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Synthesis and evaluation of new ditopic cyclophane receptors for benzoic acid

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ABSTRACT: As potential receptors for a benzoic acid guest, new ditopic cyclophane host molecules, each with a π electron-rich portion and a pyridine ring-containing portion, are synthesized. Complexation of benzoic acid guest by the potential molecular receptors is probed by infrared spectroscopy, proton magnetic resonance titration experiments and solid-state structure determination. Copyright © 2005 John Wiley & Sons, Ltd.
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KEYWORDS: molecular recognition; supramolecular chemistry; cyclophanes receptors

INTRODUCTION

During the past four decades, a wide variety of macrocyclic receptor molecules, which exhibit selectivity in binding of ionic[1] and molecular[2–4] species, has been synthesized. Molecular receptors with at least one aromatic ring bridged by at least one aliphatic *n*-membered bridge ($n \geqslant 0$) are designated as cyclophanes.

We have been using the relatively unexplored bisphenol **1**[5] (Fig. 1) as a π electron-rich hydrophobic unit for the construction of new types of cyclophanes.[6–10] By connecting the oxygen atoms of two molecules of **1** with multi-methylene spacers, the rigidity of the two α,α'-di(4-oxyphenyl)-1,4-diisopropylbenzene units provides open structures in which the dimensions of the central cavity can be varied systematically by changing the number of carbon atoms in the spacers. We have reported solid-state structures of molecular receptors **2** and their complexes with aromatic guest species.[7–9] Thus cyclophanes **2** with $n = 3$ and 5 form complexes in which *p*-xylene[7] and anthracene,[8] respectively, are located within the central cavities of the hosts. We have also prepared ditopic receptors **3** and assessed their binding of alkylammonium picrates in solution by ^{1}H NMR spectroscopy and solvent extraction.[6] For cyclophane **3** with $n = 1$, the strongest binding of *n*-propylammonium picrate was observed.

We now report the synthesis of new, ditopic cyclophanes **4** and **5** for which it was envisaged that a benzoic acid guest would be encapsulated and oriented with the phenyl ring of the guest towards the π electron-rich hydrophobic portion of the receptor and the carboxylic acid group would be hydrogen bonded to the 2,6-diaminopyridine portion. The structures of cyclophanes **4** and **5** differ in that the additional methyl groups in the latter should provide enhanced hydrophobicity.

RESULTS AND DISCUSSION

Synthesis of ditopic cyclophanes 4 and 5

For cyclophanes **4** and **5**, the hydrophobic units were formed by reaction of phenol and 2,6-dimethylphenol, respectively, with commercially available $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,4-benzenedimethanol and gaseous HCl. Resultant bisphenols **1** and **6** were alkylated with ethyl 4-bromobutanoate and K_2CO_3 in acetone to form diesters **7** and **8** in 85% and 88% yields, respectively (Fig. 2). Basic hydrolysis followed by acidification gave dicarboxylic acids **9** and **10** in 70% and 93% yields, respectively. The diacids were converted quantitatively into corresponding di(acid chlorides) **11** and **12** by reaction with thionyl chloride and a catalytic amount of DMF in benzene. Under high dilution conditions, equimolar THF solutions of the di(acid chloride) and 2,6-diaminopyridine were

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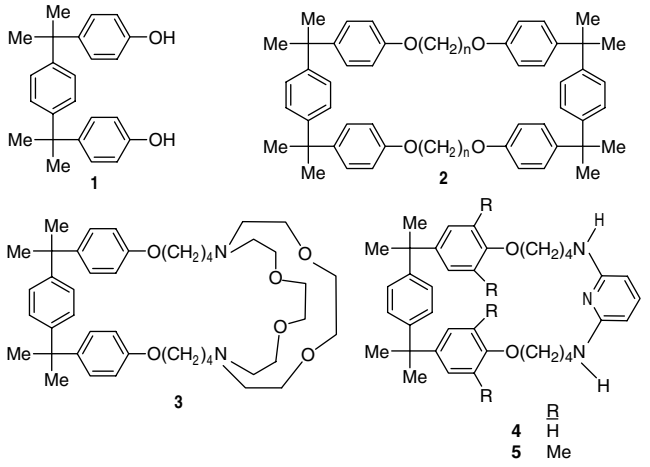

Figure 1. Structures of di-$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,4-benzenedimethanol (**1**) and cyclophanes derived therefrom

added simultaneously to a vigorously stirred mixture of K_2CO_3 in toluene to form macrocyclic diamides **13** and **14** in 35% and 29% yields, respectively. Reduction of the diamides with BH_3–THF gave 90% yields of ditopic cyclophanes **4** and **5**.

Complexation of benzoic acid by ditopic cyclophanes 4 and 5 and their precursor macrocyclic diamides 13 and 14

To determine if proton transfer took place when benzoic acid was complexed by the ditopic cyclophanes, the infrared absorptions of benzoic acid in carbon tetrachloride in the absence and presence of one equivalent of cyclophane **4** were measured. For benzoic acid alone, the carbonyl absorption was at 1690 cm^{-1}. For an equimolar solution of benzoic acid and cyclophane **4**, the carbonyl absorption shifted only slightly to 1696 cm^{-1}, revealing that proton transfer from the guest to the host was not taking place.

Association constants for interactions of benzoic acid with ditopic cyclophanes **4** and **5** and their precursor macrocyclic diamides **13** and **14** in $CDCl_3$ were measured by NMR titration. Binding was determined from the relationship of the benzoic acid (guest) concentration relative to the change in signal (in Hz) of affected nuclei in the host molecule, whose concentration was held constant. Data were analyzed using the HOSTEST II program developed by Professor Craig S. Wilcox to calculate binding constants of binary complexes by spectroscopic methods.[11,12] For this program, concentrations

