Pentamacrocyclic Tris-crown Hosts: Selective Binding of Cationic, Anionic, and Neutral Guests

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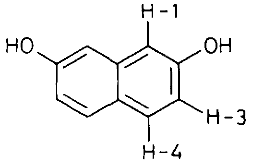
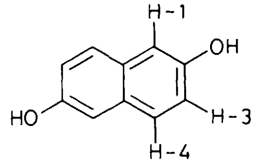
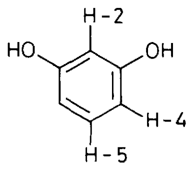
The tris-crown host compounds (**1**)—(**4**) were synthesized and the structures of (**2**) and of the 3:1 potassium complex of (**1**) (with the SCN^- anion projecting inside the cavity) were studied by *X*-ray analyses; specific organic guest molecules like β-naphthol and naphthalene diols are selectively bound inside the fitting cavities of the hosts (**2**) and (**3**) [but not (**1**) and (**4**)] in acidic water solution.

Ligands containing two crown units have been shown to complex bifunctional ammonium salts.[1] We expected unprecedented selectivities with respect to ionic and molecular recognition and inclusion of complementarily matching triply functionalized guest molecules by use of tritopic hosts of the hexamine types (**1**)—(**4**), in which three crown units are arranged at a defined, but variable, distance and relative stereochemistry to each other.

Two different strategies for the synthesis of (**1**)—(**6**) were applied. In the case of the macropentacyclic crown hexamide (**5**), a direct cyclization starting with trimesinic acid trichloride and 1,7-diaza-4,10,13-trioxocyclopentadecane ('Kryptofix-2.1') with formation of six amide bonds in one step[2] gave a 7% yield. The tris-crown (**6**) was obtained *via* a similar simple procedure in the same yield starting with the corresponding triacid chloride (of triphenylethane) and 1,10-diaza-4,7,13,16-tetraoxacyclo-octadecane ('Kryptofix-2.2').

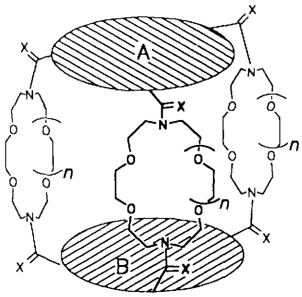
In the case of tris-crown compounds with different spacers, (**A**) and (**B**), like (**2**), and in the case of unfavourable spacers, (**A**) and (**B**), this one-step cyclization procedure was not successful because of the formation of byproducts of the type (**7**). A second strategy was applied in which the six amide bonds are connected in two consecutive steps. The spacer unit bearing three carboxylic acid functions is elongated by reaction with three molecules of the diaza crown compound to yield the corresponding tris-amides of types (**8**)—(**11**). There are no side reactions, because the crowns used have been reversibly blocked by a protecting group (carboxy benzyl) at one of the nitrogen atoms of each crown unit. After hydrogenolytically or hydrolytically splitting off the protecting group, the ligands (**8**), (**9**), and (**11**) are cyclized with the corresponding triacid chlorides to yield the macropentacyclic compounds (**1**)—(**3**) and (**6**). The overall yields in the cyclization steps here are by far higher compared to the direct cyclizations mentioned above. In the case of the macrocyclic ligand (**6**), which was synthesized according to both strategies, the yield increased from 7 to 17%. The amides were reduced using BH_3/tetrahydrofuran (THF) to the hexamines (**1**)—(**4**)

Table 1. High-field shifted protons (H-1 to H-5) of various guests and high-field shifts $\Delta\delta$ after addition of the hosts (**1**)—(**4**) in D_2O/DCl, pD 1.2, 200 MHz, 21 °C, standard defined as HDO at δ 4.8; concentrations: host 1×10^{-2} mol l^{-1}, guest 1×10^{-2} mol l^{-1}.

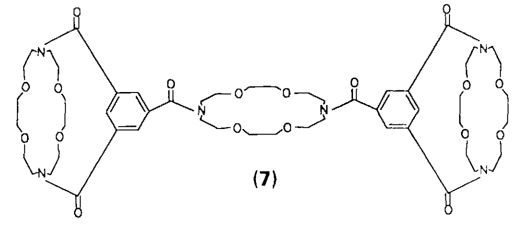
	Guest protons	Highfield shifts $\Delta\delta$ of guest protons after addition of host: (**1**)	(**2**)	(**3**)	(**4**)
	H-1 (7.03) H-3 (6.93) H-4 (7.69)	0 0 0	0.13 0.25 0.40	0.45 0.58 0.79	0 0 0
	H-1 (7.13) H-3 (7.06) H-4 (7.61)	0 0 0	0.21 0.23 0.36	0.42 0.48 0.56	0 0 0
	H-2 (6.35) H-4 (6.42) H-5 (7.11)	0 0 0	0 0 0	0 0 0	0 0 0

