How Persistent Is Cyclopropyl upon Nucleophilic Substitution, and Is Frontside Displacement Possible? A Model Study

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Quantum chemical model calculations (MP2/6-31G(d,p)) demonstrate that frontside nucleophilic substitution is not possible in the reaction between water and protonated cyclopropanol. Instead, ring opening occurs, in accordance with a well-known disrotary ring-opening mechanism. When the cyclopropane ring is embedded in a stabilizing bicyclic structure, as in protonated bicyclo-[3.1.0]hexanol, the mechanistic landscape changes. In this case frontside nucleophilic substitution occurs, and has a potential energy barrier which is lower than that of the corresponding backside substitution, which implies that the stereochemical outcome of this gas-phase nucleophilic substitution reaction is uncoupled from its kinetic order. This and similar results challenge the traditional view that nucleophilic substitution reactions should be categorized as being either S_N1 or S_N2.

Introduction

In the 1930s Hughes and Ingold introduced the concept of two distinct mechanisms for nucleophilic substitution reactions, S_N1 and S_N2.[1−3] Despite the success of this simple scheme in explaining a large body of experimental findings, pertinent evidence has made it necessary to revise and detail the original mechanistic scenario.[4−6] Among the most significant contributions is the work by Winstein,[7] which led to the notion of ion pairs, and the ideas of Jencks, Schleyer, Bentley, and many others on a continuous plethora of mechanisms between S_N1 and S_N2.[8−13]

Unless rather unsatisfactory assumptions are made, the traditional S_N1/S_N2 scheme fails to explain why many substitution reactions give enantiomeric mixtures other than the expected 100:0 (S_N2) or 50:50 (S_N1).[14] On the basis of a combined experimental and theoretical gas-phase study of water exchange in protonated alcohols

$$H_2{}^*O + R{-}OH_2^+ \rightarrow R{-}{}^*OH_2^+ + H_2O \qquad (1)$$

we recently proposed an alternative point of view.[15] In the cases studied, R = CH_3, CH_3CH_2, $(CH_3)_2CH$, and $(CH_3)_3C$), it turns out that there are two directly competing reactions, which we now call S_NB and S_NF. In the former, the nucleophile attacks the face opposite that of the nucleofuge, giving inversion of configuration (Walden inversion). In the latter mechanism, designated S_NF, the nucleophile displaces the nucleofuge on the same side, giving retention of configuration. It should be emphasized that the dilute gas phase provides a medium in which only kinetically second-order reactions are achievable. Both S_NB and S_NF are of this type. In the case of R = CH_3, the S_NF barrier is significantly higher than that for S_NB. Interestingly, however, the larger R becomes, the smaller is the difference. For R = $(CH_3)_3C$ the difference is quite small, only 10 kJ mol^{-1}. Moreover, it is also evident in this case that the interactions between the central *tert*-butyl cationic moiety and the two water molecules in the transition state is mainly due to hydrogen bonding for both S_NB and S_NF. Covalent interactions seem to be negligible. Since the distinction between the two mechanisms appears to blur out with larger R groups, this could indicate that S_NB and S_NF could merge into a degenerate situation in cases where the stability of the carbocationic moiety is even higher. The nature of this asymptotic limit and the question of whether this paradigm is transferable to the solution phase are of course of fundamental interest.

We have been made aware of an interesting discussion in the literature regarding mechanisms for substitutions of norcaryl derivatives, and similar compounds. The *exo*-enatiomer of **I** gives rise to the *exo*-enatiomer of **II** under the experimental conditions indicated in Scheme 1.[16] This led the authors to suggest that the reaction occurs according to an S_N2 retentitive mechanism, bearing close resemblance to our S_NF mechanism. This was suggested by Stohrer in 1976, and supported by HF/STO 3G calculations.[17] Another research group had also worked with the same class of compounds earlier,[18] but had suggested an S_N1 type of mechanism. The S_N1 alternative

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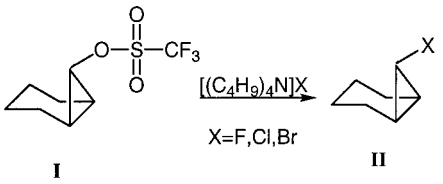
Scheme 1



found support in the fact that the corresponding norcaryl cation is stable in superacid (NMR evidence) and in vacuo (ab initio calculations).[19]

The purpose of the present work is to clarify the mechanistic scenario for nucleophilic substitution reactions in bicyclic systems containing a cyclopropyl ring and the prototype cyclopropyl systems by ab initio quantum chemical model calculations. The results will in principle only be valid for the dilute gas phase, but may also be suitable models for the essential features of the corresponding solution-phase reaction.

