Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 104 (2013) 497–504

Contents lists available at SciVerse ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Synthesis, FT-IR, ^{1}H, ^{13}C NMR, ESI MS and PM5 studies of a new Mannich base of polyether antibiotic – Lasalocid acid and its complexes with Li^+, Na^+ and K^+ cations

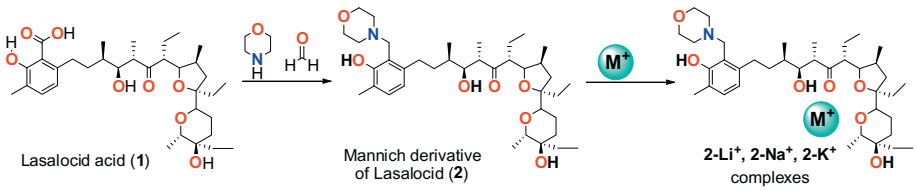
Adam Huczyński [a,*], Jacek Rutkowski [a], Bogumil Brzezinski [a], Franz Bartl [b]

[a] Faculty of Chemistry, Adam Mickiewicz University, ul. Umultowska 89b, 61-614 Poznań, Poland
[b] Institute of Medical Physics and Biophysics, Charité, Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

HIGHLIGHTS

- A new *ortho*-phenol Mannich base of Lasalocid was synthesized by chemoselective one-pot reaction.
- The compound obtained is a useful ligand for complexation of monovalent cations.
- Spectroscopic characterization of the ligand and prepared complexes is given.
- Semiempirical calculations of structures of the complexes studied are presented.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 20 August 2012
Received in revised form 24 November 2012
Accepted 29 November 2012
Available online 8 December 2012

Keywords:
Mannich base synthesis
Complexes with monovalent cations
Structural studies
Spectroscopic studies
Hydrogen bonds
Semiempirical calculations

ABSTRACT

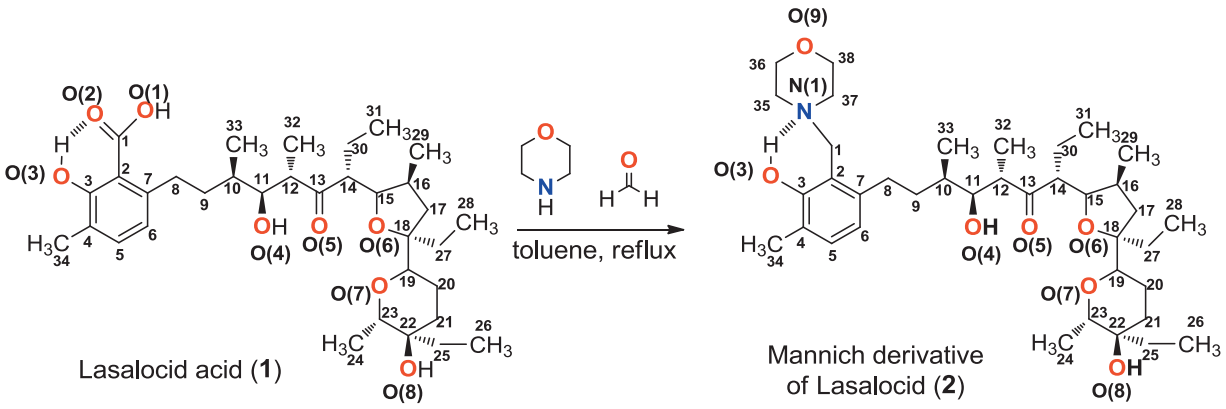
The polyether antibiotic Lasalocid acid has been converted to its Mannich base derivative by a chemoselective one-pot reaction with formaldehyde and morpholine through the decarboxylation process. Spectroscopic studies of the structure of this new derivative have shown that in this *ortho*-phenol Mannich base the O—H···N intarmolecular hydrogen bond is present. The compound forms complexes with Li^+, Na^+ and K^+ cations of exclusively 1:1 stoichiometry. The structures of these complexes have been studied and visualized by semi-empirical calculation based on results of spectrometric and spectroscopic investigation. It is demonstrated that in contrast to Lasalocid acid the novel Mannich type derivative forms preferential complexes with Li^+ cation.

Introduction

Lasalocid acid (Scheme 1) and its derivatives represent a large class of ionophore antibiotics. These compounds show a broad spectrum of bioactivity e.g. antibacterial, antifungal, antiparasitic and antiviral [1–7]. Lasalocid acid sodium salt is used as an antibiotic for poultry and as a growth promoter for ruminants [1,2]. Lasalocid acid isolated from *Streptomyces lasaliensis* is able to form complexes with monovalent and divalent cations and transport them across lipid bilayer. The influx of Na^+ into the cell of Gram-positive bacteria leads to changes in pH and to an increase in the osmotic pressure inside the cell, causing swelling and vacuolization, eventually leading to cell death. The effectiveness of this process strongly depends on the structure of the Lasalocid metal cation complexes [1–4]. In previous studies we have shown that the complex of Lasalocid with allylamine has higher anti-bacterial activity than pure Lasalocid acid [8]. We found also that Lasalocid acid and its complexes are strong cytotoxic agents towards cancer cell lines. The cytostatic activity of Lasalocid and its complexes

* Corresponding author.
E-mail address: adhucz@amu.edu.pl (A. Huczyński).

1386-1425/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.saa.2012.11.106



Scheme 1. Mannich reaction conditions.

with amines against human cancer cell lines is higher than that of cisplatin, indicating that Lasalocid and its complexes are promising candidates for new anticancer drugs [9].

