J. Org. Chem. **2002,** *67,* 1221−1226

Inversion vs Retention of Configuration in Gas-Phase Ammonium Ion/Alcohol Reactions

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Received November 5, 2001

The potential energy surface for gas-phase reactions of ammonium ion with alcohols was examined by ab initio and DFT methods. Transition structures for inversion (S_N2) and retention (S_NF) mechanisms were located for 2-propanol and *exo*-2-norbornanol. The S_NF (retention) process was found to be 6−8 kcal/mol higher in energy than the inversion S_N2 counterpart for the 2-propanol system. The retention process in the 2-*exo*-norbornanol/ammonium ion system was favored by 1.3 kcal/mol.

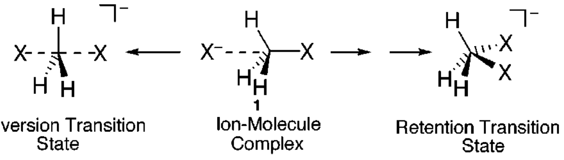
Introduction

Numerous experimental and theoretical studies have characterized the preferred stereochemical mode of bimolecular nucleophilic substitution at saturated carbon centers as inversion of configuration both in the gas phase and in solution.[1] Solution-phase reactions proceed via a single energy maximum with nucleophile and leaving group on opposite sides of the reacting carbon. In the gas phase, substitutions proceed via ion−molecule cluster formation that give rise to a “double-well” potential energy profile.[2] A recent theoretical analysis presented evidence that gas-phase identity S_N2 reactions of halide anions with methyl halides at high energies can take place with retention of configuration.[3] The calculated (overall) barriers for the Cl^-/CH_3Cl inversion and retention reactions were 2.7 and 46.3 kcal/mol, respectively. Computed intrinsic reaction paths for both inversion and retention reactions were found to proceed via the same reaction ion−molecule complex **1** (Scheme 1).[3a]

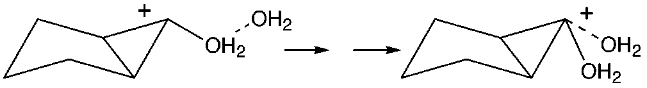
Uggerud[4a] found that frontside attack was the preferred mode for the substitution reaction between water and protonated *exo*-bicyclo[3.1.0]hexanol (Scheme 2) and suggested that reactions of this type be classified as S_NF (nucleophilic substitution with frontside attack).

In 1992 Tabet et al.[5] published a study of the substitution reactions of *exo*- and *endo*-2-norbornyl alcohols, acetates, and benzoates under ammonia/ammonium ion chemical ionization conditions. They provided stereochemical evidence for retention of configuration in the formation of norbornylammonium ions from reactions between norbornyl alcohols and ammonium ion and described the process as the S_Ni mechanism shown in Scheme 3.

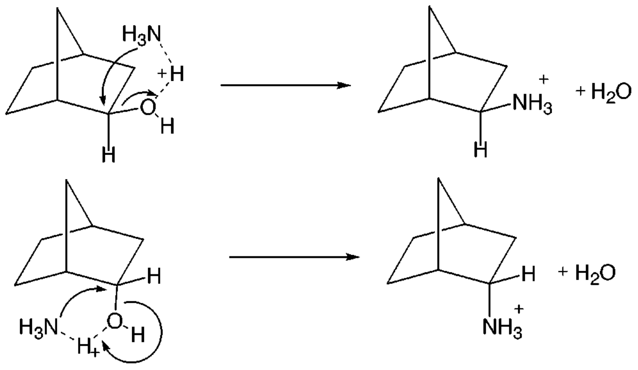
Scheme 1. Alkyl Halide/Halide Substitution Reactions



Scheme 2. Retention Reaction between Water and Protonated Bicyclo[3.1.0]hexanol



Scheme 3. Proposed S_NI Substitution Mechanisms for 2-Norbornanols



Given that most known gas-phase substitutions proceed with inversion of configuration, these results were of great interest. To better understand the underlying structural and energetic features of this novel mechanism, we initiated computational studies on ammonium ion/alcohol substitution reactions.[6] Below we describe

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[1] For a summary and references, see (a) March, J. M. *Advanced Organic Chemistry*, 4th ed. Wiley: New York, 1992; Chapter 10. (b) Carroll, F. A. *Perspectives on Structure and Mechanism in Organic Chemistry*; Brooks/Cole: Pacific Grove, CA, 1998; Chapter 8.

