Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl19

Molecular Recognition and Chemical Reactions in Lattice Inclusion Complexes of the Natural Product Gossypol

Bakhtijor Ibragimov [a] & Samat Talipov [a]
[a] Institute of Bioorganic Chemistry, H. Abdullaev Str,83, Tashkent, 700143, Uzbekistan

Version of record first published: 04 Oct 2006.

To cite this article: Bakhtijor Ibragimov & Samat Talipov (1996): Molecular Recognition and Chemical Reactions in Lattice Inclusion Complexes of the Natural Product Gossypol, Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals, 276:1-2, 305-314

To link to this article: http://dx.doi.org/10.1080/10587259608039391

Mol. Cryst. Liq. Cryst., 1996, Vol. 276, pp. 305–314
Reprints available directly from the publisher
Photocopying permitted by license only

MOLECULAR RECOGNITION AND CHEMICAL REACTIONS IN LATTICE INCLUSION COMPLEXES OF THE NATURAL PRODUCT GOSSYPOL

BAKHTIJOR IBRAGIMOV AND SAMAT TALIPOV
Institute of Bioorganic Chemistry, H.Abdullaev Str,83,
Tashkent,700143, Uzbekistan

Abstract. Two level recognition by gossypol of the organic substances during complexation is discussed. Reactions in lattice inclusion compounds of gossypol are considered.

INTRODUCTION.

Gossypol is a natural product containing in cotton seeds. It has been called so in order to designate its origin (Gossypium plants) and chemical nature (poliphenolic substance).

Gossypol show a wide spectrum of the biological activity. Most important ones are: antiviral[1,2], antitumor[3−6], antimalarial[7,8], antiparasitic [9,10] and anti−HIV[11,12]. Gossypol has attracted the world wide attention when in 1978 chinese scientists found that it is highly effective as oral male contraceptive[13].

Gossypol has optical activity due to restricted rotation around aryl−aryl bond. Bioactivities of gossypol is highly enantiospecific and reside in the (−)−isomer [4−6,14,15]. But gossypol syntezied by cotton is racemic. That is why complicated resolving procedures were used for obtaining

enantiomers from racemic substance[16-18].

INCLUSION BEHAVIOR OF GOSSYPOL.

Cotton is the main agricultural plant of Uzbekistan and therefore for many years extensive comprehensive studies of gossypol have been carried out at our republic. It is produced in the Experimental Plant of Institute of Bioorganic Chemistry from by-products of the cotton seed industry. During an elaboration of the more effective isolation procedures it has been established that physico-chemical parameters of the final product change significantly with small changes of crystallization conditions. Further investigations of this behavior lead to the discovery of the inclusion properties for this natural product: racemic gossypol forms inclusion compounds with every solvent used for crystallization[19].

Gossypol is an extremely versatile host. Over 100 inclusion compounds of gossypol have been obtained and identified. Nearly 80 of them formed single crystals of quality sufficient for crystal data determination. The structure of 32 host-guest complexes is solved by X-ray method[20].

FIRST LEVEL RECOGNITION OF GOSSYPOL.

During the formation of gossypol host-guest complexes it is occurred two level recognition by gossypol. First level takes place in the connection with the chemical nature of the including component. Gossypol divides into two large family of all complexing molecules. Substances molecules of which have polar groups for H- bonding are related to the first family. Other family substances have no polar groups in their molecules, in other words, they are hydrophobic ones. During crystallization from unpolar solvents there was formed such host matrix which has voids with completely hydrophobic walls. In the case of

polar molecules host matrix is characterized with partly hydrophilic voids or on the surface, limiting the void, at least one polar group lies. Guest molecules included to such voids H−bonded to gossypol molecules through these groups.

Hence during crystallization process it is prepared hydrophobic or hidrophilic voids within gossypol lattice depending on the polarity of the guest component, i.e. gossypol lattice is easily rearranged to accommodate in it polar or unpolar guests. Therefore crystals of host−guest complexes of gossypol with polar and unpolar guests are never isostructural. This phenomenon can be used for the separation of hydrophobic substances from hidrophilic ones.

For instance, only small amount of acetic acid added to diethyl ether solution of gossypol is sufficient to obtain pure complex of gossypol only with acetic acid though gossypol easily forms inclusion compounds with ether.

Host−guest complexes having between components only van−der−Vaals interactions we call ordinary clathrates and H−clathrates when H−bond is observed between host and guest.

