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Restricted Internal Rotation of Amino Acid Esters. Quantitative Evaluation of Rigidity of a Molecule in terms of Internal Rotation Entropy

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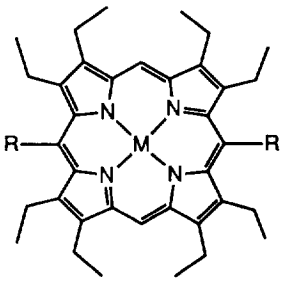
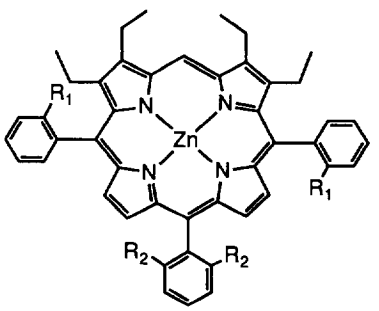
Abstract: As a model of molecular recognition of a flexible guest through multi-point recognition, the two-point fixation of the NH_2 group and the C=O group of amino acid esters to porphyrin host was investigated from thermodynamic point of view. The negative entropy change owing to restriction of internal rotation around the C_α–C(carbonyl) bond of guest as driven by the two-point fixation was calculated from the following steps: (1) *ab initio* molecular orbital calculations at the 3-21G level to generate a potential energy surface for internal rotation along the C_α–C(carbonyl) bond and the C_α–C_β bond, and (2) a calculation of partition function of the system based on classical statistical mechanics. The entropy loss due to the restriction of a rotation around the C_α–C(carbonyl) bond was 5.0 cal•K^{-1}•mol^{-1} for alanine methyl ester and 1.9 cal•K^{-1}•mol^{-1} for valine methyl ester, indicating that valine methyl ester is more rigid with respect to the C_α–C(carbonyl) rotation. This entropy loss was found to originate from the correlated rotation of the C_α–C(carbonyl) bond and the C_α–C_β bond.

INTRODUCTION

Molecular recognition is the subject of many current investigations on biofunction-related fields of chemistry. The concept of multiple recognition and preorganization of recognition groups helps in designing a good host–guest system.[1] However these views are based on the enthalpy change associated with host–guest association. Another counterpart, the entropy term, should also play an important role in molecular recognition.[2] The contribution of entropy to molecular recognition can be classified into three terms: (1) the entropy change associated with the changes in solvation upon host–guest complexation,[3] (2) the entropy change of translational and rotational motion of host and guest, and (3) the entropy change associated with changes in the motional freedom of internal rotation and vibration (intramolecular nuclear displacement). A non-linear molecule consisting of N atoms has $3N$–6 degrees of internal motional freedom. The number of motional freedom increases rapidly as the number of atoms consisting the molecule increases, that is high molecular weight compounds have many internal motional degrees. Therefore, for a large molecule, contributions of internal motional entropy to thermodynamics of molecular recognition can be quite important. In the present paper, theoretical calculations of the changes in internal rotational entropy upon molecular recognition and the contribution of the entropic term to the free energy change of recognition processes are described.

