Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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First published on: 21 September 2007

To cite this Article Virués, Claudia , Navarro, Rosa Elena , Velázquez, Enrique F. and Inoue, Motomichi(2008) 'NMR Studies of Host-guest Complexes Between Monocarboxylic Acids and Amide-based Cyclophanes in Chloroform', Supramolecular Chemistry, 20: 3, 301 — 307, First published on: 21 September 2007 (iFirst)
To link to this Article: DOI: 10.1080/10610270701245151
URL: http://dx.doi.org/10.1080/10610270701245151

Supramolecular Chemistry, April–May 2008 Vol. 20 (3), pp. 301–307

NMR Studies of Host–guest Complexes Between Monocarboxylic Acids and Amide-based Cyclophanes in Chloroform

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(Received 15 December 2006; Accepted 26 January 2007)

Formation of host–guest complexes with acetic acid and benzoic acid was studied by NMR for amide-based octaazacyclophanes having pendant methyl ester arms; the cyclophanes were tetramethyl 2,9,18,25-tetraoxo-1,4,7,10,17,20,23,26-octaaza[10.10]paracyclophane-4,7,20,23-tetraacetate, its meta-isomer and analogues. Amide NH proton and CH_2 proton adjacent to amide C═O in every cyclophane host showed down-field NMR shifts in the presence of the guest acids in $CHCl_3$-d, suggesting the formation of 1:1 complexes in which the carboxyl group of an acid molecule formed two hydrogen bonds with the amide NH and C═O moieties of a host molecule. Since the complex formation competed with the dimerization of the guest acids, the monomer–dimer equilibrium was restudied by NMR and the equilibrium constant was determined to be 330 M^{-1} for acetic acid and 518 M^{-1} for benzoic acid. By using these values, the formation constants of the host–guest complexes were determined to be 8–51 M^{-1}. The close contact between the host and guest molecules via hydrogen bonding was consistently confirmed by NMR shifts due to the ring current of aromatic group.

Keywords: Carboxylic acids; Cyclophanes; Host–guest complexes; NMR

INTRODUCTION

A variety of supramolecular assemblies, or host–guest complexes, have been reported for functionalized cyclophanes in which aromatic groups are integrated in the macrocyclic framework along with functional groups [1,2]. Binding forces for the assemblies arise from weak intermolecular interactions, including hydrogen bonding, electrostatic interaction, dipolar interaction, solvent-exclusion effect (or hydrophobic interaction) and π–π interaction. Among such binding forces, hydrogen bonding results in relatively strong interaction and plays important roles in biological systems [3]. For carboxylic acids, which have two hydrogen-bonding sites [4], a variety of host–guest complexes with strong hydrogen bonds have been reported recently, and some of them provide good models for biological systems [5–13]. We have reported previously that amide-based paracyclophanes bearing pendant carboxyl groups (**1**, **3** and **4** in Scheme 1) form host–guest complexes with dopamine in aqueous media [14,15]. The dominant binding forces are hydrophobic interaction and electrostatic interaction operative between the carboxylate group in the host and the aminium group in the guest, while hydrogen bonding is ineffective for the complex formation in aqueous media. Thus, dominative forces depend primarily on the geometrical arrangements of functional groups in constituent molecules and on the nature of solvents as well. These paracyclophanes are unsuitable for studying hydrogen bonding because of their poor solubility in organic solvents. In the present work, we have carried out esterification of **1**–**4**, and obtained cyclophanes **5**–**8** which are highly soluble in organic solvents in which hydrogen bonding may be a dominant binding force; moreover, their pendant arms no longer bear negative charge so that an electrostatic interaction is a minor binding factor. Because of these properties suitable for studying hydrogen bonding, the complex formation of the cyclophanes with acetic acid and benzoic acid has been studied by NMR in chloroform. In organic

