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Macropolycyclic Polyethers (Cages) and Related Compounds

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Contents

1. Introduction

Since Pedersen reported the synthesis and cation-complexing characteristics of the crown ethers (macromonocyclic polyethers),[1] there has been increasing interest in these compounds as complexing agents for various inorganic and organic cations.[2] Many different modifications of the crown ethers, such as changing the ring size, kind of substituents, and the types of donor atoms, have been made to enhance their complexation properties.[2–4] In order to have molecules with complexing properties superior to those of the crown ethers, the cryptands (macrobicyclic polyethers)[3–8] and other preorganized supramolecules[4,9–11] have been synthesized.

Since the first spherical macrotricyclic polyethers were reported by Lehn and co-workers,[6,12,13] hundreds of macropolycyclic polyethers with unusual shapes have been prepared and their properties have been studied.[9–11,14–17] The macropolycyclic (cage) compounds covered in this review will include macrotri(and higher)cyclic compounds but not the cryptands, which are macrobicyclic polyethers. Synthetic macropolycyclic polyethers containing intramolecular cavities and clefts of the appropriate size and shape are particularly interesting complexing reagents with regard to molecular recognition. They can form inclusion complexes in which the substrate is contained inside the molecular cage.[10] They can possess numerous branches, bridges, and connections that allow the construction of a given architecture endowed with desirable dynamic features. They can allow the arrangement of structural groups, binding sites, and reactive functions. Their structural features, controlled by chemical synthesis, determine the stability and the properties of their complexes with inorganic and organic ions, and/or neutral molecules.

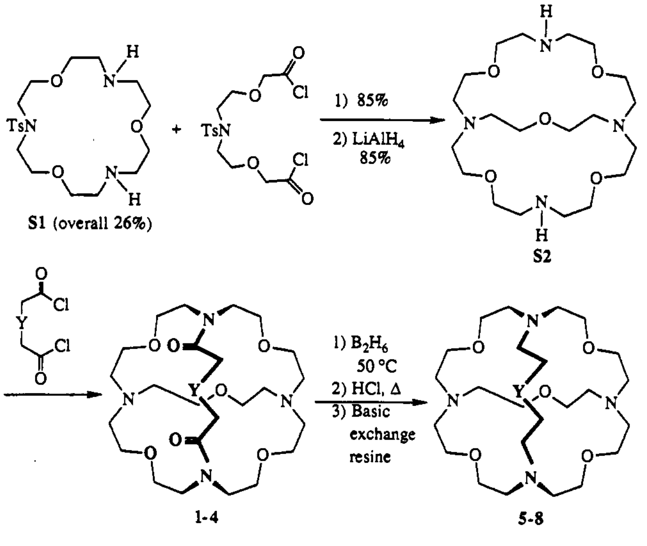
Owing to their architectural and functional plasticity, macropolycyclic systems are especially attractive for designing both biomimetic and abiotic receptor molecules for inorganic and organic substrates.[18] Spherical macrotricyclic polyethers possessing a tetrahedral recognition site selectively form complexes with the ammonium cation.[19] Some cylindrical macrotricyclic polyethers selectively form inclusion complexes with bis primary alkylammonium salts,[20–23] while cavitands[24–28] and carcerands[28–30] form stable inclusion complexes with neutral organic molecules.

This review covers the syntheses of the macrotri(and higher)cyclic (cage) crown ethers including polyethers, cryptophanes, cavitands, carcerands, quaternary ammonium salts, and azaparacyclophanes up to the beginning of 1991. A listing of these cage compounds and a brief report on some of their properties are also included. We have included the crown-capped porphyrins, but face-to-face dimers and trimers containing only porphyrin units are not included even though they are cage compounds. Cyclodextrins and macropolycyclic compounds without donor atoms are not part of this review.

2. Spherical Macrotricyclic Polyethers

Chemists have long desired to construct preorganized polyethers to coordinate with specific substrates. Selective binding of a spherical substrate requires the construction of a receptor molecule with a spherical recognition site. Graf and Lehn[12,14] were the first to synthesize a number of spherical macrotricyclic polyethers by the stepwise construction of macromonocyclic, macrobicyclic, and macrotricyclic systems as shown in procedure A (Scheme 1). Macrobicyclic intermediate S2 was obtained by cyclization of starting crown ether S1 with an *N*-tosylamino dicarbonyl dichloride followed by reductive removal of the tosyl protecting groups with

SCHEME 1. Procedure A[12,14]



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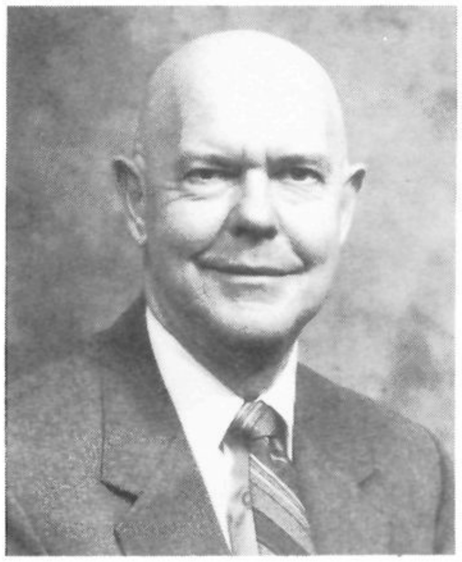
Haoyun An was born in Henan Province, P. R. China. He obtained his B.S. degree in chemistry at Zhengzhou University in 1982. He received his M.S. degree in physical organic chemistry with Professor Yangjie Wu in 1985 at Zhengzhou University. After three years working as a lecturer in Zhengzhou University, he enrolled in a Ph.D. program at Brigham Young University in 1988. He will receive the Ph.D. degree in April, 1992 with Professor Jerald S. Bradshaw on the synthesis of macropolycyclic polyethers. He is a member of the American Chemical Society. He received the 1991–1992 Charles E. and Margaret P. Maw Award from Brigham Young University and the Spring Research Conference Award from the Central Utah Section of the American Chemical Society in 1990. His research interests include the synthesis, complexation and electrochemical properties of macropolycyclic multidentate compounds, the relationship between the structure and properties of organic compounds, and the synthesis of perfumes and fragrances.

Jerald S. Bradshaw was born in Cedar City, UT, and received a B.A. degree in chemistry at the University of Utah in 1955. After four years as an officer in the U.S. Navy, he enrolled in a Ph.D. program at UCLA. He received the Ph.D. in 1963 with Professor Donald J. Cram on electrophilic substitution at saturated carbon. He received an NSF postdoctoral fellowship for the 1962–1963 academic year to work with Professor George S. Hammond at the California Institute of Technology. After three years as a research chemist at Chevron Research in Richmond, CA, he joined the faculty at Brigham Young University in 1966. He was named Professor of the Year at BYU in 1975. He was U.S. National Academy of Sciences Exchange Professor for the academic year of 1972–1973 and the Summer of 1982, working with Professor Miha Tisler at the University of Ljubljana, Yugoslavia. He also was a visiting professor with Dr. J. F. Stoddart at the University of Sheffield, England, in 1978, and a National Science Foundation Cooperative Research Fellow with Dr. L. F. Lindoy at James Cook University, Townsville, Australia, in 1988. He is a member of the American Chemical Society. He received the 1989 Utah Award from the Salt Lake and Central Utah sections of the American Chemical Society. His research interests are the synthesis and cation complexation properties of macrocyclic multidentate compounds, the photochemical reactions of heterocyclic compounds, and the preparation of new polysiloxanes for chromatography uses.

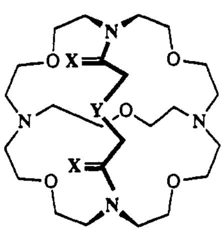


Reed M. Izatt was born in Logan, UT, and received his B.S. degree at Utah State University in 1951. He received his Ph.D. degree in 1954 with Professor W. Conard Fernelius in coordination chemistry at The Pennsylvania State University. After two years of postdoctoral work at Carnegie-Mellon University, he joined the Brigham Young University Chemistry Department in 1956. He delivered the Annual Sigma Xi lecture at BYU in 1966 and the Annual BYU Faculty Lecture in 1970 and was BYU Teacher of the Month in October 1974. He received the BYU Karl G. Maeser Research and Creative Arts Award in 1967 and was the recipient of an NIH Career Development Award (1967–1972), the Utah Award (American Chemical Society) in 1971, the Huffman Award (Calorimetry Conference) in 1983, the Willard Gardner Award of the Utah Academy of Sciences, Arts, and Letters in 1985, and the State of Utah Governor's Medal in Science in 1990. He is Chairman of the Organizing Committee for the annual International Symposium on Macrocyclic Chemistry. His research interests include the design of novel molecular recognition systems for the selective separation of cations, anions, and neutral species; calorimetry applied to metal–ligand and nonelectrolyte interactions; and the compilation of thermodynamic data.

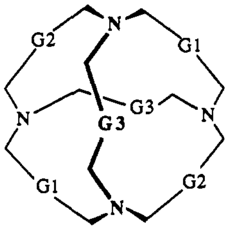
$LiAlH_4$. **S2** was then reacted with an appropriate dicarboxylyl dichloride to give spherical macrotricyclic diamides **1**–**4** which were then reduced by diborane in tetrahydrofuran (THF) to produce the corresponding spherical macrotricyclic polyethers **5**–**8**. Table 1 contains a listing of spherical macrotricyclic polyethers including melting points, product yields, synthetic procedures, and references.

Ligand **5** is one of the most aesthetically pleasing cage compounds. This material is highly symmetrical and ideal for the recognition of spherical and tetrahedral guest molecules. It accommodates Cs^+ better than any of the crown ethers, providing the most stable Cs^+ complex yet reported.[12,14] Macrotricyclic polyethers **5**–**7** form inclusion complexes with ammonium cations. **5**, in particular, has remarkable binding and selectivity properties toward NH_4^+.[19] Kinetic measurements using NMR spectroscopy showed that exchange of the ammonium cation with **5** is very slow.[14,19] The structure of the NH_4^+–**1** complex, as determined by an X-ray analysis, has the ammonium cation inside the cavity. The bridgehead nitrogens are at the corners of a tetrahedron and form linear hydrogen bonds with the protons of NH_4^+.[31] Ligand **5** is readily protonated, leading to the diprotonated and triprotonated species which form inclusion complexes with water molecules.[5,13] The tetraprotonated ligand has a high affinity and selectivity for the spherical Cl^- anion as was confirmed by an X-ray structure analysis.[31] The structure contains the Cl^- anion in the center of the cavity of the ligand. Molecular modeling studies were reported for the neutral and protonated forms of **5** and for their cation and anion complexes.[32]

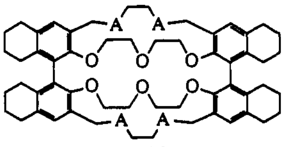
TABLE 1. Spherical Macrotricyclic Polyethers



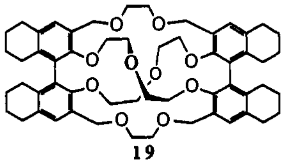
1-8



9-14



15-18



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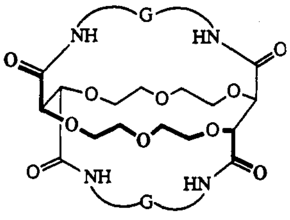
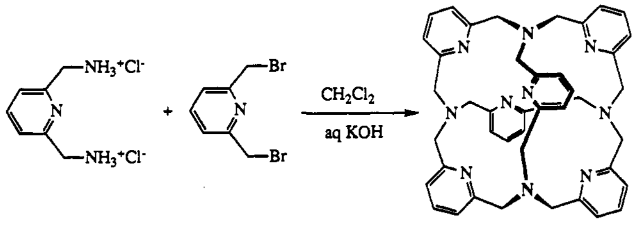


20-21

no.	remarks	mp, °C	yield, %	procedure	ref(s)
1	X = O, Y = O	220–224	52	A	12, 14
2	X = O, Y = CH_2	229–230	52	A	14
3	X = O, Y = $(CH_2)_2$	196–197	54	A	14
4	X = O, Y = $(CH_2)_3$	125–126	47	A	14
5	X = H_2, Y = O	196–200	95	A	12
		198–200	95	A	14
6	X = H_2, Y = CH_2	214–216	95	A	14
7	X = H_2, Y = $(CH_2)_2$	149	95	A	14
8	X = H_2, Y = $(CH_2)_3$	~20	80	A	14
9	G1 = G2 = G3 = 1,3-phenylene	389	6.7	B	33
10	G1 = G2 = 1,3-phenylene, G3 = 2,6-pyridinediyl	>378	8.3	B	34
11	G1 = G2 = 1,3-phenylene, G3 = 4-chloro-2,6-pyridinediyl	>312	7.1	B	35
12	G1 = G2 = 1,3-phenylene, G3 = 4-methoxy-2,6-pyridinediyl	>306	12.3	B	35
13	G1 = 1,3-phenylene, G2 = G3 = 2,6-pyridinediyl		4.3	B	34
14	G1 = G2 = G3 = 2,6-pyridinediyl		2.4	B	34
15	(*R*,*R*) A = O	310	38	C	36
16	(*R*,*S*) A = O	325	79	C	36
17	(*R*,*R*)(*S*,*S*) A = O	300	43	C	36
18	(*R*,*R*) A = S	320	20	C	36
19	(*S*,*S*)	300	43	C	36
20	G = *m*-xylylene		100	D	38
21	G = *p*-xylylene		30	D	38

Highly symmetrical cage polyethers **9–14** (Table 1) were synthesized in one step (procedure B, Scheme 2).[33–35] Hexa-*m*-xylylenetetraamine **9** was first synthesized by treating 1,3-bis(aminomethyl)benzene with 1,3-bis(bromomethyl)benzene.[33] An X-ray crystallographic analysis revealed the rigid and unique structure of cage **9**. The bridgehead nitrogens of **9** are located at the apices of an imaginary tetrahedron, and the lone electron pairs of the nitrogens are pointed toward the center of the cavity.[33] However, the cavity of **9** is too small to include any chemical species except a proton. The spherical cage polyether **10** containing two pyridine units and four benzene units was synthesized by the reaction of 1,3-bis(bromomethyl)benzene with 2,6-bis(aminomethyl)pyridine.[34] **11** and **12** were prepared in a similar manner but using 4-chloro- and 4-methoxy-2,6-bis(aminomethyl)pyridines.[35] Macrotricycle **13** containing four pyridine units was synthesized by the reaction of 1,3-bis(aminomethyl)benzene with 2,6-bis(bromomethyl)pyridine.[34] Symmetrical spherical compound **14** containing only pyridine units was synthesized from the pyridine dibromide and diamine units as shown in procedure B (Scheme 2).[34]

SCHEME 2. Procedure B[33–35]



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In general, the reactions between halides and primary amines give complex mixtures of amine products. However, the syntheses of these macrotricycles were achieved by one-step cyclizations between primary amines and halides. The yields for these reactions were not high (see Table 1), but a one-step procedure is a simple and convenient way to prepare such highly symmetrical molecules. The yields did not depend on the amine/bromide ratio or reaction conditions. Free macrotricycles **9–12** were readily isolated, but cage compounds **13** and **14** were always isolated as their potassium complexes. Demetalation of these complexes was achieved by heating them in acid solution; however, only protonated ligands were obtained. These macrotricycles could be resolved at low temperatures because the interconversion of the bridgehead nitrogen atoms was stopped. The isolated chiral materials racemized rapidly at room temperature.[35]

Cram and co-workers synthesized the 1,1′-bitetralinyl-fused cage polyethers **15–19** by treating the appropriate stereoisomeric **S3** with ethylene glycol or 1,2-ethanedithiol (procedure C, Scheme 3).[36] The structure of (*S*,*S*)-**19** was determined by X-ray crys-

SCHEME 3. Procedure C[36]

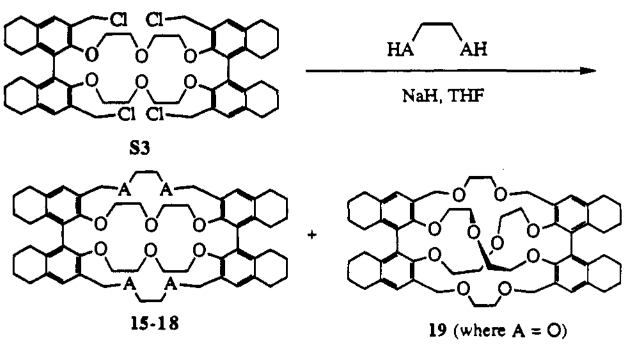
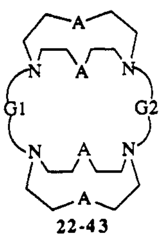
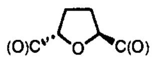
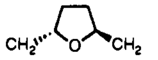
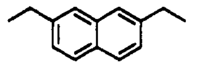
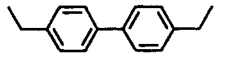
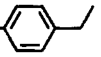
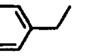
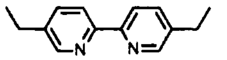


TABLE 2. Cylindrical Macrotricyclic Polyethers Containing 12-Crown-4 Units



22-43

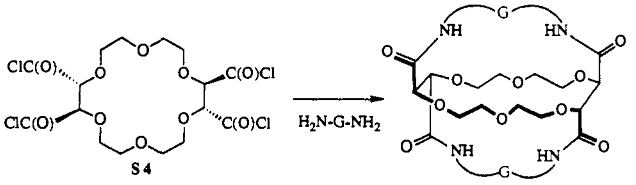
no.	remarks	mp, °C	yield, %	procedure	ref(s)
22	A = O, G1 = G2 = CH_2CH_2	144-149	80	E	48
23	A = O, G1 = $CH_2CH(CH_2Ph)CH_2$, G2 = CH_2CH_2	94-96	67	E	51, 52
24	A = O, G1 = $CH_2CH(n\text{-}C_{16}H_{33})CH_2$, G2 = CH_2CH_2	79-80	61	E	51, 52
25	A = O, G1 = $CH_2CH(CH_2Ph)CH_2$, G2 = $(CH_2)_3$		70	E	16
26	A = O, G1 = $CH_2CH[(CH_2)_6OH]CH_2$, G2 = CH_2CH_2			E	16
27	A = O, G1 = G2 = $C(O)CH_2OCH_2C(O)$	243-246	30	G	54, 55
28	A = O, G1 = G2 = $CH_2CH_2OCH_2CH_2$	54-55		G	54
		52	80	G	55
29	A = O, G1 = G2 = 	240	26	G	61
30	A = O, G1 = G2 = 	oil	51	G	61
31	A = O, G1 = G2 = $CH_2CH(OH)CH_2OCH_2CH(OH)CH_2$	73-75	15	H	62, 63
32	A = O, G1 = G2 = $CH_2CH(OH)(CH_2OCH_2)_2CH(OH)CH_2$	oil	14	H	62, 63
33	A = O, G1 = G2 = $CH_2CH(OH)(CH_2OCH_2)_3CH(OH)CH_2$	oil	6	H	62, 63
34	A = O, G1 = G2 = *p*-xylylene			F	22, 46
35	A = O, G1 = G2 = 			F	46
36	A = O, G1 = G2 = 			F	22, 46
37	A = O, G1 = $C(O)(CH_2)_7C(O)$, G2 = 	oil	52	I	68
38	A = O, G1 = $(CH_2)_9$, G2 = *p*-xylylene	oil	41	I	68
39	A = O, G1 = $(CH_2)_9$, G2 = 	oil	75	I	68
40	A = S, G1 = G2 = $C(O)CH_2OCH_2C(O)$	>250	10-30	J	69
			10-15	G	70
41	A = S, G1 = G2 = $CH_2CH_2OCH_2CH_2$	162-163	75	J	69
		161-162	32[a]	G	70
42	A = S, G1 = G2 = *p*-xylylene				45
43	A = S, G1 = G2 = 				18

[a] Overall yield.

tallography.[37] Isomer **19** possesses D_2 symmetry with all unshared electron pairs in convergent positions.

Spherical macrotricyclic tetraamide ligands **20** and **21** were synthesized in high yields by the reaction of *m*- and *p*-xylylenediamines with 18-crown-6 tetracarbonyl tetrachloride (**S4**) in THF (procedure D, Scheme 4, and Table 1).[38] Fyles and co-workers reported the spectral and structural properties of these interesting macrotricycles.[38]

SCHEME 4. Procedure D[38]



20-21

3. Cylindrical Macrotricyclic Polyethers

Cylindrical macrotricyclic polyethers contain new topological features with respect to the macromono- and macrobicyclic ligands. They are formed by linking two macrocycles together through two bridges (see the structure in Table 2), and they consist of three cavities: two lateral circular cavities and one central cavity. Changing the size of the basic macrocycle and the length and type of internal bridges changes the size of the cavity thereby changing the complexing properties of the macrotricyclic ligand.

Five synthetic strategies have been used for the construction of cylindrical macrotricyclic polyethers (I–V, Figure 1). The specific procedures corresponding to these routes will be shown later when they appear logically in the table and text. Route I allows the synthesis of symmetrical cylindrical macrotricyclic ligands containing the same macrocyclic and bridging units in one step. Routes II and III have been used to construct cylindrical macrotricycles with the same or different macrocyclic units and the same or different bridging units by the successive construction of systems of increasing cyclic order: macromono-, macrobi-, and macrotricycles and by using protection and deprotection techniques. Route IV is interesting because the first cyclization step gave two reactive sites at the same time.