Methods

The calculations were carried out using the program system GAUSSIAN 98.[20] The method used was Møller−Plesset perturbation theory to second order (MP2)[21] with the 6-31G(d,p) basis set[22] (MP2/6-31G(d,p)). All relevant critical points (reactants, transition structures, intermediates, and products) of the potential energy surface were characterized by complete optimization of the molecular geometries. Harmonic frequencies were obtained by diagonalizing the mass-weighed Cartesian force constant matrix, calculated from the analytical second derivatives of the total energy (the Hessian). Harmonic frequencies obtained in this manner were used to calculate the zero-point vibrational energies (zpve's). Total energies were calculated by including the MP2/6-31G(d,p) zero-point vibrational energies scaled by a factor of 0.9608.[23]

Results and Discussion

Some selected structures are displayed in Figure 1. The complete set of structural data from the quantum chemical calculations (Cartesian coordinates and drawings) and the corresponding total energies are given as Supporting Information.

Instability of the Cyclopropyl Cation. Figure 2 shows the potential energy diagram relevant to the cyclopropyl cation. It is evident that this cyclic molecule (**TSa**) is highly unstable, since it corresponds to a transition structure. As Figure 2 shows, it will rearrange spontaneously into the minimum-energy structure corresponding to the allyl cation (**1**). The atomic movement associated with the reaction coordinate of the formal degenerate rearrangement **1** → **1′**, as monitored for **TSa**, is that of a disrotary synchronous ring opening. The facility of the disrotary ring opening for the cyclopropyl cation was already predicted by Woodward and Hoffmann in the 1960s.[24] The instability of the cyclopropyl cation has previously been demonstrated through quantum chemical calculations using various wave functions.[25−28]

Protonated Forms of Cyclopropanol and Allyl Alcohol. Putting a water molecule onto the cyclopropyl

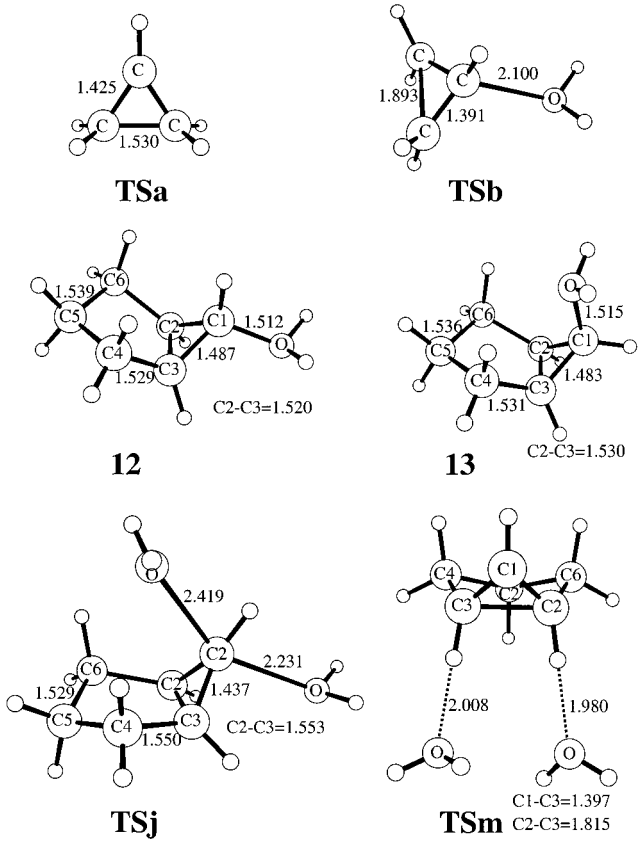


Figure 1. Selected structures of the stationary points obtained with MP2/6-31G(d,p). Bond distances indicated are in angstroms.