SECOND LEVEL RECOGNITION OF GOSSYPOL.

Second level recognition by gossypol is occurred within each family of gossypol clathrates. In this step gossypol distinguishes molecules by their geometry (size and form). This recognition will be demonstrated on the example of one family of two, namely on the example of ordinary clathrates.

In Figure 1 the morphotrophic transition for complexes of gossypol with chlorine derivatives of methane and methyl derivatives of benzene are represented. Here clathrates of gossypol with xylenes and CCl_4 central place take. Complexes of gossypol with xylenes and CCl_4 are isostructural[21,22].

In these crystals host molecules by means of H−bonds are associated

to bilayers. All polar groups are hidden inside bilayers and hydrophobic parts of gossypol molecules lie on the bilayer surface. The surface of the bilayers are not smooth, it has peaks and valleys. Voids are formed between bilayers related by translation along c axis. The shape and size of the void can be adjusted to the spatial requirements of the guest by mutual shifts of the host layers with only minor changes occurring within the

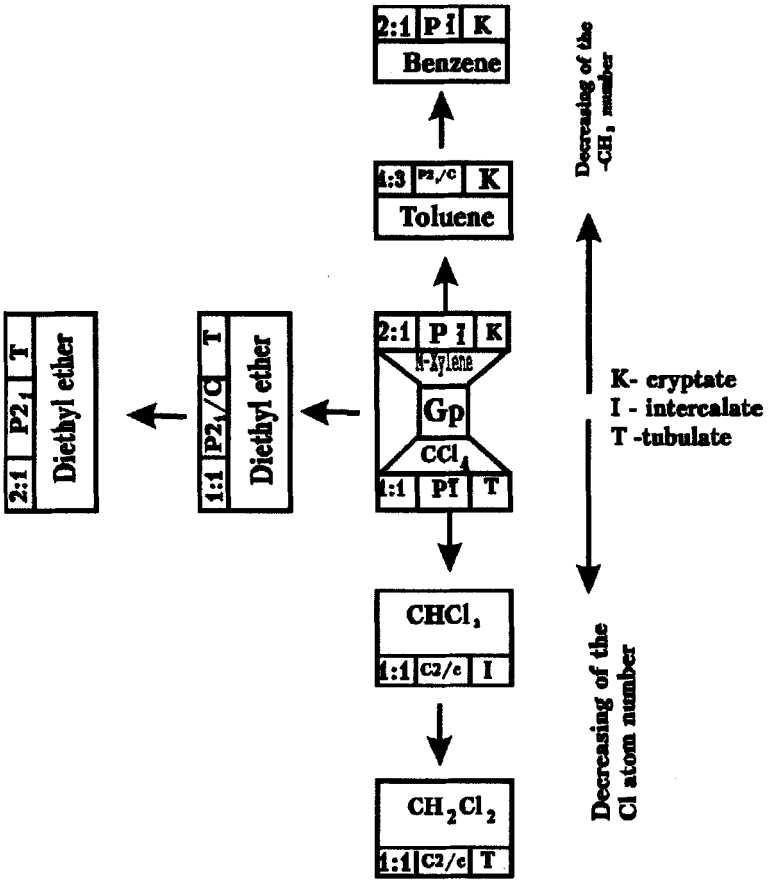


FIGURE 1 Recognition by Gp -CH derivatives of benzene and Cl derivatives of methane

layer. In such fully hydrophobic and centrosymmetrical voids two molecules of CCl_4 or one molecule of $m-$xylene are located (fig.2). As molecule of $m-$xylene unsymmetrical it is disordered and occupied two

positions in the void.

Another type of the void is observed when two nearest bilayers are related by an 2_1 axis[23] (fig.3a). The host aggregates are constructed in such a way that one surface of the bilayer is lined with the host enantiomeric molecules R while the other with S. Therefore the guest molecules are surrounded either by R or S host molecules when accommodated in a void that is formed between two twofold axis related bilayers. Diethyl ether molecules are located in channels running along c axis. This