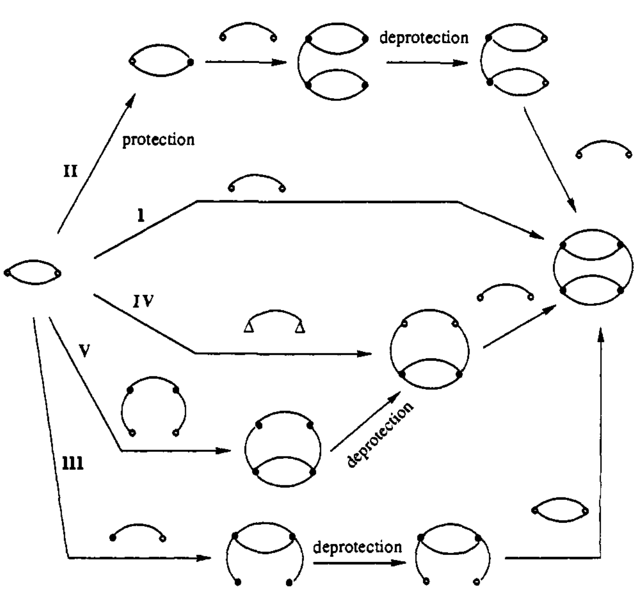


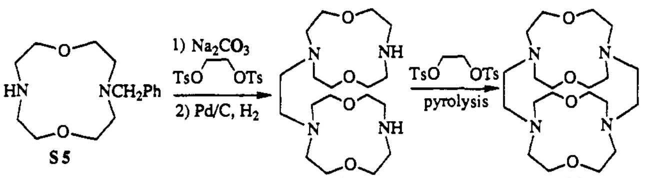
Figure 1. Synthetic strategies (I–V) for the construction of cylindrical macrotricyclic polyethers (∘ = reactive sites; Δ = epoxide ring which opens to give a reactive OH unit; • = protected or unreactive sites).

In route V protection and deprotection techniques were used for the preparation of unsymmetrical macrotricycles. Like route III, routes IV and V also were used to synthesize unsymmetrical cylindrical macrotricycles with the same bridging units and different macromonocyclic subunits.

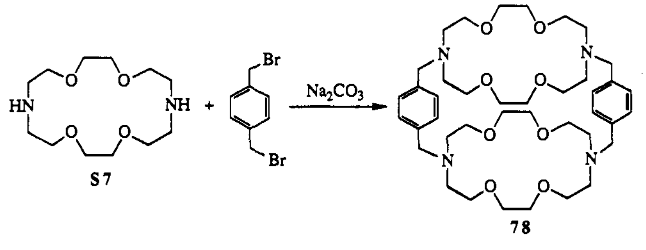
Cylindrical macrotricyclic polyethers, containing bridges short enough to make the lateral cavities cooperate with each other, formed mononuclear metal ion complexes.[16,39] Dinuclear complexes were formed when the two lateral cavities did not cooperate because of longer bridges.[40–45] Cylindrical macrotricycles with appropriate bridge lengths and macrocyclic units formed inclusion complexes with bis primary alkylammonium salts.[20–23,46,47]

Cylindrical macrotricyclic polyethers containing diaza-12-crown-4 and diaza-15-crown-5 polyether units are listed in Tables 2 and 3, respectively. Symmetrical macrotricycle 22 containing ethylene bridges was synthesized as shown in procedure E (Scheme 5).[48] This ligand also could be prepared by using procedure F (Scheme 6). Biscrown **S6** (procedure E) was obtained by treatment of monoprotected crown **S5** with ethylene ditosylate followed by reductive removal of the benzyl protecting group. Closing the second bridge was difficult. Polymer was formed when a template cation was not used and only the Na^+ complex of **S6** was isolated in the presence of Na^+. The Na^+ complex of **22** was obtained in a yield of 80% by using Li^+ as the template followed by brine in the workup. Free ligand **22** was isolated after heating the complex in vacuum. The structure of the **22**–Na^+ complex, as determined by X-ray analysis, has a cubic arrangement of the 8 donor atoms and identical helicity of the 10 ethylene units in each molecule. The crystal structures of its dihydrochloride tetrahydrate[49] and diiodide hemihydrochloride hemihydrate[50] were also determined.

SCHEME 5. Procedure E (Route II)[16,48,51,52]



SCHEME 6. Procedure F (Route I)[20,22,46,64–66,85,90,95]



Lipophilic cage ligands **23** and **24** were synthesized by using procedure E with the appropriate ditosylates.[51,52] Sodium ion was used as the template in the last step. The sodium tosylate complexes of **23** and **24** were first obtained and then the anions were exchanged to ClO_4^-, I^-, Cl^-, F^-, and CH_3O^-. Free ligands **23** and **24** were obtained by continuous extraction of solutions containing the complexes. The structure of the solid sodium perchlorate complex of **23** was determined.[52] The sodium complexes of **23** and **24** were used as anion activators.[51] Other properties of the sodium complexes of **23** and **24** also were investigated.[53] Lipophilic cage ligands **25** (Table 2) and **56** (Table 4) were synthesized by the same procedure.[16] Macrotricycle **26**, bearing a hydroxyl function, was attached to polystyrene.[16]

Cylindrical macrotricyclic ligands **27** and **28**[54,55] (Table 2) and **44**[56] (Table 3) were synthesized using procedure G (Scheme 7). Condensation of 1,7-diaza-12-crown-4 (**S8**) with diglycolyl dichloride under high dilution conditions gave tricyclic tetraamide **27** (30%) together with the cryptand (ca. 10%), a 1:1 cyclocondensation product. The macrotricyclic tetraamine **28** was obtained by reduction of **27** with diborane.[54,55] Macrotricyclic ligand **28** formed dinuclear complexes only with Cu^{2+}, Zn^{2+}, and Ag^+ and formed mononuclear complexes with other cations.[54,57,58] An X-ray structural study of the complex of **28** with Ag^+ showed that two Ag^+ cations are held close to the two 12-crown-4 units.[59] Stable 1:1 complexes of **28** with the alkaline earth cations were obtained in aqueous solution (log K = 6.52, 7.97, and 8.00 for Ca^{2+}, Sr^{2+}, and Ba^{2+}, respectively).[60] There is an intramolecular cation exchange from one 12-crown-4 unit to the other. An intermolecular cation exchange also occurs but at a slower rate.[60] The chiral macrotricyclic polyether **30** containing the *trans*-tetrahydrofuran-2,5-diylbis(methylene) subunits was ob-

SCHEME 7. Procedure G (Route I)[21,23,54–56,61,70,73–75]

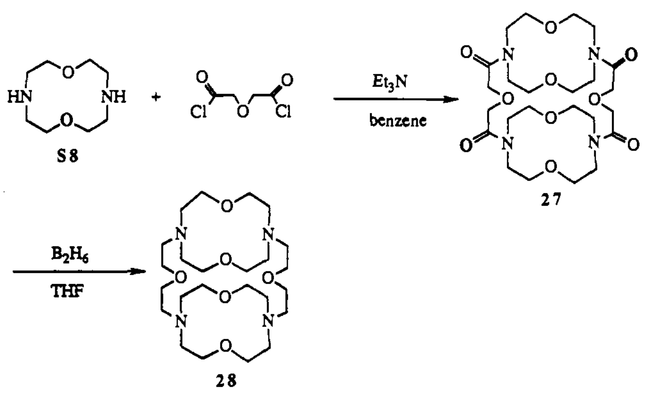
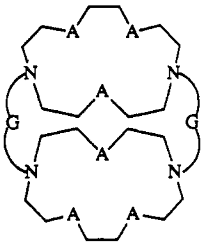
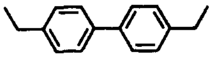
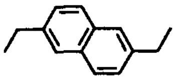
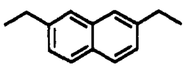
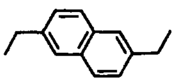


TABLE 3. Cylindrical Macrotricyclic Polyethers Containing 15-Crown-5 Units



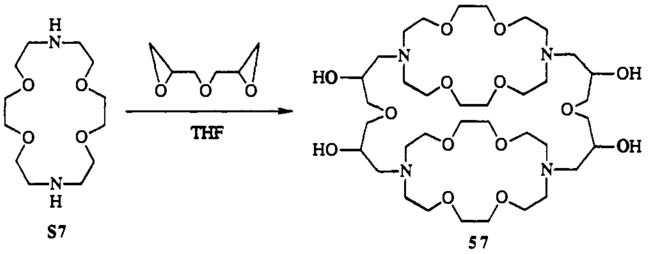
44-55

no.	remarks	mp, °C	yield, %	procedure	ref(s)
44	A = O, G1 = G2 = m-$C(O)C_6H_4C(O)$	257-259	30	G	56
45	A = O, G1 = G2 = $CH_2CH(OH)CH_2OCH_2CH(OH)CH_2$	oil	11	H	62, 63
46	A = O, G1 = G2 = p-xylylene			F	20, 22, 46
47	A = O, G1 = G2 = 			F	22
48	A = O, G1 = G2 = 			F	22
49	A = O, G1 = G2 = 		18	F	20, 46
50	A = O, G1 = G2 = m-xylylene			F	64, 65
51	A = O, G1 = G2 = $CH_2C\equiv CC\equiv CCH_2$			F	65
				J	65
52	A = O, G1 = p-xylylene, G2 = $CH_2(CH_2OCH_2)_2CH_2$	oil	51	I	22, 68
53	A = O, G =  G2 = $CH_2(CH_2OCH_2)_2CH_2$	oil	37	I	22, 68
54	A = S, G1 = G2 = $C(O)CH_2OCH_2C(O)$		50	J	70
55	A = S, G1 = G2 = $CH_2CH_2OCH_2CH_2$	144-146	50	J	70

tained via tetraamide **29**[61] by procedure G. Enantiomeric recognition properties of **29** were determined for the transport of racemic primary ammonium cations.[61] The cation-binding abilities of **30** also were investigated.[61]

Dihydroxy macrotricyclic ligands **31–33** (Table 2), **45** (Table 3), and **57–59** (Table 4) were synthesized according to procedure H (Scheme 8). The appropriate diglycidyl ether was treated with the appropriate diaza-crown ether.[62,63] The macrotricyclic ligands were separated from bicyclic products (cryptands) by chromatography to give yields of 1–15% of the desired products.

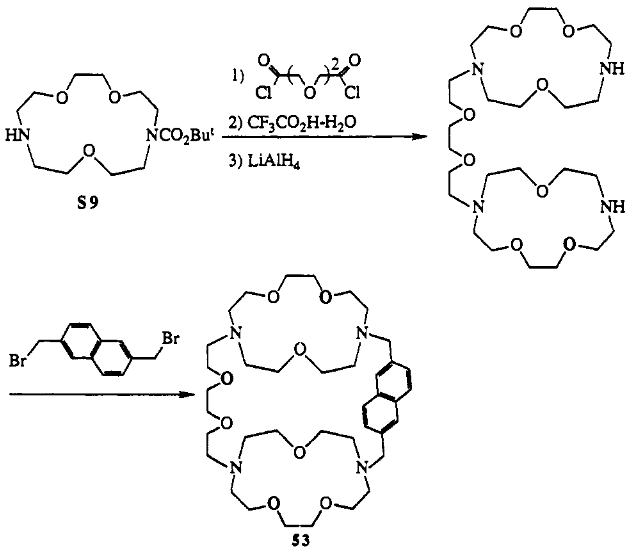
SCHEME 8. Procedure H (Route I)[16]



Macrotricycles **34–36**[22,46] (Table 2) and **46–50**[20,22,46,64,65] (Table 3) containing aromatic building groups were synthesized as shown in procedure F from the reaction of diaza-12-crown-4 (**S8**) or diaza-15-crown-5 (**S10**) with the appropriate bis(bromomethyl)arene. The complexation properties of symmetrical macrotricycles **34–36** and **46–50** were thoroughly studied using NMR spectroscopy.[21,22,46,64–67] They form 1:1 inclusion complexes with the appropriate bis primary alkylammonium salts, $^+H_3N(CH_2)_nNH_3^+$. Complexation depends on the length of the carbon chain between the two ammonium ions. Hosts **34**, **46**, and **50** with short p- or m-xylylene bridges are rigid and highly selective for $^+H_3N(CH_2)_2NH_3^+$; host **48** with rigid naphthalene-2,6-bis(methylene) bridges was selective for $^+H_3N(CH_2)_4NH_3^+$; while hosts **36** and **47** with biphenyl-4,4′-bis(methylene) bridges form the most stable complexes with bisprimary alkylammonium salts with n = 5 and 6, respectively.

Unsymmetrical macrotricycles **37–39** and **52** and **53** were synthesized by using procedure I (Scheme 9).[22,68]

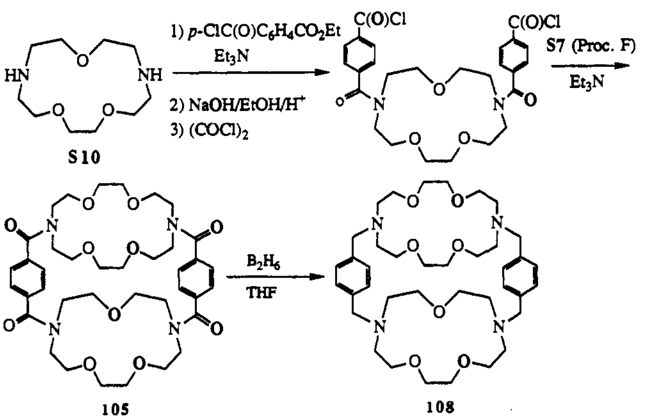
SCHEME 9. Procedure I (Route II)[22,68,65]



Monoprotected diaza-12-crown-4 or diaza-15-crown-5 was treated with the appropriate dicarbonyl dichloride followed by deprotection and reduction of amide groups to give the biscrown ether intermediate. These biscrowns were treated with the appropriate bis(bromomethyl)arene to give unsymmetrical cage hosts **37–39** and **52** and **53**. These hosts formed 1:1 complexes with various bisalkylammonium cations $^{+}H_3N(CH_2)_nNH_3^{+}$. Because they contain one flexible bridge, these unsymmetrical hosts have modified selectivity when forming complexes with bisalkylammonium cations. The conformation of these hosts influences their complexing properties. For example, host **52** complexes bisalkylammonium cations with $n = 2$, 3, and 4 at the same rate, while host **46** complexes with bisalkylammonium cations with $n = 2$ and 3 at the same rate, but at a very slow rate with $n = 4$.

Lehn and co-workers[18,45,69,70] synthesized cylindrical polythiamacrotricyclic ligands **40–43** with crown-4 units (Table 2), **54** and **55** with crown-5 units (Table 3), **60** and **61** with crown-6 units (Table 4), and **103** and **104** with a combination of crown-4 and crown-6 units (Table 5) as shown in procedure J (Scheme 10). This procedure involves: (a) attachment of two appendages to the first diaza-crown; (b) activation of the free termini of these appendages; and (c) condensation with the second diaza-crown under high dilution conditions. Macrotricycles with different crown ether units and the same bridges can be obtained in this way (strategy III, Figure 1). Macrotricycles **40** and **41** containing the same macrocyclic units and bridges were also obtained by procedure G.

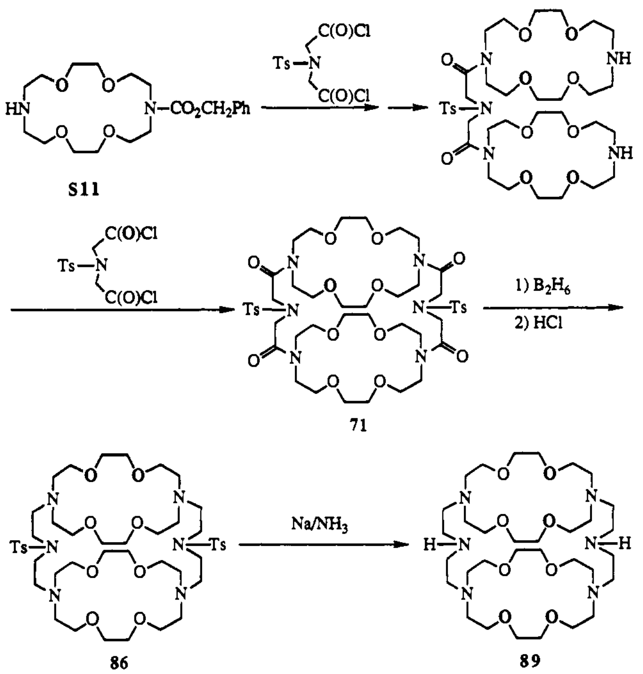
SCHEME 10. Procedure J (Route III)[21,65,69,70]



Host **41** formed dinuclear complexes with Cu^{2+} and Ag^{+}, along with a mononuclear complex with Ag^{+}.[58] Some other properties such as redox behavior,[71] electron spectroscopy,[72] and the X-ray crystal structure for the dinuclear complex of **41** with Cu^{2+} were determined. The dinuclear Cu^{2+} complex of ligand **42** exhibited a "magnetic plasticity" property.[45] **43**, which contains 2,2′-bipyridyl-5,5′-bis(methylene) bridges, formed polynuclear complexes.[18] Most of the polythiamacrotricyclic ligands formed dinuclear complexes with certain metal cations. Unsymmetrical ligand **104**, containing 12- and 18-membered rings (Table 5), formed a mixed Cu^{2+}–Cu^{+} complex in which the Cu^{+} and Cu^{2+} cations are probably located in the 18- and 12-membered rings, respectively.[69]

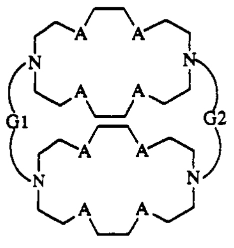
Table 4 lists a series of cylindrical macrotricyclic polyethers containing diaza- or triaza-crown-6 macrocyclic units. Cylindrical ligands **56–61** were described above. Most of the macrotricyclic tetraamides were obtained by procedures G or K, Scheme 11 (strategies I or II, Figure 1). Vögtle and co-workers[73–75] synthesized macrotricyclic tetraamides **62–65** in yields of up to 92% by a direct high dilution condensation of diaza-18-crown-6 (**S7**) with the appropriate arenedicarbonyl dichloride (procedure G). The diaza-18-crown-6 units of hosts **62–65** are held apart at fixed distances by p-phenylenedicarbonyl, 2-nitro-m-phenylenedicarbonyl, 9,10-anthracenediyldicarbonyl, and 4,4′-biphenylenedicarbonyl groups. These are model compounds for channel ion transport systems. Host **62** formed a 1:2 neutral complex with water wherein a water molecule connects two host molecules by hydrogen-bonding with carbonyl oxygen atoms of each host giving a chain-like arrangement.[76] Host **62** also formed crystalline complexes with hydroquinone, resorcinol, pyrocatechol, 2,7-naphthalenediol, and the 1,2,4-, 1,3,5-, and 1,2,3-benzenetriols. These complexes also contained water. The X-ray structure analysis of the 1:1:4 (**62**/hydroquinone/water) complex indicates that the hydroquinone is not incorporated into the cavity of the ligand and the hydrogen bonds involving water molecules lead to a more stable crystal lattice.[74] Complexation properties and the interaction of anthracene ligand **64** with dimyristyl phosphatidyl chlorine (DMPC) vesicles were studied by various techniques including relative quantum yields, lifetimes, fluorescence anisotropies, binding and fluoroscence quenching experiments and by equilibrium cooling curves.[75] Ligand **64** was also studied as a mobile fluorescence probe.[77]

SCHEME 11. Procedure K (Route II)[78,79]

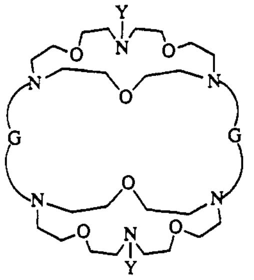


Lehn and co-workers reported the synthesis of macrotricyclic tetraamides **65–73** (Table 4).[21,23,78,79] Tetraamides **65–67** were obtained by a direct dilute condensation of diaza-18-crown-6 (**S7**) with the corresponding arenedicarbonyl dichloride (procedure G),[21,23] while stepwise procedure K was used to synthesize macrotricyclic tetraamides **68–72**. In the latter process, monoprotected diaza-18-crown-6 (**S11**) was treated with the appropriate dicarbonyl dichloride in the ratio of 2:1 followed by deprotection to give the biscrown ether intermediate (see procedure K). This intermediate was treated with the same dicarbonyl dichloride to give the macrotricyclic tetraamide. This method can be used

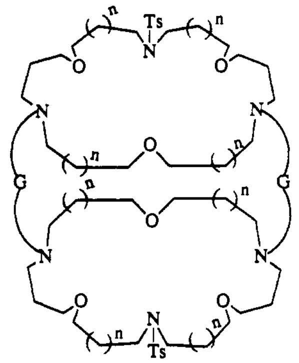
TABLE 4. Cylindrical Macrotricyclic Polyethers with Crown-6 Units