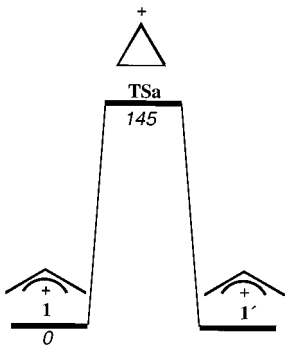


Figure 2. Potential energy diagram for the $C_3H_5^+$ system from the MP2/6-31G(d,p) calculations. Relative energies indicated are in kilojoules per mole and include zpve corrections.

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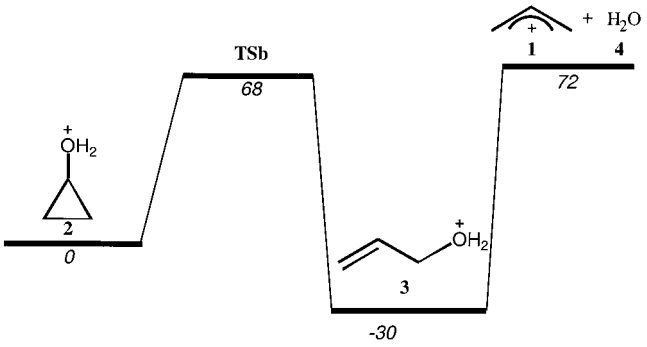

Figure 3. Potential energy diagram for $[H_2O,C_3H_5^+]$ from the MP2/6-31G(d,p) calculations. Relative energies indicated are in kilojoules per mole and include zpve corrections.

cation gives protonated cyclopropanol (**2**). In contrast to the cyclopropyl cation, protonated cyclopropanol represents a potential energy minimum (Figure 3). It is well-known that cyclopropanol should not be exposed to traces of acid (or base) as it then will isomerize slowly into propionaldehyde. Whether this occurs as the result of protonation on the ring or the hydroxyl group is of interest, and will be discussed later. Our calculations indicate that **2** may rearrange into protonated allyl alcohol (**3**) via **TSb**, and that the atomic movement leading from **2** to **TSb** corresponds to the disrotatory ring-opening mechanism studied by Woodward and Hoffmann. In our mechanism ring opening is preceded and accompanied by a substantial increase in the C−O length (Figure 1). It is interesting to notice that this partial C−O bond heterolysis leads to a molecular arrangement in which the carbon skeleton has attained a substantial cyclopropyl cation character, thereby making it unstable toward isomerization into the allyl cation structure. The combined potential energy of the fully dissociated fragments of **3**, **1**, and water (**4**) is only slightly higher than that of **TSb**. The energy of dissociation of **3** is in good agreement with earlier ab initio determinations. In an earlier report[29] a structure closely resembling **TSb** was associated with an intramolecular water molecule rearrangement within the allyl cation/water supermolecule, and not with the isomerization **2** → **3** as shown here.

Any attempt to form **3** by protonation in the gas phase (chemical ionization mass spectrometry) is likely to be unsuccessful. It is well-known that allyl alcohol is more basic at the terminal carbon than at the oxygen. This fact and the fact that there are several other lower lying $C_3H_7O^+$ isomers[30−35] have so far hampered our own experimental efforts in comparing the gas-phase reactivities of **2** and **3**. It was mentioned above that protonation of cyclopropanol gives propionaldehyde. Two different mechanisms may be envisaged, depending on the site of protonation. Protonation on the most basic hydroxyl group will most likely occur via the protonated allyl alcohol, initiated by the mechanism of Figure 3. Protonated allyl alcohol may then rearrange into protonated propionaldehyde in one or two steps, both with barriers below the energy of **3**. The other alternative—protonation on one of the less basic methylene carbons—requires a stronger proton donor, but gives protonated propionaldehyde directly. In solution, the latter mechanism seems to be in agreement with observation.[36]

