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Claudia Virués[a]; Enrique F. Velázquez[a]; Rosa Elena Navarro[a]; Motomichi Inoue[a]
[a] Departamento de Investigación en Polímeros y Materiales, Universidad de Sonora, Sonora, México

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Complexation of an anionic *meta*-cyclophane with histamine and analogous bioactive amines in aqueous media

Claudia Virués, Enrique F. Velázquez*, Rosa Elena Navarro and Motomichi Inoue

Departamento de Investigación en Polímeros y Materiales, Universidad de Sonora, Hermosillo, Sonora, México

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Molecular recognition of an anionic *meta*-cyclophane towards bioactive amines and related compounds has been studied by ^{1}H NMR titration: the *meta*-cyclophane, which is functionalised by pendant $\mathbf{CH_2CO_2^-}$ arms, is 2,9,18,25-tetraoxo-4,7,20,23-tetrakis(carboxymethyl)-1,4,7,10,17,20,23,26-octaaza[10.10]metacyclophane; the bioactive guests studied are histamine, tryptamine, tyramine, phenethylamine, imidazole, histidine, phenylalanine and 4-aminobenzoic acid. Complex formation of a *para*-cyclophane isomer has also been studied for comparison. The *meta*-cyclophane forms a complex with histamine with a formation constant of 63 M^{-1}, while the complexes with the other amines have a smaller constant in the range of 1–24 M^{-1}; the compounds other than the amines have no interaction with the host. The major binding force for the complex formation is electrostatic interaction between the $\mathbf{CH_2CO_2^-}$ arm of the hosts and the $\mathbf{CH_2CH_2NH_3^+}$ arm of the guests. The aromatic group of a guest amine molecule is encapsulated into the cavity of a host molecule, and the deepness of the encapsulation is increased with the hydrophobicity in the order histamine < tyramine ~ phenethylamine < tryptamine. In addition to hydrophobic interaction, the *meta*-cyclophane is supposed to have a dipolar interaction with a guest molecule. The combined effect of the three types of interactions stabilises the histamine complex of the *meta*-cyclophane.

Keywords: amines; cyclophanes; histamine; host–guest complexes; molecular recognition

Introduction

A variety of supramolecular assemblies, or host–guest complexes, have been reported for functionalised cyclophanes, in which the macrocyclic ring is composed of phenylene groups and is modified by functional groups such as amino, amide and carboxyl groups (*1–16*). This type of host molecules can encapsulate specific organic molecules in aqueous media as a result of hydrophobic interaction (or solvent-exclusion effect), and the resulting inclusion complexes are stabilised by additional interactions such as electrostatic interaction, dipolar interaction and hydrogen bonding. Of special interest to us are cyclophanes capable of recognising bioactive substances. Previously, we have reported that *para*-cyclophanes bearing pendant carboxyl arms form inclusion complexes selectively with dopamine and related bioactive amines in aqueous media (*17*, *18*). For the relatively simple *para*-cyclophane (pcn; Figure 1), NMR studies have confirmed that a guest molecule is inserted between two phenylene groups of a host cavity in a mode of a slipped face-to-face stack (*18*). This stacking mode is consistent with an electrostatic theory, which has proposed that a face-to-face stack is stabilised only when the π-constituents are slipped with each other in a certain slip distance (*19*). In a pcn molecule, two *p*-phenylene groups themselves are slipped in the face-to-face stack, as confirmed by an X-ray study (*20*). Preorganised geometrical relation between phenylene groups in a host molecule is supposed to be one of the controlling factors for the formation of an inclusion complex (*1–5*). When *p*-phenylene in pcn is replaced by *m*-phenylene, the resulting *meta*-cyclophane (mcn; Figure 1) will differ from pcn in the geometrical relation between the constituent phenylene rings. In addition, the local charge distribution in the phenylene group is asymmetric in mcn, inducing a local electric dipole moment on the phenylene group. These structural and electronic properties of mcn are expected to advantage interannular interaction with specific molecules so that the molecular-recognition capability may be higher than that of pcn. In this work, therefore, the complex formation of mcn has been studied by NMR titration. Since the cyclophanes have negatively charged pendant arms, target guests have been selected from ring compounds carrying a positively charged arm, including histamine, tyramine, phenethylamine and tryptamine (Figure 1). Related amino acids (i.e. histidine and phenylalanine), imidazole and 4-aminobenzoic acid were also studied for comparison. Among these guest molecules, histamine forms the most

