Generation of Plane Chirality via Specific Host-Guest Interaction by a Macrocyclic Heterocyclophane in the Crystal Phase

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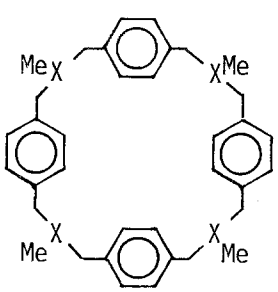
Macrocyclic cyclophanes are very suitable as completely artificial host molecules for the following reasons : a) very easy preparation, b) the well-defined molecular geometry, size, or shape, c) the readily available information concerning various physicochemical properties, e.g., macroring conformation, internal rotation etc., and d) the remarkable thermal or chemical stability. Thus, the host structures can be designed so that they may have the most appropriate size, shape, and/or functionality for the specific guest recognition. Hitherto, only a very limited number of macrocyclic cyclophane-guest pairs have been studied in the crystalline state. And most of them so far known are lattice (cavity) inclusion or channel inclusion compounds(Table I).

It has been successfully demonstrated by the authors that macrocyclic heterocyclophanes **1-3** exhibit enzyme-like or receptor-like functions with remarkable substrate specificity in the solution phase[1]. Heterocyclophane **1** is of considerable interest, since **1** forms a molecular cavity inclusion crystal which is to be differentiated from the lattice (cavity) inclusion and an interesting guest-dependent polymorphism and plane chirality in the crystalline phase have been observed[2].



1 X= N

2 X= NMe^+ BF_4^-

3 X= S^+ BF_4^-

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CRYSTAL LATTICE(CAVITY) INCLUSION

The typical examples of macrocyclic cyclophanes, e.g., cyclotriveratrylene, cyclotricatechylene, or tri-O-thymotide, form clathrate compounds.[3] Significant host-host interaction affords a cage or a channel between the host molecules for guest accomodation in these lattice (cavity) inclusion crystals, $(Host)_n \cdot (Guest)_m$.

$$\underline{\text{solution}} \qquad \underline{\text{lattice inclusion crystal}}$$

$$nH \cdot S_x + nG \cdot S_y \overset{\Delta G^a}{\rightleftharpoons} H_n \cdot G_m + (nx+my)S_x + (n-m)G \cdot S_y$$

Similarly, 6°-metacyclophane forms clathrate complexes with benzene derivatives or alicyclic compounds, where only a little guest selectivity has been found.[4] The ratio n/m of these crystal lattice (cavity) inclusion compounds varies significantly, e.g., n/m=0.3-0.6 (cyclotricatechylene), 2-6 (tri-O-thymotide). It has been found that tri-O-thymotide resolves optical isomers, e.g., 2-butyl halides, by making host-guest inclusion crystals. These optical resolutions are therefore attributable to the crystal lattice chirality that was induced by the H_nG_m crystallization.

MOLECULAR CAVITY INCLUSION

Heterocyclophane **1** forms a 1 : 1 crystalline complex with $CHCl_3$, CH_2Cl_2, CH_2BrCl, or CH_3CN. The guest molecules in these crystalline complexes of **1** were determined by NMR and Glpc(Gas liquid phase chromatography) as shown in Table II.

Table I. Classification of Host-Guest Complexes of Macrocyclic Cyclophane

type	general formula	host
molecular cavity inclusion	$(Host \cdot Guest)_n$	heterocyclophane (**1-3**)[1-2] calix[4]arene[5] 1,6,20,25-tetraaza[6.1.6.1]paracyclophane[6]
lattice cavity inclusion	$(Host)_n(Guest)_m$	cyclotriveratrylene[3] cyclotricatechylene[3] tri-O-thymotide[3] 6°-metacyclophane[4]

Table II. Molar Ratio of Inclusion Crystals of **1**

	Guest/**1**	
	^{1}H-NMR	Glpc
1·Chloroform		0.90 ± 0.01
1·Methylene Chloride	0.91 ± 0.02	0.88 ± 0.06
1·Bromochloromethane	1.07 ± 0.07	0.97 ± 0.03
1·Acetonitrile	0.9, 0.89	

The inclusion crystal of **1**·chloroform showed a strong IR absorption at 760 cm^{-1} (C-Cl stretch).

