A Molecular Orbital Study on the Partial Reactivity of Hydrogen of Various Amino Acids in the Abstraction Reaction by Hydroxyl Radical

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The reactivities of hydrogen atoms of aliphatic amino acids toward hydroxyl radicals in the hydrogen atom abstraction reaction have been studied in terms of the energy required for stretching the C-H bond which is attacked. The energy required for stretching the C-H bond by 0.5 Å from the equilibrium bond length has been calculated by the INDO method and compared with the partial rate constants experimentally assigned to the hydrogen atoms of aliphatic amino acids. The energy required has been correlated only with the partial rate constants of the hydrogen atoms on the β-carbon atom. For the hydrogen atoms on the α-carbon atom, although data was insufficient a similar situation has been observed. The reactivities of the hydrogen atoms on the γ and δ-carbon atom failed to correlate with the stretching energy. The reasons are discussed in terms of the effect raised by the configuration of amino acid molecules in solution. The stretching energy has also been found to be consistent with the electrophilicity observed in the hydrogen abstraction reaction by hydroxyl radical.

Reactions of hydroxyl radicals with amino acids have been investigated by a number of researchers with an interest in the radiation-induced damage of proteins. Hydroxyl radicals abstract hydrogen atoms from aliphatic amino acids and the rate constants for the reactions are available.

Recently, it has been reported[1] that the partial rate constants for the hydrogen atom abstraction by hydroxyl radicals may be estimated from the rate constants determined by the *p*-nitroso-*N*,*N*-dimethylaniline method[2,3] for primary, secondary, and tertiary hydrogen atoms bound to the α, β, γ, and δ-carbon atoms of simple aliphatic amino acids. The bimolecular rate constant for the hydrogen atom abstraction by hydroxyl radicals from an aliphatic amino acid has been interpreted by summation of the partial reactivities assigned to hydrogen atoms in the amino acid molecule. However, no theoretical basis of the partial reactivities has been presented.

In the present investigation, the energy required to stretch the C–H bond by 0.5 Å from the equilibrium bond length has been calculated, to ensure a quantum chemical basis to the assigned partial reactivity. This energy is possibly used as a measure of the reactivity of a hydrogen atom toward hydroxyl readicals, since it is approximately the same as the energy required for hydrogen abstraction calculated from a reacting system composed of a hydroxyl radical and an amino acid. The energies calculated for several kinds of aliphatic amino acids have been partly correlated with the assigned parital reactivities. The effect raised by configurational changes in solution has been discussed. The electrophilic behavior of hydroxyl radical observed in the hydrogen abstraction reaction with amino acids has been explained in terms of the stretching energy.

Method

The total energies for the isolated molecules as well as the reacting systems were calculated by the UHF method[4] in the INDO approximation.[5]

Results and Discussion

The total energies and the electron distributions were calculated for glycine, alanine, 2-aminobutyric acid, valine, isoleucine, and leucine. The assumed geometries of the amino acids and hydroxyl radicals are given in Fig. 1 and the total energies in Table 1. For alanine, 2-aminobutyric acid, valine, isoleucine, and leucine, the same bond lengths and bond angles as those of glycine were assumed. In order to find the stable form of valine, the total energies of the other forms were calculated and found to be less stable than that shown in Fig. 1.

Figure 1 shows a model of the hydrogen abstraction by hydroxyl radicals from glycine. It has been assumed that the hydroxyl radical approaches the H^9 atom of glycine along the extension of the C^1–H^9 bond maintaining the angle H^9OH at 104.45° (the bond angle of water) and abstracts the H^9 atom. In a previous paper,[6] the angular dependence of the energy of the CH_4–OH system (θ, the angle of HOH was varied from 90 to 180°) was studied, and it was confirmed that the approach with $\theta=104.45°$ is most favored.

