

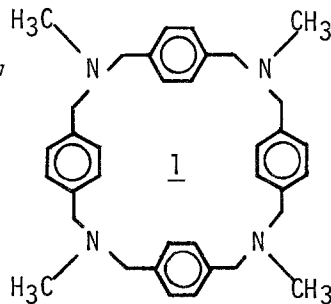
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ABSTRACT. Crystal and molecular structures of (1:1) molecular complexes of N,N',N'',N''' -tetramethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane (1) with CHCl_3 , CH_2Cl_2 , CH_3CN and CO_2 are reported. The macrocycle has square-box structure, giving hydrophobic cavity surrounded by four benzene rings. The guest molecules are included in the cavity. The uncomplexed 1 was found to have a rectangular form, indicating large conformational flexibility of 1. In solution, 1 is achiral because rapid $R \rightleftharpoons S$ interconversion, but in solid, the macrocyclic conformation is frozen as "R"-conformer or "S"-conformer. The macrocycles with the same chirality are stacked along b -axis to form chiral molecular columns, "R"-columns or "S"-columns. Complexes of 1 crystallize differently depending on the guest molecules. "R"-columns ("S"-columns) packed along a -axis produce "R"-layers("S"-layers), which are further packed along c -axis using "R"-layer to "R"-layer contact(RR) or SS and RS or SR. The crystals of 1· CHCl_3 are formulated as --RRR-- = [R]_n (Type I, chiral) and those of 1· CH_3CN or 1· CO_2 and 1· CH_2Cl_2 are represented by [RS]_n (Type IIA, racemic) and [RRSS]_n (Type IIB, racemic), respectively.

Cyclodextrins have received much attention as low molecular weight enzyme models which form one to one complexes with a variety of hydrophobic guest molecules.¹ Recently, a new class of artificial hosts (macrocyclic heterocyclophane) has been added to hydrophobic inclusion hosts, promising an interesting field for hydrophobic interaction between hosts and guests.² A macrocyclic heterocyclophane, N,N',N'',N''' -tetramethyl-2-11-20-29-tetraaza[3.3.3.3]paracyclophane (1) has a hydrophobic cavity surrounded by walls of benzene rings and can form inclusion complexes with various guest molecules, small enough to fit inside its cavity.³



Crystal structures of 1 with CHCl_3 , CH_2Cl_2 ,⁴ CH_3CN , CO_2 and

dioxane⁵ have been determined by the X-ray method. The macrocycles in these complex crystals have the shapes of square boxes with *gauche-trans* (*gtgtgt*) conformations of all four $-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_2-$ segments. The angles between benzene rings and the plane defined by four N atoms are about 60° . The guest molecules are included in the hydrophobic cavities with van der Waals stabilization. The size of the hydrophobic cavity is 4.6–6.4 Å wide and ca. 6 Å deep. On the other hand, uncomplexed 1 has a different macrocyclic conformation.⁶ The macrocycle has the shape of a rectangular box with $(-)\text{gttg}(-)\text{gttg}$ conformation of the endocyclic N-C bonds.

Table 1. Crystal data of inclusion complexes of 1

Guest	Space group and Z		Lattice constants			
			<i>a</i>	<i>b</i>	<i>c</i>	β
CHCl ₃	C2	2	25.166(8) Å	5.668(2) Å	13.438(3) Å	111.31(3)°
CH ₂ Cl ₂	C2/c	8	25.373(2)	5.486(1)	53.759(7)	111.00(1)
CH ₃ CN	C2/c	4	25.544(7)	5.406(1)	26.948(7)	109.90(4)
CO ₂	C2/c	4	25.590(6)	5.420(1)	26.900(6)	109.86(3)

Host:guest complexes of 1 crystallize differently depending on the guest molecules and are classified into three groups as shown in Table 1. Space groups and lattice constants suggest close relation among these complex crystal structures. Space groups are C2 or C2/c with the same lattice constants of *a*, *b* and β . The length of *c*-axis is nearly integral multiples of 13.4 Å. The macrocycles of the complexes in all three groups are stacked one over the other along *b*-axis to form molecular columns, where guest molecules are linearly embedded. This guest-dependent polymorphism is interpreted on the basis of different packing modes of these molecular columns. The Host:guest interaction induces slight conformational changes of the macrocycles, which affect the packing of molecular columns, i.e. column:column interaction.

