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Theoretical Study of S_N2 Reactions Involving Cationic Substrates

Krishnan Raghavachari,[*1a] **Jayaraman Chandrasekhar,**[*1b] **and R. C. Burnier**[1b]

Contribution from AT&T Bell Laboratories, Murray Hill, New Jersey 07974, and the Department of Chemistry, Purdue University, West Lafayette, Indiana 47907.

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Abstract: Ab initio calculations employing extended basis sets with polarization functions and including significant electron correlation as well as zero point vibrational energy corrections have been performed on the stationary points of the nucleophilic displacement reaction in three systems: (i) $H_2O + CH_3OH_2^+$, (ii) $CH_3OH + CH_3OH_2^+$, and (iii) $H_2O + CH_3CH_2OH_2^+$. Although the most stable structure corresponds to the "front-side" complex in which a proton is solvated by two neutral oxygen bases (complexation energy = −30, −35, and −27 kcal/mol, respectively), a backside S_N2 pathway appears feasible in all three cases, requiring no overall activation energy for the first two reactions and a small activation energy for the third reaction. The reaction profiles in these cationic systems are qualitatively similar to the gas-phase results on anions, involving double minima corresponding to loose ion–dipole complexes with unsymmetrical C–O lengths, separated by a more symmetrical transition state. The most stabilized transition state (−5 kcal/mol relative to the reactants) and hence the reaction with the highest efficiency corresponds to (ii). The results are in excellent agreement with available gas-phase studies on proton-bound alcohol dimers.

In the past decade several familiar and important condensed-phase reactions such as acid- and base-induced eliminations, nucleophilic substitution at saturated and aromatic centers, etc, have been shown to have their counterparts in gas-phase chemistry as well.[2–7] While the formal reactions are analogous, the detailed mechanisms are by no means identical in the two phases. Reactions involving ionic species are particularly sensitive to medium effects. For example, the double-well reaction surface of a typical S_N2 reaction in the gas phase[6,7] provides a striking contrast to the familiar unimodal energy surface in solution.[8,9] A detailed knowledge of potential surfaces in the gas phase is therefore essential for resolving the important role of solvation on the structure and reactivity of molecules.

Current theoretical methods are particularly suited for examining potential surfaces in the absence of medium effects. While it is impossible to examine every conceivable reaction pathway, specific mechanistic questions can often be probed. In this paper, we consider the feasibility of a reaction pathway currently under active experimental investigation, viz., the backside nucleophilic displacement reaction at a saturated carbon atom in a cationic substrate (eq 1).[10–13] Reactions of type 1 are well-known in solution chemistry,[14] while the first examples in the gas phase were reported by Holtz, Beauchamp, and Woodgate.[10a] These reactions are analogous to the more familiar nucleophilic displacements involving anionic nucleophiles and leaving groups (eq 2), which have been extensively investigated experimentally in solution[8,9] and gas phase,[6,7] as well as by theory.[15,16] The differences in the charge patterns of reactions 1 and 2 lead to several intriguing features. Due to the greater stability of neutral molecules relative to anions, reaction 1 is characterized by an excellent leaving group but also by a poor nucleophile. An S_N1 type mechanism would therefore be favored, particularly in reactions involving tertiary centers. Even if reaction 1 indeed follows an S_N2 course, an interesting variation is possible. While the favorable direction of approach for an anionic nucleophile is unquestionably toward the backside relative to the leaving group,[6–9] this is not necessarily true for the interaction between a neutral nucleophile and a cationic substrate. In fact, the optimum geometry of the ion–


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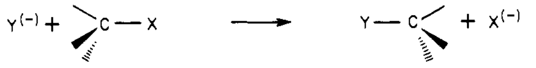
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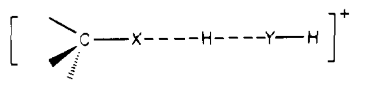
molecule complex in reaction 1 usually corresponds to a hydrogen-bonded structure, **1**.[2,10,11] Such proton-bound complexes,