TABLE 1. THE TOTAL ENERGY OF AMINO ACIDS AND HYDROXYL RADICALS CALCULATED BY THE INDO METHOD

Amino acid	Total energy (au)
Glycine	−63.6233
Alanine	−72.0652
2-Aminobutyric acid	−80.5059
Valine	−88.9413
Isoleucine	−97.3754
Leucine	−97.7260
Hydroxyl radical	−18.1505

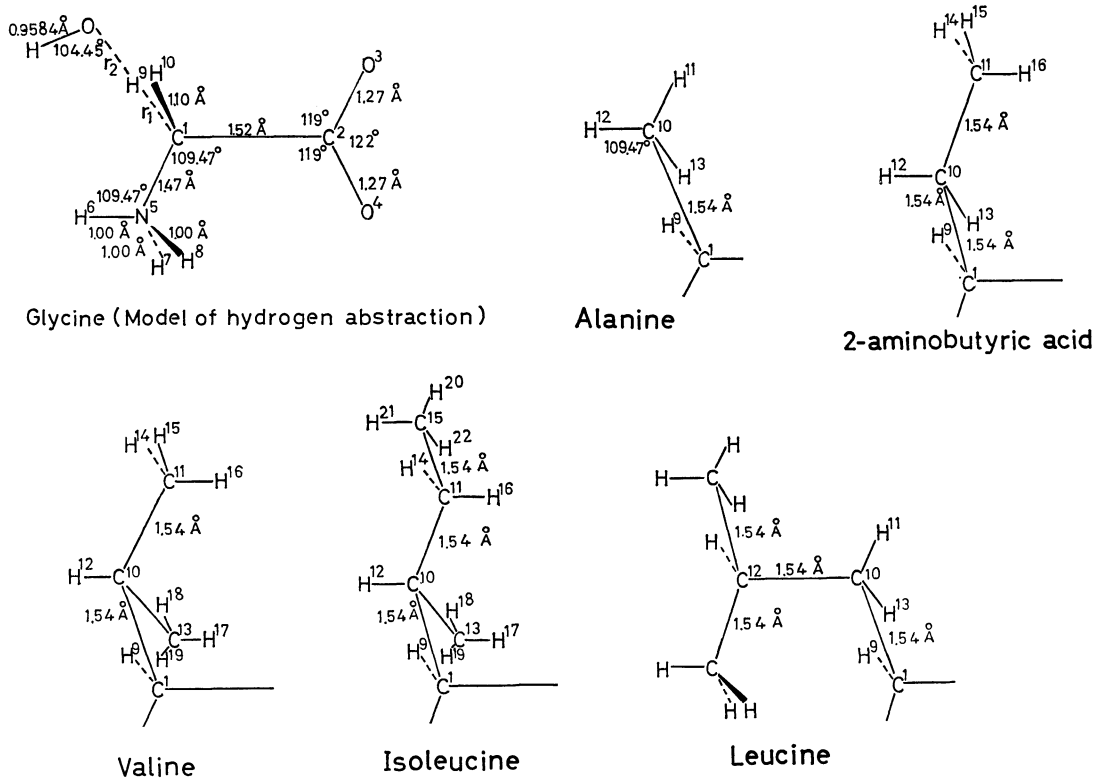

Fig 1. The geometries of amino acids and an assumed model for the abstraction by hydroxyl radical with amino acid.

Consequently, this angle has been adopted for the amino acid–OH system. The hydrogen atom of the hydroxyl radical lies in a anti-direction to the C^1–H^{10} bond with regard to the C^1–O bond. The energy dependence of the reacting system upon the intermolecular H^9–O distance, with the C^1–H^9 distance fixed at 1.10 Å was examined and the results are given in Fig. 2. The minimum quantity of energy was obtained between the intermolecular distances of 1.36 and 1.46 Å. The reacting system is more stable than the isolated state, and this is probably due to the stabilization by hydrogen-bonding between hydroxyl oxygen and the H^9 atom of glycine.

The reaction path is specified with the notation (r_1, r_2), where r_1 represents the distance in Å betweeen carbon C^1 and hydrogen H^9 which is abstracted, and r_2 that between H^9 and hydroxyl oxygen.

Figure 3 illustrates the dependence of the energy of the reacting system upon the C^1–H^9 distance r_1, when the C^1–O distance (r_1+r_2) is varied. It is conceivable that configuration interactions are important in lowering the energy for the transition state of the reacting system. However, calculation of the interactions by the UHF method is very complicated. Thus, it has been tentatively assumed that the effects of the configuration interactions are not so different, molecule to molecule in the series of aliphatic amino acid molecules, and consequently the reactivity may be compared with the energy obtained by the UHF method for the elongated C^1–H^9 bond. The following points A, B, C, and D were taken as possible reaction paths for H^9 abstraction, specified respectively by a set of r_1 and r_2 indicated in parentheses. A(1.10, 1.46), B(1.20, 1.36), C(1.30, 1.26), D(1.40, 1.16).