in order to increase the basicity and therewith the solubility in acidic water.†

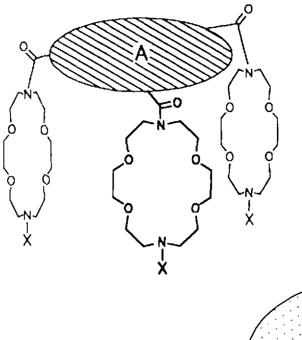
The uncomplexed host (**2**) and the potassium thiocyanate complex of the ligand (**1**) were studied by *X*-ray analyses.‡ The structure of (**2**) in the crystal reveals a threefold axis of rotation, but no mirror plane, as the three *p*-phenylene units are arranged propeller-like. The intramolecular cavity is collapsed and the distance between the centres of the benzene



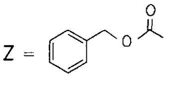
	(1)	(2)	(3)	(4)	(5)	(6)
A	I	I	II	III	I	III
B	I	I	II	III	I	III
n	1	1	1	1	0	1
X	H_2	H_2	H_2	H_2	O	O

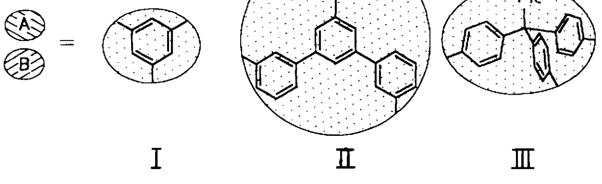


(**7**)



	(8)	(9)	(10)	(11)
A	I	II	III	III
X	H	H	Z	H

Z = 



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† All new compounds gave satisfactory spectroscopic, analytical, and mass spectral data.

‡ *Crystal data* for (**2**): $C_{72}H_{102}N_6O_{12}$, M = 1243.6, rhombohedric, space group $R\bar{3}$ (No. 148), colourless crystals, dimensions 0.3 × 0.5 × 0.5 mm³, a = 20.306(12) Å, α = 74.02(5)°, U = 7.556 nm³, Z = 4, μ(Mo-K_α) = 0.07 mm^{-1}, $\rho_{\text{ber.}}$ = 1.09 g cm^{-3}. 5799 Symmetry independent reflections ($2\theta_{\text{max.}}$ = 43°), 4019 reflections with $|F| > 4\,\sigma(F)$ were used for the structure solution (Direct Methods) and refinement (554 parameters), non-hydrogen atoms were refined anisotropically. H-atoms localized by difference electron density determination and refined using a 'riding' model. Two 1/3 molecules, one solvent molecule (diethyl ether) are located in the asymmetric unit and one water molecule in the cell. Programs see below. R = 0.104 [R_w = 0.085, $w^{-1} = \sigma^2(F)$]. For the (**1**)·KSCN complex: $C_{54}H_{90}N_6O_{12}\cdot 3KSCN\cdot 4H_2O$, M = 1378.9, monoclinic, space group $P2_1/n$ (No. 14), colourless crystals, dimensions 0.2 × 0.3 × 0.5 mm³, a = 10.861(2), b = 22.362(5), c = 29.930(5) Å, β = 93.29(1)°, U = 7.257 nm³, Z = 4, μ(Mo-K_α) = 0.33 mm^{-1}, ρ = 1.268 g cm^{-3}. 8343 Symmetry independent reflections ($2\theta_{\text{max.}}$ = 43°), 4116 with $|F| > 4\,\sigma(F)$ were used for the structure solution (Direct Methods) and refinement (742 parameters), non-hydrogen atoms were refined anisotropically, H-atoms localized by difference electron density determination and refined using a 'riding' model. Four water molecules were found in the asymmetric unit. One anion is disordered (s.o.f. S_1, C_1, N_1 = 0.56). R = 0.104 [R_w = 0.105, $w^{-1} = \sigma^2(F) + 0.0015\,F^2$]. Programs SHELXS-86 and SHELX-76: G. M. Sheldrick, SHELXS-86, 'A Program for Crystal Structure Solution,' Universität Göttingen, 1986; SHELX-76, 'A Program for Crystal Structure Determination,' Cambridge University, 1976. Atomic co-ordinates, bond lengths and angles, thermal parameters, and structure factors have been deposited at the Fachinformationszentrum Energie-Physik-Mathematik, D-7501 Eggenstein-Leopoldshafen (no. CSD-54047) and (except structure factors) also at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

