Host–Guest Complexation. 9. Macrocyclic Polyethers and Sulfides Shaped by One Rigid Dinaphthyl Unit and Attached Arms. Synthesis and Survey of Complexing Abilities[1,2]

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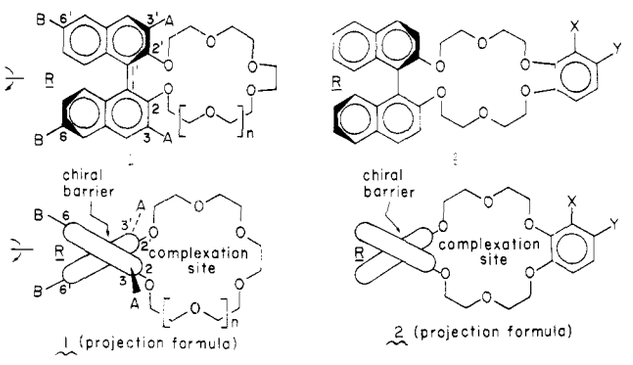
This paper reports the syntheses and characterization of a large number of stereoisomeric macrocyclic polyether and polyether–polythioether hosts that contain one 1,1′-dinaphthyl unit bound to oxygen or sulfur in the 2,2′-position. These macrocyclic compounds contain five to seven ring oxygens, or one to two sulfurs plus four to five ring oxygens. The ring heteroatoms are regularly spaced by their attachment to one another through 1,1′-dinaphthyl units, through ethylene, or through 1,2-benzene units. The heteroatoms, when turned inward, can become approximately coplanar. The naphthalene rings of the chiral 1,1′-dinaphthyl units occupy planes perpendicular to the plane of the macro ring, and these two aryls protrude from each face of the macro ring. The unshared electron pairs of the heteroatoms act as binding sites for appropriate metal or alkylammonium cations. Substituents attached at the 3,3′-positions of the 1,1′-dinaphthyl unit converge on and provide additional shape to the space surrounding the central binding hole of the macro ring. Certain of these units terminate in functional groups that provide additional ligands for cationic guests, in some cases supplying counterions for the charge on the guests. Substituents attached at the 6,6′-positions of the 1,1′-dinaphthyl unit diverge from the macro ring and its environment, and can be used to manipulate solubility properties or to bind the hosts to solid supports. Substituents attached at the 3- or 4-positions of the 1,2-benzene units, when long enough and in the proper conformations, can curl to place additional binding sites on the edge of the macro ring. The maximum rotations and absolute configurations of some of the optically active hosts were determined. Ring closures (6–65% yield) involved aryl oxide or aryl sulfide anion substitutions on appropriate alkyl ditosylates. Generalizations useful in developing synthetic strategies for these hosts are as follows. (1) Substituents in the 3-positions of the 1,1′-dinaphthyl unit had to be introduced before ring closure. (2) Alkyl, CH_2OH, and $CH_2N(CH_2CH_2)_2O$ substituents attached to the 3-positions of the naphthalene rings did not interfere with the ring-closing reactions. (3) Substituents in the 3- or 4-positions of the 1,2-benzene unit had to be introduced before ring closure. (4) Substituents attached to the 1,2-benzene unit that did not interfere with ring closures were $CH_2CH{=}CH_2$ in the 3-position and $(CH_2)_3OH$ in the 4-position. (5) Electrophilic substitution reactions of the macrocyclic ethers occurred in the 6-positions of the naphthalene rings and included bromination, acetylation, and chloromethylation. (6) Once introduced, substituents were subject to a wide variety of reactions that did not affect the configuration of the dinaphthyl or the integrity of the macrocyclic ring system. The complexing abilities of certain of the hosts toward Na^+, K^+, Ca^{2+}, Sr^{2+}, Ba^{2+}, $ArNH_3^+$, and RNH_3^+ were surveyed. In several cases in which the numbers of charges on host and guest matched, the salt complexes were characterized. The lipophilizing abilities of certain of the carboxylate-carrying hosts for Na^+, K^+, Ca^{2+}, and Ba^{2+} were compared. The complementary character of host–guest relationships is discussed.

Previous papers of this series described syntheses of macrocyclic host compounds containing one,[4,5] two,[5,6] or three[5] chiral 1,1′-dinaphthyl or 1,1′-ditetralyl[6] units. Ether oxygens were attached to the 2,2′-positions of these units and to ethylene, polyethyleneoxy,[4-6] 2,6-pyridinedimethylyl,[5] 2,5-tetrahydrofurandimethylyl,[5] or 1,3-benzenedimethyl units[5] to complete the macrocycles. The dinaphthyl or ditetralyl units act as chiral barriers, and the heteroatoms provide binding sites for alkylammonium or metal cationic guests in complexation. Paper 8 of this series describes the introduction of substituents into the 3,3′-positions of dilocular[5] cycles containing two dinaphthyl or ditetralyl units and into the 6,6′-positions of cycles containing two dinaphthyl units.[6]

Molecular models (Corey–Pauling–Koltun, or CPK) of hosts that contain one dinaphthyl unit and six ether oxygens, such as **1** (with n = 1) or **2**, indicate that, in their normal gauche conformations,[7] the six oxygens possess a roughly regular hexagonal arrangement. One of the naphthalene rings is above and in a plane tangent and perpendicular to the macro ring, and the other naphthalene ring is below and in a plane tangent and perpendicular to the macro ring. Thus the space not occupied by the naphthalene rings above and below each face of the macro ring is available for distribution of substituents a, b, and c of $abcCNH_3^+$ guest ions in complexes with these monolocular hosts. In contrast to the naphthalene rings in **2**, the benzene ring is roughly coplanar with the macro ring. Compounds **1**, when the two A groups are identical with one another and the two B groups are identical with one another, possess C_2 axes and are therefore "nonsided" (two faces of the macro ring are identical). Compounds **2**, when either substituents X or Y are other than H, are "sided", since these substituents destroy the C_2 axes of the structures.



1 (projection formula) **2** (projection formula)

Compounds represented by structure **1** are subject to variation in shapes with changes in the values of n which control hole size, and in the nature and bulk of substituents A attached to the 3-positions of the naphthalene rings. These substituents are located above and below the planes of the macro rings. When appropriately structured, substituents A can be used to place functional groups directly over and under the center of the hole of the macro ring to act as additional ligands for guests occupying that hole in the complexes. In

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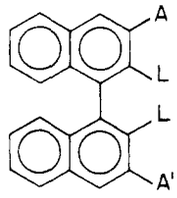
addition, these substituents can be used to further shape the chiral barrier. Because of their location with respect to the complexation site, substituents A are said to be convergent. In contrast, substituents B located in the 6-positions of the naphthalene rings diverge from the complexation site, and can be used to manipulate the solubility properties of the hosts or to attach them to solid supports. Although substituents X and Y in **2** diverge from the complexation site, when appropriately structured, they can potentially "return" to the edge of the complexation site to complex substituents a, b, and c of $abcCNH_3^+$ guests.

This paper reports on the syntheses and general survey of some of the complexing properties of compounds **1** and **2** with RNH_3^+, $ArNH_3^+$, M^+, and M^{2+} ions. Also reported are the syntheses of five cycles possessing the general structures of **1** and **2** with A = B = X = Y = H, but with some of the oxygens replaced with sulfur.

Results

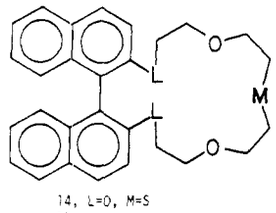
Syntheses. The following 1,1′-dinaphthyl compounds served as starting materials. Racemic and optically pure enantiomers of 2,2′-dihydroxy-1,1′-dinaphthyl (**3**) of known absolute configuration and optical stabilities have been previously reported,[5] as have racemic and optically pure enantiomers of the "dinaphthyl two-armed ditosylates"[5,6] (**4**). The two sulfhydryl units of 2,2′-disulfhydryl-1,1-dinaphthyl (**7**)



3, A=A′=H, L=OH
4, A=A′=H, L=O(CH$_2$CH$_2$O)$_2$Ts
5, A=A′=H, L=OCSN(CH$_3$)$_2$
6, A=A′=H, L=SCON(CH$_3$)$_2$
7, A=A′=H, L=SH
8, A=A′=CH$_2$OH, L=OH
9, A=CH$_2$OH, A′=H, L=OH
10, A=CH$_2$OH, A′=CH$_3$, L=OH
11, A=CH$_2$N(CH$_2$CH$_2$)$_2$O, A′=CH$_2$OH, L=OH
12, A=A′=CH$_2$N(CH$_2$CH$_2$)$_2$O, L=OH
13, A=A′=CH$_2$N(CH$_3$)$_2$, L=OH

were introduced into the dinaphthyl system by a method patterned after that of Newman,[8] and involved the sequence **3** → **5** → **6** → **7**. The 280 °C required for the rearrangement of **5** → **6** undoubtedly would have led to racemic product had optically active starting material been used.[5] Compounds **8**, (*R*)-**8**, (*S*)-**8**, and **9**–**13** were available from previous studies[6].

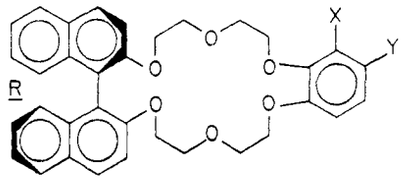
Macrocycles **14**–**18** which contained sulfur atoms as parts of their ring systems were synthesized as follows. Treatment of racemic dinaphthyl two-armed ditosylate **4** with disodium sulfide gave **14** (52%), with 1,2-ethanedithiol–NaOH gave **15**



14, L=O, M=S
15, L=O, M=SCH$_2$CH$_2$S
16, L=O, M=1,2-OC$_6$H$_4$O
17, L=O, M=1,2-OC$_6$H$_4$S
18, L=S, M=1,2-OC$_6$H$_4$O

(16%), with disulfhydrylbenzene–NaOH gave **16** (72%), and with 2-sulfhydrylphenol–KOH gave **17**. Dithiol **7** with KOH and 8,9-benzo-1,16-ditosyl-1,4,7,10,13,16-hexaoxahexadeca-8-ene[5] produced **18** (58%), which is isomeric to **16**.

The synthesis of parent host **19** with X = Y = H from ditosylate **4** and catechol was reported previously.[5] Similarly, from **4** and 3-allylcatechol–KOH,[9] a 41% yield of cycle was produced, 29% of which was **20** and 71% the corresponding allyl derivative (^{1}H NMR analysis). Accordingly, the mixture was treated with *t*-BuOH in benzene–*t*-BuOH, which completed the isomerization of the allyl to the propenyl group to produce an overall yield of 39% for **20**. This propenyl group



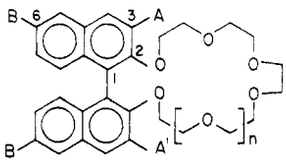
General Structure **2** (racemic)

19, X=Y=H
20, X= CH=CHCH$_3$, Y=H
21, X=H, Y=(CH$_2$)$_3$OH
22, X=CHO, Y=H
23, X=CH$_2$OH, Y=H
24, X=CH$_2$Cl, Y=H
25, X=CH$_2$N$_3$, Y=H
26, X=CH$_2$NHCOCH$_3$, Y=H
27, X=H, Y=(CH$_2$)$_3$Cl
28, X=H, Y=(CH$_2$)$_3$CO$_2$H

is a masked aldehyde group (see below), and provides an approach to attaching carbon substituents in the 3-position of the benzene ring of parent host **19**.

A route to compounds containing carbon substituents in the 4-position of the benzene ring of host **19** involves the readily available 3,4-dimethoxyallylbenzene[10] as starting material. Addition of diborane to this alkane, followed by oxidation of the adduct, gave 3-(3,4-dimethoxyphenyl)-1-propanol (84%) contaminated with 8.5% of 3-(3,4-dimethoxyphenyl)-2-propanol. The mixture was demethylated with BBr_3 to give 3-(3,4-dihydroxyphenyl)-1-propanol (78%) pure to TLC and ^{1}H NMR spectra (60% overall). When submitted to ring closure with ditosylate **4**–KOH, cycle **21** was obtained (46%). Thus the greater acidity of the phenolic hydroxyl groups over that of the alcohol group of the triol provides, with base, phenoxides in concentrations enough greater than alkoxide to direct the ring closure to the desired product **21**.

The side chains of cycles **20** and **21** were elaborated as follows. Controlled ozonolysis of alkene **20** gave aldehyde **22**, which was reduced ($LiAlH_4$) to alcohol **23** (80%, two steps). With thionyl chloride, **23** gave chloride **24** (~100%), which with NaN_3 gave azide **25** (80%). Reduction of **25** with $LiAlH_4$ gave the corresponding amine, acetylation of which produced



29, A=A′=CH$_2$OH, B=H, n=1
30, A=A′=CH$_2$OH, B=H, n=0
31, A=A′=CH$_2$OH, B=H, n=2
32, A=CH$_2$OH, A′=B=H, n=1
33, A=CH$_2$OH, A′=CH$_3$, B=H, n=1
34, A=CH$_2$OH, A′=CH$_3$, B=H, n=1
35, A=CH$_2$N(CH$_2$CH$_2$)$_2$O, A′=CH$_2$OH, B=H, n=1
36, A=A′=CH$_2$N(CH$_2$CH$_2$)$_2$O, B=H, n=1
37, A=A′=CH$_2$N(CH$_3$)$_2$, B=H, n=1
38, A=A′=CH$_2$OCH$_2$CO$_2$CH$_3$, B=H, n=1
39, A=A′=CH$_2$OCH$_2$CO$_2$CH$_3$, B=H, n=0
40, A=A′=CH$_2$OCH$_2$CO$_2$CH$_3$, B=H, n=2
41, A=CH$_2$OCH$_2$CO$_2$CH$_3$, A′=B=H, n=1
42, A=CH$_2$OCH$_2$CO$_2$CH$_3$, A′=B=H, n=0
43, A=CH$_2$OCH$_2$CO$_2$CH$_3$, A′=CH$_2$N(CH$_2$CH$_2$)$_2$O, B=H, n=1
44, A=A′=CH$_2$OCH$_2$CO$_2$H, B=H, n=1
45, A=A′=CH$_2$OCH$_2$CO$_2$H, B=H, n=0
46, A=A′=CH$_2$OCH$_2$CO$_2$H, B=H, n=2
47, A=CH$_2$OCH$_2$CO$_2$H, A′=B=H, n=1
48, A=CH$_2$OCH$_2$CO$_2$H, A′=B=H, n=0
49, A=CH$_2$OCH$_2$CO$_2$H, A′=CH$_3$, B=H, n=1
50, A=CH$_2$OCH$_2$CO$_2$H, A′=CH$_2$N(CH$_2$CH$_2$)$_2$O, B=H, n=1
51, A=CH$_2$OCH$_2$CO$_2$H, A′=CH$_2$OH, B=H, n=1
52, A=A′=CH$_2$Cl, B=H, n=1
53, A=A′=CH$_2$SCH$_2$CO$_2$H, B=H, n=1
54, A=A′=CH$_2$SCH$_2$CH$_2$CO$_2$H, B=H, n=1
55, A=A′=CH$_2$CH(CO$_2$H)$_2$, B=H, n=1
56, A=A′=CH$_2$CH$_2$CO$_2$H, B=H, n=1
57, A=A′=B=H, n=1
58, A=A′=H, B=Br, n=1
59, A=A′=H, B=COCH$_3$, n=1
60, A=A′=H, B=CH$_2$Cl, n=1
61, A=A′=B=CH$_2$Cl, n=1
62, A=A′=H, B=CO$_2$H, n=1
63, A=A′=H, B=CH$_2$OH, n=1
64, A=A′=B=CH$_2$OH, n=1
65, A=A′=H, B=CH$_2$OCH$_2$CO$_2$H, n=1
66, A=A′=H, B=CH$_2$SCH$_2$CO$_2$H, n=1
67, A=A′=B=CH$_2$SCH$_2$CO$_2$H, n=1

Table I. Abilities of Host Compounds in $CDCl_3$ to Dissolve by Complexation, Crystalline Salts of Alkylammonium, Arylammonium, Ammonium, and Hydronium Cations at Ambient Temperature

Host No.	Host Structure[a]	Salt structure	[Salt]/[host]
57[b]	D(OEOEO)$_2$E	t-BuNH$_3^+$ $(C_6H_5)_4B^-$	1.0
57[b]	D(OEOEO)$_2$E	$C_6H_5NH_3^+$ Cl^-	0.6
57[b]	D(OEOEO)$_2$E	4-$CH_3C_6H_4NH_3^+$3,5-$(NO_2)_2C_6H_3CO_2^-$	1.0
57[b]	D(OEOEO)$_2$E	4-$CH_3C_6H_4NH_3^+CHCl_2CO_2^-$	0.24
57[b]	D(OEOEO)$_2$E	4-$CH_3C_6H_4NH_3^+CCl_3CO_2^-$	1.3
57[b]	D(OEOEO)$_2$E	4-$BrC_6H_4NH_3^+Br^-$	1.3
57[b]	D(OEOEO)$_2$E	4-$CH_3OC_6H_4NH_3^+$3,5-$(NO_2)_2C_6H_3CO_2^-$	>1
57[b]	D(OEOEO)$_2$E	$C_6H_5CH(CH_3)NH_3^+$3,5-$(NO_2)_2C_6H_3CO_2^-$	0
57[b]	D(OEOEO)$_2$E	$C_6H_5CH(CH_3)NH_3^+$2,4,6-$(NO_2)_3C_6H_2O^-$	>0
57[b]	D(OEOEO)$_2$E	$NH_4^+CNS^-$	1.0
57[b]	D(OEOEO)$_2$E	$H_3O^+OTs^-$	1.0
68[b]	D(OEOE)$_2$O	t-BuNH$_3^+(C_6H_5)_4B^-$	1.0
19[c]	D(OEOEO)$_2$T	t-BuNH$_3^+(C_6H_5)_4B^-$	1.0
19[c]	D(OEOEO)$_2$T	$C_6H_5CH(CH_3)NH_3^+(C_6H_5)_4B^-$	1.5
19[c]	D(OEOEO)$_2$T	$NH_4^+SCN^-$	0.2
19[c]	D(OEOEO)$_2$T	$H_3O^+OTs^-$	1.0
26	D(OEOEO)$_2$TCH$_2$NHAc	t-BuNH$_3^+(C_6H_5)_4B^-$	1.0
28	D(OEOEO)$_2$T(CH$_2$)$_3$CO$_2$H	$NH_4^+SCN^-$	>0.2[d]
69[b]	D(OEOEOH)$_2$	t-BuNH$_3^+(C_6H_5)_4B^-$	0.3
70[e]	D(OEOEO)$_2$D	t-BuNH$_3^+(C_6H_5)_4B^-$	0.3
70[e]	D(OEOEO)$_2$D	$C_6H_5CH(CO_2CH_3)NH_3^+B(C_6H_5)_4^-$	0
70[e]	D(OEOEO)$_2$D	$C_6H_5CH(CH_3)NH_3^+$2,4,6-$(NO_2)_3C_6H_2O^-$	0
70[e]	D(OEOEO)$_2$D	$NH_4^+SCN^-$	0
47	$HO_2CCH_2OCH_2$D(OEOEO)$_2$E	t-BuNH$_3^+Br^-$	1.0
47	$HO_2CCH_2OCH_2$D(OEOEO)$_2$E	$C_6H_5NH_3^+Cl^-$	1.0

[a] D = 2,2′-disubstituted-1,1′-dinaphthyl, E = CH_2CH_2, T = 1,2-disubstituted benzene. [b] Reference 4. [c] Reference 5. [d] Spectral bands of host and guest overlap. [e] *(R,R)* isomer, ref 5.

amide **26** (57% based on azide). Alcohol **21** was converted with thionyl chloride to chloride **27** (95%), whose Grignard reagent with CO_2 gave carboxylic acid **28** (74%).