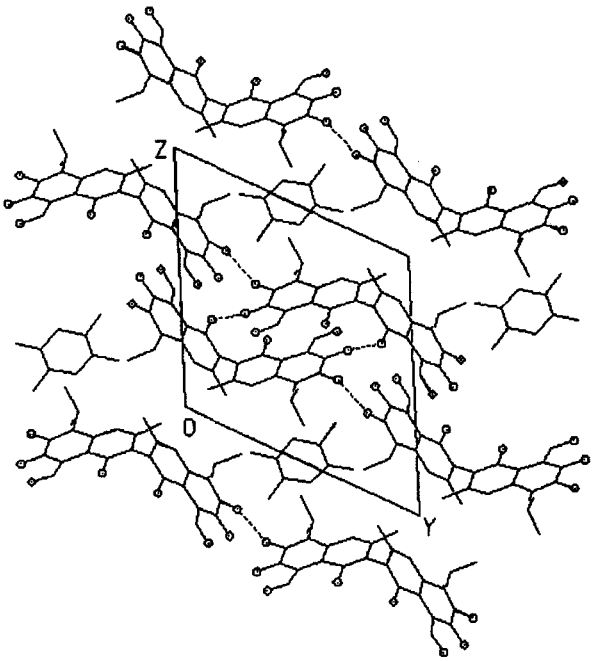


FIGURE 2 The structure of the gossypol complex with *m*−xylene

compound is unstable under ambient conditions and starts to decompose when removed from the mother solution. However, single crystals are not destroyed and decomposition process stops when a new channel type inclusion compound with host−guest ratio 2:1 is formed (fig.3b). On this transformation the unit cell parameter c is reduced by 10% and the centrosymmetric space group of the original crystal is changed to the chiral space group $P2_1$. The guest molecules had left every other interlayer space. The diethyl ether molecules located in the channels lined, say,

gossypol (R)−isomers start to leave the crystal first. As similar process in channels of the opposite chirality is somehow inhibited an enantiomorphous crystal with guest molecules placed exclusively in channels surrounded by (S)−gossypol is formed. We consider that this is the special type of the recognition of host molecules by their chirality during desolvation process. In the case of the racemic mixture of optically active guest molecules, in principle, the recognition is occured for guest molecules and it is possible to separate racemates.

If to reduce the number of CH_3 − groups of *m*−xylene two one, gossypol can't keep resulted molecules (toluene) inside the same cavity and the morphotrophic transition to other clathrate type with stochiometry 4:3 is occurred[24] (fig.4). In further reducing of the CH_3 − group number two one (benzene) a new morphotrophic transition to so called benzene group is occurred[25] (fig.5).

When we deal with the chloroderivatives of methane the similar morphotrophic transitions are occurred after each changing of the Cl atoms number. So in the case of chloroform space group P1 of CCl_4 complex changes to monoclinic C2/c and intercalate type inclusion compound is formed[25]. In it layers of the host molecules alternate with chloroform molecules layers (fig.6). Here guest molecules are disordered in 4 position.

In the case of CH_2Cl_2 gossypol gives the channel type clathrate unstable at ambient conditions [26,27]. As a crystal of the complex does not collapse during the desorption process it is possible to have two

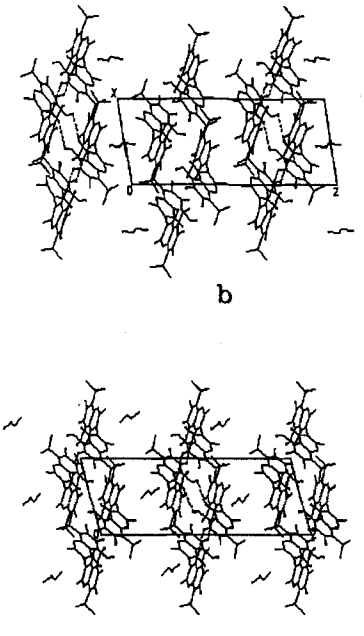


FIGURE 3 The structure of 1:1 (a) and 2:1 (b) gossypol complex with diethyl ether

experiments and hence two structures from the same crystal: one before desolvation for the complex (fig.7a) and the other after decomposition for the unsolvated form (fig.7b). In result of desolvation the unit cell volume is decreased by 4% only and enough wide channels are retained. This type