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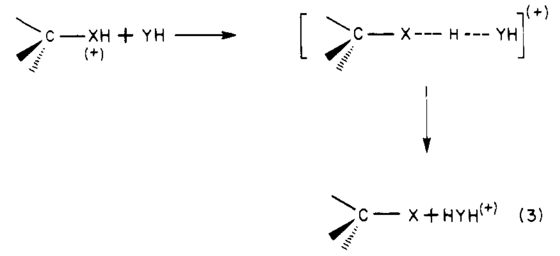
especially those involving alcohols, are quite stable and have been the subject of numerous experimental[2,10-13,17] and theoretical[18] investigations. While **1** is obviously involved in a potential proton-transfer reaction (eq 3), it can also be the precursor to a



(3)

front-side nucleophilic displacement reaction. Interestingly, reaction 1 is observed only when it is exothermic and reaction 3 is endothermic. Beauchamp and co-workers therefore made the reasonable assumption that nucleophilic displacements in cations generally involve structures like **1** and hence a front-side attack.[2,10] This, however, has no precedent in conventional S_N2 reactions (eq 2), in solution or in the gas phase.

More recently, evidence against the front-side nucleophilic displacement mechanism has been obtained in two cases. The displacement of water from protonated 2-butanol by another alcohol molecule has been shown by Hall et al. with the aid of optically pure compounds to occur via a backside attack.[13] A similar mechanism was demonstrated by Kleingeld and Nibbering for an analogous reaction involving methanol using ^{18}O labeling.[12b] Although these are unambiguous experiments, they do not provide detailed information regarding the nature of the S_N2 reaction profile in these systems. In particular, the question whether gas-phase cationic S_N2 reactions also feature a double-well potential like their anionic counterparts remains open. The energies of the stationary points of the cationic S_N2 reactions relative to the hydrogen-bonded complexes like **1** are also not available.[19] The reaction surface may also be sensitive to alkyl substitution at the substrate and the nucleophile. In order to clarify these points we have carried out high level ab initio calculations on three model cationic S_N2 reactions:

$$H_2O + CH_3OH_2^+ \rightarrow H_2OCH_3^+ + OH_2 \qquad (4)$$

$$HOCH_3 + CH_3OH_2^+ \rightarrow (CH_3)_2OH^+ + OH_2 \qquad (5)$$

$$H_2O + CH_3CH_2OH_2^+ \rightarrow H_2OCH_2CH_3^+ + OH_2 \qquad (6)$$

We have examined the stationary points (minima and transition states) of the backside nucleophilic displacement reaction as well as the hydrogen-bonded ("front-side") complexes analogous to **1**, in each case. The experimental data available for reaction 5 provide calibration for our calculations.[11] Our results for the degenerate reactions 4 and 6 which indicate the effect of varying the substrate and the nucleophile constitute predictions calling for experimental verification. The present study represents the first detailed theoretical examination of nucleophilic substitution on cationic substrates.

