since (a) the energy is not very sensitive to displacement (particularly lateral) of the cation stabilizing H_2O in H_2O + protonated isopropyl alcohol reaction, and (b) the very existence of a special salt effect implies that the interaction of ClO_4^- with the ACSI must be extremely stabilizing. Formation of this new ClO_4^-/ACSI should ultimately lead to loss of the leaving group followed by formation of product either with retained configuration (the nucleophile immediately takes the place of the leaving group) or racemization due to the formation of symmetrically solvated carbocations. The above description is summarized in Scheme I. This scheme has certain similarities and differences with those recently proposed by Sneen,[2] Bordwell,[5] and Schleyer.[13] In particular, only substitution with inversion is possible from the ACSI. Sneen[2] similarly suggested that the solvent-separated ion pair could collapse to product, but his scheme requires a product with retention of configuration. We have also included the direct SN2 substitution, which may be particularly important in primary and methyl solvolyses. The structure of the ACSI bears a strong resemblance to the "solvated ion sandwich" proposed by Bordwell.[5] Schleyer[14] proposes that the solvent-separated ion pair can only give retained R-OS, but either inverted or racemized R-N. One should note that R-N could be formed with inversion using the scheme proposed in this paper if N^- acts as a special salt and forms an ACSI/N^- analogous to the ACSI/ClO_4^- of Scheme I.

Scheme I



N = any nucleophile (including HOS)

This scheme has the particular advantage of putting the nucleophilic "solvent assistance" proposed by Schleyer[14] into a general context. In addition it accommodates the suggestion that the low nucleophilicity of trifluoroacetic acid and the high degree of internal return in this solvent might be due to nonnucleophilic cation stabilization by the CF_3 group.[15]

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Spiro Meisenheimer Complex from Catechol 2,4,6-Trinitrophenyl Ether. Rate-Limiting Proton Transfer as a Consequence of a Very Fast Intramolecular Nucleophilic Attack[1]

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Abstract: Temperature-jump experiments in 50% Me_2SO–50% water (v/v) show that the proton transfer is rate limiting in the formation of the spiro Meisenheimer complex (**9**) from catechol 2,4,6-trinitrophenyl ether. This is not because of an abnormally slow proton transfer but a consequence of a very fast rate of complex formation ($k_1 = 1.2 \times 10^9\ s^{-1}$). This rate is the highest measured to date for nucleophilic attack on an aromatic carbon.

The formation of spiro Meisenheimer complexes involves both intramolecular nucleophilic attack and proton transfer, as depicted in reaction 1. When Y = O, as in the prototype reaction 2, proton transfer is a rapid equilibrium step preceding the rate-limiting nucleophilic attack in all cases reported to date.[2-6] When Y = NR, however, as in the prototype reaction