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Stereochemistries of Aromatic *N*-Methylamides in Crystal and Solution. Temperature-dependent Conformational Conversion and Attracting Aromatic-Aromatic Interactions.

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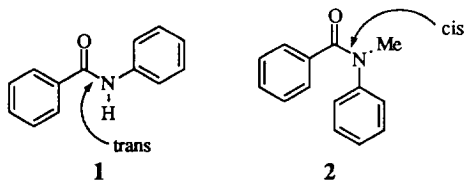
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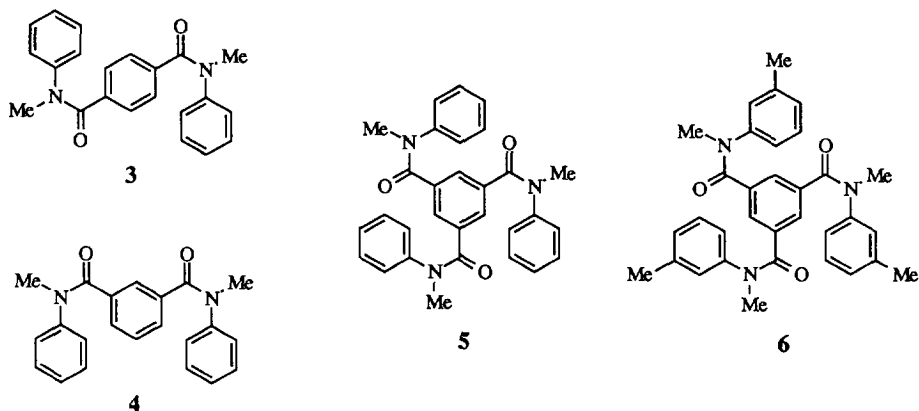
Abstract: Crystal structures and dynamic behavior in solution of some aromatic *N*-methylamides were analyzed. Every *N*-methylamide examined was in *cis* form in the crystal, and exhibited *cis*-preference in solution. Among them, *meta*-substituted amides, such as *N,N',N''*-trimethyl-*N,N',N''*-triphenyl-1,3,5-benzenetricarboxamide (**5**), exist in the all-*syn* conformation, in which all the *N*-phenyl groups are on the same side of the plane of the central benzene ring in the crystal. ¹H-NMR studies suggested that **5** existed mainly in all-*syn* conformation at low temperature as found in the crystal, while the *anti* conformation, in which one *N*-phenyl group is on the opposite side of the central benzene ring, becomes predominant at higher temperature, and a rapid equilibrium exists between the *syn* and the *anti* conformations. This is a result of the positive enthalpy ($\Delta H^\circ = +2.1$ kcal/mol) and the identical-signed large entropy ($\Delta S^\circ = +8.4$ cal/mol·K) for the conversion from *syn* to *anti* conformation. From NMR experiments, the enthalpy gained by assembly of the three phenyl groups in solution was deduced to be 2.8 kcal/mol.

The amide moiety has conformational and electronic characteristics which often determine the physicochemical or biological properties of a molecule, and it plays roles in a variety of molecular recognition events. Most compounds having a secondary amide bond (which has a proton on the nitrogen atom) exist in *trans* (*Z*) form.¹ We found in the course of investigations on various biologically active substances that *N*-methylation of aromatic secondary amides or ureas causes a dramatic loss of the biological activity due to conformational change of the amide or urea structures.² The importance of *trans/cis* stereochemistry is clear, for example, in the biochemistry of immunosuppressants.³

A *cis*-preference is general in *N*-methyl aromatic amides; that is, benzanilide (**1**) exists exclusively in the *trans* conformation both in the crystal and in solution, whereas *N*-methylbenzanilide (**2**) exists predominantly in the *cis* structure.⁴ In the ¹H-NMR spectrum of **2** in CD₂Cl₂, a major peak and a minor peak of the *N*-methyl group are observed below 233 K (the ratio is 98.6 : 1.4 at 183 K), and they coalesce at 233 K. Accordingly, the free energy difference between the two conformers (ΔG°) is 1.5 kcal/mol (at 183 K), and the *trans/cis* isomerization barrier (ΔG^\ddagger) at the coalescence point is 13.3 ± 0.3 kcal/mol (at 233 K).⁵ The chemical shift patterns at high and low temperatures are slightly different, because of the slight increase in the ratio of the minor *trans* isomer at higher temperature. The Ar-N and Ar-CO rotations are rather free and the rotational barriers are estimated to be less than 10 kcal/mol. The *cis*-preference is generally observed in *o*- and *o,o'*-substituted *N*-methylbenzanilides, and the barriers between *cis* and *trans* conformations are around 14 - 23 kcal/mol.⁵ In the



crystal, these *N*-methylated aromatic anilides exist in *cis* form. The angle made by the planes of the two aromatic rings is 60° in **2**. At present, the origin of the *cis*-preference in *N*-methylated aromatic anilides is not clear. The interaction of the two aromatic rings does not seem to be a major reason since the *cis*-preference is also observed in several non-aromatic *N*-acyl-*N*-methylanilines.⁶ However, the preference of *N*-methylated aromatic anilides to locate two aromatic rings in the *cis* position can be used for the fixation of a molecule in a shape that seems relatively unfavorable from simple stereochemical considerations.⁷ In such a case, two or more aromatic rings presumably interact spatially to elicit the unique stereochemical behavior. In this paper, we discuss the crystal structures and dynamic behavior of bis- and tris-*N*-methylanilides **3** - **6**.



Results and Discussion

Crystal Structures

The crystal structures of *N,N'*-dimethyl-*N,N'*-diphenyl-1,4-benzenedicarboxamide (**3**) and *N,N'*-dimethyl-*N,N'*-diphenyl-1,3-benzenedicarboxamide (**4**) are illustrated in Figure 1. The *N*-methylamide moieties of both compounds have the *cis* conformation, as observed in the crystal of *N*-methylbenzanilide (**2**). The orientations of the two terminal phenyl moieties, however, differ from each other. For compound **3**, the *N*-phenyl groups are located on opposite sides of the plane of the central benzene ring (*anti* conformation). On the other hand, the meta compound **4** exists in *syn* conformation, in which the *N*-phenyl groups are located on the same side. One terminal phenyl ring is nearly at right angles to the other *N*-phenyl ring (84°) and the closest atom is hydrogen at the meta position. The two *N*-phenyl groups are arranged in an L-shape or a distorted T-shape rather than in a T-shape,⁸ suggesting that aromatic-aromatic interaction between the *N*-phenyl rings is present in the crystal (Figure 3a).

