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QUANTUM MECHANICAL AND MOLECULAR MECHANICAL STUDIES OF THE HYDROLYSIS OF METHYL NITRATE AND THE SOLVENT EFFECT

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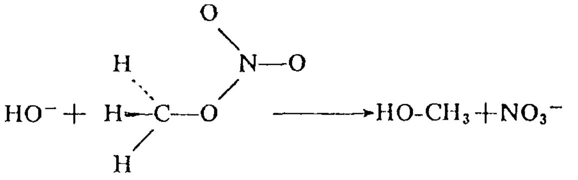
The alkaline hydrolysis reaction of methyl nitrate was simulated by quantum mechanical and molecular mechanical methods. The gas-phase reaction was calculated to proceed with no barrier when *ab initio* calculations at the STO-3G level were utilized, and with a very small barrier (5·70 kJ mol^{-1}) when the MINDO/3 method was applied. In solution, the solvation energy was estimated to be 70·33 kJ mol^{-1} by molecular mechanical calculations. Thus the activation energy (76·03 kJ mol^{-1}) of alkaline hydrolysis of methyl nitrate was found to be in good agreement with the available experimental value (82·42 kJ mol^{-1}). The results indicated that the substantial activation barrier in alkaline hydrolysis was essentially solvent-induced.

INTRODUCTION

Under the conditions for the alkaline hydrolysis of organic nitrates, RCH_2ONO_2, three simultaneous reactions may occur: (i) nucleophilic substitution (S_N2), (ii) α-hydrogen elimination (E) and (iii) β-hydrogen elimination (E_2). Experiments[1-3] clearly confirm that the alkaline hydrolysis of methyl nitrate is essentially a bimolecular substitution (S_N2) reaction (Scheme 1). Kinetic analyses indicate that the value of the second-order rate constant mainly depends on environmental factors, such as the solvent effect.

In the simulation calculation of the reaction in aqueous solution, three terms of interaction energies should be taken into account: (i) solute–solute ($E_{solu-solu}$), (ii) solute–solvent ($E_{solu-solv}$) and (iii) solvent–solvent ($E_{solv-solv}$)) interactions.



Scheme 1

Theoretical calculations have been widely applied to interpret the results and to resolve chemical ambiguities. Unfortunately, there is currently no single method that is adequate to solve all the problems in terms of both the calculated accuracy and the required computer time. Especially for the solvation effect, there are many solvent molecules involved in the calculations. Therefore, it is very important to find a method capable of reasonably evaluating solvation energies and calculating hydrated complex parameters without enormous amounts of computer time.

In recent years, a method combining quantum mechanics (QM) and molecular mechanics (MM) has been developed and applied very successfully.[4-7] Weiner *et al.*[8] used this method to study the gas- and solution-phase energy profiles of the hydroxide–formamide nucleophilic reaction, which proceeded with no potential barrier to the tetrahedral adduct when *ab initio* quantum chemical calculations were applied. Using a molecular mechanical method to analyse water–solute interactions, Weiner *et al.*[8] found a barrier of 92·05 kJ mol^{-1} to forming the tetrahedral adduct in solution. The gas- and solution-phase energetics for the reaction of hydroxide with formaldehyde

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were investigated by Madura and Jorgensen[6] using *ab initio* and Monte Carlo methods. Their results are qualitatively similar to those found by Weiner *et al.* for the hydroxide–formamide system.

Anbar *et al.*[1] and Baker and Easty[2,3] made extensive experimental studies of the alkaline hydrolysis of alkyl nitrates and discussed the mechanism of this reaction. Gaffney *et al.*[9] measured the rate of the gas-phase reaction of the hydroxyl radical with methyl nitrate using flow discharge resonance fluorescence techniques. Reactivities for OH^- to abstract specific hydrogen atoms in normal alkyl nitrates were presented and discussed.[10,11] However, theoretical calculations for hydrolysis reactions have not been reported. In this study, we calculated the activation energy of the alkaline hydrolysis of methyl nitrate in the gas and solution phases by combining QM and MM methods. The solvent effects were also explored and discussed.

