Crystal Structure of the Product of a Condensation Reaction of (±)-Gossypol with (R)-(+)-1-Phenylethylamine. Why Do Diastereoisomeric Diaminogossypols Cocrystallize?

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Abstract. The crystal structure of a compound obtained in a condensation reaction of (±)-gossypol with (R)-(+)-phenylethylamine has been determined by X-ray structure analysis. The crystals of $C_{46}H_{48}O_6N_2 \cdot (C_4H_8O_2)_2$ are monoclinic, space group $P2_1$, $a = 21.243(3)$, $b = 8.666(1)$, $c = 28.651(4)$ Å, $\beta = 108.24(1)°$, $V = 5009(3)$ Å^3, $Z = 4$, $D_x = 1.195\,\mathrm{g\,cm}^{-3}$, $\mu(\mathrm{Cu}\,K_\alpha)=0.66\,\mathrm{mm}^{-1}$, $T = 292$ K. The structure has been solved by direct methods and refined to the final R value of 0.091 for 4290 observed reflections and 1049 parameters. There are two diastereoisomeric molecules of the host and four solvent molecules in the asymmetric unit. The host molecules are H-bonded into chains with diastereoisomeric molecules alternating along the chain. The fact that the host prefers the association mode in which molecules with a different configuration of the 2,2′-binaphthyl moiety are H-bonded explains why separation of diastereoisomeric diaminogossypols by fractional crystallization has been unsuccessful. The 1,4-dioxane molecules are accommodated in infinite channels but only every second guest molecule in a channel is H-bonded to the host.

**Key words:** Gossypol, inclusion compounds, crystal structure.

1. Introduction

Gossypol (**I**, scheme) is a well known polyphenolic natural product found mainly in cottonseed kernels. The optical activity of gossypol is due to the axial dissymmetry of the molecule (atropoisomerism). Gossypol is usually isolated from the cotton plant in a racemic form as a 1 : 1 complex with acetic acid. Only racemic gossypol is able to form the complex. The optically active (+)-isomer was first isolated from the plant *Thespesia populnea* [1, 2]. Recent studies have shown that gossypol from the cotton plant is not necessarily racemic and some enantiomeric excess of either (+)- or (−)-isomer has been found in different *Gossypium* species [3–5]. Gossypol shows a broad spectrum of biological activity. Its male antifertility [6, 7], antitumor [8–10] and anti-HIV-1 [11] activity is highly enantiospecific and resides in the (−)-isomer. Gossypol is stable to racemization under conditions relevant to biological
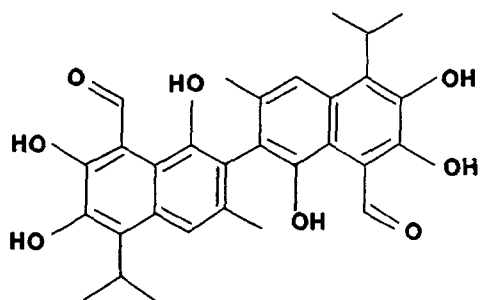
(I)
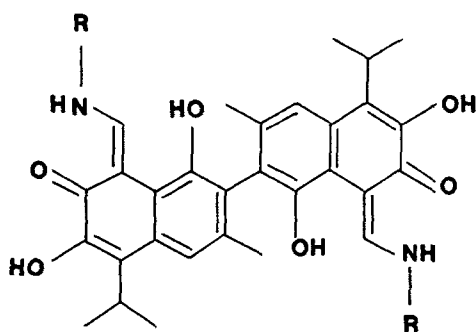
(II)   R=C_6H_5

(III)   R=$CHCH_3 C_6H_5$

studies (ambient temperature, neutral pH) [12]. From the circular dichroism data the absolute configuration of the (–)-gossypol was inferred to be R [13].

So far no natural source of pure (–)-gossypol has been found and therefore this isomer has to be prepared by resolution of the racemic mixture. However, racemic gossypol has remained surprisingly resistant to attempts to resolve it by classical chemical methods which used preparations of diastereoisomeric salts with optically active alkaloids such as morphine, quinine and cinchonine or preparation of diastereoisomeric enamine-type derivatives in a condensation reaction with optically active amines such as 1-phenylethylamine, 1-methylphenylethylamine, 1-naphthylethylamine and 2-amino-1-propanol [3, 14]. Attempts to separate those diastereoisomers by fractional crystallization using a variety of solvents have been unsuccessful and always lead to crystals which gave two equal-sized spots on TLC [14] indicating diastereoisomeric cocrystallization.

Currently, large scale resolution of racemic gossypol into its enantiomers is best achieved by chromatographic separation of enamine-type diastereoisomeric derivatives of gossypol followed by acid hydrolysis [14–19].