[2] For a recent review of organic ion/molecule reactions studied by mass spectroscopy, see: Gronert, S. *Chem. Rev.* **2001**, *101*, 329−360.

[3] (a) Glukhovtsev, M. N.; Pross, A.; Schlegel, H. B.; Bach, R. D.; Radom, L. *J. Am. Chem. Soc.* **1996**, *118*, 11258−11264. (b) Harder, S.; Streitwieser, A.; Petty, J. T.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1995**, *117*, 3253−3259 examined identity exchange reactions involving LiF and LiCl complexes.

[4] (a) Uggerud, E. *J. Org. Chem.* **2001**, *66*, 7084−7089. (b) Uggerud, E.; Bache-Andreassen, L. *Chem. Eur. J.* **1999**, *5*, 1917−1930.

[5] Despeyroux, D.; Cole, R. B.; Tabet, J. C. *Org. Mass Spectrom.* **1992**, *27*, 300−307.

[6] The inversion reaction between ammonia and protonated methanol has been studied by Uggerud, E. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1465−1467.

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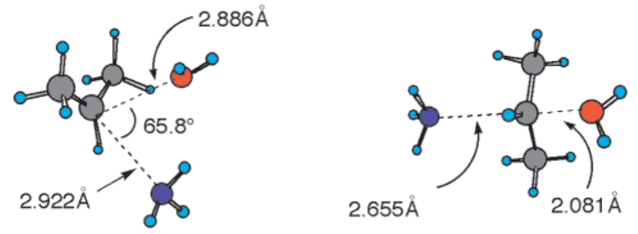

Figure 1. Transition structures for retention and inversion of configuration.

computed potential energy surfaces for retention and inversion processes for the reactions of ammonium ion with 2-propanol and *exo*-2-norbornanol.

Computational Methodology

All structures were fully optimized by analytical gradient methods using the Gaussian98 suite[7] and density functional (DFT) calculations using the exchange potentials of Becke[8a] and the correlation functional of Lee, Yang, and Parr.[8b] These results were confirmed by single point calculations and some optimizations using Møller−Plesset methods.[9] Frequencies were computed by analytical methods. Reported enthalpies were corrected for zero-point energy differences (ZPVE) (unscaled) and thermal effects at 298.150 K. Vibrational analyses established the nature of all stationary points as either energy minima (no imaginary frequencies) or first-order saddle points (one imaginary frequency). Energies in the body of the text refer to B3LYP/6-311+G* level calculations for 2-propanol and B3LYP/6-31G* for the *exo*-2-norbornanol system.

Results and Discussion

The potential energy surface for the reaction of ammonium ion with 2-propanol was searched at the B3LYP/6-311+G* level for retention and inversion transition states. Transition structures located for the two mechanisms are shown in Figure 1. Intrinsic reaction path calculations[10] confirmed the expected trajectories of the downhill processes from the two transition structures.

The unusually long C- -O and C- -N bonds for the frontside process are consistent with computational results found for halide/alkyl halide substitutions.[3] Charges on the central carbon atom were computed using Natural Population Analysis: 0.312 (inversion) and 0.380 (retention).[11] The inversion structure has a nonlinear alignment of the N- -C- -OH_2 array (150.0°), but is otherwise unexceptional.[12] The analogous angle for the retention pathway (65.8°) is significantly more acute than the angles calculated[3a] for halide−halide exchange reactions which range from 80.9° to 87.1°, but comparable to those calculated[3b] for $LiF-CH_3F$ retention transition structures (75.4°). A weak hydrogen bond may provide a small attractive force here as one of the amino protons is only 2.36 Å from the oxygen atom (N−H−O = 134.8°). The three carbon atoms and the central C−H hydrogen atom lie essentially in the same plane with a dihedral angle of 175.2°. The carbon skeleton of the retention transition structure is nearly planar having the geometry of a cation solvated on the front side by ammonia and water.

