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# Rotational Barriers and $^{15}N$ Chemical Shifts of *N*-Acyl-*N*-alkyl-substituted Amino Acids

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**Rotational barriers about the C—N bonds of several *N*-acyl-*N*-methyl-α-amino acids and their esters $R^3CO$—$N(R^4)$—$CR^1R^2$—$COOR^5$, and also *N*-Boc-protected dipeptides, were determined and the steric effects caused by the substituents $R^1$–$R^5$ are discussed by comparing them with the results of MM3 calculations on these amides. Bulky substituents on both the acyl group and the nitrogen atom were shown to have lower $\Delta G^{\ddagger}$. In the series of *N*-acylglycines with variable $R^3$, the $^{15}N$ chemical shifts were correlated with $\Delta G^{\ddagger}$. © 1997 by John Wiley & Sons, Ltd.**

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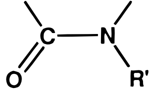
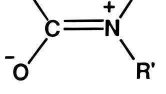
## INTRODUCTION

Since the early days of dynamic NMR (DNMR) spectroscopy, the rotational barriers of amides have been studied most extensively by this method. This is due partly to the fact that the NMR signals of these species show coalescence phenomena at ambient temperatures. Thus, a large collection of $\Delta G^{\ddagger}$ data has been accumulated.[1–10] However, few reports concerning the $\Delta G^{\ddagger}$ of peptides and relevant amides exist. Rotational barriers of *N*-acyl-α-amino acids are interesting in relation to the rigidity of the planar amide group in peptides. However, the amide linkage in peptides generally has the *s-trans* conformation almost exclusively, which prevents the determination of the rotational barriers about the C—N partial double bond.

The relatively high rotational barrier in amides comes from the partial double bond character of the C—N bond due to the mesomeric contribution of the dipolar canonical structure (II).[11] Any substituent effect, either electronic or steric, that disfavors structure II has been shown to cause a lowering of the rotational barrier.

We reported previously the linear relationship between the rotational barrier heights and the $^{15}N$ chemical shifts within a group of amides whose structure is closely related.[12] With the aim of investigating the steric effect on the rotational barriers of peptide derivatives and extending the $\Delta G^{\ddagger}$ *vs.* $\delta^{15}N$ linear relationship to biologically important amides, the rotational barriers of several *N*-acyl-*N*-methyl-α-amino acids and their esters were determined by dynamic NMR experiments and compared with their $^{15}N$ NMR chemical shifts.


(I)


(II)

Changes in relative energies and structures during the process of rotation about the C—N bond of an α-acylamino acid are illustrated schematically in Fig. 1. The trajectory of the intramolecular rotation process can be pursued either by MO or molecular mechanics calculation. A recent report by Wiberg *et al.*[13] showed that a sophisticated *ab initio* calculation gave a rotational barrier height considerably lower than that observed in solutions. We pursued the path by MM3 (92) calculation.[14] In the transition state (TS in Fig. 1), the rotation about the C—N bond is just half way; the acyl and the substituted amino counterparts of the molecule occupy positions nearly perpendicular to each other. In the transition state conformation, the steric congestion is expected to be greatly reduced in comparison with the planar ground states, i.e. *trans* and *cis* conformers (Fig. 1). Since the rotational barrier is observed as the energy difference between the more stable ground-state conformer (usually *trans*) and the nonplanar transition state (TS), steric effects on $\Delta G^{\ddagger}$ should originate from the steric congestion in the more stable ground-state conformer.

In order to determine the more stable conformer unambiguously, the signals of the *cis* and the *trans* conformers were assigned by NOE experiments. Based on the assignment, the relative stabilities ($\Delta G^{\circ}$) of the two planar (or nearly planar) conformers were also derived and are discussed.

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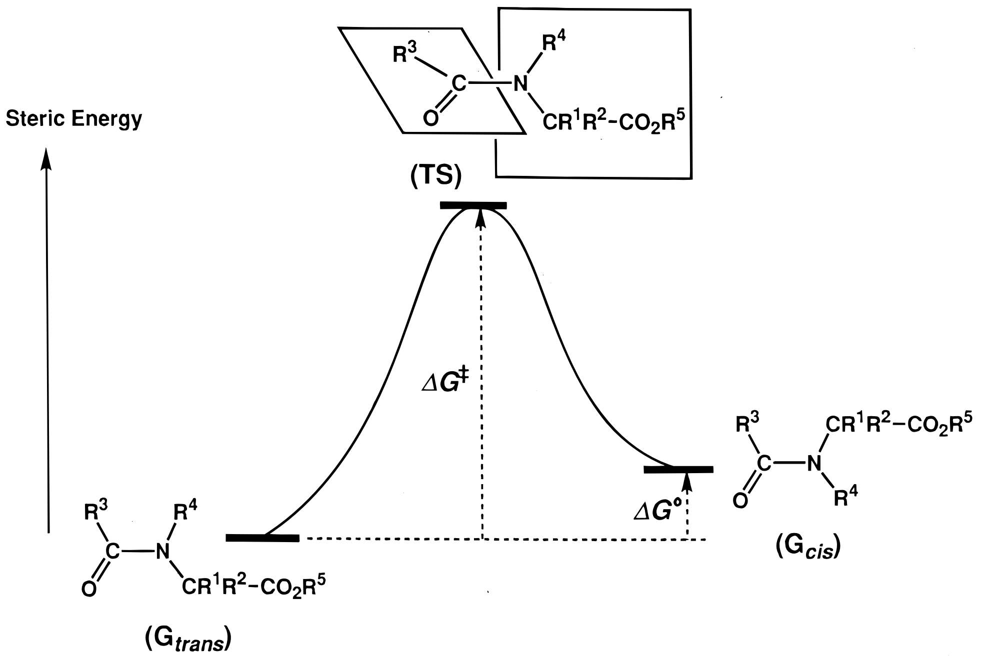


**Figure 1.** Rotational barrier and conformers of an *N*-acylamino acid.

## EXPERIMENTAL

All amides used in this investigation are known compounds and were prepared by the reported methods or their modifications.[15] The crude amides were purified by repeated recrystallization. The purity was checked by comparing their melting points with literature values and/or by their NMR and IR spectra.

$^1H$ and $^{13}C$ NMR spectra were measured using a JEOL EX-270 spectrometer using 5 mm diameter probe. $^{15}N$ spectra were recorded on a JEOL FX-90Q spectrometer using a 10 mm diameter probe. The samples for the measurements were prepared by dissolving *ca.* 100 mg of an amide in *ca.* 1.5 ml of solvent. The conditions of the measurements were given in Table 1. Temperature calibration was performed by using the external methanol reference.

The amides employed in this study are sparingly soluble in non-polar solvents. In order to overcome the difficulties arising from low solubilities and high coalescence temperatures, most measurements were carried out in DMSO-$d_6$ and pyridine-$d_5$. A series of spectra below and above the coalescence temperature were analyzed by a total lineshape analysis program.[16] The rotational barrier height ($\Delta G^\ddagger$) was obtained both by the total lineshape analysis by DNMR3 and from the coalescence temperature. In cases when more than one coalescence process was observed for a compound, the average of $\Delta G^\ddagger$ is listed (in Table 4). For example, the coalescence behaviors of the *N*-methyl, 2-methyl and formyl proton signals were used in order to calculate the $\Delta G^\ddagger$ for *N*-formyl-*N*-methyl-α-aminoisobutyric acid (**24**). The spectra for the lineshape analysis were usually collected in the range between 30 °C below and 10 °C above the coalescence temperature, $T_c$.

