Tetrahedron 67 (2011) 1468–1478

Contents lists available at ScienceDirect

Tetrahedron

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

Spectroscopic, semi-empirical and antimicrobial studies of a new amide of monensin A with 4-aminobenzo-15-crown-5 and its complexes with Na^+ cation at 1:1 and 1:2 ratios

Daniel Łowicki [a], Adam Huczyński [a,*], Joanna Stefańska [b], Bogumil Brzezinski [a,*]

[a] Adam Mickiewicz University, Faculty of Chemistry, Grunwaldzka 6, 60-780 Poznan, Poland
[b] Medical University of Warsaw, Department of Pharmaceutical Microbiology, Oczki 3, 02-007 Warsaw, Poland

ARTICLE INFO

Article history:
Received 27 August 2010
Received in revised form 18 November 2010
Accepted 13 December 2010
Available online 17 December 2010

Keywords:
Ionophores
Monensin A amide
Crown ether
Spectroscopy
Antimicrobial properties

ABSTRACT

A new amide of monensin A with 4-aminobenzo-15-crown-5 (M-AM3) was synthesised and its ability to form complexes with Na^+ cations was studied by ESIMS, ^1H, ^{13}C and ^{23}Na NMR, FTIR and PM5 semi-empirical methods. ESI mass spectrometry indicates that in the gas phase M-AM3 amide forms complexes of 1:1 and 1:2 stoichiometry with Na^+ cations. The formation of such complexes is also confirmed in the acetonitrile solution, in which the existence of equilibrium between two structures A and B is found, of which B structure is dominant. The structures of M-AM3 and its 1:1 and 1:2 complexes with Na^+ cations are stabilised by various intramolecular hydrogen bonds, which are discussed in detail. The in vitro biological tests have demonstrated that the new M-AM3 amide shows good activity towards some strains of Gram-positive bacteria (MIC 25–50 μg/ml).

1. Introduction

Monensin A is a naturally occurring ionophoric antibiotic isolated from *Streptomyces cinnamonensis*.[1] The isolation procedure for the first time was published by Honey and Hoehn in 1967.[2] This ionophore shows various antimicrobial and biological activity. Therefore, monensin A has been successfully used in veterinary medicine as a coccidiostatic drug to treat and prevent coccidiosis in poultry as well as a non-hormonal growth-promoting agent applied to stimulate the growth of ruminants.[3] The antibacterial properties of monensin A arise from its ability to coordinate metal cations inside the cavity of its molecule with particular selectivity to sodium cation. The hydrophobic exterior of the molecule allows sodium transport across cell membranes leading to death of Gram-positive bacteria.[4]

Crown ethers discovered by Pedersen in the middle of the 20th century, are a considerable part of supramolecular chemistry.[5] These particular ethers are examples of synthetic ionophores capable of making host–guest systems with metal cations. The molecule of monensin A, similarly to those of crown ethers, has the hydrophilic interior including some oxygen atoms, able to bind metal cations by dipole–ion interactions, whereas the hydrophobic exterior permits them to diffuse in the lipid bilayer.

Recently, we described the synthesis and structural studies of new monensin A amides with aniline and allylamine demonstrating the ability of these compounds to create 1:1 complexes with some monovalent metal cations and their substantial antimicrobial activity against Gram-positive bacteria.[6]