*Corresponding author. Email: evlzqz@guaymas.uson.mx

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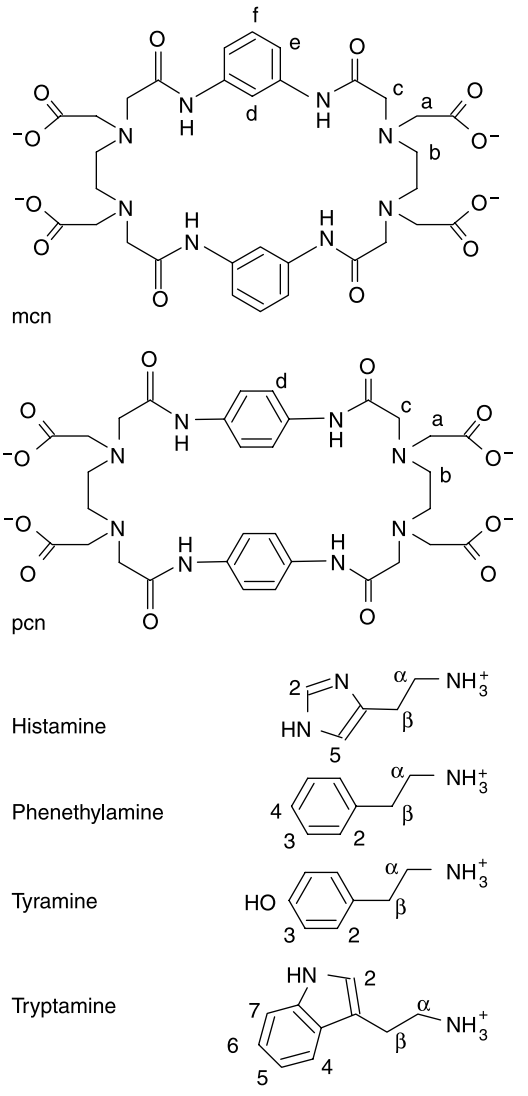

Figure 1. Anionic cyclophanes studied and target amine guests in their ionic forms.

stable complex with mcn than do the other amines, and the selectivity of mcn towards histamine is higher than that of pcn.

Results and discussion

NMR titrations and complex formation

The NMR titrations were carried at pD ~ 9 at which both hosts and guests form a single species: the host molecules are almost completely deprotonated at pD ~ 9 to form the M^{4-} species because the first logarithmic protonation constant log K_p is 7.93 for mcn and 7.77 for pcn in H_2O-d_2 (*21*); pK_a in H_2O has been reported to be 6.02 and 9.70 for histamine (*22*), 9.83 for phenethylamine (*23*), 9.30 for tyramine (*23*) and 9.92 for tryptamine (*24*), and the pK_a values of weak acids in H_2O-d_2 are approximately 0.8 higher than the corresponding values in H_2O (*25*, *26*), so that all the guest amines practically exist as the M^+ ions at pD ≤ 9 because the arms are almost protonated to be $CH_2CH_2NH_3^+$ and one of the nitrogen atoms of histamine ring is completely deprotonated (*17*, *27*). At pD ~ 9, therefore, the chemical shifts of aromatic protons in both hosts and guests are practically independent of pD so that a change in the chemical shifts upon complex formation is determinable reliably even when a small variation in pD is unavoidable. The protonated species MH_2^{2-} of the hosts is formed in a pD range of 5–6 (*21*). In this pD range, however, the solubility was too low for NMR titration. Dopamine was excluded from target guests because it was too unstable at pD > 8 for titration. In all NMR titrations at pD ~ 9, the total concentration of a host $[H]_t$ was kept constant at 5 mM (mM = 10^{-3} mol dm^{-3}) and the total concentration of a guest $[G]_t$ was changed from 10 to 50 mM.

Table 1 shows the chemical-shift changes $\Delta_H(30)$ of host protons at $[G]_t$ 30 mM and $[H]_t$ 5 mM, with reference to the chemical shift δ_H of the corresponding

Table 1. ^{1}H NMR chemical-shift changes, $\Delta_H(30) = \delta_H([G]_t\ 30\,mM) - \delta_H(0)$, of host protons (labelled as shown in Figure 1) observed at $[H]_t$ 5 mM, in the presence of guests at $[G]_t$ 30 mM, at 25°C and pD 9.