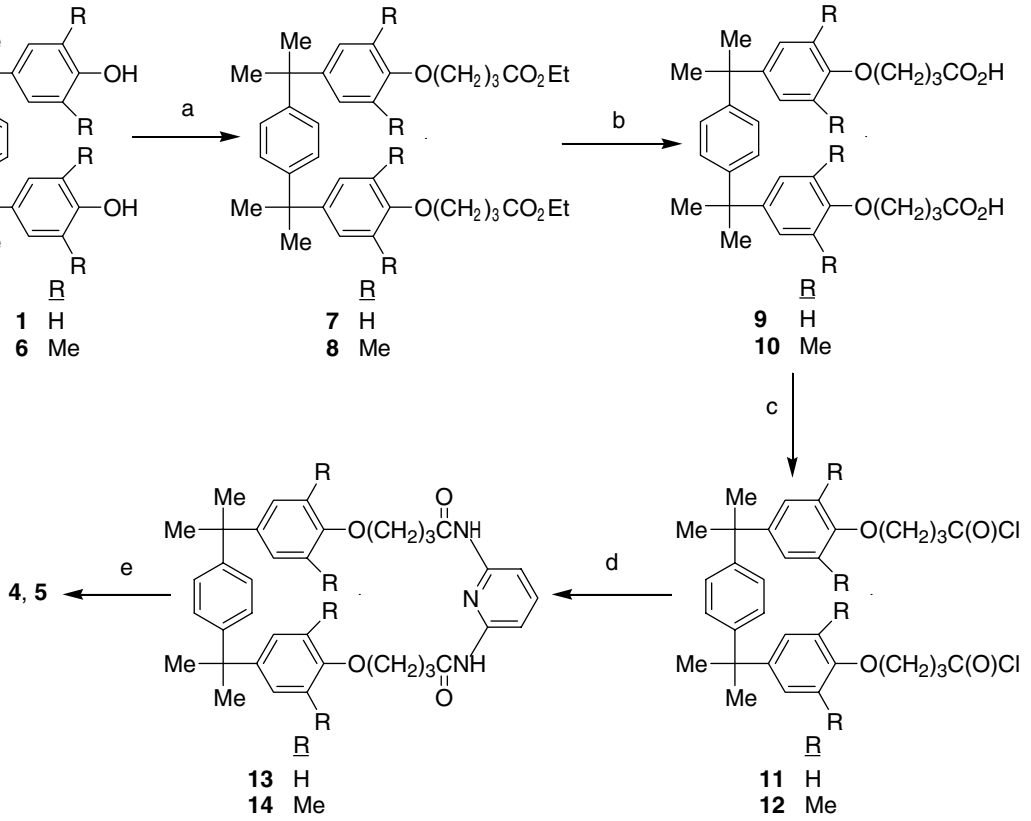

Figure 2. Synthetic scheme for the preparation of ditopic cyclophanes **4** and **5**. Reagents/solvent: (a) ethyl 4-bromobutanoate, K_2CO_3/acetone; (b) NaOH/aq. EtOH, or H_3O^+; (c) $SOCl_2$, cat. DMF/benzene; (d) 2,6-diaminopyridine, K_2CO_3/toluene; (e) BH_3–THF/THF

Table 1. Concentrations of host and guest, observed NMR signal changes, association constants and Weber *p* values for complexation of benzoic acid guest by ditopic cyclophane hosts **4** and **5** and precursor macrocyclic diamide hosts **15** and **16** in $CDCl_3$ at 23 °C

Host	[Host] (mM)	[Guest] (mM)	Proton in host[a]	Signal change (Hz)	Association constant (M^{-1})	Weber *p* value
4	0.30	0.10–0.70	H_d	−12.2	5800	0.48–0.74
			H_h	+17.5	5400	0.44–0.72
			H_x	+16.4	6400	0.42–0.75
5	0.20	0.10–0.80	H_d	−12.9	4900	0.42–0.75
			H_h	+7.1	5200	0.34–0.67
			H_x	+2.2	5100	0.42–0.76
13	2.4	7.4–95.4	H_c	−5.5	700	0.60–0.75
			H_e	+3.9	700	0.60–0.75
			H_x	+4.5	1200	0.67–0.83
14	3.5	0.0–6.9	H_c	−2.4	700	0.53–0.74
			H_e	+9.0	400	0.43–0.63
			H_x	+5.7	600	0.50–0.71

[a] See Fig. 3.

of the components in solution are entered together with the corresponding spectroscopic shifts. The program output includes a binding constant and a statistical measure of the value of the data, the Weber '*p*' value. The Weber '*p*' value should be within the range of 0.2–0.8. Values outside this range indicate that the concentrations of host and/or guest chosen for the experiment are inappropriate.

Results from the NMR titration experiments are presented in Table 1. The protons of the host for which chemical shift changes were observed upon addition of benzoic acid are shown in Fig. 3. As can be seen, association constants for the interaction of benzoic acid guest by macrocyclic diamide hosts **13** and **14** are nearly an order of magnitude lower than those for the ditopic cyclophane hosts **4** and **5**. This can be attributed to greater basicity in the polar portions of hosts **4** and **5** compared with **13** and **14**. Also, it appears that the association constants become lower when two additional methyl groups are incorporated into the host (i.e. **4** *vs*. **5** and **13**