We report here the macrocyclic conformation of the complexed and the uncomplexed host molecules, host:guest interactions, the molecular columns formed by stacking of the macrocycles and the guest dependent polymorphism (crystal structure).

RESULTS AND DISCUSSION

1. Molecular structure of 1·CHCl₃ and 1·CH₂Cl₂

X-ray analyses were carried out on 1·CHCl₃ and 1·CH₂Cl₂ single crystals.⁴ The geometries of the macrocycles are nearly the same for both complexes as shown in Figure 1. The macrocyclic conformation is essentially described by the dihedral angles of eight endocyclic N-C bonds and tilts of four benzene rings with respect to the plane defined by the four N atoms, (Table 2, Figures 1 and 3). The host molecule has a square-box structure (C₄), penetrated by a crystallographic two-fold axis for 1·CHCl₃ and a pseudo four-fold axis for both complexes by repetition of *gauche-trans* conformations in all $-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_2-$ segments.

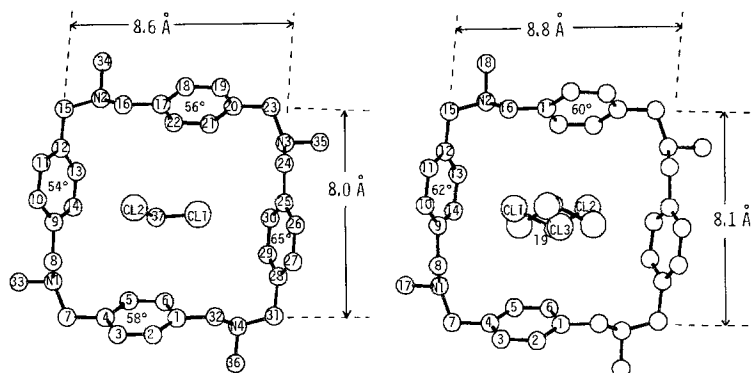


Figure 1. Perspective view of $\underline{1} \cdot \text{CHCl}_3$ and $\underline{1} \cdot \text{CH}_2\text{Cl}_2$ inclusion complexes.

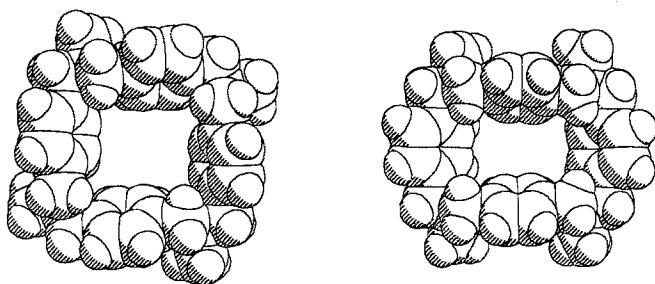


Figure 2. Comparison of macrocyclic conformation between the complexed $\underline{1}$ (left) and the uncomplexed $\underline{1}$ (right).

The benzene rings make an average angle of 61° for $\underline{1} \cdot \text{CHCl}_3$ and 58° for $\underline{1} \cdot \text{CH}_2\text{Cl}_2$ with the four N atom plane. Consequently, the size of hydrophobic cavity is 6Å in depth, ca. $4.6 \times 4.6\text{Å}$ at narrow side and ca. $6.4 \times 6.4\text{Å}$ at wide side. The guest molecule enters into the hydrophobic cavity of $\underline{1}$ from the wide side with van der Waals stabilization. The length of one side of the macrocycle is 8.8Å for $\underline{1} \cdot \text{CHCl}_3$ and 8.6Å for $\underline{1} \cdot \text{CH}_2\text{Cl}_2$, considerably longer than the other sides of 8.1Å and 8.0Å , respectively. The lengthening of one side of the macrocycle is attained by the slight change of the dihedral angles of some N-C bonds. Tilts of benzene rings in $\underline{1} \cdot \text{CHCl}_3$ are in a narrow range from 60° to 62° , while those in $\underline{1} \cdot \text{CH}_2\text{Cl}_2$ are in much wider range from 54° to 65° to get maximum van der Waals stabilization. Thus, a host molecule has a conformational flexibility, which makes it possible to place various guest molecules in the hydrophobic cavity.

