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Structure and Binding in Molecular Complexes of Cyclic Polyethers. 4. Crystallographic Study of a Chiral System: an Inclusion Complex of a Macrocyclic Ligand with Phenylglycine Methyl Ester[1]

Israel Goldberg

Contribution from the Tel-Aviv University, Institute of Chemistry, Tel-Aviv, Israel.
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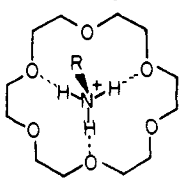
Abstract: The crystal and molecular structures of the 1:1 complex between an optically pure macrocyclic polyether host (*S*,*S*)-1 ($C_{48}H_{40}O_6$) and a hexafluorophosphate salt of (*R*)-phenylglycine methyl ester has been determined by x-ray diffraction methods at low temperature (−160 °C). The inclusion complex crystallizes with 1 mol of chloroform in the orthorhombic space group $P2_12_12_1$ with $a = 11.885$ (1), $b = 17.039$ (2), $c = 26.749$ (4) Å, and $Z = 4$. The structure was solved by Fourier and tangent formula techniques and refined to $R = 0.049$ for 3204 independent reflections measured by counter diffractometry. The geometry of the intermolecular "host-guest" type association is described in detail. The hydrophilic alkylammonium substrate is included in and hydrogen bonded to the macrocyclic cavity of the ligand. Steric repulsions involving the rigid aromatic substituents of the interacting host and guest moieties play an important role in determining the overall conformation of the complex. In the crystal, the adduct molecules are arranged in a face-to-face manner; the space between the host-guest entities is filled with chloroform molecules and hexafluorophosphate ions. The structural results are correlated with those of a recent solution study of chiral recognition in α-amino acid and ester complexation.

Recent investigations on multidentate macrocyclic systems have aroused considerable interest in several unique properties of these compounds.[2-4] For example, much attention has been given to macrocyclic polyethers,[5] macroheterobicyclic diamines,[6] and naturally occurring cyclodextrins,[7,8] and to their remarkable capability of forming stable inclusion complexes with a variety of guest molecules and ions of appropriate size. Selected series of the inclusion compounds have also been used as models for interacting biological systems in order to understand better the selective binding of substrate molecules to enzyme sites and ion carriers in biological reactions.[9,10]

Among the most interesting problems of stereochemical relationships in host-guest chemistry, those associated with properties of chiral recognition exhibited by macrocyclic ligands toward natural compounds are particularly attractive. Most recently, the cyclic polyethers have been the subject of an extensive synthetic research in which a series of chiral "crown" ethers are being developed.[11] The ability of these ligands to complex with primary alkylammonium salts and to effect resolution of racemic ammonium guest species has been demonstrated by several investigators.[12,13]

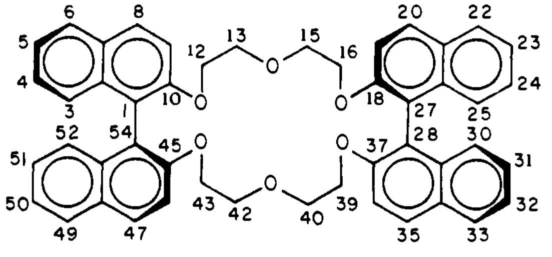


Molecular complexes of organic hosts with organic guests are often held together by hydrogen bonds. An idealized scheme of a hydrogen bonding association in ammonium complexes of hexa(ethylene oxide) macrocycles is illustrated above, suggesting also that binding interactions between the ammonium ion and the hydrophilic polyether cavity are directional to a considerable extent. Correspondingly, in a given host-guest system the geometric details of these interactions seem to be closely related to its complexation stability. Chiral recognition in the complex formation has been observed when steric and chiral barriers, in the form of bulky substituents, were incorporated into the polyether macrocycle.[11-13] The extent of the stereoselectivity in this process is a measure of the degree of complementary structural relationships between the interacting species.

A detailed x-ray study has been initiated at this laboratory in order to elucidate the structures of representative inclusion complexes with attainable precision, and to provide a quantitative description of the elementary interactions that control structural recognition between heteromacrocyclic hosts and organic guests. Two low-temperature crystal structures of alkylammonium-polyether complexes have been described previously.[14] Their geometric features suggest that hydrogen bonding associations play an important role in structuring complexes of the macrocyclic species. In both compounds, the $-NH_3^+$ group of the guest is nearly centered and tightly fitted into the ligand macrocyclic cavity, the adduct molecules being stabilized by at least two strong $N^+H\cdots O$ bonds. The spatial optimization of these as well as other (e.g., direct $N^+\cdots O$ pole-dipole) intracomplex interactions is of predominant importance in determining the observed molecular conformations of the flexible polyether ligands, while the crystal forces seem to have a minor effect. In fact, it is well known that macrocyclic compounds frequently exhibit marked conformational changes upon inclusion complex formation. A survey of the geometrical details that define the molecular structure of several complexed and uncomplexed polyether moieties in ordered crystals[15,16] indicates, however, that energetically optimal values, corresponding closely to syn-clinal torsion angles about the C-C bonds[17] and antiplanar torsion angles about the C-O bonds,[18] are attained for most of the conformational parameters in these macrorings. The deformation strain imposed on the poly(ethylene oxide) molecules by the presence of strong intraligand or ligand-substrate interactions is preferentially accommodated in a small number of torsion angles about the C-O bonds. Marked deformations of the O-C-C-O torsion angles have been observed in few structures of "empty" polyether macrocycles stabilized by intramolecular van der Waals attractions.[19,20] In this context, it is very interesting to examine further how the nature of host-guest interactions is correlated with molecular conformations, particularly in those complexes in which the intermolecular association is influenced by severe geometric constraints due to substitution of bulky groups on the interacting species.

Within the series of our studies, the present investigation is concerned with the first structure of an inclusion complex composed of optically pure host and guest moieties. The chemistry of chiral cyclic hexaether hosts containing two 2,2′-substituted-1,1′-binaphthyl units as chiral barriers has been extensively studied by Cram and his co-workers.[11,12] They have demonstrated that these polyether ligands can be effectively used to resolve, by selective complexation, the enantiomers of several amino acids and amino ester salts. The estimated differences in free energies between the two diastereomeric complexes of a particular host-guest system have also been related to the corresponding structural features, derived from molecular models. The above interesting considerations call for an accurate structure determination of a relevant model compound.

The subject of the present study is a 1:1 complex of the optically pure (*S*,*S*) host-I with the hexafluorophosphate salt of (*R*)-phenylglycine methyl ester. We describe here in detail the crystal and molecular structures of this compound as derived from three-dimensional x-ray diffraction data collected near −160 °C. The topographic details of the structure are correlated with recently reported results of the chemical study in solution.[12]



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Experimental Section

Crystals of the above compound were prepared by Cram and Timko of the University of California at Los Angeles; the complex crystallized with 1 mol of chloroform. Weissenberg and precession method photographic data collected with Mo Kα radiation indicated that the space group is orthorhombic with systematic absences corresponding uniquely to space group $P2_12_12_1$ (No. 19, D_2^4). A small well-formed parallelepiped crystal of approximate dimensions 0.2 × 0.2 × 0.1 mm was glued to a glass fiber and covered by a Lindemann glass capillary. The crystal was then mounted on an automated Syntex $P\bar{1}$ diffractometer equipped with a scintillation counter, pulse height analyzer, and a low-temperature device designed by Strouse.[21]

The diffraction experiment was carried out at low temperature of −160 ± 5 °C. The unit cell dimensions and estimated standard deviations were determined, using Cu Kα radiation (λ_{mean} = 1.5418 Å), from 2θ measurements of 15 carefully centered reflections, and refined by the method of least squares. Apparently, there is no phase transition in the range between room temperature and −160 °C.

