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For 12- and 13-membered macrocycles in which two amide linkages are integrated in the macrocyclic ring systems, the formation of 1:1 host–guest complexes with acetic and benzoic acids has been confirmed by NMR titrations. The complex formation occurs with the formation constants of 8–27 M^{-1}, under competition with the dimerisation of acid molecules. Benzoic acid tends to form more stable complexes than acetic acid. The binding force is due to a pair of hydrogen bonds, $O_{carboxyl}$—H···O=C_{amide} and C=$O_{carboxyl}$···H—N_{amide}, between the carboxyl group of a guest molecule and the amide group of a host molecule. The former bond is stronger than the latter, and defines the stability of the complexes. The formation of the pair of hydrogen bonds is accompanied by the conformational conversion of the amide group from the *trans*-form to the *cis*-form. The influence of such a conversion on the internal molecular motion is observed as a slight broadening of signal width.

Keywords: amide group; carboxylic acids; hydrogen bonds; macrocycles; NMR

Introduction

The structural and chemical characteristics of the amide group are represented in terms of the partial double bond character of the C—N bond, the planar structure, the acidity of NH, a high negative charge density on the C=O oxygen and the hydrogen-bonding capability of both NH and C=O moieties (*1*). These properties of the amide group define the 3D structures and activities of the biological substances that are composed of amino acid residues. In relation to these important properties, amide-based receptors have attracted particular interest in the field of supramolecular chemistry (*2*, *3*). The complex formation of carboxylic acids also has been extensively studied because of their biological importance (*4–13*). Some amide-based receptors have been reported to form supramolecular assemblies (or host–guest complexes) with carboxylic acids in organic solvents (*4–6*, *9*, *10*). Their major binding force is due to hydrogen bonding between amide group in the hosts and carboxyl group in the guests. Recently, we have reported the formation of host–guest complexes in which an amide-based cyclophane molecule is bound to a monocarboxylic acid molecule with a pair of hydrogen bonds, N_{amide}—H···O=$C_{carboxyl}$ and C=O_{amide}···H—$O_{carboxyl}$ (*14*). These hydrogen bonds are supposed to be arranged in a fork-like manner resembling that formed commonly in a dimeric acid molecule. The formation of such hydrogen bonding requires the conformational change of the amide group from its stable *trans*-form to the less stable *cis*-form. A similar conformational conversion may also occur in biological substances when their amino acid residues recognise acid derivatives at the two binding sites. The *trans–cis* conformational conversion is, however, naturally less probable for molecules having a higher steric hindrance (*15*). In relation to these aspects, studies of acid complexes with smaller and simpler amide-based macrocycles are expected to provide more conclusive information about the nature of the fork-shaped hydrogen bonding of amide group. In this work, therefore, an NMR study has been carried out on complex formation between monocarboxylic acids and amide-based macrocycles **1**–**4** in Scheme 1, the macrocyclic rings of which are moderately rigid to different extents.

Results and discussion

NMR titration and host–guest complex formation

Macrocycles **1**–**4** were synthesised by esterification of appropriate macrocycles having pendant carboxyl arms. Although the parent macrocycles are practically insoluble in common organic solvents, the ester derivatives are sufficiently soluble in organic solvents for NMR studies. NMR titrations were carried out by observing ^{1}H NMR shifts of host protons in $CHCl_3$-*d*. The total concentration of a host $[H]_t$ was kept constant at 5 mM (mM = 10^{-3} mol dm^{-3}), and the total

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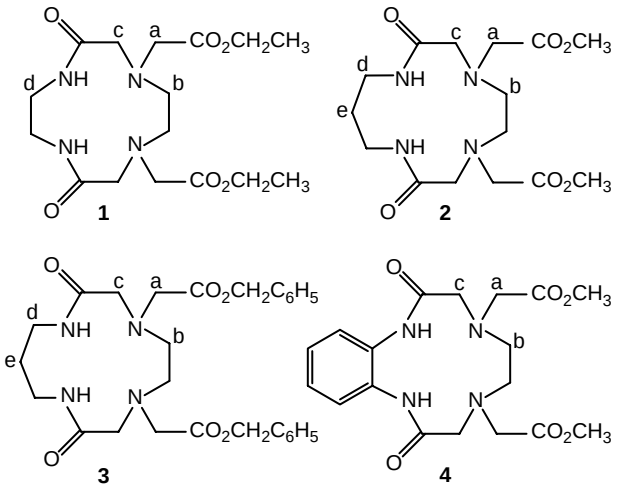

Scheme 1.

concentration of a guest $[G]_t$ was varied from 5 to 50 mM or higher.