Guests	a	b	c	d	e	f
Host: mcn						
Histamine	−0.024	−0.034	−0.034	−0.015	−0.003	−0.007
Tryptamine	−0.089	−0.112	−0.126	–[a]	−0.063	−0.051
Phenethylamine	−0.032	−0.025	−0.034	–[a]	−0.011	−0.008
Histidine	−0.010	−0.016	−0.014	−0.006	0.003	−0.000
Imidazole, phenylalanine, 4-aminobenzoic acid: $\lvert\Delta_H(30)\rvert < 0.001$ for every host proton						
Host: pcn						
Histamine	−0.013	−0.017	−0.016	−0.010		
Tryptamine	−0.069	−0.090	−0.126	−0.117		
Phenethylamine	−0.022	−0.014	−0.020	−0.023		
Histidine	−0.004	−0.007	−0.006	−0.001		
Imidazole, phenylalanine, 4-aminobenzoic acid: $\lvert\Delta_H(30)\rvert < 0.001$ for every host proton						

[a] Masked by a guest proton signal.

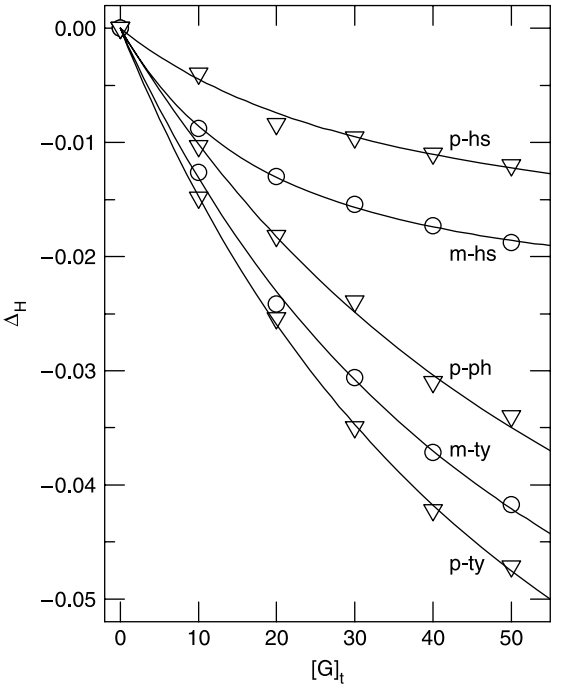

Figure 2. Chemical-shift changes Δ_H (with reference to δ in the absence of guests) observed for aromatic proton 'd' (labelled as shown in Figure 1) of mcn (*m*) and pcn (*p*) as functions of the total concentration $[G]_t$ (mM) of guests, histamine (hs), tyramine (tr) and phenethylamine (ph): $\Delta_H = \delta_H([G]_t) - \delta_H(0)$. The total host concentration is 5 mM at pD 9 and temperature 25°C. The solid lines represent the best fits obtained with K and Δ_{HC} values shown in Table 2.