Molecular force field calculations were carried out by use of MM3 (92).[14] The rotational transition state about the amide C—N bond was found as the conformation on the rotational path which gave only one imaginary vibrational frequency. Corrections to stretching force constants and bond lengths for C═O and C—N

**Table 1. Conditions of the NMR measurements**

| | $^1H$ | $^{13}C$ | $^{15}N$ |
|---|---|---|---|
| Spectrometer | EX-270 | EX-270 | FX-90Q |
| Frequency (MHz) | 270 | 68 | 9.04 |
| Pulse lengths (μs) | 5.6 | 4.5 | 18 |
| Flip angle (°) | 45 | 45 | 45 |
| Delay(s) | 4 | 2 | 3 |
| Number of data points | 32 K | 32 K | 8 K |
| Spectral width (Hz) | 5400 | 20 000 | 3000 |
| Accuracy (Hz) | 0.33 | 1.56 | 0.7 |
| Accuracy (ppm) | 0.001 | 0.018 | 0.02 |
| Number of scans | 16 | 100 | 5000–10 000 |
| Reference | TMS | TMS | $NH_3$ (external) |

in the amide groups were done by selecting a proper effective dielectric constant ($\varepsilon = 4.0$) for the polar solvent system. These corrections are necessary to reproduce the correct geometries and conformational energies of amides (or esters) in polar solvents.[14]

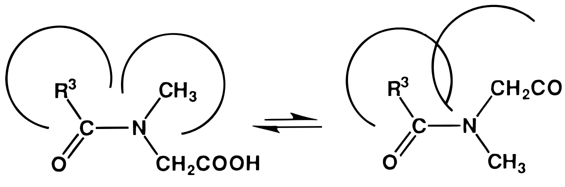
## RESULTS AND DISCUSSION

In order to investigate the nature of steric effects on the conformational preference and on the rotational barrier heights of amides of α-amino acids, a series of *N*-acyl-*N*-methyl-α-amino acids and their esters $R^3CO—N(R^4)—CR^1R^2—COOR^5$ were prepared and their dynamic behavior was examined. Thus, the effects of alkyl substituents at the α-carbon atom ($R^1$ and $R^2$), the acyl ($R^3$), the *N*-alkyl ($R^4$) and the carboxylic ester ($R^5$) groups were observed by means of dynamic NMR spectroscopy. The rotational barriers ($\Delta G^‡$) and the equilibrium free energy differences ($\Delta G°$) between the rotamers about the C—N bonds of these *N*-acyl-*N*-methyl-α-amino acid derivatives are given together with their $^{15}N$ chemical shifts in Table 2. In this paper, the terms *trans* and *cis* are used in place of the recommended *Z*/*E* nomenclature, because *Z* and *E*-isomers are reversed in *N*-primary alkyl and *N*-secondary (or tertiary) alkyl-*N*-acylglycines, which can cause serious confusion in the general discussion. The term *trans* for the *syn*-periplanar conformer of *N*-acetyl-*N*-methylglycine (**1**) was chosen according to the conventional terminology for the conformation of amide CONH group in peptides.

In the case of our *N*-acyl-*N*-methyl-α-amino acid derivatives, planar *trans* and *cis* conformers co-exist in unequal populations. In this situation, signals of the two ground-state conformers [*trans* (IIIa) and *cis* (IIIb)] should be unequivocally assigned in order to evaluate the steric and conformational effects of $\Delta G^‡$.

For this purpose, NOESY and 1D-NOE difference spectra of these amides were measured. In the cases when the amides are in fast equilibria at ambient temperature, NOE measurements at lower temperatures allow us to assign the signals of the *cis* and the *trans* conformers. Based on the assignment of *cis* and *trans* isomers by NOE experiments, the *trans* conformer is shown to be the more stable except for most of the *N*-formyl derivatives (**17**, **23**, **24**).

Even if the measurements were limited in high-boiling-polar solvents, $\Delta G^‡$ was shown to increase in order of increasing polarity of the solvents (pyridine < DMSO < $D_2O$). Previous measurements on some typical amides in various solvents had also shown that the solvent effect is normal and can be best correlated with the polarity of solvents.[17]



*trans*
(less crowded)

(IIIa)

*cis*
(more crowded)

(IIIb)

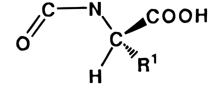
### Effect of α-alkyl substituents $R^1$ and $R^2$

Substitution of the α-carbon atom by an alkyl group ($R^1$) does not alter the rotational barrier $\Delta G^‡$ much. The $\Delta G^‡$ values are rather insensitive to both the chain length and the bulkiness of introduced alkyl group ($R^1$). However, it causes the migration of the $^{15}N$ chemical shift to higher frequency. In the *trans* conformer of *N*-acetyl-*N*-methylglycine (**1**), the repulsive steric interaction between the two methyl (*N*-methyl and acetyl) groups was estimated by MM3 calculations to be larger than the integration between the carbonyl oxygen and the carboxymethyl groups. As for the *N*-acetyl-α-monoalkyl-substituted amino acids (**2**–**8**), molecular mechanics calculations showed that they take a *trans* conformation (IV) in which the α-CH bond is nearly coplanar to the amide moiety, thus opposing the carbonyl oxygen. This conformation was confirmed to be favorable by the NOE experiments. By irradiation of $N$-$CH_3$, both the acetyl $CH_3$ (3.2%) and α-$CH_3$ (1.4%) signals were enhanced considerably, with a lesser enhancement of α-H (0.8%).

In this conformation, the shape and the bulkiness of the α-substituent ($R^1$) does not affect the geometry of the amide part of the molecule much. Thus, α-substitution by an alkyl group should result in a similar steric effect irrespective of the nature of the introduced alkyl group ($R^1$).

The rotational barriers of *N*-acetyl-*N*-methyl-α-monoalkylglycines (**2**–**8**) were found to be 6–7 kJ mol$^{-1}$ higher than those of the corresponding α-alkyl-substituted ethylamides $CH_3CON(CH_3)CHRCH_3$,[18] which implies that the ground-state conformer of **2**–**8** is considerably more stabilized than that of the ethylamides. The above conformation (IV) is geometrically favorable for the intramolecular $C—H\cdots O{=}C$ hydrogen bond. The presence of such an intramolecular hydrogen bond should stabilize the conformation IV. In this conformation, the dipole of the C—H bond is expected to interact attractively with the C=O dipole, and the *trans* conformation of **2**–**8** must be stabilized additionally by the increased polarization of the C—H bond induced by the electronegative carboxyl group on the same carbon atom.