Reactions between Water and the Protonated Forms of Cyclopropanol and Allyl Alcohol. The nucleophilic reactivity of cyclopropanol and other cyclopropyl derivatives has been thoroughly discussed in the literature.[18,24,36−39] Due to the facile ring opening under acidic and basic conditions, cyclopropanol is not suitable as a reagent for nucleophilic substitution. A better leaving group is usually required. Despite this, we have chosen the reaction between **4** and **2** only to probe the intrinsic properties of the cyclopropyl system. The results of this suitable model for nucleophilic substitution are shown in Figure 4. The backside identity S_NB displacement proceeds over **TSe**, and has a quite sizable barrier of 163 kJ mol^{-1} measured from the stable situation corresponding to **5**, in accordance with the rather poor reactivity of cyclopropyl substrates. The intermediate $H_2O\cdots c\text{-}C_3H_5OH_2^+$ complex has not been included in Figure 4, but our previous study[15] of closely similar systems has shown that "backside" complexes of this kind are bonded by approximately 45 kJ mol^{-1} relative to the separated reactants, and exist on the pathway from free reactant to transition structure. The products of this reaction are obviously identical to the reactants. One should, however, notice that the configuration of the affected carbon atom has been inverted. It is also clear that the reaction does not lead to isomerization into protonated allyl alcohol, thereby leaving the ring intact.

Despite all our efforts to locate a transition structure for frontside S_NF displacement of **2** by **4**, it was not possible to find any. On the other hand, attack by the nucleophile on the frontside, as evident from the calculations, leads to disrotary ring opening. The pathway involves the intermediate proton-bonded complex $c\text{-}C_3H_5OH_2^+\cdots OH_2$ (**5**). After passing by this structure, the minimum-energy path leads to **TSc**, and ends at the minimum corresponding to the proton-bonded complex between allyl alcohol and water (**6**) (Figure 4). Although the barrier is higher than in Figure 3, the close relationship between **TSb** and **TSc** should be noted. Structures **5** and **6** may be envisaged as formed by addition of the water dimer, $(H_2O)_2$, to **1** and the cyclopropyl cation (**TSa**), respectively. We have previously shown that the water dimer binds stronger to alkyl cations than the monomer does.[40] It is therefore not surprising that the energy cost in reaching the unstable situation necessary for ring opening, obtained by stretching the C−O bond, is higher from **5** (via **TSc**) than from **2** (via **TSb**).

In addition, there is a third higher energy route leading to frontside elimination, which passes through **TSd**. Also this reaction leaves the ring intact, giving cyclopropene (**8**) and the protonated water dimer (**9**).

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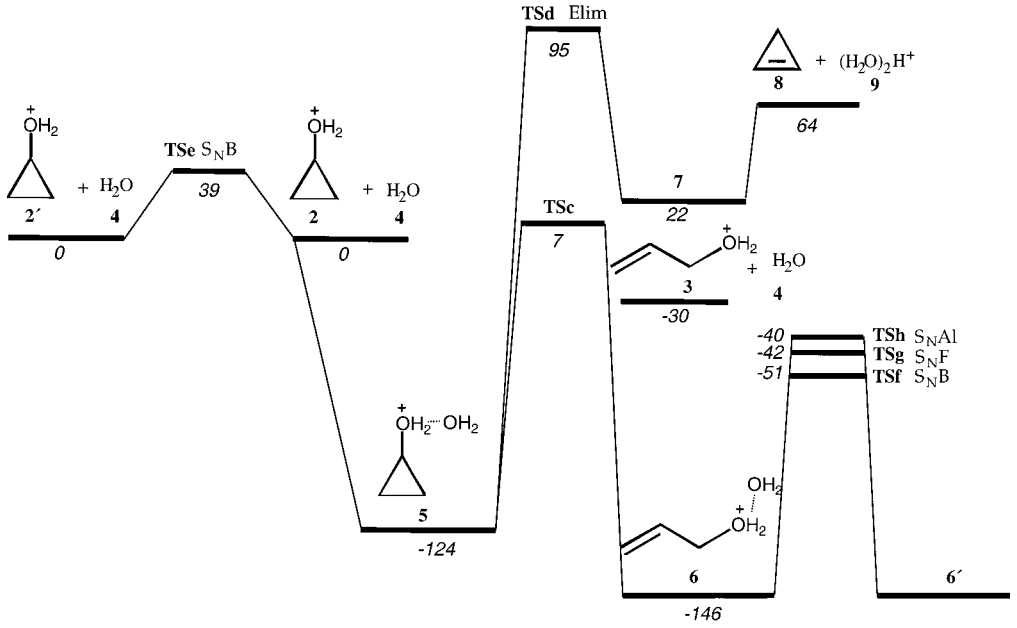
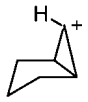