It is interesting to note that $\underline{1} \cdot \text{CHCl}_3$ forms chiral crystals and $\underline{1} \cdot \text{CH}_2\text{Cl}_2$ forms racemic crystals. $\underline{1}$ exhibits no chirality in solution because of the rapid axial-equatorial change of methylene hydrogens, but in solid the macrocyclic conformation is frozen. In the solid state, $\underline{1}$ exists as optically active isomers, "R"-conformer or "S"-conformer. The macrocycles in chiral crystals ($\underline{1} \cdot \text{CHCl}_3$) are all "R"-conformers or all "S"-conformers.

Recently, the uncomplexed host molecule was crystallized.⁶

Interestingly, the uncomplexed 1 has a completely different macrocyclic conformation from that of the complex. The shape of the macrocycle is a rectangular box (C_{2v}). The tilts of the benzene rings are 42° and 67° (Figure 2). This result indicates that the host molecule 1 has a outstanding ability to change its conformation greatly. It is reasonable to expect that the hydrophobic cavity of the rectangular macrocycle fits better with large guest molecules like anthracene than that of the square-box shape macrocycle, judging from the spatial fitness of CPK models, although the molecular complexes of 1 with C_{2v} symmetry have not yet been crystallized.

Table 2. Conformational angles of endocyclic N-C bonds($^\circ$)

<u>1</u> ·CHCl ₃		<u>1</u> ·CH ₃ CN	
C4-C7-N1-C8	-66(1)	C4-C7-N1-C8	-70(2)
C7-N1-C8-C9	159(1)	C7-N1-C8-C9	159(1)
C12-C15-N2-C16	-69(1)	C12-C15-N2-C16	-69(2)
C15-N2-C16-C1'	166(1)	C15-N2-C16-C1'	166(1)
<u>1</u> ·CH ₂ Cl ₂		<u>1</u> ·CO ₂	
C4-C7-N1-C8	-67(1)	C4-C7-N1-C8	-66(1)
C7-N1-C8-C9	156(1)	C7-N1-C8-C9	161(1)
C12-C15-N2-C16	-68(1)	C12-C15-N2-C16	-67(1)
C15-N2-C16-C17	165(1)	C15-N2-C16-C1'	167(1)
C20-C23-N3-C24	-64(1)		
C23-N3-C24-C25	158(1)		
C28-C31-N4-C32	-64(1)		
C31-N4-C32-C1	165(1)		

2. Molecular structures of 1·CH₃CN and 1·CO₂

When 1·CH₃CN and 1·CO₂ were crystallized in isomorphous forms, it was found that these complexes form second class of racemic crystals.

Data collection and reduction.

1·CH₃CN: crystals from CH₃CN, clear colourless plate, 0.35×0.20×0.08 mm, sealed in a glass capillary to avoid decomposition; 1·CO₂: crystals from n-hexane, colourless prismatic crystals, 0.58×0.36×0.30 mm, sealed in a glass capillary. 1·CH₃CN and 1·CO₂: Philips PW1100 diffractometer, graphite monochromated Mo K α radiation, cell parameters from least-squares refinement of the 25 reflections, ω -2 θ scan, three reference reflections monitored every 3 hours and no decay observed, correction for Lorentz and polarization effects, no correction for absorption, 1893 reflections (815 with $I > 3\sigma(I)$) for 1·CH₃CN and 3110 reflections (1593 with $I > 3\sigma(I)$) for 1·CO₂.

1·CH₃CN: all non-hydrogen atoms of the host molecule were obtained by application of MULTAN.⁷ A difference synthesis showed a continuous density with three broad peaks on a two-fold axis. A CH₃CN molecule was