Lowering of $\Delta G^‡$ implies a decrease in the contribution of structure II in the amide resonance, which in turn decreases the positive charge on N.[12] Thus, a low-frequency shift of the $^{15}N$ signal is expected from the electron density *vs.* chemical shift relationship. However, for **2**–**8** the direction of the $^{15}N$ chemical shift change found experimentally is opposite to the expectation from the lowering of the $\Delta G^‡$ values. The change in $\delta^{15}N$ is in accord with the general trend of the chemical shifts of amines[19] and amides;[20] the alkyl substitution



(IV)

**Table 2. $\delta^{15}N$, $\Delta G^{\ddagger}$ and $\Delta G°(=G_{cis} - G_{trans})$ values for *N*-acyl-*N*-methyl-α-amino acids and esters $R^3CONR^4CR^1R^2COOR^5$**

| No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Solvent | $\delta^{15}N$ (ppm) | Nucleus | $\delta^1H_{cis}$ | $\delta^1H_{trans}$ | $T_c$ (°C) | $\Delta G^{\ddagger}$ (kJ mol$^{-1}$) At $T_c$ | At 353 K | $\Delta G°$ kJ mol$^{-1}$) At 298 K |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (a) α-Substituted ($R^1$, $R^2$ varied) *N*-acetyl-*N*-methylamino acids ($R^5$ = H) | | | | | | | | | | | | | | |
| **1** | H | H | Me | Me | H | DMSO | 110.6*t* | *N*-$CH_3$ | 2.79 | 3.00 | 95.8 | 79.5 | 77.0 | 1.48 |
| | | | | | | | 110.2*c* | Ac | 1.91 | 2.01 | 85.4 | | 79.9 | 1.37 |
| | | | | | | | | α-$CH_2$ | 4.10 | 3.96 | 86.0 | | 76.6 | 1.50 |
| | | | | | | Pyridine | 106.1*t* | *N*-$CH_3$ | 3.05 | 3.15 | 70.8 | 78.8 | | 1.66 |
| | | | | | | | 105.4*c* | Ac | 2.10 | 2.20 | 74.2 | | | |
| | | | | | | | | α-$CH_2$ | 4.45 | 4.30 | 87.0 | | | |
| **2** | Me | H | Me | Me | H | DMSO | 119.9 | *N*-$CH_3$ | 2.66 | 2.88 | 89.6 | 78.6 | 78.0 | 2.48 |
| | | | | | | Pyridine | 116.0 | *N*-$CH_3$ | 2.99 | 3.09 | 74.6 | 74.4 | | 2.56 |
| **3** | Et | H | Me | Me | H | DMSO | 116.1 | *N*-$CH_3$ | 2.64 | 2.86 | 98.7 | 80.1 | 80.2 | 2.30 |
| | | | | | | Pyridine | 111.4 | *N*-$CH_3$ | 3.08 | 3.00 | 74.6 | 77.1 | | 2.01 |
| **4** | nPr | H | Me | Me | H | DMSO | 116.7 | *N*-$CH_3$ | 2.64 | 2.85 | 97.8 | 80.3 | 81.5 | 2.71 |
| | | | | | | | | α-CH | 5.79 | 6.11 | 114.5 | 81.3 | | |
| | | | | | | Pyridine | 110.8 | *N*-$CH_3$ | 2.32 | 2.16 | 76.1 | 77.9 | | 2.30 |
| **5** | nBu | H | Me | Me | H | DMSO | 116.8 | Ac | 1.98 | 2.00 | 64.0 | 78.7 | | 2.53 |
| | | | | | | Pyridine | 112.1 | *N*-$CH_3$ | 2.62 | 2.83 | 79.8 | 78.4 | | 2.14 |
| **6** | iPr | H | Me | Me | H | DMSO | 117.1 | Ac | 2.07 | 2.03 | 77.1 | 79.0 | 79.6 | 1.88 |
| | | | | | | | | *N*-$CH_3$ | 2.69 | 2.90 | 101.4 | 79.7 | 79.2 | |
| | | | | | | Pyridine | 112.1 | Ac | 2.37 | 2.13 | 95.8 | 78.2 | | 1.50 |
| | | | | | | | | *N*-$CH_3$ | 3.13 | 3.06 | 75.6 | 76.9 | | |
| **7** | iBu | H | Me | Me | H | DMSO | 117.5 | *N*-$CH_3$ | | | 93.8 | 80.9 | | 3.68 |
| | | | | | | Pyridine | 105.1 | Ac | 2.33 | 2.16 | 91.5 | 80.0 | | 3.68 |
| | | | | | | | | *N*-$CH_3$ | 3.11 | 3.02 | 77.6 | | | |
| **8** | tBu | H | Me | Me | H | DMSO | 118.0 | tBu | 1.07 | 1.01 | 71.9 | 80.1 | 80.4 | 4.06 |
| | | | | | | | | Ac | 2.07 | 2.04 | 65.4 | 80.0 | 80.8 | |
| | | | | | | | | *N*-$CH_3$ | 2.80 | 3.01 | 88.6 | 80.1 | 79.7 | |
| | | | | | | | | α-CH | 4.18 | 4.97 | 106.9 | 79.9 | 79.4 | |
| | | | | | | Pyridine | 109.1 | Ac | 2.34 | 2.15 | 84.0 | 79.2 | | 3.95 |
| | | | | | | | | *N*-$CH_3$ | 3.27 | 3.18 | 71.5 | 78.5 | | |
| **9** | Ph | H | Me | Me | H | DMSO | 121.3 | Ac | 2.15 | 2.08 | 54.0 | 76.6 | 76.3 | 3.99 |
| | | | | | | | | *N*-$CH_3$ | 2.57 | 2.75 | 77.2 | 77.8 | 78.1 | |
| | | | | | | | | α-CH | 5.79 | 6.11 | 83.3 | 77.4 | 77.9 | |
| | | | | | | Pyridine | 119.5 | Ac | 2.45 | 2.17 | 63.8 | 74.5 | | 4.80 |
| | | | | | | | | *N*-$CH_3$ | 3.11 | 2.95 | 55.4 | 74.2 | | |
| | | | | | | $CDCl_3$ | 121.2 | Ac | 2.29 | 2.18 | 42.8 | 74.5 | | |
| **10** | Me | Me | Me | Me | H | A–c[a] | 104.5 | Ac | | 2.09 | | | | —[b] |
| | | | | | | | | *N*-$CH_3$ | | 3.04 | | | | |
| | | | | | | | | α-$CMe_2$ | | | (*ca.* −120) | (*ca.* 35) | | |
| (b) α-Substituted ($R^1$ varied) *N*-acetyl-*N*-methylamino esters ($R^5$ = Me) | | | | | | | | | | | | | | |
| **11** | H | H | Me | Me | Me | DMSO | 108.4 | | | | | 82.3 | 81.9 | 1.93 |
| | | | | | | Pyridine | 101.3 | | | | | 78.1 | | 2.58 |
| **12** | Me | H | Me | Me | Me | DMSO | 119.0 | *N*-$CH_3$ | 2.65 | 2.90 | 88.9 | 78.1 | | 2.95 |
| | | | | | | | | $CO_2CH_3$ | 3.67 | 3.61 | 70.6 | 78.9 | 78.2 | |
| | | | | | | Pyridine | 113.4 | Ac | 2.21 | 2.06 | 78.8 | 76.9 | | 3.23 |
| **13** | Et | H | Me | Me | Me | DMSO | 115.0 | $CO_2CH_3$ | 2.03 | 2.05 | 80.0 | 80.2 | | 2.63 |
| | | | | | | | | *N*-$CH_3$ | 2.63 | 2.88 | 103.8 | 81.0 | | |
| | | | | | | Pyridine | 109.6 | Ac | 3.68 | 3.62 | 81.9 | 79.1 | | 3.06 |
| | | | | | | $D_2O$ | 118.8 | $CO_2CH_3$ | 3.87 | 3.83 | 87.7 | 83.2 | | 2.42 |
| | | | | | | $CDCl_3$ | 110.8 | *N*-$CH_3$ | 2.81 | 2.94 | | | | 3.07 |
| **14** | nPr | H | Me | Me | Me | DMSO | 115.4 | $CO_2CH_3$ | 3.67 | 3.62 | 78.1 | 80.3 | 80.2 | 3.05 |
| | | | | | | | | *N*-$CH_3$ | 2.63 | 2.87 | 100.0 | 80.8 | 81.2 | |
| | | | | | | Pyridine | 110.3 | $CO_2CH_3$ | 3.65 | 3.61 | 62.0 | 78.6 | | 3.30 |
| | | | | | | | | Ac | 2.22 | 2.11 | 82.0 | 79.2 | | |
| | | | | | | | | *N*-$CH_3$ | 2.93 | 2.88 | 56.8 | | | |
| | | | | | | $D_2O$ | 119.5 | $CO_2CH_3$ | 3.59 | 3.56 | 72.9 | 81.2 | | 2.87 |
| | | | | | | $CDCl_3$ | 111.5 | | | | | | | 3.27 |
| **15** | nBu | H | Me | Me | Me | DMSO | 115.5 | $CO_2CH_3$ | | | 76.6 | 79.8 | | 2.82 |
| | | | | | | | | *N*-$CH_3$ | | | 96.0 | 79.6 | | |
| | | | | | | | | α-CH | | | 106.2 | 80.4 | | |
| | | | | | | Pyridine | 110.2 | Ac | | | 79.6 | 78.3 | | 3.21 |
| | | | | | | | | $CO_2CH_3$ | | | 65.9 | 78.4 | | |
| | | | | | | $D_2O$ | 116.7 | | | | | | | 2.64 |
| | | | | | | $CDCl_3$ | 111.9 | | | | | | | 2.79 |