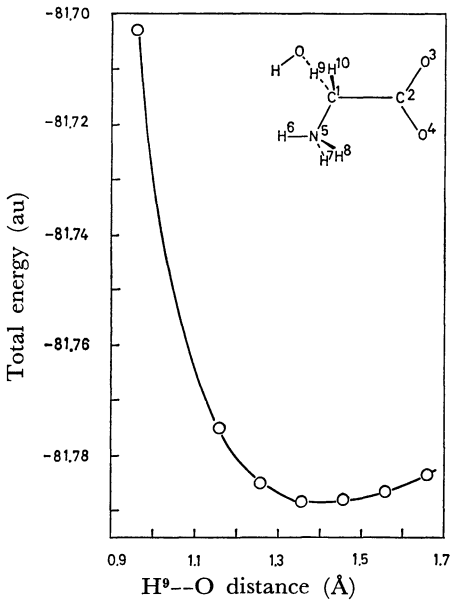

Fig. 2. Potential curve as a function of the distance between hydroxyl radical and H^9 atom in glycine-OH system.

From Fig. 3, it has been inferred that the potential curve appears to approach a maximum near D with the distance C^1–O of 2.56 Å, although the absolute value of the energy is not available. Therefore, it has been assumed that the difference in the total energy between the reacting system at D and the isolated state is an approximate measure of the reactivity of

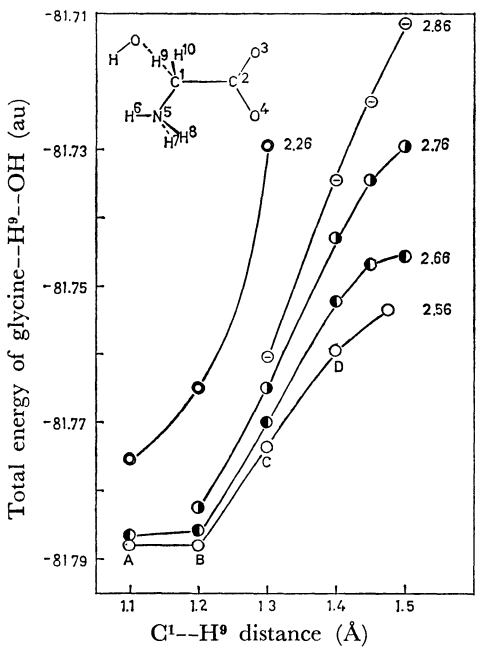

Fig. 3. Potential curves as a function of C^1–H^9 distance at various C^1–O distances in glycine–OH system. The number described near the point is C^1–O distance.

the H^9 atom (α-secondary). In order to examine the suitability of point D for other hydrogen atoms, the interaction energy between the hydroxyl radical and the H^9 atom of alanine has been calculated. As shown in Fig. 4, the favored reaction path has been found to be the same as that observed in the glycine H^9 atom. The results of Figs. 3 and 4 suggest that the path with $r_1+r_2=2.56$ Å is favored for hydrogen atoms of any type. Thus D has been taken as the reference point to compare the reactivities of hydrogen atoms bound to α, β, γ, and δ-carbon atoms.

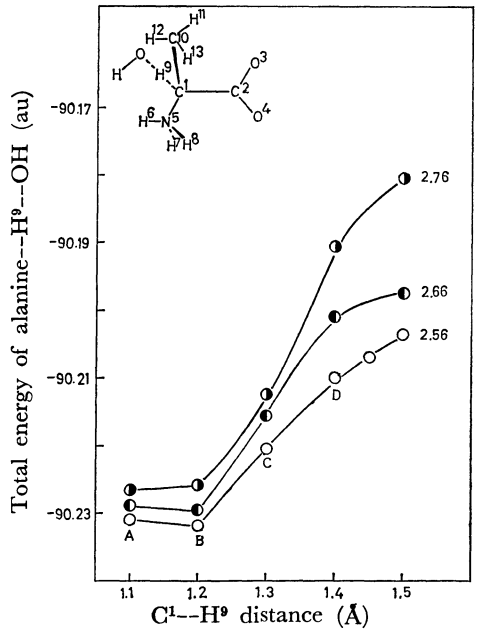

Fig. 4. Potential curves as a function of C^1–H^9 distance at various C^1–O distances in alanine–OH system. The number described near the point is C^1–O distance.