CALCULATION PRINCIPLE AND METHODS

The calculations of the gas-phase reaction (Scheme 1) were performed by using the Gaussian-82 program (STO-3G)[12] with eight single-point structures along the reaction coordinate which are presented in Figure 1(a), and by MINDO/3[13] with sixteen single-point structures, only thirteen of which are plotted in Figure 1(b). All of the geometries were optimized with an energy gradient method. The distance (R_{O-C}) from the hydroxide oxygen to the carbon of methyl nitrate was taken as the reaction coordinate. A nucleophilic substitution reaction (S_N2) was accomplished through decreasing R_{O-C} gradually along the reaction pathway.

The calculations for hydrolysis in aqueous solution were done with the MM2 program (85 version) using the same procedure as that for the gas-phase reaction. In principle, the solvent effect in aqueous solution should include the multilayers of water around the substrates. However, results presented by Chandrasekhar *et al.*[14] showed that the solvent effect in ionic solution is dominated by the first coordination shell. We focused on those water molecules in the first solvation shell. The gas-phase structures were placed in the solvation 'bath.' These modelled solute–solvent single-point structures, a type of supermolecular complex containing eleven water molecules (Scheme 2), were optimized by the MM method. The solvation energy (E_{solva}) of the system was then determined from these calculation results.

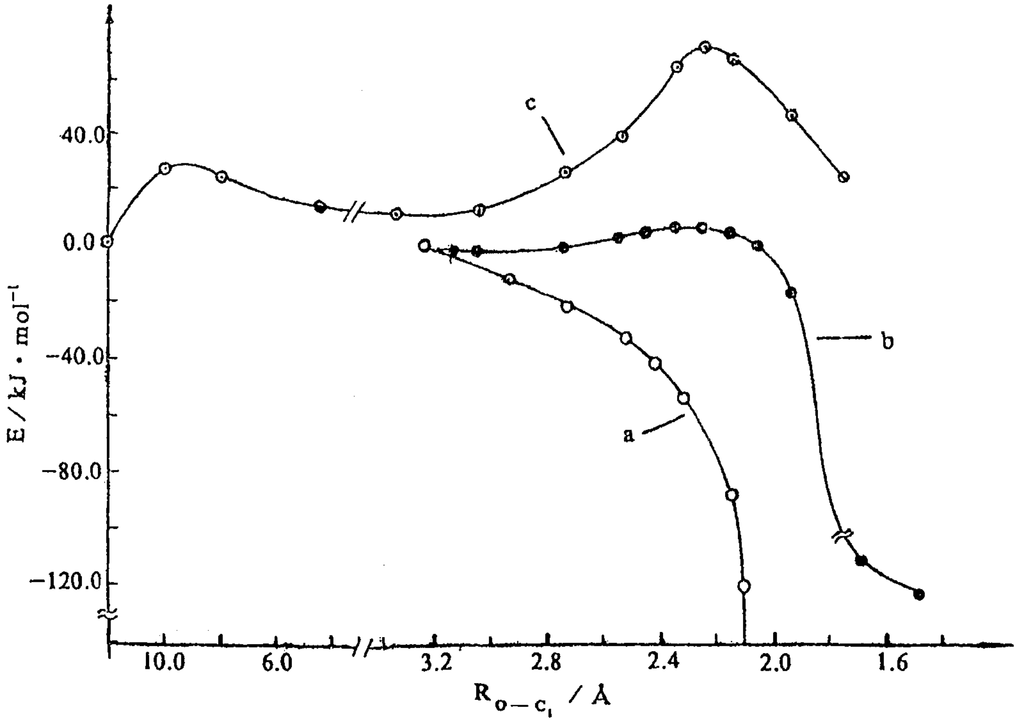
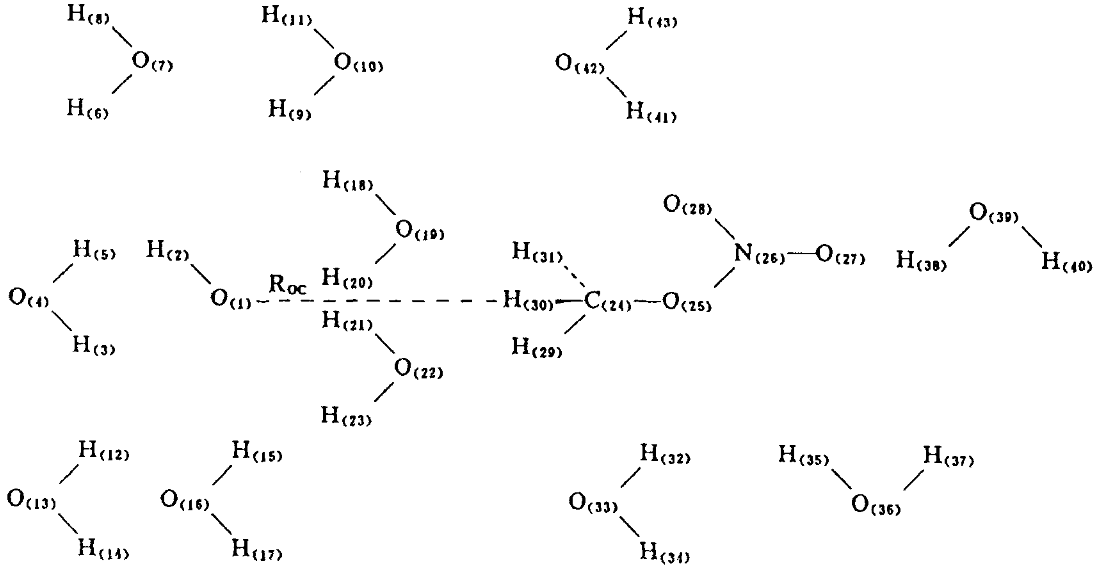