**Table 2.** *Continued*

| No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Solvent | $\delta^{15}N$ (ppm) | Nucleus | $\delta^1H_{cis}$ | $\delta^1H_{trans}$ | $T_c$ (°C) | At $T_c$ | $\Delta G^\ddagger$ (kJ mol$^{-1}$) At 353 K | $\Delta G^\circ$ kJ mol$^{-1}$) At 298 K |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **16** | iPr | H | Me | Me | Me | DMSO | 115.8 | Ac | 2.08 | 2.04 | 72.2 | 79.2 | | 2.71 |
| | | | | | | | | $CO_2CH_3$ | 3.62 | 3.40 | 78.2 | 78.2 | | |
| | | | | | | | | *N*-$CH_3$ | 2.67 | 2.92 | 94.7 | 78.1 | | |
| | | | | | | Pyridine | 106.6 | Ac | 2.26 | 2.09 | 90.3 | 79.4 | | 2.67 |
| | | | | | | | | $CO_2CH_3$ | 3.66 | 3.62 | 63.0 | 77.6 | | |
| | | | | | | | | *N*-$CH_3$ | 2.98 | 2.93 | 58.5 | 75.7 | | |
| | | | | | | $D_2O$ | 118.7 | *N*-$CH_3$ | 2.72 | 2.92 | | | | 3.04 |
| | | | | | | $CDCl_3$ | 111.9 | *N*-$CH_3$ | 2.86 | 2.98 | | | | 2.03 |
| (c) *N*-Acyl ($R^3$ varied) *N*-methylglycines ($R^5$ = H) (for $R^3$ = Me, see compound **1**) | | | | | | | | | | | | | | |
| **17** | H | H | H | Me | H | DMSO | 115.7*t* | *N*-$CH_3$ | 2.95 | 2.74 | 151.5 | 88.9 | 86.7 | −0.19 |
| | | | | | | | 115.4*c* | α-$CH_2$ | 3.95 | 4.07 | 133.7 | 87.3 | 86.2 | |
| | | | | | | | | CHO | 8.06 | 7.99 | 133.0 | 89.0 | 85.4 | |
| | | | | | | Pyridine | 110.8*t* | *N*-$CH_3$ | 2.99 | 3.08 | | 86.8 | | 0.59 |
| | | | | | | | 110.4*c* | α-$CH_2$ | 4.39 | 4.27 | | | | |
| | | | | | | | | CHO | 8.43 | 8.33 | | | | |
| **18** | H | H | Et | Me | H | DMSO | 108.3 | α-$CH_2$ | 4.09 | 3.97 | 82.4 | 77.1 | 77.3 | 1.61 |
| | | | | | | | | *N*-$CH_3$ | 2.80 | 2.98 | 91.8 | 78.1 | 77.6 | |
| | | | | | | Pyridine | 103.3 | α-$CH_2$ | 4.31 | 4.46 | 85.0 | 77.1 | | 1.67 |
| | | | | | | | | *N*-$CH_3$ | 3.17 | 3.05 | 75.5 | 75.9 | | |
| | | | | | | $CDCl_3$ | 106.6 | | | | | | | |
| **19** | H | H | iPr | Me | H | DMSO | 107.0 | α-$CH_2$ | 3.96 | 4.15 | 77.0 | 75.1 | 75.1 | 1.88 |
| | | | | | | Pyridine | 101.8 | *N*-$CH_3$ | 3.18 | 3.14 | 48.6 | 73.5 | | 2.10 |
| | | | | | | | | α-$CH_2$ | 4.40 | 4.46 | 62.7 | 75.7 | | |
| | | | | | | $CDCl_3$ | 104.7 | | | | | | | |
| **20** | H | H | tBu | Me | H | | | | | | | | | |
| **21** | H | H | Ph | Me | H | DMSO | 111.2 | *N*-$CH_3$ | 3.00 | 2.95 | 42.4 | 69.8 | 69.8 | 0.80 |
| | | | | | | | | α-$CH_2$ | 3.95 | 4.16 | 59.3 | | 68.2 | |
| | | | | | | Pyridine | 105.8 | *N*-$CH_3$ | 3.34 | 3.09 | 55.0 | 67.2 | | 0.90 |
| | | | | | | | | α-$CH_2$ | 4.29 | 4.61 | 57.6 | | | |
| **22** | H | H | tBuO | Me | H | DMSO | 78.7 | tBuO | 1.40 | 1.35 | 47.7 | 70.3 | 70.2 | 0.36 |
| | | | | | | | | *N*-$CH_3$ | 2.83 | 2.79 | 43.5 | 70.3 | 71.5 | |
| | | | | | | | | α-$CH_2$ | 3.85 | 3.83 | 35.4 | 70.2 | 71.5 | |
| | | | | | | Pyridine | 73.9 | tBuO | 1.64 | 1.63 | 30.7 | 70.4 | | 0.15 |
| | | | | | | | | *N*-$CH_3$ | 3.23 | 3.19 | 43.5 | 69.8 | | |
| | | | | | | | | α-$CH_2$ | 4.45 | 4.32 | 58.4 | 69.8 | | |
| | | | | | | $CDCl_3$ | 74.4 | tBuo | 1.47 | 1.44 | 34.7 | 68.3 | | −0.03 |
| | | | | | | | | α-$CH_2$ | 4.03 | 3.95 | 43.4 | 67.5 | | |
| (d) *N*-Formyl ($R^3$ = H) α-amino acids ($R^5$ = H) (for $R^1$ = Me, see compound **17**) | | | | | | | | | | | | | | |
| **23** | Me | H | H | Me | H | DMSO | 126.6 | *N*-$CH_3$ | 2.67 | 2.88 | 140.1 | 87.7 | 87.6 | −1.06 |
| | | | | | | | | CHO | 8.09 | 8.05 | 125.5 | 89.8 | | |
| | | | | | | Pyridine | 121.2 | α-CH | 4.63 | 5.45 | — | | | −0.73 |
| | | | | | | $CDCl_3$ | 125.8 | α-CH | 4.32 | 5.07 | | | | 0.35 |
| **24** | Me | Me | H | Me | H | DMSO | 133.4 | 2-Me | 1.52 | 1.33 | 101.5 | 80.1 | 79.4 | −0.39 |
| | | | | | | | | *N*-$CH_3$ | 2.70 | 2.92 | 104.7 | 80.2 | 80.3 | |
| | | | | | | | | CHO | 8.30 | 7.95 | 120.0 | 82.2 | | |
| | | | | | | Pyridine | 128.3 | α-$CMe_2$ | 1.67 | 1.65 | 58.6 | 78.7 | | −1.31 |
| | | | | | | | | *N*-$CH_3$ | 3.03 | 2.90 | 89.2 | 79.2 | | |
| | | | | | | | | CHO | 8.43 | 8.05 | | | | |
| | | | | | | $CDCl_3$ | 133.6 | | | | | | | −1.24 |
| **25** | H | H | H | tBu | H | DMSO | 146.2 | tBu | 1.33 | 1.31 | | — | | 7.6 |
| | | | | | | | | α-$CH_2$ | 4.06 | 3.94 | | | | |
| | | | | | | | | CHO | 7.99 | 8.40 | | | | |
| | | | | | | Pyridine | 140.6 | tBu | 1.60 | 1.34 | | — | | 7.3 |
| | | | | | | | | α-$CH_2$ | 4.31 | 4.48 | | | | |
| | | | | | | | | CHO | 8.73 | 8.84 | | | | |
| (e) *N*-Alkyl ($R^4$ varied) *N*-acetylglycines ($R^5$ = H) (for $R^4$ = Me, see compound **1**) | | | | | | | | | | | | | | |
| **26** | H | H | Me | H | H | DMSO | 116.1*t* | Ac | | 1.85 | | 94.3 | | 20.9 |
| | | | | | | Pyridine | 103.3*t* | Ac | | 2.14 | | | | |
| **27** | H | H | Me | Et | H | DMSO | 125.0*t* | Ac | 1.89 | 2.02 | 92.7 | 78.4 | 78.0 | 1.21 |
| | | | | | | | 123.8*c* | α-$CH_2$ | 4.07 | 3.90 | 92.8 | | 77.8 | |
| | | | | | | Pyridine | 118.9*t* | Ac | 2.21 | 2.10 | 75.2 | 77.8 | | 1.29 |
| | | | | | | | 118.1*c* | α-$CH_2$ | 4.31 | 4.42 | 89.8 | | | |