A change in the NMR δ of a host proton by the addition of a guest is defined as $\Delta_H([G]_t) = \delta([G]_t) - \delta(0)$. The Δ_H values observed at $[G]_t$ 50 mM are listed in Table 1; the labels of protons are given in Scheme 1. The plots of Δ_H versus $[G]_t$ are representatively shown for the reaction system of **2** and acetic acid in Figure 1. An increase in Δ_H with increasing $[G]_t$ was observed for the amide NH proton and CH_2(c) protons of every host, suggesting the formation of complexes between the macrocycles and the carboxylic acids. Carboxylic acids are readily dimerised to form two C═O···H—O hydrogen bonds in a fork-like arrangement (*1*, *16*). In the host–guest complexes studied, the carboxyl C═O oxygen of a guest molecule forms a hydrogen bond with the amide NH of a host molecule, because the NH proton shows the largest change in the chemical shift. Among the CH_2 protons only the protons of CH_2(c) group bonded to amide C═O showed a significant increase in the δ value (Table 1). This change in the chemical shift of CH_2(c) protons is not caused by the hydrogen bonding of the amide NH, because the Δ_H value of CH_2(c) protons in each host is much larger than that of protons in CH_2(d) bonded directly to the amide N. Therefore, the larger Δ_H values of CH_2(c) protons are due to hydrogen bonding formed by the amide C═O, presenting evidence for the formation of $O_{carboxyl}$—H···O═C_{amide} bond, together with C═$O_{carboxyl}$···H—N_{amide} bond, between the guest and host molecules. When benzoic acid was added as a guest, a significant change in the chemical shift was observed for the CH_2(c) protons of every host, and the corresponding changes of other CH_2 protons were very small (Table 1). The NH proton signals of hosts **1** and **4** showed a large change in δ, although the signals of **2** and **3** were masked by the signals of benzoic acid. Benzoic acid also forms the same type of hydrogen bonds as in the acetic acid complexes.

The relative stabilities of *cis*- and *trans*-conformations in solution are altered with steric effect, and the stable conformation of some molecules having high steric constraints is the *cis*-form rather than the *trans*-form (*15*). Even macrocycles **1** and **4**, which have higher steric constraints than **2** and **3**, are, however, supposed to have the *trans*-conformation in solid, as confirmed by X-ray studies of their parent macrocycles having carboxyl arms (*17*, *18*). The macrocyclic rings of the compounds have a C_2 symmetry axis along the molecular plane in solid, and as a result of a rapid internal molecular motion in solution each pair of CH_2 groups exhibits a single NMR signal. When two hydrogen bonds are formed between amide and carboxyl groups in a fork-like arrangement, rigidity around the amide group in the macrocycle is increased so that internal motion is partially hindered. Such an effect is expected to be pronounced for the CH_2(c) moiety adjacent to amide

Table 1. ^{1}H NMR shifts Δ_H of hosts ($[H]_t$, 5 mM) at a guest concentration $[G]_t$ of 50 mM, in reference to the δ values at $[G]_t = 0$, in $CHCl_3$-*d* at 25°C: $\Delta_H = \delta([G]_t\ 50) - \delta(0)$.

Hosts	NH	CH_2(a)	CH_2(b)	CH_2(c)	CH_2(d)	CH_2(e)	OCH[a]
Guest: acetic acid							
1	0.062	0.002	0[b]	0.013	0.002	–	0[b]
2	0.046	0.002	0[b]	0.016	0.001	0.009	0.001
3	0.075	0[b]	0[b]	0.021	0[b]	0.003	0[b]
4	0.039	0.002	0.002	0.013	−0.007[c]	0.004[c]	0[b]
Guest: benzoic acid							
1	0.095	0.016	0.015	0.041	0.018	–	0[b]
2	–[d]	0.015	0.012	0.053	0.014	0.027	−0.003
3	–[d]	0.013	0.010	0.055	0.019	0.007	−0.003
4	0.041	0.005	0.006	0.023	−0.001[c]	0.002[c]	0[b]

[a] OCH_3 or OCH_2 in ester arm; for the labels of the other protons, see Scheme 1.
[b] Absolute Δ_H is less than 0.001.
[c] Aromatic protons.
[d] Masked by guest signals.

