Molecular recognition of phenethylamine, tyramine and dopamine with new anionic cyclophanes in aqueous media

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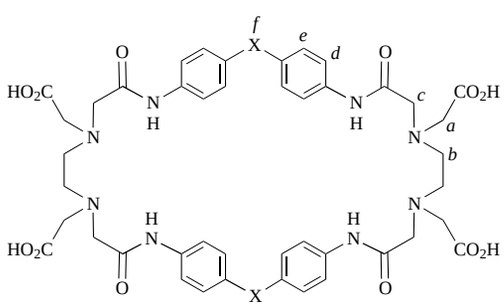
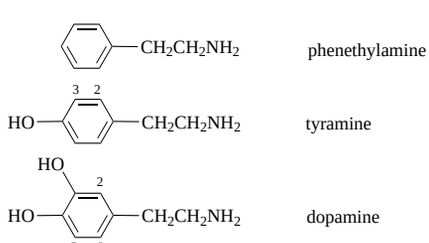
Water-soluble cyclophanes functionalized by amide groups and pendant carboxymethyl groups have been synthesized, in a single step, by a condensation reaction between ethylenediaminetetraacetic (EDTA) dianhydride and bis(4-aminophenyl) ether or bis(4-aminophenyl)methane: cyclophanes obtained are 2,9,25,32-tetraoxo-4,7,27,30-tetrakis(carboxymethyl)-1,4,7,10,24,27,30,33-octaaza-17,40-dioxa[10.1.10.1]-paracyclophane (1) and 2,9,25,32-tetraoxo-4,7,27,30-tetrakis(carboxymethyl)-1,4,7,10,24,27,30,33-octaaza[10.1.10.1]paracyclophane (2). Their complexation with 2-phenylethylamine (phenethylamine), 2-(4-hydroxyphenyl)ethylamine (tyramine) and 2-(3,4-dihydroxyphenyl)ethylamine (dopamine), which have biologically important activities, has been studied by ^{1}H NMR spectroscopy in aqueous media. The formation constants of 1 : 1 host–guest complexes, K = [HG]/[H][G], have been determined as: log K = 0.8 for 1–phenethylamine; 1.2 for 1–tyramine; 1.2 for 1–dopamine; 1.6 for 2–phenethylamine; 2.0 for 2–tyramine. Dopamine and 2 form a complex with low water-solubility. The chemical shifts of aromatic protons of the host and guest molecules suggest the formation of inclusion complexes in solutions. The formation of the host–guest complexes is assisted by a hydrogen bond and/or an electrostatic interaction between the pendant $-CH_2CO_2^-$ group of the host and the $-CH_2CH_2NH_3^+$ arm of the guest molecule. The two types of molecular recognition sites of the new cyclophanes result in the selective complex formation with the aromatic amines.

Water-soluble cyclophane-type macrocycles, which contain phenyl groups as an integral part of the macrocyclic ring, form supramolecular complexes with specific organic guest molecules in aqueous media.[1–10] One of the major binding forces arises from hydrophobic effects. Although this unique molecular recognition property of cyclophanes has attracted a great deal of interest, the binding forces involved in hydrophobic interactions are weak, and the selectivity towards a specific molecule is controlled only by the preorganization of the cyclophane cavity. The introduction of additional molecular recognition sites (*e.g.* hydrogen bonding sites and electrostatic interaction sites) to a cyclophane is, therefore, required to enhance its selectivity towards a specific molecule and to increase the stability of the resulting complex *via* multipoint molecular recognition.

We have reported that condensation reactions between alkyldiamines and ethylenediaminetetraacetic (EDTA) dianhydride give, in a single step, a new series of macrocycles with pendant carboxymethyl groups.[11] The resulting macrocycles have novel complexation properties with metal ions, due to the unique arrangements of different types of donor groups, *i.e.* amino, amide and carboxylate groups. The use of aromatic diamines, instead of aliphatic diamines, can provide a new series of functionalized cyclophanes.[12] In this work, we have synthesized two new anionic cyclophanes, 2,9,25,32-tetraoxo-4,7,27,30-tetrakis(carboxymethyl)-1,4,7,10,24,27,30,33-octaaza-17,40-dioxa[10.1.10.1]paracyclophane (**1**) and 2,9,25,32-tetraoxo-4,7,27,30-tetrakis(carboxymethyl)-1,4,7,10,24,27,30,33-octaaza-[10.1.10.1]paracyclophane (**2**), by the use of bis(4-aminophenyl) ether and bis(4-aminophenyl)methane, respectively. These cyclophanes have four phenyl groups in the ring system and, in addition, three types of functional groups, *i.e.* amino and amide groups in the ring system and carboxymethyl groups as pendant arms. The ring system is expected to have interactions with aromatic molecules due to a solvent-exclusion effect in aqueous media.[1–9] The functional groups introduced are potential molecular recognition sites *via* hydrogen bond formation and/or electrostatic interactions.[13,14] These novel structural features of the new cyclophanes will result in the formation of host–guest complexes with certain aromatic molecules that have cationic arms, due to the combined effect of a hydrophobic interaction between the aromatic groups of the host and guest molecules and an electrostatic interaction between the $-CO_2^-$ groups of the host and the $-NH_3^+$ groups of the guest. Complexation of the new cyclophanes, therefore, has been studied by means of ^{1}H NMR for 2-phenylethylamine (phenethylamine) and its biologically important derivatives, 2-(4-hydroxy-