Since various *N*-functionalized morpholines show pharmacological activity, we synthesized a new morpholine Mannich base derivative of Lasalocid acid. Such compounds are reported to exert a number of important physiological activities such as antiemetic or growth stimulant. They are also used in the treatment of inflammatory diseases, pain, migraine, and asthma [10–12]. In this contribution, the nature of complexes formed between Mannich base of Lasalocid acid with morpholine (**2**) and monovalent cations (Li^+, Na^+ and K^+) is studied using ^1H NMR, ^{13}C NMR, FTIR, ESI-MS as well as PM5 semiempirical methods. The structures of these complexes with metal cations are discussed in detail.

Experimental

Materials and methods

Lasalocid sodium salt was isolated from veterinary premix – Avatec® 20 (Alpharma Inc.), which contains about 20% pure Lasalocid sodium salt. Formaldehyde, morpholine and the perchlorates $LiClO_4$, $NaClO_4$ and $KClO_4$ were commercial products of Sigma and used without any further purification. Since the salts were hydrates, it was necessary to dehydrate them at several (6–10 times) evaporation steps from a 1:5 mixture of acetonitrile and absolute ethanol. The dehydration of perchlorates was followed by recording of their FT-IR spectra in acetonitrile.

CD_3CN and CH_3CN spectral-grade solvents were stored over 3 Å molecular sieves for several days. Handling of the compounds was performed in a carefully dried, CO_2-free glove box.

*Isolation of Lasalocid sodium salt (**1**)*

Lasalocid sodium salt was isolated from Avatec® 20 an anticoccidial feed additive distributed by Alpharma Inc. 100 g of Avatec was dissolved in dichloromethane. The solvent was evaporated under reduced pressure and the crude product obtained was purified by dry column vacuum chromatography (gradient solvent mixture hexane/dichloromethane) giving 11 g pure Lasalocid sodium salt.

Preparation of Lasalocid acid

Lasalocid sodium salt (1.5 g) was dissolved in dichloromethane (100 mL) and stirred vigorously with a layer of aqueous sulphuric acid (100 mL, $c = 0.75$ mol/L). The organic layer containing **1** was washed with distilled water and the dichloromethane was evaporated under reduced pressure to dryness to produce the acid.

*Synthesis of Mannich base of Lasalocid acid (**2**)*

A mixture of Lasalocid (1 g, 1.69 mmol), paraformaldehyde (253 mg, 8.45 mmol) and morpholine (736 mg, 8.45 mmol) in toluene (200 mL) was stirred and heated under reflux for 5 h. Water was collected in a Dean–Stark distilling trap during the reflux period. The resulting solution was diluted with petroleum ether and transferred to the separatory funnel and washed once with water and then one with 0.05 M HCl. The organic layer was evaporated under reduced pressure giving 1.6 g of pale yellow resin, which was then purified by dry column flash chromatography, giving 817 mg (75% yield) of final product. Elemental analysis calc. for $C_{38}H_{63}NO_7$: C 70.66%, H 9.83%, N 2.17%, O 17.34% found: C 70.64%, H 9.85%, N 2.14%, O 17.37%. The exemplary spectra are included in the Supplementary material.

*Synthesis of 1:1 complexes of **2** with monovalent cations*

The 0.07 mol/L solutions of 1:1 complexes of **2** with monovalent cations (Li^+, Na^+ and K^+) were obtained by adding equimolar amounts of $MClO_4$ salt (M = Li, Na, K) dissolved in water-free acetonitrile (3.5 mL, $c = 0.05$ mol/L) to acetonitrile solution of **2** (3.5 mL, $c = 0.05$ mol/L). The solvent was evaporated under reduced pressure to dryness and the oily residue was dissolved to the appropriate volume (2.5 mL) using dry CH_3CN or CD_3CN, respectively.

NMR measurements

The ^1H and ^{13}C NMR spectra of **2** and its complexes (0.07 mol/L) with Li^+, Na^+ and K^+ were recorded in CD_3CN solutions using Bruker Avance 600 MHz spectrometer. All spectra were locked to deuterium resonance of CD_3CN. The ^1H NMR measurements were carried out at the operating frequency 600.0018 MHz and the ^{13}C NMR spectra at the operating frequency 150.885 MHz. The temperature 298.0 K and TMS as the internal standard were used in both cases. No window function or zero filling was used. The errors of the ^1H and ^{13}C NMR chemical shift values were 0.01 ppm and 0.1 ppm, respectively. The ^1H and ^{13}C NMR signals were assigned using 2-D (COSY, HETCOR, NOESY and HMBC) whose examples are shown in the Supplementary materials (Figs. S1–S10). 2-D spectra were recorded using standard pulse sequences from Bruker pulse-sequence libraries.

FT-IR measurements

The FT-IR spectra of **2** and its complexes with monovalent cations were recorded in acetonitrile solution (0.07 mol/L). 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 = 64. The Happ-Genzel apodization function was used.

Mass spectrometry

The ESI (Electrospray Ionization) mass spectra were recorded on a Waters/Micromass (Manchester, UK) ZQ mass spectrometer equipped with a Harvard Apparatus syringe pump. All samples were prepared in acetonitrile. The measurements were performed for the two types of samples: the solutions of **2** (5×10^{-5} mol/L) with: (a) each of the cations Li^+, Na^+ and K^+ (2.5×10^{-4} mol/L) taken separately and (b) the cations Li^+, Na^+ and K^+ (5×10^{-5}/3 mol/L) taken together. Samples were introduced directly into the ESI source using a Harvard pump at the flow-rate of 20 μl min^{-1}. The ESI source potentials were: capillary 3 kV, lens 0.5 kV, and extractor 4 V. The standard ESI mass spectra were recorded at the cone voltages (cv) was 10, 30, 50, 70, 90, 110 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 dm^3 h^{-1}, respectively. Positive ion mode was selected for mass spectrometric experiments. Full scans were recorded in the mass range *m/z* 200–1000, and the mass resolution was of 1 unit. The ESI MS spectra of the 1:1 complex of 2 with Li^+, Na^+, and K^+ recorded at various cone voltage values are shown in the Supplementary material (Figs. S11–S14).

