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^{1}H NMR, FT-IR and MS studies and PM5 semiempirical calculations of complexes between the Schiff base of gossypol with 2-(aminomethyl)-15-crown-5 and Ca^{2+}, Pb^{2+} and Ba^{2+} cations

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ABSTRACT: A new Schiff base of gossypol with 2-(aminomethyl)-15-crown-5 (GSCB) was shown to be capable of complexation with Ca^{2+}, Ba^{2+} and Pb^{2+} cations. This process of complex formation was studied by electrospray ionization mass spectrometry, ^{1}H NMR and FT-IR spectroscopy and by the PM5 semiempirical method. It was found that gossypol Schiff base can form a 1:2 complex with Ca^{2+}, 1:1 or 1:2 complexes with Pb^{2+} and only a 1:1 complex with Ba^{2+} cation. In all complexes the Schiff base of gossypol exists as an enamine–enamine tautomer. The cations are coordinated through oxygen atoms from the crown part, lone pairs at the N-atoms and O-atoms of the $O_1H(O_1{\cdot}H)$ hydroxyl groups. The structures of these complexes were calculated by the PM5 semiempirical method and are discussed. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: gossypol; crown ethers; gossypol Schiff base; gossypol Schiff base complexes; Ca^{2+}; Pb^{2+}; Ba^{2+}; binding constants; ^{1}H NMR; COSY; Fourier transform infrared; electrospray ionization mass spectrometry; PM5

INTRODUCTION

Gossypol, 2,2′-bis(8-formyl-1,6,7-trihydroxy-5-isopropyl-3-methylnaphthalene) is a yellow, toxic compound isolated from cottonseed oil,[1–4] and has been shown to be an effective antifertility agent in the male population of different species.[5–11] It has been reported also that gossypol inhibits the growth of American and African trypanosomes because it is a powerful inhibitor of their metabolism.[12,13] Moreover, it has been found that gossypol is an unspecific inhibitor because it competes with the coenzyme NAD, and therefore it inhibits most of the dehydrogenases that use this coenzyme.[14,15] This polyphenolic compound possesses reversible inhibition activity to calcineurin[16] and in the presence of Cu^{2+} and Fe^{3+} cations it is also capable of nicking supercoiled DNA.[17] Furthermore, this compound and its derivatives have been extensively studied as possible antimalarial drugs,[18] and as potential cures for diseases such as HIV infections[19–21] and cancer.[22–24]

Gossypol Schiff bases also possess biological activity similar to that of gossypol but their lower toxicity due to the absence of aldehyde groups means that they can be safely used in medical therapy.[17,25]

Gossypol Schiff bases can occur in imine–imine and enamine–enamine tautomeric forms, which are analogues of aldehyde–aldehyde and ketol–ketol tautomeric forms of gossypol, respectively (Scheme 1).[21,26–29] Different tautomers of gossypol and gossypol Schiff bases form complexes with various metal cations.[30–33] The new Schiff base studied in this paper is a combination of two parts characterized by two different functions: the crown ether part well known as an effective and highly selective agent in the reaction of complexation of alkali and alkaline earth metal cations,[34–41] and the gossypol part showing high biological activity. Mutual competition of these parts of gossypol Schiff base in the complexation of various metal cations is a very interesting problem, and stimulated our study of the properties of complexation of gossypol Schiff base with Ca^{2+}, Pb^{2+}, Ba^{2+}, Sr^{2+}, Mg^{2+}, Co^{2+}, Ni^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+} and Bi^{3+} cations by electrospray ionization (ESI) mass spectrometric, spectroscopic and semiempirical methods.

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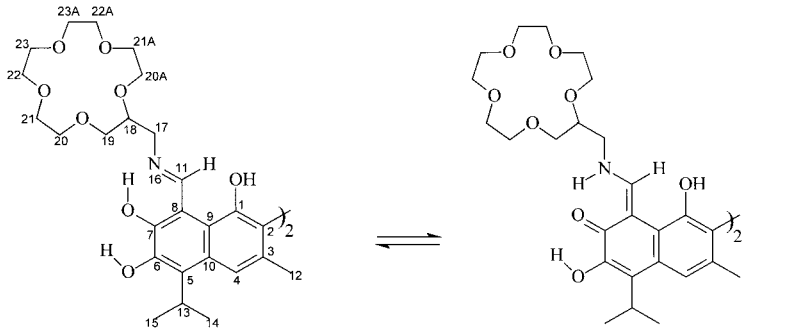


imine - imine (GSCB) enamine - enamine (GSCB)

Scheme 1

EXPERIMENTAL

The Schiff base of gossypol with 2-aminomethyl-15-crown-5 was synthesized as described previously.[28] The perchlorates $Ca(ClO_4)_2$, $Pb(ClO_4)_2$ $Ba(ClO_4)_2$, $Sr(ClO_4)_2$, $Mg(ClO_4)_2$, $Co(ClO_4)_2$, $Ni(ClO_4)_2$, $Fe(ClO_4)_2$, $Cu(ClO_4)_2$, $Zn(ClO_4)_2$, $Fe(ClO_4)_3$ and $Bi(ClO_4)_3$ were obtained from Sigma and were used without any purification. The salts are hydrates, however, and it was necessary to dehydrate them by several (6–10) evaporations from a 1:5 mixture of acetonitrile and absolute ethanol. The dehydration of the perchlorates was detected by the FT-IR spectra in acetonitrile.