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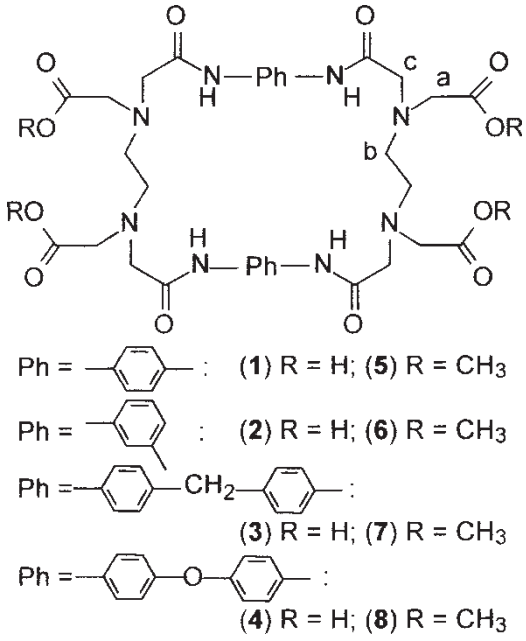
ISSN 1061-0278 print/ISSN 1029-0478 online © 2008 Taylor & Francis
DOI: 10.1080/10610270701245151



SCHEME 1

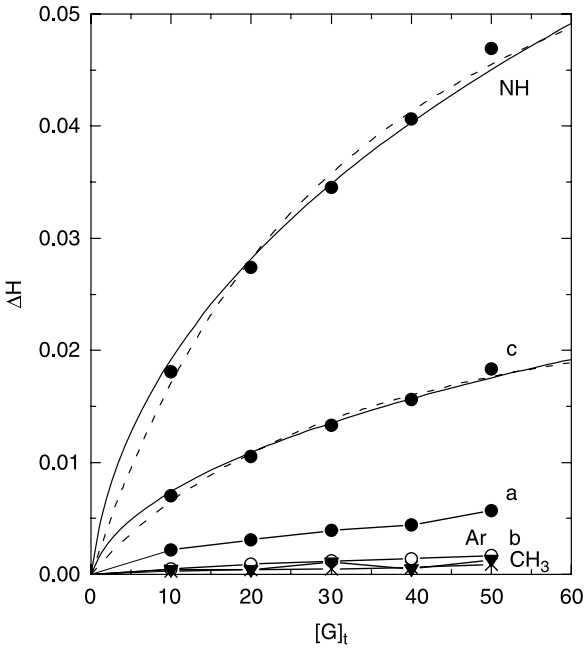


FIGURE 1 Changes in proton NMR shifts δ of host **5** ($[H]_t$ 5 mM) as functions of concentration of coexisting acetic acid guest $[G]_t$ (mM or mmol dm^{-3}) in $CHCl_3$-d at 25°C: the ordinate Δ_H is δ referenced to the value at $[G]_t = 0$, i.e. $\Delta_H = \delta([G]_t) - \delta(0)$. For the labels of protons see Scheme 1. The solid lines are calculated for probe protons NH and CH_2(c) with K_{prop} and K_{dm}(acetic acid), and the broken lines with K_{app} without considering the dimerization of the guest acid; the values of the formation constants are given in Table I. The solid lines for other protons connect the observed data for the aid of view: CH_2(a) proton (triangle); aromatic proton (open circle); methyl proton (cross).

solvents, the guest acids readily undergo dimerization [4], which competes with the formation of the host–guest complexes. Such a self-assembling effect of guest acids, which was neglected in most previous reports, has been included in the calculation of formation constants in this work.

RESULTS AND DISCUSSION

NMR Shifts and Complex Formation

In NMR titrations, the total concentration of a host $[H]_t$ was kept constant at 5 mM (mM = mmol dm^{-3}) and the total concentration of a guest $[G]_t$ was varied from 5 to 50 mM. Figure 1 shows changes in δ referenced to that at $[G]_t = 0$, i.e. $\Delta_H([G]_t) = \delta([G]_t) - \delta(0)$, for host **5** in the presence of acetic acid as a guest; the labels of protons are given in Scheme 1. The amide NH and CH_2(c) protons clearly showed increasing down-field shifts with increasing $[G]_t$, while no significant shift was observed for other protons. This mode of NMR spectra was observed for every host–guest system. Table I lists $\Delta_H([G]_t)$ values for NH and CH_2(c) at $[G]_t/[H]_t$ ratios of 6 and 10. The increase in δ observed for NH and CH_2(c) indicates the formation of host–guest complexes.