Racemic gossypol was shown to form crystalline inclusion compounds with a large variety of organic molecules [20] of which the above mentioned gossypol-acetic acid (1/1) is the best known representative. Similar abilities were revealed by dianilinogossypol (II, scheme) which is a condensation product of gossypol

with two molar equivalents of aniline [21–23]. Crystal structure analyses of their inclusion compounds indicated that while gossypol can form a large variety of H-bonded aggregates, dianilinogossypol (which has a reduced number of proton-acceptor groups), is less versatile and forms only two types of host aggregates. The fact that (±)-dianilinogossypol in crystals tends to form aggregates comprising both the R and S enantiomers of the host suggested that this preferred association mode might be at the root of the failure of diastereoisomeric separation by fractional crystallization.

This work, which reports the crystal structure of the enamine-type condensation product of racemic gossypol and (R)-(+)-1-phenylethylamine recrystallized from 1,4-dioxane, has been undertaken to address the question of whether H-bond inter-action between diastereoisomeric molecules can lead to host aggregates similar to those present in dianilinogossypol inclusion compounds.

2. Experimental

Compound **III** (1,1′6,6′-tetrahydroxy-3,3′-dimethyl-8,8′-bis[[(1-phenylethyl) amino]methylene]-[2,2′-binaphthalene]-7,7′(8H,8′H)-dione, see scheme) was pre-pared from (±)-gossypol and (R)-(+)-1-phenylethylamine following the procedure of Shirley and Sheehan [24]. An orange crystalline solid was filtered off and recrys-tallized from 1,4-dioxane. A dark red crystal with dimensions 0.1 × 0.2 × 0.5 mm was chosen for all measurements on a KM-4 diffractometer. Lattice parameters were determined by a least-squares fit of the setting angles of 25 reflections with 2θ in the range 13–45°.

The crystal data are as follows: $C_{46}H_{48}O_6N_2 \cdot (C_4H_8O_2)_2$, monoclinic, space group $P2_1$, $a = 21.243(3)$, $b = 8.666(1)$, $c = 28.651(4)$ Å, $\beta = 108.24(1)°$, $V = 5009(3)$ Å^3, $Z = 4$, $D_x = 1.195$ g cm^{-3}, μ(Cu K_α)=0.66 mm^{-1}, $T = 292$ K.

Reflection intensities were measured with graphite-monochromatized Cu K_α radiation up to $2\theta_{max} = 130°$. No significant intensity variation was observed for two standard reflections monitored after each group of 100 reflections. The intensities were corrected for Lorentz and polarization factors but not for absorption and were reduced to structure factors by the DATARED program from the KM-4 package [25]. Out of the 8678 reflections measured, only 4290 had $F > 2.5\sigma(F)$ and those were used in further calculations. The structure has been solved by direct methods using the program SHELXS86 [26]. The atoms forming the naphthalene skeleton of the molecules and some of the substituents were located from the first E-map. Subsequent difference Fourier syntheses were necessary to reveal the positions of the phenyl substituents and of the four solvent molecules. The asymmetric unit comprises a pair of diastereoisomeric molecules formed in the condensation reaction and four 1,4-dioxane molecules. With the exception of the solvent molecule designated DA, the 1,4-dioxane molecules exhibit disorder. In molecule DB atoms C(1) and C(4), and in molecule DC atoms C(2) and C(5) have their primed counterparts. In the fourth solvent molecule, none of the atomic

positions of the primed (DD′) and unprimed (DD) orientations, overlap. It was not possible to distinguish between the O and C atoms in the DB and DD/DD′ molecules. The structure has been refined by the full-matrix least-squares method with the program SHELX76 [27]. The phenyl groups C(41A)–C(46A), C(33B)–C(38B), C(41B)–C(46B), have been treated as regular hexagons with 1.395 Å C–C bonds and refined as rigid groups. Initially, 42 constraints were imposed on interatomic distances in the DB, DC and DD/DD′ solvent molecules by adding extra observational equations to the least-squares matrix with weights proportional to $1/\sigma^2$ ($\sigma = 0.01$ Å). In the final stages of the refinement, the solvent molecules DB, DC and DD/DD′ were treated as rigid groups. Except for the H atoms from the phenyl groups refined as rigid fragments and the H atoms from DB, DC and DD/DD′ solvent molecules which were not determined, the remaining H atoms, were placed in idealized positions, assuming C–H, N–H and O–H distances of 0.96, 0.90 and 0.85 Å, respectively, and an overall isotropic temperature factor $U = 0.08$ Å^2. The positions of the H atoms in the hydroxyl and amino groups were calculated assuming intramolecular hydrogen bonds analogous to those observed in dianilinogossypol [23, 24]. Except for the atoms from the three disordered 1,4-dioxane molecules refined with isotropic temperature factors, the non-H atoms were refined anisotropically. The refinement converged with final $R = 0.091$ and $wR = 0.083$ for 1049 refined parameters and 4290 reflections. Structure-factor weights were assigned as $w = 1/[\sigma^2(F) + 0.0002F^2]$ and the quantity minimized was $\Sigma w(F_0 - F_c)^2$. The maximum Δ/σ value in the final cycle of refinement was less than 0.1. The final difference Fourier map had electron density between –0.33 and 0.55 e Å^{-3} with highest features near the disordered DD/DD′ solvent molecule. Atomic scattering factors used were those incorporated in SHELX76 [27]. Final atomic coordinates are given in Table I. Lists of bond lengths and angles, anisotropic thermal parameters, H-atom coordinates and lists of structure factors have been deposited with the British Library Lending Division, and copies may be ordered quoting Sup. No. 82167 (27 pp.). The numbering scheme of the atoms is shown in Figure 1.