In chemical reactions, it has been recognized that the delocalization of electrons between a reactant and a reagent is a major factor in determining reactivity.[7,8] Although the potential curve should be obtained for the system including both a hydroxyl radical and an amino acid, the interaction energy could not always be obtained, because of divergence in the SCF calculation. This divergence may make the absolute values of the total energy unreliable. However, the relative values of the energy may be useful for a discussion of the relative reactivity. Thus, it has been assumed that the interaction energy could be approximated by the energy change due to the stretching of C–H bond. This model was checked in detail as follows. Several factors contribute to the abstraction reaction, for example, a) the strength of the R–H bond broken, b) the strength of forming the H–X bond, c) the stabilization energy due to delocalization of electrons, d) solvation, and so on. The relative reactivities of hydrogen atoms toward the same attacking reagent have been investigated in the present study and it appears that factors a) and c) dominate. If c) does not vary with types of C–H bonds or if a) and c) correlate linearly with each other, the reactivities of the hydrogen atoms for abstraction may be approximated to the strength of the C–H bond. The interaction energy of the glycine–OH system along the reaction path(A, B, C, D) has been compared with the total energy of glycine obtained by stretching the C^1–H^9 bond from 1.10 to 1.40 Å, in the singlet state. From a linear correlation between the total energy of the composite system and that of glycine at the same bond distance of the C^1–H^9 (Fig. 5), it has been concluded that the reactivity of the H^9 atom may be evaluated in terms of the energy required to stretch the C^1–H^9 bond by a

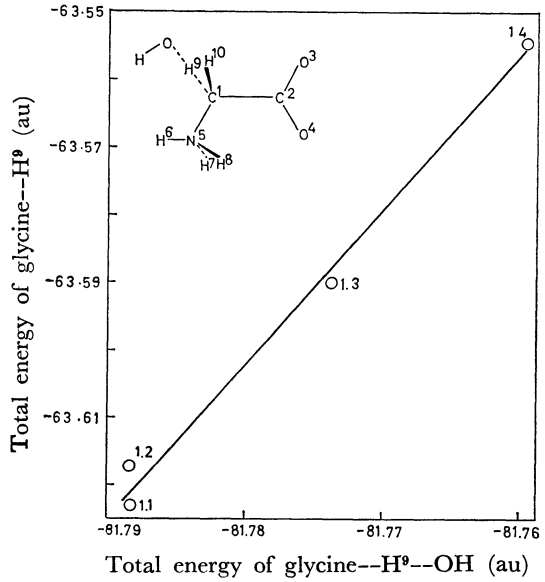

Fig. 5. The linear relationship between the energy changes by elongation of the C-H bond in question in presence and absence of OH group for glycine. The number described near the point is the bond length of the stretching C-H bond.

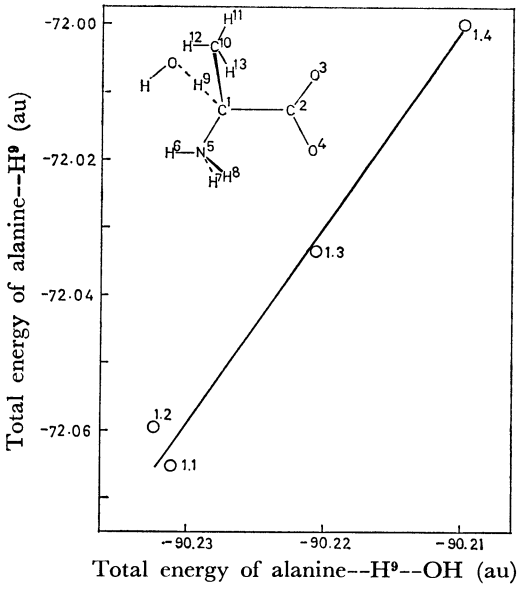

Fig. 6. The linear relationship between the energy changes by elongation of the C-H bond in question in presence and absence of OH group for alanine. The number described near the point is the bond length of the stretching C-H bond.

certain distance from the equilibrium bond length. The same argument is valid for the H^9 (α-tertiary) atom of alanine as shown in Fig. 6.

