Theoretical Study of a Reaction Path *via* a Hydrogen-bonded Intermediate for the Alkaline Hydrolysis of Esters in the Gas Phase

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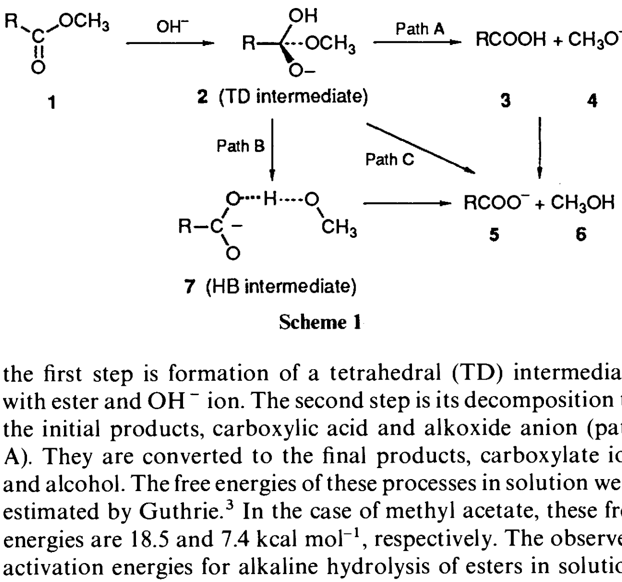
Two steps are considered for the alkaline hydrolysis of methyl acetate in the gas phase. The first step is the formation of a tetrahedral intermediate and the second is its decomposition. In the present paper, the mechanism for the second step is discussed by using *ab initio* molecular orbital calculations. The path releasing acetic acid and methoxide anion is an energetically unfavourable path, as easily expected by their pK_a values. The final products, acetate ion and methanol, are more stable than the tetrahedral intermediate. We found a hydrogen-bonded acetate–methanol molecule as the intermediate that was more stable than both the tetrahedral intermediates and the final products. We searched and found the transition state which connected the tetrahedral intermediate with the hydrogen-bonded intermediate. The activation energy of the path through the transition state was calculated to be 8.7 kcal mol^{-1} (MP2/6–31 + G**//RHF/6–31G: 5.8). This mechanism explains well the alkaline hydrolysis of esters in the gas phase.

Alkaline hydrolysis of esters is one of the most fundamental reactions in organic chemistry. The reaction mechanism in solution has been well studied[1] and is considered to be very simple as described in many text books.[2] As shown in Scheme 1, the first step is formation of a tetrahedral (TD) intermediate with ester and OH$^-$ ion. The second step is its decomposition to the initial products, carboxylic acid and alkoxide anion (path A). They are converted to the final products, carboxylate ion and alcohol. The free energies of these processes in solution were estimated by Guthrie.[3] In the case of methyl acetate, these free energies are 18.5 and 7.4 kcal mol^{-1}, respectively. The observed activation energies for alkaline hydrolysis of esters in solution are in the range of 12–15 kcal mol^{-1}.(4)



Scheme 1

Alkaline hydrolyses of esters were also observed in the gas phase. As it was very difficult to detect the TD intermediate in the gas phase reaction, Takasima *et al.* suggested that it was more likely a local transition state than a stable intermediate.[5] Later, they proposed the path B which includes hydrogen-bonded carboxylate–methanol species as another intermediate from their gas-phase experiment with CF_3COOCH_3 and OH$^-$.[6] They postulated an extremely high barrier on the basis of the crude molecular orbital (MO) calculations by Alagona *et al.*[7] Johlman *et al.* have performed a detailed analysis of the gas-phase reaction of methyl formate.[8] Quantum mechanical calculations indicated the existence of the stable TD intermediate. In the case of methyl formate (R = H), 6–31 + G* level MO calculations[9] estimated the reactants, methyl formate and hydroxide ion, to be less stable than the TD intermediate by 35.15 kcal mol^{-1}. Therefore, the first step in the gas phase spontaneously proceeds to form the TD intermediate.