3. Discussion

3.1. MOLECULAR STRUCTURE

There are two diastereoisomeric molecules and four solvent molecules in the asymmetric unit. The molecule designated A represents the isomer formed from (R)-gossypol while molecule B is derived from (S)-gossypol. Even though the bond lengths and angles are accompanied by high standard errors as a consequence of the limited number of observed reflections and do not warrant detailed discussion of the molecular geometry, the bond lengths (Table II) in the O(3)–C(7)–C(8)–C(22)–N(1) and O(7)–C(17)–C(18)–C(27)–N(2) fragments support an enamine and not a Schiff-base, type structure for both diastereoisomers. The products of a conden-

TABLE I. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($\text{Å}^2 \times 10^3$).

	x	y	z	U(eq)
C(1A)	5078(4)	2047(11)	6902(2)	51(3)
C(2A)	5694(4)	2470(12)	7212(3)	62(4)
C(3A)	5981(4)	3833(11)	7107(3)	52(3)
C(4A)	5646(4)	4694(11)	6699(3)	56(3)
C(5A)	4685(4)	5267(10)	5962(3)	55(3)
C(6A)	4045(5)	4939(13)	5733(3)	79(4)
C(7A)	3683(5)	3689(11)	5839(3)	68(4)
C(8A)	4043(4)	2525(11)	6184(3)	57(3)
C(9A)	4710(4)	2915(10)	6483(3)	47(3)
C(10A)	5016(4)	4248(12)	6385(3)	57(3)
C(21A)	6638(5)	4349(16)	7441(3)	89(4)
C(22A)	3739(4)	1092(11)	6169(3)	56(3)
C(23A)	5057(5)	6497(12)	5790(3)	67(4)
C(24A)	4781(6)	8097(14)	5853(4)	94(5)
C(25A)	5038(6)	6242(18)	5261(3)	98(5)
C(31A)	2836(5)	−798(12)	5788(4)	74(4)
C(32A)	2125(6)	−615(18)	5450(5)	117(6)
C(33A)	2856(4)	−1670(13)	6237(4)	64(4)
C(34A)	2899(5)	−1053(14)	6686(5)	86(5)
C(35A)	2874(6)	−1995(20)	7071(5)	91(6)
C(36A)	2793(6)	−3471(23)	7017(6)	103(7)
C(37A)	2764(6)	−4159(17)	6583(6)	104(7)
C(38A)	2796(6)	−3253(16)	6190(4)	96(6)
O(1A)	4773(3)	738(8)	6995(2)	67(2)
N(1A)	3108(4)	774(10)	5900(3)	69(3)
O(3A)	3077(3)	3534(8)	5585(3)	90(3)
O(4A)	3680(3)	5891(9)	5355(2)	88(3)
C(11A)	6115(4)	1722(11)	8093(3)	53(3)
C(12A)	6075(4)	1443(10)	7613(3)	51(3)
C(13A)	6394(5)	98(13)	7505(3)	70(4)
C(14A)	6770(4)	−785(11)	7893(3)	57(3)
C(15A)	7237(4)	−1497(10)	8771(3)	49(3)
C(16A)	7276(4)	−1135(11)	9247(3)	53(3)
C(17A)	6961(4)	153(10)	9375(3)	52(3)
C(18A)	6590(4)	1173(10)	9014(3)	50(3)
C(19A)	6518(4)	861(10)	8503(2)	44(3)
C(20A)	6851(4)	−479(10)	8388(2)	45(3)
C(26A)	6349(6)	−347(15)	6988(3)	91(5)
C(27A)	6355(4)	2556(11)	9167(3)	54(3)
C(28A)	7590(5)	−2905(12)	8668(3)	72(4)
C(29A)	7336(7)	−4381(15)	8826(4)	102(6)
C(30A)	8354(6)	−2718(19)	8868(5)	117(7)
C(39A)	6205(6)	4324(15)	9781(3)	84(5)

