

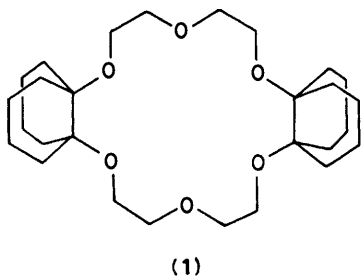
Water-soluble Macrocyclic Paddlanes and Propellane as a New Class of Host Molecules

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A new class of water-soluble macrocyclic polyamine host molecules containing bicyclo[2.2.2]octane or bicyclo[4.4.0]decane subcyclic units, tetra-azabispaddlane (**2a**), hexa-azatrispaddlane (**3a**), and tetra-azabispropellane (**4a**), have been synthesized. While trispaddlane (**3a**) and bispropellane (**4a**) showed only line broadening of the n.m.r. spectra at -59°C , bispaddlane (**2a**) exhibited coalescence behaviour at -31°C , (benzyl protons), -35°C (*N*-methylene protons adjacent to the bicyclo-octane unit), and -50°C (ArH). The association constants of (**2a**)—(**4a**) and the fluorescent hydrophobic guest, 1-anilino-naphthalene-8-sulphonate, were determined in KCl—HCl buffer of pH 1.68 to be $2.7 \times 10^2 \text{ M}^{-1}$, $1.1 \times 10^3 \text{ M}^{-1}$, and $2.2 \times 10^2 \text{ M}^{-1}$, respectively.

There has been considerable interest in the design and synthesis of water-soluble macrocyclic compounds having hydrophobic cavities of well defined size and shape. For this reason, a number of water-soluble paracyclophane-type host molecules have been synthesized and their inclusion abilities for hydrophobic guests have been examined.¹ The cavities of the above molecules are constructed by joining aromatic rings, which serve both as the lipophilic wall of the cavity and also as a rigid spacer extending the cavity diameter, with aliphatic chains (see e.g. polyazaparacyclophanes²). Alicyclic ring systems having appropriate shape and rigidity, such as bicyclo[2.2.2]octane and *cis*-bicyclo[4.4.0]decane (*cis*-decalin), have also been recognised as providing the lipophilic wall of polyalicyclic host molecules. For example, we have recently found that didecalino-18-crown-6 (**1**), having two *cis*-bicyclo[4.4.0]decane



moieties fused to the opposite sides of the crown ether ring, exhibit excellent complexing ability and stoichiometric selectivity toward alkali-metal cations because of the embedding effect of the decalin wall.³ In the context, we disclose herein the synthesis of a new class of water-soluble host molecules which contain bicyclo[2.2.2]octane and bicyclo[4.4.0]decane rings as subcyclic ring systems, namely tetra-azabispaddlane (**2a**),⁴ hexa-azatrispaddlane (**3a**),⁴ and tetra-azabispropellane (**4a**),^{4,5} and report the study of their conformational properties and complex formation with a hydrophobic guest in aqueous solution.

