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Sorption of Ammonia, Methylamine and Methanol by the $P3$ Polymorph of Gossypol. Synthesis of Unsymmetrical Monoamine Derivatives of Gossypol by a Solid-state Reaction

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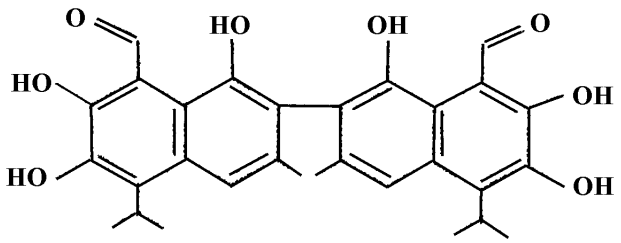
Abstract. The $P3$ polymorph of gossypol has wide, empty channels and strongly absorbs linear amines. One of the two gossypol aldehyde groups is located near the channel wall. This situation allows reaction of the amines with half of a gossypol molecule, yielding unsymmetric monoaminoderivatives of gossypol in high yield and by a simple, solid-state method.

Key words: Gossypol host-guest complex, sorption, monoaminoderivatives of gossypol.

1. Introduction

Gossypol (Scheme I) is a versatile host molecule which forms inclusion complexes with all (over 100) guest substances that have been tested to date [1–7]. It is also characterized by a unique polymorphism [8]. Two polymorphs were obtained directly by crystallization from solution, while five other structures resulted from decomposition (guest desorption) of channel type clathrates. Of the latter polymorph structures, the most interesting one is denoted $P3$. It forms as a result of decomposition of the gossypol host-guest complex with dichloromethane or dibromomethane and contains rather large open channels [9]. One of the two gossypol aldehyde groups is located close to the channel wall. This situation was the basis for a prediction that it might be used for the synthesis of unsymmetrical Schiff's base-type gossypol monoderivatives using a solid-state reaction. In order to check this prediction we first studied the sorption of ammonia, methylamine and methanol into the $P3$ polymorph, and then the possibility of a solid state reaction being carried out in the matrix of this organic host.



Gossypol

Scheme I.

2. Experimental

Gossypol produced by the Institute of Bioorganic Chemistry of the Uzbekistan Academy of Sciences was recrystallized from dichloromethane solution by slow evaporation of the solvent at ambient temperature. A powder of the $P3$ polymorph of gossypol with enclathrated dichloromethane was obtained [8]. In order to remove the absorbed guest molecules the product was evacuated at 50°C. Isotherms were studied by using the experimental apparatus and procedure described in Ref. [10] with a Mettler AE-100 balance and an external reservoir of guest vapours. The temperature in the apparatus was maintained with an accuracy of ± 0.2°C, pressure was measured by a Hg manometer with an accuracy of ± 0.5 torr. Errors in the determination of x (the number of guest molecules per single host molecule) were less than ± 0.1 for small x and less than ± 0.05 for maximum x. For measurement of sorption curves 100 mg samples of the $P3$ polymorph were used.

In order to synthesise the monoaminoderivatives of gossypol 100 mg of the crystalline polymorph was inserted into an evacuated vessel and methylamine or ammonia atmosphere with a pressure of about 50 torr was used at room temperature. The temperature was raised to 50°C in the case of methylamine and 60°C in the case of ammonia, and maintained for 2 h.

Thin-layer chromatography of the solid-state reaction product was performed using a 4 : 1 benzene : ethylacetate solvent system and silyphol plates. Preparative separation of the components of the reaction mixture was performed on a chromatographic column filled with silicagel of type silner 100/160. A 9 : 1 benzene : ethylacetate mixture was used as eluent. XRD traces were recorded on a DRON-UM-1 diffractometer with Ni-filtered CuK_α radiation and 1 degree/min scan speed. The melting temperatures were determined using a Koffler thermomicroscope. NMR spectra of 5% solutions in acetone-d_6 were recorded on a 'XL-100' spectrometer (Varian, USA) using TMS as internal standard. Mass-spectra were recorded on a MX-1310 mass spectrometer (USSR). In this equipment a direct entry system was used at the temperature of the ionization chamber (170°C), an ionization voltage

of 70 eV, an ionization current of 30 μA and the temperature of the evaporating ampule was 120–130°C.

