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# Spectroscopic and semiempirical studies of new Schiff base of gossypol with allylamine in solution

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## Abstract

The Schiff base of racemic gossypol with allylamine (GSBAL) has been studied by FT-IR, $^{1}$H and $^{13}$C NMR spectroscopy as well as by the PM5 semiempirical method. The spectroscopic methods have shown that GSBAL Schiff base exists in chloroform solution as enamine–enamine tautomer. The structure of GSBAL and the hydrogen bonds within this structure have been calculated to show that the allyl groups are out-of-planes of naphthalene rings. The strongest intramolecular hydrogen bond within the structure of GSBAL is formed between $O_7\cdots H–N_{16}$ atoms and it belongs to the medium strong bonds. The other hydrogen bonds, although very weak, play a very important role in stabilising the GSBAL enamine–enamine structure.

*Keywords:* Gossypol; Schiff bases; Allylamine; $^{1}$H NMR; $^{13}$C NMR; COSY; HETCOR; FT-IR; PM5 semiempirical calculation; Hydrogen bonds

## 1. Introduction

Gossypol is a very important and interesting compound known for its biological activity [1–10]. Its relatively high toxicity, related to the presence of two aldehyde groups, is the main obstacle in using this polyphenolic compound in medical therapy [11,12]. The Schiff bases of gossypol show lower toxicity and still are biologically active so they could be used instead of gossypol as therapeutic agents [13]. Significant interest in these compounds has prompted our study of several Schiff bases containing methyl esters of L-amino acids [14–16], crown ether amines [17], oxaalkyl amines [18,19], *n*-butylamine [20] and (*R*)-tetrahydrofurfuryl amine [21]. The results have shown that in all newly synthesised Schiff bases as well as their complexes with monovalent and bivalent metal cations [22–31], the enamine–enamine tautomeric form is always present. Furthermore, in the Schiff bases of gossypol with methyl esters of L-amino acids, additionally a process of epimerisation has also been detected [14]. In contrast to the studies of the Schiff bases of gossypol as well as their complexes, we have proved the occurrence of the N-imine–N-imine tautomeric form in new hydrazones of gossypol [32,33]. Analogously, the formation of the imine–imine tautomeric forms has also been observed after protonation of the Schiff bases of gossypol [22,24,27–31].

As a continuation of our earlier studies a new Schiff base of gossypol with allylamine has been synthesised and its structure has been investigated by NMR and FT-IR spectroscopic methods as well as by semiempirical calculations.

## 2. Experimental

Racemic gossypol was extracted from cotton seeds of *Gossypium herbaceum* following the procedure given in Ref. [34]. Purity of this compound was controlled by $^{1}$H NMR spectra.

The allylamine as well as spectral-grade solvents $CHCl_3$ and $CDCl_3$ were commercial products of Aldrich.

### 2.1. Synthesis of new Schiff base of gossypol with allylamine

The Schiff base of gossypol with allylamine was synthesised by addition of a solution of 20.26 μl of allylamine ($2.702\times10^{-4}$ mol) in 5 cm$^{3}$ absolute ethanol to

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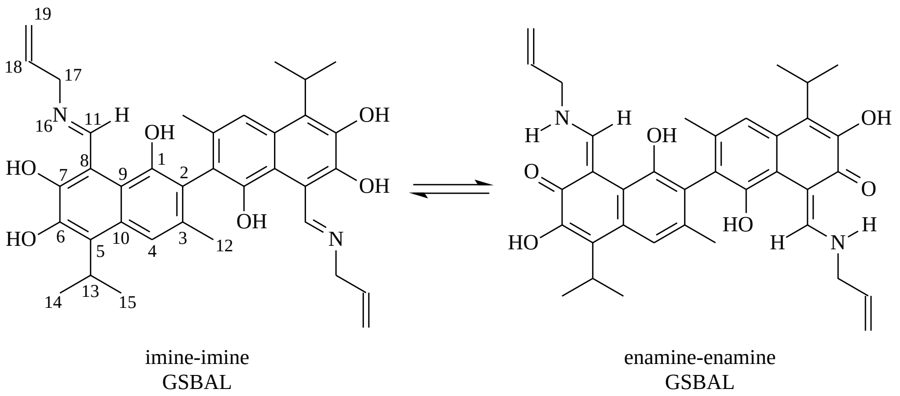

Scheme 1.

