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Inclusion Complexes of the Natural Product Gossypol. The Formation of Different Gossypol Polymorphs on Decomposition of Channel Type Inclusion Complexes

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Abstract. The existence of seven gossypol polymorphs has been established. Two of them are obtained by direct crystallization from solution. The remaining five polymorphs are the products of desolvation of channel type complexes (tubulates). Each isostructural group of the complexes on decomposition gives one polymorph. Gossypol thus possesses specific peculiarities in terms of the decomposition of its tubulates, and also the absence of thermotropic polymorphic transitions.

Key words: Gossypol, clathrate, polymorph, desolvation.

1. Introduction

As long ago as 1937, after recrystallization of gossypol from diethyl ether, chloroform and ligroin, Adams obtained samples with melting points of 184, 199, and 214°C, respectively [1, 2]. He suggested that these samples were various polymorphic modifications of gossypol. However, our studies have shown that only the sample with the melting point of 214°C is a nonsolvated compound [3], while the samples with melting points of 184° and 199°C are complexes with diethyl ether [4, 5] and chloroform [6], respectively.

Subsequent studies showed that besides its unique clathrate-forming properties [7] gossypol possesses unusual polymorphism.

2. Experimental

Monocrystals of the **P1** polymorph were obtained from a solution of gossypol in diethyl ether (60 mg/mL) prepared at 28–30°C. An equal volume of hexane at the same temperature was added. The solution was kept in a thermostat at 28–30°C. Monocrystals were formed during a 12-h period. The **P2** polymorph crystals were formed by adding an equal volume of hexane to a more dilute ether solution of gossypol (20 mg/mL) at a temperature of 23–25°C.

In order to obtain the **P3** polymorph crystals of the gossypol complex with CH_2Cl_2 were first grown from solution in dichloromethane (15 mg/mL) at 23–25°C. Separation of the monocrystals of the complex from the solution led to immediate decomposition with formation of **P3** polymorph monocrystals. The remaining **P4–P7** polymorphs were obtained as follows.

The **P4** polymorph was formed as a result of drying the gossypol complex with ethanol in vacuum (10^{-1} Torr) at a temperature of 23–25°C for 3 h. The **P5** polymorph was obtained by desolvating the gossypol complex with diethyl ether *in vacuo* (10^{-1} Torr) at 25-27°C for 3 h and then at 10^{-2} Torr at 60°C for 20 h. The **P6** polymorph was obtained by drying the gossypol complex with acetone *in vacuo* (10^{-2} Torr) at 60°C for 20 h. The **P7** polymorph was formed from the gossypol complex with pyridine by drying *in vacuo* (10^{-2} Torr) at 50°C for 20 h.

The phase purity of specimens was checked by their NMR spectra recorded on an XL-200 spectrometer. The XRD traces were recorded on a DRON-UM-1 diffractometer, CuK_α radiation, Ni filter, 1 degree/min scan speed. Crystallographic parameters were determined on a 'Syntex-$P2_1$' diffractometer. The decomposition temperatures of the complexes were determined using a Kofler thermomicroscope [8].

3. Results and Discussion

Of the seven gossypol polymorphs obtained by us only the **P1** and **P2** polymorphs are crystallised from solution. The **P1** polymorphic modification was obtained from gossypol solutions in ligroine and from mixtures of butylacetate+hexane and diethyl ether+hexane. The **P2** polymorph was produced by crystallization only from the latter solution. Diffractograms of the polymorphs are shown in Figure 1. Crystallographic characteristics of the **P2** polymorph are: $a = 42.032(9)$, $b = 15.980(4)$, $c = 32.785(5)$ Å, $\beta = 110.30(2)°$, $V = 20653$ Å^3, Sp.gr. C2/c, $\rho = 1.33$ g/cm^3, $Z = 32$. Crystal data for polymorphs **P1** and **P3** were given earlier in [3] and [9], respectively.

Slow removal of the guest molecules from the channel type gossypol clathrates gives a range of new gossypol polymorphs. The **P3** polymorph is formed as a result of decomposition of the dichloromethane and dibromomethane complexes at room temperature. The **P4** polymorph can be obtained from the decomposition of gossypol complexes with methylformate, methylacetate, methanol, ethanol and formic acid [10]. Gossypol complexes with methylformate and formic acid are desolvated at room temperature, but decomposition of the methylacetate and ethanol solvates requires temperatures of 50 and 40°C respectively. The **P5** polymorph is formed by a two stage desolvation of the gossypol 1 : 1 complex with diethyl ether. Heating at room temperature removes exactly half of the guest molecules transforming the initial monosolvate to the semisolvate. Only further heating to 140° removes all the remaining guest molecules [5]. The acetone tubulate of gossypol decomposes near to 145°C. On vacuum drying of the acetone complex of gossypol the **P6** polymorph

