Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Ibragimov, B. T. , Talipov, S. A. and Zorky, P. M.(1994) 'Inclusion complexes of the natural product gossypol', Supramolecular Chemistry, 3: 2, 147 — 165
To link to this Article: DOI: 10.1080/10610279408029853
URL: http://dx.doi.org/10.1080/10610279408029853

SUPRAMOLECULAR CHEMISTRY, Vol. 3, pp. 147–165
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Inclusion complexes of the natural product gossypol

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(Received June 27, 1993)

Gossypol, a biologically active compound with a wide spectrum of action (antiviral, immunosuppressive, antifertile, etc.), is a unique compound in the sense of inclusion complex formation. It gives clathrates with all 110 tested low-molecular organic substances. For 80 clathrates single cyrstals have been obtained and their crystallographic parameters have been determined. By the method of X-ray diffraction the structures of 30 inclusion complexes has been solved. The extreme divergence of gossypol clathrate structures is established: clathrates (H-clathrates) with cavities as isolated cells (cryptates), channels (tubulates), intersecting channels (intercalates), clathrates with mixed host-guest matrix and autoclathrates are observed. The existence of 20 groups of isostructural gossypol clathrates is found.

INTRODUCTION

Gossypol (**Gp**), 2,2′-[1,1′,6,6′7,7′-hexahydroxy-3,3′-dimethyl-5,5′-diisopropyl-8,8′-diformyl]-naphthalene, with empirical formula $C_{30}H_{30}O_8$, is found in the plants of *Gossypium speciese.*[1] Its highest content is discovered in the seeds and root bark of cotton.[2,3] For many years **Gp** was considered as an injurious toxic substance.[4,5,6] These considerations changed over a 60 year period due to the initiative of E.M. Vermel[7] and A.S. Sadykov.[8] Antitumor,[7,9] antiviral,[10,11,12] interferon inducing,[13] antiparasitogenic[14] and other properties of **Gp** have been revealed. The most interesting is the possibility of the use of **Gp** as a male contraceptive agent,[15,16,17] because of its antifertility activity.

However, the wide adoption of **Gp** into medical practice as a contraceptive drug is impeded by its toxic side effects.[18] Not long ago the results of *in vitro* experiments showed that **Gp** has the ability to inactivate the AIDS virus.[19] **Gp** is an effective antioxidant[1] which presents the possibility of its use in industry to protect natural drying oils.[20]

Recently more attention has been given to the study of the polymorphism of medical substances with the aim of obtaining new crystal modifications, possessing more optimal biopharmaceutical properties.[21] Data from the literature showed the possibility of the existence of various crystal forms of **Gp**. As long ago as 1937. Adams[22] reported three possible polymorphs and four clathrates of **Gp** with the first four homologs of carbonic acids. In connection with this we began the study of polymorphic modifications and clathrates of **Gp**.

RESULTS AND DISCUSSION

We have obtained eight polymorphs and 100 molecular complexes of **Gp**. The latter represent inclusion compounds of **Gp** with different low molecular weight organic substances. Three polymorphs and 80 clathrates have been obtained as single crystal, for which crystallographic parameters have been determined. The structure of two polymorphs and 28 clathrates have been determined by X-ray structure analysis (Table 1). In the inclusion complexes molecules of the guests are located in closed cells (cryptates), in channels (tubulates) and in layers (intercalates). Host and guest molecules interact by van der Waals forces (normal for clathrates) or specific forces such as electrostatic, dipole-dipole and H-bonds. For the latter Weber[23,24] suggested the name coordinatoclathrates. We call such coordinatoclathrates as **H**-clathrates. Accordingly, **H**-clathrates, in which guest molecules are disposed in the cavities, channels and layers are given the name **H**-cryptate, **H**-tubulate and **H**-intercalate, respectively.

Two types of the crystals may be distinguished under the heading clathrates: those in which the host matrix is produced from the participation of different molecules (clathrates on the base of the mixed host matrix), and those in which chemically identical

Table Crystallographic characteristics of gossypol crystal forms

	Polymorphs		*Cryptates*	
Parameters	**P1**	**P3**	**CC(A)/BNZ** (*benzene*)	**CC(B)/MXL** (*m-xylene*)
a(Å)	13.468(2)	21.298(8)	11.241(3)	8.487(1)
b(Å)	21.376(3)	19.079(4)	14.986(4)	14.087(2)
c(Å)	8.784(1)	15.267(2)	17.380(4)	14.411(2)
α(°)	90	90	98.84(2)	115.38(1)
β(°)	97.23(1)	113.19(2)	99.86(2)	75.11(1)
γ(°)	90	90	98.91(2)	86.80(1)
V(Å^3)	2511	5678	2800	1475
Sp. gr.	$P2_1/c$	$C2/c$	$P\bar{1}$	$P\bar{1}$
m:n	—	—	2:1	2:1
Z	4	8	4	2
ρ_{calc}(g/cm^3)	1.37	1.22	1.32	1.29
N	2144	2470	6146	3900
R	4.9	6.8	5.0	8.5

	Cryptates		*Tubulates*	
Parameters	**CC(B)/EBZ** (*ethylbenzene*)	**CC(B)/FCC** *fourchlorine carbon*)	**CT(A)/DER** (*dyethyl ether*)	**CT(B)/DER** (*dyethyl ether*)
a(Å)	8.451(1)	8.847(1)	8.557(2)	8.497(4)
b(Å)	14.195(3)	14.300(6)	14.474(5)	14.546(6)
c(Å)	14.398(3)	14.395(5)	25.651(5)	23.031(7)
α(°)	114.89(2)	102.54(3)	90	90
β(°)	77.45(4)	69.53(3)	107.12(2)	99.53(2)
γ(°)	87.79(4)	91.12(3)	90	90
V(Å^3)	1470	1547	3034	2807
Sp. gr.	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1$
m:n	2:1	1:1	1:1	2:1
Z	2	2	4	4
ρ_{calc}(g/cm^3)	1.29	1.44	1.30	1.34
N	3224	2559	2600	716
R	6.8	8.8	5.9	18.3

	Tubulates		*Itercalates*	
Parameters	**CT(C)/DCM** (*dychloromethane*)	**CT(D)/DXN** (*1,4-dioxane*)	**CI(A)/CLE** (*chloroform*)	**CI(A)/IVA** (*isovaleric acid*)
a(Å)	21.320(4)	25.459(9)	28.464(4)	28.835(7)
b(Å)	19.199(6)	11.923(3)	8.948(1)	9.063(2)
c(Å)	15.765(1)	13.608(2)	26.480(4)	26.880(4)
α(°)	90	90	90	90
β(°)	113.05	90	108.46(2)	109.66(1)
γ(°)	90	90	90	90
V(Å^3)	5916	4130	6380(2)	6615(2)
Sp. gr.	$C2/c$	$Pbcn$	$C2/c$	$C2/c$
m:n	1:1	1:3	1:1	1:1
Z	8	4	8	8
ρ_{calc}(g/cm^3)	1.35	1.26	1.33	1.25
N	2090	1610	1980	1114
R	9.4	6.8	10.0	13.2

			H-cryptates	
Parameters	**HC(A)/EAT** (*ethylacetate*)	**HC(A)/BAT** (*butylacetate*)	**HC(A)/MPT** (*methylpropionate*)	**HC(A)/ACE** (*acetoacetic ether*)
a(Å)	11.130(2)	11.221(2)	11.079(3)	11.095(2)
b(Å)	30.892(12)	30.538(9)	30.724(7)	30.604(9)
c(Å)	11.472(3)	17.023(2)	16.515(5)	15.955(5)

Table continued

	Polymorphs		*Cryptates*	
Parameters	**P1**	**P3**	**CC(A)/BNZ** (*benzene*)	**CC(B)/MXL** (*m-xylene*)
$\alpha(^\circ)$	90	90	90	90
$\beta(^\circ)$	89.69(2)	89.32(1)	90.46(2)	88.27(2)
$\gamma(^\circ)$	90	90	90	90
V(Å^3)	5650	5833	5621	5754
Sp. gr.	C2/c	C2/c	C2/c	C2/c
m:n	2:1	2:1	2:1	2:1
Z	8	8	8	8
ρ_{calc}(g/cm^3)	1.32	1.31	1.33	1.35
N	2465	2388	1899	2502
R	9.3	8.9	5.9	5.6

	H-*cryptates*		**H-*tubulates***	
Parameters	**HC(B)/AAL** (*amylacrylate*)	**HC(C)/BAD** (*benzaldehyde*)	**HT(A)/ACT** (*acetone*)	**HT(A)/CHN** (*cyclohexanone*)
a(Å)	14.425(2)	10.959(2)	10.665(2)	10.803(4)
b(Å)	15.519(1)	14.——6(2)	11.135(2)	11.157(5)
c(Å)	16.409(2)	11.418(2)	14.379(3)	14.692(6)
$\alpha(^\circ)$	97.89(1)	73.62(1)	76.47(2)	75.39(3)
$\beta(^\circ)$	117.80(1)	92.27(1)	108.67(1)	104.73(3)
$\gamma(^\circ)$	90	91.71(1)	77.72(1)	76.66(3)
V(Å^3)	2986	1693	1493	1573
Sp. gr.	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
m:n	2:1	2:3	1:1	1:1
Z	4	2	2	2
ρ_{calc}(g/cm^3)	1.31	1.33	1.28	1.30
N	5155	2499	2542	1879
R	5.9	5.4	7.7	7.1

	H-*tubulates*			
Parameters	**HT(A)/THF** (*tetrahydrofuran*)	**HT(A)/ANL** (*acetonitrile*)	**HT(A)/IPL** (*isopropanol*)	**HT(A)/MAA** (*m-acrylic acid*)
a(Å)	10.788(2)	10.938(1)	10.861(5)	10.996(2)
b(Å)	10.979(3)	10.982(2)	11.035(3)	11.065(3)
c(Å)	13.880(2)	14.162(2)	14.142(7)	13.452(2)
$\alpha(^\circ)$	80.11(2)	77.99(1)	78.40(3)	81.76(2)
$\beta(^\circ)$	103.87(1)	112.24(1)	110.49(3)	107.09(2)
$\gamma(^\circ)$	77.96(2)	.25(1)	79.55(3)	85.70(2)
V(Å^3)	1518	1453	1496	1536
Sp. gr.	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
m:n	1:1	1:1	1:1	1:1
Z	2	2	2	2
ρ_{calc}(g/cm^3)	1.29	1.28	1.28	1.31
N	2701	2360	2484	1910
R	5.2	4.9	6.4	7.0