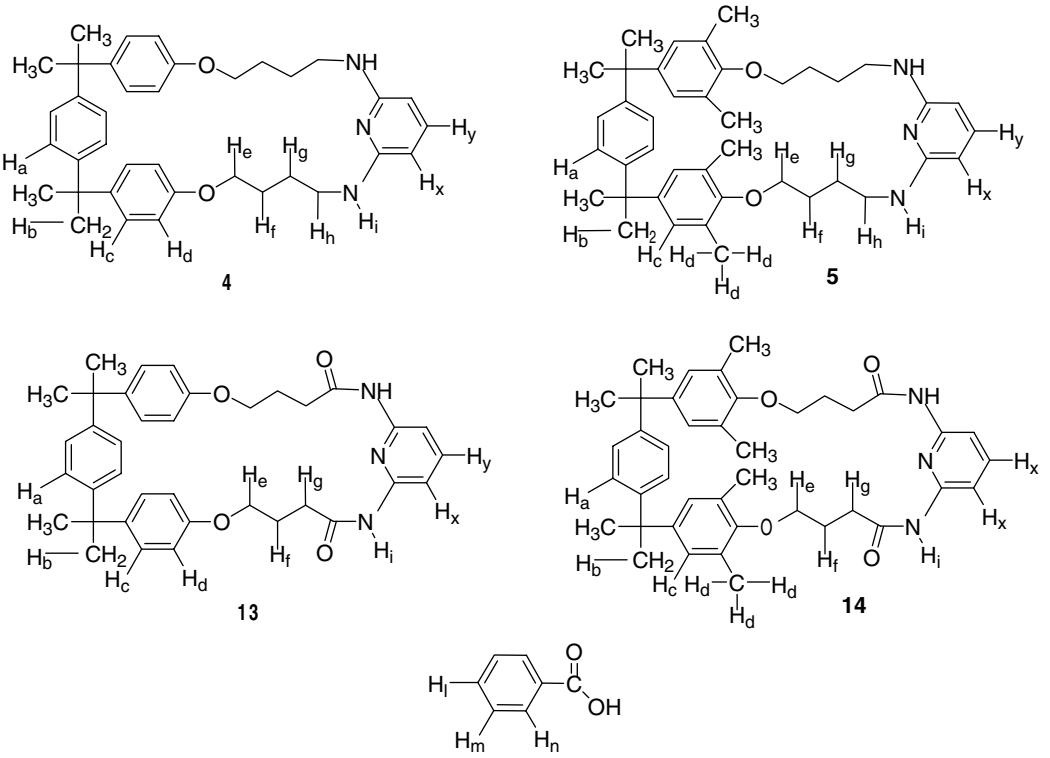

Figure 3. Protons in cyclophane hosts **4**, **5**, **13** and **14** affected by addition of benzoic acid in NMR titration experiments

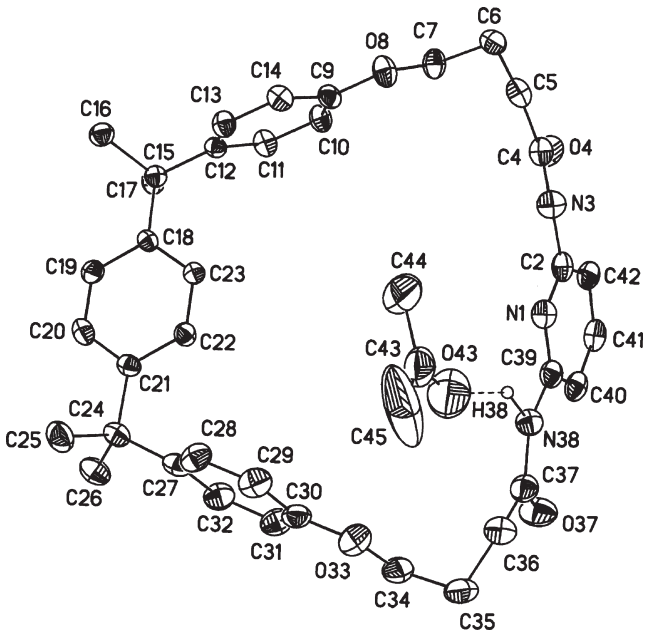

Figure 4. An ORTEP drawing with numbering system for one structure of cyclophane diamide **13** with a solvating molecule of acetone. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms of **13** (except for H38) and the solvating acetone molecule are omitted for clarity

vs. **14**). This could arise from unfavorable steric interactions between the guest and the hydrophobic portions of host **13** compared with **4** and host **14** compared with **5**. Although the observed shifts in NMR signals for some of the protons on the terminal phenylene groups and in the polymethylene chains connecting the hydrophobic and polar portions of the cyclophane are consistent with complexation of the benzoic acid guest within the cavities of the host molecules, the NMR signal shifts observed for H_x, the *meta* protons on the pyridine ring, are not.

Solid-state structure determinations

In an effort to obtain additional information about the structures of the new cyclophane host molecules and their complexes with benzoic acid guest, attempts were made to grow crystals suitable for x-ray structure determination. These efforts were successful only for macrocyclic diamide **13** and a complex of cyclophane triamine host **4** with benzoic acid. The asymmetric unit of **13** consisted of two very similar molecules.

An ORTEP drawing for one of the two molecules of **13•acetone** is shown in Fig. 4. (An ORTEP drawing for the second molecule is shown in Fig. ES1 in the electronic supplement.) For both molecules, there is an associated molecule of acetone solvent located above the plane of the molecule. The carbonyl oxygen of the acetone is hydrogen bonded to the N—H of one amide group. The hydrogen bond data are given in Table 2. This host molecule is seen to be in an open conformation with a well-formed cavity.

An ORTEP drawing for the 1:1 complex of benzoic acid with ditopic cyclophane host **4** is presented in Fig. 5. Instead of the expected inclusion complex with the guest located within the central cavity of the host, the molecule of **4** is folded with the pyridine ring nitrogen and the hydrogens on the two amine groups pointed outward towards an *external* benzoic acid molecule. The benzoic acid guest is disordered in two sites to allow the carboxyl oxygen to hydrogen bond (Table 2) with one or the other amine hydrogens. It was not possible to locate the acid hydrogen atom of the carboxylic acid group of either partial benzoic acid. However, it appears that the carboxyl oxygens are hydrogen bonded to the two amine groups of the host (see Fig. 5). The hydrogen bond data are given in Table 2. This folding of the cyclophane host to hydrogen bond with an external benzoic acid guest is consistent with the unexpected shifts of *meta* pyridyl ring hydrogens, H_x, upon addition of benzoic acid to cyclophanes **4**, **5**, **13** and **14** in the NMR titration experiments (*vide infra*).

Nuclear Overhauser effect studies of ditopic cyclophane 4 and macrocyclic diamides 13 and 14 in solution

For further investigation of the cyclophane host structures, nuclear Overhauser effect (NOE) studies were performed for macrocycles **4**, **13** and **14** and for **4** in the presence of equimolar benzoic acid in $CDCl_3$ solution.

