An ab Initio Study of Intramolecular Hydrogen Bondings in α-Hydroxy Ketomethylene Dipeptide Isostere†

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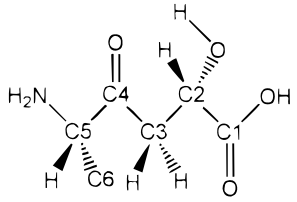
Ab initio calculations of the representative α-hydroxy ketomethylene dipeptide isostere (2*S*,5*S*)-5-amino-2-hydroxy-4-oxohexanoic acid (**1**) are described. All calculations including full geometry optimizations were performed at the MP2/6-31G* level. In the gas phase, 12 low-energy conformers are located by minimizing geometries assembled from stable molecular fragments. Among these conformers, six structurally similar conformers, in which the 2-hydroxyl group forms hydrogen bondings with both the O atom of the 4-carbonyl group in 1,3-fashion and the O atom of 1-carboxylic acid in 1,2-fashion simultaneously, are found to be particularly stable. Thus, the conformational preference of **1** appears to be governed by arrangements and strength of intramolecular hydrogen bondings. To examine conformational natures of **1** in solutions more accurately, we corrected the thermochemical properties and carried out self-consistent reaction field calculations. Going from the gas phase to solutions, the basic features of the conformational preferences in **1** also appear to be maintained in solutions including a highly polar aqueous medium, despite slight changes in the population of each conformer.

Introduction

α-Hydroxy ketomethylene dipeptide isostere was first introduced as a novel isostere in 1993[1] and successfully applied to angiotensin converting enzyme inhibitors[2] and HIV-1 protease inhibitors.[3] Ketomethylene dipeptide isostere[4] is a well-known isostere and has been widely used to prepare metabolically stable peptides and various enzyme inhibitors.[5] Compared with ketomethylene dipeptide isostere, α-hydroxy ketomethylene dipeptide isostere is believed to have one important merit in conformational control. The problem of conformational mobility faced in ketomethylene dipeptide isostere can be effectively solved in α-hydroxy ketomethylene dipeptide isostere due to the intramolecular hydrogen bonding between the hydroxyl group and carbonyl oxygen. Thus, α-hydroxy ketomethylene dipeptide isostere may be considered as a conformationally controlled analogue of ketomethylene dipeptide isostere. To figure out the conformational rigidity of α-hydroxy ketomethylene dipeptide isostere, ab initio calculations of the representative (2*S*,5*S*)-5-amino-2-hydroxy-4-oxohexanoic acid (**1**) were carried out. Our speculation on the conformation of α-hydroxy ketomethylene dipeptide isostere is well supported by the ab initio calculations, and we report here detailed molecular calculation results and rationalization of conformational control based on these data.



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Computational Methods

All ab initio calculations were carried out using the GAUSSIAN-94 series of programs.[6] Throughout this study, geometries were fully optimized with the 6-31G* basis set[7] at the MP2 level of theory[8] with the frozen core approximation in order to take the electron correlation effect into account. No symmetrical restrictions were imposed during the geometry optimization. The harmonic frequencies were calculated to confirm that the optimized geometries are true minima. In addition,

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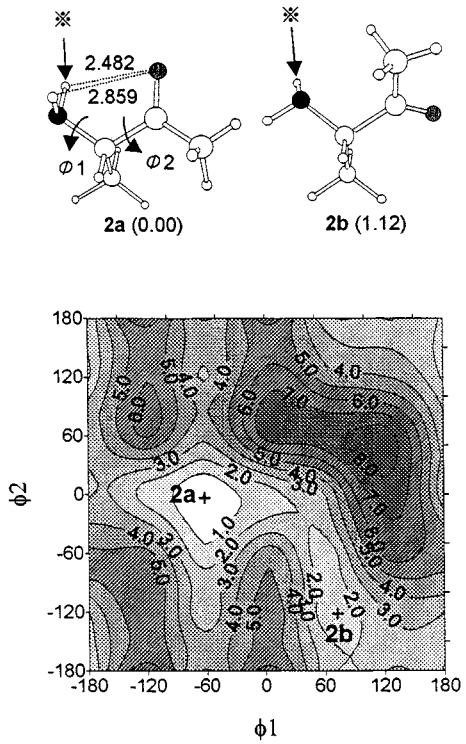