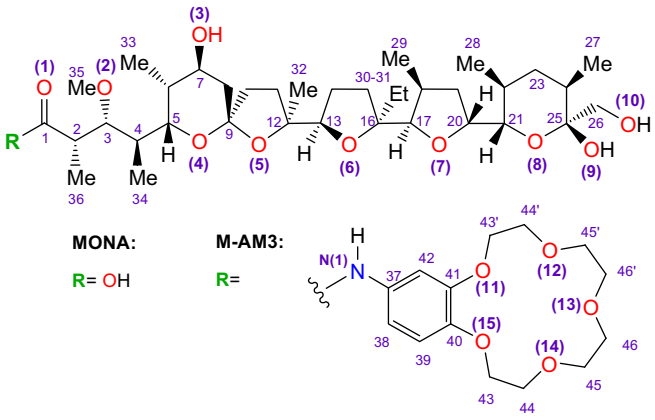
In this paper we synthesised a new amide of monensin A with 4-aminobenzo-15-crown-5 (M-AM3) and studied its complexation properties of sodium cations using ^1H, ^{13}C and ^{23}Na NMR, FTIR, ESIMS, as well as PM5 semi-empirical methods. This new amide possesses two hydrophilic sites able to coordinate metal cations in comparison to monensin A amides discussed previously, i.e., the crown ether moiety and the sphere of the monensin A molecule both showing high affinity to sodium cation because the cation diameter well matches the molecule cavity size.[7–12] Therefore, two questions arise, if the new amide is able to form a complex of 1:2 stoichiometry with sodium cations, and which of the two moieties can complex the first cation primarily. In this paper we try to answer these questions and we also report the microbiological activity of the newly synthesised amide M-AM3 against Gram-positive bacteria.

2. Results and discussion

The structures of monensin A and M-AM3 together with the atom numbering are shown in Scheme 1. The numbers of oxygen atoms are shown in brackets.

* Corresponding authors. Tel.: +48 61 829 1330; fax: +48 61 829 1505; e-mail addresses: adhucz@amu.edu.pl (A. Huczyński), bbrzez@amu.edu.pl (B. Brzezinski).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.12.033



Scheme 1. The structures and atom numbering of MONA and M-AM3.

2.1. Synthesis

M-AM3 amide was synthesised in the reaction between the monensic acid (MONA) and 4-aminobenzo-15-crown-5 (AB15C5) in the presence of 1,3-dicyclohexylcarbodiimide (DCC) with the addition of 1-hydroxybenzotriazole (HOBt) as a catalyst (Scheme 2). This one-pot reaction led to M-AM3 obtained with 71% yield. It is interesting to note that without the addition of the HOBt catalyst, under the same reaction conditions, no expected amide was formed.