Dewar and Stroch discussed the difference between the activation energies in gas phase and in solution.[10] They concluded that the barriers observed for alkaline hydrolysis in solution are due entirely to the energy needed to desolvate hydroxide ion so that the other reactant can approach. Madura and Jorgensen[9] estimated the activation energy for nucleophilic addition of OH$^-$ to formaldehyde by use of *ab initio* MO and Monte Carlo calculations. The estimated value of 28 kcal mol^{-1} was much larger than that observed in solution. Kollman and co-workers also pointed out that the solvent effect is also critical for the first step in the case of formamide by *ab initio* MO and molecular dynamic calculations.[11] The experimental and theoretical studies indicated the rate-determining step in solution to be the first step.

In the decomposition of the TD intermediate, the second step, formation of alkoxide anion, is not favoured according to the pK_a values of carboxylic acid and alcohol. 4–31 + G level MO calculations[12] estimated that the initial products, formic acid and methoxide anion, are also less stable than the TD intermediate by 30.5 kcal mol^{-1}. Path A requires a higher barrier than this energy difference in gas phase. On the other hand, the final products, HCOO$^-$ and CH_3OH, are more stable by 43.2 kcal mol^{-1} than the TD intermediate. It is, therefore, possible to draw another path that directly forms carboxylate ion and alcohol as the final products (path C). Ewig and co-workers[12] suggested the path C for the gas phase reaction, *i.e.*, the reactants are quite hot so that, if the TD intermediate is formed, it will probably fall apart quickly into the observed, thermodynamically more stable reaction products.

We can also expect such a path that methoxide anion extracts a hydrogen from the carboxylic acid to form a hydrogen bonded (HB) intermediate (B path). As the hydrogen bond is not so strong, the HB intermediate easily decomposes to RCOO$^-$ and CH_3OH in the gas phase. This mechanism explains well gas phase experiments.[5,6,8] We can draw a schematic reaction profile in gas phase as displayed in Fig. 1.

If path B is a better route for the second step than path A in the gas phase, it should satisfy two conditions.

(1) There should exist an HB intermediate which is more stable than the TD intermediate and reactants.

(2) There should be a reaction path from the TD to the HB intermediate and this path should have an activation energy smaller than that for the path A.

It is impossible to examine these conditions by use of

Table 1 Total energies and optimized bond lengths, bond and dihedral angles[a] for the tetrahedral (**2**), and hydrogen-bonded (**7**) intermediates and the transition state (TS) for path B

	2	TS	**7**	**5** and **6**
E(6–31 + G)[b]	−0.117 98	−0.104 17 (8.7)	−0.168 13 (−31.5)	−0.139 40 (−13.4)[c]
E(MP2/6–31 + G**)[b]	−0.281 82	−0.272 58 (5.8)	−0.326 05 (−27.8)	−0.298 66 (−10.6)[c]
O(1)–C(2)	1.325	1.237	1.254	1.265[d]
C(2)–C(3)	1.522	1.504	1.527	1.533[d]
C(2)–O(4)	1.493	1.995	3.892	—
O(4)–C(5)	1.418	1.400	1.420	1.435[e]
C(2)–O(6)	1.451	1.402	1.274	1.264[d]
O(4)–H(7)	2.721	1.928	0.972	0.950[e]
O(6)–H(7)	0.952	0.959	1.717	—
∠C(3)–C(2)–O(1)	116.3	121.4	117.7	116.0[d]
∠O(4)–C(2)–C(3)	105.9	95.6	102.2	—
∠C(5)–O(4)–C(2)	117.3	116.8	108.3	—
∠O(6)–C(2)–C(3)	105.5	112.6	115.6	116.4[d]
∠H(7)–O(6)–C(2)	107.0	106.0	155.0	—
τ[O(4)–C(2)–C(3)–O(1)]	−126.0	−117.4	−179.8	—
τ[C(5)–O(4)–C(2)–C(1)]	−24.1	−14.3	0.3	—
τ[O(6)–C(2)–C(3)–O(1)]	125.4	152.4	180.0	178.5[d]
τ[H(7)–O(6)–C(2)–C(3)]	205.3	99.6	0.6	—