Figure 1. The CES and stable conformations of **2** calculated at the MP2/6-31G* level. Values in the parentheses are relative energies (in kcal/mol). The H atom indicated by ∗ is used to define the Φ1 torsional angle.

calculated frequencies were used to obtain (1) zero-point vibrational energy (ZPVE) and thermal vibrational energy (TVE) with the scaling factor of 0.94[9,10] and (2) entropies at each isomer. Eventually, the free energy differences at 298 K (ΔG(298 K)) were calculated by correcting the thermochemical properties mentioned above.[10] Solvent effects were introduced by means of a self-consistent reaction field (SCRF) method, in which solvents were treated as a dielectric continuum that interacts with the solute charge distribution.[11] The SCRF calculations were carried out at the MP2/6-31G* levels at two different media, $\epsilon = 2.0$ and 78.0, which simulate nonpolar and highly polar aqueous media. Geometries optimized in the gas phase were also utilized in SCRF calculations, and the cavity sizes were computed by using keyword, volume. (2*S*,5*S*)-5-amino-2-hydroxy-4-oxohexanoic acid (**1**) was selected as the model compound, which is a typical example of α-hydroxy ketomethylene dipeptide isostere. Our approach to find stable conformations of **1** consists of two steps: (1) conformational energy scans of small molecules that constitute key molecular fragments of **1** and (2) optimizations of selected numbers of **1** conformations, of which initial structures are constructed by hooking up stable conformations of molecular fragments. 3-Amino-2-butanone (**2**), 3-hydroxypropanal (**3**), 2-hydroxylpropanoic acid (**4**), and 2-hydroxy-4-oxobutanoic acid (**5**) were found to be key molecular fragments of **1**. The conformational energy surfaces (CESs) of these fragments were scanned by rotating one or two key torsional angle(s) with an increment of 60°. We believe that this approach will provide low-energy conformations with an efficient manner, since full conformational searches of **1**, which is relatively large in size and has numerous rotatable bonds, are extremely computationally laborious.

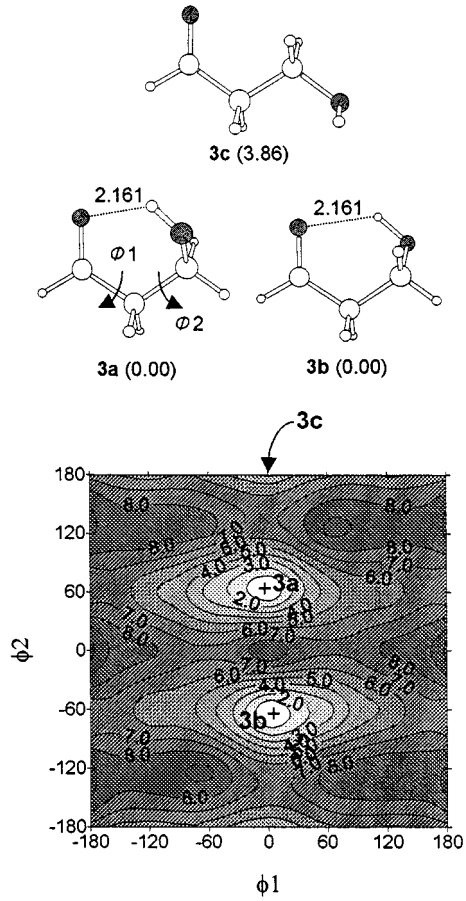

Figure 2. CES and stable conformations of **3** calculated at the MP2/6-31G* level. Values in the parentheses are relative energies (in kcal/mol).