Figure 4. Potential energy diagram for $[2H_2O,C_3H_5^+]$ from the MP2/6-31G(d,p) calculations. Relative energies indicated are in kilojoules per mole and include zpve corrections.

Chart 1



We have also investigated nucleophilic attack of **4** on **3**. We have found three different pathways for this degenerate water substitution. The lowest goes via **TSf**, and corresponds to an S_NB mechanism, while the transition structure **TSg** for the second mechanism—a variant of the S_NF reaction, but with nucleophilic attack on the allylic carbon—is slightly higher in energy. All attempts to locate an S_NF transition structure where the nucleophilic attack occurs on the same carbon and at the same face as those from which the nucleofuge is departing were in vain. The third route (via **TSh**) also corresponds to an allylic substitution, but in this case the nucleophile enters the allylic framework at the face opposite the leaving group. Nice examples of these mechanisms for allylic substitutions have been demonstrated in elegant experiments.[41−43]

Bicyclo[3.1.0]hexyl Cation. As mentioned in the Introduction, the *exo*-forms of norcaryl derivatives and similar bicyclic systems tend to give substitution products with retention of configuration. Before this point is discussed in more detail, it is useful to analyze the potential energy surface of the prototype system of the bicyclo[3.1.0]hexyl cation (Chart 1). Our computations of the semiplanar system **TSi** (Figures 1 and 5) showed a situation similar to that for the cyclopropyl cation (cf. **TSa** of Figure 2). Outward disrotary rotation from **TSi** of C1 gives the allylic cation **11**. The corresponding inward disrotary movement (en route to give an inward allylic cation) cannot be fully accomplished since it is hindered by the methylene groups and the restrictions imposed by the six-membered ring. The result is the compromise "half-open" bicyclic structure **10**. The unusual atomic arrangement of **10** is signified by the C2−C3 bond distance of 1.838 Å. This structure is already known and was characterized by its NMR spectrum in superacidic solution,[44] and later verified by HF/6-31G(d) calculations.[19]

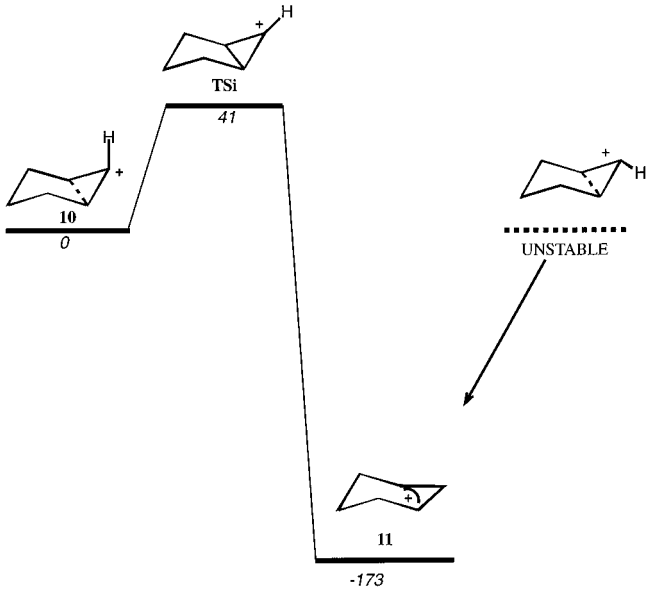


Figure 5. Potential energy diagram for the bicyclo[3.1.0]hexyl cation system, $C_6H_9^+$, from the MP2/6-31G(d,p) calculations. Relative energies indicated are in kilojoules per mole and include zpve corrections.