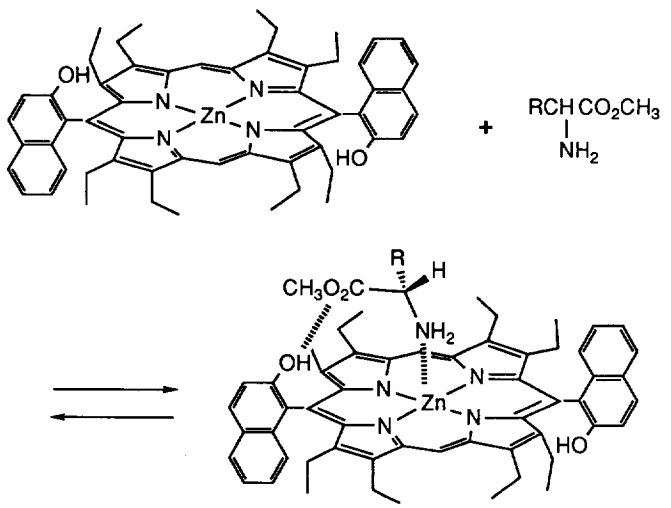




	R_1	R_2
3	OH	CH_2COOCH_3
4	H	CH_2COOCH_3
5	H	H

In the previous study we reported the binding of amino acid esters by functionalized porphyrin hosts **1–5**.[4] Hosts **1** and **3** have both the coordination site (the Zn ion) and the hydrogen bonding site (the OH group) and can bind amino acid esters by fixing two-points (the NH_2 group and the C=O group), while hosts **2**, **4**, and **5** have only the coordination site and bind amino acid esters by fixing one point (the NH_2 group). The two-point fixation by hosts **1** and **3** was confirmed by circular dichroism studies, ^1H NMR studies and thermodynamic studies (see Scheme 1). This binding mode leads to the restriction of the internal rotation along the C_α–C(carbonyl) bond and the restriction may affect the rotation along the C_α–C_β bond.[4a] The binding becomes stronger as the side chain group of amino acid ester becomes bulkier (Table 1).[4] For example, the binding constant of valine methyl ester by host **1** was 8100 M^{-1} while that of alanine methyl ester was 2200 M^{-1} in chloroform at 25°C. Similar tendency was also observed for host **3**.[4b] The main issue we focus on is why the bulkier amino acid esters are bound more strongly than the less bulky ones.

Scheme 1.



There seems to be two explanations for this preference for bulky guest: (1) the larger stabilization due to the difference in van der Waals attraction between host and guest and host/guest and solvent for the bulkier guest than the less bulky one, and (2) the difference in the intrinsic motional entropy of a guest molecule between bulky amino acid ester and

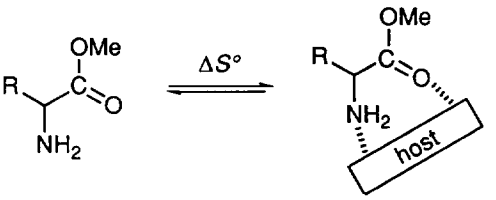
Table 1. Association Constants for the Binding of Amino Acid Esters to Porphyrin Hosts **1–5** (M^{-1}) in $CHCl_3$ [4]

	1	2	3	4	5
L-Gly–OMe	3500	920			
L-Ala–OMe	2200	330	1590	720	740
L-Val–OMe	8100	350	6130	650	1240
L-Leu–OMe	10900	270	6160	680	1130

less bulky one. As shown in Table 1, the binding constant for one-point recognition hosts **2**, **4**, and **5** showed different trends. These hosts **2** and **4** did not exhibit a preference for bulky guests, and host **5** exhibited a weak preference for the bulky guest. Therefore these results suggest that the preference for bulky guest found for hosts **1** and **3** may be caused by two-point fixation of the guest through concurrent coordination and hydrogen bonding interactions. These considerations lead us to investigate the contribution of the conformational change of the guest to the overall thermodynamics of the recognition. We focus on the entropy change originating from the conformational change of the guest in the present study. In order to evaluate the entropy changes of conformational origin, we developed the calculation procedure of the internal rotational entropy of amino acid esters, and examined whether this term may make important contributions to the free energy change of molecular recognition.

THEORETICAL BACKGROUND

We consider the entropy change of the following equilibrium. Upon molecular association, motional freedom of translation, rotation, and internal rotation of host and guest would be affected to a large extent. The entropy change of host–guest complexation equilibrium (ΔS_{total}) is given by

