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Schiff bases of gossypol: an NMR and DFT study

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Schiff bases of gossypol with benzylamine, methylamine, 4-aminoacetophenone and 4-fluoroaniline have been synthesized and characterized by NMR spectroscopy. All the Schiff bases of gossypol are in the enamine form according to ^3J(HC,NH) and ^1J(N,H) coupling constants. The spectra are basically unchanged by change of solvent (CD_2Cl_2, THF-d_8 and CD_3OD) and by variation of temperature. For the derivative of benzylamine, deuterium isotope effects on ^{13}C chemical shifts are determined. They support strongly the enamine form and serve as a reference for other tautomeric Schiff bases. Structures and NMR nuclear shieldings of model compounds (the second monomer is replaced by a 2-hydroxybenzene ring) have been calculated by density functional theory (DFT) methods. A good correlation is observed between calculated ^{13}C nuclear shieldings of the enamine form and observed ^{13}C chemical shifts. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: gossypol; Schiff bases; isotope effects; ^{13}C chemical shifts; ^1H NMR; DFT calculations; enamine; ^{15}N–H coupling constants

INTRODUCTION

Schiff bases have attracted much attention because of their tautomeric properties[1–12] (and consequently proton transfer) and because of interesting biological properties.[13–17] Schiff bases of *o*-hydroxybenzaldehydes and *o*-hydroxyacetophenones and, in many cases, the corresponding naphthalene derivatives have been investigated in great detail.[1,3,7,9,11] Structures have been determined both by X-ray[18] and NMR methods.[1–11,19–24] For Schiff bases of simple aldehydes such as salicylaldehyde, the imine form is the only observed form.[6,9] However, most of the Schiff bases show tautomerism (Scheme 1). For the so-called proton transfer (enamine) form much discussion has concerned the actual form.[25] Two resonance forms are given in Scheme 1. In the results section only one form is shown for simplicity. So far, no compounds of this type have been found to be fully in the enamine form at ambient temperature, although compounds such as 6-nitro-2-hydroxynaphtaldehyde are shifted very much towards the enamine form.[7] However, recent reports for Schiff bases of gossypol indicate that some of these are in the enamine form,[12,26,27] although an earlier report disagrees.[28] Furthermore, solvent may play a crucial role.

Schiff bases of gossypol have shown interesting biological properties.[13–17] and thus knowledge about their tautomerism is essential. The present work describes the synthesis and NMR spectroscopic properties of Schiff bases of gossypol with aliphatic and aromatic amines of varying base strength. The ^1H and ^{13}C NMR chemical shifts, ^3J(HC,NH) and ^1J(N,H) coupling constants and deuterium isotope effects on ^{13}C chemical shifts are measured to describe the system with respect to tautomeric vs. non-tautomeric behaviour. Furthermore, spectra are recorded in solvents of different polarities and at varying temperature. The main aim is to find parameters for the enamine form for future use in describing tautomeric Schiff bases in general.