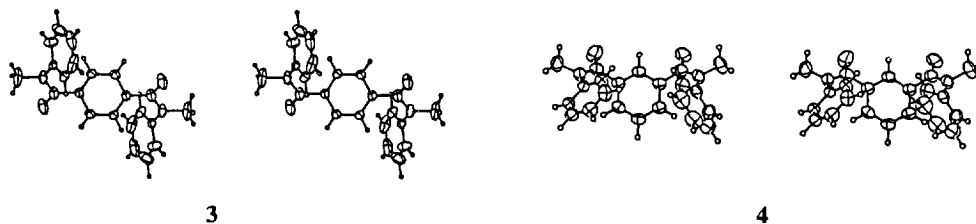


Figure 1. ORTEP stereoviews of compounds **3** (left) and **4** (right)

The crystal structure of *N,N,N''*-trimethyl-*N,N',N''*-triphenyl-1,3,5-benzenetricarboxamide (**5**) is shown in Figure 2. The stereochemistry of all three amide bonds is *cis*, as expected, and surprisingly, the three *N*-Ph groups are all located on the same side of the plane of the central benzene ring (all-*syn* structure). The molecule in the crystal nearly has a three fold axis of symmetry, the torsion angles of the three amide bonds

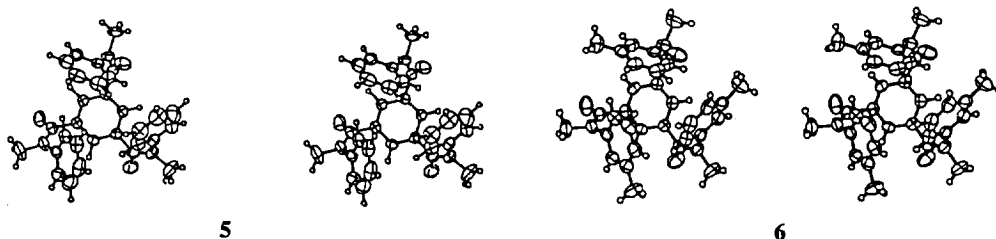


Figure 2. ORTEP stereoviews of compounds 5 (left) and 6 (right)

($C_{ph}-C-N-C_{ph}$) being 3° , 0° and 7° , those of Ar-CO being 48° , 59° and 48° , and those of Ar-N(C_{Me}) being 61° , 68° and 61° , respectively.⁹ The angles made by the planes of the pairs of *N*-phenyl rings are 74° , 79° and 83° . Though the distances between the centers of the pairs of *N*-phenyl rings are slightly larger than that of the optimized T-shaped benzene dimer (Table I, Figure 3), this conformation is compact and sterically crowded, and looks less favorable in terms of free energy. Thus, the stabilization of the all-syn structure is possibly due to mutual bonding interactions of the three benzene rings. The angles made by the benzene rings in the crystal structure suggest that these interactions are three L- or distorted T-shaped interactions of pairs of *N*-phenyl rings (Figure 3b), and the bonding energy may be significant, as discussed by Jorgensen and Severance^{8a} or Hobza et al.^{8b}

The all-syn structure as observed in compound 5 was maintained when a methyl group was introduced at the meta position of each *N*-phenyl ring. Figure 2 shows the crystal structure of *N,N,N'*-trimethyl-*N,N,N'*-tris(3-methylphenyl)-1,3,5-benzenetricarboxamide (6). The molecule has three *cis*-amide bonds, and the three *N*-(*m*-tolyl) groups are on the same side of the plane of the central benzene ring, as in the case of 5. All three *meta*-methyl groups are directed outside of the molecule, as expected. For compound 6, three L- or distorted T-shaped structures of pairs of *N*-phenyl rings are also observed in the crystal (Figure 3c). The distances between the centers of the pairs of *N*-phenyl rings are smaller than in compound 5, and are very close to that of the optimized distorted T-shaped benzene dimer (Table I, Figure 3e).

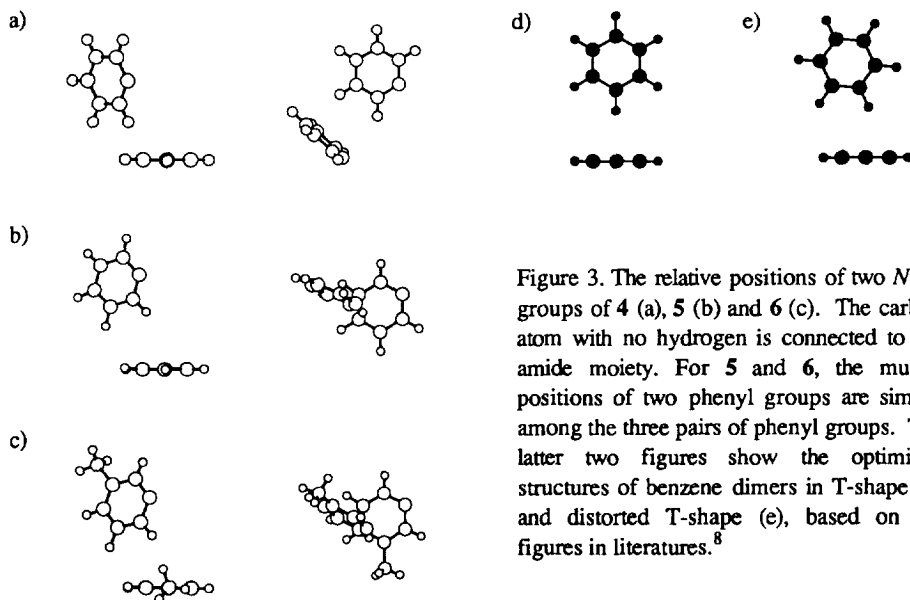


Figure 3. The relative positions of two *N*-Ph groups of 4 (a), 5 (b) and 6 (c). The carbon atom with no hydrogen is connected to the amide moiety. For 5 and 6, the mutual positions of two phenyl groups are similar among the three pairs of phenyl groups. The latter two figures show the optimized structures of benzene dimers in T-shape (d) and distorted T-shape (e), based on the figures in literatures.⁸

Table I. Comparison of ring center-ring center distances between the *N*-phenyl groups of aromatic *N*-methylanilides **4** - **6** and optimized benzene dimers^a

Compound	Ring center-ring center distance (Å)	
4	6.36	
5	5.28, 5.49, 5.42	
6	4.99, 5.00, 5.00	
Calculated optima		
T-shaped	5.19 ^a	5.00 ^b
distorted T-shaped	4.99 ^a	5.05 ^b

^a Ref. 8a. ^b Ref. 8b.