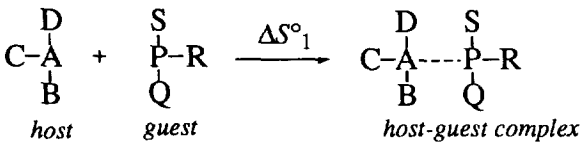


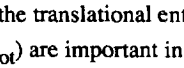
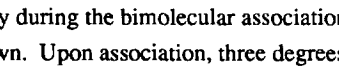
$$\Delta S_{total} = \sum_{complex} S_{trans} + S_{rot} + S_{int.rot} + S_{vib} + S_{electronic} + S_{solvation} - \sum_{host} S_{trans} + S_{rot} + S_{int.rot} + S_{vib} + S_{electronic} + S_{solvation} - \sum_{guest} S_{trans} + S_{rot} + S_{int.rot} + S_{vib} + S_{electronic} + S_{solvation} = \Delta S_{trans} + \Delta S_{rot} + \Delta S_{int.rot} + \Delta S_{vib} + \Delta S_{electronic} + \Delta S_{solvation}$$

If the host is rigid, the entropy of host can be considered as unchanged. Under these conditions,

$$\Delta S_{total} = \sum_{guest\ in\ complex} S_{trans} + S_{rot} + S_{int.rot} + S_{vib} + S_{electronic} + S_{solvation} - \sum_{guest} S_{trans} + S_{rot} + S_{int.rot} + S_{vib} + S_{electronic} + S_{solvation}$$

Table 2. Motional Changes upon Bimolecular Association [a]



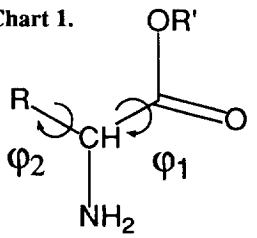
Motional Change		Change in Motional Freedom	ΔS
translation	PQRS	–3	–30 eu
rotation	PQRS	–3	–30 eu
vibration	A---P	+1	~0 eu
vibration		+2	~0 eu
internal rotation		+3	5~10 × 3 eu

[a] Only changes in motional freedom of guest are indicated.

Among these entropy terms, the translational entropy (ΔS_{trans}), the rotational entropy (ΔS_{rot}), and the internal rotational entropy ($\Delta S_{int.rot}$) are important in molecular recognition in non-polar media. Table 2 shows the interconversion of entropy during the bimolecular association. In Table 2, only changes in motional freedom of the guest are shown. Upon association, three degrees of translational and three degrees of rotational motion of guest are converted to three degrees of vibration and three degrees of internal rotation. Among these entropy terms internal rotational entropy ($\Delta S_{int.rot}$) is the most sensitive to molecular structure. If selectivity or specificity of molecular recognition is concerned, internal rotational entropy may play an important role. Thus we discuss the internal rotational entropy in detail. Because porphyrin hosts **1–5** are relatively rigid molecules, changes in motional freedom of internal rotational motion of host will be minimal and ignored in the present treatment. We also assumed that the vibrational motion and electronic motion change little upon complexation and ignored the change in the vibrational entropy (ΔS_{vib}) and electronic entropy ($\Delta S_{electronic}$) of host and guest.

The internal rotational entropy was calculated from the following steps: (1) calculation of potential energy surface for the guest, (2) calculation of the partition function of the guest, and (3) calculation of the entropy from the partition function. Following treatment can be applied to evaluate entropy changes owing to changes of internal rotations of a molecule in general. The potential energy (electronic and nuclear) U of a molecule can be calculated as a function of internal coordinates of a molecule. We focused on the dependence of the potential energy U on the dihedral angle φ.[5] The potential energy U was calculated as a function of two dihedral angles φ_1 and φ_2 (Chart 1) by molecular orbital calculations. Owing to practical reasons, the energy U can be calculated as a function of discrete values of φ_1 and φ_2. Then a finite Fourier-

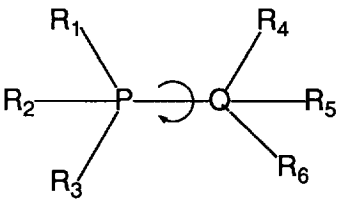
Chart 1.



series expansion gives the energy U as a function of continuous values of φ_1 and φ_2. Once the energy U is obtained as a function of φ_1 and φ_2, we can calculate the partition function on the basis of classical statistical mechanics. By use of this partition function, entropy associated with the motional freedom of internal rotation can be calculated. These procedures are shown below.

