Solid-State Inclusion Compounds of New Host Macrocycles with Uncharged Organic Molecules.[1] Host Synthesis, Inclusion Properties, and X-ray Crystal Structure of an Inclusion Compound with 1-Propanol

Edwin Weber,*[2a] Hans-Peter Josel,[2a] Heinrich Puff,[2b] and Sybille Franken[2b]

Institut für Organische Chemie und Biochemie and Anorganisch-Chemisches Institut der Universität, D-5300 Bonn-1, Federal Republic of Germany

Received October 19, 1984

A series of organic macrocycles composed of a systematically varied combination of ethano, propano, benzeno, pyridino, and analogous groups, mainly ether-linked (see Chart I), are reported, and their abilities to function as solid-state inclusion hosts are studied. It is found that **3–5**, **11–13**, **18b**, and **21** form crystalline inclusion compounds with a number of low-molecular-weight alcohols such as methanol, ethanol, 1- and 2-propanol, 1-butanol, ethylene glycol, and/or with dimethylformamide and acetonitrile as CH-acidic guests. The observed inclusion selectivities and the stoichiometries of the various host–guest compounds are discussed showing that by and large both chemical and steric host–guest fits apply in the formation of the aggregates. The crystal structure of the inclusion compound of the bipyridino host **11** with 1-propanol (1:1) has been determined from single-crystal X-ray diffraction. There are eight host and guest molecules in each unit cell of dimension a = 2665.2 pm, b = 813.8 pm, c = 2667.4 pm, β = 105.61°; space group $C2/c$; R = 0.088 for 2884 unique reflections. The host macrocycle shows a hollow-type conformation with the 1-propanol molecule coordinated via a moderately stable H-bond to one of the bipyridine nitrogens (O···N = 300 pm). The packing diagram characterizes the host–guest topology largely as a channel-like clathrate (actually "tubulato-coordinatoclathrate"). A number of general conclusions that will facilitate the future design of selectively binding hosts for solid-state inclusion are given.

Since the discovery of crown compounds in 1967[3] there have been endless illustrations of their superior complexation properties for cations of either metal[4a] or ammonium type.[4b] Extensive reviews of this work are available.[5,6] In comparison however, crystalline "complexes"[7] of crowns with uncharged molecules have remained almost unexplored until lately.[8] This is surprising because interactions between uncharged organic species play a fundamental role in many biochemical processes.[9] Admittedly the theoretical background involved in this field of molecular aggregation phenomena, mainly called weak molecular interactions, has seen considerable progress.[10] Nevertheless, it is still difficult to suggest an organic host which will bind a specific uncharged guest. Formation of stable host–guest inclusions of neutral components is promoted by the acidity of certain methyl and methylene groups which show coordination to oxygen donors and lead to well-ordered crystalline solids.[8] In addition, there is good evidence for hydrogen bonding of crown ethers to NH-acidic guests in the crystalline state.[11] OH-acidic organic molecules, assumed to be even better proton donors, have long been tested as guest components without substantial success.[12]

Recently we gave a preliminary report of the successful formation of crystalline inclusion compounds of the macrocycle **1** (Chart I) with various alcohols and projected a new inclusion strategy (see Figure 1).[13] Some special features are exhibited by the constitution of **1**: the favorably positioned pyridine ring as a specific acceptor

(1) Previous paper in this series: Weber, E.; Vögtle, F.; Josel, H.-P.; Newkome, G. R.; Puckett, W. E. *Chem. Ber.* **1983**, *116*, 1906.

(2) (a) Institut für Organische Chemie und Biochemie. (b) Anorganisch-Chemisches Institut.

(3) (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495, 7017. (b) Discovery of crown ethers: Pedersen, C. J. In "Synthetic Multidentate Macrocyclic Compounds"; Izatt, R. M., Christensen, J. J., Eds.; Academic Press: New York, 1978.

(4) Recent examples: (a) Blasius, E.; Rausch, R. A.; Andreetti, G. D.; Rebizant, J. *Chem. Ber.* **1984**, *117*, 1113. Merz, A.; Dietl, F.; Tomahogh, R.; Weber, G.; Sheldrick, G. M. *Tetrahedron* **1984**, *40*, 665. Czech, B.; Czech, A.; Kang, S. I.; Bartsch, R. A. *Chem. Lett.* **1984**, 37. Nakatsuji, Y.; Mori, T.; Okahara, M. *Tetrahedron Lett.* **1984**, *25*, 2171. (b) Cram, D. J.; deGrandpre, M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 3286. Davidson, R. B.; Bradshaw, J. S.; Jones, B. A.; Dalley, N. K.; Christensen, J. J.; Izatt, R. M. *J. Org. Chem.* **1984**, *49*, 353. Beadle, J. R.; Gokel, G. W. *Tetrahedron Lett.* **1984**, *25*, 1681.

(5) (a) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8. (b) Lehn, J. M. *Acc. Chem. Res.* **1978**, *11*, 49. (c) Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85. (d) DeJong, F.; Reinhoudt, D. N. In "Advances in Physical Organic Chemistry"; Gold, V., Berthell, D., Eds.; Academic Press: London, 1980; Vol. 17, p 279. (e) Vögtle, F.; Weber, E. In "The Chemistry of Functional Groups"; Patai, S., Ed.; Wiley: New York, 1980; Suppl. E., p 59 ff. (f) Weber, E. *Kontakte (Merck)* **1984**(1), 26, and preceding contributions of this series.

(6) Monographs: (a) "Synthetic Multidentate Macrocyclic Compounds"; Izatt, R. M., Christensen, J. J., Eds.; Academic Press: New York, 1978. (b) "Coordination Chemistry of Macrocyclic Compounds"; Melson, G. A., Ed.; Plenum Press: New York, 1979. (c) "Progress in Macrocyclic Chemistry"; Izatt, R. M., Christensen, J. J., Eds.; Wiley Interscience: New York, 1979 and 1981; Vol. 1 and 2. (d) "Macrocyclic Polyether Syntheses"; Gokel, G. W., Korzeniowski, S. H., Eds.; Springer: Berlin, 1982. (e) "Crown Compounds"; Hiraoka, M., Ed.; Elsevier: Amsterdam, 1982. (f) "Host Guest Complex Chemistry", Part I–III; Vögtle, F., Weber, E., Eds.; Topics in Current Chemistry; Springer: Berlin, 1981, Vol. 98; 1982, Vol. 101; and 1984, Vol. 121.

(7) New proposal for the classification and nomenclature of host–guest-type compounds: Weber, E.; Josel, H.-P. *J. Inclusion Phenom.* **1983**, *1*, 79.

(8) (a) Review: Vögtle, F.; Sieger, H.; Müller, W. M. *Top. Curr. Chem.* **1981**, *89*, 107. (b) van Zon, A.; deJong, F.; Reinhoudt, D. N.; Torny, G. J.; Onwezen, Y. *Recl. J. R. Neth. Chem. Soc.* **1981**, *100*, 453. (c) Elbasyouny, A.; Brügge, H. J.; von Deuten, K.; Dickel, M.; Knöchel, A.; Koch, K. U.; Kopf, J.; Melzer, D.; Rudolph, G. *J. Am. Chem. Soc.* **1983**, *105*, 6568.