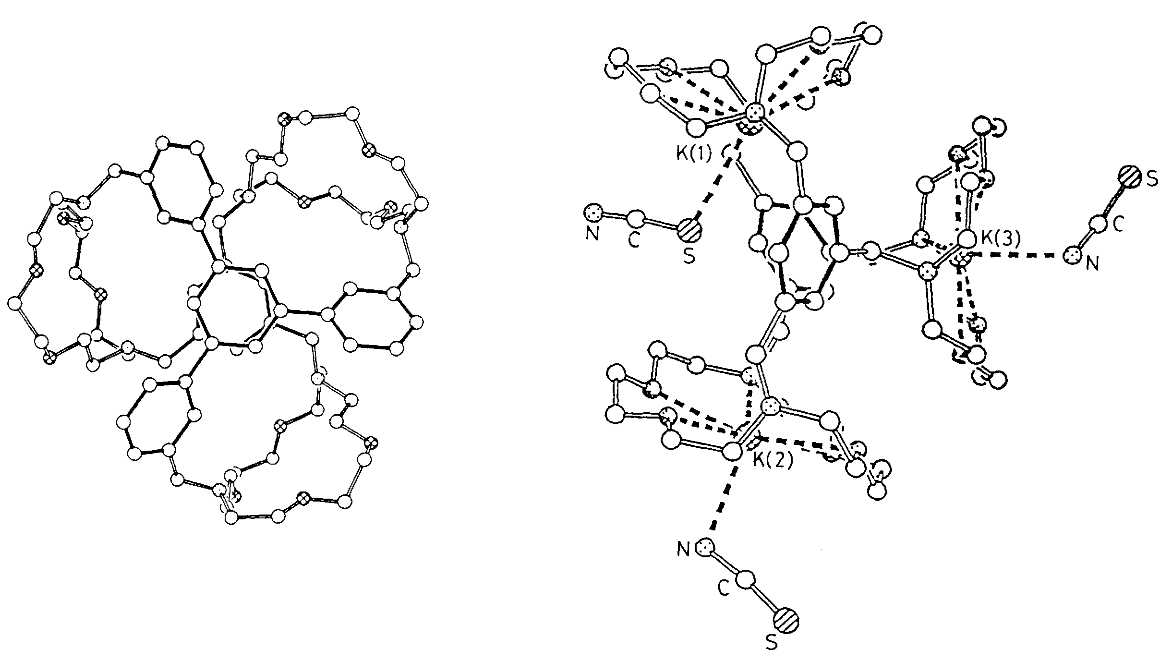

Figure 1. *X*-Ray structures of (**2**) (left) and of the 3 : 1-KSCN complex of (**1**) (right).

rings only amounts to 483 pm. The crown units consequently are bent to the outside. The distance between the central points of the crown units and the threefold molecular axis of rotation is 547 pm. Thus the skeleton of (**2**) does not seem to be well preorganized for the uptake of neutral organic guests.

Addition of KSCN to a solution of the ligand (**1**) (in ethyl acetate) yielded a crystalline 3 : 1 (guest : host) complex. The *X*-ray structural analysis shows that in this complex the molecular skeleton forms a more suitable cavity. The distance between the two centres of the benzene rings here is much larger (639 pm). The molecule does not possess a threefold axis of symmetry, whereas the thiocyanate anions are arranged in different ways with respect to the crown ether units, amongst which the potassium cations are located. Two of the three thiocyanate anions are situated outside the pentamacrocyclic skeleton and in each case *vis-à-vis* to the potassium cation, whereas the N-atom of the thiocyanate is ligated to the potassium cation. The third thiocyanate anion in contrast to this arrangement is disordered with respect to the SCN- (NCS-) sequence between two crown ether units and as a consequence lies partly inside the interior of the molecular cavity. The distance between the central point of the S atoms of the SCN^- anion and the line connecting the centres of the benzene rings is only 300 pm; for the other two SCN^- anions this distance is 950 pm. Thus, the potassium ion K(1) (*cf.* Figure 1) is drawn relatively far into the cavity, because its distance to the connection lines mentioned above only amounts to 361 pm, whereas the two other potassium cations are 439 and 449 pm from the connection lines, respectively.[3] Remarkably, the benzene rings are not parallel to each other, but the distance between them is greater where the SCN^- anion projects inside the cavity. The distances between the corresponding C-atoms lying above each other range from 576 to 704 pm. A crystalline complex of (**3**) with RbI (1 : 3) also could be isolated (from ethyl acetate). A guanidinium$^+$ SCN^- complex of (**3**) was obtained in ethyl acetate solution, which also proved to have the stoicheiometry 1 : 3 (host : guest). We assume a similar structure with the three guanidinium ions bound to the three crown units outside the cavity, as in the case of the alkali metal complex.

