J Incl Phenom Macrocycl Chem (2009) 65:31–38
DOI 10.1007/s10847-009-9617-7

ORIGINAL ARTICLE

Interaction of hydroquinone and substituted derivatives with two cyclophane-like hosts: X-ray, molecular modelling and NMR studies

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Received: 15 June 2009 / Accepted: 20 June 2009 / Published online: 8 July 2009

Abstract An investigation of the interaction of hydroquinone and selected substituted derivatives with the 28-membered tetrabenzo-cyclophane-type receptor **1** and a tetramethoxy-substituted variant, **2**, each incorporating an O_4N_2-heteroatom set, is reported. In a preliminary solution study, aromatic solvent introduced shift (ASIS) experiments had indicated that deuterated benzene is intercalated between the two xylyl bridges of cyclophane **1**. In parallel with this result, a further NMR study was consistent with the inclusion of hydroquinone between the xylyl groups of **1** to produce a face-to-face π-stacked arrangement, with additional host–guest stability being provided by a pair of simultaneous hydrogen bonds between host and guest. Owing to limited $CHCl_3$ or CH_2Cl_2 solubilities no association constant (K) for this host–guest system could be determined. However, use of the more soluble substituted guests 2,5-di-*tert*-butylquinone and 2,3-dimethylquinone enabled K values for **1** and **2** (ranging from 54 to 162 $dm^3\ mol^{-1}$) to be determined. Single crystal X-ray structure determinations of (solvated) **1** and **2** are reported, their highly different conformations reflecting their change in substitution pattern.

Keywords Host–guest · X-ray structure · Hydroquinone · Cyclophane · Association constant

Authors dedicate this article to Prof. Jack Harrowfield and Dr. Jacques Vicens in celebration of their 65th birthdays.

Electronic supplementary material The online version of this article (doi:10.1007/s10847-009-9617-7) contains supplementary material, which is available to authorized users.

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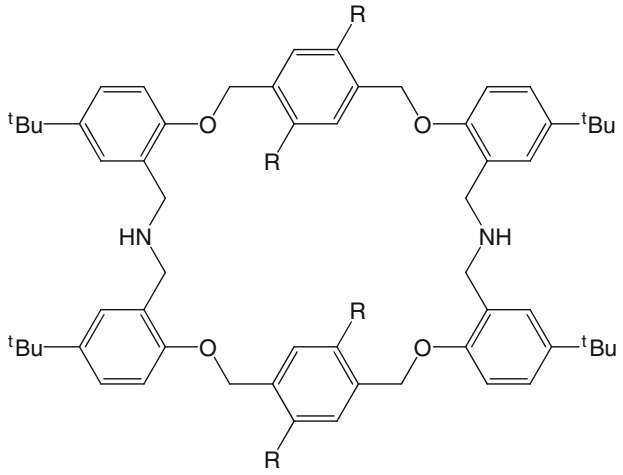
Introduction

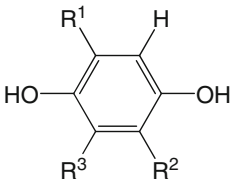
As part of a programme concerned with the design and synthesis of new molecular cages [1–3] we have described the synthesis of a number of large ring precursor macrocycles that include the 28-membered tetrabenzo-macrocycle **1** incorporating two *p*-xylyl linked dibenzylamine bridges and a N_2O_4-heteroatom set [4]. In this report we describe the synthesis of the corresponding tetramethoxy derivative **2** as well as the X-ray structures of both these macrocyclic products. We also describe an investigation of the interaction of hydroquinone and two of its substituted derivatives with both **1** and **2**, with the latter macrocycles representing a new category of host–guest receptor for this guest type. While literature reports of synthetic receptors for hydroquinone and its derivatives are quite rare [4, 5], two examples of this type (both non-macrocyclic) have been the subject of recent reports [6, 7].

Experimental

Routine ^1H and ^{13}C NMR spectra were determined on a Bruker AM300 spectrometer in $CDCl_3$ unless specified



1 R = H
2 R = OCH_3



3a $R^1 = R^2 = R^3 = H$
3b $R^1 = R^2 = {}^tBu$, $R^3 = H$
3c $R^1 = H$, $R^2 = R^3 = Me$

otherwise. The electrospray mass spectrum was obtained on a Finnigan LCQ-8 spectrometer. Melting points are uncorrected. 2,5-Di-*tert*-butylhydroquinone and 2,3-dimethylhydroquinone were obtained commercially. ^{1}H NMR titrations to determine association constants were carried out at 298 K in deuterated CD_2Cl_2 on a Varian Inova 500 MHz spectrometer; the constants were determined using the non-linear curve fitting program, EQNMR [8]. Molecular mechanics structure minimisations were carried out using Spartan 5.1 (MM2 force field; SPARTAN 5.1, Wavefunction Inc., 18401 Von Karman Ave, Ste. 370 Irving, CA, 92612 USA), with additional (semi-empirical) minimisation of individual structures employing AM1 [9].