Absorptions for the different protons in the 300 MHz NMR spectrum of macrocyclic diamide **13** (see Fig. 3 for

Table 2. Hydrogen bonding in the two molecules **13•acetone** and in **4•benzoic acid**

Molecule	D	H	A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···O (°)
13•Acetone	N38	H38	O43	1.18	2.11	3.17	148
	N88	H88	O93	0.86	2.39	3.18	154
4•Benzoic	N3	H3	O51′	1.18	1.89	2.99	153
acid	N38	H38	O51	1.17	1.71	2.79	151

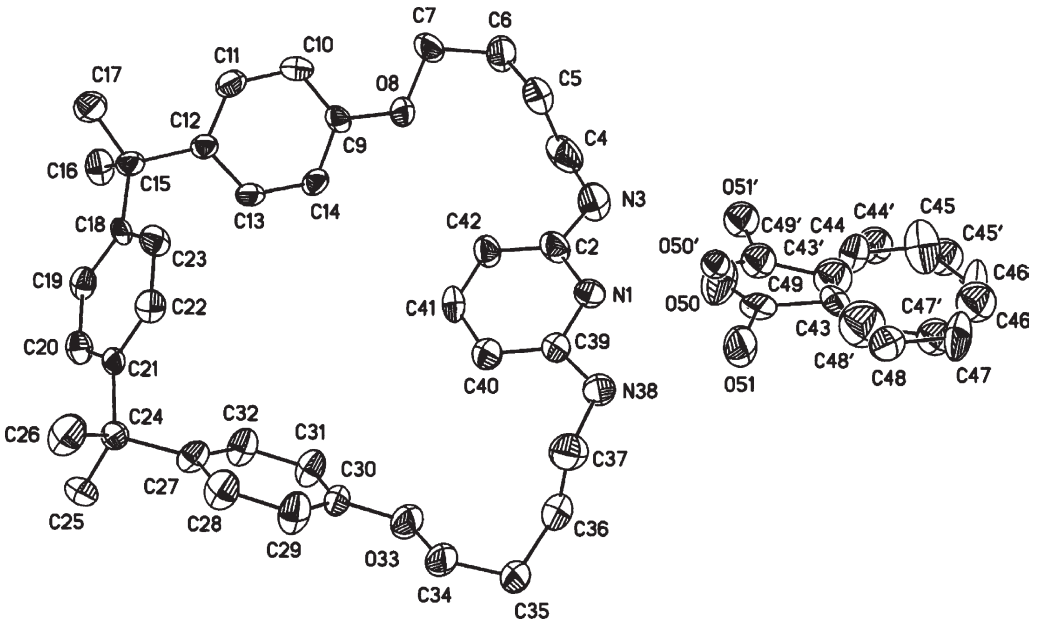

Figure 5. An ORTEP drawing with numbering system for the 1:1 complex of cyclophane **4** and benzoic acid. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms of **4** and benzoic acid are omitted for clarity

proton designations) are identified as δ: 1.63 (s) H_b; 2.20 (p) H_f; 2.58 (t) H_g; 3.93 (t) H_e; 6.69 (d) H_d; 7.98 (s) H_a; 7.12 (d) H_c; 7.61 (br s) H_i; 7.63 (t) H_y; 7.89 (d) H_x. Upon irradiation of the signal for H_d, only the signals for adjacent protons H_c and H_e exhibited the NOE. When the signal for H_x was irradiated, the NOE was observed only for the adjacent pyridyl ring proton H_y. In both instances, only nuclei near the irradiated nuclei gave signal enhancements. This is in agreement with an open conformation of the type found in the solid-state structure (Fig. 4).

For macrocyclic diamide **14** (see Fig. 3 for proton designations), the proton absorptions in the 300 MHz NMR spectrum are identified as δ: 1.63 (s) H_b; 2.07 (s) H_d; 2.20 (p) H_f; 2.68 (t) H_g; 3.76 (t) H_e; 6.59 (s) H_c; 7.17 (s) H_a; 7.63 (t) H_y; 7.72 (br s) H_i, 7.94 (d) H_x. Irradiation of the singlet for H_d gave signal enhancements for neighboring protons H_c and H_e. There was also a small, but clearly discernable, enhancement for the amide proton H_i, suggesting some folding of the molecule. When the signal for H_x was irradiated, the NOE was noted only for the adjacent pyridyl ring proton H_y.

Absorptions for the different protons (see Fig. 3 for the proton designations) in the macrocyclic triamine **4** are identified as δ: 1.58 (s) H_b; 1.69 (p) H_g; 1.73 (p) H_f; 3.14 (q) H_h; 3.92 (t) H_e; 4.24 (br t) H_i; 5.55 (d) H_y; 6.66 (d) H_d; 6.97 (s) H_a; 7.02 (t) H_x; 7.02 (d) H_c. Irradiation of the signal for H_d gave the NOE only of signals for adjacent protons H_c and H_e. When the signal for H_e was irradiated, signal enhancements were observed only for neighboring protons H_f and/or H_g (these protons are indiscernible in the difference spectra) and H_d. Irradiation of the signal for H_x produced the NOE for adjacent pyridyl ring proton H_y and amine proton H_i, with possible enhancements for more distant H_h and H_e. When the signal for H_h was irradiated, the expected NOE of the signals for adjacent protons H_f and/or H_g was observed. In addition, there was an unanticipated NOE of the signal for H_x. This is only possible if the pyridine ring in **4** is flipped so that the pyridyl nitrogen points away from the macrocylic cavity.

Attention then was shifted to solutions that contained equimolar amounts of cyclophane triamine **4** and benzoic acid. Upon irradiation of the signal for H_d, the NOE was observed for the signals of H_c and H_e with a small enhancement of the signal for H_x. No signal enhancement was noted for H_l, H_m, or H_n of the benzoic acid guest (see Fig. 3 for proton designations). With irradiation of the signal for H_x, signal enhancement for H_h was evident. The intensity of this NOE was greater in the presence of benzoic acid than in its absence. Also, weak signal enhancement for H_f and/or H_g was evident. Irradiation of the signal for H_e gave an NOE only of the signals for neighboring H_d and indistinguishable H_f and/or H_g. When the signal for H_h was irradiated there was an intense NOE for the signal of H_x. This enhancement of the H_x signal was much greater than when the signal for H_h in cyclophane **4** was irradiated in the absence of benzoic acid.

Finally, nuclei of the benzoic acid guest were probed to see if any intermolecular NOEs could be detected. However, irradiation of signals for the aromatic ring protons H_l, H_m and H_n gave an NOE only for signals of the other aromatic ring protons. Thus, no intermolecular NOEs between benzoic acid and host **4** were observed.