Structural Behavior in Solution

Equilibrium Constant and Entropy/Enthalpy

In the case of two conformers A and B (the existence ratios are x_A and $x_B = 1 - x_A$, respectively) in equilibrium with each other, the equilibrium constant $K = (1 - x_A)/x_A$ is generally correlated with enthalpy and entropy by the relation $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -RT \ln K$, where T is temperature and R is the gas constant. The equation can be transformed to $-\ln K = \Delta H^\circ/RT - \Delta S^\circ/R$, and there is a first-order correlation between $-\ln K$ and $1/T$ through the enthalpy ΔH° , but the entropy ΔS° . Then, putting $K = (1 - x_A)/x_A$, we obtain $x_A = 1/(\exp[(\Delta S^\circ - \Delta H^\circ/T)/R] + 1)$. If ΔH° is zero, the equation can be written as $x_A = 1/(\exp[\Delta S^\circ/R] + 1)$, which shows that the existence ratio is not affected by temperature. If ΔS° is zero where x_A is $1/(\exp[-\Delta H^\circ/RT] + 1)$, or if the sign of ΔH° is opposite to that of ΔS° , there is no temperature in which the existence ratio reverses itself, and the ratio of the minor conformer (enthalpically unfavorable) increases to a certain limited value (less than 0.5) as the temperature is increased. *Only when ΔH° is not 0 and its sign is the same as that of ΔS° can a most significant change (inversion of conformer ratio) occur as the temperature is varied.*

The theory is straightforward, but few examples of detailed analysis of such organic systems in solution have been reported. Moreover, the change of existence ratio can be observed in the NMR spectrum as a change of chemical shifts depending on the temperature only when there is a sufficiently large difference of chemical shifts of two conformers in rapid equilibrium. The following results can be well understood in terms of these concepts.

N,N'-Dimethyl-*N,N'*-diphenyl-1,4-benzenedicarboxamide (**3**) and *N,N'*-Dimethyl-*N,N'*-diphenyl-1,3-benzenedicarboxamide (**4**)

The different conformers of these bisanilides (**3**, **4**) arise from the configuration of the amide groups (cis or trans), as well as the difference of torsional angles of the *N*-phenyl bond with the amide plane and the difference of torsional angles of the carbonyl planes with the central benzene ring. In these compounds, the *N*-phenyl rotation can generally be neglected because the rotation of *N*-phenyl bonds is so fast on the ¹H-NMR time scale that the two ortho protons on the *N*-phenyl group cannot be distinguished. The configuration of the *N*-methanamide moiety will be denoted as "c" (for cis) or "t" (for trans), and the configuration of the *N*-phenylcarbamoyl moiety with respect to the plane of the central benzene ring will be denoted by adding an apostrophe, as in "c'" or "t'" where the apostrophe indicates that the *N*-phenyl group lies below the central benzene ring (absence of the apostrophe indicates that the *N*-phenyl group lies above the central benzene ring). Therefore, for example, the expressions (c, c) and (c', c') indicate the same conformation. Furthermore, the expressions (c, c') and (c', c) indicate the same conformation for compound **3**, or the two anti enantiomers for compound **4**. (t) and (t') should not be discriminated in the experiments, because of their fast interconversion and small difference in chemical shifts. These conformational classifications are summarized in Figure 4.

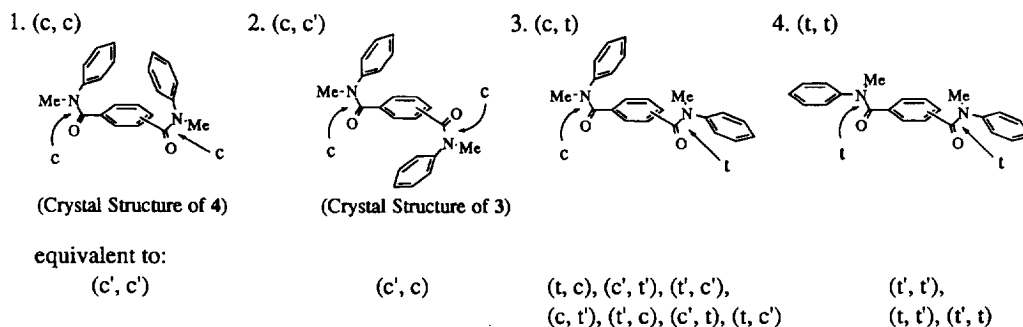


Figure 4. Conformational classification of compounds **3** and **4**. Representative structures and experimentally equivalent conformations

Figure 5 shows the temperature dependence of the $^1\text{H-NMR}$ spectrum of 1,4-bisanilide (**3**), which is very similar to that of *N*-methylbenzanilide (**2**). The chemical shifts in the aromatic region suggest that the two amides of the major conformer are in *cis* form. The peak broadening at 253 - 273 K suggests that there is an equilibrium of a species with a *trans* isomer which exists in a small amount, as in the case of **2**, as judged from the signals of the *N*-methyl hydrogens (Table II). The barrier to this isomerization is calculated to be 13 - 14 kcal/mol (at 243 K),¹⁰ which corresponds to the *trans/cis* isomerization barrier of **2**.⁵ Above the coalescence point of *N*-CH₃ (243 K), the observed chemical shifts are averaged ones of all 4 conformers (c, c), (c, c'), (c, t), (c, t') in rapid equilibrium, with slight increases in the contributions of the minor *trans*-amide structures [(c, t) and (c, t')] as in the case of *N*-methylbenzanilide at higher temperatures. Below the coalescence point,

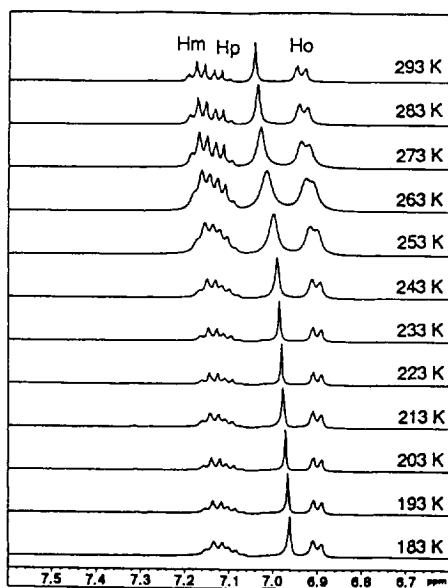


Figure 5. The temperature dependence of $^1\text{H-NMR}$ signals of **3** in the aromatic region.