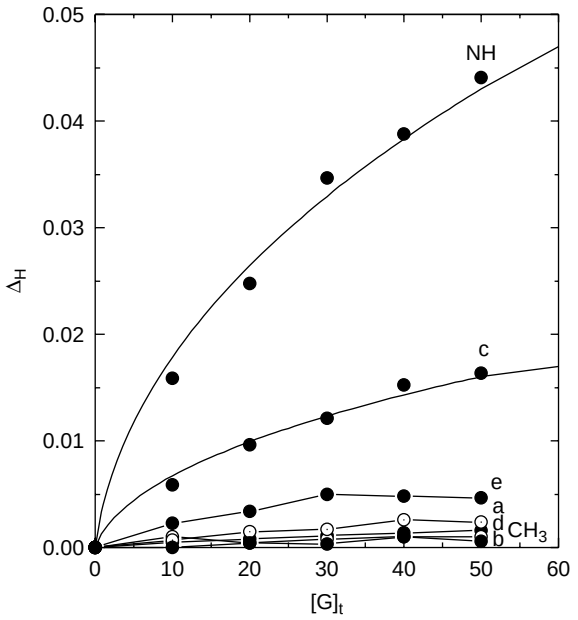

Figure 1. Changes in proton NMR shifts δ of host **2** as functions of the total concentration of coexisting acetic acid guest $[G]_t$ (mM or mmol dm^{-3}) at a constant host concentration $[H]_t$ of 5 mM in $CHCl_3$-*d* at 25°C: the ordinate Δ_H is δ referenced to the value at $[G]_t = 0$, i.e. $\Delta_H = \delta([G]_t) - \delta(0)$. For the labels of protons, see Scheme 1. The solid lines for protons NH and CH_2(c) are calculated with K_{dm} (M^{-1}) = 330 and K (M^{-1}) = 10.0 for CH_2(c) and 7.7 for NH. The solid lines for other protons connect the observed data for the aid of view.

C═O. The CH_2(c) proton signal of every host tended to be broadened by the addition of acetic acid; the FWHM (full width at half maximum) value was increased by about 20% or more at $[G]_t$ 50 mM, although the accurate value was difficult to determine because of its extreme sensitiveness to sample conditions. Such a slight increase in the signal width may be a sign of a slower internal motion related to the hydrogen bond formation which is accompanied by the *trans–cis* interconversion.

Stability of complexes and hydrogen bonds

The Δ_H versus $[G]_t$ curves observed for CH_2(c) protons were used for the determination of the formation constants of the complexes, because the signal was observable for both the acetic acid and benzoic acid complexes; in addition, the large signal width of the NH proton observed for the acetic acid complexes probably caused a relatively large scatter in the δ values (Figure 1). The CH_2 protons of every host–guest system showed a single NMR signal, and hence the equilibrium of the complex formation is rapid when compared with the NMR observation time scale. In such a fast-exchange case, the Δ_H value is proportional to the mole fraction of the host–guest complex, $[HG]/[H]_t$, as given by:

$$\Delta_H = \Delta_{CH}[HG]/[H]_t, \quad (1)$$

Here, Δ_{CH} is the Δ_H value of the complex, or $\Delta_{CH} = \delta([G]_t = \infty) - \delta(0)$. Since dimerisation of carboxylic acids competes with the complex formation with a host, the formation constant $K = [HG]/[H][G]$ of a 1:1 complex is given by (*14*)

$$K = 4K_{dm}(\Delta_H/\Delta_{CH})/[(1 - \Delta_H/\Delta_{CH})(B - 1)]. \quad (2)$$