3. Results and Discussion

Sorption equilibria in the systems $P3$ gossypol polymorph-gaseous ammonia, methylamine and methanol were studied in the 5–30°C temperature interval (Figure 1). According to Ref. [9] the channels present in this polymorph have about 5.5 Å diameter, and their diameter increases with increasing guest uptake. The increase of the unit cell volume may reach 9.4%, which allows accommodation of a CH_2Br_2, guest molecule up to a 1 : 1 host : guest ratio [9]. According to Ref. [12], the volumes of the CH_2Br_2, ammonia, methylamine and methanol molecules are about 69, 22, 45 and 37 Å^3, respectively. The sorption isotherms indicate that only the methylamine molecule fills the available channels space as effectively as the CH_2Br_2 molecule. Sorption of ammonia molecules continues to a 1 : 2 host to guest ratio, and the total volume of sorbed guest is significantly lower in this case. Sorption of methanol molecules does not achieve saturation at methanol vapour pressures close to the vapour pressures over liquid methanol at a corresponding temperature. The enthalpies of guest sorption were estimated from equilibrium guest pressure – temperature dependence and actual experimental errors were taken into account. It was found that the enthalpy of ammonia and methylamine sorption are in the range 90–180 kJ/mol. The enthalpy of methanol sorption was found to fall in the 10–60 kJ/mol range. Comparison of the crystal structure (Figure 2) and sorption equilibrium data allowed us to interpret the sorption of the molecules under consideration in the following way. Specific host-guest interactions (hydrogen bonding between the aldehyde group of gossypol and the amino group of the guest) is the factor which determines the high enthalpy of sorption of the ammonia and methylamine molecules.

The sorption isotherm of ammonia reaches a plateau when all the aldehyde groups are bonded. Sorption of methylamine (and, most probably, other amines) is controlled by the filling of the channel space by the guest molecules, but host-guest hydrogen bonding takes place in this case. In the case of less polar guest molecules (such as methanol), host-guest hydrogen bonding does not play a significant role.

The product of the solid state reaction between the $P3$ polymorph and ammonia melts at 241–242°C, while the melting point of the pure $P3$ polymorph is 182–184°C. The XRD of the product is nearly identical with the XRD of the initial polymorph (Figure 3). NMR spectra reveal the existence of both aldehyde and Schiff base groups in the solid state reaction product, but this does not permit an estimation to be made of the quantities of gossypol, the mono- and diamino derivatives (Scheme IIa) in a mixture because the NMR signal is independently recorded from each half of gossypol or the gossypol derivative molecule. An attempt to separate the components of the mixture using column chromatography