(9) (a) "Intermolecular Interactions and Biomolecular Organization"; Hopfinger, A. J., Ed.; Wiley-Interscience: New York, 1977. (b) Bioorganic Chemistry (A Chemical Approach to Enzyme Action)"; Dugas, H., Penney, C., Eds.; Springer: New York, 1981. (c) "Bio-organische Chemie"; Fuhrhop, J. J., Ed.; Thieme: Stuttgart, 1982.

(10) (a) Lehn, J. M. *Struct. Bonding* **1973**, *16*, 1. (b) Cram, D. J. In "Applications of Biochemical Systems in Organic Chemistry" Part II; Jones, J. B., Sih, C. J., Perlman, D., Eds.; Techniques of Chemistry; Wiley: New York, 1976, Vol. X, p 815. (c) Hayward, R. C. *Chem. Soc. Rev.* **1983**, *12*, 285. (d) Diederich, F. *Chem. Unserer Zeit* **1983**, *17*, 105. (e) Cram, D. J.; Cram, J. M. In "Selectivity–a Goal for Synthetic Efficiency"; Bartmann, W., Trost, B. M., Eds.; Workshop Conferences, Hoechst; Verlag Chemie: Weinheim, 1984; Vol. 14, p 43.

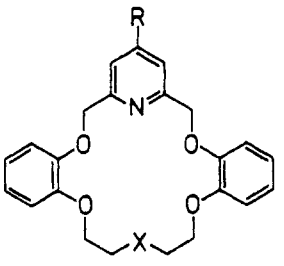
(11) (a) Knöchel, A.; Kopf, J.; Oehler, J.; Rudolph, G. *J. Chem. Soc., Chem. Commun.* **1978**, 595. (b) Vögtle, F.; Müller, W. M. *Chem. Ber.* **1980**, *113*, 2081. (c) Harkema, S.; van Hummel, G. J.; Daasvatn, K.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1981**, 368. (d) Weber, G. *Acta Crystallogr., Sect. B* **1982**, *B38*, 2712; **1983**, *C39*, 896. (e) See also: Colquhoun, H. M.; Lewis, D. F.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1983**, 607.

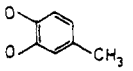
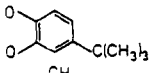
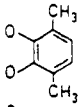
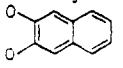
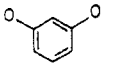
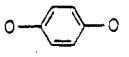
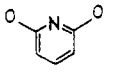
(12) Cf. (a) Vögtle, F.; Müller, W. M.; Weber, E. *Chem. Ber.* **1980**, *113*, 1130. (b) Vögtle, F.; Müller, W. M. *Chem. Ber.* **1981**, *114*, 3179. (c) Grossie, D. A.; Watson, W. H.; Vögtle, F.; Müller, W. M. *Acta Crystallogr., Sect. B.* **1982**, *B38*, 3157. (d) Watson, W. H.; Galloy, J.; Grossie, D. A.; Vögtle, F.; Müller, W. M. *J. Org. Chem.* **1984**, *49*, 347.

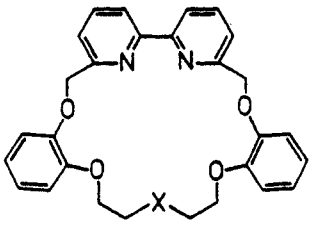
(13) Weber, E.; Vögtle, F. *Angew. Chem.* **1980**, *92*, 1067; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1030.

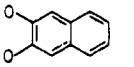
0022-3263/85/1950-3125$01.50/0

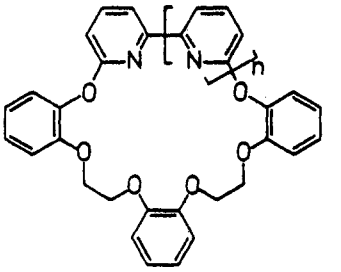
Chart I



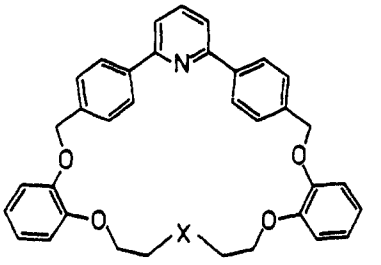
no.	X	R
1		H
2		Cl
3		OCH_3
4		H
5		H
6		H
7		H
8		H
9		H
10		H



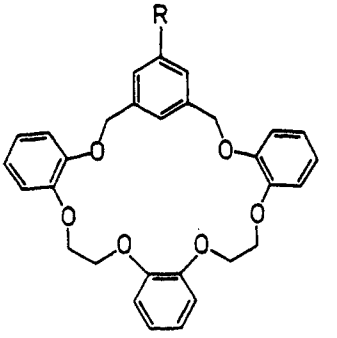
no.	X
11	O
12	
13	



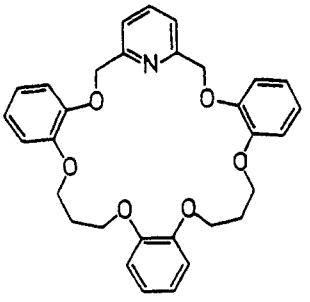
no.	n
14	0
15	1



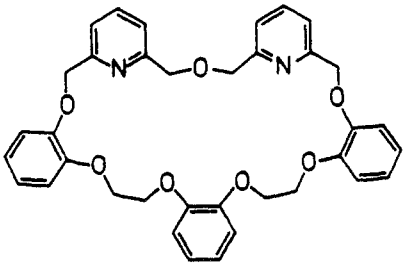
no.	X
16	O
17	



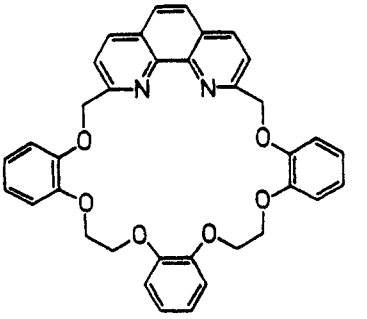
no.	R
18a	H
18b	$C(CH_3)_3$



19



20



21

group for H-bonds and a sort of trigonal symmetry connected with the appended benzene units. Variation of the general building elements of 1, as presented in Figure 1, gave rise to new hosts (e.g., **7**, **12**, **21**) with altered inclusion selectivities.[1] An X-ray crystal structure of **1**·2MeOH was determined,[14] showing the host–guest relation to be of cavitate-type.[7,15] Meanwhile the structure of a 1:1 inclu-

(14) Weber, G.; Jones, P. G. *Acta Crystallogr., Sect. C; Cryst Struct. Commun.* **1983**, *C39*, 1577.

