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Efficiency of Bulky Protic Solvent for S_N2 Reaction

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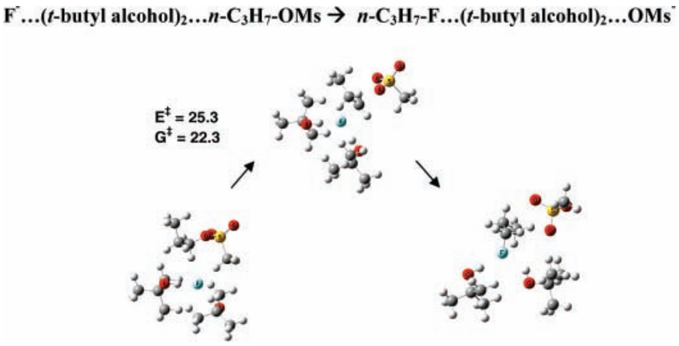
ABSTRACT



We calculate and compare the effects of aprotic vs protic solvent on the rate of S_N2 reaction [$F^- + C_3H_7OMs \rightarrow C_3H_7F + OMs^-$]. We find that aprotic solvent acetonitrile is more efficient than a small protic solvent such as methanol. Bulky protic solvent (*tert*-butyl alcohol) is predicted to be quite efficient, giving the rate constant that is similar to that in CH_3CN. Our calculated relative activation barriers of the S_N2 reaction in methanol, *tert*-butyl alcohol, and CH_3CN are in good agreement with experimental observations.

The bimolecular nucleophilic substitution (S_N2) reactions,[1−16] which are one of the most fundamental and useful chemical reactions, have long been envisaged as occurring by a backside attack of the nucleophile via a single transition state. Although this simplified picture could explain many features of the S_N2 reaction, the detailed mechanism has recently been under intensive study, questioning the traditional concepts. For example, Uggerud[7] proposed that some S_N2 reactions

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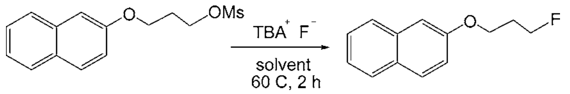
may occur via frontside attack of the nucleophile, based on the different yields of optical isomers experimentally observed. The reaction of F^- in the form of an ion pair (Cs^+F^-)[9a] was invoked to explain the phenomenal efficiency of fluorination in protic solvent (*tert*-butyl alcohol).[9b]

Chi and co-workers[17] observed that S_N2 reaction in an ionic liquid can be very efficient, which indicates that ionic species may affect the reaction rate in an intricate fashion that has so far not been considered. These new findings may require a fundamental revision to long-held "common sense" concerning the S_N2 reaction.

The influence of solvent on the efficiency of S_N2 reaction is one of the features that requires more careful investigation because the knowledge of solvent effects has largely been based on intuition. For example, a protic solvent has long been considered as deterring the S_N2 reaction due to the unfavorable interactions with the nucleophile, and experimental and theoretical studies for smaller protic solvents such as water and methanol have confirmed this viewpoint. In this work, we focus on the effects of *tert*-butyl alcohol for the S_N2 reaction (see Scheme 1) as an example of a bulky protic solvent, presenting a quantum chemical analysis to compute and compare the mechanism and activation barriers in the presence of protic (methanol, *tert*-butyl alcohol) and aprotic (acetonitrile) solvent for predicting their role and efficiency. In contrast with our earlier work,[9a] we exclude the cation here to isolate the influence of solvent on the nucleophile and to study the S_N2 reaction involving a "naked" nucleophile that may be obtained by using bulky cations such as *tert*-butylammonium ion. We treat the solvent as explicit molecules (not as a continuum) by employing the cluster approach to examine the solvent−nucleophile interactions at the molecular level.

Scheme 1



Density functional theory method (MPW1K)[18,19] is employed with the 6-311++G** basis set, as implemented in the GAUSSIAN 03 set of programs.[20] Stationary structures are confirmed by ascertaining that all of the harmonic frequencies are real. The structure of the TS is confirmed by carrying out the intrinsic reaction coordinate (IRC) analysis along the reaction pathway. Zero point energies (ZPE) are taken into account, and default criteria are used for all optimizations.

