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Ab Initio Molecular Orbital Studies on the Aspirin Solvolysis and Ester Hydrolysis

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In the solvolysis of aspirin and acyl-α-chymotrypsin, the significant fact is the rate acceleration by the addition of alcohol in water solution. The authors reported that the rate acceleration of the hydrolysis occurs as the content of alcohol increases, since a water of the monomer state reacts with the ester part of aspirin or acyl-α-chymotrypsin. The mechanism was clarified by using nonempirical molecular orbital method.

The proton removal energy for methanol corresponds to that for 1.4 waters. The difference of the proton removal energy between CH_3OH and H_2O is attributed to the electrostatic interaction term. On the other hand the main contributor for the difference between CH_3OH and $(H_2O)_2$ is the polarization interaction term. Moreover the difference between H_2O and $(H_2O)_2$ is due to the electrostatic interaction term.

For the interaction energies between ester and hydroxyl ion and between ester and water, the charge transfer interaction term and the electrostatic interaction term, respectively, were significant.

Keywords——molecular orbital; nonempirical molecular orbital; *ab initio*; aspirin; aspirin hydrolysis; ester; chymotrypsin; enzymatic reaction; hydrolysis; proton affinity

The reaction mechanisms of serine protease, cysteine protease and modified protease have been researched extensively.[2)] Interesting were the "charge relay system" composed of serine, histidine and aspartate in serine protease, the hydrogen bond system composed of asparagine, histidine and cysteine in papain and the hydrogen bond system composed of serine, histidine and cysteine in thiolsubtilisin. In α-chymotrypsin, aspartate lowers the barrier of the proton transfer from serine to histidine.[2a,c)] In papain the barrier of the proton transfer from cysteine to histidine was much smaller than that from serine to histidine.[2d)] In thiolsubtilisin, the charge relay is impossible since the hydrogen bond system is composed of aspartate (anion), histidine(neutral) and cysteine(anion).[2d)] Moreover the solvent effects on the solvolysis of acyl-α-chymotrypsin and aspirin were also interesting. As the content of methanol or ethanol for water increases, the solvolysis rate of acyl-α-chymotrypsin or aspirin is facilitated in the process of general base catalysis. The conclusion was attributed to the difference of the proton affinity OH^- and CH_3O^- by using semiempirical CNDO/2 method.[2b)] Several calculations of proton affinities for OH^- and CH_3O^- have been carried out by using nonempirical method.[3)] All the papers showed that the proton affinity energy of OH^- is larger than that of CH_3O^-. Accordingly it is reasonable that the rate acceleration of solvolysis of acyl-α-chymotrypsin and aspirin with the increase of alcohol content is attributed to the difference of the proton affinity

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2) *a*) H. Umeyama, A. Imamura, C. Nagata, and M. Hanano, *J. Theor. Biol.*, **41**, 485 (1973); *b*) H. Umeyama, *Chem. Pharm. Bull.* (Tokyo), **22**, 2518 (1974); *c*) H. Umeyama, A. Imamura, and C. Nagata, *Chem. Pharm. Bull.* (Tokyo), **23**, 3045 (1975); *d*) S. Nakagawa and H. Umeyama, *Chem. Pharm. Bull.* (Tokyo), **25**, 909 (1977).

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between OH^- and CH_3O^- in the process of the general base catalysis. In hydrolysis of enzymes, ester substrates as well as amide substrates are hydrolysed. In α-chymotrypsin serine anion part ($-CH_2O^-$) approaches to the ester carbon ($-\overset{\overset{O}{\|}}{C}-O-$). In acyl-α-chymotrypsin, polarized water($OH^-\cdots H^+$) attacks the ester carbon($-\overset{\overset{O}{\|}}{C}-O$) by general base mechanism. In aspirin polarized water ($OH^-\cdots H^+$) attacks the ester carbon ($-\overset{\overset{O}{\|}}{C}-O-$) by intramolecular general base mechanism. The alkyl substituent effect in the proton affinity of amines, alcohols and ethers was already reported in detail by Umeyama and Morokuma[4] by using nonempirical calculations, and was shown that the polarization energy was a major component of the effect. The decomposition of the interaction energy for molecular complexes has been studied by many researchers.[5] Umeyama and Morokuma clarified the origin of strong complexes $OC-BH_3$, H_3N-BH_3, $(CH_3)_3N-BH_3$, H_3N-BF_3 and $(FHF)^-$,[6] and the origin of weak complexes H_3N-F_2, H_3N-Cl_2, H_3N-ClF, CH_3H_2N-ClF, H_2CO-F_2, $HF-ClF$, and F_2-F_2.[7] From these facts the decomposition of the interaction energy between ester group and OH^-, H_2O or polarized water ($HO^-\cdots H^+$) is useful in order to clarify the hydrolysis of ester substrates by enzymes or the hydrolysis of molecules with ester group. The interaction energy(ΔE) between ester group and OH^- or H_2O can be decomposed into five terms,