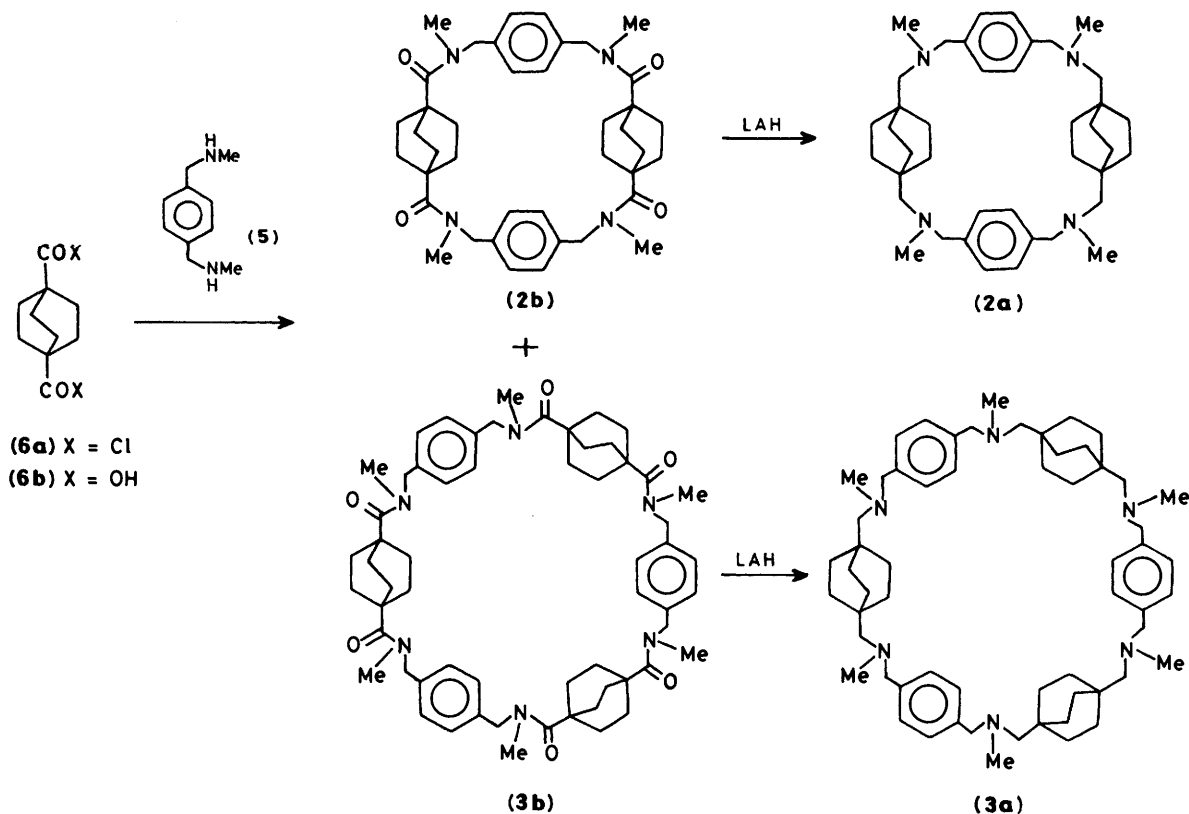
The syntheses of compounds (**2a**)—(**4a**) are shown in Schemes 1 and 2. In order to construct polycyclic paddlanes and propellanes having defined cavities, it is desirable to conjoin the subcyclic units with a rigid molecule which extends the requisite cavity. For this reason, *N,N'*-dimethyl-*p*-xylylenediamine (**5**), which itself composes the lipophilic wall, was chosen as a rigid spacer. Thus, condensation of (**5**) with the diacid chloride (**6a**) prepared from bicyclo[2.2.2]octane-1,4-

dicarboxylic acid (**6b**)⁶ in benzene under high dilution conditions gave the tetra-lactam (**2b**) (decomp. *ca.* 180°C) and the hexa-lactam (**3b**) (decomp. *ca.* 180°C) in 13 and 16% yields, respectively. The lactams (**2b**) and (**3b**) were reduced by lithium aluminium hydride in tetrahydrofuran to afford the corresponding tetra-azabispaddlane (**2a**) (m.p. $213\text{--}215^{\circ}\text{C}$) and hexa-azatrispaddlane (**3a**) (m.p. $177\text{--}179^{\circ}\text{C}$) in moderate yield. Similarly, the tetra-azabispropellane (**4a**) (m.p. $197\text{--}198^{\circ}\text{C}$) was obtained by condensation of (**5**) with the diacid chloride (**7a**) derived from 1,6-bis(carboxymethyl)bicyclo[4.4.0]decane (**7b**)⁷ (17% yield) followed by lithium aluminium hydride reduction of the tetra-lactam (**4b**) (m.p. $> 300^{\circ}\text{C}$).