$$B = [1 + 8K_{dm}([G]_t - (\Delta_H/\Delta_{CH})[H]_t)]^{1/2}. \quad (3)$$

Here, K_{dm} is the formation constant of the acid dimer, $K_{dm} = [G - G]/[G]^2$, which can be determined by concentration dependence of chemical shifts (*16*, *19*). The K_{dm} value obtained in $CHCl_3$-*d* was 330 M^{-1} for acetic acid and 518 M^{-1} for benzoic acid as reported previously (*14*). The unknown parameters K and Δ_{CH} in Equation (2) were determined in the following manner: (1) K and Δ_{CH} were determined without considering K_{dm} with a repeated linear least squares method (the K values thus obtained are denoted K_{app} and listed in Table 2) (*20*, *21*) and (2) by using these K and Δ_{CH} values together with the appropriate K_{dm} values, a Δ_H versus $[G]_t$ curve was simulated, and then the set of K and Δ_{CH} was searched so as to minimise the SD of K as well as the residual factor $[\Sigma w(\Delta_{H,obs} - \Delta_{H,calc})^2/\Sigma\Delta^2_{H,obs}]^{1/2}$ (where w is a weight related to a gradient in the δ_{obs} versus concentration curve) (*14*). The obtained values are listed in Table 2. These parameters well reproduced the observed curves as representatively shown in Figure 1 for the **2** – acetic acid system. The mole fraction of the dimeric acid is much larger than that of the complex for every host–guest system: in the system of host **1** and benzoic acid guest, for example, $[HG]/[H]_t$ is 0.07, $[HG]/[G]_t$ 0.03, and $[G - G]/[G]_t$ 0.35 at $[H]_t = 5$ mM and $[G]_t = 10$ mM; $[HG]/[H]_t$ 0.15, $[HG]/[G]_t$ 0.015, and $[G - G]/[G]_t$ 0.43 at $[H]_t = 5$ mM and $[G]_t = 50$ mM. For chloroacetic acid which has a much higher acidity,

Table 2. Formation constants and Δ_{CH} values obtained the NMR shifts of CH_2(c) protons for host–guest complexes in $CHCl_3$-*d* at 25°C.

	Acetic acid			Benzoic acid		
	K_{app}[a]	K[b]	Δ_{CH}	K_{app}[a]	K[b]	Δ_{CH}
1	22(1)	8(2)	0.202	35(3)	27(2)	0.265
2	27(3)	10(2)	0.217	43(4)	24(2)	0.390
3	33(3)	12(1)	0.239	43(3)	27(2)	0.366
4	28(4)	11(1)	0.170	30(4)	13(2)	0.284

[a] K_{app}(M^{-1}) = [HG]/[H][G] calculated by ignoring the dimerisation of the guests.
[b] K (M^{-1}) = [HG]/[H][G] calculated by including a K_{dm}(M^{-1}) of 330 for acetic acid and 518 for benzoic acid.

the dimerisation constant K_{dm} was indeterminable because the acid proton signal was too broad for locating the peak position and was unobservable below 30 mM. As a consequence, the proper formation constants K of the complexes of the acid were unable to be calculated. The following discussion, therefore, focuses on acetic and benzoic acids, which have moderate acidities.

Table 2 indicates the following tendencies for the formation constants: (1) the complexes of aliphatic hosts **1**–**3** with an identical acid guest have practically identical stability, and the benzoic acid complex of every aliphatic host is more stable than the corresponding acetic acid complex and (2) the complex of aromatic macrocycle **4** with benzoic acid is less stable than the benzoic acid complexes of the aliphatic hosts while the acetic acid complexes show no difference in stability. The δ value of the amide NH proton was observed in a range of 7.94–8.07 for aliphatic macrocycles **1**–**3**, as described in the Experimental section. This small difference in δ indicates that the amide NH moieties of these hosts have an almost identical acidity, and hence their capabilities of forming the N_{amide}—H···$O_{carboxyl}$ bond are almost identical. On the other hand, benzoic acid has a higher acidity than acetic acid. This acidity difference may result in the higher stability of the benzoic acid complexes. The aromatic protons of macrocycle **4** did not show significant shifts upon complex formation with benzoic acid, suggesting the absence of interaction between the aromatic groups of the host and guest. The only binding force is also the hydrogen bonding in this complex. The δ value of the amide NH proton of aromatic macrocycle **4** amounts to 9.58, which is much larger than the corresponding values observed for the aliphatic macrocycles. The NH of the aromatic macrocycle, therefore, has a higher acidity than the aliphatic macrocycles. As a consequence of the higher acidity, the aromatic macrocycle could form stronger N_{amide}—H···$O_{carboxyl}$ bonds. However, the formation constants of the complexes of **4** are by no means higher than those of the corresponding acid complexes of the aliphatic macrocycles; with benzoic acid, on the contrary, aromatic host **4** forms a less stable complex than the aliphatic hosts. These observations suggest that the stability of the complexes is correlated with the strength of the $O_{carboxyl}$—H···O_{amide} bond rather than the N_{amide}—H···$O_{carboxyl}$ bond; the hydrogen bonding is, therefore, dominated by the former bond. This conclusion is consistent with a spectral change in the OH signal of acetic acid, as described below.