Macrocycles with substituents A and A′ attached at the 3-positions of the 1,1′-dinaphthyl unit were prepared by ring-closing reactions between tetra-, penta-, or hexaethylene glycol ditosylate[4,11] and optically pure enantiomers or racemates of tetrol **8**.[6] In THF–t-BuOK, the five-oxygen cycles **30** were formed in only 6–10% yield, but the six- and seven-oxygen cycles **29** and **31** were formed in 50–60% yields, respectively. Similarly, **9**–**13**[6] underwent ring-closing reactions with the appropriate ditosylates to give **32**–**37** in 31–64% yields. Thus CH_2OH, $CH_2N(CH_2CH_2)_2O$, and $CH_2N(CH_3)_2$ substituents in the 3,3′-positions of 2,2′-dihydroxy-1,1′-dinaphthyl (**1**) do not interfere with the ring closures.

The cycles containing CH_2OH groups in either the 3- or 3′- (or both) positions served as starting materials for side-chain elaboration. For example, **29** with NaH and $BrCH_2CO_2CH_3$ gave diester **38** in 60% yield. Similarly, (−)-(*S*)-**29** gave (−)-(*S*)-**38**, (−)-(*S*)-**30** gave (−)-(*S*)-**39**, **30** gave **39**, (−)-(*R*)-**31** gave (−)-(*R*)-**40**, **31** gave **40**, **32** gave **41**, **33** gave **42**, and **35** gave **43** (yields varied from 35 to 70%). Hydrolysis of these esters with barium hydroxide octahydrate in methanol gave, after acidification with hydrochloric acid, the corresponding acids (35–80%) (−)-(*S*)-**44**, **44**, (−)-(*S*)-**45**, **45**, (−)-(R)-**46**, **46**, **47**, **48**, **49**, and **50**. The use of less NaH and $BrCH_2CO_2CH_3$ with **29** and (+)-(*R*)-**29** led to the corresponding hydroxy esters, hydrolysis of which gave the respective hydroxy acids **51** (8% overall) and (+)-(*R*)-**51** (11% overall).

Treatment of diols **29** and (−)-(*S*)-**29** with thionyl chloride gave dichlorides **52** (91%) and (−)-(*S*)-**52** (81%), respectively. These arylmethyl chlorides reacted readily with thioglycolic or β-sulfhydrylpropionic acids to give diacids **53** (96%), (+)-(*S*)-**53** (72%), **54** (97%), and (−)-(*S*)-**54** (58%), respectively. With sodium dimethyl malonate, **52** gave tetraester, hydrolysis of which gave tetraacid **55** (59% overall). When heated, **55** decarboxylated to give diacid **56** (92%), which contains two propanoic acid side chains. Similarly, dichloride (−)-(*S*)-**52** gave (−)-(*S*)-**56** (37% overall).

Interestingly, the optical rotations of some of the carboxylic acids changed sign at λ 578 and 546 nm when the solvent was changed from THF to $CHCl_3$. This behavior was observed for (*S*)-**44**, (*R*)-**51**, (*S*)-**54**, and (*S*)-**56**.

Macrocycles with β substituents attached to the 6-positions of the 1,1′-dinaphthyl were prepared making use of the directing effects of the ether oxygens of parent host **57**[4] in the electrophilic substitution. When brominated in CH_2Cl_2 with Br_2 without catalyst, **57**[4] gave dibromide **58** (67%), whose structure was established by the splitting patterns of the aromatic protons in the ^1H NMR spectrum of the compound (see Experimental Section). With acetyl chloride–aluminum chloride in nitrobenzene, the 6,6′-diacetyl derivative **59** (36%) was produced. The structure of this compound was also established from its ^1H NMR spectrum. Chloromethylation of **57** with chloromethyl methyl ether in $CHCl_3$–$SnCl_4$ at −60 °C gave 6,6′-bis(chloromethyl) derivative **60** (50%). Likewise, chloromethylation of cycle **52** already containing two chloromethyl groups in the 3,3′-positions gave cycle **61** containing four chloromethyl groups in the 3-, 3′-, 6-, and 6′-positions. Spectral comparisons (^1H NMR) of **57**, **52**, **60**, and **61** established the positions of chloromethylation of **57** to give **60** and of **52** to give **61**.

Compounds **59**, **60**, and **61** served as starting materials for modification of the side chains in the 6- and 3-positions of the naphthalene rings. Oxidation of diacetyl cycle **59** with KOBr in THF gave diacid **62** (84%), reduction of which ($LiAlH_4$) produced diol **63** (74%). Tetrol **64** was produced by acetolysis of tetra(chloromethyl) cycle **61** to give the tetraacetate of **64** (76%), reduction of which ($LiAlH_4$) produced **64** (90%). With NaH–$BrCH_2CO_2CH_3$, diol **63** gave the dimethyl ester of diacid **65**, hydrolysis of which gave diacid **65** (41% overall). Bis(chloromethyl) cycle **60** with thioglycolic acid gave diacid **66** (75%), whereas tetra(chloromethyl) cycle **61** gave tetraacid **67** (96%).

Table II. Abilities of Host Compounds in $CDCl_3$ to Extract Alkylammonium Thiocyanate Salts from D_2O into $CDCl_3$ by Complexation at Ambient Temperature

Host No.	Host Structure[a]	Salt cation	[Salt]/[host][b]
57[c]	$D(OEOEO)_2E$	$C_6H_5CH(CH_3)NH_3^+$	2.0
57[c]	$D(OEOEO)_2E$	$C_6H_5CH(CO_2CH_3)NH_3^+$	0.8
19[d]	$D(OEOEO)_2T$	$C_6H_5CH(CH_3)NH_3^+$	1.9
19[d]	$D(OEOEO)_2T$	$C_6H_5CH(CO_2CH_3)NH_3^+$	0.7
28	$D(OEOEO)_2T(CH_2)_3CO_2H$	$C_6H_5CH(CO_2CH_3)NH_3^+$	0.8

[a] D = 2,2′-disubstituted-1,1′-dinaphthyl, E = CH_2CH_2, T = 1,2-disubstituted benzene. [b] ^1H NMR spectral criteria. [c] Reference 4. [d] Reference 5.

Survey of Abilities of Hosts to Complex Ammonium, Arylammonium, and Hydronium Salts. In the abbreviated formulas of the tables and following sections, D stands for the 1,1′-dinaphthyl unit bound to oxygen at its 2,2′-position, E stands for the 1,2-ethylene unit, and T stands for the benzene unit attached to oxygen at its 1,2-positions.

Through use of ^1H NMR integration techniques, hosts **57, 68, 19, 26, 28, 69, 70,** and **47** were examined for their abilities to enhance, by complexation, the solubilities of a variety of crystalline salts in $CDCl_3$ at ambient temperature. Direct evidence for complexation of the host was found in changes in chemical shifts of the naphthyl OCH_2 protons when salt was present. Table I reports the results.

A second study determined the capacity of hosts dissolved in $CDCl_3$ to extract, by complexation, alkylammonium salts from D_2O solution. Hosts **57, 19,** and **28** and guests $C_6H_5CH(CH_3)NH_3^+SCN^-$ and $C_6H_5CH(CO_2CH_3)NH_3^+SCN^-$ were examined. Table II reports the results.

The complexing of dilocular host **70** [$D(OEOEO)_2D$] with CH_3OD was also demonstrated by extraction. The high melting point and low solubility of (*RR*), (*S,S*)-**70** in CS_2 required that (*R,R*)-**70** be used. A solution of (*R,R*)-**70** in CS_2 was shaken at −78 °C with a 20% by volume solution of D_2O in CH_3OD which was 0.66 M in $LiPF_6$. The layers were carefully separated at −78 °C. The ^1H NMR spectrum of the organic layer at ambient temperature revealed the presence of equimolar quantities of host and CH_3OD. Repetition of the experiment in the absence of host gave no detectable CH_3OD. Thus, (*R,R*)-**70** complexes only 1 mol of CH_3OD in CS_2 at −78 °C.

Two crystalline 1:1 complexes of primary amine salts with hosts were prepared for determinations of their compositions and X-ray structures. The first involved the five-oxygen cycle **68** [$D(OEOE)_2O$] and *t*-$BuNH_3^+B(C_6H_5)_4^-$, and was obtained by mixing the components in $CDCl_3$. The second complex involved optically pure (*R*)-$C_6H_5CH(CO_2CH_3)NH_3^+PF_6^-$, which was extracted at −13 °C from a 4 M $LiPF_6$–D_2O solution into a $CDCl_3$ solution of optically pure (*S,S*)-**70**[5] [$D(OEOEO)_2D$]. Analysis showed the compound contained 1 mol of chloroform. The detailed X-ray structure of this compound is reported elsewhere.[12]

Several metal salts of hosts **50, 44, 45,** and **46** were prepared and examined. Amino ester **43** was hydrolyzed with KOH and the product was acidified with hydrochloric acid and extracted with $CHCl_3$. The extracted material when evaporated gave a powder whose mass spectrum gave a parent molecular ion at M^+ 713, but no peak at 675, the molecular weight of the parent amino acid **50.** Apparently the complex of **50** with KCl was extracted into $CHCl_3$, and HCl was lost when the complex was heated in the inlet tube of the mass spectrometer. The complex is, in effect, the hydrochloride of the amine and the potassium salt of the carboxylic acid. The potassium salt was made by neutralization of **50** with KOH and evaporation of the aqueous solution to give a powder.

Similar hydrolysis of amino ester **43** with $Ba(OH)_2$, acidification of the product with acetic acid, and extraction of the aqueous solution with $CHCl_3$ gave material that chromatographed on silica gel, 2:3 methanol–ether (v/v), to produce the barium salt of amino acid **50.** The analysis of this material indicated two ligand assemblies per barium ion. The ^1H NMR spectrum of the host portion of the salt was typical for complexed cycles, and was dramatically different from uncomplexed host **50.** The complex was slightly soluble in water and soluble in methanol, $CHCl_3$, and acetic acid. Thus the salt complex possesses mixed hydrophilic–lipophilic character. A solution of the complex in methanol–water was acidified with 5% sulfuric acid. No precipitate of $BaSO_4$ appeared.

The alkaline earth metal complexes of diacid **44** containing one dinaphthyl unit and six oxygens were prepared by hydrolyzing diester **38** with the appropriate $M(OH)_2$. The salts formed were extracted into $CHCl_3$, and the solutions were evaporated to give the salt complexes as powders. Their ^1H NMR spectra indicate the macrocycles are complexed. Application of the same procedure to the five-oxygen cyclic diester **39** with $Ca(OH)_2$ and to the seven-oxygen cyclic diester **40** with $Ba(OH)_2$ gave the corresponding salt complexes of diacids **45** and **46.**

Diester **38** was hydrolyzed with excess $Ba(OH)_2$ which was 0.8% in $Sr(OH)_2$. After washing with CH_2Cl_2, the aqueous solution was acidified with excess acetic acid and extracted with $CHCl_3$. The mass spectrum of the material extracted gave not only M^+ 664 for the host diacid **44,** but also M^+ for the strontium salt complex of **44.** No M^+ was observed for the barium salt complex of diacid **44.** Thus diacid **44** scavenged strontium ion from bulk barium ion, and the strontium salt complex was selectively extracted from an aqueous acetic acid solution.

The relative lipophilizing abilities of the anions of monoacid 6-ring oxygen host **47** and 5-ring oxygen host **48** for Na^+, K^+, Ca^{2+}, and Ba^{2+} were estimated as follows. The salt complexes of these two acids and four cations were prepared by neutralization, CH_2Cl_2 extraction procedures. Metal content determinations were made for the two Ca salts by atomic absorption, and for the two Na and two K salts by air–acetylene flame emission.[14] Unfortunately, the method could not be applied to the two Ba salts due to the low sensitivity for this element with the air–acetylene flame analysis. The salts were assumed to contain two cyclic ligands for each Ba^{2+} ion by analogy with the salt complex with **50.**

The salt complexes in CH_2Cl_2 exhibited a carbonyl-stretching frequency at only 1724 cm^{-1} for those derived from **48** (the free acid gave 1575 cm^{-1}), and at only 1724 cm^{-1} for those of **47** (the free acid gave 1580 cm^{-1}). The band frequencies of the salt complexes were essentially independent of which metal ion was complexed. The UV extinction coefficients of the eight salt complexes were determined in CH_2Cl_2 at their λ_{max} of 337, 324, 294, 286, and 276 nm. The ^1H NMR spectra of the salt complex solutions in $CDCl_3$ were dramatically different from those of the free acids **47** and **48.** For example, the $ArCH_2$ protons of **48** appear as a singlet at δ 4.99

Table III. Ability of Host Acids to Distinguish between Metal Ions in Lipophilization

Conditions	Host	Metal anion	Ratios of q_A (q'_A)
CH_2Cl_2, I	48	Ca^{2+}	8.0
	48	Ba^{2+}	4.9
	48	Na^+	3.6
	48	K^+	1.0
CH_2Cl_2, I	47	K^+	13
	47	Na^+	3.6
	47	Ca^{2+}	1.3
	47	Ba^{2+}	1.0
Toluene, II	48	Ca^{2+}	480
	48	Na^+	1.4
	48	K^+	1.0
Toluene, II	47	Ca^{2+}	43
	47	Na^+	1.5
	47	K^+	1.0
Toluene, III	48	Ca^{2+}	53
	48	Ba^{2+}	1.0
Toluene, III	47	Ca^{2+}	38
	47	Ba^{2+}	1.0

in the acid, but as a quartet in its Ba^{2+} salts. Additionally, the $ArOCH_2$ and OCH_2O proton bands are moved in the salts with respect to where they are in the free acids. Clearly, the conformational organizations of the ligands in the salt complexes are different from those in the free acids.

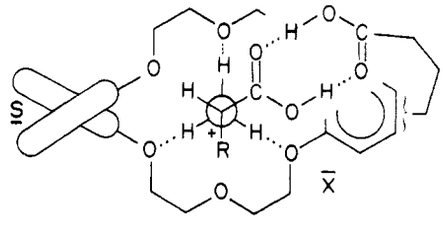
Distribution experiments were performed for the eight salt complexes between water–CH_2Cl_2 and water–toluene at 25 °C. Ultraviolet spectroscopy was used to determine the total ligand concentration in the organic and aqueous phases through the use of standards. The results were used to calculate for the four metal ions the ligand distribution ratios (q_A) between the two phases. The distribution ratio is defined as $q_A = 1a0_o/[A]_w$, where A is the anion of **47** or **48**, $[A]_o$ is the concentration of ligand in the organic solvent, and $[A]_w$ the concentration of ligand in water at equilibrium. The values of q_A vary with experimental conditions, and, therefore, comparisons of q_A values for the various salts are valid only when those values are obtained under the same conditions.[15] Comparisons of q_A as a lipophilization parameter for monovalent ions can be made directly. A semiquantitative comparison of values of this parameter between monovalent and divalent ions is provided by the assumption that $q'_A = q_A/2$, where q'_A applies to divalent ions and q_A values for monovalent ions are only compared with q'_A values for divalent ions, and when the experimental conditions for the extraction remain constant.

For the distribution experiments between water and CH_2Cl_2, all eight salt complexes were measured under one set of concentrations (water, 10^{-4} M in **47** or **48**, 10^{-2} M in NaOH, KOH, $Ca(OH)_2$, or $Ba(OH)_2$, 10^{-3} M in LiOH). In the experiments involving water–toluene, two sets of conditions were required because the range of lipophilization parameters was larger. The first set of conditions involved water, 2×10^{-3} M in **47** or **48**, 0.50 M in NaCl, KCl, or $CaCl_2$, 4.3×10^{-3} M in LiOH. The second set involved water 10^{-4} M in **47** or **48**, 0.95 M in $CaCl_2$ or $Ba(OH)_2$, and 10^{-3} M in LiOH. The LiOH was present to ensure that **47** and **48** were in the anionic form. Control experiments demonstrated that essentially no Li salt was extracted under the conditions used, and that the lithium salts present did not "salt out" the other salt complexes into the organic medium (see Experimental Section). In the tabulation of results, ratios of q_A (q'_A) values are listed for various combinations of the two different ligands, four different metal ions, and two different solvents. With CH_2Cl_2 as the organic solvent, all eight salt complexes could be distributed under the same conditions (conditions I). With toluene, two sets of concentrations had to be used (conditions II and III). Table III reports the results.

Discussion

Prior sections describe the syntheses of a large number of multiheteromacrocycles and determinations of their capacities to complex and lipophilize cations. Further studies will be described in future papers of this series.

Macrocycles **26** and **28** were prepared to test their abilities to act as hosts for complexing amino acids. With CPK models, amino acid salt complexes of **26** and **28** can be constructed in which the NH_3^+ group of the guest is bound to the ether oxygens of the host by hydrogen bonds, and the CO_2H group of the guest is hydrogen bonded to the $NHCOCH_3$ or the CO_2H group of the host. In the models of the complexes, either the R or the H group attached to the asymmetric center of the amino acid salt ($RCH^*(NH_3^+)CO_2H\ X^-$) is thrust into the chiral barrier (the binaphthyl group), depending on which diastereoisomeric complex is prepared. With amide **26** as host, the four stereoisomeric complexes that can be constructed using the two faces of the host do not provide a clear-cut prediction as to their stability order. In acid **28**, the arm carrying the CO_2H group is located almost on a C_2 axis of the host. Structure A represents the possible complexes between (*S*)-**28** and L-amino acid salts. These complexes are predicted



A

to be more stable than the corresponding diastereoisomeric complexes involving (*S*)-**28** and D-amino acid salts. The test of this prediction will involve the synthesis of the enantiomers of **28**. The synthesis of racemic **28** described in this paper indicates a feasible route to optically active **28**.