PM5 semi-empirical calculation

PM5 calculations were performed using the Win Mopac 2007 program at the semiempirical level (Cache Work System Pro Version 7.5.085 – Fujitsu) [13,14]. PM5 quantum semiempirical method uses the Schrödinger equation to determine bond strengths, atomic hybridizations, partial charges, and orbitals from the positions of the atoms and the net charge.

Results and discussion

Synthesis

*Synthesis of Mannich base of Lasalocid acid (**2**)*

Design of procedures to obtain semi-synthetic derivatives of Lasalocid acid (**1**) (Scheme 1) is challenging because its structure is stable neither in strongly acidic nor in strongly basic conditions. Additionally, since the structure of Lasalocid comprises many different functional groups (i.e. carboxylic, ketone, aromatic, etheric hydroxyl groups) it was important for the synthetic transformation to be highly chemoselective. Taking into account the above it was deduced that a Mannich reaction would be ideal for conversion of carboxylic group of Lasalocid to dialkylaminomethyl group since the reaction can be carried out under neutral conditions and is compatible with all of the other functional groups of Lasalocid. The Mannich reaction is a classic method for the preparation of nitrogen-containing compounds and therefore a very important carbon–carbon bond-forming reaction in organic synthesis [15–17]. It has been successfully employed as a key step in syntheses of natural products and in medicinal chemistry [17–19]. When chemically different reactive sites, capable of reacting independently with the aminomethylating agent, are present in the substrate's molecule, the selectivity of the reaction is substantially determined by the relative reactivity of each reactive centre. In the Lasalocid acid molecule three types of reactive sites are present, i.e. alkyl keto group, positions 5 and 6 in salicylic acid moiety, and carboxylic group. Previous studies have shown that aminomethylation of phenols is achieved with formaldehyde and amines under acidic conditions using the Mannich reaction, which occurs readily in *ortho*- and *para*-positions affording substituted phenols [20,21]. It has also been shown that alkyl keto group readily reacts under acidic conditions [22,23]. However, Lasalocid is very unstable in acidic environment and higher temperatures. For this reason we chose mild conditions for the Mannich reaction using only three substrates (Lasalocid acid, morpholine and paraformaldehyde 1:1:1) to perform a one-pot reaction in toluene solutions under reflux. Mannich base of Lasalocid acid (**2**) was easily isolated in pure form after purification by dry column vacuum chromatography yielding a pure product with relatively low 12% yield (Scheme 1). The low yield of the reaction was unsatisfactory therefore we performed this reaction with five fold excess of morpholine and paraformaldehyde. The change in stoichiometry of the reaction gave a yield of 75%. Note that the chemoselectivity of this reaction did not change and that the second aminomethyl group was not introduced to the Lasalocid acid molecule under these reaction conditions.

*Synthesis of complexes of **2** with metal cations*

The solutions of 1:1 complexes of **2** with monovalent cations (Li^+, Na^+ and K^+) were obtained by adding equimolar amounts of $MClO_4$ salt (M = Li, Na, and K) dissolved in acetonitrile to acetonitrile solution of **2**. The solvent was evaporated under reduced pressure to dryness and the oily residue was dissolved to the appropriate volume using dry CH_3CN or CD_3CN, respectively. The complexes have no tendency to crystallize and therefore were studied in the solution.

The structures of product **2** and its complexes were determined using the ESI-MS, FT-IR, ^1H NMR, ^{13}C NMR and PM5 semiempirical methods and are discussed in detail herein. The ^1H- and ^{13}C NMR signals were assigned using two-dimensional spectra such as COSY, HETCOR, NOESY, HMBC shown in the Supplementary materials.

*Spectroscopic studies of **2***

FT-IR spectroscopy

In Fig. 1 the FT-IR spectrum of Lasalocid acid (**1**) (dashed line) is compared with that of its Mannich base (**2**) (solid line). In the spectrum of **2** (solid line), the bands assigned to the ν(O—H) and ν(C=O) stretching vibrations of the carboxylic group, present in the spectrum of Lasalocid acid at 3200–2700 cm^{-1} and 1652 cm^{-1}, vanish completely indicating the absence of carboxylic group with the formation of the respective Mannich base **2**. The band assigned to the ν(C=O) vibrations of the ketone group is present at 1712 cm^{-1} in FT-IR spectra of **1** and **2** indicating that the Mannich reaction was chemoselective and no transformation of ketone group occurs.

^1H and ^{13}C NMR spectroscopy

In the ^{13}C NMR spectrum of Mannich base **2** (Table S1), the most characteristic signal of C(1) atom of the methylene group at *N* atom was observed at 57.6 ppm, while the signal of C(1) atom of carboxyl group of Lasalocid acid (**1**) was at 173.2 ppm. The assignment of the salicylic aromatic ring moiety was carried out on the basis of two- and three-bond long-range correlation detected in the HMBC spectrum. The correlation of the proton of methylene group $C(1)H_2$ at 3.76 ppm with the ^{13}C NMR signals at 118.9 ppm (C-2), 157.4 ppm (C-3) and 140.5 ppm (C-7) indicated the presence of a morpholinemethyl group on C-2 atom (Table S1, Supplementary materials) and led to a conclusion that the morpholinemethyl group is present at C-2 atom (Scheme 1).