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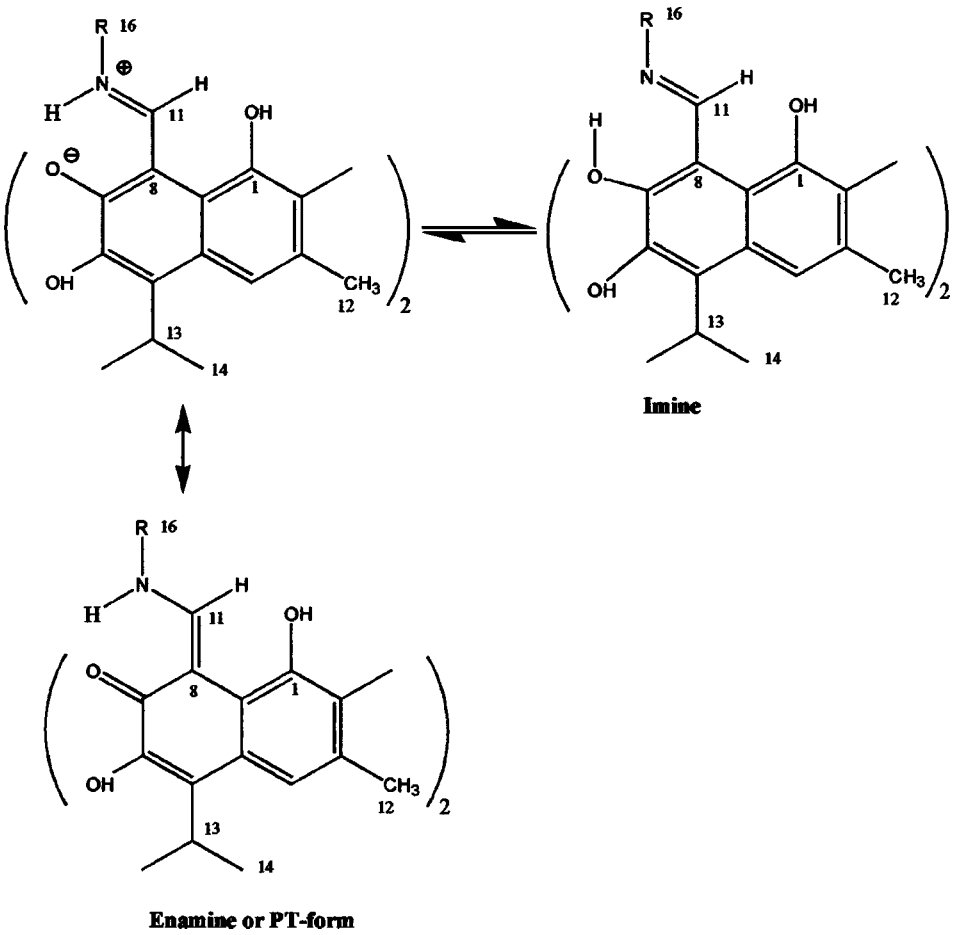
RESULTS

The Schiff bases of gossypol (**1**–**4**; see Scheme 2) have been prepared using gossypol acetic acid and the amines benzylamine, methylamine hydrochloride, methylamine ^{15}N hydrochloride, 4-aminoacetophenone and 4-fluoroaniline.

The reaction with benzylamine is almost finished after 1 h whereas 4-aminoacetophenone reacted much more slowly. The reaction mixture of the latter after 1 h consisted of gossypol, a Schiff base reacted at one of the aldehyde groups and a Schiff base reacted at both aldehyde groups.

The ^1H NMR data are given in Table 1. Resonances of three XH protons are observed. The NH chemical shifts fall into two groups, that of **1** and **2** and that of **3** and **4**. In the former case the NH proton chemical shift is close to 13.5 ppm, the OH-6 proton shift is at ~8 ppm and the OH-1 proton shift is at 5.6 ppm. In the latter group the NH ^1H chemical shift is close to 15.0 ppm and the two OH resonances are again at 8 and 5.6 ppm. For the NH proton no great variation in position is found by a change of temperature. However, the OH-1 proton is shifted considerably to high frequency when the spectrum is recorded in THF-d_8 (Table 2).

The ^3J(HC,NH) coupling constant in all cases is close to 12 Hz. Cooling of the sample to −25 °C gave almost no change in this coupling constant. For **1** and **2** the coupling



Scheme 1. Tautomeric equilibrium and resonance forms.

under non-exchanging conditions is 12.6 Hz and for **3** and **4** it is 11.7 Hz. For the ^{15}N-enriched compound **2**, a ^{1}J(N,H) coupling constant of 88.7 Hz could be obtained at ambient temperature in THF-d_8, together with ^{3}J(CH,NH) = 12.3 Hz, ^{3}J(CH$_3$, NH) = 5.2 Hz and ^{2}J(CH$_3$,^{15}N) = 4.2 Hz.