For a rotation around a bond P–Q (Chart 2), kinetic energy can be calculated if the moments of inertia are known. Let the moment of inertia of substituents on P around P–Q axis be I_{ai} and that of substituents on Q be I_{bi}. The kinetic energy of rotation of a molecule as a whole is related to rotational entropy (S_{rot}), not internal rotational entropy ($S_{int.rot}$), so that kind of motion is not included in the present treatment. Accordingly, we give a restriction that the total angular momentum around the P–Q axis is zero. The relative angular motion of substituents on P to those on Q is taken as a generalized coordinate and denoted as φ_i. Then the kinetic energy associated with the rotation is given by

Chart 2.



$$T = \sum_{i=1}^{n} \frac{1}{2} \frac{I_{ai} I_{bi}}{I_{ai} + I_{bi}} \varphi_i^2 \qquad (1)$$

Because the Lagrangian function of the molecule in terms of the internal rotational freedom is

$$L = \sum_{i=1}^{n} \frac{1}{2} \frac{I_{ai} I_{bi}}{I_{ai} + I_{bi}} \varphi_i^2 - U(\varphi_1, \varphi_2, \cdots \varphi_n), \qquad (2)$$

the associated conjugate momentum p_i is written as

$$p_i = \frac{\partial L}{\partial \varphi_i} = \frac{I_{ai} I_{bi}}{I_{ai} + I_{bi}} \varphi_i \,. \qquad (3)$$

The Hamiltonian is thus:

$$H = \sum_{i=1}^{n} \frac{1}{2} \frac{I_{ai} + I_{bi}}{I_{ai} I_{bi}} p_i^2 + U(\varphi_1, \varphi_2, \cdots \varphi_n). \qquad (4)$$

The molecular partition function q is then given by

$$q = \frac{1}{h^n}\int_0^{2\pi} e^{-U(\varphi_1, \varphi_2, \cdots \varphi_n)/kT} d\varphi_1 d\varphi_2 \cdots d\varphi_n \int_{-\infty}^{+\infty} exp(-(\sum_{i=1}^{n} \frac{I_{ai} + I_{bi}}{I_{ai} I_{bi}} p_i^2)/2kT) dp_1 dp_2 \cdots dp_n \tag{5}$$

$$= (\sqrt{\frac{2\pi kT}{h^2}})^n \prod_{i=1}^{n} \left(\sqrt{\frac{I_{ai} I_{bi}}{I_{ai} + I_{bi}}}\right) \int_0^{2\pi} e^{-U(\varphi_1, \varphi_2, \cdots \varphi_n)/kT} d\varphi_1 d\varphi_2 \cdots d\varphi_n.$$

where h is the Planck's constant and k is the Boltzmann constant.

In a system consisting of N molecules, the partition function Q is given by

$$Q = \frac{1}{N!} q^N. \tag{6}$$

The contribution from internal rotation of n degrees of freedom to entropy can be calculated from Q:

$$S = Nk \left[1 + \frac{\int_0^{2\pi} \frac{U}{kT} e^{-U/kT} \, d\varphi_1 \, d\varphi_2 \cdots d\varphi_n}{\int_0^{2\pi} e^{-U/kT} \, d\varphi_1 \, d\varphi_2 \cdots d\varphi_n} + \right. \tag{7}$$

$$\left. ln \left\{ \frac{(2\pi kT)^{n/2}}{h^n} \prod_{i=1}^{n} \sqrt{\frac{I_{ai} \, I_{bi}}{(I_{ai} + I_{bi})}} \int_0^{2\pi} e^{-U/kT} \, d\varphi_1 \, d\varphi_2 \cdots d\varphi_n \right\} \right] .$$

The two integrals of the above equation were evaluated numerically by use of U expressed in a finite Fourier series.

RESULTS

Calculation of the Entropy of Alanine Methyl Ester and Valine Methyl Ester Associated with Two Degrees of Internal Rotation.