Results from the NOE experiments reveal some folding of cyclophane triamine **4** into conformations in which the

pyridine ring nitrogen is oriented away from the macrocyclic cavity. This folding is accentuated by the presence of an equimolar amount of benzoic acid guest. These findings suggest that the host–guest geometrical relationship for cyclophane **4** and benzoic acid in solution resembles that found in the solid-state structure for the complex (Fig. 5).

EXPERIMENTAL

General methods and materials

Unless specified otherwise, reagent-grade reactants and solvents were used as received from chemical suppliers. Acetone was distilled from and stored over anhydrous K_2CO_3. Tetrahydrofuran was distilled from benzophenone-sodium ketyl and used immediately. Dimethyl formamide was distilled from BaO and stored over 4 Å molecular sieves. Reagent-grade benzene and toluene were stored over sodium ribbon.

Infrared (IR) spectra were obtained with a Perkin-Elmer 1600 FTIR spectrophotometer and are reported in wavenumbers. The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained with a Bruker IBM AF-200 (200 MHz) or AF-300 (300 MHz) spectrometer. Chemical shifts (in ppm) are reported downfield from TMS. Mass spectra (MS) were recorded with a Hewlett-Packard GC/MS 5995 spectrometer. Combustion analysis was performed by the Desert Analytics Laboratory of Tucson, Arizona.

Synthesis of compounds

Bisphenol **1**[5]. A 500-ml, three-neck flask was charged with $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,4-benzenedimethanol (50.00 g, 0.26 mol) and phenol (240.00 g, 2.60 mol) and the mixture was heated to 80 °C. Upon melting of the reactants, mechanical stirring was initiated and HCl gas was introduced under the surface of the liquid through a glass tube. The reaction mixture was saturated with gaseous HCl for 30 min, after which the addition of HCl was terminated. Stirring was continued for 3 h and the mixture was poured into water (500 ml). Repeated washing of the crude oil with water gave a light brown solid. Recrystallization from EtOH produced **1** (54.20 g, 65%) as a white powder, m.p. 188–189 °C. ν_{max} (deposit on a NaCl plate from CH_2Cl_2 solution) (cm^{-1}): 3241 (OH) and 1244 (C—O). δ_H (200 MHz, $CDCl_3$): 1.55 (s, 12H), 6.68 (d, $J = 6.5$ Hz, 4H), 7.00 (d, unresolved, 4H), 7.02 (s, 4H), 7.10 (s, 2H). δ_C (50 MHz, $CDCl_3$): 30.77, 41.62, 114.57, 126.00, 127.67, 142.08, 147.76, 154.03. MS (EI, 70 eV)[*m/e*, (%)]: 17.90 (100), 18.20 (99.19), 331.30 (62.94), 135.15, (29.01), M + 346.30 (16.74), M+1 (4.18), M+2 (0.69).

Bisphenol **6**. The procedure was identical to that given for the preparation of bisphenol **1**, except for the replacement of phenol with 2,6-dimethylphenol. Crude bisphenol **6** was recrystallized from EtOH to give very large prisms (76.00 g, 73%), m.p. 156–157 °C. ν_{max} (deposit on a NaCl plate from CH_2Cl_2 solution) (cm^{-1}): 3478 (OH) and 1183 (C—O). δ_H (200 MHz, $CDCl_3$): 1.62 (s, 12H), 2.19 (s, 12H), 4.46 (s, 2H), 6.83 (s, 4H), 7.11 (s, 4H). δ_C (50 MHz, $CDCl_3$): 16.09, 30.85, 41.58, 122.19, 126.08, 126.93, 142.35, 147.80, 149.86. MS (EI, 70 eV)[*m/e*, (%)]: 41.10 (38.55) 186.00 (31.38), 387.35 (100), M + 402.35 (29.56), M+1 (8.10), M+2 (1.50). Found: C, 83.79; H, 8.50. Calc. for $C_{28}H_{34}O_2$: C, 83.54; H, 8.51.

Diester **7**. To acetone (250 ml) in a 500-ml flask was added bisphenol **1** (22.00 g, 63 mmol), anhydrous K_2CO_3 (34.00 g, 252 mmol) and ethyl 4-bromobutanoate (37.00 g, 189 mmol). The mixture was refluxed for 24 h and evaporated *in vacuo*. To the residue, CH_2Cl_2 was added and the mixture was filtered. The filtrate was evaporated *in vacuo* to provide a pale yellow oil. After addition of warm EtOH (20 ml) and allowing the solution to stand for 2 days at room temp, 31.00 g (85%) of diester **7** was obtained as large needles, m.p. 64–65 °C. ν_{max} (deposit on NaCl plate from $CDCl_3$ solution) (cm^{-1}): 1734 (C═O) and 1249 (C—O). δ_H (200 MHz, $CDCl_3$): 1.23 (t, $J = 7.1$ Hz, 6H), 1.61 (s, 12H), 2.07 (d of t, $J = 7.9$ and 6.3 Hz, 4H), 2.48 (t, $J = 7.2$ Hz, 4H), 3.95 (t, $J = 6.0$ Hz, 4H), 4.12 (q, $J = 7.0$ Hz, 4H), 6.75 (d, $J = 6.7$ Hz, 4H), 7.07 (s, 4H), 7.12 (d, $J = 6.7$ Hz, 4H). δ_C (50 MHz, $CDCl_3$): 14.20, 24.65, 30.81, 30.85, 41.79, 60.38, 66.52, 113.70, 126.16, 127.72, 142.96, 147.79, 156.57, 173.27. MS (EI, 70 eV)[*m/e*, (%)]: 42.95 (12.33), 87.00 (33.57), 115.10 (100), M + 574.45 (6.03), M+1 (2.19), M+2 (0.43). Found: C, 75.40; H, 8.03. Calc. for $C_{36}H_{46}O_6$: C, 75.23; H, 8.07.