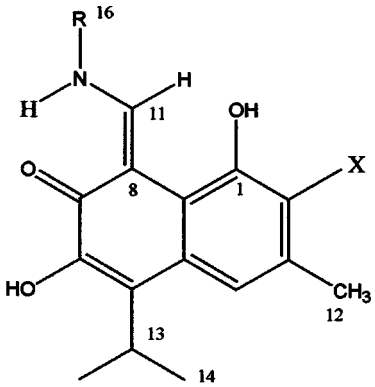
Deuterium isotope effects on ^{13}C chemical shifts have been measured in **1** in $CDCl_3$ and in THF-d_8 at ambient temperature. The isotope effects are given in Scheme 3. At ambient temperature only one isotope effect is observed, namely that of C-11. In $CDCl_3$ at −25 °C effects are also seen at C-7 (−0.19 ppm), C-8 (0.09 ppm), C-1 (0.10 ppm), C-16 (0.19 ppm) and C-6 (broadening). The effects at C-1 and C-6 are believed to originate from deuteration of the C-1 and C-6 OH groups, respectively. This is supported by the finding that both of the corresponding OH resonances are sharp at low temperature. The OH-1 resonance was the sharpest. For **1** in THF-d_8 at ambient temperature, deuterium isotope effects were found at C-7, C-8, C-11 and C-16 but not at C-6 or C-1, but at −25 °C both C-1 and C-8 show distinct isotope effects (not shown in Scheme 3) and C-6 shows a broadening just as in $CDCl_3$, whereas at −55 °C all six carbon resonances C-1, C-6, C-7, C-8, C-11 and C-16 show well-resolved isotope effects. In addition, an extra splitting is observed at the C-7 carbon resonance (see Scheme 3).

Theoretical calculations

The molecular geometries were optimized using the Gaussian 98 suite of programs.[29] The calculations are done in density functional theory (DFT) using B3LYP[30,31] and a 6-31G* basis set. Chemical shifts were calculated using the GIAO approach.[32,33]

Structures and NMR chemical shifts have been calculated for the three derivatives: **1aOH, 2a, 2aOH**; and **2b, 3aOH**, **4a** (see Scheme 2). Calculations for all four molecules show that the enamine form has the lowest energy in the gas phase. The energy differences between the enamine and imine form are: 27.1 kJ, for **1aOH**, 25.4 kJ for **2a**, 26.8 kJ for **2aOH**, 24.7 kJ for **2b** and 23.6 kJ for **4a**.

A plot of calculated ^{13}C nuclear shieldings for the enamine form of **1aOH** vs. observed chemical shifts for **1** in $CDCl_3$ is shown in Fig. 1. A similar plot can be obtained for data of **3a** vs. **3** or **4a** vs. **4**. In the correlations, data points for C-2 have been left out to compensate for the fact that the calculated and measured compounds are not fully identical. The correlation coefficients of 0.999 are very good. It is also seen that no major differences exist whether the model used is of type **a,b** or **aOH** (see Scheme 2). The calculated nuclear shieldings are very similar from compound to compound, as are the chemical shift (nuclear shielding) differences (Table 3). These data also reveal quite large differences between carbon resonances of enamine and imine forms, so that these forms can be distinguished easily by ^{13}C NMR. The fact that there is a large difference in chemical shifts means that for an equilibrium a change of temperature or deuterium substitution[7,11] would give rise to a large change. This is not found experimentally.



	R	X
1	CH_2Ph	second half of dimer
1aOH	CH_2Ph	2-hydroxyphenyl
2	CH_3	second half of dimer
2a	CH_3	phenyl
2aOH	CH_3	2-hydroxyphenyl
2b	CH_3	CH_3
3	4-acetylphenyl	second half of dimer
3aOH	4-acetylphenyl	2-hydroxyphenyl
4	4-fluorophenyl	second half of dimer
4a	4-fluorophenyl	phenyl

Scheme 2. Compounds **1**–**4**.