56-94



95-100



101-102

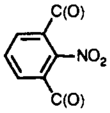
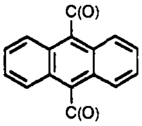
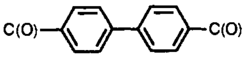
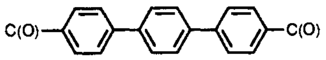
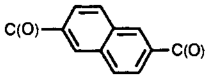
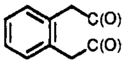
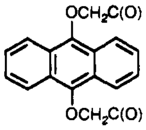
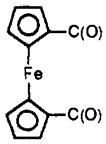
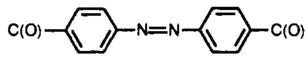
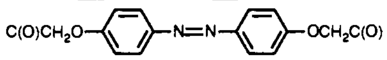
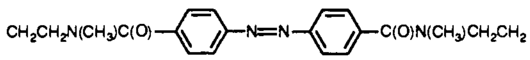
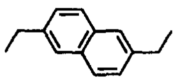
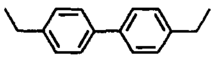
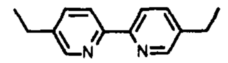
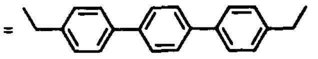
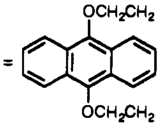
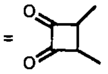
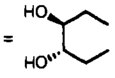
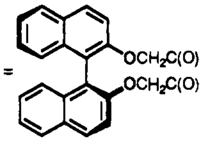
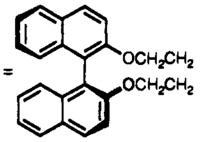
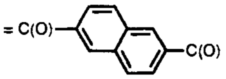
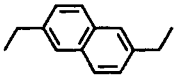
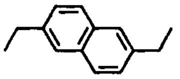
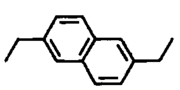
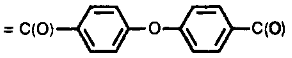
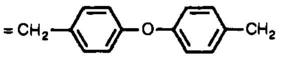
no.	remarks	mp, °C	yield, %	procedure	ref(s)
56	A = O, G1 = $CH_2CH(CH_2Ph)CH_2$, G2 = CH_2CH_2		10	E	16
57	A = O, G1 = G2 = $CH_2CH(OH)CH_2OCH_2CH(OH)CH_2$	oil	10	E	16
58	A = O, G1 = G2 = $CH_2CH(OH)(CH_2OCH_2)_2CH(OH)CH_2$	oil	1	H	62, 63
59	A = CH_2, G1 = G2 = $CH_2CH(OH)CH_2OCH_2CH(OH)CH_2$	oil	10	H	62, 63
60	A = S, G1 = G2 = $C(O)CH_2OCH_2C(O)$	190–191	60	J	69
61	A = S, G1 = G2 = $CH_2CH_2OCH_2CH_2$	130–131	80	J	69
62	A = O, G1 = G2 = *p*-$C(O)C_6H_4C(O)$	190	38	G	73
		216–220		G	74
63	A = O, G1 = G2 = 	295–296	52	G	73
64	A = O, G1 = G2 = 	185–192	92	G	75
65	A = O, G1 = G2 = 	180	69	G	73
		192	85	G	21
66	A = O, G1 = G2 = 			G	23
67	A = O, G1 = G2 = 	250	70	G	21, 78
68	A = O, G1 = G2 = 	258–260	70	K	78
69	A = O, G1 = G2 = 	195–250	50	K	79
70	A = O, G1 = G2 = $C(O)CH_2OCH_2C(O)$	185	70	K	78
71	A = O, G1 = G2 = $C(O)CH_2N(Ts)CH_2C(O)$	223	55	K	78
72	A = O, G1 = G2 = $C(O)(CH_2)_3C(O)$	185–186	75	K	78
73	A = O, G1 = G2 = $C(O)(CH_2)_8C(O)$	glassy	65	J	21
74	A = O, G1 = G2 = 	243.5–245	26	G	80, 81
75	A = O, G1 = G2 = 	224–226	21	G	82, 83
76	A = O, G1 = G2 = 	219–221	37	G	83
77	A = O, G1 = G2 = 	166–167	12	L	84
78	A = O, G1 = G2 = *p*-xylylene	111–113		G	74
		116		G	23
				F	64–66
79	A = O, G1 = G2 = 	210	93	G	21
80	A = O, G1 = G2 = 	174	92	G	21
				F	64–66

TABLE 4 (Continued)

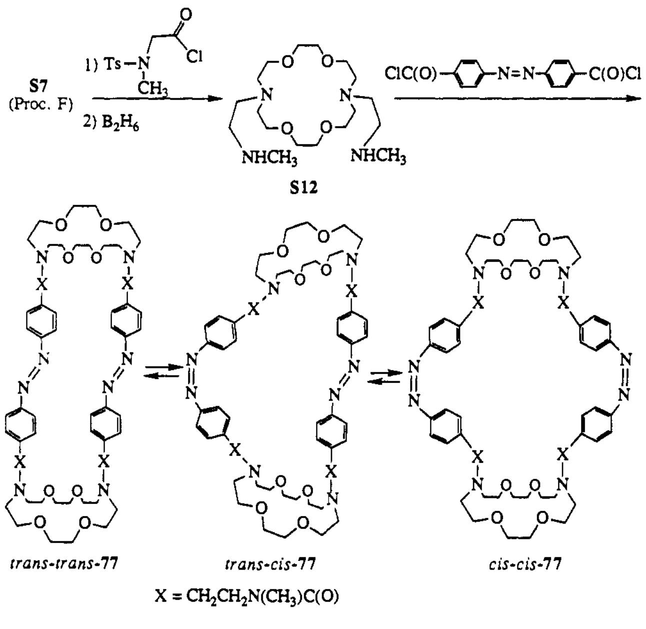
no.	remarks	mp, °C	yield, %	procedure	ref(s)
81	A = S, G1 = G2 = 			G	18
82	A = O, G1 = G2 = 	210		G	23
83	A = O, G1 = G2 = o-$CH_2CH_2C_6H_4CH_2CH_2$	oil	80	K	78
84	A = O, G1 = G2 = 	212	20	K	79
85	A = O, G1 = G2 = $CH_2CH_2OCH_2CH_2$	64	90	K	78
86	A = O, G1 = G2 = $CH_2CH_2N(Ts)CH_2CH_2$	152	80	K	78
		152	90	K	78
87	A = O, G1 = G2 = $(CH_2)_5$	45–46	90	K	78
88	A = O, G1 = G2 = $(CH_2)_8$	oil	92	J	21
89	A = O, G1 = G2 = $CH_2CH_2NHCH_2CH_2$	92–94	70	K	78
90	A = O, G1 = G2 = $CH_2C{\equiv}CC{\equiv}CCH_2$	132–133	15	F	85
91	A = O, G1 = G2 = 	229–230	12	F	90
92	A = O, G1 = G2 = 	oil	11	M	91
93	A = O, G1 = C(O)CH2OCH2C(O), G2 = 	glassy	50	K	92, 93
94	A = O, G1 = CH2CH2OCH2CH2, G2 = 	oil	90	K	92, 93
95	G =  Y = Ts	152	80	G	94
96	G =  Y = Ts			G	94
97	G =  Y = H	138	80	G	94
		138	80	G	94
98	G =  Y = Me	glassy	57	G	94
99	G =  Y = Ts			G	94
100	G =  Y = H			G	94
101	n = 1, G = p-$C(O)C_6H_4C(O)$	foam	30	J	95
102	n = 0, G = p-xylylene	gum	27	F	95

to prepare symmetrical and unsymmetrical macrotricycles. Macrotricyclic tetraamide **73** was obtained in a stepwise fashion using procedure J. Use of procedure G to prepare **73** gave the macrobicyclic product (cryptand). Treatment of diaza-18-crown-6 (**S7**) with $ClC(O)(CH_2)_6CO_2C_2H_5$ gave the diamide diester which was hydrolyzed to the corresponding diacid and then converted to the reactive dicarbonyl dichloride (see procedure J). High dilution condensation of this reactive intermediate dichloride with **S7** gave the desired macrotricyclic tetraamide **73**.[21]

Condensation of 1,1′-bis(chloroformyl)ferrocene with diaza-18-crown-6 (**S7**) gave macrotricyclic tetraamide **74** (procedure G, Table 4) containing bisferrocene bridges and some macrobicyclic (cryptand) byproduct.[80,81] High temperatures favored the formation of the cryptand, while the macrotricycle was favored at low temperatures.[81]

Photoresponsive cylindrical ligands **75** and **76** (Table 4) were synthesized in benzene from equimolar amounts of diaza-18-crown-6 (**S7**) and azobis[4-(chloroformyl)-benzene] or azobis[4-[(chloroformyl)methoxy]benzene] in the presence of an excess of triethylamine under high dilution (procedure G).[82,83] Photoresponsive cylindrical ligand **77**[84] was synthesized by procedure L (Scheme 12). Reactive intermediate **S12** was first obtained by acylation of **S7** followed by reduction. As in procedure G, condensation of intermediate **S12** with azobis[4-

SCHEME 12. Procedure L (Route I)[84]



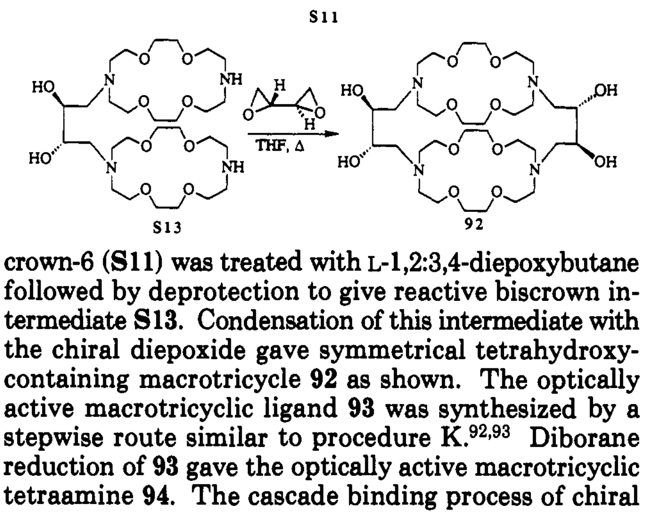
(chloroformyl)benzene] gave macrotricycle 77. Because of the two photoresponsive azobenzene bridges between the diaza-crown ethers, macrotricycles 75–77 change their binding ability for polymethylene diammonium salts and metal cations in response to photoirradiation. In these cases, the distances between two crown units are changed by the photoinduced cis–trans isomerism of the azobenzenes. For example, *trans,trans*-75 extracted $^+H_3N(CH_2)_{10}NH_3^+$ selectively from an aqueous solution, while *cis,cis*-75 was more selective for $^+H_3N(CH_2)_6NH_3^+$.[82,83] *trans,trans*-75 and -76 had very little affinity for the alkali metal cations. However, the affinity for alkali metal cations significantly increased when *cis,cis*-75 and -76 were formed under UV-light irradiation.[83] This so-called "all-or-nothing" control of cation binding ability by these ligands using UV light also would be applicable to solvent extraction, membrane transport, the spatial distance between two metal cations, etc. Some other photoresponsive properties of ligand 77 were also studied.[84] These switching mechanisms have been reviewed.[2e]

Cylindrical macrotricyclic tetraamines 78–88 (Table 4) were obtained by reduction of the corresponding tetraamides with diborane. Tetraamine ligands 78 and 80 were also obtained by a direct condensation of diaza-18-crown-6 (S7) with the corresponding bis(bromomethyl)arene (procedure F).[64–66] Detosylation of macrotricycle 86 with Na/NH_3 (procedure K) gave diazamacrotricycle 89 which could be used as an intermediate for the synthesis of more complicated macropolycyclic polyethers.[78] Tetraacetylene-containing macrotricycles 51 (Table 3) and 90 (Table 4) were synthesized by condensing the appropriate diaza-crown with $TsOCH_2C{\equiv}CC{\equiv}CCH_2OTs$.[85] X-ray crystallographic and NMR studies of macrotricycle 90 show that 90 has a channellike structure and selectively accommodates both metallic and organic cations within its compartment.

Various studies have been carried out using cylindrical tetraamines 78–88. An X-ray crystal structure of free ligand 78[86] and mass spectroscopic studies of free ligands 78 and 79[87] were reported. Most of these macrotricycles form dinuclear complexes with metal cations,[40,41,79,88,89] and some may also form mononuclear complexes.[89] Crystal structures of the dinuclear complexes of ligands 84[79] and 85[40,41] with Rb^+ and Na^+, respectively, have been reported. These cylindrical macrotricycles selectively form inclusion complexes with various bis primary alkylammonium salts $[^+H_3N(CH_2)_nNH_3^+]$. Macrotricyclic ligands 78, 85, 79, 80, 81, 84, and 82 selectively form complexes with the bis primary alkylammonium cations with n values of 3, 4, 5, 6 or 7, 7, 7, and 10 or 11, respectively.[18,21,23,64,65,79] This inclusion phenomenon was confirmed by the crystal structure of the 79–$^+H_3N(CH_2)_5NH_3^+$ complex.[47] The substrate is held inside coreceptor molecule 79 by simultaneous binding to the two crown ether subunits.

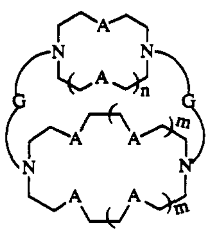
Using procedure F, dimethyl squarate was treated with diaza-18-crown-6 (S7) to give macrotricyclic ligand 91 (Table 4) containing very rigid bridges.[90] 91 formed crystalline complexes with KSCN, RbI, and CsCl. Chiral macrotricycle 92 was obtained by using procedure M (Scheme 13).[91] Monoprotected diaza-18-crown-6 (S11) was treated with L-1,2:3,4-diepoxybutane followed by deprotection to give reactive biscrown intermediate S13. Condensation of this intermediate with the chiral diepoxide gave symmetrical tetrahydroxy-containing macrotricycle 92 as shown. The optically active macrotricyclic ligand 93 was synthesized by a stepwise route similar to procedure K.[92,93] Diborane reduction of 93 gave the optically active macrotricyclic tetraamine 94. The cascade binding process of chiral ligand 94 is of special interest. Complexation of a metal cation by one of the diaza-18-crown-6 units leads to extraction of a mandelate or a chiral amino acid anion. In forming an ion pair, the anion probably penetrates, at least partially, into the central molecular cavity.[8,93] Complexation, extraction, and transport properties of chiral ligands 93 and 94 of organic ammonium salts, alkali metal ions and molecular anions have been reported.[93]

SCHEME 13. Procedure M (Route II)[91]

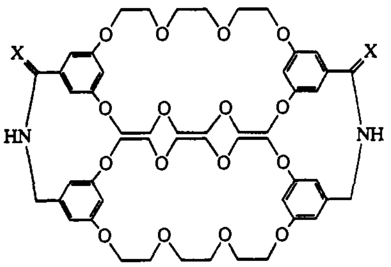


Lehn and co-workers[94] synthesized cylindrical macrotricycles 95 and 96 (Table 4) containing triaza-18-crown-6 units by a method similar to procedure G. The monoprotected triaza-18-crown-6 (S1), obtained as an intermediate in the synthesis of spherical macrotricycles (procedure A), was condensed with naphthalene-2,6-dicarbonyl dichloride under high dilution conditions to give diprotected tetraamide 95 in an 80% yield. Ligand 95 was converted into macrotricycle 97 either in two steps via 96 (reduction with diborane; detosylation with HBr/AcOH/phenol; 55%), or directly from 95 by reduction with $LiAlH_4$ in tetrahydrofuran (80%). The latter route was better because two reactions were done in one step with a resulting higher overall yield. The

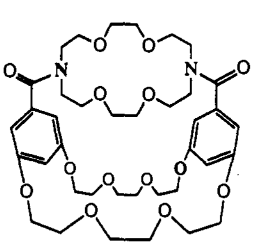
TABLE 5. Cylindrical Macrotricyclic Polyethers with Various Ring Sizes



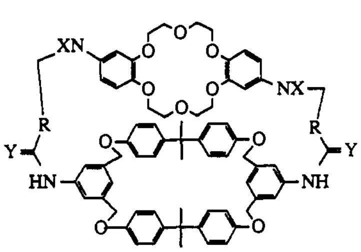
103-110



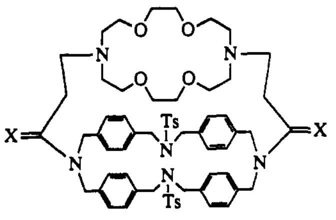
111-112



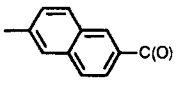
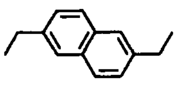
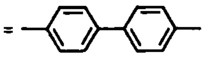
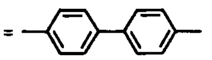
113



114-115

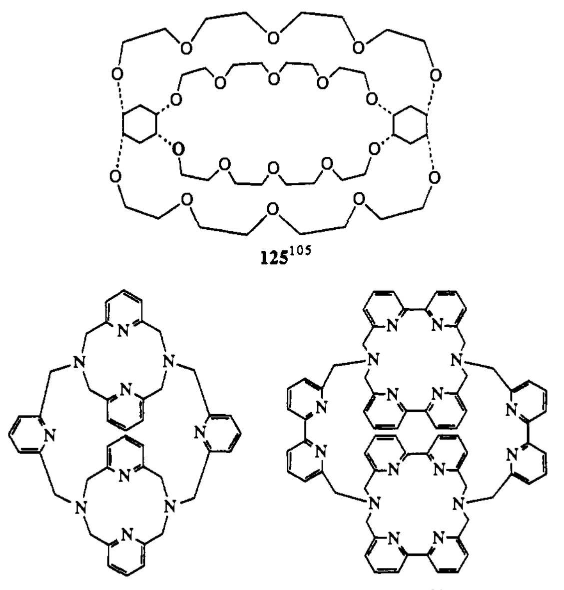


116-117

no.	remarks	mp, °C	yield, %	procedure	ref(s)
103	A = S, $n = m = 1$, G = $C(O)CH_2OCH_2C(O)$	glassy	50	J	69
104	A = S, $n = m = 1$, G = $CH_2CH_2OCH_2CH_2$	135-136	80	J	69
105	A = O, $n = 2$, $m = 1$, G = p-$C(O)C_6H_4C(O)$			J	64-67
106	A = O, $n = m = 2$, G = p-$C(O)C_6H_4C(O)$			J	64-67
107	A = O, n = 2, m = 1, G = C(O)  C(O)			J	64-67
108	A = O, $n = 2$, $m = 1$, G = p-xylylene			J	64-67
109	A = O, $n = m = 2$, G = p-xylylene			J	64-67
110	A = O, n = 2, m = 1, G = 			J	64-67
111	X = O	146	32	J	96
112	X = H_2	oil	82	J	96
113		75	35	J	97
114	R =  X = Ts, Y = O		13	J	98
		263-265	64	J	99
115	R =  X = H, Y = H_2	263-265		J	98
		263-264	44	J	99
116	X = O		27	J	8
117	X = H_2		92	J	100

Eschweiler–Clarke N-methylation of ligand **97** gave macrotricyclic hexaamine **98**. Macrotricyclic ligands **99** and **100** were obtained by the same procedures. Bis secondary amine-containing macrotricyclic ligands **97** and **100** were used as key intermediates for the synthesis of macrotetracycles **160** and **161** (see section 5, Table 9). Macrotricyclic tetraamide **101** was synthesized using procedure J by the condensation of the monoprotected triaza-24-crown-6, while macrotricyclic amine **102** was obtained by procedure F from monoprotected triaza-20-crown-6 and α,α'-dibromo-p-xylene.[95]

Table 5 lists a series of cylindrical macrotricyclic polyethers with various ring sizes and bridges. Macrotricyclic tetraamides **105–107** were synthesized by procedure J.[64-67] As mentioned above, diborane reduction of these tetraamides gave the corresponding tetraamines **108–110**. This procedure can be used to synthesize cylindrical macrotricycles with the same bridges and different or the same crown ether units. Ligands **108–110** selectively form inclusion complexes with the bis primary alkylammonium salts, $^+H_3N(CH_2)_nNH_3{}^+$, with n values of 2 or 3, 3 or 4, and 4 or 5, respectively. Macrotricycles **111–113** also were synthesized by procedure J.[96,97] Ligand **111** was obtained by the condensation of the appropriate bis(aminomethyl)- and bis(chloroformyl)dibenzocrown ethers,[96] while ligand **113** was obtained by treating the bis(chloroformyl)dibenzocrown ether with diaza-18-crown-6 (**S7**).[97] Diborane reduction of ligand **111** gave the corresponding macrotricycle **112** which can be used to prepare macropentacyclic polyethers **188** and **189** (see section 6, Figure 6).[96] Cylindrical macrotricyclic polyethers **114–117** containing crown ether and cyclophane units also were synthesized by procedure J.[98-100] Condensation of the appropriate diaminocyclophane and



125[105]

126[106]

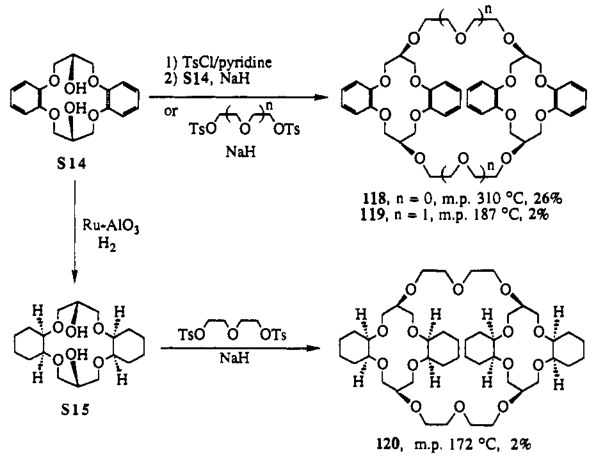
127[106]

Figure 2. Other cylindrical macrotricycles.

reactive dichloride derivative of the appropriate crown ether gave amide 114 or 116 which were reduced to amine 115 or 117 with diborane. The interaction of 115 with various (ω-phenylalkyl)ammonium picrates [$Ph(CH_2)_nNH_3^+Pi^-$, where n = 3–9] to form 1:1 inclusion complexes was reported.[98,99] The results indicated that the stability constant values of the complexes with (5-phenylpentyl)ammonium (n = 5) and (6-phenylhexyl)ammonium (n = 6) picrates were more than 3 times as large as those for complexes with other ammonium picrates. The inclusion complexes of ligand 117 with alkylammonium picrate salts were also studied by an NMR technique.[100]

Macrotricycles 118–120 with only oxygen donor atoms were synthesized as shown in procedure N (Scheme 14).[101] Dicyclohexanediol S15 was obtained by high-pressure hydrogenation of dibenzenediol S14 over $Ru-Al_2O_3$. The other isomers of S15 were separated by fractional crystallization. Reaction of diol S14 with tosyl chloride give the corresponding intermediate ditosylate which was treated with S14 to give macrotricycle 118 in a 26% yield. Diol S14 or S15 was treated with 1,5-bis(tosyloxy)-3-oxapentane to give macrotricyclic polyether 119 or 120 together with the corresponding 1:1 macrobicyclic (cryptand-like) product.

