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First Solvation Shell Effects on Ionic Chemical Reactions: New Insights for Supramolecular Catalysis

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This article presents a detailed discussion on medium effect on ionic S_N2 reactions. Ion pairing and the first solvation shell play the main role on reactivity. Ab initio calculations are used to show that a combination of apolar molecular cavity with polar hydroxyl groups can have catalytic effects on these reactions. The present results open an avenue of development for supramolecular catalysts able to control bimolecular ionic reactions. In particular, this new catalytic concept could be useful in nucleophilic fluorinations.

Introduction

Nucleophilic substitution reactions involving anionic species are very useful and fundamental in organic chemistry.[1-3] Anions are usually reactive species in the gas phase and are highly deactivated in protic solvents.[4-12] Ideal solvents for promoting their reactivity are dipolar aprotic or low polarity solvents due to smaller anion solvation ability of these media. However, even more important than reactivity is selectivity. Many anions are ambident nucleophiles, leading to different products,[13-18] whereas others are strong bases and able to promote E2 reactions.[19-25] In fact, it is not easy to achieve fast and selective reactions through changing only the solvent polarity. In many situations, low yield of S_N2 reactions are observed.

The present approach for performing anionic S_N2 reactions, either using aprotic solvents or phase-transfer catalysis[26] in apolar solvents, has been used since the 1960s. The main idea is to decrease the anion solvation, with the result that apolar solvents combined with large counterions would produce *naked* ions.[24,25,27-33] This idea has dominated the field in the last 30 years and no new concepts related to medium effect emerged aimed at improving our ability to control the kinetics and product outcome of these reactions. Nevertheless, recent theoretical[19,34-38] and experimental[39-41] studies have provided new insights on medium effects and pointed out that it is possible to accelerate and to take control of the product outcome through hydrogen bonding. The aim of this paper is to present a deeper development of new ideas on this very important subject.

A General View of the Solvent and Ion-Pairing Effects on Ionic S_N2 Reactions. An important outcome of experimental and theoretical studies of ion–molecule chemical reactions, both in gas phase and in solution, was to realize the critical role of the solvent for inducing free energy barrier. A more polar medium leads to a higher barrier and small reaction rate, whereas a less polar one should lead to a smaller barrier and faster kinetics. However, the general behavior of the activation free energy barrier in relation to the solvent polarity is not monotonic, because ion pairing and even the formation of greater aggregates (dimers, trimers, etc.) produces an important effect on the reaction kinetics, mainly in low polarity medium. A general overview of the medium and ion-pairing effects on the activation barrier is presented in Figure 1 and is based on recent results.[27]
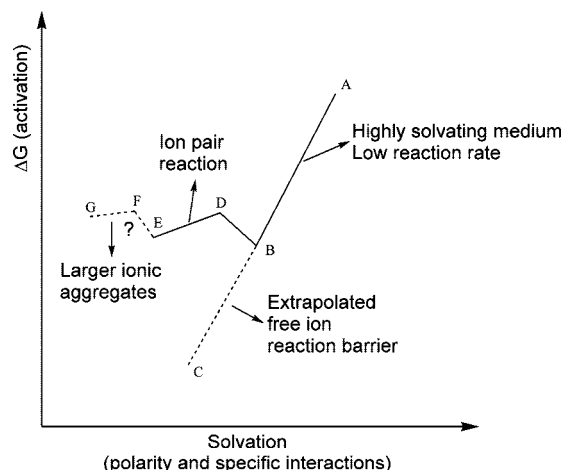

Figure 1. Anion reactivity as a function of the solvation ability of the medium.