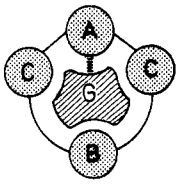
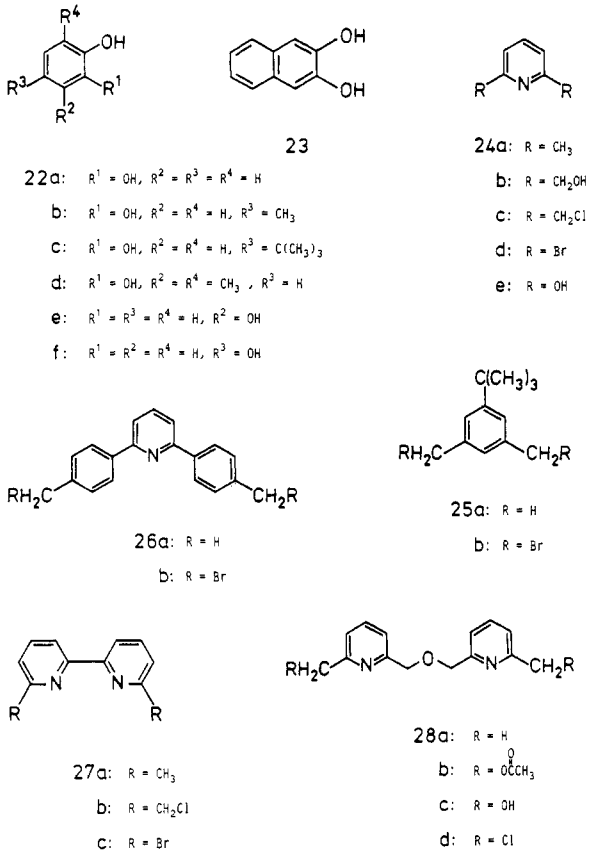


Figure 1. Inclusion strategy and abstracted structure of the new inclusion hosts: (A) H-bond-mediating section of the host skeleton; (B) handle-type section; (C) flanking group; (G) guest inclusion; H-bond interaction represented by a dashed line.

Chart II



sion compound of methanol with a bicyclic host has also been reported.[16]

The present investigations were undertaken in order to get further insight into the factors affecting the selective solid-state inclusion of a hydrogen-bonded (hydroxylic) guest substrate by an organic host. We report the syntheses of the new macrocycles (Chart I, exclusive of **1–3**, **7**, **12**, **14**, **18a**, **21**, whose preparation is described elsewhere[1]) corresponding to Figure 1, discuss their inclusion properties, also in comparison with the known representatives of this host type, and present an X-ray structure of one of the new inclusion compounds (**11**·1-PrOH).

Results and Discussion

Synthesis of the Hosts. The synthetic strategy of the macrocycles studied here is characterized by a stepwise assemblage of ethano, propano, benzeno, pyridino, bipyridino, or analogous building elements (cf. Chart II, **22–28**), respectively, mostly via ether linkage. Use is made of temporary blocking of individual phenolic groups by the benzyl unit.[17] An outline is given in Scheme I showing

(15) Cram, D. J. *Science (Washington, D.C.)* **1983**, *219*, 1177.
(16) Bandy, J. A.; Hughes, D. L.; Truter, M. R. *Acta Crystallogr., Sect. B: Struct. Crystallog. B38*, 2648.

Table I. Crystalline Inclusion Compounds

host no.	guest compd	host:guest mol ratio[a]	thermal dec, °C[c]
3	methanol	2:1	55–65
	ethanol	(≈2:1)[b]	58–66
	2-propanol	(≈5:2)[b]	69–73
	ethylene glycol	1:1	73–86
	acetonitrile	(≈1:1)[b]	60–75
4	methanol	(≈3:2)[b]	>48
	ethanol	2:3	>50
	2-propanol	1:2	>50
5	2-propanol	2:3	>45
11	ethanol	1:1	>56
	1-propanol	1:1	>54
	2-propanol	(≈2:1)[b]	>45
12	ethanol	1:1	>75
	1-propanol	3:2	75–100
	1-butanol	(≈2:1)[b]	76–91
	ethylene glycol	1:1	75–85
	dimethylformamide	3:2	52–60
	acetonitrile	3:2	70–95
13	ethanol	1:2	>66
	1-propanol	1:2	>55
	2-propanol	1:1	>100
18b	acetonitrile	1:1	58–66
21	ethanol	(≈2:1)[b]	90–110
	1-propanol	(≈2:1)[b]	173–181
	dimethylformamide	1:1	85–90

[a] Determined by NMR integration after a dying period of 12 h at 15 torr (room temperature). [b] Unstoichiometric. [c] Value given first is indicative of the onset of opacity, shrinking or edge melting of the crystals.

that the most useful starting component of the various reaction sequences is monobenzyl-blocked catechol **29**.[18] This was reacted either with 2-chloroethanol (**30**), 3-chloro-1-propanol (**31**), or dichloride **40**[3a] to give the phenolic ethers **32–33** and **41** in 48%, 59%, and 68% yields, respectively. The last compound was directly deblocked to the corresponding diphenol **42**. This method for **42** was found superior in the yield to the one-step procedure described earlier[3a,19] (58% vs. 23%). The diphenols **38a–38h** and **39a** were obtained from hydroxy ethers **32** and **33** via tosylation (**34** and **35**) with subsequent reaction with the appropriate dihydroxy compounds **22a–22f**, **23** or **24e**, respectively, to give **36a–36h** or **37a** as intermediates which finally were catalytically hydrogenolyzed (cf. ref 13). Good overall yields (50–60%) within this reaction sequence were achieved except for **38d** (27%), **38e** (37%), and **38h** (21%).

The diphenols **38a–38h**, **39a**, and **42** were the starting materials for the critical ring-closing reactions. Their treatment with the corresponding halogen-containing pyridino, bipyridino, and 1,3-xylyleno components (Chart II) in DMF using Cs_2CO_3 as a base (cf. ref 1) yielded the macrocycles **1**, **4–6**, **8–11**, **13**, **16**, **17**, **18b**, **19**, and **20** in 6.5–70% (see Experimental Section). This procedure proved to be superior to that reported in an earlier paper,[13] where KOH in ethanol is used as the base system, and a three-component high dilution technique applies. For example, the 21-membered macroring **1** was obtained by the present method in 70% yield compared with a 26% yield with KOH.[13] This provides further evidence of the effectiveness of Cs^+ assistance in the synthesis of sterically problematic macrorings.[20] The bipyridino host **15** was synthesized in 13.5% yield from diphenol **38a** with 6,6′-

(17) Cf. Weber, E. *Liebigs Ann. Chem.* **1983**, 770.
(18) Jones, J. H.; Young, G. T. *J. Chem. Soc. C* **1968**, 436.
(19) (a) Weber, E.; Vögtle, F. *Chem. Ber.* **1976**, *109*, 1803. (b) Oepen, G.; Dix, J. P.; Vögtle, F. *Liebigs Ann. Chem.* **1978**, 1592.
(20) (a) Review: Klieser, B.; Rossa, L.; Vögtle, F. *Kontakte (Merck)* **1984**(1), 3. (b) Vriesema, B. K.; Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 110 and references cited therein.

dibromo-2,2′-bipyridine (**27c**)[21] and KOH in refluxing *o*-xylene.[22]

Solid-State Inclusion Properties. Crystalline inclusion compounds of several of the new macrocycles with a variety of OH- and CH-acidic uncharged molecules could be isolated. A list of the various examples with their characterization is given in Table I.

Unbranched alcohols of low molecular weight seem to be favored in guest inclusion by a large majority of the hosts. Moreover, a few inclusion compounds with acetonitrile and/or dimethylformamide (DMF) as CH-acidic solvents are also formed, e.g., by hosts **3**, **12**, and **21**. Host **18b** is an exception: it allows the isolation of an inclusion compound only with acetonitrile. This specific behavior of **18b** clearly demonstrates the role of the endocyclic pyridino N in the successful inclusion of alcohols (cf. ref 1). A promoting effect of the *tert*-butyl substituent may be operating in **18b**, since for the present macrocycle **18a** no inclusion compound whatever could be isolated.[1] Discrepancies in the guest inclusion properties with the series of pyridino hosts in general are due to the nature of the building blocks (cf. e.g., **3**, **4**, and **5** among one another and with **8**, **9**, or **19**, respectively). Thus, the presence of an additional pyridino unit in the macroring (see, **10**–**13**, **15**, **20**) does not necessarily mean an improvement in the lattice uptake of hydroxylic guests (cf. **10**, **15**, and **20**), just because of the extended possibilities of induci· g mutual H-bonds.