SCHEME 14. Procedure N (Route I)[101]



S14

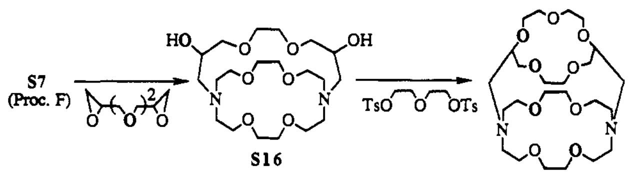
S15

118, n = 0, m.p. 310 °C, 26%
119, n = 1, m.p. 187 °C, 2%

120, m.p. 172 °C, 2%

Cylindrical macrotricyclic ligand 121 containing methylene bridges between the crowns was synthesized as shown in procedure O (Scheme 15).[102] Condensation of diaza-18-crown-6 (S7) with the diglycidyl ether derivative of triethylene glycol gave the intermediate dihydroxy cryptand S16 in a 95% yield. S16 was condensed with $TsOCH_2CH_2OCH_2CH_2OTs$ to give macrotricycle 121 in a 19% yield.

SCHEME 15. Procedure O (Route IV)[102]

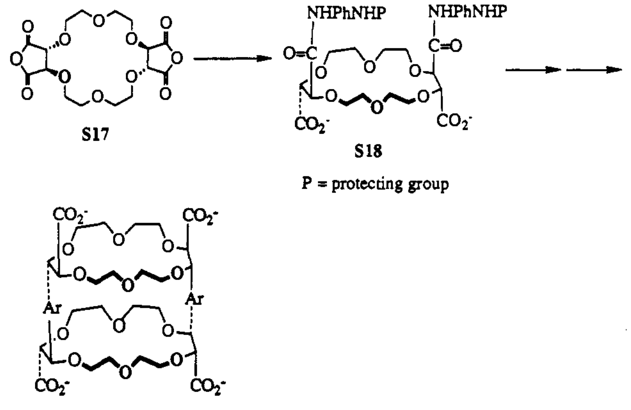


S16

121, oil, 19%

Dianhydride S17 was treated with monoprotected 1,3-diaminobenzene (procedure P, Scheme 16).[103] The desired *syn*-dicarboxylic acid-containing macrocycle S18 was isolated in a 90% yield. S18 was quantitatively deprotected and then condensed with an equimolar amount of S17 under high dilution conditions to give macrotricyclic tetracarboxylate 122 in a 20% yield. A crystal structure analysis of the (2-hydroxyethyl)ammonium complex of 122 confirmed the structure.[103]

SCHEME 16. Procedure P (Route III)[103]



S17

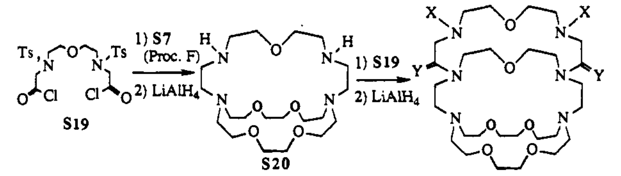
S18

P = protecting group

122, Ar = m-$C(O)NHC_6H_4NHC(O)$
20%

Vögtle[104] synthesized cylindrical macrotricycles 123 and 124 by a stepwise construction method as shown in procedure Q (Scheme 17). The condensation of protected dicarbonyl dichloride S19 with diaza-18-crown-6 (S7) followed by reduction with $LiAlH_4$ gave intermediate cryptand S20. This intermediate reacted with S19 to give diamide 123 which was reduced to macrotricycle 124. Other more complicated macropolycycles can be constructed by this repetitive procedure.

SCHEME 17. Procedure Q (Route V)[104]



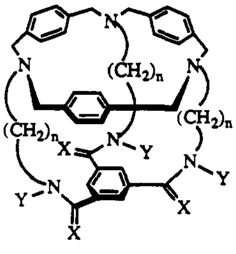
S19

S20

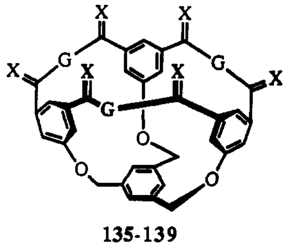
123, X = Ts, Y = O
124, X = H, Y = H_2

Figure 2 shows the structures of other cylindrical macrotricycles (125–127). Ligand 125 with only oxygen donor atoms was an unexpected product of the con-

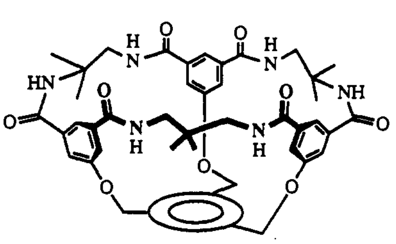
TABLE 6. Basket-Shaped Macrotricyclic Polyethers



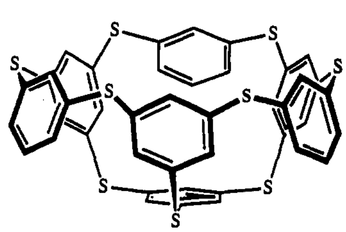
129-134



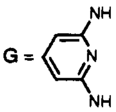
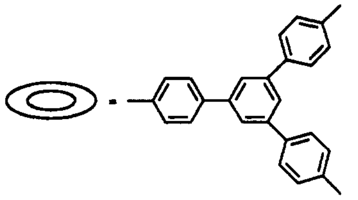
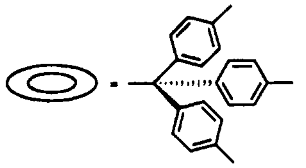
135-139



140-141



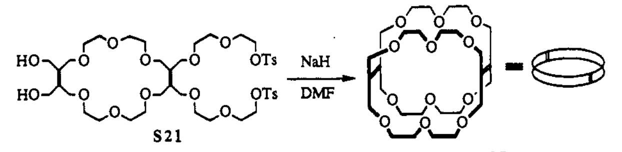
142

no.	remarks	mp, °C	yield, %	procedure	ref(s)
129	$n = 2$, X = O, Y = H		13	S	109
130	$n = 3$, X = O, Y = H		33	S	109
131	$n = 4$, X = O, Y = H		42	S	109
132	$n = 3$, X = H_2, Y = Ts		20	S	109
133	$n = 3$, X = H_2, Y = H		90	S	109
			95		109
134	$n = 4$, X = H_2, Y = H		90	S	109
135	X = O, G = $NHCH_2C(CH_3)_2CH_2NH$	369	37	T	110
		347-350	51	T	111
136	X = O, G = $NH(CH_2)_3NH$	367	21	T	110
137	X O, G = 	>400	22	T	110
138	X = H_2, G = $NHCH_2C(CH_3)_2CH_2NH$	oil	10	T	110
139	X = O, G = $OCH_2C(CH_3)_2CH_2O$	299	28	T	111
140		>350	0.4	T	111
141		347-350	0.6	T	111
142			1.5		112

densation of *cis*-1,2,4,5-tetrahydroxycyclohexane with tetraethylene glycol ditosylate. The crystal structure of its complex with potassium picrate was reported.[105] Cylindrical ligand 126, containing pyridine bridges, was synthesized by a one-step reaction of 2,6-bis(aminomethyl)pyridine with 2 equiv of 2,6-bis(bromomethyl)pyridine.[106] Macrotricycle 127, containing bipyridine bridges, was obtained from bis(aminomethyl)bipyridine and bis(bromomethyl)bipyridine.[106]

Macrotricyclic tetrakis(hydroxymethyl)ethylene (THYME)-containing fused-crown ether 128, was synthesized as shown in procedure R (Scheme 18).[107,108]

SCHEME 18. Procedure R[107,108]



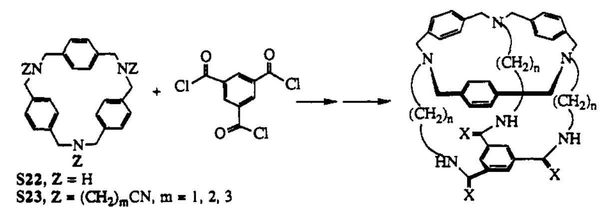
128, m.p. 118-123 °C
33-35%

Key intermediate diol ditosylate S21 was constructed by a stepwise method.[107] The intramolecular condensation of S21 under high dilution conditions gave macrotricyclic THYME cage 128. The crystal structure of toluene-solvated 128 was determined by X-ray analysis. The crystal structure of the trinuclear cascade complex $[K_2(H_2O)\cdot 128]^{2+}[PtCl_3\cdot(CH_3)_2SO]_2^-$, in which the two potassium cations are bound in the two 20-crown-6 ring cavities, demonstrates that host 128 does behave as a hydrophilic cylinder containing two 20-crown-6 analogues, at least in the crystalline phase. The similar macrotetra- and pentacyclic THYME polyethers 178–181 (Figure 4) will be discussed in section 5.

4. Basket-, Suitcase-, and Folder-Shaped Macrotricyclic Polyethers

In addition to spherical and cylindrical macrotricyclic polyethers, some other variously shaped macrotricycles also have been synthesized. In this section we will discuss the preorganized basket-, suitcase-, and folder-shaped macrotricyclic polyethers. Table 6 lists basket-shaped macrotricycles 129–142. Lehn and coworkers[109] synthesized basket-shaped polyazamacro-

SCHEME 19. Procedure S[109]



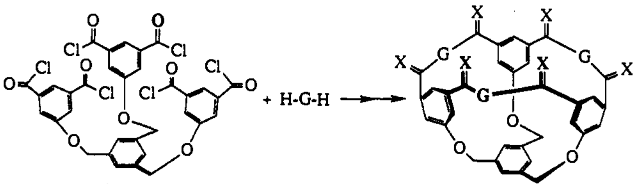
S22, Z = H
S23, Z = $(CH_2)_mCN$, m = 1, 2, 3
S24, Z = $(CH_2)_nNH_2$, n = 2, 3, 4
S25, Z = $(CH_2)_3NHTs$

129-131, 133-134

tricycles 129–134 of the cyclophane type using procedure S (Scheme 19). 2,11,20-Triaza[3.3.3]paracyclophane S22 was the starting material for these macrotricycles. Branched macrocycles S24 (n = 2–4) were prepared by the attachment of nitrile-bearing side-chains to S22 (to form S23) and subsequent reduction with $LiAlH_4$ or B_2H_6. The synthesis of macrotricycles 129–131 was carried out by a direct coupling of triply branched macrocycles S24 with 1,3,5-benzene tricarbonyl trichloride under high dilution conditions. Reduction of amides 130 and 131 with diborane gave the macrotricyclic hexaamines 133 and 134, respectively, in yields of 90%. An alternative synthesis of 133 was achieved by condensation of S25 with 1,3,5-tri(bromomethyl)benzene to give the tritosyl triamide 132 which was treated with $LiAlH_4$ to remove the tosyl groups in a 95% yield. Anion binding studies of these macrotricycles as determined by NMR spectroscopy were reported.[109]

Vögtle and co-workers[110,111] synthesized macrotricyclic hosts 135–141 with basket-shaped cavities by procedure T (Scheme 20). The condensation of hexacarbonyl hexachloride S26 with the appropriate diamine or 2,2-dimethyl-1,3-propanediol under high dilution conditions gave basket-shaped hexaamides 135–137 and hexaester 139, respectively. Basket-shaped amides 140 and 141 were synthesized in a similar fashion by the reaction of 1,3-diamino-2,2-dimethylpropane with the appropriate hexacarbonyl hexachloride.[111] Diborane reduction of amide 135 gave basket-shaped polyamine 138. Host hexaamine 138 formed the first reported inclusion complex with tetrahydrofuran in water.[110] Macrotricycles 135, 140, and 141 selectively formed crystalline adducts with ethanol, but macrotricyclic hexaester 139 formed no such complex.[111]

SCHEME 20. Procedure T[110,111]

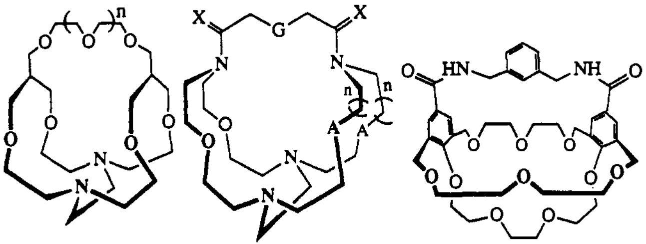


S26

135-139

Treatment of 1,3,5-trimercaptobenzene with an excess of 1,3,5-trifluorobenzene in the presence of $NaN(SiMe_3)_2$ gave 1,3,5-tris[(3,5-difluorophenyl)thio]benzene (65%). This material was then treated with 1,3,5-trimercaptobenzene at moderate dilution in the presence of $NaN(SiMe_3)_2$ (6 equiv) to give basket-shaped (or bowl-shaped) macrotricycle 142 (Table 6).[112] The crystal structure of the 142–$CHCl_3$ inclusion complex was confirmed by X-ray crystallography.

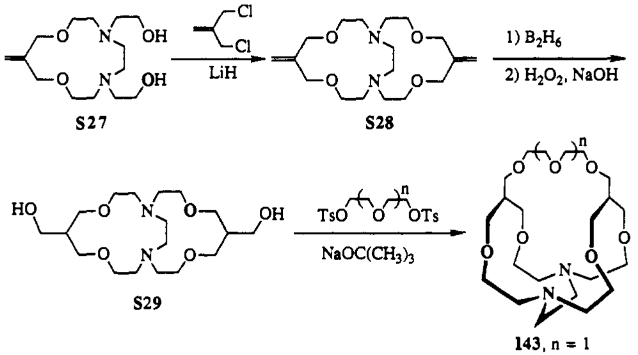
TABLE 7. Suitcase-Shaped Macrotricyclic Polyethers



143, 144 145-152 153

no.	remarks	mp, °C	yield, %	procedure	ref
143	$n = 1$	oil	30	U	113
144	$n = 2$	oil	20	U	113
145	$X = H_2, n = 1, A = G = OCH_2CH_2O$	oil	29	V	113
146	$X = H_2, n = 1, A = OCH_2CH_2O, G = OCH_2C({=}CH_2)CH_2O$	oil	40	V	113
147	$X = H_2, n = 2, A = O, G = OCH_2CH_2O$	oil	41	V	113
148	$X = H_2, n = 2, A = O, G = OCH_2C({=}CH_2)CH_2O$	oil	27	V	113
149	$X = O, n = 1, A = OCH_2CH_2O, G = O$	oil	40	W	113
150	$X = H_2, n = 1, A = OCH_2CH_2O, G = O$	oil	59	W	113
151	$X = O, n = 2, A = O, G = O$	oil	51	W	113
152	$X = H_2, n = 2, A = O, G = O$	oil	53	W	113
153		249–250	73		114

SCHEME 21. Procedure U[113]

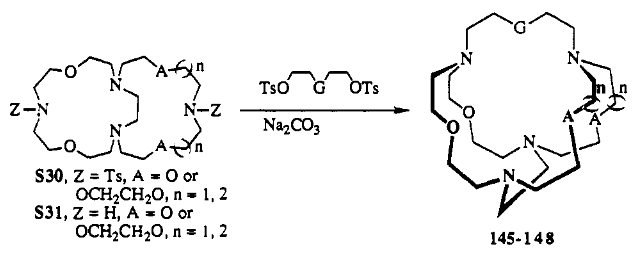


S27 S28 S29

143, n = 1
144, n = 2

A series of suitcase-shaped macrotricyclic polyethers 143–152 (Table 7) have been prepared.[113] Suitcase-shaped macrotricycles 143 and 144 were synthesized using procedure U (Scheme 21). Condensation of N,N'-bis(2-hydroxyethyl)ethylenediamine with 3-chloro-2-(chloromethyl)-1-propene using anhydrous cesium carbonate as the base gave dilariat crown S27. Macrocycle S27 was treated with the above dichloride using lithium hydride to give macrobicycle S28. Hydroboration–oxidation of S28 gave the key intermediate dihydroxyl macrobicycle S29, which was condensed with di- and triethylene glycol ditosylate to give suitcase-shaped macrotricycles 143 and 144, respectively. Protected macrobicycles S30 (procedure V, Scheme 22)

SCHEME 22. Procedure V[113]

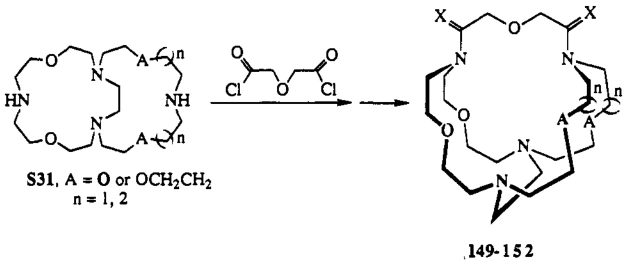


S30, Z = Ts, A = O or OCH_2CH_2O, n = 1, 2
S31, Z = H, A = O or OCH_2CH_2O, n = 1, 2

145-148

were prepared by a similar strategy from N,N'-bis(2-hydroxyethyl)ethylenediamine and N-protected aminotosylates. The tosyl groups of **S30** were removed with $LiAlH_4$ to give the key reactive intermediates **S31**. Condensation of **S31** with the appropriate ditosylate under high dilution gave suitcase-shaped macrotricycles **145–148**. Macrotricyclic diamides **149** and **151** were synthesized by the condensation of **S31** with diglycolyl dichloride (procedure W, Scheme 23). Reduction of diamides **149** and **151** with diborane gave suitcase-shaped macrotricyclic tetraamines **150** and **152**.

SCHEME 23. Procedure W[113]

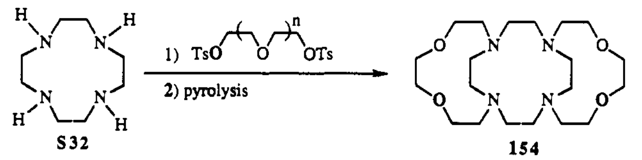


log K values for the interaction of some of these suitcase-shaped macrotricycles with proton and various metal ions in aqueous solution were determined by a potentiometric technique.[113] Ligand **150** formed very stable complexes with Cu^{2+} (log K = 6.32) and Cd^{2+} (log K = 6.57) and was selective for Pb^{2+} (log K = 12.90). Ligand **152** was selective for Hg^{2+} (log K = 10.10). The monoprotonated form of **147** formed a strong complex with F^- (log K = 13.0) but did not complex with NO_3^- or Cl^-.

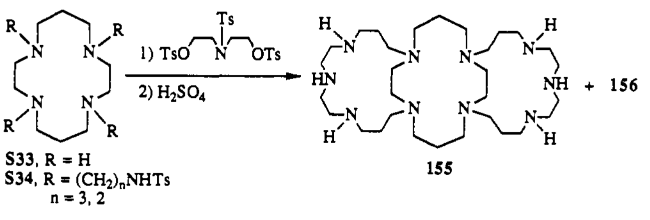
Suitcase-shaped macrotricycle **153** was synthesized in eight steps starting from 4-bromo-2,6-dimethylphenol with an overall yield of 1.25% (Table 7).[114] The X-ray crystal structures of free host **153** and its 2:1 complex with $[Pt(NH_3)_4][PF_6]_2[Me_2CO]_2$ were reported.