assigned to this density and refined as a group molecule. The structure was refined by full-matrix least-squares with anisotropic temperature factors for all non-hydrogen atoms of 1 and isotropic ones for group parameters. Hydrogen atom positions except for those of CH_3CN were calculated and fixed through refinements. Final refinement gave $R=0.087$ and $R_w=0.088$ for 815 observed reflections. The refined occupancy factor of the guest was 0.91 which is in good agreement with observed density. 1· CO_2 : The arrangements of host molecules in crystal are isomorphous with that of 1· CH_3CN . A CO_2 molecule was located on a two-fold axis and treated as the group molecule in the following refinements. Full-matrix least-squares refinement with anisotropic temperature factors for non-hydrogen atoms of 1 and isotropic ones for group atoms led to convergence at $R=0.076$ and $R_w=0.077$ for 1593 observed reflections. At final stage of refinements, the occupancy factor of the guest was fixed as 1.0 since the refined occupancy factors were always greater than 0.96.⁷ Positional and equivalent isotropic thermal parameters for non-hydrogen atoms of 1· CH_3CN and 1· CO_2 are listed in Table 3.⁸

Table 3. Fractional coordinates and temperature factors

<u>1</u> · CH_3CN					<u>1</u> · CO_2				
ATOM	X	Y	Z	B(EQ) OR B	ATOM	X	Y	Z	B(EQ) OR B
C(1)	0.3279(6)	0.720(3)	0.1936(5)	6.0(6)	C1	0.3278(2)	0.723(1)	0.1937(2)	4.7(2)
C(2)	0.3033(5)	0.565(3)	0.2199(6)	6.3(6)	C2	0.3037(2)	0.563(1)	0.2199(2)	5.4(2)
C(3)	0.3086(6)	0.617(3)	0.2736(6)	6.1(6)	C3	0.3091(2)	0.611(1)	0.2736(2)	5.4(2)
C(4)	0.3378(5)	0.824(3)	0.2985(6)	5.3(6)	C4	0.3374(2)	0.816(1)	0.2995(2)	4.5(2)
C(5)	0.3606(6)	0.974(3)	0.2704(7)	6.4(7)	C5	0.3596(3)	0.977(1)	0.2715(2)	5.7(2)
C(6)	0.3581(7)	0.927(4)	0.2192(6)	7.4(7)	C6	0.3546(3)	0.928(1)	0.2193(2)	5.7(2)
C(7)	0.3442(5)	0.864(3)	0.3565(5)	7.0(6)	C7	0.3439(3)	0.868(2)	0.3553(2)	5.6(2)
C(8)	0.4343(6)	0.669(4)	0.3948(6)	6.8(6)	C8	0.4343(3)	0.678(1)	0.3930(3)	5.3(2)
C(9)	0.4974(6)	0.717(3)	0.4113(5)	5.0(6)	C9	0.4963(2)	0.724(1)	0.4104(2)	4.5(2)
C(10)	0.5353(8)	0.560(3)	0.4430(5)	5.7(6)	C10	0.5338(3)	0.561(1)	0.4418(3)	5.7(2)
C(11)	0.5909(7)	0.586(4)	0.4538(5)	6.8(7)	C11	0.5909(3)	0.590(1)	0.4532(2)	5.9(2)
C(12)	0.6117(5)	0.781(4)	0.4338(6)	6.2(6)	C12	0.6113(2)	0.789(1)	0.4338(2)	4.9(2)
C(13)	0.5746(8)	0.956(3)	0.4030(6)	6.5(6)	C13	0.5743(3)	0.960(1)	0.4038(3)	6.5(3)
C(14)	0.5162(7)	0.926(3)	0.3900(5)	6.5(7)	C14	0.5168(3)	0.931(1)	0.3920(3)	6.3(3)
C(15)	0.6728(6)	0.813(4)	0.4440(6)	7.5(7)	C15	0.6731(3)	0.822(2)	0.4451(2)	6.0(2)
C(16)	0.6739(6)	0.656(3)	0.3633(5)	6.5(6)	C16	0.6729(3)	0.660(2)	0.3618(2)	5.6(2)
C(17)	0.4035(6)	1.002(5)	0.4410(6)	7.6(7)	C17	0.4058(4)	0.996(2)	0.4411(3)	6.2(3)
C(18)	0.7455(6)	0.943(6)	0.4101(6)	9.9(9)	C18	0.7436(3)	0.943(2)	0.4101(3)	7.6(3)
N(1)	0.4020(4)	0.907(2)	0.3899(4)	5.4(4)	N1	0.4020(2)	0.904(1)	0.3888(2)	4.5(2)
N(2)	0.6854(5)	0.872(2)	0.3963(4)	6.1(5)	N2	0.6857(2)	0.872(1)	0.3966(2)	5.1(2)
C(19)	0.50000(0)	0.73(1)	0.25000(0)	30.(3)	C19	0.0	(0)	0.860(7)	25000(0)
C(20)	0.50000(0)	0.46(1)	0.25000(0)	22.(2)	D1	0.0	(0)	0.560(8)	25000(0)
N(3)	0.50000(0)	0.24(1)	0.25000(0)	21.(2)	O2	0.0	(0)	1.117(6)	25000(0)