Diester **8**. The procedure was the same as that employed in the synthesis of diester **7** except for the use of bisphenol **6** (20.00 g, 50 mmol) instead of bisphenol **1**. Large transparent needles of diester **8** (27.20 g, 88%) with m.p. 74–75 °C were crystallized after addition of warm EtOH (20 ml) to the crude oil product. ν_{max} (deposit on a NaCl plate from $CDCl_3$ solution) (cm^{-1}): 1731 (C═O) and 1224 (C—O). δ_H (200 MHz, $CDCl_3$): 1.26 (t, $J = 7.1$ Hz, 6H), 1.61 (s, 12H), 2.08 (d of t, unresolved, 4H), 2.19 (s, 12H), 2.58 (t, $J = 6.2$ Hz, 4H), 3.76 (t, $J = 6.0$ Hz, 4H), 4.15 (q, $J = 7.1$ Hz, 4H), 6.83 (s, 4H), 7.10 (s, 4H). δ_C (40 MHz, $CDCl_3$): 14.24, 16.46, 25.70, 30.85, 30.92, 41.84, 60.37, 70.56, 126.15, 127.19, 129.76, 145.79, 147.71, 153.43, 173.40. MS (EI, 70 eV)[*m/e*, (%)]: 87.00 (35.55), 115.10 (100), M + 630.70 (1.49), M + 1 (0.73). Found: C, 76.33; H, 8.79. Calc. for $C_{40}H_{54}O_6$: C, 76.16; H, 8.63.

Diacid **9**. To a solution of diester **7** (32.00 g, 56 mmol) in EtOH (200 ml) was added a solution of KOH (15.00 g,

268 mmol) in H_2O (150 ml). The suspension was refluxed for 1 h, cooled to 0 °C and acidified with 15% aqueous HCl. After stirring the mixture gently overnight to promote aggregation, the crude product was filtered. The solid was dissolved in toluene and dried with a Dean-Stark trap. The dried toluene solution was placed in a freezer overnight to afford **9** (22.00 g, 70%) as a white powder, m.p. 218–219 °C. ν_{max} (deposit on a NaCl plate from THF solution) (cm^{-1}): 3300–2500 (COOH) and 1692 (C═O). δ_H (200 MHz, DMSO-d_6): 1.55 (s, 12H), 1.88 (t of t, $J = 7.2$, 7.2, 6.6, 6.6 Hz, 4H), 2.35 (t, $J = 7.2$ Hz, 4H), 3.91 (t, $J = 6.4$ Hz, 4H), 6.79 (d, $J = 8.6$ Hz, 4H), 7.07 (s, 4H), 7.11 (d, $J = 8.6$ Hz, 4H), 12.16 (br s, 2H). δ_C (50 MHz, DMSO-d_6): 24.30, 30.15, 30.55, 41.36, 66.42, 113.84, 125.97, 127.46, 142.26, 147.51, 156.29, 174.15. MS (EI, 70 eV)[*m/e*, (%)]: 40.95 (30.3), 331.20 (100), 417.30 (30.1), M + 518.40 (2.97), M + 1 (1.02). Found: C, 74.35; H, 7.38. Calc. for $C_{32}H_{38}O_6$: C, 74.11; H, 7.38.

Diacid **10**. The procedure described for the synthesis of diacid **9** was utilized with the exception that diester **8** (27.00 g, 43 mmol) was a reactant. Recrystallization of the crude product from toluene gave diacid **10** (26.00 g, 93%) as a white powder, m.p. 243–246 °C. ν_{max} (deposit on a NaCl plate from THF solution) (cm^{-1}): 3424–2519 (COOH) and 1716 (C═O). δ_H (200 MHz, DMSO-d_6): 1.61 (s, 12H), 2.05 (p, unresolved, 4H), 2.19 (s, 12H), 2.51 (t, $J = 7.3$ Hz, 4H), 3.78 (t, $J = 6.3$ Hz, 4H), 6.89 (s, 4H), 7.12 (s, 4H). δ_C (50 MHz, DMSO-d_6):16.23, 25.36, 30.18, 30.44, 41.35, 70.46, 125.95, 126.77, 129.37, 145.19, 147.30, 153.19, 174.20. MS (EI, 70 eV)[*m/e*, (%)]: 163.15 (21.0), 387.25 (100), 388.35 (32.6), M + 574.45 (7.3). Found: C, 75.03; H, 7.77. Calc. for $C_{36}H_{46}O_6$: C, 75.23; H, 8.07.

Di(acid chloride) **11**. To a solution of diacid **9** (1.00 g, 1.8 mmol) in benzene (10 ml) was added thionyl chloride (0.47 g, 4.0 mmol) and two drops of DMF. The solution was refluxed for 3 h and evaporated *in vacuo*. To the residue, benzene was added and the mixture was filtered through an oven-dried, sintered glass funnel. The filtrate was evaporated *in vacuo* leaving a pale yellow solid (1.00 g) with m.p. 91–92 °C, which was utilized without purification in the next step. ν_{max} (deposit on a NaCl plate from $CDCl_3$ solution) (cm^{-1}): 1797 (C═O). δ_H (200 MHz, $CDCl_3$): 1.63 (s, 12H), 2.16 (t of t, $J = 7.0$, 5.9, 5.8, 7.0 Hz, 4H), 3.13 (t, $J = 5.8$ Hz, 4H), 3.77 (t, $J = 5.8$ Hz, 4H), 7.07 (s, 4H), 7.13 (d, $J = 8.8$ Hz, 4H). δ_C (50 MHz, $CDCl_3$): 24.92, 30.84, 41.85, 43.81, 65.46, 113.70, 126.18, 127.82, 143.38, 147.79, 156.25, 173.68.

Di(acid chloride) **12**. To a solution of diacid **10** (2.00 g, 3.5 mmol) in benzene (15 ml) were added thionyl chloride (0.86 g, 7.2 mmol) and two drops of DMF. The remaining procedure and work-up were the same as employed in the synthesis of di(acid chloride) **11** providing di(acid chloride) **12** (2.10 g) as a yellow solid with m.p. 101–102 °C. This solid was used directly in the next step. ν_{max} (deposit on a NaCl plate from $CDCl_3$ solution) (cm^{-1}): 1798 (C═O). δ_H (200 MHz, $CDCl_3$): 1.62 (s, 12H), 2.16 (t of t, unresolved, 4H), 2.19 (s, 12H) 3.21 (t, $J = 7.2$ Hz, 4H), 3.77 (t, $J = 5.9$ Hz, 4H), 6.84 (s, 4H), 7.09 (s, 4H). δ_C (50 MHz, $CDCl_3$): 16.47, 25.91, 30.83, 41.86, 43.86, 69.27, 126.17, 127.31, 129.64, 146.11, 147.66, 153.10, 173.73.