The conclusion is that the energy change due to stretching of the C–H bond interacting the hydroxyl radical may be approximated by the energy change in the absence of the hydroxyl radical. The validity of this conclusion has been examined for other types of hydrogen-atoms and the results are given in Fig. 7. ΔE_{OH} and ΔE have been difined for the reactivities of the hydrogen atoms in the following equations and have been calculated by two methods.

$$\Delta E_{OH} = E_{\text{amino acid-OH}} \text{ at D(1.40, 1.16)} - E_{\text{amino acid-OH}} \text{ at (1.10, } \infty) \quad (1)$$

$$\Delta E = E_{\text{amino acid}}(\text{C-H } 1.60) - E_{\text{amino acid}}(\text{C-H } 1.10) \quad (2)$$

Where D(1.40, 1.16) and (1.10, ∞) represent the points on the reaction path as previously defined and (C–H 1.60) and (C–H 1.10) indicate the C–H bond length. The point (C–H 1.60) has been tentatively selected in order that ΔE might approximate to ΔE_{OH}, although the absolute value of the energy may be unreliable.

The ΔE for several kinds of hydrogen atoms was found to have a close correlation with ΔE_{OH} with a few exceptions. Consequently, ΔE given by Eq. 2 has been used as an index to represent the reactivity of the hydrogen atoms of amino acids toward hydroxyl radicals in order to avoid the problem of divergency in the SCF calculation of ΔE_{OH}. Here, it should be noticed that the hydrogen atoms bound to the same carbon atom show different reactivities according to the orientation in the amino acid molecule as shown for the H^{11}, H^{12}, and H^{13} atoms of alanine in Fig. 7. This will be discussed in detail below.

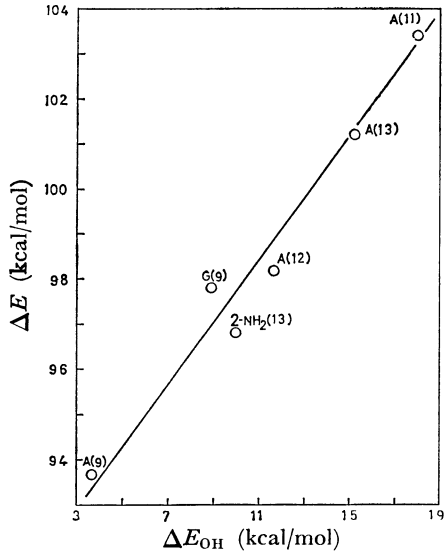

Fig. 7. Comparison of ΔE with ΔE_{OH} for different types of hydrogen atoms. G: glycine, A: alanine, 2-NH_2: 2-aminobutyric acid. The number in parenthesis indicates hydrogen atoms in Fig. 1.

TABLE 2. THE REACTIVITY OF HYDROGEN ATOMS OF AMINO ACIDS CALCULATED BY ΔE

Amino acid		Type of C–H bond	ΔE(au)[b]
Glycine	H^9	α-sec[a]	0.1560
Alanine	H^9	α-tert	0.1498
	H^{11}	β-prim	0.1468
	H^{12}	β-prim	0.1565
	H^{13}	β-prim	0.1614
2-Aminobutyric acid	H^{12}	β-sec	0.1491
	H^{13}	β-sec	0.1544
	H^{14}	γ-prim	0.1617
	H^{15}	γ-prim	0.1601
	H^{16}	γ-prim	0.1490
Valine	H^{12}	β-tert	0.1428
	H^{14}	γ-prim	0.1601
	H^{15}	γ-prim	0.1599
	H^{16}	γ-prim	0.1488
	H^{17}	γ-prim	0.1617
	H^{18}	γ-prim	0.1610
	H^{19}	γ-prim	0.1555
Isoleucine	H^{14}	γ-sec	0.1538
	H^{16}	γ-sec	0.1430
	H^{20}	δ-prim	0.1610
	H^{21}	δ-prim	0.1604
	H^{22}	δ-prim	0.1601
Leucine	H^{11}	β-sec	0.1574
	H^{13}	β-sec	0.1543
	H^{14}	γ-tert	0.1494

a) α-sec: α-secondary, α-tert: α-tertiary, β-prim: β-primary, β-sec: β-secondary, β-tert: β-tertiary. b) Atomic unit.

To compare ΔE with the experimentally assigned values of the partial reactivities of hydrogen atoms, ΔE's were calculated for various kinds of hydrogen

atoms. The calculated values of ΔE are listed in Table 2. In the case of γ-primary hydrogen atoms (H^{14}, H^{15}, H^{16}) of 2-aminobutyric acid or valine, the prediction is that H^{16} is more reactive than H^{14} or H^{15}.

The differences in the reactivities of hydrogen atoms bound to the same carbon atom have been neglected when the partial reactivities were estimated from the observed rate constants. Therefore, the reactivity of γ-primary hydrogen atoms (also, β-primary, β-secondary, and so on) has been approximated by the average reactivity of H^{14}, H^{15}, and H^{16} atoms assuming Maxwell-Boltzmann distribution among the ΔE's. The results are in Table 3.