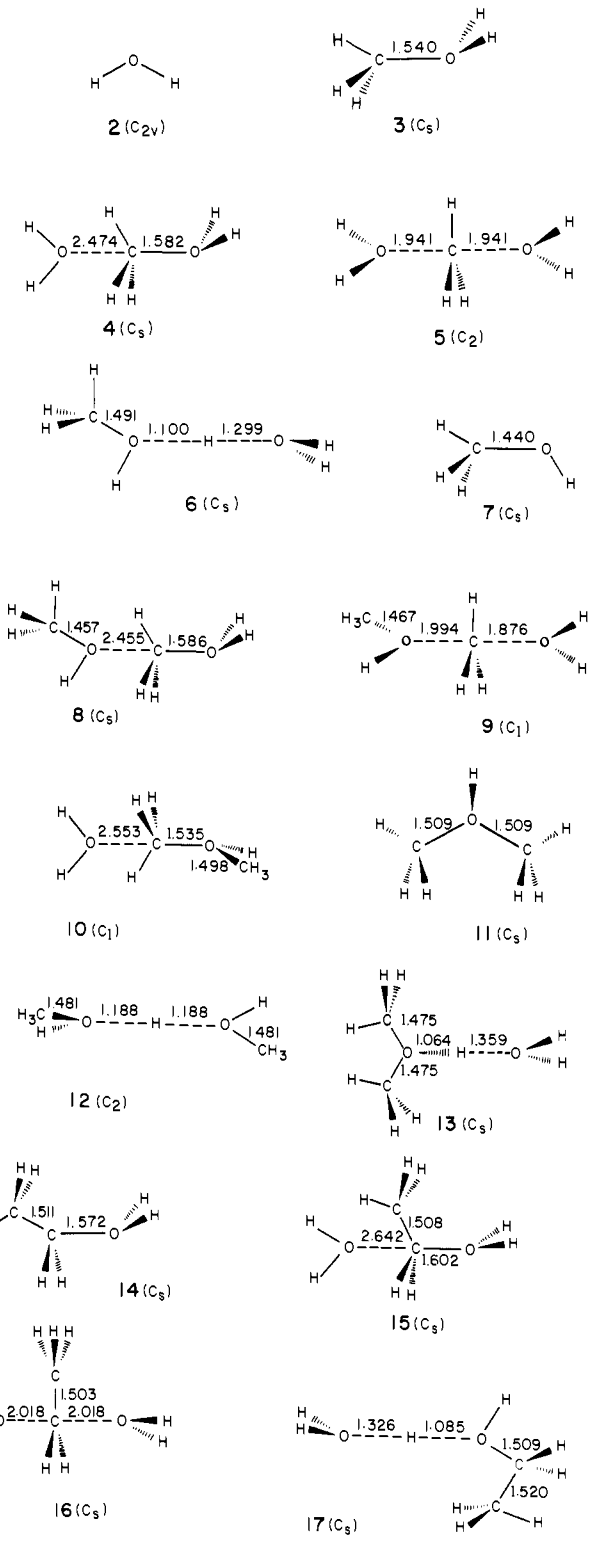


Figure 1. Stationary points considered in this study for reactions 4–6. Bond lengths are in angstroms, and bond angles are in degrees.

Computational Details

The geometries of all structures considered, **2**–**17** (Figure 1), were fully optimized at the Hartree–Fock level with the split-valence 3-21G basis set using analytical energy gradients.[20] The calculated minima and transition states were rigorously characterized by diagonalizing the analytically evaluated matrix of force constants.[21] These geometries

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Table I. Total and Relative Energies[a] for the Stationary Points of Reaction 4 ($H_2O + H_3C\text{-}OH_2^+$)

structure	HF[b]	$\epsilon^{(2)b}$	$\epsilon^{(3)b}$	$\epsilon_{vib}{}^c$	E_{rel}	$E_{exptl}{}^e$
$H_2O + H_3C\text{-}OH_2^+$ (**2** + **3**)	-191.37700	-527.76	-26.30	55.6	0.0	0.0
$[H_2O\cdots CH_3\text{-}OH_2]^+$ (**4**)	-191.39496	-529.91	-25.63	57.5	-10.3	
$[H_2O\cdots CH_3\cdots OH_2]^+$ (**5**)[d]	-191.38089	-528.78	-24.73	56.9	-0.8	
$[H_2O\cdots H\cdots OH\text{-}CH_3]^+$ (**6**)	-191.42037	-538.26	-23.61	58.1	-29.6	
H_2O (**2**)	-76.02228	-197.04	-6.29	13.7		
$H_3C\text{-}OH_2^+$ (**3**)	-115.35472	-330.72	-20.01	41.9		
H_3O^+	-76.30766	-195.66	-7.89	22.0		
$H_3C\text{-}OH$	-115.04486	-336.45	-17.53	34.2		
$H_3O^+ + H_3C\text{-}OH$	-191.35252	-532.11	-25.42	56.2	13.8	11.9

[a] Total energies in hartrees, correlation energies in millihartrees, vibrational and relative energies in kcal/mol. Geometries optimized with the 3-21G basis were used throughout. [b] Obtained with the 6-31G** basis. [c] Obtained with the 3-21G basis. [d] Transition structure. [e] Reference 28.