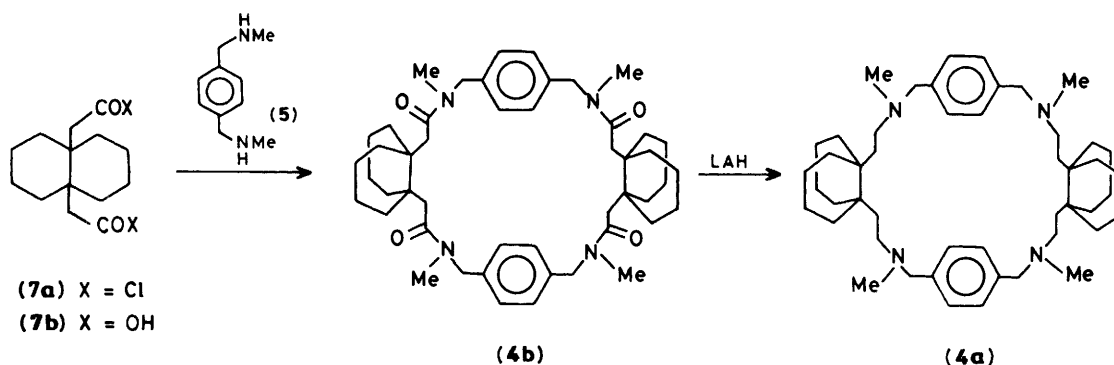
In order to investigate the conformational properties of the paddlanes (**2a**) and (**3a**) and the propellane (**4a**), the temperature dependence of their ^1H n.m.r. spectra was examined. The chemical shifts at 26°C and the line broadening at -59°C in CDCl_3 solution are listed in Table 1. The n.m.r. spectra of (**2a**) and (**3a**) at 26°C consisted of five sharp singlets. It should be noted that the bicyclo-octane methylene protons and the *N*-methylene protons adjacent to the bicyclo-octane units of (**2a**) appeared at *ca.* 0.2 p.p.m. higher field compared with those of (**3a**) owing to shielding by the benzene rings. Similarly, the aromatic, benzyl, and *N*-methyl protons of (**4a**) appeared as sharp singlets at 26°C . As shown in the Table, while all three compounds (**2a**), (**3a**), and (**4a**) showed line broadening at low temperatures, only (**2a**) exhibited coalescence behaviour under the conditions examined. Thus, the benzyl protons and the *N*-methylene protons adjacent to the bicyclo-octane units coalesced at -31 and -35°C , respectively, and split into AB quartets below these temperatures (benzyl protons: $\Delta\nu_{\text{AB}}$ 78 Hz, J_{AB} 12 Hz; *N*-methylene protons adjacent to the bicyclo-octane units: $\Delta\nu_{\text{AB}}$ 38 Hz, J_{AB} 13 Hz). Moreover, the aromatic protons also coalesced at -50°C and separated into an AB quartet at -65°C ($\Delta\nu_{\text{AB}}$ 20 Hz, J_{AB} 7 Hz). The ΔG^\ddagger values for the above conformational change were calculated to be 11.6 (-31°C), 11.7 (-35°C), and 11.2 (-50°C) kcal/mol, respectively, according to equation (1)⁸ where $k_c = \pi\Delta\nu/\sqrt{2}$.

$$\Delta G^\ddagger = 2.303RT_c(10.319 - \log k_c + \log T_c) \quad (1)$$

Since the above energy barriers are so similar, it is assumed that they are ascribed to the same conformational process. Taking the conformations of the related paracyclophanes into account,^{1,9,10} examination of molecular models indicates that (**2a**) is locked at low temperatures in a conformation in which the $\text{CH}_2\text{--N}(\text{CH}_3)\text{--CH}_2$ segments have an *anti* [C(7)—N(1)]-*gauche* [N(1)—C(8)]/*gauche* [C(17)—N(2)]-*anti* [N(2)—C(18)]



Scheme 1.



Scheme 2.

conformation because of steric repulsion between the congested bicyclo-octane units (see Figure 1). In the above conformation, the geminal protons on both *N*-methylene groups [*i.e.* H(7A) and H(7B) or H(8A) and H(8B)] are diastereotopic (pseudo-

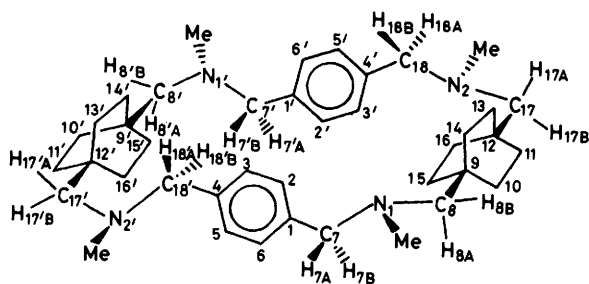


Figure 1.

