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Spectroscopic and PM5 semiempirical studies of new hydrazone of gossypol with 3,6-dioxaheptylhydrazine

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Abstract

A new hydrazone of gossypol with 3,6-dioxaheptylhydrazine (GHDO) has been synthesised and its structure has been studied by FT-IR, ^{1}H NMR, ^{13}C NMR as well as PM5 semiempirical methods. All the studies have provided clear evidence of the existence of GHDO in the solution in the *N*-imine–*N*-imine tautomeric form. The structure and the spectroscopic behaviour of this tautomer are discussed in details. It is shown the structure of GHDO is strongly stabilised by different types of intramolecular hydrogen bonds. In two of them the oxygen atoms of the oxaalkyl chains are also engaged. The strongest intramolecular hydrogen bond is formed between the O_7H proton and N_{16} atom from the hydrazone group.

Keywords: Gossypol; Hydrazones; 3,6-Dioxaheptylhydrazine; ^{1}H NMR; ^{13}C NMR; COSY; HETCOR; FT-IR; PM5 Calculations; Hydrogen bonds

1. Introduction

Hydrazones of gossypol are very interesting compounds because they occur as *N*-imine–*N*-imine tautomers [1–9], whereas the studies of the gossypol Schiff bases and their complexes with monovalent and bivalent metal cations have been shown to occur in the enamine–enamine tautomeric form [10–24]. The protonation of gossypol Schiff bases has always resulted in transformation of the enamine–enamine into the imine–imine tautomeric form [16,18–24].

As a contribution to our earlier studies a new hydrazone of gossypol with 3,6-dioxaheptylhydrazine was synthesised and its structure was investigated by spectroscopic methods and PM5 semiempirical calculations.

2. Experimental

3,6-Dioxaheptylhydrazine was synthesised following the procedure in Ref. [25]. The purity of this compound was controlled by ^{1}H NMR spectra.

Hydrazone of gossypol (GHDO) was synthesised by addition of a solution of 51.74 mg (3.85×10^{-4} mol) of 3,6-dioxaheptylhydrazine in 5 cm^3 absolute ethanol to 100 mg of gossypol (1.92×10^{-4} mol) in 25 cm^3 absolute ethanol. The solutions were stirred under reflux for 3 h under argon atmosphere in 70 °C. After cooling of the mixture, the product crystallised as a brown-yellow powder. The product was dried under reduced pressure and recrystallised from absolute ethanol. All manipulations were performed under argon atmosphere. Yield (61.7%). Melting point 168–170 °C with decomposition.

Elementary analysis $C_{40}H_{54}N_4O_{10}$: calculated: C=63.98%, H=7.25%, N=7.46%; found: C=63.96%, H=7.26%, N=7.42%.

2.1. FT-IR measurements

The FT-IR spectra of gossypol and its hydrazone with 3,6-dioxaheptylhydrazine (GHDO) were recorded in methylenchloride and chloroform (0.05 mol dm^{-3}), respectively, at 300 K using a Bruker IFS 113v spectrometer. Chloroform and methylenchloride 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).

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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.

2.2. NMR measurements

The NMR spectra of GHDO 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 have been assigned independently for each species using one or two-dimensional (COSY, HETCOR) spectra. The ^1H NMR spectrum of GHDO was also measured after an addition of one drop of CD_3OD to identify the signals of OH and NH protons.

2.3. PM5 semiempirical calculations

PM5 semiempirical calculations were performed using the Win Mopac 2003 program [26]. For the calculations full geometry optimisation was carried out without any symmetry constraints [27,28].

2.4. Elementary analysis

The elementary analysis was carried out on Perkin–Elmer CHN 240 apparatus.

3. Results and discussion

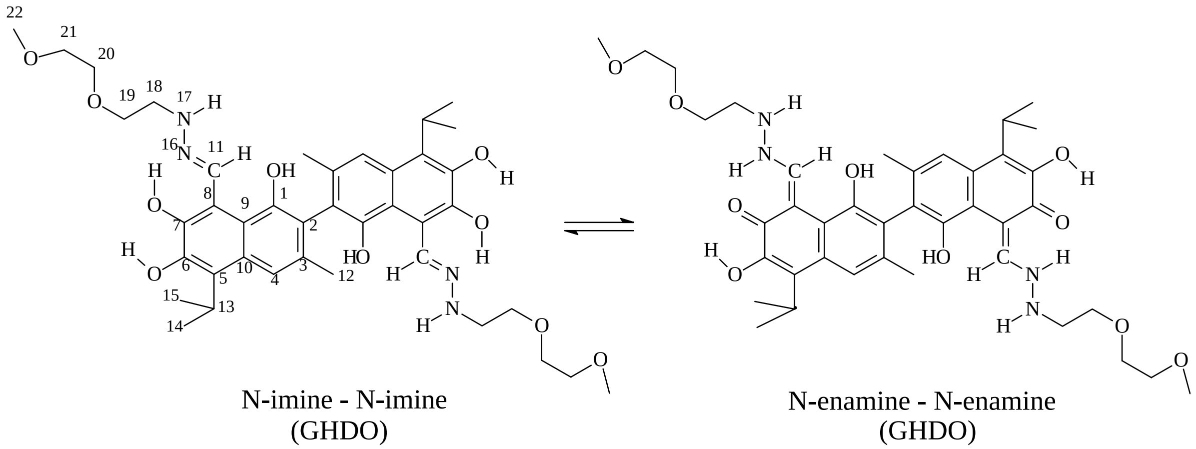
The formula and the atom numbering of the hydrazone of gossypol with 3,6-dioxaheptylhydrazine (GHDO) are shown in Scheme 1.

3.1. NMR studies

The chemical shifts of the signals observed in the ^1H and ^{13}C NMR spectra of GHDO are shown in Tables 1 and 2, respectively. These signals were assigned independently using one- and two-dimensional COSY and HETCOR spectra shown in Figs. 1 and 2, respectively, as well as after the addition of CD_3OD to the probe.

In the ^1H NMR spectrum of GHDO, the signals of the protons of OH and that of N–H groups are observed separately. After the addition of CD_3OD these signals vanish completely. The highest chemical shift of the $O_7H\cdots N_{16}$ intramolecular hydrogen-bonded proton is observed at 14.47 ppm. It is interesting to note that this chemical shift is slightly higher when compared to that of the respective intramolecular hydrogen bond observed in the ^1H NMR spectrum of earlier studied gossypol hydrazones (14.43 and 14.37 ppm) [8,9]. The signal of the O_6H proton is found at 6.78 ppm, and its position is the same as in the spectra of all other hydrazones studied. This result is understandable because this proton is engaged in the $O_6H\cdots O_7$ weak intramolecular hydrogen bond. In contrast, the position of the O_1H proton signal at 5.66 ppm is slightly shifted toward higher frequencies if compared with the respective signals observed in the spectra of other hydrazones. This shift is probably evoked by the formation of a weak intramolecular hydrogen bond between the O_1H proton and O_{21-22} oxygen atom from the oxaalkyl chain, which is in agreement with the ^{13}C NMR chemical shit of the C_1 atom as well as with the PM5 semiempirical calculations discussed below.

In the ^{13}C NMR spectrum of GHDO (Table 2), the signal of the C_7 atom is observed at 150.2 ppm. This chemical shift



Scheme 1. Tautomeric forms of GHDO.