Although the computed activation enthalpy for the inversion transition structure at the B3LYP/6-311+G* level is 6.1 kcal/mol lower[14] than that for the retention transition structure, a complete understanding of the course of these reactions requires a more detailed analysis of the potential energy profiles. To this end, entrance and exit channel ion−molecule complexes were sought. The energies and structures of these complexes are shown in Scheme 4 along with other relevant points for the retention reaction.

The relative energy of the ion−molecule complex [R−OH- -NH_4^+] is comparable to the −26.4 kcal/mol estimated for the NH_4^+/2-norbornanol system.[5] The estimated overall reaction energy change for *exo*-2-norbornanol system was estimated to be −19.6 kcal/mol in fair agreement with our calculated value of −14.6 kcal/mol. The computed overall activation enthalpy for the ammonia/2-propanol reactions is 14.0 kcal/mol, and the $\Delta H^\ddagger$ from the ion−dipole complex (also known as the central barrier) is ca. 40 kcal/mol. Not shown is the relative energy of the proton-transfer product ROH_2^+. In view of the endothermicity (14 kcal/mol) of this process, the protonated alcohol is not a likely intermediate. Attempts to locate a backside complex between ammonia and protonated 2-propanol were unsuccessful.

In contrast to the retention reaction, we were unable to locate an entrance channel ion−molecule complex [NH_4^+ - - -ROH] with ammonium ion positioned at the backside of the C−OH group. Structures with this initial geometry invariably rearranged to the frontside complex upon optimization. A loose exit channel complex was located which is shown with other relevant points in the reaction profile in Scheme 5. The central barrier lies ca.. 34 kcal/mol above the ion−molecule complex.

While the overall barrier for the Cl^-/CH_3Cl inversion reaction is lower than that found for the NH_4^+/ROH inversion reaction, the reverse situation holds for the retention reaction. The NH_4^+/ROH retention reaction undoubtedly profits from hydrogen bonding between NH protons and the lone pairs on oxygen.

These results represent a straightforward characterization of two pathways for the gas-phase ammonium ion/alcohol substitution reactions, one involving a classical S_N2 process, the other a variant of the S_Ni reaction or, more accurately, an S_NF mechanism.[4,5,15] Our results

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[7] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

[8] (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

[9] Møller, C.; Plesset, M., S. *Phys. Rev.* **1934**, *46*, 618.

[10] Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem*. **1990**, *90*, 5523.

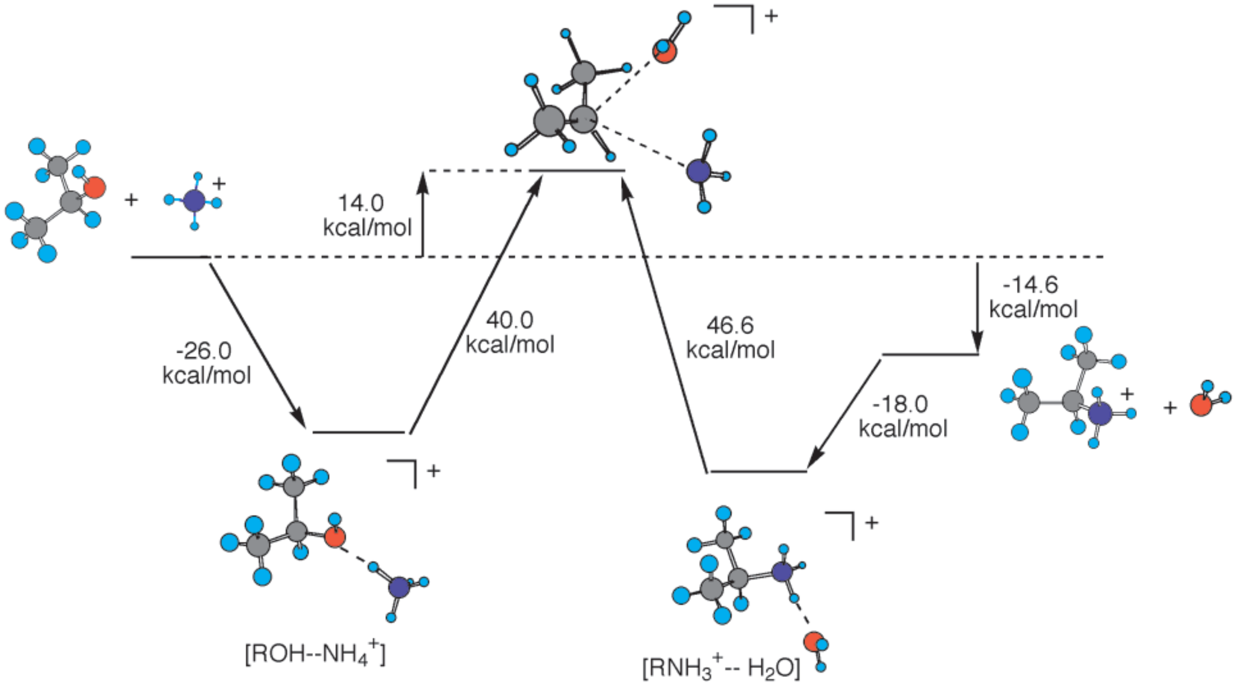
[11] NPA utilized NBO 3.1 E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, and F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison, 1996.