axial or pseudo-equatorial) and one of the geminal protons on each pair of *N*-methylene units [*i.e.* H(7A) or H(8A)] is homotopic with those in the same environments [*i.e.* H(7'A), H(18A), and H(18'A) or H(8'A), H(17A), and H(17'A)]. Consequently, the AB quartets of the *N*-methylene protons are ascribed to the above conformation. Similarly, the vicinal aromatic protons [*i.e.* 2-H and 3-H] are diastereotopic and, therefore, separated into an AB quartet. At higher temperatures, the pseudo-axial-pseudo-equatorial conformational change involving inversion of the *N*-methyl groups¹¹ takes place and the signals become sharp singlets. The *N*-methyl and the bicyclo-octane protons of (2a) did not split until -65°C but remarkable line broadening of the latter protons were observed. As can be seen in Table, the magnitude of the line broadening of (4a) was greater than that of (3a) though the peak separation was not observed for these compounds. Consequently, it is deduced that the conformational flexibility of the macrocyclic ring systems is in the order of (3a) \geq (4a) > (2a).

Table. Chemical shifts and line broadening in the ^1H n.m.r. spectra of (2a)—(4a).

Compd.	Proton	Chemical shift ^a	Line broadening ^b
(2a)	Aromatic	7.22	c
	Benzyl	3.36	c
	N-CH ₃	2.32	7.2
	NCH ₂ C	1.87	c
	Bicyclo-octane	1.11	29
(3a)	Aromatic	7.24	4.5
	Benzyl	3.44	11
	N-CH ₃	2.17	7.5
	NCH ₂ C	2.07	14
	Bicyclo-octane	1.35	11
(4a)	Aromatic	7.23	5.1
	Benzyl	3.38	27
	NCH ₃	2.24	19

^a δ In p.p.m. in CDCl_3 solution at 26 °C. ^b Half-width in Hz at -59 °C. ^c Below the coalescence temperature.

Examination of space-filling molecular models (CPK) indicates that (2a) and (4a) have rectangular cavities (diameters, $3 \times 6 \text{ \AA}$ and $5 \times 6 \text{ \AA}$, respectively) which can include a benzene ring and that (3a) has a large circular cavity (diameter, 10 \AA) which can incorporate larger molecules such as naphthalene assuming the 'face' conformation^{1,10} of the benzene rings. The interaction of the host molecules (2a)—(4a) with a hydrophobic guest was studied by using the fluorescence probe, 1-anilinonaphthalene-8-sulphonate (1,8-ANS);^{1,2} in KCl-HCl buffer of pH 1.68 at 20 °C; concentrations of 1,8-ANS and (2a)—(4a), $1.02 \times 10^{-5} \text{ M}$ and $1.94\text{--}10.1 \times 10^{-4} \text{ M}$, respectively; excitation wavelength, 375 nm; fluorescence intensity, measured at 505 nm. Remarkable enhancement of fluorescence intensity and considerable blue shift of the emission λ_{max} of 1,8-ANS were observed with increasing concentration of (2a)—(4a), especially in the case of (3a). The reciprocal of fluorescence intensity ($1/I_f$) was plotted as a function of reciprocal concentration of (2a)—(4a) on the basis of the Benesi-Hildebrand relationship¹² giving straight lines as shown in Figure 2; this indicated that (2a)—(4a) formed 1:1