The AB line corresponds to free anion reaction and BC is an extrapolated behavior. The BC line is not observed because ion pairing can take place, producing the BD line. On this line, the anion is forming an ion pair but the reaction takes place with the dissociated species. In the case of DE line, the ion pair is the reactant and it is active in the transition state. The EFG line corresponds to formation of a greater aggregate (dimer) and its behavior was estimated. We can observe that ion pairing does not allow the reaction rate to become very fast in apolar solvents. In fact, it works like a buffer and as the solvation ability decreases, the barrier should increase, because larger aggregates are even less reactive. This phenomenon sets an important limitation on our ability to produce fast kinetics on ionic reactions in solution. In addition, we do not have an adequate control of the product outcome.

The reader should observe we are using the term *solvation* instead of *solvent polarity* because the solute may have both a strong first solvation shell interaction (like hydrogen bonding and solvent coordination) as well as electrostatic interactions (dielectric constant) with the bulk solvent molecules.

Structured Environment: Transition State Stabilization. An interesting observation related to molecular solvents is the fact they consist of mobile small molecules. The environment around the solute is determined by its charge distribution, which influences the solvent configuration. Small molecules can better
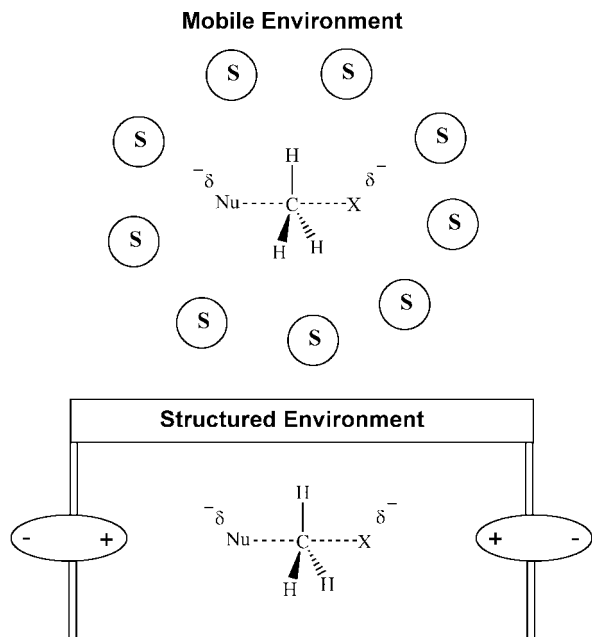
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Mobile Environment

Structured Environment

Figure 2. Solvent has a mobile environment, inducing a high free energy barrier due to better stabilization of charge-centered species. A rigid structured environment could produce selective stabilization of the transition state, leading to rate acceleration and control of the product ratio.

fit around the solute cavity, leading to greater stabilization of charge-centered species in relation to species with charge dispersion like S_N2 transition states. As a result, the solvent induces an activation barrier. In a sense, we can say the solvent has a mobile environment (Figure 2). This is a key observation and suggests that a carefully designed structured medium can take control of the reaction. In the case of the ionic S_N2 transition state, a medium with an adequate charge orientation in the space could lead to selective stabilization of this species as proposed in the Figure 2. The interaction with the free ionic nucleophile should be weaker, resulting in a catalytic effect.

Solvents able to make hydrogen bonding induce a high activation barrier for anionic S_N2 reactions, retarding the reaction. This view has dominated chemists thinking for many years. Nevertheless, the retarding effect is due to greater stabilization of the nucleophile in relation to the transition state. If we are able to provide a better stabilization of the transition state, it should be possible to observe a decrease of the barrier. This goal can be achieved with an adequate orientation of the hydroxyl groups, providing selective hydrogen bonds and stabilization of the transition state. A molecule able to form these hydrogen bonds is 1,4-benzenedimethanol, which was recently investigated in a set of theoretical studies.[19,34−36] In this work, a more complete analysis was performed of the role of hydrogen bonds on the activation barrier. The effect of molecules with one to four hydroxyl groups, i.e., methanol, *tert*-butanol, 1,4-benzenedimethanol (BDM), and a tetraol (BETROL) was investigated. The respective structures are presented in Scheme 1. The model system considered here involves complexes of these molecules with the fluoride ion in DMSO solution and the effect on the activation barrier for the F^- + CH_3Cl reaction.