[12] The computed (MP2/6-31G*) Cl−C−Cl angle for the chloride ion−isopropyl chloride transition state is 158.5°. Jensen, F. *Chem. Phys. Lett.* **1992**, *196*, 368−376.

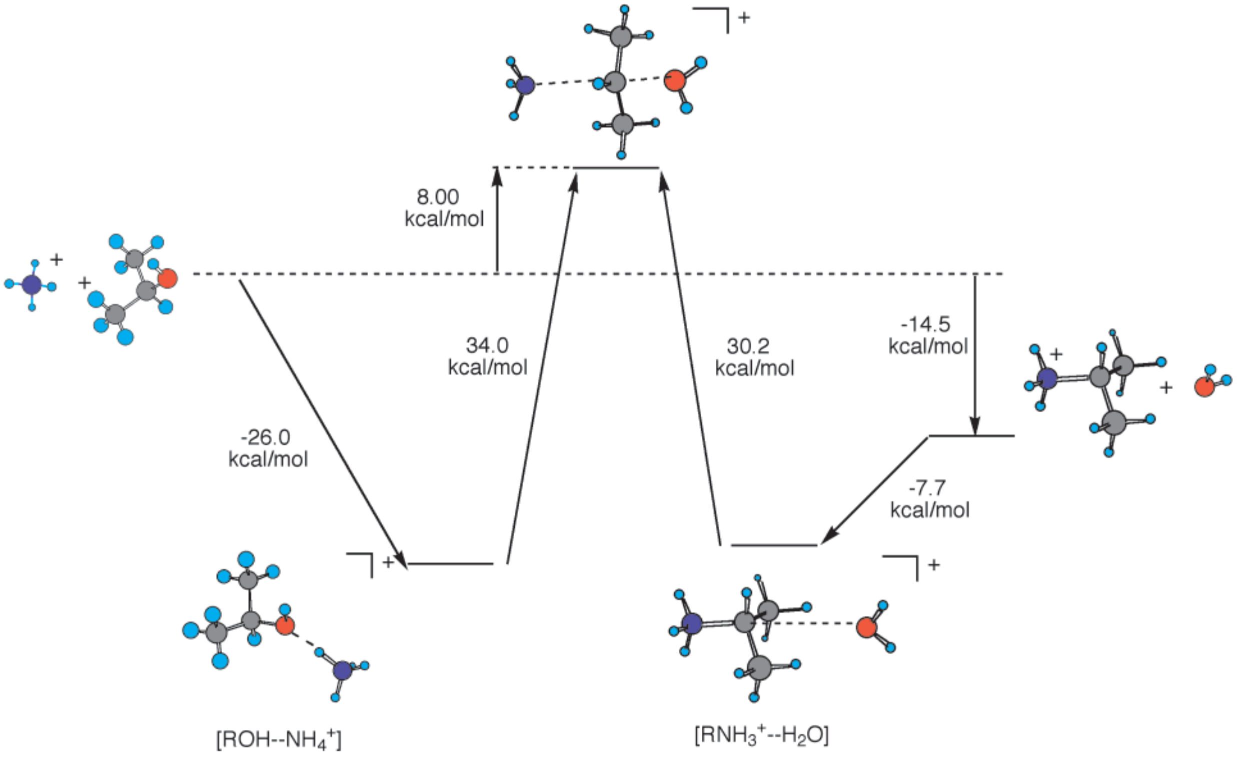
[13] The two chlorine atoms in the frontside transition state for the chloride ion methyl chloride exchange reaction are separated by 3.268 Å with bond lengths of 2.438 Å and a Cl−C−Cl angle of 84.2°.