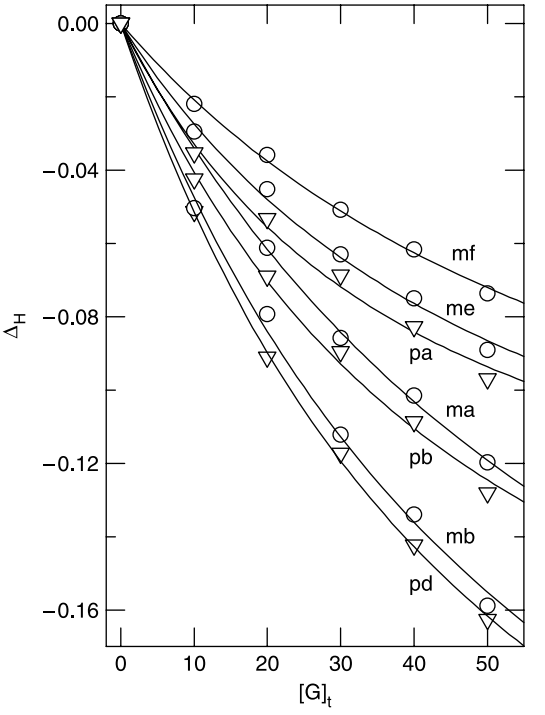

Figure 3. Chemical-shift changes Δ_H (with reference to δ in the absence of guests) of selected protons of mcn (*m*) and pcn (*p*) as functions of the total concentration $[G]_t$ (mM) of tryptamine: $\Delta_H = \delta_H([G]_t) - \delta_H(0)$. The labels of the protons are shown in Figure 1. The total host concentration is 5 mM at pD 9 and temperature 25°C. The solid lines for aromatic protons represent the calculated curves with K and Δ_{HC} values shown in Table 2. The solid lines for aliphatic protons show the best fits with K (M^{-1}) of (proton 'a') 13 and (proton 'b') 17 for the mcn complex; (proton 'a') 27 and (proton 'b') 21 for the pcn complex; the Δ_H versus $[G]_t$ plot of proton 'c' resembles that of proton 'b' in either complex, and gives $K \sim 22$ for mcn and 23 for pcn.

protons in the absence of guests: $\Delta_H(30) = \delta_H([G]_t\ 30\,mM) - \delta_H(0)$. The presence of the guest amines including histamine, tryptamine, tyramine and phenethylamine results in a significant change in the chemical shifts of the aromatic protons of the hosts. The δ_H values decrease with increasing $[G]_t$, as representatively shown for selected aromatic protons in Figures 2 and 3, in which chemical-shift change, $\Delta_H = \delta_H([G]_t) - \delta_H(0)$, is plotted against $[G]_t$. The observed saturation curves indicate the complex formation of the bioactive amines with the hosts. The $\delta_H(0)$ values of aliphatic protons of the hosts are strongly pD-dependent around pD 8 (*21*). As a result, a small variation in pD around 9 still caused a relatively large uncertainty of the Δ_H values of the aliphatic protons, whereas such a pD effect is negligible for the aromatic protons. Despite this difficulty, the $\Delta_H(30)$ values of the aliphatic protons are also significant (Table 1), and the Δ_H versus $[G]_t$ plots show saturation curves similar to those of the aromatic protons, as shown in Figure 3 for selected aliphatic protons in the presence of tryptamine. These observations consistently support the complex formation concluded from the aromatic proton signals. In contrast to the bioactive amines, the other substances give no evidence of interaction with the hosts; although histidine causes a small change in δ_H of some host protons, the change of every aromatic proton, which is insensitive to pD variation, is negligible (Table 1), and, moreover, the Δ_H versus $[G]_t$ plot of any proton does not tend to a definitive saturation; phenylalanine and imidazole are absolutely ineffective on δ_H (Table 1). Only the amines interact with the hosts strongly enough to form their definite complexes.

The common structural feature of the guests that form complexes with the hosts is the possession of a $-CH_2CH_2NH_3^+$ arm at pD ~ 9. The cationic arm is supposed to interact strongly with the $-CH_2CO_2^-$ group of a host molecule. Such an electrostatic interaction is absolutely absent in the case of imidazole, the amino acids bearing a zwitter-ion arm, and aminobenzoic acid carrying $-CO_2^-$ and NH_2 groups. These observations conclude that the electrostatic interaction between the $-CH_2CH_2NH_3^+$ and $-CH_2CO_2^-$ arms is a dominative binding force for the complex formation.

Formation constants of host–guest complexes

For the host–guest complexes of the amines, the formation constants were determined from changes in Δ_H with $[G]_t$. Since every host proton shows a single NMR signal as a result of a fast exchange in the equilibrium of complex formation, the concentration of a complex [HG] can be determined from Δ_H as follows:

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

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

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

On the basis of Equations (1) and (2), two unknown parameters K and Δ_{HC} were determined for each proton by employing Lang's method, which is a repeated linear least-squares calculation with a linearised equation (*17*, *28*). Table 2 shows the K and Δ_{HC} values obtained for the aromatic protons whose Δ_H values are reliable; the parameters well reproduce the observed shifts as shown in Figures 2 and 3. Least-squares calculation by assuming 1:2 host–guest complexation gave large standard deviations of the parameters, and the calculated curves showed a systematic deviation from the observed data. These results of calculations concluded the formation of 1:1 complexes. Although the Δ_H values of aliphatic protons involved large uncertainty due to unavoidable pD variation, the K values obtained for three aliphatic proton signals of a host by assuming 1:1 complexation were similar in magnitude to one another in every host–guest system (cf. caption of Figure 3). For reference, therefore, the approximate K values averaged over the aliphatic protons are also included in Table 2. The formation constants determined cannot be strictly compared with one another, owing to the difficulty in controlling ionic strength (cf. Experimental). Despite this limitation, it is apparent that the stability of the mcn complexes tends to increase in the order phenethylamine < tyramine ~ tryptamine < histamine. A similar tendency is found for the pcn complexes, but the difference in the stability is more pronounced for the mcn complexes than for the pcn complexes. This difference is a result of the introduction of *m*-phenylene in the place of *p*-phenylene.

Chemical shifts of guests and interannular interaction

Similar to the shifts of the host protons in the presence of the guests, the protons of the guests also exhibited up-field shifts in the presence of the hosts. Table 3 shows the chemical-shift changes Δ_G of guest protons at $[G]_t$ 5 mM and $[H]_t$ 30 mM: $\Delta_G(30) = \delta_G([H]_t\ 30\ mM) - \delta_G(0)$. The chemical-shift changes Δ_{GC} of guest protons in the complexes were determined on the basis of the relation $\Delta_{GC} = \Delta_G(30)\cdot[G]_t/[HG]$, in which complex concentration [HG] was calculated with the formation constants given in Table 2. The obtained Δ_{GC} values are presented in Table 3.

The electrostatic interaction of $CH_2CH_2NH_3^+$ in a guest molecule with $CH_2CO_2^-$ in a host molecule may cause NMR shift of protons in $CH_2(\alpha)$ bonded directly to NH_3^+. This effect, even if exists, attenuates along the aliphatic chain so rapidly as to be irresponsible for the shifts observed for the ring protons. The up-field shifts of the aromatic protons, therefore, suggest the coexistence of another type of interaction between host and guest molecules. The possibility of charge-transfer interaction is ruled out because both host and guest protons shift to the same direction of field upon complex formation, and hydrogen bonding is also ruled out for the same reason. Hydrophobic interaction does not directly cause a chemical-shift change. In the resulting inclusion complexes, however, the close contact between aromatic groups leads to a large chemical shift due to mutual

Table 2. Formation constants K (M^{-1}) calculated on the basis of host proton signals, and the chemical-shift change of the complexes, $\Delta_{HC} = \delta_H([G]_t\ \infty) - \delta_H(0)$, at 25°C and pD 9.

	K				Δ_{HC}			
	hst	trp	tyr	phn	hst	trp	tyr	phn
mcn								
d	63(4)	24(4)	18(2)	–[a]	−0.025(1)	−0.23(3)	−0.090(8)	–[a]
e	–[a]	20(2)	17(6)	8(4)	–[a]	−0.18(3)	−0.05(2)	−0.05(2)
f	–[a]	14(2)	14(5)	1(4)	–[a]	−0.18(3)	−0.06(2)	−0.2(5)
CH_2[b]	80	15	20	0				
pcn								
d	31(7)	20(2)	18(2)[c]	14(2)[c]	−0.021(4)	−0.34(2)	−0.103(5)	−0.088(8)
CH_2[b]	50	25	20	20				

Abbreviation of guests: hst, histamine; trp, tryptamine; tyr, tyramine; phn, phenethylamine. For the abbreviation of hosts and labels of protons, see Figure 1.

[a] Undeterminable due to very small chemical-shift changes.

[b] Aliphatic protons; approximate values averaged over three CH_2 proton signals.

[c] Reported values at pD 8 (reference (*18*)): K = 20(2) for tyramine and 17(2) for phenethylamine.

Table 3. ^{1}H NMR chemical shifts of guest protons (labelled as shown in Figure 1) with reference to the δ values at $[H]_t = 0$, $\Delta_G(30) = \delta_G([H]_t\ 30\ mM) - \delta_G(0)$, observed at $[G]_t$ 5 mM and pD 9, the shifts of the guest protons in the complexes, $\Delta_{GC} = \delta_G([H]_t \infty) - \delta_G(0)$, and distances d of the aromatic protons along the molecular plane from the normal to the host ring centre.