Abilities of Hosts to Complex by Hydrogen Bonding Ammonium, Alkylammonium, Arylammonium, and Hydronium Salts and Methanol. The results of Table I indicate that most of the cycles examined possessed the ability to solubilize in $CDCl_3$, NH_4^+, RNH_3^+, $ArNH_3^+$, and H_3O^+ salts in the crystalline state. Very likely, this lipophilization is due to complexation through a tripod arrangement of $^+NH\cdots O$ or $^+OH\cdots O$ hydrogen bonds, as has been found in several X-ray structures[12,16] and as is formulated in envisioned complex A.

All of the hosts tried complexed 1 mol of *t*-$BuNH_3^+$-$B(C_6H_5)_4^-$ except the open-chain model compound **69** [D(OEOEOH)$_2$][4] and the dilocular host **70** [D(OEOEO)$_2$D],[5] each of which complexed about 0.3 mol of salt. The lack of molecular organization of the host appears to reduce its complexing ability in the case of **69**. The lowered basicity of the four aryl oxygens of **70**, coupled with steric inhibition of complexation (CPK molecular model examination), are the factors that probably lower the binding power of **70**, as compared to **57**. Monolocular host **57** [D(OEOEO)$_2$E][4] complexed various para-substituted anilinium salts to give [salt]-/[host] ratios that varied from 0.24 to 1.3. With $NH_4^+SCN^-$ and $H_3O^+OTs^-$, **57** gave 1:1 complexes, whereas **19** [D(OEOEO)$_2$T][5] complexed only 0.2 mol of $NH_4^+SCN^-$ and dilocular host **70** complexed none. The lower basicity of the four ArO oxygens of **19** and **70** appear responsible for their lower complexing abilities of the NH_4^+ ion. The fact that **19** complexes 1.5 mol of $C_6H_5CH(CH_3)NH_3^+(C_6H_5)_4B^-$ provides a second example in which a host complexes more than one

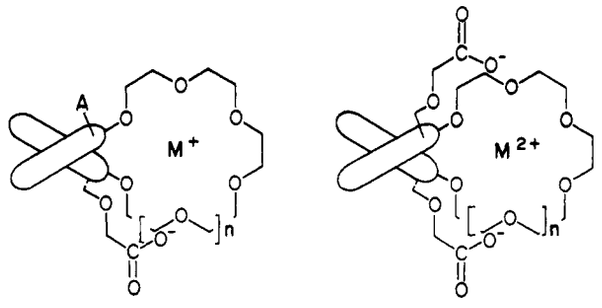
guest molecule. This might occur by one guest being bound to each face of the host, or by the complex involving only one or two hydrogen bonds between host and guest. The carboxyl-terminated arm of host **47** in the proper conformation can center the CO_2H group directly under the hole of the host (CPK molecular models), and this structural feature of the compound is probably responsible for **47** complexing 1 mol of $C_6H_5NH_3^+Cl^-$, as compared with the 0.6 mol complexed by the parent host **57**. The host whose carboxyl-terminated arm reaches only to the rim of the macrocycle (**28**) complexes $NH_4^+SCN^-$ somewhat better than its parent host **19**. The CO_2H group might provide a hydrogen bonding site for one end of the SCN^- ion, the other end being associated with the fourth N–H bond not hydrogen bonded to the host.

The results of Table II indicate that hosts **57**, **19**, and **28** in $CDCl_3$ are able to extract $RNH_3^+SCN^-$ salts from water. Cycle D(OEOEO)$_2$E extracted 2.0 mol and **19** [(D(OEOEO)$_2$T] about 1.9 mol of $C_6H_5CH(CH_3)NH_3^+SCN^-$, whereas their corresponding bromides were not extracted detectably. No detectable salt was extracted in the absence of host. The delocalization of negative charge in SCN^- and localization in Br^- suggests that more energy of solvation has to be overcome in transferring Br^- than SCN^- ion from D_2O into $CDCl_3$. Possibly 1 mol of guest cation is complexed at each face of the host. The less lipophilic salt, $C_6H_5CH(CO_2CH_3)NH_3^+$, was extracted to the extent of 0.8 mol by **57**, 0.7 mol by **19**, and 0.8 mol by **28**, which contains the carboxyl-terminated arm attached to the benzene ring. This arm appears to enhance the complexing ability of its host only to a small extent, possibly by hydrogen bonding the ester group. The structure envisioned resembles that of complex A.

The remarkable observation that (*R*,*R*)-**70** in CS_2 solution extracts at −78 °C from 80% CH_3OD–20% D_2O (by volume) only 1 mol of CH_3OD per mole of host is explained as follows. Molecular models (CPK) of a 1:1 complex can be constructed in which the CH_3OD group is hydrogen bonded to an inward-turned oxygen of (*R*,*R*)-**70**, which allows the CH_3 group to nicely occupy the space between the two naphthalene walls of the host. Another attractive explanation that is compatible with the structures of host and guest involves insertion of the $S{=}C^+$ portion of a $S{=}C^+\text{-}S^-\cdots DOCH_3$ species into the hole of (*R*,*R*)-**70** much as the N_2^+ part of ArN_2^+ inserts into host compounds.[4]

Complexation and Lipophilization of Metal Ions. Molecular models (CPK) of hosts that contain $CH_2OCH_2CO_2H$ side chains substituted in the 3-positions of the naphthalene rings indicate that one oxygen of one carboxylate group can center directly under, and that of the second carboxylate, if present, directly over the hole of the macrocycle. When metal cations occupy that hole, the carboxylate anions are ideally positioned (both with respect to conformations and length of the side chain) to act as contact counterions for the complexed metals. Since the number of carboxylates and the sizes of the holes are subject to design, it seemed probable that hosts could be tailored to the valence and ligand preferences (number, type, and arrangement) of various metal cations.

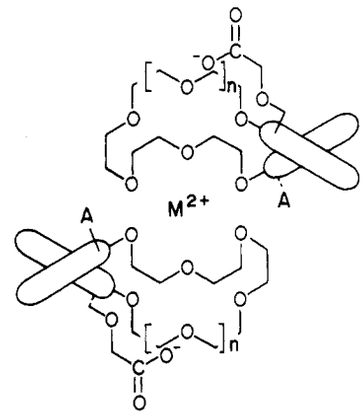
Three structures of differing charge type are envisioned as possible for the complexes. In **71–73**, the charge of a monovalent metal ion matches the charge of one carboxylate group of the host. In **74–78**, the charge of the divalent metal ion matches the charge of the two carboxylate groups of the host. In **79–81**, the charge of the divalent metal does not match the single carboxylate of the host, and thus two hosts per metal ion are required to balance the charge. The structures are drawn in such a way to maximize the number of metal ion to oxygen contacts, with the carboxylate and ether oxygens acting cooperatively. In the last type of complex, the number of contacts can be maximized only by sandwiching the metal ion between two macro rings, with an oxygen of a carboxylate



71, A=$CH_2N(CH_2CH_2)_2O$, M=K, n=1
72, A=H, M=K, n=0
73, A=H, M=Na, n=0

74, M=Ca, n=1
75, M=Sr, n=1
76, M=Ba, n=1

77, M=Ca, n=0
78, M=Ba, n=2



79, A=$CH_2N(CH_2CH_2)_2O$, M=Ba, n=1
80, A=H, M=Ca, n=1
81, A=H, M=Ba, n=1

82, A=H, M=Ca, n=0
83, A=H, M=Ba, n=0

occupying the center of each ring. Such an arrangement is compatible with CPK molecular models (coupled with appropriate spheres)[13] of **79**, **81**, and **83** that involve Ba^+. In these structures, the metal ions are completely covered with a lipophilic skin of C–H bonds. However, Ca^{2+} is too small to contact both O^- groups at the same time when each O^- is centered in the middle of a five- or six-oxygen macro ring. Thus **80** and **82** are sterically incompatible structures. The structures for the two Ca^{2+} salt complexes which are sterically the most compatible involve six or seven oxygen–Ca contacts with one of the two ligands, and two oxygen–Ca contacts with the other (the labeled oxygens of the $CH_2\dot{O}CH_2C(=O)O^-$ group).

The interesting question arises as to how well the ionic diameters of the different metal cations match the holes of the different macro ring systems. To answer this question, graded ball bearings[13] were inserted into the centers of the holes of CPK molecular models of cycles containing five, six, or seven oxygens, with all the electron pairs of the oxygens turned inward, and all the OCH_2CH_2O units in gauche conformations. The diameters of those spheres that just contacted the oxygens of the macro ring with the O's coplanar are listed in Table IV for the minimum and maximum dihedral angles (θ) between the planes of the two naphthalene rings of the dinaphthyl unit. The minimum θ values place the two naphthyl oxygens as close together as do gauche oxygens of ethylene glycol. A second set of minimum diameters is also listed in which θ is minimized, the OCH_2CH_2O units are gauche, and the ring oxygens are as noncoplanar and staggered as possible. Table IV also contains the diameters of metal cations of interest here.

The hole diameters vary over a wide range of 1.7–4.0 Å, depending on the ring size (O's in ring), θ, and the staggering of the oxygens. With five ring oxygens, it can vary from 1.7 to 2.3 Å, and therefore the five-oxygen hosts might nicely accommodate Na^+ and Ca^{2+}, whose diameters are 1.90 and 1.98

Table IV. Comparisons of Hole Diameters of Hosts (All Gauche Conformations) with Ionic Diameters of Metals

No. of O's in ring of host	Hole diameter, Å: Minimum θ^a (~60°) O's coplanar	Minimum θ^a (~60°) O's staggered	Maximum θ, O's coplanar
5	1.9	1.7	2.3 (θ^a = 90°)
6	2.7	2.3	3.3 (θ^a = 95°)
7	3.2	2.8	4.0 (θ^a = 110°)

Guest	Ionic diameter, Å
Na^+	1.90
K^+	2.66
Ca^{2+}	1.98
Sr^{2+}	2.26
Ba^{2+}	2.70

[a] Dihedral angle between planes of two naphthalene rings.

Å, respectively. With six ring oxygens, it varies from 2.3 to 3.3 Å, and thus the six-oxygen hosts might nicely complex Sr^{2+}, K^+, and Ba^{2+}, whose diameters are 2.26, 2.66, and 2.70 Å, respectively. With seven ring oxygens, it varies from 2.8 to 4.0 Å, which is greater than the diameter of any of the ions, but is closest to Ba^{2+} (2.70 Å).

The qualitative results obtained with hosts **50** and **44–46** are interpreted in terms of the above structural parameters. The six ring oxygen host **50** containing one $CH_2OCH_2CO_2H$ and one $CH_2N(CH_2CH_2)_2O$ side chain formed particularly stable salt complexes with K^+ and Ba^{2+}. Structure **71** is probable for the salt complex formed from K^+ and **50**. The valences and diameters match, and the complex is stable enough to give a parent molecular ion at *m/e* 713 in its mass spectrum. Structure **79** is probable for the salt complex formed from Ba^{2+} and **50**. In this structure, the barium ion has 14 contact binding sites. The two O^- groups of the CH_2O-$CH_2CO_2^-$ arms protrude into the two holes of the macrocycles to contact the Ba^{2+}. The two sets of six ethers in their macro rings form "halos" opposite one another with Ba^{2+} in the center. This structure involves a minimum θ and hole diameter, and orientations of the oxygen's electron pairs toward the barium. Molecular models of **79** appear sterically compatible, although many conformations must be adjusted to have all ring oxygens contact Ba^{2+}. The Ba^{2+} is completely enveloped by the two ligand assemblies. The (*R*),(*S*) diastereoisomer that is formulated possesses a center of symmetry, but the racemate is equally likely. The stability of the complex to chromatography and to sulfuric acid is probably associated with the steric unavailability of Ba^{2+} to other ions or molecules of solvent.

The salt complexes of hosts **44–46** are presumed to have structures **74–78**. These structures are unique in the sense that the two carboxylate groups attached to the same molecule are separated by the macro ring and cannot converge and contact a divalent metal cation unless that metal is in the hole of the macro ring. The analysis of possible hole and metal ion diameters in Table IV suggests that all oxygens can contact all metal ions in structures **75, 76,** and **77,** but that the holes of **44** and **46** are too big for Ca^{2+} and Ba^{2+}, respectively.

The fact that **44** (six ring oxygens) scavenged trace amounts of Sr^{2+} from bulk Ba^{2+} indicates that complex **75** is more stable than **76**. The hole of **44** with $\theta \sim 60°$ can vary between 2.3 (O's staggered) and 2.7 Å (O's coplanar), whereas the diameters of Sr^{2+} and Ba^{2+} are 2.26 and 2.70 Å, respectively. These facts suggest that more stable salt complexes are formed when the oxygens are staggered than when coplanar. Models of **75** (the Sr^{2+} complex salt of **44**) indicate that the six ring oxygens must pucker maximally to contact the metal ion, and that they approach an octahedral arrangement. Thus the puckered all-gauche oxygen conformation in these salt complexes appears to be more stable than a coplanar, all-gauche oxygen arrangement. Attempts to grow crystals of these salt complexes suitable for X-ray structure determination failed.

The relative lipophilizing abilities of the anion of monoacid host **47** (six ring oxygens) and monoacid host **48** (five ring oxygens) for sodium, potassium, calcium, and barium cations (Table IV) are discussed in terms of structures **72, 73,** and **80–83**. As expected on basis of fits between host hole and guest diameters (Table IV), in CH_2Cl_2 the five ring oxygen ligand lipophilizes Na^+ more than K^+, and the six ring oxygen system lipophilizes K^+ more than Na^+. Surprisingly, the factor in each case was only about 4. In the same solvent, $Ca^{2+} \gtrsim Ba^{2+}$, in spite of the size changes in both host and guest. For the five ring oxygen ligand, Ca^{2+} or $Ba^{2+} \gtrsim Na^+$ or K^+, but for the six ring oxygen ligand, K^+ or $Na^+ > Ca^{2+}$ or Ba^{2+}.

In the less polar toluene solvent, the differences in lipophilizing abilities of the anions of the five and six ring oxygen ligands for Na^+ and K^+ becomes miniscule. However, in this solvent, Ca^{2+} is lipophilized 300–500 times more by the anion of the five-oxygen cycle, and 30 and 40 times more by the anion of the six-oxygen cycle than are Na^+ or K^+. Also, Ca^{2+} is lipophilized 50 times better by the five-oxygen cyclic anion and 40 times better by the six-oxygen cyclic anion than is Ba^{2+}. In other words, Ca^{2+} is lipophilized 1.5–2.5 powers of 10 better by the two cyclic ligands than by any of the other three ions.

The monovalent complexes probably possess a "nesting" type of structure typified by **72–73,** in which the metal ion is not far from being in the best plane of the surrounding ring oxygens. Possibly a mole of water is drawn into the organic phase to complete the coordination sphere of the metal ion on the side opposite the O^- group. The difference in energy cost of placing a molecule of water in this position in H_2O, CH_2Cl_2, and $C_6H_5CH_3$ solvents could be an important structural parameter that affects the changes in lipophilization of the Na^+ and K^+ ions.

Examinations of CPK molecular complexes of the sandwich type (**80–83**) provide more conclusions as to what structures are impossible than as to what structures probably exist. Barium ion is large enough for structures **81–83** to apply to the complex salts with the larger and smaller ring systems. Calcium ion is too small to contact both O^- groups and all 10 or 12 ring oxygens at the same time. Therefore, structures **80** and **82** cannot apply to the salt complexes of Ca^{2+}, and anion ligand and metal cation are not entirely complementary. The fact that Ca^{2+} is much more lipophilized than the other three ions in $C_6H_5CH_3$, but not in CH_2Cl_2, indicates that solvent polarity greatly affects the structures of the salt complex when host and guest are not entirely complementary. What is surprising is that the predicted complementary structural relationship between Ba^{2+} and its two ligand assemblies leads to lower lipophilization than the partially noncomplementary structural relationship between Ca^{2+} and its two ligand assemblies. A probably complicated and as yet nonunderstood set of superimposed effects must be responsible.

The important feature of these results is that Ca^{2+} is much more lipophilized by the anionic ligands in the solvent ($C_6H_5CH_3$) that most resembles cell membranes than are the Na^+ or K^+ ions. Thus the anion of **48** is a calcium selective ionophore of potentially important physiological significance.[17]

Experimental Section

General. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. All ^1H NMR chemical shifts are given in δ ppm from internal Me_4Si unless otherwise indicated, and were recorded on a Varian HA-100 or T-60 spectrometer. Optical rotations were obtained with a Perkin-Elmer 141 polarimeter in a 1-dm ther-

mostatted cell. Infrared spectra were determined with a Beckman IR-5 spectrometer. Gel permeation chromatograms were run on a 3/8 in. × 20 ft column of styragel 100-Å beads in CH_2Cl_2(30–70 μm particle size, exclusion limit of 1500 molecular weight) at a flow rate of about 4 mL min^{-1} and a pressure of 200–400 psi. Mass spectra were taken at 70 EV on an AEI model MS-9 double-focusing spectrometer. All chemicals were reagent grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Dimethylformamide (DMF) was distilled from CaH_2 prior to use. All reactions that involved KOH, KOBu-*t*, $LiAlH_4$, or NaH were conducted in an inert atmosphere of N_2 or Ar. Organic extracts were dried with $MgSO_4$. All noncrystalline macrocycles, once synthesized, were slightly air sensitive, and were therefore stored under Ar at 0 °C.

2,2′-Disulfhydryl-1,1′-dinaphthyl (7). To a stirred solution under N_2 of 60 g of diol **3** in 450 mL of dry DMF at 0 °C was added (2 h) 20.2 g of a 50% dispersion of NaH in mineral oil. To the resulting mixture was added 52 g of *N,N*-dimethylthiocarbamoyl chloride.[8] The stirred mixture was warmed over a 1-h period to 85 °C, and after 1 h at 85 °C the slurry was cooled and shaken with 1500 mL of 1% KOH in water. The solid that separated was collected, dried at 25 °C, and recrystallized from benzene–cyclohexane to give 83.5 g (86%) of 2,2′-bis(*N,N*-dimethylthiocarbamoyloxy)-1,1′-dinaphthyl (**5**): mp 208–209.5 °C; M^+ 260. Anal. Calcd for $C_{26}H_{24}O_2S_2N_2$: C, 67.79; H, 5.25. Found: C, 68.01; H, 5.07.