Preparation of **1** and **2**

The preparation and characterisation of **1** has been described previously [4]. Slow recrystallization of this product from toluene yielded crystals suitable for X-ray diffraction studies. Macrocycle **2** was prepared by an analogous procedure: the required precursor dialdehyde **4** was first converted to the corresponding dioxime which was then reduced to the corresponding diamine **5**. Schiff base condensation of the diamine and dialdehyde species followed by cyanoborohydride reduction yielded **2**. Slow recrystallization from a methanol–chloroform mixture yielded crystals suitable for the X-ray work.

1,4-Bis[(2′-formyl-4′-*t*-butylphenoxy)methyl]-2,5-dimethoxybenzene (**4**)

A solution of 4-*tert*-butyl salicylaldehyde (2 g, 11.0 mol) in toluene (20 cm^3) was added to a solution of tetrabutylammonium bromide (0.375 g, 1.1 mmol) and NaOH (0.5 g, 12.5 mmol) in water (20 cm^3) and the mixture was stirred at reflux under nitrogen for 30 min. 1,4-bis(bromomethyl)-2,5-methoxybenzene (1.71, 5.2 mmol) in hot toluene (50 cm^3) was added and the solution was stirred at 80 °C under nitrogen for 1 h then allowed to stand (with stirring) at room temperature overnight. The organic layer was separated and washed with NaOH (2 M) several times then with water. The organic phase was again separated and dried over anhydrous Na_2SO_4. The toluene was removed on a rotary evaporator and the resulting brown solid was purified by vacuum chromatography (Kieselgel 60H) using dichloromethane as the eluent. The glassy material obtained was recrystallised from ethanol to yield **4** as an off-white solid; yield 1.03 g, 41%. ^{1}H NMR, δ 1.31 (s, ^{t}Bu, 18H), 3.82 (s, CH_3O, 6H), 5.13 (s CH_2O, 4H), 6.96 (d, $J = 8$ Hz, H6′, 2H) 7.03 (s, 2H, H3, 6), 7.37 (d, $J = 3$ Hz, H3', 2H), 7.76 (s, $J = 2$ Hz, 2H), 8.59 (s, CHO, 2H).

1,4-Bis[(2′-aminomethyl-4′-*t*-butylphenoxy)methyl]-2,5-dimethoxybenzene)] (**5**)

Dialdehyde 4 (5.0 g, 10.2 mmol) was suspended in ethanol (200 cm^3) and a solution of $NH_2OH{\cdot}HCl$ (2.5 g, 36 mmol) and NaOH (1.5 g, 37.5 mmol) in water (50 cm^3) was added. The mixture was stirred for 2 h and was then made slightly acidic with 1 M HCl and the solid that formed was removed by filtration then recrystallised from a chloroform/petrol (bp 60–80 °C) mixture (1:1) to yield the intermediate dioxime, 1,4-bis[(2′-oximinomethyl-4′-*t*-butylphenoxy)methyl]-2,5-dimethoxybenzene; yield 5.22 g, 95%. ^{1}H NMR, $CDCl_3$, $\delta = 1.32$ (s, ^{t}Bu, 18H), 3.81 (s, CH_3O, 6H), 5.14 (s, CH_2O, 4H), 6.97 (d, $J = 8.5$ Hz, H6′, 2H), 7.03 (d, $J = 2.5$ Hz, H3′, 2H), 7.27 (s, H3, 6, 2H), 7.37 (dd, $J = 2.5$, 8.5 Hz, H5′, 2H), 7.78 (s, NOH, 2H), 8.60 (s, CHN, 2H). The above product (3.0 g, 5.4 mmol) was dissolved in dry THF (50 cm^3), $LiA1H_4$ (0.5 g, 13.2 mmol) was added, and the reaction mixture was stirred under nitrogen at reflux for 4 h. Water (0.5 cm^3), 20% NaOH (0.5 cm^3) and again water (1.5 cm^3) were added in sequence and the mixture was filtered through celite. The

celite was washed several times with hot chloroform. The organic phase was separated and washed with 1 M NaOH solution then with distilled water. Routine work up yielded the required diamine **5**; yield 2.2 g, 75%.