Cyclophane diamide **13**. A solution of di(acid chloride) **11** (1.10 g, 1.90 mmol) in THF (40 ml) was drawn into an oven-dried, 50-ml glass syringe. A solution of 2,6-diaminopyridine (0.21 g, 1.90 mmol) in THF (40 ml) was drawn into a second oven-dried, 50-ml glass syringe. With two Sage Instruments syringe pumps, the two solutions were added simultaneously over an 8-h period at room temperature to a vigorously stirred suspension of anhydrous K_2CO_3 (1.30 g, 9.5 mmol) in toluene (300 ml) in a flame-dried, 1-l Morton flask. The mixture was stirred for an additional 48 h after the addition was completed. The mixture was filtered and evaporated *in vacuo*. The resultant light brown oil was dissolved in CH_2Cl_2 and the solution was passed through a short column of flash silica gel (2.4 × 10 cm) with EtOAc–hexane (1:3) as eluent. The eluent was evaporated *in vacuo* and the resultant pale yellow oil was chromatographed on a flash silica gel column (2.4 × 40 cm) with EtOAc–hexane (1:19) as eluent to provide a cream-colored solid. Recrystallization by slow evaporation of its $CHCl_3$–hexane (9:1) solution gave cyclophane diamide **13** (0.40 g, 35%) as a white solid, m.p. 244–246 °C. ν_{max} (deposit on a NaCl plate from $CDCl_3$ solution) (cm^{-1}): 3436, 3272 (N—H) and 1684 (C═O). δ_H (200 MHz, $CDCl_3$): 1.61 (s, 12H), 2.19 (t of t, unresolved, 4H), 2.59 (t, $J = 5.8$ Hz, 4H), 3.93 (t, $J = 6.0$ Hz, 4H), 6.69 (d, J = 6.8 Hz, 4H), 6.69 (s, 4H) 7.12 (d, $J = 6.8$, 4H), 7.63, br s, 2H), 7.69 (t, $J = 8.0$ Hz, 1H), 7.90 (d, $J = 8.0$ Hz, 2H). δ_C (50 MHz, $CDCl_3$): 24.43, 30.53, 33.51, 41.62, 65.50, 109.41, 113.57, 125.89, 127.70, 140.86, 142.42, 148.11, 149.26, 156.43, 170.77. MS (EI, 70 eV)[*m/e*, (%)]: 18.00 (70.33), 178.10 (49.59), 246.15 (100), M+591.40 (2.73). Found: C, 74.82; H, 6.84; N, 6.83. Calc. for $C_{37}H_{41}N_3O_4$: C, 75.10; H, 6.98; N, 7.10.

Cyclophane diamide **14**. Using the procedure described for the preparation of cyclophane diamide **13**, solutions of di(acid chloride) **12** (5.00 g, 8.2 mmol) in THF (50 ml) and 2.6-diaminopyridine (0.89 g, 8.2 mmol) in THF (50 ml) were added simultaneously over a 12-h period at room temperature to a vigorously stirred suspension of K_2CO_3 (11.3 g, 82 mmol) in 2.5 l of toluene. Following the addition, the suspension was stirred for another 18 h and then filtered. The filtrate was evaporated *in vacuo* to give a brown oil that was dissolved in CH_2Cl_2 and passed through a short column of flash silica gel (4.3 × 8.0 cm)

with EtOAc-hexane (3:17) as eluent. After evaporation of the eluent *in vacuo*, the resultant yellow oil was chromatographed on flash silica gel (2.4 × 40 cm) with EtOAc-hexane (1:19) as eluent to give a white powder (1.53 g, 29%), m.p. 272–273 °C. ν_{max} (deposit on a NaCl plate from $CDCl_3$ solution) (cm^{-1}): 3429, 3300 (N—H) and 1682 (C═O). δ_H (200 MHz, $CDCl_3$): 1.63 (s, 12H), 2.06 (s, 12H), 2.18 (p, unresolved, 4H), 2.65 (d of t, $J = 2.6$, 5.8 Hz, 4H), 3.73 (t, $J = 5.9$ Hz, 4H), 6.58 (s, 4H), 7.16 (s, 4H), 7.65 (t, $J = 8.1$ Hz, 1H), 7.68, br s, 2H), 7.93 (d, $J = 8.0$ Hz, 2H). δ_C (50 MHz, $CDCl_3$): 16.40, 25.52, 30.33, 33.64, 41.83, 69.07, 109.19, 126.53, 127.15, 129.57, 140.83, 147.14, 147.34, 149.32, 152.97, 170.98. MS (EI, 70 eV)[*m/e*, (%)]: 178.10 (25.07), 219.15 (26.46), 246.15 (100), M + 647.55 (0.60), M + 1 (0.28). Found: C, 76.02; H, 7.60; N, 6.59. Calc. for $C_{41}H_{49}N_4O_3$: C, 76.01; H, 7.62; N, 6.49.

