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Solvents effect on S_N2 reactions

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We attempt to find out the origin of rate difference of the S_N2 reaction in the gas phase and in the aqueous solution which is about twenty orders of magnitude. To do this, we calculate the interaction energies of both reactant-complex and activated-complex of the S_N2 reaction with the hydrated water molecules and their interaction energy differences, varying the number of hydrated water molecules step by step. The calculated results show that the rate of the S_N2 reaction decreases with an increase of the number of hydrated water molecules due to the increase of the reaction barrier height and also about sixty or more water molecules are needed to explain the rate difference of the S_N2 reaction in the gas phase and solution.

Key words: Reaction barrier height—Solvents effect

1. Introduction

The studies on the bimolecular nucleophilic substitution (S_N2) reactions in solution [1-3] and in the gas phase [4-10] have been done extensively. They have shown that S_N2 reactions involving anions and polar molecules proceed up to twenty orders of magnitude faster in the gas phase than in solution.

The double-well form of the potential energy surface for the S_N2 reaction in the gas phase has been confirmed by the extensive studies of Brauman et al. [4-7] and by the considerable progresses made in characterizing the energetics of S_N2 reactions in the gas phase through the application of quantum mechanical methods [11-22]. The unimodal form [1-3] of the potential energy surface for the S_N2 reaction in solution has been generally accepted and confirmed by the statistical mechanical study of Chandrasekhar et al. [23] through the Monte Carlo simulation, especially in the case of the aqueous solution. Therefore, we can schematically draw the symmetric potential energy profiles of the S_N2 reaction both in the gas phase and in solution shown in Fig. 1, when the nucleophile is equal to the leaving group such as

$$Cl^- + Ch_3Cl \rightleftharpoons ClCH_3 + Cl^- \quad (1)$$

In case the nucleophile is not equal to the leaving group such as

$$F^- + CH_3Cl \rightleftharpoons FCH_3 + Cl^- \quad (2)$$

we can also schematically draw the unsymmetric potential energy profiles of the S_N2 reaction both in the gas phase and in solution shown in Fig. 2.

There are some attempts [24–26] to bridge the gap between the rate of the S_N2 reaction in the gas phase and that in aqueous solution. Morokuma [25] has

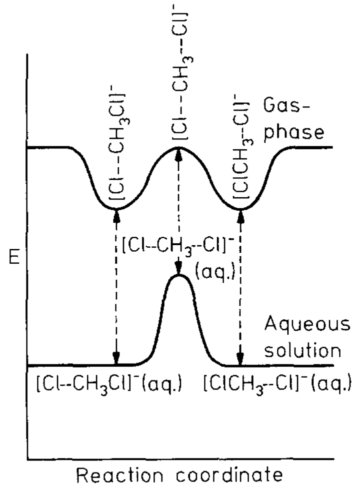

Fig. 1. The schematic symmetric potential energy profiles of S_N2 reaction such as $Cl^- + CH_3Cl \rightleftharpoons ClCH_3 + Cl^-$

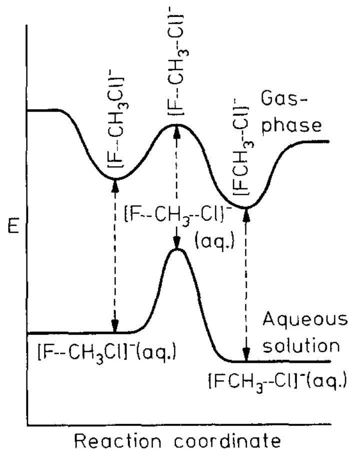

Fig. 2. The schematic unsymmetric potential energy profiles of S_N2 reaction such as $F^- + CH_3Cl \rightleftharpoons FCH_3 + Cl^-$

presented the results of *ab initio* SCF calculations of potential energy surfaces on the S_N2 reaction

$$Cl^-(H_2O)_n + CH_3Cl \rightleftarrows ClCH_3 + Cl^-(H_2O)_n \tag{3}$$

for $n = 0$(unhydrated), 1, and 2, and found that the barrier of the reaction increases significantly with the introduction of only one or two hydrated water molecules. These hydrated cluster reactions, however, do not include sufficient numbers of water molecules which are necessary to reasonably explain the solvents effect on the S_N2 reaction because the explicit inclusion of many water molecules is beyond the scope of current quantum mechanical methods. Similarly, Bohme and Mackay [26] have also presented the results obtained by the experiment and found that the rate constant of the reaction

$$OH^-(H_2O)_n + CH_3Br \rightleftarrows Br^-(H_2O)_n + CH_3OH \tag{4}$$

decreases gradually from $n = 0$ to $n = 3$. However, these hydrated cluster reactions do not also include sufficient numbers of water molecules because of the limitation of the experiment.