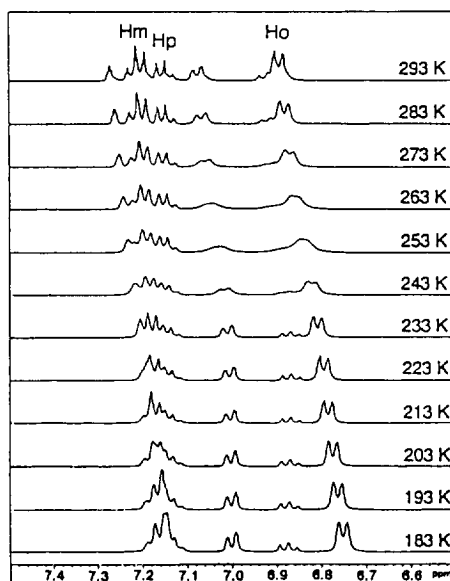
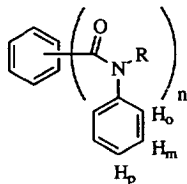


Figure 6. The temperature dependence of $^1\text{H-NMR}$ signals of **4** in the aromatic region.

the $N\text{-CH}_3$ signals split into two sets of peaks, of which the minor peaks (3.42 ppm, 1.2 %; 3.14 ppm, 1.2 %) were assigned to the $N\text{-CH}_3$ of *cis*-amide and the $N\text{-CH}_3$ of *trans*-amide of the conformer (c, t) [and conformer (c, t'): the two conformations should be in rapid equilibrium], and the major peak was assigned to conformers (c, c) and (c, c') in rapid equilibrium. The presence of conformers with two *trans*-amide bonds (t, t) or (t, t') is not indicated (judging from the small existence ratio of *trans*-amide, it should be negligible). Because no temperature dependence of the chemical shifts [that is, no change in the ratio of conformers (c, c) and (c, c')] was observed in the temperature range below 243 K, although a large difference of chemical shifts between (c, c) and (c, c') would be expected, the difference (ΔH°) of enthalpy terms may be almost zero, that is, the two N -phenyl rings interact little (neither attracting nor repelling).

Figure 6 shows the temperature dependence of the $^1\text{H-NMR}$ spectrum of 1,3-bisanilide (4). The chemical shift of Ho proton of 4 is more shielded to higher field than that of 3 (Table II). Since a chemical shift difference between the signals at high and low temperatures is observed, the composition of conformational structures (*trans/cis* or *syn/anti*, or both) depends on temperature. The coalescence point of $N\text{-CH}_3$ peaks at 233 K is due to the *trans/cis* conversion ($\Delta G^\ddagger = 13$ kcal/mol).¹⁰ The temperature dependence of the chemical shifts of the major species [conformers (c, c) and (c, c')] below the coalescence point is particularly important: this indicates that the existence ratio of the conformer (c, c) increases as the temperature is lowered, since the chemical shifts of the ortho protons (Ho) in the conformer (c, c) are expected to be at higher field than those of conformer (c, c') because of the aromatic anisotropic effects. The enthalpy and the entropy difference

Table II. Chemical shifts and coalescence point of N -methyl peaks and temperature dependence of Ho chemical shifts of aromatic N -methylanilides (3 - 6)



Compound	Temp. (K)	Chemical shift of N -phenyl group(s)			Chemical shift and existence ratio ^a of N -methyl peaks	
		Ho	Hm	Hp	major peak	minor peak(s)
1 Benzanilide (R=H)	293	7.63	7.36	7.14	none	none
2 N -Methylbenzanilide (R=Me)	293	7.04	7.21	7.12	3.43	
	233 ^b	7.01	7.21	7.10	3.41	
3	183	7.00	7.20	7.10	3.39 (98.6%)	3.25 (1.4%)
	293	6.93	7.17	7.11	3.37	
	243 ^b	6.90	7.15	7.10	3.36	
4	183	6.90	7.13	7.09	3.33 (97.6%)	3.42 (1.2%), 3.14 (1.2%)
	293	6.89	7.21	7.15	3.36	
	233 ^b	6.81	7.19	7.13	3.35	
5	183	6.75	7.17	7.13	3.33 (98.0%)	3.43 (1.0%), 2.71 (1.0%)
	293	6.66	7.22	7.23	3.28	
	233 ^b	6.50	7.19 - 7.22		3.28	
	183	6.39	7.17	7.22	3.24 (98.8%)	3.36 (0.8%), 2.34(0.4%)

^a The total of $N\text{-CH}_3$ peak areas is taken as 100 %.

^b Coalescence point (± 5 K) of the major peak of $N\text{-Me}$ and the minor peak in lower field.

between (c, c) and (c, c') can be calculated if the temperature dependence of the existence ratio of the components is obtained. The existence ratio can not be directly obtained because the conformers are in rapid equilibrium, but it can be obtained from the equation $C_{\text{OBS}} = x_A C_A + (1-x_A)C_B$, where C_{OBS} is the observed chemical shift (Ho), C_A is the chemical shift (Ho) of conformer (c, c), and C_B is that of conformer (c, c'). For compound **4** (as well as other benzanilides), the equilibrium is so fast even at low temperature that the chemical shifts of the individual conformers (c, c) and (c, c') can not be obtained. Therefore, they need to be estimated in an indirect way. C_B is estimated to be 7.00 ppm, which is the chemical shift (Ho) of *N*-methylbenzanilide (**2**), because the anisotropic effect of one *N*-phenyl group may scarcely affect the hydrogen of the other *N*-phenyl group. Consequently, the chemical shifts (C_A) of conformer (c, c), and the enthalpy (ΔH°) and the entropy (ΔS°) are deduced to be 6.54 ppm, 0.72 kcal/mol and 3.6 cal/mol·K, respectively, to make the observed points (below 233 K, the coalescence point related to the amide conversion) agree with the equation $\Delta H^\circ - T\Delta S^\circ = -RT \ln K$ ($= -RT \ln [(1-x_A)/x_A] = -RT \ln [(C_{\text{OBS}}-C_A)/(C_B-C_{\text{OBS}})]$). These chemical shift values and thermodynamic constants reproduce the observed chemical shifts exactly (correlation between calculated and observed values is 0.99991, Figure 7). It is important to notice that the syn structure (c, c) is more stable in terms of enthalpy, in spite of the steric repulsion between the phenyl rings. In other words, the repulsive energy is cancelled by an attractive force between the two phenyl rings. That is, an attracting force between two phenyl rings in 1,3-positions exists, which is in contrast to the case of 1,4-bisanilide (**3**).