[a] Total energy in Hartree, bond lengths (X–Y) in Å, and bond angles (∠XYZ) and dihedral angle (τWXYZ) in °. W, X, Y and Z refer to atoms as in Fig. 1. [b] Total energies +342.0 or +343.0 Hartree for RHF/6–31 + G and MP2/6–31 + G**//RHF/6–31 + G calculations, respectively. [c] Sum of the total energies of **5** and **6**. [d] Optimized parameters for acetate ion. [e] Optimized parameters for methanol.

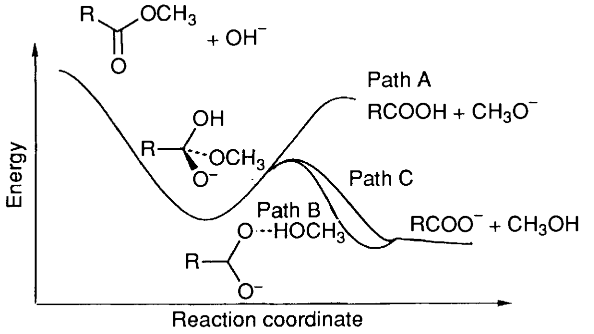


Fig. 1 Schematic representation of energy profiles of the reaction mechanisms for the alkaline hydrolysis of esters in the gas phase

experimental techniques. In this study, the reaction mechanisms for alkaline hydrolysis of esters, especially the path B of the second step, were examined by *ab initio* MO calculations.

Method of Calculation.—The *ab initio* MO calculations were performed using the GAUSSIAN86 program[13] at the Institute for Molecular Science and the GAUSSIAN90 program for the Fujitsu S4/2 (SUN SPARCstation 2) computer.[14] Methyl acetate (**1**; R = CH_3) was adopted as a model molecule. We used the 6–31 + G basis sets[15] to describe accurately the anions for all calculations. For a better energy description of the reaction, we performed MP2/6–31 + G**//RHF/6–31 + G calculations.[16,†] Molecular geometries including a transition state (TS) were optimized by use of the energy gradient method and checked with vibration frequency calculations. It was ascertained that the acetate ion with C_s symmetry is a transition state. However, the fully optimized structure without symmetry is more stable only by 0.004 kcal mol^{-1}. To obtain a proposed reaction profile, the intrinsic reaction coordinate (IRC)[17] was also calculated.

Results and Discussions

Geometries of the TD, HB Intermediates and the Transition State.—It has been considered that the TD intermediate **2** (R = CH_3) is produced at the first step of alkaline hydrolysis of esters in the gas phase. The optimized parameters of **2** are summarized in Table 1. C(2) has a tetrahedral environment since τ[O(6)–C(2)–C(3)–O(1)] is 125.4°, as is also understood from Fig. 2(*a*). The vibration frequency calculation for the optimized structure of **2** gave all positive force constants, *i.e.*, the molecule with the TD environment is not a TS but a stable intermediate. H(7) occupies the position which can interact with neither O(1) nor O(4). The O(1)–C(2) length (1.325 Å) is shorter than C(2)–O(6) (1.451 Å) and C(2)–O(4) (1.493 Å) because of its double bond nature. The total energy of **2** was calculated to be − 342.117 98 (−343.281 82) Hartree, respectively. The value in parentheses is the energy from the MP2/6–31 + G**//RHF/6–31 + G calculation. Fig. 3 displays the energy relation among reactants and the products.

