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Spectroscopic studies of the equilibrium between complexes of lasalocid acid with propargylamine and metal cations

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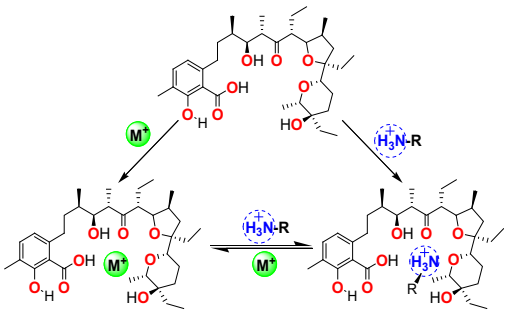
HIGHLIGHTS

- The crystal structure of the lasalocid complexes with propargylamine is studied.
- Lasalocid forms concurrent complexes with metal cations and amines existing in equilibrium.
- Lasalocid is a useful ligand for complexation of amines and metal cations.

GRAPHICAL ABSTRACT

The polyether ionophore antibiotic – lasalocid acid forms concurrent complexes with metal cations and amines existing in equilibrium.



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ABSTRACT

The molecular structure of 1:1 complex formed between the naturally occurring polyether ionophore, called lasalocid acid (LAS) and propargylamine (PROP) is studied by X-ray, FT-IR, ^{1}H NMR, ^{13}C NMR and ESI-MS methods. The complex formed between deprotonated LAS acid and protonated PROP molecule is stabilized by intra- and inter-molecular hydrogen bonds. The protons of the protonated amine group are hydrogen bonded to etheric and hydroxyl oxygen atoms of the LAS anion. The similarity of the FT-IR spectra of the LAS–PROP complex in solid state and in solution demonstrated that the molecular structures of the complex in both states are comparable. It is shown that LAS in solution can form concurrent complexes with metal cations (M = Li^+, Na^+, K^+) and amine existing in equilibrium. Analysis of the structures of lasalocid complexes is important for a better understanding of the antibacterial and anticancer properties of lasalocid acid.

Introduction

Polyether ionophores represent a large group of naturally occurring compounds which are able to form complexes with metal cations in order to transport them across lipid bilayer of cells, thereby disturbing natural gradient of biologically important cations. For this reason a lot of polyether ionophores show a broad spectrum of bioactivity ranging from antibacterial, antifungal, antiparasitic, antiviral, and anti-tumour cell cytotoxicity [1–4].

Lasalocid acid (LAS, Scheme 1) specified as X-537A is a well-known carboxylic polyether ionophore isolated from

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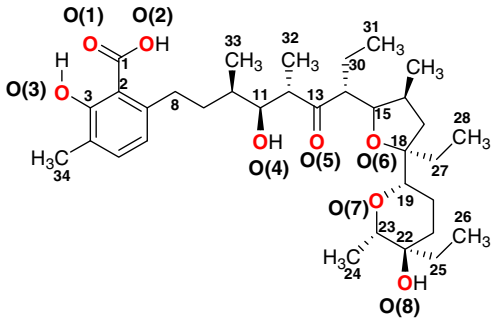

Scheme 1. The formula and atom numbering of LAS.

Streptomyces lasaliensis. Its sodium salt (Bovatec, Avatec) is one of the most commonly used veterinary antibiotics. It has found wide application as growth-promoting agent and coccidiostat in beef, cattle, sheep, chicken and turkeys [5–19].

Our previous studies have clearly demonstrated that the biological activity of derivatives of polyether ionophores depends strongly on their structures [20–25]. Recently we have discovered that LAS is able to form stable complexes with *N*-bases such as 1, 5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) [26], 1,1,3,3-tetramethylguanidine (TMG) [27] and with amines such as allylamine [28], phenylamine and butylamine [29], benzylamine and ammonia [30]. In previous studies we have shown that the complex of LAS with allylamine has a higher antibacterial activity than pure LAS [28] and also that LAS and its complexes with phenylamine and butylamine are relatively strong cytotoxic agents towards cancer cell lines [29]. It is interesting to note that the cytotoxic activity of LAS and its complexes with amines against human cancer cell lines is higher than that of *cisplatin* – a standard anticancer drug [29].

Table 1
Crystallographic data and structure refinement parameters.