The entropy of alanine methyl ester and valine methyl ester associated with the two degrees of internal rotation was calculated. We considered the rotation around the Cα–C(carbonyl) bond and the Cα–Cβ bond. The dihedral angle for the former bond is φ_1 and that for the latter bond is φ_2 (Chart 1). The electronic energy $U(\varphi_1, \varphi_2)$ was calculated for the 144 pairs of φ_1 and φ_2 at φ_1 and φ_2 intervals of 30° by an *ab initio* molecular orbital calculation at the 3–21G level.[6–7] The geometry was fully optimized except for the two dihedral angles φ_1 and φ_2. The results for alanine methyl ester and valine methyl ester are summarized in Tables 3 and 4. The total potential energy for a nuclear geometry with fixed φ_1 and φ_2 was then obtained

Table 3. Conformational Energy (kcal•mol^{-1}) of Valine Methyl Ester Calculated at the 3–21G Level as a Function of Dihedral Angles φ_1 and φ_2 (deg) [a]

$\varphi_1 \backslash \varphi_2$	0	30	60	90	120	150	180	210	240	270	300	330
0	5.49	3.03	0.00	3.43	9.22	8.68	4.02	2.39	6.31	6.82	3.91	3.36
30	8.14	5.71	2.07	6.98	15.3	14.2	6.99	4.68	11.4	12.5	6.72	4.83
60	10.7	7.70	5.50	13.1	18.8	14.5	6.76	9.88	16.7	13.6	5.27	6.6
90	9.61	6.75	6.81	12.0	14.3	8.87	6.13	10.3	13.7	7.93	2.94	6.3
120	7.93	5.23	4.24	7.76	9.79	6.13	4.33	6.73	8.93	5.16	1.88	4.48
150	7.87	4.73	2.06	5.43	8.84	6.77	2.90	3.90	7.05	5.75	2.38	3.82
180	7.57	4.89	1.87	5.44	11.0	9.99	4.63	3.61	8.29	8.46	4.31	4.24
210	7.20	4.72	1.82	6.32	13.4	11.8	4.75	4.03	10.4	10.4	4.24	3.94
240	7.47	5.14	2.70	8.32	14.1	10.5	3.46	6.06	11.9	8.99	2.60	4.14
270	8.77	6.19	4.28	9.73	13.5	8.83	4.23	7.91	12.1	7.69	2.61	5.30
300	8.77	6.18	3.89	8.49	11.3	7.29	4.11	6.96	10.1	6.55	2.88	5.47
330	6.49	3.52	0.73	4.77	7.79	5.49	2.05	3.33	6.21	4.40	1.76	3.34

[a] The total energy of the reference ($\varphi_1 = 0°$, $\varphi_2 = 60°$) is –273928.91 kcal•mol^{-1}

from the above values by a Fourier series expansion of the form

$$U(\varphi_1, \varphi_2) = \frac{a_{00}}{2} + \sum_{m,n}^{\infty} \{a_{mn} \cos(m\varphi_1 + n\varphi_2) + b_{mn} \sin(m\varphi_1 + n\varphi_2)\} \quad (8)$$

where a_{mn} and b_{mn} are given by

$$a_{mn} = \frac{(\Delta\varphi)^2}{2\pi^2} \sum_{i,j} U(\varphi_i, \varphi_j) \cos(m\varphi_i + n\varphi_j) \quad (9)$$

Table 4. Conformational Energy (kcal•mol^{-1}) of Alanine Methyl Ester Calculated at the 3–21G Level as a Function of Dihedral Angles φ_1 and φ_2 (deg) [a]

