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Spectroscopic, crystallographic and theoretical studies of lasalocid complex with ammonia and benzylamine

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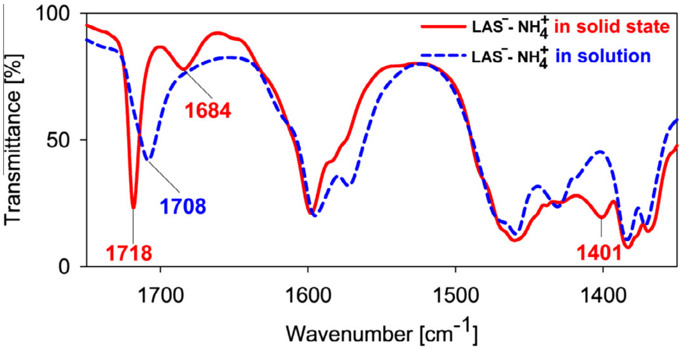
HIGHLIGHTS

- New Lasalocid complexes were synthesized.
- Lasalocid is a useful ligand for complexation of NH_4^+ and benzylamine.
- The crystal structure of the complexes were studied.
- Structures of Lasalocid complexes were visualised using DFT method.

GRAPHICAL ABSTRACT

The presence of band at 1684 cm^{-1} and 1401 cm^{-1} present in the FT-IR spectrum of crystalline complex formed between ionophore antibiotic lasalocid acid and ammonia are no longer observed in chloroform solution. This phenomenon is accompanied by a change in the coordination geometry of NH_4^+ cation.



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ABSTRACT

A natural antibiotic – Lasalocid is able to form stable complexes with ammonia and organic amines. New complexes of lasalocid with benzylamine and ammonia were obtained in the crystal forms and studied using X-ray, FT-IR, ^1H NMR, ^{13}C NMR and DFT methods. These studies have shown that in both complexes the proton is transferred from the carboxylic group to the amine group with the formation of a pseudo-cyclic structure of lasalocid anion complexing the protonated amine or NH_4^+ cation. The spectroscopic and DFT studies demonstrated that the structure of the complex formed between Lasalocid and benzylamine in the solid is also conserved in the solution and gas phase. In contrast, the structure of the complex formed between lasalocid and ammonium cation found in the solid state undergoes dissociation in chloroform solution accompanied with a change in the coordination form of the NH_4^+ cation.

Introduction

Structural and spectroscopic studies of synthetic and natural receptors for inorganic and organic ammonium cations have been performed intensively for many years. The information gathered help to understand better the individual contributions of different forces involved in ammonium cation binding [1–3]. Many types of synthetic and natural receptors of organic ammonium ion are available, ranging from crown ethers [1–3], cryptands [1,4], cyclodextrins [5], and cyclopeptides [1,6], cucurbiturils [1,7] natural ionophores [1,8–9]. Typical interactions observed in the complexes

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of amines are ionic and dipolar interactions, dispersive forces such as van der Waals or hydrogen bonds [1,10].

Lasalocid acid (LASH, Scheme 1) also known as X-537A isolated from *Streptomyces lasaliensis* is a well-known representative of polyether antibiotics – highly bioactive molecule which exhibits interesting activities such as antibacterial, antifungal, antiparasitic, antimalarial, antiviral and anti-inflammatory [11–12]. LASH is currently used as a growth-promoting agent and as a coccidiostat in veterinary medicine [13].

The structural studies of polyether antibiotics and their derivatives together with the elucidation of their biological activity have recently become a very important field of research. It has been shown that some polyether antibiotics (*e.g.* salinomycin, monensin) exhibit high activity against the proliferation of various cancer cells, including those that display multidrug resistance (MDR) and cancer stem cells (CSC) [14–20]. Furthermore, polyether ionophores are recognized as potential anticancer drugs [21,22] and preclinical and clinical studies of their therapeutic potential are in progress [23,24].

Our previous studies have clearly demonstrated that the biological activity of derivatives of polyether ionophores depends strongly on their structures [25–30]. Thus, it is very important to obtain detailed information on their structures. Recently we have discovered that LASH is able to form stable complexes with *N*-bases such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) [31], 1,1,3,3-tetramethylguanidine (TMG) [32] and several amines such as allylamine [33], phenylamine and butylamine [34]. In previous studies we have shown that the complex of LASH with allylamine has higher antibacterial activity than pure LASH [33] and also that LASH and its complexes with phenylamine and butylamine are relatively strong cytotoxic agents towards cancer cell lines [34]. It is interesting to note that the cytostatic activity of LASH and its complexes with amines against human cancer cell lines is higher than that of *cisplatin* – a standard anticancer drug [34].