Spectral-grade CH_3CN solvent was stored over 3Å molecular sieves for several days. All manipulations with the substances were performed in a carefully dried and CO_2-free glove-box.

Preparation of complexes of gossypol Schiff base with Ca^{2+}, Pb^{2+} and Ba^{2+} cations

The 1:1 and 1:2 complexes of Schiff base of gossypol with Ca^{2+}, Pb^{2+} and Ba^{2+} cations were obtained by adding suitable amounts (1.96×10^{-4} or 3.92×10^{-4} mol) of $M(ClO_4)_2$ (M = Ca, Pb, Ba) dissolved in acetonitrile to the gossypol Schiff base (1.96×10^{-4} mol) dissolved in absolute ethanol. The solvents were evaporated to dryness under reduced pressure and the oil residue was dissolved in dry CH_3CN for FT-IR or in CD_3CN for ^1H NMR measurements. All complexes were orange–brown.

The purity of the complexes was controlled by NMR and elemental analysis: $C_{52}H_{72}N_2O_{32}Ca_2Cl_4$ (calculated C 42.81, H 4.97, N 1.92; found C 42.82, H 4.95, N 1.91%); $C_{52}H_{72}N_2O_{24}PbCl_2$ (calculated C 45.02, H 5.23, N 2.02; found C 45.04, H 5.21, N 2.01%); $C_{52}H_{72}N_2O_{32}Pb_2Cl_4$ (calculated C 34.83, H 4.05, N 1.56; found C 34.82, H 4.04, N 1.55%); $C_{52}H_{72}N_2O_{24}$-$BaCl_2$ (calculated C 47.41, H 5.51, N 2.13; found C 47.39, H 5.52, N 2.15%).

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

Mass spectrometric measurements

ESI mass spectra were recorded on a Waters/Micromass (Manchester, UK) ZQ mass spectrometer equipped with a Harvard Apparatus syringe pump. All sample solutions were prepared in acetonitrile. The measurements were performed for the solutions of the Schiff base of gossypol (2×10^{-6} mol dm^{-3}) with Ca^{2+}, Pb^{2+}, Ba^{2+}, Sr^{2+}, Mg^{2+}, Co^{2+}, Ni^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+} and Bi^{3+} cations (1×10^{-5} mol dm^{-3}) taken separately. The samples were infused into the ESI source using a Harvard pump at a flow-rate of 20 µl min^{-1}. The ESI source potentials were capillary 3kV, lens 0.5 kV and extractor 4 V. In the case of standard ESI mass spectra the cone voltage was 30 V. The source temperature was 120 °C and the desolvation temperature was 300 °C. Nitrogen was used as the nebulizing and desolvation gas at flow-rates of 100 and 300 l h^{-1}, respectively.

^1H NMR measurements

NMR spectra of the 1:1 and 1:2 complexes of gossypol Schiff base with $Ca(ClO_4)_2$, $Pb(ClO_4)_2$ and $Ba(ClO_4)_2$ were recorded in CD_3CN using a Varian Gemini 300 MHz spectrometer. All spectra were locked to the deuterium resonance of CD_3CN.

^1H NMR measurements in CD_3CN were carried out at operating frequency 300.075 MHz, flip angle pw = 45°, spectral width sw = 4500 Hz, acquisition time 2.0 s, relaxation delay $d_1 = 1.0$ s and $T = 293.0$ K and using TMS as the internal standard. No window function or zero filling was used. The digital resolution was 0.2 Hz per point. The error of chemical shift value was 0.01 ppm.

FT-IR measurements

The FT-IR spectra of gossypol Schiff base and its 1:2 complex with $Ca(ClO_4)_2$ and also 1:1 complexes with $Pb(ClO_4)_2$ and $Ba(ClO_4)_2$ were recorded in 0.05 mol dm^{-3} acetonitrile solutions. The spectrum of the solvent was subtracted form the spectra of the complexes and the ranges of its absorption were omitted.

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, Germany) equipped with a DTGS detector, resolution 2 cm^{-1}, NSS = 125.

Elemental analysis

Elemental analysis was carried out on a Perkin-Elmer CHN 240 instrument.

Semiempirical PM5 calculations

PM5 semiempirical calculations were performed using the Win Mopac 2002 program.[42] In all cases full geometry optimization was carried out without any symmetry constraints.[43]

RESULTS AND DISCUSSION

The structures of the imine–imine and enamine–enamine tautomers of the studied Schiff base together with the atom numbering are shown in Scheme 1.

Electrospray mass spectrometry

ESI mass spectrometric data for the mixtures of GSCB with various cations are given in Table 1. They show the disappearance of the characteristic *m/z* signals which could be assigned to the respective complexes formed between GSCB and cations such as Sr^{2+}, Mg^{2+}, Co^{2+}, Ni^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+} and Bi^{3+}. Thus, GSCB molecules are not able to form stable complexes with these cations.

