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X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES. XXVIII. SEPARATION OF THE DILACTOL TAUTOMERIC FORM OF GOSSYPOL HEXAMETHYL ETHER INTO INDIVIDUAL STEREOISOMERS AND EVALUATION OF THEIR CLATHRATE-FORMING CAPACITY

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All three possible stereoisomers of gossypol hexamethyl ether in the dilactol tautomeric form have been separated with the aid of fractional crystallization and have been identified crystallographically. These stereoisomers have been subjected to x-ray stuctural investigation, and their configurations and clathrate-forming properties have been determined.

Many questions of the structure of gossypol hexamethyl ether — the product of the complete methylation of gossypol — have remained unanswered up to the present time. Various, sometimes contradictory, results relating to its melting point, color, and solubility have been reported [1-5]. Sources of these discrepancies may be tautomerism and atropo- and diastereoisomerism caused by the appearance of an asymmetric carbon atom in the lactol form and also the possibility of the existence of gossypol hexamethyl ether in several crystalline modifications (polymorphism and clathrate formation).

Theoretically, gossypol hexamethyl ether can exist in lactol, aldehyde, and quinoid forms. Numerous studies of the tautomerism of gossypol hexamethyl ether have shown the existence of only the first two forms [5-8, 9]. At the same time, since the two halves of the molecule may differ, the realization is permissible of three tautomeric states of this ether: dialdehyde, aldehydo-lactol, and dilactol. In the lactol form, the asymmetric carbon atom may assume one of two conformations: R and S. Thus, six different states of the gossypol hexamethyl ether molecule are possible, and if atroposteroisomerism (r or s) is taken into account the number of possible states is doubled.

Sadykov et al. [9], by changing the reaction conditions, separated the dialdehyde, aldehydo-lactol, and dilactol forms of gossypol hexamethyl ether, while Seshadri and Sharma [5] have reported the isolation of the dilactol tautomeric form. However, these authors did not succeed in separating their samples into individual stereoisomers.

Our aim was to study the clathrate-forming capacity of gossypol when all its polar groups are eliminated. With such a modification of gossypol, its hexamethyl ether is produced in just the dilactol tautomeric form. Consequently, to achieve the aim set it was necessary to solve a subsidiary problem — to obtain the dilactol form of gossypol hexamethyl ether as individual stereoisomers and to identify them by determining their configurations.

The dilactol form of gossypol hexamethyl ether was obtained by the method of Morris and Adams [10] in the shape of three fractions. From solutions of the first fraction in alcohol it was possible to grow single crystals of two varieties: first, prismatic crystals formed (stereoisomer A, Table 1) and then crystals of acicular form (A+ethanol, Table 2). Likewise, single crystals of two habituses precipitated successively from alcoholic solutions of the second fraction of gossy-

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TABLE 1. Crystallographic Characteristics of Gossypol Hexamethyl Ether in the Dilactol Tautomeric Form

Parameters	Stereoisomers			Polymorphs	
	A	B	C	D	E
a(Å)	15.581(3)	9.708(2)	21.175(5)	10.293(4)	16.261(6)
b(Å)	20.815(4)	10.113(2)	10.570(2)	11.941(3)	9.623(3)
c(Å)	10.364(2)	16.813(4)	15.070(2)	14.672(4)	20.817(8)
α(deg.)	90	81.82(2)	90	92.74(2)	90
β(deg.)	96.98(2)	104.87(2)	92.80(1)	90.00(3)	94.41(3)
γ(deg.)	90	92.34(2)	90	115.51(2)	90
V(Å^3)	3364	1579	3355	1625	3248
Sp. gr.	$P2_1/c$	$P\bar{1}$	$C2/c$	$P\bar{1}$	$P2_1/c$
Z	4	2	4	2	4
ρ(g/cm^3)	1.20	1.26	1.20	1.23	1.23

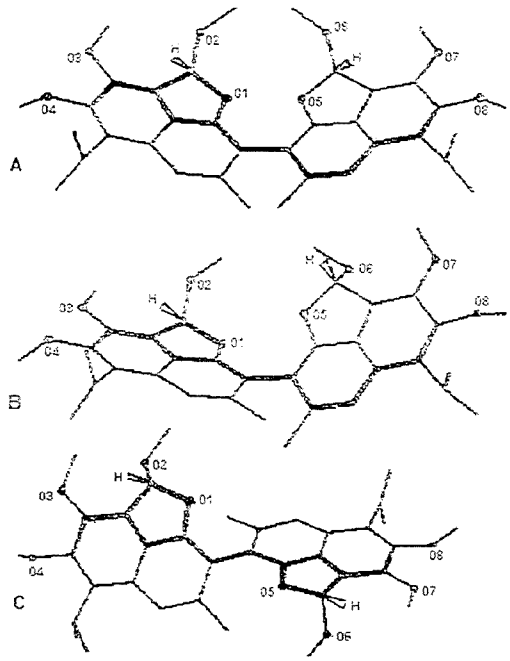

Fig. 1. Molecules of the stereoisomers of gossypol hexamethyl ether in the dilactol tautomeric form:
A) RsR (SrS); B) RsS (SrR); C) RrR (SsS).

pol hexamethyl ether: acicular crystals (stereoisomer B) and a few crystals of prismatic form (stereoisomer C). An alcoholic solution of the third fraction deposited mainly type C crystals together with a small amount of type B crystals (see Table 1). NMR investigations showed that the crystals of types A, B, and C contained no molecules of the solvent.

The crystals differed greatly in habitus, and, where necessary, it was possible to pick them out visually and accumulate them. It must be mentioned that the separation of a mixture in this way is carried out fairly rarely.