[14] The barrier for the inversion reaction is 8.6 kcal/mol lower than that for inversion at the MP2/6-311+G* level.

Scheme 4. Relative Enthalpies at 298.15 K for the Retention Reaction



Scheme 5. Relative Enthalpies at 298.15 K for the Inversion Reaction



support a preferred inversion mechanism in view of the large computed difference in activation enthalpies (6.0−8.6 kcal/mol). Since the isopropyl system does not model the norbornyl system accurately, we also studied the reaction of *exo*-2-norbornanol with ammonium ion at the B3LYP/6-31G* level. Figure 2 displays the two transition structures for the inversion and retention processes.[16,17] The geometry of the retention transition structure is relatively planar about the reacting carbon analogous to the 2-propanol system (178°).

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[15] For related computational studies on the reactions of alkyl chlorosulfite decompositons, see: Schreiner, P. R.; Schleyer, P. von R.; Hill, R. K. *J. Org. Chem*. **1994**, *59*, 1849−1854. Schreiner, P. R.; Schleyer, P. von R.; Hill, R. K. *J. Org. Chem*. **1993**, *58*, 2822−2829.

[16] The stereochemical assignments were based by analyses of low energy collision-activated decomposition spectra and may not be quantitative.

[17] The isomeric retention transition state with the ammonia and water components interchanged had a slightly higher activation energy.

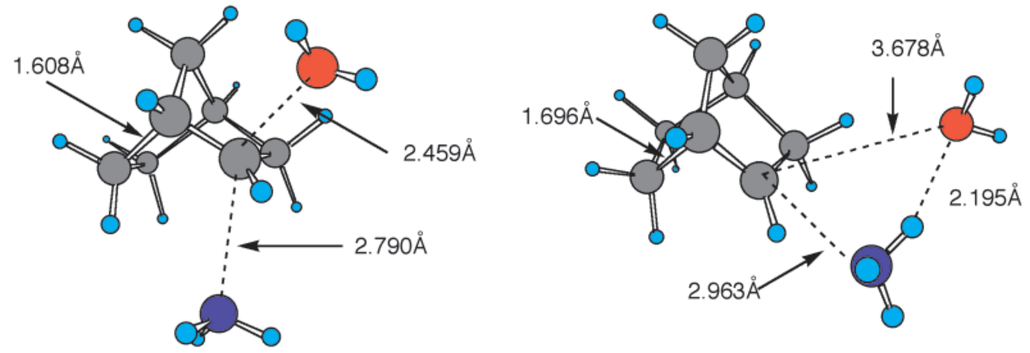
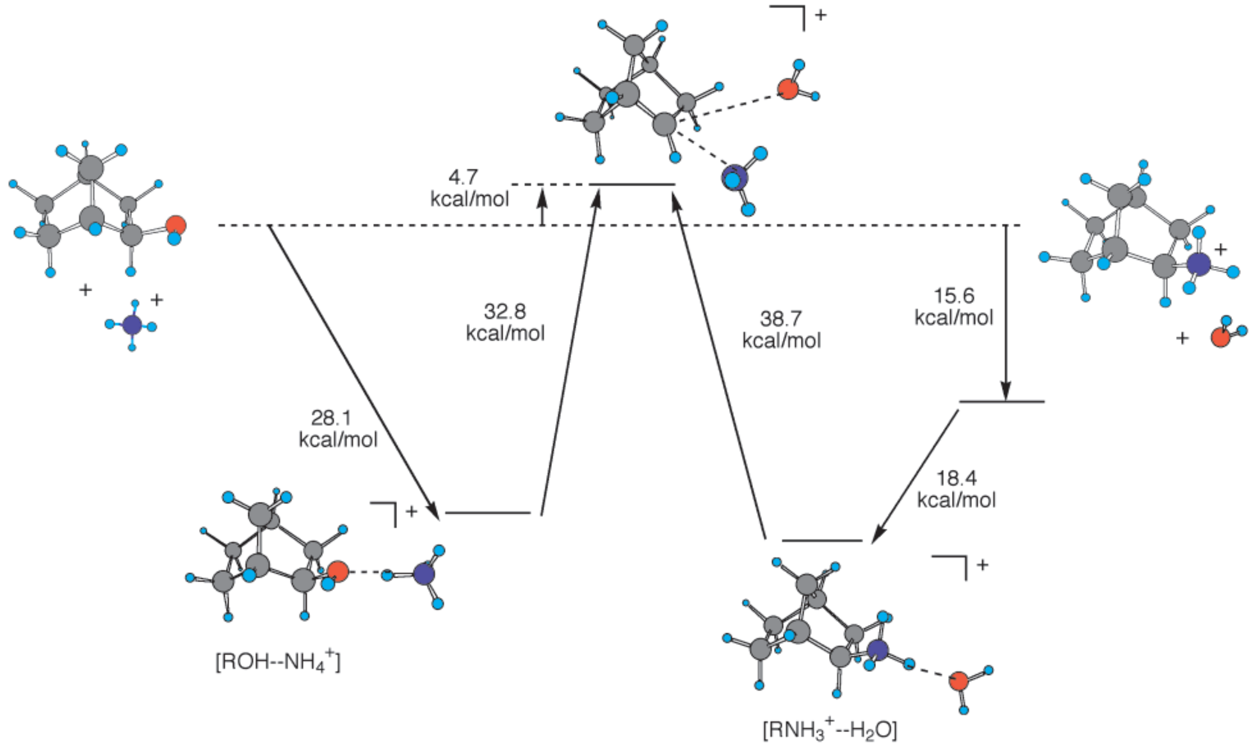