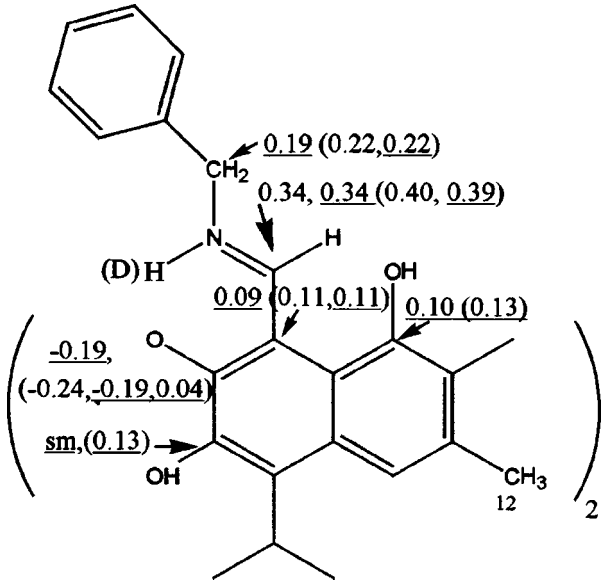
The choice of model turned out to be revealing for understanding the structure. Originally the second monomer unit was replaced either by a CH_3 group as in **2b** or by a phenyl group as in **2a** This gave a structure with the OH group out of the ring plane and pointing towards C—H_{ald}, which resulted in poor prediction of the OH-1 and NH chemical shifts. By introducing a 2-hydroxyphenyl ring as the second ring a much better fit was achieved, showing that OH-1 is almost in the ring plane and that the two aromatic rings are almost perpendicular. The calculated ^{1}H nuclear shieldings are given in Table 3 and a plot vs. the observed ^{1}H chemical shifts is given in Fig. 1(b).

The calculated structures of the derivatives show the formation of a hydrogen bond between the NH proton and the oxygen at position 6 (Table 4). The OH-6 proton is pointing towards the O-7 oxygen.

As seen in Table 4, the difference in bond lengths is moderate between **2a** and **2aOH**. Furthermore, the *N*-methyl derivative (**2**) can be used as a model for an *N*-benzyl derivative (**1**).

DISCUSSION

The Schiff bases may exist as a tautomeric mixture as seen in Scheme 1. However, the observation of a large positive deuterium isotope effect at C-11, a ^1J(N,H) of 88.6 Hz and



Scheme 3. Deuterium isotope effects on ^{13}C chemical shifts of **1** in $CDCl_3$. Values in parentheses are recorded in THF-d_8. Values that are underlined are at low temperature: for $CDCl_3$, at −25 °C; for THF-d_8, at −55 °C.

a ^3J(HC,NH) of 12.8 Hz point towards the enamine form being dominant. The finding that neither isotope effects nor coupling constants change with solvent or temperature points towards the enamine being the only constituent. This is also supported by the finding that the ^{13}C chemical shifts do not change very much with temperature and by the finding that the majority of the ^{13}C chemical shifts are very similar in **1, 3** and **4** as well as in the butylamine derivative of gossypol.[13] The finding that the Schiff bases of gossypol are exclusively in the enamine form irrespective of the amine or solvent used make these Schiff bases a unique model for extracting basic parameters for the enamine form, parameters that have proved very difficult to extract from other tautomeric Schiff bases. The ^1J(N,H) of 88.6 Hz is close to the value of 92.6 Hz found by Kurkovskaya.[1] More recently a ^1J(N,H) coupling of 80 Hz has been found by extrapolation in Schiff bases of nitro derivatives of 2-hydroxyacetophenone.[7]

The deuterium isotope effects on chemical shifts indicate rather strong hydrogen bonding of this enamine. The $^2\Delta$C-α(ND) of 0.34 ppm is clearly larger than is found for aliphatic keto-enamines.[34] At −25 °C compound **1** in both $CDCl_3$ and THF-d_8 shows a well-resolved isotope effect at C-1 most likely due to deuteriation at OH-1. Deuteriation at OH-6 leads only to a broadening at this temperature, showing that exchange with external hydrogens is still too fast. This is also confirmed by the slight broadness of this OH proton resonance. At −55 °C in THF-d_8 C-6 shows a well-resolved splitting. At the same time C-7 shows an additional splitting that can be ascribed to the presence of a hydrogen bond from OH-6 to O-7. Deuteriation at OH-6 will give rise to a small isotope effect, as is seen for intramolecular hydrogen-bonded systems.[35]