Ab Initio Calculations. The potential energy surface for the species involved in this work was explored at the HF/6-31(+)G(d) level of theory for gas phase. The 6-31(+)G(d) basis set corresponds to 6-31G(d) for H and C and 6-31+G(d) for F, O, and Cl. Because small and charge-centered anions are

SCHEME 1

1 (MeOH)   **2 (tBuOH)**

3 (BDM)   **4 (BETROL)**
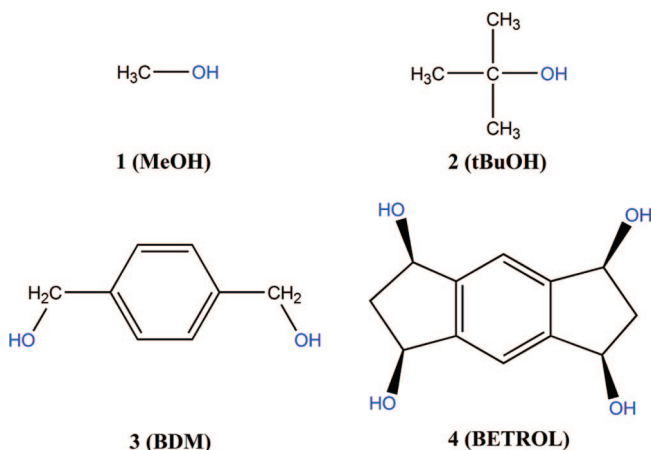
involved, the solvent could have an important effect on the activation barrier. Thus, more optimizations were done in solution at the PCM/HF/6-31(+)G(d) level, where the solvation method, PCM (polarizable continuum model),[42−46] considers the solvent as a dielectric medium. Dimethyl sulfoxide (DMSO) was considered the solvent with the use of cavity parameters proposed by Pliego and Riveros.[47] Recent studies have shown this approach provides a very good description of solvent effect on ionic process in DMSO.[11−13,19,48]

In order to obtain more reliable gas phase contribution to the potential energy surface, single-point calculations were done at the MP2 level using the 6-31(+)G(d) and 6-311+G(2df,2p) basis set. Harmonic frequency calculations were done for the transition state structures to confirm they are first-order saddle points. Only for the large $(F^-)_2(BDM)_2TBA$ complex frequency calculations were not performed.

In the investigation of the medium effect on the reaction, it was analyzed the potential of mean force surface $W(\mathbf{R})$,[49−51] defined by the relation

$$W(\vec{R}) = E(\vec{R}) + \Delta G_{solv}(\vec{R})$$

where the first term on the right side is the gas phase contribution, determined at the MP2 level and the second term is the solvation contribution, obtained at the PCM/HF/6-31(+)G(d) level. All the gas-phase calculations were done using the PC Gamess/Firefly program[52] while the solvation effect and liquid-phase optimizations[53] were done with the Gamess program.[54]

