
5,21-Dimethyl-8,24-pentamethylenedioxy-1,10,17,26-tetra-aza[2,2](mo)₂-cyclophane

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The synthesis and properties of a tetra-aza-cryptand (**3**; R = H) are described; its diacetate (**4**; R = Ac) is a secondary diamine in which inversion at the amino-nitrogen atoms is inhibited at ambient temperature.

In earlier studies the synthesis and properties of the crown ethers (**1**) and (**2**) as hosts for the inclusion of alcohols and phenols were investigated.¹ The tetra-aza-analogue (**3**; R = H) of (**2**) was obtained (16%) by reaction of 1,5-bis(2',6'-bisbromo-methyl-4'-methylphenoxy)pentane¹ with *o*-phenylenediamine. X-Ray analysis of the tetra-aza-cryptand showed the molecule to adopt a 'V' shaped conformation (Figure) analogous to the hexa-oxacyclophane (**1**; R = Me). The hydrogen sites on N-17 and N-26 are ordered and unambiguous, since the alternative sites are, in each case, in conflict with the hydrogen atoms on the adjacent methylene group (Figure; ●). The hydrogen sites on N-1 and N-10 are both acceptable stereochemically and are both shown (Figure); for each of N-1 and N-10 one of these sites forms a short contact (~2.4 Å) to N-17 and N-26 respectively. The high symmetry and conformational flexibility

of the aza-cryptand (**3**; R = H) at ambient temperature is shown by its NMR characteristics. Thus, the ¹H NMR spectrum shows the eight benzylic protons as a pair of four proton doublets (δ 4.36 and 4.07, with a geminal coupling of 12.0 Hz) and the ¹³C NMR spectrum displays just 12 carbon signals. The aza-cryptand readily formed bis-acyl derivatives but all attempts to generate tetra-acyl compounds failed. Dialkylation (MeI or BrCH₂CO₂Et, NaH) but not tetra-alkylation was possible. The proton NMR spectrum of the bis-acetate (**4**; R = Ac) contained several distinctive features—the four aromatic protons of the *p*-cresol rings appeared as a pair of two proton singlets, the two aromatic methyl groups as two singlets, and the four protons of the outermost methylene groups (next to oxygen) in the central C-5 chain as two triplets. Most significant, however, was the appearance of the eight benzylic

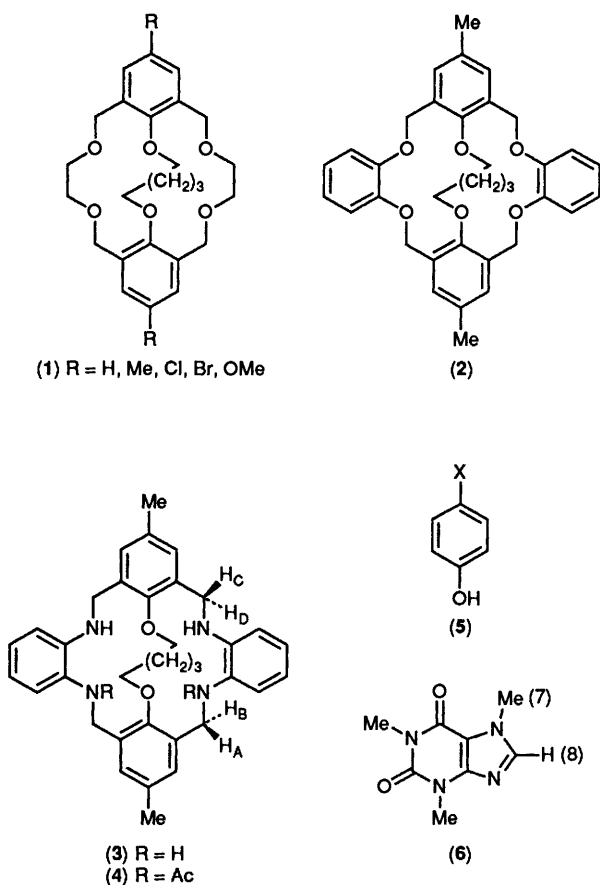
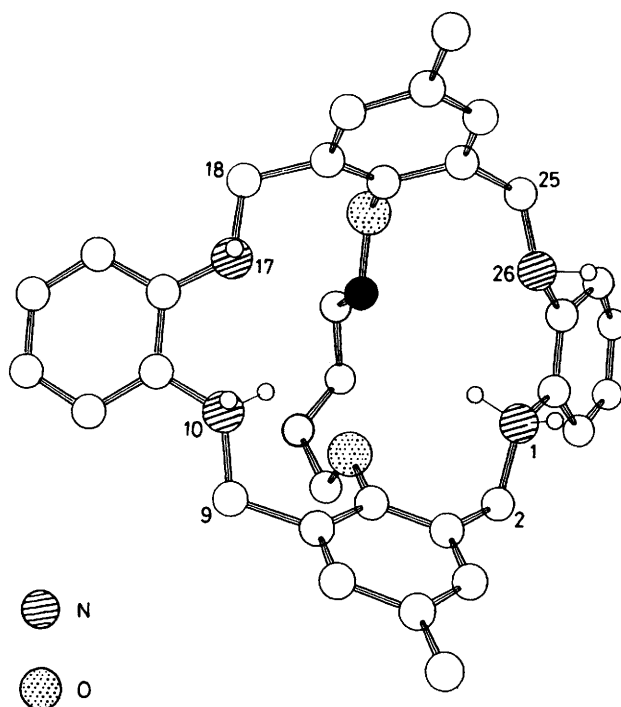