Results and Discussion

CESs of Molecular Fragments in 1: 2−5. The CES of **2** was fully characterized by rotating both H−N−C−C and N−C−C═O torsional bonds and is depicted in Figure 1. We were able to locate only two minima, i.e., **2a** and **2b**. **2a** is the global minimum, which is stabilized by intramolecular hydrogen bondings between the O atom of a carbonyl group and the H atoms of an amino group in a 1,3-relationship. The CES of **3** was also examined by rotating both O═C−C−C and C−C−C−O(−H) torsional angles with posing the C−C−O−H torsional angle in an energetically favorable fashion. The computational results are illustrated in Figure 2. As shown in Figure 2, intramolecular hydrogen bonding is also a dominant factor to determine stable conformations in **3**. Two global minima, i.e., **3a** and **3b**, which are mirror images to each other, can be found. They can be converted to each other by overcoming an energy barrier of ca. 7 kcal/mol. These two conformers are identical in **3** but cause a significant difference when they are hooked into **1**, which has a chiral center at the C2 position. **3c** is the other stable minimum with a relative energy of 3.86 kcal/mol higher than the global minima. In **4**, where COOH and OH groups are adjacent, we also noticed that an intramolecular hydrogen bonding between two adjacent groups governs the stable conformation (Figure 3). The global

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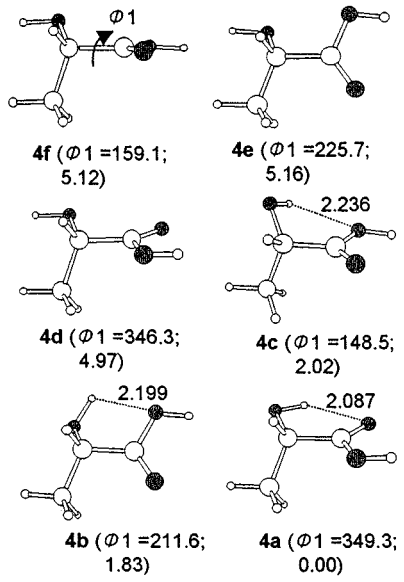

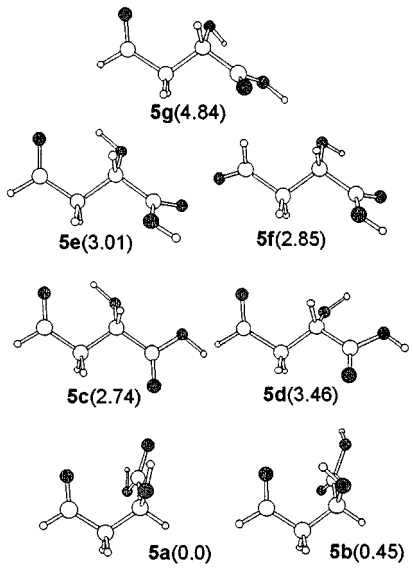

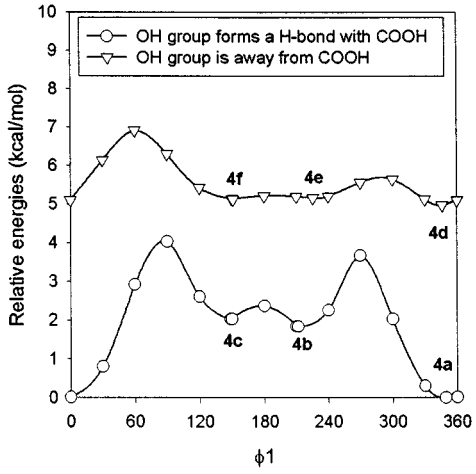

Figure 3. Conformational energy changes of **4** due to the rotation of the 2-OH group. Six stable conformers of **4** are also depicted. Values in parentheses are relative energies (in kcal/mol). Absolute energy of **4a** is −342.6130827 hartree. The Φ1 torsional angle is defined by (H−)O−C−C=O.

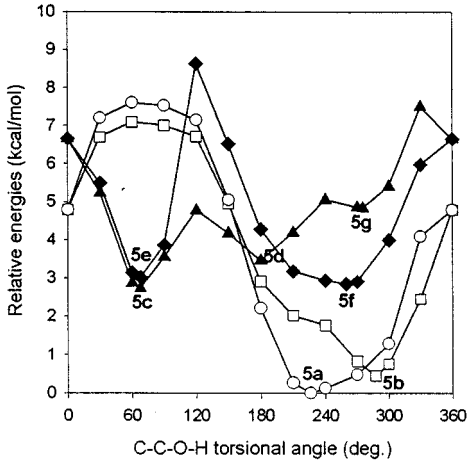

Figure 4. Conformational energy changes of **5** due to the rotation of the 2-OH group. Seven stable conformers of **5** also are depicted. Values in parentheses are relative energies (in kcal/mol). Absolute energy of **5** is −455.6335171 hartree.