Figure 1 presents the S_N2 reaction $[F^- + C_3H_7OMs \rightarrow C_3H_7F + OMs^-]$ in the aprotic solvent CH_3CN. We treat the reaction of F^- that is "fully" solvated by allowing the nucleophile and the reactant to interact with as many as solvent molecules as possible and find that three CH_3CN molecules may interact with F^- in the first shell. Although this situation may be different from the reaction in the solution phase in which numerous molecules CH_3CN exist in and beyond the second shell around the reacting species exerting an electrostatic influence, it is extremely useful for elucidating the effects of detailed interactions between the nucleophile and solvent on the reaction rate, as discussed below.

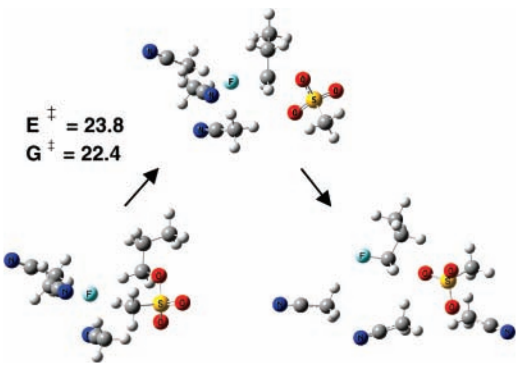


Figure 1. Calculated S_N2 mechanism in acetonitrile. Energy in kcal/mol and bond lengths in Å.

It is useful to note that F^- interacts with CH_3CN by forming weak links with methyl hydrogen atoms, rather than with the polar CN bond. Although the carbon atom in the CN group possesses a partial positive charge, the electronegative nitrogen atom seems to prevent F^- from interacting with the CN group. The electrostatic influence of the CH_3CN molecules may still be strong but seems to be less important than hydrogen-bonding that is shown below to be profound in the case of the protic solvents.

This situation basically provides the reason that aprotic solvents are known to give rise to S_N2 reactions. It is

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interesting to observe that the C_3H_7 side chain in the reactant, which forms weak interactions with one of the methanol molecules in the pre-reaction complex flips over to the other side, via the transition state in which the C−C−C backbone is almost planar. The activation energy (free energy) is calculated to be 23.8 (22.4) kcal/mol.

Figure 2 presents the same S_N2 reaction occurring under the interactions with three methanol molecules, a typical small protic solvent. We find that all three OH groups bind with F^-, which act as a Lewis acid. Since the OH group is fairly acidic, methanol is expected to significantly decrease the nucleophilicity of F^-, thus retarding the S_N2 reaction. The calculated activation energy (free energy) is 27.7 (27.6) kcal/mol, much larger (by 3.9 (5.2) kcal/mol) than that in the aprotic solvent CH_3CN. Accordingly, the rate constant of fluorination under the influence of three methanol molecules is predicted to be several hundred times smaller than that in CH_3CN at 60 °C, and methanol may be considered as a poor solvent for S_N2 reactions for the same reason as water.

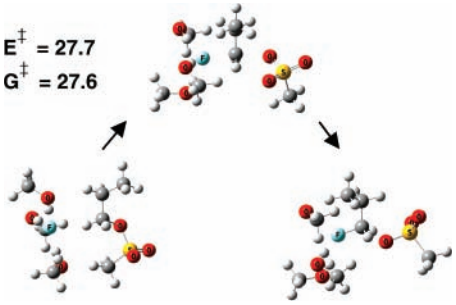

Figure 2. Calculated S_N2 mechanism in methanol. Energy in kcal/mol and bond lengths in Å.

We calculated the mechanism and the activation barrier of the same S_N2 reaction in a bulky protic solvent (*tert*-butyl alcohol) to scrutinize the effects of the size of protic solvent by comparison with the reaction in the small protic solvent CH_3OH and aprotic solvent CH_3CN. We find that two *tert*-butyl alcohol molecules directly interact with F^- in the first shell, as depicted in Figure 3. The nucleophile F^- binds with the acidic OH group in the pre-reaction complex, and the reaction is predicted to proceed via the activation energy (free energy) of 25.3 (22.3) kcal/mol. This barrier is only 1.5 (0.1) kcal/mol larger (smaller) than that in CH_3CN, and *tert*-butyl alcohol is predicted to be as efficient as CH_3CN. The difference from the small protic solvent methanol is, however, calculated to be even larger, with the activation energy (free energy) smaller by 2.4 (5.3) kcal/mol. Therefore, *tert*-butyl alcohol seems to be a quite good solvent for S_N2 reactions because of limited interactions with the nucleophile F^- due to the bulkiness of solvent molecules.