Figure 1. Potential curves for alkaline hydrolysis of methyl nitrate. (a) *Ab initio* total energy; (b) MINDO/3 heat of formation; (c) MM2 solvation energy



Scheme 2

In all of the calculations we ensured that the activation energy (E_{act}) can be represented as a sum of two terms:

$$E_{\mathrm{act}} = E_{\mathrm{solu-solu}} + E_{\mathrm{solva}} \tag{1}$$

$$E_{\mathrm{solu-solu}} = E^{\mathrm{TS}}_{\mathrm{solu}} - E^{\mathrm{BS}}_{\mathrm{solu}} \tag{2}$$

where $E^{\mathrm{TS}}_{\mathrm{solu}}$ and $E^{\mathrm{BS}}_{\mathrm{solu}}$ represent the intrinsic energy of the transition state and adduct (OH^- and $MeONO_2$), respectively and are taken directly from the gas-phase quantum mechanical calculations. E_{solva} is the solvation energy:

$$E_{\mathrm{solva}} = E_{\mathrm{solu-solv}} - E_{\mathrm{solv-solv}} \tag{3}$$

where $E_{\mathrm{solu-solv}}$ is the solute–solvent (water) interaction energy and $E_{\mathrm{solv-solv}}$ represents the interaction energy between water molecules in the first shell. $E_{\mathrm{solu-solv}}$ and $E_{\mathrm{solv-solv}}$ come from the molecular mechanics calculations.

In our calculations, the MM calculation parameters were taken from Ref. 15. As the C—O bond lengths (L_{CO}) were changed along the reaction pathway, the force constants (K_{OC}) were adjusted according to Badger's rule:[16]

$$K_{\mathrm{OC}} = 1\cdot 86/(L_{\mathrm{CO}} - 0\cdot 68) \tag{4}$$

Because the hydroxide ion bears a unit negative charge, the dipole interaction was replaced by a charge interaction. The charge distribution was calculated by the MINDO/3 method.

All of the calculations were performed on the VAX-II/780 computer in the Laboratory of Computer Chemistry, Chinese Academy of Science, Shanghai Institute of Organic Chemistry.

RESULTS AND DISCUSSION

Reaction in gas phase

The adduct of methyl nitrate with OH^- was optimized by Gaussian-82 program at the STO-3G level. No equilibrium and transition state of the adduct were found. The potential curve along the reaction path is like a 'downhill' process with no barrier [Figure 1(a)] as the distance $R_{\mathrm{O—C}}$ is reduced from infinity to 1·9 Å. The result is similar to that of Weiner *et al.*'s calculations for the hydroxide–formamide nucleophilic addition.[8] When the MINDO/3 method was used, an equilibrium geometry of the adduct at $R_{\mathrm{O—C}} = 3\cdot 1$ Å was obtained. The energy profile subsequently slightly increases after $R_{\mathrm{O—C}} = 3\cdot 1$ Å and reaches a maximum at $R_{\mathrm{O—C}} = 2\cdot 3$ Å. This single-point structure becomes a transition state [TS, Figure 2(a)]. A gradual decrease in energy occurs from $R_{\mathrm{O—C}} = 2\cdot 2$ to 1·5 Å. The potential curve is shown in Figure 1(b).