Table 8 shows folder-shaped macrotricycles **154–158** which were synthesized as shown in procedures X and Y (Schemes 24 and 25). Buøen and Dale[115] synthesized folder-shaped macrotricycle (tri-ptychand) **154** by the condensation of tetraaza-12-crown-4 (**S32**) with 2 equiv of triethylene glycol ditosylate (procedure X). The free host was obtained from its sodium complex by pyrolysis. Branched tetraazacrown **S34** (n = 3) was prepared from cyclam **S33** (procedure Y).[116]

SCHEME 24. Procedure X[115]

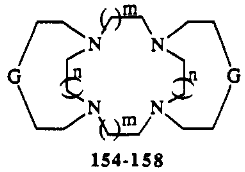


SCHEME 25. Procedure Y[116]



Condensation of **S34** (n = 3) with tritosylated diethanolamine followed by detosylation gave an isomeric mixture of macrotricycles **155** and **156**. The magnetic properties of their copper(II) and nickel(II) trinuclear complexes were reported.[116] The reaction of branched tetraaza-crown **S34** (n = 2) with 1,3-propanediyl ditosylate $[TsO(CH_2)_3OTs]$ gave tetratosylated macrotricycle **157** (procedure Y).[117] Detosylation of **157** gave folder-shaped macrotricyclic polyether **158**. The copper(II), nickel(II), and cobalt(II) binuclear complexes of macrotricycle **158** were prepared and characterized by elemental analyses; IR, electronic absorption, and reflectance spectroscopies; magnetic susceptibility; and X-ray crystal structure determinations. The macrotricyclic p-*tert*-butylcalix[4]arenebis-crown-5 ligand (**159**) was obtained as a byproduct in the condensation of p-*tert*-butylcalix[4]arene (**S35**) with tetraethylene glycol ditosylate (procedure Z, Scheme 26).[118]

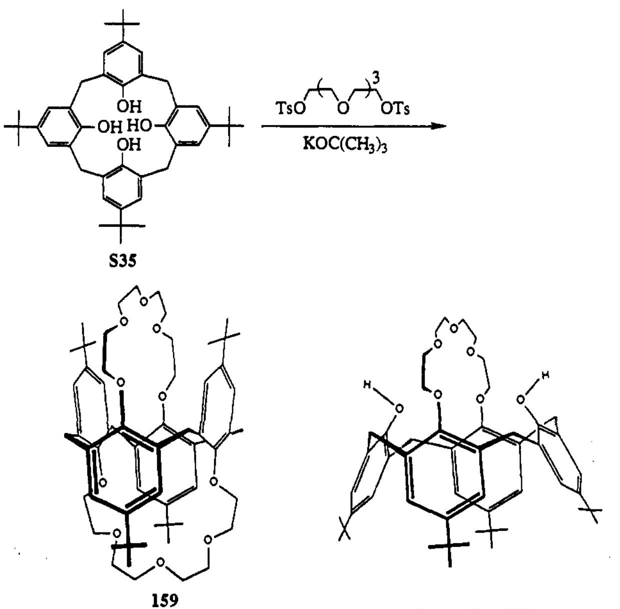
TABLE 8. Folder-Shaped Macrotricyclic Polyethers



154-158

no.	remarks	mp, °C	yield, %	procedure	ref
154	$m = n = 1$, G = OCH_2CH_2O	125–129	43	X	115
155	$m = 2, n = 1$, G = $(CH_2NHCH_2)_3$			Y	116
156	$m = 1, n = 2$, G = $(CH_2NHCH_2)_3$			Y	116
157	$m = 2, n = 1$, G = $NTs(CH_2)_3NTs$	250	40	Y	117
158	$m = 2, n = 1$, G = $NH(CH_2)_3NH$	oil	57	Y	117

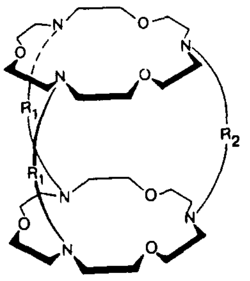
SCHEME 26. Procedure Z[118]



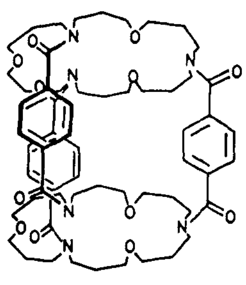
5. Macrotetracyclic Polyethers and Polycyclic THYME Polyethers

There are three general kinds of macrotetracyclic polyethers: cylindrical, speleand, and trinuclear. Table 9 shows triply bridged cylindrical macrotetracycles

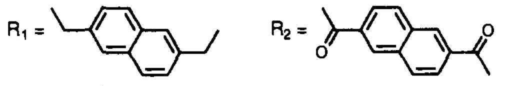
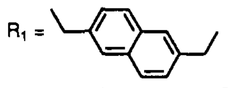
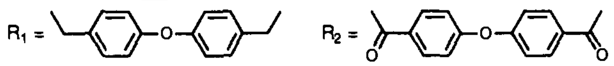
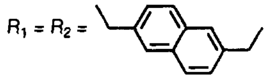
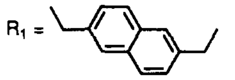
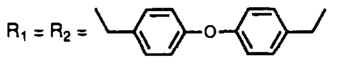
TABLE 9. Cylindrical Macrotetracyclic Polyethers



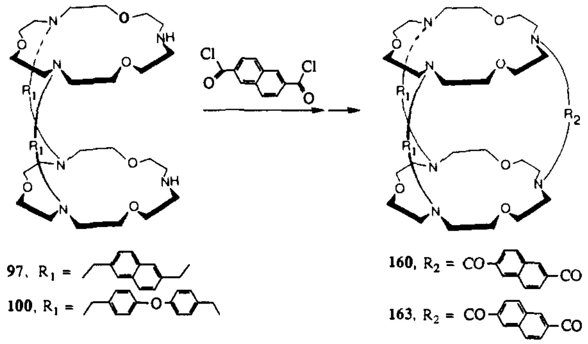
160-165



166

no.	remarks	mp, °C	yield, %	procedure	ref
160		glassy	55	AA	94
161	 $R_2 = C(O)(CH_2OCH_2)_2C(O)$	glassy	46	AA	94
162				AA	94
163		>260	75	AA	94
164	 $R_2 = CH_2(CH_2OCH_2)_2CH_2$	140	78	AA	94
165				AA	94
166		272-273	28	BB	95

SCHEME 27. Procedure AA[94]



SCHEME 28. Procedure BB[95]

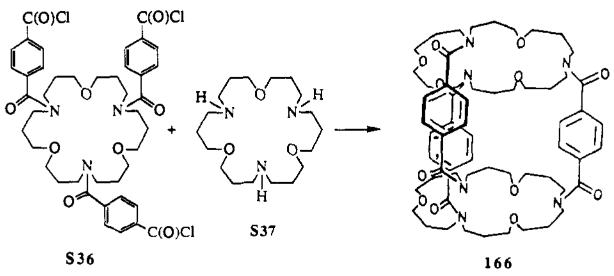
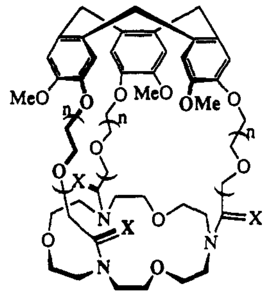


TABLE 10. Macrotetracyclic Speleands with a Cyclotriveratrylene Unit

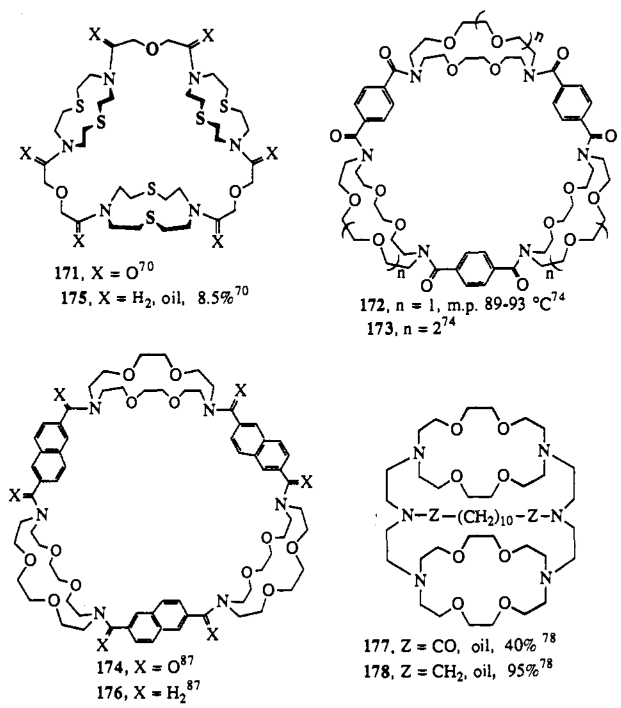


167-170

no.	remarks	mp, °C	yield, %	procedure	ref
167	$n = 0, X = O$	325	35	BB	119
168	$n = 1, X = O$	glassy	40	BB	119
169	$n = 0, X = H_2$	230	85	BB	119
170	$n = 1, X = H_2$	glassy	65	BB	119

160–166 which were synthesized using procedures AA[94] or BB[95] (Schemes 27 and 28). Condensation of macrotricycle **97** with naphthalene-2,6-dicarbonyl dichloride and triglycolyl dichloride gave triply bridged macrotetracyclic amides **160** and **161**, respectively (procedure AA).[94] Diborane reduction of diamides **160** and **161** gave the corresponding macrotetracyclic hexaamines **163** and **164**, respectively. Macrotetracyclic diamide **162** and hexaamine **165** were synthesized in a similar manner from macrotricycle **100**.[94] Triply bridged macrotetracyclic hexaamide **166** was synthesized by the condensation of triaza-24-crown-6 containing three acid chloride side chains (**S36**) and unsubstituted triaza-24-crown-6 (**S37**) as shown in procedure BB.[95] The three bridges connecting the two triazacrown ethers keep the macrocycles at a fixed distance and delineate a central cavity. Triply bridged cylindrical macrotetracycles **163** and **164** selectively formed 1:1 complexes with $^{+}H_3N(CH_2)_5NH_3^{+}$ dipicrate.[94] The complexation data indicated that substrate binding is more restricted for **163** and **164** than for macrotricycle **79** (Table 4), which has two naphthalenyl bridges.

Macrotetracyclic speleands with one cyclotriveratrylene unit and one triaza-crown unit were synthesized by a method similar to procedure BB (Table 10).[119] Condensation of 1,7,13-triaza-18-crown-6 with the appropriate cyclotriveratrylenetricarbonyl tri-



171, X = O[70]
175, X = H_2, oil, 8.5%[70]

172, n = 1, m.p. 89-93 °C[74]
173, n = 2[74]

174, X = O[87]
176, X = H_2[87]

177, Z = CO, oil, 40%[78]
178, Z = CH_2, oil, 95%[78]

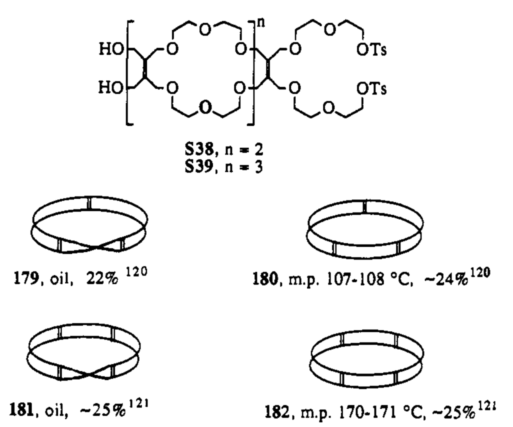
N–Z–$(CH_2)_{10}$–Z–N

Figure 3. Other macrotetracyclic polyethers.

chlorides gave triamides **167** and **168**. The reduction of these triamides with diborane gave triamine speleands **169** and **170**. Macrotetracycles **169** and **170** represent a new type of macropolycyclic molecules containing both a receptor site and a rigid shaping unit. They combine the features of cylindrical macrotetracycles (Table 9) and the cyclotriveratrylene molecular cages (see section 8). Speleand **169** binds methylammonium ions, forming both external and internal complexes. In the latter case, the cation end of the guest coordinates with triaza-crown ether, while the aliphatic end ($-CH_3$) points toward the cyclotriveratrylene unit.

Trinuclear macrotetracyclic polyethes **171**–**174**[70,74,87] (Figure 3) are the 3:3 cyclocondensation products of the reaction of the diaza-crowns and a dicarbonyl dichloride. Macrotricycles **40** (Table 2), **62** (Table 4), and **67** (Table 4) are the 2:2 cyclocondensation products corresponding to **171**, **172**, and **174**, respectively. Reduction of hexaamides **171** and **174** gave hexaamines **175** and **176**, respectively. Macrotetracycle **177** was synthesized by the reaction of macrotricycle **89** (Table 4) and dodecanedicarbonyl dichloride.[78] Hexaamine **178** was obtained by the reduction of **177** with diborane. Trinuclear macrotetracycle **172** formed crystalline complexes with 1,3,5-benzenetricarboxylic acid and benzenehexacarboxylic acid with melting points of 237–245 °C and 166–173 °C, respectively.[74] The structure of the 2:2 cyclocondensation product **79** (Table 4) and the 3:3 cyclocondensation product **176** were determined by mass spectroscopy.[87]

In a manner similar to the synthesis of macrotricyclic THYME polyether **128** (procedure R), the macrotetracyclic and macropentacyclic THYME polyethers **179** and **180**[120] and **181** and **182**[121] were synthesized by the intramolecular condensation of the appropriate diol ditosylate substituted biscrown ether **S38** and triscrown ether **S39** in high dilution conditions (Figure 4). The twisted macrotetracycle **179** and cylindrical macrotetracycle **180** were obtained in yields of 22% and 24%, respectively. The structure of symmetrical (D_{3h}) macrotetracycle **180** was confirmed from an X-ray structure analysis and from NMR spectroscopy.[120] The stereochemistry of **179** was also reported. The twisted macropentacycle **181** and cylindrical macrotetracycle **182** were isolated in about equal amounts (total yield 50%).[121] An X-ray structure analysis confirmed the structure of cylinder **181**. Ozonolysis of **181** and **182** was also carried out in order to clarify the structures.



S38, n = 2
S39, n = 3

179, oil, 22%[120]

180, m.p. 107-108 °C, ~24%[120]

181, oil, ~25%[121]

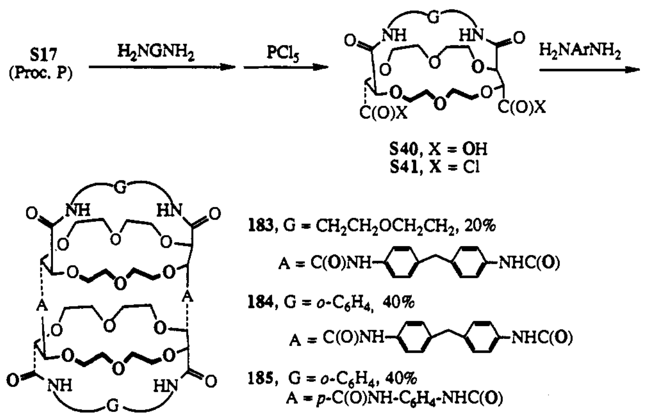
182, m.p. 170-171 °C, ~25%[121]

Figure 4. Macrotetracyclic and macropentacyclic THYME polyethers.

6. Macropenta(and higher)cyclic Polyethers

Highly preorganized macropentacyclic polyethers generally contain two or three crown units; therefore, they form polynuclear complexes with various substrates. Macropentacyclic polyethers **183**–**185** were synthesized as shown in procedure CC[103] (Scheme 29).

SCHEME 29. Procedure CC[103]



S40, X = OH
S41, X = Cl

183, G = $CH_2CH_2OCH_2CH_2$, 20%

184, G = o-C_6H_4, 40%

185, G = o-C_6H_4, 40%
A = p-C(O)NH-C_6H_4-NHC(O)

The high dilution reaction of dianhydride **S17** with the appropriate diamine proceeded quantitatively and selectively to give macrocyclic diacid **S40**. Diacid **S40** was activated with PCl_5 and the resulting crude dicarbonyl dichloride **S41** was condensed under high dilution with the appropriate aromatic diamine to give the macropentacycles **183**–**185**. A crystal structure analysis of **184** showed that the molecule has a boatlike shape with a water molecule strongly bound on top of each macrobicyclic subunit. An NMR study showed that there is a strong 1:1 association of **183** and **184** with $^+H_3NCH_2CH_2$-p-C_6H_4-$CH_2CH_2NH_3^+$.[103]

Cylindrical macropentacycle **186** was synthesized by a high dilution coupling of macrocyclic tetraamine **S42** with 2 equiv of *syn*-diester dicarbonyl dichloride **S43** (Figure 5).[122] The macroheptacyclic polyether **187**,

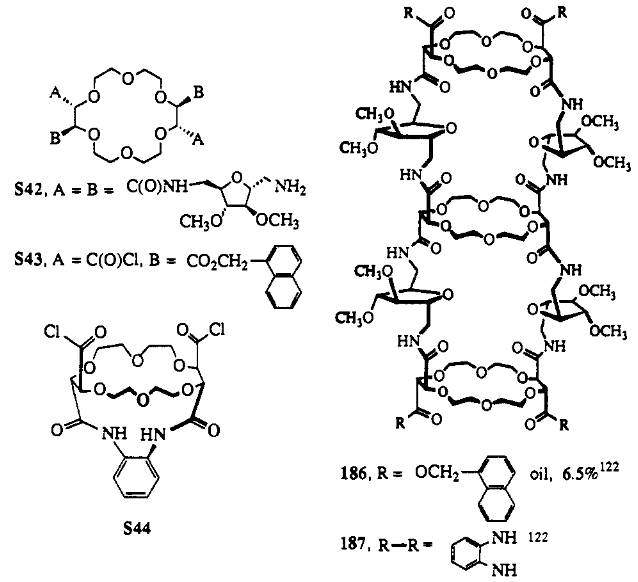


Figure 5. Synthesis of cylindrical macropolycyclic polyethers.

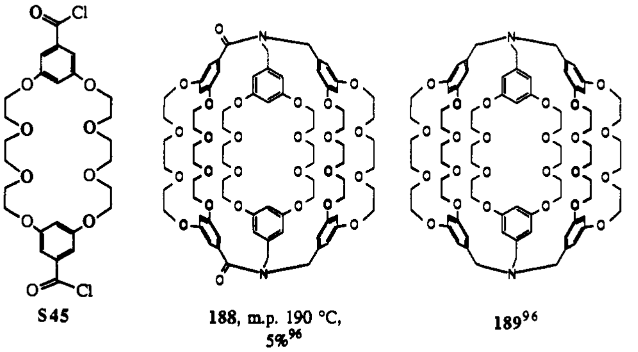
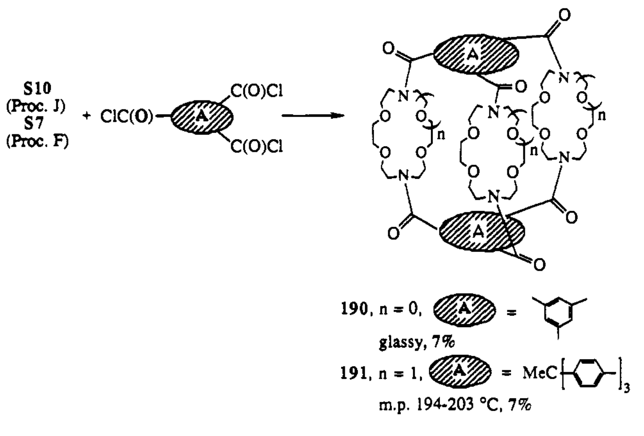


Figure 6. Other macropentacyclic polyethers.

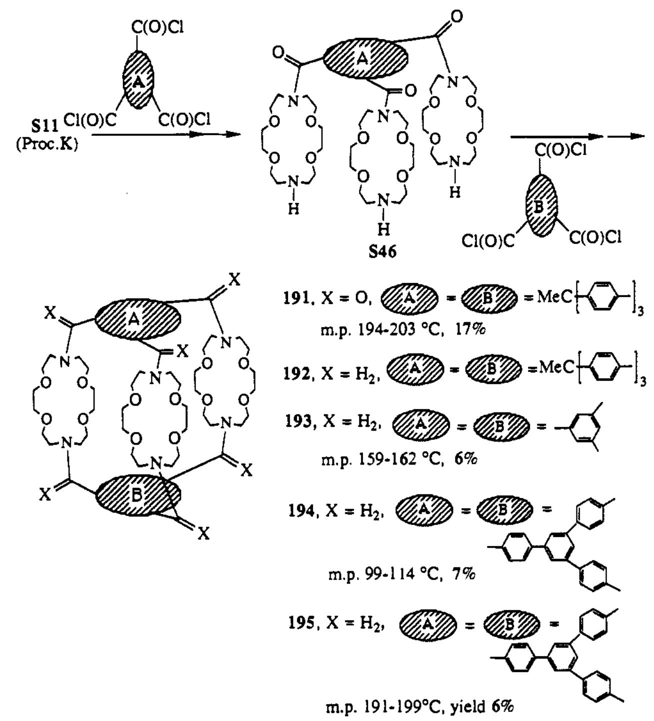
where the two carbonyls on the top and bottom are each connected together, was similarly synthesized from **S42** and macrobicycle **S44**. The high dilution condensation of macrotricycle **112** (Table 5) with macrocyclic dicarbonyl dichloride **S45** gave trinuclear macropentacyclic diamide **188** (Figure 6).[96] Diborane reduction of diamide **188** gave macropentacyclic diamine **189**.