Substitution Mechanisms of Bicyclo[3.1.0]hexyl Derivatives. We find that both the *exo* (**12**) and the *endo* (**13**) forms of protonated bicyclo[3.1.0]hexanol are minima of the potential energy surface, having nearly the same energy (Figure 1). Upon reaction with water an S_NB exchange mechanism connects the two configurational

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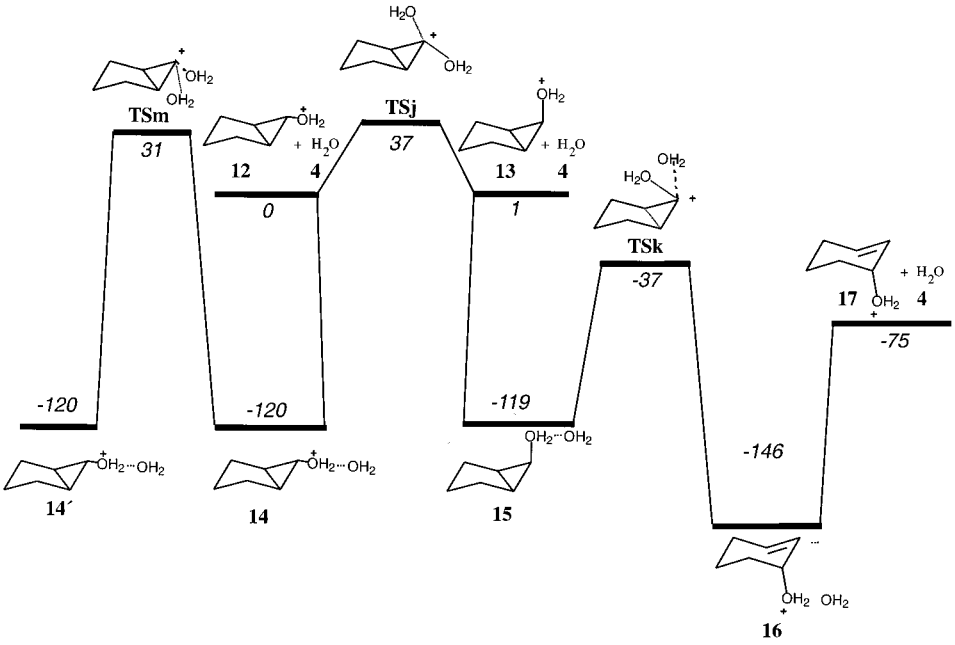

Figure 6. Potential energy diagram for the reaction between water and protonated bicyclo[3.1.0]hexanol, [$2H_2O$,$C_6H_9^+$]. Relative MP2/6−31g(d) energies indicated are in kilojoules per mole and include zpve corrections. Bond distances indicated are in angstroms.

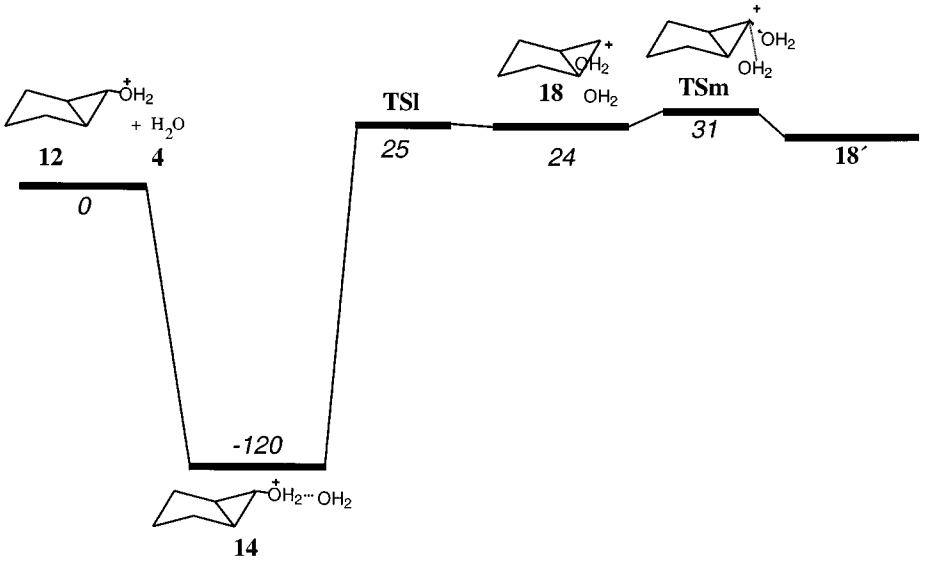

Figure 7. Detail of the potential energy diagram for the central part of the frontside displacerment mechanism in the reaction between water and protonated bicyclo[3.1.0]hexanol. Relative MP2/6−31g(d,p) energies indicated are in kilojoules per mole and include zpve corrections. Bond distances indicated are in angstroms.