Macrocycle **2**

Separate solutions of the dialdehyde **4** (3.5 g, 7.64 mmol) in a 1:1 mixture of toluene:ethanol (25 cm^3) and diamine **5** (3.5 g, 78.65 mmol) in ethanol (250 cm^3) were added dropwise (1 drop every 3 s) to a refluxing solution of absolute ethanol (1,000 cm^3) containing 4 Å molecular sieves (20 g). The mixture was stirred and heated under reflux overnight. Sodium cyanoborohydride (1.75 g, 26 mmol) was then added and the solution was heated at reflux for 3h. The mixture was then filtered through celite and any solid washed with hot chloroform (3 × 50 cm^3) and the solution shaken with 2 M NaOH (100 cm^3 × 3). Evaporation of the organic phase yielded a cream solid which was recrystallised from a chloroform/petrol (bp 60–80 °C) mixture to yield **2**. Yield 3.12 g, 44%; mp 227-228 °C. ESI-MS *m/z* 1006.6 (MH^+). ^{1}H NMR, $CDCl_3$, δ 1.34 (s, ^{t}Bu, 36H), 3.63 (s, MeO, 12H), 3.90 (s, CH_2N, 8H), 4.91 (s CH_2O, 8H), 6.75 (s, H3, 6, 4H), 6.93 (d, $J = 3$ Hz, H3′, 4H), 7.29 (dd, $J = 3$, 9 Hz, H5′, 4H), 7.38 (d, $J = 9$ Hz, H6′, 4H). Slow recrystallisation of the above product from a methanol–chloroform mixture yielded crystals suitable for X-ray diffraction.

Structure determinations

Single-counter data sets were measured for **1** and **2** on capillary-mounted specimens at ca. 295 K (monochromatic Mo Kα radiation, $\lambda = 0.7107_3$ Å; $2\theta/\theta$ scan mode) yielding N unique reflections, N_o with $F > 4\sigma(F)$ being considered 'observed'. Solution of the structures modelled **1** as its toluene mono-solvate and **2** as its methanol tri-solvate. At a later date it proved possible to redetermine the structure of **2** at ca. 153 K using a CCD area-detector instrument; the solvation model adopted in that ('isomorphous') determination was $2.21CHCl_3{\cdot}0.79MeOH$. A total of 26,774 total reflections merged to 12,178 unique ($R_{int} = 0.040$) after 'empirical'/multiscan absorption correction ('T'$_{min,max} = 0.83$). In all cases all unique data were used in the full matrix least squares refinements on F^2, refining anisotropic displacement parameter forms for the non-hydrogen atoms, hydrogen atom treatment following a 'riding' model. (Reflection weights: $\left(\sigma^2(F_o^2) + (aP)^2 + (+bP)\right)$ $\left(P = \left(F_o^2 + 2F_c^2\right)/3\right)$. Neutral atom complex scattering factors were employed within the SHELXL 97 program [10]. Pertinent results are given below and in the text and figures. Full .cif depositions reside with the Cambridge Crystallographic Data Centre, CCDC #733224, 733226, 733227.

Crystal/refinement data

1 $C_7H_8 \equiv C_{67}H_{78}N_2O_4$, $M = 975.3$. Monoclinic, space group $C2/c$ (C_{2h}^6, No. 15), $a = 21.148(7)$, $b = 10.369(5)$, $c = 29.660(10)$ Å, $\beta = 115.07(3)°$, $V = 5{,}891$ Å^3. D_c ($Z = 4$) = 1.10_4 g m^{-3}. $\mu_{Mo} = 0.067$ mm^{-1}; specimen: 0.95 × 0.40 × 0.30 mm. $2\theta_{max} = 50°$; $N = 5{,}085$, $N_o = 2{,}897$, $R1 = 0.068$, $wR2 = 0.17$ (a = 0.10), $S = 0.99$. $|\Delta\rho_{max}| = 0.23$ Å^{-3}.

Variata. The *tert*-butyl groups were each modelled as rotationally disordered about their pendants over two sets of sites, major component occupancies 0.869(4), 0.770(5). The toluene molecule is disordered about a crystallographic inversion centre (isotropic displacement parameter forms, also for the minor disordered components).

2 $3CH_3OH \equiv C_{67}H_{91}N_2O_{11}$, $M = 1100.5$. Triclinic, space group $P\bar{1}$ (C_i^1, No. 2), $a = 18.318(9)$, $b = 14.751(10)$, $c = 14.662(13)$ Å, $\alpha = 108.46(6)$, $\beta = 99.34(5)$, $\gamma = 95.67(5)°$, $V = 3{,}660$ Å^3. D_c ($Z = 2$) = 0.998 g m^{-3}. $\mu_{Mo} = 0.067$ mm^{-1}; specimen: 0.85 × 0.45 × 0.35 mm. $2\theta_{max} = 45°$; N_t (sphere) = 18,002, $N = 9{,}555$ ($R_{int} = 0.056$), $N_o = 3{,}643$, $R1 = 0.081$, $wR2 = 0.20$ (a = 0.35), $S = 0.91$. $|\Delta\rho_{max}| = 0.23$ Å^{-3}.

Variata. One *tert*-butyl group was modelled as rotationally disordered about its pendant, major component occupancy 0.678(10). The solvent was modelled as six methanol sites, each assigned occupancy 0.5 after trial refinement; associated hydrogen atoms were not located.