The reason why Schiff bases of gossypol are exclusively in the enamine form (PT form) compared with numerous other

Table 1. The ^{13}C chemical shifts of compounds **1, 3** and **4**[a]

	1 ($CDCl_3$ 25 °C)	**1** ($CDCl_3$ −25 °C)	**1** (THF-d_8 25 °C)	**1** (THF-d_8 −25 °C)	**3** (THF-d_8 25 °C)	**4** ($CDCl_3$ 25 °C)	**4** (THF-d_8 25 °C)	Butyl[b] ($CDCl_3$)
C-1	149.0	149.0	151.1	151.3	152.0	149.5	151.5	148.9
C-2	114.6	114.4	116.5	116.4	113.7	114.5	115.9	115.7
C-3	132.0	132.1	132.8	132.7	134.6	133.0	133.9	131.7
C-4	118.8	118.0	119.0	119.2	120.2	120.0	118.5	118.1
C-5	127.4	128.8	129.7	129.1	131.3[d]	129.1	129.3	127.1
C-6	147.1	147.0	148.0	148.0	147.9	147.2	147.8	147.2
C-7	173.1	172.6	174.3	174.0	177.0	174.5	175.4	172.1
C-8	103.4	103.4	104.9	104.8	107.8	105.3	106.7	103.0
C-9	115.8	115.7	118.1	117.6 (broad)	118.9	116.4	119.6	114.7
C-10	128.2	129.1	128.7	128.6	130.3[d]	130.0	130.1	128.9
C-11	163.0	163.1	164.0	164.1	153.4	154.7	155.2	162.9
C-12[c]	20.1	20.2	20.9	20.7	20.5	20.5	20.4	20.0
C-13	27.4	27.3	28.4	28.4	n.o	27.8	28.4	27.4
C-14[c]	20.3	20.2	20.8	20.7	20.5	20.5	20.7	20.3
C-15[c]	20.3	20.2	20.5	20.7	20.5	20.4	20.6	20.4
C-1′	136.2	136.1	138.9	139.0	135.2	136.1	137.6	50.5
C-2′	129.1	129.1	129.7	129.7	131.2	120.08[e]	120.65[e]	32.5
						119.98	120.54	
C-3′	127.4	127.4	128.7	128.2	118.2	117.16[e]	117.55[e]	19.7
						116.85	117.24	
C-4′	—	127.5	127.5	127.3	144.9	162.46[e]	163.09[e]	13.5
						159.20	159.85	
C-16	54.5	54.6	54.8	54.6	30.8	—	—	—

[a] The ^{13}C NMR spectrum of compound **2** could not be recorded because of the low solubility.

[b] Taken from Ref. 13.

[c] Assignments may be interchanged.

[d] Assignment tentative.

[e] Splittings are due to C–F couplings.

Schiff bases of *o*-hydroxy aromatic aldehydes and ketones is not immediately obvious. One contributing factor could be the hydrogen bond formed between the OH group at C-6 and the oxygen function at C-7, although the OH-6 chemical shift of ~8 ppm is not signalling a very strong hydrogen bond. However, the fact that the frequency of OH-6 is shifted by >2 ppm compared with gossypol itself indicates that the hydrogen bonding has been strengthened. Furthermore, at low temperature, when exchange is slowed down sufficiently, the hydrogen bond is recognized by means of an isotope effect at C-7 (see previously). The steric interaction formed by H-11, C-11, C-8, C-9, C-1 and O-1 is clearly pushing the NH bond versus O-7, thereby causing a favourable hydrogen bond. The N—O distance is calculated as ~2.58 Å (Table 4). The NH chemical shift of ~13.5 ppm for **1** and **2** points towards a medium-strength hydrogen bond. The increase in chemical shift to 15.0 ppm for **3** and **4** can be ascribed partly to a slightly stronger hydrogen bond and partly to ring current effects.