		$\Delta_G(30)$		Δ_{GC}[a]		d (Å)	
Guest proton		mcn	pcn	mcn	pcn	mcn	pcn
Histamine	α	−0.028	−0.025	−0.045	−0.054		
	β	–[b]	−0.026	–	−0.056		
	2	−0.017	−0.015	−0.027	−0.032	4.5	4.5
	4	–[b]	−0.029	–	−0.063	–	4.2
Tryptamine	α	−0.057	–[b]	−0.163	–		
	β	−0.062	−0.060	−0.177	−0.166		
	2	−0.073	−0.064	−0.209	−0.177	3.5	3.6
	4	−0.062	−0.057	−0.177	−0.158	3.6	3.7
	5	−0.045	−0.027	−0.129	−0.075	3.8	4.1
	6	−0.041	−0.035	−0.117	−0.097	3.6	4.0
	7	−0.048	−0.043	−0.137	−0.119	3.8	3.9
Tyramine	α	−0.053	−0.055	−0.169	−0.163		
	β	–[b]	−0.059	–	−0.175		
	2	−0.056	−0.045	−0.179	−0.133	3.6	3.8
	3	−0.040	–[b]	−0.128	–	3.9	–
Phenethylamine	α	−0.048	−0.050	–[c]	−0.175		
	β	−0.048	–[b]	–[c]	–		
	Ar[d]	−0.04	−0.05	–[c]	−0.175	–	3.7

[a] Calculated with K determined for aromatic protons (Table 2); the averaged value 19 was employed for mcn–tryptamine and 16 for mcn–tyramine.
[b] Masked by a host proton signal.
[c] Undeterminable due to very small formation constants.
[d] Averaged over all aromatic proton signals.

ring-current effect. The chemical shift δ_{rc} (in ppm) that is induced by a benzene ring on a nearby resonant proton is given by (*29*):

$$\delta_{rc} = 27.6(1 - 3\cos^2\theta)/R^3. \quad (3)$$

Here, R is the distance (in Å) between the resonant proton and the ring centre, and θ is the angle between the $\boldsymbol{R}$ vector and the normal to the ring centre. Magnetic field induced by other types of aromatic rings also has the nodal surface on the two sides of which the sign of δ_{rc} is reversed. Since both host and guest protons show a decrease in δ upon complex formation, the protons are located in the region of negative δ_{rc} above the ring plane of the counter molecule, and hence the host and guest molecules are stacked in a face-to-face manner rather than in an edge-to-face contact (*18*, *20*). A similar molecular arrangement is assumable for mcn complexes, as tentatively visualised in Figure 4. When the face-to-face stack is formed with the van der Waals contact of 3.4 Å (*30*), the R and cos θ of a resonant guest proton are derived from the distance d along the ring plane of the guest from the normal to the phenylene ring centre of the host, as $R^2 = 3.4^2 + d^2$ and $\cos\theta = 3.4/R$. Since two phenylene groups of a host molecule are geometrically equivalent on the time average, δ_{rc} induced by one of the two groups on a resonant guest proton can be equated to half the Δ_{GC} value of the proton. Thus, the distance d was calculated for the aromatic protons of the guests, as