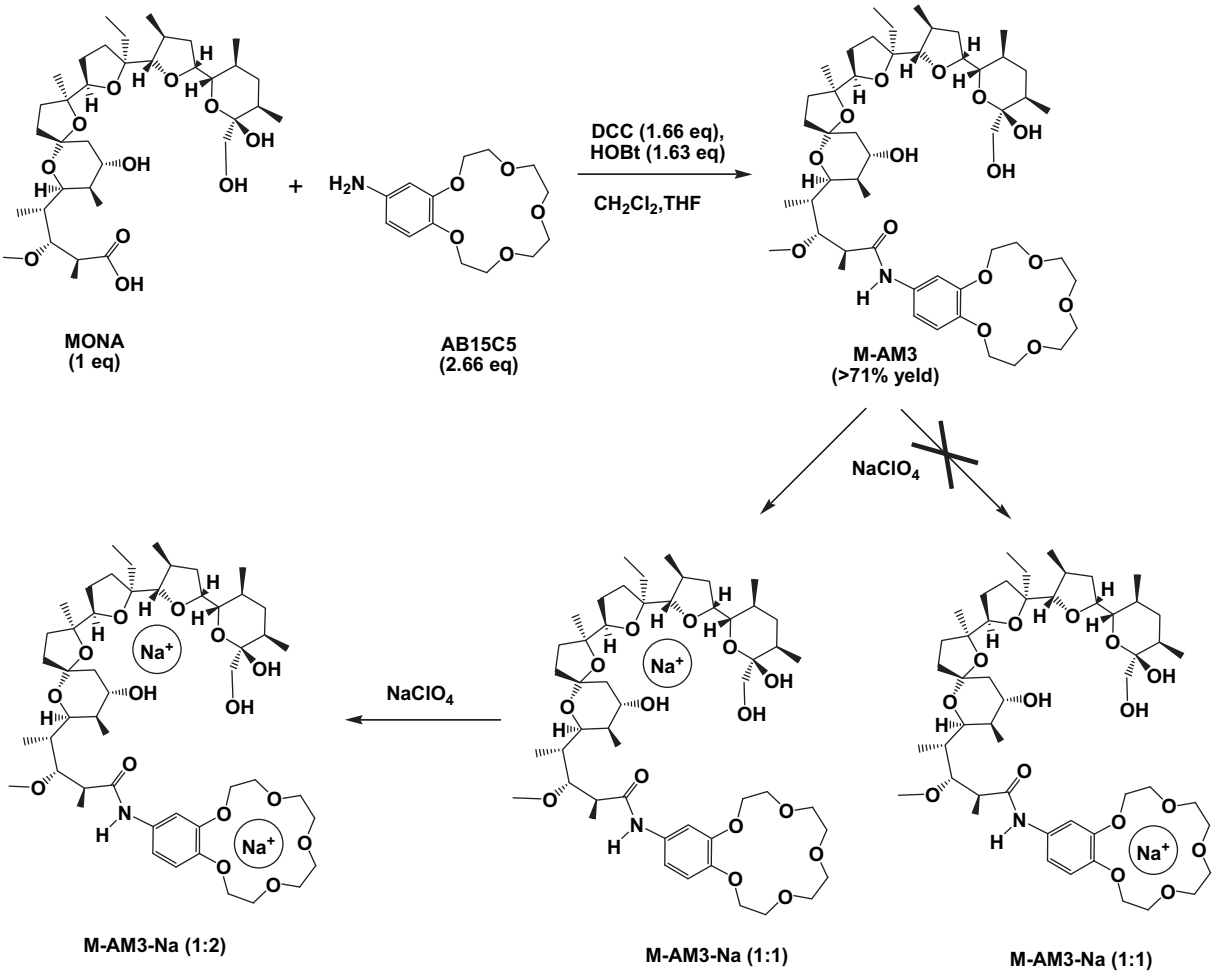
2.2. ^{1}H and ^{13}C NMR measurements

The ^{1}H and ^{13}C NMR data of M-AM3 and its 1:1 and 1:2 complexes with Na^{+} cations all in CD_3CN are shown in Tables 1 and 2, respectively. The ^{1}H and ^{13}C NMR signals were assigned using one- and two-dimensional (COSY, HETCOR, HMQC, HMBC and NOESY) spectra as well as by the ^{1}H NMR measurements with the addition of CD_3OD to the sample.

In the ^{1}H NMR spectra of M-AM3, its 1:1 and 1:2 complexes with Na^{+} cations (Table 1), the signals of the protons of all three OH and one NH groups are separate as illustrated in Fig. 1. The OH proton signals observed in the spectrum of M-AM3 at 4.07 ppm, 3.86 ppm, 2.75 ppm and 8.38 ppm are assigned to the O(3)H, O(9)H, O(10)H and N(1)H groups, respectively, whereas in the spectra of the complexes at 1:1 and 1:2 ratio the O(9)H and O(10)H proton signals are shifted to higher frequencies suggesting various involvement of these groups in formation of hydrogen bonds within the complexes.

A comparison of the ^{13}C NMR chemical shifts in the spectra of the complexes with those observed in the spectrum of M-AM3 reveals (Table 2) that not only the chemical shifts of the carbon atoms neighbouring the oxygen atoms involved in the coordination of Na^{+} cation but also the chemical shifts of some carbon atoms from the lipophilic sphere are visibly changed.

These changes indicate that upon complexation also conformational modifications of the M-AM3 molecule skeleton occur. The most interesting results regarding to the complexation process are connected with the ^{13}C NMR chemical shifts of the crown ether moiety.



Scheme 2. The diagram of synthesis of M-AM3 and its complexes with sodium perchlorate.