	H-*tubulates*			
Parameters	**HT(C)/OAD** (*oil aldehyde*)	**HT(A)/TCA** (*t-chloroacetic acid*)	**HT(B)/FOA** (*formic acid*)	**HT(B)/MTL** (*methanol*)
a(Å)	10.190(2)	11.178(2)	14.249(3)	13.420(3)
b(Å)	11.355(1)	11.178(2)	6.969(1)	7.156(2)
c(Å)	16.613(2)	13.139(2)	14.620(4)	14.208(3)
$\alpha(^\circ)$	73.04(1)	82.93(2)	90.07(2)	93.51(2)

continued

Table continued

Parameters	*Polymorphs* P1	P3	*Cryptates* CC(A)/BNZ (*benzene*)	CC(B)/MXL (*m-xylene*)
β(°)	108.46(1)	107.39(2)	92.82(2)	98.17(2)
γ(°)	81.07(1)	84.94(2)	99.09(2)	85.05(2)
V(Å^3)	1530	1575	1431	1372
Sp. gr.	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
m:n	1:1	1:1	1:1	1:1
Z	2	2	2	2
ρ_{calc}(g/cm^3)	1.28	1.44	1.31	1.33
N	2961	236–	2603	2664
R	6.8	8.9	4.8	6.3

Parameters	**H-*tubulates*** HT(B)/DMS (*DMSO*)	HT(C)/PRD (*pyridine*)
a(Å)	15.102(2)	10.726(3)
b(Å)	7.207(1)	20.38(4)
c(Å)	14.726(3)	19.159(6)
α(°)	90.90(2)	90
β(°)	66.94(2)	93.95(2)
γ(°)	96.15(2)	90
V(Å^3)	1468	4002
Sp. gr.	$P\bar{1}$	$P2_1/c$
m:n	1:1	1:3
Z	2	4
ρ_{calc}(g/cm^3)	1.35	1.25
N	2040	3864
R	5.7	6.6

molecules simultaneously play the role both of host and guest (autoclathrates).

For further identification purposes the symbols **P1–P8** are used for **Gp** polymorphs. **Gp** clathrates are indicated by six-letter symbols (Table 1). The first letter indicates the type of clathrate. The second letter defines the topology of the empty space (isolated cells, channels, layers). Letters **A**, **B**, **C**,... put in brackets in the third position correspond to the group of the isostructural clathrates. Further, there is an oblique stroke, which is followed by the shortened (three-letter) name of the guest component (from the Table it is clear how the names of the guests are shortened). It is implied that in all cases the host is **Gp** (exceptions are clathrates on the basis of the mixed gossypol-dioxane matrix). For example, **CT(A)** denotes the **A** group of isostructural clathrates having cavities as channels. By symbol **HC(B)/AEA** we mean a **Gp H**-clathrate with amylic ether of acrylic acid with cavities as cells.

The composition m(host)·n(guest) of a given clathrate is determined by use of the m:n ratio and the symbol **z** shows the number of **Gp** molecules in the unit cell.

The structure of the gossypol molecule in its crystal forms

The **Gp** molecule may be in lactol, aldehyde and quinoid tautomeric forms.[1] However, in the crystalline state the **Gp** molecule is only found in the aldehyde tauromeric one. Dihedral angles between naphthyl groups $\mathscr{AB}$ and $\mathscr{CD}$ (Fig 1) are found in the range 72.3–105.5°.

Isopropyl groups of **Gp** molecules have one of two different orientations, differing from each other by rotations around the C(5)-C(23) and C(15)-C(28) bonds of 180°. In most structures in $\mathscr{AB}$ the H(4) atoms and H(23) atoms, and in $\mathscr{CD}$ accordingly H(14) and H(28) atoms turn to each other. Only in the polymorph **P1** and clathrates **HC(A)** the orientation of the $\mathscr{CD}$ isopropyl group changes: the H(28) atom is directed to the nearest O(8)-H hydroxyl group.

H-bonds of two types exist in the molecule: C=O...H-O form six-membered cycles $\mathscr{F}$ and $\mathscr{F}'$, consisting of atoms O(2)-C(22)-C(8)-C(7)-O(3)-H and O(6)-C(27)-C(18)-C(17)-O(7)-H, and O-H...O form five-membered cycles $\mathscr{E}$ and $\mathscr{E}'$, consisting of O(3)-C(7)-

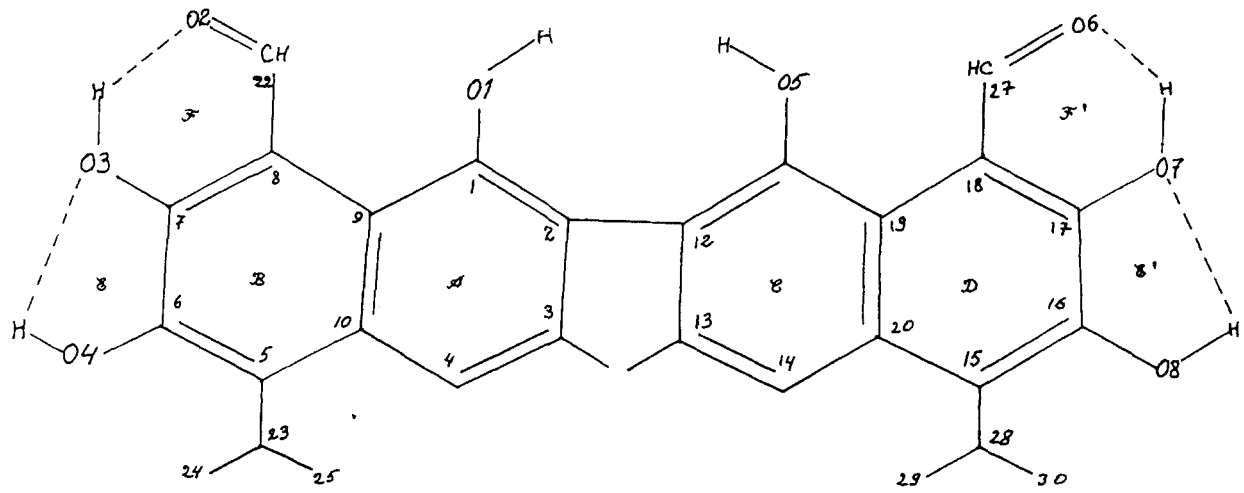

Figure 1 Gossypol molecule.

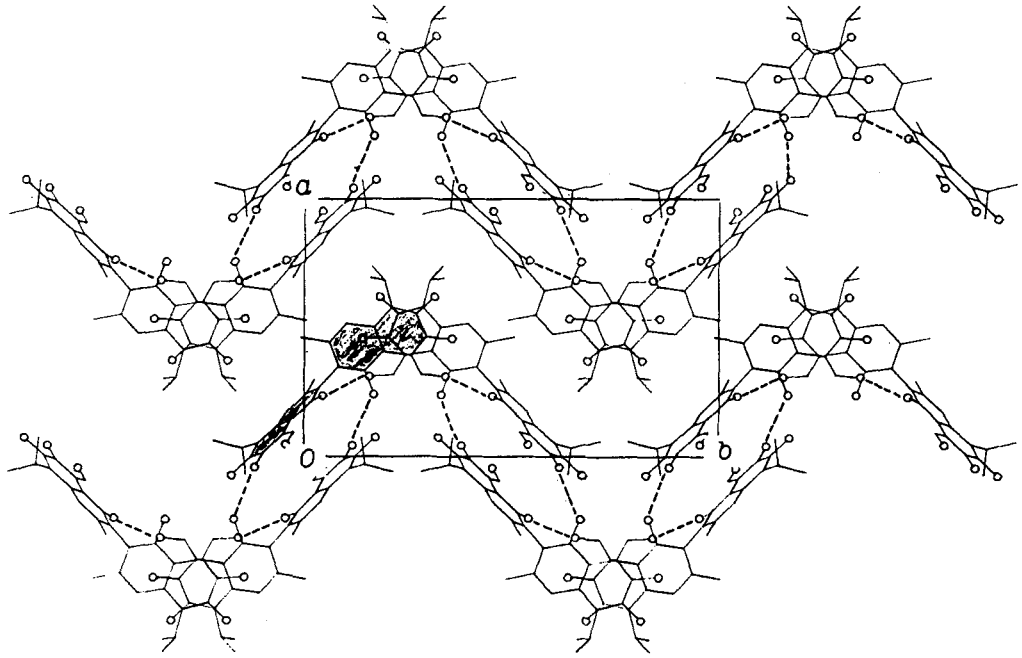

Figure 2 The structure of the **P1** polymorph.

C(6)-O(4)-H and O(7)-C(17)-C(16)-O(8)-H (Fig 1). These intramolecular H-bonds are similar to those found in related structures.

In many **Gp** crystal forms the naphthyl groups are coplanar to within 0.04 Å. Atoms of $\mathscr{CD}$ nuclei of the **P1** polymorph and atoms of one of two symmetrically independent molecules in **HC(B)/AAL** are characterised by the lowest coplanarity (0.14 Å).