1 : X = –O– **2** : X = –CH_2–



phenyl)ethylamine (tyramine) and 2-(3,4-dihydroxyphenyl)-ethylamine (dopamine); dopamine is of special importance because it belongs to a family of catecholamine neurotransmitters.

Experimental

Syntheses of cyclophanes

Cyclophane **1** was synthesized by adding dropwise 3.9 g of bis(4-aminophenyl) ether (Aldrich) in 70 cm^3 of dimethylformamide (DMF) to 4.9 g of ethylenediaminetetraacetic (EDTA) dianhydride (Aldrich) in DMF (300 cm^3) under a nitrogen atmosphere. The light yellow solution obtained was concentrated and mixed with water. A pale brown solid was obtained. This crude cyclophane was converted to the lithium salt, and was recrystallized twice from hot water. Acidification (pH ≈ 3) of the purified lithium salt gave cyclophane **1** in the acid form as a colourless solid. Yield: 25% (Calc. for $C_{44}H_{48}N_8O_{14}\cdot H_2O$: C, 56.78; H, 5.41; N, 12.03. Found: C, 57.17; H, 5.52; N, 12.02%) (the elemental analyses were performed at Desert Analytics, Tucson, AZ, USA); $\delta_H(D_2O$, pD = 8.4; 250 MHz; DSS) 2.97 (8H, s, proton *b*), 3.38 (8H, s, *a*), 3.55 (8H, s, *c*), 6.84 (8H, d, *J* 8.9, *e*), 7.20 (8H, d, *J* 8.9, *d*); $\delta_C(D_2O$, pD = 8.4; 62.9 MHz; DSS) 55.7 (carbon *b*), 61.2, 61.5 (*a*, *c*), 121.3 (*e*), 125.5 (*d*), 134.8 (phenyl *C*–N), 155.9 (phenyl *C*–O), 173.6 (*C*=O), 180.4 (CO_2^-); *m*/*z* (electrospray ionization) 911.5 [$(M - H)^-$, 6%], 455.4 [$(M - 2H)^{2-}$, 67], 303.1 [$(M - 3H)^{3-}$, 100].

Cyclophane **2** was synthesized by essentially the same method as for **1** by the use of the diamine, bis(4-aminophenyl)methane (Aldrich). The crude product was converted to the lithium salt, which was recrystallized from 50% ethanol. When an aqueous solution of the purified lithium salt was acidified with dilute HCl to pH ≈ 3, cyclophane **2** in the acid form was obtained as a colourless solid. The product was washed with water. Yield: 10% (Calc. for $C_{46}H_{52}N_8O_{12}\cdot 2H_2O$: C, 58.46; H, 5.97; N, 11.86. Found: C, 58.76; H, 5.64; N, 11.83%); $\delta_H(D_2O$, pD = 10.4; 250 MHz; DSS) 2.82 (8H, s, *b*), 3.29 (8H, s, *a*), 3.38 (8H, s, *c*), 3.79 (4H, s, *f*), 6.99 (8H, d, *J* 8.1, *e*), 7.13 (8H, d, *J* 8.1, *d*); $\delta_C(D_2O$, pD = 10.2; 62.9 MHz; DSS) 42.7 (*f*), 55.7 (*b*), 61.6, 61.8 (*a*, *c*), 124.0 (*e*), 131.9 (*d*), 137.4 (phenyl *C*–N), 140.5 (phenyl *C*–CH_2), 175.0 (*C*=O), 181.9 (CO_2^-); *m*/*z* (electrospray ionization) 907.6 [$(M - H)^-$, 7%], 453.3 [$(M - 2H)^{2-}$, 62], 301.8 [$(M - 3H)^{3-}$, 100].