Crystal Data. $C_{58}H_{53}Cl_3F_6NO_8P$, mol wt 1143.4, space group $P2_12_12_1$, a = 11.855 (1), b = 17.039 (2), c = 26.749 (4) Å, V = 5416.9 Å^3, ρ_c = 1.402 g cm^{-1}, Z = 4, $F(000)$ = 2368, μ(Cu Kα) = 24.7 cm^{-1}.

Intensity data were collected in the θ-2θ scan mode out to 2θ = 153° ($(\sin\theta)/\lambda$ = 0.63 Å^{-1}) with graphite-crystal monochromatized Cu Kα radiation. Reflections were scanned at a constant rate of 2° min^{-1} from 1.0° below Kα_1 to 1.0° above Kα_2. The scan method was utilized with stationary background measurements both at the beginning and end of each scan; the ratio of the total background time to scan time was 0.8. The intensities of three check reflections were frequently remeasured throughout the data collection to monitor possible crystal deterioration. The standard reflections showed no significant deviations.

Data processing was carried out in the usual manner. After the data were corrected for background, the intensities were assigned standard deviations according to the formula: $\sigma(I) = [\sigma_s^2 + (pI)^2]^{1/2}$, where σ_s is the standard deviation due to counting statistics. The parameter p, introduced to avoid overweighting the strong reflections, was set to 0.04. The values of I and $\sigma(I)$ were corrected for Lorentz and polarization effects. Because of the small size of the crystal, absorption corrections were not considered necessary. The intensities of 5324 independent reflections accessible in the reciprocal lattice hkl octant were measured. Only 3204 observations with $I \geqslant 3.0\sigma(I)$ were in-

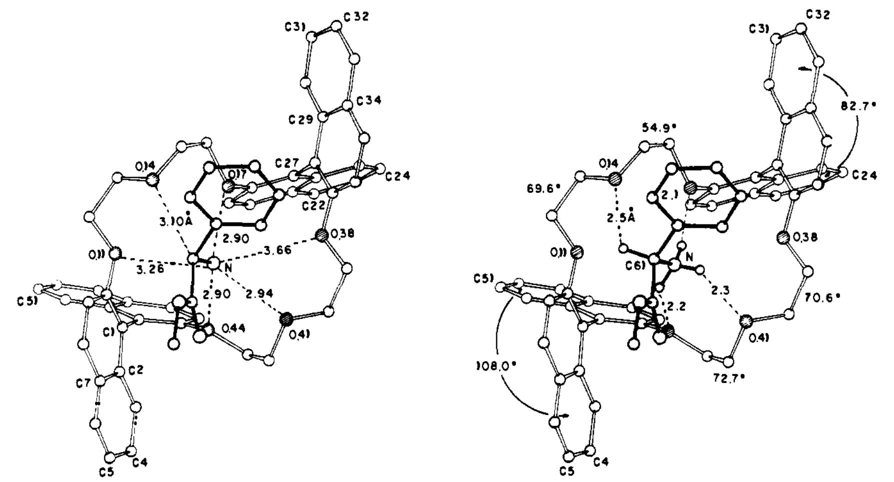

Figure 1. A perspective drawing of the host-guest complex. All N⋯O and H⋯O contacts which describe the hydrogen bonding association are shown.

cluded in further calculations. Distribution of the observed structure factors among the eight parity groups of reflection indices indicated a presence of a *B*-type pseudocentering in the unit cell; the ratio between the height of a Patterson peak at 0.5, 0, 0.5 and that at the origin is 0.34.

Structure Determination. Many difficulties were encountered in solving the $P2_12_12_1$ structure with 77 atoms (not including the hydrogens) of four different chemical species in the asymmetric unit. Probable positional parameters of the P atom and orientational parameters of the naphthalene fragments were first derived from a visual inspection of sharpened and unsharpened Patterson syntheses. A systematic vector verification method[22] was then applied in order to find the approximate locations of the semirigid binaphthyl groups. All subsequent Fourier calculations phased by the various partial sets of atomic parameters obtained from the Patterson maps were, however, unsuccessful in producing an acceptable trial model of the structure. Simultaneous attempts at solving the phase problem by direct methods were based on the use of cosine seminvariant relations[23] and tangent formula phase refinement techniques.[23,24] In fact, many of the solutions arrived at converged to the same result: a solution which is characterized by a very strong self-consistency of the phase determination procedure. The corresponding *E* map contained one large peak relating to the actual position of the PF_6 group. Nevertheless, a correct representation of the structure was not recognizable neither from distribution of the other peaks on this map, nor from maps describing other solutions. Similar difficulties experienced in application of direct methods to the structure determination of alborixin antibiotic have been recently discussed by Buseta.[25]

The final breakthrough came when the tactics employed in our trials to solve the structure by phase refinement was modified in two respects: (a) the approximately known geometry of the naphthalene, benzene, and PF_6 rigid fragments was taken into account in computation of spherically averaged molecular scattering factors and consecutive conversion of *F*'s to normalized structure factors; and (b) a limited number of phases but as large as possible number of triple-phase relationships were included in the calculations. More recently, it has been shown that these particular elements of structure determination via the MULTAN procedure played in fact an important role in a successful solution of several complex structures.[26]

The modified calculations were carried out using the MULTAN 74 system of computer programs.[27] Phases of 444 reflections with $|E| > 1.62$ were developed from a starting set including three origin defining general phases (1,9,19, $E = 2.69$; 7,9,8, $E = 2.44$; 4,9,10, $E = 2.29$) and three permutated restricted phases (0,14,6, $E = 3.47$; 4,0,2, $E = 3.35$; 0,15,12, $E = 3.13$). A total of 4000 Σ_2 relationships were used. At this stage, it was possible to identify 58 atoms of the desired structure on the *E* map corresponding to a solution with the highest combined figure of merit. All the missing nonhydrogen atoms, including those of the chloroform molecule, were found after two successive computations of structure factors and Fourier maps. The respective space group enantiomorph was selected to conform with the absolute configuration assigned to the host-guest compound in a previous study.[12a] One cycle of an overall isotropic refinement of the trial model so derived led to $R = \sum|F_o - |F_c||/\sum F_o = 0.16$ for a small set of reflections with $(\sin\theta)/\lambda \leqslant 0.38$.

The coordinates of the 77 heavy atoms and the corresponding anisotropic parameters of thermal motion were subjected to a block-diagonal least-squares refinement: $R = 0.07$ for 2360 observations below $(\sin\theta)/\lambda = 0.50$. In subsequent structure factor calculations the contributions of hydrogen atoms attached to the aromatic and methylene carbon atoms were introduced in calculated positions (C-H = 1.04 Å). The locations of the remaining H atoms were obtained directly from electron density difference maps. The positions located for hydrogens of the C(66) methyl group correspond to rather diffused electron density peaks and are, therefore, not reliable. The isotropic temperature factor of each H atom was set to 0.04 Å^2 ($B = 3.2$). No attempt was made to refine the hydrogen atom positions or thermal parameters because the data to parameters ratio was already low. In the final cycles of the refinement 3204 structure factors contributed to the adjustment of 694 independent parameters. The atomic parameters were grouped in 11 blocks due to limitations of the computer memory. These blocks were constructed in such a way that the scale factor was refined in one block, while atomic parameters of the five aromatic substituents, the PF_6 ion, the chloroform molecule, the two bis(ethylene oxide) fragments, and the methylglycinate residue corresponded respectively to the other ten blocks.

The refinement of the structure converged to $R = 0.049$ (weighted $R = 0.053$); the estimated standard deviation of an observation of unit weight is 1.27. The function minimized was $\sum w(\Delta F)^2$ with $w = 1/\sigma^2(F)$. A final difference synthesis had no peaks of magnitude greater than 0.2 e/Å^3. The scattering factors for the nonhydrogen atoms were taken from ref 28, those for the H atoms from ref 29. The anomalous dispersion terms were ignored. Finally, least-squares calculations have also been carried out on a structural model defined by a smaller number of parameters, constraining the geometry of the assumedly rigid aromatic and PF_6 fragments of this compound. The improvement of the results is, however, not significant with respect to the following discussion.