Gossypol polymorphs

The structure of polymorphs **P1** and **P3** is determined. The symmtrically related pair of H-bonds O(5)-H...O(3) joints **Gp** molecules in centrosymmetric dimers, which are characteristic for many **Gp** crystal forms. H-bonds O(1)-H...O(6) form from such centrosymmetric dimers the crimped bilayers, the central planes of which are perpendicular to the x axis (Fig 2). The bilayer structure has an important peculiarity: all polar (hydrophilic) groups are directed to the inside of the bilayers and on the surface only hydrophobic portions of **Gp** molecules are situated. As a result an ideal separation of hydrophobic and hydrophilic areas is observed. The structure of the **P3** polymorph will be discussed below together with the

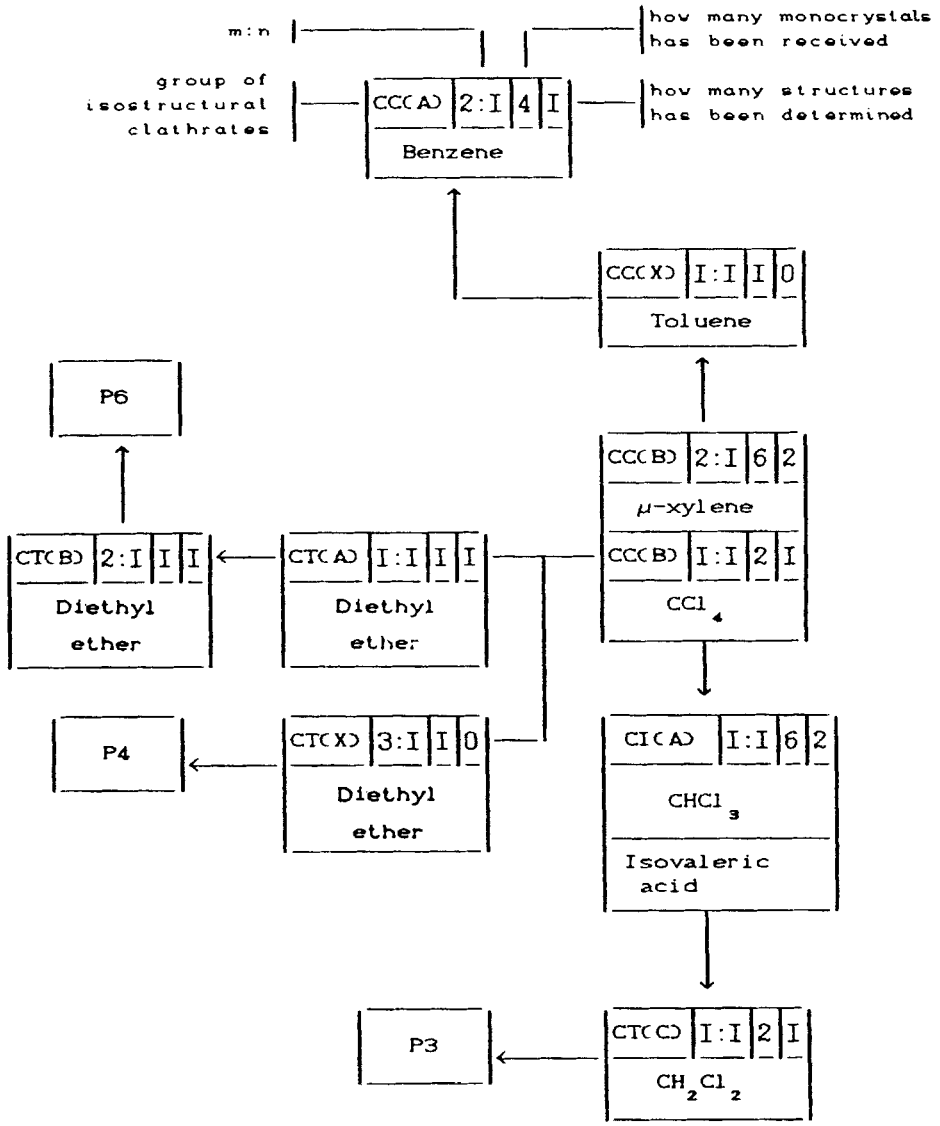

Figure 3 Family of gossypol clathrates and correlation between its members.

tubulates of the **CT(C)** group, from which it is formed by decomposition.

The **P1** and **P2** polymorphs are produced by crystallization from the solution and all other polymorphs **P4–P4** are obtained be decomposition of tubulates, belonging to different groups. The **P4** polymorph is formed by **CT(X)/DER** decomposition; **P5** is produced by desolvation-clathrates with **MTL**, ethanol, formic aicd and methylformate; **CT(B)/DER** gives **P6**; **P7** is found after decomposition of **HT(A)/ACT** and **P8-HT(C)/PRD**. Change from room temperature to the melting point does not produce transformation among polymorphs.

Gossypol clathrates

Gp forms clathrates of all possible types: cryptates, tubulates and inercalates. Cryptates are represented by two groups of isostructural complexes, **CC(A)** and **CC(B)**; tubulates are represented by three groups, **CT(A)**, **CT(B)**, and **CT(C)**; intercalates by only one, **CI(A)**. Figure 3 shows the family of **Gp** clathrate and the relation between its members (some morphotropic transitions). In the Scheme cryptates **CC(B)** occupy the central place. In the cryptates of this group **Gp** molecule (I(x,y,z) and molecule II(2-x,1-y,1-z) are combined by H-bonds O(5)-H ... O(3) into typical centrosymmetric dimers.[25] The I(x,y,z) molecule also forms pairs by means of O(1)-H ... O(2) bands with molecule III(2-x,1-y,1-z), resulting in the uniting of **Gp** molecules in the columns in the x direction (Fig 4). The H-bond between the O(8)-H group of molecule I(x,y,z) and O(4) of molecule IV($x+1,y+1,z$) units the colums into bilayers parallel to the *ab* plane. As in the

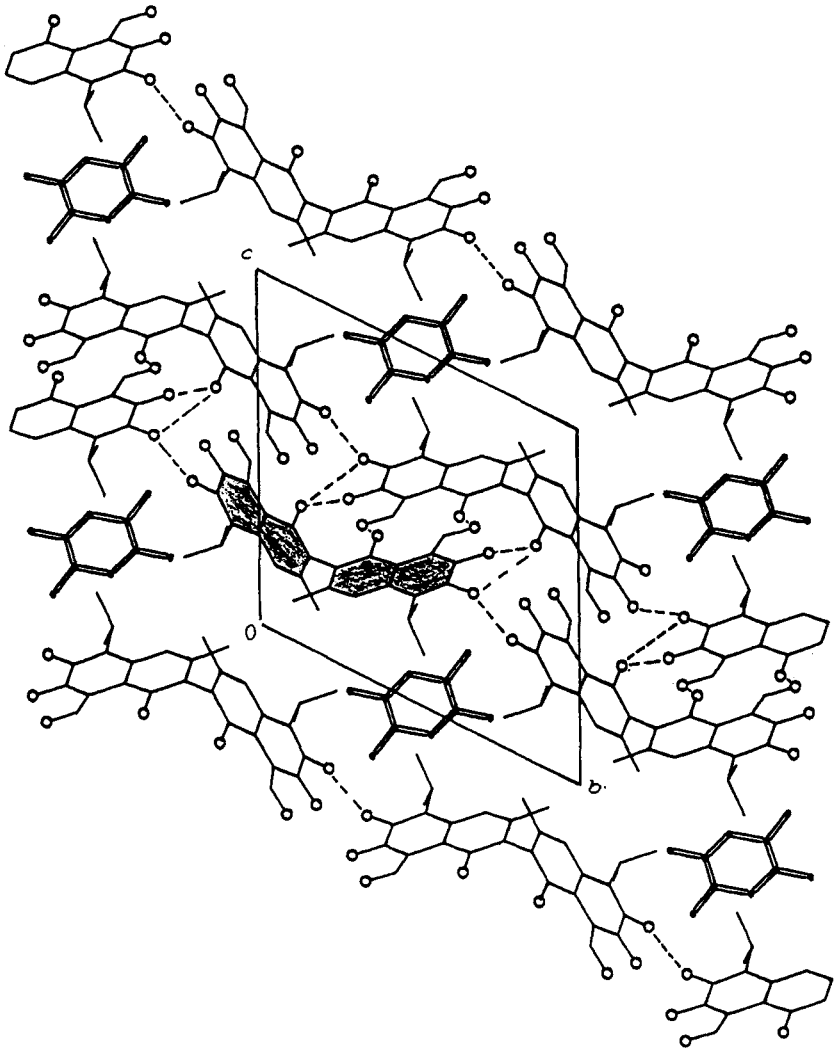

Figure 4 The structure of **CC(B)/MXL**.

P1 structure all polar groups are directed toward the inside of the bilayers and on their surface, only hydrophobic regions of **Gp** molecules are situated. This, the interaction between bilayers is entirely van der Waals. The layer surface has projections and cavities. The cavities are formed by the contact of molecules I(x,y,z) and V(x,$y+1$,z), between naphtyl nuclei $\mathscr{AB}$ and $\mathscr{CD}$ of these molecules. The cavities of the neighboring bilayers are situated opposite each other, and a hydrophobic centrosymmetric cavity in the form of a prism is formed. In the direction of the y axis the cavities are connected by rather narrow crosses. The relation of the bilayers is determined in part by the size and shape of the guest molecules.

With regard to the **CC(B)** group eight different clathrates are attributed. In the cavities one molecule of **MXL** (Fig 4) or two molecules of **FCC** (Fig 5) may be disposed. The **FCC** molecule may leave the crystals at higher temperature by means of the crosses connecting the cavities, whereas the **MXL** molecules are released only upon melting. This example clearly shows the reason for the classifications of the clathrate as cryptates, tubulates and intercalates. The **CC(B)/MXL** complex is a typical cryptate, but the isostructural **CCB()/FCC** complex is referred to as a tubulate because here the crosses between the cells are large enough to permit diffusion of the **FCC** molecules.

In the **CT(A)** tubulate analogous bilayers are also present. For **DER** inclusion, the bilayers expand such that typical channels form. The **DER** molecules in the channels are tightly packed (Fig 6), but held so weakly that after removal of the crystals from the mother liquor immediate desolvation begins. The ***DER*** molecules are isolated from the channels having the same chirality. As a result of desolvation of the **CT(B)/DER** structure 50% of the solvent molecules are removed (Fig 7). It is noteworthy that the single crystals are not destroyed. If chiral guest molecules

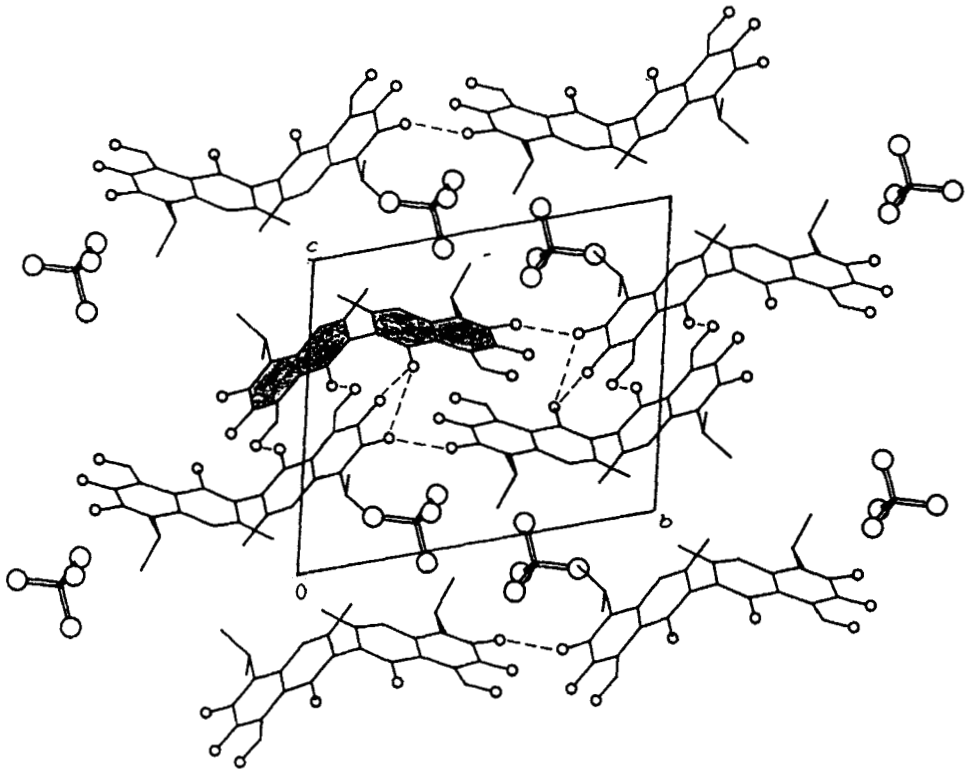

Figure 5 The structure of **CC(B)/FCC**.