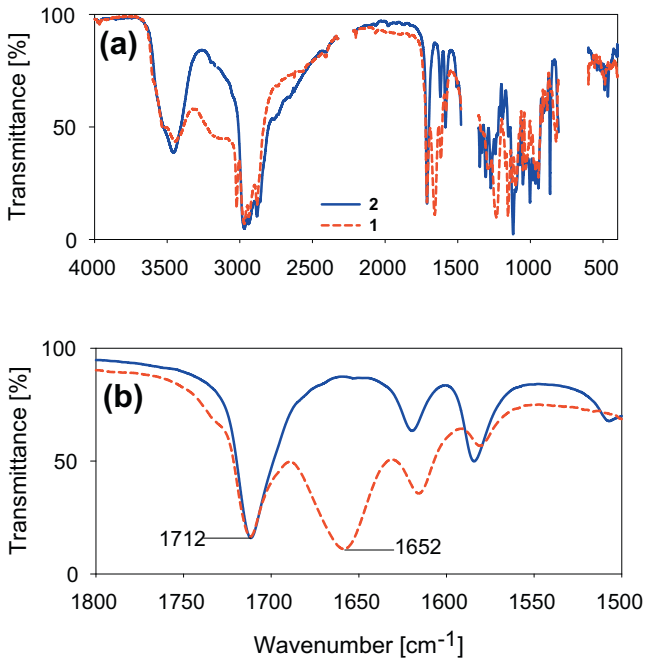


Fig. 1. The FT-IR spectra of: **1** (- - -) and **2** (––), recorded in CH_3CN: (a) 4000–400 cm^{-1}; (b) 1800–1500 cm^{-1}.

Table 1
Heat of formation (kcal/mol) of **2** and its complexes with the cations calculated by PM5 method.

Complex	HOF (kcal/mol)	ΔHOF (kcal/mol)
2	−378.16	–
2+$Li^+_{uncomplexed}$	−254.91	−72.21
2+$Li^+_{complexed}$	−327.12	
2+$Na^+_{uncomplexed}$	−236.11	−33.96
2+$Na^+_{complexed}$	−270.07	
2+$K^+_{uncomplexed}$	−261.12	−29.47
2+$K^+_{complexed}$	−290.68	

$\Delta HOF = HOF_{2+M\ complexed} - HOF_{2+M\ uncomplexed}$, M-metal cation.

Phenolic Mannich bases having the aminomethyl group in the *ortho* position form the O—H···N intramolecular hydrogen bond. The equilibrium between hydrogen-bonded and proton transfer forms was also observed and discussed by several authors [24,25].

In the ^{1}H NMR spectrum of **2** the most significantly shifted signal at 11.20 ppm is assigned to the proton of the O(3)H group at the aromatic ring involved in the intramolecular O(3)H···N hydrogen bond.

*Spectroscopic studies of 1:1 complexes of **2** with Li^+, Na^+ and K^+ cations*

ESI mass spectrometry

The ESI MS spectra of the 1:1 complexes of **2** with Li^+, Na^+, and K^+ recorded at various cone voltage values are shown in the Supplementary material in Figs. S11–S13 (Supplementary information), respectively. The ESI mass spectra of the complexes of **2** with Li^+, Na^+ and K^+, recorded at cone voltage 10 V, show intense peaks at *m/z* 652, 668, 684 respectively, indicating the formation of complexes of exclusively 1:1 stoichiometry. With increasing cone voltage, the intensity of the *m/z* signals of the 1:1 complexes (ion **A** in Scheme 2) decreases and the intensity of two fragment ion signals increases as shown in Figs. S11–S13. The fragmentary cation **B** is formed by abstraction of the part of the molecule containing a morpholine moiety group due to the charge-remote fragmentation mechanism [31,32] giving the respective cation observed at *m/z* 565, 581, 597, respectively. The ESI MS data of the complexes of **2** indicate that no abstraction of water molecule in the fragmentation process occurs, while dehydration process has always been observed during the ESI MS fragmentation process of Lasalocid and its ester derivatives. Furthermore, the ESI spectra of the Li^+, Na^+ and K^+ complexes with **2** show characteristic signals at *m/z* 361, 377, 393, respectively, assigned to fragment ion **C**, formed directly from the molecular cation, by cleavage of the C(11)—C(12) bond. Previously, Lopes et al. proposed a mechanism of the formation of fragment ion **C** for complexes of the Lasalocid salts with monovalent cations [26]. In this mechanism a six-membered intermediate facilitates a E_i type β-elimination leading to cation **C** (Scheme 2) [26–28] This mechanism is promoted by the monovalent metal cation withdrawing electron density from the carbonyl group due to the ion–dipole interaction [28] and is characteristic of Lasalocid salts and Lasalocid ester complexes [28–31].

The ESI-MS spectrum of the 1:1:1:3 mixture of $LiClO_4$, $NaClO_4$, $KClO_4$ and **2**, measured at *cv* = 10 V (Fig. S14) shows three signals at *m/z* 652, 668 and 684 characteristic of the 1:1 complexes of **2** with Li^+, Na^+ and K^+ cations, respectively. The intensity of the signal assigned to the **2**–Li^+ complex is the highest, clearly indicating that **2** preferentially forms complexes with Li^+ cations. The intensities of the signals of **2**–Na^+ and **2**–K^+ complexes are comparable, but significantly lower than that of **2**–Li^+ complex, demonstrating that **2** shows much lower affinity to Na^+ and K^+ cations.