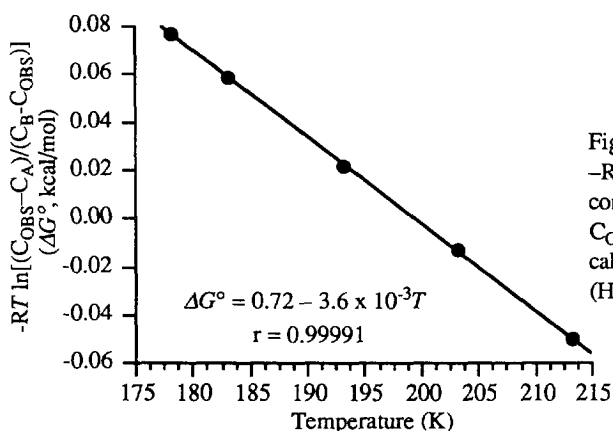


Figure 7. Plot showing the correlation between $-RT \ln K$ ($= \Delta G^\circ$) and temperature (K) for compound **4**, where $K = [(C_{\text{OBS}}-C_A)/(C_B-C_{\text{OBS}})]$: C_B is 7.00 ppm and C_A is 6.54 ppm, as calculated from the extrapolated chemical shift (Ho) of compound **6**.

N,N',N''-Trimethyl-*N,N',N''*-triphenyl-1,3,5-benzenetricarboxamide (**5**) and *N,N',N''*-Trimethyl-*N,N',N''*-tris(3-methylphenyl)-1,3,5-benzenetricarboxamide (**6**)

Table III shows the conformational classification of these compounds, which can be discriminated experimentally as in the case of the bisanilides. These compounds exist in conformation (c, c, c) in the crystal. Analysis of the $^1\text{H-NMR}$ spectra of these trisanilides was conducted to obtain information on the solution stereochemistry and phenyl-phenyl interactions. The spectra are strongly dependent on temperature.

Table III. Conformations of **5** and **6** which can be discriminated^a

(c, c, c)	(c, c, c')	(c, c, t)	(c, c', t)	(c, t, t)	(t, t, t)
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^a (c, c, c) is equivalent to (c', c', c'). Equivalent structures, for example, of (c, c, c') are shown in Figure 12. (t) and (t') cannot be discriminated because of their similar NMR chemical shifts. Conformers having more than two *trans*-amides can not be observed experimentally because of their small amounts.

In the NMR spectrum of the compound **5** at 183 K, there is a major singlet peak at 3.24 ppm accompanied with two minor singlets (3.36 ppm and 2.34 ppm, 2:1) in the *N*-methyl proton region (Table II). In a similar way to the case of the *trans/cis* isomerization (in CD₂Cl₂ at 183 K) of **2**, **3** and **4**, the latter two *minor* singlets can be attributed to the methyl protons of the conformers with two *cis*-amides and a *trans*-amide, that is, the conformers (c, c, t), (c, c, t'), and (c, c', t) which are in rapid equilibria. The smaller peak (0.4%, 2.34 ppm) of higher chemical shift is assigned to the *N*-methyl protons of the *trans*-amide moiety of the conformations in rapid equilibria, and the other (0.8%, 3.36 ppm), to those of *cis*-amide moieties. These minor peaks coalesced at 233 ± 5 K, in good agreement with the general coalescence point of *trans/cis* equilibrium.

Figure 8 shows the temperature dependence of the aromatic region of compound **5**. The signals of aromatic protons appear over a wide range of chemical shifts, but the assignments of Hc (the hydrogen of the central benzene ring: 6.84 ppm at 183 K and 7.00 ppm at 293 K) and Ho (the hydrogens ortho to the amide bond on the *N*-phenyl group: 6.39 ppm at 183 K and 6.66 ppm at 293 K) are obvious. The chemical shifts in the aromatic region are much more shielded than those observed for **4** (Table II). Decrease of the temperature broadened all the peaks at around 263 K. The estimated coalescence point is around 233 K, and corresponds to an energy barrier of 13 kcal/mol,¹⁰ which can be interpreted in terms of *trans/cis* isomerization, as in the case of *N*-methylbenzanilide or the 1,3- and 1,4-bisanilides. A further temperature decrease causes further sharpening of the peaks and change of the chemical shift. At 183 K, the peak of Ho only (protons of *N*-phenyl groups ortho to the amide bond) becomes broad again. This broadening phenomenon is due to the coalescence derived from the restricted rotation of the N-Ph bonds, which may differentiate the two kinds of ortho protons. In a simple *N*-methylamide, this N-Ph rotation barrier is less than 10 kcal/mol, as in the case for the CO-Ph bond.^{5,10} The coalescence in this compound, however, was observed at a relatively higher temperature, due to the benzene-benzene steric interaction accompanying N-Ph rotation and the large difference of chemical shifts between the protons on the inside and outside of the molecule.

The temperature dependence of the chemical shifts of *N*-phenyl protons is much greater than in the case of 1,3-bisanilide (Table II). The signal assigned to Ho moved to 6.66 ppm, which is still very high, at 293 K. Though the conformers (c, c, t), (c, c, t'), (c, c', t) and their equivalents exist, they are minor because the essential *cis*-amide preference is not greatly changed by change of the temperature, as found for *N*-methylbenzanilide (**2**), **3** and **4**, and the amount of the *trans*-amide is at most about 1 - 2 %. Therefore, the major species observed at 293 K are assigned as the anti conformers (c, c, c'), (c, c', c), (c', c, c), whereas the major conformer at 183 K is the all-syn structure (c, c, c) as observed in the crystal. In order to confirm this assignment, the stereochemistry of *N,N,N'*-trimethyl-*N,N',N''*-tris(3-methylphenyl)-1,3,5-benzene-tricarboxamide (**6**) was examined.

Compound **6** exists in conformation (c, c, c) and the three Ho protons are located over the central benzene ring in the crystal (Figure 2). The steric bulkiness of the *meta*-methyl group will restrict N-Ph bond rotations, and favor the conformation in which three *meta*-methyls are directed outside of the molecule. Furthermore, two kinds of ortho position to the amide nitrogen are expected to be distinguishable in solution by NMR. If

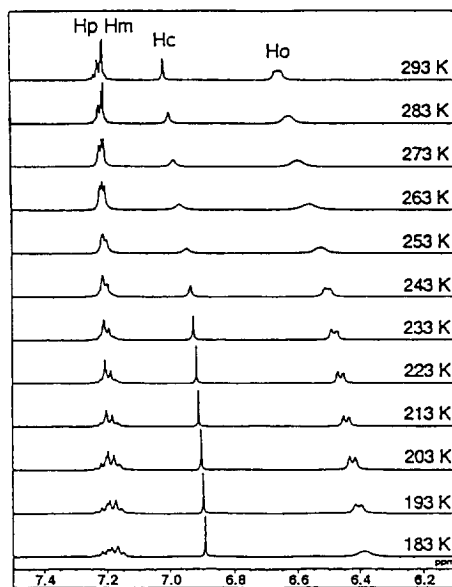


Figure 8. The temperature dependence of ¹H-NMR signals of **5** in the aromatic region.

compound **6** exists in all-syn-cis conformation and H_o is in the inside of the molecule (the left structure in Figure 10), as in the crystal structure, the H_o protons should be strongly shielded. On the other hand, signals of H_o' protons outside of the molecule should be observed at normal positions because they are not affected by the aromatic rings on the outside of the molecule in the all-syn-cis conformation (c, c, c). If the ratio of anti conformation increases, the peaks of H_o and H_o' protons should shift to lower and higher field, respectively.