The above material, 75.3 g, was heated at 280 °C for 40 min. A high-boiling liquid refluxed. The metal was cooled, dissolved in 500 mL of $CHCl_3$, and chromatographed through a silica gel column. The column was washed with 4 L of $CHCl_3$, and the desired product eluted with 7 L of 1% methanol–99% $CHCl_3$. Evaporation of this eluate and crystallization and recrystallization of the residue from $CHCl_3$ gave 30.5 g (40%) of 2,2′-bis(*N,N*-dimethylcarbamoylthia)-1,1′-dinaphthyl (**6**): mp 245–247 °C; M^+ 460. Anal. Calcd for $C_{26}H_{24}O_2S_2N_2$: C, 67.79; H, 5.25. Found: C, 67.74; H, 5.24.

A slurry of 18.9 g of this material in 500 mL of methanol was refluxed under N_2 for 0.5 h. A 10% NaOH solution (100 mL, oxygen-free) was added (0.5 h), and the mixture was refluxed under N_2 for an additional 9 h, cooled, and concentrated. The solid produced was dissolved in 250 mL of oxygen-free water, washed with CH_2Cl_2, acidified carefully with 15 mL of concentrated H_2SO_4, crystallized, collected, and dried. This material was recrystallized twice from benzene to give 7.1 g (55%) of white **7**: mp 152.5–153.5 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 7.95–6.85 (m, ArH, 12), 3.2 (s, SH, 2). Anal. Calcd for $C_{20}H_{14}S_2$: C, 75.43; H, 4.43. Found: C, 75.38; H, 4.31.

3-Hydroxymethyl-2,2′-dihydroxy-1,1′-dinaphthyl (9). This synthesis is superior to that reported previously.[6] A solution of 50 g of 2,2′-dihydroxy-1,1-dinaphthyl (**3**) in 210 mL of $(C_2H_5OCH_2CH_2)_2O$ and 125 g of *N*-butoxymethylmorpholine[6] was heated and stirred under N_2 at 165 °C for 72 h. The solution was cooled and the solvent was evaporated at 0.1 mm. The residue was mixed with 300 mL of CH_2Cl_2 and 100 g of silica gel and the CH_2Cl_2 was evaporated at 30 mm and added as a slurry in 30% pentane in CH_2Cl_2 (by volume) to the top of a 300-g silica gel column. The product was eluted with the same solvent (6 L), the solvent was evaporated, and the residue was dissolved in 400 mL of CH_2Cl_2. The solution was stirred with 100 mL of 20% HCl in water for ½ h, and the hydrochloride of 3-morpholinomethyl-2,2′-dihydroxy-1,1′-dinaphthyl (separated) was collected and washed with 280 mL of CH_2Cl_2. The unreacted **3** remained in CH_2Cl_2 and the dihydrochloride of 3,3′-dimorpholino-2,2′-dihydroxy-1,1′-dinaphthyl (**12**)[6] remained in the aqueous phase. The desired monosubstituted salt was shaken with 500 mL of saturated $NaHCO_3$–H_2O solution and 100 mL of CH_2Cl_2. The aqueous layer was extracted with two additional 100-mL portions of CH_2Cl_2. The combined organic layers were dried and evaporated and the product was crystallized: mp 226–228 °C; wt 17.5 g or 54% based on unrecovered starting material. From the aqueous layer 21 g of **3** was recovered. The monomorpholino material (21 g) was heated at reflux under N_2 in 470 mL of Ac_2O for 8 days, and the solvent was distilled under reduced pressure. The residue was dried at 100 °C under 0.1 mm of pressure to give 23 g (95%) of 3-acetoxymethyl-2,2′-diacetoxy-1,1′-dinaphthyl. This material (23 g) in 400 mL of dry THF was added dropwise to 13 g of $LiAlH_4$ in dry ether under N_2, and the product, 3-hydroxymethyl-2,2′-dihydroxy-1,1′-dinaphthyl (**9**) was isolated in the usual way: wt 15 g (92%); mp 206–207 °C.[6]

2,3:4,5-Di(1,2-naphtho)-1,6,9,15-tetraoxa-12-thiacycloheptadeca-2,4-diene (14). A solution of 1.25 g of racemic dinaphthyl two-armed ditosylate[5] (**4**) in 400 mL of butanol and 40 mL of dioxane was stirred under N_2 at reflux, and 0.391 g of disodium sulfide nonahydrate in 15 mL of distilled water and 100 mL of butanol was added. The mixture was refluxed under N_2 for 17 h and concentrated under reduced pressure and the residue was triturated with $CHCl_3$. The mixture was filtered and the filtrate was evaporated and chromatographed on 200 g of silica gel. Product was eluted in fractions 10–14 of 100 mL each of 2% ethyl acetate–98% $CHCl_3$ (by volume) to give after recrystallization from methanol 0.386 g (52%) of **14**: mp 125–127 °C. A recrystallized sample gave: mp 127–128 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 8.0–7.7 (m, Ar, 4), 7.5–7.0 (m, ArH, 8), 4.5–3.8 (m, $ArOCH_2$, 4), 3.8–3.3 (m, ROCH, 8), 3.0–2.1 (m, SCH_2, 4), M^+ 460. Anal. Calcd for $C_{28}H_{28}O_4S$: C, 73.01; H, 6.13. Found: C, 72.97; H, 5.98.

2,3:4,5-Di(1,2-naphtho)-1,6,9,18-tetraoxa-12,15-dithiacycloeicosa-2,4-diene (15). To a solution of dinaphthyl two-armed ditosylate[5] (**4**; 10.0 g) and 1,2-ethanedithiol (1.22 g) in 800 mL of THF under N_2 was added 1.04 g of NaOH in 10 mL of water. The mixture was refluxed for 40 h, concentrated to 200 mL, and partitioned between 500 mL of CH_2Cl_2 and 600 mL of water. The layers were separated and the aqueous phase was extracted with two 200-mL portions of CH_2Cl_2. The combined organic phases were dried and evaporated and the residue was chromatographed on 150 g of basic alumina. The column was washed with benzene (2 L), 49:1 benzene–ether, 48:2 benzene–ether and 19:1 benzene–ether (v/v, 2 L each), and 9:1 benzene–ether (v/v, 3 L) to give 1.05 g (16%) of **15** in the final eluate, mp 85–90 °C. Recrystallization of this material gave: mp 85–90 °C; M^+ 520; ^1H NMR (60 MHz, $CDCl_3$) δ 7.96–7.00 (m, ArH, 12) and 4.30–2.30 (m, OCH_2, SCH_2, 20). Anal. Calcd for $C_{30}H_{32}O_4S_2$: C, 69.22; H, 6.20. Found: C, 69.01; H, 6.12.

2,3:4,5-Di(1,2-naphtho)-13,14-benzo-1,6,9,18-tetraoxa-12,15-dithiacycloeicosa-2,4,13-triene (16). The substance 1,2-disulfhydrylbenzene (0.1676 g) in 80 mL of butanol was stirred under N_2 for 0.5 h and 0.0965 g of NaOH pellets was added. Water was azeotropically distilled from the refluxing solution and then 0.9078 g of dinaphthyl two-armed ditosylate[5] (**4**) in 30 mL of N_2-flushed dioxane (purified) was added. The resulting slurry was stirred at reflux for 11 h. The reaction mixture was cooled and filtered and the solid washed well with $CHCl_3$ to give 0.356 g of NaOTs. The filtrate was concentrated under reduced pressure and the residual oil was chromatographed on 150 g of silica gel. Elution of column with $CHCl_3$ gave 0.618 g of crude product in fractions 7–12 (125 mL each), recrystallization of which from acetone twice gave 0.484 g (72%) of **16**: mp 149.5–151 °C; M^+ 568; ^1H NMR (60 MHz, $CDCl_3$) δ 7.9–7.6 (m, 4, ArH), 7.4–6.9 (m, 12, ArH), 4.1–3.7 (m, 4, $ArOCH_2$), 3.5–3.2 (m, 8, CH_2OCH_2), 3.0–2.7 (m, 4, $ArSCH_2$). Anal. Calcd for $C_{34}H_{32}O_4S_2$: C, 71.79; H, 5.67. Found: C, 72.00; H, 5.53.

2,3:4,5-Di(1,2-naphtho)-13,14-benzo-1,6,9,12,18-pentoxa-15-thiacycloeicosa-2,4,13-triene (17). The substance 2-sulfhydrylphenol (1.26 g) was stirred under N_2 in 1 L of THF and 2.24 g of *t*-BuOK and 30 mL of H_2O were added at reflux, followed by a solution of 7.70 g of dinaphthyl two-armed ditosylate[5] (**4**) in 300 mL of N_2-flushed THF and 60 mL of H_2O. The reaction mixture was held at reflux for 48 h and an additional 0.504 g of 2-sulfhydrylphenol and 0.88 g of 85% KOH were added. After refluxing for 24 h, the solution was evaporated under reduced pressure. The residue was slurried in $CHCl_3$ and filtered and the solid was washed with $CHCl_3$ to give 3.87 g (99%) of KOTs. The filtrate was washed with 5% NaOH solution, water, and brine, dried, and evaporated. The white paste was chromatographed on activity grade III dry-pack silica gel (775 g) in 0.5% EtOAc–99.5% $CHCl_3$ (by volume). After development of the 75-cm column with 2.4 L of the same solvent mixture, the column was sectioned and the product eluted in that part 6–26 cm from the bottom with 70% $CHCl_3$–30% CH_3OH (by volume). This material (2.26 g) was crystallized (slowly) from 160 mL of absolute ethanol to give 2.053 g (38%) of **17**, mp 106–113 °C, whose ^1H NMR spectrum was identical with that of an analytical sample: mp 111–113 °C. This material gave: M^+ 552; ^1H NMR (60 MHz, $CDCl_3$) δ 8.0–6.68 (m, 16, ArH), 4.2–3.86 (m, 6, $ArOCH_2$), 3.75–3.2 (m, 8, CH_2OCH_2), 3.2–2.5 (m, 2, $ArSCH_2$). Anal. Calcd for $C_{34}H_{32}O_5S$: C, 73.88; H, 5.84. Found: C, 73.93; H, 5.86.

2,3:4,5-Di(1,2-naphtho)-13,14-benzo-9,12,15,18-tetraoxa-1,6-dithiacycloeicosa-2,4,13-triene (18). To a solution 1.0 g of 2,2′-disulfhydryl-1,1′-dinaphthyl (**7**) and 0.434 g of KOH in 40 mL of H_2O stirred under N_2 was added (in 200 mL of THF and 28 mL of purified dioxane) 1.86 g of 8:9-benzo-1,16-ditosyl-1,4,7,10-13,16-hexaoxahexadeca-8-ene[5]. The resulting solution had a pH 7–8, which decreased to 5–6 after refluxing for 15 h. The solution was evaporated under reduced pressure and the residue was mixed with 50 mL of CH_2Cl_2 and filtered. The KOTs that separated was collected and washed with CH_2Cl_2 to give 0.903 g (69%) of salt. The filtrate was washed with 10% KOH in water and water and brine, dried, and evaporated under reduced pressure. The residue was crystallized from benzene and recrystallized from 50% benzene–50% cyclohexane (v/v) to give 1.14 g of **18** as a solvate, mp 154–155 °C, which after drying at 81 °C and 50 μm for 24 h gave 1.10 g (58%) of **18**: mp 167–168 °C; M^+

568; ^{1}H NMR spectrum (60 MHz, $CDCl_3$) δ 8.1–6.9 (m, naphtho-H, 12), 6.85 (s, benzo-H, 4), 4.2–3.9 (m, $ArOCH_2$, 4), 3.9–3.6 (m, CH_2OCH_2, 8), 3.3–2.9 (m, $ArSCH_2$, 4). Anal. Calcd for $C_{34}H_{32}O_4S_2$: C, 71.79; H, 5.67. Found: C, 71.65; H, 5.85.

2,3:4,5-Dinaphtho-13,14-(3-propenyl-1,2-benzo)-1,6,9,12,15,-18-hexaoxacycloeicosa-2,4,13-triene (20). Procedure 1. A solution of 38.3 g of dinaphthyl two-armed ditosylate[5] (**4**) in 200 mL of purified dioxane was added (15 min) to a refluxing and stirred (under N_2) mixture of 8.0 g of 3-allylcatechol,[9] 6.9 g of 85% KOH, and 400 mL of butanol. The resulting mixture was refluxed for 7 h, cooled, and filtered. The filtrate was concentrated to give 37 g of oil which was chromatographed on 1 kg of neutral alumina. Elution of the column with 10 L of benzene–ether (7:3, v/v) gave on concentration and drying at 100 °C (50 μm) for 24 h 11.7 g (41%) of macrocycle. The 100-MHz ^{1}H NMR spectrum of this material in $CDCl_3$ gave a multiplet at δ 4.95 (C=CH_2) as well as a d of d at δ 1.81, whose integration indicated the presence of 71% of the allyl and 29% of the 1-propenyl derivative. Accordingly, the mixture was dissolved in 700 mL of dry benzene which was mixed at 25 °C with 10 mL of 1 M *t*-BuOK in *t*-BuOH for 6 h, conditions that completed the isomerization of the allyl to the propenyl derivative. The solution was extracted with three 200-mL portions of 0.5 M hydrochloric acid, dried, concentrated, and film dried at 100 °C (50 μm) for 24 h to give 11.1 g (95%) of cycle **20** as a colorless glass, M^+ 576. The ^{1}H NMR spectrum (100 MHz) in $CDCl_3$ gave δ 7.8 (m, naphthyl ArH, 4), 7.5–6.5 (complex m, naphthyl and benzo ArH and olefinic CH, 12), 6.2 (m, olefinic CH, 1), 4.0 (m, $ArOCH_2$, 7), 3.6 (m, CH_2OCH_2, 9), and 1.84 (d of d, J_1 = 7 Hz, J_2 = 2 Hz, CH_3, 3). Anal. Calcd for $C_{37}H_{36}O_6$: C, 77.06; H, 6.29. Found: C, 77.11; H, 6.25.

4-(3′-Hydroxypropyl)catechol. To a solution of 42.6 g of 4-allylveratrole[10] in 250 mL of dry THF was added 110 mL of a 0.1 M solution of diborane in THF, and the solution was stirred for 0.75 h. A solution of 1 mL of 3 M aqueous NaOH in 16 mL of water was added carefully, followed by 31 mL of 3 M aqueous NaOH, followed by careful addition of 42 mL of a 30% solution of hydrogen peroxide. The resulting mixture was stirred for 1 h and 120 g of K_2CO_3 and 100 mL of water were added, and the mixture was stirred for 1 h. The layers were separated and the THF layer was dried and concentrated to give 43.9 g of an oil. This material was distilled under vacuum to give three fractions: F1, 0.64 g, bp 60–110 °C at (50 μm); F2, 34.5 g, bp 110–112 °C (50 μm); F3, 4.9 g, bp 112–113 °C (50 μm). Fraction F2 was shown by its ^{1}H NMR spectrum to be a 9:1 mixture of primary to secondary alcohol, and F3 contained <0.5% of secondary alcohol. Fractions F2 and F3 together provided 39.4 g (84%) of a 9.15:0.85 mixture of the primary to secondary alcohol. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.35; H, 8.12.

This veratrole derivative was demethylated as follows. A solution of 104 g of BBr_3 in 150 mL of dry CH_2Cl_2 was added to 35.0 g of the above mixture of alcohols dissolved in 400 mL of dry CH_2Cl_2 at −77 °C under N_2. The resulting solution was warmed to 25 °C over 1 h, poured into 1 kg of ice water, and stirred vigorously for 12 h. The layers were separated and the CH_2Cl_2 solution was dried and concentrated to give 3.5 g of olefinic material derived from the unwanted secondary alcohol. The aqueous layer was extracted with five 600-mL portions of ether and the combined extracts were dried, concentrated, and dried as a film at 110 °C (50 μm) for 15 h: wt 21.5 g (78%) of viscous oil. This 4-(3-hydroxypropyl)catechol was pure to TLC and gave: M^+ 168; ^{1}H NMR (CD_3COCD_3 containing several drops of D_2O) δ 6.7 (m, ArH, 3), 3.58 (t, J = 6.5 Hz, CH_2OH(D), 2), 2.57 (m, $ArCH_2$, 2) and 1.83 (m, $CH_2CH_2CH_2$, 2). There was no trace of a d in the region of δ 1.2, attributable to a methyl group of a secondary alcohol. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.24.

2,3:4,5-Dinaphtho-13,14-[4-(4-oxabutyl)-1,2-benzo]1,6,9,12,-15,18-hexaoxacycloeicosa-2,4,13-triene (21). Application of procedure I to dinaphthyl two-armed ditosylate[5] (**4**) and 4-(3-hydroxypropyl)catechol gave cycle **21** in 46% yield as a colorless glass: ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.8 (m, naphthyl ArH, 4), 7.2 (complex m, naphthyl ArH, 8), 6.7 (m, benzo ArH, 3), 4.0 (complex m, $ArOCH_2$, 8), 3.5 (complex m, CH_2OCH_2 and CH_2OH, 10), 2.57 (m, aryl-CH_2, 2), and 1.78 (m, $CH_2CH_2CH_2OH$, 3). Anal. Calcd for $C_{37}H_{38}O_7$: C, 74.73; H, 6.44. Found: C, 74.84; H, 6.56.

2,3:4,5-Dinaphtho-13,14-(3-aldehydo-1,2-benzo)-1,6,9,12,15,-18-hexaoxacycloeicosa-2,4,13-triene (22). Into 500 mL of CH_2Cl_2 at −77 °C was bubbled on ozone–oxygen mixture until the deep blue color did not intensify. This solution was added to a stirred solution of 5.8 g of cyclic alkene **21** in 125 mL of dry CH_2Cl_2 at −77 °C. The colorless solution was stirred for 0.3 h, 1.8 g of Zn was added, and the stirred solution was slowly warmed (5 h) to 25 °C. The solution was concentrated and the residue dissolved in dry THF, whereupon a solid separated. A portion of this material (aldehyde **22**) was purified as follows, and the remainder was used directly in the next reaction (**22** → **23**). The white solid (0.15 g) was recrystallized from THF to give cubic crystals of a 1:1 solvate (^{1}H NMR): mp 100–110 °C (bubbles, solidification, and remelting at 159–160 °C). The solid was heated at 100–110 °C at 50 μm for 24 h, and the amorphous aldehyde **22** was characterized: IR ($CDCl_3$) C=O band at 1695 cm^{-1}; 100-MHz ^{1}H NMR ($CDCl_3$) δ 10.36 (s, O=CH, 1), 7.8 (m, naphthyl ArH, 4), 7.5–6.9 (complex m, naphthyl and benzo ArH, 11), 4.1 and 3.6 (overlapping complex m, OCH_2, 16). Anal. Calcd for $C_{35}H_{32}O_7$: C, 74.45; H, 5.71. Found: C, 74.22; H, 5.80.