**Table 2.** *Continued*

| No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Solvent | $\delta^{15}N$ (ppm) | Nucleus | $\delta^1H_{cis}$ | $\delta^1H_{trans}$ | $T_c$ (°C) | $\Delta G^‡$ (kJ mol$^{-1}$) | | $\Delta G°$ kJ mol$^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | At $T_c$ | At 353 K | At 298 K |
| **28** | H | H | Me | nPr | H | DMSO | 123.2*t* | Ac | 1.90 | 2.02 | 92.7 | 78.4 | | 1.18 |
| | | | | | | | 121.9*c* | α-$CH_2$ | 4.07 | 3.89 | 92.4 | | | |
| | | | | | | Pyridine | 118.4*t* | Ac | 2.23 | 2.16 | 74.5 | 77.6 | | 1.07 |
| | | | | | | | 117.5*c* | α-$CH_2$ | 4.34 | 4.43 | 87.3 | | | |
| **29** | H | H | Me | nBu | H | DMSO | 123.1*t* | Ac | 1.90 | 2.02 | 94.2 | 78.6 | 78.1 | 1.03 |
| | | | | | | | 121.7*c* | α-$CH_2$ | 4.07 | 3.89 | 94.2 | | | |
| | | | | | | Pyridine | 118.4*t* | Ac | 2.24 | 2.18 | 73.8 | 77.6 | | 1.07 |
| | | | | | | | 117.4*c* | α-$CH_2$ | 4.35 | 4.45 | 87.7 | | | |
| **30** | H | H | Me | iBu | H | DMSO | 122.8*t* | Ac | 1.91 | 2.01 | 93.2 | 79.5 | 80.6 | 1.01 |
| | | | | | | | 121.7*c* | α-$CH_2$ | 4.07 | 3.88 | 98.6 | | | |
| | | | | | | Pyridine | 118.2*t* | Ac | 2.26 | 2.18 | 78.0 | 78.2 | | 1.03 |
| | | | | | | | | α-$CH_2$ | 4.35 | 4.42 | 87.9 | | | |
| **31** | H | H | Me | iPr | H | DMSO | 134.6*t* | Ac | 1.89 | 2.04 | 92.7 | 77.5 | 78.8 | 0.83 |
| | | | | | | | 132.3*c* | α-$CH_2$ | 3.98 | 3.77 | 92.8 | | 77.3 | |
| | | | | | | Pyridine | 128.3*t* | Ac | 2.26 | 2.19 | 69.9 | 76.7 | | 0.63 |
| | | | | | | | 126.4*c* | α-$CH_2$ | 4.26 | 4.31 | 80.5 | | | |
| **32** | H | H | Me | tBu | H | DMSO | — | Ac | 1.92 | | | | | — |
| | | | | | | | 135.4*c* | α-$CH_2$ | 4.06 | | | | | |
| | | | | | | Pyridine | — | Ac | 2.23 | | | | | |
| | | | | | | | 130.2*c* | α-$CH_2$ | 4.36 | | | | | |
| | | | | | | $CDCl_3$ | | α-$CH_2$ | | | (−32.2) | (48.7) | (49.0) | 5.27 |
| **33** | H | H | Me | Ph | H | DMSO | 135.3 | Ac | 2.19 | 1.88 | 38.3 | 71.4 | 73.7 | 8.6 |
| | | | | | | | | α-$CH_2$ | 4.52 | 4.32 | 31.8 | — | | — |
| | | | | | | Pyridine | 118.4 | Ac | 2.42 | 1.99 | 37.3 | | | 8.5 |

[a] Measured in acetone–chloroform (5 : 2) solution.
[b] Only one species, presumably the *trans* isomer, could be detected.
[c] Calculated values for the corresponding acids.

on the α-carbon atom induces a high-frequency shift in this series of α-amino acids.[21] Even in this case, the rotational barrier height can be correlated with $\delta^{15}N$ fairly well (slope = − 1.64, $r = 0.904$). Nevertheless, the rationalization for the linear plot seems difficult.

The free energy difference between the rotamers increases as a function of the bulkiness of the α-substituent $R^1$, as evidenced by the $\Delta G°$ *vs.* $E_s$ correlation ($r = 0.874$) in Fig. 2. $E_s$ is the steric substituent constant defined by Taft[22] in order to evaluate the bulkiness of a substituent. Although both the *trans* and *cis* conformers can suffer from the steric hindrance by the $R^1$ substituent, its effect must be more significant with the sterically more stringent *cis* conformer. Therefore, the increase in $\Delta G°$ should originate to a major extent from the increase in the steric energy of the *cis* conformer.