Table 1. Changes in chemical shift (δ) of the protons *ortho* ($\Delta\delta_o$) and *meta* ($\Delta\delta_m$) to the phenolic group of *p*-XC₆H₄OH (5) upon complexation with the cryptands (3; R = H) and (2). Changes in the chemical shift of the protons of the methyl groups ($\Delta\delta_{Me}$) of the cryptands. Concentrations of both phenol and cryptands in CDCl₃ = 0.2 mmol l⁻¹. Measurements at 250 MHz.

Cryptand	X	p <i>K</i> _a	$\Delta\delta_o$	$\Delta\delta_m$	$\Delta\delta_{Me}$
(2)	NO ₂	7.2	-0.30	-0.71	-0.39
(2)	Cl	9.4	-0.30	-0.58	-0.31
(3; R = H)	NO ₂	7.2	-0.23	-0.35	-0.07
(3; R = H)	Cl	9.4	-0.16	-0.26	-0.07

protons and the NH signal. Four of the benzylic protons at (C-2 and C-9) occur as a pair of doublets as in the original cryptand (δ 4.10 and 5.35, with a geminal coupling of 16 Hz) but with one pair now deshielded by -1.0 ppm, presumably by the adjacent quasi-axial *N*-acetyl groups (N-1, N-10). The remaining four benzylic protons were present as a pair of double doublets (δ 4.40 and 3.73, geminal coupling 10.5 Hz and additional coupling to the N-H proton of 6.0 and 2.5 Hz respectively). The amino protons in the aza-cryptand (3; R = H) appear as a broad singlet but in the diacetate as a distinctive double doublet (δ 4.01, *J* = 2.5 and 6.0 Hz) from ambient temperatures to 70 °C. This suggests that both of the NH protons occupy a fixed stereochemical position and cannot change chemical environments by inversion at nitrogen. On the basis of this evidence the diacetate is formulated as (4; R = Ac) with a conformation fixed by stereochemical constraints at nitrogen.

Binding studies with the cryptand (3; R = H) and various substrates were carried out in an analogous manner to those with the oxa-analogue (2) (Table 1). With phenolic guests (5) the most significant chemical shift changes ($\Delta\delta$) occurred in the

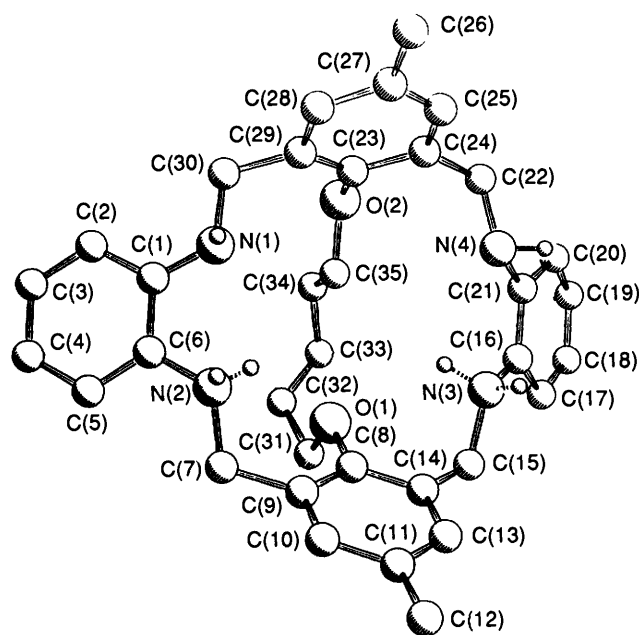


position of the host NH protons which experienced downfield shifts of 0.6–1.3 ppm consistent with hydrogen bonding of the hydroxy group to nitrogen. Binding was invariably weaker to the aza-cryptand (3; R = H) than to the oxa-cryptand (2). Although the NH groups of (3; R = H) may also act, in principle, as hydrogen bond donors the ability of the aza-cryptand (3; R = H) to bind caffeine (6) was very similar to that of the oxa-cryptand (2). On the basis of chemical shift changes ($\Delta\delta$, CDCl₃) observed in the substrate, association takes place in both cases by preferential insertion of the 5-membered ring of caffeine (6) into the cavity of the cryptands.