Results and Discussion

The results of the calculations are presented in Figure 3. For the direct reaction of the free fluoride ion, the activation barrier $(\Delta W^\dagger)$ is 17.0 kcal mol^{-1}. In the case of methanol−fluoride complex, its stabilization energy is 11.8 kcal mol^{-1} and the barrier becomes 20.8 kcal mol^{-1}. This high stabilization of the complex indicates it is present in liquid phase and has a very important effect on the activation barrier, increasing it by almost 4 kcal mol^{-1}. This is the well-established retarding effect, known from experimental studies, on going from dipolar aprotic to protic solvents. However, when *tert*-butanol is used, the complex is weaker and the transition state is slightly more stabilized. The final effect on the activation barrier is smaller and it becomes 19.8 kcal mol^{-1}. In recent experimental studies, Kim and co-workers have reported this interesting property of bulk alcohols and explored this effect for caring out nucleophilic
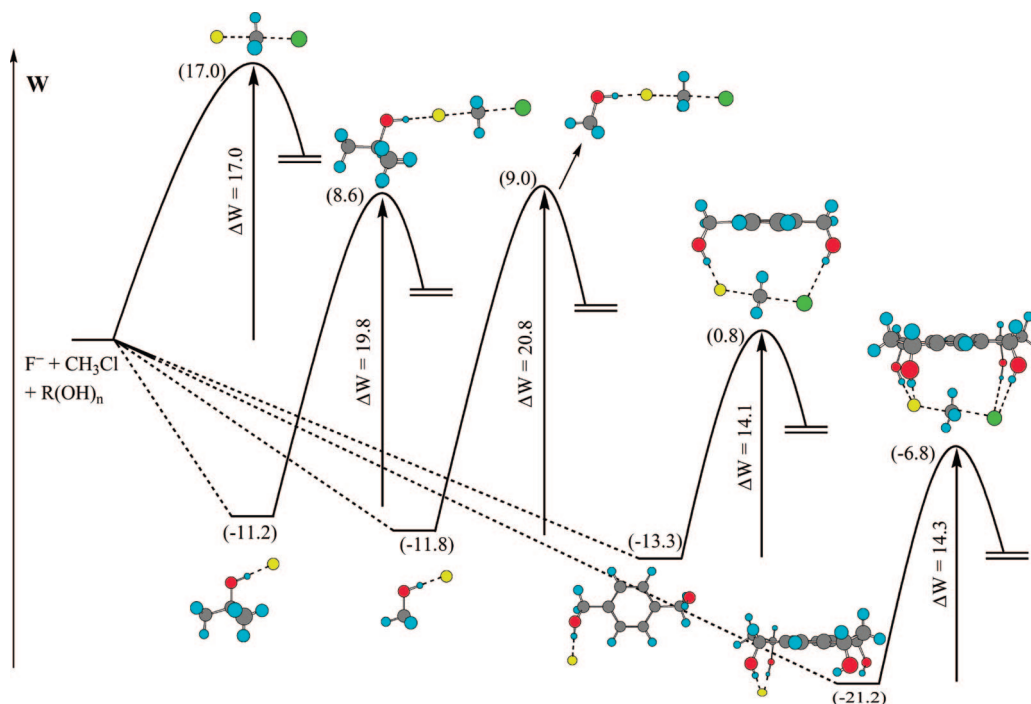
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Figure 3. Potential of mean force surface for $CH_3Cl + F^-(R(OH)_n)$ reaction in DMSO solution, where $R(OH)_n$ can be methanol, *tert*-butanol, BDM, or BETROL. Units of kcal mol^{-1}. Calculations at MP2/6-311+G(2df,2p) level for gas-phase contribution and PCM/HF/6-31(+)G(d) level for solvation. Optimized structures obtained at PCM/HF/6-31(+)G(d) level.
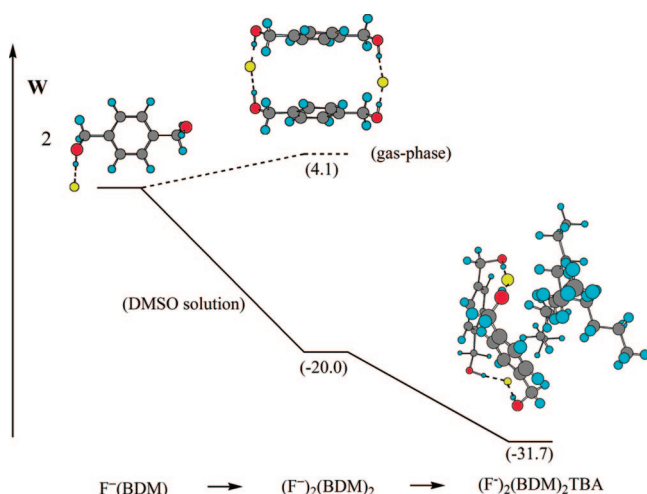

Figure 4. Association equilibriums involving fluoride ion, BDM, and TBA in gas phase (traced line) and DMSO solution (solid line). Units of kcal mol^{-1}. Calculations at MP2/6-31(+)G(d) level for gas-phase contribution and PCM/HF/6-31(+)G(d) level for solvation. Geometries obtained at HF/6-31(+)G(d) level.