NMR measurements

The NMR spectra were recorded on a Bruker AM 250 spectrometer. The internal reference for aqueous solutions was sodium 3-(trimethylsilyl)propanesulfonate (sodium 4,4-dimethyl-4-silapentane-1-sulfonate, DSS).† The pH values of sample solutions were determined with a Beckman Phi 72 pH meter equipped with an Aldrich ultra-thin long stem combination electrode (calomel reference) after the NMR measurements, and converted to pD values by $pD = pH_{measured} + 0.4$.[15] NMR titrations were carried out at a pD of 8 and at a probe temperature of 23 °C. The ^{1}H NMR signals of a cyclophane molecule were used as a probe for complex formation, and the concentration of the cyclophane in the sample solutions was kept constant at 5 mmol dm^{-3}. The concentrations of the guest molecules were varied from 5 to 50 mmol dm^{-3}. The guest compounds, phenethylamine hydrochloride and tyramine hydrochloride, were supplied from Aldrich and dopamine hydrochloride from Sigma, and used without further purification. The stock solutions of the host and the guest compounds were prepared by dissolving them in 99.9% D_2O (Cambridge Isotope Laboratories), and the pD of the stock solutions was adjusted to 8 by adding a minimum amount of solid Na_2CO_3.‡ The concentration of the internal standard, DSS, in sample solutions was kept constant at approximately 0.2 mmol dm^{-3}, which was much lower than the host and guest concentrations, in order to minimize electrostatic effects that might be caused by the presence of DSS.† Dopamine was gradually oxidized in an aqueous solution in the presence of air. Freshly prepared sample solutions were, however, stable enough for NMR measurements without taking special care for the removal of oxygen at the pD studied; sample solutions were colourless for the duration of NMR measurements and no impurity peaks were observed in the ^{1}H NMR spectra.

Results and discussion

Cyclophanes

Condensation reactions between aromatic diamines and EDTA dianhydride gave cyclophanes **1** and **2** in each of which two diamine units and two EDTA units were linked by four amide bonds. The formation of the cyclophanes was confirmed by ^{1}H and ^{13}C NMR and electrospray ionization mass spectroscopy. These new cyclophanes in the acid form are practically insoluble in water. The sodium salt of **1** is, however, highly water-soluble; the sodium salt of **2** is less water-soluble but sufficiently soluble for NMR measurements. The amide groups of the cyclophanes are involved in the conjugated system of the phenyl groups, and hence the –NH–CO–C– atoms in each amide group are on the same molecular plane of the aromatic ring to which the amide group is bonded. This planarity defines the geometry of the cyclophane cavities. The three functional groups, *i.e.* amino, amide and pendant carboxylate groups, contribute to the water-solubility, and are potential molecular recognition sites. The negatively charged pendant carboxylate groups will enhance the molecular recognition of aromatic cations as a result of ion paring.

Fig. 1 shows the pD dependence of the chemical shifts observed for cyclophane **1**. The aliphatic protons, *a*, *b* and *c*, shifted downfield with decreasing pD in the range 7–9. These simultaneous shifts of the three proton signals indicate that the amine nitrogens are protonated prior to the carboxylate oxygens, thereby resulting in the formation of a zwitterion structure. Phenyl proton *e* showed a small upfield shift in the pD range where protonation occurred, and this pD dependence was pronounced at high sample concentrations (Fig. 1). The protonated molecules are, therefore, aggregated in concentrated solutions. The shift of *e* proton may be caused by a change in the angle between the molecular planes of two neighbouring phenyl groups, because the shielding field due to the ring current of the adjacent phenyl group is angle-dependent.[16] Fig. 2 shows pD dependence of ^{1}H NMR signals observed for cyclophane **2**. Protonation occurred on amine nitrogen in almost the

† DSS can be used as an internal reference for the anionic cyclophanes, because the chemical shifts referenced to DSS were practically independent of the DSS concentration: the shifts of each cyclophane (5 mmol dm^{-3}) at the DSS concentrations of 0.2 and 5 mmol dm^{-3} agreed within 0.004 ppm. In the titrations with the aromatic guest amines, however, the concentration of DSS in sample solutions was kept as low as possible, and constant, to minimize its possible electrostatic interaction with host and guest molecules.

‡ The NMR shifts of the sodium salts of the cyclophanes agreed with those of the corresponding lithium and potassium salts, within ±0.003 ppm at pD = 8. When a large amount of NaCl or KCl (30–50 mmol dm^{-3}) was added to a sample solution (5 mmol dm^{-3}) of pD = 8, the *e* proton signal of **1** shifted by 0.01–0.02, and the *e* and *f* protons of **2** by 0.01–0.03 ppm; the shifts of other protons (including the *d* protons) of both cyclophanes were less than 0.002 ppm. These observations show that no complexation occurs with the alkali metal ions. The presence of a large amount of an electrolyte, however, influences the formation of complexes with the guest amines: in the presence of KCl at a concentration of 0.1 mol dm^{-3}, the aromatic proton signals of the cyclophanes (5 mmol dm^{-3}) shifted to a higher field with increasing concentration of a guest amine, but no saturation curve was observed up to $[G]_t$ = 50 mmol dm^{-3}. A minimum amount of Na_2CO_3 was, therefore, used to adjust the pD of the stock solutions so that a possible electrolyte effect on the complexation was minimized.