Empirical formula	$C_{37}H_{59}NO_8$
Formula weight	645.85
Temperature (K)	293(2)
Wavelength	1.54178 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 10.0590(1) Å
	b = 18.5610(1) Å
	c = 19.7388(1) Å
Volume	3685.15(3) Å^3
Z	4
Calculated density	1.164 g cm^{-3}
Absorption coefficient	0.648 mm^{-1}
$F(000)$	1408
Crystal size	0.25 × 0.20 × 0.15 mm
θ Range for data collection	3.27–73.81°
Limiting indices	$-8 \leqslant h \leqslant 12$, $-23 \leqslant k \leqslant 22$, $-24 \leqslant l \leqslant 24$
Reflections collected/unique	30,193/7320 R_{int} = 0.0127
Completeness to θ = 73.82	99.2%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	7320/0/427
Goodness-of-fit on F^2	1.038
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0401, wR_2 = 0.1202
R indices (all data)	R_1 = 0.0412, wR_2 = 0.1219
Absolute structure parameter	−0.01(15)
Largest diff. peak and hole	0.260 and −0.139 eÅ^{-3}

Table 2
Parameters of the hydrogen bonds (Å, °) in the crystal of LAS–PROP complex.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H···O1	0.82	1.73	2.461(2)	148(4)
O4—H···O2	0.82	1.83	2.636(2)	168(4)
O8—H···O1	0.82	1.94	2.721(2)	160(4)
N1—H1···O8	0.83(3)	1.99(3)	2.766(2)	155(2)
N1—H2···O4	0.97(4)	2.29(4)	3.137(2)	145(3)
N1—H3···O6	0.84(3)	2.21(3)	2.934(2)	143(3)

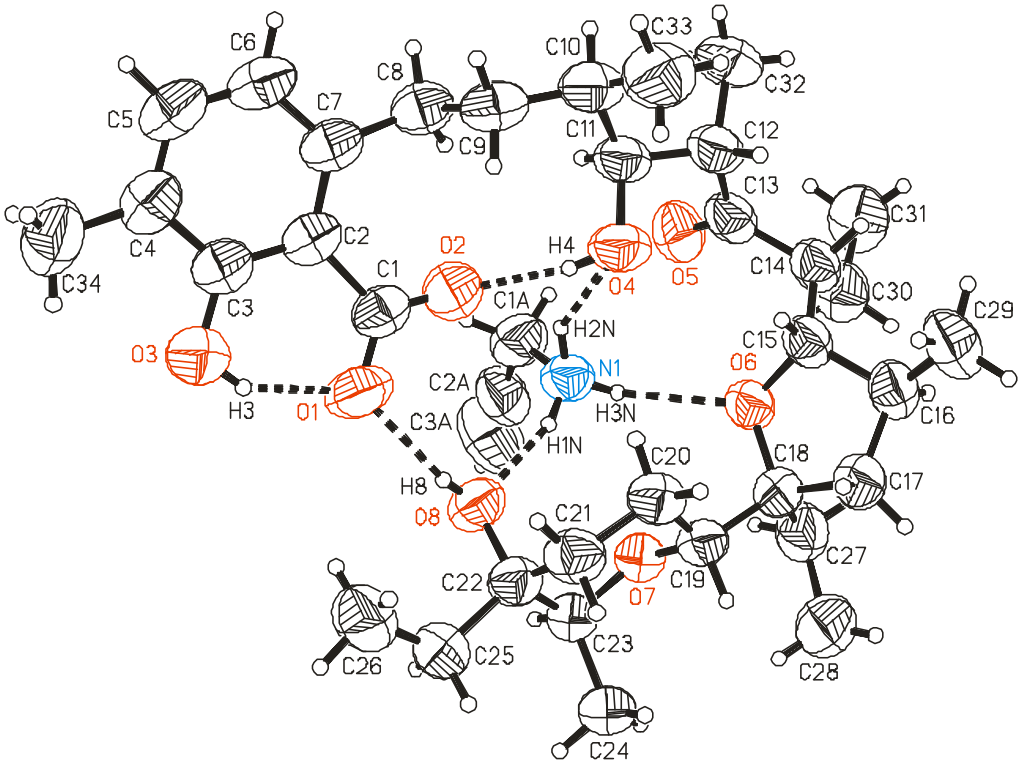

Fig. 1. Perspective ORTEP drawing of the molecular structure of host-guest complex LAS–PROP with atom numbering. The thermal ellipsoids are shown at the 50% probability level. The dashed lines represent three intramolecular O—H···O hydrogen bonds in the LAS anion and its three N—H···O bonds to the PROP cation.