Figure 5. Molecular cavity, named BDMCV, derived from the BDM.

fluorination.[39,40] They have also performed a theoretical analysis of this effect.[37,38]

When the diol (BDM) is complexing with fluoride, the stabilization energy increases to 13.3 kcal mol^{-1}. This greater stability can be attributed to extra interaction with the aromatic hydrogen. As reported in previous papers,[19,36] the stabilization of the transition state is greater, producing low activation barrier, only 14.1 kcal mol^{-1}. This effect is the opposite of that observed for methanol and *tert*-butanol, indicating this diol structure is able to catalyze this S_N2 reaction. The difference in relation to previous reports is that now we have provided a direct comparison with the effect of monoalcohols. Thus, Figure 3 provides computational support for the catalytic effect.

We can explore more details of the role of hydroxyl groups on the transition state stabilization. For example, what is the
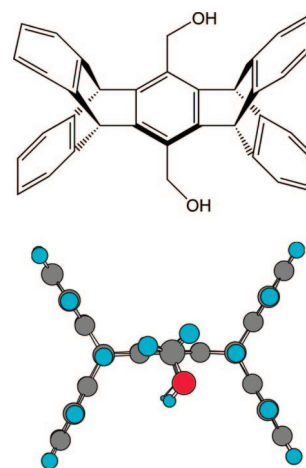
effect of adding new hydroxyl groups? The BETROL molecule was designed for analyzing this effect. The calculations show the fluoride ion is more stabilized, with complexation energy of 21.2 kcal mol^{-1}. This indicates a very stable species in solution. Similarly, the transition state is also strongly stabilized, but the final effect on the activation barrier is close to that observed for BDM, leading to a barrier of 14.3 kcal mol^{-1}. Thus, although the complex is more stable, the catalytic effect is the same. On the other hand, two hydrogen bonds between the BETROL and the fluoride are important for reactions occurring in less polar solvents. In this case, the counterion will have a stronger binding energy with the fluoride ion and formation of a stable complex is critical in order to dissociate the ion pair. Since it is expected that less polar medium will decrease the activation barrier, a structure like BETROL should be more effective than BDM for reactions in low polarity solvents.