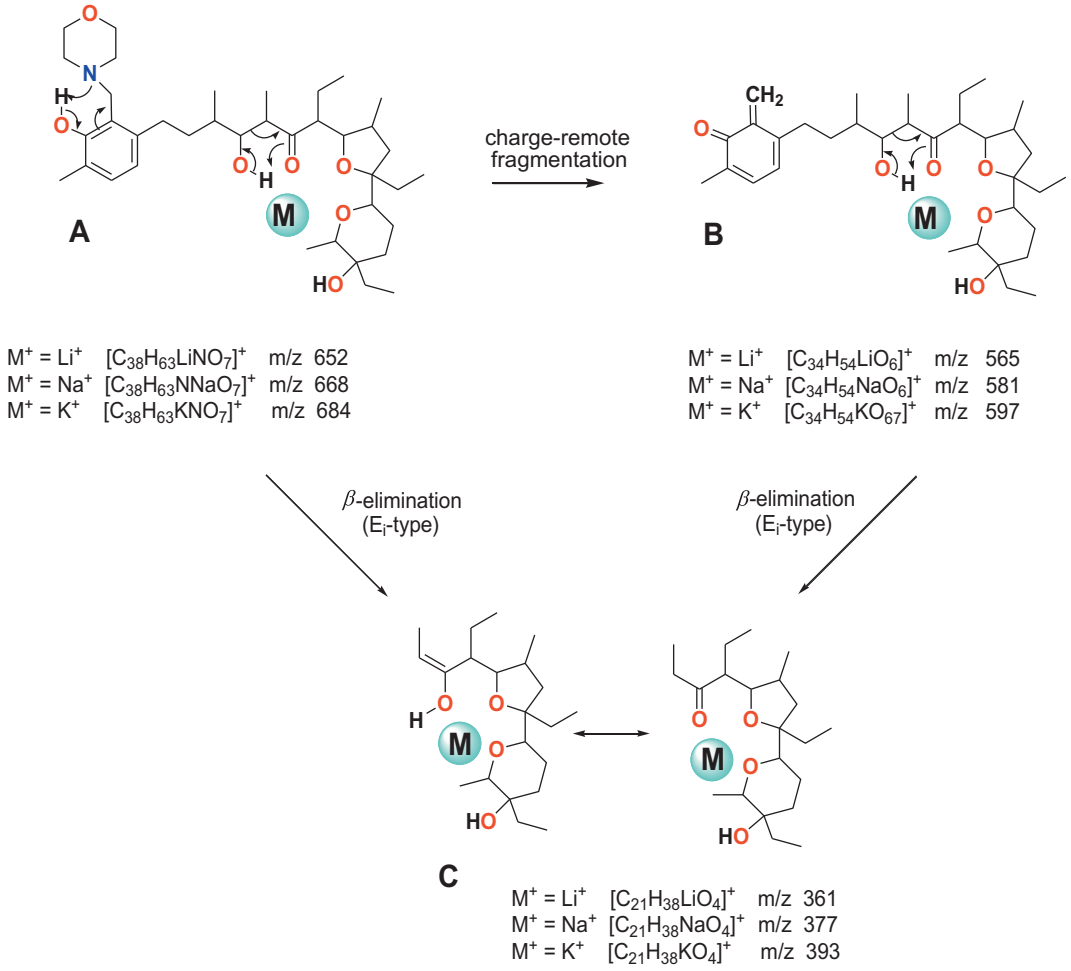
^{1}H and ^{13}C NMR spectroscopy

The most important differences Δ(ppm) between the respective chemical shifts observed in the spectrum of **2** and the spectra of its 1:1 complexes with Li^+, Na^+ and K^+ cations all in CD_3CN are collected in Supplementary materials (Table S1). The signals assigned to the O(4)H and O(8)H protons in the ^{1}H NMR spectrum of **2** arise as a doublet at 2.74 ppm and a singlet at 2.99 ppm, respectively, indicating that both protons are involved in only weak hydrogen bonds (Fig. 2). In the ^{1}H NMR spectra of 1:1 complexes formed between **2** and $LiClO_4$, $NaClO_4$, and $KClO_4$, the most shifted signals are found at *ca.* 11.35 ppm, assigned to O(3)H proton of the phenolic group, demonstrating that in the complexes the intramolecular O(3)H···N hydrogen bond is still present. In these spectra the signals of O(4)H and O(8)H protons are separate (Fig. 2) and shifted, depending on the kind of the cation, towards lower ppm values indicating that the hydrogen bonds in which these groups are involved, are weaker than and different from those present in the structure of **2**.

The interactions between the oxygen atoms of the molecule of **2** with Li^+ cation are clearly indicated in the ^{13}C NMR spectra by the shifts of C(13) carbon signal of the ketone group from 214.8 ppm (uncomplexed **2**) to 223.8 ppm (**2**–$LiClO_4$ complex) and the shifts of the signals of C(18), C(19), C(22) and C(23) carbon atoms (Tables S1 and S2), i.e. the atoms which are close the O atoms coordinating Li^+ cation. The same applies to the chemical shifts of the signals of all carbon atoms close to the O atoms which coordinate Na^+ and K^+ cations within the 1:1 complexes, although all the chemical shift changes are significantly lower in comparison with those observed in the ^{13}C NMR spectrum of **2**–$LiClO_4$ complex. These results demonstrate that the interactions of **2** with Na^+ or K^+ cations are clearly weaker than those with Li^+ cation (Table S1), which is also in agreement with the PM5 semiempirical calculations discussed below.

FT-IR spectroscopy

In Fig. 3 the FT-IR spectra of **2** and its 1:1 complexes with Li^+, Na^+ and K^+ are compared. In the spectrum of **2** (solid line) the broad band assigned to the O—H stretching vibrations arising in the range 3700–3250 cm^{-1} shows a complex structure following



Scheme 2. The proposed in source fragmentation pathways of **2** complexes with monovalent cations (M = Li^+, Na^+, and K^+). The calculated formula of fragment ion and exact *m/z* values of fragment ion added for clarity.