Figure 2. Transition structures for *exo*-2-norbornyl substitutions.

Scheme 6. Relative Enthalpies at 298.15 K for the 2-*exo*-Norbornanol Retention Reaction



In contrast to the results for the 2-propanol/ammonium ion reaction, the calculated $\Delta H^{\ddagger}$ for the retention pathway was slightly lower (1.1 kcal/mol) than that for inversion (Schemes 6 and 7).[18] The energy gap increased to 1.3 kcal/mol at the B3LYP/6-311+G* level [$\Delta(\Delta G^{\ddagger}) = 1.4$ kcal/mol]. Single point calculations at other levels confirmed this preference with $\Delta(\Delta H^{\ddagger})$ values ranging from 0.36 kcal/mol [MP4(sdq)6-31+G**] to 3.2 kcal/mol [MP2-6-311G**]. Surprisingly, these findings were not the result of a more sluggish inversion pathway, but rather the result of a more facile retention process compared to the 2-propanol system.

Because the calculated activation energies for these substitution reactions may be too high for an observable gas-phase reactions, we considered the intervention of clusters. Speranza and co-workers[19] studied the substitution reactions of CH_3F and CH_3Cl with H_2O/H_3O^+ and found that related reactions are pressure-dependent. They concluded that displacement reactions on thermally excited hydrogen-bonded clusters were involved and that excess water molecules provided effective third body stabilization:

$$CH_3F + H_3O+ \underset{K_-}{\overset{K_+(H_2O)}{\rightleftharpoons}} [CH_3F\text{---}H\text{---}OH]_{exc}^{+} \xrightarrow{H_2O} CH_3OH_2^{+} + HF + H_2O$$

It was emphasized that these proton-induced nucleophilic displacements are governed by factors beyond relative proton affinities and overall exothermicities. Clustering and collisional deactivation of excited complexes may play a decisive role in determining reaction mechanisms under these conditions. Uggerud and Bache-Andreassen[4b] demonstrated computationally that explicit solvation lowered the transition structure energy as well as that of intermediates in the identity substitution reactions between water and protonated alcohols. They