To determine the configuration of the gossypol hexamethyl ether molecule, a complete x-ray structural analysis of these three types of crystals was performed. The configuration of the asymmetric carbon atom was readily determined on the basis of the usual rules employed in stereochemistry [11]. To determine the configurations of the atropoisomeric molecules of gossypol hexamethyl ether, we used the following rule. We considered a projection of the molecule along the bond linking the naphthyl nuclei from the direction of the (C1-C10) half. If the minimal rotation of the O atom of the lactol ring conjugated with the C1-C10 nucleus in the direction of the same atom in the C11-C20 nucleus takes place clockwise, the atropostereoisomerism corresponds to the r- configuration, and if this rotation takes place anticlockwise the configuration is s-. The configurations of the molecules of gossypol and its other derivatives can be found analogously.

TABLE 2. Crystallographic Characteristics of Clathrates of Stereoisomer A (gossypol hexamethyl ether)

Parameters	Group G*						
	I		II				
	Ethanol	Acetone	Methyl acetate	Benzene	1,4-Dioxane	Diethyl ether	*p*-Xylene
a(Å)	7.964(5)	8.082(7)	8.231(2)	8.871(5)	8.819(2)	8.141(4)	8.955(2)
b(Å)	19.94(2)	20.14(2)	13.832(2)	13.347(9)	13.427(3)	15.338(4)	15.772(3)
c(Å)	22.67(1)	22.47(1)	16.832(3)	17.11(1)	17.354(5)	15.332(4)	15.680(3)
α (deg.)	90	90	95.92(2)	99.88(6)	92.11(3)	95.36(2)	111.91(1)
β (deg.)	90	90	100.20(2)	103.15(5)	106.50(3)	100.86(3)	104.29(2)
γ (deg.)	90	90	79.13(1)	74.49(5)	73.26(2)	79.12(3)	87.22(1)
V(Å^3)	3600	3657	1793	1887	1871	1830	1967
Sp. gr.	Pbcn	Pbcn	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
ρ(g/cm^3)	1.29	1.30	1.26	1.19	1.24	1.23	1.24

On the basis of this rule, the molecules in stereoisomers A, B, and C were identified as RsR (or SrS), RsS (or SrR), and RrR (or (SsS)), respectively (Fig. 1). Consequently, the crystals of these stereoisomers are the racemates RsR+SrS, RsS+SrR, and RrR+SsS.

When the third fraction of gossypol hexamethyl ether was crystallized from solutions in ethanol at temperatures above 26-28°C, crystals with tabular (D) and acicular (E) habitus deposited (see Table 1). They were most probably polymorphs of some one or more of the stereoisomers described above, since the structures of crystals D and E have not been deciphered and the configuration of the gossypol hexamethyl ether molecule in these phases remains unknown.

Stereoisomers B and C prefer to crystallize from ethanolic and acetone solutions in nonsolvated form, while stereoisomer A likes to include the majority of the guest molecules tested, with the formation of two groups of isostructural clathrates (see Table 2). It must be mentioned that the group II clathrates are given by both polar (methyl acetate) and hydrophobic guest molecules. In this respect, gossypol hexamethyl ether behaves differently from gossypol itself.

Thus, when all the polar groups are eliminated, the clathrate-forming capacity of gossypol deteriorates greatly. While the hydrophobic substance so obtained does form clathrates, in these clathrates the host no longer distinguishes the guest molecule by their chemical nature (polarity).

EXPERIMENTAL

Gossypol hexamethyl ether in the dilactol form, obtained by alkylation with dimethyl sulfate [10], was used for separation into stereoisomers. Separation was achieved by column chromatography on silica gel Sil'ner 100/160. The starting material was dissolved in benzene. The concentrated solution formed was deposited on the column and eluted with benzene. The three fractions obtained were concentrated, and each, separately, was redeposited on a column of silica gel. Elution was conducted with benzene, and three fractions of equal volume were collected.

Crystallization was carried out from saturated solutions at room temperature by slow evaporation. Crystallographic parameter were determined on a Syntex-$P2_1$ diffractomter, and the NMR study was conducted on an XL-200 spectrometer (Varian, USA) at a working frequency of 200 MHz.

REFERENCES

1. R. C. Morris and R. Adams, J. Am. Chem. Soc., **59**, 1731 (1937).
2. R. T. O'Connor, P. Van der Haar, E. F. Dupre, and L. E. Brown, J. Am. Chem. Soc., **76**, 2368 (1954).
3. K. S. Murty and T. R. Seshadri, Proc. Indian Acad. Sci., **16A**, 146 (1942).
4. S. C. Datta, V. V. Murty, and T. R. Seshadri, Indian J. Chem., **10**, 691 (1972).
5. T. R. Seshadri and N. N. Sharma, Indian J. Chem., **13**, 865 (1975).
6. N. I. Baram, A. I. Ismailov, V. B. Leont'ev, F. G. Kamaev, and A. S. Sadykov, Dokl. Akad. Nauk SSSR, **195**, No. 5, 1097 (1970).
7. N. I. Baram, A. I. Ismailov, V. B. Leont'ev, and F. G. Kamaev, in: The Chemistry of Plant Substances [in Russian], Fan UzSSR, Tashkent (1972), p. 66.
8. N. I. Baram, A. I. Ismailov, and A. S. Sadykov, Zh. Obshch. Khim., **2**, 230 (1972).
9. F. G. Kamaev, N. I. Baram, A. I. Ismailov, V. B. Leont'ev, and A. S. Sadykov, Izv. Akad. Nauk SSSR, Ser. Khim., 1003 (1979).
10. R. C. Morris and R. Adams, J. Am. Chem. Soc., **59**, 1731 (1937).
11. V. M. Potapov, Stereochemistry [in Russian], Khimiya, Moscow (1976).