Therefore, in this study, we include many hydrated water molecules in order to reasonably explain the solvents effect on the S_N2 reaction and find out how the rate constant of the S_N2 reaction, that is, the barrier of reaction changes with a increase of the number of hydrated water molecules. We believe that the solvents effect is important to understand the origin of the rate difference of the S_N2 reaction in the gas phase and in solution. We also think that the rate difference of the S_N2 reaction in the gas phase and in aqueous solution, which is about twenty orders of magnitude, may be mainly due to the difference between the interaction energy of reactant-complex of the S_N2 reaction with the hydrated water molecules ($V_{R.C.}$) and that of the activated-complex of the S_N2 reaction with the hydrated water molecules ($V_{A.C.}$).

In this study, we choose two S_N2 reactions (Eqs. 1, 2) and represent the water molecule as a Soft Sphere Point Dipole (SSPD) [27], which is a very simple model for the water molecule, in order to include many water molecules and to reeasonably explain the solvents effect on the S_N2 reaction. In particular, the SSPD model can be reasonably used not only in the complete solute-solvent system but also in the system of an ion solvated by a limited number of solvent molecules, because the potential parameters for the SSPD model are parametrized by fitting the calculated potentials of clusters with a different number of water molecules (20–100) to the corresponding experimental energies. The validity of the model is also confirmed by the fact that interaction energies of reactant-complex and activated-complex with a single water molecule each obtained with the SSPD model are in agreement with *ab initio* results, even though there are small discrepancies. We hydrate both reactant-complex and activated-complex of the S_N2 reaction with the equal number of water molecules and calculate interaction energies, varying the number of hydrated water molecules step by step until the difference between $V_{R.C.}$ and $V_{A.C.}$ converges approximately.

In order to calculate the interaction energies, we optimize the positions and orientations of hydrated water molecules. The method of calculations are given in detail in the next section.

2. Method of calculations

As mentioned before, we use the simple model, that is, the SSPD model for water molecules in order to include many water molecules and to reasonably explain the solvents effect on the S_N2 reaction. This model represents each water molecule as a point dipole attached to the center of a compressible soft sphere. Therefore, the interaction between the pair of water molecules is represented by dipole-dipole and van der Waals potential functions. The interactions between water molecules and atoms of the reactant-complex or the activated-complex are represented by dipole-charge and van der Waals potential functions. Thus, the potential function to calculate the interaction energy of complex with hydrated water molecules is given by

$$\begin{aligned} V = & -\sum_{ij} Q_i \mathbf{r}_{ij} \boldsymbol{\mu}_j / r_{ij}^3 + \sum_{j>j'} \boldsymbol{\mu}_j [\nabla(\boldsymbol{\mu}_{j'} \mathbf{r}_{jj'} / r_{jj'}^3)] \\ & + \sum_{ij} V_{vdw}(r_{ij}) + \sum_{j>j'} V_{vdw}(r_{jj'}) \end{aligned} \tag{5}$$

where Q_i is the atomic charge of the complex and $\boldsymbol{\mu}_j$ is the water dipole moment vector and V_{vdw} is the van der Waals potential function. The van der Waals potential function between the pairs of water molecules is given by

$$V_{vdw}(r_{jj'}) = 2\varepsilon^*((r^*/r_{jj'})^9 - (3/2)(r^*/r_{jj'})^6) \tag{6}$$

where $r_{jj'}$ is the distance between the centers of indicated point dipoles and ε^* and r^* are the van der Waals parameters taken from [27]. The van der Waals potential function between the water molecule and the atom of the complex is given by

$$V_{vdw}(r_{ij}) = \varepsilon^*((r^*/r_{ij})^{12} - 2(r^*/r_{ij})^6), \tag{7}$$

where r_{ij} is the distance between the center of dipole and the atom of the complex and ε^* and r^* are the van der Waals parameters. The van der Waals parameters of interaction between the atom of the complex and the water molecule are determined using the arithmetic mean law for r^* and the geometric mean law for ε^* respectively. The van der Waals parameters used in this study are listed in Table 1. In order to represent the finite dipole properties of water molecules by point dipoles, the length of the dipole moment vector in the dipole-dipole interaction term is replaced by

$$|\boldsymbol{\mu}| = \boldsymbol{\mu}_0 + \Delta\boldsymbol{\mu}'/(1 + (r_{jj'}/r_0)^2) \tag{8}$$

The parameter $\boldsymbol{\mu}_0$ is taken as the dipole moment of an isolated water, i.e., $\boldsymbol{\mu}_0 = 1.88$ D and r_0 is fixed at 6 Å. The parameter $\Delta\boldsymbol{\mu}'$ is taken from Ref. [27]. The same type of function is also used for the dipole-charge interaction term using different $\Delta\boldsymbol{\mu}'$ value. Such parameters are also listed in Table 1. The details about the potential functions are given in [27].