Table 3. Comparison of ΔE with the experimentally assigned partial reactivity

Type of C-H bond	Partial reactivity $M^{-1}s^{-1}$	ΔE(kcal/mol)
α-Secondary	8.5×10^{6}	97.835
α-Tertiary	1.7×10^{7}	93.715
β-Primary	2.07×10^{7}	98.188
β-Secondary	1.77×10^{8}	93.540[a]
		96.862[b]
β-Tertiary	3.54×10^{8}	89.575
γ-Primary	4.85×10^{7}	93.465[a]
		93.343[c]
γ-Secondary	5.12×10^{8}	89.701
γ-Tertiary	1.02×10^{9}	93.715
δ-Primary	6.75×10^{7}	100.597

a) Obtained from 2-aminobutyric acid. b) From leucine. c) From valine.

The relationship between the logarithm of the experimental reactivity and ΔE is shown in Fig. 8. If the type of hydrogen atoms is not taken into consideration, no clear correlation can be found. However, when the argument is restricted to only β-hydrogen atoms, a correlation betweeen ΔE and $\ln k$ is observed, though it is not well defined. For α-hydrogen atoms, only two points are available, and consequently no conclusive statement can be inferred. However, the slope is similar to that in the $\ln k \approx \Delta E$ correlation of β-hydrogen atoms. In the case of γ-hydrogen atoms, no correlation was found. To obtain a quantitative relation between the experimentally determined rate constant and the calculated interaction energy, the configurational changes of molecules in solution needs to be taken into consideration. In the present procedure, ΔE has been calculated for the fixed geometry of the amino acid molecule. The effect of the protonated amino group on the reactivity of a given hydrogen atom may vary with the position of the atom in three-dimentional space. For γ-hydrogen atoms, the fluctuation of the reactivity due to the configurational change is probably larger than the α or β-hydrogen atoms.

With regard to the values of ΔE in Table 3, two values of ΔE are given for β-secondary and γ-primary hydrogen atoms. The ΔE of the β-secondary hydrogen atom has been evaluated to be 93.540 kcal/mol as the average for H^{12} and H^{13} atoms of 2-aminobutyric acid, whereas 96.862 kcal/mol has been obtained as the average for H^{11} and H^{13} atoms of leucine. As ΔE for the H^{13} atom of leucine is approximately the same as that for the H^{13} atom of 2-aminobutyric acid, the difference in averaged ΔE's is attributable to the difference in ΔE between the H^{11} atom of leucine and the H^{12} atom of 2-aminobutyric acid. The value for γ-primary hydrogen atoms, 93.465 kcal/mol has been obtained from H^{14}, H^{15}, and H^{16} atoms of 2-aminobutyric acid and it was approximately consistent with 93.343 kcal/mol obtained from the H^{14}, H^{15}, and H^{16} atoms of valine. This suggests that the effect of another CH_3 group (C^{13}, H^{17}, H^{18}, H^{19}) of valine upon the reactivitiy of γ-primary hydrogen atoms is not large and the same value may be used for 2-aminobutyric acid and valine. If the molecular backbone is different, the same value cannot always be applied to represent the reactivity as shown in the cases of 2-aminobutyric acid and leucine, because the reactivity of the hydrogen atom is closely related to the orientation in the molecule. As already described, there is a remarkable difference in ΔE among primary and secondary hydrogen atoms. For γ-primary hydrogen atoms of 2-aminobutyric acid, for example, the large reactivity of the H^{16} atom compared with that of the H^{14} and H^{15} atoms is ascribed to the difference in the two-center interaction energy. The two-center energy in the INDO method[5] is equal to that in the CNDO/2 method by Pople *et al.*[9,10] and consists of the three terms with different characters.

