Journal of Molecular Structure 936 (2009) 92–98

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Lasalocid acid as a lipophilic carrier ionophore for allylamine: Spectroscopic, crystallographic and microbiological investigation

Adam Huczyński [a], Jan Janczak [b], Jacek Rutkowski [a], Daniel Łowicki [a], Anna Pietruczuk [c], Joanna Stefańska [c], Bogumil Brzezinski [a,*], Franz Bartl [d]

[a] Faculty of Chemistry, A. Mickiewicz University, Grunwaldzka 6, 60-780 Poznan, Poland
[b] Institute of Low Temperature and Structure Research, Polish Academy of Sciences, P.O. Box 1410, 50950 Wroclaw, Poland
[c] Medical University of Warsaw, Department of Pharmaceutical Microbiology, Oczki 3, 02-007 Warsaw, Poland
[d] Institute of Medical Physics and Biophysics Charité – Universitätsmedizin Berlin Campus Charité Mitte, Ziegelstr. 5/9, 10117 Berlin, Germany

ARTICLE INFO

Article history:
Received 12 June 2009
Received in revised form 20 July 2009
Accepted 20 July 2009
Available online 24 July 2009

Keywords:
Ionophores
Allylamine
Anti-bacterial activity
Structure
Complexes
Staphylococcus aureus

ABSTRACT

A new complex of lasalocid acid with allylamine (LAS–AM) is synthesised and studied by X-ray, FT-IR, ^{1}H NMR and ^{13}C NMR, ESI MS methods. In the solid state allylamine is protonated and all protons of NH_3^+ are hydrogen bonded. We show that in the gas, liquid and solid states lasalocid forms 1:1 complexes with allylamine and that its structures of all states are comparable, which indicates that the complex LAS–AM is very stable. The stability of the LAS–AM complex is achieved by some intra-molecular hydrogen bonds. Due to these interactions the outside of the complex is hydrophobic enabling its transport across the biological membranes. This property of the complex is reflected in its anti-microbial activity, which is discussed.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

Ionophore antibiotics are lipophilic chelating agents of cations and are able to transport cations across lipid membranes of cells upsetting the gradients of biological important cations, causing cell death [1–3]. Lasalocid acid (Scheme 1) is well known carboxylic polyether ionophore isolated from *Streptomyces lasaliensis*. Its sodium salt (Bovatec™, Avatec™) is one of the most commonly used veterinary antibiotics since it is an widely spread anticoccidial agent [4–7]. The mechanism of lasalocid activity is clearly attributed to its ionophoric properties. Especially the influx of Na^+ in the cell of Gram-positive and anaerobic bacteria causes swelling, vacuolization and finally death [1].

The molecule of lasalocid acid (Scheme 1) consists of a salicylic acid moiety, tetrahydrofuran and tetrahydropyran rings, ketone group and two hydroxyl groups. The pseudo-cyclic conformation of the lasalocid molecule is stabilized by intra-molecular hydrogen bonds formed between the carboxyl and hydroxyl groups. The inside of this pseudo-cyclic structure is hydrophilic, rich in oxygen atoms, and is able to coordinate metal cations of different radii and charges such as alkali, alkaline earth, rare earth, and transition metal cations [8–13]. The outside of the lasalocid molecule is hydrophobic permitting penetration of its complexes through the biological membranes.

Only a few authors have reported about complexes of lasalocid with biogenic amines such as dopamine, norepinephrine, 2-aminoheptane as well as tyramine and their transport across the biological membrane [14–20]. The formation of the lasalocid complexes with biogenic or organic amines can also influence the anti-bacterial activity of this ionophore, which was never investigated so far.

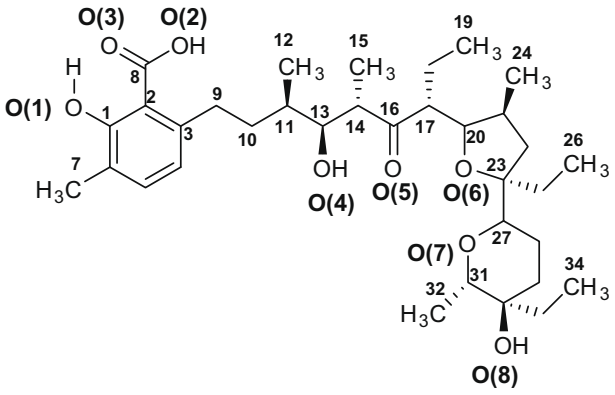
The aim of the present paper is to study a new complex of lasalocid acid (LAS) with allylamine (LAS-AM). This amine was chosen because it is a known toxin metabolized *in vitro* to acrolein [21]. It was shown that both allylamine and acrolein strongly influence the mitochondrial electron transport [21–27]. The structure of this new LAS-AM host–guest complex in the solid and in solution was studied by X-ray crystallography, FT-IR, ^{1}H and ^{13}C NMR spectroscopic methods. The anti-microbial activity of the LAS-AM complex was also investigated and compared with the activity of pure lasalocid acid.

2. Experimental

Lasalocid sodium salt was extracted from Avatec. It was dissolved in dichloromethane and stirred vigorously with a layer

* Corresponding author. Tel.: +48 618291330.
E-mail addresses: adhucz@amu.edu.pl (A. Huczyński), bbrzez@main.amu.edu.pl (B. Brzezinski).