If the second step of the hydrolysis includes decomposition of **2** to form the initial products, acetic acid (**3**) and methoxide anion (**4**, path A), this process is expected to require a high barrier as represented in Fig. 1. The present calculations indicated a trend that was similar to the previous calculations.[10,12] The total energies of **3** and **4** were calculated to be −227.708 73 (−228.467 75) and −114.366 03 (−114.769 00) Hartree, respectively. The total energies of acetate anion (**5**) and methanol (**6**) as the final products were calculated to be −227.145 44 (−227.906 44) and −114.993 96 (−115.392 22) Hartree, respectively. They are more stable than **2** by 13.4 (10.6) kcal mol^{-1}. On the other hand, the reactants, **3** and **4**, are less stable than **2** by 27.1 (28.3) kcal mol^{-1}. This trend is easily explained by the energy difference between the neutral and anionic species. That for the CH_3OH–CH_3O^- pair was calculated to be 394.0 (391.1) kcal mol^{-1} and that for the CH_3COOH–CH_3COO^- pair to be 353.5 (352.2) kcal mol^{-1}. This means that acetic acid is more easily ionized than methanol, which is consistent with the expectation from their pK_a values. If the methoxy fragment can withdraw a proton from the carboxylic fragment during the decomposition through the path B, the activation energy should be smaller

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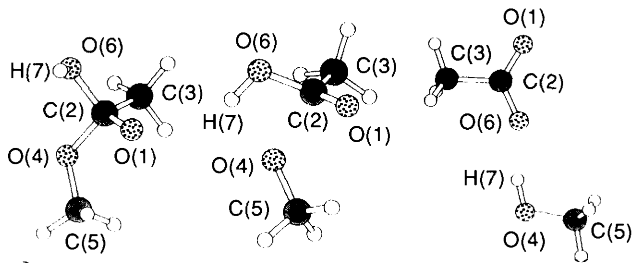
† The MP2/6–31 + G**//RHF/6–31 + G energy means the MP2 energy which uses the 6–31 + G** basis set and the RHF/6–31 + G optimized geometry.



(*a*) TD intermediate 0.0(0.0) (*b*) Transition state 8.7(5.8) (*c*) HB intermediate 31.5(27.8)

Fig. 2 Optimized structures for (*a*) the TD intermediate, (*b*) the transition state and (*c*) the HB intermediate

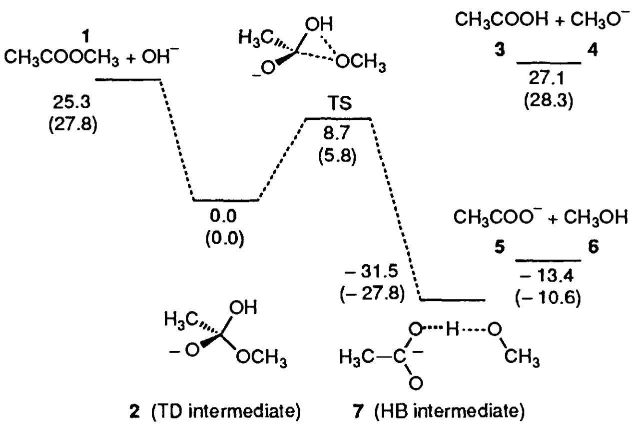


Fig. 3 Energy-level diagram of alkaline hydrolysis of methyl acetate in the gas phase

than that expected from the energy difference for the path A.