ΔE = electrostatic interaction energy (ES)
+ exchange repulsion energy (EX)
+ polarization interaction energy (PL)
+ charge transfer interaction energy (CT)
+ mixing interaction energy (MIX)

Method

All calculations were performed within the framework of closed shell single determinant *ab initio* LCAO SCF MO theory, using the Gaussian 70 programming system.[8] As primitive functions, the following two sets are used as Gaussian-type orbitals (GTO). (a) STO-3G. Scale factors are those recommended by Hehre, *et al.*[9] This set gives total energy higher than the STO minimal set, but valence properties calculated with this set are comparable to the STO set. (b) 4-31G set. This larger set produces results which are comparable to the double zeta STO set. The exponents and scale factors are those by Ditchfield, *et al.*[10]

Monomer Geometries——The geometry of methanol for geometry optimization was taken from experiment: for CH_3OH $r(CO)=1.428$ Å, $r(OH)=0.96$ Å, $r(CH)=1.095$ Å, $<HOC=109.0°$, and $<OCH=109.5°$.[11] The geometries of methanol and water for energy decomposition are as follows: for CH_3OH the same structure as that described above and for H_2O, $r(OH)=0.956$ Å and $<HOH=105.2°$.[12] The geometries of HCOOH, OH^-, and H_2O for ester reaction: for HCOOH $r(CO)=1.202$ Å and 1.343 Å, $r(CH)=1.097$ Å, $r(OH)=0.972$ Å,

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$<$OCO$=124.9°$, $<$HCO$=124.1°$, and $<$COH$=106.3°$,[12] for H_2O the same structure as that described above,[12] and for OH^- $r(OH)=0.985$ Å.[3e]

Energy Decomposition——The following procedure to calculate energy components are used. After the SCF MO's (MO°'s) for isolated moleculaes are calculated, the sum of energy of both moleculaes is called E_0. By using MO°'s as the initial guess in the standard SCF procedure, Schmidt orthogonalization for MO°'s are carried out. The wave function and energy in the first cycle (before diagonalization) are

$$\phi_3,\ E_3 = E_o + E_{ES} + E_{EX}$$

and the wave function and energy after the SCF is converged are

$$\phi_4,\ E_4 = E_o + E_{ES} + E_{EX} + E_{CT} + E_{PL} + E_{MIX}$$
$$= E_o + \Delta E$$

where ES, EX, CT, PL and MIX refer to electrostatic, exchange, charge transfer, polarization and coupling terms, respectively, and ΔE is the total interaction energy. Next, after dropping all the one and two electron integrals involving a differential overlap between the isolate molecules, the similar calculations to those described above are carried out. The first cycle gives

$$\phi_1,\ E_1 = E_o + E_{ES}$$

and the converged SCF gives

$$\phi_2,\ E_2 = E_o + E_{ES} + E_{PL}$$

The above procedure leads to the decomposition into E_{ES}, E_{EX}, E_{PL} and E_{CT+MIX}. Next the Hartree–Fock and overlap matrices are transformed from the AO basis to the MO° basis. By keeping only interaction matrix elements connecting the occupied MO's of a molecule with the vacant MO's of the other molecule in addition to the diagonal blocks, the process is repeated until the SCF is converged. The first cycle is

$$\phi_5,\ E_5 = E_o + E_{ESX}$$

and the converged SCF is

$$\phi_6,\ E_6 = E_o + E_{ESX} + E_{CT}$$

where ESX refers to the electrostatic plus exchange integral part of the exchange term. E_{CT} is obtained as the difference between E_6 and E_5.

Calculations were carried out by using HITAC 8700—8800 Computer of the University of Tokyo and IBM 370 Computer of Mitsubishi-Kasei Kogyo Company.