Some more detailed points crystallize from a comparison of the various hosts. Methoxy-substituted host **3** behaves largely like the unsubstituted macrocycle **1**,[13] whereas chloro-substituted **2** proved ineffective in guest inclusion.[1] Host **5** in one respect (prefered inclusion of 2-propanol, though with altered stoichiometry) resembles **7**; host **4** exhibits an inclusion behavior roughly intermediate between the parent macrocycle **1**[13] and **7**.[1] Either a 3- or a 6-positioned methyl group at the benzeno unit under discussion (cf. **6**) paralyzes the inclusion activity. The same breakdown occurs when the 1,2-disubstituted phenylene ring of **1** under consideration is exchanged for a 1,3- or 1,4-disubstituted phenylene subunit. This handicap remains uncompensated even when a 2,6-disubstituted pyridino ring (cf. **10**) is introduced into the specified position. While a ring extension of the **16**-, **17**-, or **19**-fashion starting, e.g., from **1** results in a loss of the inclusion activity, the insertion of an additional pyridine nucleus, as verified in the 2,2′-bipyridines **11**–**13**, is promoting (for **12**, see ref 1). Nevertheless, the presence of benzylic C positions is also required in the favorable bipyridine case, since neither **14**[1] nor **15** shows host properties. In contrast to **12**, macrocycle **20**, having the pyridino moieties separated by an additional oxybismethylene unit, also fails to form an appropriate inclusion compound. The phenanthrolino macrocycle **21**,[1] however, which coincides in the ring size as well as in the nature and position of the heteroatoms with **12** (except for the native coplanarity of the heterocyclic N atoms in **21**) logically exhibits a similar inclusion behavior, though different stoichiometries are found in the two instances.

In most of the other cases the steric relationship and the fit between the host and the guest is more obvious from the inclusion stoichiometries (Table I), in outline at least. For instance, **1**[13] as well as **3** forms a stable 2:1-stoichiometric inclusion compound with methanol, whereas **5** which is substituted by a voluminous *tert*-butyl group, is unable to retain methanol in its crystal lattice. The last like the naphthalino analogue **7**,[1] however, binds 2-propanol. Correspondingly, the methyl-substituted host **4** has complexing behavior intermediate between **1** and **5** (3:2 stoichiometry in its inclusion compound with methanol). The stoichiometries of the ethanol inclusions with **1**,[13] **12**,[1] and **13** are 2:1, 1:1, and 1:2, respectively, and are in accordance with the extended ring size and steric bulk of the hosts; **11** combines with one stoichiometric equivalent of 1-propanol, the more spacious **13** with two, etc.

The strict 1:1 stoichiometry in the inclusion compounds of **3** and **12** with ethylene glycol is presumably a consequence of the bivalency of the guest component.[23]

As a matter of course, insight into the specific host conformations in the crystalline state allows a more detailed consolidation of the inclusion properties under discussion. For that purpose, some X-ray analyses of analogous host–guest systems have been carried out in former studies.[14,24] The inclusion compound of **11** with 1-propanol was chosen as the structural probe since our knowledge of the characteristic 2,2′-bipyridinyl building block within this general type of macrocyclic hosts is only poor.

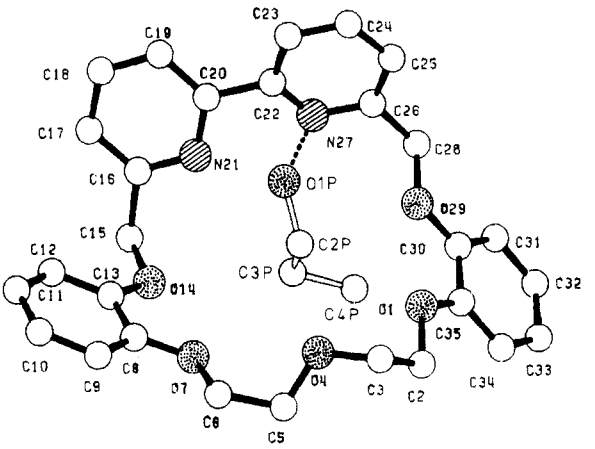


Figure 2. Molecular structure of 11·1-PrOH: top view giving indication of the numbering scheme for the atoms (H atoms have been omitted; solid and dashed lines represent covalent and hydrogen bonds, respectively).

X-ray Analysis: Structure Description of 11·1-PrOH (1:1). Atomic coordinates, thermal parameters, bond distances, bond angles, and torsion angles are collected in Tables II–VII (supplementary material). A view of the structure is presented in Figure 2; stereodrawings (top and side view) and a space-filling stereoscopic diagram of the host–guest unit in the supplementary material (Figures 4–6, respectively). The packing of the crystal is shown in Figure 3.

Bond lengths (Table V) and bond angles (Table VI) of the host structure generally conform to the values expected from previous studies of bipyridines[25] and crown compounds/coronates.[5e,26] Average lengths for various bond

(21) Parks, J. E.; Wagner, E. B.; Holm, R. H. *J. Organomet. Chem.* **1973**, *56*, 53.

(22) Cf. Newkome, G. R.; Nayak, A.; McClure, G. L.; Danesh-Khoshboo, F.; Broussard-Simpson, J. *J. Org. Chem.* **1977**, *42*, 1500; see also ref 1.

(23) For a similar situation on the coordinatoclathrate sector, see: Weber, E.; Csöregh, I.; Stensland, B.; Czugler, M. *J. Am. Chem. Soc.* **1984**, *106*, 3297.

(24) Weber, G. *Acta Crystallogr., Sect. C: Crystal. Struct. Commun.* **1984**, *C 40*, 592.

(25) E.g.: (a) Newkome, G. R.; Pappalardo, S.; Gupta, V. K.; Fronczek, F. R. *J. Org. Chem.* **1983**, *48*, 4848. (b) Newkome, G. R.; Gupta, V. K.; Fronczek, F. R. *Inorg. Chem.* **1983**, *22*, 171.

(26) Reviews: (a) Hilgenfeld, R.; Saenger, W. *Top. Curr. Chem.* **1982**, *101*, 1. (b) Dalley, N. D. In ref 6a; p 207. (c) Dale, J. *Isr. J. Chem.* **1980**, *20*, 3.