Among the ionic S_N2 reactions, nucleophilic fluorinations[24,55,56] are singled out as very important and fluorinated organic
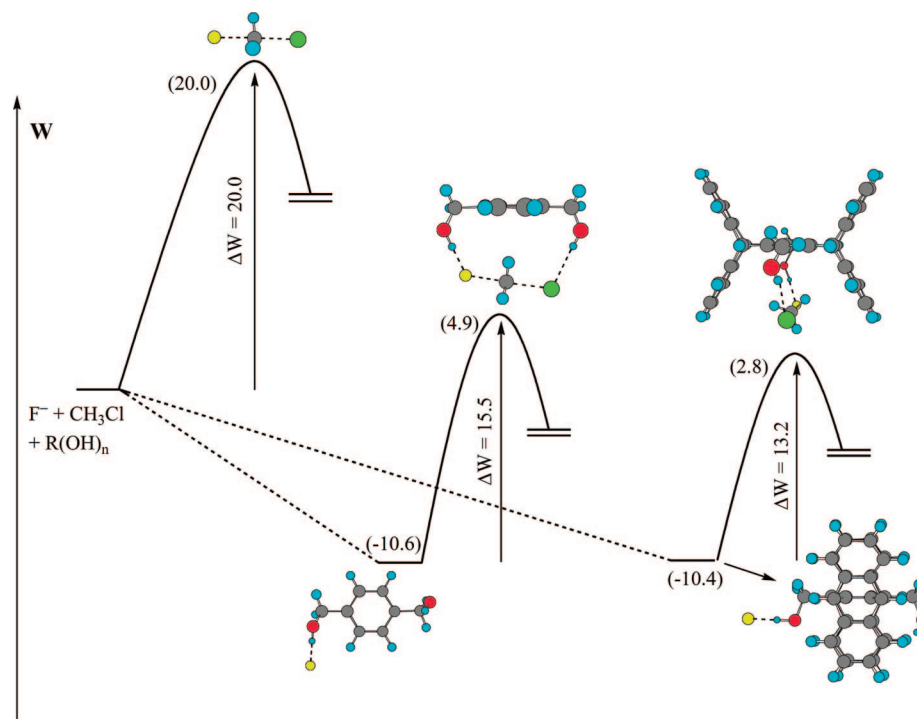
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Figure 6. Potential of mean force surface for $CH_3Cl + F^-(R(OH)_n)$ reaction in DMSO solution, where $R(OH)_n$ can be BDM or BDMCV. Units of kcal mol^{-1}. Calculations at MP2/6-31+G(d) level for gas-phase contribution and PCM/HF/6-31(+)G(d) level for solvation. Optimized structures obtained at the PCM/HF/6-31(+)G(d) level.

compounds have received an increased interest as more potent drugs.[57] Nevertheless, direct reaction of the fluoride ion with secondary alkyl halides leads to an E2 process as the main pathway. The approach proposed in this paper could resolve this issue, and a recent report[19] has suggested an increased selectivity toward S$_N$2 product could be achieved. Experimental studies using bulk alcohols as a solvent have also indicated good selectivity and reactivity in this media.[39,40] The effect of BDM and bulk alcohols is similar. The bulk alcohols are not able to form many hydrogen bonds with the fluoride ion while the wider transition state does. In addition, the fluoride ion is less stabilized in *tert*-butanol in relation to methanol. As a consequence, there is a decrease of the activation barrier and enhanced reactivity in bulk alcohols.

Catalysis Deactivation: Self-Association and Ion Pairing. The previous analysis indicates an important new catalytic effect due to selective solvation of the transition state. In the absence of any other equilibrium, catalysis should be observed. However, there is the possibility of a fluoride−BDM complex to form a dimer, producing an extra equilibrium in solution. In addition, the TBA cation could associate with this charged species, leading to ion pairing. We have theoretically investigated these possibilities and the calculations support this view. Figure 4 presents the relative W for the processes both in the gas phase and in DMSO solution. In the gas phase, the dimerization of the fluoride−BDM complex is unfavorable, leading to energy of 4.1 kcal mol^{-1} above the monomer. Thus, this dimeric structure is not stable in gas phase. However, when we consider the DMSO solvent, the situation inverts. The $(F^-)_2(BDM)_2$ complex becomes more stable by 20.0 kcal mol^{-1}, indicating the solvent has a very important effect on stabilizing the $(F^-)_2(BDM)_2$ complex. As a consequence, this very stable dimer seems able to eliminate the catalytic effect of the BDM on this S$_N$2 reaction.

Because the solvent plays an important role on the stability of the $(F^-)_2(BDM)_2$ complex, one possibility would be to use an apolar solvent. However, in this case ion pairing could become very important. In a previous study,[27] it has been found that one water molecule is able to dissociate the $F^-(TBA)$ ion pair in DMSO solution and the same effect should be expected for BDM. On the other hand, in the case of the $(F^-)_2(BDM)_2$ complex, its higher charge could lead to stronger association with one TBA cation. The calculations support this view, and Figure 4 presents the structure of the $(F^-)_2(BDM)_2$TBA complex. The ΔW for formation of this species from $2F^-(BDM)$ + TBA is −31.7 kcal mol^{-1}, 11.7 kcal mol^{-1} below of $(F^-)_2(BDM)_2$ complex. Entropy effects are important for determining the ΔG for association, but this system is very large for frequency calculations. In addition, it is not clear if simple harmonic frequency analysis is adequate for such floppy species. Anyway, the $(F^-)_2(BDM)_2$ complex seems be stable enough for eliminating the catalysis in DMSO, whereas the $(F^-)_2(BDM)_2$TBA complex should be important in less polar medium.