The final atomic positional and thermal parameters are listed in Table I; their standard errors were estimated from the inverse matrix of the normal equations (see paragraph at end of paper regarding supplementary material).

Discussion of Results

The Intermolecular Association. A major feature of the present structure is the host-guest type association of optically pure organic species, and we focus our attention on the intermolecular interactions which apparently affect the arrangement of the component molecules in the solid.

From the two diastereomeric complexes resolved in solution, this structure corresponds to the less stable isomer. In the host compound, the four rigid naphthyl substituents extend above and below the mean plane of the six ether O atoms and divide the space around the macroring into four equivalent cavities, two on each side of the ring. The host-guest interaction (Figure 1) is confined to one face of the ligand. Presumably, hydrogen

Table I. Final Atomic Fractional Coordinates and Temperature Factors[a]

	X	Y	Z	U_{11}	U_{22}	U_{33}	U_{12}	U_{23}	U_{31}
C(1)	7540(6)	6419(4)	678(2)	187(44)	198(31)	206(30)	-31(32)	31(25)	-31(30)
C(21	7793(6)	7203(4)	556(2)	245(48)	209(32)	197(30)	-23(33)	-42(25)	-43(31)
C(3)	7413(6)	7872(4)	597(2)	203(46)	233(32)	232(32)	-15(34)	-55(27)	-9(32)
C(4)	7595(7)	8616(4)	789(2)	277(51)	239(34)	303(37)	29(36)	12(29)	-20(36)
C(5)	8163(7)	8729(4)	1247(2)	279(49)	240(35)	307(35)	16(35)	-71(28)	59(35)
C(6)	8526(7)	8088(4)	1510(2)	347(55)	289(37)	262(34)	-6(37)	-93(29)	0(36)
C(7)	8357(7)	7325(4)	1323(2)	306(50)	201(32)	269(32)	-2(35)	-25(27)	-40(36)
C(8)	8749(6)	6655(4)	1595(2)	288(52)	305(37)	288(34)	-36(38)	-11(30)	-121(34)
C(9)	8579(7)	5912(4)	1418(2)	432(59)	247(35)	221(31)	25(38)	17(27)	-175(36)
C(10)	8022(6)	5805(4)	956(2)	284(50)	221(33)	202(31)	14(34)	21(25)	-79(32)
O(11)	7755(4)	5067(3)	775(2)	462(36)	192(22)	288(23)	-32(25)	37(20)	-149(24)
C(12)	8372(7)	4386(4)	943(2)	356(52)	225(34)	365(38)	87(38)	5(30)	-20(39)
C(13)	7601(8)	3702(4)	839(3)	706(68)	186(35)	295(36)	117(42)	-64(30)	-122(43)
O(14)	6687(5)	3768(3)	1182(2)	512(40)	214(24)	461(30)	-27(27)	-15(23)	-114(31)
C(15)	5865(8)	3153(4)	1152(3)	648(69)	190(35)	533(47)	-97(43)	23(34)	-69(50)
C(16)	5173(8)	3188(4)	699(3)	678(72)	185(34)	533(48)	83(43)	-18(33)	-180(51)
O(17)	4660(4)	3959(2)	667(2)	375(35)	201(22)	342(25)	-25(26)	24(20)	-71(25)
C(18)	4035(7)	4034(4)	222(2)	444(59)	191(33)	222(33)	2(38)	-47(26)	10(36)
C(19)	4592(7)	4294(4)	-208(3)	329(53)	286(38)	374(38)	-9(38)	22(31)	82(39)
C(20)	4003(7)	4349(4)	-648(2)	456(59)	303(37)	199(32)	5(40)	21(28)	98(36)
C(21)	2846(7)	4149(4)	-670(21	349(55)	180(32)	235(34)	0(35)	-12(26)	38(34)
C(22)	2230(8)	4209(4)	-1118(3)	637(71)	235(37)	242(37)	55(43)	25(30)	49(42)
C(23)	1114(8)	4049(4)	-1140(3)	565(67)	181(33)	350(40)	48(41)	-82(30)	-5(43)
C(24)	550(7)	3831(4)	-694(3)	383(59)	220(36)	503(46)	-4(39)	24(33)	-23(44)
C(25)	1117(7)	3755(4)	-247(3)	405(60)	164(33)	329(37)	1(37)	24(27)	69(38)
C(26)	2287(7)	3908(4)	-225(2)	325(56)	187(32)	239(34)	10(35)	-25(26)	42(34)
C(27)	2911(7)	3844(4)	226(2)	361(56)	174(31)	243(34)	25(34)	-37(26)	107(34)
C(28)	2354(6)	3604(4)	699(2)	278(48)	195(31)	212(29)	-17(33)	34(25)	-44(32)
C(29)	2110(6)	2802(4)	805(2)	231(50)	261(35)	258(34)	-31(35)	34(28)	0(33)
C(30)	2477(6)	2171(4)	489(2)	241(48)	219(33)	302(35)	-43(34)	-23(28)	-11(34)
C(31)	2291(7)	1402(4)	623(3)	299(52)	181(32)	425(42)	-5(35)	-16(31)	-134(39)
C(32)	1700(8)	1218(4)	1067(3)	417(57)	257(38)	471(43)	-31(41)	63(33)	-24(46)
C(33)	1309(7)	1803(4)	1369(3)	326(57)	355(41)	345(40)	-59(39)	55(33)	-97(39)
C(34)	1506(7)	2603(4)	1255(2)	334(51)	275(36)	219(30)	-88(36)	24(28)	-4(35)
C(35)	1132(7)	3212(4)	1574(2)	419(58)	336(40)	243(35)	-156(40)	-35(30)	81(37)
C(36)	1392(7)	3974(4)	1470(2)	300(54)	326(39)	255(32)	-109(39)	-11(30)	42(34)
C(37)	1997(7)	4165(4)	1033(2)	437(57)	245(35)	252(33)	-80(38)	18(27)	91(37)
O(38)	2328(4)	4924(3)	922(2)	465(36)	209(23)	270(23)	-53(26)	-34(20)	155(25)
C(39)	1754(7)	5556(4)	1163(2)	464(58)	216(33)	363(38)	-55(40)	0(31)	131(42)
C(40)	2235(7)	6297(4)	957(3)	333(55)	196(34)	432(42)	26(36)	-22(30)	-25(39)
O(41)	3351(4)	6405(2)	1132(1)	313(32)	213(23)	232(21)	-20(24)	-33(18)	3(23)
C(42)	3865(7)	7115(4)	972(2)	363(53)	139(30)	345(36)	5(35)	39(27)	4(37)
C(43)	4375(7)	7026(4)	463(2)	469(61)	322(39)	306(39)	23(42)	36(32)	73(40)
O(44)	5366(4)	6553(3)	511(1)	283(31)	269(23)	216(21)	21(25)	9(19)	-17(22)
C(45)	6008(6)	6411(4)	95(2)	238(49)	213(32)	176(30)	0(33)	-24(26)	35(31)
C(46)	5519(6)	6363(4)	-391(2)	252(51)	290(37)	262(33)	-36(38)	-10(30)	21(34)
C(47)	6198(7)	6155(4)	-787(2)	483(62)	198(32)	228(34)	-2(37)	-56(27)	-63(37)
C(48)	7342(6)	5992(4)	-726(2)	290(50)	173(31)	200(30)	20(33)	35(25)	-24(32)
C(49)	8040(8)	5777(4)	-1136(2)	516(61)	193(33)	270(35)	13(38)	-22(28)	39(39)
C(50)	9143(7)	5629(4)	-1072(2)	435(60)	285(37)	270(35)	25(42)	23(30)	43(38)
C(51)	9633(7)	5686(4)	-583(3)	394(55)	247(35)	407(40)	17(40)	17(33)	32(43)
C(52)	8993(7)	5895(4)	-180(2)	336(54)	165(31)	317(36)	-10(35)	-22(28)	65(35)
C(53)	7830(6)	6054(3)	-235(2)	301(52)	134(29)	240(33)	25(32)	7(25)	14(32)
C(54)	7131(7)	6292(4)	172(2)	365(56)	182(31)	185(31)	-39(34)	75(25)	-27(33)
C(55)	5855(7)	4098(4)	2364(3)	379(53)	300(36)	363(40)	87(38)	29(33)	-13(41)
C(56)	5342(8)	3576(4)	2694(3)	521(62)	338(39)	251(33)	50(43)	90(32)	-13(41)
C(57)	4179(8)	3592(4)	2753(3)	454(59)	282(37)	365(42)	-53(41)	56(33)	65(41)
C(58)	3550(7)	4117(5)	2486(3)	311(54)	515(48)	429(45)	-15(43)	71(39)	21(43)
C(59)	4061(7)	4639(4)	2150(2)	391(56)	277(35)	255(34)	-44(38)	24(29)	58(36)
C(60)	5218(7)	4623(4)	2092(2)	393(57)	259(35)	235(33)	5(38)	2(29)	74(38)
C(61)	5803(7)	5216(4)	1763(2)	323(52)	286(39)	267(35)	32(37)	-57(28)	-11(36)
N(62)	5260(5)	5324(3)	1260(2)	514(46)	256(28)	153(24)	-45(32)	14(22)	40(30)
C(63)	5924(7)	6020(4)	1999(3)	278(50)	301(38)	292(37)	-17(39)	-35(30)	-56(35)
O(64)	5714(5)	6635(3)	1794(2)	510(40)	225(23)	290(24)	35(27)	-10(21)	-47(26)
O(65)	6295(5)	5949(3)	2465(2)	647(42)	304(26)	292(25)	-24(28)	14(22)	-144(28)
C(66)	6491(8)	6688(4)	2778(3)	621(66)	386(43)	349(39)	-46(46)	-150(35)	-177(45)
P(67)	9785(2)	4993(1)	2667(1)	307(12)	209(7)	158(6)	37(9)	19(7)	10(8)
F(68)	10471(4)	5442(2)	2232(1)	427(31)	318(20)	253(19)	-108(22)	42(17)	21(20)
F(69)	8884(4)	5683(2)	2664(1)	593(32)	446(25)	264(19)	237(24)	-85(19)	10(23)
F(70)	10700(4)	4311(2)	2668(1)	619(34)	415(24)	373(22)	298(24)	47(20)	-45(25)
F(71)	9079(4)	4534(2)	2251(1)	526(31)	341(21)	268(20)	-114(24)	8(18)	-75(22)
F(72)	10502(4)	5458(2)	3083(1)	554(35)	490(25)	203(19)	-57(26)	-35(18)	-115(22)
F(73)	9121(4)	4560(3)	3099(1)	691(37)	558(28)	258(21)	-122(29)	122(20)	122(24)
C(74)	8171(8)	1991(4)	2440(3)	577(59)	261(34)	391(41)	90(40)	0(32)	-42(45)
CL(75)	8444(2)	2623(1)	2944(1)	770(20)	529(13)	528(12)	-6(14)	-109(11)	-175(14)
CL(76)	8254(2)	2514(1)	1881(1)	853(20)	643(15)	408(10)	-298(16)	202(11)	-32(14)
CL(77)	6850(2)	1558(1)	2499(1)	616(16)	615(13)	457(11)	-244(13)	37(10)	77(12)
H(61)	6606	5008	1678	400					
H(62a)	5030	5000	1037	400					
H(62b)	4583	5441	1415	400					
H(62c)	5625	5735	1132	400					
H(74)	8784	1548	2435	400					