Figure 9 shows the temperature-dependent 1H -NMR spectrum of **6** in CD_2Cl_2 . Peak broadening is seen at around 253 K - 283 K, as always observed for the other *N*-methylamides and attributed to the trans/cis isomerization of the amides. The H_o' protons were observed at 6.84 ppm as a broad singlet at 293 K, and shifted to lower field with more broadening as the temperature was lowered. On the other hand, H_o protons were observed as a broad singlet (6.32 ppm at 293 K), and shifted to higher field with more broadening. At 178 K, this peak assigned to H_o was observed at anomalously high field (5.20 ppm) as a doublet. Thus, at low temperature, **6** exists mainly in the all-syn-cis conformation. The chemical shift of the other *ortho*-position proton (H_o') of *N*-Ph is seen at relatively low field (7.11 ppm), as expected. The movement of the H_o proton chemical shifts seems to stop below 183 K. The integration of the peak of H_o proton accounts for 68% of all H_o , and two broad minor peaks are observed at 5.55 ppm and at 5.99 ppm in the ratio of about 2 : 1. The other minor peaks are considered to be in the region of 6.8 - 7.2 ppm, deduced from the integrations. These minor peaks at higher field could be assigned to H_o' or H_o protons (which are on the inside of the molecule) of a minor conformer caused by rotation of an *N*-Ph bond (Figure 10), but definitely not to H_o protons of the anti conformer, because the chemical shifts are at much higher field than those of **5** at 183 K (6.38 ppm). Thus, both the conformers at the low temperature are all-syn conformers. In contrast, the chemical shifts seem to converge above 283 K, and therefore the anti conformers [(c, c, c'), *etc.*] exist predominantly above this temperature.

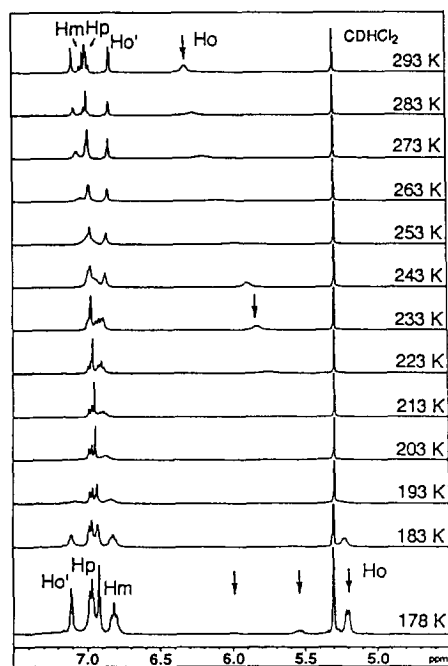


Figure 9. The temperature dependence of 1H -NMR signals of **6** in the aromatic region.

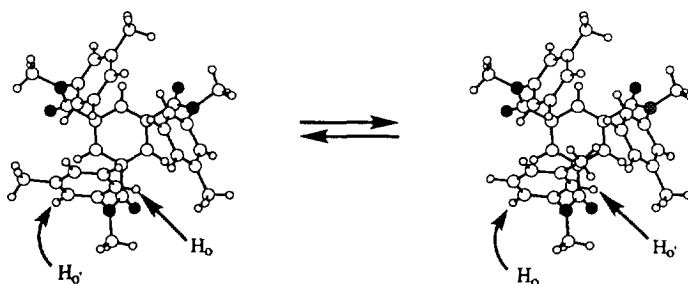


Figure 10. The *N*-Ph bond rotation of **6**

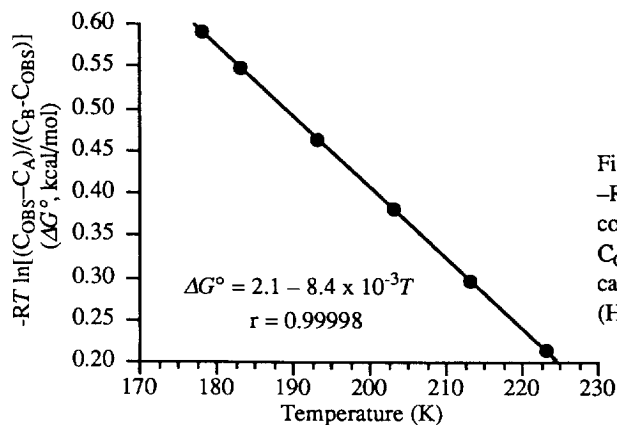


Figure 11. Plot showing the correlation between $-RT \ln K$ ($= \Delta G^\circ$) and temperature (K) for compound 5, where $K = [(C_{\text{OBS}} - C_A)/(C_B - C_{\text{OBS}})]$: C_B is 6.69 ppm and C_A is 6.32 ppm, as calculated from the extrapolated chemical shift (Ho) of compound 6.

From the results described above, the static Ho chemical shift of conformer (c, c, c) of compound 5 was initially estimated to be 6.32 ppm by extrapolation of the averaged chemical shifts of Ho and Ho' of compound 6 at lower temperature, allowing for the electronic effect of the methyl group on the chemical shift. The static averaged chemical shift of the ortho position of the conformer (c, c, c') of 5 was initially estimated to be 6.85 ppm from the averaged chemical shifts of the conformers of compound 4 [a ratio of 2:1 of (c, c') and (c, c)]. These chemical shifts were modified in order to reproduce the observed chemical shift movements, and the final best-fit values were $C_A = 6.32$ and $C_B = 6.69$, where the enthalpy (ΔH°) and the entropy (ΔS°) differences between compound 5 isomers (c, c, c) and (c, c, c') could be calculated to be 2.1 kcal/mol and 8.4 cal/mol·K, respectively (Figure 11), from the temperature dependence of the chemical shifts of Ho below the coalescence point. Thus, the free energy relationship between (c, c, c) and (c, c, c') is expressed by $\Delta G^\circ = -RT \ln K = 2.1 - 8.4 \times 10^{-3} T$.