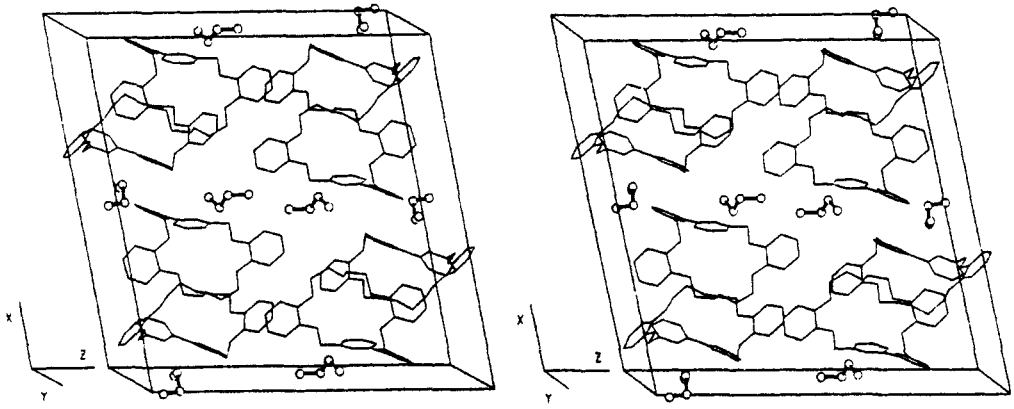


Figure 3. Stereoview of the unit cell packing of 11·1-PrOH (the host molecule is represented as a line drawing, the guest in ball and stick fashion).

type are 138.3 pm for pyridinylene C–C, 134.0 pm for pyridinylene C–N, 138.5 pm for phenylene C–C, 150.6 pm for C(sp^2)–C(sp^3), 147.4 pm for C(sp^3–sp^3), 136.3 pm for C(sp^2)–O, and 145.4 pm for C(sp^3)–O; central bipyridine bond 148.6 pm. The remarkably short aliphatic C–C distances are due to a "macrocyclic C–C shortening effect"[27] and the average C–O–C angle is 117.1°. The 1-propanol molecules are subject to a partial structural disorder.[23,28]

The conformations of individual molecules are as depicted in Figure 2. A characterization is given by the torsion angles: 1-propanol shows *ac* torsion [O(1P)–C(2P)–C(3P)–C(4P), 112.0°]. The endocyclic torsion angles of the host (Table VII) coincide with the usual anti for C–X–C–C (X = O, N), ±gauche for O–C–C–O, and syn for 1,2-disubstituted benzene[26] except for C(2)–C(3)–O(4)–C(5) and C(13)–O(14)–C(15)–C(16), which are gauche (88.0, −75.1°, respectively) instead of anti. The bipyridine moiety possesses the syn conformation with the N(21)–C(20)–C(22)–N(27) torsion angle 25.6°, and hence is in contrast to other bipyridino-containing macrocycles.[25a] Nevertheless, in the considerably nonsymmetric conformation of the host molecule the five oxygen atoms are nearly coplanar [maximum deviation out of the compensating plane, O(1) = −39.9 pm]. A further remarkable feature of the host appearance arises from the appended aromatic/heteroaromatic units: the two pyridine rings are bent out of the best plane defined by the oxygen atoms by angles of approximately 64° and 91°. One of the phenylene rings is positioned above, the other is turned beneath the aforesaid plane (Figure 2), thus giving the whole molecule the shape of an irregular hollow. In this particular conformation one of the basic sites of the bipyridine grouping [N(27)] seems well-designed for the successful approach of a proton-donating 1-propanol molecule to form a hydrogen bond. However, the bonding distances [O(1P)···N(27) = 3.00 Å, H atom not localized] specifies this interaction as rather weak (cf. ref 14 and 16). On the whole, the host–guest aggregate exhibits the character of a lattice void inclusion (clathrate type[29]) rather than a molecular inclusion (cavitate type[15]).[7]

Packing in the crystal (Figure 3) is such that the angular host units in pairs gear together to form a layered aggregate. Thereby channel-type cavities are generated which run through the crystal near the *z* direction and contain the weakly coordinated guest molecules. A further essential feature of the packing mode is seen in the stacking of the uncoordinated pyridine rings, which helps to propagate the building blocks through the crystal. Following a recently developed classification and nomenclature system for any host–guest relationship,[7] the present situation should appropriately be termed as "tubulato-coordinatoclathrate".

Conclusions

The following general conclusions can be drawn from the results of this work and with regard to the former findings.[1,12a,13] (1) The ring size of the host seems to determine decisively whether a guest molecule is included at all. (2) The host macrorings favoring neutral molecule inclusion have 21 and 24 members. (3) Ethano and 1,2-benzeno building blocks are established as the favorable bridging units. (4) Although a rather high degree of conformational rigidity of the host skeleton is required, a hollow-type molecular conformation ought to be formed in the crystalline state (cf. also the "dentist chair" structures of **3**[14] and of its lower phenylene homologue[24] in their inclusion compounds with alcohols). (5) Similarly the lateral catechol moieties, combined with the benzylic positions flanking the central aromatic/heteroaromatic subunit (2,6-pyridino, 6,6′-bipyridino, 2,9-phenanthrolino, 1,3-benzeno), prove to be an essential feature of the host structures. (6) The presence of an intraannular N atom is seen as a prerequisite for the binding of alcohols. (7) The introduction of substituents on the parent host is a critical point, since the consequences are difficult to estimate: the ring conformation as well as the whole lattice structure may be affected. (8) Notwithstanding this, the bulk of the group at position B of the macroring (cf. Figure 1) was found a suitable instrument for interfering with the stereocontrol of the guest inclusion.

We are now in a position to interpret the inclusion properties of the various macrocycles more precisely. With this mental equipment the design of highly selective hosts at will seems near at hand. Certainly, structural variations of position C of Figure 1 are a promising object for the future.

Experimental Section

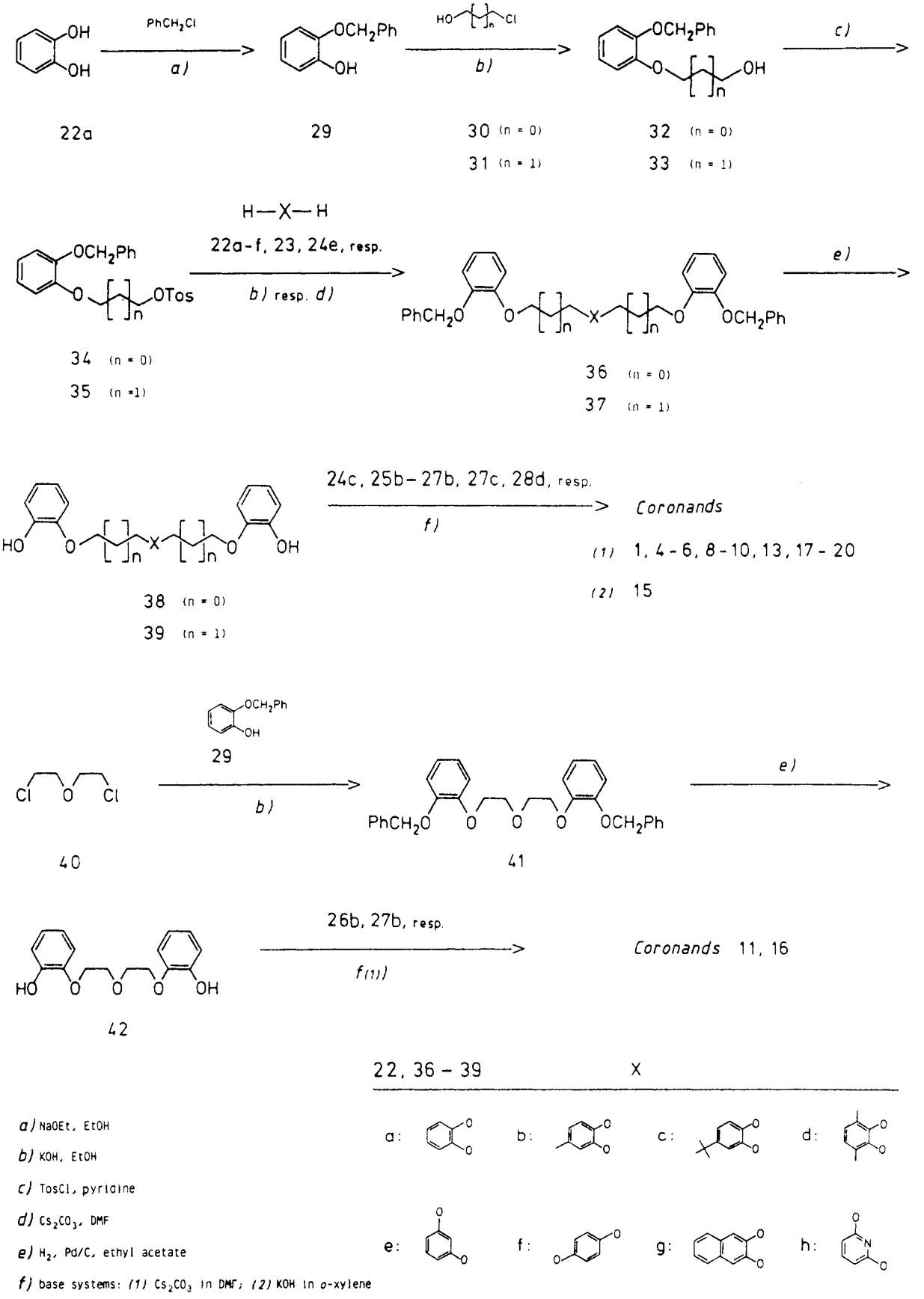
(1) General Methods. All temperatures are uncorrected. Melting points were obtained on a Kofler apparatus (Reichert, Wien). The ^1H NMR spectra were taken on a Varian EM-360 (60 MHz) or a Bruker WH-90 (90 MHz) spectrometer in $CDCl_3$;