3 $2.21CHCl_3{\cdot}0.79CH_3OH \equiv C_{67}H_{87.37}Cl_{6.63}N_2O_{8.79}$, $M = 1296.4$. Triclinic, space group $P\bar{1}$, $a = 13.704(2)$, $b = 14.985(2)$, $c = 18.307(3)$ Å, $\alpha = 92.405(2)$, $\beta = 95.179(2)$, $\gamma = 112.317(2)°$, $V = 3{,}452$ Å^3. D_c ($Z = 2$) = 1.24_7 g m^{-3}. $\mu_{Mo} = 0.33$ mm^{-1}; specimen: 0.31 × 0.20 × 0.20 mm. $2\theta_{max} = 50°$. $N_o = 6{,}960$, $R1 = 0.075$, $wR2 = 0.26$ (a = 0.15, b = 3.72), $S = 1.09$. $|\Delta\rho_{max}| = 0.97$ Å^{-3}.

Variata. Chloroform molecule 1 was modelled as disordered over a pair of sites, occupancies set at 0.5 after trial refinement. Chloroform molecule 2 was well-behaved. The remaining residues were modelled in terms of chloroform and methanol fragments, occupancies 0.208(4) and complement respectively.

Results

Synthesis and crystal structures of **1** and **2**

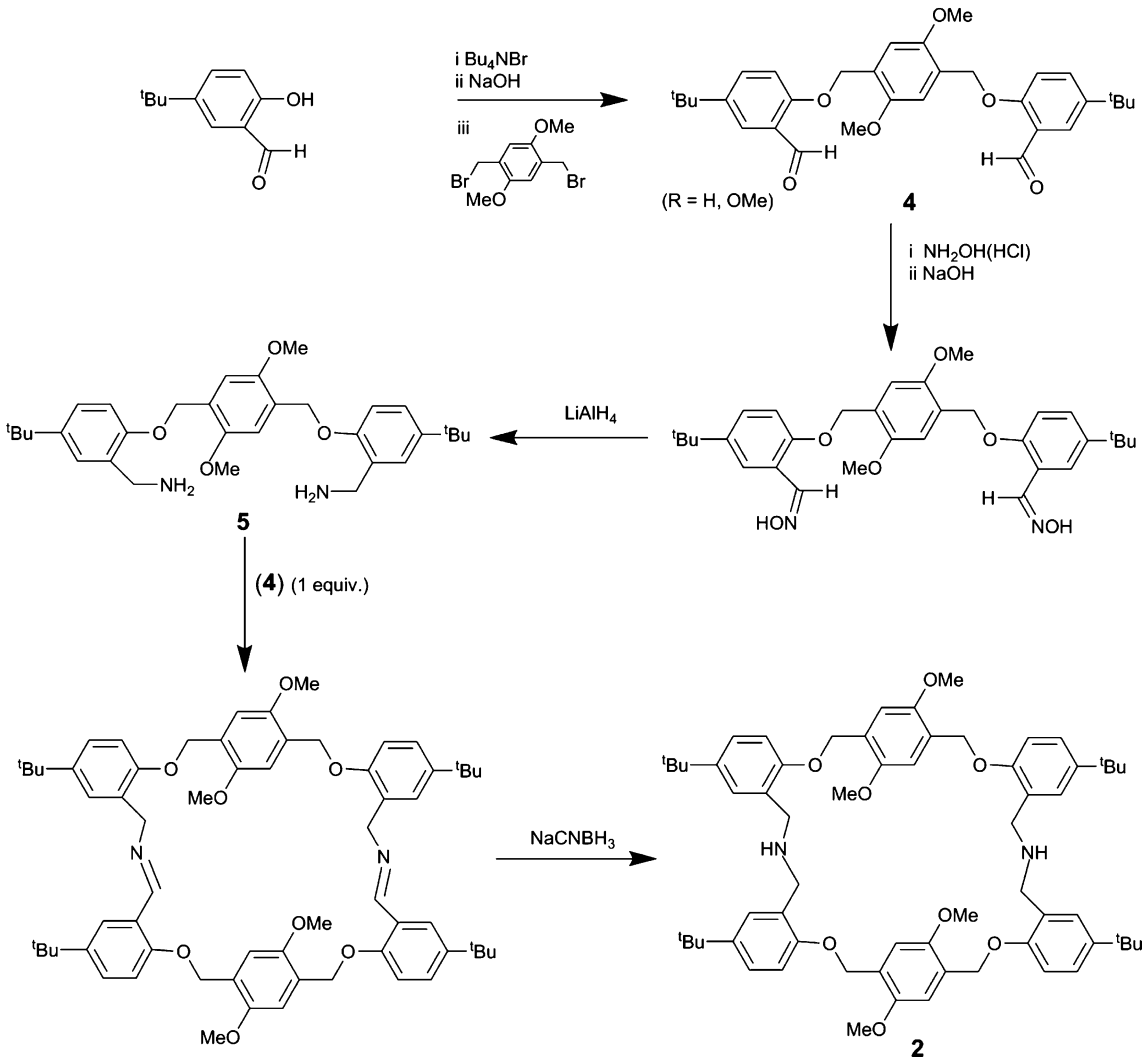
The synthesis of **1**, via Schiff base condensation of the corresponding diamine and dialdehyde precursors, followed by in situ reduction of the product with sodium cyanoborohydride in dry methanol, has been reported previously by us [4]. The synthesis of the related

tetramethoxy macrocycle **2** employed a similar procedure starting from the corresponding dimethoxy dialdehyde and diamine (Scheme 1).