TABLE I. *continued*

	x	y	z	U(eq)
C(40A)	6796(7)	5084(14)	10144(4)	108(6)
C(41A)	5628(4)	4129(13)	9971(3)	82(5)
C(42A)	5731	3749	10462	215(16)
C(43A)	5192	3571	10637	282(25)
C(44A)	4549	3774	10320	215(18)
C(45A)	4445	4154	9828	294(27)
C(46A)	4984	4332	9654	209(14)
O(5A)	5805(3)	2961(8)	8208(2)	72(3)
N(2A)	6417(4)	2887(9)	9623(2)	66(3)
O(7A)	7024(3)	312(8)	9832(2)	66(2)
O(8A)	7635(3)	−2053(7)	9625(2)	70(2)
C(1B)	−805(4)	7638(12)	2376(3)	59(3)
C(2B)	−729(3)	8074(12)	2857(3)	58(4)
C(3B)	−1041(4)	9376(13)	2943(3)	64(4)
C(4B)	−1427(4)	10245(13)	2558(3)	64(4)
C(5B)	−1962(4)	10688(12)	1660(3)	61(4)
C(6B)	−2098(4)	10112(12)	1197(3)	64(4)
C(7B)	−1787(4)	8741(11)	1080(3)	59(4)
C(8B)	−1294(4)	8036(11)	1455(3)	53(3)
C(9B)	−1204(4)	8477(11)	1962(3)	53(3)
C(10B)	−1520(4)	9809(12)	2059(3)	57(3)
C(21B)	−977(6)	9878(16)	3464(3)	93(5)
C(22B)	−868(5)	7058(12)	1318(3)	61(4)
C(23B)	−2243(6)	12232(14)	1737(4)	86(5)
C(24B)	−3012(6)	12184(17)	1599(4)	106(6)
C(25B)	−2008(7)	13551(16)	1479(5)	117(6)
C(31B)	−449(5)	5688(15)	716(4)	76(4)
C(32B)	−254(8)	6567(17)	327(5)	119(7)
C(33B)	−732(5)	4103(11)	553(3)	86(5)
C(34B)	−1295	4001	141	139(8)
C(35B)	−1551	2558	−37	188(13)
C(36B)	−1244	1219	196	182(16)
C(37B)	−681	1321	607	167(14)
C(38B)	−425	2764	786	145(9)
O(1B)	−507(3)	6324(8)	2280(2)	78(3)
N(1B)	−933(4)	6602(10)	870(3)	73(3)
O(3B)	−1961(3)	8342(8)	627(2)	74(3)
O(4B)	−2550(3)	10829(9)	806(2)	85(3)
C(11B)	316(4)	7238(12)	3492(3)	56(3)
C(12B)	−351(4)	6990(12)	3271(3)	59(3)
C(13B)	−678(4)	5798(15)	3419(3)	74(4)
C(14B)	−312(5)	4928(14)	3815(3)	76(4)
C(15B)	715(4)	4206(13)	4482(3)	66(4)
C(16B)	1368(4)	4489(11)	4720(3)	56(3)

TABLE I. *continued*

	x	y	z	$U(\text{eq})$
C(17B)	1722(4)	5687(11)	4557(3)	53(3)
C(18B)	1414(4)	6532(10)	4127(3)	49(3)
C(19B)	696(4)	6323(11)	3886(3)	55(3)
C(20B)	363(4)	5156(12)	4059(3)	57(3)
C(26B)	−1392(5)	5474(19)	3182(4)	112(6)
C(27B)	1815(4)	7408(10)	3922(3)	51(3)
C(28B)	395(5)	2723(18)	4607(5)	103(6)
C(29B)	710(11)	1287(20)	4515(6)	174(10)
C(30B)	407(9)	2845(23)	5148(6)	169(11)
C(39B)	2888(5)	8349(13)	3904(3)	67(4)
C(40B)	3572(5)	7684(16)	4104(4)	91(5)
C(41B)	2874(4)	10004(9)	3958(4)	78(5)
C(42B)	3074	10690	4422	157(11)
C(43B)	3045	12290	4466	258(25)
C(44B)	2816	13203	4046	334(41)
C(45B)	2616	12517	3582	290(29)
C(46B)	2645	10918	3538	134(8)
O(5B)	625(3)	8428(9)	3336(2)	74(3)
N(2B)	2453(3)	7581(9)	4126(3)	61(3)
O(7B)	2335(3)	5883(8)	4815(2)	74(2)
O(8B)	1717(3)	3620(8)	5101(2)	82(3)
1,4-Dioxane DA				
O(1DA)	4844(5)	8407(9)	7669(3)	105(4)
C(2DA)	4708(8)	7239(16)	7269(4)	107(6)
C(3DA)	4517(7)	5848(17)	7406(4)	109(6)
O(4DA)	4963(4)	5242(9)	7822(3)	103(4)
C(5DA)	5041(8)	6241(17)	8207(4)	112(6)
C(6DA)	5255(7)	7751(17)	8102(4)	106(6)
1,4-Dioxane DB				
C(1DB)	3942(10)	3181(25)	8503(7)	182(15)
C(1′B)	3875	1414	8619	158(23)
C(2DB)	3280	2483	8498	211(9)
C(3DB)	2850	2485	7967	242(11)
C(4DB)	3134	1104	7778	134(11)
C(4′B)	3246	2833	7620	190(28)
C(5DB)	3801	1647	7743	242(12)
C(6DB)	4238	1916	8267	239(11)
1,4-Dioxane DC				
O(1DC)	355(5)	3999(8)	2660(4)	150(4)
C(2DC)	−205	3020	2400	123(10)
C(2′C)	293	3187	2209	83(10)
C(3DC)	39	1553	2227	139(5)
O(4DC)	434	830	2681	138(3)
C(5DC)	995	1693	2974	102(8)