The OH-1 protons of the gossypol Schiff bases cannot simultaneously form hydrogen bonds. Model calculations using **2aOH** show that the OH group is in the ring plane but not hydrogen bonded. Such a picture is also in line with the distinct solvent dependence of the OH-1 proton resonance, a feature not seen for the other XH resonances.

The chemical shift of C-7 points to the C7—O bond having considerable double bond character, as does the calculated C7—O bond length (Table 4). The enamine function is probably resonance assisted[36] (see also Scheme 1) but only to a minor degree. The present enamine definitely can be seen as different to that of the 3-nitro-5-chloro-2-hydroxyacetophenone, in which the C═NH group has a more positive charge.

EXPERIMENTAL

Compounds

±Gossypol (1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-5,5′-diisopropyl[2,2′-binaphthalene]-8,8′-dicarboxaldehyde) acetic acid was reacted with methylamine hydrochloride, methylamine ^{15}N hydrochloride, 4-aminoacetophenone, benzylamine and 4-fluoroaniline in the two solvents chloroform and ethanol. With methylamine hydrochloride and methylamine ^{15}N hydrochloride, ethanol was used; with 4-aminoacetophenone both ethanol and chloroform were used, whereas with benzylamine and 4-fluoroaniline only chloroform was used. All reactions were performed at ambient temperature. The pH of the reaction mixtures was adjusted to ~5–7 by adding sodium hydroxide in ethanol to methylamine hydrochloride and methylamine

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Table 2. The ^{1}H chemical shifts of compounds **1**–**4**[a]

	1 ($CDCl_3$)	**1** (THF-d_8)[b]	**2** ($CDCl_3$)	**2** (THF-d_8)[b]	**3** ($CDCl_3$)	**3** (THF-d_8)[b]	**4** ($CDCl_3$)	**4** (THF-d_8)[b]
NH	13.59	13.74 (13.76) [13.85]	13.24 (13.26)	13.30	14.85	15.01	15.00	15.12
$CH_{aldehyde}$	9.74	9.89 (9.96) [10.07]	9.62 (9.68)	9.78	10.16	10.43	10.08	10.35
OH-6	7.94	8.25 (8.38) [8.57]	7.98 (8.01)	8.25	7.8	8.21	7.84	8.21
CH_{arom}	7.59	7.52 (7.54) [7.63]	7.59 (7.61)	7.52	7.64	7.60	7.63	7.60
OH-1	5.61	7.30 (7.32) [7.81]	5.58 (5.64)	7.10	Not observed	7.25[e]	5.73	7.48
CH	3.72	3.72 (3.71) [3.78]	3.72 (not observed)	Overlap	3.72	3.75	3.73	3.77
CH_xN	4.65	4.71 (4.75) [4.86]	3.30 (3.33)[c]	3.27[d]	—	—	—	—
CH_3C_{arom}	2.11	2.01 (2.01) [2.08]	2.11 (2.12)	2.02	2.16	2.08	2.15	2.08
CH_3	1.52	1.49 (1.50) [1.54]	1.55 (1.54)	1.50	1.56	1.54	1.55	1.54
CH_3	1.51	1.47 (1.49) [1.58]	1.52 (1.53)	1.48	1.54	1.51	1.54	1.51
H-2′	~7.27	~7.3 (~7.3) [~7.4]	—	—	7.91	7.99	7.25	7.37
H-3′	~7.27	~7.3 (~7.3] [~7.4]	—	—	7.34	7.41	7.06	7.15

[a] Values in parentheses are recorded at −25 °C and values in square brackets at −55 °C.

[b] For THF-d_8 the CH_2 resonance at 3.58 ppm was used as reference. No temperature compensation is included.

[c] Showed a splitting of 5.1 Hz at −25 °C.

[d] The ^{15}N-enriched compound showed a splitting of 4.2 Hz.

[e] Assignment uncertain.