minimum of **4** displayed a hydrogen bond between the carbonyl O atom of the carboxyl group and the H atom of the hydroxyl group. In **4**, another hydrogen bond is also found between the O(−H) atom of the carboxyl group and the H atom of the hydroxyl group, although its strength appears to be slightly smaller than the former one. Thus, in all the molecular fragments of **1** that we have studied in this work so far, intramolecular hydrogen bonding is the most dominant factor to determine the stable conformation.

Compound **5**, which comprises **3** and **4**, is a more realistic model for **1**. The conformational preference of **5** does not appear to be as straightforward as that of those model compounds mentioned earlier. On the basis of the conformational analyses of **3** and **4**, an intramolecular hydrogen bonding in **5** possibly forms in a competitive fashion because the 2-hydroxyl group can form a hydrogen bond with either the 4-carbonyl group in a 1,3-relation or the 1-carboxylate group in a 1,2-relation. In addition, the C2 atom becomes a chiral center, and the moieties of **3a** and **3b** are not identical any more. The *pro-S* hydrogen attached to the C2 atom is replaced by a carboxylate group. Thus, conformations of **5** with the **3b** moiety have the arrangement in which both 1-carboxylate and 4-carbonyl groups stay in a relatively close distance to the 2-hydroxyl group. On the other hand, conformations with a **3a** moiety are extended, and the 1-carboxylate group resides on the opposite side of the 4-carbonyl group. Thus, in these conformations, intramolecular hydrogen bonding of 2-hydroxyl group should be formed by choosing one of these acceptors.

We have surveyed the CES by rotating the 2-hydroxyl group with both **3a** and **3b** moieties. In addition, the two possible orientations of the 1-carboxylate group led us to investigate four different potential curves. The potential curves and numerous stable conformations in these potential curves are shown in Figure 4. As shown in Figure 4, two exceptionally stable conformations, **5a** and **5b**, are observed from the potential curves at conformations with the **3a** moiety. These conformations are more than 2 kcal/mol stable, when compared with those with the **3b** moiety. We believe that this additional stability

Table 1. Relative Energies (ΔE(0 K), in kcal mol^{-1}) and Relative Free Energies (ΔG(298 K), in kcal mol^{-1}) for the Conformers of 1 Both in the Gas Phase and in Solutions Calculated at the MP2/6-31G* Level

	gas phase		solution with $\epsilon = 2.0$		solution with $\epsilon = 78.0$	
	ΔE(0 K)	ΔG (298 K)[a]	ΔE(0 K)[b]	ΔG (298 K)[c]	ΔE(0 K)[b]	ΔG (298 K)[c]
1a	0.00[d]	0.00	0.00[e]	0.00	0.00[f]	0.00
1b	0.86	0.95	0.79	0.88	0.68	0.77
1c	2.02	1.10	1.79	0.87	1.38	0.46
1d	0.36	1.19	0.57	1.40	0.93	1.76
1e	0.00	1.26	0.22	1.49	0.59	1.85
1f	1.64	1.36	0.97	0.68	−0.23	−0.52
1g	1.15	1.52	1.02	1.39	0.79	1.16
1h	2.67	2.05	2.72	2.10	2.81	2.19
1i	3.37	2.78	3.59	3.00	3.95	3.36
1j	3.17	2.66	2.90	2.39	2.41	1.90
1k	2.77	3.33	2.80	3.36	2.84	3.40
1l	3.62	3.34	3.47	3.20	3.22	2.95