Experimental

Tetra-aza-cryptand (3; R = H).—A solution of freshly sublimed *o*-phenylenediamine (2.4 g, 22 mmol) in anhydrous THF (80 ml) was added (over 4 h) to a stirred, refluxing solution of 1,5-bis(2',6'-bisbromomethyl-4'-methylphenoxy)pentane (6.56 g, 10 mmol) in anhydrous THF (600 ml) containing anhydrous potassium carbonate (12.0 g, 87 mmol). After being heated (with stirring) under reflux for a further 6 days, the mixture was evaporated to dryness and the organic material extracted (Soxhlet) with chloroform (3 days). The bright orange powder was separated by medium-pressure liquid chromatography (silica 100 g; elution with ethyl acetate–light petroleum, 1:8) to give, after crystallisation from ethyl acetate, the aza-cryptand (0.86 g, 16%) as pale yellow needles, m.p. 266–268 °C (Found: C, 76.2; H, 7.3; N, 10.6. C₃₅H₄₀N₄O₂ requires C, 76.6; H, 7.3; N, 10.2%). Molecular ion *m/z* 548 (C₃₅H₄₀N₄O₂ requires 548); δ_H (CDCl₃, TMS) 7.09 (4 H, s, Ar-H), 6.89 (4 H, m, Ar-H), 6.80 (4 H, m, Ar-H), 4.36 (4 H, *d*, *J* 12 Hz), 4.07 (4 H, *d*, *J* 12 Hz), 3.99 (4 H, t, *J* 6 Hz), 2.31 (6 H, s, Ar-Me), and 1.0–0.8 (6 H, m, CH₂); δ_C (CDCl₃, TMS) 155.2, 137.4, 133.3, 131.8, 131.4, 118.9, 110.4, 71.4, 47.2, 28.5, 20.8, and 20.5; *R*_F 0.47 [in light petroleum (b.p. 40–60 °C)–ethyl acetate, 8:1].

The diacetate (4; R = Ac), prepared with acetic anhydride and pyridine and purified by medium-pressure liquid chromatography, crystallised from ethyl acetate as needles, m.p. 295–7 °C;

Table 2. Atom co-ordinates ($\times 10^4$)

Atom	x	y	z
O(1)	-495(11)	-532(6)	2 068(3)
O(2)	-583(11)	874(6)	515(3)
N(1)	-2 263(12)	2 164(7)	1 496(4)
N(2)	-2 125(15)	1 285(8)	2 406(4)
N(3)	2 994(14)	-700(7)	1 675(4)
N(4)	3 132(13)	334(8)	786(4)
C(1)	-3 629(19)	2 030(9)	1 753(4)
C(2)	-5 109(18)	2 310(10)	1 570(6)
C(3)	-6 525(17)	2 110(9)	1 840(6)
C(4)	-6 470(15)	1 670(10)	2 319(5)
C(5)	-4 955(17)	1 419(8)	2 500(5)
C(6)	-3 599(16)	1 565(10)	2 220(4)
C(7)	-1 960(20)	614(11)	2 842(5)
C(8)	442(19)	-349(9)	2 495(5)
C(9)	-197(16)	242(10)	2 879(5)
C(10)	688(19)	512(10)	3 319(5)
C(11)	2 198(18)	124(11)	3 372(6)
C(12)	3 168(16)	504(10)	3 826(5)
C(13)	2 827(18)	-407(10)	2 983(6)
C(14)	1 966(14)	-709(9)	2 549(5)
C(15)	2 584(15)	-1 276(9)	2 141(5)
C(16)	3 342(15)	-1 183(8)	1 202(5)
C(17)	3 592(18)	-2 196(11)	1 192(6)
C(18)	3 910(22)	-2 630(13)	711(8)
C(19)	3 985(28)	-2 110(13)	255(7)
C(20)	3 899(19)	-1 117(11)	279(5)
C(21)	3 430(19)	-683(10)	743(5)
C(22)	2 716(16)	844(10)	326(5)
C(23)	199(17)	1 707(9)	612(4)
C(24)	1 810(17)	1 763(8)	455(4)
C(25)	2 533(17)	2 633(8)	474(4)
C(26)	2 652(18)	4 438(8)	662(5)
C(27)	1 860(17)	3 465(9)	646(5)
C(28)	280(19)	3 362(11)	792(5)
C(29)	-530(16)	2 483(10)	787(4)
C(30)	-2 246(17)	2 493(12)	976(5)
C(31)	-1 398(16)	-1 407(12)	2 088(7)
C(32)	-2 423(24)	-1 412(13)	1 622(8)
C(33)	-1 867(27)	-1 481(13)	1 109(7)
C(34)	-1 810(23)	-597(13)	790(7)
C(35)	-776(18)	189(9)	945(5)