Commonly, both oxygen atoms of a carboxyl group participate in hydrogen-bond formation [4]. The C═O oxygen of the guest acid in every host–guest system forms a hydrogen bond definitely with the amide NH of the host, because the NH proton signal shifts down-field upon complexation. Toward OH in the guest acid, every host molecule has three potential binding sites, i.e. amino nitrogen, amide oxygen and ester oxygen. Among the three types of CH_2 protons in a host, only proton in CH_2(c) adjacent to amide C═O shifts down-field, as shown in Fig. 1. Therefore, the binding site toward acid OH is amide C═O oxygen rather than amino nitrogen or ester C═O oxygen. When an amide group forms two hydrogen bonds with a single carboxyl group, the conformation of the amide group must be changed from its stable *trans*-form to the less stable *cis*-form. This thermodynamic disadvantage can be compensated by stabilization resulting from the hydrogen-bond formation. For determination of the formation constants of the host–guest complexes, amide NH and CH_2(c) protons were used as probes, as described below.

Formulation and Calculation of Formation Constants

Since every probe proton showed a single NMR signal, the equilibrium of the complex formation is rapid in comparison with the NMR observation time scale. In such a fast-exchange case, the concentration of a complex [HG] can be determined from Δ_H as follows:

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

TABLE I NMR shifts and formation constants of the complexes of hosts **5**–**8** with acetic acid and benzoic acid as guests in $CHCl_3$-d at 25°C: NHR-shift differences Δ_H of probe protons of the hosts (5 mM) in the presence of a guest (30 mM and 50 mM), the apparent formation constants K_{app}, the proper constants K_{prop}, and the shift differences Δ_{CH} calculated for the complexes

Hosts	protons	$\Delta_H(30)$	$\Delta_H(50)$	K_{app}[†,¶]	K_{prop}[‡,¶]	Δ_{CH}[‡]
Guest: acetic acid						
5	NH	0.035	0.047	34(4)	15(3) [14(3)]	0.421 [0.537]
	CH_2(c)	0.013	0.018	33(5)	12(3) [10(2)]	0.205 [0.281]
6	NH	0.011	0.014	36(6)	28(8) [29(7)]	0.075 [0.086]
	CH_2(c)	0.007	0.010	54(12)	51(9) [53(9)]	0.035 [0.039]
7	NH	0.026	0.034	34(2)	14(3) [19(3)]	0.334 [0.303]
	CH_2(c)	0.010	0.013	40(2)	19(3) [22(3)]	0.099 [0.106]
8	NH	0.025	0.033	38(3)	20(3) [22(3)]	0.233 [0.261]
	CH_2(c)	0.011	0.015	44(4)	30(3) [30(3)]	0.075 [0.087]
Guest: benzoic acid						
5	NH	0.044	0.059	35(3)	15(3)	0.657
	CH_2(c)	0.024	0.032	34(3)	15(3)	0.356
6	NH	0.019	0.026	35(3)	15(3)	0.280
	CH_2(c)	0.015	0.020	31(3)	9(3)	0.349
7	NH	0.034	0.047	35(7)	17(3)	0.469
	CH_2(c)	0.020	0.027	36(7)	22(5)	0.213
8	NH	0.027	0.040	22(4)	8(3)	0.781
	CH_2(c)	0.018	0.025	26(4)	8(3)	0.482

[†] $K_{app}(M^{-1}) = [HG]/[H][G]$, calculated by ignoring dimerization of acids. [‡] $K_{prop}(M^{-1}) = [HG]/[H][G]$, calculated by assuming a monomer–dimer equilibrium constant K_{dm} (M^{-1}) of 330 for acetic acid and 518 for benzoic acid; for acetic acid, K_{prop} and Δ_{HC} calculated with K_{dm} 518 are shown in the brackets for comparison. [¶] The numbers in the parentheses are estimated uncertainties for the formation constants.

Here Δ_{CH} is the Δ_H value of the complex, or $\Delta_{CH} = \delta([G]_t = \infty) - \delta(0)$. The formation constant of a 1:1 host–guest complex is defined by:

$$K = [HG]/[H][G]. \quad (2)$$

On the basis of Eqs. (1) and (2), formation constants and Δ_{CH} values were determined by employing Lang's method, which is a repeated linear least squares calculation with a linearized equation [14,15,19]. Table I shows the obtained constants, which are denoted K_{app}. The observed change in δ is well elucidated by the calculated value $\Delta_H(calc) = \Delta_{CH}[HG]/[H]_t$, as representatively shown for **5**-acetic acid in Fig. 1. Assumption of HG_2-type complexes did not well interpret the observed Δ_H versus $[G]_t$ plots; as suggested by the observation of a single NMR signal for every host proton, a guest molecule is exchanged among the amide groups of a host molecule at so high a rate that the 1:1 complex is formed in the NMR time scale.