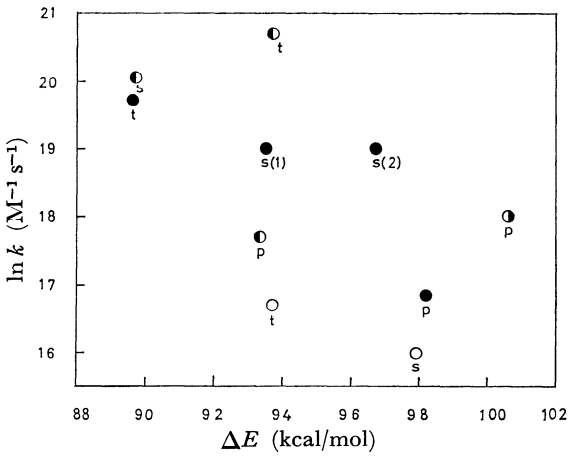

Fig. 8. Comparison of ΔE with the experimentally assigned partial reactivity. ○: α-, ●: β-, ◐: γ-, ◑: δ-, p: primary, s: secondary, t: tertiary. s(1) and s(2) are obtained from 2-aminobutyric acid and leucine respectively, see Table 3.

$$E_{A-B} = \sum_{\mu}^{A}\sum_{\nu}^{B} 2P_{\mu\nu}\beta_{\mu\nu} - \frac{1}{2}\sum_{\mu}^{A}\sum_{\nu}^{B} P_{\mu\nu}^{2}\gamma_{AB} + [Z_A Z_B R_{AB}^{-1} - P_{AA}V_{AB} - P_{BB}V_{BA} + P_{AA}P_{BB}\gamma_{AB}] \quad (3)$$

The first term is called the resonance term, the second the exchange term and the third the electrostatic term. The two-center energies calculated for 2-aminobutyric acid are shown in Table 4. ΔE_{C-H}, defined by the following equation, is the local energy required in stretching a C–H bond.

$$\Delta E_{C-H} = E_{C-H\ 1.60} - E_{C-H\ 1.10}, \quad (4)$$

where $E_{C-H\ 1.10}$ and $E_{C-H\ 1.60}$ are the interatomic interaction energies between carbon and hydrogen atoms at the C–H distance of 1.10 and 1.60 Å, respectively. E_{O-H} (C–H 1.10) and E_{O-H} (C–H 1.60) are the interatomic interaction energies between O^3 oxygen and hydrogen atoms (H^{14}, H^{15}, H^{16} of 2-aminobutyric acid) obtained at the C–H distance of 1.10 and 1.60 Å, respectively. ΔE, defined by Eq. 2, is the total energy required for the stretching and gives an index of the reactivity of hydrogen atoms. From the viewpoint of the energy required to stretch the C–H bond ΔE_{C-H}, the H^{16} atom is expected to the less reactive than the H^{14} and H^{15} atoms. However, ΔE gives the reverse results. For the interatomic interaction energy between O^3 and (H^{14}, H^{15}, H^{16}) atoms (E_{O-H} in Table 4), large stabilization is observed between O^3 and H^{16} atoms when the C^{11}–H^{16} bond is stretched. In the case of H^{14} and H^{15} atoms, destabilization occurred. In order to clarify the effect of the carboxyl group upon the reactivity of the H^{16} atom, a similar calculation was conducted by rotating the carboxyl group around the C^1–C^2 bond by 90°. The stabilization energy due to the interaction between O^3 and H^{16} atoms then reduces to approximately a tenth compared with the case without rotation of the carboxyl group. Accordingly, three hydrogen atoms have approximately equal reactivity as predicted from the magnitude of ΔE_{C-H}.

The interatomic interaction energy between O^3 and H^{16} atoms was further investigated by decomposing it into three components as in Eq. 3. The results given in Table 5 indicate that the resonance term is the most important and the main reason for the negative value of the O^3–H^{16} energy. Consequently it

TABLE 4. INTERATOMIC INTERACTION ENERGY OF 2-AMINOBUTYRIC ACID (au)

(A) Carboxyl group lies on the same plane with C^1, C^2, and N_5 atoms.

	C^{11}–H^{14}	C^{11}–H^{15}	C^{11}–H^{16}
E_{C-H} 1.10	−0.7536	−0.7481	−0.7470
E_{C-H} 1.60	−0.5475	−0.5433	−0.5239
ΔE_{C-H}	0.2061	0.2038	0.2231
ΔE	0.1617	0.1601	0.1490
	O^3–H^{14}	O^3–H^{15}	O^3–H^{16}
E_{O-H} (C–H 1.10)	0.0012	0.0018	−0.0179
E_{O-H} (C–H 1.60)	0.0055	0.0050	−0.0717

(B) After rotating carboxyl group by 90° around C^1–C^2 bond.