Reaction Inside a Molecular Cavity. The previous results point out that adequate stabilization of the transition state can be achieved through two or more hydrogen bonds with adequate orientation. However, because self-association and complexation with the counterion can lead to more stabilization of the anion, a new structure able to avoid these problems must be designed. On the other hand, an apolar environment around the reactants could produce more rate acceleration. Taking these points in consideration, a new structure was designed, named BDMCV, presented in the Figure 5. The BDM was taken as the reference species to build the BDMCV. The idea is that the transition state will be enclosed in an apolar environment and interact with the hydroxyl

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groups. The cavity is able to avoid self-association. In this way, the new structure would avoid the main drawback of the BDM.

The effect of the BDMCV interacting with the S$_N$2 transition state was also investigated at the theoretical level. The results of the calculations and the optimized structures are presented in the Figure 6. The formation of the F$^-$(BDMCV) complex can be observed. The most stable structure corresponds to fluoride ion outside the apolar cavity. However, for the reaction to proceed via complexaton with BDMCV, the transition state stays inside the cavity. For comparison, we have included the bare F$^-$ + CH$_3$Cl system and its interaction with BDM. Because it was not possible to perform single-point MP2/6-311+G(2df,2p) calculations for this large system, the calculations were done at MP2/6-31(+)G(d)//PCM/HF/6-31(+)G(d) level. For the F$^-$ + CH$_3$Cl system, the barrier becomes 20.0 kcal mol^{-1}, while considering the interaction with BDM, the barrier changes to 15.5 kcal mol^{-1}. For comparison, the previous values (obtained at higher level) are 17.0 and 14.1 kcal mol^{-1}, respectively. When we consider the BDMCV, the barrier is even more reduced to 13.2 kcal mol^{-1}, producing additional stabilization by 2.3 kcal mol^{-1} in relation to BDM. It is interesting to mention that Halls and Raghavachari[58] have reported a theoretical study of an ionic S$_N$2 reaction (Cl$^-$ + CH$_3$Cl) inside a carbon nanotube, and they have found the nanotube environment induces a small activation barrier of only 6.6 kcal/mol for this reaction. Therefore, our conjecture that the BDMCV could lead to further rate acceleration has a computational support. In addition, the self-association involving four hydrogen bonds is not possible in this case, indicating the BDMCV has enhanced catalytic activity on ionic S$_N$2 reactions.

Final Considerations

Control of chemical reactions is a very important subject. The idea of creating artificial enzymes through design of structured environments has received a lot of attention.[59,60] However, it involves synthesis of complex structures and it would be very desirable to have available methods useful for projecting promising molecular species. In the same way, hydrogen bonds have been used in organocatalyzed reactions.[61,62] In this paper, it was shown that molecular cavities with hydrogen bonds placed at specific positions can be effective for promoting ionic S$_N$2 reactions. The proposed catalytic concept is a molecular cavity able to interact selectively with the transition state and to avoid self-association. Therefore, the foundations of this new effect have been presented in this paper and the author hopes these results will provide an incentive for experimental chemists to perform studies in this direction. It should be noticed that a structure similar to BDMCV species was synthesized by Yang and co-workers,[63,64] and it would not be difficult to add hydroxyl groups. In addition, new hydroxylated molecular cavities could be designed. One potential application of these ideas is increasing selectivity of nucleophilic fluorinations.[19]

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