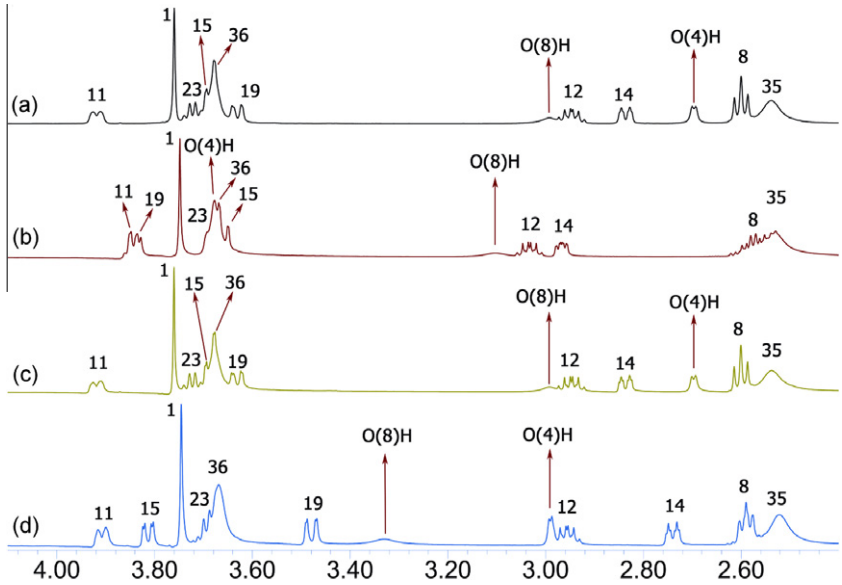


Fig. 2. Parts of the ^1H NMR spectra of: (a) **2**, (b) **2**–$LiClO_4$ complex, (c) **2**–$NaClO_4$ complex, (d) **2**–$KClO_4$ complex. The corresponding proton assignments to the structures of **2** and its complexes are shown.

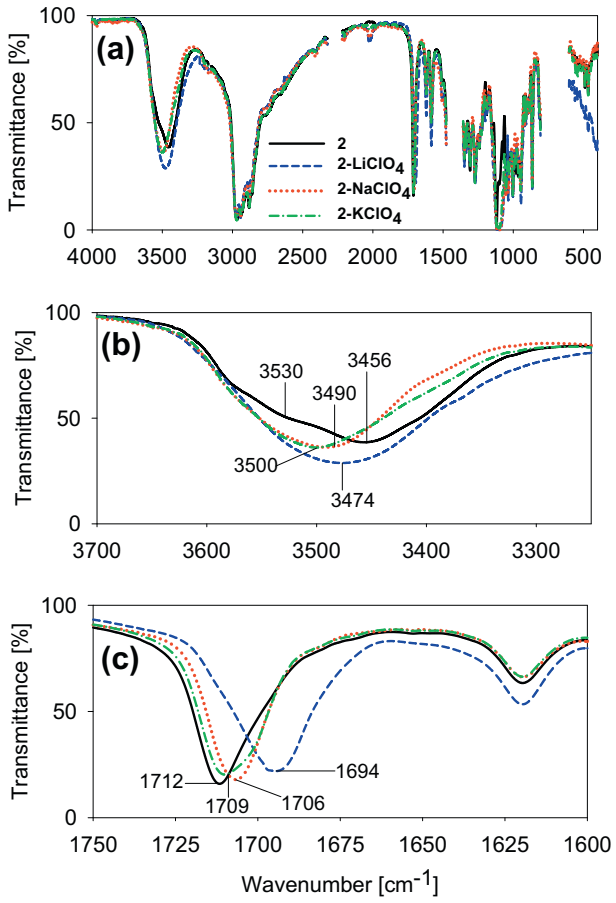


Fig. 3. FT-IR spectra of: (––) **2**, (—) **2**–$LiClO_4$, (···) **2**–$NaClO_4$, and (––) **2**–$KClO_4$ recorded in CD_3CN in the ranges of: (a) 4000–400 cm^{-1}; (b) ν(OH) and (c) ν(C=O) stretching vibrations.

from the involvement of O(4)H and O(8)H hydroxyl groups in intramolecular hydrogen bonds of various strength. The structure of this broad band changes with the complexation process and with the type of metal cation in the complex. The same is true with the band assigned to C=O stretching vibration of the ketone group. In the spectra of the 1:1 complexes of **2** with Li^+ (dashed line), Na^+ (dotted line), K^+ (dash-dotted line) the respective bands arise at 1694 cm^{-1}, 1706 cm^{-1} and 1709 cm^{-1}, respectively. This demonstrates that the carbonyl group ceases to be hydrogen bonded and is engaged in the coordination process of the metal cations. The interaction of C(13)=O oxygen atom with Li^+ cation is the strongest.

PM5 calculations

On the basis of the above-discussed, spectroscopic data of the structure of **2** is calculated using the PM5 semiempirical method (Tables 1 and 2). In this structure, shown in Fig. 4, the O(3)H phenolic group is hydrogen-bonded to the nitrogen atom of morpholine moiety in the Mannich base fragment and the C(13)=O(5) keto group is not involved in a hydrogen bond. The calculated parameters of the intramolecular O(3)H···N hydrogen bond present in **2** are similar to those calculated previously for *ortho*-dimethylaminomethylphenol by Koll et al. [32]. The molecule of **2** forms pseudo-cyclic structure stabilised by O(4)H···O(6) and O(8)H···O(4) intramolecular hydrogen bonds.

The calculated heat of formation (HOF) of the structure of **2** with O(3)H···N hydrogen bond is lower than that of its alternative structure without this bond or with a proton transferred to the nitrogen atom as shown in Scheme S1 (Supplementary materials), indicating that this structure is more favourable than that of both alternative types. This result is in agreement with the experimental FT-IR and ^{1}H NMR data. The data collected in Table 1 also show that the formation of complexes of **2** with the cations is energetically favourable. The calculated structures of **2** and its 1:1 complexes with various monovalent cations are shown in Fig. 4.