The attractive enthalpic force very plausibly arises from the three-fold phenyl-phenyl interactions. Since the conversion from (c, c, c) to (c, c, c') decreases two Ph-Ph interactions among the three, 2.1 kcal/mol is attributed to two such interactions. In other words, the three Ph-Ph interactions are estimated to amount to 2.8 kcal/mol, because (c, c, c') has still one Ph-Ph interaction similar to that observed in 1,3-bisanilide (4; $\Delta H^\circ = 0.7$ kcal/mol). Since the major equilibrium among (c, c, c) and (c, c, c') and the equivalent conformers is attained simply through easy and fast CO-Ph rotations (Figure 12), the exchange is rapid. The isomer ratio in the equilibrium, however, is controlled by temperature.

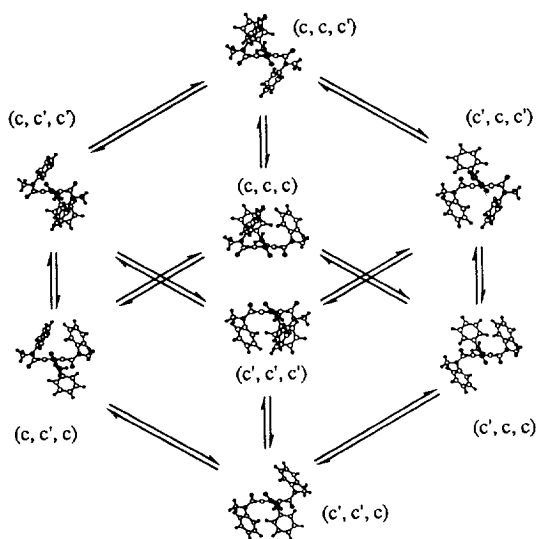


Figure 12. Schematic representation of fast equilibria between all-syn conformers and syn-anti conformers. Conformers (c, c, c) and (c', c', c') are predominant at low temperature. (c, c, c') and its equivalents are predominant at higher temperatures.

Temperature Dependence of the Energy Profile

For the trisanilides (**5**, **6**) with *N*-methylamide structures at meta positions, the syn conformation is the most stable in terms of enthalpy. The stability seems to be derived from an attractive interaction among the terminal *N*-phenyl groups. Accordingly, at lower temperature, predominance of the syn conformation is observed. At higher temperature, the anti conformer is more stable because the contribution of the entropy is relatively larger (Figure 13). The temperature (T_E) at which the existence ratio of the two conformers (c, c, c) and (c, c, c') is unity, depends on the entropy and the enthalpy. Since the temperature is within the range used in the NMR spectroscopy, the change of the most stable conformer can be observed. For the *meta*-bisanilide (**4**), the same tendency exists, but the temperature dependence of the existence ratio of conformers (c, c) is smaller because both the enthalpy and the entropy are rather small.

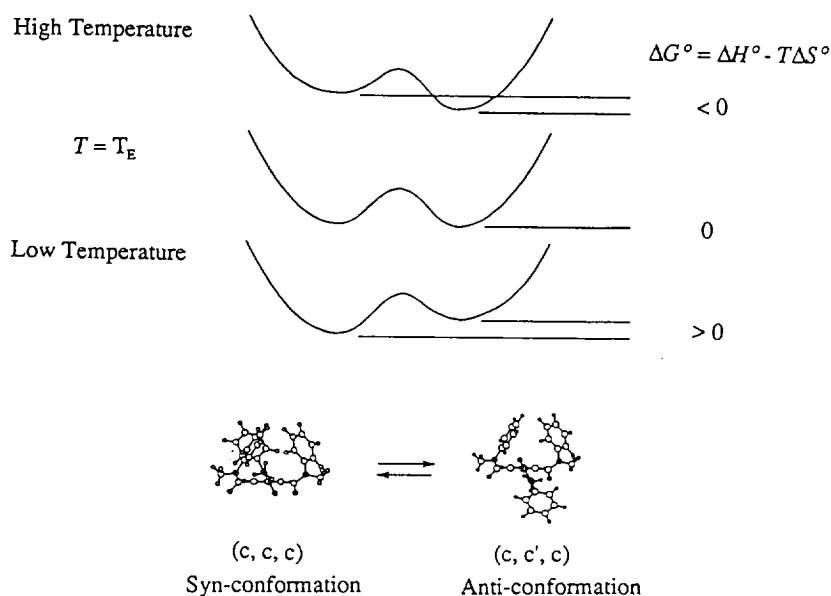


Figure 13. The temperature dependence of the energy profile of **5**

Conclusion

The phenomenon of exchange of stable conformations depending on temperature requires a moderate enthalpy and a large entropy which have identical sign, and for observation of the phenomenon by NMR spectroscopy, a large difference of the chemical shifts of species in rapid equilibrium is needed. The compounds discussed here satisfy these conditions, and such an example is also found in the conformational behavior of dihydrotitylbiphenyls.¹¹ Furthermore, an attractive aromatic-aromatic interaction certainly exists in the aromatic compounds, discussed here.

The *cis* preference of an aromatic *N*-methylamide structure and the attractive aromatic-aromatic interaction would be useful for constructing a specific three-dimensional structure of functionalized molecules. Such molecules with suitable functional groups may be useful as sophisticated probes in chemistry and biology. Furthermore, the temperature-dependent change of stable conformers could be useful for constructing a temperature-sensitive device.

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Experimental Section

Materials.

Bis- or tris-anilides (**3** - **6**) were prepared by the condensation of the corresponding benzenedi- or tricarboxylic acid chloride and *N*-methylaniline in dry dichloromethane and pyridine. All the compounds subjected to measurement were purified several times by recrystallization. Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Tokyo and were within $\pm 0.3\%$ of the theoretical values. The physical data are listed in Table IV.

Table IV. Physical data of aromatic *N*-methylanilides (**3** - **6**)

	Crystal form	Recrystn. solvent	mp, °C	Formula	Elemental Analysis			
					C	H	N	
3	colorless needles	AcOEt- <i>n</i> -hexane	214-215	C ₂₂ H ₂₀ N ₂ O ₂	Calcd	76.72	5.85	8.13
					Found	76.73	5.81	8.33
4	colorless prisms	AcOEt- <i>n</i> -hexane	165-166	C ₂₂ H ₂₀ N ₂ O ₂	Calcd	76.72	5.85	8.13
					Found	76.89	5.86	8.09
5	colorless prisms	AcOEt- <i>n</i> -hexane	262-263	C ₃₀ H ₂₇ N ₃ O ₃	Calcd	75.45	5.70	8.80
					Found	75.15	5.68	8.54
6	colorless prisms	AcOEt- <i>n</i> -hexane	185-185.5	C ₃₃ H ₃₃ N ₃ O ₃	Calcd	76.28	6.40	8.09
					Found	76.02	6.43	7.97

X-ray Crystallography¹²

The X-ray crystal structure analyses were performed on crystals of compounds **3** - **6**. Intensity data were collected with a Rigaku AFC5 diffractometer using graphite-monochromated Cu K α , radiation ($\lambda = 1.54050$ Å) by the ω - 2θ scan method. The typical ω scan width was $(1.3 + 0.41 \tan \theta)^\circ$. Intensities were corrected for Lorentz and polarization factors, but no correction was made for absorption.