TABLE I. *continued*

	x	y	z	U(eq)
C(5'C)	416	1713	3106	210(26)
C(6DC)	760	3234	3108	142(5)
	1,4-Dioxane DD/DD'			
C(1DD)	822(10)	7139(35)	1639(7)	114(8)
C(2DD)	951	8724	1920	219(20)
C(3DD)	1154	8034	2449	299(35)
C(4DD)	1878	7567	2523	85(6)
C(5DD)	1810	6133	2200	199(18)
C(6DD)	1534	6669	1673	191(17)
C(1'D)	1586(22)	8692(44)	2322(13)	197(17)
C(2'D)	1893	7998	1919	423(60)
C(3'D)	1174	7771	1508	188(16)
C(4'D)	1097	6076	1708	117(9)
C(5'D)	862	6520	2150	468(75)
C(6'D)	1531	6981	2532	285(33)

* Equivalent isotropic U defined as one third of the
  trace of the orthogonalized U_{ij} tensor.
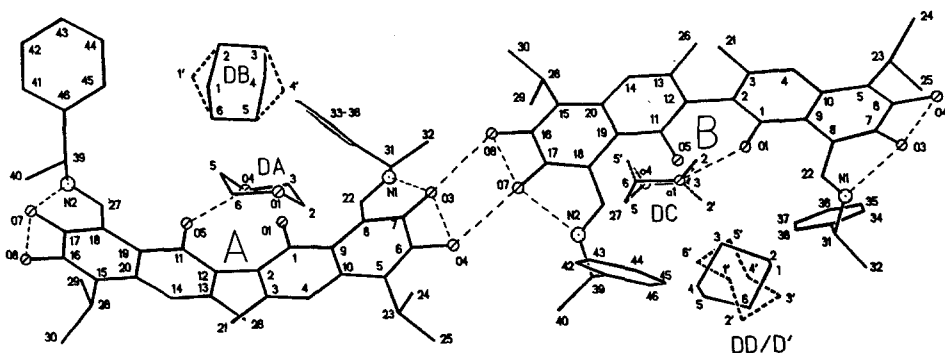
Fig. 1.   Atom labeling scheme.

sation reaction of gossypol with primary amines, termed diaminogossypols, may
exist, like gossypol, in three tautomeric forms [28]. Only the enamine form has
been observed in the solid state so far [21, 22]. There are two strong and two rather
weak intramolecular H-bonds within each molecule (Table II). The N–H. . .O bonds
are parts of six-membered conjugated ring systems while the O–H. . .O bonds close
five-membered rings. The naphthyl moieties within molecules A and B are nearly
perpendicular, the dihedral angles between their least-squares planes being 99 and
91°, respectively. Those moieties are non-planar to a different extent. The largest
deviations are observed in the C(1A)–C(10A) ring system with atom C(7A) located

TABLE II. Selected bond distances (Å).

bond	Mol. A	Mol. B	bond	Mol. A	Mol. B
C(1)–O(1)	1.373(12)	1.372(12)	C(11)–O(5)	1.354(12)	1.370(12)
C(6)–O(4)	1.390(11)	1.375(10)	C(16)–O(8)	1.368(9)	1.343(10)
C(6)–C(7)	1.416(16)	1.449(14)	C(16)–C(17)	1.407(13)	1.443(13)
C(7)–O(3)	1.272(11)	1.281(9)	C(17)–O(7)	1.279(9)	1.292(9)
C(7)–C(8)	1.452(12)	1.387(11)	C(17)–C(18)	1.400(11)	1.406(11)
C(8)–C(22)	1.395(14)	1.384(14)	C(18)–C(27)	1.419(13)	1.399(13)
C(22)–N(1)	1.349(11)	1.308(12)	C(27)–N(2)	1.302(11)	1.306(11)
C(31)–N(1)	1.475(13)	1.471(15)	C(39)–N(2)	1.444(15)	1.439(14)
N(1)...O(3)	2.55(1)	2.56(1)	N(2)...O(7)	2.55(1)	2.54(1)
O(4)...O(3)	2.60(1)	2.61(1)	O(8)...O(7)	2.59(1)	2.63(1)