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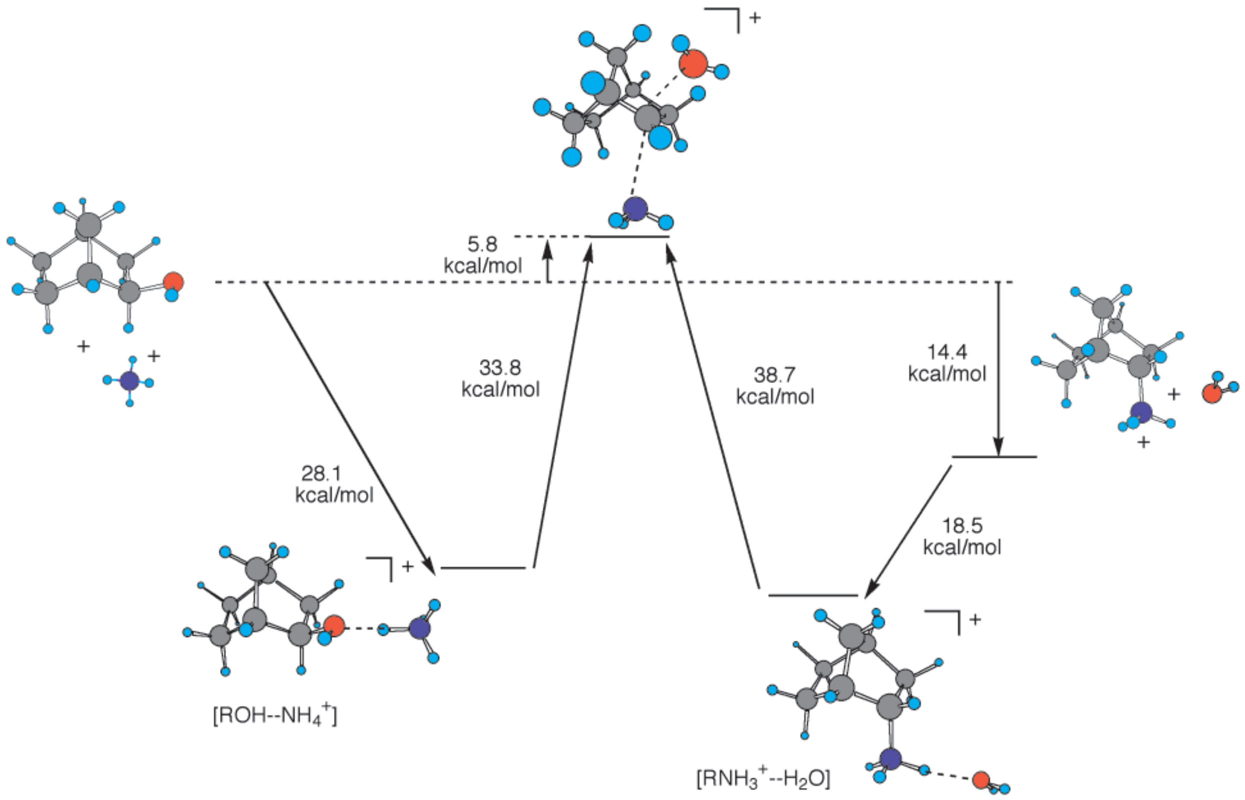
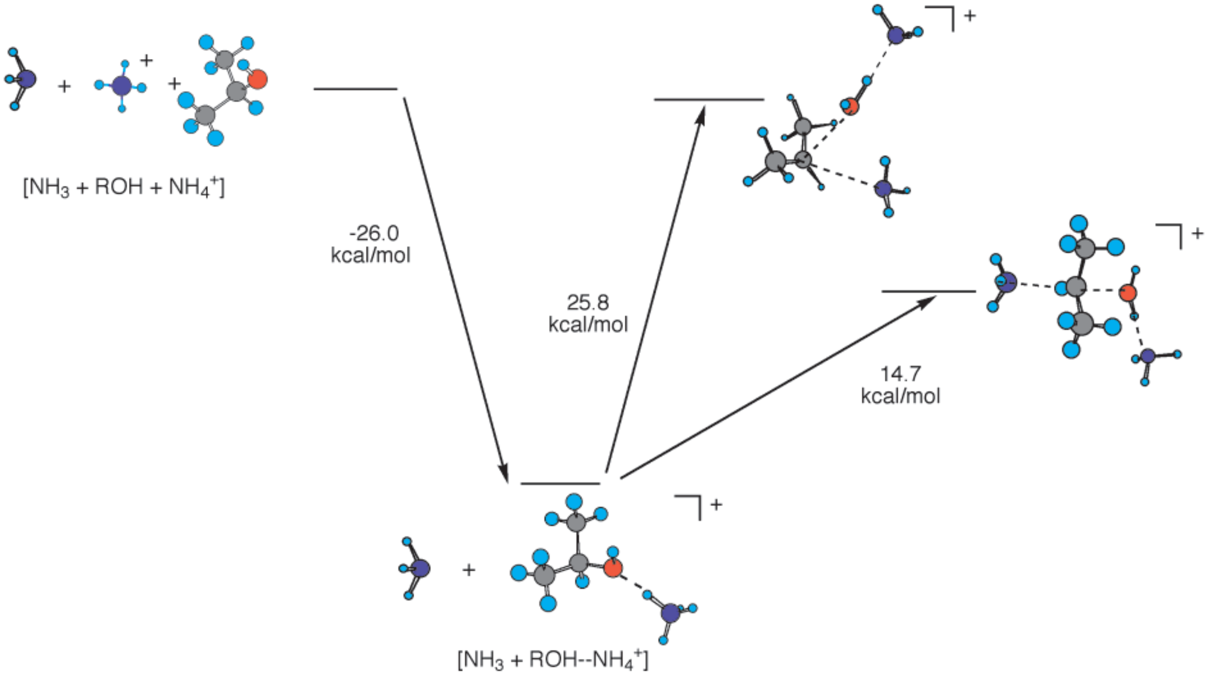
[18] We were unable to locate backside entry complexes between ammonium ion and *exo*-2-norbornanol or between ammonia and protonated *exo*-2-norbornanol.