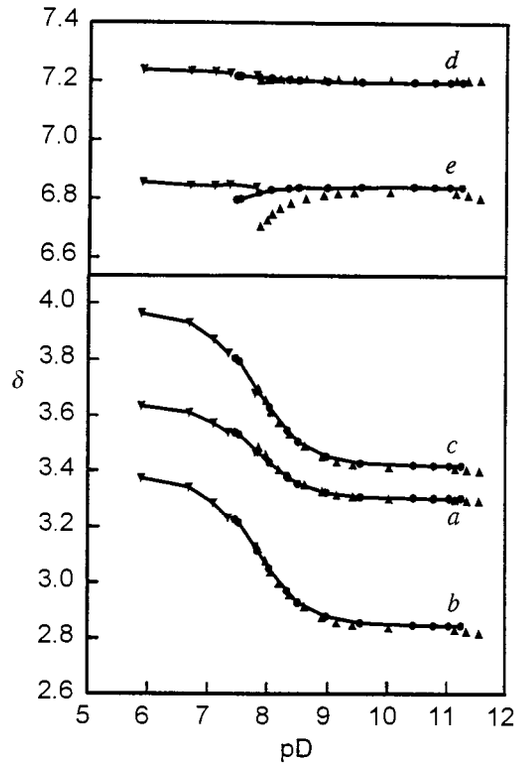


Fig. 1 Plots of ^{1}H NMR chemical shifts (referenced to DSS) of cyclophane **1** in D_2O as functions of pD at 5 mmol dm^{-3} (●) and 30 mmol dm^{-3} (▲). At pD below 7.5, the shifts were determined at a concentration less than 1 mmol dm^{-3} (▼), because of the low solubility. For labelling, see formula.

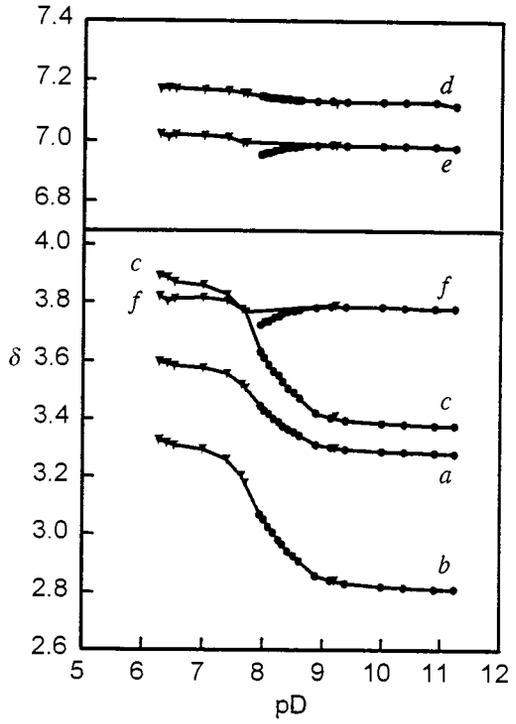


Fig. 2 Plots of ^{1}H NMR chemical shifts (referenced to DSS) of cyclophane **2** in D_2O as functions of pD at 5 mmol dm^{-3} (●). At pD below 8, the shifts were determined at a concentration less than 1 mmol dm^{-3} (▼), because of the extremely low solubility. For labelling, see formula.

same pD range as for **1**. The basicities of the amine nitrogens in the two cyclophanes are, therefore, almost identical. Upon protonation, *d*, *e* and *f* proton signals shifted, as a result of a change in the geometrical relation between two neighbouring phenyl rings. The water-solubility of **2** decreased rapidly with decreasing pD in the range where protonation occurred, and hence NMR experiments were carried out at 5 mmol dm^{-3} or lower; the *e* and *f* protons tended to shift to a higher field with increasing sample concentration in the pD range where protonation occurred.

Complexation of cyclophane 1

The ^{1}H NMR signals of cyclophane **1** showed significant shifts in the presence of phenethylamine, tyramine or dopamine, and no new peak was observed. Table 1 shows the chemical shifts of aromatic protons *d* and *e* with reference to the corresponding signals in the absence of the guest amines. The ^{1}H NMR signals of the guest amines shifted upfield in the presence of the cyclophane (Table 2). These observations suggest that there are interactions between the aromatic groups of the host and guest molecules. Probably the cyclophane molecule encapsulates an aromatic amine molecule in the cyclophane cavity.