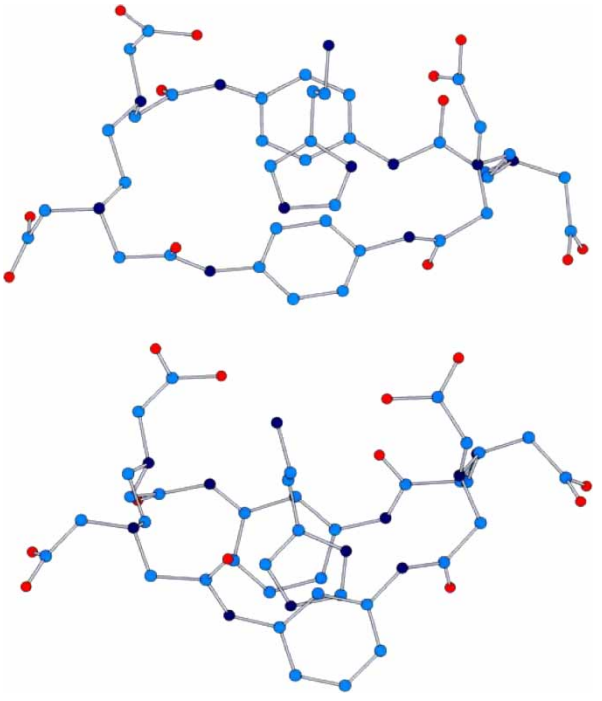

Figure 4. Possible molecular arrangements in histamine complexes with (top) pcn and (bottom) mcn. The structures were drawn with molecular mechanics in the program HyperChem, only for visualising encapsulation of histamine and electrostatic interaction between $-CH_2CH_2NH_3^+$ and $-CH_2CO_2^-$ arms.

presented in Table 3; protons in the $CH_2CH_2NH_3^+$ arms were not included in the calculation because they deviate from the ring plane of the relevant guest molecule. Practically, the same *d* values were obtained for the complexes of mcn and pcn with a common guest, suggesting that the mode of encapsulation is essentially identical in the two complexes.

In a host–guest assembly, the $CH_2CH_2NH_3^+$ arm of the guest orients towards one of the potential minima formed by the $CH_2CO_2^-$ groups of the host, as shown in Figure 4, during a certain lifetime. As a result of fast complexation equilibrium and conformational changes, the host molecule takes equivalent orientations in an equal probability in such a way that four equivalent subunits (involving $CH_2CO_2^-$) of the host have the same geometrical relation with the guest on a time average; the rate of this molecular reorientation is much higher than the NMR time scale, because every proton shows a single NMR signal. The *d* values, therefore, give the time-averaged positions of aromatic protons which are relocated synchronously with the molecular reorientation of the aromatic ring to which the aromatic protons are bonded. Since the *d* values of all aromatic protons in a guest molecule are practically identical, the relocation of all aromatic protons is supposed to occur around a common centre, which is most probably the centre of the aromatic ring to which the protons are attached. Therefore, the mean *d* value of a guest shows the position of the ring centre of the guest molecule with respect to the ring centre of the host, or it is equated to the slip distance d_s by which the aromatic rings of the host and guest molecules are slipped away from each other along their molecular planes, as schematically shown in Figure 5. The slip distance d_s thus defined is approximately 4.4 Å for the histamine complexes and 3.8 Å for the tyramine, phenethylamine and tryptamine complexes (Table 3). In the assumed stacking mode illustrated in Figure 5, the time-averaged position of an aromatic hydrogen atom can be represented by the distance d_H from the normal to the ring centre of the counter host molecule. The d_H value estimated from the slip distance d_s was found to be 2.2 Å for histamine, 1.4 Å for phenethylamine and tyramine, and 0.2 Å (along the major axis) for tryptamine, by assuming 1.4 Å for the radius of a six-membered ring, 1.2 Å for the radius of a five-membered ring and 1.0 Å for the C—H bond distance; the indole ring is approximated by an ellipse with a major radius of 2.6 Å and a minor radius of 1.4 Å. The obtained d_H values describe the stacking modes as follows: in the tryptamine complexes, a hydrogen atom residing along the major axis in a guest ring is located almost vertically above the ring centre of the counter host molecule; in the phenethylamine and tyramine complexes, an aromatic H atom in a guest molecule is above an aromatic carbon atom in the counter host molecule; in the histamine complexes, a ring H atom of the guest is above an aromatic C—H bond in the host molecule (Figure 5). The degree of the overlap between host and guest rings, or the deepness of insertion, is increased in the order histamine < tyramine ~ phenethylamine < tryptamine. This relation is correlated with the hydrophobicity of the guests; the more hydrophobic ring is more deeply inserted in a host cavity. The deepness of the insertion, however, is not correlated with the stability of the complexes; on the contrary, the most stable complex of mcn is formed by histamine, which is less hydrophobic than the other guests, and the stability of the tryptamine complexes are by no means higher than that of the other complexes despite the deepest insertion. The hydrophobic interaction may motivate the encapsulation of a guest molecule into a host cavity, but the resulting complexes should be stabilised by additional interannular interaction.

