X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES.

X. UNUSUAL INCLUSION COMPOUNDS BASED ON GOSSYPOL

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More than 100 crystalline molecular complexes of gossypol with various organic molecules have been obtained and identified, and for 67 of them single crystals have been grown and their crystallographic parameters have been determined. On the basis of an interpretation of the structures of 30 complexes by the method of x-ray structural analysis, it has been shown that gossypol exhibits unusual including properties. Thus, in addition to all possible types of inclusion compounds this substance forms five polymorphic modifications, solvates, and a coordinoclathrate. The inclusion compounds of gossypol clearly distinguish polar guest molecules from nonpolar ones.

In preceding communications of this series of papers, the x-ray crystal structures of complexes of gossypol (GP) with a number of organic solvents were considered. As a result of a study of all these new molecular complexes, we have established that the complexes of GP are inclusion compounds (ICs). The phenomenon of the inclusion of neutral molecules in intermolecular cavities formed in crystals of certain compounds is fairly common [1-3] and has been studied intensively in recent years for a number of ICs in connection with the development of the technique of x-ray structural analysis [4]. A substance the crystal lattice of which includes various molecules is called a host, and an included substance, a guest [5]. According to the shape of the including cavity, ICs are divided into cellular (clathrates), channel, and layer types [6, 7]. Classical examples of substances giving ICs of these types are hydroquinone [8], urea [9], and nickel cyanide [10, 11], respectively. The ICs the guest molecules in which are bound in the cavity to the framework by hydrogen bonds are called semiclathrates. As an example of a semiclathrate we can give the IC of hexakis(p-hydroxyphenoxy) benzene with pyridine [12].

We have obtained and identified more than 100 ICs of GP. For 67 of them single crystals have been grown and their crystallographic parameters have been measured. The structures of 30 ICs have been determined by x-ray structural analysis. The available information indicates an unusual nature of the including properties of GP.

This unusualness consists primarily in the fact that in addition to all possible types of ICs, GP forms several polymorphic modifications, crystal solvates, and coordinoclathrates (the last term is taken from a recent publication [13] for those ICs in which several H-bonds of the type of coordination bonds exists between the guest molecules and the host molecules). In addition, GP as host differentiates guest molecules according to the sign of their polarity. In contrast to ordinary ICs such as, for example, clathrates of hydroquinone [8] or Dianin's compounds [7, 14] in the cells of which both polar and nonpolar guest components may be included, GP forms an adduct of a definite type either only with hydrophobic or only with polar molecules. Below we give brief characteristics of the ICs that we have investigated.

I. GP ICs of Layer Type A. In the case of certain hydrophobic guest molecules, infinite bimolecular walls are formed in the crystals as the result of the closure of H-bonds between the host molecules. Then the polar parts of the GP molecules are hidden within the wall and the hydrophobic part form its surface. Cavities are formed between the parallel walls within which the guest molecules are located.

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TABLE 1. Crystallographic Parameters of Some Inclusion Compounds of Gossypol

Type	Guest	a	b	c	α	β	γ	V Å³	Space group	Composition, host: guest
		Å			град					
I	m-Xylene	8,477	14,087	14,411	115,38	75,11	86,60	1475	P$\bar{1}$	2:1
I	Diethyl ether	8,558	14,474	25,651	90	107,22	90	3035	$P2_1/c$	1:1
I	CCl_4	8,847	13,221	14,504	78,05	91,12	71,64	1547	P$\bar{1}$	1:1
II	$CHCl_3$	28,693	9,068	26,262	90	108,66	90	6472	C2/c	1:1
III	Benzene	11,241	14,986	17,380	98,89	80,14	81,69	2800	P$\bar{1}$	2:1
IV	Dichloromethane	21,320	19,129	15,765	90	113,05	90	5916	C2/c	1:1
IV	Toluene	20,615	19,329	16,150	90	90	109,13	6079	C2/c	1:1
V	Diethyl ether	20,721	26,018	27,957	90	90	96,83	14965	B2/b	3:1
VI	Ethyl acetate	11,125	16,469	30,689	90	90	89,69	5623	B2/b	2:1
VI	Isobutyl acetate	11,445	16,522	30,724	90	90	88,17	5806	$P2_1/b$	2:1
VII	Amyl acrylate	14,433	15,547	16,413	81,89	62,10	67,03	2992	P$\bar{1}$	2:1
VIII	Acetone	10,655	11,135	14,859	111,75	75,65	77,72	1493	P$\bar{1}$	1:1
IX	Formic acid	14,249	6,969	14,620	90,07	92,87	99,09	1432	P$\bar{1}$	1:1
IX	n-Valeric acid	14,652	6,947	19,420	96,12	100,95	93,05	1917	P$\bar{1}$	1:2
X	1, 4-Dioxane	25,450	11,923	13,608	90	90	90	4130	P bcn	1:3
XI	Pyridine	10,263	19,171	20,392	90	90	93,97	4003	$P2_1/b$	1:3
XII	—	13,467	8,794	21,376	90	90	97,22	2511	$P2_1/b$	1:0
XII	—	21,208	19,079	15,267	90	113,19	90	5678	C2/c	1:0

The molecules of o-xylene, p-xylene, m-xylene*, p-chlorotoluene, and ethylbenzene* give isostructural layer complexes with GP. The following class of layer ICs is formed by diethyl ether, and two polymorphic modifications of this IC exist: α* – with a ratio of host to guest of 1:1, and β* – with a ratio of 2:1. A third isostructural class is formed in the case of the guest molecules CCl_4* and paraldehyde. It must be mentioned that on passing from one isostructural class to another the shape and size of the cavity between the bimolecular walls change.