Single crystals of **1**, grown from toluene as the toluene mono-solvate, were employed for an X-ray crystal structure determination (Fig. 1a) and showed that this macrocycle adopts a solid state configuration of quasi-D_{2h} symmetry in which all of its aromatic rings are essentially coplanar; one half of the formula unit comprises the asymmetric unit of the structure, both components being disposed about crystallographic inversion centres. The rms deviation from the macrocycle plane for all atoms excluding hydrogens and those in the *tert*-butyl groups is 0.39 Å, with interplanar dihedral angles between the sequence of C_6 aromatic rings between the pair of nitrogen atoms being 15.5(1) (1/2), 22.5(1), 21.6(2)° (1,2/3).

Highly disordered toluene solvent molecules lie adjacent to the *p*-xylyl rings of the macrocycle; they are arranged such that the plane of each toluene ring lies approximately perpendicular to the plane of a *p*-xylyl ring of the macrocycle (interplanar dihedral angle 76.1(4)°) in a manner that appears to involve a T-stacking π-interaction. However, the toluene molecules lie outside the cavity leaving the latter empty. The area of the macrocyclic cavity is approximately 42 $Å^2$. The lone pairs on the two nitrogen atoms are directed *exo* with respect to the cavity, the two nitrogen atoms being 10.3 Å apart. In the lattice, macrocycle molecules are stacked on top of one another such that the macrocyclic rings are parallel with their N–N axes parallel.

The two solvated forms of **2**, although differing appreciably in their cell dimensions and detailed conformations (Table 1), are essentially isomorphous; discussion will be conducted in terms of the more precisely determined low-temperature study of the mixed chloroform/methanol solvate.



Scheme 1 The synthesis of macrocycle 2

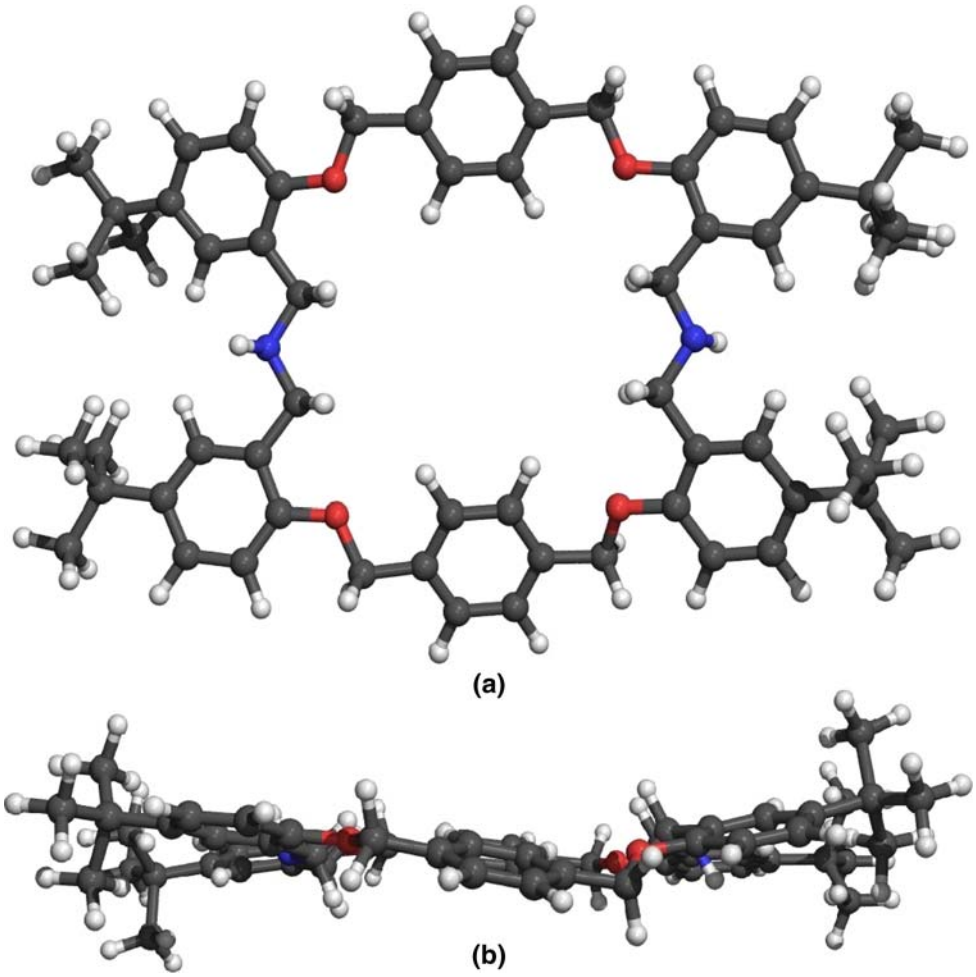


Fig. 1 Projections of a single molecule of **1**: **a** normal to and **b** through the macrocycle plane