φ_1\φ_2	0	30	60	90	120	150	180	210	240	270	300	330
0	4.03	2.08	0.00	1.78	4.02	2.17	0.00	1.86	4.03	2.18	0.01	1.77
30	5.61	3.93	1.90	3.19	5.58	3.97	1.70	3.31	5.59	4.04	1.72	3.27
60	7.87	6.23	3.90	5.46	7.85	6.19	3.88	5.55	7.84	6.31	3.89	5.57
90	7.30	5.64	3.44	5.01	7.30	5.58	3.43	5.03	7.29	5.66	3.43	5.06
120	6.06	4.37	2.04	3.65	6.06	4.37	2.04	3.64	6.05	4.39	2.04	3.64
150	6.30	4.37	1.97	3.71	6.29	4.43	1.97	3.73	6.29	4.40	1.98	3.66
180	5.97	4.35	1.88	3.79	5.96	4.00	1.88	3.88	5.96	4.01	1.89	3.8
210	4.80	3.91	1.47	2.96	4.79	3.18	1.47	3.06	4.79	3.25	1.47	3.04
240	4.71	3.53	1.71	2.85	4.69	3.48	1.70	2.93	4.69	3.58	1.71	2.94
270	6.14	4.99	2.76	3.82	6.14	4.94	2.73	3.87	6.12	5.03	2.75	3.88
300	7.14	5.59	3.04	4.53	7.14	5.58	3.03	4.54	7.12	5.62	3.04	4.53
330	5.33	3.23	1.02	2.92	5.32	3.32	1.02	2.94	5.33	3.28	1.03	2.86

[a] The total energy of the reference ($\varphi_1 = 0°$, $\varphi_2 = 60°$) is –225207.45 kcal•mol^{-1}

$$b_{mn} = \frac{(\Delta\varphi)^2}{2\pi^2} \sum_{i,j} U(\varphi_i, \varphi_j) \sin(m\varphi_i + n\varphi_j) \qquad (10)$$

The contour map of the conformational energy $U(\varphi_1,\varphi_2)$ was obtained from eq 8 and shown in Figure 1. The contour lines are drawn at 2 kcal•mol^{-1} intervals. As can be seen from Figure 1, the two conformation energy surfaces are quite different with each other: valine methyl ester has deeper potential surface than alanine methyl ester.

The moment of inertia was calculated for the most stable conformer ($\varphi_1 = -11.25°$, $\varphi_2 = 55.94°$). The calculated entropy ($S_{\text{int.rot}}$ (φ_1, φ_2)) from eq 7 at 25 °C was 9.2 cal•K^{-1}•mol^{-1} for alanine methyl ester and 7.0 cal•K^{-1}•mol^{-1} for valine methyl ester (Table 5). This difference in entropy reflects the fact that alanine methyl ester is more freely changing its molecular shape than valine methyl ester is. Therefore these values of entropy can be used as a measure of rigidity of the molecule.