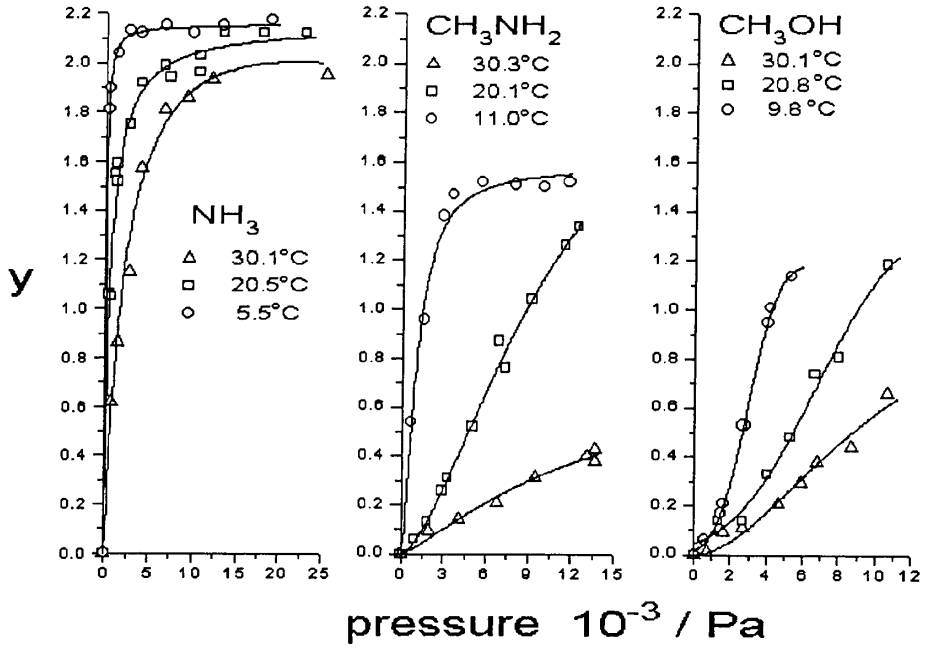


Figure 1. Sorption isotherms of ammonia, methylamine and methanol on the *P*3 polymorph of gossypol at different temperatures. The equilibrium pressure of the guest vapours is shown on the horizontal axis. The composition of the equilibrium inclusion compound (y = number of guest molecules per single host molecule) is shown on the vertical axis.

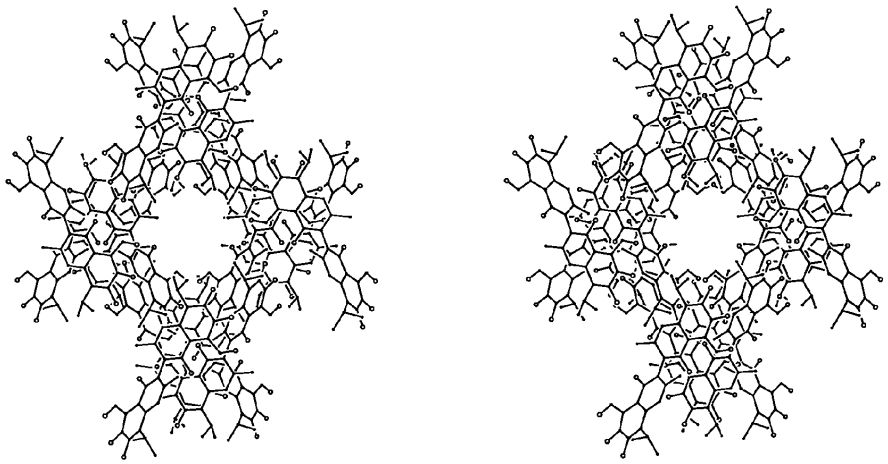


Figure 2. Stereoview of the channel in the *P*3 polymorph.

failed. The NH_2 group of aminogossypol probably reacts with the free aldehyde group to form dimers, trimers etc., with Al_2O_3 acting as catalyst.

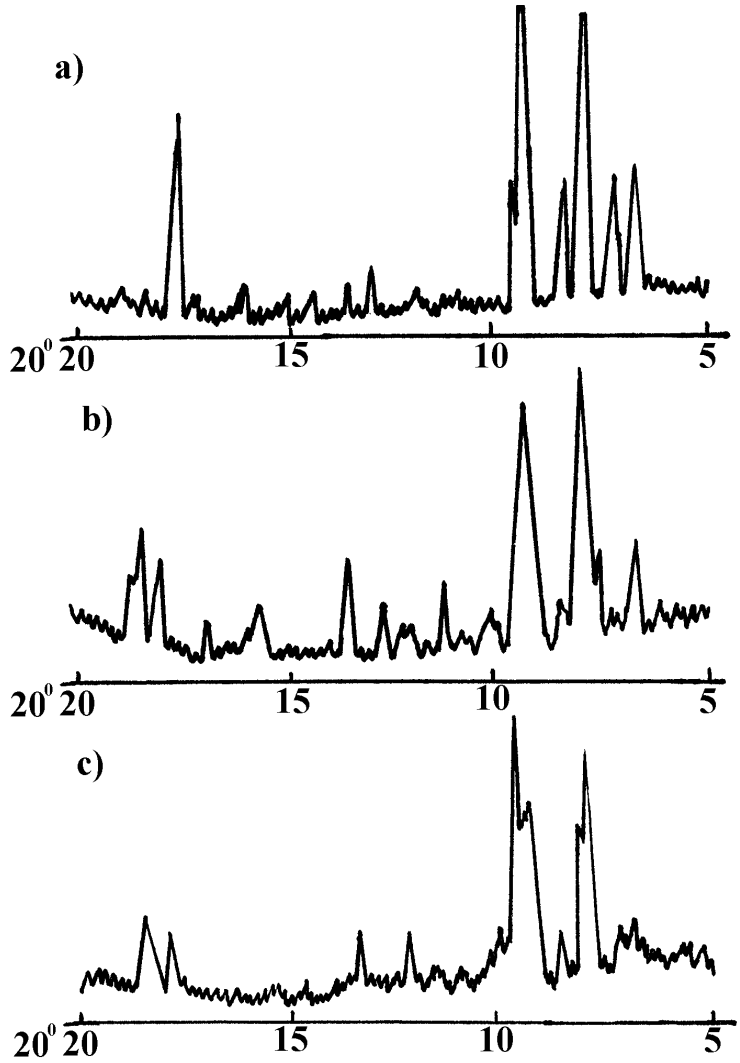
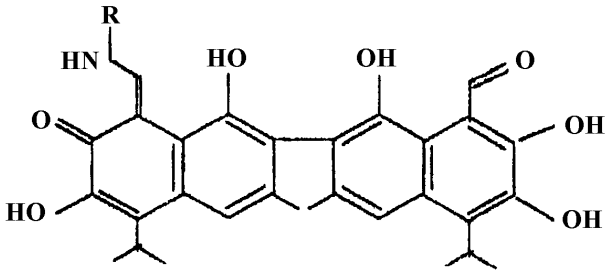