Table II. Total and Relative Energies[a] for the Stationary Points of Reaction 5 ($H_3C\text{-}OH + H_3C\text{-}OH_2^+$)

structure	HF[b]	$\epsilon^{(2)b}$	$\epsilon^{(3)b}$	$\epsilon_{vib}{}^c$	E_{rel}	$E_{exptl}{}^e$
$H_3C\text{-}OH + H_3C\text{-}OH_2^+$ (**3** + **7**)	-230.39958	-667.17	-37.54	76.1	0.0	0.0
$[H_3C\text{-}OH\cdots CH_3\text{-}OH_2]^+$ (**8**)	-230.41731	-670.02	-36.76	77.3	-11.2	
$[H_3C\text{-}OH\cdots CH_3\cdots OH_2]^+$ (**9**)[d]	-230.40681	-670.03	-35.58	76.6	-4.6	
$[H_3C\text{-}OH\text{-}CH_3\cdots OH_2]^+$ (**10**)	-230.43444	-670.64	-36.78	77.2	-22.5	
$H_3C\text{-}OH\text{-}CH_3^+ + OH_2$ (**2** + **11**)	-230.41837	-667.92	-37.41	75.3	-13.0	-12.0
$[H_3C\text{-}OH\cdots H\cdots OH\text{-}CH_3]^+$ (**12**)	-230.44865	-678.43	-34.66	77.1	-35.1	
$[(H_3C)_2\text{-}OH\cdots H\cdots OH_2]^+$ (**13**)	-230.45612	-678.43	-34.71	77.7	-39.2	
$H_3C\text{-}OH$ (**7**)	-115.04486	-336.45	-17.53	34.2		
$H_3C\text{-}OH_2^+$ (**3**)	-115.35472	-330.72	-20.01	41.9		
H_2O (**2**)	-76.02228	-197.04	-6.29	13.7		
$[H_3C\text{-}OH\text{-}CH_3]^+$ (**11**)	-154.39609	-470.88	-31.12	61.6		
H_3O^+	-76.30766	-195.66	-7.89	22.0		
$H_3C\text{-}O\text{-}CH_3$	-154.07178	-478.85	-27.92	53.7		
$H_3O^+ + H_3C\text{-}O\text{-}CH_3$	-230.37944	-674.51	-35.81	75.7	21.7	20.1

[a] Total energies in hartrees, correlation energies in millihartrees, vibrational and relative energies in kcal/mol. Geometries optimized with the 3-21G basis were used throughout. [b] Obtained with the 6-31G** basis. [c] Obtained with the 3-21G basis. [d] Transition structure. [e] Reference 28.

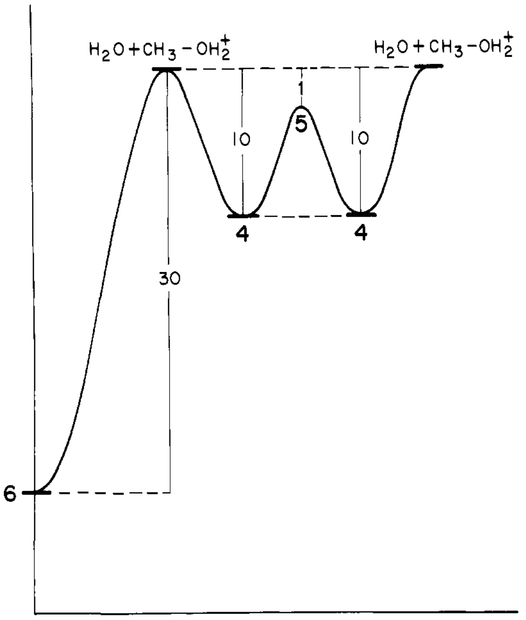

Figure 2. Calculated energy profile for reaction 4 ($H_2O + H_3C\text{–}OH_2^+$). Energy differences are in kcal/mol.