(a)

(b)
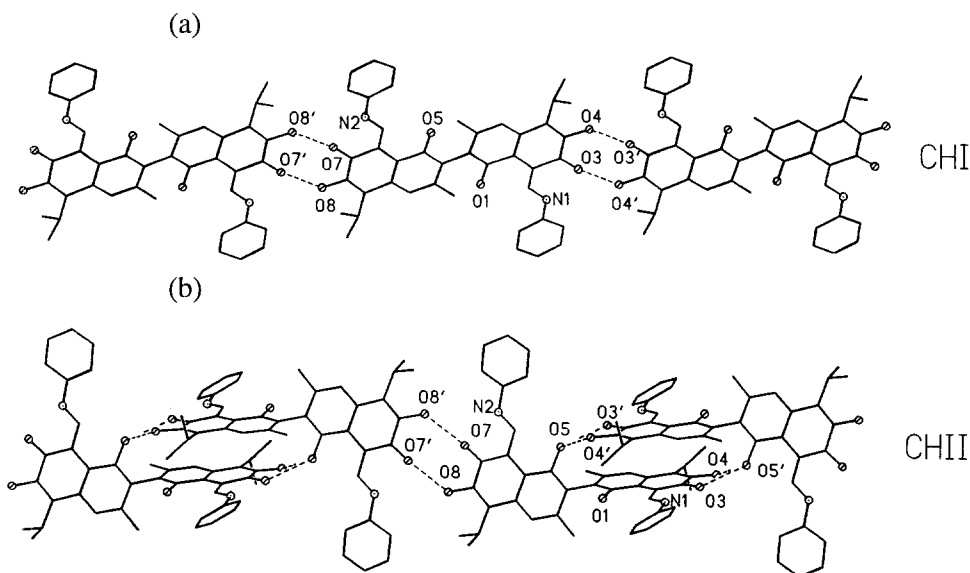
Fig. 2. Structure of H-bonded chain aggregates observed in dianilinogossypol inclusion compounds: (a) chain CHI; (b) chain CHII. Only intermolecular H-bonds are marked.

0.17 Å from the ring 'best' plane. The highest possible molecular symmetry for both diastereoisomers is C_2, with the two fold axis intersecting the C(2)–C(12) bond. However, this symmetry is distorted in both molecules (Table II).

3.2. CRYSTAL PACKING

The diastereoisomeric molecules A and B have their proton-donor and proton-acceptor groups arranged analogously to dianilinogossypol. Two types of H-bonded aggregates of the host molecules have been observed in dianilinogossypol inclusion compounds [22, 23] (Figure 2). In chain CHI, shown in Figure 2a, α-ketoenol
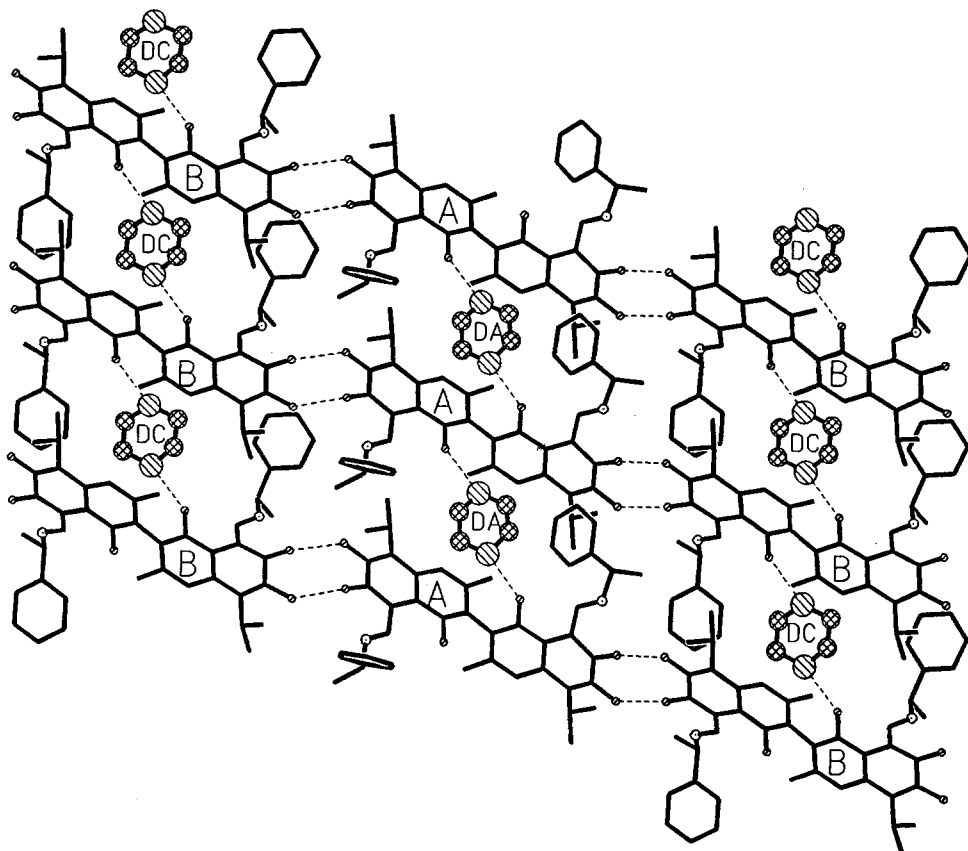
Fig. 3.   Structure of the host–guest aggregate. H-atoms have been omitted for clarity. Only intermolecular H-bonds are marked with dashed lines.