^{15}N hydrochloride and by the addition of acetic acid to 4-aminoacetophenone, benzylamine and 4-fluoroaniline. The crude products were purified by thin-layer chromatography (TLC) with the eluent system chloroform–methanol–hexane (8 : 1 : 1) or chloroform–acetone–hexane (8 : 1 : 1). The former was used for products between gossypol and methylamine hydrochloride or methylamine ^{15}N hydrochloride, whereas the latter was used for products between gossypol and 4-aminoacetophenone, benzylamine or 4-fluoroaniline.

NMR

The ^{1}H and ^{13}C NMR spectra of samples of non-deuterated and deuterated compounds were measured in $CDCl_3$ solutions using a Varian Mercury 300 spectrometer. Other solvents such as CD_2Cl_2 and tetrahydrofuran-d_8 were also used, the former at low temperature. The ^{1}H NMR spectra were recorded at 300 MHz with an acquisition time of 4.29 s and the ^{13}C spectra at 75.46 MHz with an acquisition time of 1.6 s. Tetramethylsilane (TMS) was used as internal reference.

The HMQC spectrum was recorded with an acquisition time of 0.2 s, a spectral width of 7000 Hz, 2048 points in the ^{1}H dimension and 30 kHz spectral width in the ^{13}C dimension; 512 increments and, aiming at a long-range coupling constant of 7.5 Hz, 288 transients were recorded for each increment, with a relaxation delay of 1.7 s.

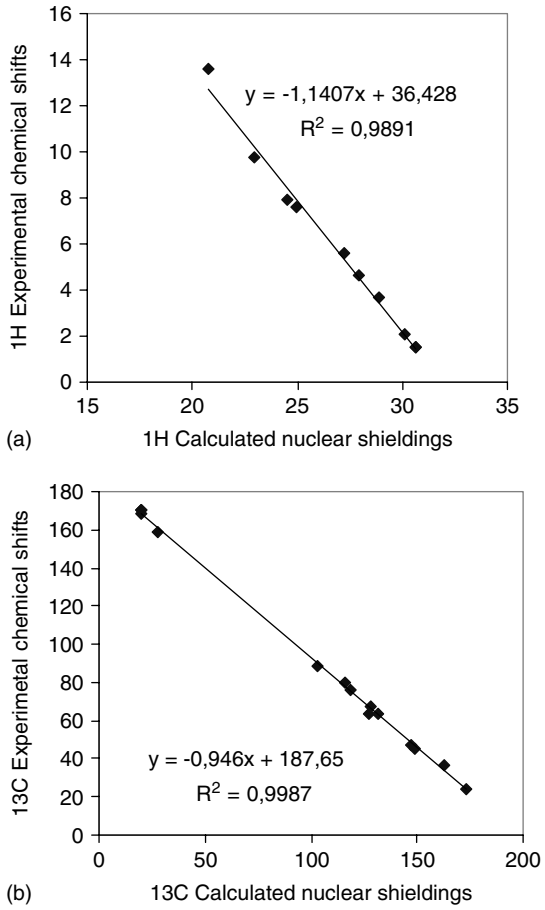

Figure 1. Plot of calculated ^{13}C nuclear shieldings of compound **1aOH** vs. measured chemical shifts of **1** (in $CDCl_3$).

Table 3. The ^{13}C and ^{1}H calculated nuclear shielding differences.[a]