Carboxylic acids are well known to undergo monomer–dimer equilibrium in organic solvents [4]. In fact, the δ value of CO_2H proton observed for acetic acid in $CHCl_3$-d was decreased slowly with decreasing concentration above 10 mM, and below this concentration decreased sharply (Fig. 2), while the δ value of CH_3 proton was practically independent of the concentration; δ = 2.103 at 10 mM and 2.104 at 50 mM. This observation indicates the occurrence of monomer–dimer equilibrium [4,20]. The host–guest complexation, therefore, occurs under competition with the dimerization of the guest acids; K_{app} described above gives just apparent constants (or conditional constants) for the host–guest complexes. The total concentrations of host and guest in every system studied are given by:

$$[G]_t = [G] + [HG] + 2[G_2], \quad (3)$$

$$[H]_t = [H] + [HG]. \quad (4)$$

Dimer concentration $[G_2]$ is related to monomer–dimer equilibrium constant K_{dm} as:

$$K_{dm} = [G_2]/[G]^2. \quad (5)$$

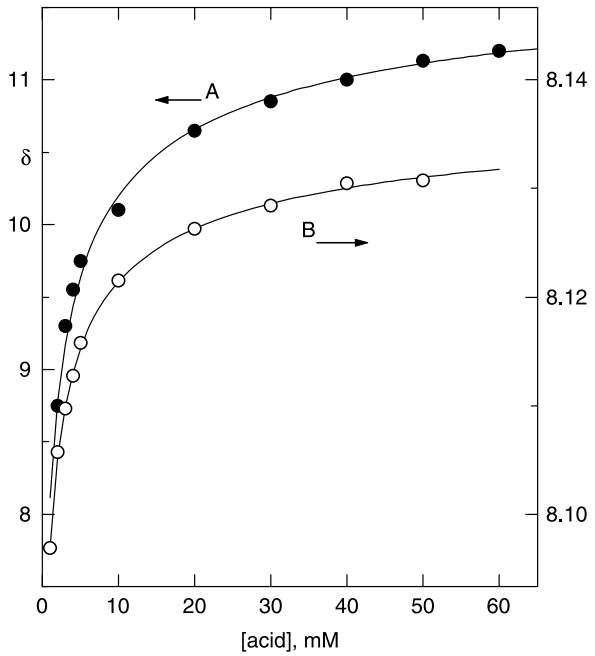


FIGURE 2 Concentration dependence of NMR shifts δ of (A) CO_2H proton of acetic acid and (B) ortho proton of benzoic acid in $CHCl_3$-d at 25°C. The solid curves are calculated with the following parameters: for acetic acid, $K_{dm} = 330\,M^{-1}$, δ(monomer) = 6.34 and δ(dimer) = 12.02; for benzoic acid, $K_{dm} = 518\,M^{-1}$, δ(monomer) = 8.0696 and δ(dimer) = 8.1402.

The combination of Eqs. (1), (3) and (5) leads to:

$$[G] = (B - 1)/4K_{dm}, \quad (6)$$

$$B = [1 + 8K_{dm}([G]_t - (\Delta_H/\Delta_{CH})[H]_t)]^{1/2}. \quad (7)$$

Substitution of Eqs. (1), (4) and (6) into Eq. (2) gives the proper formation constant K_{prop} of a host–guest complex composed of a carboxylic acid guest, as follows:

$$K_{prop} = 4K_{dm}(\Delta_H/\Delta_{CH})/[(1 - \Delta_H/\Delta_{CH})(B - 1)]. \quad (8)$$