The X-ray crystal structure of **2** (Fig. 2) shows a very different arrangement to that discussed above for **1**. The molecule adopts a conformation of quasi-2 symmetry in which the two bis(methoxy)-*p*-xylyl groups are involved in a classic offset face-to-face π–π interaction. The interplanar distance between the two bis(methoxy)-*p*-xylyl groups is 3.4 Å with the centroids offset by 2.3 Å. The two rings are rotated relative to each other about the normals of their respective planes (Table 1) such that when the centroids are aligned, a carbon atom of one ring sits over the centre of a bond in the other. The arrangement of the substituents on the two bis(methoxy)-*p*-xylyl groups relative to each other is in close accordance with the expected outcome based on the rules for π–π interaction postulated by Hunter and Sanders [11]. The N···N distance in the X-ray structure of **2** is also 10.3 Å, comparable to the analogous distance in **1** discussed above despite the change in conformation.

Molecular modelling and ASIS NMR studies

As expected, an investigation of low energy conformers for **1** using molecular mechanics (MM2 force field) yielded several energetically similar local minima, with the respective structures showing insignificant change on application of further semi-empirical (AM1) minimisation. One of these minimum energy conformations corresponded to a structure in which the two *p*-xylyl groups adopt a face-to-face arrangement, similar to that observed in the X-ray structure of **2**.

In a preliminary experiment aimed at probing the possibility that such a configuration might act as a host for a small aromatic guest, an aromatic solvent induced shift (ASIS) [12–15] involving a ^{1}H NMR study of **1** in C_6D_6 (as well as a parallel study of this molecule in $CDCl_3$), was undertaken. The technique is based on the expectation that when the ^{1}H NMR spectrum of an aromatic molecule is measured in an aromatic solvent, upfield (deshielded) shifts for the solute signals will be observed relative to the corresponding signals for non-aromatic solvent signals when the aromatic solvent solvates the solute in such a way that individual protons experience the shielding π-face of the solvent. The aromatic xylyl proton signal of **1** showed an upfield shift of 0.10 ppm, as did the signals due to the CH_2O (0.19 ppm) and the aromatic CH (0.09) signal ortho

Table 1 C_6/C_6 interplanar dihedral angles in **2** (2.21$CHCl_3$·0.79 MeOH) (degrees)

	Xy_A	A′	B	Xy_B	B′
A	14.3(2)	46.7(2)	71.7(2)	16.2(2)	20.7(2)
	10.7(4)	*50.8(4)*	*75.8(4)*	*11.5(4)*	*24.5(4)*
Xy_A		70.9(2)	70.4(2)	4.9(2)	18.3(2)
		61.4(4)	*72.8(3)*	*2.3(3)*	*14.3(3)*
A′			89.1(2)	71.9(2)	52.7(2)
			79.3(4)	*62.3(4)*	*75.2(4)*
B				71.9(2)	69.3(2)
				70.5(3)	*64.6(4)*
Xy_B					23.2(2)
					13.0(3)

To either side of each central xylyl ring the rings are labelled. A–Xy_A–A′ and B–Xy_B–B′ (A proximal to B and A′ to B′). Counterpart values for the room temperature study of the 3 MeOH solvate are given in italics

to the $COCH_2$ fragment while the remaining signals shifted downfield. The former two signals are those in the immediate vicinity of the xylyl aromatic rings, while the other signals (including the methylene protons adjacent to the nitrogen) experience a downfield shift as expected for them falling in the deshielding zone of any intercalated benzene molecule. The ^{1}H NMR spectrum of **1** was also acquired using various mole fractions of C_6D_6 and $CDCl_3$ and the expected variation of the ASIS values for the respective signals with mole fraction of benzene in the mixture was observed. While clearly not unequivocal, these results nevertheless are compatible with face-to-face π–π interaction occurring between the xylyl groups of **1** and an incalcated C_6D_6 molecule. Unfortunately, in an attempt to investigate the corresponding solid state situation, several attempts to obtain single crystals of the benzene adduct by slow evaporation of a benzene solution of the macrocycle proved unsuccessful.

The relative disposition of the two secondary amine groups in **1** also suggested the possibility of combining the π–π interaction mentioned above with hydrogen bonding interactions offering the prospect that **1** might host an appropriately sized aromatic disubstituted phenol such as hydroquinone. For this to be efficient it is noted that the separation between the hydrogen-bonding protons in hydroquinone was estimated to be ~6.4 Å, suggesting that **1** would need to adopt an *endo–endo* conformation to accommodate a hydrogen bonded hydroquinone substrate.