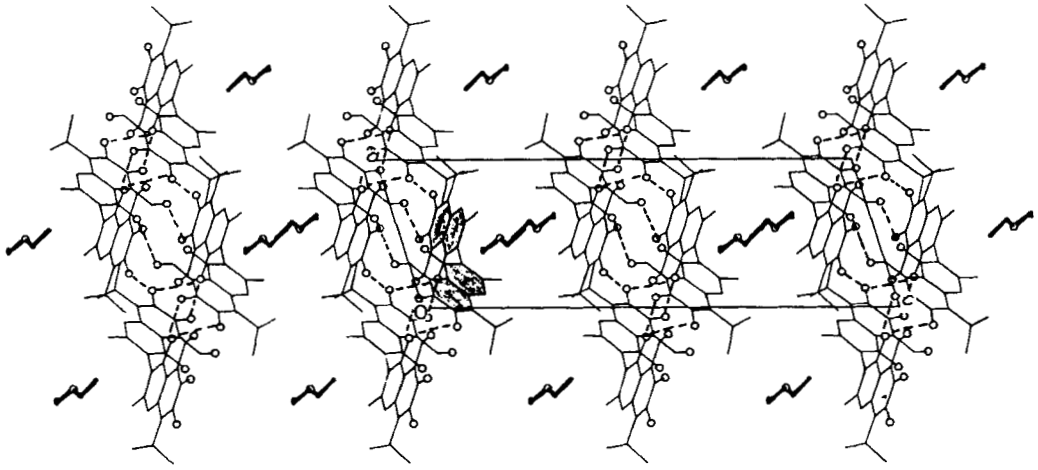

Figure 6 The structure of **CT(A)/DER**.

not capable of racemization are used instead of **DER** in **CT(A)**, the crystal produced after the **CT(A)-> CT(B)** transition contains only one of enantiomers. This represents a met method of racemate separation. At 140–142° the **CT(B)/DER** crystals completely desolvate with the formation of the **P6** polymorph.

DER also forms another type of clathrate, **CT(X)/DER**. On desolvation of the clathrate the powder diffractogram does not change and the **P4** polymorph is formed. This fact (and other reasons) shows that this clathrate is a tubulate.

The reduction of methyl groups from two to one on the transition from m-xylene (**MKL**) to toluene leads to the formation of **CC(X)** clathrates of the undetermined structure. For benzene, transition to the **CC(A)** group occurs. This group contains four

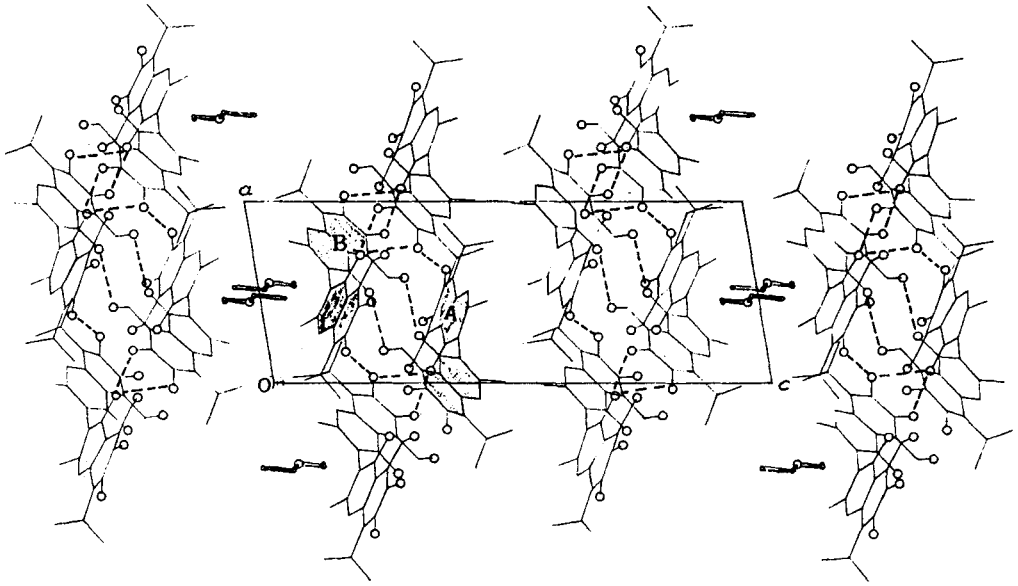

Figure 7 The structure of **CT(B)/DER**.

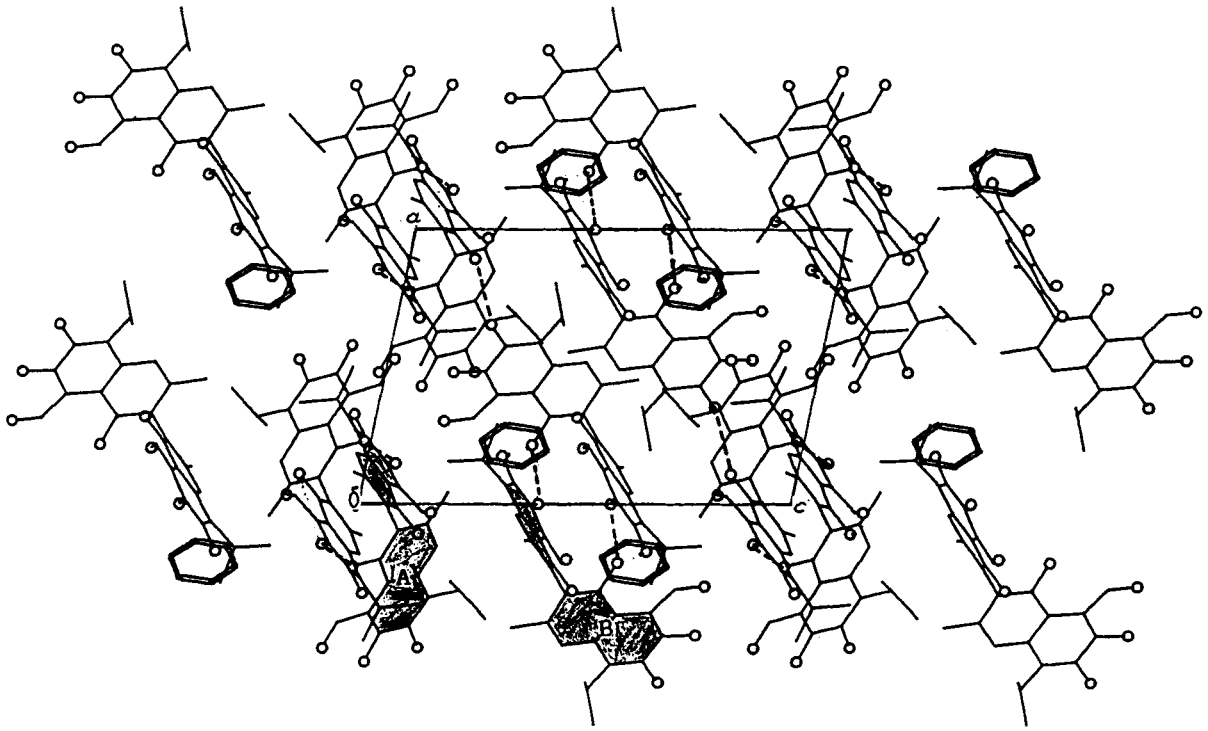

Figure 8 The structure of **CC(A)/BNZ**.

cryptates. In **CC(A)/BNZ**[26,27] centrosymmetric dimers are combined to form columns which are packed to produce closed cavities (Fig 8).

The different chlorine-containing derivatives of methane each produce different results as guests. *$CHCl_3$ forms a* ***Gp*** *intercalate.*[27,28] Clathrates of seven other organic substances such as 1,2-dichlorethane, diiodomethane, and isovaleric acid also form intercalates. In these intercalates centrosymmetric dimers are combined by O(1)-H...O(8) and O(8)-H...O(4) H-bonds for form columns parallel to the [101] direction (Fig 9). By translation in the *y* direction columns form layers of host molecules. Guest molecules are situated in the interlayer space. $CHCl_3$ molecules display strong