isomers through the transition structure **TSj** (Figure 6). The structure is analogous to **TSe** (Figure 4), and also this reaction leaves the cyclopropyl ring intact. Also in analogy with the free cyclopropyl system (**TSc** of Figure 4), frontside encounter between **4** and the *endo*-epimer **13**, via the hydrogen-bonded adduct **15**, gives the ring-opened allyl alcohol **17**, via **TSk** and the dimer **16**.

On the other hand, frontside encounter between **4** and the *exo*-epimer **12** has a completely different outcome. Analysis of the potential energy surface shows that the first stage corresponds to formation of the adduct **14**. From this structure a minimum-energy pathway leads to transition structure **TSl** (see Figure 7), resulting in C−O bond dissociation and formation of a hydrogen-bonded trimeric complex (**18**) consisting essentially of one *exo*-norcaryl cation (**10**) and two water molecules. Further, through **TSm**, the waters may exchange roles, and the incoming water becomes the hydrogen bond donor in **18′**. Formation of the final substitution products **4** and **12′** is then the result of following the retour via **TSl′**, and **14′**. Through this series of events an identity nucleophilic substitution reaction has been completed.

Formally, this is a multistep reaction, but the flatness of the potential surface in the region where the actual chemical transformation takes place indicates that essentially it is a one-step reaction. Under the conditions of the dilute gas phase it is first order in both reactants, with an overall order of two. Unfortunately, Ingold did not include the possibility that second-order processes may give retention of configuration. A key assumption of the Ingold theory is the direct connection between the molecularity of the reaction and the stereochemical

outcome. As this example shows, this simple connection does not necessarily hold, at least not in the dilute gas phase. The timing of the complete sequence **14** → **14′** is probably short, and it would have been interesting to study the dynamical details during the lifetime of the collision complex by high-level ab initio reaction trajectory calculations. For the time being, only smaller systems are accessible for such studies.

In conclusion, if we extend our model to the solution phase, we see that the outcome of our model calculation is in accord with the observation that the *exo*-form of such bicyclic systems may undergo nucleophilic substitution with retention of configuration, and not inversion. Using the nomenclature already introduced by us, the reaction follows an S_NF mechanism. In addition, it represents the first example where an S_NF mechanism is shown to have a lower potential energy barrier than the corresponding S_NB mechanism. Although the result presented here applies to the gas phase, it has clear implications for the situation in solution. As pointed out by us[15] and others,[45,46] there are inherent weaknesses in the traditional S_N1/S_N2 mechanistic regime utilized to describe the mechanistic features of nucleophilic substitution reactions. It is highly relevant that these weaknesses have been noticed previously, and that frontside substitution is a well-established phenomenon. Terms such as "solvent-assisted S_N1", "neigboring group participation", "ion-pair S_N2", and S_Ni have been introduced to describe similar situations when the classical S_N1/S_N2 paradigm is inappropriate.[5,47,48] Further studies will hopefully show how the theory for nucleophilic substitution should be redefined to incorporate the idea of a bimolecular frontside mechanism.

Acknowledgment. I thank the Norwegian Research Council (NFR) for the grants that made this work possible. The calculations were made possible thanks to support through the NFR Programme for Supercomputing. I am indebted to Professor Dieter Lenoir for addressing the question of frontside substitution in cyclopropanols, and for interesting and informative discussions. Dr. Jon K. Lærdahl and Professors Paul v. R. Schleyer and Maurizio Speranza are acknowledged for their helpful comments on the manuscript.

Supporting Information Available: Cartesian coordinates and total energies of all the optimized structures. This information is available free of charge via the Internet at http://pubs.acs.org.

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