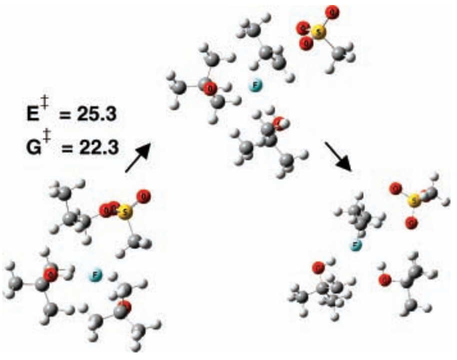

Figure 3. Calculated S_N2 mechanism in *tert*-butyl alcohol. Energy in kcal/mol and bond lengths in Å.

Based on the observed relative rate constants (1:74.8:166.2) (Table 1) of fluorination reaction[21] (Scheme 1) in methanol, *tert*-butyl alcohol, and CH_3CN, the relative activation barriers for the two former solvents with respect to that for CH_3CN are 3.4 and 0.5 kcal/mol, respectively, at 60 °C.

Table 1. Experimentally Observed Relative Rate Constants and Experimental and Calculated Relative Barriers (in kcal/mol) of S_N2 Reaction in Methanol, *tert*-Butyl Alcohol, and CH_3CN

	methanol	*tert*-butyl alcohol	CH_3CN
relative rate constant	1	74.8	166.2
relative activation barrier (exptl)	3.4	0.5	0
relative activation barrier $E^\ddagger$ (calcd)	3.9	1.5	0
relative free energy of activation $G^\ddagger$ (calcd)	5.2	−0.1	0

Our calculated relative activation energy (free energy) of the S_N2 reaction in methanol and *tert*-butyl alcohol are 3.9 (5.2) and 1.5 (−0.1) kcal/mol, respectively, in reasonable agreement with experimental observations in the solution phase.[21] This indicates that the electrostatic influence of other numerous solvent molecules beyond the first shell around the nucleophile may be considered more or less similar, and that the activation barriers may be shifted by a similar amount by the electrostatic influence of the solvent continuum of methanol, *tert*-butyl alcohol, and CH_3CN, and the relative activation barriers of S_N2 reaction in various solvents are determined mostly by interactions with the solvent molecules directly binding with the nucleophile. Thus, it seems that the S_N2 reaction studied here may well be modeled as a cluster reaction[22,23] comprising the nucleophile, reactant, and a few solvent molecules as depicted in Figures 1−3, at least for comparing the efficiency of solvents for S_N2 reaction.

Good agreement between experimental observations and theoretical calculations for the relative rate constants of S_N2

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reaction in various solvents presented in this work indicates that the mechanism is the nucleophilic attack of a “naked” F^-, rather than that of a contact ion pair for the S_N2 reaction of CsF.[9a] Experimental and theoretical observations presented in this work seem to be in line with Pliego and co-workers’ very interesting proposal[24] that employs a diol as a solvent that can give a higher S_N2 reaction rate (and higher selectivity) than dipolar aprotic solvents, in that the difference in rate constants in methanol and *tert*-butyl alcohol is to be understood in terms of differential degrees of solvation due to the size of solvent molecules; less solvation by a bulkier protic solvent (*tert*-butyl alcohol) leads to a lower stabilization of F^- than methanol, whereas the difference in the corresponding effects on the transition state would be smaller due to larger distances between the solvent molecules and F^-, thus producing a lower (higher) net barrier (rate constant) for *tert*-butyl alcohol. Our results also suggest that an even bulkier protic solvent would be more efficient than *tert*-butyl alcohol, as will be discussed elsewhere.[21]

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Supporting Information Available: Table of energy (*E*), ZPE, and Gibbs energy. This material is available free of charge via the Internet at http://pubs.acs.org.

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