Spectral changes of acetic acid and hydrogen bonding

The acidic proton of acetic acid showed a very broad signal, the FWHM value of which amounted to 300 Hz at a concentration of 10 mM. The signal was still broader in the presence of the hosts, probably as a result of complex formation; at $[\text{acetic acid}]_t$ 10 mM and $[H]_t$ 5 mM, the FWHM (in Hz) was about 1200 for host **1**, 550 for **2** and **3**, and 300 for **4**. The OH proton shifted down-field upon addition of hosts, and the increase in δ at $[\text{acetic acid}]_t$ 10 mM amounted to about 0.3–0.6 at $[H]_t$ 5 mM; above this $[H]_t$, the peak position of the signal was difficult to locate because of the very large the signal width. The δ values, and hence their changes with $[H]_t$, contained a very large uncertainty due to many influencing factors. Obviously, however, the observed change in δ is much larger than that observed for the NH proton of the hosts (Table 1). This fact may support that the $O_{carboxyl}$—H···O_{amide} bond is stronger than the N_{amide}—H···$O_{carboxyl}$ bond. This relative strength of these two hydrogen bonds is consistent with the difference between the acidities of NH and CO_2H groups and also with the general rule that oxygen atom has a greater hydrogen-bonding capability than nitrogen atom (*1*, *16*). Amide C=O oxygen carries a large negative charge density, which facilitates the formation of a strong hydrogen bond.

The methyl proton of acetic acid does not show NMR shift upon hydrogen bond formation, while the aromatic-proton signals of benzoic acid shift sensitively to hydrogen bond formation (*14*). If the methyl-proton signal of acetic acid is shifted upon complex formation, the shift is ascribable to the magnetic field induced by the mobile electrons of a host molecule in a complex. The δ value of the CH_3 proton was decreased when hosts were added; the difference in δ value, $\delta([H]_t\ 30\,\text{mM}) - \delta(0)$, was -0.037 for **1** and **4**, -0.033 for **2** and -0.046 for **3** at $[G]_t$ 5 mM. These changes may be due to a spatial effect from amide group in proximity (*15*). Another spatial effect predicted for hosts **3** and **4**, which involve aromatic group, is the ring-current effect. A benzene ring produces an angle-dependent magnetic field around a resonant proton, which undergoes a shift due to the ring-current effect δ_{rc} given by (*22*, *23*):

$$\delta_{rc} = 27.6(1 - 3\cos^2\theta)/R^3, \qquad (4)$$

Here, R is the distance (in Å) between the resonant proton and the benzene-ring centre, and θ is the angle between the **R** vector and the normal to the ring centre. The difference between the chemical shift changes of **2** and **3** is attributable to the ring-current effect from the phenyl group of the pendant arm in **3** (*24*). The 12-membered macrocycles **1** and **4** showed no difference in the chemical shift change. When hydrogen bonds formed between host **4** and acetic acid are on the same molecular plane as the phenylene plane of the host (i.e. $\theta = 90°$), the δ_{rc} of the methyl proton of the acetic acid molecule is calculated to be about $+0.07$ on the basis of geometrical

parameters assumed as $r(C_{phenylene}—C_{phenylene}) = 1.4$ Å, $r(C_{phenylene}—C_{carboxyl}) = 1.5$ Å, $r(C═O) = 1.2$ Å, $\angle OCO = 120°$, and $r(N_{amide}—H\cdots O_{carboxyl}) = 3$ Å. When the plane of the hydrogen bonding rotates about the amide N—C bond so as to be perpendicular to the phenylene plane, the values of R and θ are 6.5 Å and 37°, respectively, which lead to the δ_{rc} value −0.09. The δ_{rc} value of the methyl proton in the complex of **4** should vary between these positive and negative values depending on the orientation of the hydrogen bonds. The chemical shift change, $\delta([H]_t) - \delta(0)$, of the guest methyl proton in the presence of **1** and **4** were exactly identical at $[H]_t$ 30 mM, as described above. This observation indicates that the δ_{rc} value is almost 0 for the methyl proton of acetic acid in its complex with **4**. In the time-averaged structure, therefore, the methyl proton resides on a plane close to the nodal plane (i.e. $\theta = 54.7°$) of the magnetic field induced by the ring current. For such a location of the methyl proton, the plane of the hydrogen bonding is rotated by about 70° around the N—C bond from the plane of the phenylene group of the host molecule. This arrangement is probably defined by the stable orientation of the amide group. In the complex of **4** with benzoic acid, the guest molecule is supposed to have a similar orientation, which is not favourable to $\pi-\pi$ interaction between the host and guest as predicted from the stability.