Vögtle and co-workers reported a series of macropentacyclic triscrown hosts **190–195** (see procedures DD and EE, Schemes 30 and 31).[123] Two different strategies for the synthesis of **190–195** are shown. Procedure DD is a one-step method which can be used to synthesize a triscrown with the same connecting groups, while the procedure EE is a stepwise route to the triscrown with different connecting groups. Monoprotected diaza-18-crown-6 (**S11**) (procedure EE) was treated with the appropriate tricarbonyl trichloride followed by deprotection to give key intermediate **S46** which was then condensed with the another tricarbonyl trichloride to give the triscrown hosts with different or the same connecting groups.

SCHEME 30. Procedure DD[123]



SCHEME 31. Procedure EE[123]

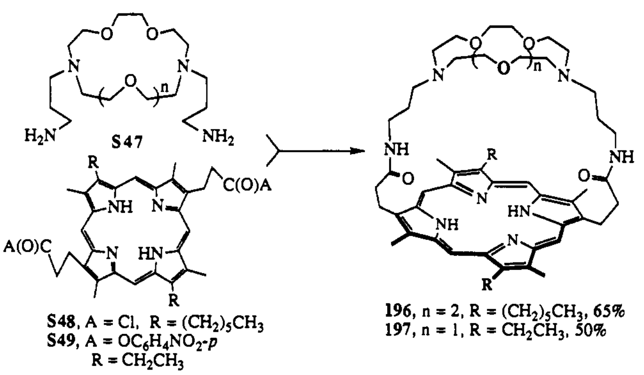


Triscrown **191** was obtained in a 7% yield by the direct cyclization of diaza-18-crown-6 (**S7**) and tricarbonyl trichloride of 1,1,1-triphenylethane (procedure DD). Hexaamide **191** also was obtained by stepwise procedure EE but in a higher yield (17%). The diborane reduction of hexaamide **191** gave the corresponding macropentacyclic hexaamine **192**. The intermediate hexaamides for **193–195** were not isolated and characterized. The crystal structures of free host **194** and the potassium thiocyanate complex of host **193** were reported.[123] NMR studies showed that specific organic molecules, such as β-naphthol and some dihydroxynaphthalenes, were selectively bound inside the cavities of macropentacycles **194** and **195** but not in **192** and **193**.[123]

7. Crown-Capped Porphyrins

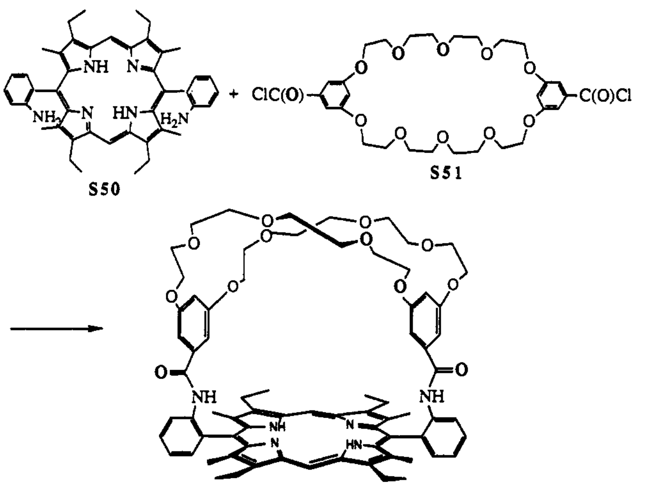
Multisite complexing agents, which incorporate subunits for binding both metal ions and organic substrates (heterotopic coreceptors), might allow reactions between metal-centered reactive sites and cobound molecular substrates. Crown ether and porphyrin units can be combined together to form such multisite complexing agents, the crown-capped porphyrins.[124-130] Macrotricyclic crown-capped porphyrins containing one crown and one porphyrin subunit can be synthesized either by the condensation of activated porphyrin dicarboxylic acid with a diamine-substituted crown ether[124,125] or by the condensation of activated crown ether dicarboxylic acid with a diamine-substituted porphyrin.[126] In pro-

SCHEME 32. Procedure FF[124,125]



cedure FF (Scheme 32), the reaction of diamine-substituted crown ethers **S47** (n = 2 or 1) with porphyrin dicarbonyl dichloride **S48**[124] or the corresponding bis(*p*-nitrophenyl) ester **S49**[124] gave the crown-capped porphyrins **196** and **197**, respectively. The properties of crown-capped porphyrin **196** was studied by ^{13}C, ^{23}Na, and ^{133}Cs NMR and UV spectroscopies.[124] The metalloporphyrin of **197** is potentially a host for anionic and cationic species. Association constants of the interaction of this capped porphyrin with various metal ions and of its zinc(II) metalloporphyrin association with ammonium salts were reported.[125] The crown-capped porphyrin **198** containing four benzene rings was synthesized by the condensation of α,α'-diaminoporphyrin **S50** and crown dicarbonyl dichloride **S51** (procedure GG, Scheme 33).[126] The ability of **198** to complex with paraquat in acetone was systematically examined by NMR spectroscopy.[126]

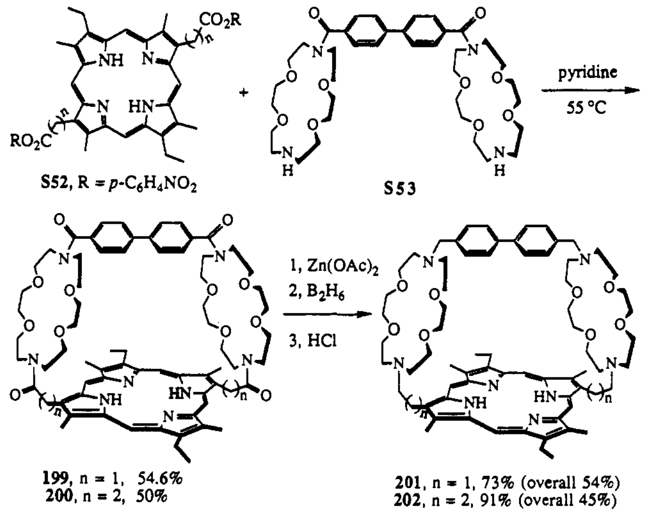
SCHEME 33. Procedure GG[126]



198

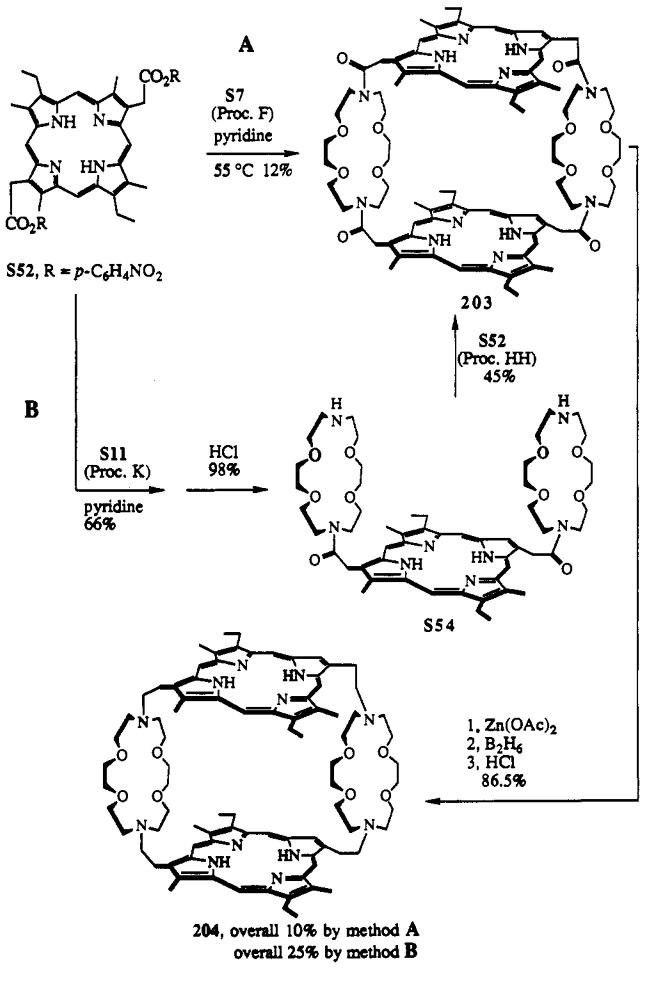
Lehn and co-workers[127–129] reported a series of macrotetracyclic crown-capped porphyrins **199–202** containing two crowns and one porphyrin (procedure HH, Scheme 34) and macropentacyclic crown-capped porphyrins **203** and **204** containing two crowns and two porphyrins (procedure II). The coupling of biphenylene-bridged biscrown ether **S53** with the bis(*p*-nitrophenyl) ester of porphyrin dicarboxylic acid (**S52**) in warm pyridine gave tetraamides **199** and **200** (procedure HH). Tetraamines **201** and **202** were obtained in high yields from tetraamides **199** and **200** by using a three-step sequence which involved (i) preparation of the zinc(II) derivatives, (ii) reduction with diborane, and (iii) treatment with concentrated HCl to effect hydrolysis and demetalation. Poor yields were obtained when the free macrotetracycles **199** and **200** were reduced directly by diborane. Formation of the zinc complex serves to protect the porphyrin ring from reaction with diborane. Photoinduced electron transfer from the singlet excited state of a zinc porphyrin to cobound silver(I) ions within **201** formed a long-lived charge-separated species.[129]

SCHEME 34. Procedure HH[127]



Two strategies were employed to synthesize the macropentacyclic tetraamide **204** (procedure II, Scheme 35).[127] In method A, key intermediate tetraamide **203** was produced directly by a 2:2 condensation of activated

SCHEME 35. Procedure II[127]

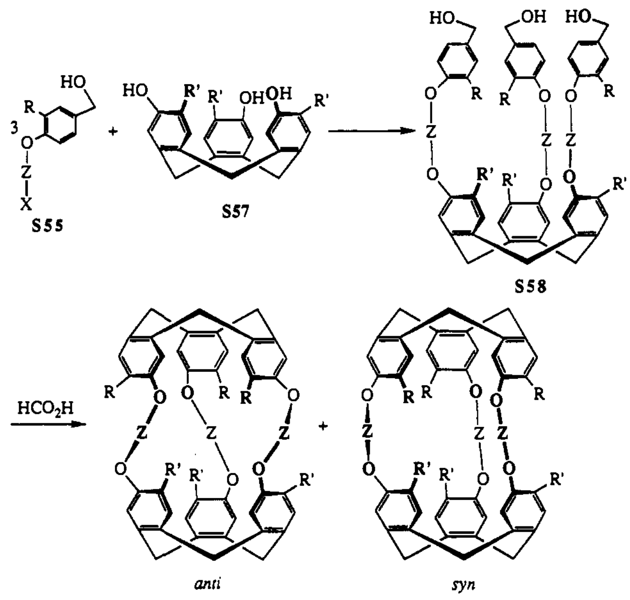


porphyrin **S52** with diaza-18-crown-6 (**S7**) under high dilution conditions. The crude product was subjected directly to the three-step reducing procedure mentioned above to give **204** in a 10% overall yield. Better yields of **204** were obtained by using stepwise method B. In this approach, the monoprotected crown ether **S11** was first condensed with **S52** followed by deprotection to give the porphyrin-bridged biscrown **S54** in a good yield. Condensation of intermediate **S54** with **S52** gave tetraamide **203** which was reduced to **204** in an overall yield of 25%. Crown-capped porphyrins **201**, **202**, and **204** formed inclusion complexes with ${}^{+}H_3N(CH_2)_9NH_3{}^{+}$. This organic cation also complexed with **201**, **202**, and **204** which contained the Zn(II) cations in the center of the porphyrin rings. Mutual interactions between these and other cobound substrates could provide means for regulating the physical properties and chemical reactivity of supramolecular species.[127,128]

8. Macropolycyclic Cryptophanes

The name cryptophane designates host molecules made of two cyclotriveratrylene units linked together face-to-face. These materials are powerful complexing agents for neutral lipophilic molecules.[130] Two types of cryptophanes have been synthesized. One cryptophane has the R and R′ substituents in an anti relationship and the other in a syn relationship as shown in Table 11 and procedure JJ (Scheme 36). Historical developments of the cyclotriveratrylenes and some cryptophanes were reviewed in 1987.[130] In this section, we show all macropolycyclic cryptophanes synthesized so far and discuss their general synthetic methods and properties. Two synthetic routes, procedures JJ and KK, have been employed. The ω-halogenated vanillyl alcohol derivative **S55**, prepared from vanillyl alcohol **S56**, was treated with cyclotriveratrylene derivative **S57** to give key intermediate **S58**. The intramolecular trimerization of **S58** under high dilution in formic acid gave the *anti*- and *syn*-cryptophane isomeric mixture (procedure JJ).[131-137]

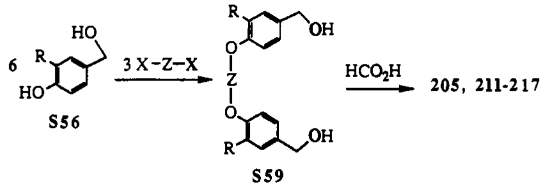
SCHEME 36. Procedure JJ[131-137]



204, 205, 211 and 216-218
(see Table 11 for Z)

New perspectives in cryptophane chemistry were opened by the recent discovery of a short and easy synthesis of these compounds in two steps from vanillyl alcohol **S56** (procedure KK, Scheme 37).[138] Bis(vanillyl alcohol) derivative **S59**, obtained from the reaction of a dihalide with **S56**, was converted into a cryptophane in formic acid in a 10–20% isolated yield (Table 11). In addition to its simplicity and convenience, this new method has the advantage of not requiring high dilution conditions. Macropolycyclic cryptophanes **205**, **206**, **211**, and **216–218** were synthesized by procedure JJ,[131-137] and cryptophanes **205** and **211–217** were obtained by procedure KK.[138] From Table 11, we can see that the anti isomer was the major product in the most cases, while the syn isomers of **211** and **216** were obtained preferentially by procedure JJ. Macropolycyclic cryptophanes **207–210** were obtained by chemical transformations of the peripheral substituents. The six methyl groups of *anti*-**205** were cleaved by lithium diphenylphosphide to give hexahydroxy cryptophane **207**.[135] This compound gave the hexaacetate **208** on acetylation and **209** on reaction with methyl bromoacetate. Saponification of **209** eventually afforded water-soluble cryptophane hexaacid **210** in a quantitative yield.[139] Optical resolution of some cryptophanes was carried out by liquid chromatography.[140]

SCHEME 37. Procedure KK[138]



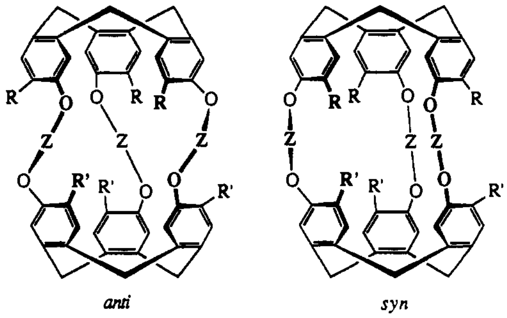
(see Table 11 for Z)

Cryptophane *anti*-**206** selectively formed an internal 1:1 inclusion complex with dichloromethane in chloroform.[137] The structure of this complex was determined.[132] Cryptophane *anti*-**206** also was used for optical resolution of bromochlorofluoromethane (CHFClBr).[133] *syn*-**206** formed 1:1 inclusion complexes with CH_2Cl_2 and CH_2Br_2 and the structure of the *syn*-**206**·CH_2Cl_2 complex was determined.[141] The cavity of *anti*-**205** containing OCH_2CH_2O bridges is not large enough to complex with $CHCl_3$, while cryptophane *anti*-**211**, with $O(CH_2)_3O$ bridges, formed very stable inclusion complexes with $CHCl_3$, $CHBr_3$, and CH_2Cl_2.[134] The structure of the *anti*-**211**·$CHCl_3$ inclusion complex has been confirmed by X-ray crystallography.[142] Water-soluble cryptophane **210** complexed $CHCl_3$ and CH_2Cl_2 strongly in D_2O, with binding constants in the range of 10^3–10^4 dm^3/mol.[139] Cryptophane *anti*-**211** formed a radical cation on oxidation and hence represents a new family of organic donors.[143] The radical cation species can be stabilized by delocalization over the entire molecule. The structure of the three-dimensional charge transfer salt [(*anti*-211^{+})·(PF_6^{-})·($CHCl_3$)] was determined.[143]

9. Cage Cavitands and Carcerands

Cram and co-workers[24,25,28,144] designated the name cavitand for the synthetic organic compounds that contain enforced cavities large enough to embrance simple molecules or ions. By this definition, the cavitands include spherands, cyclotriveratrylenes, cryptophanes, calixarenes, and others. In this review, only synthetic molecular vessels and cage-shaped cavitands

TABLE 11. Macropolycyclic Cryptophanes



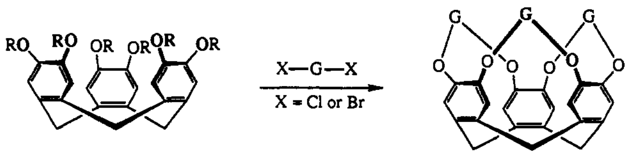
205-218

no.	remark		mp, °C	yield, %	procedure	ref(s)
105	Z = $(CH_2)_2$, R = R′ = OCH_3	*anti*	>350	60	JJ	131
		syn		0		
		anti		80	JJ	132
		syn		0		
		anti		70–80	JJ	135
		syn		0		
		anti		5	KK	138
		syn		0		
206	Z = $(CH_2)_2$, R = OCH_3, R = H	*anti*	325	25	JJ	132, 133
		syn	290	5		137
207	Z = $(CH_2)_2$, R = R′ = OH	*anti*	>260	60		135, 139
208	Z = $(CH_2)_2$, R = R′ = OC(O)CH_3	*anti*	>260			135, 139
209	Z = $(CH_2)_2$, R = R′ = OCH_2CO_2Me	*anti*	195	65		135, 139
210	Z = $(CH_2)_2$, R = R′ = OCH_2CO_2H	*anti*	220–230	100		139
210	Z = $(CH_2)_3$, R = R′ = OCH_3	*anti*	>300	27	JJ	134
		syn	>300	50		
		anti	>260	27	JJ	136
		syn		50		
		anti		17	KK	138
		syn		0		
212	Z = $(CH_2)_4$, R = R′ = OCH_3	*anti*		8	KK	138
		syn		2		
213	Z = $(CH_2)_5$, R = R′ = OCH_3	*anti*		11.5	KK	138
		syn		5.5		
214	Z = $(CH_2)_6$, R = R′ = OCH_3	*anti*		7.5	KK	138
		syn		2		
215	Z = $(CH_2)_7$, R = R′ = OCH_3	*anti*		4.5	KK	138
		syn		0		
216	Z = *cis*-$CH_2CH{=}CHCH_2$, R = R′ = OCH_3	*anti*		25	JJ	136
		syn		50		
		anti		10	KK	138
		syn		8		
217	Z = *trans*-$CH_2CH{=}CHCH_2$, R = R′ = OCH_3	*anti*		34	JJ	136
		syn		4.5		
		anti		5	KK	138
		syn		<1		
218	Z = $CH_2C{\equiv}CCH_2$, R = R′ = OCH_3	*anti*	>260	43	JJ	135
		syn	>260	20		

containing donor atoms will be discussed. The shell closure of two hemispherical cavitands forms another kind of synthetic molecular vessel, the carcerands, which are closed-surface hosts with enforced interiors large enough to imprison ordinary solvent molecules.[25,28,145]

A series of cyclotriveratrylene-based cavitands **219–223** (Table 12) were synthesized by procedure LL[146] (Scheme 38). Demethylation of cyclotriveratrylene **S60** ($R = CH_3$) gave its hydroxy derivative **S60** (R = H). Treatment of dry hexol **S60** (R = H) with the appropriate dichloride in the presence of Cs_2CO_3 gave the corresponding cavitands **219–223**. Most of them were obtained as solvates as shown in Table 12. These inclusion complexes were formed during purification or by solvent exchange. The crystal structure of cavitand **219** inclusion complex with CH_2Cl_2 was determined by X-ray crystallography.[146]

SCHEME 38. Procedure LL[146]

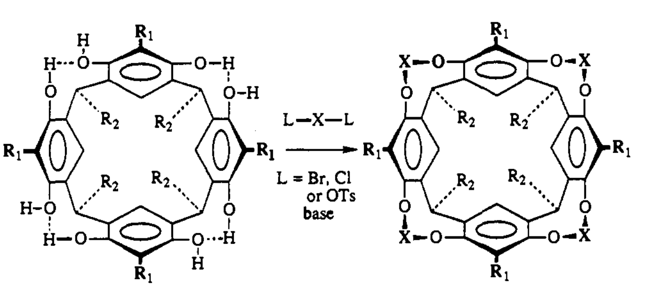


S60, R = CH_3, H

219-223

Cyclophane-based cavitands **224–239**, **263–268**, and **270–276** (Table 13) were synthesized by procedure MM (Scheme 39). Cyclophane octols **S61** were prepared by the condensation of resorcinol or its 2-methyl and 2-bromo derivatives with the appropriate aldehyde (R_2CHO) in the presence of hydrochloric acid and ethanol. The treatment of the appropriate octol **S61** with excess CH_2BrCl under basic conditions gave the corresponding cyclophane-based cavitands **224–239**.[26,27,30,144,147-153] Similarly, cavitands **263** and **264** and **265** and **266** containing $(CH_2)_2$ and $(CH_2)_3$ bridges were synthesized by treatment of the appropriate octol