[a] Includes corrections for ZPVE, TVE, and entropy. ZPVEs and TVEs are corrected with a scaling factor of 0.94. Calculated ZPVE/TVE (both scaled, in kcal mol^{-1})/entropies (in cal mol^{-1} K^{-1}) are 107.78/113.94/109.96 (**1a**), 107.79/113.92/109.69 (**1b**), 107.59/113.92/112.36 (**1c**), 108.08/114.12/108.80 (**1d**), 108.15/114.07/107.44 (**1e**), 107.69/113.82/111.23 (**1f**), 108.10/114.11/110.39 (**1g**), 107.67/113.93/111.68 (**1h**), 107.86/114.02/112.48 (**1i**), 107.64/113.92/111.20 (**1j**), 108.00/114.06/109.22 (**1k**), and 107.79/113.96/110.99 (**1l**). [b] Radii of cavity sizes (in Å) are 4.49 (**1a**), 4.63 (**1b**), 4.33 (**1c**), 4.60 (**1d**), 4.37 (**1e**), 4.28 (**1f**), 4.32 (**1g**), 4.50 (**1h**), 4.55 (**1i**), 4.34 (**1j**), 4.56 (**1k**), and 4.34 (**1l**). [c] Thermal corrections performed at the gas phase are used. [d] Absolute energy is −589.1634831 hartree. [e] Absolute energy is −589.1652463 hartree. [f] Absolute energy is −589.1658966 hartree.

appears to be attributed to favorable contributions of two intramolecular hydrogen bondings.

Conformational Preference of 1. We have built numerous conformations of **1** by hooking up stable conformations of molecular fragments, bearing all the consequences of model compounds in mind. Although we have assembled 23 conformations, eight of them have ended up as the same conformations as others during the geometry optimization. We have found 12 conformations whose relative energies are less than 4.0 kcal/mol. By performing vibrational frequency calculations, we have fully confirmed that all these conformers are true minima in the CES. At the same time, frequency calculations also allow us to compute the free energy differences at 298 K, which are more realistic values compared with the experimental ones rather than the energy differences at 0 K. The ΔG(298 K) as well as the ΔE(0 K) values of the 12 conformers of **1** are summarized in Table 1. As shown in Table 1, the effects of ZPVE and TVE corrections are relatively small, but the effect of entropy correction appears to be somewhat large. Among some changes in the figures, notable are the large increase in **1d** and **1e** and the substantial decrease in **1c**. However, **1a** remains as the global minimum after thermal corrections.

The 12 conformations are illustrated in Figure 5 along with their ΔG(298 K) values. Although we fully understand that our conformational search in **1** is quite limited, the extensive conformational search of **1** by rotating six rotatable bonds is extremely expensive with the level of theories employed in this study. We feel confident that we have surveyed stable conformations with an efficient manner. In particular, the 12 stable conformations we searched in this study appear to be compatible with the conformational analyses of the molecular fragments. All of them have rigid structures by bearing more than two intramolecular hydrogen bondings. This also supports the idea that we may have most of the stable conformations of **1**, since there are only a limited number of possibilities to construct more than two hydrogen bondings out of a few hydrogen-bonding donors and acceptors. In addition, we also have found that a large number of initial geometries are also converted to the conformations illustrated in Figure 5, as mentioned previously.

Although CES of **1** becomes a little complex by adding an amino group, the fundamental conformational nature of **1** in the gas phase remains the same as that of **5**. Conformational preferences of **1** in the gas phase also appear to be governed by the arrangements and strength of intramolecular hydrogen bondings. In all 12 conformations, the 2-hydroxyl group can form intramolecular hydrogen bondings with the O atom of the 4-carbonyl group in a 1,3-fashion and/or with the O atoms of 1-carboxylic acid in a 1,2-fashion. As shown in **5**, these two hydrogen bondings, the strength of which is nearly the same, probably compete with one another. This relationship appears to remain in some conformations of **1**. Conformations **1c**,**i**,**l** have a hydrogen bond between the 2-hydroxyl group and the 4-carbonyl group in a 1,3-fashion, while **1c**,**h**,**j**,**k** have a hydrogen bond between the 2-hydroxyl group and the 1-carboxylate group in a 1,2-fashion. As can be seen in their relative free energy values, the stability is nearly the same, except in **1c**, where some favorable, but small, interactions may supplement its additional stability. A large group of much more stable conformations, that is, **1a**,**b**,**d**−**g**, have the molecular arrangement where these two intramolecular hydrogen bondings are maintained simultaneously. These conformations have basically the same molecular arrangement, but with only a small change. For instance, **1a** and **1b** are almost identical, except for a slight torsional change in the 2-hydroxyl group. **1b** and **1d** also have a similar nature, but a different orientation in 1-carboxylate group. Another group of conformations, **1e**, **1f**, and **1g**, have the same molecular arrangement with **1a**, **1b**, and **1d**, respectively, except for a different conformation in the amino group. The stability of these conformations is, of course, higher than those with only one hydrogen bond. When we apply the Boltzmann distribution by using free energy values of these conformations at 297 K, the portion of conformational populations in these conformations is estimated to be more than 88%, which implies that these conformers are absolutely major in the CES of **1** in the gas phase.