The key to path B is the existence of an intermediate (**7**) which should, at least, have stability comparable with the TD intermediate. The total energy of **7** was calculated to be −342.168 13 (−343.326 05) Hartree and is more stable than **2** by 31.5 (27.8) kcal mol^{-1}. **7** is also more stable than the final products, **5** and **6**, by 18.0 (17.2) kcal mol^{-1}. This energy corresponds to the hydrogen bond energy between methanol and acetate ion. The HB intermediate satisfies the condition (1) (see earlier). It is noteworthy that in this geometry H(7) is no longer connected to O(6) owing to the long O(6)–H(7) length (1.717 Å). These atoms make a bond in the TD intermediate. On the other hand, the O(4)–H(7) length is calculated to be 0.972 Å, and H(7) produces a new bond with O(4) as shown in Fig. 2(*c*). All the heavy atoms and H(7) stay on almost the same plane. The O(6)–O(4) length and ∠ O(6)–H(7)–O(4) are calculated to be 2.668 Å and −165.3°, respectively. These values are typical in hydrogen-bonded systems. The C(2)–O(1) and C(2)–O(6) lengths are 1.254 and 1.274 Å, respectively. τ[O(6)–C(2)–C(3)–O(1)] was calculated to be 180.0°, which indicates C(2) to be sp^2 hybridized. The upper fragment of Fig. 2(*c*) is almost an acetate ion. According to all the optimized parameters for **7**, the lower fragment has geometrical parameters similar to those of methanol. Therefore, **7** is constructed with an acetate ion and methanol with a hydrogen bond between O(6) and H(7)–O(4).

If there is a reaction path leading the TD intermediate to HB and it has a barrier smaller than that of path A, path B should be preferable to path A as the mechanism of the second step. A TS with the imaginary frequency of 258.3*i* cm^{-1} was obtained. Fig. 1(*b*) displays the structure of the TS and its optimized parameters are also summarized in Table 1. The total energy of the TS was calculated to be −342.104 17 (−343.272 58) Hartree. The energy difference between **2** and the TS (the activation energy) is only 8.7 (5.8) kcal mol^{-1}. The energy is smaller than the energy difference of 27.8 (28.3) kcal mol^{-1} between the TD intermediate and the initial products, **3** and **4**. The TS satisfies the condition (2). τ[O(6)–C(2)–C(3)–O(1)] of the TS is calculated to be 152.4°. Therefore, C(2) does not completely lose sp^3 nature. In this structure, the acetate fragment still keeps H(7) because the O(6)–H(7) length is 0.959 Å. This structure resembles the TD rather than the HB intermediate.

Intrinsic Reaction Coordinate.—The IRC calculation was performed in order to obtain the reaction path which passes through the obtained TS. Fig. 4 displays structures of the points with s = −2.77, −1.38, 0.00 (TS), 1.38, 2.77, 3.98, 4.75 and 5.51 amu$^{\frac{1}{2}}$Bohr along the IRC. The geometry of s = −2.77 amu$^{\frac{1}{2}}$Bohr resembles the TD intermediate (**2**). The structure at s = 5.51 has a hydrogen bond of the type O(6)···H(7)–O(4), although all the heavy atoms are not in the same plane like the HB intermediate. We can expect that this structure will converge to that of the HB intermediate **7**. Therefore, the TS connects **2** with **7**. The reaction from **2** to **7** *via* the obtained TS satisfies all the conditions as mentioned above. However, the reactants in the gas phase reaction are so hot that the HB intermediate may not be formed. In this case, the reaction through the obtained TS leads directly to the final products, **5** and **6**, such as *via* path C.

Fig. 5 displays the energy profile of the reaction along the IRC together with the parameters which greatly change their values. The potential curve is divided into three parts. While the energy rises during the first part from s = −3.5 to 0.0, the next part from 0.0 to 4.0 amu$^{\frac{1}{2}}$Bohr decreases the energy by *ca.* 7 kcal mol^{-1}. The third part beginning from s = 4.0 amu$^{\frac{1}{2}}$Bohr quickly decreases the energy of the system. This energy profile is closely related to the geometrical parameters as shown in Fig. 4(*b*) and 4(*c*).