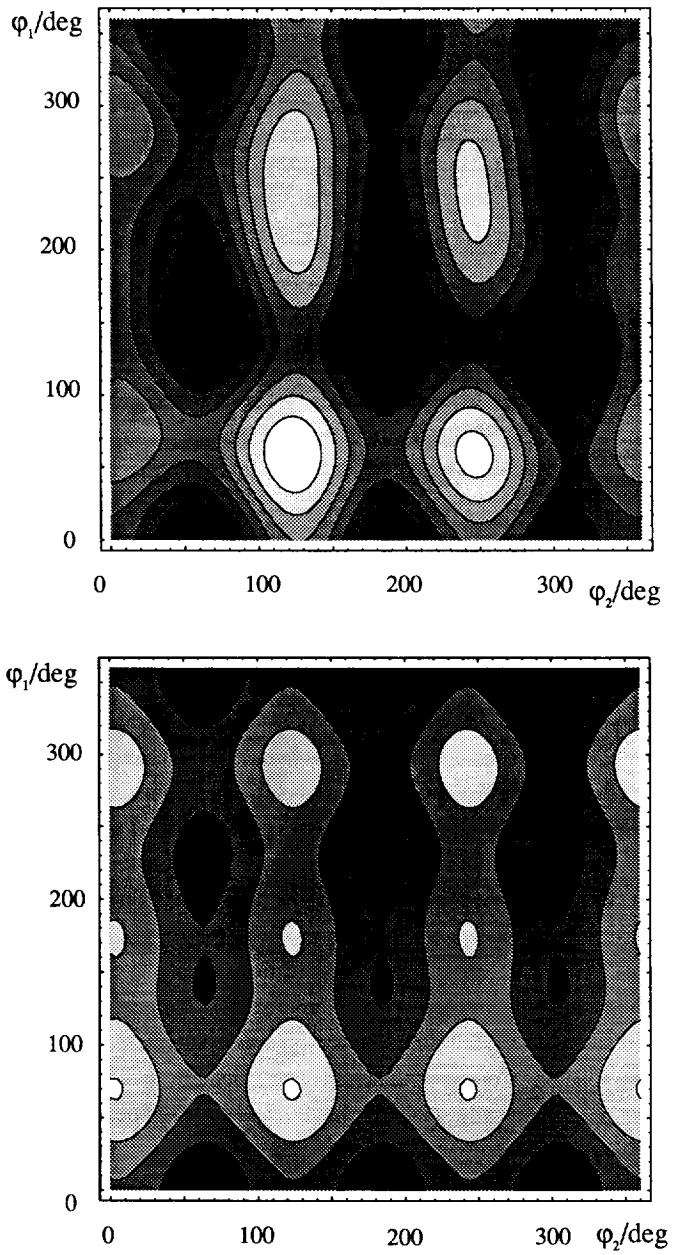


Figure 1. The contour map of the potential energy $U(\varphi_1,\varphi_2)$ of valine methyl ester (top) and alanine methyl ester (bottom) as a function of dihedral angles φ_1 and φ_2. The potential energy was calculated from eq 8. The contour lines are drawn at 2 kcal•mol^{-1} intervals. The black region is the stable conformer.

Calculation of the Entropy of Alanine Methyl Ester and Valine Methyl Ester Associated with One Degree of Internal Rotation. The entropy of internal rotation associated with the internal rotation along the C_α–C_β bond (φ_2) was similarly calculated. Semi-empirical molecular orbital calculations by the PM3 method indicated that φ_1 is −14° in the most stable conformation of the complex between host **1** and leucine methyl ester.[8] The dihedral angle φ_1 was fixed to be −14°. The calculated entropy at 25 °C was 4.2 cal•K^{-1}•mol^{-1} for alanine methyl ester and 5.1 cal•K^{-1}•mol^{-1} for valine methyl ester (Table 5). From the difference between the entropy with φ_1 and φ_2 rotating (Sint.rot (φ_1, φ_2)) and that with only φ_2 rotating (Sint.rot (φ_2)), we can estimate the entropy loss upon the fixation of the dihedral angle φ_1 to −14°. The entropy loss for φ_1 fixation is 5.0 cal•K^{-1}•mol^{-1} for alanine methyl ester and 1.9 cal•K^{-1}•mol^{-1} for valine methyl ester. Therefore the entropy loss upon constraint of internal rotation (φ_1) imposed by, for example, two point fixation of amino acid ester by host **1** is less for valine methyl ester than alanine methyl ester. This reflects the rigidity of valine methyl ester compared with alanine methyl ester.

The entropy loss for φ_1 fixation can also be calculated by using the potential energy U as a function of only one dihedral angle φ_1. How-

Table 5. Internal Rotational Entropy (cal•K^{-1}•mol^{-1}) for Alanine Methyl Ester and Valine Methyl Ester at 25°C

	$S_{int.rot}(\varphi_1, \varphi_2)^a$	$S_{int.rot}(\varphi_2)^b$
alanine methyl ester	9.2	4.2
valine methyl ester	7.0	5.1

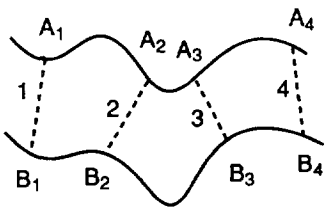
ever, the potential curves obtained as a function of φ_1 were very similar in shape between alanine methyl ester and valine methyl ester. Therefore there was almost no difference in internal rotational entropy between alanine methyl ester and valine methyl ester when the entropy was calculated from $U(\varphi_1)$. Therefore this result suggests that the difference in the internal rotational entropy between alanine methyl ester and valine methyl ester is ascribed to the correlated rotation around the C_α–C(carbonyl) bond and the C_α–C_β bond.