As is easily understood from the energy profile in Fig. 1, the congestion in the more stable *trans* conformer is expected to destabilize the ground state and decrease the energy difference between the ground and the transition states, which is measured as $\Delta G^‡$. From this point of view, $\Delta G^‡$ of the α,α-dialkyl derivative is interesting. The MM3 steric energy suggests that the introduction of a second alkyl group ($R^2$) on the α-carbon atom should cause a very abrupt decrease in the rotational barrier. The *N*-methyl $^{13}C$ signal of *N*-acetyl-*N*-methyl-2-aminoisobutyric acid (**10**) showed coalescence behavior at −120 °C [in acetone–chloroform (5:2)], which corresponds to a rotational barrier $\Delta G^‡$ of *ca.* 35 kJ mol$^{-1}$. However, the equilibrium between the two conformers of **10** should lie far on the side of the *trans* conformer, according to the MM3 steric energy difference (21.0 kcal mol$^{-1}$). For this reason, the coalescence was suspected to have a different origin. Comparing the similar coalescence behavior of **32**, the coalescence of **10**

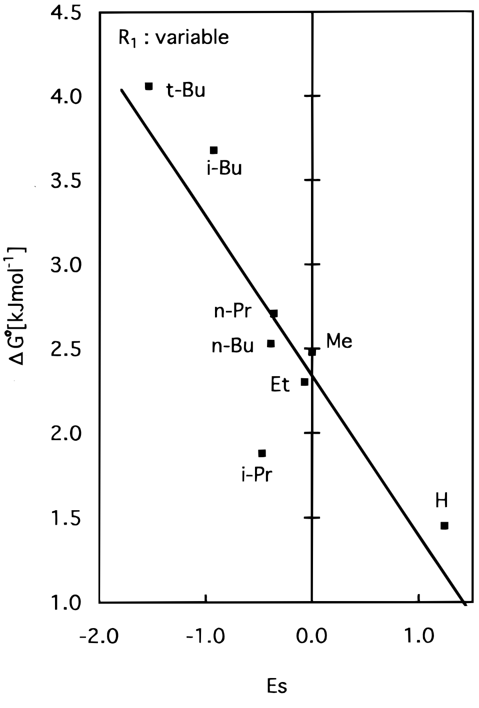


**Figure 2.** Steric effect by α-alkyl ($R^1$) substituent on the equilibria between the *cis* and *trans* conformers.

is assumed to come from the slow rotation about N—$C_\alpha$ bond. In contrast, introduction of an additional α-methyl group to *N*-formyl-*N*-methylalanine (**23**) causes a regular and moderate decrease in $\Delta G^\ddagger$ for *N*-formyl-*N*-methyl-2-aminoisobutyric acid (**24**) [Table 2(d)].

In elucidating the reason for the anomalously low $\Delta G^\ddagger$, the behavior of the $^{15}N$ chemical shifts is also very informative. *N*-Formyl derivatives of glycine (**17**), alanine (**23**) and α-aminoisobutyric acid (**24**) have resonance signals at 115.7, 126.6 and 143.4 ppm, respectively, in the $^{15}N$ NMR spectra (relative to external $NH_3$). Regular and normal high-frequency shifts common to alkylamine derivatives were observed with this series of *N*-formyl compounds, which indicates their planar ground states. In sharp contrast, $\delta(^{15}N)$ of **10** shifts towards low frequency (104.5 ppm, in contrast to 116.0 ppm for **2**), which suggests a considerable steric hindrance due to the planar geometry of the amide moiety. The phenomenon is best explained by assuming a non-planar ground state for the *N*-acetyl-α,α-dimethyl derivative **10**. The non-planarity should originate from the steric hindrance between acetyl and α-methyl groups.

## Effect of acyl group $R^3$

Variation of the alkyl group of the acyl moiety ($R^3$) causes a gradual decrease in the rotational barrier as $R^3$ becomes bulkier (Fig. 3). Since the rotational transition state (TS in Fig. 1) is expected to be less crowded than the planar ground-state conformers, the barrier height is actually governed by the steric effect on the more stable *trans* conformer ($G_{trans}$). The congestion in the *trans* conformer should destabilize the ground state and decrease the energy difference between the ground and the transition states, which is measured as the decrease in $\Delta G^\ddagger$. A steric effect of similar trend was reported recently in the series of *N*-ethyl-*N*-methyl-alkanecarboxamides.[23]

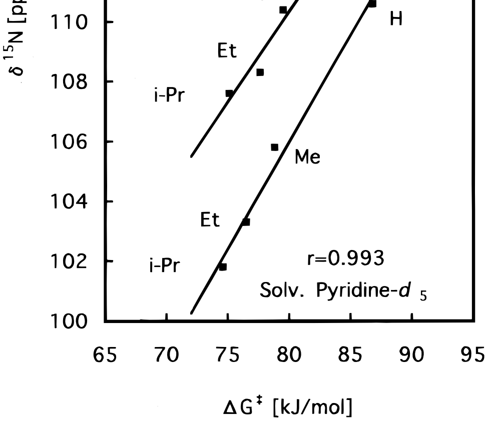


**Figure 3.** Linear correlation between the rotational barriers ($\Delta G^\ddagger$) and the $^{15}N$ chemical shifts ($\delta^{15}N$) of *N*-acyl ($R^3$)-*N*-methylglycines.

The bulkiness of $R^3$ affects less straightforwardly the free energy difference ($\Delta G^\circ$) between the *trans* and *cis* conformers. In pyridine and DMSO, $\Delta G^\circ$ tends to increase as $R^3$ becomes bulkier when we compare the sequence of $R^3$: H < Et < iPr < tBu. This trend can be explained by the steric effect, which is more severe in the *cis* than in the *trans* conformer because the carboxymethyl group is apparently bulkier than the *N*-methyl group. As a result, $\Delta G^\circ$ increases slightly as the substituent $R^3$ becomes bulkier. The substituent effect is considerably dependent on the solvent used, however.

Reflecting the increase in the steric hindrance of the ground state, which is unfavorable for the amide mesomerism (II), the $^{15}N$ chemical shift is expected to move to lower frequency as $R^3$ becomes bulkier. In accord with this deduction, the $\Delta G^\ddagger$ *vs.* $\delta^{15}N$ plot in Fig. 3 constitutes a straight line of positive slope. It should be noted that the linear plot provides a method for the prediction of the rotational barrier from much more easily observable $^{15}N$ chemical shift within a limited range.

Judging from the very abrupt decrease in its $\Delta G^\ddagger$, pivaloyl amide (**20**, $R^3$ = tBu) must have a non-planar ground-state conformation owing to very severe steric hindrance between the *N*-methyl and acyl *tert*-butyl groups. The torsional angle [$\omega_{C(R^3)—C—N—CH3}$] about the C—N bond was estimated to be 6.5° from MM3 calculations for the *trans* conformer of **20**. This is a smaller deformation than expected from the drastic decrease in $\Delta G^\ddagger$. As expected, even though more planar conformations were predicted with the other amides **17–19**. [Calculated $\omega_{C—N}$ values for **17**, **1**, **18** and **19** are 2.5°, 4.2°, 4.0° and 4.3°, respectively.]

When the acyl group is benzoyl (**21**) or *tert*-butoxycarbonyl (**22**), the rotational barrier also tends to be lowered owing to the conjugation within the ester or aroyl chromophore which suppresses the alternative amide conjugation. Thus, the lowering of the rotational barriers comes from a common origin, i.e. the decrease in the double bond character of the amide C—N bond.

## Effect of *N*-alkyl group $R^4$

Within this the series of *N*-$R^4$-substituted amides (**1**, **27–31**), the steric hindrance between acetyl methyl and *N*-alkyl groups in the more stable *trans* conformer must be the most stringent factor controlling both free energy ($\Delta G^\circ$ and $\Delta G^\ddagger$) values. Similar discussions as in the case of $R^3$ lead to the conclusion that $\Delta G^\ddagger$ should be lowered as $R^4$ becomes bulky. This trend is qualitatively in accord with the experimental findings. However, the effect is slight and less predominant than in the case of $R^3$, probably because the C—N—$R^4$ angle is less rigid than the N—C—$R^3$ angle, which allows the C—N—$R^4$ angular deformation to occur more easily.