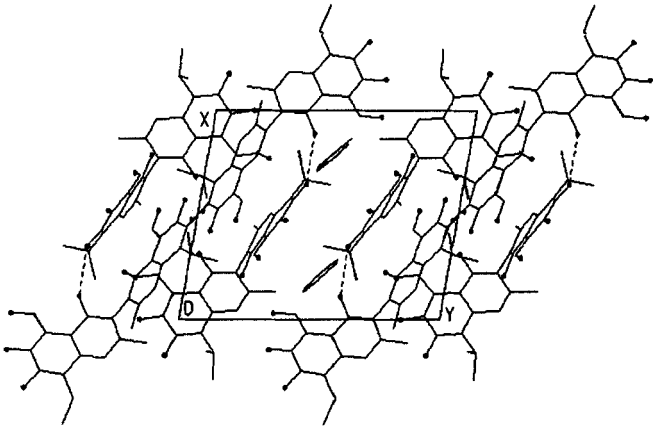


FIGURE 4 The structure of the gossypol complex with toluene

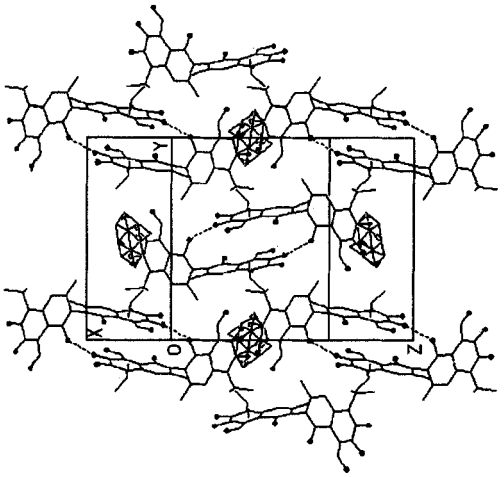


FIGURE 5 The structure of the gossypol complex with benzene

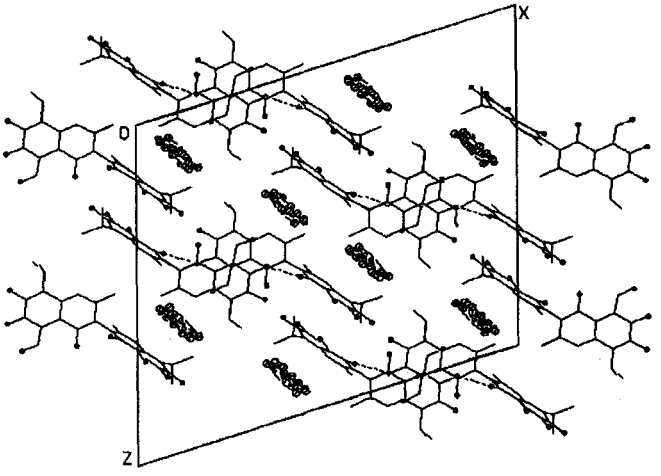
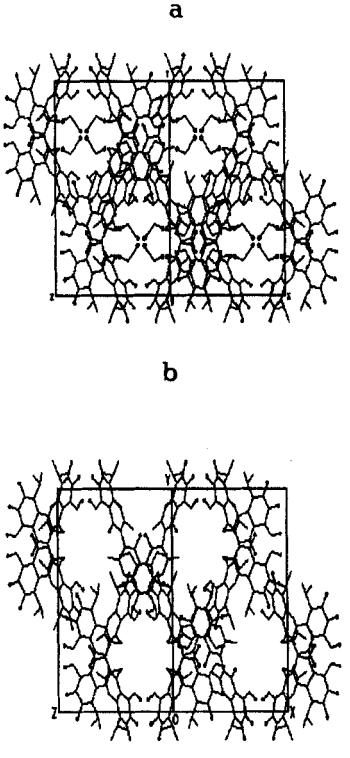


FIGURE 6 The structure of the gossypol complex with chloraform

FIGURE 7 The structure of the gossypol complex with CH_2Cl_2 (a) and unsolvated form (b)



of gossypol clathrate behave like organic zeolites. The channels are not empty, they contain atmospheric gases freely moving along them. The analysis of the host matrix showed that on the channel walls aldehyde group of the one half of gossypol molecule is located while other such group is hidden inside crystal.

This situation predicts us existing of a good possibility to obtain unsymmetrical Shiff base type derivatives of gossypol using solid state reaction. Indeed, when

we used linear amines such as methyl, ethyl or prophyl amines we were able to syntezise highly pure monoderivatives with high yield. This is important for obtaining a new type biologically active unsymmetrical gossypol derivatives.