Table 1. Parameters for calculations

van der Waals parameters			
$\varepsilon^*(H_2O)^a$	0.16 kcal/mol	$r^*(H_2O)^a$	3.66 Å
$\varepsilon^*(C)^a$	0.067 kcal/mol	$r^*(C)^a$	4.24 Å
$\varepsilon^*(H)^a$	0.018 kcal/mol	$r^*(H)^a$	2.81 Å
$\varepsilon^*(Cl)^b$	0.144 kcal/mol	$r^*(Cl)^b$	4.96 Å
$\varepsilon^*(F)^b$	0.268 kcal/mol	$r^*(F)^b$	3.08 Å
Other parameters			
μ_0^a	1.88 Debye		
r_0^a	6.0 Å		
$\Delta\mu'(H_2O—H_2O)^a$	1.6 Debye		
$\Delta\mu'(H_2O—Solute)^a$	0.8 Debye		

[a] Parameters taken from [27]
[b] Parameters fitted with ion-water interaction energies data in [28]

For the geometries and atomic charges of both reactant-complex and activated-complex, we use the data obtained by *ab initio* SCF calculations. For the S_N2 reaction (Eq. 1), we use the geometries and atomic charges of both reactant-complex and activated-complex obtained by Chandrasekhar et al. [23] through *ab initio* SCF calculations. The geometries of both the reactant-complex and the activated-complex for S_N2 reaction (Eq. 1) are shown in Fig. 3 and the atomic charges are listed in Table 2. For the S_N2 reaction (Eq. 2), we also use the

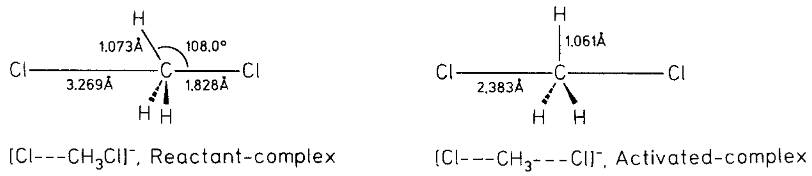

Fig. 3. Geometries of reactant-complex and activated-complex for S_N2 reaction, $Cl^- + CH_3Cl \rightleftarrows ClCH_3 + Cl^-$

Table 2. Atomic charges of reactant-complex and activated-complex for S_N2 reaction, $Cl^- + CH_3Cl \rightleftarrows ClCH_3 + Cl^-$ (In units of electron charge, *e*)

Reactant-complex	
$\underline{Cl}—CH_3Cl$	−0.973
$Cl—\underline{C}H_3Cl$	−0.188
$Cl—C\underline{H}_3Cl$	0.136
$Cl—CH_3\underline{Cl}$	−0.247
Activated-complex	
$\underline{Cl}—CH_3—Cl$	−0.77
$Cl—\underline{C}H_3—Cl$	−0.24
$Cl—C\underline{H}_3—Cl$	0.26
$Cl—CH_3—\underline{Cl}$	−0.77

$[F{-}{-}{-}CH_3Cl]^-$, Reactant-complex

$[F{-}{-}{-}CH_3{-}{-}{-}Cl]^-$, Activated-complex

Fig. 4. Geometries of reactant-complex and activated-complex for S_N2 reaction, $F^- + CH_3Cl \rightleftarrows FCH_3 + Cl^-$

Table 3. Atomic charges of reactant-complex and activated-complex for S_N2 reaction, $F^- + CH_3Cl \rightleftarrows FCH_3 + Cl^-$
(In units of electron charge, *e*)

Reactant-complex	
$\underline{F}$—CH_3Cl	−0.969
F—$\underline{C}H_3Cl$	−0.383
F—$C\underline{H}_3Cl$	0.244
F—$CH_3\underline{Cl}$	−0.377
Activated-complex	
$\underline{F}$—CH_3—Cl	−0.896
F—$\underline{C}H_3$—Cl	−0.252
F—$C\underline{H}_3$—Cl	0.250
F—CH_3—$\underline{Cl}$	−0.604

geometries and atomic charges obtained by Morokuma et al. [29] through *ab initio* SCF calculations. The geometries of both the reactant-complex and the activated-complex for the S_N2 reaction (Eq. 2) are shown in Fig. 4 and the atomic charges are listed in Table 3.

As mentioned before, the positions and orientations of hydrated water molecules having the minimum interaction energy are generated by minimizing the interaction energy function described above. Optimization method [30] is used to minimize the interaction energy. Because the minimization involves many degrees of freedom when the number of hydrated water molecules increases, it is important to ensure that the calculated minimum energy is the lowest one possible. To determine this, the calculation is repeated many times varying the initial coordinates of hydrated water molecules.