Cyclophane triamine **4**. To a solution of diamide **13** (100 mg, 0.17 mmol) in THF (10 ml) at 0 °C was added 1.0 M BH_3–THF in THF (0.51 ml, 0.51 mmol). The solution was refluxed for 4 h and allowed to cool to room temperature. A few drops of 10% aqueous HCl were added and the THF was removed *in vacuo*. To the residue, EtOAc (50 ml) was added. The suspension was washed with 10% aqueous $NaHCO_3$ (3 × 25 ml), distilled water (2 × 25 ml) and brine (25 ml). The organic layer was dried over anhydrous $NaHCO_3$ and evaporated *in vacuo* to produce a white solid that was dissolved in a minimal amount of THF. Chromatography of this solution on an alumina column (2.4 × 17 cm) with EtOAc–hexanes (1:1) as eluent gave cyclophane triamine **4** (86 mg, 90%) as a white solid, m.p. 226–227 °C. ν_{max} ($CDCl_3$ solution) (cm^{-1}): 3426 (N—H) and 1249 (C—O). δ_H (200 MHz, $CDCl_3$): 1.63 (s, 12H), 1.79 (t of t, unresolved, 4H), 1.82 (t of t, unresolved, 4H), 3.21 (d of t, $J = 5.9$, 6.7, 4H), 3.99 (t, $J = 5.9$ Hz, 4H), 4.20 (t, $J = 5.9$ Hz, 2H), 5.64 (d, $J = 7.9$ Hz, 2H), 6.73 (d, $J = 8.8$ Hz, 4H), 7.04 (s, 4H), 7.09 (d, $J = 8.8$ Hz, 4H), 7.09 (t, unresolved), 1H) δ_C (50 MHz, $CDCl_3$): 26.02, 26.53, 30.45, 41.70, 41.88, 67.28, 94.55, 113.88, 126.06, 127.72, 139.12, 142.82, 148.08, 156.65, 157.98. MS (EI, 70 eV) [*m/e*, (%)]: 134.15 (82.28), 135.15 (75.06), 176.20 (100), M + 563.40 (50.67), M + 1 (19.63), M + 2 (4.45). Found: C, 78.66; H, 8.16; N, 4.80. Calc. for $C_{37}H_{45}N_2O_3$: C, 78.55; H, 8.02; N, 4.95.

Cyclophane diamine **5**. To a solution of diamide **14** (0.50 g, 0.80 mmol) in THF (15 ml) at O °C was added 1.0 M BH_3–THF (3.2 ml, 3.2 mmol). The solution was allowed to warm to room temperature and then refluxed for 6 h. After cooling the reaction solution in an ice bath, a few drops of aqueous 1.0 M HCl were added. The solution was evaporated *in vacuo*. The residue was made basic with aqueous 1.0 M Na_2CO_3 and then EtOAc (50 ml) was added. The suspension was washed with 1.0 M Na_2CO_3 (2 × 20 ml), distilled water (2 × 20 ml) and brine (20 ml). The organic layer was dried over anhydrous $NaHCO_3$ and evaporated *in vacuo* to provide a tan, light-sensitive oil, which was dissolved in a minimum amount of CH_2Cl_2. The solution was loaded onto an alumina column (2.4 × 15 cm). The column was eluted with EtOAc–hexanes (1:49) under pressure until the more mobile components were evident upon TLC analysis of the eluent. When the desired product was predicted by TLC to be the next off the column, the eluent was changed to EtOAc–hexanes (3:2). The product appeared as the brightest of several fluorescing purple spots on TLC (silica gel) when visualized with an UV lamp. (When in solution, this compound was very sensitive to UV light.) The desired fractions were evaporated *in vacuo* to yield diamine **5** (430 mg, 90%) as a white solid, m.p. 182–183 °C. ν_{max} (deposit on a NaCl plate from $CDCl_3$ solution) (cm^{-1}): 3394 (N—H). δ_H (200 MHz, $CDCl_3$): 1.53 (s, 12H), 1.64 (t of t, unresolved, 4H), 1.70 (t of t, unresolved, 4H), 2.04 (s, 12H), 3.12 (d of t, $J = 6.0$, 6.0, 4H), 3.67 (t, $J = 6.6$ Hz, 4H), 4.06 (t, $J = 6.0$ Hz, 2H), 5.55 (d, $J = 7.9$ Hz, 2H), 6.58 (s, 4H), 7.00 (s, 4H), 7.06 (d, $J = 7.9$ Hz, 1H). δ_C (50 MHz, $CDCl_3$): 16.81, 26.06, 27.89, 30.24, 41.75, 41.90, 72.18, 94.68, 126.27, 127.11, 129.53, 138.73, 146.21, 147.73, 153.79, 158.29. MS (EI, 70 eV) [*m/e*, (%)]: 176.20 (25.82), 218.25 (100), 302.35 (14.39), M + 619.55 (38.76), M + 1 620.54 (17.11), 621.55 (4.23) 622.45 (0.56). Found: C, 79.28; H, 8.63; N, 6.60. Calc. for $C_{41}H_{52}N_3O_2$: C, 79.44; H, 8.62; N, 6.78.

Solid-state structure determination for 13-acetone and 4-benzoic acid

Crystals of macrocyclic diamide **13•acetone** were grown from acetone. Slow partial evaporation of an equimolar solution of cyclophane triamine **4** and benzoic acid in CH_2Cl_2–hexane (3:2) gave the 1:1 complex.

The crystal and intensity data were obtained with a Siemens R3m/V automated diffractometer with graphite monochromated Mo Kα radiation. The crystal data and a summary of the experimental details are listed in Table ES1 (see electronic supplement). The structures were solved using the SHELXTL-PLUS[13] program package and the final refinements and display of the structures were performed with the SHELXTL-PC program package.[14] Both structures were solved using direct methods and refined using a full matrix least-squares procedure based on F^2. Positions for hydrogen atoms bonded to carbon atoms were calculated, whereas positions for hydrogens bonded to nitrogen atoms were obtained from difference maps. The two partial benzoic acid molecules were refined as rigid bodies with bond lengths of the hexagon carbons fixed at 1.39 Å and bond angles fixed at 120°. It was not possible to locate the acid hydrogen for either site of the partial benzoic acid molecules.

Solutions of the structures revealed that the benzoic acid guest of the **4•benzoic acid** complex was disordered

and that the asymmetric unit of **13** contained two molecules, each linked to an acetone solvent molecule. The disorder of the benzoic acid in **4•benzoic acid** was resolved using difference maps. The occupancy factor for the unprimed benzoic acid was 0.70 whereas that of the primed molecule was 0.30.

Tables of atomic coordinates, equivalent isotropic displacement parameters, bond lengths and angles for the two molecules of **13•acetone** and for **4•benzoic acid** are provided in the electronic supplement.

Crytallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC, 12 Union Road, Cambridge, CB2 1E2, UK). The deposited structure numbers are CCDC 271325 for **13•acetone**; and CCDC 271326 for **4•benzoic acid**.

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