[a] All parameters are multiplied by 10^4. Standard deviations are given in parentheses in units of the last decimal place. The anisotropic temperature factor for the nonhydrogen atoms is in the form $\exp[-2\pi^2(h_ia_i)(h_ja_j)U_{ij}]$, where h_i and a_i are reflection indices and reciprocal unit-cell edges, respectively. Positions of hydrogen atoms bonded to aromatic and methylene carbon atoms were computed from the molecular skeleton and are not given in this table.

bonding between the substrate and the macrocyclic receptor site is the greatest stabilizing force within the complex. The $-NH_3^+$ group of the alkylammonium salt penetrates into the polyether ring and forms three NH···O bonds with the ligating O atoms. Secondary interactions involve the three substituents attached to the asymmetric center of the guest phenylglycine derivative. These substituents differ in their relative size. They are distributed into two of the initially equivalent host cavities is such a way that the large phenyl group and the small H atom are located in one cavity, while the medium ester group resides

Table II. Geometry of the Hydrogen Bonds

RH· · ·OR'	R–H, A	R· · ·O, A	H· · ·O, A	RH· · ·O, deg	H· · ·OR', deg
(1) N(62)–H(62a)· · ·O(17)–C(16)	0.87	2.90	2.1	160	132
–C(18)					115
(2) N(62)–H(62b)· · ·O(41)–C(40)	0.93	2.94	2.3	124	127
–C(42)					115
(3) N(62)–H(62c)· · ·O(44)–C(43)	0.89	2.90	2.2	136	123
–C(45)					115
(4) C(61)–H(61)· · ·O(14)–C(13)	1.04	3.10	2.5	116	116
–C(15)					128

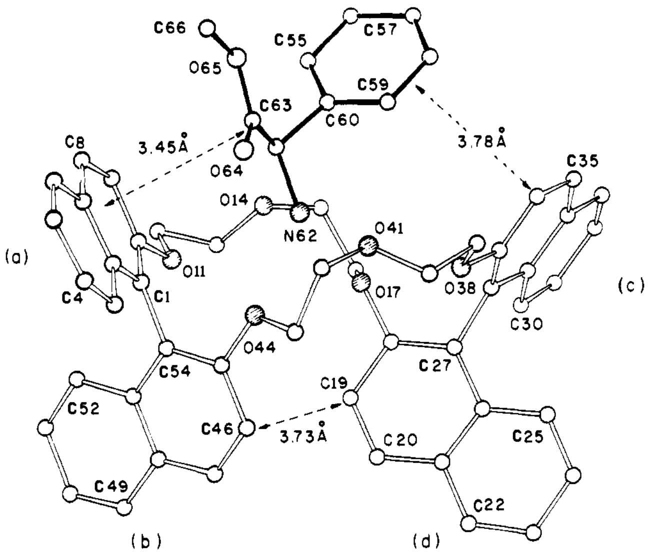

Figure 2. An illustration of the main steric interactions within the inclusion compound.

in the other site (Figure 1). The periphery of the formed adduct is hydrophobic. These main structural features are consistent with previous predictions of the approximate structure and relative stability of the two diastereomeric complexes, which were made on purely steric grounds.[11b,12a] Furthermore, the observed attraction of an organic guest to an organic host via specific interaction of the ammonium ion with the polyether cavity is similar, in general terms, to that described for other inclusion compounds in the solid[14] and in solution.[13,30]

However, the topological details of the relevant interactions that stabilize the structure and influence the selectivity of the present host-guest compound differ significantly from those assumed from models and magnetic resonance studies, and in this respect the structure determination proved particularly rewarding. Thus, e.g., an idealized four-point binding model, according to which three alternate ether O atoms of the 22-membered polyether ring are involved in hydrogen bonds with the ammonium ion and a fourth oxygen interacts with the ester group of the guest, has been proposed to describe the (*S*,*S*)-(*R*) isomer of the complex.[11b] It has also been anticipated that in this diastereomer the phenyl substituent of the substrate lies parallel to and possibly interacts (via charge transfer) with one of the aryl groups of the host. As illustrated in Figures 1 and 2, there seems to be poor correlation between the above model and the observed binding scheme.