A single crystal X-ray crystallographic study has revealed that the **1**·chloroform crystal belongs to the monoclinic space group C2(chiral) having cell dimensions a=25.166(8), b=5.668(2), c=13.438(4), β=111.31°, and Z=2(Table III). The shape of heterocyclophane **1** resembles a "square box" (Fig 1) with the wall formed by four benzene rings and the floor being the plane containing four N atoms.

This unique molecular shape results from the conformation of the slightly tilted benzene walls (ca. 60°) with respect to the plane containing the four N atoms. The dihedral angle of the linkage ($-CH_2$-NMe-CH_2-) is 156-166° for C(7)-N(4)-C(8)-C(9) or C(15)-N(2)-C(16)-C(1), 66-69° for C(4)-C(7)-N(1)-C(8) or C(12)-C(15)-N(2)-C(16), respectively, revealing that gauche-trans conformation of the linkage constitutes the characteristic feature of the macrocycle.

Thus, a molecular cavity (4.6-6.4 Å side width, ca. 6Å depth) is provided by **1** so that it includes chloroform as a guest molecule in its molecular cavity with a nearly maximum van der Waals interaction.

Table III Crystal Data

	space group	cell dimensions
$CHCl_3$	C2	a=25.166(8) Å b=5.668(2) c=13.438(4) β=111.31(3)° Z=2
CH_2Cl_2	C2/c	a=25.359(5) Å b=5.485(8) c=50.565(8) β=96.92(3)° Z=8

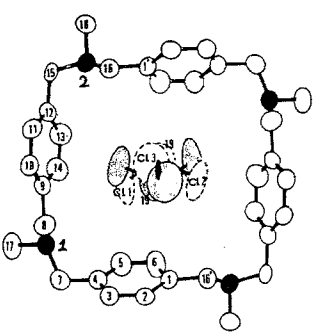


Fig 1. **1**·$CHCl_3$

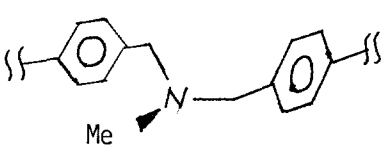
Therefore, it is most appropriate to classify $1 \cdot CHCl_3$ as a molecular (cavity) inclusion crystal.

$$\underline{\text{solution}} \qquad \overset{\Delta G^b}{\rightleftharpoons} \qquad \underline{\text{host-guest molecular inclusion crystal}}$$

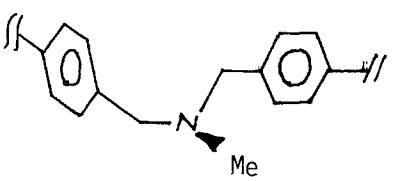
$$n\ \text{Host}\cdot G_x + n\ \text{Guest}\cdot S_y \rightleftharpoons (\text{Host}\cdot\text{Guest})_n + n(x+y)S$$

1. Type I Inclusion Crystal

The host molecule **1**, in the crystalline state, has no symmetry element except the C_2 axis. Namely, **1** exists as optically active isomers, the "R"-conformer or the "S"-conformer (Type I, chiral inclusion crystal) [For the R,S assignment, we followed the proposal by Cahn, Ingold, and Prelog]. In solution phase, the conformation change R ⇄ S is very rapid, and the optical rotation measurement of a $CHCl_3$ solution of $1 \cdot CHCl_3$ single crystal indicated that $[\alpha_D]$ is zero within the accuracy of the polarimeter, i.e., 0.000 ± 0.005(c, 0.01). However, when **1** crystallizes with chloroform, the conformational freedom is frozen, because lattice energy operates between host molecules. The conformation is thus fixed either in an all-R or all-S state, whose probability is 50% and 50%, respectively.