70 mg of gossypol ($1.35\times10^{-4}$ mol) in 30 $cm^3$ absolute ethanol. The solutions were stirred under reflux for 2 h under argon atmosphere. After cooling the mixture, the product crystallised as a brown–yellow powder. The product was dried under reduced pressure and recrystallised from absolute ethanol. Yield (55.1%). Melting point 234–236 °C with the decomposition.

Elementary analysis $C_{36}H_{40}N_2O_6$: Calculated: C=72.46%, H=6.76%, N=4.69%; Found: C=72.42%, H=6.79%, N=4.70%.

### 2.2. FT-IR measurements

The FT-IR spectra of gossypol and its Schiff base with allylamine were recorded in methylenechloride and chloroform (0.05 mol $dm^{-3}$), respectively, at 300 K using a Bruker IFS 113v spectrometer. Chloroform and methylenechloride spectral-grade solvents were stored over 3 Å molecular sieves for several days.

A cell with Si windows and wedge-shaped layers was used to avoid interferences (mean layer thickness 170 μm). The spectra were taken with an IFS 113v FT-IR spectrophotometer (Bruker, Karlsruhe) equipped with a DTGS detector; resolution 2 $cm^{-1}$, NSS=125. The Happ-Genzel apodisation function was used.

All manipulations with the substances were performed in a carefully dried and $CO_2$-free glove box.

### 2.3. NMR measurements

The NMR spectra of GSBAL were recorded in $CDCl_3$ using a Varian Gemini 300 MHz spectrometer. All spectra were locked to deuterium resonance of $CD_3OD$ or $CDCl_3$, respectively. The error in ppm values was 0.01.

All $^1H$ NMR measurements were carried out at the operating frequency 300.075 MHz; flip angle, pw=45°; spectral width, sw=4500 Hz; acquisition time, at=2.0 s; relaxation delay, $d_1=1.0$ s; $T=293.0$ K and TMS as the internal standard. No window function or zero filing was used. Digital resolution=0.2 Hz/point.

$^{13}C$ NMR spectra were recorded at the operating frequency 75.454 MHz; pw=60°; sw=19,000 Hz; at=1.8 s; $d_1=1.0$ s; $T=293.0$ K and TMS as the internal standard. Line broadening parameters were 0.5 or 1 Hz. The $^1H$ and $^{13}C$ NMR signals were assigned independently for each species using one or two-dimensional (COSY, HETCOR) spectra.

### 2.4. PM5 semiempirical calculations

PM5 semiempirical calculations were performed using the Win Mopac 2003 program [35,36]. In all cases, full geometry optimisation of GSBAL was carried out without any symmetry constraints [37].

## 3. Results and discussion

### 3.1. NMR studies

The formulae of the two tautomeric forms and the carbon atoms numbering in GSBAL are shown in Scheme 1.

The $^1H$ and $^{13}C$ NMR data of GSBAL in $CDCl_3$ are shown in Tables 1 and 2, respectively. The $^1H$ and $^{13}C$

Table 1
$^1H$ NMR chemical shifts (ppm) of proton of GSBAL in $CDCl_3$

| Compound | Chemical shift (ppm) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $O_1H$ | $CH_3$ | $C_4H$ | $O_6H$ | $C_{11}H$ | $C_{13}H$ | $C(CH_3)_2$ | $N_{16}H$ | $C_{17}H$ | $C_{18}H$ | $C_{19}H$ |
| GSBAL | 5.60 (s) | 2.10 (s) | 7.59 (s) | 7.98 (s) | 9.62 (d) | 3.72 (sept) | 1.53 (d),<br>1.52 (d) | 13.34 (bs) | 4.08 (d) | 5.93 (m) | 5.32, 5.27 (dd) |

s, singled; bs, broad singled; d, doublet; dd, double doublet; sept, septet; m, multiplet.