The parameters describing the hydrogen bonding interaction are given in Figure 1 and in Table II. The ammonium protons are donated to nonalternate oxygen atoms of the macroring O(17), O(41), and O(44). All the corresponding N···O (2.90–2.94 Å) and H···O (2.1–2.3 Å) distances are in the normally accepted range for a typical NH···O bonding;[31] the H···O distances are significantly shorter than the ideal van der Waals contact. The C–NH_3^+ bond is nearly perpendicular to a plane defined by the three O atoms acting as hydrogen acceptors. It is also interesting to note that the hydrogen bonding contacts are not linear. The corresponding NH···O angles are: NH···O(17), 160°; NH···O(41), 124°; and NH···O(44), 136° (Table II).

Figure 2 illustrates that the ester moiety of the guest lies nearly parallel to and partially overlaps one of the naphthyl substituents. The average distance of the carbonyl group from the aromatic ring is 3.45 Å. We assume that charge-transfer interactions between the naphthaleneoxy group acting as π base and the -$COOCH_3$ group acting as π acid provide an additional contribution to the stability of the structure. A possible indication of another weak attractive interaction is the relatively short distance, 2.5 Å, involving the basic O(14) and (slightly) acidic H(61) atoms (Figure 1). One should keep in mind, however, that the observed spatial disposition of these two atoms is mostly a result of the steric requirements associated with the more powerful pattern of binding (see above) and repelling (see below) forces within the complex.

Chiral recognition among optically pure species is largely controlled by steric forces. It has been shown, e.g., that the complexation selectivity in reactions involving the above discussed ligand, or its close derivative, is influenced by the size of the substituents attached to the polyether macrocycle as well as to the asymmetric center of the interacting substrate.[12c] Figures 1 and 2 demonstrate the steric host-guest relationships in the present structure. The overall conformation of the polyether ligand is determined by the shape and dimensions of the particular guest. The phenylglycine derivative is oriented into the host cavity in such a way that its longest molecular axis lies roughly parallel to the planes of the enclosing naphthalene rings (a) and (c). As a result of geometric constraints associated with the intermolecular attraction, the naphthalene substituents on one face of the macrocycle are pushed away from each other, while those on the noninteracting side of the hexaether ring are in close contact with each other. This is reflected in a relatively short distance C(19)···C(46) at 3.73 Å, as well as in the average distances between centers of the aryl groups (a) and (c) and (b) and (d), at 10.8 and 6.9 Å, respectively. The guest inclusion is characterized by the following details. The ester group is placed parallel to one of the naphthalene moieties within the range of the usual van der Waals contact (Figure 2). Atom O(64) resides in a pocket formed between naphthalene barrier (a) and a fraction of the polyether ring extending from O(41) through O(44); the nonbonding distances C(42)···O(64) and H(42b)···O(64) are 3.21 and 2.4 Å, respectively. The phenyl substituent is placed against the steric barrier on the other side of the ligand cavity. This barrier consists of naphthalene (c) and the fraction -O(38)-CH_2(39) attached to it. The related contacts include C(36)···C(58), 3.74 Å, and C(36)···C(59), 3.83 Å.

Two other features of the intermolecular attraction correlate well with the fact that the stability constants of alkylammonium complexes with macrocyclic polyether ligands containing binaphthyl substituents are usually rather low.[32] (a) In the observed configuration of the binding site, the nitrogen atom

Table III. Torsion Angles within the Ligand

Atoms 1	2	3	4	Angle 1–2–3–4, deg	Distance 1–4, Å
C(45)	C(54)	C(1)	C(10)	110.7	3.478
C(54)	C(1)	C(10)	O(11)	−9.3	2.741
C(1)	C(10)	O(11)	C(12)	161.5	
C(10)	O(11)	C(12)	C(13)	158.5	
O(11)	C(12)	C(13)	O(14)	−69.6	2.774
C(12)	C(13)	O(14)	C(15)	−178.5	
C(13)	O(14)	C(15)	C(16)	−70.9	
O(14)	C(15)	C(16)	O(17)	−54.9	2.795
C(15)	C(16)	O(17)	C(18)	176.8	
C(16)	O(17)	C(18)	C(27)	91.7	
O(17)	C(18)	C(27)	C(28)	3.2	2.807
C(18)	C(27)	C(28)	C(37)	81.4	3.260
C(27)	C(28)	C(37)	O(38)	−7.9	2.707
C(28)	C(37)	O(38)	C(39)	163.2	
C(37)	O(38)	C(39)	C(40)	−177.2	
O(38)	C(39)	C(40)	O(41)	−70.6	2.856
C(39)	C(40)	O(41)	C(42)	−177.4	
C(40)	O(41)	C(42)	C(43)	−84.2	
O(41)	C(42)	C(43)	O(44)	−72.7	2.924
C(42)	C(43)	O(44)	C(45)	−177.6	
C(43)	O(44)	C(45)	C(54)	151.0	
O(44)	C(45)	C(54)	C(1)	−8.0	2.749

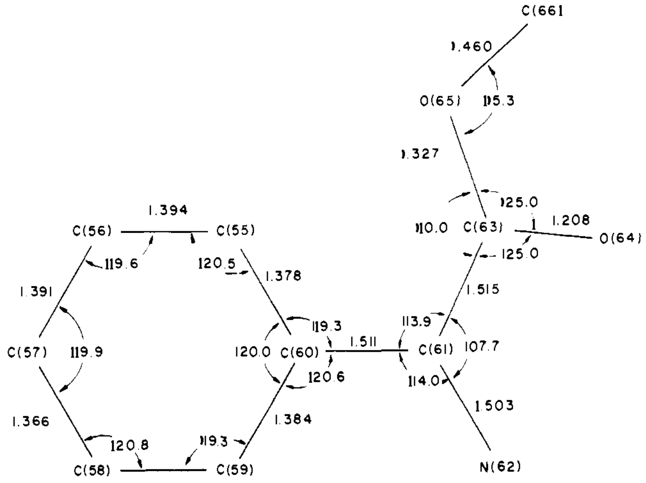

Figure 3. Bond distances and angles in the ammonium ion of phenylglycine methyl ester. Averaged standard deviations of a bond length and a bond angle are 0.010 Å and 0.6°, respectively.

of the guest species is in a close contact with only three of the six ether O atoms. The distances N···O(11), N···O(14), and N···O(38) at 3.27, 3.15, and 3.66 Å are significantly larger than the sum of the van der Waals radii of O and N, which suggests that the corresponding pole-dipole N^+···O direct interactions have a relatively small effect on the binding energy. (b) The hydrogen-bonding scheme involves two aryl O atoms of the host, O(17) and O(44). The electrons of the aryl atoms are delocalized to some extent into the nearest π systems, thus limiting the potential strength of the hydrogen bonds.

Host and Guest Conformations. The observed conformation of the polyether macrocycle is described in Table III in terms of the torsion angles along the 22-membered ring. Within the aliphatic parts of the ligand, all torsion angles about C–C bonds correspond to a gauche conformation, while those about most of the C–O bonds are close to 180°. Such features are characteristic of a preferred unstrained conformation in poly(ethylene oxide) compounds.[17,18] A significant deformation of this pattern of torsion angles in the present complex is evident only in torsions about the O(14)–C(15) (−71°) and O(41)–C(42) (−84°) bonds. Similar observations have been reported for a variety of structures involving the crown ether complexes[14-16] (see Introduction).

Further details describing the ligand geometry are included in Table IV. In correlation with the above discussed interactions, we also note that the hexagon defined by the six ether O atoms is contracted along the O(17)···O(44) direction. The corresponding diagonal distances within the cavity are O(11)···O(38), 6.47 Å, O(14)···O(41), 5.99 Å, and O(17)···O(44), 4.52 Å. The conformation of the semirigid binaphthyl unit is characterized by a single dihedral angle between planes of the two naphthalene rings. The two binaphthyl dihedral angles in the present chiral structure differ by about 25° owing to the different steric environments on each side of the binding site (Figure 1). This gives rise to unequal separations of the adjacent aryl O atoms: O(11)···O(44), 3.87 Å, and O(17)···O(38), 3.29 Å.