Host–guest NMR studies

Excess hydroquinone (**3a**) was added to a $CDCl_3$ solution of **1**, undissolved hydroquinone then removed, and the ^{1}H NMR spectrum of the solution obtained (hydroquinone has only a low solubility in $CDCl_3$ but that is increased in the presence of **1**). The spectrum clearly showed a single (shifted) peak for the hydroquinone aromatic protons as well as changes in the spectrum of 'free' **1**; although the induced chemical shifts tend to be small, they were shown to be quite reproducible. The ^{1}H chemical shifts (together with the corresponding ^{13}C NMR shifts) for both free and bound **3** are listed in Table 2. Thus the ^{1}H NMR spectrum (298 K) of the mixture displays a single set of resonances,

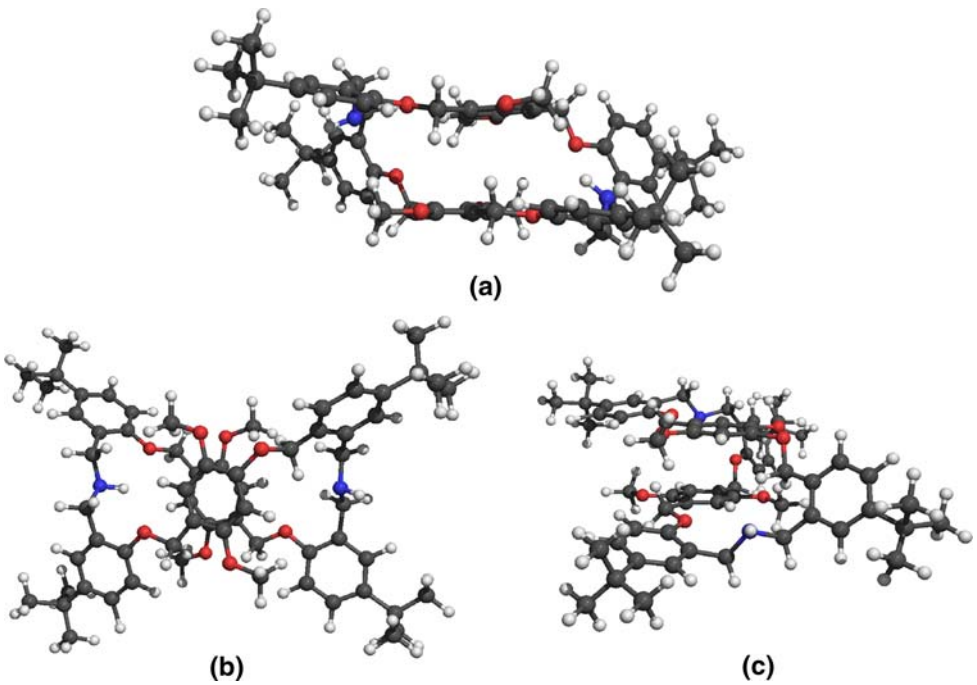
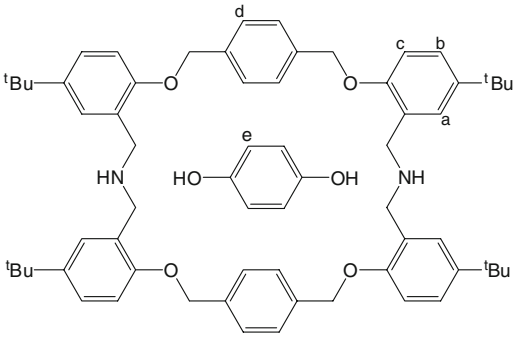


Fig. 2 X-ray crystal structure of **2**: **a** from "side on", **b** from "above" at an angle normal to the two bis(methoxy)-*p*-xylyl groups and **c** slightly offset from the N–N axis

in keeping with a resulting complex corresponding to the fast exchange regime, with integration of the spectrum indicating an approximate 1:1 stoichiometry. The hydroquinone aromatic protons are significantly shielded upon complexation and move upfield by 0.39 ppm while the *p*-xylyl protons of the host are also shielded and shifted upfield by 0.12 ppm on complex formation. These complementary shifts are in accord with the aromatic rings of the host and the guest being oriented face-to-face in the complex. While the CH_2N proton signals for the host show a relatively small shift (0.05 ppm upfield) upon the addition of hydroquinone, the ^{13}C signal for the methylene carbon moves 1.2 ppm upfield as expected for hydrogen bond formation between the phenol groups of **3a** and the amine nitrogens of **1**.