The determination of a proper formation constant requires the K_{dm} value known. The dimerization of carboxylic acids is strongly dependent on the environment including the nature of solvent and a trace of water involved unavoidably in reagents used, and consequently K_{dm} reported for acetic acid in $CHCl_3$-d is scattered over the range 100–400 $(mol/kg)^{-1}$ [4]. For this reason, the dimerization of the acids was restudied in this work by using the substances and solvent supplied from the same source as for the study of the host–guest complexation. On the basis of the concentration dependence of the δ value, K_{dm} was determined as $330(\pm 25)\,M^{-1}$ for acetic acid by searching a set of K_{dm}, δ(monomer) and δ(dimer) that minimized the standard deviation of K_{dm} as well as the residual factor $\left[\sum w(\delta_{obs} - \delta_{calc})^2/\sum \delta_{obs}^2\right]^{1/2}$ (w is a weight related to a gradient in the δ_{obs} versus concentration curve) under the condition that $\delta_{obs} \rightarrow$ δ(monomer) with $[G]_t \rightarrow 0$, by using a repeated linear least squares method; the calculated curve reproduced well the observed shifts as shown in Fig. 2. The relatively large uncertainty arose in part from the large line width of the signal: fwhm (full width at half maximum) is 200–350 Hz in a concentration range of 2–50 mM. A more dominant origin for the uncertainty was that the least-squares calculations gave a shallow minimum of the standard deviation because both δ(monomer) and δ(dimer) had to be included as unknown parameters; the deviation was larger than the experimental fluctuation between different runs. Although accurate determination of K_{dm} was difficult as pointed out already [4,20], the obtained value was reasonable when compared with the reported range 100–400 $(mol/kg)^{-1}$ [4]. For benzoic acid, the CO_2H proton signal was not useful for determination of K_{dm}, because the signal was much broader than that of acetic acid, and was not observable below 10 mM; fwhm ~ 450 Hz at concentrations of 10–50 mM. The ortho-proton signal, on the other hand, was so sharp as to be observable down to 1 mM, and the δ showed clear concentration dependence (Fig. 2), which gave K_{dm} $518(\pm 25)\,M^{-1}$. The K_{dm} values obtained for the two acids are largely different, probably because of their different acidities. The effect of water involved unavoidably in the reagents used, however, cannot be ruled out because even a trace of water may effectively break hydrogen bonding. Since the reagents from the same source were used for the study of host–guest complexation, the K_{dm} values determined individually for the two acids in the present experiment were employed for calculation of K_{prop} in Eq. (8). For acetic acid, K_{dm} $518\,M^{-1}$ was also employed for comparison so that the derived conclusion was verified.

In calculation of K_{prop} and Δ_{CH}, their initial values were selected to be K_{app} and the corresponding Δ_{CH} which were determined without considering K_{dm}, and then the standard deviation of K_{prop} as well as the residual factor of simulated Δ_H versus $[G]_t$ was minimized in an acceptable range. Obtained K_{prop} and Δ_{CH} are listed in Table I. The two K_{dm} values used for acetic acid gave practically identical K_{prop} values within the estimated uncertainties. The Δ_H(calc) values, which are $\Delta_{CH}([HG]/[H]_t)$, well reproduced the observed shifts as representatively shown for **5**-acetic acid in Fig. 1. The mole fraction of the monomeric species of an acid decreases with increasing the concentration of the acid as a result of monomer–dimer equilibrium; for example, K_{dm} $330\,M^{-1}$ of acetic acid gives $[G]/[G]_t = 0.32$ at $[G]_t$ 10 mM and 0.16 at 50 mM. Since only monomeric acid molecule participates in host–guest complexation (but the dimer does not), the Δ_H versus $[G]_t$ curve approaches to a saturation more rapidly than that predicted for a simple complexation equilibrium, which would not compete with the monomer–dimer equilibrium. Therefore, K_{app} gives overestimation for the true formation constant and is larger than the corresponding K_{prop}. For example, the mole fraction of each species is calculated for K_{prop} $28\,M^{-1}$ (determined from NH proton for **6**-acetic acid) and $K_{dm} = 330\,M^{-1}$ as: $[HG]/[H]_t = 0.08$, $[HG]/[G]_t = 0.04$ and $[G]/[G]_t = 0.31$ at $[H]_t$ 5 mM and $[G]_t$ 10 mM; $[HG]/[H]_t = 0.18$, $[HG]/[G]_t = 0.02$ and $[G]/[G]_t = 0.16$ at $[H]_t$ 5 mM and $[G]_t$ 50 mM. On the other hand, K_{app} $36\,M^{-1}$ of the same system gives $[HG]/[H]_t = 0.24$ and $[HG]/[G]_t = 0.12$ at $[H]_t$ 5 mM and $[G]_t$ 10 mM; $[HG]/[H]_t = 0.63$ and $[HG]/[G]_t = 0.06$ at $[H]_t$ 5 mM and $[G]_t$ 50 mM. The ratio of the mole fraction $[HG]/[H]_t$ at $[G]_t$ 50 mM to that at 10 mM is 2.3 in the former calculation model and 2.6 in the latter. Thus, the ratio is not largely dependent on the calculation models employed so that either model can well reproduce the observed curves. Obviously, however, the absolute values of the mole fractions are quite different, and the neglect of the self-assembling effect of the acid leads to a large overestimation of the mole fraction of the complex and consequently an overestimation of the formation constant.