Since the orientation of the 2-hydroxyl group appears to be important in the skeleton of **1**, we have further surveyed the CES by rotating the C3−C2−O−H torsion angle. This survey enables us (1) to find additional stable conformations, if any, and (2) to understand the conformational nature of **1** in this stable skeleton. The resultant curves are summarized in Figure 6. We have obtained two conformational energy curves due to a different orientation of the 1-carboxylate group. According to these curves, we feel confident that **1a**,**b**,**d** are all the possible minima within this motion. In addition, it would be of interest to find that the CES is quite flat due to the orientation of C3−C2−O−H torsional angle. Especially, when the carbonyl O atom in 1-carboxylic acid is close to the 2-hydroxyl group, relative energies remain less than 2 kcal/mol even at a substantial deformation of the C3−C2−O−H torsion angle from −180° to −40°. Furthermore, we can find that the energy barrier between

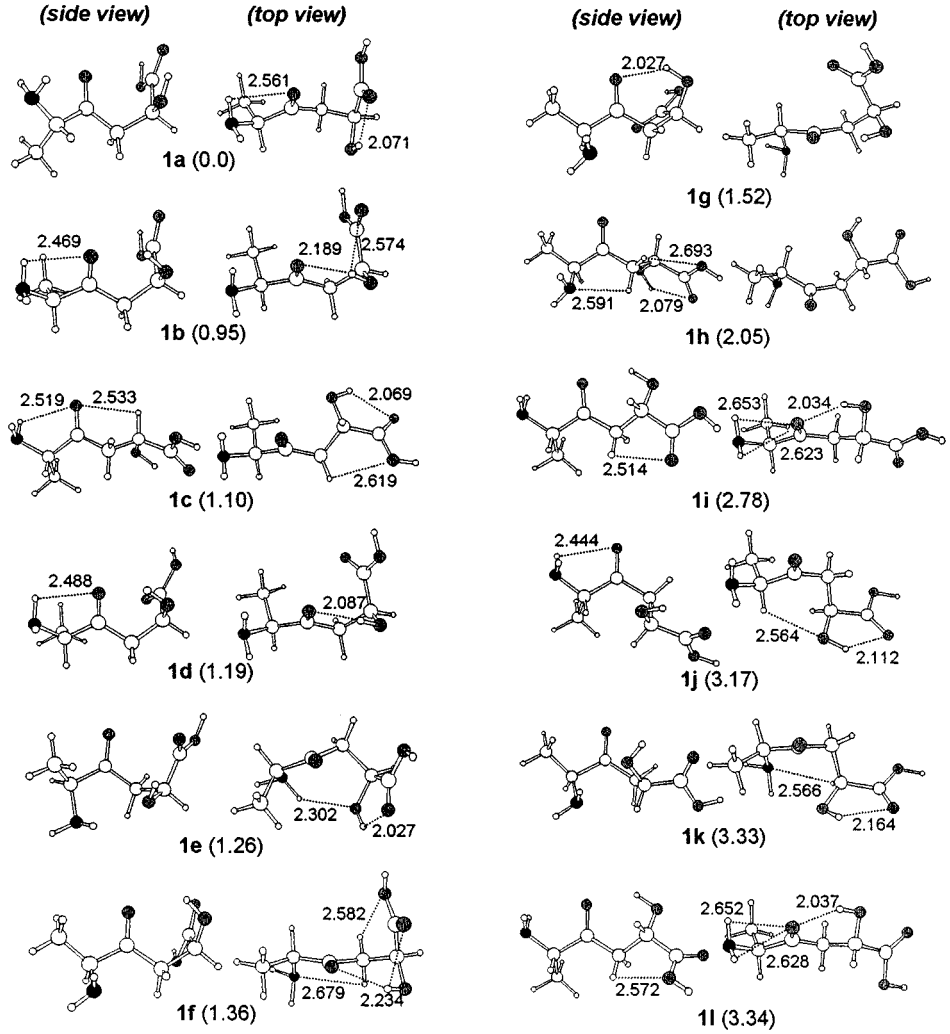

Figure 5. Side and top views of 12 stable conformations of **1** at the MP2/6-31G* level. Values in parentheses are relative free energies (in kcal/mol) at 298 K calculated in the gas phase.

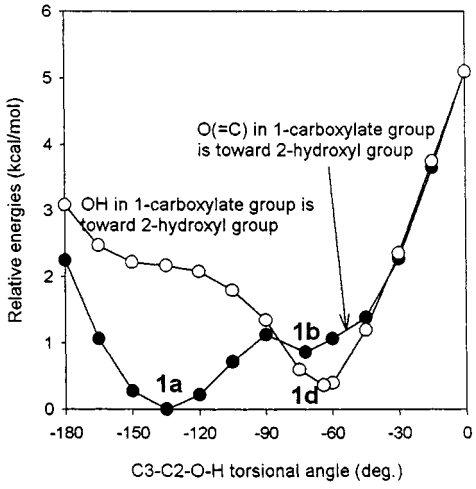

Figure 6. Conformational energy changes of **1** due to the rotation of the 2-OH group when both the O atom of 4-carbonyl group and the O atoms in 1-carboxylic acid are aligned to form hydrogen bonds with the 2-OH group.

1a and **1b** is extremely tiny. This extremely flat energy surface may also contribute further to the increase of population of these conformations owing to an entropic effect.[12] On the other hand, the energy minimum, i.e., **1d**, is quite distinctive when the hydroxyl O atom in 1-carboxylic acid is close to the 2-hydroxyl group. Of course, we believe that the same analysis can be applied to **1e**−**g**.