fragments of the host molecule interact *via* hydrogen bonds with analogous fragments of two other molecules related by inversion centers. Thus, those chains comprise both enantiomers. Two hydroxyl groups, O(1)–H and O(5)–H, *ortho* to the naphthyl–naphthyl bond are not involved in the interhost interactions and, therefore, the host molecules may coordinate, *via* H-bonds, two guest molecules. In chain CHII (Figure 2b) only one α-ketoenol fragment of the host interacts with an analogous part of another host molecule. The second fragment is H-bonded to O(5)–H of an inversion-center related molecule to form an aggregate similar to the so-called centrosymmetric O(5)–H...O(3) dimer of gossypol [22]. Analogously to chain CHI, chain CHII is also built from *R* and *S* host molecules but only one hydroxyl, O(1)–H, is available for host–guest interaction.

The diaminogossypol discussed in this paper forms chains CHI with alternating diastereoisomeric molecules A and B along the chain (Figure 3). The axial dissymmetry of the 2,2′-binaphthyl nucleus seems to be crucial for this mode of
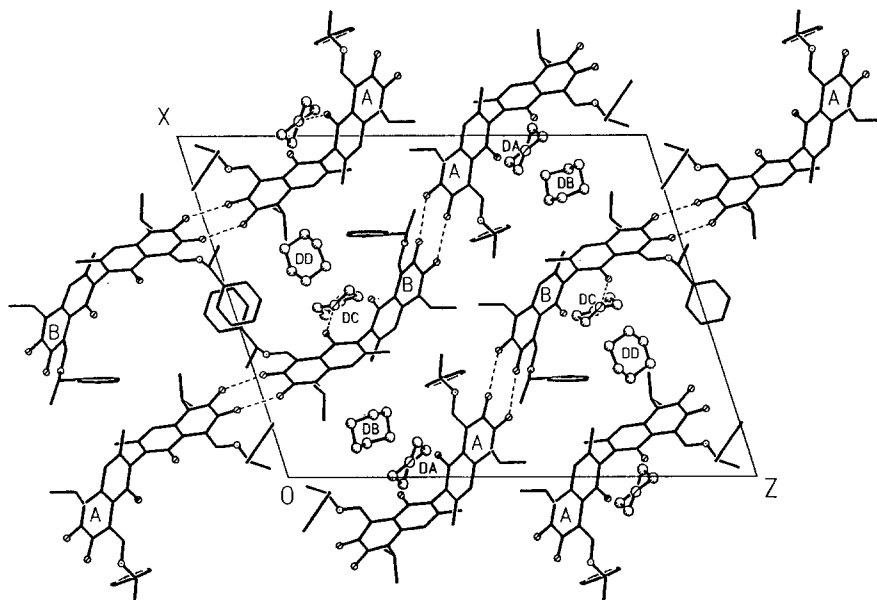
Fig. 4.   Crystal packing viewed along [010].

inter-host interaction and the configuration at the asymmetry centers in the amine parts of the molecule seems to be a minor factor. The fact that diastereoisomeric diaminogossypol represented by compound **III**, tends to form in the crystal chain-like aggregates with alternating isomeric molecules along the chain explains why diastereoisomeric products of the condensation reaction of ($\pm$)-gossypol with optically active primary amines could not be separated by fractional crystallization.

Compound **III** behaves analogously to gossypol and dianilinogossypol and forms with 1,4-dioxane inclusion compounds of host : guest ratio lower than 1. The host chains described above are connected *via* hydrogen bonds with 1,4-dioxane molecules to form layer-type host-guest aggregates shown in Figure 3. The hydroxyls O(1)–H and O(5)–H of molecules A and B act as donors, and the oxygen atoms O(1) and O(4) of 1,4-dioxane molecules DA and DC act as acceptors in those bonds. When these host–guest layers pack in the crystal (Figure 4), there is an empty space in the inter-layer area in which two additional guest molecules, DB and DD/DD$'$, not H-bonded to the host, can be accommodated. All 1,4-dioxane molecules are located in two types of wavy channels running along [010]. One of the channels is occupied by alternating guest molecules DA and DB, while the other by molecules DC and DD/DD$'$. The behavior of compound **III** resembles that of gossypol which in its 1 : 3 inclusion compound with 1,4-dioxane forms a layer-type host–guest aggregate with two solvent molecules involved in H-bonding to the host and the third molecule loosely packed in a channel [29]. Dianilinogossypol, which has H-bonding ability identical to compound **III**, forms in its inclusion compound

with 1,4-dioxane [23] a CHII-type aggregate with only one of the guest molecules H-bonded to the host. There are at least two other solvent molecules which are enclosed in cavities formed between chain-type host–guest aggregates.