All these calculated complex structures are stabilised by intramolecular hydrogen bonds whose parameters depend on the coordinating cations (Table 2). This result is in agreement with the conclusion from the ^{1}H NMR and FT-IR spectra discussed above (see Figs. 2 and 3). The structures of the **2**–Li^+ and **2**–Na^+ complexes are stabilized by four intramolecular hydrogen bonds such as O(3)—H···N(1), O(8)—H···O(4), O(8)—H···O(7) and O(4)—H···O(6) which are shown in Fig. 4 and their geometric parameters are collected in Table 3. Additionally the structures of the **2**–Li^+ and **2**–Na^+ complexes are stabilized by four oxygen atoms coordinating the respective cation. In contrast, the **2**–K^+ complex is stabilized by three hydrogen bonds and five oxygen atoms coordinating K^+ cation. The interatomic distances between the coordinated cations and the coordinating oxygen atoms together with their partial charges are summarized in Table 2. These data demonstrate that with increasing ionic radii of the cations the coordination spheres of these cations change. Different are also the interatomic distances between the cations and the coordinating oxygen atoms, as well as their partial charges.

Table 2
The interatomic distances (Å) and partial charges for O atoms of **2** coordinating metal cations in complexes structures calculated by PM5 method.

Complex with monovalent cation	Monovalent cation partial charge	Coordinating atom	Coordinating atom partial charge	Distance (Å) coordinating atom → cation
2–Li^+	+0.492	O(4)	−0.443	2.11
		O(5)	−0.355	2.03
		O(6)	−0.379	2.00
		O(7)	−0.368	2.02
2–Na^+	+0.573	O(4)	−0.424	2.37
		O(5)	−0.364	2.32
		O(6)	−0.399	2.34
		O(7)	−0.389	2.31
2–K^+	+0.581	O(4)	−0.437	2.84
		O(5)	−0.360	2.80
		O(6)	−0.396	2.82
		O(7)	−0.375	2.75
		O(8)	−0.440	2.83

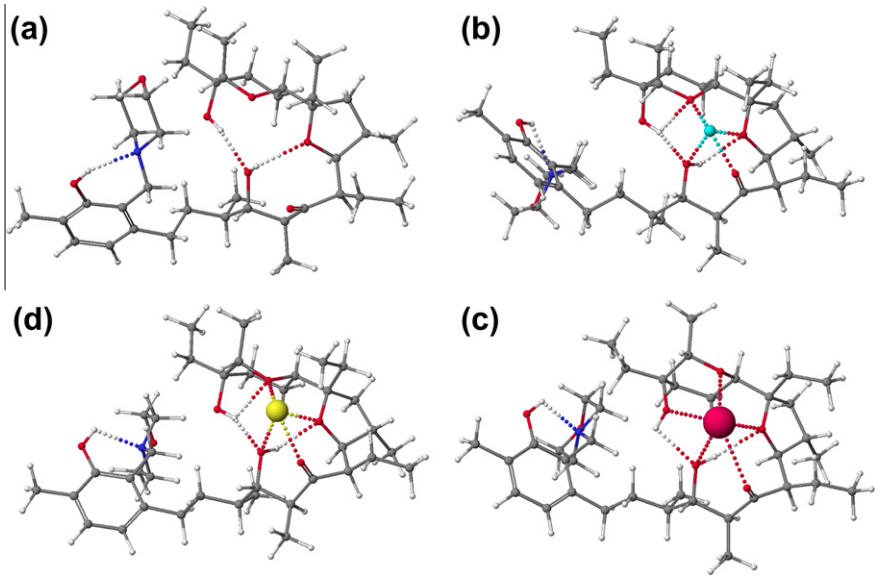


Fig. 4. The structures of: (a) **2** and its complexes, (b) **2**–Li^+, (c) **2**–Na^+, (d) **2**–K^+ calculated by PM5 semiempirical method (WinMopac 2007).

Table 3
The lengths (Å) and angles (°) of the hydrogen bond for **2** complexes calculated by PM5 method.

Compound	Atoms engaged in hydrogen bonds	Length (Å)	Angle (°)
2	O(3)—H···N(1)	2.70	147
	O(4)—H···O(6)	2.73	113
	O(8)—H···O(4)	2.85	161
2–Li^+	O(3)—H···N(1)	2.71	148
	O(8)—H···O(4)	2.95	165
	O(8)—H···O(7)	2.72	115
	O(4)—H···O(6)	2.53	111
2–Na^+	O(3)—H···N(1)	2.71	148
	O(8)—H···O(4)	2.97	160
	O(8)—H···O(7)	2.70	114
	O(4)—H···O(6)	2.60	109
2–K^+	O(3)—H···N(1)	2.71	148
	O(8)—H···O(4)	2.46	106
	O(4)—H···O(6)	2.97	140

Conclusions

For the first time the Lasalocid Mannich base derivative (**2**) and its 1:1 monovalent metal cation complexes have been obtained and characterized by spectroscopic (FT-IR, ^{1}H- and ^{13}C NMR), mass spectrometry (ESI-MS) and PM5 semiempirical methods. Lasalocid acid (**1**) a well known polyether antibiotic has been converted to its Mannich base derivative (**2**) by a simple one-pot reaction. Spectroscopic studies of the structure of **2** have shown that in this *ortho*-phenol Mannich base the O–H···N intarmolecular hydrogen bond is present. The ability to form complexes with Li^+, Na^+ and K^+ cations by **2** has been studied in detail. It has been demonstrated that **2** preferentially forms a complex with Li^+ cations. The electrospray ionization mass spectra indicated the formation of stable complexes of 1:1 stoichiometry. With increasing cone voltage values the fragmentation of the respective complexes is detected and is connected with the E_i type β-elimination, charge-remote fragmentation mechanism and dehydration processes. The formation of the complexes as well as the intramolecular hydrogen bonds stabilizing their structures is demonstrated by ^{1}H and ^{13}C NMR, FT-IR spectra and PM5 semiempirical calculations. It is shown that in the structure of **2** the oxygen atom of the C=O ketone group is always involved in coordination process of metal cation, especially with Li^+ because it is demonstrated that the strongest intramolecular hydrogen bonds are formed within structure of the **2**–Li^+ complex. In the complexes of **2** with monovalent cations we observe that the nitrogen atom of Mannich base, phenolic oxygen atom as well as morpholine moiety play no role in the complexation process.