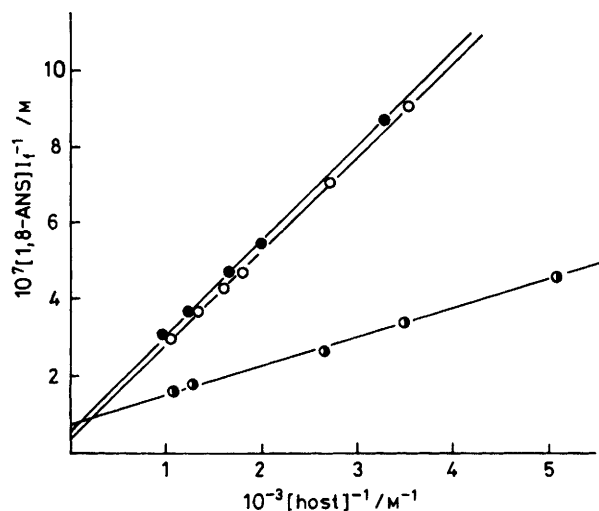


Figure 2. The Benesi-Hildebrand plot of 1,8-ANS and (2a), (3a), and (4a).

complexes with 1,8-ANS in the concentration range examined. The association constants were calculated to be $2.7 \times 10^2 \text{ M}^{-1}$ for (2a), $1.1 \times 10^3 \text{ M}^{-1}$ for (3a), and $2.2 \times 10^2 \text{ M}^{-1}$ for (4a),

which were comparable with those for the related water-soluble cyclophane-type host molecules.^{1,2} The difference in the association constants for (2a)—(4a) is reasonably attributed to the difference in the size of the cavities: while the cavities of (2a) and (4a) are too small to incorporate the naphthalene residue of 1,8-ANS, (3a) has a large cavity enough to accommodate the whole of 1,8-ANS.

In conclusion, a new class of water-soluble macrocyclic host molecules, tetra-azabispaddlane (2a), hexa-azatrispaddlane (3a), and tetra-azabispropellane (4a), have been successfully synthesized and it has been shown that they can include a hydrophobic guest into the lipophilic cavity consisting of bicycloalkane subcyclic units in aqueous solution.

Experimental

I.r. spectra were obtained on a Hitachi 260-10 spectrometer. ^1H N.m.r. spectra were taken with a JEOL JMN-PS-100 spectrometer in CDCl_3 solutions unless otherwise noted with SiMe_4 as the internal standard. Mass spectra were obtained on a Hitachi RMU-6E instrument. Fluorescence spectra were measured with a Hitachi MPF-3 spectrometer. The diacid chlorides (6a) and (7a) were prepared from the corresponding diacids (6b)⁶ and (7b)⁷ by heating with an excess of oxalyl chloride under reflux for 1–2 h followed by evaporation, and were used without further purification [ν_{max} (neat) 1780 cm^{-1}]. 1,8-ANS (sodium salt) was purified as its magnesium salt (Tokyo Kasei Kogyo) according to the literature procedure¹³ and the purity was checked by t.l.c.¹³ and u.v. spectroscopy.¹⁴

Tetra-azabispaddlane (2a) and Hexa-azatrispaddlane (4a).—A solution of (6a) prepared from (6b) (1.13 g, 5.71 mmol) in dry benzene (300 ml) and a solution of *N,N'*-dimethyl-*p*-xylylenediamine (5) (2.30 g, 14.4 mmol) in dry benzene (300 ml) were added dropwise with stirring to the same solvent (900 ml) during 20 h with heating under reflux in a nitrogen atmosphere. After completion of the addition, the mixture was refluxed for a further 1 h. The mixture was filtered, the filtrate was evaporated, and the residual solid chromatographed on silica gel with ethyl acetate-methanol (9:1) as eluant to give the tetra-lactam (2b) (240 mg, 13%) and the hexa-lactam (3b) (303 mg, 16%); (2b) decomposed at ca. 180 °C; ν_{max} (KBr) 1620 cm^{-1} (CO); δ 1.73 (24 H, s, CH_2 of bicyclo-octane), 2.91 (12 H, s, $4 \times \text{NCH}_3$), 4.61 (8 H, br s, benzyl), and 7.03 (8 H, s, ArH); m/z 652 (M^+ , 37%), 492 (100); (3b) decomposed at ca. 180 °C; ν_{max} (KBr) 1615 cm^{-1} (CO); δ (CD_3OD) 1.95 (36 H, s, CH_2 of bicyclo-octane), 2.99 (18 H, s, $6 \times \text{NCH}_3$), 4.60 (12 H, br s, benzyl), and 7.15 (12 H, s, ArH); m/z 950 (M^+ , not detected), 652 (28%), 492 (100), 327 (40), 167 (58), 133 (64), and 109 (44).