The formation constants of the host–guest complexes were determined by ^{1}H NMR titrations at pD ≈ 8. The pD at which the NMR titrations were performed was limited (1) by the solubility of the cyclophane which rapidly decreased with decreasing pD and also (2) by the properties of the guest amines. The ^{1}H NMR spectra of the amines showed two sets of signals at pD above about 9.0, indicating the presence of two species with an exchange rate lower than the NMR timescale. Moreover, tyramine and dopamine were unstable at higher pD. Since the chemical shifts of the cyclophane signals showed a concentration-dependence, the concentration of the cyclophane was kept constant at 5 mmol dm^{-3} where its aggregation was still insignificant. Aromatic protons *d* and *e* of the cyclophane were used as probe signals for determination of formation constants.

The aliphatic proton signals were not useful as probe signals, because their large pD dependence at pD ≈ 8 resulted in a large uncertainty in the formation constants (Fig. 1). Fig. 3 shows the chemical shifts of the aromatic protons of **1** as functions of the concentrations of the guest amines; the shifts were referenced to the corresponding signals in the absence of the guest molecules. The observed saturation curves support the formation of host–guest complexes. When host and guest molecule, H and G, are in equilibrium with their complex molecule HG, the formation constant of the complex, $K = [HG]/[H][G]$, can be calculated by Lang's method.[17] When a signal of the host is used as a probe and the total concentration of the host is kept constant in a titration, Lang's equation is given by eqn. (1), where $[H]_t$ is the

$$[G]_{t,i}/\Delta_i = \{[G]_{t,i} + [H]_t - (\Delta_i/\Delta_c)[H]_t\}(1/\Delta_c) + 1/(K\Delta_c) \quad (1)$$

total concentration of the host, $[G]_{t,i}$ is the total concentration of the guest in the *i*th sample solution, Δ_i is the shift of the probing signal in the *i*th sample solution with reference to the corresponding signal at $[G]_t = 0$, and Δ_c is the shift at infinite $[G]_t$. The *K* and Δ_c calculated by using a locally developed computer program are collected in Table 1. The solid lines in Fig. 3 show calculated Δ_i *vs.* $[G]_t$ curves, which fit the experimental data quite well. The formation constants that were determined, based on the shifts of the two protons, agree well. Curves calculated by assuming formation of 2:1 complexes systematically deviated from the experimental data. This is indirect confirmation that only the 1:1 complex is formed in each host–guest system.

Complexation of cyclophane 2

The *e* proton signal of cyclophane **2** in the presence of phenethylamine shifted to a greater extent than the corresponding signal of cyclophane **1** at the same guest concentration (Table 1), and the shift observed for **2** reached a saturation value at a lower amine concentration than that for **1** (Fig. 4). The *d* proton signal shifted downfield in the presence of the amine, differing from the **1**–phenethylamine system. Proton *f* in a CH_2 group located between two phenyl groups showed a

Table 1 ^{1}H NMR shifts Δ (ppm) of aromatic proton signals of the cyclophane hosts (5 mmol dm^{-3}) in the presence of aromatic amine guests with concentrations $[G]_t$/mmol dm^{-3} = 5 and 30, formation constants $K = [HG]/[H][G]$ and Δ_c (Δ at infinite concentration of amines)[a]

Host–guest	Proton	Δ,[b] $[G]_t = 5$	Δ,[b] $[G]_t = 30$	log K[c]	Δ_c[b]
1–phenethylamine	*d*	0.005	0.026	1.0	0.12
	e	0.016	0.089	0.8	0.55
1–tyramine	*d*	0.006	0.037	1.2	0.11
	e	0.021	0.097	1.2	0.30
1–dopamine	*d*	0.011	0.050	1.3	0.13
	e	0.031	0.145	1.2	0.42
2–phenethylamine	*d*	−0.018	−0.046	1.9	−0.069
	e	0.067	0.199	1.6	0.37
	f	0.107	~0.29[d]	1.9[d]	0.39[d]
2–tyramine	*d*	−0.015	−0.017[e]	2.7[e]	−0.026[e]
	e	0.084	0.176	2.0	0.25
	f	0.128	~0.24[d]	2.3[d]	0.27[d]
2–dopamine[f]	*d*	−0.014			
	e	0.080			
	f	0.124			

[a] In D_2O with pD = 8.0 ± 0.1. [b] The negative sign shows downfield shifts and the positive sign upfield shifts, with reference to the corresponding signals at $[G]_t = 0$. [c] The estimated uncertainty of log K is ±0.1, unless otherwise noted. [d] The signal overlapped with its neighbouring signal at high guest concentrations; the formation constants were determined from the data at low guest concentrations. [e] A larger downfield shift of −0.023 was observed at $[G]_t$ = 20 mmol dm^{-3}; above this concentration the shift tended to decrease with increasing concentration. The approximate formation constant was obtained on the basis of the data for $[G]_t \leqslant 20$ mmol dm^{-3}. [f] At higher guest concentrations, a water-insoluble host–guest complex was formed.