During the first part, τ[H(7)–O(6)–C(2)–O(3)] is decreased by *ca.* 30°. This involves shortening the O(4)–H(7) length by 0.218 Å. The cleavage of the C(2)–O(4) bond accompanies the increase of τ[O(6)–C(2)–C(3)–O(1)], which modifies C(2) from sp^3 to sp^2 hybridization. However, these changes in the geometrical parameters do not largely alter the energy of the system. While the O(4)–H(7) length continuously decreases from s = −3.0 to 4.0 amu$^{\frac{1}{2}}$Bohr, O(6) keeps binding with H(7) because the O(6)–H(7) length does not change at all. The largest energy decrease occurs in the third part. The characteristic of the geometry change of the third part is that H(7) suddenly begins to leave O(7) for O(4) around s = 4.0. The O(6)–H(7) and O(4)–H(7) lengths are calculated to be 1.213 and 1.247 Å in the structure of s = 4.75 amu$^{\frac{1}{2}}$Bohr. The HB intermediate is more stable by 30.1 kcal mol^{-1} than the structure. Therefore, the migration of H(7) is not complete at the point on the IRC. The O(4)–H(7) and C(2)–O(4) lengths differ by 1.742 and 2.839 Å between the TD and the HB intermediates. As H(7) is the important atom for the hydrogen bond between the acetate and the methanol fragments, the O(6)–H(7) length is lengthened only by 0.760 Å after the reaction has completed.

Concluding Remarks.—Three paths were considered for alkaline hydrolysis of methyl acetate in the gas phase. The HB intermediate is more stable than the reactants, the final products and the TD intermediate. The activation energy for the path B is 8.7 (5.8) kcal mol^{-1}. The hydrogen bond energy between the methanol and acetate ion was estimated to be 18.0 (17.2) kcal mol^{-1}. The energy was not so large as compared with those of reactants in the gas phase reaction. This mechanism accurately describes the alkaline hydrolysis of esters.[5,6,8] On the other hand, the alkaline hydrolysis in the gas phase may follow path C because the reactants are very hot. The mechanism through