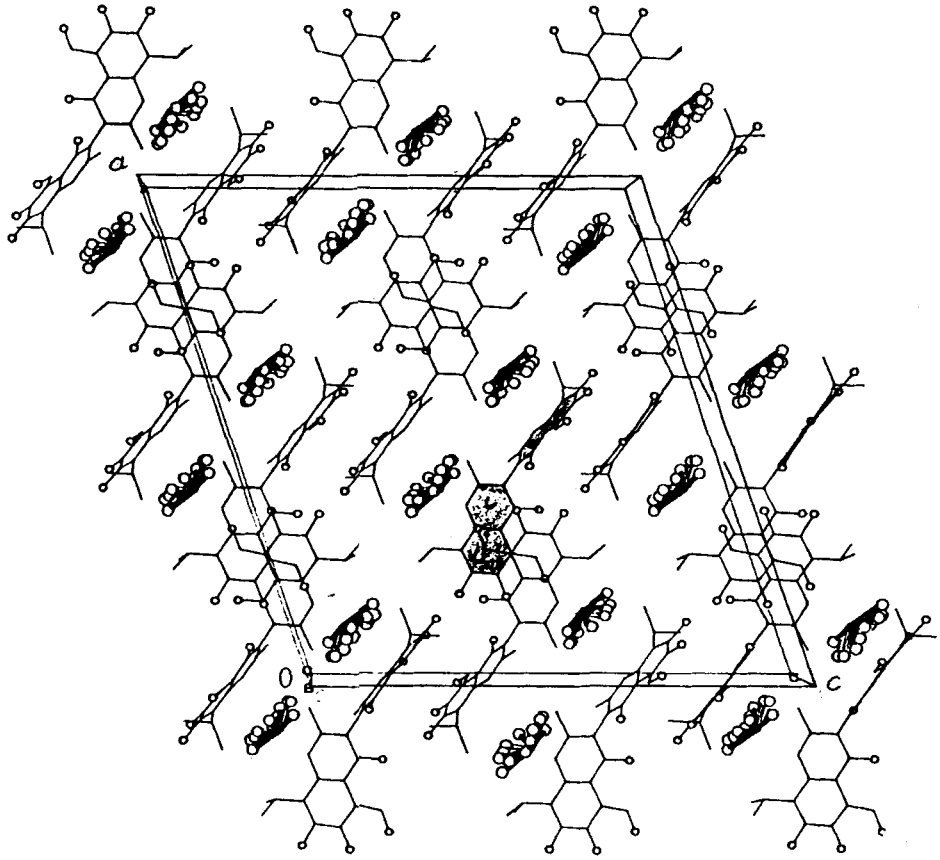

Figure 9 The structure of **CI(A)/CLF**.

disorder. They are distributed among our orientations, differing by a rotation of ~30° about the C-H bond. Molecules of isovaleric acid in **CI(A)/IVA**[28,29] exist as centrosymmetric dimers and thus behave as hydrophobic guest molecules.

CH_2Cl_2[30] and CH_2Br_2 form unstable clathrates, belonging to the **CT(C)** group. For the diffraction experiment a single crystal of **CT(C)/DCM** was mounted in a capillary. After completion of the data collection the capillary was carefully broken. Four hours later the experiment was updated: it showed that on desolvation the **P3** polymorph had formed. On tubulate decomposition reconstruction of the host lattice does not take place: crystal compression of 4% is observed in case of **CT(C)/DCM** and 9.4% in case of CT(C)/CH_2Br_2 (Fig 10).

The channels present in the polymorph **P3** crystals have ~4 Å diameter. This is large enough to accommodate gas molecules of air. Spectrophotometric studies of the purity of various unsolvated **Gp** samples show maximal content of admixtures in the **P3** polymorph is also characterized by the worst chemical stability: on storage it changes colour and decomposes. The channel walls of **P3** contain polar groups of $\mathscr{CD}$ nuclei of the **Gp** molecules. Oxygen and ammonia, if it present, react with these groups and accelerate the transformation of **Gp**.

The **Gp** complex with 1,4-dioxane represents a specific clathrate because two **DXN** molecules from the three take place in the construction of the gossypol-dioxane matrix (Fig 11). The latter is constructed from H-bonds of the type **Gp**...**DXN**. Each **Gp** molecule has H-bonds with four **DXN** molecules, and each **DXN** molecule, with two **Gp** molecules. Packing of the mixed host layers parallel to the *ac* plane forms channels in the *z* direction. Other **DXN** molecules (one of the three) appear as disordered guests in these channels. Thus, this complex represents an auto-clathrate on the basis of the mixed host matrix. Other molecules of suitable size may take the place of the **DXN** molecules in the channels leading to a new clathrate family on the basis of the gossypol-dioxane matrix.

H-clathrates of gossypol

The existence of three groups of isostructural **H**-cryptates and the same number of tubulates groups

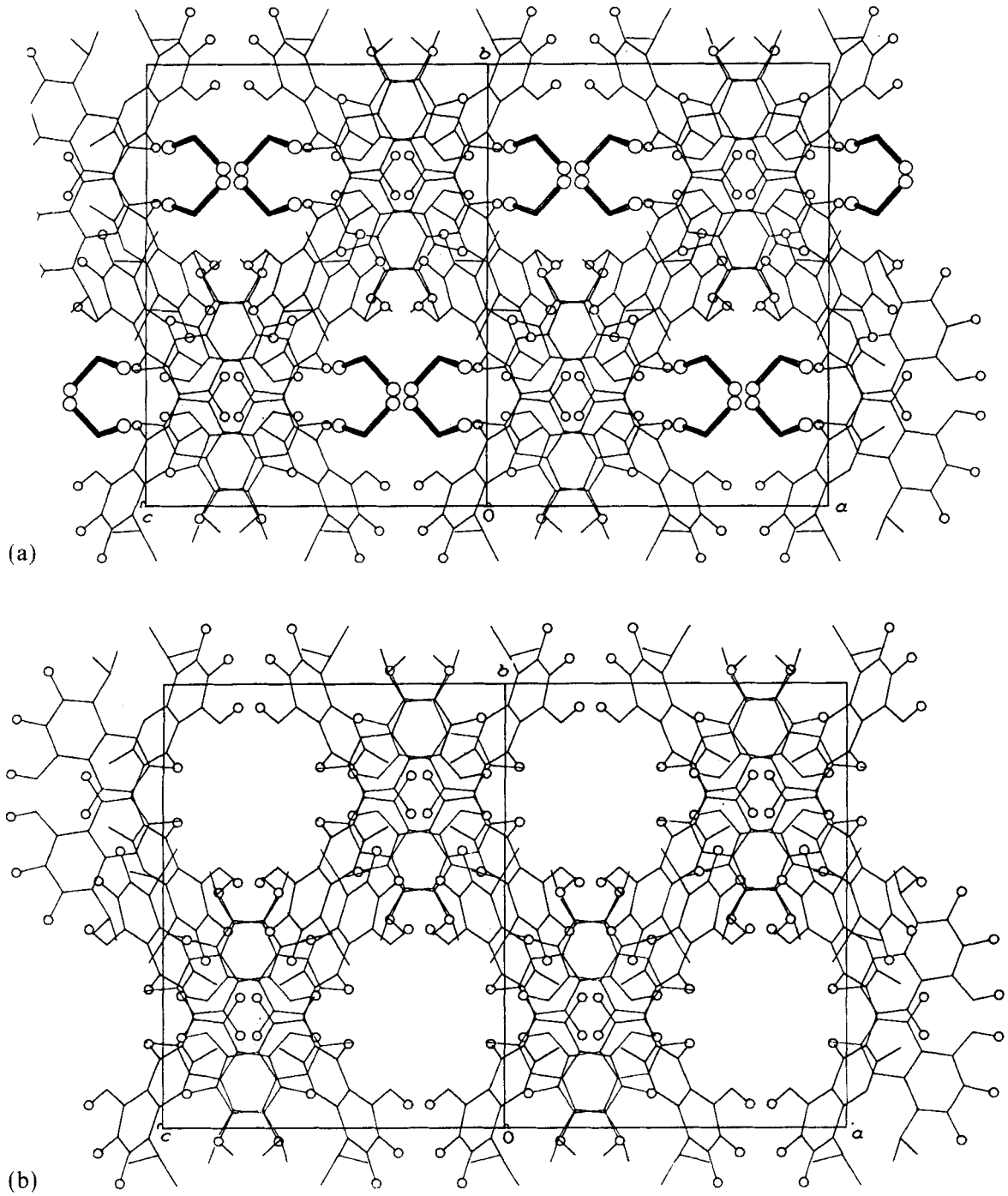

Figure 10 The structure of (a) **CT(C)DCM** and (b) **P3**.

has been established. Figure 12 shows the family of **Gp H**-clathrates and the relation between its members (some morphotropic transitions). The group **HT(A)**, having the greatest number of representatives (19), occupies the central place.[31,32] Typical centrosymmetric dimers are present in the most of these **H**-tubulates. With the help of O(8)-H ... O(4) H-bonds these are combined into columns, which pack to form channels parallel to the z axis (Fig 13). At the same time, depending on the size and shape of the guest molecules, the host substructure may change a little. In **HT(A)/THF** and **HT(A)/CHN** H-bonds combining dimers to the columns are absent, and in **HT(A)/OAD** centrosymmetric dimers of another structural type (H-bonds O(3)-H ... O(5) and O(5)-H ... O(2) instead of O(5)-H ... O(3)) are connected to the columns.

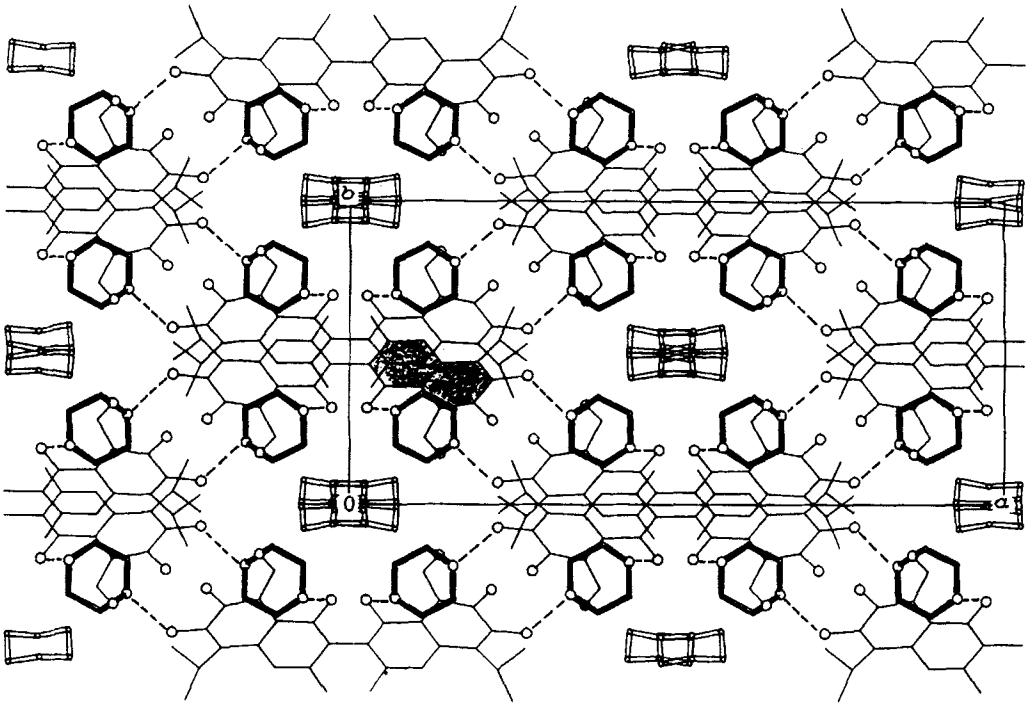

Figure 11 The structure of **CT(D)/DXN**.