II. GP ICs of Layer Type B. Dichloroethane, $CHCl_3$, dibromoethane, diiodomethane, and isovaleric acid give with GP ICs of a different layer type. In this case, the GP molecules form by means of intermolecular H-bonds infinite ribbons which are united by Van der Waals forces into layers.

III. Clathrates. Benzene*, bromobenzene, trichloroethylene, and isopropyl bromide give densely packed clathrates.

IV. ICs of Channel Type A. Dichloromethane* and dibromomethane form ICs of this type which are isostructural with one of the polymorphic modifications of GP. In the case of the IC of toluene with GP, the symmetry of the crystal is different.

V. ICs of Channel Type B. Pentane,† hexane, heptane,† and diethyl ether form ICs of this type. The width of the channel is different and longer molecules cannot locate themselves in it.

VI. Semiclarthrates of the Ester Series of Type A. Ethyl acetate*, butyl acetate*, acetoacetic ester*, methyl propionate*, methyl acrylate, and acetylacetone complex with GP to form isomorphous semiclathrates in which a H-bond exists between the carbonyl oxygen of the ester of ketone molecule and a hydroxy group of the GP molecule. It has been shown that all other esters and ketones the linear part of the hydrocarbon chain of which contains from five to seven nonhydrogen atoms also give ICs with GP in this isostructural class. In the case of esters with branched chains, such as isobutyl acetate, the type of IC is retained but the crystals have a different symmetry (a different class of the given type).

VII. Semiclathrates of the Ester Series of Type B. Esters with lengths of the carbon-oxygen chain greater than seven atoms, such as amyl acrylate* and amyl acetate, give this type of ICs.

VIII. Semiclathrates of the Usual Type. Ketones, cyclic esters, ethers, alcohols, aldehydes, monocarboxylic acid, etc., give this type of semiclathrates. The guest molecule also forms a H-bond with a hydroxy group of the host molecule in the semiclathrates of acetone*, MEK, DMFA, cyclohexanone,* propyl, isopropyl,* butyl, isobutyl, isoamyl, and amyl alcohols, isobutyric and methacrylic* acids, butyraldehyde*, benzaldehyde, crotonaldeyhde, tetrahydrofuran*, ethyl trichloroacetate* and acetonitrile with GP.

IX. Semiclathrates of Monocarboxylic Acids. GP ICs of this type are close to the coordinoclathrates. Formic, acetic,‡ propionic, butyric, and acrylic acids bind the host molecules into a strong framework through the formation of H-bonds between the polar groups of the guest molecules and GP. These ICs are isostructural with the ICs of methanol*, ethanol*, methyl acetate, DMSO*, and methyl formate* with GP. However, the molecules of alcohols with one-proton-donating group and of DMSO, methyl acetate, and methyl formate, each with one proton-accepting group, have only one H-bond with the GP molecules in each case.

Consequently, in spite of the isomorphousness of these these ICs and the ICs of carboxylic acids, they are, semiclathrates rather than coordinoclathrates. Valeric acid gives a nonisostructural semiclathrate.

X. Coordinoclathrates. The IC of 1,4-dioxane* with GP is a coordinoclathrate in which the host:guest ratio is 1:3. Two dioxane molecules cross-link GP molecules with the aid of H-bonds into a dioxane-gossypol framework in the cavities of which guest molecules are also located.

*An asterisk denotes those guest molecules the ICs of which with GP have been deciphered by the method of x-ray structural analysis.

†A dagger denotes GP ICs for which no single crystals have yet been obtained.
‡The crystal structure of the GP IC with acetic acid has been deciphered by Chinese authors [15].

XI. Solvates. Pyridine* forms a solvate with GP having a GP:pyridine ratio of 1:3. It is possible that salicylaldehyde also forms a crystal solvate with GP.

XII. Polymorphic Modifications. Only one polymorphic modification (α*) crystallizes directly from solutions. The polymorphs β*, γ, δ†, and ε† are formed in the desolvation of certain ICs.

In addition to the ICs mentioned with crystallographic parameters that have already been measured, as stated above, GP forms another series of ICs among which must be mentioned, the complexes of GP with solid substances — naphthalene†. Table 1 gives the crystallographic characteristics of one typical representative of such an isostructural class of GP ICs.

At the present time, the determination of the structures of hitherto undeciphered GP ICs is continuing and publications are being prepared on the structures of ICs of the types considered above.

SUMMARY

More than 100 crystalline molecular complexes of glossypol have been obtained and identified, and for 67 of the single crystals have been grown and their crystallographic parameters have been determined. On the basis of the decipherment of the structures of 30 crystalline complexes by the method of x-ray structural analysis it has been shown that gossypol exhibits unusual inclusion properties.

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