The characteristic *m/z* signals of various types of GSCB complexes with Ca^{2+}, Pb^{2+} and Ba^{2+} cations are found in the ESI spectra (Table 1). In the presence of excess amount of Ca^{2+} cations, GSCB forms only complexes of 1:2 stochiometry because no *m/z* signal of $[GSCB + M]^{2+}$ cation characteristic of the 1:1 complex is detected in the ESI mass spectrum. Under the same experimental conditions, the GSCB molecule forms two various types of complexes with Pb^{2+}, which is indicated by the *m/z* signals assigned to the 1:1 complex $[GSCB + M]^{2+}$ and 1:2 complex $[GSCB + 2M]^{4+}$ in the ESI spectrum. In contrast to the situation with Pb^{2+} cations, the GSCB molecule forms only the 1:1 complex with the Ba^{2+} cation.

Table 1. ESI mass spectrometric data for complexes of gossypol Schiff base with various cations[a]

M^{x+}	*m/z*		
	$[AC + M]^{2+}$	$[GSCB + M]^{2+}$	$[GSCB + 2M]^{4+}$
Mg^{2+}	—	—	—
Ca^{2+}	144	—	265
Sr^{2+}	—	—	—
Ba^{2+}	193	559	—
Zn^{2+}	—	—	—
Pb^{2+}	228	594	348
Ni^{2+}	—	—	—
Co^{2+}	—	—	—
Cu^{2+}	—	—	—
Fe^{2+}	—	—	—
Fe^{3+}[b]	—	—	—
Bi^{3+}[b]	—	—	—

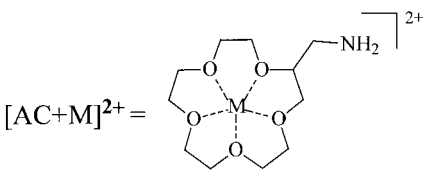
[a] GSCB = gossypol Schiff base with 2-(aminomethyl)-15-crown-5; AC = 2-(aminomethyl)-15-crown-5.
[b] $[AC + M]^{3+}$, $[GSCB + M]^{3+}$, $[GSCB + 2M]^{6+}$.

Apart from the signals assigned to $[GSCB + M]^{2+}$ and $[GSCB + 2M]^{4+}$ complexes, the ESI mass spectra also revealed a signal characteristic of $[AC + M]^{2+}$ cation. This signal was assigned to the cation of the complexed aminomethyl crown part after fragmentation of GSCB (Scheme 2). Further information on the structures of the complexes of GSCB with the cations studied was obtained from spectroscopic and semiempirical studies.

The binding constants (K_a) for GSCB complexes with Ca^{2+}, Ba^{2+} and Pb^{2+} were obtained from the ESI mass spectra, following the method described in Ref. 44. The values of $\log K_a$ determined by the ESI method are shown in Table 2.

NMR studies

The ^1H NMR data of GSCB and its 1:1 and 1:2 complexes with Ca^{2+}, Pb^{2+} and Ba^{2+} cations are given in Table 3. The COSY spectra of all complexes demonstrate the existence of the enamine–enamine



M = Ca, Pb, Ba.

Scheme 2

Table 2. Binding constants for GSCB–2Ca^{2+}, GSCB–2Ba^{2+}, GSCB–Pb^{2+} and GSCB–2Pb^{2+} complexes derived by ESI-MS

Complex	Solvent	ESI logK_a
GSCB–Pb^{2+}	CH_3CN	2.6
GSCB–2Pb^{2+}	CH_3CN	4.2
GSCB–2Ba^{2+}	CH_3CN	8.5
GSCB–2Ca^{2+}	CH_3CN	10.4

tautomer of GSCB within these complexes. This is confirmed by the coupling between the $N_{16}H$ (12.36 ppm) and $C_{11}H$ (9.70 ppm) or $C_{17}H$ (4.02 ppm) protons. An examplary COSY spectrum of the complex GSCB with Ca^{2+} cations is shown in Fig. 1.

In all ^1H NMR spectra the signals of the O_1H ($O_{1'}H$), O_6H ($O_{6'}H$) and $N_{16}H$ ($N_{16'}H$) protons are observed separately in the ranges 6.41–7.02, 7.69–8.15 and 12.36–13.28 ppm, respectively. With the formation of the complexes of GSCB with 2Ca^{2+} cations, the signals of the O_1H ($O_{1'}H$) protons are shifted slightly towards lower frequencies. Thus, the strength of the hydrogen bonds in which these OH groups are involved becomes more comparable. In the spectra of GSCB–Pb^{2+} and GSCB–Ba^{2+} complexes the chemical shifts of the signals of O_1H and ($O_{1'}H$) protons are different. One signal remains in the same position and the other is shifted towards lower frequencies. This result shows that one of the OH groups is more strongly hydrogen bonded than the other. The chemical shifts of the signals of O_6H and ($O_{6'}H$) protons are comparable to those observed in the GSCB spectrum, whereas the chemical shift of the $N_{16}H$ ($N_{16'}H$) protons is shifted towards higher frequencies. This result indicates the decreasing strength of the intramolecular NH···O=C hydrogen bond both due to the involvement of the lone electron pair on N_{16} atom and the conformational changes about the C_{11}—N_{16} ($C_{11'}$—$N_{16'}$) bond in the complexation process.