m/z 633 (MH^+ . $C_{39}H_{44}N_4O_4$ requires 632); ν_{max} (Nujol) 1 655 cm^{-1} ; δ_H ($CDCl_3$, TMS) 7.22 (2 H, dt, J 7, 1 Hz, N(COMe)Ar-H], 7.06 (2 H, s, Ar-H), 7.03 (2 H, dd, J 7, 1 Hz, N(COMe)Ar-H], 6.83 (2 H, s, Ar-H) 6.80 (2 H, dd, J 7, 1 Hz, Ar-H), 6.71 (2 H, dt, J 7, 1 Hz, NHAr-H), 5.35 (2 H, d, J 16 Hz), 4.40 (2 H, dd, J 10.5, 6 Hz), 4.10 (2 H, d, J 16 Hz), 4.01 (2 H, dd, J 6, 2.5 Hz, NH), 3.73 (2 H, dd, J 10.5, 2.5 Hz), 3.40 (2 H, t, J 7 Hz, $ArOCH_2$), 3.26 (2 H, t, J 7 Hz, $ArOCH_2$), 2.32 (3 H, s, Ar-Me), 1.97 (6 H, s, MeCO), 1.83 (3 H, s, Ar-Me), 1.30–1.15 (4 H, m, CH_2), and 0.95–0.80 (2 H, m, CH_2); δ_C ($CDCl_3$, TMS) 173.3 (CO), 154.1, 151.4, 144.5, 134.0, 133.7, 131.9, 131.1, 130.5, 130.2, 129.5, 128.7, 126.8, 117.2, 110.7 (all aromatic C), 75.4, 75.2 ($ArOCH_2$), 48.3, 43.3 ($ArCH_2N$), 27.5, 27.3, 22.6 (CH_2), and 21.4, 21.1, 20.6 (Me).

Crystal Data for $C_{35}H_{40}N_4O_2$ (3; R = H).— $M = 548.73$; crystallises from Et(OAc) as colourless faceted needles; crystal dimensions 0.90 \times 0.15 \times 0.20 mm. Orthorhombic, $a = 8.445(15)$, $b = 13.79(5)$, $c = 25.87(5)$ Å, $U = 3 011(14)$ Å³, $D_c = 1.210$ g cm^{-2} , $Z = 4$; space group $P2_12_12_1$ (D_2^4 , No. 19); Mo- K_α radiation ($\lambda = 0.710 69$ Å), μ (Mo- K_α) = 0.71 cm^{-1} , $F(000) = 1 175.79$.

Three-dimensional, room temperature X-ray data were collected in the range $3.5 < 2\theta < 40^\circ$ on a Nicolet R3 diffractometer by the omega scan method. The 974 independent reflections (of 1 668 measured) for which $|F|/\sigma(|F|) > 3.0$ were corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by blocked cascade least squares. Hydrogen atoms were placed in calculated positions, with isotropic thermal parameters related to those of the supporting atom, and refined in riding mode. The positions of the hydrogen atoms on two of the four secondary amines [N(1) and N(4)] were clearly determined to be 'out-of-plane', because of the steric interference of the alternative sites by the hydrogen atoms on C(35). For the remaining two secondary amines, the hydrogens were deemed to be disordered between the two sites with equal occupancy. It is noteworthy that the pairs of 'in-plane' sites on N(1) and N(2), and on N(3) and N(4) would have been mutually incompatible (too close $H \cdots H$ contacts) and the restrictions placed on N(1) and N(4) permit the disorder on N(2) and N(3). The refinement converged at a final R 0.0803, $R_w = 0.0738$ (376 parameters, final mean and maximum values of Δ/σ 0.116 and 0.787 respectively), with allowance for thermal anisotropy of all non-hydrogen atoms. A weighting scheme of $w^{-1} = [\sigma^2(F) + 0.001 25(F)^2]$ was used in the final cycles of refinement. A final difference electron density synthesis showed minimum and maximum values of -0.25 and $+0.27$ eÅ⁻³ respectively. Scattering factors were taken from the program package SHELXTL, as implemented on the Data General Nova 3 computer, which was used throughout the refinement. Atomic positions with estimated standard deviations are listed in Table 2. Full listings of bond lengths and bond angles, hydrogen co-ordinates, and thermal parameters are available, on request, from the Cambridge Crystallographic Data Centre [see Instructions for Authors (1990), *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1].

References

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Paper 0/01655A
Received 12th April 1990
Accepted 31st May 1990