Thus, in complexes of a given type, guest molecules may exclude some groups from participation in the intermolecular H-bonds, but they may also stimulate the formation of the new H-bonds. Despite the peculiarities of the structures of clathrates with **THF**, **CHN** and **OAD**, they are attributed to the **HT(A)** group, because of the similarity of the cell parameters (Table) and because of the location of the **Gp** molecules.

Guest molecules arranged in the channels of **H**-clathrates **HT(A)** may have only proton acceptor groups (ketones, aldehydes, cyclic ethers), only hydroxylic groups (alcohols) or both (carbonic acids). **Gp** molecules of the first type form H-bonds with the O(1)-H group of the **Gp** molecules. Alcohols participate in H-bonds with O(1)-H (hydroxyl) or they may donate the proton to O(6) of other **Gp** molecules. Acids form H-bonds with the O(1)-H group and the O(6) atom of different **Gp** molecules.

H-clathrates of the **HT(B)** group are also formed with the three types of guest molecules described above. However, for the formation of these group complexes only the lowest members of the complex ethers series (methyl formate, methyl acetate), alcohols (methanol, ethanol) and carbonic acids (C(1)–C(4) are found. Ten **H**-clathrates belonging to **HT(B)** group have been discovered. In **H**-clathrates of the acids and alcohols H-bonded associates exist only as centrosymmetric dimers. They are packed in the crystals in such a way that channels are formed in the *y* direction (Fig 14). Each molecule of the carbonic acid has four H-bonds with the surrounding **Gp** molecules. It is noteworthy that **HT(B)/FOA** single crystals, prepared from **Gp** solutions of industrial formic acid containing 0.1% acetic acid in fact have the content **HT(B)**/(0.82**FOA** + 0.18**AEA**), where **AEA** is acetic acid. This means that the ability of **Gp** to clathrate with acetic acid is much higher than with its near homolog. Alcohol molecules in **H**-clathrates form three H-bonds with the **Gp** molecules. In **HT(B)/DMS** the number of H-bonds decreases to two, but DMSO moves the **Gp** molecules aside to form O(8)-H... O(8) H-bonds, combining dimers into columns (Fig 15).

Normal ketones and complex ethers, containing more than four carbon atoms in the molecule, and also simple ethers whose molecules contain more than five carbon atoms, form **HC(A)** clathrates (Fig 16). This group has 16 representatives.[33] These complexes are characterised by the absence of the typical centrosymmetric dimers. Two independent H-bonds, O(4)-H... O(8) and O(8)-H... O(4), combine **Gp** molecules into chiral bilayers parallel to the *ac* plane. Guest molecules, having at least one photon acceptor group and containing from five to seven nonhydrogen atoms in the chain, are arranged in the symmetrical cavities (twofold axis). Guest molecules may form H-bonds with the O(1)-H groups of the host molecules, arranging the proton acceptor groups (more often

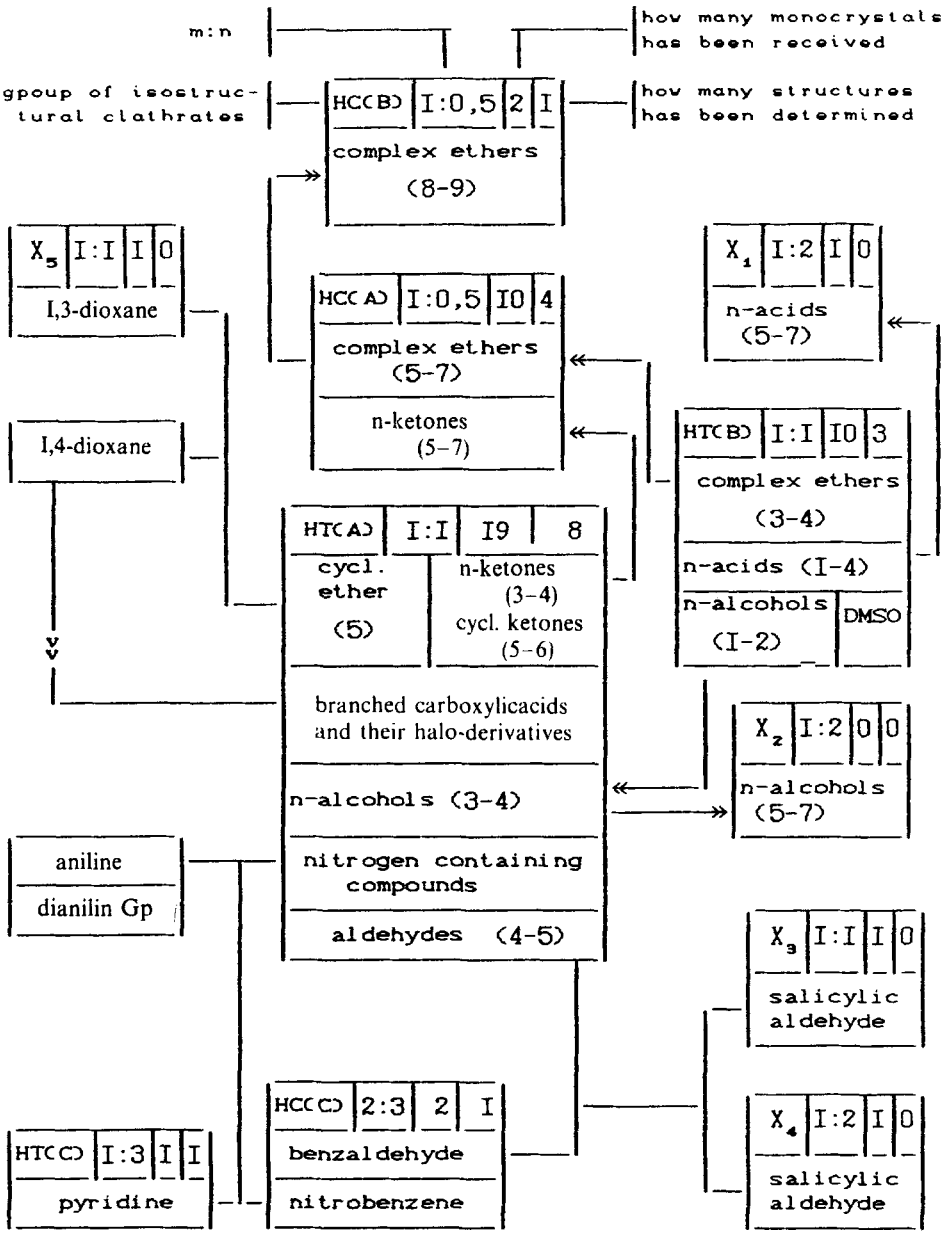

Figure 12 Family of gossypol **H**-clathrates and correlation between its members (figures shows C atoms numbers; in case of the complex ethers O atom included into nonbranched chain is added).

oxygen atoms), in various positions inside the cavity. Most probable is the distribution of proton acceptor group in three positions, marked in Fig 17 with numbers 0, ± 1 abd ± 2. All modes of arrangement and some of their combinations have been realized. Nonsymmetrical molecules are found to be disordered in the symmetrical cavities.

Amyl acrylate and amyl acetate, containing in the chain accordingly eight or nine nonhydrogen atoms, do not form **HC[A]** group clathrates; they lead to the formation of the new **HC(B)** group. The molecules form typical centrosymmetric dimers. The **B** molecules are attached to the dimers by O(1A)-H...O(8B), O(1B)-H...O(8A) and O(8B)-H...O(4A) H-bonds, forming centrosymmetric tetramers, in which **A** and **B** molecules are related by a twofold axis (Fig 18). By O(4A)-H...O(6A) H-bonds tetramers, along the *y* axis are combined into the columns. Two guest molecules, having three H-bonds with **Gp** molecules are arranged in the centrosymmetric cavities (Fig 19). Guest

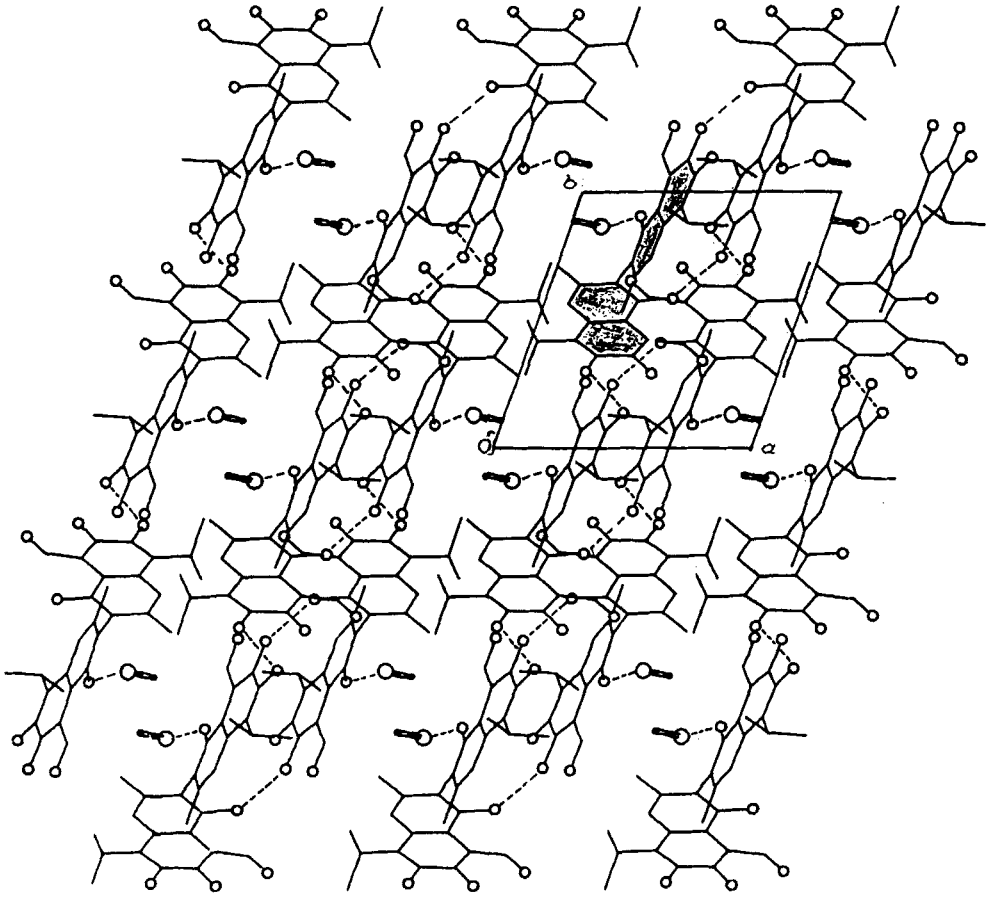

Figure 13 The structure of **HT(A)/ANL**.

molecules are folded so as to fit in the cavity. It is possible that these conformations are not typical for the isolated molecule.