The signals of the protons from the crown part are observed in the GSCB spectrum in the range 3.35–3.84 ppm as a multiplet. With the complex formation of the GSCB molecules with the studied Ca^{2+}, Pb^{2+} and Ba^{2+} cations, the corresponding signals shift towards lower frequencies and occur in a slightly wider range, indicating different interactions of these cations with the oxygen atoms of the crown part. Probably these interactions are not fixed but different oxygen atoms can be involved in them. The strongest interactions between the oxygen atoms of the crown part are observed for the GSCB–2Ca^{2+} complex, because in this case the signals of the protons are strongly shifted toward higher ppm values and the multiplet occurs in the widest range.

FT-IR studies

Figure 2(a) presents the FT-IR spectrum of the 1:2 complex of GSCB with $Ca(ClO_4)_2$, and the spectra of the 1:1 complexes of GSCB with $Pb(ClO_4)_2$ and $Ba(ClO_4)_2$ are given in Fig. 2(b) and (c), respectively. All spectra are compared with that of GSCB in acetonitrile solution. The GSCB molecule and its complexes with Ca^{2+}, Pb^{2+} and Ba^{2+} cations in acetonitrile solution exist as the enamine–enamine tautomer, as indicated by the absence of the bands characteristic of the imine–imine tautomer assigned to the naphthalene ring vibrations at about 1550 cm^{-1}.[27]

In the range 3700–3000 cm^{-1}, where ν(O–H) vibrations occur, there are two bands at 3484 and 3375 cm^{-1} in the GSCB spectrum. The band at 3484 cm^{-1} can be assigned to the stretching vibrations of O_1H and $O_{1'}H$ groups, and the band at lower wavenumbers (3375 cm^{-1}) to the stretching vibrations of O_6H and $O_{6'}H$ groups, both engaged in relatively weak intramolecular hydrogen bonds. This assignment is confirmed by the ^1H NMR data and is in agreement with the PM5 semiempirical calculations. It is also in agreement with our interpretation of the FT-IR spectra of gossypol discussed in earlier papers.[27,45] Furthermore, according to these interpretations, the vibrations of the strongest hydrogen-bonded proton in the O···HN hydrogen bond should be observed

Table 3. ^1H NMR chemical shifts (ppm) and coupling constants J (Hz) between $C_{11}H$–$N_{16}H$ protons for GSCB and its complexes with Ca^{2+}, Pb^{2+} and Ba^{2+} cations in CD_3CN solutions[a]

	Chemical shift (ppm)										
Compound	$C(CH_3)_2$	CH_3	$HC(CH_3)_2$	H–O_1	H–C_4	H–O_6	H–C_{11}	H–N_{16}	H_{17}	H_c[b]	$J_{C11H–N16H}$
GSCB	1.48 (d)	2.00 (s)	3.44 (sept)	6.41 (s)	7.59 (s)	8.12 (s)	9.71 (d)	13.28 (m)	3.48 (t)	3.35–3.84 (m)	13.85
GSCB–2Ca^{2+}	1.50 (d)	2.00 (s)	3.47 (sept)	6.46 (s) 6.48 (s)	7.59 (s)	7.69 (s)	9.70 (d)	12.36 (m)	4.02 (t)	3.69–4.46 (m)	13.36
GSCB–Pb^{2+}	1.51 (d)	2.00 (s)	3.76 (sept)	6.42 (s) 6.93 (s)	7.59 (s)	8.14 (s)	9.72 (d)	12.87 (m)	3.46 (t)	3.41–4.35 (m)	12.42
GSCB–Ba^{2+}	1.52 (d)	2.00 (s)	3.82 (sept)	6.42 (s) 7.02 (s)	7.59 (s)	8.15 (s)	9.71 (d)	12.95 (m)	3.49 (t)	3.39–4.14 (m)	12.59

[a] s, Singled; d, doublet; t, triplet; sept, septet; m, multiplet.
[b] H_c: the proton signals from the crown ether part of the gossypol Schiff base.