Results and Discussion

Geometry Optimization for CH_3OH and CH_3O^-

In the gas phase the proton affinity of methoxide is less than that of hydroxide.[3] There are many calculations[3] for the experiment. However, the comparison after the geometry optimization was not carried out. In order to clarify this result the optimization for CH_3OH and CH_3O^- was carried out by using 4-31G basis set. The optimization for H_2O and OH^- by using 4-31G basis set was already calculated.[3e] Table I shows the result of geometry optimization of CH_3OH and CH_3O^-. Figure 1 shows the result obtained from Table I. By the proton removal r(CO) is by 0.029 Å smaller, r(CH) is by 0.028 Å longer, and $<$OCH is by 5.09° bigger. The change of the angle $<$OCH is thought to be due to negative net charges of three protons and oxygen in CH_3O^-. Accordingly the energy of the proton removal in CH_3OH is shown by the equation,

$$CH_3O^- - CH_3OH = 0.6536 \text{ atomic unit}$$

On the other hand the proton removal energies for water are shown by the equations,

$$OH^- - H_2O = 0.6788 \text{ atomic unit}$$
$$OH^-(H_2O) - (H_2O)_2 = 0.6270 \text{ atomic unit}$$
$$OH^-(H_2O)_2 - (H_2O_3) = 0.6044 \text{ atomic unit}$$

from the results by Newton and Ehrenson.[3e] Figure 2 shows the plot of the proton removal energy against the water number. From three points for water a parabolic fit curve is obtained. A closed circle was obtained from the assumption that the value of the proton removal energy

TABLE I

r (CO) (Å)	r (OH) (Å)	<HOC (Degree)	r(CH) (Å)	<OCH (Degree)	Total energy (Atomic unit)
(a) Geometry optimization of CH_3OH(4-31G basis set)					
1.428	0.96	109.0	1.095	109.5	−144.869875
1.448	0.96	109.0	1.095	109.5	−144.869838
1.408	0.96	109.0	1.095	109.5	−144.869367
1.43662	0.96	109.0	1.095	109.5	−144.869922
1.43662	0.99	109.0	1.095	109.5	−144.868640
1.43662	0.93	109.0	1.095	109.5	−144.869465
1.43662	0.95288	109.0	1.095	109.5	−144.869985
1.43662	0.95288	112.0	1.095	109.5	−144.870328
1.43662	0.95288	115.0	1.095	109.5	−144.870135
1.43662	0.95288	112.4193	1.095	109.5	−144.870332
1.43662	0.95288	112.4193	1.105	109.5	−144.869558
1.43662	0.95288	112.4193	1.085	109.5	−144.870731
1.43662	0.95288	112.4193	1.07935	109.5	−144.870782
1.43662	0.95288	112.4193	1.07989	109.5	−144.870783[a]
1.43662	0.95288	112.4193	1.07989	111.5	−144.870291
1.43662	0.95288	112.4193	1.07989	107.5	−144.869890
1.43662	0.95288	112.4193	1.07989	109.7898	−144.870798
(b) Geometry optimization of CH_3O^- (4-31G basis set)					
1.43662			1.07898	109.79	−144.210551
1.39662			1.07898	109.79	−144.210949
1.35662			1.07898	109.79	−144.209403
1.40843			1.07898	109.79	−144.211013
1.40843			1.05989	109.79	−144 208092
1.40843			1.09989	109.79	−144.212352
1.40843			1.10683	109.79	−144.212479
1.40843			1.10843	109.79	−144.212484[a]
1.40843			1.10843	112.790	−144.216358
1.40843			1.10843	115.790	−144.216989
1.40843			1.10843	114.8739	−144.217153

a) Value obtained from a parabolic fit.

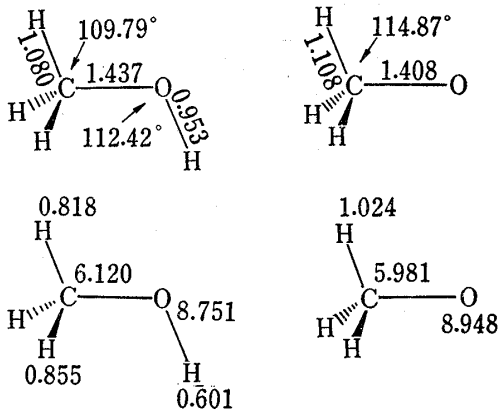

Fig. 1. Structure and Atomic Population of CH_3OH and CH_3O^- obtained from Geometry Optimization

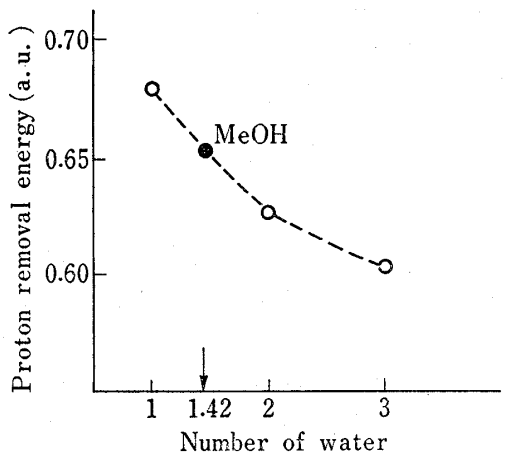

Fig. 2. Plot of the Proton Removal Energy against the Water Number

Open Circle is obtained from water. Closed circle is obtained from the proton removal in CH_3OH.