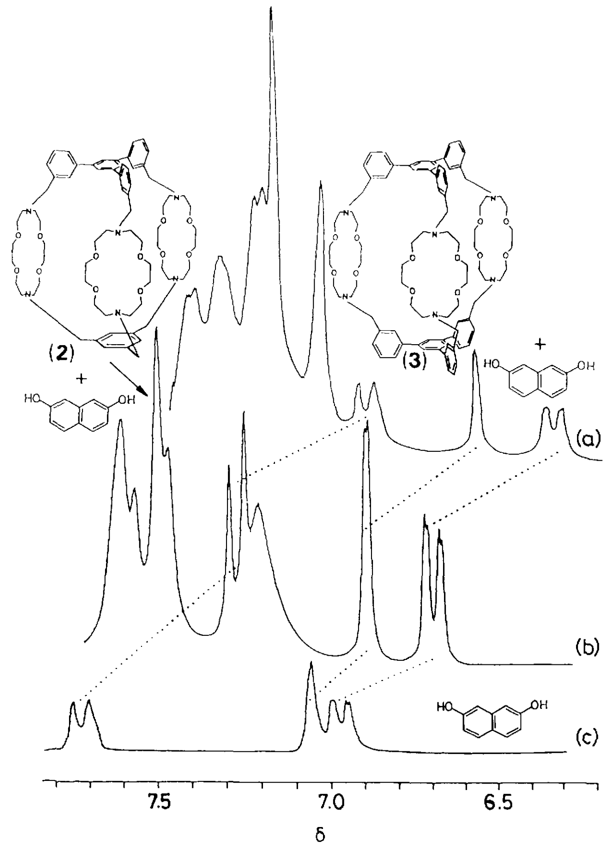

Figure 2. NMR spectra (section) of (a) host (**3**) after addition of the guest naphthalene-2,7-diol; (b) host (**2**) after addition of the guest naphthalene-2,7-diol; (c) naphthalene diol; all in D_2O/DCl, pD 1.2, 200 MHz.

Unexpectedly, the host compounds (**2**) and (**3**) in acidic water solution form inclusion complexes with some isomeric naphthalene diols, but not with a series of other phenolic substrates. Table 1 gives an overview with respect to the binding of these and related guests. The hosts (**2**) and (**3**), in contrast to the crown compounds (**1**) and (**4**), selectively form complexes with specific phenolic substrates which match the size of the cavity and can bind to one or two of the crown units in the interior of the cavity. Whereas β-naphthol as well as naphthalene-1,2-, -1,3-, -1,5-, -1,6-, -2,6-, and -2,7-diols are complexed by (**2**) and (**3**) [but not by (**1**) and (**4**)], similar, but smaller phenolic molecules like phenol itself, pyrocatechol, resorcinol, pyrogallol, phloroglucinol, and benzene-1,2,4-triol, are not bound significantly. The dramatic high-field shifts[4] obtained with the fitting guests are illustrated in Figure 2 and listed in Table 1. Figure 2 also shows that the hosts (**2**) and (**3**) with the same guest naphthalene-2,7-diol lead to different high-field shifts of the guest protons. High-field shifts of a similar order of magnitude had been previously observed, using similar guests, with hosts of different types bearing more lipophilic diphenylmethane walls around the cavity.[2,5]

Remarkably, more acidic guests like benzene tricarboxylic acid, benzene-trithiol, and benzene-tris(methylammonium) do not lead to highfield shifts and did not yield crystalline complexes with the host (**3**).§ We recently observed similar highly selective host/guest behaviour with a host bearing three bipyridine units.[7]

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3 Similar structures, in which the anion lies between two crown ether units and the cation is placed outside the crown ether ring, are only known from crown ether complexes with alkali metal salts, in which the cation possesses a diameter too large and consequently does not fit into the crown ether. This seems comparable with the 4-nitrobenzo[18]crown-6 complex. *Cf.* D. Hlavatá, J. Hašek, and K. Huml, *Acta Crystallogr., Sect. B,* 1978, **34**, 416. See also the dimer CsSCN/[18]crown-6 sandwich type complex, in which the crown ether units are bridged by an anion. *Cf.* M. Dobler and R. P. Phizackerly, *Acta Crystallogr., Sect. B,* 1974, **30**, 2746; 2748.

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§ Measurements of the association constants of (**3**) towards the fluorescing guest 1,8-ANS (1,8-anilinonaphthalene sulphonate)[6] were undertaken using fluorescence spectroscopy. Only weak effects were registrated in MeOD/DCl solution with this guest.