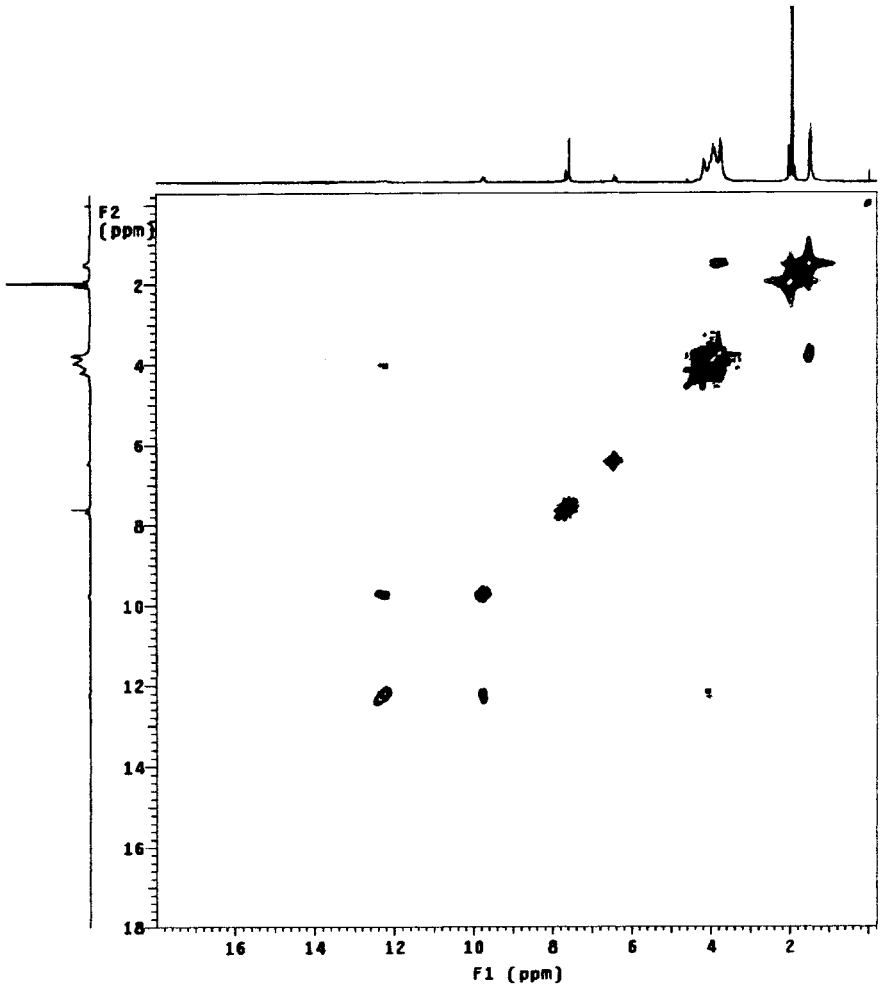


Figure 1. Two dimensional COSY spectrum of the 1:2 complex of GSCB with Ca^{2+} in CD_3CN solution

in the FT-IR spectrum in the region of about 3000 cm^{-1}. This absorption is readily visible in the spectra taken in chloroform solutions.[27] The low intensity of this absorption can be explained by the fact that the proton is more localized at the N_{16} atom than at the O_7 atom and that in the intramolecular $N_{16}H\cdots O_7$ hydrogen bond it shows almost imperceptible proton polarizability.[46–49]

The FT-IR spectrum of the 1:2 complex of GSCB with Ca^{2+} cations is shown in Fig. 2(a) and the corresponding spectrum on an extended scale in the range 1675–1500 cm^{-1} in Fig. 3(a). As a result of complexation of Ca^{2+} cations by the GSCB molecule, some changes in the spectrum in the range 3500–3000 cm^{-1} and a new band at 1632 cm^{-1} are observed. The appearance of the new band at 1632 cm^{-1} indicates that the intramolecular hydrogen bonds formed between $N_{16}H$ ($N_{16'}H$) and O_7 ($O_{7'}$) atoms from the carbonyl groups of the GSCB molecule have weakened. On the other hand, because of the interaction of the N_{16}, $N_{16'}$ lone electron pairs with Ca^{2+} cations, the NH protons have become more acidic i.e. the $NH\cdots O{=}C$ hydrogen bond should be stronger. This contradiction can be explained by the conformational changes about the N_{16}—C_{11} bond after the complex formation of GSCB with Ca^{2+} cations. Such an explanation is in good agreement with the ^1H NMR data and also with our PM5 semiempirical calculation.

The interaction of the Ca^{2+} cations with the lone electron pairs of the N_{16} and $N_{16'}$ atoms can be directly concluded from the so-called Bohlmann band characteristic of N-bases with lone electron pair at the nitrogen atom, which occurs in the region 3000–2800 cm^{-1} (Fig. 4). In the spectrum of GSCB the Bohlmann band is observed at 2873 cm^{-1}, whereas in the spectrum of the GSCB–$2Ca^{2+}$ complex this band vanishes completely and a new band arises at about 2895 cm^{-1}.

The $\nu(O_1H)$ and $\nu(O_6H)$ vibrations arise as an intense broad band in the GSCB–$2Ca^{2+}$ spectrum with a maximum at 3426 cm^{-1} instead of two separate bands observed in the spectrum of GSCB. This result demonstrates that both types of OH groups are hydrogen bonded with more comparable strength than in the case of other GSCB–cation complexes. This is also confirmed by the ^1H NMR data (Table 3). Furthermore, PM5 calculations show that these OH groups are involved in different types of hydrogen bonds.