3. Results and discussion

We calculate the interaction energies of reactant-complex with the hydrated water molecules ($V_{R.C.}$) and those of activated-complex with the hydrated water molecules ($V_{A.C.}$), step by step varying the number of hydrated water molecules. We also calculate the difference between $V_{R.C.}$ and $V_{A.C.}$, which is an important factor to determine the barrier of the reaction, that is, the activation energy. The difference between $V_{R.C.}$ and $V_{A.C.}$ can be related to the rate constant by the following equation

$$k_s = k_g \exp(-\Delta V/RT), \tag{9}$$

where ΔV is the difference between $V_{R.C.}$ and $V_{A.C.}$. k_g and k_s are the rate constants of the S_N2 reaction in the gas phase and the hydrated state respectively. From Eq. 9, we calculate the ratios of k_s/k_g, in which we are interested to find out

Table 4. Results for S_N2 reaction, $Cl^- + CH_3Cl \rightleftharpoons ClCH_3 + Cl^-$

Number of hydrated water molecules	$V_{A.C.}$[a]	$V_{R.C.}$[a]	ΔV[a]	$\log(k_s/k_g)$[b]
2	−18.9	−24.0	5.1	−3.76
18	−174.9	−192.1	17.2	−12.66
34	−370.7	−391.2	20.5	−15.01
42	−488.3	−511.2	22.9	−16.74
54	−627.1	−656.5	29.4	−21.61
66	−763.7	−794.5	30.8	−22.61

[a] Units in kcal/mol

[b] The values calculated from Eq. (9) at 298K

Table 5. Results for S_N2 reaction, $F^- + CH_3Cl \rightleftharpoons FCH + Cl^-$

Number of hydrated water molecules	$V_{A.C.}$[a]	$V_{R.C.}$[a]	ΔV[a]	$\log(k_s/k_g)$[b]
2	−35.0	−39.9	4.9	−3.60
18	−194.3	−210.3	16.0	−11.73
34	−386.8	−406.1	19.3	−14.15
42	−506.6	−527.9	21.3	−15.64
54	−646.1	−672.8	26.7	−19.58
66	−784.3	−812.8	28.5	−20.89

[a] Units in kcal/mol

[b] The values calculated from Eq. (9) at 298K

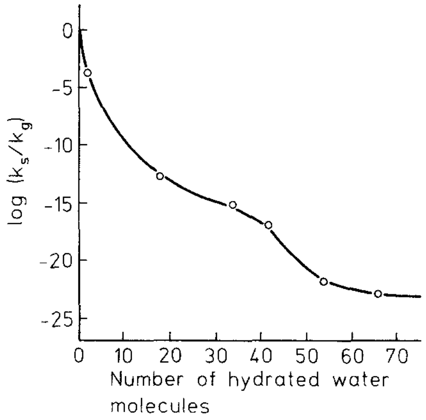

Fig. 5. $\log(k_s/k_g)$ vs number of hydrated water molecules for S_N2 reaction, $Cl^- + CH_3Cl \rightleftharpoons ClCH_3 + Cl^-$

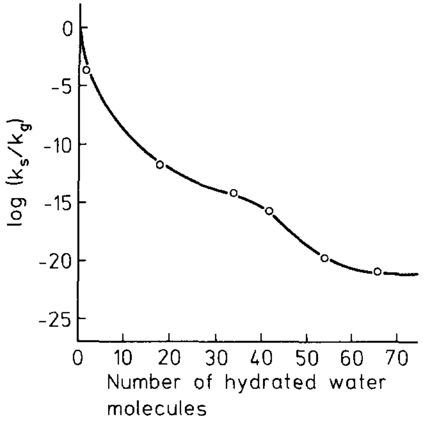

Fig. 6. $\log(k_s/k_g)$ vs number of hydrated water molecules for S_N2 reaction, $F^- + CH_3Cl \rightleftarrows FCH_3 + Cl^-$

how many water molecules are needed to explain the rate difference of the S_N2 reaction in the gas phase and in aqueous solution which is about twenty orders of magnitude.

The calculated results for the reactions (Eqs. 1 and 2) are summarized in Tables 4 and 5, respectively. Figs. 5 and 6 also represent the calculated results for the reactions (Eqs. 1, 2), respectively.

In conclusion, the rate of the S_N2 reaction decreases with an increase of the number of hydrated water molecules due to the increase of the reaction barrier height. From Figs. 5 and 6, we also know that about sixty or more water molecules are needed to explain the rate difference of the S_N2 reaction in the gas phase and in aqueous solution. That is, the hydrated clusters having about sixty or more water molecules may represent solution-like behaviors.

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