A bibliographic search through the Cambridge Data Files[33] reveals that detailed structural data have not yet been published for any derivative of a phenylglycine species. It is interesting, therefore, to characterize the spatial geometry of this moiety. The dihedral angle between least-squares planes of the ester group and the phenyl substituent is, in this structure, 81.7°. The torsion angle N(62)–C(61)–C(63)–O(64) is −6.3°, the nitrogen atom deviating only 0.08 Å from the plane of the ester group. In the observed conformation the C(60), H(61), and C(63) atoms form a staggered arrangement relative to the hydrogen-bonded ammonium H atoms.

Molecular Structure. Bond lengths and angles of the guest ion shown in Figure 3, and those of the host molecule listed in Tables V and VI, exhibit no extraordinary features. Most of the chemically equivalent dimensions agree well within the experimental error. The intramolecular distances in the host moiety are similar to those usually reported for ethylene oxide oligomers and naphthalene species in other structures.[14] The bond distances C(15)–C(16) (too short) and C(16)–O(17) (too long) are the only exception, probably due to a minor conformational disorder present in this part of the macroring. The assumed disorder is reflected in the relatively large thermal parameters of C(15) and C(16) (Table I). Moreover, it is in agreement with the observed pattern of crystal packing, since all intermolecular contacts involving $-CH_2(15)$ and $-CH_2(16)$ are significantly larger than the corresponding van der Waals distances.

The dimensions of the guest species are as expected. The PF_6 ion forms an almost perfect octahedron. The observed F–P–F bond angles involving adjacent F atoms vary within 89.2 (2)–91.1 (2)°; the P–F bond lengths range from 1.582 (5) to 1.613 (5) Å. In the chloroform molecule, the averaged C–Cl distances and Cl–C–Cl angles are 1.747 ± 0.007 Å and 110.2 ± 0.8°, respectively.

Molecular Packing. The crystal structure viewed down the *a* axis is shown in Figure 4. The packing arrangement can be conveniently described in terms of alternately stacked layers which consist of different molecular species and lie parallel to the (001) plane. Layers centered at $z = 0$ and $z = \frac{1}{2}$ consist of the large ligand molecules, those at $z = \frac{1}{4}$ and $z = \frac{3}{4}$ contain the smaller alkylammonium, PF_6, and chloroform moieties. Apparently, such pattern allows an efficient crystal packing of molecular species that are markedly different in their shape and size. In this respect, there exists an interesting similarity between the present structure and that of the α-cyclodextrin-*p*-iodoaniline complex.[34] In both cases the macrocyclic ligands formed cage-type adducts with guest species that were too large to be entirely enclosed within the host cavities. Although the corresponding inclusion complexes much vary in their dimensions, both compounds are packed typically in an opposite face-to-face orientation in space group $P2_12_12_1$. Such an arrangement of the molecular adducts creates empty spaces in the respective crystal structures which are filled by molecules

Table IV. Least-Squares Planes

(a) Equations (as $Ax + By + Cz = D$) and Definition of Planes[a]

	A, A	B, A	C, A	D, A	Definition	
(1)	11.153	0.488	−9.209	5.048	Ester group	Guest
(2)	1.139	11.438	19.660	9.998	Benzene ring	
(3)	10.410	0.810	−12.844	7.594	Naphthalene (a)	Host
(4)	10.236	−0.883	13.523	3.037	Naphthalene (c)	
(5)	0.503	1.243	26.654	2.903	22-membered ring	
(6)	6.796	−0.536	21.929	4.418	O(17), O(41), O(44)	

(b) Deviations (A) from the Planes

(1) C(1) 3.16; C(7) 3.41; C(10) 3.30; C(42) −1.29; N(62) −0.08
(2) O(17) −3.63; C(61) 0.09
(3) O(11) 0.11; O(44) 2.13; N(62) 3.30; C(63) 3.51; O(64) 3.41
(4) O(17) 2.28; O(38) 0.16; C(58) 3.60; C(59) 3.62; N(62) 3.58
(5) O(11) 0.18; O(14) 1.05; O(17) −0.40; O(38) 0.28; O(41) 1.08; O(44) −0.45; N(62) 1.38; O(64) 2.99
(6) O(11) 2.28; O(14) 2.52; O(38) −1.08; N(62) 1.63

(c) Angles between Normals to the Planes, deg

(1) and (2)	.82	(3) and (4)	121
(1) and (3)	9	(3) and (5)	64
(1) and (5)	108	(4) and (5)	58

[a] x, y, z are fractional coordinates of a point in a plane and D is the distance of the plane from unit-cell origin.

Table V. Bond Distances (A) in the Polyether Ligand

C(1) - C(2)	1.430(9)	C(27) - C(28)	1.484(9)
C(1) - C(10)	1.362(9)	C(28) - C(29)	1.426(9)
C(1) - C(54)	1.498(9)	C(28) - C(37)	1.376(9)
C(2) - C(3)	1.408(9)	C(29) - C(30)	1.437(9)
C(2) - C(7)	1.432(9)	C(30) - C(31)	1.376(9)
C(3) - C(4)	1.385(9)	C(31) - C(32)	1.416(11)
C(4) - C(5)	1.412(9)	C(32) - C(33)	1.363(10)
C(5) - C(6)	1.370(9)	C(33) - C(34)	1.416(10)
C(6) - C(7)	1.407(9)	C(34) - C(29)	1.439(9)
C(7) - C(8)	1.432(9)	C(39) - C(35)	1.417(9)
C(8) - C(9)	1.366(9)	C(35) - C(36)	1.363(10)
C(9) - C(10)	1.414(9)	C(36) - C(37)	1.409(10)
C(10) - O(11)	1.384(7)	C(37) - O(38)	1.385(8)
O(11) - C(12)	1.443(8)	O(38) - C(39)	1.428(8)
C(12) - C(13)	1.507(10)	C(39) - C(40)	1.491(10)
C(13) - O(14)	1.426(10)	C(40) - O(41)	1.419(9)
O(14) - C(15)	1.434(10)	O(41) - C(42)	1.421(8)
C(15) - C(16)	1.465(12)	C(42) - C(43)	1.499(10)
C(16) - O(17)	1.450(8)	C(43) - O(44)	1.433(9)
O(17) - C(18)	1.403(8)	O(44) - C(45)	1.372(8)
C(18) - C(14)	1.402(10)	C(45) - C(46)	1.428(9)
C(18) - C(27)	1.374(12)	C(45) - C(54)	1.366(11)
C(19) - C(20)	1.372(10)	C(46) - C(47)	1.380(10)
C(20) - C(21)	1.418(11)	C(47) - C(48)	1.397(11)
C(21) - C(22)	1.408(10)	C(48) - C(53)	1.436(9)
C(21) - C(26)	1.423(9)	C(48) - C(49)	1.425(10)
C(22) - C(23)	1.356(13)	C(49) - C(50)	1.346(12)
C(23) - C(24)	1.420(11)	C(50) - C(51)	1.434(10)
C(24) - C(25)	1.374(11)	C(51) - C(52)	1.367(10)
C(25) - C(26)	1.416(12)	C(52) - C(53)	1.416(11)
C(26) - C(27)	1.425(10)	C(53) - C(54)	1.433(10)