were employed in higher level calculations with the 6-31G** basis set which includes a set of d-type polarization functions on all non-hydrogen atoms and a set of p-type polarization functions on hydrogen atoms. Electron correlation effects were evaluated by means of third order Moller–Plesset perturbation theory (MP3) with the 6-31G** basis.[22]

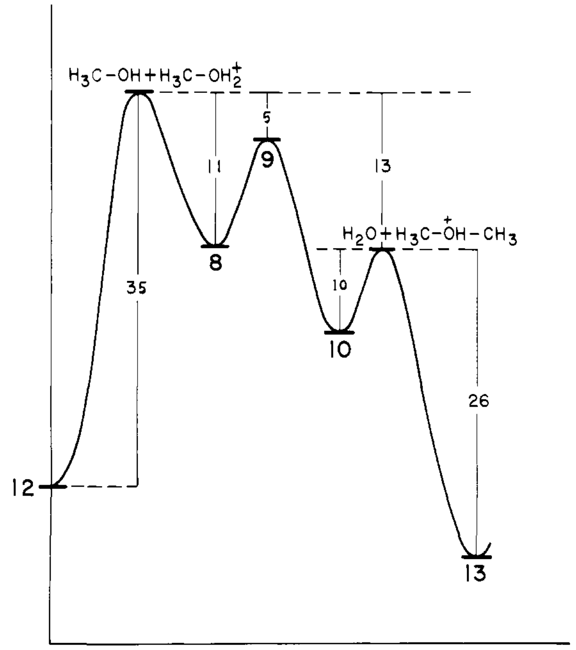

Figure 3. Calculated energy profile for reaction 5 ($H_3C\text{–}OH + H_3C\text{–}OH_2^+$). Energy differences are in kcal/mol.

The calculated total energies are presented in Tables I–III. The relative energies of the species involved in reactions 4–6 are also given. These latter values include zero-point vibrational energy corrections (at 0 K) obtained from the 3-21G vibrational frequencies. The calculated reaction profiles are graphically shown in Figures 2–4. Key geometrical features are indicated in structures **2**–**17** (Figure 1).

Results and Discussion

Reaction 5 with a calculated exothermicity of 13.0 kcal/mol (experiment, 12 kcal/mol)[2,11] differs from reactions 4 and 6 in

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Table III. Total and Relative Energies[a] for the Stationary Points of Reaction 6 ($H_2O + C_2H_5\text{-}OH_2^+$)

structure	HF[b]	$\epsilon^{(2)b}$	$\epsilon^{(3)b}$	$\epsilon_{vib}{}^c$	E_{rel}	$E_{exptl}{}^e$
$H_2O + C_2H_5\text{-}OH_2^+$ (**2** + **14**)	-230.42785	-670.54	-37.13	74.6	0.0	0.0
$[H_2O\cdots C_2H_5\text{-}OH_2]^+$ (**15**)	-230.44392	-672.98	-36.60	76.4	-9.5	
$[H_2O\cdots C_2H_5\cdots OH_2]^+$ (**16**)[d]	-230.42978	-669.77	-36.55	75.7	1.5	
$[H_2O\cdots H\cdots OH\text{-}C_2H_5]^+$ (**17**)	-230.46707	-681.46	-34.44	77.3	-27.1	
H_2O (**2**)	-76.02228	-197.04	-6.29	13.7		
$C_2H_5\text{-}OH_2^+$ (**14**)	-154.40557	-473.50	-30.84	60.9		
H_3O^+	-76.30766	-195.66	-7.89	22.0		
$C_2H_5\text{-}OH$	-154.08819	-480.03	-28.07	53.5		
$H_3O^+ + C_2H_5\text{-}OH$	-230.39585	-675.69	-35.96	75.5	18.5	17.3