Experimental

Macrocycles **1**–**4** were synthesised by esterification of the appropriate macrocycles having pendant carboxyl arms; the parent macrocycles were obtained by methods reported previously, and the purities were checked by ^{1}H NMR (*18*, *25*, *26*). The esterification was performed by the use of ethyl iodide for **1**, benzyl bromide for **3** and methyl iodide for **2** and **4** in basically the same procedure as reported previously for **1** (*27*, *28*). Ester **3** was, for example, prepared from the corresponding acid derivative as follows. The parent macrocycle (0.99 g, 3 mmol) was dried in vacuum at 80°C for 8 h, and suspended in 10 ml of dimethylformamide in a 100 ml three-necked flask equipped with nitrogen-gas inlet and outlet tubes and a joint, through which was added $KHCO_3$ (1.2 g, 12 mmol) dried in advance under a nitrogen stream. Successively, benzyl bromide (2.3 ml, 9.6 mmol) was added. The reaction mixture was stirred for 20 h at room temperature and then 30 ml of water was added. An organic phase was separated from the inorganic phase. The extraction with dichloromethane (10 ml) was repeated for three times. The extract was washed successively with 10 ml of 5% sodium sulphite solution, 10 ml of saturated NaCl solution and 10 ml of water, and then dried over sodium sulphate. Evaporation of the solvent at room temperature provided the product as colourless crystalline solid. Yield, 83.7%. Mp 159°C. Anal.: C, 63.71; H, 6.50; N, 10.60%. Calcd for $C_{27}H_{34}N_4O_6$: C, 63.51; H, 6.71; N, 10.97%. ^{1}H NMR (400 MHz, $CHCl_3$-*d*, TMS): δ 1.76 (qn, 2H, He), 2.73(s, 4H, Hb), 3.24 (s, 4H, Hc), 3.37 (s, 4H, Ha), 3.42 (A_2B, $J_{d\text{-}e}$ 5 Hz, $J_{d\text{-}NH}$ 5.6 Hz, 4H, Hd), 5.14 (s, 4H, ph—CH_2), 7.37 (m, 5H, arH); 8.03 (t, 2H, 5.6 Hz, NH); signals attributable to organic solvents used for the synthesis were not detected.

Other esters were synthesised in essentially the same manner. For **2**, yield, 87.5%. Mp 153°C. Anal.: C, 49.39; H, 6.78; N, 15.44%. Calcd for $C_{15}H_{26}N_4O_6$ C, 50.27; H, 7.31; N, 15.63%. ^{1}H NMR (400 MHz, $CHCl_3$-*d*, TMS) δ 1.84 (qn, 2H, He), 2.76(s, 4H, Hb), 3.25(s, 4H, Hc), 3.38 (s, 4H, Ha), 3.50 (m, 4H, Hd), 3.74(s, 6H, CH_3), 8.07 (s, 2H, NH). For **4**, yield, 76%. Mp 168°C. Anal.: C, 54.91; H, 6.04; N, 14.35%. Calcd for $C_{18}H_{24}N_4O_6$: C, 55.09; H, 6.16; N, 14.28%. ^{1}H NMR (400 MHz, $CHCl_3$-*d*, TMS): δ 2.88 (s, 4H, Hb), 3.41(s, 4H, Hc), 3.50 (s, 4H, Ha), 3.75 (s, 6H, CH_3), 7.25 (dd, J 3.6 Hz, 2.2 Hz, 2H, arH), 7.70 (dd, J 3.6 Hz, J 2.2 Hz, 2H, arH), 9.58 (s, 2H, NH).

NMR spectra were obtained with a Bruker AVANCE 400 spectrometer operating at 400 MHz at a temperature of 25°C. The solvent used for studies of complex formation was $CHCl_3$-*d* (99.9% atom D) supplied from Aldrich, and the internal standard was TMS. The guests were glacial acetic acid (99.8%, Aldrich) and benzoic acid (99 + %, Aldrich), which were used without further purification.

Conclusion

The observed NMR shifts have shown that both NH and C═O moieties of an amide group participate in hydrogen bond formation with a carboxyl group, and that the $O_{carboxyl}—H\cdots O═C_{amide}$ bond is stronger than the $C═O_{carboxyl}\cdots H—N_{amide}$ bond as a result of a large negative charge density on C═O oxygen. This pair of hydrogen bonds is arranged in a fork-like manner, and the amide group changes its conformation from the *trans*-form to the *cis*-form. A similar conformational conversion may also occur readily in biological systems upon hydrogen bond formation with a carboxylic acid when the receptors have some flexibility.

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