(27) (a) Shoham, G.; Lipscomb, W. N.; Olsher, U. *J. Chem. Soc., Chem. Commun.* **1983**, 208. (b) Hartman, J. A. R.; Wolf, R. E.; Foxman, B. M.; Cooper, S. R. *J. Am. Chem. Soc.* **1983**, *105*, 131 and references cited therein.

(28) Gavezzotti, A.; Simonetta, M. *Chem. Rev.* **1982**, *82*, 1.

(29) Recent and most comprehensive presentation of the clathrate inclusion topic: "Inclusion Compounds"; Atwood, J. L., Davies, J. E. D., MacNicol, D. D.; Eds.; Academic Press: New York, 1984; Vol. I–III.

Scheme I



δ values in ppm, Me_4Si as internal reference; s, singlet; t, triplet; qu, quintet; m, multiplet (c, centered) and br, broad; J in hertz. Mass spectra were recorded on a A.E.I. MS-50 mass spectrometer. For column chromatography Al_2O_3 (Woelm, basic, grade I or Brockmann, grade II–III; Woelm, Eschwege, West Germany) and silica gel (0.063–0.1 mm; Merck, West Germany) were used. Satisfactory elemental analytical data (±0.3% for C, H, and N) were obtained for all new compounds.

(2) Materials. All solvents were of reagent quality (Baker) or purified by distillation before use. Starting compounds **22a**–

22c, 22e, 22f, 23, 24a, 24d, 24e, 25a, 26a, 30, and **31** were purchased from Janssen (Nettetal-2, West Germany) and *N*-bromosuccinimide (NBS) from Riedel-de Haën (Seelze, Hannover, West Germany). A 10% Pd/C catalyst of type E10N (Degussa, West Germany) was used in catalytic hydrogenations.

(3) Synthesis of the Halogen-Containing Cyclization Components (Chart II). 2,6-Bis(chloromethyl)pyridine (24c) was prepared from **24b** and $SOCl_2$ following the literature procedure.[30]

5-*tert*-Butyl-1,3-bis(bromomethyl)benzene (25b). A stirred mixture of 5-*tert*-butyl-1,3-xylene (**25a**) (16.2 g, 100 mmol), of NBS (40.2 g, 226 mmol) and of azobis(isobutyronitrile) (AIBN, 100 mg) in 200 mL of methyl formate was irradiated with a 200-W bulb for 3 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in 200 mL of CH_2Cl_2. The extract was washed twice with an aqueous solution of $NaHCO_3$ and then with water (100 mL each time), dried (Na_2SO_4), and evaporated in vacuo. Purification of the solid residue by recrystallization from hexane gave 18.0 g (56%) of colorless needles; mp 112–114 °C (lit.[31] mp 110–112 °C).

2,6-Bis[4-(bromomethyl)phenyl]pyridine (26b). A mixture of 2,6-di-*p*-tolylpyridine (**26a**) (10.0 g, 38.5 mmol), NBS (15.0 g, 84.3 mmol), and AIBN (100 mg) in 100 mL of dry CH_2Cl_2 was reacted under conditions (200 W, 5 h) analogous to those described for **25b**. The same workup of the reaction mixture (evaporated half to its volume) applies. Recrystallization from CH_2Cl_2/EtOH gave 5.20 g (32%) of colorless crystals: mp 150–153 °C; ^1H NMR δ 4.60 (s, benzyl H), 7.20–8.33 (m, 11 H, Ar H, py H); MS 417 (*m/e* value, M^+).

6,6′-Bis(chloromethyl)-2,2′-bipyridine (27b) was obtained from **27a** and prepared as described.[32] **6,6′-Dibromo-2,2′-bipyridine (27c).** To a stirred solution of 2,6-dibromopyridine (**24d**) (2.32 g, 10 mmol) in 250 mL of dry Et_2O was dropped at −78 °C and under an atmosphere of N_2 7.0 mL of a 1.6 N solution of *n*-BuLi in *n*-hexane. Stirring was continued for 2 h at the same temperature. Then anhydrous $CuCl_2$ (2.0 g, 14.9 mmol) was added and a steam of dried O_2 was bubbled through the solution, until its color turned from brown to green and the precipitation of the product occurred. The mixture was hydrolyzed by cautiously adding 200 mL of 2 N HCl. The precipitate was collected by suction filtration and thoroughly washed with water. Subsequent recrystallization from THF yielded 1.70 g (54%) of colorless crystals: mp 218–220 °C [lit.[21] mp 221–223 °C (from benzene)].

Bis[[6-(hydroxymethyl)-2-pyridyl]methyl] ether (28c) was prepared from 2,6-lutidine (**24a**) following the literature procedures,[30,33,34] except for some minor modifications: bis[(6-methyl-2-pyridyl)methyl] ether (**28a**) was advantageously recrystallized from methylcyclohexane rather than from cyclohexane/pentane.[34] Bis[[6-(acetoxymethyl)-2-pyridyl]methyl] ether (**28b**) was prepurified by flash chromatography[35] on SiO_2 (elution with EtOAc). For the continuous extraction of **28c**, CH_2Cl_2 was used instead of $CHCl_3$[34] and the overall yield (8 steps) was 2%.