A mixture of the tetra-lactam (2b) (190 mg, 0.29 mmol) and lithium aluminium hydride (300 mg, 7.9 mmol) in tetrahydrofuran (THF) (40 ml) was heated under reflux with stirring for 16 h. After the mixture had been cooled, 5% aqueous sodium hydroxide (1 ml) was added to it and the whole refluxed for 1 h and then filtered. The filtrate was evaporated and the residue recrystallized from ether-THF to afford (2a) (94 mg, 54%), m.p. 213–215 °C (Found: C, 80.2; H, 10.1; N, 9.65. $\text{C}_{40}\text{H}_{60}\text{N}_4$ requires C, 80.48; H, 10.13; N, 9.39%); ν_{max} (KBr) 2770 cm^{-1} (N- CH_3); δ 1.11 (24 H, s, $2 \times$ bicyclo-octane CH_2), 1.87 (8 H, s, $4 \times \text{NCH}_2\text{C}$), 2.32 (12 H, s, $4 \times \text{NCH}_3$), 3.36 (8 H, s, benzyl), and 7.22 (8 H, s, ArH); m/z 596 (M^+ , 100%), 582 (38), 474 (40), 223 (38), 201 (48), and 104 (79).

Reduction of (3b) (217 mg, 0.23 mmol) with lithium aluminium hydride (250 mg, 6.0 mmol) in THF (30 ml) as described above gave (3a) (84 mg, 41%) after recrystallization from ether, m.p. 177–179 °C (Found: C, 80.25; H, 10.1; N, 9.25. $\text{C}_{60}\text{H}_{90}\text{N}_6$ requires C, 80.48; H, 10.13; N, 9.39%); ν_{max} (KBr) 2770 cm^{-1} (N- CH_3); δ 1.35 (36 H, s, $3 \times$ bicyclo-octane CH_2),

2.07 (12 H, s, 6 × NCH₂C), 2.17 (18 H, s, 6 × NCH₃), 3.44 (12 H, s, benzyl), and 7.24 (12 H, s, ArH); *m/z* 894 (*M*⁺, 2%), 597 (17), 402 (37), 352 (38), 299 (52), 164 (38), 148 (95), 105 (100), and 104 (57).

Tetra-azabispropellane (4a).—Condensation of (7a) prepared from (7b) (0.617 g, 2.47 mmol) and (5) (1.00 g, 6.25 mmol) as described for (2b) and (3b) afforded the tetra-lactam (4b) (155 mg, 17%), m.p. > 300 °C (Found: C, 75.2; H, 8.85; N, 7.44. C₄₈H₆₈N₄O₄ requires C, 75.35; H, 8.96; N, 7.32%); *v*_{max.} (KBr) 1 620 cm⁻¹ (CO); δ 1.0—2.0 (32 H, m, 2 × decalin CH₂, 2.14 (8 H, s, 4 × COCH₂C), 2.90 (12 H, br s, 4 × NCH₃), 4.60 (8 H, br s, benzyl), and 7.20 (8 H, br s, ArH); *m/z* 764 (*M*⁺, 7%), 631 (35), 559 (30), 175 (100), 133 (83), and 104 (33).

Reduction of (4b) (235 mg, 0.26 mmol) with lithium aluminium hydride (910 mg, 25 mmol) in dioxane (60 ml) was carried out as described for (2a) and (3a) to give (4a) (52 mg, 28%) after recrystallization from dioxane, m.p. 197—198 °C (Found: C, 80.9; H, 10.65; N, 7.8. C₄₈H₇₆N₄ requires C, 81.30; H, 10.80; N, 7.90%); *v*_{max.} (KBr) 2 780 cm⁻¹ (NCH₃); δ 0.9—2.6 (60 H, m, contains br s at 2.24, 2 × decalin CH₂, 4 × NCH₂-CH₂C, and 4 × NCH₃), 3.38 (8 H, s, benzyl), 7.23 (8 H, s, ArH); *m/z* 708 (*M*⁺, 18%), 456 (23), 352 (100), 220 (34), and 104 (41).

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