[a] Total energies in hartrees, correlation energies in millihartrees, vibrational and relative energies in kcal/mol. Geometries optimized with the 3-21G basis were used throughout. [b] Obtained with the 6-31G** basis. [c] Obtained with the 3-21G basis. [d] Transition structure. [e] Reference 28.

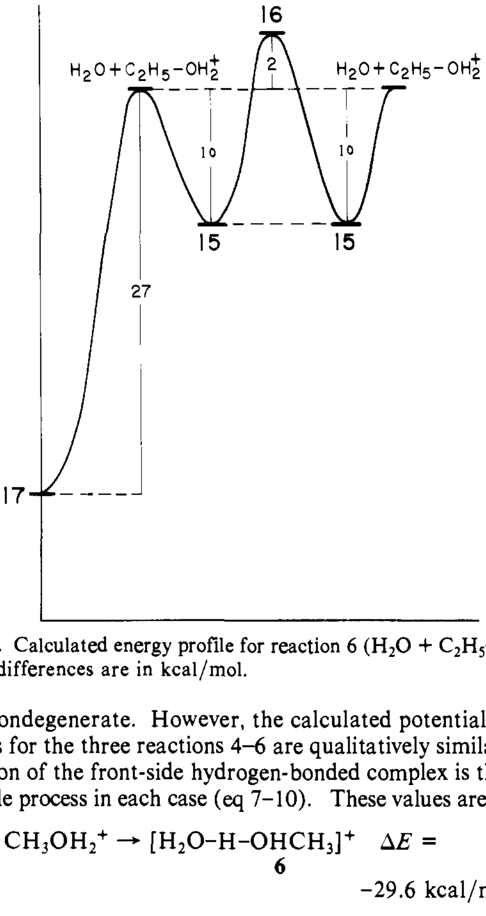

Figure 4. Calculated energy profile for reaction 6 ($H_2O + C_2H_5\text{-}OH_2^+$). Energy differences are in kcal/mol.

being nondegenerate. However, the calculated potential energy surfaces for the three reactions 4–6 are qualitatively similar. The formation of the front-side hydrogen-bonded complex is the most favorable process in each case (eq 7–10). These values are similar

$$H_2O + CH_3OH_2^+ \rightarrow \underset{\mathbf{6}}{[H_2O\text{-}H\text{-}OHCH_3]^+} \quad \Delta E = -29.6 \text{ kcal/mol} \quad (7)$$

$$CH_3OH + CH_3OH_2^+ \rightarrow \underset{\mathbf{12}}{[CH_3HO\text{-}H\text{-}OHCH_3]^+} \quad \Delta E = -35.1 \text{ kcal/mol} \quad (8)$$

$$H_2O + (CH_3)_2OH^+ \rightarrow \underset{\mathbf{13}}{[H_2O\text{-}H\text{-}O(CH_3)_2]^+} \quad \Delta E = -26.2 \text{ kcal/mol} \quad (9)$$

$$H_2O + C_2H_5OH_2^+ \rightarrow \underset{\mathbf{17}}{[H_2O\text{-}H\text{-}OHC_2H_5]^+} \quad \Delta E = -27.1 \text{ kcal/mol} \quad (10)$$

to the enthalpy changes involved in the formation of proton-bound dimers of water, methanol, and dimethyl ether (32, 33, and 31 kcal/mol, respectively).[2] Hirao et al. also obtained a value of 36.4 kcal/mol for the energy change in reaction 8 from calculations with the 4-31G basis set.[18a] This agreement is partly due to the cancellation of the effects of polarization functions and electron correlation (Table II), although the 4-31G basis seems to be superior to the smaller 3-21G basis set for hydrogen-bonding studies.