SCHEME 39. Procedure MM[26,27,30,144,147-153]



S61

224-239, 263-268, 270-276

R_1 = H, CH_3, Br
R_2 = CH_3, Ph, CH_2CH_2Ph, $(CH_2)_4CH_3$, *p*-$C_6H_4CH_3$, *p*-C_6H_4Et, *p*-C_6H_4Br, *p*-C_6H_4I, *p*-$C_6H_4Sn(CH_3)_3$, *p*-$C_6H_4C{\equiv}CSi(CH_3)_3$, ferrocene, 4′-benzo-15-crown-5

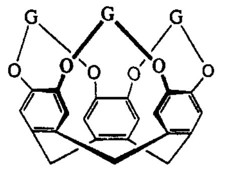
S61 with excess $TsO(CH_2)_2OTs$ and $TsO(CH_2)_3OTs$, respectively.[26] 1,4-Diazanaphthalene-bridged cavitands **267** and **268**[144,145] were synthesized from the appropriate **S61** and 2,3-dichloro-1,4-diazanaphthalene, and silicone-bridged cavitands **270–276**[27,155] were synthesized from the appropriate **S61** and dialkyldichlorosilanes. Redox-active cavitands **238** and **239** were obtained by the reaction of ferrocene-1,1′-dicarbonyl dichloride with the corresponding octol **S61**.[152] Unsymmetrical cavitand **269** was prepared from 2,3-dichloro-1,4-diazanaphthalene and the three-quarter cavitand corresponding to **224** (3X = CH_2 with OH on the other two aromatic rings).[147]

The other cavitands listed in Table 13 were prepared by functional transformations. The tetraiodo cavitand **240** was prepared by tetralithiating **224** and treating the organolithium with I_2.[26] Tetrabromo cavitand **234** was metalated with BuLi and *N*-formylmorpholine was added to give tetraaldehyde **240**.[156] Metalation of tetrabromo cavitand **234** with *t*-BuLi at −78 °C and treating the organometallic compound with $(CH_3O)_3B$ gave the aryl boron intermediate, which was oxidized with H_2O_2/NaOH to produce tetrol **242** and triol **243**.[30,150] Tetraester cavitands can be prepared by three different methods. Tetrabromocavitands **230–232** and **234** and **235** were lithiated with BuLi, and the organometallics were treated with $ClCO_2CH_3$ to give the corresponding tetraesters **245–249**.[27,149] Tetraester **244** was synthesized from both cavitand **224** and tetrabromo cavitand **229**. Metalation of **224** with PhLi at 0 °C and treatment of the organometallic with $ClCO_2CH_3$ gave tetraester **244** in an 89% yield.[29] Alternatively, tetrabromide **229** was metalated with BuLi and the product treated with CO_2 to give the corresponding tetraacid, which without characterization was treated with CH_2N_2 to give tetraester **244** in a 50% yield.[29,144] Tetraesters **244**, **245**, and **247–249** were reduced with $LiAlH_4$ to their corresponding tetrols **250–254**.[27,29,145,149] When treated with $CH_3(CH_2)_3I$/NaH, tetrols **251** and **252** gave the corresponding tetraethers **255** and **256**, respectively.[27] Treatment of tetrols **250**, **253**, and **254** with Ph_3P and *N*-chlorosuccinimide gave the corresponding tetrachlorides **257–259**.[29,145,149] Thiolation of these chlorides with thiourea in DMSO and hydrolysis of the intermediates with base led to tetrathiols **260–262**, respectively.[29,145,149]

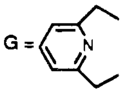
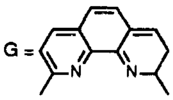
These cavitands look like bowls of different depths and shapes, varying with the character of the substituents R_1 and R_2, and the bridges. The cavitands with small substituents, e.g., H, CH_3, have shallow cavities, while those with large substituents, e.g., aromatic compounds, have deep cavities. The cavities of the cavitands with X = silicone (**270–276**), ferrocene (**236**, **238**, and **239**), and 1,4-diazanaphthalene (**267–269**) are deeper than those with other bridges. Most of the cavitands crystallized as solvates. The crystal structure of some inclusion complexes of the cavitands with solvents (caveplexes) have been determined. These structures have a variety of bowl shapes and host–guest interactions. The crystal structures of the **224**,[26] **236**,[151,152] and **264**[26] inclusion complexes with CH_2Cl_2 were determined by X-ray crystallography. The crystal structure of **226**·C_6H_6,[27] **226**·$(CH_3)_2CO/CH_2Cl_2$,[27] **228**·CH_3CN,[26] **228**·$(CH_2)_6$·C_6H_6,[26] **229**·$CHCl_3$,[26] **232**·$C_6H_5CH_3$,[27] **234**·$2H_2O$,[150] **240**·$C_6H_5CH_3$,[26] **246**·$(CH_3)_2CO$,[27] **263**·$(CH_2)_6$,[26] and **263**·$2C_6H_6$[26] inclusion complexes also were reported. The vest-shaped cavitand **267** was isolated as its inclusion complex with DMF. Although this guest could not be removed at high temperature and low pressure, it easily was displaced with $CHCl_3$.[144] The crystal structure of the **268**·$3(CH_3)_2CO$ complex was determined by X-ray crystallography.[154] Cavitand **268** selectively binds aromatic compounds, for example, benzene, toluene, chlorobenzene, fluorobenzene, and benzonitrile, in organic solvents.[154] Silicone bridged cavitands **270–272** have deep well-shaped cavities. They formed inclusion complexes with linear carbon disulfide and propyne.[155] Association constants for the interaction of **270–272** with carbon disulfide were determined by NMR spectroscopy, and the crystal structure of the **270**·CS_2 complex was confirmed by an X-ray structure determination.[155] Cavitand **275** was crystallized from diethyl ether without inclusion of solvent molecules and thereby provided the first crystal structure of a host of this series in a non-complexed state.[27] The electrochemical properties of cavitands **236**, **238**, and **239**, which contain multiple ferrocenyl redox centers, also were reported.[151,152]

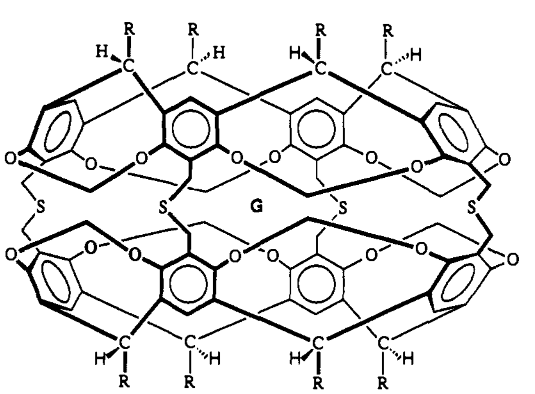
Most of the cavitands were synthesized in order to study their physical properties. Tetraaldehyde **241**, tetrol **242**, tetrachlorides **257–259**, and tetrathiols **260–262** were synthesized as key intermediates for the

TABLE 12. Cyclotriveratrylene-Based Cavitands



219-223

no.	remarks (guest)	mp, °C	yield, %	procedure	ref(s)
219	G = *m*-xylylene (CH_2Cl_2)	>360	42	LL	146
220	G = 4-*tert*-butyl-*m*-xylylene ($1.5H_2O$)	153	5	LL	146
221	G = 4-bromo-*m*-xylylene (THF or $CHCl_3$)	>360	38	LL	146
222		>360	25	LL	146
223	 (CH_2Cl_2)	>360	17	LL	146



277, R = CH_3, G = DMF, THF, CsCl, Ar, m.p. >360 °C, ~29%[29,145]

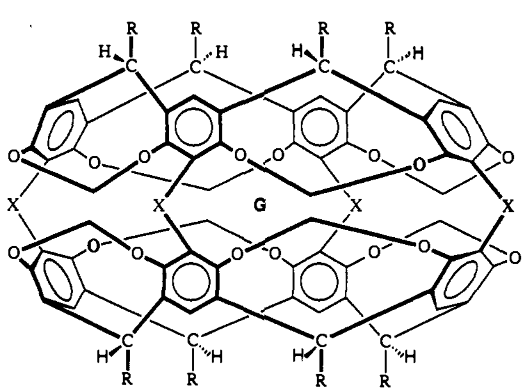
278, R = CH_2CH_2Ph[148,149]
G = $2CH_3OH$ (22%)
G = CH_3CN (11%)
G = $2CH_3CN$ (14%)

279, R = $(CH_2)_4CH_3$[148,149]
G = CH_3CH_2OH (20%)
G = $(CH_3)_2NCHO$ (20%)
G = $CH_3COCH_2CH_3$ (32%)
G = $CH_3CH_2C(O)CH_3$ (23%)

Figure 7. Carcerands and carceplexes obtained by direct coupling of two different cavitands.

syntheses of the more complicated carcerands (Figures 7 and 8). The shell closure of two hemispherical cavitands forms the carcerands. These materials are very powerful complexing agents for small neutral molecules. Nearly all of the carcerands were isolated as inclusion complexes (carceplexes) with certain solvent molecules. The shell-closure reaction of tetrachlorides **257–259** and tetrathiols **260–262** gave the corresponding carceplexes **277–279**, respectively (Figure 7). This critical shell-closure reaction was conducted under an atmosphere of Ar or $ClCF_2CF_2Cl$ at moderately high dilution and at 60–80 °C. Rb_2CO_3, Cs_2CO_3, or K_2CO_3 was used as the base. Carcerand **277** was obtained as a mixture of free host and its carceplex containing DMF, THF, Ar, and CsCl as indicated in Figure 7.[29,145] Carceplexes **278** and **279** contained only solvent molecules as indicated in Figure 7.[148,149] No shell closure occurred with benzene as the solvent.

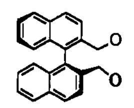
The shell-closure reaction of tetrol **242** with CH_2BrCl under high dilution conditions in various solvents at 60–100 °C with Cs_2CO_3 as the base gave the carceplexes **280** (Figure 8).[30,150] The crystal structure of carceplex **280**·$(CH_3)_2NC(O)CH_3$ was reported.[150] Similarly, carceplexes (*R*)-**281**·$CHCl_3$ and (*S*)-**281**·$CHCl_3$ were obtained by shell closure of tetrol **242** with enantiomerically pure (*R*)- and (*S*)-2,2′-[binaphthalene]yldimethyl dichloride followed by guest exchange with $CHCl_3$ (Figure 8).[157] When the **281**·$CHCl_3$ isomers were heated in neat solvents, guest exchange occurred to give 1:1 carceplexes with 1,4-$(CH_3)_2C_6H_4$, $CH_3CHICH_2CH_3$, $CH_3CH(OH)CH_2CH_3$, and $BrCH_2CH(CH_3)_2$. Judice and Cram studied the chiral diastereomeric complexes of these chiral cavitands.[157] Carcerand **282** was synthesized by the condensation of tetraaldehyde **241** with 1,3-diaminobenzene under an argon atmosphere at 65 °C (Figure 8).[156] Fourteen 1:1 carceplexes were prepared by heating **282** to 80–120 °C in neat hexachlorobutadiene, triethyl phosphate, tripropyl phosphate, menthol, or hexamethylphosphoramide or by heating **282** in solutions of tripiperidylphosphine oxide



R = $C_6H_5CH_2CH_2$

280, X = OCH_2O[30,150,158]
G = $(CH_3)_2SO$ (61%, m.p. >360 °C)
G = $(CH_3)_2NC(O)CH_3$ (54%, m.p. >360 °C)
G = $(CH_3)_2NCHO$ (49%, m.p. >360 °C)

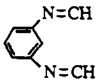
281, X =



(*R* or *S*)[157]

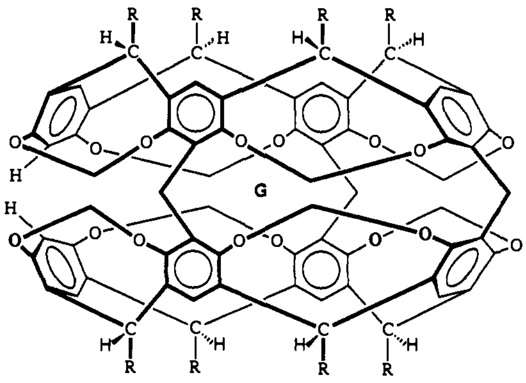
(*R*)-**281**·$CHCl_3$ (12%)
(*S*)-**281**·$CHCl_3$ (13%)

282, X =



(45%, m.p. 240° C)[156]

Figure 8. Carcerands and carceplexes obtained by the reaction of cavitands with different connectors.



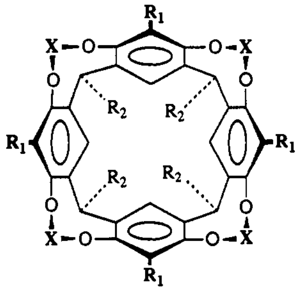
283, R = CH_2CH_2Ph[158,159]
G = $(CH_3)_2SO$ (51%)
G = $(CH_3)_2NC(O)CH_3$ (42%)
G = $(CH_3)_2NCHO$ (20%)
G = $(CH_3)_2NCHO \cdot 2CH_3CN \cdot 2CHCl_3$

Figure 9. Hemicarcerand and hemicarceplexes.

containing [2.2]paracyclophane, anthraquinone, anthracene, camphor, ferrocene, ruthenocene, amantadine, hexamethylenetetramine, or adamantane. The kinetic stability order of the complexes are **282**·ferrocene > **282**·[2.2]paracyclophane > **282**·adamantane > **282**·ruthenocene > **282**·amantadine > **282**·hexamethylenetetramine > **282**·camphor > **282**·anthraquinone > **282**·tripropyl phosphate > **282**·anthracene > **282**·menthol > **282**·triethylphosphate ≈ **282**·hexachlorobutadiene.[156]

Hemicarcerand **283** (Figure 9) was synthesized as its complex with various solvents from triol **243** and CH_2BrCl under similar conditions as those used for the synthesis of **280**.[158,159] The crystal structure of carceplex **283**·$(CH_3)_2NCHO \cdot 2CH_3CN \cdot 2CHCl_3$ shows that the

TABLE 13. Cyclophane-Based Cavitands-Synthetic Molecular Vessels



224-276

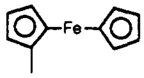
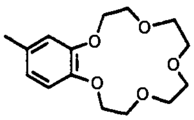
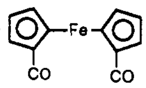
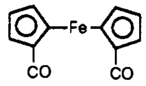
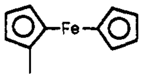
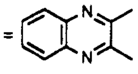
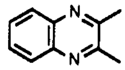
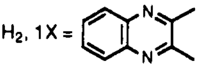
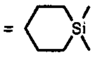
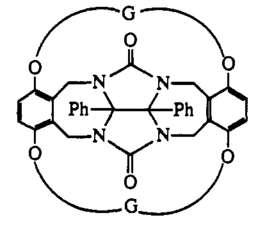
no.	remarks	mp, °C	yield, %	procedure	ref(s)
224	X = CH_2, R_1 = H, R_2 = CH_3	>360	23	MM	26
			14	MM	144
225	X = CH_2, R_1 = H, R_2 = $(CH_2)_4CH_3$	226-228	10	MM	147
226	X = CH_2, R_1 = H, R_2 = Ph	>390	5	MM	27
227	X = CH_2, R_1 = H, R_2 = p-$C_6H_4CH_3$	>390	0.9	MM	27
228	X = CH_2, R_1 = R_2 = CH_3	>360	63	MM	26
229	X = CH_2, R_1 = Br, R_2 = CH_3	≥360	55	MM	26
			4.2	MM	144
230	X = CH_2, R_1 = Br, R_2 = Ph	>360	10.4	MM	27
231	X = CH_2, R_1 = Br, R_2 = p-$C_6H_4CH_3$	>360	5.3	MM	27
232	X = CH_2, R_1 = Br, R_2 = p-C_6H_4Et	>360	49	MM	27
233	X = CH_2, R_1 = Br, R_2 = p-C_6H_4Br	>360	46	MM	27
234	X = CH_2, R_1 = Br, R_2 = CH_2CH_2Ph	280-290	52-53	MM	30
					149, 150
235	X = CH_2, R_1 = Br, R_2 = $(CH_2)_4CH_3$		56	MM	148, 149
236	X = CH_2, R_1 = H, R_2 = 		1[a]	MM	151
		>250	2[a]	MM	152
237	X = CH_2, R_1 = H, R_2 = 		4[a]	MM	153
238	X =  , R_1 = H, R_2 = CH_3	>250	4[a]	MM	152
239	X =  , R_1 = H, R_2 = 	>250	2[a]	MM	152
240	X = CH_2, R_1 = I, R_2 = CH_3	>360	40		26
241	X = CH_2, R_1 = CHO, R_2 = CH_2CH_2Ph		75		156
242	X = CH_2, R_1 = OH, R_2 = CH_2CH_2Ph	300	53		30, 150
243	X = CH_2, $3R_1$ = OH, $1R_1$ = H, R_2 = CH_2CH_2Ph	300	23		150
244	X = CH_2, R_1 = CO_2Me, R_2 = CH_3		40-56		29, 144
		>360	89		29
245	X = CH_2, R_1 = CO_2Me, R_2 = Ph	>360	74		27
246	X = CH_2, R_1 = CO_2Me, R_2 = p-$C_6H_4CH_3$	>360	57		27
247	X = CH_2, R_1 = CO_2Me, R_2 = p-C_6H_4Et	>360	64		27
248	X = CH_2, R_1 = CO_2Me, R_2 = CH_2CH_2Ph		82		149
249	X = CH_2, R_1 = CO_2Me, R_2 = $(CH_2)_4CH_3$		80		149
250	X = CH_2, R_1 = CH_2OH, R_2 = CH_3	360	77		29, 145
251	X = CH_2, R_1 = CH_2OH, R_2 = Ph		88		27
252	X = CH_2, R_1 = CH_2OH, R_2 = p-C_6H_4Et		55		27
253	X = CH_2, R_1 = CH_2OH, R_2 = CH_2CH_2Ph		85		149
254	X = CH_2, R_1 = CH_2OH, R_2 = $(CH_2)_4CH_3$		90		149
255	X = CH_2, R_1 = $CH_2O(CH_2)_3CH_3$, R_2 = Ph	271-273	52		27
256	X = CH_2, R_1 = $CH_2O(CH_2)_3CH_3$, R_2 = p-C_6H_4Et	272-274	15		27
257	X = CH_2, R_1 = CH_2Cl, R_2 = CH_3		65		29
		>360	99		145
258	X = CH_2, R_1 = CH_2Cl, R_2 = CH_2CH_2Ph		72		148, 149
259	X = CH_2, R_1 = CH_2Cl, R_2 = $(CH_2)_4CH_3$		65		148, 149
260	X = CH_2, R_1 = CH_2SH, R_2 = CH_3	>360	56		29
		>360	71		145
261	X = CH_2, R_1 = CH_2SH, R_2 = CH_2CH_2Ph		80		148, 149
262	X = CH_2, R_1 = CH_2SH, R_2 = $(CH_2)_4CH_3$		60		148, 149
263	X = $(CH_2)_2$, R_1 = R_2 = CH_3	330	43	MM	26
264	X = $(CH_2)_2$, R_1 = Br, R_2 = CH_3	>360	35	MM	26
265	X = $(CH_2)_3$, R_1 = R_2 = CH_3	>360	16	MM	26
266	X = $(CH_2)_3$, R_1 = Br, R_2 = CH_3	>360	50	MM	26
267	X =  , R_1 = H, R_2 = CH_3		34	MM	144

TABLE 13 (Continued)

no.	remarks	mp, °C	yield, %	procedure	ref(s)
268	X = , R_1 = H, R_2 = $(CH_2)_4CH_3$		88	MM	154
269	3X = CH_2, 1X = , R_1 = H, R_2 = $(CH_2)_4CH_3$	124–140	7		147
270	X = Me_2Si, R_1 = H, R_2 = CH_3	>320	37	MM	155
271	X = Et_2Si, R_1 = H, R_2 = CH_3	>320	9	MM	155
272	X = , R_1 = H, R_2 = CH_3	>320	7	MM	155
273	X = n-Bu_2Si, R_1 = H, R_2 = p-C_6H_4Br	>300	63	MM	27
274	X = n-Bu_2Si, R_1 = H, R_2 = p-C_6H_4I	326–327	79	MM	27
275	X = n-Bu_2Si, R_1 = H, R_2 = p-$C_6H_4SnMe_3$	250	66	MM	27
276	X = n-Bu_2Si, R_1 = H, R_2 = p-$C_6H_4C{\equiv}CSiC(CH_3)_3$	349–350	53	MM	27

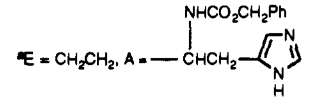
[a] Overall yields.