Our calculations have further displayed the solvent effect by performing SCRF calculations. These results are also summarized in Table 1. We carried out calculations at two significantly different solvent media; one is nonpolar solvent and the other is highly polar aqueous medium. One of the notable changes in relative energies in solutions is a significant stabilization of **1f**, of which the stability exceeds that of **1a** in aqueous media. Additionally, **1c** also becomes quite stable in solutions, and the relative energies of **1c** is only about 0.5 kcal/mol higher than the one of **1a**. Except for these changes, the basic feature of major conformations in solvents appears to be similar with that in the gas phase. If populations of conformers are calculated with the ΔG(298 K) values and the Boltzmann distribution, the total populations of the **1a**,**b**,**d**−**g** conformers are still absolutely major in various solvents, e.g., 86.2% at the solvents with $\epsilon = 2$ and 87.9% at the aqueous medium. Thus, we believe that

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the majority of **1** stays in the conformations where two strong intramolecular hydrogen bonds are retained.

Conclusions

The conformation of **1** appears to be determined mainly by the arrangements and strength of intramolecular hydrogen bondings. In the gas phase, three conformers with much lower energies are observed in the region where two strong intramolecular hydrogen bondings are maintained at the same time. The conformational energy surface in this region is significantly lower than other areas and quite flat according to the orientational change of the 2-hydroxyl group. Thus, an entropic effect as well as favorable enthalpy is responsible for the fact that most of the conformers stay in the major conformations. By correcting the thermochemical properties and incorporating the solvent effects, we have found that major portions of conformers of **1** in the gas phase are retained in a molecular skeleton in which 2-hydroxyl groups can form intramolecular hydrogen bonds with both the 1-carboxylate group and the 4-carbonyl group simultaneously. This result in vacuo appears to be valid in various solutions including the highly polar aqueous medium. We believe that these conformers may play an important role in the interaction of α-hydroxy ketomethylene dipeptide isostere analogues with enzyme.

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