in MeOH is on the parabolic curve. The closed circle corresponds to the number 1.4 of water. Accordingly it was shown that the proton removal energy in CH_3OH corresponds to the proton removal energy of 1.4 waters. In other words the proton removal energy in poly water molecules is smaller than that in MeOH. Table II shows the proton removal energies calcu-

Table II. Proton Removal Energies Calculated by Many Researchers and the Authors in kcal/mol

	(1)	(2)	(3)	(4)	(5)
CH_3OH	384	534.4	496.0	419.7	410.2[a]
H_2O	390	568.0	510.4	433.8	426.0[b]
Difference	6	32.6	14.4	14.1	15.8

(1) Reference 3*a*. Experimental value.
(2) Reference 3*b*. STO-3G basis set. Molecular geometries for the neutral molecules were chosen to a standard model. The same bond lengths and tetrahedral angles were used in negative ion.
(3) Reference 3*c*. Complete optimization of Slater exponents and molecular geometries of water, hydroxy ion, methanol and methoxide ion was accomplished at the STO-3G level.
(4) Reference 3*d*. The exponents and contraction coefficients used have been optimized for C and O atoms by Huzinaga and Basch, *et al.* for H. This basis set consists of double-zeta basis functions. CH_3O^- is not optimized.
(5) *a*) Value obtained by the authors in this report. *b*) Reference 3*e*. All parameters are the same as these in this report.

lated by many researchers. For the proton removal energy in CH_3OH the value 410.2 kcal/mol obtained in this report is the smallest. The value 15.8 kcal/mol of the difference between the proton removal energies in MeOH and H_2O is almost the same as the values by Owen, *et al.* and Tel, *et al.* Accordingly the result of the calculation obtained after geometry optimization in double-zeta basis set explains the experiment. However the result of the calculation is by 10 kcal/mole larger than the experiment. Moreover the result in Table II is in accordance with the previous report[2b] that the effect for the aspirin hydrolysis by methanol addition is due to the difference between the proton removal energies in CH_3OH and H_2O.

Energy Decomposition of Proton Removal Energy

The proton removal energy in CH_3OH is smaller than that in H_2O, but it is larger than that in $(H_2O)_2$. In order to clarify this result energy decomposition analysis were carried out for the proton removal in those molecules. Table III shows the results. Structures used for anion molecules were assumed to be the same as those for neutral structures. The electrostatic energy for the proton removal energies is main contributor and the charge transfer energy is secondly important. The larger value of the proton removal energy in H_2O in comparison with that in CH_3OH is attributed to the electrostatic interaction energy. On the other hand the smaller value in $(H_2O)_2$ is due to the polarization interaction energy. For the difference of the proton removal energy between H_2O and $(H_2O)_2$, main contributor is the electrostatic term. The contribution of the polarization energy is reverse. The charge transfer energy term is the second contribution. Accordingly the result that the proton removal energy in CH_3OH is between those in H_2O and $(H_2O)_2$ is due to the different value of the ES term of the proton removal energies between H_2O and water dimer.

Interaction between Ester and Water

Hydrolysis of ester is described by the equation,

$$RCOOR' + H_2O \rightleftarrows RCOOH + R'OH$$

Interaction between RCOOR' and H_2O is significant. In this report the interaction energy between HCOOH and H_2O was calculated. Figure 3 shows the structure calculated. Table

13) T.R. Dyke and J.S. Muenter, *J. Chem. Phys.*, **60**, 2929 (1974).

Table III. Energy Decomposition Analysis of Proton Removal in CH_3OH, H_2O and $(H_2O)_2$ in kcal/mol[a] (4-31G basis set)

	$CH_3OH \rightarrow CH_3O^-$	$H_2O \rightarrow OH^-$	$(H_2O)_2 \rightarrow OH^-(H_2O)$
ΔE	411.1	425.8	400.6
E_{ES}	261.7(64%)	292.8(69%)	265.7(66%)
E_{EX}	0	0	0
E_{PL}	41.5(10%)	21.6(5%)	28.0(7%)
E_{CT}	98.1(24%)	95.9(23%)	92.9(23%)
E_{MIX}	9.8(2%)	15.4(4%)	14.1(4%)
$\Delta\Delta E$	0	14.7	−10.5
ΔE_{ES}	0	31.1	3.9
ΔE_{EX}	0	0.0	0.0
ΔE_{PL}	0	−19.1	−13.6
ΔE_{CT}	0	−2.2	−5.2
ΔE_{MIX}	0	5.6	4.3
$\Delta\Delta E'$		0	−25.2
$\Delta E_{ES}'$		0	−27.2
$\Delta E_{EX}'$		0	0
$\Delta E_{PL}'$		0	6.4
$\Delta E_{CT}'$		0	−3.0
$\Delta E'_{MIX}$		0	−1.3