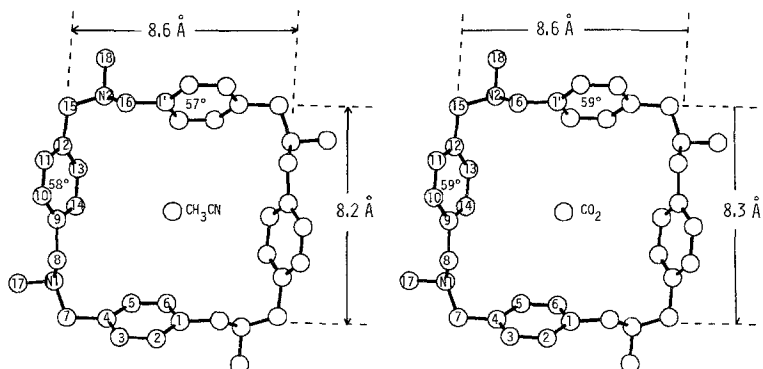
Figure 3. Perspective view of 1· CH_3CN and 1· CO_2 inclusion complexes.

Figure 3 shows that the molecular complexes of $\underline{1} \cdot \text{CH}_3\text{CN}$ and $\underline{1} \cdot \text{CO}_2$ are exactly in the same conformation. The macrocycle simulates square-boxes using *gauche-trans* conformations of all $-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_2-$ segments. Therefore, this conformation is essentially the same as that found in $\underline{1} \cdot \text{CHCl}_3$ and $\underline{1} \cdot \text{CH}_2\text{Cl}_2$. The size of the boxes are $8.2 \times 8.6 \text{ \AA}$ and $8.3 \times 8.6 \text{ \AA}$, respectively. The host molecules in $\underline{1} \cdot \text{CH}_3\text{CN}$ and $\underline{1} \cdot \text{CO}_2$ have more rectangular shape when compared with those in $\underline{1} \cdot \text{CHCl}_3$ and $\underline{1} \cdot \text{CH}_2\text{Cl}_2$. This may be due to the high symmetry of guest molecules (CH_3CN and CO_2). The guest molecules are included in the hydrophobic cavity made up of four benzene walls and situated on crystallographic two-fold axes. CH_3CN and CO_2 , not so bulky as CHCl_3 and CH_2Cl_2 molecules, are too small to occupy the hydrophobic cavities. This reflects on the abnormal high thermal motions of CH_3CN and CO_2 guest molecules.

3. Molecular column

In all three types of complex crystals of $\underline{1}$, the macrocycles are stacked along the *b*-axis to give a molecular column with a continuous hydrophobic cavity, where guest molecules are included one after another with host:guest = 1:1 (Figure 4). A column penetrated by a pseudo four-fold axis has a period of 5.5 \AA along *b*-axis and a square section with variable side lengths from 4.6 – 6.4 \AA , which restrict the size of guest molecules. Guest molecules at x, y, z are located in the space between the neighbouring two macrocycles at x, y, z and $x, 1+y, z$ in the column. Although guest molecules interact with two host molecules, most of the contacts were found with the host at x, y, z .

In the solid state, the macrocycle $\underline{1}$ exists as "R"-conformer or "S"-conformer. A molecular column is chiral because a column consists of all "R"-conformers or all "S"-conformers. Thus, "R"-conformers make "R"-columns and "S"-conformers make "S"-columns. Chiral crystals of $\underline{1} \cdot \text{CHCl}_3$ consists of all "R"-columns or all "S"-columns, while racemic crystal of $\underline{1} \cdot \text{CH}_2\text{Cl}_2$ consists of both "R"-columns and "S"-columns.