Table VI. Bond Angles (deg) in the Polyether Ligand

C(10)-C(1)-C(2)	119.6(6)	C(27)-C(28)-C(37)	120.0(6)
C(10)-C(1)-C(54)	121.1(5)	C(27)-C(28)-C(29)	121.7(6)
C(2)-C(1)-C(54)	119.2(5)	C(29)-C(28)-C(37)	118.2(6)
C(1)-C(2)-C(7)	119.0(6)	C(28)-C(29)-C(34)	119.6(6)
C(7)-C(2)-C(3)	117.5(6)	C(30)-C(29)-C(34)	117.9(6)
C(2)-C(3)-C(4)	120.5(6)	C(29)-C(30)-C(31)	120.7(6)
C(3)-C(4)-C(5)	121.5(6)	C(30)-C(31)-C(32)	120.6(6)
C(4)-C(5)-C(6)	119.2(6)	C(31)-C(32)-C(33)	120.2(6)
C(5)-C(6)-C(7)	120.6(6)	C(32)-C(33)-C(34)	121.3(7)
C(6)-C(7)-C(2)	120.8(6)	C(29)-C(34)-C(33)	119.3(6)
C(2)-C(7)-C(8)	118.7(6)	C(29)-C(34)-C(35)	119.2(6)
C(7)-C(8)-C(9)	121.0(6)	C(34)-C(35)-C(36)	120.2(6)
C(8)-C(9)-C(10)	119.4(6)	C(35)-C(36)-C(37)	120.3(6)
C(9)-C(10)-C(1)	122.3(6)	C(28)-C(37)-C(36)	122.4(6)
C(9)-C(10)-O(11)	122.0(5)	C(36)-C(37)-O(38)	122.6(6)
C(1)-C(10)-O(11)	115.6(5)	C(28)-C(37)-O(38)	114.9(6)
C(10)-O(11)-C(12)	120.4(5)	C(37)-O(38)-C(39)	118.1(5)
O(11)-C(12)-C(13)	104.8(6)	O(38)-C(39)-C(40)	106.7(6)
C(12)-C(13)-O(14)	106.5(5)	C(39)-C(40)-O(41)	110.3(6)
C(13)-O(14)-C(15)	115.1(5)	C(40)-O(41)-C(42)	114.4(5)
O(14)-C(15)-C(16)	113.6(6)	O(41)-C(42)-C(43)	111.2(5)
C(15)-C(16)-O(17)	108.7(6)	C(42)-C(43)-O(44)	107.9(5)
C(16)-O(17)-C(18)	110.8(5)	C(43)-O(44)-C(45)	118.8(5)
O(17)-C(18)-C(19)	118.4(7)	O(44)-C(45)-C(54)	116.6(5)
O(17)-C(18)-C(27)	118.8(6)	O(44)-C(45)-C(46)	121.6(6)
C(19)-C(18)-C(27)	122.8(7)	C(46)-C(45)-C(54)	121.8(6)
C(18)-C(19)-C(20)	119.0(7)	C(45)-C(46)-C(47)	118.6(7)
C(19)-C(20)-C(21)	121.0(6)	C(46)-C(47)-C(48)	122.0(6)
C(20)-C(21)-C(26)	119.1(6)	C(47)-C(48)-C(53)	119.1(6)
C(26)-C(21)-C(22)	119.4(7)	C(49)-C(48)-C(53)	119.1(7)
C(21)-C(22)-C(23)	122.1(7)	C(48)-C(49)-C(50)	121.1(6)
C(22)-C(23)-C(24)	118.6(7)	C(49)-C(50)-C(51)	120.0(7)
C(23)-C(24)-C(25)	121.5(8)	C(50)-C(51)-C(52)	120.8(7)
C(24)-C(25)-C(26)	120.0(7)	C(51)-C(52)-C(53)	120.5(7)
C(25)-C(26)-C(21)	118.5(6)	C(48)-C(53)-C(52)	118.6(6)
C(21)-C(26)-C(27)	119.4(7)	C(48)-C(53)-C(54)	118.9(7)
C(26)-C(27)-C(28)	120.9(7)	C(53)-C(54)-C(1)	119.8(7)
C(18)-C(27)-C(26)	118.7(6)	C(53)-C(54)-C(45)	119.6(6)
C(18)-C(27)-C(28)	120.4(6)	C(45)-C(54)-C(1)	120.6(6)

of the solvent. The intercomplex cavities in this structure are occupied by the PF_6 counterions as well as by chloroform molecules.

Some relatively short intermolecular distances are shown in Table VII. They reflect, in particular, a close packing of the host molecules about the screw axes parallel to a, short contacts between the PF_6 and naphthalene moieties, and a probable hydrogen bonding interaction involving chloroform and PF_6^-. The structural data also suggest that the ion pairing between N^+ and PF_6^- has little effect on the geometry of the formed complex. All distances between N^+ and the F atoms exceed 5.4 A. The charge separation in the structure is stabilized by delocalization of the negative charge in the relatively large anions, as well as by their hydrogen bonding to chloroform.

Remarks on Chiral Recognition.[35] Detailed structural results describing the stabler diastereomer of this compound are not yet available. Nevertheless, it is interesting to correlate the present data with results of recently published studies on chiral recognition in complexation of α-amino acids and esters.[12] The most striking example deals with selective complexation of phenylglycine esters by a close derivative of the ligand shown at the outset, in which two methyl groups are substituted in the 3 positions of one binaphthyl unit. According to atom numbering in the present work, this corresponds to substitution of the methyls on atoms C(9) and C(46) or C(19) and C(36) of the ligand. In fact, an increase of nearly 1 kcal/mol in the free energy difference $\Delta(\Delta G)$ between the two diastereomerically related complexes has been observed on introduction of such

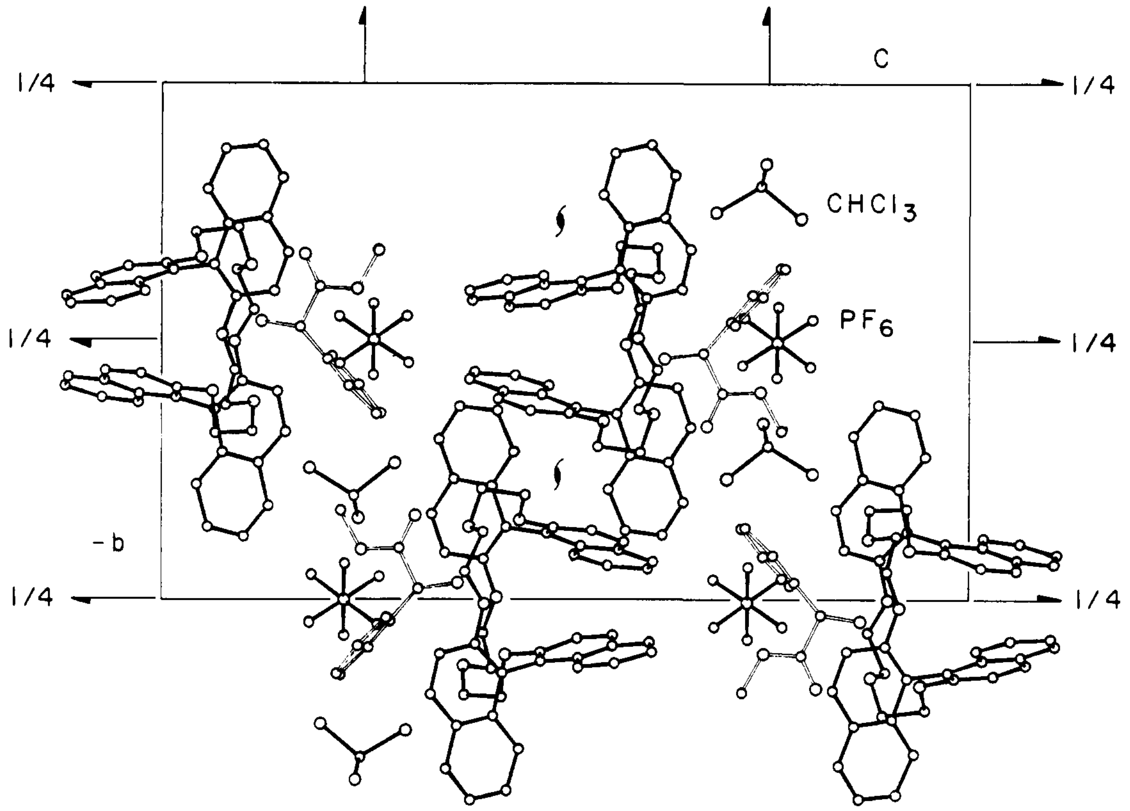

Figure 4. Crystal structure viewed down the *a* axis. Symbols for some of the symmetry elements are marked on the figure.