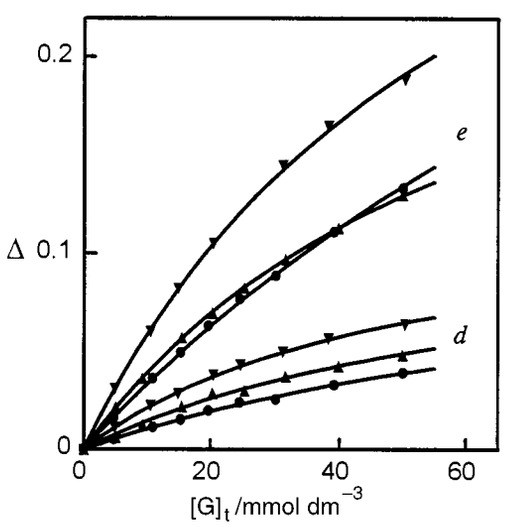


Fig. 3 NMR shifts, Δ (ppm) = $\delta - \delta_0$, of *d* and *e* proton signals of cyclophane host **1** at different guest concentrations $[G]_t$ (mmol dm^{-3}), with reference to the chemical shifts δ_0 of the corresponding signals at $[G]_t = 0$. The total concentration of the host $[H]_t$ was kept constant at 5 mmol dm^{-3}; temperature ≈ 23 °C; pD = 8.0. The guests are phenethylamine (●), tyramine (▲) and dopamine (▼). The solid lines were calculated by the use of eqn. (1) with the formation constants listed in Table 1.

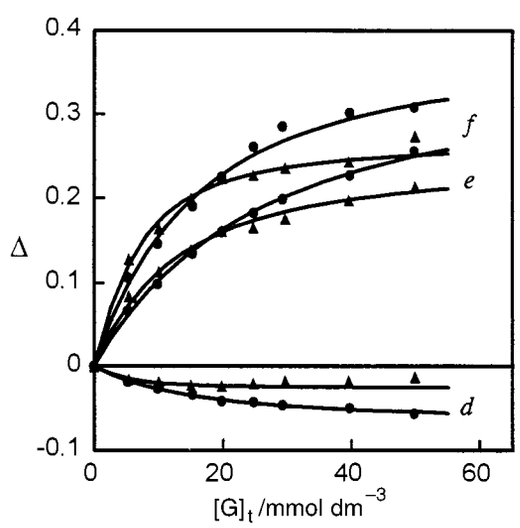


Fig. 4 NMR shifts, Δ (ppm) = $\delta - \delta_0$, of *d*, *e* and *f* proton signals of cyclophane host **2** at different guest concentrations $[G]_t$ (mmol dm^{-3}) with reference to the chemical shifts δ_0 of the corresponding signal at $[G]_t = 0$. The total concentration of the host $[H]_t$ was kept constant at 5 mmol dm^{-3}; temperature ≈ 23 °C; pD = 8.0. The guests are phenethylamine (●) and tyramine (▲). The solid lines were calculated by the use of eqn. (1) with the formation constants listed in Table 1.

larger upfield shift than the *e* proton. The formation constant of phenethylamine–**2** is significantly larger than that for the corresponding complex of **1** (Table 1).

In the presence of tyramine, the *e* and *f* proton signals of **2** shifted upfield, and the shifts reached a saturation value at a lower concentration than in the presence of phenethylamine. The *d* proton showed an unusual concentration-dependence: the *d* proton signal shifted downfield with increasing tyramine concentration up to $[G]_t \approx 20$ mmol dm^{-3}, but, above this concentration, the shift tended to decrease (Fig. 4). Tentatively, the formation constant was determined by using the data for $[G]_t \leqslant 20$ mmol dm^{-3}. A 1:1 tyramine–**2** complex has a larger formation constant than the phenethylamine–**2** complex (Table 1).