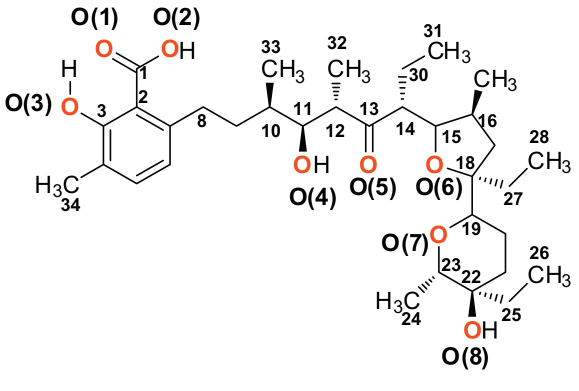
As a continuation of these studies, we synthesized two new hydrogen-bonded complexes of the LASH with the benzylamine ($BnNH_2$) and ammonia (NH_3) and characterised them using X-ray crystallography, FT-IR and NMR spectroscopy, as well as DFT calculations.

Experimental

General

Lasalocid sodium salt was isolated from veterinary premix – Avatec® 20 (Alpharma Inc.), which contains about 20% pure Lasalocid sodium salt.

Benzylamine ($BnNH_2$), ammonium hydroxide (NH_4OH) water solution (5.0 mol dm^{-3}) and solvents were obtained from Sigma–Aldrich or Fluka and used without any further purification.



Scheme 1. The formula and atom numbering of LASH.

Preparation of $LAS^{(-)}-BnNH_3^{(+)}$ *and* $LAS^{(-)}-NH_4^{(+)}$ *complexes*

Lasalocid sodium salt (1.0 g, 1.70 mmol) was dissolved in dichloromethane (150 ml) and stirred vigorously with a layer of diluted aqueous sulphuric acid (pH = 1.5) (100 ml). The organic layer containing Lasalocid acid (LASH) was washed three times with distilled water. Subsequently dichloromethane was evaporated under reduced pressure to dryness giving LASH (0.75 g; 1.27 mmol).

The crystals of 1:1 complex of $LAS^{(-)}-BnNH_3^{(+)}$ and 1:1 complex of $LAS^{(-)}-NH_4^{(+)}$ were obtained by crystallization from acetonitrile solution using a 1:1 M ratio of LASH and benzylamine ($BnNH_2$) and ammonium hydroxide (NH_4OH), respectively.

Mp = 179–181 °C ($LAS^{(-)}-BnNH_3^{(+)}$) and 183–186 °C ($LAS^{(-)}-NH_4^{(+)}$). Elemental Analysis: Calculated for $LAS^{(-)}-BnNH_3^{(+)}$ complex ($C_{41}H_{63}NO_8$): C, 70.56; H, 9.10; N, 2.01; Found:70.44; H, 9.23; N, 2.03; Calculated for $LAS^{(-)}-NH_4^{(+)}$ complex ($C_{34}H_{57}NO_8$): C,67.19; H, 9.45; N, 2.30;C, Found: C, 67.02; H, 9.66; N, 2.23.

X-ray measurements

Single crystal X-ray diffraction measurements of $LAS^{(-)}-BnNH_3^{(+)}$ (**1**) and $LAS^{(-)}-NH_4^{(+)}$ (**2**) were carried out at 295 K on a four-circle KUMA KM4 diffractometer equipped with two-dimensional CCD area detector. Graphite monochromatized Mo Kα radiation (λ = 0.71073 Å) and ω-scan technique ($\Delta\omega$ = 1°) were used for data collection. Data collection and reduction along with absorption correction were performed using *CrysAlis* software package [35]. The structures were solved by direct methods using *SHELXS-97* [36], which revealed the positions of almost all non-hydrogen atoms. The remaining atoms were located from subsequent difference Fourier syntheses. The structure was refined using *SHELXL-97* [36] with the anisotropic thermal displacement parameters. Visualizations of the structures were made with the Diamond 3.0 program [37]. Details of the data collection parameters, crystallographic data and final agreement parameters are collected in Table 1.

DFT calculations

Theoretical calculations with geometry optimization of $LAS^{(-)}-BnNH_3^{(+)}$ and $LAS^{(-)}-NH_4^{(+)}$ as well as the lasalocid acid (LASH) and its dissociated $LAS^{(-)}$ anion were performed with the Gaussian03 program package [38]. All calculations were carried out with the DFT level using the Becke3–Lee–YangParr correlation functional (B3LYP) [39–40] with the 3-21 + G* basis set assuming the geometry resulting from the X-ray diffraction study as the starting structure. As convergence criterions the threshold limits of 0.00025 and 0.0012 a.u. were applied for the maximum force and the displacement, respectively.

Spectroscopic measurements

The ^1H and ^{13}C NMR spectra of LASH, $LAS^{(-)}-BnNH_3^{(+)}$ and $LAS^{(-)}-NH_4^{(+)}$ (0.1 mol dm^{-3}) were recorded in $CDCl_3$ solutions using Bruker Avance 600 MHz spectrometer. All spectra were locked to deuterium resonance of $CDCl_3$. 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 and temperature 298.0 K using TMS as the internal standard 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 *1*H and *13*C NMR signals were assigned using 2-D (COSY, HETCOR, NOESY and HMBC). 2-D spectra were recorded using standard pulse sequences from Bruker pulse-sequence libraries.