TABLE 14. **Basket-Shaped Cavitands**



284-294

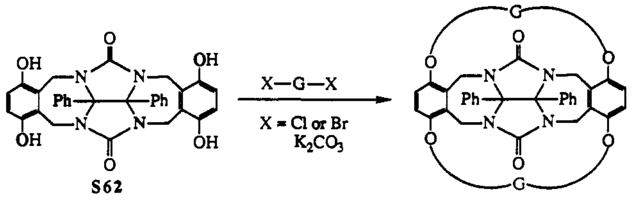
no.	remarks	mp, °C	yield, %	procedure	ref(s)
284	G = $(CH_2)_6$		34	NN	161
285	G = $CH_2(CH_2OCH_2)_2CH_2$		16	NN	161
286	G = $CH_2(CH_2OCH_2)_3CH_2$		75	NN	160, 161
287	G = $CH_2(CH_2OCH_2)_4CH_2$		55	NN	161
288	G = EOEN(EOEOH)EOE[a]	>195	40	OO	162
289	G = EOEN(CH_2Ph)EOE[a]	>185	52	OO	162
290	G = EOENHEOE[a]	>200	70		162
291	G = $CH_2CH_2N(CH_2Ph)CH_2CH_2$	>200	73	OO	163
292	G = $CH_2CH_2NHCH_2CH_2$	>200	95		163
293	G = EOEN-[EOEOC(O)A]EOE[a]	>165	46		162
294	G = EOEN-[EOEOC(O)CH_3]EOE[a]	>190	40		162

[a] E = CH_2CH_2, A = 

$(CH_3)_2NCHO$ guest was firmly lodged within the cavity and the other molecules acted as solvates outside the cavity. Upon heating in solvents that were too large to occupy the cavity, the complexes of **283** released their guests to give free hemicarcerand **283**.[158]

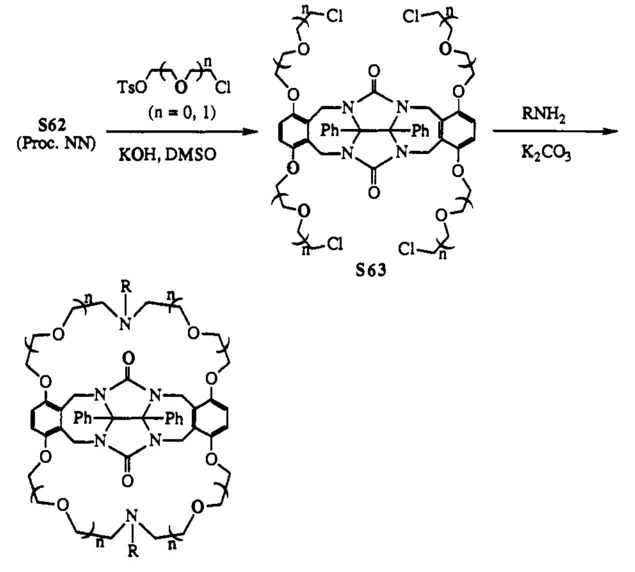
The series of basket-shaped cavitands listed in Table 14 was synthesized from the novel concave building block **S62**, which was prepared from urea, benzil, hydroquinone, and formaldehyde (procedure NN, Scheme 40).[160-163] This building block contains two fused 2-imidazolidone rings, which are flanked by two o-xylylene units. Its overall shape is concave, and its convex side is shielded by two phenyl substituents. The basket-shaped cavitands **284–287** were synthesized as shown in procedure NN by treating **S62** with 2 equiv of 1,6-dibromohexane or the appropriate polyethylene glycol dichloride in DMSO with K_2CO_3 as the base.[160,161] The reaction of **S62** with a slight excess of 1-(tosyloxy)-5-chloro-3-oxapentane or 2-chloroethyl tosylate in DMSO with KOH as the base gave **S63** with four oxyethylene chains terminated by a chloride (procedure OO, Scheme 41). **S63** (n = 1) was treated with 2-(2-aminoethoxy)ethanol or benzylamine, using potassium carbonate as the base and catalytic amounts of potassium iodide, to give basket-shaped cavitands **288** and **289**, respectively.[162] Cavitand **291** was prepared from **S63** (n = 0) and benzylamine.[163] Hydrogenation of **289** and **291** using 10% Pd/C in acetic acid gave **290** and **292** in yields of 70 and 95%, respectively.[162,163] Compound **293** was synthesized by the treatment of **288** with N-(benzyloxycarbonyl)-L-histidine. **288** was acetylated using acetic anhydride in pyridine to yield **294**.

SCHEME 40. **Procedure NN**[160,161]



S62 **284-287**

SCHEME 41. **Procedure OO**[162,163]



S63

288-289, 291

Complexation of these basket-shaped cavitands with alkali metal ions and ammonium guests, as well as with aliphatic and aromatic diammonium cation guests, has been studied. The oxygen atoms of the urea units and

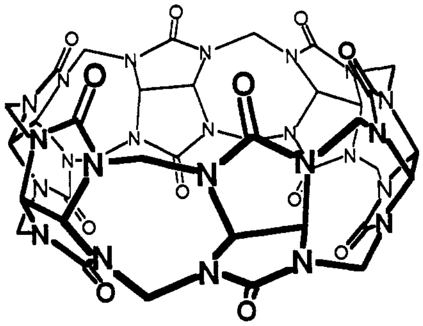


Figure 10. Cavitand cucurbituril 295.[164-170]

the oxyethylene bridges in these cavitands form two receptor sites at the far end of the molecules. Cavitand **285** formed 1:1 inclusion complexes with all alkali metal and ammonium picrate salts in $CHCl_3$ saturated with H_2O.[161] **286**, **288–290**, and **293** formed 1:1 complexes with potassium picrate in the same solvent system.[161,162] Cavitand **287**, containing a large ring, formed 1:1 as well as 1:2 complexes with K^+ and Cs^+ ions depending on the concentration of the guests.[161] UV spectral studies indicated that these 1:1 complexed salts exist as separated ion pairs because the hosts completely encapsulated the cations. The association constants and free energies for the interaction of baskets **285–290** and **293** with Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and t-$BuNH_3^+$ picrates were determined by the extraction method.[161,162] Hosts **288–290** and **293** have strong affinity for the NH_4^+ ion and exhibit the same binding pattern: $NH_4^+ > CH_3NH_3^+ > t\text{-}BuNH_3^+$.[162] Because of the presence of two receptor sites in these cavitands, they form complexes with aliphatic and aromatic diammonium dipicrates. In the complexes, the diammonium guests are situated between the *o*-xylylene rings. The experimental results revealed that **286** and **287** formed 1:1 complexes with aliphatic diammonium salts $^+H_3N(CH_2)_nNH_3^+$ with $n \geq 5$, and 1:2 host–guest complexes with $n = 3$.[161] The association constant and free energy values show that **286** and **287** formed the most stable complexes with aliphatic diammonium salts with $n = 8$ and 9, while **288**, **289**, and **293** formed the most stable complexes with $n = 4$ and **290** with $n = 3$.[162] Association constants for their interaction with *p*- and *m*-xylylenediammonium and *p*- and *o*-phenylenediammonium dipicrates indicated that **286** formed more stable complexes with *p*- and *m*-xylylenediammonium salts, while **288–290** and **293** formed the most stable complexes with *o*-phenylenediammonium salts.[161,162] The properties of the **293** complex with Zn(II) was also studied.[162] Cages **289–292** strongly bound the dihydroxybenzenes in organic solvents.[163] The association constants have values of up to 3×10^5 M^{-1}. The guest was sandwiched between the *o*-xylylene walls of the host and formed hydrogen bonds to the receptor sites.

Cavitand cucurbituril **295** (Figure 10) was first reported without structural information; however, it was found to form crystalline complexes with a variety of metal salts and dye stuffs.[164] This compound was recently rediscovered,[165] and its structure was determined.[166] Cucurbituril **295** is a nonadecacyclic cage structure of hexagonal symmetry. It is readily assembled by acid-catalyzed condensations of urea, glyoxal, and formaldehyde.[167] Inclusion complexation properties of this compound with various aliphatic primary, secondary, and diammonium salts in aqueous formic acid have been studied in 1:1 (v/v) HCO_2H/H_2O.[167-169] The results indicated that the cavity of **295** can accommodate an isobutyl group, a phenyl group, or an aliphatic ring of up to five members. Among the straight-chain aliphatic monoamines, $H(CH_2)_nNH_2$, *n*-butylamine formed the most stable complex, and the order of complex stability follows the trend $n = 1 < 2 < 3 < 4 > 5 > 6 > 7$. α,ω-Alkanediamines $[H_2N(CH_2)_nNH_2]$ formed stronger complexes with **295** than the monoamines. 1,6-Hexanediamine ($n = 6$) formed the most stable complex with the following stability order for the diamines: $n = 3 < 4 < 5 < 6 > 7 > 8 > 9 > 10$. Cyclopentylmethanamine formed the most stable complex among the cycloalkylmethanamine series. The guest with more amine groups formed the more stable complex with **295**.[167-169] The stability of the spermine $[H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2]\cdot$**295** complex was 85 times greater than that of spermidine $[H_2N(CH_2)_4NH(CH_2)_3NH_2]$, which bound 9 times more tightly than did 1,4-butanediamine $[H_2N(CH_2)_4NH_2]$. A thioether-containing guest bound more strongly to **295** than an (oxy)ether-containing guest, but less strongly than the corresponding alkylamine, e.g., $H_2N(CH_2)_5NH_2 > H_2N(CH_2)_2S(CH_2)_2NH_2 > H_2N(CH_2)_2O(CH_2)_2NH_2$. Cucurbituril **295** has also been shown to be an effective catalyst for a specific cycloaddition reaction.[170]

10. Macrotricyclic Quaternary Ammonium Salts

Quaternization of spherical macrotricycle **5** (Table 1) yielded the corresponding macrotricyclic quaternary ammonium salt **296** (Table 15).[13] Since ligand **296** formed inclusion complexes with spherical anions,[13] various other macrotricyclic quaternary ammonium salts **297–308** (Table 15) have been synthesized. Two methods have been used to synthesize these anion receptors. Symmetrical macrotricyclic quaternary ammonium salts **297** and **298** were synthesized by procedure PP (Scheme 42). Ring closure of **S64** was achieved by reaction with the appropriate dicarbonyl dichloride to give the tricyclic amides **S65** (40–50%) which were reduced with diborane to the tetrahedral tetraamine **S66** (65–75%).[171,172] Quaternization with methyl fluorosulfate or methyl *p*-toluenesulfonate in nitromethane converted **S66** into the corresponding tetraammonium salts **297** and **298**. Salts of these ligands with other anions were obtained by an exchange method.[172,173]

SCHEME 42. Procedure PP[170,173]

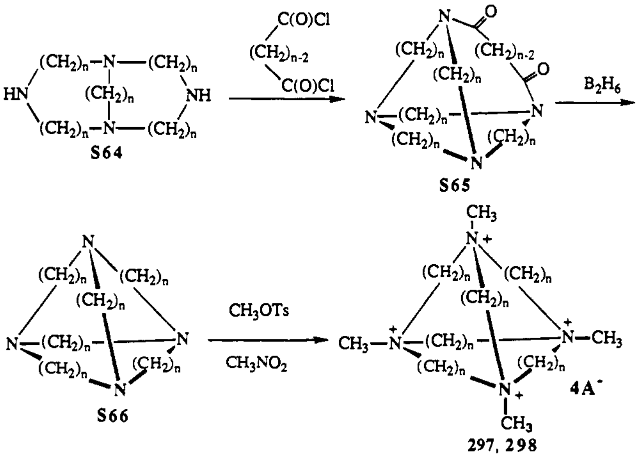
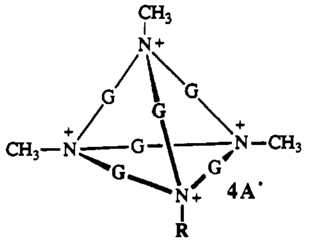


TABLE 15. Macrotricyclic Quaternary Ammonium Salts

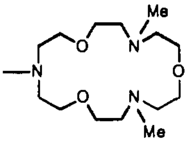


$A^- = FSO_4^-$, $p\text{-}MeC_6H_4SO_3^-$, BF_4^-, F^-

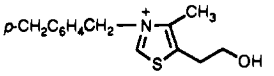
296-308

no.	remarks	mp, °C	yield, %	procedure	ref(s)
296	R = CH_3, G = $CH_2CH_2OCH_2CH_2$			PP	13
297	R = CH_3, G = $(CH_2)_6$	>300	85	PP	172, 173
298	R = CH_3, G = $(CH_2)_8$	>290	98	PP	172, 173
299	R = $p\text{-}CH_2C_6H_4CO_2CH_3$, G = $(CH_2)_6$	>300	74	QQ	174
			80	QQ	175
300	R = $p\text{-}CH_2C_6H_4CO_2H$, G = $(CH_2)_6$	>300	92	QQ	174
			85		175
301	R = $p\text{-}CH_2C_6H_4CH_2OH$, G = $(CH_2)_6$	>300	92		176
302	R = $p\text{-}CH_2C_6H_4CH_2Br$, G = $(CH_2)_6$	>300	95		176
			88		177
303	R = $p\text{-}CH_2C_6H_4C(O)TACr$,[a] G = $(CH_2)_6$	208–210	85	QQ	174
			100	QQ	175
304	R = $p\text{-}CH_2C_6H_4CH_2TACr$,[a] G = $(CH_2)_6$	202–204	93	QQ	174
			65	QQ	175
305	R = STOL,[b] G = $(CH_2)_6$		32[c]	QQ	176
306	R = STOL,[b] G = $(CH_2)_8$		50[c]	QQ	176
307	R = $p\text{-}CH_2C_6H_4CH_2\text{-}W$,[d] G = $(CH_2)_6$, X = $(CH_2)_8$		44	QQ	178
			54	QQ	177
308	R = $p\text{-}CH_2C_6H_4CH_2\text{-}U$,[e] G = $(CH_2)_6$, X = $(CH_2)_8$		50	QQ	177

[a] TACr =

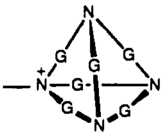


[b] STOL =

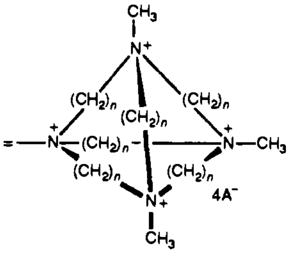


[c] Overall yields.

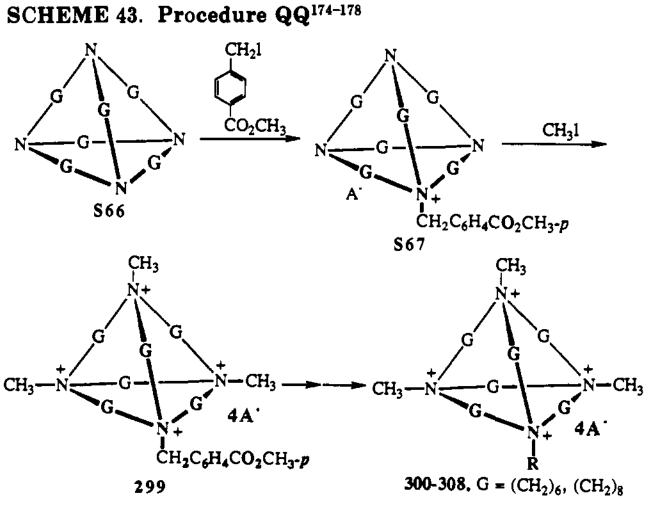
[d] W =



[e] U =

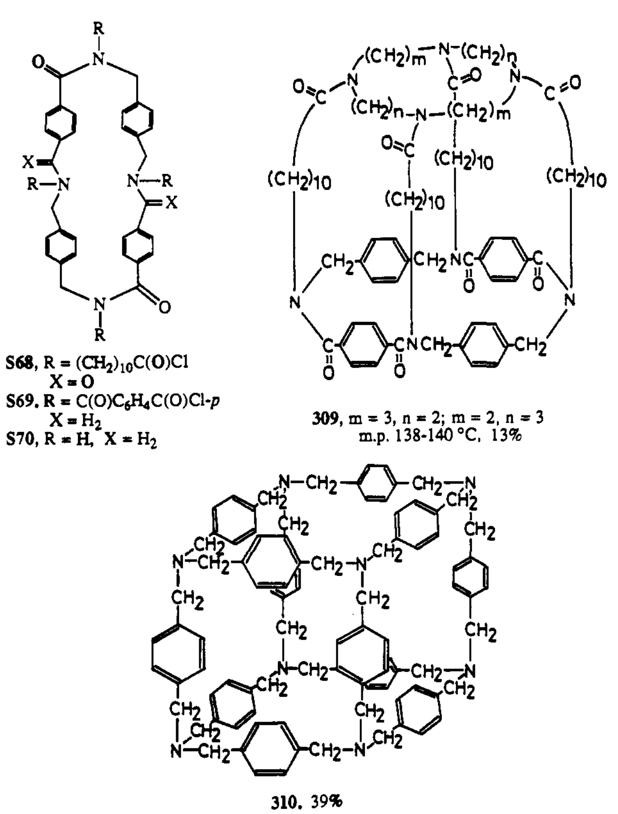


SCHEME 43. Procedure QQ[174-178]



Unsymmetrical macrotricycles **299–306**, containing three *N*-methyl groups and an N-para-substituted benzyl group, were synthesized by a stepwise method (procedure QQ, Scheme 43).[175-177] Monoquaternization of tetraamine **S66** by the substituted benzyl iodide gave **S67**. **S67** was treated with CH_3I to give ester **299** which was hydrolyzed to the corresponding acid **300**. Reduction of ester **299** using borane–dimethyl sulfide/nitromethane gave **301** which also was obtained by an alternative procedure.[176] Cleavage of the benzylammonium bond in **299** produced the triquaternized compound which was allowed to react with 4-(bromomethyl)benzyl alcohol to give **301**. The transformation of **301** into bromide **302** was readily accomplished in concentrated aqueous HBr. Macrotricycle **303**, containing a triaza-crown ether substituent, was obtained by coupling acid **300** and dimethylated triaza-18-crown-6. This compound was reduced to form **304** using the $BH_3{\cdot}S(CH_3)_2$ complex in nitromethane.[175] Macrotricycles **305** and **306**, containing the thiazolium heterocycle was synthesized by quaternizing the thiazole derivative with bromide **302** to give overall yields of 32% and 50% for **305** and **306**, respectively.[176] The reaction of **302** with excess tetraamine **S66** gave bistricycle **307** which was quaternized into bismacrotricyclic quaternary ammonium salt **308**.[177,178]

The macrotricyclic quaternary ammonium compounds **297** and **298** formed stable inclusion complexes with anionic guests in water.[172,173] Their complexes with the bromide anion were more stable than their complexes with nearly all other anions. The crystal structure of inclusion complex $[297^{4+}{\cdot}I^-]{\cdot}3I^-{\cdot}3CH_3CN{\cdot}H_2O$ showed that one iodide anion is symmetrically encapsulated into the spherical intramolecular cavity of the macrotricycle.[179] Macrotricycle **298** catalyzed binuclear aromatic and aliphatic nucleophilic substitution reac-



S68, R = $(CH_2)_{10}C(O)Cl$, X = O
S69, R = $C(O)C_6H_4C(O)Cl$-*p*, X = H_2
S70, R = H, X = H_2

309, m = 3, n = 2; m = 2, n = 3
m.p. 138-140 °C, 13%

310, 39%

Figure 11. Macropentacyclic azaparacyclophanes.

tions,[180-182] as well as the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate.[183] Ditopic host molecule **304** selectively bound amino carboxylates over simple ammonium salts in 9:1 (v/v) methanol/H_2O,[175] and it preferentially bound hydrophobic amines in H_2O.[184] Ditopic **308** has a 3-fold greater attraction for amino acids than do monotopic receptors.[177,178,184] Macrotricycles **305–306** exhibited enhanced substrate selectivity and catalytic activity in decarboxylations of α-ketoacids compared to simpler salts lacking the receptor substructure.[176]

11. Macropentacyclic Azaparacyclophanes

Murakami and co-workers[185-188] synthesized capped-azaparacyclophane **309** and cubic azaparacyclophane **310** (Figure 11). Host **309** was synthesized by condensation of tetraundecoyl tetrachloride **S68** with 1,4,8,11-tetraazacyclotetradecane under high dilution conditions.[185,186] Cubic cyclophane **310**, which has a hydrophobic cavity surrounded by six faces each containing the 2,11,20,29-tetraaza[3.3.3.3]paracyclophane ring, was prepared by treating **S69** with **S70** under high dilution conditions followed by reduction with borane–dimethyl sulfide.[187,188] Host **309** has a cavity that is deep enough to incorporate a number of hydrophobic substrates. Cubic azaparacyclophane **310** provides a rigid, hydrophobic, three-dimensional cavity. Binding constants for the formation of inclusion complexes of these hosts with various fluorescent substrates were determined by fluorescence spectroscopy.[185-188] The restricted and rigid geometry of **310** makes it sensitive to guest size and allows **310** to have regioselective molecular recognition. *N*-Phenyl-1-naphthylamine (α-PNA) fits best in the cavity of **310** compared to other neutral arenes studied.[189] 2,7-Naphthalenedisulfonate fits most favorably in the cavity compared to all the naphthalene disulfonates tested. Cubic azaparacyclophane **310** also behaved as a polycationic host in acidic aqueous media and exhibited pH-dependent binding of 8-anilinonaphthalene-1-sulfonate.[190]

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