	C^{11}–H^{14}	C^{11}–H^{15}	C^{11}–H^{16}
E_{C-H} 1.10	−0.7507	−0.7496	−0.7507
E_{C-H} 1.60	−0.5476	−0.5467	−0.5461
ΔE_{C-H}	0.2031	0.2029	0.2046
ΔE	0.1615	0.1610	0.1613
	O^3–H^{14}	O^3–H^{15}	O^3–H^{16}
E_{O-H} (C–H 1.10)	0.0015	0.0011	−0.0033
E_{O-H} (C–H 1.60)	0.0046	0.0047	−0.0084

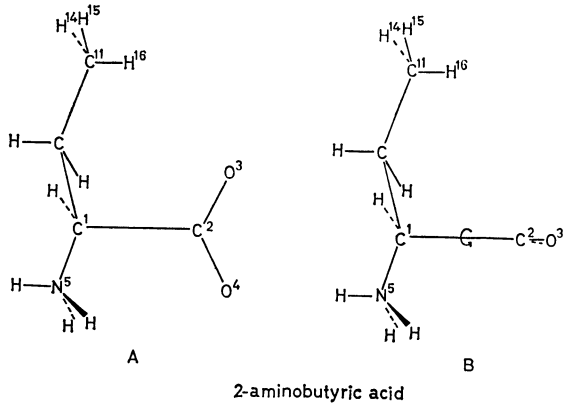

Fig. 9. Carboxyl group lies on the same plane with C^1, C^2, and N^5 atoms in A form, whereas in B form, the carboxyl group is rotated by 90° around C^1–C^2 bond.

may be concluded that the resonance interaction between O^3 and H^{16} atoms leads to an intramolecular hydrogen-bonding and this stabilization results in the large reactivity of the H^{16} atom despite the large value of ΔE_{C-H} of the C^{11}–H^{16} bond.

The reaction mechanism of the hydrogen abstraction by the hydroxyl radical from amino acids will now be discussed in terms of the electronic structure. The bond indices given by Wiberg[11] for the glycine–OH system are listed in Table 6, and the spin density and the charge transferred from glycine to the hydroxyl radical are listed in Table 7. It has been assumed that the hydroxyl readical has four valence electrons of α-spin and three valence electrons of β-spin. As shown in Tables 6 and 7, the approach of the hydroxyl radical decouples the electron pairing in the C^1–H^9 bond. The β-spin electron moves toward the H^9 atom while the α-spin electron in the opposite direction. In accordance with this spin movement, the α-spin

TABLE 5. THE DECOMPOSITION OF THE INTERATOMIC INTERACTION ENERGY BETWEEN O^3 AND H^{16} ATOMS(au)

Resonance term	−0.0617
Exchange term	−0.0101
Electrostatic term	0.0001
E_{O-H} (C–H 1.60)	−0.0716[a]

a) The interatomic interaction energy between O^3 and H^{16} atoms in Table 4 (A).

TABLE 6. BOND INDICES FOR THE GLYCINE–OH SYSTEM

Path point	C^1–H^9 bond indices		H^9–O bond indices	
	α-Spin	β-Spin	α-Spin	β-Spin
(1.10, 1.56)[a]	0.231	0.222	0.007	0.018
(A)	0.227	0.214	0.010	0.027
(B)	0.209	0.195	0.022	0.045
(C)	0.169	0.155	0.061	0.082
(D)	0.103	0.091	0.108	0.150

a) The values 1.10 and 1.56 denote the C^1–H^9 bond distance and H^9–O bond distance respectively.

Table 7. Spin density and charge transfer quantities for the glycine-OH system

Path point	Spin density			CT[b]
	C^1	H^9	O	
(1.10, 1.56)[a]	0.010	−0.044	0.015	−0.020
(A)	0.016	−0.061	0.016	−0.031
(B)	0.029	−0.120	0.015	−0.044
(C)	0.047	−0.209	0.011	−0.071
(D)	0.053	−0.239	0.006	−0.128

a) The values 1.10 and 1.56 denote the C^1–H^9 bond distance and H^9–O distance respectively. b) The charge transfer quantity from glycine to hydroxyl radical.

C^1–H^9 bond is weakened, and the β-spin H^9–O bond begins to form. This can reasonably be explained by the three-stage model proposed by Nagase *et al.*[12–14]

Glycine $C^1\uparrow\downarrow H^9 + \uparrow OH \rightarrow$ Gly $C^1\cdots\uparrow\downarrow\cdots H^9\cdots\uparrow OH$

$\rightarrow$ Gly $C^1\uparrow + H_2O$

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