Table VII. Selected Intermolecular Contact Distances (Å)[a]

C(74)···F(68^{I})	3.22	H(74)···F(68^{I})	2.3
C(74)···F(72^{I})	3.35	H(74)···F(72^{I})	2.5
C(6)···F(70^{I})	3.17	H(6)···F(70^{I})	2.4
C(9)···F(71)	3.23	H(9)···F(71)	2.3
C(33)···F(69^{II})	3.22	H(33)···F(69^{II})	2.4
C(36)···F(68^{III})	3.41	H(36)···F(68^{III})	2.4
C(39)···F(68^{III})	3.25	H(39b)···F(68^{III})	2.5
C(47)···F(73^{IV})	3.24	H(47)···F(73^{IV})	2.3
C(49)···F(73^{IV})	3.33	H(49)···F(73^{IV})	2.4
C(16)···C(24^{V})	3.47	H(16b)···C(24^{V})	3.0
C(19)···C(31^{V})	3.59	H(19)···C(31^{V})	2.8
C(43)···C(3^{VI})	3.65	H(43a)···C(3^{VI})	2.8
C(43)···C(52^{VI})	3.68	H(43b)···C(52^{VI})	2.7
C(46)···C(4^{VI})	3.63	H(46)···C(4^{VI})	2.7
C(51)···C(24^{VII})	3.36	H(51)···C(24^{VII})	3.0
H(4)···H(51^{VI})	2.2		

[a] Superior roman numerals refer to the following equivalent positions relative to the reference asymmetric unit at x, y, z: (I) $2 - x, -\frac{1}{2} + y, \frac{1}{2} - z$; (II) $1 - x, -\frac{1}{2} + y, \frac{1}{2} - z$; (III) $-1 + x, y, z$; (IV) $\frac{3}{2} - x, 1 - y, -\frac{1}{2} + z$; (V) $\frac{1}{2} + x, \frac{1}{2} - y, -z$; (VI) $-\frac{1}{2} + x, \frac{3}{2} - y, -z$; (VII) $1 + x, y, z$.

change into the host structure.[12] Inspection of Figure 2 could provide a possible explanation of this effect, if we assume that the overall structure of the corresponding dimethyl compound is similar to the structure reported here. Evidently, the methyl substitutions cause an extension of one of the chiral barriers adjacent to the binding site, as well as an increase of steric hindrance between the naphthalene rings (b) and (d). The (*S,S*)-(*R*) (or equivalently (*R,R*)-(*S*)) isomer of the dimethyl complex is, therefore, more crowded than the unsubstituted compound. The stronger repulsive interactions contribute to further destabilization of the less stable diastereomer of the modified system, which accounts at least in part for the observed increase in $\Delta(\Delta G)$. The decrease in chiral recognition exhibited by the bis(binaphthyl) polyether ligands toward the smaller amino esters of valine and methionine could be interpreted on purely steric grounds by opposite reasoning. Finally, it should be noted that the reported $\Delta(\Delta G)$ values for diastereomeric complexes with phenylglycine methyl ester as guest are smaller than those found for complexes of *p*-hydroxyphenylglycine ester. We cannot offer at this point a reasonable explanation. Further study of related diastereomeric systems may provide the missing structural information.

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Supplementary Material Available. Table listing observed and calculated structure factors (11 pages). Ordering information is given on any current masthead page.

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(35) It should be kept in mind that the results of the chemical studies of chiral recognition referred to in this paper pertain to solution, the structural proposals being based on space-filling molecular models and ^{1}H NMR interpretations. On the other hand, the present work deals with conformational aspects of the chiral complex in the solid state.

Optical Resolution of Asymmetric Amines by Preferential Crystallization as Lasalocid Salts[1]

J. W. Westley,* R. H. Evans, Jr., and J. F. Blount

Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received February 21, 1977*

Abstract: The ability of the polyether antibiotic lasalocid to transport catecholamines across lipid membranes led to an investigation into the nature of the lasalocid-amine complexes. On finding that the naturally occurring *R* enantiomer of norepinephrine gave a highly crystalline, equimolar salt with lasalocid, the possibility occurred to us that the antibiotic might be able to resolve racemic amines by fractional crystallization as lasalocid salts. As a consequence, several types of amines were successfully resolved, and in one case the resolved complex was analyzed by x-ray crystallography. The results of this analysis provided a possible explanation for the high enantioselectivity displayed by lasalocid on preferential crystallization of salts formed from the antibiotic with racemic amines.

Lasalocid (**1**) is a member of the class of naturally occurring ionophores known as polyether antibiotics.[1] Produced by *Streptomyces lasaliensis*,[2] **1** is both an effective coccidiostat[3] and a cardiotonic agent.[4] Close correlation[5] between the cardiac effects and the ability of a number of derivatives of lasalocid[6] to transport norepinephrine across artificial membranes led to this study of the nature of the interaction between **1** and various organic amines.

In preliminary experiments, three typical catecholamines, dopamine (**2a**), norepinephrine (**2b**), and epinephrine (**2c**), were found to be soluble in a methylene chloride (CH_2Cl_2) solution of the antibiotic **1**. Crystallization of the antibiotic-base salts from these CH_2Cl_2 solutions was attempted by addition of hexane (n-C_6H_{14}) and removal of CH_2Cl_2 by evaporation. Both **2a** and **2b** gave crystalline salts containing equimolar amounts of the amine and antibiotic, but all attempts to crystallize the lasalocid salt of **2c** were unsuccessful. It is interesting to note that permeability coefficients[5] measured in lipid bilayer membranes containing **1** were ten times higher for **2a** and **2b** than for **2c**.

Since norepinephrine (**2b**) has an asymmetric center (*R* configuration), the possibility occurred to us that lasalocid might have the ability to resolve racemic amines. The results of attempts to resolve racemic 1-amino-1-phenylethane (**3a**), 1-amino-1-(4-bromophenyl)ethane (**3b**), 1-dimethylamino-1-phenylethane (**3d**), 1-amino-1-naphthylethane (**4**), 2-aminoheptane (**5**), tetrahydrofurfurylamine (**6**), and 2-amino-1-(3′,4′-dimethoxyphenyl)propane (**7**) by crystallization as a salt of **1** from various solvents are given in Table I.

Each of the first four amines tested (**3a**, **3b**, **4**, **5**) contained an asymmetric carbon atom attached directly to the primary amino group and each gave crystalline salts in which the *R isomer* of the amine predominated to an extent of 6 to 10 times over the *S* isomer when the salt was crystallized from the CH_2Cl_2-C_6H_{14} solvent system. The absolute configuration and optical purity of the amines after each crystallization step were determined by the gas-liquid chromatographic (GLC) analysis of the diastereoisomeric *N*-trifluoroacetyl-*S*-prolyl derivatives[8] formed by direct reaction of TPC reagent[9] with 1-5 mg of crystalline salt. This technique has the advantage that the salt can be analyzed without tedious conversion to the amine followed by spectropolarimetry. A number of solvents can thus be rapidly screened for their relative efficiency in preferential crystallization. To further investigate the high enantioselectivity in the formation of crystalline salts of **1** with substituted 2-aminoalkanes, advantage was taken of the heavy atom (Br) in the **3b** salt of **1** to carry out an x-ray crystallographic analysis of the salt, which was shown to have an optical