Because the restricted solubilities of both the macrocyclic host **1** and hydroquinone guest **3a** limited the scope of the solution studies, we instigated further studies in which the tetramethoxy-substituted derivative **2** was also employed as a guest and the more soluble alkyl-substituted hydroquinone substrates **3b** and **3c** were substituted for **3a** in an attempt to obtain related host–guest systems exhibiting enhanced solubilities in $CDCl_3$ or CD_2Cl_2.

Table 2 The 'free' (F), 'bound' (B) and induced ($\Delta\delta$) ^1H and ^{13}C NMR shifts (ppm) of the respective signals for **1** and **3a** ($CDCl_3$, 300 MHz, 298 K)



Signal	^1H(F)	^1H(B)	$\Delta\delta^1H$	^{13}C(F)	^{13}C(B)	$\Delta\delta^{13}C$
CH_2O	4.86	4.92	−0.06	69.5	69.4	0.1
CH_2N	3.91	3.86	0.05	50.4	49.2	1.2
a	6.77	6.77	0.00	111.1	110.9	0.2
b	7.20	7.21	0.01	124.6	125.1	−0.5
c	7.38	7.29	0.09	128.3	128.3	0.0
d	7.27	7.15	0.12	126.9	126.6	0.3
e	6.72	6.33	0.39	–	116.1	–
tBu	1.29	1.30	−0.01	31.5	31.5	0

$\Delta\delta$ ($\delta_{free} - \delta_{bound}$); positive values are upfield shifts. A similar pattern of induced shift behaviour was observed when CD_2Cl_2 was substituted for $CDCl_3$ as the NMR solvent

A ^1H NMR titration of **1** in CD_2Cl_2 with **3b** resulted in a gradual upfield shift of all CH signals, with the respective induced shifts levelling off at a molar ratio of ~8:1 (**3b**:**1**). Even at the latter ratio the induced shifts were small, the largest (0.09 ppm) occurring for the CH_2N protons of **1**; all other shifts were 0.05 ppm or less. Also the induced shift pattern differed from that observed when hydroquinone (**3a**) was used as the guest, suggesting that a different host–guest structure may occur with the more sterically bulky guest **3b**. The small magnitude of the induced shifts (at 298 K) coupled with the high ratio of guest **3b** to **1** required to obtain 'saturation' host–guest complex formation indicate that the binding of **3b** to **1** is quite weak. Even so, the NH signal for **1** moved downfield, consistent with each of these groups being involved in hydrogen bonding.

A similar titration employing the tetramethoxy host **2** (incorporating more electron rich substituted xylyl moieties) once again yielded only very small induced CH proton shifts (0.03 ppm or less, but nevertheless again quite reproducible) with the individual induced shifts not levelling out until a **3b**:**2** ratio of ~9 was reached, again in keeping with weak host–guest interaction for this system. Titration curves for both this and the previous system are given in the electronic supplementary material as Figs. 1S and 2S. Once again the induced shift pattern could not be interpreted as 'simple' incalcation of **3b** between parallel xylyl rings of **2**. Nevertheless, it needs to be noted that for each system upfield shifts of both the aliphatic and aromatic hydroquinone derivative CH proton signals were observed, perhaps indicating that they fall in the shielding region of the aromatic host (but not necessarily in a π–π stacked arrangement).

The above ^1H titration data were employed to obtain 1:1 association constants for the interaction of **3b** and **3c** with both **1** and **2**. Attempts to fit the data to a 2:1 model were in each case unsuccessful. The results are presented in Table 3. Clearly, the stabilities of all four complexes do not vary greatly, with the results suggesting that host **1** yields slightly more stable complexes with **3b** and **3c** than does **2**, perhaps reflecting increased steric hindrance to complexation arising from the presence of the methoxy substituents in the latter case.

Finally we note that the K values listed in Table 3 fall in the same general range (but in each case of somewhat greater magnitude) as the recently reported value of 10.6 $dm^3\ mol^{-1}$ in 4:1 $CHCl_3/CH_3CN$) for the 1:1 complex of hydroquinone with the new bispyridyl cleft-like synthetic receptor mentioned previously [7].

Conclusion

In this study we have determined the X-ray structures of two (solvated) 28-membered O_4N_2-macrocycles, **1** and **2**,

Table 3 Association constants (298 K) for the 1:1 complexes between hosts **1** and **2** and guests **3b** and **3c** in CD_2Cl_2

Host	Guest	K (dm^3 mol^{-1})
1	**3b**	80 ± 20
2	**3b**	69 ± 20
1	**3c**	162 ± 40
2	**3c**	54 ± 20

and guided by the results of molecular modelling studies, demonstrated that both form 1:1 host–guest complexes with hydroquinone as well as with two of its (more soluble) substituted derivatives. There appear to be no previous literature reports of K determinations involving synthetic macrocyclic receptors and hydroquinone derivatives related to those employed in the present study, and we report binding constants for **1** and **2** and the latter hydroquinone derivatives which have been determined in CD_2Cl_2.

Acknowledgement We thank the Australian Research Council for support.

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