Bis[[6-(chloromethyl)-2-pyridyl]methyl] Ether (28d). To an ice-cooled and stirred mixture of **28c** (7.50 g, 28.5 mmol) and of pyridine (4.5 mL, 57 mmol) was slowly dropped $SOCl_2$ (9.0 mL, 120 mmol). Stirring was continued for 2 h at 60 °C. The excess of $SOCl_2$ was removed by vacuum distillation. Water was added to the residue, and the mixture was neutralized with Na_2CO_3. The product was extracted with ether, isolated by evaporation of the solvent, and used without further purification (pure by NMR): yield 3.75 g (44%); ^1H NMR δ 4.70 (s, 4 benzyl H), 4.83 (s, 4 benzyl H), 7.30–8.00 (m, 6 py H).

(4) Synthesis of the Phenolic Cyclization Components (Scheme I). 3,6-Dimethylcatechol (22d). This compound was prepared from catechol (**22a**) by applying the procedures of Cadwell and Thompson,[36] Fields and Reynolds,[37] and Sinhababu and Borchardt[38] in order. The product was obtained (overall yield 31%) without prior isolation of the corresponding diacetate (method A in ref 38): colorless crystals; mp 100–101 °C (lit.[38] mp 99–101 °C).

2-(Benzyloxy)phenol (29) was synthesized according to the literature procedure.[18]

2-[[2-(Benzyloxy)phenyl]oxy]ethanol (32) and 3-[[2-(Benzyloxy)phenyl]oxy]propanol (33). KOH (14.0 g, 250 mmol) in 250 mL of boiling EtOH is stirred for 30 min under an atmosphere of N_2 with 2-(benzyloxy)phenol (**29**) (50.0 g, 250 mmol). The temperature is maintained and 2-chloroethanol (**30**) (20.1 g, 250 mmol) or 3-chloro-1-propanol (**31**) (23.6 g, 250 mmol), respectively, is added dropwise. After 6 h under reflux the mixture is filtered and the solvent is removed under reduced pressure. The resulting residue is dissolved in CH_2Cl_2, washed with 0.2 N NaOH and then with water, and dried (Na_2SO_4). Distillation gave **32** and **33**, respectively, as colorless oils [**32**: bp 166–168 °C (0.5 torr); **33**: bp 175–178 °C (0.5 torr)] which solidified on standing. They were recrystallized from *n*-heptane.

32: yield 29.3 g (48%) of colorless crystals; mp 40–41 °C; ^1H NMR δ 2.98–3.20 (s, br, 1 H, OH), 3.65–4.13 (m, 4 H, OCH_2), 5.02 (s, 2 benzyl H), 6.83 (s, 4 H, phenylene), 7.29 (mc, 5 H, phenyl); MS 244 (*m/e* value M^+).

33: Yield 37.8 g (59%) of colorless crystals; mp 46–48 °C; ^1H NMR δ 2.02 (qu, J = 6, 2 H, $CH_2CH_2CH_2$), 2.72 (s, br, 1 H, OH), 3.60–4.30 (m, 4 H, OCH_2), 5.04 (s, 2 benzyl H), 6.88 (mc, 4 H, phenylene), 7.33 (mc, 5 H, phenyl); MS 258 (*m/e* value, M^+).

2-[[2-(Benzyloxy)phenyl]oxy]ethanol *p*-Toluenesulfonate (34) and 3-[[2-(Benzyloxy)phenyl]oxy]propanol *p*-Toluenesulfonate (35). The corresponding hydroxy compounds **32** and **33** were tosylated under the usual conditions with *p*-toluenesulfonyl chloride. The pure products were obtained by recrystallization from *n*-heptane. Compound **35** was previously chromatographed on a SiO_2 column (elution with $CHCl_3$).

34: yield 84% of colorless crystals; mp 44–46 °C (from *n*-heptane; ^1H NMR δ 2.30 (s, 3 H, CH_3), 3.97–4.40 (m, 4 H, OCH_2), 4.98 (s, 2 benzyl H), 6.65–7.82 (m, 13 Ar H); MS 398 (*m/e* value, M^+).

35: yield 63% of colorless crystals; mp 47–49 °C (from *n*-heptane): ^1H NMR δ 2.09 (qu, J = 6, 2 H, $CH_2CH_2CH_2$), 2.32 (s, 3 H, CH_3), 3.94 (t, J = 6, 2 H, CH_2OAr), 4.21 (t, J = 6, 2 H, CH_2OTos), 4.95 (s, 2 benzyl H), 6.70–7.80 (m, 13 Ar H); MS 412 (*m/e* value, M^+).

1,5-Dichloro-3-oxapentane (40) was prepared in the usual way.[3a]

General Procedure for the Synthesis of the Benzyl-Blocked Diphenols 36a–36g, 37a, and 41. To a stirred solution of KOH (2.80 g, 50 mmol) in 250 mL of EtOH was added under N_2 25 mmol of the corresponding diphenol (see Table VIII); in case of **41** a solution of 2-(benzyloxy)phenol (**29**) (10.0 g, 50 mmol) in 50 mL of EtOH was added. The resulting suspension was heated to reflux, and 50 mmol of the tosylate **34** (18.9 g) or **35** (20.6 g), respectively, in the case of **41** a solution of dichloride **40** (3.85 g, 25 mmol) in 10 mL of EtOH, was added in portions. After being boiled for 6 h, the mixture was filtered while hot. The solution was evaporated under reduced pressure, and the resulting residue was extracted with CH_2Cl_2. The extract was washed with 0.2 N NaOH and then with water and dried over Na_2SO_4. Evaporation under reduced pressure left the crude compounds either as solid residues or viscous oils which were purified by column chromatography (SiO_2, elution with $CHCl_3$) and recrystallization. Details and data for the individual compounds are collected in Table VIII.

(30) Baker, W.; Buggle, K. M.; McOmie, J. F. W.; Watkins, D. A. M. *J. Chem. Soc.* **1958**, 3594.
(31) Moore, S. S.; Tarnowski, L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398.
(32) Newkome, G. R.; Puckett, W. E.; Kiefer, G. E.; Gupta, V. K.; Xia, Y.; Kohli, D. K.; Baker, G. R.; Coreil, M.; Hackney, M. A. *J. Org. Chem.* **1982**, *47*, 4116.
(33) Boekelheide, V.; Linn, W. J. *J. Am. Chem. Soc.* **1954**, *76*, 1286.
(34) Newcomb, M.; Timko, J. M.; Walba, D. M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6392.
(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(36) Caldwell, W. T.; Thompson, T. R. *J. Am. Chem. Soc.* **1939**, *61*, 765, 2354.
(37) Fields, D. L.; Miller, J. B.; Reynolds, D. D. *J. Org. Chem.* **1964**, *29*, 2640.
(38) Sinhababu, A. K.; Borchardt, R. T. *Synth. Commun.* **1982**, *12*, 983.
(39) Cf. Stott, P. E.; McCausland, C. W.; Parish, W. W. *J. Heterocycl. Chem.* **1979**, *16*, 453. A possible explanation for the occurence of different crystal phases refers to a preformed inclusion compound with the used solvent. Without being in contact with the mother liquor it could be unstable, but retain the former lattice build-up. Other solvents for recrystallization (e.g., *n*-heptane) led to the formation of a glass.