The calculated interaction energies in eq 7–10 are significantly larger than the hydrogen-bond energies involving neutral molecules.[23] These values are, however, not surprising since the importance of such enhanced hydrogen-bond strengths and their attenuation with increasing cluster size in ion–molecule complexes have been the subject of several previous studies.[2,17f,18]

The remarkable result from Table II is the stability associated with complexes **4**, **8**, **10**, and **15** in which the nucleophiles are aligned for a backside displacement reaction. These are non-hydrogen-bonded structures which are held just by ion–dipole interactions. The four complexes are more stable than the corresponding ion and dipole at infinite separation by an almost constant value, 10 ± 1 kcal/mol. This value is comparable to the ion–dipolar interaction energy of 8.6 kcal/mol between Cl^- and CH_3Cl,[24] the prototypical anionic S_N2 intermediate. In fact, the entire reaction profile for eq 4–6 is qualitatively not different from the usual double-well potential characteristic of gas-phase anionic S_N2 reactions.[2,6,7] Thus, the ion–dipole complexes are separated by a more symmetrical transition state in each reaction. The energy of the transition state is lower than that of the separated reactants for reactions 4 and 5 and only slightly (1.5 kcal/mol) higher for the forward reaction 6, at the highest theoretical level used. As pointed out by Brauman et al.,[7] the stability of the transition state relative to the reactants is a measure of the efficiency of the substitution reaction, i.e., the probability that a binary collision will lead to the products. The most favorable case in this regard is the reaction involving methanol and protonated methanol, eq 5, with a negative activation energy of -4.6 kcal/mol. In fact, this reaction represents one of the two experimentally confirmed examples of backside nucleophilic substitution reaction.[12b] The reaction involving water and protonated methanol has an activation energy of -0.8 kcal/mol. The least favorable case is the reaction involving protonated ethanol and water, whose transition state is slightly less stable than the reactants. The calculations clearly define a trend of substituent effect; alkyl substitution at the substrate destabilizes the S_N2 transition state, while such substitution at the nucleophile provides the opposite effect. The observation of backside S_N2 reaction involving 2-butanol and its protonated form by Morton et al. indicates the cancellation of the alkyl group effect on the substrate and the nucleophile involved.[13] On this basis, the reaction of 1-propanol with its protonated form follows a similar S_N2 pathway.[17b] However, in the case of tertiary alcohols, alternative processes like elimination or an S_N1 reaction are likely to become more favorable than a backside S_N2 reaction.[10]

In addition to the overall activation energy, the intrinsic barrier, i.e., the energy difference between the transition state and the ion–dipole complex, is another quantity of interest.[7] The calculated intrinsic barriers are nearly identical (≈10 kcal/mol) for the degenerate reactions 4 and 6. In the unsymmetrical case, eq 5, the forward reaction has a smaller intrinsic barrier (7 kcal/mol), while that of the reverse reaction is correspondingly higher (18 kcal/mol). This is entirely in accord with the Hammond postulate: for exothermic reactions, the geometry of the transition state

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resembles that of the reactants to a greater extent.[25] The validity and usefulness of this concept in interpreting the geometries of S_N2 transition states in anionic systems have been examined in detail recently by Wolfe et al.[16] In the case of reaction 5, the transition-state structure, **9** (and its energy), is closer to the complex involving the reactants CH_3OH and $CH_3OH_2^+$ (**8**).