From $R_{\mathrm{O—C}} = 3\cdot 1$ to 1·50 Å, the principal changes involve Warlton turnover of the methyl group and lengthening of the C—O bond. The C—O bond is 3·86 Å given by auto-optimization when $R_{\mathrm{O—C}}$ is reduced to 1·70 Å. The O—H bond length hardly changes from 0·97 Å throughout the reaction. The charges calculated from Mulliken population analysis are transferred during the reaction. Both the hydroxyl oxygen and the nitroxy group (NO_3) show a smooth change of their charge along the reaction path. The hydroxyl oxygen starts with a charge of −1·809e and ends with −0.263e, whereas NO_3 goes from 0·247e to

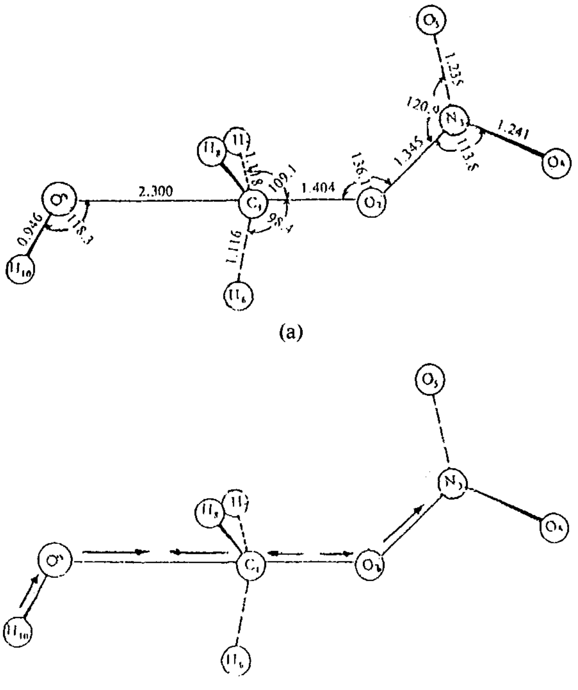


Figure 2. Transition state for gas reaction. (a) Geometry; (b) vibration model

− 1·00e. The hydroxyl hydrogen starts with 0·089e and ends with 0·29e.

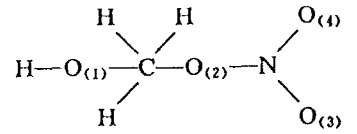
Vibration analysis [Figure 2(b)] shows that the transition state is verified as having only one imaginary frequency, at 209·9 cm^{-1}. Frequency calculations provide further characterization of the transition state. The apparent minimum turns out to be a saddle point along the reaction path. However, the calculated activation energy is only 5·70 kJ mol^{-1} according to equation (2), which is inconsistent with experimental value of 82·42 kJ mol^{-1}.[2] This shows that the simulation calculation does not reflect the reality of the reaction owing to neglect of solvent perturbation. For this reason, it is necessary to consider the solvent effect so that the hydrolysis in basic media can be reasonably described.

Reaction in aqueous solution

In order to determine the number of water molecules around the reaction substrates (OH^- and $MeONO_2$), we put as many as possible water molecules around the substrates and it was found that there may be fourteen water molecules present in the first shell of the substrates.

This hydration complex model was optimized by MM calculations in which the hydrogen bonds between water molecules and the substrate were taken into account. After the molecular mechanics minimization, the complex was found to have a stronger hydrogen-bonding network. The calculated non-bonding distances between the solute and water molecules are given in Table 1.