The FT-IR spectra of the 1:1 complexes of GSCB with

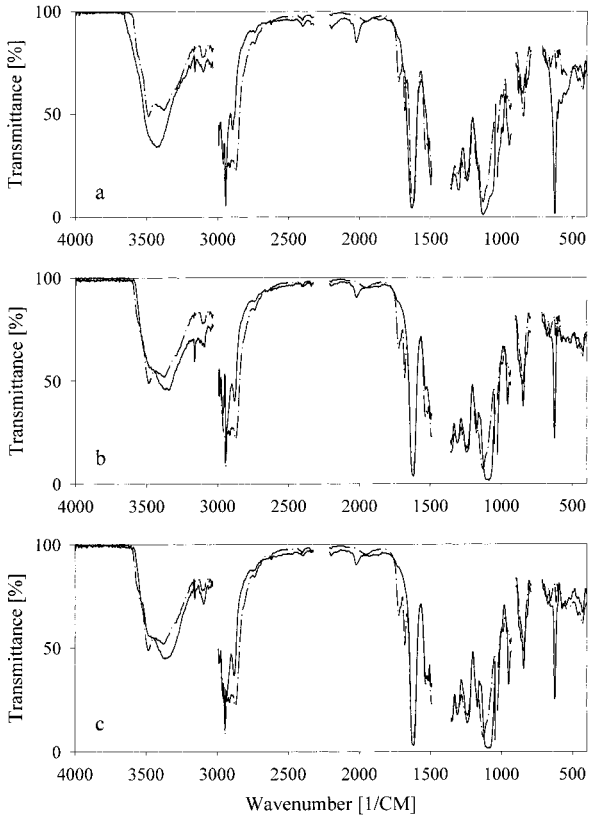


Figure 2. FT-IR spectra of the acetonitrile solutions of (solid lines) the complexes of GSCB with cations and (dot-dashed lines) for comparison spectra of GSCB, (a) 1:2 complex with Ca^{2+}, (b) 1:1 complex with Pb^{2+} and (c) 1:1 complex with Ba^{2+}

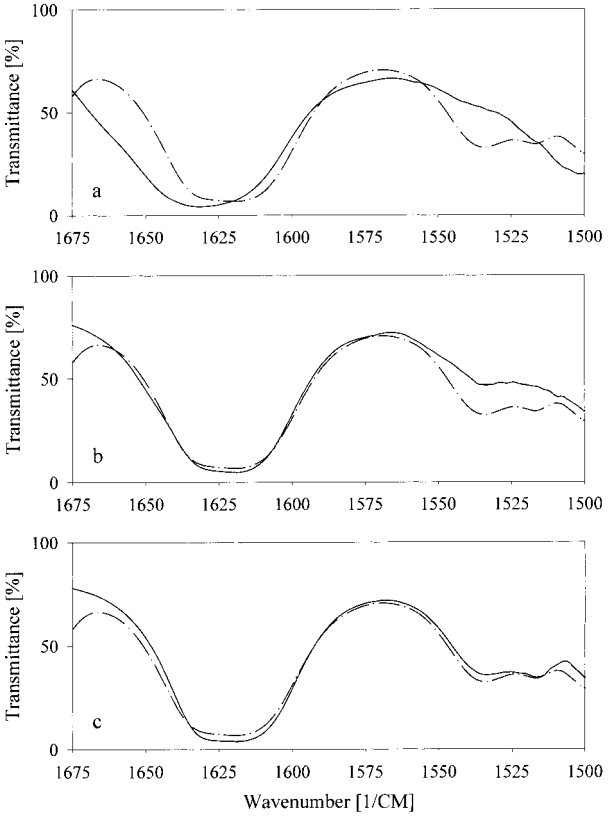


Figure 3. FT-IR spectra of acetonitrile solutions on an extended scale of (solid lines) the complexes of GSCB with cations and (dot-dashed lines) for comparison spectra of GSCB, (a) 1:2 complex with Ca^{2+}, (b) 1:1 complex with Pb^{2+} and (c) 1:1 complex with Ba^{2+}

Pb^{2+} and Ba^{2+} cations are shown in Fig. 2(b) and (c) and the corresponding spectra on an extended scale in the range 1675–1500 cm^{-1} in Fig. 3(b) and (c), respectively. After complexation of Pb^{2+} or Ba^{2+} cations by GSCB, the changes in both spectra are very similar. In these spectra the band at 3484 cm^{-1} assigned to the $\nu(O_1H)$ stretching vibrations partially vanishes and a new band at 3344 cm^{-1} appears, whereas the band at a lower wavenumbers (3375 cm^{-1}) of the $\nu(O_6H)$ vibrations remains at an almost unchanged position at 3378 cm^{-1}. The position of the new band at 3344 cm^{-1} indicates the involvement of one of the O_1H or $O_{1'}H$ hydroxyl groups in a slightly stronger intramolecular hydrogen bond within the GSCB–Pb^{2+} or GSCB–Ba^{2+} complexes. This result is in agreement with NMR and semiempirical data.

The information on the interactions of the free electron pairs at N_{16} and $N_{16'}$ atoms with Pb^{2+} and Ba^{2+} cations in the respective complexes can be extracted from the FT-IR spectra shown in Fig. 4. The Bohlmann band observed in the FT-IR spectrum of GSCB shifts slightly in the spectra of the 1:1 complexes of GSCB with Pb^{2+} and Ba^{2+} cations from 2873 to 2882 cm^{-1}. This shift however, is weaker than that in the spectrum of the 1:2 GSCB–Ca^{2+} complex. This result indicates that the nitrogen atom coordinates Ca^{2+} cations more strongly than Pb^{2+} and Ba^{2+} cations and no differences in the coordination strength between the Pb^{2+} and Ba^{2+} are observed.