Geometrical Relation Between Host and Guest Molecules

The formation constants of the benzoic acid complexes are almost identical with the values of the corresponding acetic acid complexes, and hence the strength of hydrogen bonding is almost identical. On the other hand, the δ values observed in the presence of benzoic acid are larger than the corresponding values in the presence of acetic acid. As a consequence, the chemical-shift change, Δ_{CH}, of the host NH proton in every complex of the aromatic acid is much larger than that of the corresponding aliphatic acid complex: for example, the difference Δ_{CH}(benzoic acid) − Δ_{CH}(acetic acid) amounts to 0.24 for **5** and 0.21 for **6** (Table I). Since the hydrogen-bond strength is almost identical for the complexes of the two acids with the same host, their Δ_{CH} values due to hydrogen bonding should be almost equal. The observed differences in Δ_{CH} are, therefore, ascribable to the spatial effect from the ring current of the aromatic acid that is bound to the amide group with hydrogen bonding. The ring current of a benzene ring induces angle-dependent magnetic field around a resonant proton, resulting in a shift of the resonant proton as given by [21,22]:

$$\delta_{rc} = 27.6(1 - 3\cos^2\theta)/r^3 \qquad (9)$$

Here r is the distance (in Å) between the resonant proton and the benzene-ring center, and θ is the angle between the ***r*** vector and the normal to the ring center. When the $C\cdots O_{acid}—H_{amide}$ bond is assumed to form on the same molecular plane as the phenyl ring plane of the acid molecule (i.e. $\theta = 90°$), the Δ_{CH} differences 0.24 and 0.21 lead to $r = 4.9$ Å and 5.1 Å, respectively, from which the $O_{acid}\cdots H_{amide}$ distance is calculated to be 1.3–1.5 Å 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 and $\angle OCO = 120°$. The estimated $O_{acid}\cdots H_{amide}$ distance is reasonable for $O\cdots H—N$ hydrogen bonds [23], when the roughness of the calculation is taken into account, providing a supporting evidence for the intermolecular hydrogen bonding formed between the carboxyl and amide groups. The use of K_{dm} 518 M^{-1} for acetic acid gives larger Δ_{CH} values for the complexes. The differences from the corresponding values of the benzoic acid complexes, 0.12 for **5** and 0.19 for **6**, lead to $r = 6.1$ and 5.3 Å, respectively, from which the $O_{acid}\cdots H_{amide}$ distance is calculated to be 1.7–2.5 Å. These distances are still in the range that supports hydrogen-bond formation.

The Δ_{CH} value of CH_2(c) proton in a benzoic acid complex is also significantly larger than the value of the corresponding acetic acid complex. This observation indicates that the resonant proton in the host is under the influence of ring current field of the aromatic acid, supporting the formation of hydrogen bonding between OH in the guest and amide O═C in the host. The Δ_{CH} difference amounting to 0.2–0.3 suggests that the $O\cdots H$ distance in $O_{acid}—H—O_{amide}$ is of the same order of magnitude as in $O_{acid}\cdots H—N_{amide}$, although the former distance cannot be calculated because the resonant proton in CH_2(c) deviates from the plane of the benzene ring.

The δ values of aromatic protons in benzoic acid are changed with the concentration of the acid itself as a result of hydrogen-bond formation accompanied by the dimerization. In contrast, the δ value of methyl proton in the aliphatic acid is insensitive to the dimerization and practically independent of the concentration: δ(50 mM) − δ(10 mM) ∼ 0.001. If the δ value of the methyl proton is changed upon complex formation, such a change is ascribable to the influence of ring-current field produced by phenylene group in the host of the complex. In fact, the methyl proton shows a significant up-field shift, as shown in Table II, which lists the δ values referenced to the value in the absence of a host, i.e. $\Delta_G = \delta_{([H]t)} - \delta(0)$, at $[G]_t = 5$ mM and at $[H]_t = 20$ and 30 mM. The Δ_G value of a complex, Δ_{CG}, can be calculated from the relation $\Delta_{CG} = \Delta_G([H]_t/[HG])$ with K_{prop}. The means of the Δ_{CG} values calculated at the two host concentrations are shown in Table II. These values are related to the time-averaged position of the methyl group in the complexes. Half the value of **5** can be equated to δ_{rc} in Eq. (9), because two phenylene groups of the macrocyclic ring in the host are supposed to be geometrically equivalent on the time average [24]. When a methyl group is assumed to reside on the plane that is parallel to a phenyl ring plane with an interplane distance equal to the van der Waals radius sum of methyl group (2 Å) and phenyl group (1.7 Å) [25], the distance d from the normal to the phenylene-ring center, i.e. $r^2 = 3.7^2 + d^2$ in Eq. (9), is calculated to be 3.9 Å. The same assumptions for **6** gave $d = 4.0$ Å. These d values are much larger than the benzene ring radius, indicating that the methyl group is far apart from the phenylene group. Probably the same geometrical situation occurs in the benzoic acid complexes so that