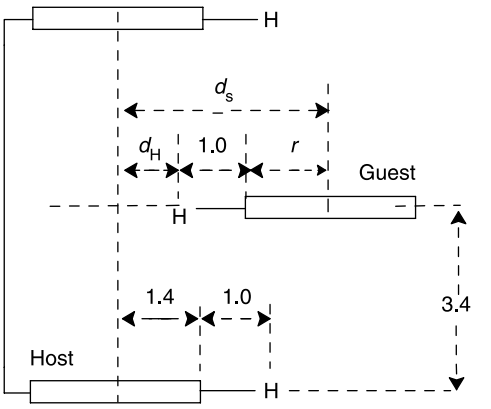

Figure 5. Stacking mode proposed for the time-averaged structure of the host–guest complexes of the cyclophanes with the bioactive amines. The ring radii and the C—H bond distances are shown in Å. The slip distance d_s (Å), the ring radius *r* (Å) of a guest and the distance d_H (Å) of a guest proton from the normal to the phenylene ring centre of the host are approximately given as follows: $d_s = 4.4$, $r = 1.2$ and $d_H = 2.2$ for histamine; $d_s = 3.8$, $r = 1.4$ and $d_H = 1.4$ for tyramine and phenethylamine; $d_s = 3.8$, $r_{major} = 2.6$ and $d_H = 0.2$ (along the major axis) for tryptamine.

The phenylene rings of mcn carry a local electric dipole moment, which is induced by amide groups attached at the *meta* positions. This electronic property is the most significant difference from the *para*-cyclophane whose phenylene rings have no local electric dipole moment. Among the ring systems of the guest amines studied, histamine ring is supposed to have the largest local electric dipole moment and phenethylamine ring has the smallest moment. Dipolar interaction is, therefore, operative most strongly between mcn and histamine, and the stability of the mcn complexes is correlated with the magnitude of the local dipole moment of the guests.

Experimental

The host cyclophanes were synthesised by the methods reported previously (*21*, *31*) and the purity was checked by ^{1}H NMR. The guests were commercially supplied and used

as received: histamine hydrochloride (99%, Aldrich), tryptamine hydrochloride (99%, Aldrich), tyramine hydrochloride (99%, Sigma), phenethylamine hydrochloride (99%, Aldrich), L-histidine monohydrochloride monohydrate (99%, Aldrich), L-phenylalanine (99%, Aldrich) and 4-aminobenzoic acid (99%, Aldrich).

^{1}H NMR spectra were obtained with a Bruker AVANCE NMR spectrometer operating at 400 MHz at 25°C. The solvent was H_2O-d_2 supplied from Aldrich (99.9 atom% *d*) and was mixed with H_2O-d_2 (Aldrich) containing 1% w/w sodium 3-(trimethylsilyl)-1-propanesulphonate (DSS) as the internal standard. The concentration of DSS was kept constant and as low as possible to minimise possible interaction with guest molecules (*17*). The pH values of sample solutions were determined with an Aldrich ultra-thin combination electrode (calomel reference) calibrated with standard buffers, and converted to pD on the basis of the relation $pD = pH_{measured} + 0.45$ (*32*). The pD values of sample solutions were adjusted with solid Na_2CO_3 to a value between 8.8 and 9.1; the pD variation among sample solutions in each run of titration was less than ± 0.05. In the presence of a large excess of electrolyte, no complex formation occurred, as reported for analogous anionic cyclophanes (*17*); the ionic strength of sample solutions was not controlled, and a minimum quantity of Na_2CO_3 was used to adjust pD so that the interference of electrolyte with complexation was minimised.

Conclusion

The *meta*- and *para*-cyclophanes form host–guest complexes with the bioactive amines. The major binding force for the complex formation is electrostatic interaction between the cationic arm of a guest molecule and the anionic arm of a host molecule, because imidazole as well as the amino acids having a zwitter-ion arm does not form a complex with the hosts. Hydrophobic interaction probably motivates encapsulation of the aromatic group of a guest molecule into the cavity of a host molecule, so as to define the orientation of the guest molecule in the host cavity. As a result, the tryptamine, which is most hydrophobic, is most deeply encapsulated. Furthermore importantly in the mcn complexes, dipolar interaction is operative between the phenylene group of the host and the aromatic group of the guests. The combined effect of these different types of interactions results in the selective recognition of the anionic *meta*-cyclophane towards histamine.

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