2,3:4,5-Dinaphtho-13,14-(3-hydroxymethyl-1,2-benzo)-1,6,9,-12,15,18-hexaoxacycloeicosa-2,4,13-triene (23). The remaining unpurified aldehyde **22** (see above) in 150 mL of THF was slowly added to 380 mg of $LiAlH_4$ in 150 mL of dry THF. The mixture was refluxed for 0.5 h, treated with 2.5 mL of water, filtered, and concentrated. The residue was chromatographed on 300 g of silica gel with $CHCl_3$–ethanol (49:1, v/v) as eluent. Alcohol **23** was eluted with 12 L of solvent, which when evaporated gave a glass. This material was film dried at 100 °C (50 μm) for 24 h to give 4.4 g (80% based on olefin **20**) of **23**: IR (KBr) OH band at 3440 cm^{-1}; 100-MHz ^{1}H NMR ($CDCl_3$) δ 7.8 (m, naphthyl ArH, 4), 7.2 (complex m, naphthyl ArH, 8), 6.8 (m, benzo ArH, 3), 4.72 and 4.34 (ABq, J_{AB} = 12 Hz, CH_2OH, 2) and 4.2–3.1 (complex m, CH_2O and OH, 7). Anal. Calcd for $C_{35}H_{34}O_7$: C, 74.19; H, 6.05. Found: C, 74.03; H, 5.97. This material crystallized as a solvate from THF, mp 90–100 °C (bubbles).

2,3:4,5-Dinaphtho-13,14-(3-chloromethyl-1,2-benzo)-1,6,9,-12,15,18-hexaoxacycloeicosa-2,4,13-triene (24). A solution of 5.8 g of thionyl chloride in 210 mL of dry benzene was added dropwise to a solution of 12.8 g of alcohol **23** in 620 mL of dry benzene and 4 mL of dry pyridine. The mixture was refluxed for 1 h, filtered, and concentrated and the residue was dissolved in 500 mL of CH_2Cl_2. The solution was washed with water, dried, and concentrated to give 13.2 g (100% crude) of **24** as a yellow glass film dried at 70 °C (50 μm) for 1 h. A 100-mg sample was crystallized and recrystallized from THF to give a 1:1 solvate: mp 90–100 °C (bubbles). Anal. Calcd for $C_{35}H_{33}ClO_6 \cdot C_4H_8O$: C, 71.27; H, 6.29. Found: C, 71.27; H, 6.42. The sample when heated at 100 °C (50 μm) for 48 h gave **24** as a glass. Anal. Calcd for $C_{35}H_{33}ClO_6$: C, 71.86; H, 5.69. Found: C, 71.74; H, 5.69.

2,3:4,5-Dinaphtho-13,14-(3-azidomethyl-1,2-benzo)-1,6,9,12,-15,18-hexaoxacycloeicosa-2,4,13-triene (25). A mixture of 12.8 g of chloride **24**, 14 g of sodium azide, and 700 mL of 95% ethanol was stirred at reflux for 15 h and concentrated. The residue was partitioned between 500 mL of CH_2Cl_2 and 150 mL of water. The organic layer was washed with water, dried, and concentrated to give after film drying at 100 °C (50 μm) (2 h) 10.1 g (80%) of a glass. A 150-mg sample was chromatographed on neutral alumina wtih benzene–ether (4:1) as eluent to give azide **25** as a glass, whose IR spectrum ($CDCl_3$) showed a strong band at 2105 cm^{-1} (N_3 asymmetric stretch). Anal. Calcd for $C_{35}H_{33}N_3O_6$: C, 71.05; H, 5.58. Found: C, 71.00; H, 5.62.

2,3:4,5-Dinaphtho-13,14-(3-*N*-acetylaminomethyl-1,2-benzo)-1,6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene (26). A solution of 9.8 g of crude azide **25** (see above) in 500 mL of dry THF was added slowly to 2.5 g of $LiAlH_4$ in 100 mL of dry THF. The resulting mixture was refluxed for 0.5 h, cooled, and treated carefully with 32 mL of water and 500 mL of CH_2Cl_2. The mixture was filtered, dried, and concentrated to give a glass. This amine (8.6 g) was dissolved in 240 mL of dry CH_2Cl_2 and 4.6 g of triethylamine, and the solution was treated with a solution of 1.61 g of acetyl chloride in 100 mL of dry CH_2Cl_2. The mixture was stirred for 0.5 h, washed with water, dried, and evaporated to give 8.2 g of glass. This material was chromatographed on 500 g of neutral alumina with ether–ethanol (99:1, v/v) as eluent. Fractions of 500 mL were collected. Fractions 12–24 were evaporated to give 5.6 g of a white solid which was crystallized from ether–benzene. This amide (**26**) as fine needles was dried at 165 °C at (50 μm) for 24 h to give 5.1 g (57%) of pure material: mp 193–194 °C; IR ($CDCl_3$) N–H band at 3333, C=O band at 1661 cm^{-1}; M^+ 607; ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.8 (m, naphthyl, ArH, 4), 7.2 (complex m, naphthyl ArH, 8), 6.8 (m, benzo ArH and NH, 4), 4.1 (complex m, $ArOCH_2$ and $ArCH_2N$, 10), 3.5 (complex m, CH_2OCH_2, 8), and 1.75 (s, CH_3, 3). Anal. Calcd for $C_{37}H_{37}NO_7$: C, 73.17; H, 6.14. Found: C, 73.27; H, 6.11.

2,3:4,5-Dinaphtho-13,14-[4-(3-chloropropyl)-1,2-benzo]-1,-6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene (27). Alcohol **21** (4.0 g) in 70 mL of dry benzene and 2.5 mL of dry pyridine was treated with 1.6 g of thionyl chloride in 70 mL of dry benzene. The resulting mixture was refluxed for 3.5 h and stirred at 25 °C with 1 mL of water. The benzene layer was concentrated and the residue was chromatographed on 300 g of silica gel with $CHCl_3$ as eluting agent. Product was eluted with 3 L of $CHCl_3$, concentration of which gave after drying at 110 °C (50 μm) for 24 h 3.9 g (95%) of chloride **27**. Anal. Calcd for $C_{37}H_{37}ClO_6$:

C, 72.71; H, 6.10. Found: C, 72.70; H, 6.05.

2,3:4,5-Dinaphtho-13,14-[4-(3-carboxypropyl)-1,2-benzo]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene (28). A solution of 8.0 g of ethyl bromide in 100 mL of dry THF was added slowly to 2.2 g of Mg turnings covered by 30 mL of dry THF under N_2. After about half the ethyl bromide had been added, a solution of 4.75 g of chloride **27** in 20 mL of dry THF was added to the remaining ethyl bromide solution, and the addition was completed. The resulting reaction mixture was refluxed for 8 h, cooled to −25 °C, and dry carbon dioxide gas was bubbled through the reaction mixture for 1 h. The solution was warmed to 25 °C and diluted with 10 mL of brine and the mixture was shaken. The organic layer was filtered and concentrated and the residue was dissolved in 200 mL of CH_2Cl_2. The solution was washed with dilute hydrochloric acid and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated and the residue was chromatographed on 300 g of silica gel with chloroform–ethanol–acetic acid (98:2:0.2, v/v/v) as eluting agent. Elution of the column with 1.5 L of solvent gave 0.5 g of byproducts. Elution with an additional 2 L of solvent gave product acid **28,** obtained as a glass by evaporation of the solvent and film drying at 120 °C (50 μm) for 24 h; wt 3.6 g (74%); IR ($CDCl_3$) broad OH band at 3000, C=O band at 1720 cm^{-1}; 100-MHz ^1H NMR ($CDCl_3$) δ 9.3 (br s, CO_2H, 1), 7.8 (m, naphthyl ArH, 4), 7.2 (complex m, naphthyl ArH, 8), 6.68 (narrow m, benzo ArH, 3), 4.0 and 3.5 (overlapping complex m, CH_2O, 16), 2.56 and 2.31 (overlapping m's; former is phenyl-CH_2–, latter is HO_2CCH_2, 4) and 1.92 (m, $CH_2CH_2CH_2$, 2); mass spectrum base peak M^+ 622. Anal. Calcd for $C_{38}H_{38}O_8$: C, 73.29; H, 6.15. Found: C, 72.99; H, 6.34.

2,3:4,5-Bis[1,2-(3-hydroxymethylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (29). Procedure 2. A solution of 12.6 g of tetrol **8**[6] in 900 mL of THF was stirred at 25 °C under N_2 for 30 min. To the clear solution was added 4.5 g of KOH dissolved in 80 mL of water. The mixture was warmed to 65 °C (homogeneous) and with stirring 26 g of pentaethylene glycol ditosylate[4,11] dissolved in 100 mL of THF was added. The solution was refluxed for 48 h, cooled, concentrated to 200 mL at 30 mm, and partitioned between water and CH_2Cl_2. The water layer was extracted with additional CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and concentrated to 100 mL. This solution was chromatographed on 500 g of neutral alumina packed in CH_2Cl_2. Elution of the column with 2 L of CH_2Cl_2, 2 L of 1% 2-propanol–CH_2Cl_2, and 2 L of 2% 2-propanol–CH_2Cl_2 produced after removal of solvents 12.0 g (60%) of **29** as a colorless glass, which tenaciously retains solvent. When heated as a thin film at 145 °C (0.05 mm) for 6 h, the solvent evaporated. A crystalline sample of **29,** mp 132–134 °C, was obtained by concentrating a 2-propanol solution (1 g in 50 mL) at 25 °C. The solid material after drying at 25 °C for 48 h and 0.1 mm still contained a trace (^1H NMR) of 2-propanol. **29:** ^1H NMR (100 MHz, $CDCl_3$) δ 7.90 (s, ArH^4, 2), 7.85 (m, $ArH,^5$ 2), 7.28 (m, ArH, 6), 4.95 (AB q, J_{AB} = 13 Hz, $ArCH_2O$, 4), and 7.28 (complex m, OCH_2, 20); mass spectrum base peak M^+ 548 (see Table V for analysis).

(−)-(*S*)-2,3:4,5-Bis(1,2-[3-(2,5-dioxa-4-oxohexyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene [(−)-(*S*)-38]. Procedure 3. To a solution of optically pure (−)-(*S*)-**29** (Table V) (5.8 g) in 250 mL of THF was added NaH as a 50% suspension in oil (2.4 g, 50 mmol) and the mixture was stirred at 25 °C for 2 h. Methyl bromoacetate (7.6 g) was added to the above suspension and the mixture was heated to reflux for 6.5 h. The reaction mixture was cooled and filtered and the solid was washed with THF. The combined filtrate was evaporated to an oil that was chromatographed on 150 g of silica gel. Elution of the column with 1.4 L of CH_2Cl_2 gave nonnaphthalene-containing products (^1H NMR). Elution with 3.5 L of 2% methanol–ether (by volume) gave (−)-(*S*)-**38.** The eluate was evaporated to give 3.2 g (44%) of this product as a glass, which was dried at 165 °C (0.07 mm) for 1 h: $[\alpha]^{25}_{546}$ −25.7° (*c* 1.0, THF); M^+ 692; 100 MHz ^1H NMR ($CDCl_3$) δ 7.7–8.05 (m, ArH, 4), 7.0–7.5 (m, ArH, 6), 5.0 (s, $ArCH_2O$, 4), 4.35 (s, OCH_2CO_2, 4), 3.80 (s, OCH_3, 6), 2.8–3.8 (m, OCH_2CH_2O, 20). Table V records the analysis.

2,3-(1,2-[3-(2,5-Dioxa-4-oxohexyl)naphtho])-4,5-[1,2-(3-methylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (Methyl Ester of 49). Application of procedure 3 to monomethylmonool **34** (Table V) gave the methyl ester of **49** as a glass (72%); M^+ 604; ^1H NMR (60 MHz, $CDCl_3$) δ 8.10–6.84 (m, ArH, 10), 4.98 (s, $ArCH_2$, 2), 4.32 (s, CH_2CO_2, 2), 4.05–2.76 (m, CH_2O, 20), 3.72 (s, OCH_3, 3) and 2.55 (s, $ArCH_3$, 3). Anal. Calcd for $C_{35}H_{40}O_9$: C, 69.52; H, 6.67. Found; C, 69.29; H, 6.48.

2,3-(1,2-[3-(2,5-dioxa-4-oxohexyl)naphtho])-4,5-[1,2-(3-hydroxymethylnaphtho)]-1,6,9,12,15,18-hexaoxyacycloeicosa-2,4-diene (Methyl Ester of 51). Application of a modified procedure 3 to diol **29** (Table V) gave the methyl ester of monoacid **51.** To a solution of 5.5 g of **29** in 500 mL of THF under N_2 was added 3.0 g of NaH (50% mineral oil dispersion). The mixture was heated to reflux and 2.2 g of methyl bromoacetate in 25 mL of THF was added, and the mixture was refluxed for 12 h, cooled, filtered, and evaporated under vacuum. The residue was shaken with 400 mL each of water and CH_2Cl_2 and the organic layer was dried and concentrated. The residue was chromatographed on 200 g of silica gel and the column was washed with 2 L of CH_2Cl_2, 2 L of CH_2Cl_2–methanol (99:1, v/v), and 2 L of CH_2Cl_2–methanol (49:1, v/v). Then 2 L of 19:1 (v/v) CH_2Cl_2–methanol gave 2.2 g (35%) of diester **38,** identified by TLC and ^1H NMR spectrum. Elution of the column with 2 L of 9:1 and 3 L of 4:1 (v/v) CH_2Cl_2–methanol gave upon evaporation and drying 0.60 g (10%) of the methyl ester of monoacid **51** as a glass: M^+ 620; ^1H NMR (60 MHz, $CDCl_3$) δ 8.02 (s, ArH^4, 1), 7.86 (s, ArH at ArH^4, 1), 7.95–6.85 (m, ArH, 8), 4.88 (s, $ArCH_2O$, 2), 4.90 (ABq, CH_2OH, 2), 4.26 (s, OCH_2CO_2, 2), 3.75 (s, OCH_3, 3), and 3.92–2.80 (m, OCH_2, 20). Anal. Calcd for $C_{35}H_{40}O_{10}$: C, 67.73; H, 6.50. Found: C, 67.90; H, 6.51.

Application of this same procedure to optically pure (+)-(*R*)-**29** gave (14%) the methyl ester of the monoacid, (−)-(*R*)-**51,** identified by TLC and ^1H NMR spectral comparisons with racemic ester.

(−)-(*S*)-2,3:4,5-Bis(1,2-[3-(2,5-dioxa-4-oxopentyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene [(−)-(*S*)-44]. Procedure 4. A mixture of (−)-(*S*)-**38** (Table V) (5.2 g) and barium hydroxide octahydrate (7.1 g) in 250 mL of methanol was heated at reflux for 4 h and evaporated to dryness. The residue was dissolved in water and the aqueous solution was washed with a mixture of CH_2Cl_2 and ether. The aqueous layer was filtered and acidified with hydrochloric acid to pH 1 to give a milk-like emulsion, which was extracted twice with CH_2Cl_2. The combined extracts were washed once with 5% aqueous hydrochloric acid and three times with water and dried. Evaporation of the CH_2Cl_2 gave 4.65 g (90%) of optically pure (−)-(*S*)-**44** as a glass. A sample dried as a thin film at 165 °C (0.07 mm) for 1 h gave: $[\alpha]^{25}_{546}$ +76.2° (*c* 1.0, $CHCl_3$), $[\alpha]^{25}_{546}$ −24.4° (*c* 1.0, THF); M^+ 664; 100-MHz ^1H NMR ($CDCl_3$) δ 7.7–8.1 (m, ArH, 4), 6.9–7.5 (m, ArH, 6), 4.97 (s, $ArCH_2O$, 4), 4.30 (s, OCH_2CO_2, 4), 3.0–4.0 (m, OCH_2CH_2O, 20). The analysis is given in Table V.

Procedure 4 when applied to the hydrolysis of the methyl ester of **49** gave (85%) **49** as a glass: M^+ 590; ^1H NMR (60 MHz, CD_3CO_2D) δ 8.15–6.95 (m, ArH, 10), 5.10 (s, $ArCH_2$, 2), 4.42 (s, CH_2CO_2, 2), 4.20–2.95 (m, OCH_2, 20), and 2.60 (s, $ArCH_3$, 3). Table V records the analysis.

Procedure 4 when applied to the methyl ester of monoacid **51** gave (77%) acid **51** as a glass: M^+ 606; ^1H NMR (60 MHz, $CDCl_3$) δ 8.07 (s, ArH^4, 1), 7.96 (s, ArH^4, 1), 7.95–6.88 (m, ArH, 8), 4.90 (m, $ArCH_2OH$ and $ArCH_2OCH_2$, 4), 4.25 (s, OCH_2CO_2, 2), and 3.92–2.80 (m, OCH_2, 20). Table V records its analysis.

Procedure 4 applied to the methyl ester of monoacid (+)-(*R*)-**51** gave (82%) (+)-(*R*)-**51** as a glass: $[\alpha]^{25}_{578}$ −68.3°, $[\alpha]^{25}_{546}$ −80.4° (*c* 1.0, $CHCl_3$), $[\alpha]^{25}_{578}$ +20.7°, and $[\alpha]^{25}_{546}$ +24.2° (*c* 1.0, THF). Table V records the analysis.