TABLE II NHR-shift differences Δ_G of methyl proton of acetic acid in the presence of hosts **5**–**8** at total concentrations of $[G]_t = 5$ mM and $[H]_t = 20$ and 30 mM in $CHCl_3$-d at 25°C, and the corresponding shift differences Δ_{CG} calculated for the host–guest complexes

	$\Delta_G(20)^\dagger$	$\Delta_G(30)^\dagger$	$\Delta_{CG}{}^\ddagger$
5	−0.019	−0.024	−0.157(8)
6	−0.026	−0.034	−0.128(4)
7	−0.029	−0.041	−0.270(3)
8	−0.034	−0.045	−0.225(8)

† $\Delta_G = \delta([H]_t) - \delta(0)$ at $[H]_t = 20$ or 30 mM. ‡ Mean of values calculated from Δ_G(20 mM) and Δ_G(30 mM) with $K_{dm} = 330\ M^{-1}$ and K_{prop} shown in Table I for NH proton: numbers in the parentheses are deviation in the least significant digits.

no π−π interaction is operative between the host and guest molecules. This is consistent with the formation constants which are almost identical with those of the corresponding acetic acid complexes.

Molecular-recognition Capability

Some amide-based bicyclic and ditopic cyclophanes have been reported to form highly stable inclusion complexes with acetic acid and benzoic acid, with a formation constant of the order of $10^3\,M^{-1}$ [5,6]. For di- and tricarboxylic acids, which have multiple hydrogen-bonding sites, a variety of stable inclusion complexes have been reported [7,10,11]. Most formation constants reported have been calculated without taking into account the dimerization of the acids, and hence the definition of the reported constants corresponds to that of K_{app} rather than K_{prop} defined in our work. The K_{app} values obtained in the different concentration ranges of the guest acids cannot be directly compared, because the mole ratio of the monomeric to dimeric species is changed to a greater extent in a lower concentration range especially below 10 mM, as predicted from Fig. 2. Despite the difference in the concentration range studied, the stability reported for the complexes of the bicyclic and ditopic cyclophanes is obviously much higher than that of our systems. The high stability of these complexes is due to the complete encapsulation of a guest molecule in the rigid cavity with multiple binding sites [5]. In contrast, the guest molecule in our systems is located far apart from the phenylene-ring center of the host, as suggested by the NMR shift of methyl proton of acetic acid. This incomplete encapsulation may be a reason for the lower stability of the complexes.

The host molecules **5**–**8** have different sizes of macrocyclic cavity, but the formation constants of their complexes are not largely different. The formation constants of the benzoic acid complexes are almost identical with those of the corresponding acetic acid complexes, although **6** and **8** tend to have a higher stability with acetic acid. The absence of significant size and substituent effects suggests that the complex formation is performed merely by hydrogen bonding; other binding forces including π−π interaction and solvent-exclusion effect are negligible, in contrast to the complex formation of the parent cyclophanes in water [14,15].

In the presence of phenol, which has a single hydrogen-bonding site, the NH proton of **6** showed a chemical-shift change ($\Delta_H = 0.02$ at $[H]_t = 5$ mM and $[G]_t/[H]_t = 10$), but the K_{app} value was determined to be $12\,M^{-1}$, which was smaller than the corresponding value $35\,M^{-1}$ of the benzoic acid complex. For phenethylamine ($C_6H_5CH_2CH_2NH_2$), which is another type of a guest having a single binding site, a chemical shift change observed for every host proton was less than 0.004 even at $[G]_t/[H]_t = 10$; the host molecules do not recognize the aromatic amine. Obviously, the stability of the benzoic acid complexes arise from interaction at two hydrogen-bonding sites.