The **HT(C)/PRD** complex is the second example of the absence of the typical centrosymmetric dimers. The **Gp** molecules are surrounded mainly by **PRD** molecules in this complex, moreover each host molecule forms H-bonds with three guest molecules (Fig 20). Among the few **Gp**...**Gp** contacts there is only a weak O(8)-H...O(4) H-bond.

The **HC(C)** group consists of two **H**-clathrates, in addition to **HC(C)/BZD**, the complex with nitrobenzene belongs to it. The only type of **Gp H**-associates present in these crystals are centrosymmetric dimers formed by O(5)-H...O(3) bonds. The dimers have contacts mainly with guest molecules which form H-bonds with **Gp** (Fig 21).

CONCLUSION

Gossypol is a unique substance, giving clathrates with practically all low-molecular organic compounds (for 110 tested substances exceptions were not observed).

Gossypol possesses unusual polymorphism, consisting in the formation of eight crystallographically identified polymorphs, six of which are produced only by decomposition of channel type clathrates.

Single crystals of 80 clathrates and three gossypol polymorphs have been obtained and their crystallographic parameters determined. The X-ray crystal structures of 28 clathrated and two polymorphs have been solved.

The extreme variability of gossypol clathrate structures has been noted. It is observed that clathrates with cavities in the form of isolated cells (cryptates), channels (tubulates), intersecting channels (intercalates), clathrates with a mixed host matrix, and autoclathrates exist. Twenty groups of gossypol isostructural clathrates has been established.

For the crystal forms of gossypol the high extent of spatial isolation of hydrophilic and hydrophobic areas is observed. During clathration, hydrophobic cavities for the inclusion of nonpolar molecules and hydrophilic cavities for the inclusion of molecules capable of forming H-bonds are formed. This leads to the

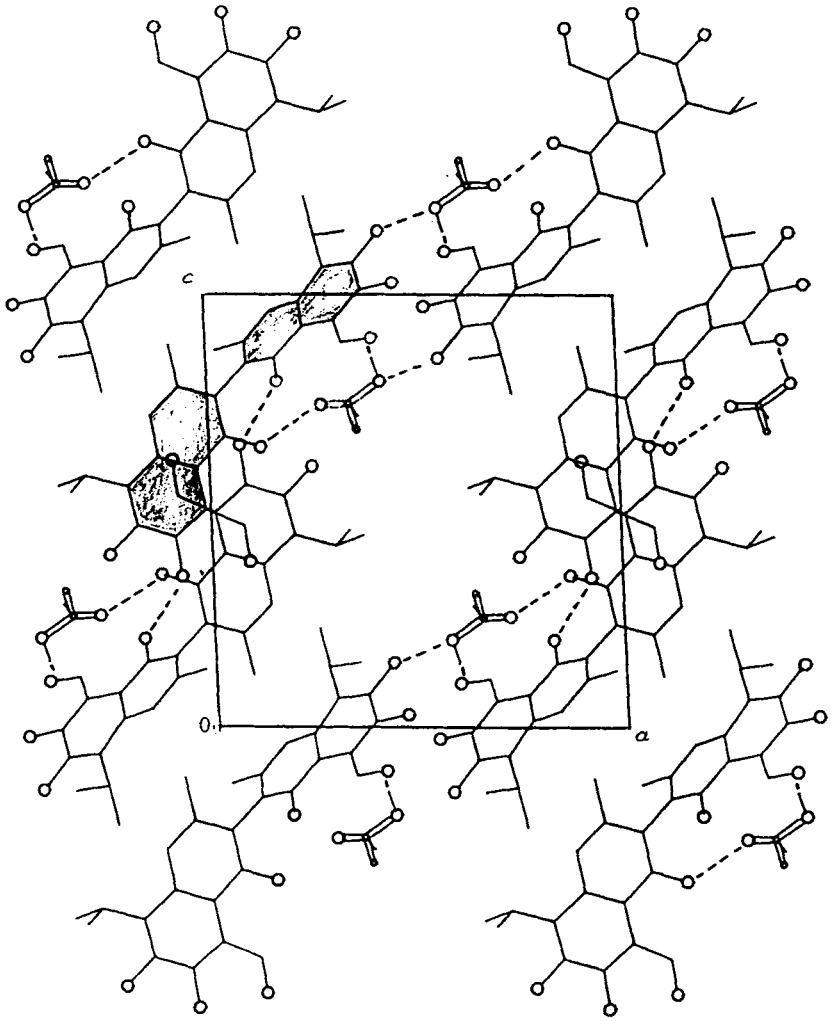

Figure 14 The structure of **HT(B)/FOA**.

availability of structurally variable families of true clathrates and **H**-clathrates. The structure of clathrates of each family depends to a large extent on the size and fom of the guest molecules. Even within of one homologous series of guests, numerous morphotropic transitions take place.

ACKNOWLEDGMENT

We are grateful to professors T.F. Aripov, Z. Kosturjiewicz, A.A. Abduvakhabov for the interest in the work and for their support. This work was also supported by Rockefeller Foundation's Grant RE 90034 Allocation 73.

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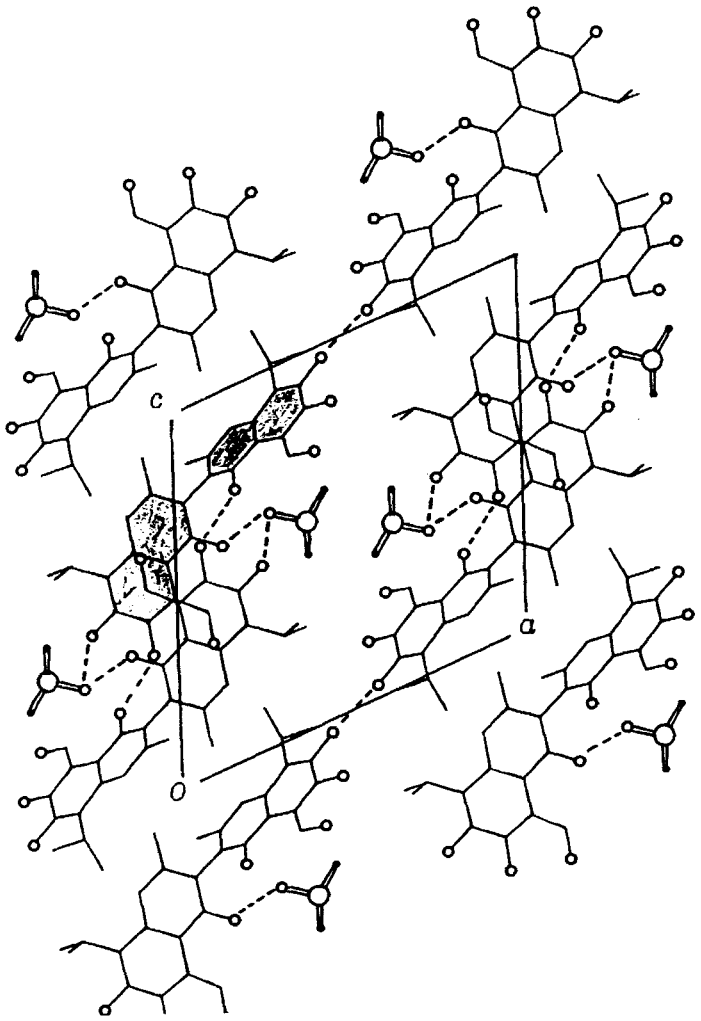

Figure 15 The structure of **HT(B)/DMS**.

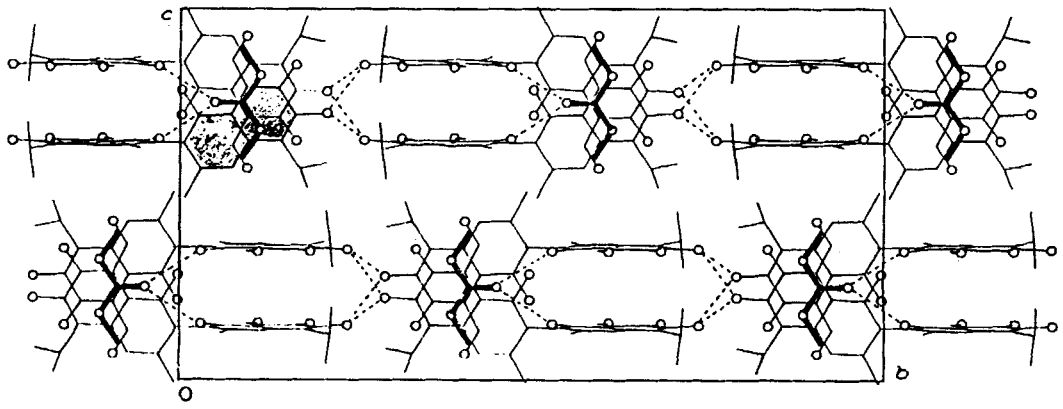

Figure 16 The structure of **HC(A)/EAT**.