2,3:4,5-Bis[1,2-(3-chloromethylnaphto)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (52) and (−)-(*S*)-52. Procedure 5. To a suspension of 4.0 g of **29** in 50 mL of benzene was added 4.0 g of thionyl chloride at 25 °C. The mixture became homogeneous, and after stirring at 25 °C for 8 h the solvent was evaporated under vacuum and the residue was dissolved in 100 mL of CH_2Cl_2. The solution was extracted with a 100-mL portion of sodium bicarbonate saturated water, and the water layer was washed with 50 mL of CH_2Cl_2. The combined organic extracts were dried, evaporated, and chromatographed on 100 g of silica gel. The column was washed with 500 mL of CH_2Cl_2 and 500 mL of CH_2Cl_2–ether (19:1, v/v). Product **52** was eluted with 2 L of CH_2Cl_2–ether (9:1) and 1 L of 4:1 (v/v) CH_2Cl_2–ether as an oil: wt 3.9 g (91%); M^+ 584; ^1H NMR (60 MHz, $CDCl_3$) δ 8.05 (s, ArH^4, 2), 7.98–7.14 (m, ArH, 8), 5.50 (ABq, CH_2Cl, 4), and 3.93–2.75 (m, OCH_2, 20). Table V reports the analysis. Optically pure enantiomer, (−)-(*S*)-52, similarly prepared from optically pure (−)-(*S*)-**29,** gave $[\alpha]^{25}_{578}$ −7.0°, $[\alpha]^{25}_{546}$ −9.5°, $[\alpha]^{25}_{436}$ −38.4° (*c* 1.0, $CHCl_3$).

2,3:4,5-Bis(1,2-[3-(5-oxa-4-oxo-2-sulfapentyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (53) and (+)-(*S*)-53. Procedure 6. To a stirred solution of racemic **52** (2.0 g) and 3.7 g of thioglycolic acid in 200 mL of THF under N_2 was added 3.2 g of NaOH dissolved in 30 mL of water. The mixture was refluxed for 20 h, cooled, and concentrated under vacuum to 20 mL. The solution was diluted to 100 mL with water and 6 N hydrochloric acid was added until a pH of 1 was obtained. An oil separated and the mixture was allowed to stand at 25 °C for 10 h. The aqueous solution was decanted and the oily residue was washed three times with 50 mL of water. The residue was dissolved in 150 mL of CH_2Cl_2 and the solution was washed with water, dried, and evaporated under vacuum. The residue was dried

Table V. Compound Numbers, Procedures, Yields, Physical Properties, and Analyses of Macrocycles

Compd no.			Product							
Starting material[a]	Product	Procedure no.[b]	Mp, °C	Yield, %	$[\alpha]^{25}_{546}$ (c 1.0, THF)[c]	Anal. Calcd for, % Formula	C	H	Found, % C	H
(−)-(S)-8	(−)-(S)-29	2	Glass	55	−34.0°	$C_{32}H_{36}O_8$	70.05	6.61	69.89	6.82
8	29	2	132–134	60		$C_{32}H_{36}O_8$	70.05	6.61	69.91	6.70
(−)-(S)-8	(−)-(S)-30	2	Glass	6	−56.1°	$C_{30}H_{32}O_7$	71.41	6.39	71.45	6.45
8	30	2	Glass	10		$C_{30}H_{32}O_7$	71.41	6.39	71.21	6.53
(+)-(R)-8	(−)-(R)-31	2	Glass	57	−16.4°	$C_{34}H_{40}O_9$	68.90	6.80	69.02	6.80
8	31	2	Glass	50		$C_{34}H_{40}O_9$	68.90	6.80	68.73	6.98
9	32	2	136–137	50		$C_{31}H_{34}O_7$	71.80	6.61	71.57	6.64
9	33	2	151–152	31		$C_{29}H_{30}O_6$	73.39	6.37	73.33	6.26
10	34	2	159	59		$C_{32}H_{36}O_7$	72.16	6.81	72.12	7.06
11	35	2	Glass	55		$C_{36}H_{43}NO_8$	70.00	7.02	69.76	7.22
12	36	2	Glass	65		$C_{40}H_{50}N_2O_8$	69.95	7.34	69.71	7.38
13	37	2	Glass	64		$C_{36}H_{46}N_2O_6$	71.73	7.69	71.70	7.62
(−)-(S)-24	(−)-(S)-38	3	Glass	44	−25.7°	$C_{38}H_{44}O_{12}$	65.87	6.40	65.99	6.27
24	38	3	Glass	60		$C_{38}H_{44}O_{12}$	65.87	6.40	65.63	6.27
(−)-(S)-25	(−)-(S)-39	3	Glass	51	−95.7°	$C_{36}H_{40}O_{11}$	66.65	6.22	66.50	6.05
25	39	3	Glass	55		$C_{36}H_{40}O_{11}$	66.65	6.22	66.46	6.15
(−)-(R)-26	(−)-(R)-40	3	Glass	54	−19.5°	$C_{40}H_{48}O_{13}$	65.20	6.57	65.05	6.50
26	40	3	Glass	50		$C_{40}H_{48}O_{13}$	65.20	6.57	65.06	6.39
28	41	3	Glass	70		$C_{34}H_{38}O_9$	69.14	6.48	68.95	6.71
29	42	3	128–130	71		$C_{32}H_{34}O_8$	69.91	6.05	70.09	6.26
35	43	3	Glass	35		$C_{39}H_{47}NO_{10}$	67.91	6.87	67.98	6.89
(−)-(S)-38	(−)-(S)-44	4	Glass	90	−24.4°	$C_{36}H_{40}O_{12}$	65.05	6.07	65.00	6.23
38	44	4	Glass	80		$C_{36}H_{40}O_{12}$	65.05	6.07	64.87	6.28
(−)-(S)-39	(−)-(S)-45	4	Glass	65	−107.4°	$C_{34}H_{36}O_{11}$	65.79	5.85	65.86	5.94
39	45	4	Glass	85		$C_{34}H_{36}O_{11}$	65.79	5.85	65.92	5.87
(−)-(R)-40	(−)-(R)-46	4	Glass	50	−15.0°	$C_{38}H_{44}O_{13}$	64.39	6.26	64.18	6.06
40	46	4	Glass	75		$C_{38}H_{44}O_{13}$	64.39	6.26	64.14	6.42
41	47	4	Glass	70		$C_{33}H_{36}O_9$	68.74	6.29	68.95	6.63
42	48	4	128–130	35		$C_{31}H_{32}O_8$	69.91	6.05	70.09	6.26
31	49	3,4	Glass	85		$C_{34}H_{38}O_9$	69.14	6.48	69.78	6.47
43	50	4[e]	Glass	65		$C_{38}H_{45}NO_{10}$	67.53	6.71	67.41	6.74
24	51	3,4	Glass	77		$C_{34}H_{38}O_{10}$	67.31	6.31	67.63	6.29
(+)-(R)-24	(+)-(R)-51	3,4	Glass	82	+24.2°	$C_{34}H_{38}O_{10}$	67.31	6.31	67.30	6.21
24	52	5	Glass	91		$C_{32}H_{34}Cl_2O_6$	65.61	5.86	65.89	5.91
(−)-(S)-24	(−)-(S)-52	5	Glass	81	−9.5°[d]	$C_{32}H_{34}Cl_2O_6$	65.61	5.86	65.87	6.01
52	53	6	Glass	96		$C_{36}H_{40}O_{10}S_2$	62.06	5.79	61.90	6.16
(−)-(S)-52	(+)-(S)-53	6	Glass	72	+12.0°	$C_{36}H_{40}O_{10}S_2$	62.06	5.79	62.21	6.01
52	54	6	Glass	97		$C_{38}H_{44}O_{10}S_2$	62.98	6.12	62.86	6.15
(−)-(S)-52	(−)-(S)-54	6	Glass	58	−33.6°	$C_{38}H_{44}O_{10}S_2$	62.98	6.12	62.67	6.27
52	55	7	140	91		$C_{38}H_{40}O_{14}$	63.33	5.59	63.15	5.82
55	56	7	Glass	92		$C_{36}H_{40}O_{10}$	68.34	6.37	68.30	6.51
(−)-(S)-52	(−)-(S)-56	7	Glass	85	−94°[d]	$C_{36}H_{40}O_{10}$	68.34	6.37	68.10	6.40

[a] Optically pure when optically active, ref 6. [b] See Experimental Section. [c] Unless otherwise noted. [d] c 1. $CHCl_3$. [e] Lithium hydroxide was substituted for barium hydroxide.

at 95 °C (5 μm) for 1 h to give 2.3 g (96%) of **53** as a glass: M^+ 696; ^1H NMR (60 MHz, CD_3CO_2D) δ 8.02 (s, ArH^4, 2), 8.00–6.90 (m, ArH, 8), 4.22 (ABq, $ArCH_2S$, 4), 3.40 (s, SCH_2CO_2, 4), and 4.10–2.90 (m, OCH_2, 20). Table V records the analysis.

Optically pure (+)-(S)-**53** was similarly prepared: $[\alpha]^{25}_{546}$ +204° (c 1.3, $CHCl_3$) and $[\alpha]^{25}_{546}$ +12.0° (c 1.0, THF). Table V records the analysis.

2,3:4,5-Bis(1,2-[3-(6-oxa-5-oxo-2-sulfahexyl)naphtho])-1,-6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (54) and (−)-(S)-54 by Procedure 6. Racemic **54** was similarly prepared from racemic **52** except β-sulfhydrylpropionic acid was substituted for thioglycolic acid. The product gave: M^+ 724; ^1H NMR (60 MHz, CD_3CO_2D) δ 8.02 (s, ArH^4, 2), 8.02–6.90 (m, ArH, 8), 4.18 (AB q, $ArCH_2$, 4), and 4.20–2.50 (m, OCH_2, $SCH_2CH_2CO_2$, 28). Table V records the analysis.

Optically pure (−)-(S)-**54** prepared from optically pure (−)-(S)-**52** gave $[\alpha]^{25}_{546}$ +61.5° (c 1.15, $CHCl_3$) and $[\alpha]^{25}_{546}$ −33.6° (c 1.21, THF). Table V records the analysis.

2,3:4,5-Bis(1,2-[3-(2-carboxy-4-oxa-3-oxobutyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (55), 2,3:4,5-Bis(1,2-[3-(4-oxa-3-oxobutyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (56), and (−)-(S)-56. Procedure 7. To a solution under N_2 of 3.0 g of **52** and 2.0 g of dimethyl malonate in 100 mL of dry toluene was added with stirring 0.720 g of NaH (50% mineral oil dispersion). The mixture was stirred for 1 h at 25 °C, at reflux for 2 h, and an additional 6 h at 25 °C. The solution was cooled and shaken with 200 mL of CH_2Cl_2 and 200 mL of water. The aqueous layer was extracted with 50 mL of CH_2Cl_2 and the combined organic layers were dried and evaporated under vacuum. The residue was chromatographed on 100 g of silica gel. The column was washed with 1 L of CH_2Cl_2, 1 L of 49:1 (v/v) CH_2Cl_2–ether, and 1 L of 19:1 (v/v) CH_2Cl_2–ether. Elution of the product (tetraester) came with 2 L of 9:1 and 2 L of 4:1 (v/v) CH_2Cl_2–ether: wt 2.6 g (65%) of glass; M^+ 776; ^1H NMR (60 MHz, $CDCl_3$) δ 7.92–6.90 (m, ArH, 10), 4.10 (m, $CH(CO_2CH_3)_2$, 2) and 3.90–2.70 (m, $ArCH_2$, OCH_2, OCH_3, 36). Anal. Calcd for $C_{42}H_{48}O_{14}$: C, 64.94; H, 6.23. Found: C, 64.85; H, 6.16.

To a solution of 2.0 g of the above tetraester in 100 mL of ethanol was added 2.0 g of NaOH in 15 mL of water. The mixture was refluxed for 8 h, concentrated under vacuum to 10 mL and diluted with 75 mL of water. The solution was acidified with 6 N hydrochloric acid to a pH of 1. Tetraacid **55** crystallized and was collected, washed with water, and vacuum dried at 25 °C to give 1.7 g (91%) of white solid, mp 140 °C, with loss of carbon dioxide: ^1H NMR (60 MHz, Me_2SO-d_6) δ 8.04–6.80 (m, ArH, 10) and 4.20–3.16 (m, CH_2O, $CH_2CH(CO_2H)_2$, 26). Table V records the analysis.

Tetraacid **55**, 0.36 g, was heated at 160 °C (30 mm) for 2 h. The resulting oil was cooled and dissolved in 50 mL of CH_2Cl_2 and the solution was washed with water and dried. The solution was evaporated under vacuum and dried to give 0.30 g (92%) of **56** as a glass; M^+ 632; ^1H NMR (100 MHz, CD_3CO_2D) δ 8.0–6.8 (m, ArH, 10) and 4.5–2.60

(m, CH_2O, $ArCH_2CH_2CO$, 28). Table V records the analysis.

By procedure 7 optically pure (−)-(*S*)-**52** was converted to optically pure (−)-(*S*)-**56**. The tetraester intermediate was obtained in 44% yield (glass): $[\alpha]^{25}_{578}$ −64.7°, $[\alpha]^{25}_{546}$ −75.5°, $[\alpha]^{25}_{436}$ −152.4° (*c* 1.0, $CHCl_3$). This material was decarboxylated to give (−)-(*S*)-**56** by the above method. Table V records the analyses.

2,3:4,5-Bis[1,2-(6-bromonaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (58). To 3 g of parent cycle **57**[4] dissolved in 100 mL of CH_2Cl_2 was added 0.3 mL of bromine and the reaction mixture was heated to reflux. After 1 h, 0.35 mL more bromine was added and the solution was refluxed an additional 7.5 h. The solution was cooled and shaken with 25 mL of a 10% $NaHSO_3$ solution. The organic phase was separated, washed successively with water, saturated $NaHCO_3$ solution, and brine, and dried. Evaporation of the solvent left 4.17 g of an orange oil. This material was dissolved in ether and the solution was cooled to give 2.65 g (67%) of **58**: mp 138–139.5 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 3.40–3.62 (m, CH_2OCH_2, 16), 3.86–4.26 (m, $ArOCH_2$, 4), 7.40 (ArH^3), 7.76 (ArH^4, $J_{3,4}$ = 9 Hz), 7.93 (ArH^5), 7.20 (ArH^7, $J_{5,7}$ = 2 Hz), 6.90 (ArH^8, $J_{7,8}$ = 9 Hz). This ^1H NMR spectrum is uniquely consistent with the bromines being substituted in the 6- and 6′-positions of **58**. Anal. Calcd for $C_{30}H_{30}O_6Br_2$: C, 55.74; H, 4.68. Found: C, 55.98; H, 4.55.

2,3:4,5-Bis[1,2-(6-acetylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (59). Aluminum chloride (4.55 g) was added to 21.6 mL of nitrobenzene and the mixture was cooled to 0 °C. Acetyl chloride (2.52 g) and parent cycle **57**[4] (2.01 g) were then added in rapid succession and the mixture was stirred at 0 °C for 1 h. The cold mixture was stirred into an ice-concentrated hydrochloric acid mixture, which was subsequently extracted with CH_2Cl_2. The organic phase was washed successively with water, saturated $NaHCO_3$ solution, and brine and dried. Solvent was evaporated under reduced pressure to give an oil that was chromatographed on 100 g of neutral alumina. Fractions (100 mL) were collected of eluent. After 500 mL of ether eluate, 1% ethanol (by volume) in ether brought off the desired product in fractions 13–17, which on evaporation gave 0.982 g of **59**: mp 107–109 °C. Recrystallization of this material from acetone–hexane gave: 0.86 g (36%); mp 103–104 °C; IR (KBr) strong band at 1675 cm^{-1} (C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 2.5 (s, CH_3, 6), 3.30–3.58 (m, CH_2OCH_2, 16), 3.92–4.34 (m, $ArOCH_2$, 4), 7.50 (ArH^3), 8.04 (ArH^4, $J_{3,4}$ = 9 Hz), 8.46 (ArH^5), 7.72 (ArH^7, $J_{5,7}$ = 2 Hz), 7.10 (ArH^8, $J_{7,8}$ = 9 Hz). Anal. Calcd for $C_{34}H_{36}O_8$: C, 55.74; H, 4.68. Found: C, 55.98; H, 4.55.

2,3:4,5-Bis[1,2-(6-chloromethylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (60). Procedure 8. To 2.0 g of parent cycle **57**[4] and 10 g of chloromethyl methyl ether in 25 mL of $CHCl_3$ stirred at −60 °C was added (15 min) 3 mL of anhydrous stannic chloride. The solution was stirred for 1 h at −60 °C and shaken with 50 mL of water and 100 mL of CH_2Cl_2. The organic layer was washed with 100 mL of saturated $NaHCO_3$ solution, dried, and concentrated. The residue was chromatographed on 75 g of silica gel and the column was washed with 500 mL of CH_2Cl_2 and 500 mL of 19:1 (v/v) CH_2Cl_2–ether. Product was eluted with 1 L of 4:1 and 2 L of 1:1 (v/v) CH_2Cl_2–ether to give 1.2 g (50%) of **60** as a glass: M^+ 584; ^1H NMR (60 MHz, $CDCl_3$) δ 7.90–7.02 (m, ArH, 10), 4.62 (s, $ArCH_2$, 4), 4.02 (m, $ArOCH_2$, 4), and 3.70–3.18 (m, OCH_2, 16). Anal. Calcd for $C_{32}H_{34}Cl_2O_6$: C, 65.61; H, 5.86. Found: C, 65.58; H, 5.80.

2,3:4,5-Bis(1,2-[3,6-di(chloromethyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (61). Procedure 8 applied to di(chloromethyl) cycle **52** gave **61** (82%) as a glass: M^+ 680; ^1H NMR (60 MHz, $CDCl_3$) δ 8.00 (s, ArH^4, 2), 7.80 (s br, ArH^5, 2), 7.34–6.90 (m, $ArH^{7,8}$, 4), 4.98 (ABq, 3,3′-CH_2Cl, 4), 4.64 (s, 6,6′-CH_2Cl, 4), and 4.05–2.90 (m, OCH_2, 20). Anal. Calcd for $C_{34}H_{36}Cl_4O_6$: C, 59.83; H, 5.33. Found: C, 61.01; H, 5.67.

2,3:4,5-Bis[1,2-(6-carboxynaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (62). To a solution of 32 g of KOH in 100 mL of water at 5 °C was added 24 g of bromine. A solution of 4.5 g of diacetyl compound **59** in 200 mL of THF was added and the resulting mixture was held at reflux for 12 h with vigorous stirring. The reaction mixture was cooled, 100 mL of 10% $NaHSO_3$ solution was added, and the solution was concentrated under vacuum to 150 mL. The aqueous solution was diluted with 300 mL of water, washed with 200 mL of ether, and acidified with 6 N HCl to pH 1. The product that separated was collected, washed with water, and dried at 100 °C (50 μm) to give 3.8 g (84%) of diacid **62**, which gave: mp 291–292 °C (from methanol); ^1H NMR (100 MHz, $(CD_3)_2SO$) δ 7.70 (m, ArH^3 and ArH^7, 4), 8.24 (d, ArH^4, $J_{3,4}$ = 9 Hz, 2), 8.61 (d, ArH^5, $J_{5,7}$ = 2 Hz, 2), 6.98 (d, ArH^8, $J_{7,8}$ = 9 Hz, 2), 4.16 (m, $ArOCH_2$, 4), and 3.36 (m, CH_2O, 16). Anal. Calcd for $C_{32}H_{32}O_{10}$: C, 66.66; H, 5.59. Found: C, 66.53; H, 5.63.