0022-2860/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.molstruc.2009.07.021



Scheme 1. Structure of lasalocid acid.

of diluted aqueous sulphuric acid (pH = 1.5). The organic layer containing lasalocid acid was washed with distilled water. Subsequently dichloromethane was evaporated under reduced pressure to dryness.

The crystals of 1:1 complex of lasalocid with allylamine were obtained by the crystallization from their equimolar amounts in dried acetonitrile solution. M_p = 199–200 °C, Elemental analysis: Calculated for $C_{37}H_{61}NO_8$: C, 68.59%; H, 9.49%; N, 2.16%. Found: C, 68.61%; H, 9.59%; N, 2.01%, FAB-MS $[M + H]^+$ 648.4.

2.1. X-ray measurements

A colourless single crystal of LAS-AM with the edges of 0.42 × 0.22 × 0.16 mm was measured on a KUMA KM-4 CCD diffractometer with graphite monochromatized Mo Kα (λ = 0.71073 Å) radiation at room temperature. The final unit cell parameters were refined by the least-squares method on the basis of 1856 reflections. 49125 reflections (9415 independent, R_{int} = 0.0917) were measured up to 59° in 2θ covering over 99% of the Ewald sphere. Data collections were made using the CrysAlis CCD program [28], integration, scaling of the reflections and absorption corrections were performed with CrysAlis Red program [28]. The structure was solved by direct methods using the SHELXS-97 and refined using the SHELXL-97 program [29]. The hydrogen atoms were located from the $\Delta\rho$ maps, but in the final refinement they were constrained. The final differences Fourier maps showed no peaks of chemical significance. The largest peaks on the final $\Delta\rho$ map were +0.187 and −0.194 eÅ^{-3}. Details of the data collection parameters, crystallographic data and final agreement parameters are collected in Table 1. Visualization of the structure was made with the Diamond 3.0 program [30].

Table 1
Crystallographic data and structure refinement parameters.

Crystal data	
Formula	$C_{32}H_{61}NO_8$
M (g mol^{-1})	647.87
Crystal size	0.42 × 0.22 × 0.16
Crystal system	Orthorhombic
Space group	$P\,2_1\,2_1\,2_1$ (No. 19)
a (Å)	10.151(2)
b (Å)	18.801(4)
c (Å)	19.346(4)
V (Å^3)	3692.3(13)
Z	4
μ (mm^{-1})	0.081
ρ_{obs}; ρ_{calc} (g cm^{-3})	1.16; 1.165
Data collection	
Radiation, λ (Å)	Mo Kα (0.71073)
θ_{max}(°)	29.5
Absorpt. correct. (T_{min}; T_{max})	0.9721; 0.9880
No. collected reflections	49125
No. unique reflections	9415 (R_{int} = 0.0917)
No. observed reflections	4934 ($I > 2\sigma(I)$)
Refinement	
R [$F^2 > 2\sigma(F^2)$]	0.0624
$wR(F^2)$[a]	0.1293
Flack parameter	0.3(2)
GooF	1.004
$\Delta\rho_{min}$; $\Delta\rho_{max}$ (eÅ^{-3})	+0.187; −0.194

[a] $w = 1/[\sigma^2(F_o^2) + (0.065P)^2 + 0.0935P]$ where $P = (F_o^2 + 2F_c^2)/3$.

2.2. Spectroscopic measurements

The NMR spectra were recorded in $CDCl_3$ using a Varian Gemini 300 MHz spectrometer. All spectra were locked to deuterium

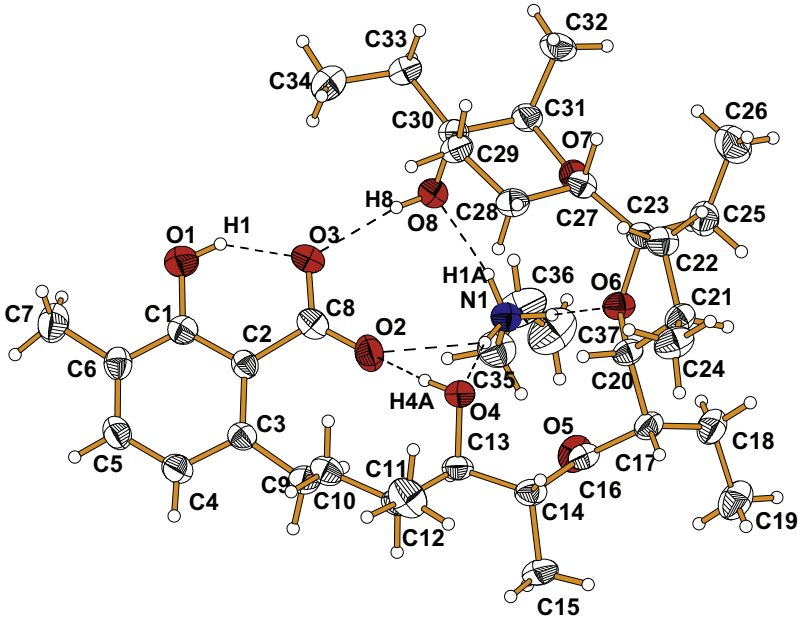


Fig. 1. View of the asymmetric unit of the crystal with the labelling of the atoms. Displacement ellipsoids are show at the 50% probability level.

Download English Version:

https://daneshyari.com/en/article/1411294

Download Persian Version:

https://daneshyari.com/article/1411294

Daneshyari.com