The calculated geometries of the ion–dipole complex and the S_N2 transition state for reactions 4–6 reveal an intriguing feature involving the orientation of the nucleophile and the leaving group. The geometries of **4** and **5** are illustrative. In **4**, the two H_2O units have their p-type lone pairs orthogonal to each other. The H_2O fragment corresponding to the leaving group has the orientation found in the unperturbed substrate, $CH_3OH_2^+$, **3**. The nucleophile, on the other hand, lies in the molecular plane of symmetry. The two H_2O units twist relative to each other during the formation of the transition state, **5**, which has C_2 symmetry. One should be cautious in interpreting geometrical features obtained at only the 3-21G level, which generally underestimates the pyramidality at trigonal oxygen.[26,27] However, it is interesting to find the same kind of twisting of the nucleophile and the leavng group relative to each other in all three reactions studied.

In the reaction profiles (Figures 2–4), the formation of the front-side hydrogen-bonded complex and the backside ion–dipole complex have been arbitrarily indicated as two alternative reaction pathways, the former being a "dead end", while the latter leads to substitution. The hydrogen bonded complex can, in principle, be involved in a proton-transfer reaction (eq 3). However, the potential nondegenerate proton processes are all highly endothermic:[28,29]

$$H_2O + H_3C\text{–}OH_2^+ \rightarrow H_3O^+ + H_3C\text{–}OH \quad \Delta E = +11.9 \text{ kcal/mol}$$

$$H_2O + C_2H_5\text{–}OH_2^+ \rightarrow H_3O^+ + C_2H_5\text{–}OH \quad \Delta E = +17.3 \text{ kcal/mol}$$

$$H_2O + (H_3C)_2OH^+ \rightarrow H_3O^+ + (H_3C)_2O \quad \Delta E = +20.1 \text{ kcal/mol}$$

The calculated reaction energies at the level of theory employed in this paper (+13.8, +18.5, +21.7 kcal/mol, respectively, for the three reactions) are all within 2 kcal/mol of the corresponding experimental values. None of the above reactions is likely to compete with the S_N2 reactions 4–6. However, another interesting possibility remains. A rearrangement of the proton-bound complex leading to the ion–dipole complex or perhaps directly to the transition state without a significant activation barrier is conceivable. But the question is beyond the slope of the present calculations, whose objective is the examination of the feasibility of the backside nucleophilic displacement reaction.

Conclusions

Nucleophilic substitution is calculated to proceed without significant overall activation energy in three model cationic systems. The reaction profiles have all the characteristics of typical gas-phase S_N2 reactions involving anions, viz., (i) a double-well potential surface, (ii) unsymmetrical minima held by ion–dipole interaction, and (iii) a more symmetrical transition state. Alkyl substitution at the nucleophile enables it to disperse the cationic charge from the substrate more effectively, leading to a more stable transition state. Alkyl groups at the saturated carbon of the substrate lead to destabilization of the S_N2 transition state. The calculated results are in accord with the recent unequivocal mechanistic investigations of reaction 5 and a similar reaction involving protonated 2-butanol. Confirmation of our predictions concerning reactions 4 and 6 as well as rate measurements on all the systems considered here to obtain detailed energetics would be of considerable interest.

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Note Added in Proof. Recently, on the basis of theoretical modeling of the temperature and pressure dependence of the rate constants of reaction 5, Bass et al.[30] find Nibbering's proposal of an S_N2 mechanism[12b] questionable. The reaction is alternatively formulated as involving a tight transition state (of unspecified geometry) separating the front-side hydrogen-bonded minima **12** and **13**. Our calculations fully support Nibbering's conclusion that the back-side S_N2 displacement is an observable reaction if not the only viable pathway in this system. However, the present study may also be reconciled with the results of Bass et al. if it is assumed that a channel exists for the rearrangement of **12** and **13** to the ion–dipole complexes **8** and **10** or to the S_N2 transition state, **9** (see text above). Interestingly, the energy of the tight transition state relative to the reactants (−6.7 ± 2.3 kcal/mol) estimated by Bass et al. is close to the activation energy of −4.6 kcal/mol obtained in this study for the S_N2 reaction.

Registry No. $CH_3OH_2^+$, 17836-08-7; $CH_3CH_2OH_2^+$, 18639-79-7.

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