2,3:4,5-Bis[1,2-(6-hydroxymethylnaphtho)]-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (63). Procedure 9. To a refluxing solution of 3.8 g of $LiAlH_4$ in 300 mL of THF was added, via Soxhlet extraction, 4.0 g of diacid **62**. The mixture was refluxed for 16 h and cooled and ethanol was cautiously added. The mixture was shaken with 500 mL of ether and 200 mL of 6 N hydrochloric acid and the resulting mixture was stirred for 8 h. The ether layer was separated and the aqueous layer extracted with two 200-mL portions of ether. The combined organic layers were washed with 100 mL of saturated aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed on 150 g of alumina. The column was washed with 2 L of ether and the product eluted with ether–2-propanol, 2 L of 49:1 and 2 L of 19:1 (v/v), to give 2.8 g (74%) of diol **63** as a glass: M^+ 548; ^1H NMR (60 MHz, $CDCl_3$) δ 7.88–7.00 (m, ArH, 10), 4.62 (s, $ArCH_2$, 4), and 4.22–3.05 (m, OCH_2CH_2O, 20). Anal. Calcd for $C_{32}H_{36}O_8$: C, 70.06; H, 6.61. Found: C, 70.22; H, 6.59.

2,3:4,5-Bis(1,2-[6-(2,5-dioxa-4-oxopentyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (65). By procedure 3, diol **63** was converted with methyl bromoacetate to the dimethyl diester **65** (55%), which was a glass; M^+ 692; ^1H NMR (60 MHz, $CDCl_3$) δ 7.98–7.04 (m, ArH, 10), 4.72 (s, $ArCH_2$, 4), 4.16 (s, CH_2CO_2, 4), 3.73 (s, OCH_3, 6), and 4.24–3.10 (m, OCH_2CH_2O, 20). Anal. Calcd for $C_{38}H_{44}O_{12}$: C, 65.88; H, 6.40. Found: C, 65.85; H, 6.60.

By procedure 4, this diester was hydrolyzed to diacid **65** as a glass (75%): M^+ 664; ^1H NMR (60 MHz, $CDCl_3$) δ 7.98–7.00 (m, ArH, 10), 4.70 (s, $ArCH_2$, 4), 4.10 (s, CH_2CO_2, 4), and 4.20–3.20 (m, OCH_2CH_2O, 20). Anal. Calcd for $C_{36}H_{40}O_{12}$: C, 65.05; H, 6.07. Found: C, 65.20; H, 6.11.

2,3:4,5-Bis(1,2-[6-(5-oxa-4-oxo-2-sulfapentyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (66). By procedure 6 the bis(chloromethyl) cycle **60** was converted to diacid **66**, which was an oil (75%): M^+ 696; ^1H NMR (60 MHz, CD_3CO_2D) δ 8.00–6.85 (m, ArH, 10), 3.96 (s, $ArCH_2$, 4), 4.15 (m, $ArOCH_2$, 4), 3.50 (m, OCH_2, 16), and 3.18 (s, CH_2CO_2, 4). Anal. Calcd for $C_{36}H_{40}O_{10}S_2$: C, 62.06; H, 5.79. Found: C, 61.94; H, 5.71.

2,3:4,5-Bis(1,2-[3,6-di(hydroxymethyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (64). Tetrachloro compound **61** was subjected to acetolysis to produce the tetraacetate of **64** as follows. To an acetic acid solution (150 mL), 1 M in KOAc, was added 5.50 g of **61** and the solution was refluxed for 18 h. The solution was cooled and shaken with a mixture of 400 mL each of water and CH_2Cl_2 and the organic layer was washed with two 100-mL portions of $NaHCO_3$-saturated water, dried, and evaporated. The product was chromatographed on 100 g of silica gel and the column was washed with 250 mL of CH_2Cl_2 and 0.5 L of 19:1 and 0.5 L of 9:1 (v/v) CH_2Cl_2–ether. The tetraacetate was eluted with CH_2Cl_2–ether, 1 L of 4:1 and 2 L of 1:1 (by volume), to give 4.8 g (76%) of the tetraacetate of **64** as a glass: M^+ 776; ^1H NMR (60 MHz, $CDCl_3$) δ 7.98 (s, ArH^4, 2), 7.83 (s br, ArH^5, 2), 7.10 (m, $ArH^{7,8}$, 4), 5.50 (s, 3,3′-$ArCH_2$, 4), 5.20 (s, 6,6′-$ArCH_2$, 4), 3.82–2.80 (m, OCH_2CH_2O, 20), 2.18 (s, 3,3′-$COCH_3$, 6), and 2.05 (s, 6,6′-$COCH_3$, 6). Anal. Calcd for $C_{42}H_{48}O_{14}$: C, 64.94; H, 6.23. Found: C, 64.90; H. 6.15.

To a refluxing solution of 3.8 g of $LiAlH_4$ in 300 mL of THF under N_2 was added dropwise a solution of 4.8 g of the above tetraacetate in 150 mL of THF. The mixture was refluxed for 8 h and cooled to 5 °C, ethanol was cautiously added, and the mixture was shaken with 200 mL of 6 N hydrochloric acid and 300 mL of ether. The aqueous layer was washed with three 150-mL portions of 2:1 ether–THF and combined with the original organic layer. The solution was dried and evaporated under reduced pressure to give 3.4 g (90%) of tetrol **64** as a glass; M^+ 608; ^1H NMR (60 MHz, $CDCl_3$) δ 7.82 (s, ArH^4, 2), 7.72 (s, br, ArH^5, 2), 7.00 (m, $ArH^{7,8}$,4), 4.82 (ABq, 3,3′-$ArCH_2$, 4), 4.63 (s, 6,6′-$ArCH_2$, 4) and 4.20–2.70 (m, OCH_2CH_2O, 20). Anal. Calcd for $C_{34}H_{40}O_{10}$: C, 67.09; H, 6.62. Found: C, 66.82; H, 6.90.

2,3:4,5-Bis(1,2-[3,6-di(5-oxa-4-oxo-2-sulfapentyl)naphtho])-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene (67). By procedure 6 except that the relative amount of thioglycolic acid was doubled, tetrachloride **61** was converted to tetraacid **67** (96%) as a glass (no M^+ observed): ^1H NMR (60 MHz, CD_3CO_2D) δ 8.02 (s, ArH^4, 2), 7.86 (s, ArH^5, 2), 7.40–6.90 (m, $ArH^{7,8}$, 4), 4.20 (s, 3,3′-$ArCH_2$, 4), 3.95 (s, 6,6′-$ArCH_2$, 4), 3.40 (s, 3,3′-CH_2CO_2, 4), 3.18 (s, 6,6′-CH_2CO_2, 4), and 4.30–2.62 (m, OCH_2, 20). Anal. Calcd for $C_{42}H_{48}O_{14}S_4$: C, 55.73; H, 5.35. Found: C, 56.04; H, 5.43.

Solubilization in Deuteriochloroform of Crystalline Amine Salts by Complexation with Various Host Compounds. Tetraphenylborate salts of *t*-$BuNH_3^+$, $C_6H_5CH(CH_3)NH_3^+$, and $C_6H_5CH(CO_2CH_3)NH_3^+$ ions were prepared[18] by adding an aqueous solution of the hydrochloride of the amine to an aqueous solution of sodium tetraphenylborate. The precipitated salt was filtered, water washed, and dried at 50 °C (50 μm). The other salts were made by standard procedures or purchased. The abilities of various hosts to solubilize these amine salts were determined as follows. The cyclic

ether (~90 mg) was dissolved in 0.4 mL of $CDCl_3$ and its 100-MHz ^1H NMR spectrum recorded. Excess salt (3–4 mol per mole of cyclic ether) was shaken with this solution, which was then filtered, and the ^1H NMR spectrum again taken. The relative number of moles of the cyclic ether to the dissolved salt was determined (±5%) by integrating the appropriate signals of the protons of the cycle vs. those of the salt. After the spectra were run, all solutions were returned to contact with the excess salt, and the mixtures were shaken intermittently for 24 h without spectral change. With each salt, a parallel experiment was performed in which the host was absent. Unless noted otherwise, no signal was observed for the salt in the absence of the host, indicating the salt alone to be too insoluble to be detected. Table I records the results.

Extraction into Deuteriochloroform from Deuterated Water of Amine Salts by Complexation with Various Host Compounds. Hosts (~90 mg) were dissolved in 0.7 mL of $CDCl_3$ and shaken with 0.8 mL of D_2O containing 6 mol (relative to the cyclic ether) each of KSCN and either α-phenylethylammonium bromide or the hydrobromide of methyl α-phenylglycinate. The organic layer was separated and dried with magnesium sulfate, and the 100-MHz ^1H NMR spectrum was examined.

The relative amounts of cyclic ether and complexed salt were determined (±5%) by integration of appropriate ^1H NMR peaks of the host and guest entities. In parallel runs made without host present, or alternatively without the KCN present, peaks due to the salts were absent from the $CDCl_3$ layer's spectra. Table II records the results.

Extraction into Carbon Disulfide from Deuterated Water–Deuterated Methanol of Methanol by Complexation with (*R,R*)-70.[5] A 0.112 M solution of (*R,R*)-**70** in carbon disulfide (80 mg in 1.0 mL) was cooled to −78 °C and shaken with 1.5 mL of a 20% solution (by volume) of D_2O in CH_3OD which was 0.66 M in $LiPF_6$ (152 mg) at −78 °C. The layers were carefully separated at this temperature. Integrations of the ^1H NMR spectrum of the CS_2 layer taken (100 MHz) at 25 °C gave the relative amounts of CH_3OD [δ 3.18 (s, CH_3, 3 H)] and of (*R,R*)-**70** [δ 7.68 (m, $ArH^{4,5}$, 8), 7.00 (m, $ArH^{3,6,7,8}$, 12), 3.62 (m, $ArOCH_2$, 8), 3.00 (m, CH_2OCH_2, 8)].

Integrals	$ArH^{4,5}$	$ArH^{3,6,7,8}$	$ArOCH_2$	CH_2OCH_2 + CH_3OD
Calcd for 1:1 complex	75	150	75	103
Found	75	150	75	100

Repetition of the experiment except that the (*R,R*)-**70** was omitted gave no observable amount of CH_3OD in the CS_2 layer, although <10% of the observed in the original experiment would have been detected.

Preparation of Crystalline Host–Guest Complexes that Involve Amine Salts. Treatment of a solution of five-oxygen cycle **68**[4] (44.4 mg) in 2 mL of $CDCl_3$ with 46 mg of *tert*-butylammonium tetraphenylborate gave a clear solution, which after standing at 25 °C for 14 h deposited crystals: wt 75 mg (80%); mp 118–120 °C; ^1H NMR spectrum of this material in $DCCl_3$ indicated it to be 1:1. Anal. Calcd for $C_{56}H_{60}O_5NB$: C, 80.29; H, 7.17. Found: C, 80.30; H, 7.34.

A crystalline complex was formed by extracting 1.5 mL of a D_2O solution 4 M in $LiPF_6$ (pH 4.0) and 1.2 M in (*R*)-phenylglycine methyl ester hydrochloride with 3 mL of a 0.2 M solution of optically pure (*S,S*)-**70**[5] in $CDCl_3$ at −13 °C. The $CDCl_3$ layer was dried and its ^1H NMR spectrum showed it contained a 1:1 complex. After 0.5 h the complex crystallized and was collected and recrystallized from $CHCl_3$ to give 0.41 g (75%) of complex: phase change and bubbles 142–145 °C; mp 222–224 °C dec. The analysis and an X-ray molecular weight determination demonstrated that a 1:1 complex had formed and that 1 mol of $CHCl_3$ was present as solvate.[12] Anal. Calcd for $C_{57}H_{52}F_6NO_8P \cdot HCCl_3$: C, 60.93; H, 4.67; Cl, 9.30. Found: C, 60.75; H, 4.55; Cl, 8.91.

Preparation of Solid Host–Guest Complexes that Involve Metal Ions. A solution of 350 mg of amino ester **43** and 120 mg of KOH in 100 mL of methanol–water (9:1, v/v) was refluxed under N_2 for 6 h. The solution was evaporated (30 mm) and the residue was partitioned between 150 mL of water and 200 mL of ether. The ether layer was dried ($MgSO_4$), filtered, and evaporated to give <10 mg of material. The aqueous layer was extracted with four 100-mL portions of $CHCl_3$, which were combined, dried ($MgSO_4$), and evaporated to give 50 mg of material. The ^1H NMR spectrum (60 MHz) of this substance in $CDCl_3$ gave signals indicative of complexed material: δ 6.98–8.18 (complex m, ArH, 10), 4.98 (ABq, $ArCH_2O$, 2), 4.20 (s br, OCH_2CO, 2), 2.85–4.15 (m, OCH_2CH_2O, $ArCH_2N$ and OCH_2CH_2N, 26) and 2.40–2.70 (m, NCH_2CH_2O, 4). A 30-mL portion of the above aqueous solution was brought to pH 1 with 6 N hydrochloric acid and continuously extracted with $CHCl_3$ for 8 h. The $CHCl_3$ extract was dried ($MgSO_4$), filtered, and evaporated to dryness to give a powder. A 70-eV mass spectrum of the residue (40 mg) showed a parent M^+ 713 (potassium salt of host amino acid), but no peak at 675 (molecular ion of amino acid **50**). The hydrochloride, potassium salt of the amino acid was apparently extracted into $CHCl_3$. Neutralization of amino acid **50** with KOH gave the potassium salt of the amino acid as a powder (**71**). Anal. Calcd for $C_{38}H_{44}O_{10}NK$: C, 63.94; H, 6.22; K, 5.49. Found: C, 62.21; H, 6.12; K. 5.64.

A solution of 3.5 g of amino ester **43** and 3.2 g of $Ba(OH)_2 \cdot 8H_2O$ in 400 mL of methanol–water (4:1, v/v) under N_2 was refluxed for 8 h. The solution was concentrated (30 mm) to 40 mL and 300 mL of water and 75 mL of acetic acid were added to the mixture. The aqueous solution was extracted three times with 300-mL portions of $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and concentrated to 40 mL. The crude product was chromatographed on 200 g of silica gel made up in benzene. Elution of the column with up to 1:4 (v/v) 2-propanol–ether mixture gave only traces of material. Elution of the column with 3 L of methanol–ether (1:4) and 2 L of methanol–ether (2:3, v/v) gave 1.5 g (40%) of the barium salt of amino acid **50** as a powder (**79**). The 1:2 complex is readily soluble in water, methanol, $CHCl_3$, and acetic acid, which demonstrates its mixed hydrophilic–lipophilic character: 100-MHz ^1H NMR ($CDCl_3$) δ 6.90–8.20 (complex m, ArH, 10), 4.82 (ABq, J_{AB} = 7 Hz, $ArCH_2O$, 2), 4.72 (s br, OCH_2CO_2, 2), 2.85–4.10 (m, OCH_2, $ArCH_2N$, 24) and 2.80 (m, NCH_2CH_2O, 4). The spectrum is dramatically different from that of the uncomplexed amino acid hydrochloride. Anal. Calcd for $C_{76}H_{88}O_{20}N_2Ba$: C, 61.37; H, 5.92; Ba, 9.24. Found: C, 61.98; H, 6.10; Ba, 9.58.

A solution of this complex in methanol–water was acidified with 5% sulfuric acid. No precipitate of $BaSO_4$ was formed.

The alkaline earth metal complexes of the diacids containing one dinaphthyl unit and five, six, or seven oxygens (macrocycles **45, 44,** and **46,** respectively) were prepared by a method illustrated as follows. A solution of 0.70 g (1 mmol) of methyl ester **38** and 2 mmol of $M(OH)_2$ (M = Ca, Sr, or Ba) in 200 mL of methanol–water (4:1) was refluxed under N_2 for 8 h. The solution was concentrated to about 20 mL and 150 mL of water was added. The aqueous solution was extracted with two 50-mL portions of CH_2Cl_2 to remove neutral material. The water layer was then extracted with five 100-mL $CHCl_3$–methanol (3:1) portions to give $CHCl_3$ solutions of the salts. The combined organic extracts were dried with the metal sulfates corresponding to the $M(OH)_2$ used in the hydrolysis. The dried solutions were evaporated to give the metal salt complexes as white powders. Since $BaSO_4$ was an inefficient drying agent, benzene was added during the evaporation to help dry the solution when M = Ba. The yields of the salts ranged from 80% for Ca and Sr to ~50% for Ba. The extraction of the barium salt was considerably less efficient than for the other two ions. The ^1H NMR spectra (60 MHz) of the salts in CD_3CO_2D were consistent with highly complexed macrocyclic ether structures with the differences for the three complexes not significant enough to correlate with possible metal positioning within the macrocycle. The ^1H NMR spectrum (60 MHz) of the barium salt **76** in CD_3CO_2D gave δ 7.00–8.20 (complex m, ArH, 10), 4.98 (ABq, J_{AB} = 12 Hz, $ArCH_2$, 4), 4.38 (s br, OCH_2CO_2, 4), and 2.95–4.20 (m, OCH_2CH_2, 20). Anal. Calcd for $C_{36}H_{38}O_{12}Ba$: C, 54.04; H, 4.80; Ba, 17.16. Found: C, 53.68; H, 4.77; Ba, 15.47.

The ^1H NMR spectrum (60 MHz) for the strontium salt **75** in CD_3CO_2D gave δ 7.08–8.22 (complex m, ArH, 10), 5.04 (ABq, J_{AB} = 13 Hz, 4), 4.42 (s br, OCH_2CO_2, 4), and 2.90–4.05 (m, OCH_2CH_2, 20). Anal. Calcd for $C_{36}H_{38}O_{12}Sr$: C, 57.63; H, 5.10; Sr, 11.68. Found: C, 57.33; H, 5.84; Sr, 10.88.

The ^1H NMR spectrum (60 MHz) for the Ca salt **74** in CD_3CO_2D gave δ 7.10–8.18 (complex m, ArH, 10), 4.80 (ABq, J_{AB} = 12 Hz, $ArCH_2$, 4), 4.22 (br s, OCH_2CO_2, 4), and 2.90–4.20 (m, OCH_2CH_2, 20). Anal. Calcd for $C_{36}H_{38}O_{12}Ca$: C, 61.52; H, 5.45. Found: C, 62.04; H, 6.03.