In the presence of dopamine in an equimolar amount, the shifts of the *d*, *e* and *f* proton signals are almost identical with those in the presence of tyramine. The host–guest interaction is, therefore, almost identical for the two amines. At higher amine concentrations, a colourless solid formed, and an NMR titration could not be performed. The solid formed was soluble in dimethyl sulfoxide, and its ^{1}H NMR spectrum indicated that the solid was a 2:1 dopamine–**2** complex.§ Since the NMR titrations of other systems show that the 1:1 complexes are formed in solution, it is probable that, in the solid state of the 2:1 dopamine–**2** complex, one dopamine molecule is encapsulated in the cyclophane cavity whereas the second dopamine molecule is involved as a countercation outside the cavity; the structure in the solid state may, however, differ from that in solution.

Molecular recognition

For both cyclophanes, the formation constants of their complexes with the amines show an increase in the order,

§ ^{1}H NMR of **2**–dopamine complex ([$^2H_6$]DMSO; 250 MHz). Cyclophane: 2.76 (8H, s, *b*); 3.20 (8H, s, a); 3.32 (8H, s, *c*); 3.78 (4H, s, *f*); 6.98 (8H, d, *J* 8.1, *e*); 7.55 (8H, d, *J* 8.1, *d*). Dopamine: 2.63 (2 × 2H, t, *J* 7.7, CH_2NH$_3$); 2.89 (2 × 2H, t, *J* 7.7, CH_2–Ph); 6.42 (2 × 1H, d, *J* 7.1, H6); 6.62 (2 × 1H, s, H2); 6.64 (2 × 1H, d, *J* 7.1, H5).

Table 2 ^{1}H NMR shifts[a] of aromatic amine guests (5 mmol dm^{-3}) in the presence of cyclophane hosts **1** and **2** with the concentrations $[H]_t$/mmol dm^{-3} = 5 and 30 in D_2O with pD = 8

Guest–host	$[H]_t$	CH_2–NH_3	CH_2–Ph	Aromatic protons[b]
phenethylamine–**1**	5	0.035	0.031	0.04 (average)
	30	0.139	~0.15[c]	~0.18[c]
tyramine–**1**	5	0.043	0.038	0.036 (H2), 0.044 (H3)
	30	0.185	~0.14[c]	0.142 (H2), 0.198 (H3)
dopamine–**1**	5	0.056	0.046	0.061 (H6), 0.048 (H5), ~0.04[c] (H2)
	30	0.204	~0.14[c]	0.192 (H6), 0.150 (H5), ~0.15[c] (H2)
phenethylamine–**2**[d]	5	0.131	0.116	0.08 (average)
tyramine–**2**[d]	5	0.185	0.147	0.095 (H2), 0.157 (H3)
dopamine–**2**[d]	5	0.186	~0.1[c]	0.168 (H6), 0.094 (H5), 0.114 (H2)

[a] Upfield shift (ppm) referenced to the value at $[H]_t = 0$. [b] For labelling, see formula. [c] Overlapped with a host signal. [d] The water-solubility of **2** was too low for NMR measurements at higher host concentrations.

phenethylamine < tyramine ≈ dopamine. For the same guest molecule, the complexes of **2** have higher formation constants than the corresponding complexes of **1**. The aromatic proton shifts of both host and guest molecules are also larger in the complexes of **2** than in the corresponding complexes of **1**.

The observed NMR shifts of the aromatic protons suggest that inclusion complexes are formed as a result of hydrophobic effects. In these systems, however, the hydrophobic interaction is not the only principal driving force for the complex formation, because no significant host–guest interaction was observed with the aromatic anion, phenylacetate $C_6H_5CH_2$-CO_2^-, and the aromatic zwitterion, phenylalanine $C_6H_5CH_2$-$CH(NH_3^+)CO_2^-$. In a solution containing cyclophane **1** (5 mmol dm^{-3}) and phenylacetic acid (30 mmol dm^{-3}), for example, the *d* proton shifted only by 0.003 ppm (upfield), and the *e* proton by 0.02 (upfield) at pD = 8; in the presence of phenylalanine (30 mmol dm^{-3}), the *d* proton shifted by 0.006 (upfield) and the *e* proton by 0.008 (upfield). The formation of the complexes with the aromatic amines is, therefore, driven by additional interactions between the cyclophane and guest amine molecules. The amino and phenolate groups of the guest amines are protonated at the pD studied: $pK_a = 9.83$ for phenethylamine; 9.3 and 10.9 for tyramine.[18] The $-CH_2CH_2NH_3^+$ arm of the aromatic amine molecule can form an ion pair with a pendant $-CH_2CO_2^-$ group of the cyclophane, *via* a hydrogen bond or electrostatic interaction. The formation of an $-N-H^+\cdots O^--CO-$ link was confirmed by the observation that the CH_2 protons in $-CH_2NH_3^+$ of the guest molecule significantly shifted upfield upon complexation (Table 2); the upfield shift indicates that the electron density of the carbon atom bonded to NH_3^+ increases as a result of a partial deprotonation of NH_3^+ in the linkage. This ion-pairing stabilizes the host–guest complex.