Acknowledgements

References

1. T.J. King and L.B. de Silva: *Tetrahedron. Lett.*, 261 (1968).
2. D.S. Bhakuni, M.M. Dhar, and V.N. Sharma: *Experientia* **24**, 109 (1968).
3. J.M. Dechary and P. Pradel: *J. Am. Oil Chem. Soc.* **48**, 563 (1971).
4. R.H. Zhou and X.D. Lin: *Contraception* **37**, 239 (1988).
5. Q.B. Cass, E. Tiritan, S.A. Matlin, and E.C. Freire: *Phytochemistry* **30**, 2655 (1991).
6. Y.-E. Wang, Y.-D. Luo, and X.-C. Tang: *Acta Pharm. Sinica* **14**, 662 (1979).
7. S.A. Matlin, R.H. Zhou, G. Bialy, R.P. Blye, R.H. Naqvi, and M.C. Lindberg: *Contraception* **31**, 141 (1985).
8. V. Band, A.P. Hoffer, H. Band, A.E. Rhinehardt, R.C. Knapp, S.A. Matlin, and D.J. Anderson: *Genecol. Oncol.* **32**, 273 (1989).
9. Y.-W. Wu, C.L. Chik, and R.A. Knazek: *Cancer Res.* **49**, 3754 (1989).
10. N. Tanphaichitr, L.M. Fitzgerald, and S.A. Matlin: *J. Androl.* **9**, 270 (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. J.W. Jaroszewski, T. Strøm-Hansen, and L.L. Hansen: *Chirality* **4**, 216 (1992).
13. L. Huang, Y.-K. Si, G. Snatzke, D.-K. Zheng, and J. Zhou: *Coll. Czech. Chem. Commun.* **53**, 2664 (1988).
14. L. Huang, D.-K. Zheng, and Y.-K. Si: *J. Ethnopharmacol.* **20**, 13 (1987).
15. D.-K. Zheng, Y.-K. Si, and L. Huang: *J. Chem. Soc. Chem. Commun.*, 168 (1985).
16. D.S. Sampath and P.A. Balaram: *J. Chem. Soc. Chem. Commun.*, 649 (1986).
17. S.A. Matlin and R.H. Zhou: *J. High Res. Chromatogr. Chromatographic Commun.* **7**, 629 (1984).
18. S.A. Matlin, R.H. Zhou, A. Belenguer, R.G. Tyson, and A.N. Brookes: *J. High Res. Chromatogr. Chromatographic Commun.* **10**, 86 (1987).
19. S.A. Matlin, R.H. Zhou, and A. Belenguer: *Contraception* **37**, 229 (1988).
20. B.T. Ibragimov, S.A. Talipov, B.N. Dadabaev, G.B. Nazarov, and T.F. Aripov: *Khim. Prir. Soed.*, 675 (1988): *Chem. Abstr.* **111**, 58080c (1989).
21. B.T. Ibragimov, G.B. Nazarov, and S.A. Talipov: *Khim. Prir. Soed.*, 666 (1988); *Chem. Abstr.* **111**, 174421p (1989).
22. G.B. Nazarov, B.T. Ibragimov, and T.F. Aripov: *Khim. Prir. Soed.*, 661 (1988); *Chem. Abstr.* **111**, 174420n (1989).
23. M. Gdaniec: *J. Incl. Phenom.*, in preparation.
24. D.A. Shirley and W.C. Sheehan: *J. Org. Chem.* **21**, 251 (1956).
25. Kuma Diffraction: KM-4 User's Guide, Ver. 3.1. Wrocław, Poland (1989).
26. G.M. Sheldrick: SHELXS86. *Program for the solution of crystal structures*, Univ. of Götingen, Germany (1986).
27. G.M. Sheldrick: SHELX76. *Program for crystal structure determination*, University of Cambridge, England (1976).
28. L. Biktemirov, N.I. Baram, A.I. Ismailov, F.G. Kamaev and V.B. Leontev: *Khim. Prir. Soed.*, 286 (1975); *Chem. Abstr.* **83**, 77932b (1975).
29. B.T. Ibragimov, M. Gdaniec, S.A. Talipov, B.N. Dadabaev, and K.M. Beketov: *Khim. Prir. Soed.*, in press (1993).