[19] (a) Attina, M.; Angelini, G.; Speranza, M. *Tetrahedron* **1981**, *37*, 1221−1226. (b) Speranza, M.; Angelini, G. *J. Am. Chem. Soc.* **1980**, *102*, 3115−3120.

Scheme 7. Relative Enthalpies at 298.15 K for the *exo*-2-Norbornanol Retention Reaction



Scheme 8. Cluster Reactions of 2-Propanol with Ammonia (B3LYP/6-311+G*)



also showed that frontside substitution would play a minor role in the corresponding reactions with protonated 2-propanol/water.

In an effort to simulate the role of clusters, we evaluated the energetics of substitution and inversion reactions of the alcohol:ammonium ion complexes (Scheme 8). The overall energy of both transition structures decreased significantly in the presence of an additional ammonia molecule to the extent that the calculated barrier for the inversion process was below that of the sum of the energies of the reactants.

Full optimization of the transition structures with an additional ammonia molecule led to a reduction of the energy of both structures by about ∼16 kcal/mol. Under these conditions, the inversion process was favored by ca. 0.3 kcal/mol (B3LYP/6-31+G*) with $\Delta(\Delta G^{\ddagger}) = 1.2$ kcal/mol.

In summary, our results describe the geometry and relative energies for inversion and retention processes for alcohol:ammonium ion substitution reactions. The results support a preferred inversion mechanism for 2-propanol and a dominant[16] retention process for the 2-*exo*-norbornanol system. Although the calculated energy gaps are relatively small for the latter, it is likely that higher level calculations would reveal greater energy differences. In any event, correlation of computed energies with mass spectral results may be problematic due to lack of information on the effects of clustering.

Acknowledgment. We are grateful to the Center for Computational Neuroscience, Rutgers University, Newark, NJ, for computational resources. Helpful discussions with J. K. Lee and constructive comments from a referee are gratefully acknowledged.

Supporting Information Available: Cartesian coordinates, total energies, and enthalpies at 298.14 K for all structures. Imaginary frequencies for all transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016267D