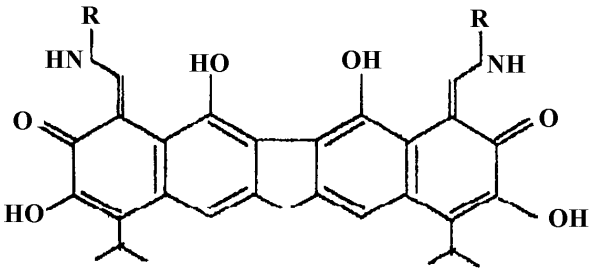
Figure 3. Powder diffractograms of the gossypol $P3$ polymorph (a); the monoamino derivative of gossypol (b); and monomethylaminogossypol (c) obtained by the solid state reaction with gossypol in $P3$ polymorph form. (CuK_α radiation, Ni filter, 1 deg/min scan speed).

For this reason we decided to use methylamine instead of ammonia. The melting point of the solid-state reaction product is 278–280°C in this case. The XRD of the product is slightly different from the diffractogram of the $P3$ polymorph (Figure 3). NMR spectra reveal that the reaction product contains molecules with gossypol and methylaminogossypol (Scheme IIb). Thin-layer chromatography of the solid-state reaction product was carried out. In addition to the minute amounts of unreacted gossypol, the monomethylaminoderivative (R_f = 0.77) and dimethylaminogossy-



Monoaminoderivative of gossypol

a) R = H
b) R = CH_3



Diaminoderivative of gossypol

Scheme II.

pol (R_f = 0.50) were detected. Comparision of the spot sizes has shown that the main compound is monomethylaminogossypol. Separation of monomethylaminogossypol from the reaction mixture was performed on a chromatographic column with a yield of about 80%. The identity of the gossypol and dimethylaminogossypol components was proved by comparison of their R_f values with those of the pure compounds under similar conditions. The identity of the monomethylaminogossypol was confirmed by mass and NMR spectra of the individual products.

The mass spectrum of dimethylaminogossypol (Scheme II) consists of peaks at: 544(M^+), 527($M-OH)^+$, 513($M-NH_2CH_3)^+$, 498($M-NH_2CH_2CH_3)^+$, 496($M-NH_2$ $CH_2OH)^+$, 482($M-2NH_2CH_3)^+$; and the monoderivative is represented by peaks at: 531(M^+), 514($M-OH)^+$, 513($M-H_2O$, 500($M-NH_2CH_3)^+$, 482($M-NH_2CH_2H_2O)^+$.

Thus an unsymmetric monoaminoderivative of gossypol has been obtained in a simple manner and large yield by a condensation reaction of gossypol with linear amines in the solid state. The unsymmetric monoderivatives obtained may be used for preparing other gossypol derivatives, for example, unsymmetric diaminoderivatives.

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