EXPERIMENTAL

Parent cyclophanes **1**–**4** were synthesized by the methods reported previously [14,16], and dried in vacuum at 80°C for 8 h before use. Esterification of the cyclophanes was performed by a reaction with iodomethane [17,18]. For synthesis of **5**, 0.4 g (0.54 mmol) of **1** was loaded into a 100 mL three-necked flask equipped with nitrogen-gas inlet and outlet tubes, a septum and a bent joint to a container in which 0.43 g (4.3 mmol) of $KHCO_3$ dried in advance was loaded. Under a nitrogen stream, 10 mL of dimethylformamide (DMF) was added with a syringe. To the resulting suspension, $KHCO_3$ was transferred, and successively 0.2 mL (3.2 mmol) of iodomethane was added with a syringe. The reaction mixture was stirred for 20 h at room temperature, and then 24 mL of water was added. An organic phase was separated from an inorganic phase. Extraction with 10 mL of dichloromethane was repeated for three times. The extract was washed successively with 10 mL of 5% sodium sulfite solution, 10 mL of saturated NaCl solution and 10 mL of water, and then dried over sodium sulfate. Evaporation of the solvent at room temperature provided the product as colorless crystalline solid. Yield, 35%. Anal. found: C, 53.50; H, 6.10; N, 13.31. Calc. for $C_{36}H_{48}N_8O_{12}\cdot H_2O$: C, 53.85; H, 6.28; N, 13.96. ^{1}H NMR (400 MHz, $CHCl_3$-d, TMS): δ 2.80 (s, 8H, assigned to proton b in Scheme 1), 3.31 (s, 8H, c), 3.37 (s, 8H, a), 3.80 (s, 12H, CH_3), 7.09 (s, 8H, ar), 9.24 (s, 4H, NH); signals attributable to organic solvents used for the synthesis were not detected.

Other esters **6**–**8** were derived from the appropriate cyclophanes by the same method as for **5** in a yield of about 35%. For **6**, anal. found: C, 54.03; H, 6.26; N, 13.55%. Calc. for $C_{36}H_{48}N_8O_{12}\cdot H_2O$: C, 53.85; H, 6.28; N, 13.96%. ^{1}H NMR (400 MHz, $CHCl_3$-d, TMS): δ2.86(s, 8H, b), 3.36 (s, 8H, c), 3.46 (s, 8H, a), 3.53 (s, 12H, CH_3), 7.51 (s, 2H, ar), 7.73 (A_2B pattern, 6H, ar), 9.77 (s, 4H, NH). For **7**, anal. found: C, 61.64; H, 6.60; N, 11.36%. Calc. for $C_{50}H_{60}N_8O_{12}\cdot H_2O$: C, 61.09; H, 6.36; N, 11.40. ^{1}H NMR (400 MHz, $CHCl_3$-d, TMS): δ 2.83 (s, 8H, b), 3.34 (s, 8H, c), 3.42 (s, 8H, a), 3.65 (s, 4H, ph−CH_2), 3.85 (s, 12H, CH_3), 7.00 (d, 8H, ar), 7.47 (d, 8H, ar), 9.50 (s, 4H, NH). For **8**, anal. found: C, 59.10; H, 6.02; N, 11.46. Calc. for $C_{48}H_{56}N_8O_{14}\cdot H_2O$: C, 58.41; H, 5.92; N, 11.35. ^{1}H NMR (400 MHz, $CHCl_3$-d, TMS): δ 2.81 (s, 8H, b),

3.35 (s, 8H, c), 3.46 (s, 8H, a), 3.67 (s, 12H, CH_3), 6.79 (d, 8H, ar), 7.35 (d, 8H, ar), 9.63 (s, 4H, NH).

NMR spectra were obtained with a Bruker AVANCE 400 spectrometer operating at 400 MHz at a temperature of 25°C. Solvent used for studies of complexation 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.

Acknowledgements

This work was supported in part by the Consejo Nacional de Ciencia y Tecnología de México (Grant No. P44427-Y). The NMR spectrometer was operated under the support of the Secretaría de Educación Pública, México (SES-SEP, project No. P/PEF 2005-26-11). C. V. thanks CONACYT for graduate scholarship.

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