Table 1. Non-bonding distances (Å) for solute–solvent in $HO—CH_3ONO_2(H_2O)_{14}$[a]



$O_{(1)}$—H_{w1}	1·828	$O_{(2)}$—H_{w8}	1·984
$O_{(1)}$—H_{w2}	1·772	$O_{(2)}$—H_{w9}	3·773
$O_{(1)}$—H_{w3}	1·905	$O_{(3)}$—H_{w10}	2·058
$O_{(1)}$—H_{w4}	1·686	$O_{(4)}$—H_{w11}	2·072
$O_{(1)}$—H_{w5}	3·280	O_{w12} − H_{M1}	2·956
$O_{(1)}$—H_{w6}	4·200	O_{w13} − H_{M2}	2·851
$O_{(1)}$—H_{w7}	1·742	O_{w14} − H_{M3}	3·621

[a] H_{Wn} is the hydrogen of water molecle n, O_{Wn} is the oxygen of water molecule n and H_{Mn} is the hydrogen of the methyl group.

As can be seen from Table 1, there are eight water molecules which form stronger hydrogen bonds with the solute at a distance ranging from 1·69 to 2·07 Å. Three water molecules are separated from the solute by 3·62–4·20 Å. This shows that in the first hydration shell of the substrates only eleven water molecules may be accommodated. As an approximation, we neglect interactions of the furthest three water molecules and consider only those interactions of the water molecules closer to solutes. Hence, the above reaction model (Scheme 2) involves eleven water molecules. Gas-phase structures were placed in the solvent 'bath' and optimized by a molecular mechanical method. We found that the distances between the water hydrogens and the substrate oxygens increase as hydroxide approaches. In the structure with $R_{O—C}$ = 10·5 Å, E_{solva} is increased and there are seven water molecules forming hydrogen bonds with distances ranging from 1·73 to 2·07 Å. The two water molecules are separated by 8·57 and 5·80 Å from the solutes. At $R_{O—C}$ = 8·5 Å, E_{solva} is decreased and the distances between the two water molecules and the solute are 55·8 and 64·9 Å, respectively (see Tables 2 and 3). It is suggested that the two water molecules are squeezed from the first solvent shell. We neglected these two water molecules and the nine-water complex was used for the subsequent calculations along the reaction coordinate. E_{solva} decreases and reaches a minimum at 3·5–3·0 Å. E_{solva} increases gradually after reaching 3·0 Å and is maximum at 2·2 Å. This single-point structure corresponds to the transition state (Figure 3) of the hydrated complex. A gradual decrease in energy occurs after

Table 2. Non-bonding distances at various R_{O-C}

	R_{O-C} (Å)					
A—B (Å)[a]	10·5	8·5	4·5	3·0	2·2	1·7
$O_{(1)}$—$H_{(3)}$	4·05	1·84	1·97	1·97	2·14	1·99
$O_{(1)}$—$H_{(6)}$	1·78	1·89	1·98	1·74	2·10	2·25
$O_{(1)}$—$H_{(9)}$	1·81	1·72	1·73	1·72	2·11	2·39
$O_{(1)}$—$H_{(12)}$	1·73	1·77	1·87	1·84	2·13	3·50
$O_{(1)}$—$H_{(15)}$	2·07	3·65	—	—	—	—
$O_{(1)}$—$H_{(18)}$	8·57	64·9	—	—	—	—
$O_{(1)}$—$H_{(21)}$	1·79	1·87	1·71	1·80	1·99	1·91
$O_{(25)}$—$H_{(32)}$	3·87	4·00	3·10	3·40	2·40	1·87
$O_{(25)}$—$H_{(35)}$	5·80	55·8	4·37	2·47	1·99	1·73
$O_{(27)}$—$H_{(38)}$	2·06	2·09	2·10	2·08	2·03	2·00
$O_{(28)}$—$H_{(41)}$	2·05	2·08	2·09	2·08	2·03	2·01

[a] See Scheme 1 for labelling of atoms.