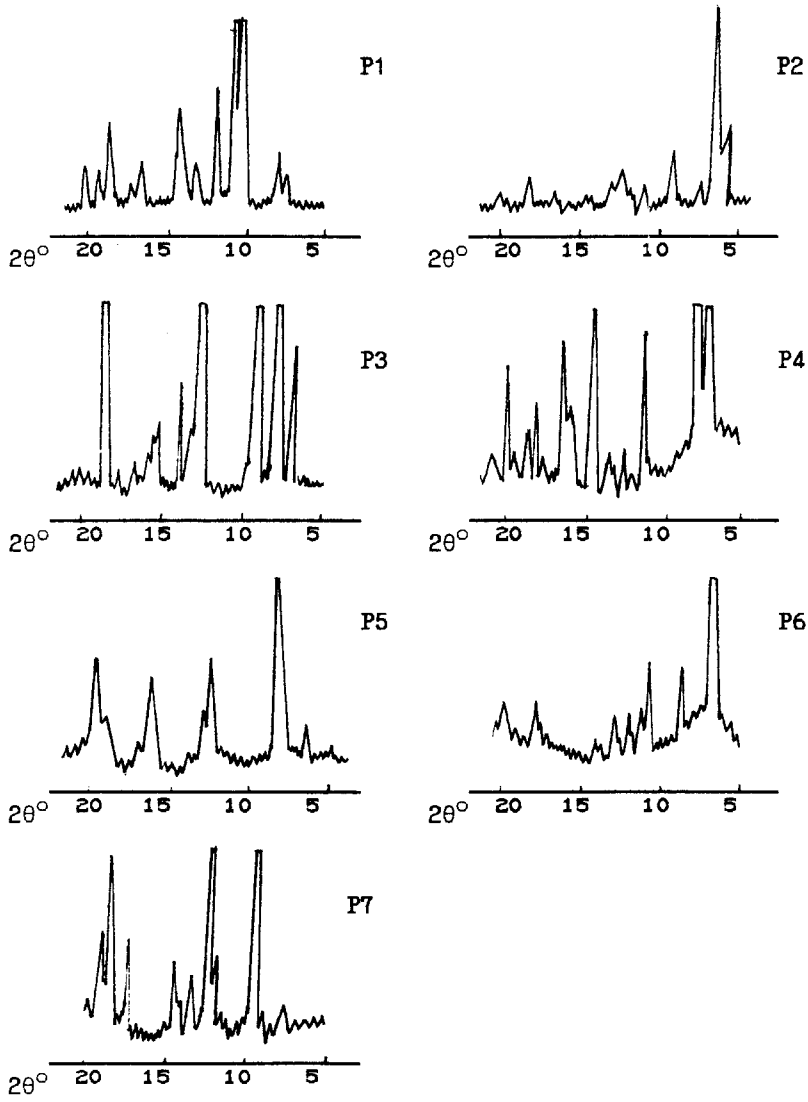

Fig. 1. Powder diffractograms of the gossypol polymorphs (DRON-UM-1 diffractometer, CuK_α radiation, Ni filter, 1 degree/min scan speed).

is produced [11]. The complex of gossypol with pyridine is stable up to 112°C. So the final **P7** polymorph is a product of desolvation of gossypol tripyridine *in vacuo* [12].

Of these seven gossypol polymorphic modifications, the structures of only **P1** [3] and **P3** [9] have been determined crystallographically. It was impossible to

carry out a complete determination of the structure of the other polymorphs (apart from **P2**) because of the absence of monocrystals.

Organic substances often form 2–3 but seldom 4–5 polymorphic modifications. Gossypol is therefore very unusual in forming such a large number of polymorphs. Decomposition of different crystallosolvates of a given chemical compound usually gives rise to one and the same nonsolvated modification (gomomolecular crystal), which is thermodynamically stable under the given conditions. Furthermore the various modifications of a nonsolvated compound are usually transformed into each other by changing the conditions.

In this respect gossypol behaves in a different way: on decomposition of its complexes, belonging to a definite group of isostructural channel type clathrates, the polymorph specific for this group is formed, and on increasing the temperature such polymorphs are *not* transformed into each other. Such unusual gossypol behaviour shows that in its crystal forms packings with similar energy are achieved, among which there is no one preferred form. This is probably explained by the fact that the gossypol molecule contains a considerable number of functional groups – donors and acceptors of proton, the spatial dispositions of which are fixed. As a rule simultaneous participation of all these groups in the system of H-bonds is impossible because of steric reasons, which are combined with the need for creation of high optimal packing. In gossypol polymorphs whose structures have been solved only some of the functional groups take part in intermolecular H-bonds.

Thus, gossypol possesses specific peculiarities as to the decomposition of its complexes and the absence of thermotropic polymorphic transitions. We may use the variability of the clathrates and the unique gossypol behaviour on desolvation for producing modifications, possessing various physicochemical and therefore biopharmaceutic properties, that is very valuable for medical preparations.

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