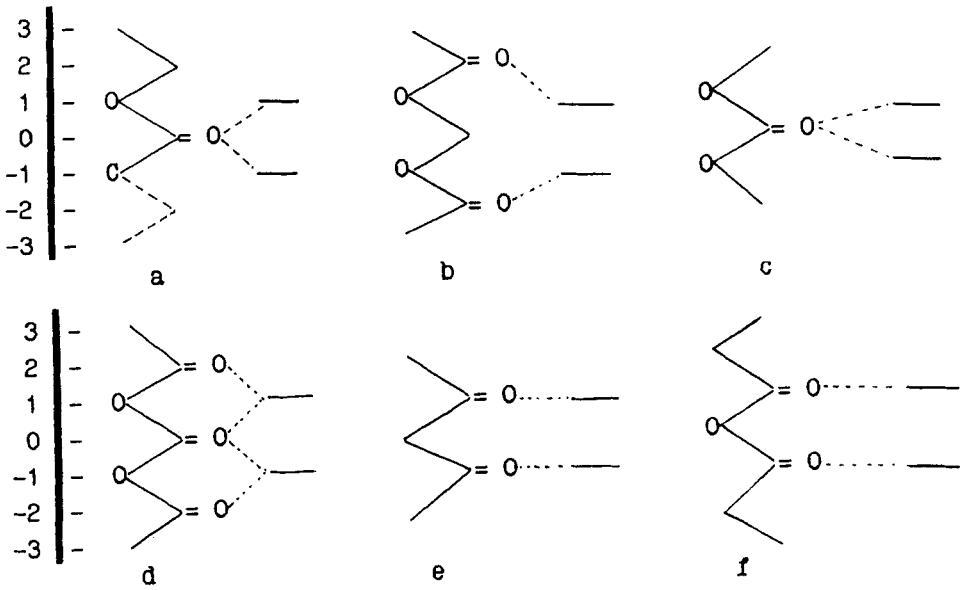

Figure 17 Scheme of gossypol H-bonding in (a) **HK(A)/EAT**, (b) **HK(A)/BAT**, (c) **HK(A)/MPT**, (d) **HK(A)/AAL**, (e) **HK(A)**/acetyl acetone and (f) **HK(A)**/propyl propionate.

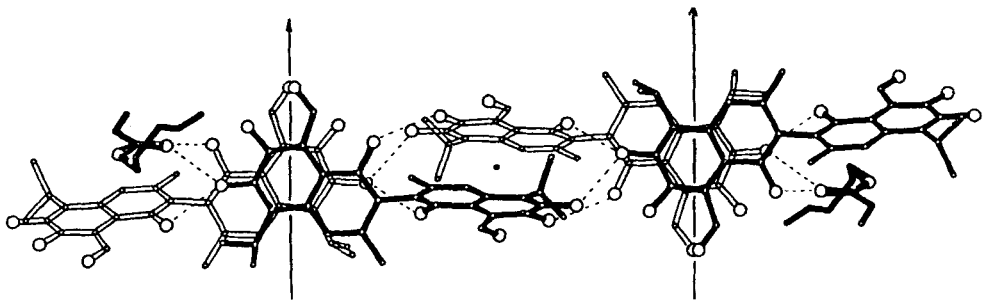

Figure 18 Tetramer structure in **AHK(B)/AAL**.

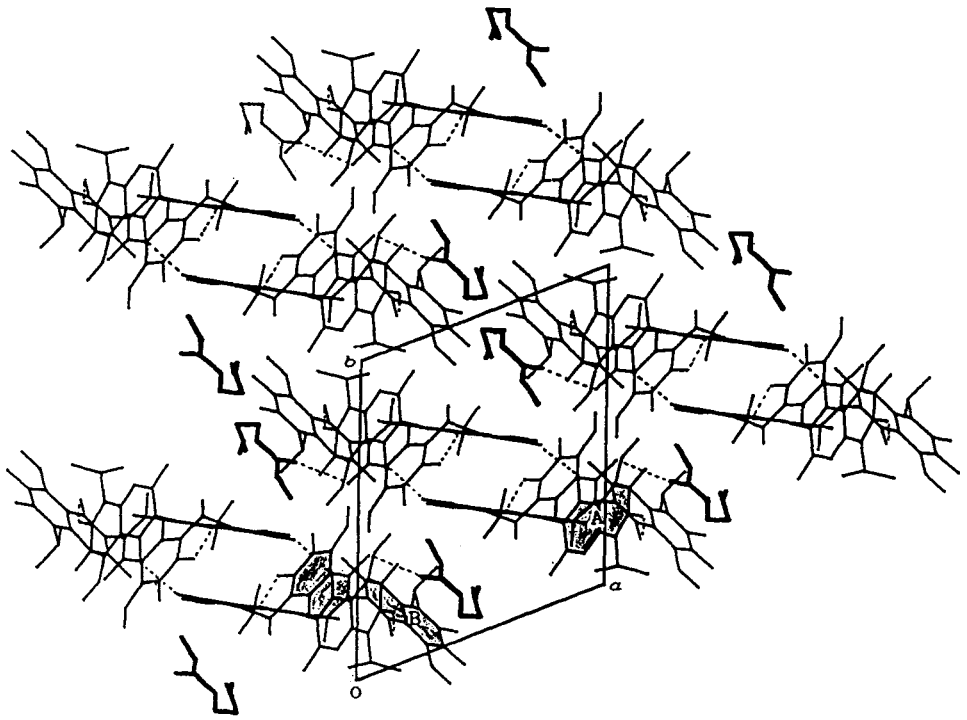

Figure 19 The structure of **HC(B)/AAL**.

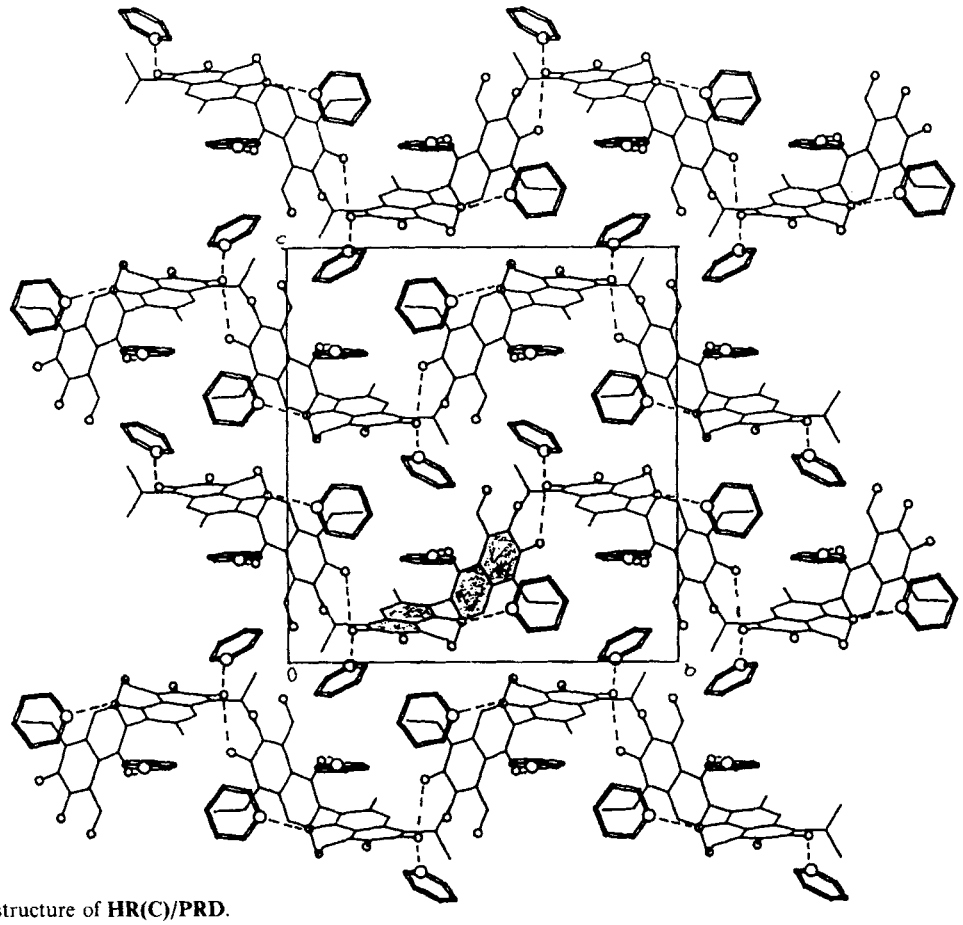

Figure 20 The structure of **HR(C)/PRD**.

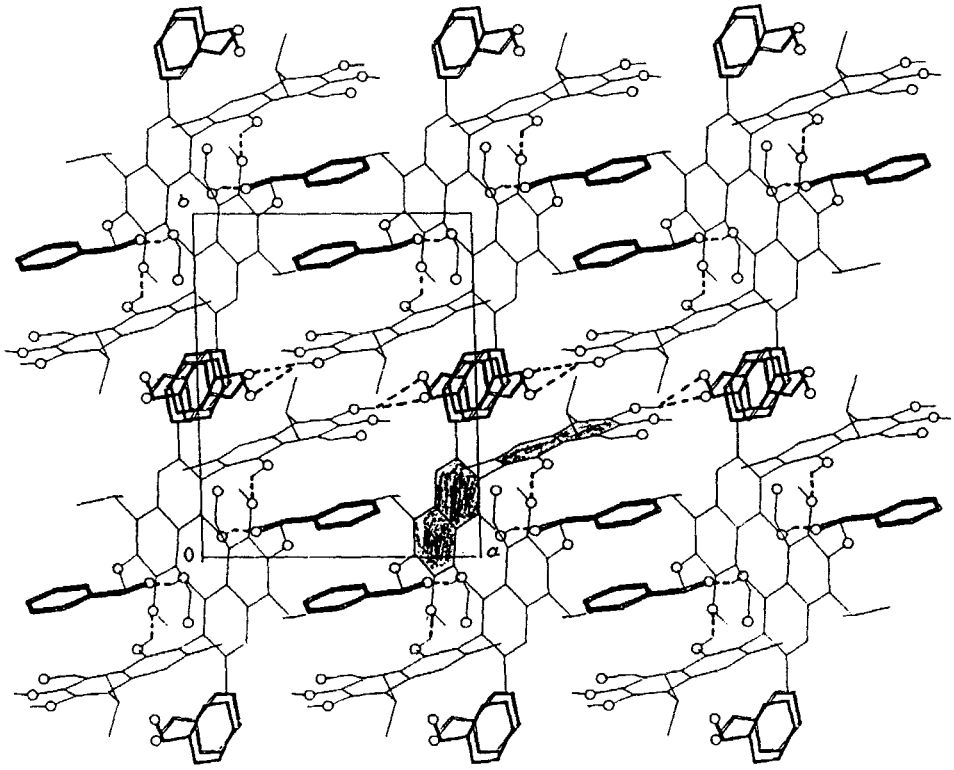

Figure 21 The structure of **HC(C)/BZL**.

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