Application of this same method to diester **39** and calcium hydroxide produced calcium salt **77** (~80%). Anal. Calcd for $C_{34}H_{34}O_{11}Ca$: C, 61.98; H, 5.21. Found: C, 60.81; H, 5.54.

Application of this same method to diester **40** and barium hydroxide gave barium salt **78** (~75%). Anal. Calcd for $C_{38}H_{42}O_{13}Ba$: C, 54.07; H, 5.02; Ba, 16.27. Found: C, 53.89; H, 5.20; Ba, 16.04.

Application of this method to diester **38** and a 10 mmol of $Ba(OH)_2$ which was 0.8% $Sr(OH)_2$ gave a solution which after hydrolysis and the CH_2Cl_2 wash was acidified with excess acetic acid. The solution was extracted by the above method, dried with $MgSO_4$, and evaporated to a gum. The mass spectrum of this material contained M^+ of both diacid **44** at M^+ 664, and more interestingly, that of the strontium salt **75** at M^+ 750. Thus diacid **44** scavenged strontium from bulk barium, and the strontium was carried through the acidification and

Table VI. Distribution Ratios (q_A or q'_A)[a] for Carboxylate Ligands from Hosts 48 and 47 between Organic Phases and Aqueous Solutions of Metal Hydroxides–Lithium Hydroxides at Ambient Temperature

Run no.	Organic phase		Aqueous Phase						[Ligand] × 10^5 M at equilibrium		q_A for Na^+ or K^+, and q'_A for Ca^{2+}[a]
			Ligand		Metal compd						
	Kind	Vol, mL	Kind	Concn, M	Vol, mL	Kind	Concn, M	LiOH concn,M	Organic phase	Water phase	
1	CH_2Cl_2	5	48	0.00010	10	NaOH	0.010	0.0010	9.18	5.47	1.68
2	CH_2Cl_2	5	48	0.00010	10	KOH	0.010	0.0010	3.47	7.36	0.47
3[b]	CH_2Cl_2	3	48	0.00010	10	$Ca(OH)_2$	0.010	0.0010	24.5	3.24	3.77 ± 0.04
4[b]	CH_2Cl_2	3	48	0.00010	10	$Ba(OH)_2$	0.010	0.0010	23.7	3.23	2.3 ± 0.1
5[b]	CH_2Cl_2	10	47	0.00010	10	NaOH	0.010	0.0010	10.2	1.07	9.5 ± 0.6
6[b]	CH_2Cl_2	10	47	0.00010	10	KOH	0.010	0.0010	10.6	0.299	35.6 ± 0.8
7[b]	CH_2Cl_2	3	47	0.00010	10	$Ca(OH)_2$	0.010	0.0010	22.8	3.16	3.6 ± 0.2
8[b]	CH_2Cl_2	3	47	0.00010	10	$Ba(OH)_2$	0.010	0.0010	21.9	4.10	2.67 ± 0.02
9	$C_6H_5CH_3$	110	48	0.0020	5	LiCl	0.50	0.0043	0.098	99.2	9.9×10^{-4}
10	$C_6H_5CH_3$	110	48	0.0020	5	NaCl	0.50	0.0043	0.266	94.5	2.8×10^{-3}
11[c]	$C_6H_5CH_3$	110	48	0.0020	5	NaCl	0.50	0.0043	0.241	94.5	2.5×10^{-3}
12[c]	$C_6H_5CH_3$	110	48	0.0020	5	KCl	0.50	0.0043	0.174	94.4	1.8×10^{-3}
13	$C_6H_5CH_3$	20	48	0.0020	5	$CaCl_2$	0.50	0.0043	22.6	13.1	8.6×10^{-1}
14	$C_6H_5CH_3$	110	47	0.0020	5	LiCl	0.50	0.0043	0.197	102	1.9×10^{-3}
15	$C_6H_5CH_3$	110	47	0.0020	5	NaCl	0.50	0.0043	1.03	81.7	1.2×10^{-2}
16[c]	$C_6H_5CH_3$	110	47	0.0020	5	NaCl	0.50	0.0043	0.954	83.0	1.1×10^{-2}
17[c]	$C_6H_5CH_3$	110	47	0.0020	5	KCl	0.50	0.0043	0.602	80.6	7.4×10^{-3}
18	$C_6H_5CH_3$	20	47	0.0020	5	$CaCl_2$	0.50	0.0043	18.4	29.0	3.2×10^{-1}
19[d]	$C_6H_5CH_3$	21	48	0.00010	10	$CaCl_2$	0.95	0.0010	1.75	5.56	1.6×10^{-1}
20	$C_6H_5CH_3$	21	48	0.00010	10	$BaCl_2$	0.95	0.0010	0.0556	9.21	3.0×10^{-3}
21	$C_6H_5CH_3$	52	47	0.00010	10	$CaCl_2$	0.95	0.0010	0.625	8.12	3.8×10^{-2}
22[d]	$C_6H_5CH_3$	52	47	0.00010	10	$BaCl_2$	0.95	0.0010	0.0202	9.80	1.0×10^{-3}

[a] q_A values are reported for monovalent cations and $q'_A = q_A/2$ values for divalent cations. [b] Average values from two to four determinations. [c] The aqueous phases in these runs were initially 0.5 M in additional LiCl. [d] Average values of two determinations which were at least within 10% of one another.

extraction procedure.

Determination of the Lipophilizing Abilities of the Anions of Hosts 48 and 47 for Sodium, Potassium, Calcium, and Barium Cations. In these experiments, monocarboxylic acid hosts **48** and **47** were used to lipophilize Na^+, K^+, Ca^{2+}, and Ba^{2+} through salt complex formation. Aqueous solutions of these salts of **48** and **47** in conductivity water were prepared from reagent-grade metal hydroxide and analytically pure acid, and were extracted with spectral grade CH_2Cl_2. The stoichiometric composition of the extracted material was determined by its isolation and by measuring the amount of metal ion (by atomic absorption for Ca^{2+} and flame emission spectroscopy for Na^+ and K^+). The preparations of these salts and determinations of their compositions are first described.

All the equipment used for the preparation of the salts and for the metal determinations was washed with detergent, washed twice with dilute aqueous nitric acid, and rinsed five times with distilled water and five times with deionized water. All the glassware was made of borosilicate glass. Weighings of <10 mg were made with a Cahn balance. Compounds **48** or **47** (~10 mg) were completely dissolved in ~25 ml of ~0.020 M aqueous metal hydroxide solution. The aqueous solution was then extracted with three 50-mL portions of redistilled spectral quality CH_2Cl_2. The organic layers were separated after centrifugation, combined, and evaporated. The residual salt was dried at 165 °C in high vacuum for 24 h before use. The modifications involved in this procedure were for the calcium salts of **48** and **47** and the barium salt of **47**. In these preparations, **48** or **47** was first completely dissolved in 20 mL of ~0.01 M aqueous LiOH to which 20 mL of 0.5 M aqueous metal chloride was then added, and the aqueous solution was extracted as described. For each metal determination, blanks, samples, and standard solutions were run at least twice each and average values were obtained. All solutions were run as long as necessary to produce a stable reading (3–7 s). The wavelengths used for the determinations were 4226Å for Ca, 5890 Å for Na, and 7660 Å for K.

A PE-303 spectrophotometer was used for all the metal determinations. A calcium vapor lamp was used for the determination of calcium by atomic absorption and sodium and potassium were determined by air–acetylene flame emission. The salts used for the standards were reagent quality except for the calcium carbonate for the calcium standards (a primary standard). The solvent in which the determinations were made was reagent-grade DMF. For determination of sodium, a sample of 0.994 mg of the dried salt of **48** and 0.0916 mg of that of **47** was dissolved in DMF to give 10.00 mL of solution. Standards were prepared by dissolving 45.1 mg of NaBr in 100 mL of DMF. An aliquot of 25 mL was diluted to 250 mL to produce a solution that contained 10.08 μg/mL of Na. Aliquots (50 and 25 mL) of this solution were each diluted to 100 mL to produce three standard solutions. In determination of potassium, 1.280 mg of **48** and 0.906 mg of **47** as dried salts were each dissolved in DMF to give 10.00 mL of solution. For standards, 32.0 mg of KBr was dissolved in 100 mL of DMF. An aliquot of 25 mL of this solution was diluted with DMF to 250 mL to give a standard solution containing 10.5 μg/mL of K. Aliquots (50 and 25 mL) of this solution were each diluted to 100 mL to give two additional standard solutions of 5.20 and 2.65 μg/mL, respectively. In determination of calcium, the solution used for preparing both sample and standards was obtained by dissolving 5.85 g of lanthanum oxide in ~50 mL of aqueous hydrochloric acid and evaporating to dryness. The residue was dissolved in DMF and diluted to 500 mL with DMF. A sample of each of the calcium salts (0.830 mg and 1.587 mg of the salts of **48** and **47**, respectively) was dissolved quantitatively in the lanthanum-containing solution of DMF and diluted to 10.00 mL with the same solution. Calcium carbonate (14.6 mg) was dissolved in aqueous hydrochloric acid and the solution was evaporated to dryness. The residue was diluted with the same lanthanum solution to 100 mL to give a solution containing 58.5 μg/mL of calcium and 10 000 μg/mL of lanthanum. Further dilution as before gave additional standard solutions containing 5.85 and 2.92 μg/mL of calcium (respectively) and 10 000 μg/mL of lanthanum.

In the analyses for all three metals, the metal content of the samples was between 3 and 6 μg/mL and the standards had metal contents that ranged higher and lower than the unknowns. A calibration curve of absorbance vs. μg/mL was plotted for each metal, which was linear for Ca and nearly so for Na and K. The concentration of metal in the unknown samples was then read from the calibration curve. Unfortunately, these methods could not be applied to Ba due to this element's low sensitivity when an acetylene–air flame is used. The results for the other salts are as follows. Anal. for the Na salt of **48**. Calcd for $C_{31}H_{31}NaO_8$: Na, 4.14. Found: Na, 3.90. Anal. for the K salt of **48**. Calcd for $C_{31}H_{31}KO_8$: K, 6.85. Found: K, 6.42. Anal. for the Ca salt of **48**. Calcd for $C_{62}H_{62}CaO_{16}$: Ca, 3.63. Found: Ca, 3.80. Anal. for the Na salt of **47**. Calcd for $C_{33}H_{35}NaO_9$: Na, 3.84. Found: Na, 3.60. Anal. for the K salt of **47**. Calcd for $C_{33}H_{35}KO_9$: K, 6.36. Found: K, 5.98. Anal. for the Ca salt of **47**. Calcd for $C_{66}H_{70}CaO_{18}$: Ca, 3.36. Found: Ca, 3.53.

The salt distribution experiments between water and CH_2Cl_2 were carried out with UV spectra (Cary Model 14 spectrometer) as an an-

alytical probe. Spectral-grade solvents and analytically pure **48** and **47** were used. Extinction coefficients for the metal salts of **48** and **47** (see above) in CH_2Cl_2 and water at about 10^{-4} M concentration were determined at their λ_{max} of 337, 324, 294, 286, and 276 nm. All extraction experiments were performed by the following procedure. Table VI reports the volumes and concentrations. All measuring and transferring of solutions was done with volumetric pipettes and flasks.

An accurately weighed sample (~10 mg) of host **48** or **47** was dissolved in enough of the appropriate standardized metal hydroxide solution (~10^{-2} to 10^{-3} N) to give 10.00 mL of solution. Measured aliquots of this solution were mixed (in pear-shaped separatory funnels or in flasks fitted with magnetic stirrers and stoppers) with appropriately measured aliquots of aqueous metal chloride or hydroxide solutions and with measured aliquots of the organic solvent. The separatory funnels were shaken 200–300 times, or the flasks' contents were stirred for ~12 h. In either method, after centrifugation the layers were separated and their UV spectra were determined. The aqueous phases were measured directly using cells with appropriate pathlengths (1 or 0.1 cm). For the organic phases, where the solvent was CH_2Cl_2, the UV spectra were obtained directly on the solutions or by suitable dilution with the same solvent of measured aliquots of the solutions. Cells of appropriate pathlengths (0.1, 1, 2, or 4 cm) were employed. For organic phases where the solvent was not CH_2Cl_2, a measured aliquot was evaporated to dryness under vacuum. The residue was transferred quantitatively with CH_2Cl_2 to a volumetric flask and diluted with CH_2Cl_2 to the mark. The UV spectra of both the aqueous and CH_2Cl_2 solutions were recorded at about 10^{-4} M concentrations of carboxylate ligand. The concentrations of that ligand in both layers were calculated from the extinction coefficients of the unknowns as compared to those of the known salt solutions at the five λ_{max} wavelengths. The concentrations recorded in Table VI represent the average values calculated at different wave lengths. The barium salt was assumed to have the composition $C_{66}H_{70}BaO_{18}$.

Registry No.—**3,** 602-09-5; **4,** 55441-94-6; **5,** 55441-97-9; **6,** 55441-98-0; **7,** 55441-99-1; (+)-**8,** 55515-95-2; (*S*)-(−)-**8,** 42167-06-6; (*R*)-(+)-**8,** 42167-07-7; (+)-**9,** 55442-32-5; **9** triacetate, 65942-49-6; **10,** 55442-35-8; **11,** 55442-31-4; **12,** 55442-26-7; **13,** 55442-28-9; **14,** 55442-03-0; **15,** 55442-04-1; **16,** 55442-91-6; **17,** 55442-90-5; **18,** 55442-92-7; **20,** 55442-88-1; **21,** 55442-89-2; **22,** 55442-93-8; **23,** 55442-94-9; (±)-**24,** 55442-95-0; (*S*)-(−)-**24,** 65981-87-5; (*R*)-(+)-**24,** 65981-88-6; (±)-**25,** 55442-96-1; (*S*)-(−)-**25,** 65981-85-3; (±)-**26,** 55442-97-2; (*R*)-(−)-**26,** 65981-86-4; **27,** 55442-98-3; **28,** 55442-99-4; (±)-**29,** 55442-40-5; (*S*)-(−)-**29,** 55516-00-2; (±)-**30,** 55516-03-5; (*S*)-(−)-**30,** 55442-50-7; (±)-**31,** 55516-06-8; (*R*)-(−)-**31,** 55442-52-9; **32,** 55500-30-6; **33,** 55442-43-8; **34,** 55442-59-6; **35,** 55442-47-2; **36,** 55442-41-6; **37,** 55442-42-7; (±)-**38,** 55516-01-3; (*S*)-(−)-**38,** 42167-09-9; (±)-**39,** 55516-04-6; (*S*)-(−)-**39,** 55442-51-8; (±)-**40,** 55516-07-9; (*R*)-(−)-**40,** 55442-53-0; **41,** 55442-44-9; **42,** 65942-48-5; **43,** 55442-48-3; (±)-**44,** 55516-02-4; (*S*)-(−)-**44,** 42167-01-1; (±)-**45,** 55516-05-7; (*S*)-(−)-**45,** 42167-02-2; (±)-**46,** 55516-08-0; (*R*)-(−)-**46,** 42167-03-3; **47,** 55442-45-0; **47** Na Salt, 65943-28-4; **47** Ca Salt, 65995-88-2; **47** K Salt, 65943-29-5; **48,** 55442-46-1; **48** Na Salt, 65943-26-2; **48** K salt, 65943-27-3; **48** Ca salt, 65995-87-1; **49,** 55442-60-9; **49** methyl ester, 55442-65-4; **50,** 55442-49-4; (±)-**51,** 55529-01-6; (*R*)-(±)-**51,** 55442-61-0; **51** methyl ester, 55516-13-7; (±)-**52,** 55442-54-1; (*S*)-(−)-**52;** 55516-09-1; (±)-**53,** 55442-55-2; (*S*(−(+)-**53,** 55516-10-4; (±)-**54,** 55442-56-3; (*S*)-(−)-**54,** 55516-11-5; **55,** 55442-57-4; (±)-**55** tetramethyl ester, 55500-31-7; (*S*)-(−)-**55** tetramethyl ester, 55821-99-3; (±)-**56,** 55442-58-5; (*S*)-(−)-**56,** 55516-12-6; **57,** 63783-48-2; **58,** 55442-72-3; **59,** 55442-73-4; **60,** 55442-75-6; **61,** 55442-76-7; **62,** 55442-77-8; **63,** 55442-80-3; **64,** 55442-82-5; **64** tetraacetate, 55442-81-4; **65,** 55442-85-8; **65** dimethyl ester, 55442-84-7; **66,** 55442-83-6; **67,** 55824-36-7; **68,** 55515-78-1; **68** *t*-$BuNH_3 \cdot BPh_4$ complex salt, 66070-44-8; (*R,R*)-**70,** 41024-95-7; (*S,S*)-**70,** 41024-93-5; (*S,S*)-**70** methyl *R*-phenylglycinate PF_6 complex salt, 66070-43-7; **71,** 55522-34-4; **74,** 55522-35-5; **75,** 55522-33-3; **76,** 55522-32-2; **77,** 55522-36-6; **78,** 65969-59-7; **79,** 65995-86-0; *N*-butoxymethylmorpholine, 5625-84-3; 3-morpholine-2,2′-dihydroxy-1,1-dinaphthyl hydrochloride, 65942-46-3; 3-morpholino-2,2′-dihydroxy-1,1-dinaphthyl, 65942-47-4; 1,2-ethanedithiol, 540-63-6; 1,2-disulfhydrylbenzene, 17534-15-5; 2-sulfhydrylphenol, 1121-24-0; 8,9-benzo-1,16-ditosyl-1,4,1,10,13,16-hexoxohexadeca-8-ene, 41024-87-7; 3-allylcatechol, 1125-74-2; 4-(3′-hydroxypropyl)catechol, 46118-02-9; 4 allylveratrole, 93-15-2; 2,3:5,6-dinaphtho-13,14-(3-allyl-1,2-benzo)1,6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene, 55442-87-0; 3-(3,4-dimethoxyphenyl)-1-propanol, 3929-47-3; 3-(3,4-dimethoxyphenyl)-2-propanol, 19578-92-8; 2,3:4,5-Dinaphtho-13,14-(3-aminomethyl-1,2-benzo)-1,6,9,12,15,18-hexaoxacycloeicosa-2,4,13-triene, 65942-45-2; pentaethylene glycolditosylate, 41024-91-3; thioglycolic acid, 68-11-1; β-sulfhydrylpropionic acid, 107-96-0; dimethyl malonate, 108-59-8; (R)-phenylglycine methyl ester hydrochloride, 19883-41-1.

References and Notes

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