Acknowledgements

Financial support from budget funds for science in years 2012–2013 – Grant *"Iuventus Plus"* of the Polish Ministry of Science and Higher Education-No. 0179/IP3/2011/71, is gratefully acknowledged. The financial support of the DAAD (The German Academic Exchange Service) is gratefully acknowledged by Adam Huczyński.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2012.11.106.

References

[1] R. Martineau, C. Benchaar, H.V. Petit, H. Lapierre, D.R. Ouellet, D. Pellerin, R. Berthiaumef, J. Dairy Sci. 90 (2007) 5714.
[2] M. Mitrovic, E.G. Schildknecht, Poultry Sci. 54 (1975) 750.
[3] J.W. Westley, Polyether Antibiotics Naturally Occurring Acid Ionophores, 1, Marcel Dekker Inc., New York, 1982.
[4] B.C. Pressman, Antibiotics and their complexes, 1, Marcel Dekker Inc., New York, 1985.
[5] A. Kart, A. Bilgili, Anim. J. Vet. Adv. 7 (2008) 748.
[6] A. Huczyński, A. Domańska, I. Paluch, J. Stefańska, B. Brzezinski, F. Bartl, Tetrahedron Lett. 49 (2008) 5572.
[7] R. Pankiewicz, D. Remlein-Starosta, G. Schroeder, B. Brzezinski, J. Mol. Struct. 783 (2006) 136.
[8] A. Huczyński, J. Janczak, J. Rutkowski, D. Łowicki, A. Pietruczuk, J. Stefańska, B. Brzezinski, F. Bartl, J. Mol. Struct. 936 (2009) 92.
[9] A. Huczyński, J. Rutkowski, J. Wietrzyk, J. Stefańska, E. Maj, M. Ratajczak-Sitarz, A. Katrusiak, B. Brzezinski, F. Bartl, J. Mol. Struct. 1032 (2013) 69.
[10] J.J. Hale, S.G. Mills, M. MacCross, C.P. Dorn, P.E. Finke, R.J. Budhu, R.A. Reamer, W.P. Huskey, D. Luffer-Atlas, B.J. Dean, E.M. McGowan, W.P. Feeney, S.H.L. Chiu, M.A. Cascieri, G.G. Chicchi, M.M. Kurtz, S. Sadowski, E. Ber, F.D. Tattersall, N.M.J. Rupniak, A.R. Williams, W. Raycroft, R. Hargreaves, J.M. Metzger, D.E. MacIntyre, J. Med. Chem. 43 (2000) 1234.
[11] P. Avramova, N. Danchev, R. Buyukliev, T. Bogoslovova, Arch. Pharm. 331 (1998) 342.

[12] R.S. Varma, R. Prakash, M.M. Khan, A. Ali, Indian Drugs 23 (1986) 345.
[13] CAChe 5.04 UserGuide, Fujitsu, 2003.
[14] P. Przybylski, A. Huczyński, B.J. Brzezinski, J. Mol. Struct. 826 (2007) 156.
[15] H.T. Cao, T. Roisnel, A. Valleix, R. Gree, Eur. J. Org. Chem. (2011) 3430.
[16] C.-H. Zhao, L. Liu, D. Wang, Y.-J. Chen, Eur. J. Org. Chem. (2006) 2977.
[17] A. Ting, S.E. Schaus, Eur. J. Org. Chem. (2007) 5797.
[18] T. Hirose, T. Sunazuka, D. Yamamoto, E. Kaji, S. Omura, Tetrahedron Lett. 46 (2006) 6761.
[19] E.J. Corey, R.D. Balansom, J. Am. Chem. Soc. 96 (1974) 6516.
[20] K. Matsumoto, K. Joho, S. Mimori, H. Iida, H. Hamana, A. Kakehi, Heterocycles 76 (2008) 106.
[21] K. Bujnowski, A. Adamczyk-Woźniak, L. Synoradzki, Arkivoc 13 (2008) 106.
[22] N. Holy, R. Fowler, E. Burnett, R. Lorenz, Tetrahedron 35 (1979) 613.
[23] K. Manabe, S. Kobayashi, Org. Lett. 1 (1999) 1965.
[24] M. Rospenk, L. Sobczyk, Magn. Res. Chem. 27 (1989) 445.
[25] M. Rospenk, J. Mol. Struct. 109 (1990) 221.
[26] C. Cheng, M.L. Gross, Mass Spectrom. Rev. 19 (2000) 398.
[27] M.L. Gross, Int. J. Mass Spectrom. 200 (2000) 611.
[28] N.P. Lopes, P.J. Gates, J.P.G. Wilkins, J. Staunton, Analyst 127 (2002) 1224.
[29] A. Huczyński, J. Rutkowski, B. Brzezinski, Struct. Chem. 22 (2011) 627.
[30] A. Huczyński, M. Ratajczak-Sitarz, A. Katrusiak, B. Brzezinski, J. Mol. Struct. 998 (2011) 206.
[31] G.J. Francis, M. Forbes, D.A. Volmer, D.K. Bohme, Analyst 130 (2005) 508.
[32] A. Koll, S.M. Melikova, A. Karpfen, P. Wolschann, J. Mol. Struct. 559 (2001) 127.