	1aOH ^{13}C	**2a** ^{13}C	**2aOH** ^{13}C	**2b** ^{13}C	**4a** ^{13}C		**1aOH** ^{1}H
C-1	−1.7	−0.4	−1.8	0.2	−0.1	H_{arom}	−0.20
C-2	0.6	0.25	0.7	0	0.3	CH_3C-3	−0.05
C-3	−0.2	−0.3	−0.3	−0.8	0.1	H_{ald}	−0.26
C-4	1.2	0.9	0.7	0.7	1.1	OH-1	−2.14
C-5	−2.7	−2.0	−2.2	−1.8	−2.2	OH-6	1.31
C-6	3.3	3.3	3.3	3.3	3.3	NH	−3.91
C-7	18.1	20.2	18.0	20.1	21.8	CH	−0.72
C-8	−4.0	−3.2	−4.0	−3.0	−2.3	CH_3C	−0.06
C-9	−0.3	−1.2	−0.3	−1.5	−1.6	CH_3C	−0.06
C-10	1.0	0.5	0.9	0.2	0.8	CH_2	−0.29
C-11	−11.1	−11.8	−9.7	−12.2	−16.8		
C-12	−0.2	−0.2	−0.3	0	−0.2		
C-13	−0.6	−0.7	−0.6	−0.7	−0.7		
C-14	−0.3	−0.2	−0.3	−0.5	−0.5		
C-15	−0.1	−0.2	0.3	−0.2	−0.1		
C-16	−8.1	−10.3	−9.4	−10.3	—		

[a] Nuclear shielding of imine—enamine. Nuclear shieldings can be converted to chemical shifts by plotting chemical shift vs. nuclear shielding (see Fig. 1).

Table 4. Calculated (B3LYP DFT) bond lengths (in Å)

Bond	**1aOH**	**2a**	**2aOH**	**3aOH**
C1—C2	1.404	1.397	1.403	1.402
C2—C3	1.413	1.412	1.413	1.407
C3—C4	1.385	1.389	1.385	1.386
C4—C4a	1.413	1.411	1.414	1.411
C4a—C5	1.464	1.465	1.463	1.466
C5—C6	1.367	1.369	1.367	1.366
C6—C7	1.458	1.458	1.146	1.455
C7—C8	1.439	1.442	1.437	1.447
C8—C8a	1.468	1.467	1.468	1.471
C4a—C8a	1.436	1.430	1.437	1.435
C8—C11	1.406	1.401	1.408	1.397
C3—C12	1.512	1.512	1.512	1.510
C5—C13	1.529	1.528	1.530	1.529
C11—N	1.330	1.333	1.328	1.345
N—Cl6	1.455	1.450	1.449	1.398
Cl—O	1.374	1.385	1.374	1.376
C6—O	1.356	1.389	1.356	1.358
C7—O	1.272	1.270	1.274	1.270
O1—H	0.975	0.972	0.975	0.974
O6—H	0.988	0.986	0.988	0.987
N—H	1.030	1.029	1.030	1.031
C11—H	1.081	1.086	1.081	1.077
C4—H	1.092	1.083	1.082	1.082
N—O7	2.582	2.608	1.575	2.579

Assignments

The assignment of **1** in $CDCl_3$ at ambient temperature is done based on a HMBC spectrum showing the following cross-peaks, all values in ppm: 9.74, H_{ald} (54.5, CH_2; 173.1, C-α (one-bond); 7.52, H-4 (114.6, C-2; 118.8, C-4 (one-bond); ~7.27, H-2′, H-3′, H-4′ (129.1, 127.4 and 127.5, not resolved); 4.65, CH_2 (129.1, C-2′; 136.2, C-1′; 173.1, C-α); 3.72, CH (127.4, C-5; 128.2, C-10; 147.1, C-6); 2.11, CH_3 (20.1, CH_3(12) (one-bond); 114.6, C-2; 118.8, C-4; 132.0, C-3); $(CH_3)_2$, 20.3 (20.3, $(CH_3)_2$ (one-bond); 27.4, CH; 128.2, C-5). These peaks lead to an unambiguous assignment. The assignment of compounds **2, 3** and **4** is done by analogy because the chemical shifts are very similar and the compounds are too insoluble for HMBC analysis. The assignments are confirmed by comparison with the butylamine Schiff base of gossypol.[13] For C-α the assignment is assured by observation of the variation in chemical shift as a function of the substituent at N, something that is not found to any large degree for the remaining carbons. For compound **4** the assignment of the carbon resonances of the extra benzene ring can be done based on C–F coupling constants. The assignments reached are very similar to those of the butylamine derivative of Ref. 13.

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