The hydrophobic effect of the guest amines with the cyclophane cavity may weaken in the order, phenethylamine > tyramine > dopamine, due to the presence of hydrophilic OH groups in tyramine and dopamine. On the contrary, the stabilities of the tyramine and dopamine complexes are higher than the corresponding complexes of phenethylamine, and the NMR shifts of the aromatic protons of the host and guest molecules are larger in the tyramine and dopamine complexes (Tables 1 and 2). The OH group of the guest molecule contributes to the stabilization of the host–guest complex, probably *via* the formation of a hydrogen bond with one of potential hydrogen bonding sites (amine nitrogen and carboxylate oxygen) of the host. For a solution containing phenol (5 mmol dm^{-3}) and cyclophane **1** (30 mmol dm^{-3}), however, the aromatic protons of phenol showed a very small upfield shift of 0.02 ppm referenced to the signals in the absence of cyclophane **1**; no significant shift was observed for the *e* proton of **1** (5 mmol dm^{-3}) in the presence of phenol (30 mmol dm^{-3}). Thus, there was no indication of complex formation between phenol and the cyclophane. Interaction of the OH group itself with the host molecule is not strong enough to form a host–guest complex.

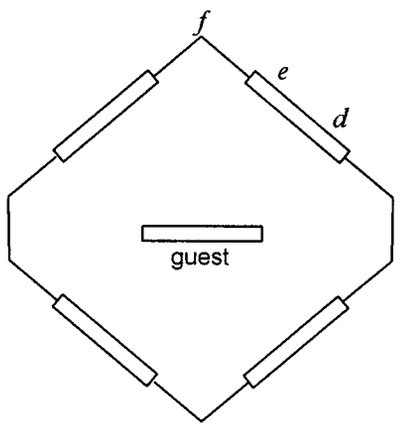


Fig. 5 A possible time-averaged orientation of a guest benzene ring in a cyclophane cavity in accordance with the ^{1}H NMR shifts. The rectangles indicate phenyl groups projected along their molecular plane. The locations of protons *d*, *e* and *f* of the host are shown schematically.

When the cyclophane and tyramine or dopamine form an inclusion complex, however, the OH group of the guest molecule is located close to a hydrogen bonding site of the host, and increases the stability of the complex.

The ring current of a phenyl group produces an angle-dependent magnetic shielding field in its neighbourhood.[16] A proton located along the molecular axis normal to the molecular plane of the phenyl group experiences the largest upfield shift, and a proton in the molecular plane of the π-system undergoes the largest downfield shift. The nodal surface of the zero-shielding field exits at about 35° from the molecular plane. This ring current effect gives information about the orientation of an aromatic molecule encapsulated in the cyclophane cavity. Proton *d* of **2** shifts downfield upon complexation, whereas protons *e* and *f* of **2** shift upfield, the shift of the latter proton being larger. For the complexes of **1**, proton *d* shifts upfield but the shift is much smaller than that of proton *e*. The encapsulated aromatic amine molecule, therefore, has the time-averaged orientation that is illustrated in Fig. 5: the molecular plane faces the $-CH_2-$ or $-O-$ group of the cyclophane molecule, and the *d* protons of the host molecule are located near the nodal surface of the shielding field produced by the guest π-system. This is consistent with an electrostatic calculation,[19] in which it was reported that an attractive interaction is operative between the π-systems of host and guest molecules arranged as shown in Fig. 5.

The complexes of **2** are more stable than those of **1**. This difference is attributed to the group that links two phenyl groups in the cyclophanes. One of the plausible factors is the steric effect of the CH_2 group which defines the geometry of the cavity in **2** more strictly than does the ether oxygen in **1**. A cavity well-defined by aromatic fences favours the inclusion of an aromatic molecule.[2]

Conclusions

The new anionic cyclophanes form host–guest complexes with the aromatic amine cations, phenethylamine, tyramine and dopamine, and do not recognize aromatic anions and aromatic zwitterions. There are two main binding forces between the cyclophanes and aromatic amines: (1) a hydrophobic interaction between the phenyl groups and (2) hydrogen bond formation and/or ion-pairing between the pendant CO_2^- and NH_3^+ arms. The OH groups of the guest molecules contribute to the stabilization of the host–guest complexes to some extent. These multipoint molecular recognition properties of the new cyclophanes result in the selective complexation with the aromatic amines. It is noteworthy that cyclophane **2** forms a water-insoluble solid specifically with dopamine. The molecular recognition sites of **2** are probably more favourably arranged for complexation with dopamine.

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