PM5 calculations

The heats of formation (HOF) of the enamine–enamine form of GSCB and its complexes with Ca^{2+}, Pb^{2+} and

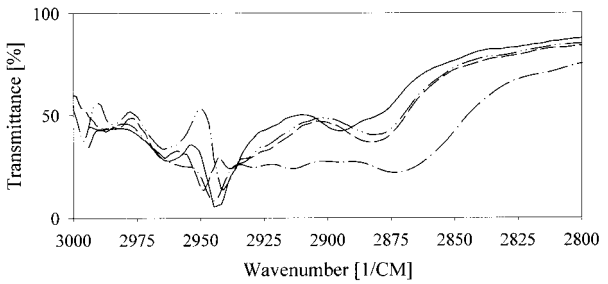


Figure 4. FT-IR spectra of the acetonitrile solutions on an extended scale of GSCB with (solid line) 1:2 complex with Ca^{2+}, (double dot-dashed line) 1:1 complex with Pb^{2+}, (dashed line) 1:1 complex with Ba^{2+} and (dot-dashed line) for comparison spectrum of GSCB

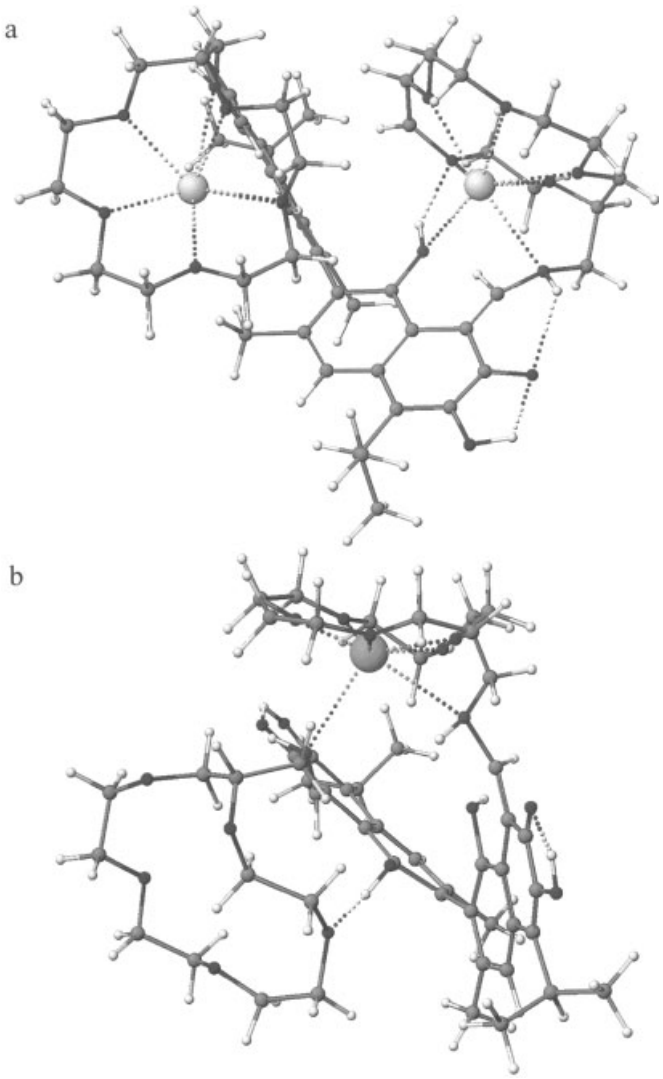
Table 4. Heat of formation of GSCB (in enamine–enamine form) and its complexes with Pb^{2+} and Ca^{2+} cations calculated by the PM5 method (WinMopac 2002)

Compound	HOF (kcal mol^{-1})[a]
GSCB	−414.49
GSCB–Pb^{2+} (complexed)	−618.29
GSCB–Pb^{2+} (non-complexed)	−393.45
GSCB–$2Pb^{2+}$ (complexed)	−624.22
GSCB–$2Pb^{2+}$ (non-complexed)	−372.79
GSCB–Ca^{2+} (complexed)	−607.56
GSCB–Ca^{2+} (non-complexed)	−400.35
GSCB–$2Ca^{2+}$ (complexed)	−639.78
GSCB–$2Ca^{2+}$ (non-complexed)	−386.33

[a] 1 kcal = 4.184 kJ.

Ba^{2+} cations are displayed in Table 4. Unfortunately, the structure of the GSCB–Ba^{2+} complex cannot be calculated by the PM5 method.

The data in Table 4 demonstrate that the most stable complexes are formed between GSCB and two Ca^{2+} cations. For the 1:1 complex of GSCB with Ca^{2+} only half of the GSCB molecule is involved in the coordination of Ca^{2+} cation and the other half remains free. This explains the preferential formation of the 1:2 complex between GSCB and Ca^{2+} cations in the presence of excess of these cations in the solution. In the case of Pb^{2+} cation, the formation of the 1:1 and 1:2 complexes is possible and the structure of the 1:2 complex is slightly favoured.



Scheme 3

The calculated structures of the GSCB:$2Ca^{2+}$ and GSCB:Pb^{2+} are given in Scheme 3(a) and (b), respectively. It is interesting that the structure of the GSCB–$2Pb^{2+}$ complex is very similar to that of the GSCB–$2Ca^{2+}$ complex.