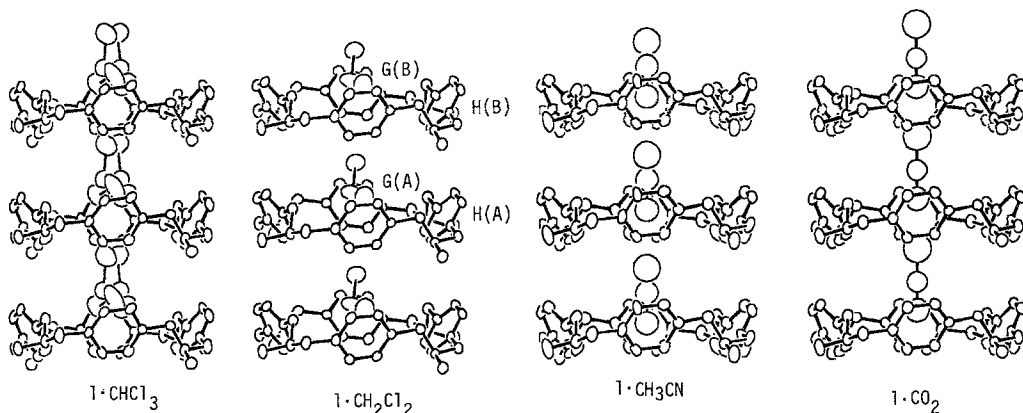


Figure 4. Molecular columns formed by stacking of the macrocycles along *b*-axis.

4. Host:guest Interaction

A column is stabilized by host:guest, host:host and guest:guest van der Waals interactions, which were calculated by the molecular mechanics method for $\underline{1} \cdot \text{CH}_2\text{Cl}_2$ complex.⁹ Each interaction is approximated as H(A):H(B) for host:host, H(A):G(A) and H(B):G(A) for host:guest and G(A):G(B) for guest:guest (H(A) = host at x, y, z , H(B) = host at $x, 1+y, z$, G(A) = guest at x, y, z and G(B) = guest at $x, 1+y, z$.) Sum of the calculated intermolecular van der Waals interaction of a column amounts to 32.9 kcal/mol, of which host:guest interaction is 13.3 kcal/mol, much greater than 0.9 kcal/mol of guest:guest interaction. H(A):G(A) interaction is by 4.7 kcal/mol greater than H(B):G(A) interaction.

5. Guest dependent polymorphism

The host:guest complexes of $\underline{1}$ crystallize differently depending on the guest molecules as is shown in Figure 5. The crystal structure viewed along the b -axis displays the packing of the molecular columns, parallel to the b -axis. "R"-columns or "S"-columns are packed along the a -axis by c -translation ($1/2, 1/2, 0$) to produce "R"-layer or "S"-layer, abbreviated as R or S in Figure 5. "R"-layer consists of all "R"-columns and "S"-layer consists of all "S"-columns. Thus, "R"-columns make "R"-layer and "S"-columns make "S"-layer. The guest dependent polymorphism is interpreted in terms of the packing mode of these "R"-layers and "S"-layers. These layers are further packed along c -axis using "R"-layer to "R"-layer contact (=RR) or SS and "R"-layer to "S"-layer