The free energy difference $\Delta G^\circ$ decreases regularly as the substituent $R^4$ becomes bulky. Thus, the $\Delta G^\circ$ in DMSO could be correlated with steric substituent constant $\Omega_s$ [24] with $r = 0.940$, $n = 6$. In the cases of

$R^4$ = iPr (**31**) and tBu (**32**), the *trans* conformer becomes less stable than the *cis* conformer, which implies that isopropyl and *tert*-butyl groups are bulkier than the carboxymethyl (—$CH_2COOH$) group. This supports the assumption that the steric effect operates predominantly in the more stable *trans* conformer. Judging from $\Delta G°$, the *trans* conformer of *N*-acetyl-*N*-phenylglycine (**33**) is extraordinarily stable. In this molecule, the phenyl group is expected to lie perpendicular to the amide N—C=O plane and to be facing the acetyl $CH_3$ group as illustrated in V. This conformation is favorable for CH–$\pi$ interaction to occur,[25] which results in additional stabilization.

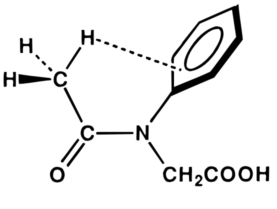
*N*-Formylglycine is assumed to take a *cis* conformation in which NH and the carboxyl group are located *syn*-periplanar in order to avoid a larger steric hindrance between carbonyl and carboxymethyl groups in the *trans* conformation. In the case of *N*-formyl-*N*-methylglycine (**17**), still the same trend holds because $CH_2COOH$ is bulkier than $CH_3$. However, the energy difference between the two conformers is small, in accord with the MM3 calculations. As the *N*-alkyl group ($R^4$) becomes more bulky, the order of the stabilities of the two conformers tends to be reversed and the *trans* conformers become the more stable.

## Effect of structural modification of the carboxyl group COOR$^5$

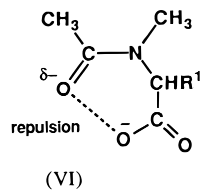
By comparison of the $\Delta G^‡$ values of **1**–**6** with those of **11**—**16**, it was shown that esterification of the carboxyl group does not alter the rotational barrier height significantly. Variation of the ester alkoxyl group again does not affect $\Delta G^‡$ much; $\Delta G^‡$ values for the methyl, ethyl, propyl and isopropyl esters of *N*-acetyl-*N*-methylalanine are 78.1, 80.6, 80.6 and 78.5 kJ $mol^{-1}$, respectively, in DMSO at the coalescence temperature.

Dissociation of the carboxyl group forming the corresponding carboxylate anion causes a decrease in the free energy difference between the *trans* and *cis* conformers. It must originate from the excess destabilization of the *trans* conformer (VI) due to the negative charge–dipole repulsion operating between the carboxylate ion and the carbonyl group in a closer distance than in the *cis* conformer.

The dissociation process could be followed by measuring the $\delta^1H$ (of the methine proton, for instance) as a function of pH. The inflection point (indicated by arrows in the figure) of the $\delta^1H$ *vs.* pH curve gave the $pK_a$ values of *trans* and *cis* conformers separately.[26] As can easily be seen from the $pK_a$ values in Table 3, the *trans* conformer is a slightly weaker acid than the *cis* conformer owing to the above-mentioned repulsion which prevents the dissociation of the acid. This agreed with the decrease in $\Delta G°$ by ionization.



(V)



(VI)

## Comparison of experimental ΔG‡ and ΔG° values with those from MM3 calculations

The $\Delta G^‡$ and $\Delta G°$ values in DMSO are summarized in Table 4 together with the theoretical values calculated as the differences in the steric energies from MM3. The averages of the free energy values obtained with various species of protons in DMSO are given. The $\Delta G^‡_{\text{exptl}}$ *vs.* $\Delta G^‡_{\text{calcd}}$ and the $\Delta G°_{\text{exptl}}$ *vs.* $\Delta G°_{\text{calcd}}$ plots are shown in Fig. 4. The correlation is generally good ($r = 0.905$ and 0.944, respectively) and the slopes of the plots are nearly unity. This implies that the MM3 method can be used

**Table 3. Acidities of the *cis* and *trans* conformers of some *N*-acyl-α-amino acids**

| Compound | $pK_a$ (*cis*) | $pK_a$ (*trans*) |
|---|---|---|
| **1** | 3.1 | 3.5 |
| **12** | 3.3 | 3.8 |
| **16** | 3.2 | 3.8 |
| **17** | 3.1 | 3.3 |
| **19** | 3.2 | 3.5 |
| **24** | 4.8 | 3.9 |

**Table 4. Experimental and calculated rotational barriers and conformational free energy differences (kcal mol$^{-1}$)[a]**

| Compound | $\Delta G^{‡\,b}_{\text{exptl}}$ | $\Delta G^‡_{\text{calcd}}$ | $\Delta G^{°\,b}_{\text{exptl}}$ | $\Delta G°_{\text{calcd}}$ |
|---|---|---|---|---|
| **1** | 78.2 | 78.2 | 1.45 | 2.14 |
| **2** | 78.0 | 76.1 | 2.48 | 3.12 |
| **3** | 80.2 | 81.4 | 2.30 | 3.44 |
| **4** | 81.5 | 78.3 | 2.71 | 3.40 |
| **5** | (78.7)[c] | 78.2 | 2.53 | 3.42 |
| **6** | 79.4 | 77.8 | 1.88 | 3.03 |
| **8** | 80.4 | 83.2 | 4.06 | 6.22 |
| **10** | — | 62.7 | — | 21.0 |
| **17** | 86.2 | 90.1 | −0.65 | 1.10 |
| **18** | 77.5 | 76.8 | 1.61 | 2.36 |
| **19** | 75.1 | 72.3 | 1.88 | 2.34 |
| **20** | — | 40.2 | — | 5.27 |
| **24** | 79.9 | 79.0 | −0.39 | 0.55 |
| **25** | — | 88.4 | 7.6 | 8.52 |
| **26** | — | 94.3 | — | 20.9 |
| **27** | 77.9 | 79.5 | 1.21 | 0.73 |
| **31** | 78.0 | 78.7 | 0.83 | −0.38 |
| **32** | — | 70.3 | — | −19.7 |

[a] Measurements were carried out in DMSO-$d_6$. The average value is given when determined from various $^1H$ species.
[b] When available, the $\Delta G^‡$ from the rate data by DMNR3 are given.
[c] $\Delta G^‡$ from $T_c$.