DISCUSSION

Molecular recognition is caused by a set of attractive interactions such as hydrogen bonding, coordination interaction, hydrophobic interaction and so on. Large enthalpy gain (negative enthalpy change in the system) is then compensated for by entropy loss (negative entropy change of the system). The entropy loss is associated with changes in motion upon association. The largest entropy loss is caused by the changes in translational degree of motion. For example, the changes of translational entropy associated with six degrees of motion of host and guest into translational and vibrational entropy (three degrees of translational and three degree of vibrational motion) for the association depicted in Scheme 1 is calculated to be 34.6 cal•K^{-1}•mol^{-1}.[9] This entropy loss is primarily compensated for by the coordination interaction between the zinc ion of the host and the amino group of the guest, and concurrent stripping of solvent molecules from the zinc ion and the amino group. Entropy associated with rotational motion (ΔS_{rot}) also makes an important contribution to the energetics of molecular association. Compared to these entropy changes, an entropy change associated with *internal* rotation ($\Delta S_{int.rot}$) is generally small. However, the number of degrees of internal rotation increases as the molecular weight of the host and guest increases. Also as the number of recognition groups increases, the enthalpy gain of the interaction of the *i*th recognition group is used mainly to restrict internal motion as schematically depicted in Figure 2. It is anticipated that the contribution from the internal rotations is important for flexible molecules. Therefore the internal rotational entropy should become important for molecular recognition by a large molecule, especially by biopolymers.

Quantum-mechanical calculation of the conformational energy as a function of φ_1 and φ_2 listed in Tables 3 and 4 indicates that potential energy barrier is higher for valine methyl ester than alanine methyl ester. The minimum potential energy occurred always at φ_2 of 180° irrespective of the values of φ_1 for alanine methyl ester whilst it occurred at either φ_2 of 60° or 300° depending on the value of φ_1 for valine

Figure 2. Free energy changes in multi-point host–guest complexation.



$$\Delta G_1 = \Delta H_1 - T(S_{trans} - S_{vib})$$
$$\Delta G_2 = \Delta H_2 - T(S_{rot} - S_{vib})$$
$$\vdots$$
$$\begin{cases} \Delta G_i = \Delta H_i - T(S_{int.rot} - S_{vib}) \\ or \\ \Delta G_i \approx \Delta H_i \end{cases} \quad (i \geq 3)$$

methyl ester. This indicates that if conformational energy calculation was carried out with φ_1 fixed and all the other internal coordinates optimized, then the potential energy surface is discontinuous in terms of φ_2 coordinate for valine methyl ester. This result demonstrates that the rotation around the Cα–C(carbonyl) axis and that around the Cα–Cβ axis are strongly correlated in the case of valine methyl ester. The classical statistical mechanical calculations of the entropy associated with internal rotation of valine methyl ester and alanine methyl ester indicate that the entropy loss upon constraint of internal rotation around the Cα–C(carbonyl) bond is smaller for valine methyl ester than alanine methyl ester. This is in agreement with experiment where valine methyl ester is bound more strongly to porphyrin hosts **1** and **3** than alanine methyl ester. The free energy difference ($\Delta\Delta G = -T(\Delta S_{Ala} - \Delta S_{Val})$) between valine methyl ester and alanine methyl ester due to the internal rotational entropy is then 0.9 kcal•mol^{-1}, which can account for 4 to 5 times difference in the association constant.

It should be noted that the internal rotational entropy is sensitive to the changes in molecular structures while the translational and rotational entropy is not. In the present example, substitution of two hydrogen atoms of alanine methyl ester by two methyl groups resulted in the entropy change of 3.1 cal•K^{-1}•mol^{-1}, indicating that a relatively small structural change in guest can result in a relatively large change in internal rotational entropy. Therefore precise estimation of the internal rotational entropy is important for the molecular design of a host–guest system. Also, internal rotational entropy may play an important role in a variety of biological functions.

The present calculation not only afforded a quantitative estimate of rigidity of a molecule but also gave a general method to evaluate correlation of two internal rotations. This correlation of internal motion should be important for understanding conformational equilibria and functions of biologically important molecules.

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