"R"-conformer



"S"-conformer

2. Type II Inclusion Crystal

A racemic inclusion crystal is also obtained when the guest molecule is other than chloroform. **1** forms a similar 1:1 molecular cavity inclusion complex with methylene chloride, but in a different space group C2/c (Table III). In marked contrast to the type I crystal, the heterocyclophane in the CH_2Cl_2 complex takes both "R"- and "S"-conformations (Type II, racemic inclusion crystal). A schematic picture of the host-guest packing in the methylene chloride complex is shown in Fig 2.

This racemic(RRSS) complex has two types of host-host contact, (1) R---S intercolumn contact which is characterized by a symmetry center. "S"-**1** has the inverted orientation of the adjacent "R"-**1** host (2)R---R (or S---S) contact which closely resembles that of the type I crystal. The R---R (or S---S) contact is related by a C_2 axis.

Another type of racemic crystal, viz., $[(R\text{-}1 \cdot G)(S\text{-}1 \cdot G)]_n$ (RS racemic) was also found when the guest molecule is acetonitrile, thus

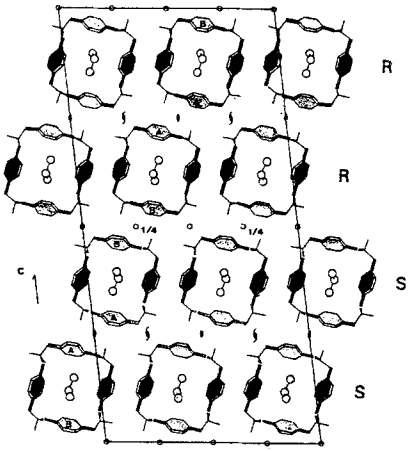


Fig 2. Two types of host-guest contacts in the $1 \cdot CH_2Cl_2$ molecular inclusion crystal

disclosing the first clear case of guest dependent polymorphism and plane chirality in the crystalline host-guest packing.

Type I (chiral) crystal $(R\text{-}\mathbf{1}\cdot G_I)_n$ or $(S\text{-}\mathbf{1}\cdot G_I)_n$

Type II(RRSS racemic) crystal $[(R\text{-}\mathbf{1}\cdot G_{II})_2(S\text{-}\mathbf{1}\cdot G_{II})_2]_n$

Type III(RS racemic) crystal $[(R\text{-}\mathbf{1}\cdot G_{III})(S\text{-}\mathbf{1}\cdot G_{III})]_n$

This unique polymorphism of H·G packing is the result of small conformation changes of the host molecule, depending on the shape and/or the size of the guest molecule. For example, the host-guest stabilization of the $1 \cdot CH_2Cl_2$ complex is optimized by a slight decrease in the cavity size (especially in the c-axis direction) and the slightly increased tilt of the benzene walls. Thus, the selection of crystal type, Type I(chiral), Type II(RRSS racemic), or Type III(RS racemic) is mainly determined by the host-guest pairwise interaction. The interaction energy in a single host-guest pair is probably very small. However, it can be amplified or accumulated, in the crystal phase, to a magnitude large enough to alter the intercolumn interaction.

References

1. Tabushi, Yamada, Yoshida,Oda,Tetrahedron,27,4845(1971),Tabushi et al., ibid.,28,3381(1972),Tabushi et al.,J.Amer.Chem.Soc.,98,5727(1976), Tetrahedron Lett.,8827(1976),J.Amer.Chem.Soc.,100,1304(1978),J.Amer. Chem.Soc.,103,6486(1981).
2. Tabushi,Yamamura,Nonoguchi,Hirotsu,Higuchi,J.Amer.Chem.Soc.,106,2621 (1984).
3. Hyatt et al.,J.Org.Chem.,45,5074(1980),Powell,Nature,155(1952), A-Yellin et al.,Tet.Lett.,387(1977).
4. Ichikawa et al., Japan Kokai,51329(1977).
5. Andreetti,Ungara,Pochinic,JCS,Chem.Commun.,1005(1979).
6. Odashima,Itai,Iitaka,Koga,J.Amer.Chem.Soc.,102,2504(1980).