Structures were solved by using the SAPI85 version of the program package MULTAN.¹³ The refinement was carried out by the full-matrix least-squares method with anisotropic thermal parameters for non-hydrogen atoms. The function minimized was $\sum w(|F_o|)^2 - (|F_c|)^2$ with $w = 1/[\sigma^2(F_o) + 0.02(F_o)^2]$, while $\sigma(F_o)$ was determined from counting statistics. All H atoms located from the difference map and from theoretical calculations were refined. All calculations were performed by using a Panafacom computer with the RCRYSTAN (Rigaku Corp., 1985) X-ray analysis program system. The atomic scattering factors were taken from the International Tables for X-ray Crystallography (1974). The final atomic coordinates and thermal parameters for the crystals have been deposited as supplementary material.

Table V. Crystal data of aromatic *N*-methylamides (3 - 6)

Compound	3	4	5	6
Formula	C ₂₂ H ₂₀ N ₂ O ₂	C ₂₂ H ₂₀ N ₂ O ₂	C ₃₀ H ₂₇ N ₃ O ₃	C ₃₃ H ₃₃ N ₃ O ₃
<i>M_r</i>	344.41	344.41	477.56	519.65
Crystal system	monoclinic	monoclinic	monoclinic	orthorhombic
Space group	<i>P</i> 2 ₁ /a	<i>P</i> 2 ₁ /n	<i>P</i> 2 ₁ /n	<i>Pbca</i>
<i>a</i> / Å	12.417(1)	18.2005(8)	20.898(2)	17.862(1)
<i>b</i> / Å	9.644(2)	11.839(5)	15.184(1)	17.863(1)
<i>c</i> / Å	7.835(1)	8.771(1)	8.771(1)	17.816(1)
β / °	96.59(1)	100.24(1)	98.97(1)	
<i>V</i> / Å ³	932.0(2)	1859.7(9)	2578.8(6)	5684(2)
<i>D_x</i> / Mgm ⁻³	1.227	1.230	1.230	1.214
<i>Z</i>	2 ^a	4	4	8
No. of unique reflections	1201	2351	3261	3513
<i>R</i>	0.072	0.064	0.057	0.067

^a 1/2 molecule in an asymmetric unit.

¹H-NMR Analysis

¹H-NMR spectra were recorded on a JEOL GSX 400-MHz spectrometer. The temperatures indicated by the NMR instrument were checked by measuring the differences of chemical shift between methyl protons and the hydroxyl proton of methanol.¹⁴ A solvent used for the measurements (with range of temperature, and internal standard) was dichloromethane-*d*₂ (183 K - 293 K, CDHCl₂ as 5.30 ppm), and all measurements were started at room temperature (293 K) and done by decreasing the temperature in steps of 10 K. The concentration of each solution was 10 mg/ml; no change of spectra was observed at lower concentration (2 mg/ml).

References

- In this paper, the term "cis" and "trans" are used to show the relative position of *substituents* connected to the amide group. The designation can be easily understood at a glance, though, ordinarily, "cis-amide" and "trans-amide" should be named (*E*)- and (*Z*)-amide, respectively.
- (a) Kagechika, H.; Himi, T.; Kawachi, E.; Hashimoto, Y.; Shudo, K. *J.Med.Chem.* **1989**, *32*, 2292-2296. (b) Toriumi, Y.; Kasuya, A.; Itai, A. *J.Org.Chem.* **1990**, *55*, 259-263. (c) Okamoto, T.; Shudo, K.; Takahashi, S.; Kawachi, E.; Isogai, Y. *Chem.Pharm.Bull.* **1981**, *29*, 3748-3750. (d) Yamaguchi, K.; Shudo, K. *J.Agric.Food Chem.* **1991**, *39*, 793-796.
- Seebach, D. *Aldrichchimia Acta* **1992**, *25*, 59-66, and the references cited therein.
- The crystal structure of benzanilide: Kashino, S.; Ito, K.; Haisa, M. *Bull.Chem.Soc.Jpn.* **1979**, *52*, 365-369. The structure of *N*-methylbenzanilide in the crystal or in solution: (a) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177-6180. (b) Azumaya, I.; Kagechika, H.; Fujiwara, Y.; Itoh, M.; Yamaguchi, K.; Shudo, K. *J.Am.Chem.Soc.* **1991**, *113*, 2833-2838.
- Azumaya, I.; Yamaguchi, K.; Kagechika, H.; Saito, S.; Itai, A.; Shudo, K. *Yakugaku Zasshi* **1994**, *114*, 414-430.

- 6 Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J.Am.Chem.Soc.* **1992**, *114*, 10649-10650.
- 7 Yamaguchi, K.; Matsumura, G.; Kagechika, H.; Azumaya, I.; Ito, Y.; Itai, A.; Shudo, K. *J.Am.Chem.Soc.* **1991**, *113*, 5474-5475.
- 8 (a) Jorgensen, W. L.; Severance, D. L. *J.Am.Chem.Soc.* **1990**, *112*, 4768-4774. (b) Hobza, P.; Selzle, H. L.; Schlag, E. W. *J.Am.Chem.Soc.* **1994**, *116*, 3500-3506.
- 9 Attempts to analyze the crystal structure in terms of a three fold axis were unsuccessful.
- 10 The rotation barriers were calculated from coalescence point and the chemical shift differences. see Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH Publishers, Inc.Florida, 1985.
- 11 Grossel, M. C.; Cheetham, A. K.; Hope, D. A. O.; Weston, S. C. *J.Org.Chem.* **1993**, *58*, 6654-6661.
- 12 Yamaguchi, K. *Chem.Pharm.Bull.* **1993**, *41*, 424-429.
- 13 SAPI85: Yao, J.-X.; Zheng, C.-D.; Qian, J.-Z.; Han, F.-S.; Gu, Y.-X.; Fan, H.-F. (1985); MULTAN78: Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. (1978).
- 14 Van Geet, A. L. *Anal. Chem.* **1970**, *42*, 679-680.

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