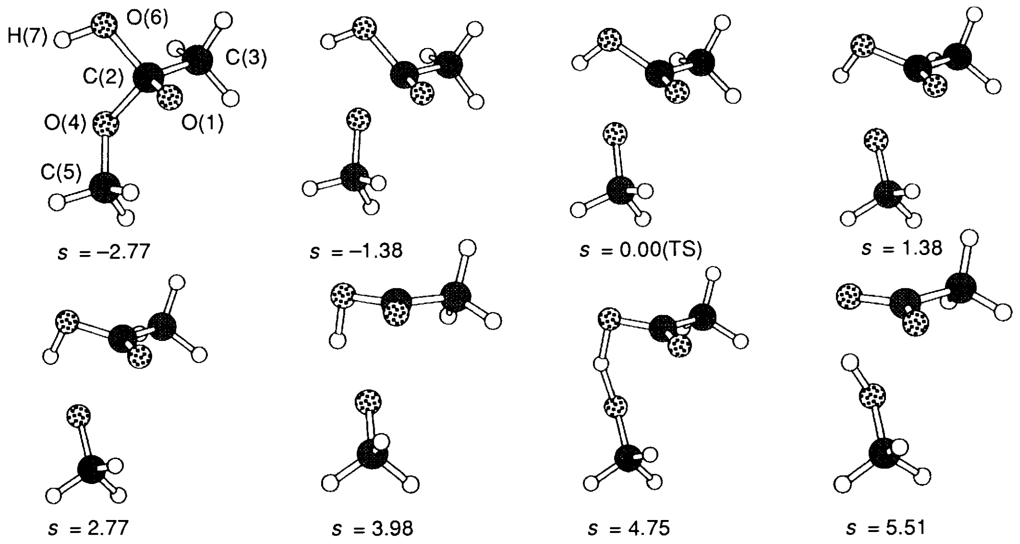


Fig. 4 Change of the geometry along the IRC calculated for path B

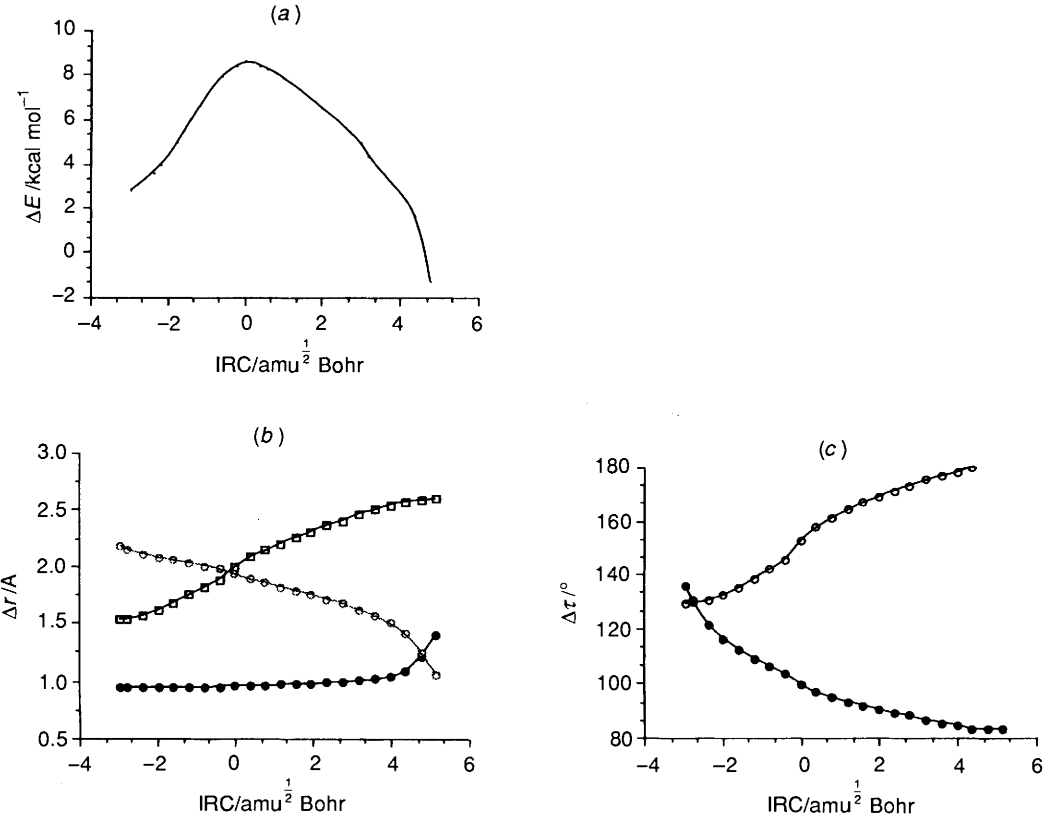


Fig. 5 Potential energy profile (*a*), the change of bond lengths C(2)–O(4), (□), O(6)–H(7) (●) and O(4)–H(7) (○), (*b*) and dihedral angles O(6)–C(2)–C(3)–C(1) (○) and H(7)–O(6)–C(2)–C(3) (●), (*c*) along the IRC for path B

path B may also be applicable to alkaline hydrolysis in solution.

Path A, which is widely accepted as the mechanism of the second step, is an energetically unfavourable path in the gas phase. It is because this process requires a high barrier for the decomposition of the TD intermediate to carboxylic acid and alkoxide anion. This is easily anticipated by the pK_a values of carboxylic acid and alcohol.

Acknowledgements

The author thanks the Computer Center, Institute for Molecular Science at the Okazaki National Research Institutes for the use of the HITAC M-600 and S-820/80 computers and the Library Program GAUSSIAN86. This work was supported in part by a Grant-in-Aid for Science Research from the Ministry of Education and Culture, Japan.

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Paper 2/00841F
Received 17*th February* 1992
Accepted 21*st May* 1992