a) Structure used for CH_3O^-, OH^- and $OH^-(H_2O)$ were assumed to be the same as those for CH_3OH, H_2O and $(H_2O)_2$. Reference 13 was referred to the structure for water dimer: $r(OO)=2.98$ Å, and the proton acceptor molecule inclines at 60° from O–O axis. The proton of the proton acceptor water is removed.

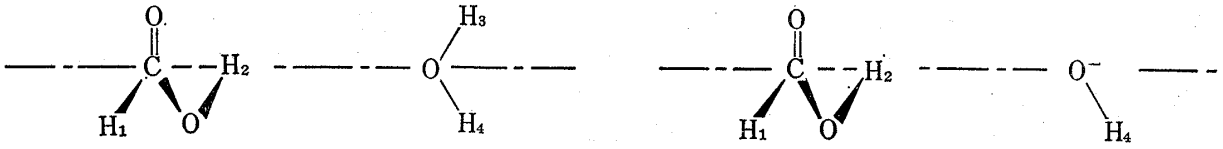

Fig. 3. Structure for Interaction Between HCOOH and H_2O or OH^-

C_{2v} in water is perpendicular against the plain of HCOOH and is above the carbon in HCOOH.

Table IV. Interaction Energy between HCOOH and H_2O at Various Separations between the Oxygen in H_2O and the Carbon in HCOOH in Atomic Unit (STO-3G Basis Set)

Separation (Å)	Total energy (Atomic unit)
2.0	−261.155587
2.5	−261.178549
3.0	−261.179560
3.4	−261.178960
∞	−261.177794

Table V. Energy Decomposition Analysis for the Interaction between HCOOH and H_2O at the Separation 3.0Å in kcal/mol (STO-3G Basis Set)

Decomposition term	Decomposition energy
ΔE	−1.1
E_{ES}	−1.1(77%)
E_{EX}	0.4
E_{PL}	−0.0(3%)
E_{CT}	−0.3(20%)
E_{MIX}	0.0

IV shows the result in STO-3G basis set. It is assumed that water in its C_{2v} geometry approachs above the carbon in HCOOH as described in Fig. 3. At a parabolic fit by using the values corresponding to 2.5, 3.0, and 3.4 Å the value for the separation 3.0 Å was minimum. Energy decomposition analysis was carried out at the separation 3.0 Å. The result is shown in Table V. The main contributor was the electrostatic term.

Interaction between Ester and OH^-

In general base catalysis and alkali hydrolysis for ester, the interaction energies between ester and water ($OH^-..H^+$) and between ester and OH^-, respectively, are significant. In this paper the interaction energies between HCOOH and OH^- were calculated. The same structure as that in Fig. 3 was used. H^3 in H_2O was removed for OH^- structure. The result is shown in Table VI. At a parabolic fit by using the values corresponding to 1.6, 1.8, and 2.0 Å, the value at the separation 1.86 Å was minimum. Moreover the energy decomposition analysis at the separation 1.86 Å was carried out. Table VII shows the result. The main

Table VI. Interaction Energy between HCOOH and OH^- by Using STO-3G Basis Set in Atomic Unit at Various Separations between the Carbon in HCOOH and the Oxygen in OH^-

Separation (Å)	Total energy (Atomic unit)
3.0	−260.284832
2.5	−260.301380
2.0	−260.327343
1.86	−260.331856
1.8	−260.331028
1.6	−260.316299

Table VII. Energy Decomposition Analysis at the Separation 1.86 Å between the Carbon in HCOOH and the Oxygen in OH^- in kcal/mol (STO-3G Basis Set)

Decomposition term	Decomposition energy
ΔE	−35.2(−37.5)[a]
E_{ES}	−29.0(−29.8)[a]
E_{EX}	70.0(72.3)[a]
E_{PL}	−4.8(−4.8)[a]
E_{CT}	−47.9(−49.1)[a]
E_{MIX}	−23.6(−26.1)[a]

a) Values in the parentheses are for the angle 120° of ∠COH, where C is in HCOOH and OH is in OH^-.

contributor is the charge transfer term. Secondly the electrostatic term is important. The slight change of the complex structure gives the similar result shown as the values in parentheses.

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