The interatomic distances between oxygen atoms and cations and partial charges of the cations and O-atoms are given in Table 5. The lengths and angles of the hydrogen bonds formed between the O-atom from the crown and O_1H and $O_{1'}H$ protons are collected in Table 6. The partial charge of the cations increases for weaker cation complexation by the N- and O-atoms from the GSCB.

The semiempirical calculations on the GSCB–$2Ca^{2+}$ and GSCB–$2Pb^{2+}$ complexes have shown that not only oxygen atoms of the crowns but also the oxygen atoms of the O_1H and $O_{1'}H$ groups interact strongly with the cation. Furthermore, these groups form intramolecular hydrogen bonds with O-atoms of the crown parts (Table 6). These hydrogen bonds are stronger in the GSCB–Pb^{2+} complex than in the GSCB–$2Pb^{2+}$ and GSCB–$2Ca^{2+}$ complexes, which is in agreement with FT-IR and NMR data discussed above.

CONCLUSIONS

A new Schiff base of gossypol with 2-(aminomethyl)-15-crown-5 was shown to be characterized not only by potential biological activity but also by the ability to form selective complexes with Ca^{2+}, Pb^{2+} and Ba^{2+} cations. It was demonstrated that many other cations (Sr^{2+}, Mg^{2+}, Co^{2+}, Ni^{2+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+} and Bi^{3+}) cannot form stable complexes with the new Schiff base.

Ca^{2+} cations form stable 1:2 complexes, whereas the Pb^{2+} and Ba^{2+} form 1:1 complexes with GSCB. Additionally with Pb^{2+} cation GSCB can also form stable complex of 1:2 stoichiometry. The formation of such complexes was established from the ESI mass spectra.

Spectroscopic measurements and semiempirical calculations showed that the structures of 1:2 complexes of GSCB with Ca^{2+} and Pb^{2+} cations are comparable. The same is true for the 1:1 complexes of GSCB with Pb^{2+} and Ba^{2+} cations. In all complexes the cations are coordinated in the enamine–enamine tautomeric form by the lone pairs of N-atoms and oxygen atoms from the crown part of the molecules.

Table 5. Interatomic distances (Å) and partial charges for O and N atoms of GSCB and coordinated cation in Pb^{2+} and Ca^{2+} complexes calculated by the PM5 method (WinMopac 2002)

Complex	Cation partial charge	O, N-atom	O, N-atom partial charge	O, N-atom–cation distance (Å)
GSCB–Pb^{2+}	0.904	$N_{16}H$	−0.494	2.72
		$N_{16'}H$	−0.492	2.71
		$O_{19–20}$	−0.358	2.20
		$O_{21–22}$	−0.356	2.19
		$O_{23–23A}$	−0.357	2.19
		$O_{21A–22A}$	−0.358	2.20
		$O_{18–20A}$	−0.357	2.19
		O_1H	−0.702	3.97
		$O_{1'}H$	−0.692	4.87
GSCB–$2Pb^{2+}$	0.898	$N_{16}H$	−0.279	2.25
		$O_{19–20}$	−0.355	2.19
		$O_{18–20A}$	−0.357	2.22
		$O_{21A–22A}$	−0.355	2.20
		$O_{21–22}$	−0.359	2.22
		$O_{23–23A}$	−0.360	2.21
		O_1H	−0.385	2.51
		$O_{1'}H$	−0.387	2.50
GSCB–Ca^{2+}	0.885	$N_{16}H$	−0.263	2.16
		$O_{19–20}$	−0.358	2.25
		$O_{18–20A}$	−0.360	2.25
		$O_{21–22}$	−0.365	2.26
		$O_{21A–22A}$	−0.378	2.29
		$O_{23–23A}$	−0.378	2.29
		O_1H	−0.396	2.63
		$O_{1'}H$	−0.861	6.35
GSCB–$2Ca^{2+}$	0.882	$N_{16}H$	−0.264	2.15
		$O_{19–20}$	−0.357	2.23
		$O_{18–20A}$	−0.360	2.25
		$O_{21–22}$	−0.364	2.27
		$O_{21A–22A}$	−0.378	2.29
		$O_{23–23A}$	−0.378	2.29
		O_1H	−0.392	2.62
		$O_{1'}H$	−0.397	2.63

Table 6. Length (Å) and angle (°) of the hydrogen bond formed between hydroxyl groups and O-atoms of the crown ether part (O_1H) for some GSCB–cation complexes calculated by the PM5 method (WinMopac 2002)

Complex	O-atom	Hydrogen bond length (Å)	Hydrogen bond angle (°)
GSCB–Pb^{2+}	$O_{19'–20'}$	2.57	157.2
GSCB–$2Pb^{2+}$	$O_{18–20A}$	2.81	153.5
GSCB–Ca^{2+}	$O_{21A–22A}$	2.74	159.8
GSCB–$2Ca^{2+}$	$O_{21A–22A}$	2.76	156.8

In the 1:2 complexes of GSCB with Ca^{2+} or Pb^{2+}, both oxygen atoms from the O_1H and ($O_{1'}H$) groups are also engaged in coordination process and simultaneously hydrogen bonded with the O-atoms of the crowns.

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