Synthesis of 2,2′-[2,6-Pyridinediylbis(oxy-2,1-ethanediyloxy)]diphenyl Dibenzyl Ether (36h). To a stirred solution of 2,6-dihydroxypyridine (**24e**) (3.60 g, 25 mmol) in 300 mL of MeOH under an atmosphere of N_2 was added Cs_2CO_3 (12.2 g, 37.5 mmol). When the evolution of gaseous CO_2 had ceased, the solvent was evaporated under reduced pressure. Traces of water in the remaining solid were removed by drying in vacuo (0.5 torr). Then 100 mL of dry DMF, followed by a solution of tosylate **34** (19.9 g, 50 mmol) in 150 mL of dry DMF were added to the residue. After having stirred at 65 °C for 12 h, the mixture was freed from the solvent by evaporation under reduced pressure and the residue partitioned between CH_2Cl_2 and water. The organic layer was separated, washed twice with 0.2 N NaOH and then with water, and dried (Na_2SO_4). The compound was purified by column chromatography (Al_2O_3), eluted with $CHCl_3$, and subsequently recrystallized from EtOH. Yield and characterization data in Table VIII.

Catalytic Hydrogenation to the Diphenols 38a–38h, 39a, and 42. General Procedure. A suspension of 25 mmol of the corresponding dibenzyl ether (see Table VIII) and of 10% Pd/C (1.5–2.0 g) in 50–100 mL of EtOAc was hydrogenated in a Parr apparatus at 3 atm H_2 and at 25 °C for 4 h. The filtrate after evaporation solidified and was recrystallized. Data for each compound are given in Table IX.

(5) Cyclization Reactions. (a) Synthesis of the Pyridino, Bipyridino, and 1,3-Xyleno Macrocycles 1, 4–6, 8–11, 13, 16, 17, 18b, 19, and 20 (Cs_2CO_3-Assisted Ring Formation. General Procedure.). The respective diphenol (10 mmol) and 10 mmol of the corresponding dihalide (see Table X) in separate 250-mL portions of dry DMF were simultaneously added over a period of 8 h and under N_2 to a vigorously stirred suspension of Cs_2CO_3 (3.26 g, 10 mmol) in 1 L of dry DMF at 65–70 °C. Stirring was continued for 5 h at the same temperature. The solvent was removed under reduced pressure. Traces of DMF were removed by coevaporation with three 100-mL portions of water, followed by coevaporation with EtOH. The residue was extracted with CH_2Cl_2 and filtered from the salt. Purification by column chromatography: **1**, **5**, and **9** on Al_2O_3, elution with $CHCl_3$; **4** and **19** on Al_2O_3, elution with hexane/acetone (4:1) and $CHCl_3$/*n*-heptane (3:2), respectively; **6**, **8**, **10**, **11**, **13**, **16**, **17**, **18b**, and **20** on SiO_2, elution with CH_2Cl_2. Subsequently, the compounds were recrystallized. Details and data for the individual compounds are collected in Table X.

(b) Synthesis of Bipyridino Macrocycle (15). To a stirred suspension of powdered KOH (1.12 g, 20 mmol) in 50 mL of *o*-xylene under an atmosphere of N_2 was added a solution of diphenol **38a** (3.82 g, 10 mmol) in 75 mL of gently warmed *o*-xylene. After having stirred for 15 min, a solution of **27c** (3.14 g, 10 mmol) in 200 mL of *o*-xylene was dropped in, and the mixture was heated to reflux for 24 h. The solvent was removed under reduced pressure, and the residue was extracted with boiling CH_2Cl_2. The extract was chromatographed on an Al_2O_3 column (elution with CH_2Cl_2) and recrystallized from EtOH. Yield and characterization in Table X.

(6) Preparation of the Crystalline Inclusion Compounds. General Procedure. The corresponding host compound was dissolved under heating in a minimum amount of the respective guest solvent. If necessary for dissolution, toluene or acetonitrile are used as cosolvents. The solution was placed into a heated water bath to prevent it from rapid cooling and to ensure slow crystallization of the adduct. In some cases the addition of a small amount of hexane is needed to initiate the crystallization. After storage for 12 h at 4 °C, the crystals which formed were collected by suction filtration and dried. Specific details and data for each compound are given in Table I.

(7) Crystallography. (a) Sample Preparation and Data Collection. Single crystals of **11**·1-PrOH were obtained from a solution of **11** in 1-PrOH as described above. Intensity data were collected at 293 K on a four-circle diffractometer CAD 4 (Enraf Nonius) using graphite-crystal monochromatized Mo K_α radiation.

Crystal Data for **11**·1-PrOH: $C_{28}H_{26}N_2O_5 \cdot C_3H_8O$; M_r = 530.5; monoclinic space group $C2/c$ (No. 15); Z = 8; a = 2665.2 (6) pm, b = 813.8 (4) pm, c = 2667.4 (6) pm; β = 105.61 (3)°; V = 5.785 nm^3, d = 1.21 g·cm^{-3}, μ = 0.52 cm^{-1}.

(b) Structure Determination and Refinement. All calculations were made on a IBM 3081K computer of the "Regionales Hochschulrechenzentrum der Universität Bonn". The structure was solved by direct methods (MULTAN80[40]); final R = 0.088 for 2884 unique reflexions [$\theta < 23°$, $F > 3\sigma(F)$], using unit weights. H atoms of the host molecule—but not for the guest—could be localized in a difference Fourier map. Large temperature factors and unacceptable bond distances and angles were found for the atoms of the guest, so that a disorder was assumed. The refinement (339 parameters) was carried out with blocked-matrix least-squares methods (SHELX76[41]). Anisotropic temperature factors were applied for the C, N, and O atoms of the host molecule. H atoms were included with constraints (C–H, 108.0 pm) and a common temperature factor for each block. For the guest molecule the positional parameters were refined with two fixed distances, C(2P)–C(3P), C(3P)–C(4P), and one fixed angle, C(2P)–C(3P)–C(4P), using individual isotropic temperature factors. Final atomic coordinates, thermal parameters, and bonding dimensions are summarized in the Tables II–VII (supplementary material).

Acknowledgment. We are indebted to Prof. G. R. Newkome (Lousiana State University, Baton Rouge, LA) for gratefully supplying us with 6,6′-bis(chloromethyl)-2,2′-bipyridine as one of the vital starting materials for this study. The technical assistance of Mrs. E. Kloppe and Mrs. G. Dittmann (both University of Bonn) is appreciated. We also thank Prof. F. Vögtle (University of Bonn) for his support to this project. Prof. R. M. Izatt (Brigham Young University, Provo, UT), Prof. W. H. Watson (Texas Christian University, Fort Worth, TX), and Dr. M. Czugler (Central Research Institute for Chemistry, Budapest, Hungary) are acknowledged for helpful discussions.

Supplementary Material Available: Lists of positional parameters and anisotropic temperature factors of the non-hydrogen atoms (Tables II and III), positional parameters and isotropic temperature factors for the hydrogen atoms (Table IV), bond lengths and bond angles involving non-hydrogen atoms (Table V and Table VI), endocyclic torsion angles for the host macrocycle (Table VII), figures with different stereoscopic representations of the host–guest unit (Figures 4–6), and physical data for the benzyl-blocked diphenols **36a–h**, **37a**, **41**, the diphenols **38a–h**, **39a**, **42**, and macrocycles **1**, **4–6**, **8–11**, **13**, **15–17**, **18b**, **19**, and **20** (Tables VIII, IX, and X) (12 pages). Ordering information is given on any current masthead page. A listing of observed and calculated structure factors is available directly from the author.

(40) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declerq, J. P.; Woolfson, M. M. "MULTAN 80: A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data"; York, 1980.

(41) Sheldrick, G. M. "SHELX 76: A Program for Crystal Structure Determination"; Cambridge, 1976.