REFERENCES

1. S.A.Vichkanova and L.V.Goryunova, Antibiotiki, 13,828(1968), (Chem.Abstr., 1968, 69, 94802n).
2. K.Wichmann, A.Vaheri and T.Luukkainen, Am.J.Ostet. Gynecol., 142,593(1982).
3. E.M.Vermel, Acta Unio Intern. Contra Cancrum, ,20,211(1964).
4. V.Band, A.P.Hoffer, H.Bands, A.E.Rhinehardt, R.C.Knapp,S.A.Matlin and D.J.Anderson, Gynecol.Oncol., , 32, 273(1989).
5. Y.−W.Wu, C.L.Chik and R.A.Knazek, Cancer Res., , 49, 3754(1989).
6. N.Tanphaichitr, L.M.Fitzgerald and S.A.Matlin, J.Androl.,, 9, 270(1988).
7. J.E.Heidrich, L.A.Hunsacker and D.L.Vander Jagt, IRCS, Med.Sci., 11, 304(1983).
8. D.L.Vander Jagt, B.R.Baack, N.M.Campos, L.A.Hunsacker and R.E.Royer, IRCS, Med.Sci., 12, 845(1984).
9. E.E.Montamat, C.Burgos, N.M.Geres de Burgos, L.E.Rovai, A.Blanco and E.L.Sugera, Science, 218, 288(1982).
10. J.E.Eid, H.Ueno, C.C.Wang and J.E.Donelson, Exp. parasitol., 66, 140(1988).
11. T.−S.Lin, R.Schinazi, B.P.Griffith, E.M.August, B.F.H.Eriksson, D.−K. Zheng, L.Huang and W.H.Prusoff, Antimicrob. Agents Chemother., 33, 2149(1989).
12. B.Polsky, S.J.Segal, P.A.Baron, J.W.H.Gold and H.Ueno, Contraception, 39, 579(1989).
13. National Coordinating Group on Male Antifertility Agents, Chin. Med.J., 91, 417(1978).
14. Y.E.Wang,Y.D.Luo and X.C.Tang,Acta Pharmaceutica Sinica,14,662(1979.

15. .A.Matlin, R.H.Zhou, G.Bialy, R.P.Blye, R.H.Naqvi and M.C.Lindberg, Contraception, 31, 141(1985).

16. L.Huang, D.−K.Zheng and Y.−K.Si, J.Ethnopharmacol., 20,13(1987).

17. S.A.Matlin and R.H.Zhou, J.High Resolution Chromatogr. and Chromatographic Commun., 7, 629(1984).

18. S.A.Matlin, R.H.Zhou, A.Belenguer, R.G.Tyson and A.N.Brookes, J.High Resolution Chromatogr. and Chromatographic Commun., 10, 86(1987).

19. B.T.Ibragimov, S.A.Talipov, B.N.Dadabaev, G.B.Nazarov and T.F.Aripov, Khim. Prir.Soedin., 675(1988) (Chem.Absr.,1989, 111, 58080c).

20. B.T.Ibragimov, S.A.Talipov and P.M.Zorky, Supramol. Chem., 3, 147(1994).

21. B.T.Ibragimov, S.A.Talipov, G.B.Nazarov, R.G.Mardanov, T.F.Aripov, A.I.Ismailov and A.S.Sadykov, Khim. Prir. Soedin., 113(1986) (Chem. Abstr., 1986, 105, 227069).

22. B.T.Ibragimov, S.A.Talipov, T.F.Aripov and A.S.Sadykov, J.Inclusion Phenom. Mol. Recognit. Chem., 8, 323(1990).

23. S.A.Talipov, B.T.Ibragimov, G.N.Tishchenko, T.F.Aripov, G.B.Nasarov, B.V.Strokopytov and K.M.Polyakov, Kristallografija, 33, 384(1988), (Chem.Abstr., 1988, 109, 170100).

24. M.Gdaniec, Polish J.Chem., 68, 733(1994).

25. M.Gdaniec, B.T.Ibragimov and S.A.Talipov, J.Inclusion Phenom. Mol. Recognit. Chem., 9, 231(1990).

26. S.A.Talipov, B.T.Ibragimov, G.B.Nazarov, T.F.Aripov and A.S.Sadykov, Khim. Prir.Soedin., 835(1985) (Chem.Abstr., 1986, 104, 139743d).

27. B.T.Ibragimov, S.A.Talipov and T.F.Aripov, J.Inclusion Phenom. Mol.Recognit. Chem., 17, 317(1994).