Table 3. Reaction pathway energies (kJ mol^{-1}) calculated using MM2 in aqueous solution[a]

R_{O-C} (Å)	$E_{\text{solu-solv}}$	$E_{\text{solv-solv}}$	E_{solva}	H_2O[b]	E'_{solva}
∞	−318·86	53·98	−372·84	11	0·00
10·5	−286·86	58·79	−345·65	11	27·18
8·5	−293·16	55·77	−348·93	11	23·90
4·5	−312·67	39·16	−351·83	9	18·81
3·5	−314·97	44·14	−359·11	9	11·53
3·0	−324·97	34·52	−359·49	9	11·15
2·7	−312·87	32·47	−335·34	9	25·30
2·5	−305·17	32·40	−337·57	9	33·07
2·3	−283·97	25·02	−308·99	9	61·65
2·2	−273·57	26·74	−300·31	9	70·33
2·1	−278·07	27·15	−305·22	9	65·42
1·9	−299·77	25·19	−324·96	9	45·68

[a] $E_{\text{solu-solv}}$ is the solute–solvent interaction energy, $E_{\text{solv-solv}}$ is the solvent–solvent interaction energy, $E_{\text{solva}} = E_{\text{solu-solv}} - E_{\text{solv-solv}}$ and E'_{solva} is the same as E_{solva} but relative to the reactant ($OH^- + CH_3ONO_2$) and eleven water molecules.

[b] The number of water molecules considered.

$R_{O-C} = 2{\cdot}1$ Å. During the course of the reaction, as NO_3 takes on more negative ion character, the strength of hydrogen bonding between nitroxyl oxygens and water molecules increases, whereas the number and strength of hydrogen bonds around the hydroxyl oxygen decrease.

Table 3 summarizes the energies calculated by the molecular mechanical method. It is clear that the solvent dramatically changes the gas-phase potential curve. The perturbations of the solvent in the first shell are found to be greatest for the reaction. The energy profile [Figure 1(c)] was drawn from these molecular mechanical calculations.

The transition state is located at $R_{O-C} = 2{\cdot}2$ Å. The location of the transition state shows a shift from the gas phase ($R_{O-C} = 2{\cdot}3$. Å) to the aqueous solution which is similar to Weiner *et al.*'s results for the base-catalysed hydrolysis of formamide.[8] Based on the energy profile of the hydrolysis reaction of the hydrated complex, the contribution of the solvation energy to the activation energy of hydrolysis is estimated from equation (3) to be 70·33 kJ mol^{-1}. Therefore, an activation energy [the sum of solvation energy (70·33 kJ mol^{-1}) and gas-phase activation energy (5·7 kJ mol^{-1})] of 76·03 kJ mol^{-1} is obtained, which is in good agreement with the available experimental

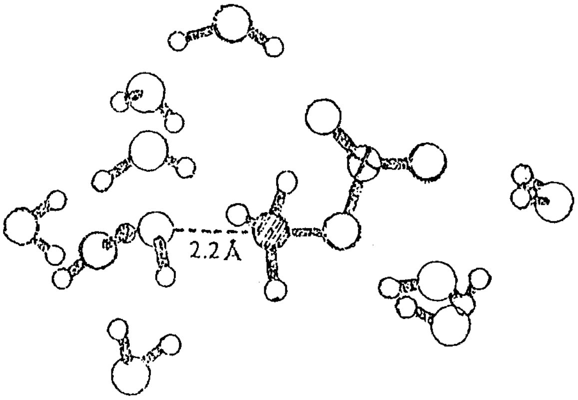


Figure 3. Transition-state geometry of $[OH + (CH_3ONO_2) + (H_2O)_9]^-$ for solution reaction. ○ —H atom; ◯—O atom; ▨—C atom; ⊗—N atom

value ($82{\cdot}42\ kJ\,mol^{-1}$). This indicates that the activation energy on alkaline hydrolysis of methyl nitrate is essentially solvent-induced.

CONCLUSIONS

Applying *ab initio* calculations, we have found that the S_N2 reaction of methyl nitrate proceeds with no barrier in the gas phase, whereas a small activation energy of $5{\cdot}70\ kJ\,mol^{-1}$ was given by the MINDO/3 method. The large difference between the calculated and observed activation energies can be accounted for by considering the contribution of the solvent effect. The solvation energy in aqueous solution calculated by the MM method is $70{\cdot}33\ kJ\,mol^{-1}$. The calculated activation energy ($76{\cdot}03\ kJ\,mol^{-1}$) obtained with a method combining quantum mechanics and molecular mechanics, is in agreement with the available experimental value ($82{\cdot}42\ kJ\,mol^{-1}$). The results indicate that the substantial activation barrier to hydrolysis of methyl nitrate in alkaline media is essentially solvent-induced.

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