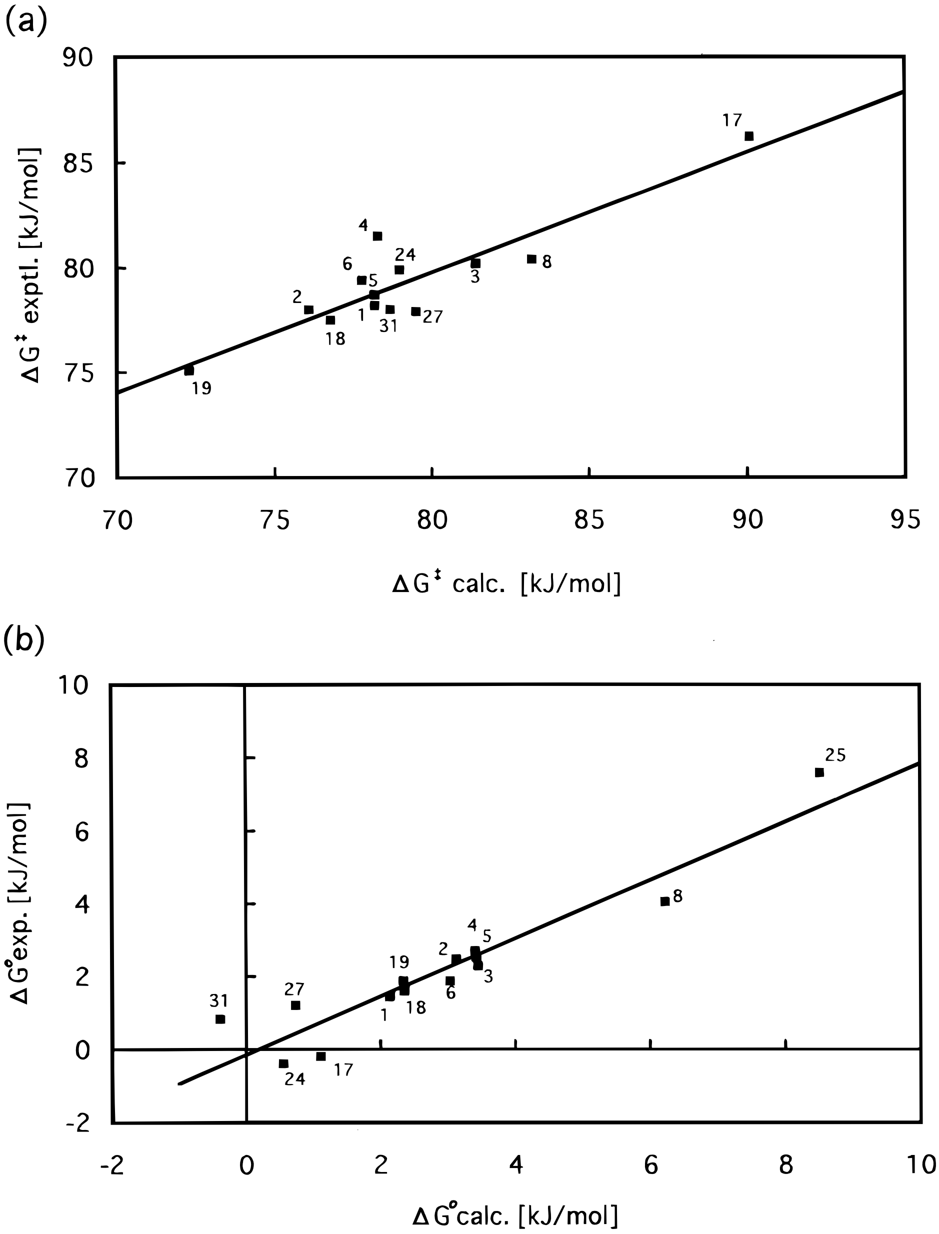


**Figure 4.** Correlations between the experimental and the calculated (MM3) rotational barriers (a) and free energy difference between the *trans* and *cis* conformers (b).

to predict $\Delta G^\circ$ and $\Delta G^\ddagger$. However, the subtle $\Delta G^\ddagger$ and $\Delta G^\circ$ differences among the α-monosubstituted series (**2**–**6**) could not be reproduced by the calculations.

## Rotational barriers of Boc-protected dipeptides

The results for *N*-acyl amino acids were compared with the dynamic properties of dipeptides. Thus, the rotational barriers about the C—N(2) bonds of some $N^1$-butoxycarbonyl(Boc)-$N^2$-(α-aminoacyl)-$N^2$-methylglycine methyl esters (**34**–**37**) were determined for this purpose (Table 5).

In contrast to the simple *N*-acyl series, methyl L-valyl-*N*-methylglycinate (**36**) has a rotational barrier higher than its less bulkier homologs [glycyl (**34**), L-alanyl (**35**) and L-leucyl (**37**) derivatives]. Judging from the $N^1$ $^1$H signal of the Boc-protected L-valyl group appearing at a lower field than others, the NH group is expected to take a conformation (VII) suitable to form a stronger hydrogen bond with the carbonyl group of the same amino acid residue. This, in turn, contributes to stabilizing its *N*-methylamide chromophore by dispersing the negative charge on the carbonyl oxygen and increases the rotational barrier.

## Acknowledgements

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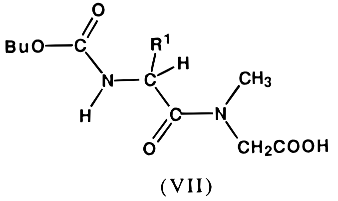

(VII)

**Table 5. $\delta^{15}N$, $\Delta G^{\ddagger}$ and $\Delta G^{\circ}(=G_{cis}-G_{trans})$ values for $N^1$-Boc-$N^2$-(α-aminoacyl)-$N^2$-methylglycine methyl esters $Bu^tOCON^1HCHRCON^2MeCH_2COOMe$**

| No. | R | Solvent | $\delta^{15}N$ (ppm) N$^1$ | N$^2$ | $\delta^1H(N^1H)$ (ppm) | Nucleus | $\delta^1H_{cis}$ | $\delta^1H_{trans}$ | $T_c$ (°C) | $\Delta G^{\ddagger}$ (kJ mol$^{-1}$) At $T_c$ | At 353 K | $\Delta G^{\circ}$ (kJ mol$^{-1}$) At 298 K |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **34** | H (Gly) | DMSO | 82.8 | 104.8 | 6.75 | $N$-$CH_3$ | 2.82 | 2.99 | 80.4 | 76.0 | 76.1 | 1.87 |
| | | | | | | $CO_2CH_3$ | 3.69 | 3.64 | 69.6 | 77.0 | 75.6 | |
| | | | | | | α-$CH_2$ | 4.24 | 4.09 | 75.4 | 75.4 | 76.6 | |
| | | Pyridine | 77.9 | 99.9 | 7.42 | $N$-$CH_3$ | 3.03 | 2.95 | 62.2 | 74.2 | | 1.86 |
| | | | | | | $CO_2CH_3$ | 3.61 | 3.55 | 60.9 | 74.9 | | |
| **35** | Me (Ala) | DMSO | 98.7 | 102.4 | 6.93, 6.91*t* | $CO_2CH_3$ | | | 62.3 | 76.2 | 76.0 | 2.46 |
| | | | | | 7.02, 7.00*c* | | | | | | | |
| | | Pyridine | 93.7 | 98.2 | 7.92, 7.89*t* | $N$-$CH_3$ | 3.05 | 3.13 | 68.4 | 75.7 | | 2.76 |
| | | | | | 8.25, 8.22*c* | $CO_2CH_3$ | 3.66 | 3.54 | 69.2 | 75.1 | | |
| **36** | iPr (Val) | DMSO | 93.7 | 108.3 | 7.99, 7.95*t* | $CO_2CH_3$ | 3.67 | 3.63 | 68.6 | 79.1 | 79.3 | 3.11 |
| | | | | | 8.35, 8.31*c* | | | | | | | |
| | | Pyridine | 89.1 | 102.9 | 6.76, 6.73*t* | $N$-$CH_3$ | 3.08 | 3.23 | 80.0 | 78.1 | | 3.31 |
| | | | | | 6.92, 6.89*c* | $CO_2CH_3$ | 3.66 | 3.55 | 74.8 | 77.7 | | |
| **37** | iBu (Leu) | DMSO | 96.3 | 105.6 | 6.91, 6.88*t* | $CO_2CH_3$ | 3.68 | 3.63 | 64.7 | 76.9 | 77.4 | 2.67 |
| | | | | | 7.01, 6.98*c* | | | | | | | |
| | | Pyridine | 91.3 | 100.3 | 8.05, 8.02*t* | $N$-$CH_3$ | 3.08 | 3.23 | 77.6 | 77.3 | | 3.14 |
| | | | | | 8.38, 8.35*c* | $CO_2CH_3$ | 3.18 | 3.55 | 73.2 | 76.6 | | |

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