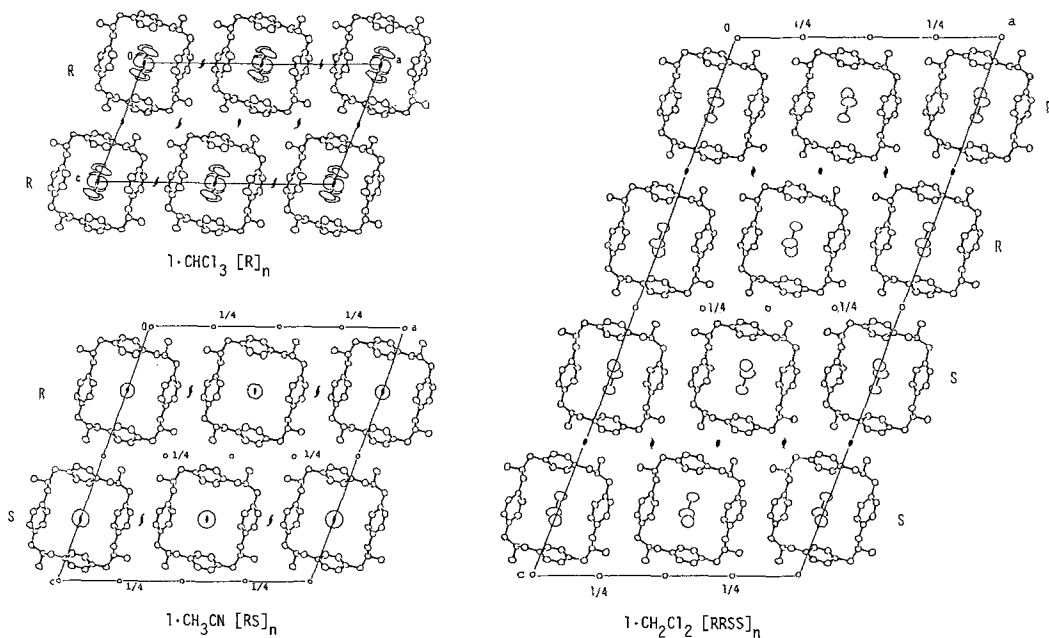


Figure 5. Crystal structures of $\underline{1} \cdot \text{CHCl}_3$, $\underline{1} \cdot \text{CH}_3\text{CN}$ and $\underline{1} \cdot \text{CH}_2\text{Cl}_2$ complexes.

contact(=RS) or SR. The RR contact is characterized by the presence of C_2 axis between two layers, while the RS (or SR) contact is characterized by the presence of symmetry center between two layers.

The crystal structure of $\underline{1}\cdot\text{CHCl}_3$ is formulated as $---\text{RRRR}--- = [\text{R}]_n$ (Type I, chiral) and those of $\underline{1}\cdot\text{CH}_3\text{CN}$ and $\underline{1}\cdot\text{CH}_2\text{Cl}_2$ are represented by $[\text{RS}]_n$ (Type IIA, racemic) and $[\text{RRSS}]_n$ (Type IIB, racemic), respectively.

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References.

1. (a) M.L. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer-Verlag: West Berlin and Heidelberg, 1978.
(b) I. Tabushi, *Acc. Chem. Res.*, 1982, 15, 66.
2. (a) I. Tabushi, Y. Kimura, K. Yamamura, *J. Am. Chem. Soc.*, 1981, 103, 6486.
(b) Y. Murakami, A. Nakano, R. Miyata and Y. Matsuda, *J. Chem. Soc., Perkin Trans.1*, 1979, 1669.
3. I. Tabushi, Y. Kuroda and Y. Kimura, *Tetrahedron Lett.*, 1976, 3327.
4. I. Tabushi, K. Yamamura, H. Nonoguchi, K. Hirotsu and T. Higuchi, *J. Am. Chem. Soc.*, 1984, 106, 2621.
5. S.J. Abott, A.G.M. Barret, C.R.A. Godfrey, S.B. Kalindjian, G.W. Simpson and D.J. Williams, *J. Chem. Soc., Chem. Commun.*, 1982, 796.
6. Crystals of $\underline{1}$ uncomplexed are monoclinic, space group $P2_1/a$ with $a=21.491(2)$, $b=15.123(1)$, $c=10.020(1)\text{\AA}$ and $\beta=97.26(1)^\circ$; $Z=4$. The structure was solved by direct method and refined to $R=0.083$ for 1269 reflections with $I>3\sigma(I)$. Full details will be published elsewhere.
7. The following library of major crystallographic programs was employed: MULTAN, G. Germain, P. Main and M.M. Woolfson, *Acta Crystallogr.*, 1970, B26, 274; ORFLS, W.R. Busing, K.O. Martin and H.A. Levy, Oak Ridge National Laboratory Report ORNL-TM-305; ORTEP, C.K. Johnson, Oak Ridge National Laboratory Report ORNL-TM-3794.
8. W.C. Hamilton, *Acta Crystallogr.*, 1959, 12, 609.
9. N.L. Allinger, *J. Am. Chem. Soc.*, 1977, 99, 8127. MM2 is available from Indiana University's Quantum Chemistry Program Exchange as program number 395.