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EFFECT OF HYDRATE WATER ON THE HYDROGEN BOND FORMATION IN DIMETHYLAMINOARGLABINE SALTS WITH HYDROCHLORIDE AND HYDRONITRATE

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The crystal structure of crystalline hydrates of dimethylaminoarglabine hydrochloride and dimethylaminoarglabine hydronitrate is determined by single crystal X-ray diffraction. It is established that in a crystal, water breaks the hydrogen bond between the anion and the cation in dimethylaminoarglabin hydrochloride and weakens it in dimethylaminoarglabin hydronitrate, which improves the solubility of salts in water.

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INTRODUCTION

Many organic compounds exhibiting biological activity are insoluble or poorly soluble in water. Therefore, drugs based on them have been usually prepared with their water soluble derivatives. Biologically active compounds occur sometimes in the ion form in nature, e.g., B1 vitamin (thiamine) and its phosphorus derivatives, and do not require its conversion into the water soluble form [1]. A drug form is most often obtained based on a salt of the respective physiologically active compound. For instance, the antispastic drug adapromine (α-propyl-1-adamantylethylamine hydrochloride) or the antiviral drug dimedrochinum (1,2α-dimethyl-4e-ethinyl-trans-decahydroquinolol-4α hydrochloride) [2].

A new sesquiterpene lactone arglabine has been previously extracted from *Artemisia glabella*, which exhibited a pronounced antitumor activity in vitro [3]. In order to further test the biological activity of arglabine, well water-soluble dimethylamino arglabine hydrochloride (**1**) (Scheme 1) was synthesized [4]. The in vivo tests of **1** have shown the good clinical efficacy of the drug [5, 6]. The analysis of the structure of compound **1** revealed that a strong hydrogen bond between the cation and the anion was observed in the crystal. To study the effect of water molecules on the interaction between counterions a single crystal X-ray diffraction analysis of the crystal structures of crystal hydrates of dimethylamino arglabinea hydrochloride (**2**) and dimethylamino arglabine hydronitrate (**3**) was performed (Scheme 1).

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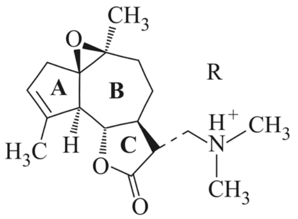

(**1**) R = Cl^-; (**2**) R = $Cl^- \cdot H_2O$; (**3**) R = $NO_3^- \cdot H_2O$

Scheme 1. Structural formulas of compounds **1-3**.

EXPERIMENTAL

Synthesis. A solution of 1 g arglabine in 10 mL of ethanol was treated with 10 mL of aqueous dimethylamine until the complete consumption of the starting material (controlled by thin-layer chromatography). Ethanol was distilled off in vacuo and the residue was extracted by chloroform (3×100 mL). The chloroform layer was dried above Na_2SO_4 and evaporated in a rotary evaporator. The oily mixture obtained was dissolved in ethanol (10 mL) and bubbled through an HCl solution to pH 5.3, after which ethyl acetate was added. The precipitate formed was filtered off and dried in vacuo. About 1 g of a colorless compound with T_{melt} 183-185 °C (dimethylaminoarglabine hydrochloride (**1**)) was obtained. Compound **1** was recrystallized from chloroform. Monohydrate of dimethylamino argolamine hydrochloride (**2**) was obtained by recrystallization from H_2O (T_{melt} 176-178 °C).

A precursor for the synthesis of the monohydrate of dimethylamino arglabine hydronitrate (**3**) was dimethylaminoarglabine hydrochloride (**1**). Nitrate of the compound under study was obtained by the following exchange reaction:

$$C_{17}H_{25}O_3NHC1 \text{ (solution, } H_2O) + AgNO_3 \text{ (solid)} =$$
$$= AgCl \text{ (solid)} + C_{17}H_{25}O_3NHNO_3 \text{ (solution, } H_2O).$$

The AgCl precipitate was filtered off. A white crystalline compound with T_{melt} 160-162 °C (monohydrate of dimethylamino arglabine hydronitrata (**3**)) was obtained from filtrates in vacuo and recrystallized from H_2O.

Single crystal X-ray diffraction study of the crystal hydrates of dimethylamine oarglabine hydrochloride (**2**) and dimethylamino arglabine hydronitrate (**3**).

Cell parameters and reflection intensities of **2** and **3** were measured on Bruker APEX-II CCD and Bruker P4 diffractometers respectively (MoK_α, graphite monochromator) at 296 K. The initial set of the measured reflections was processed and the absorption correction was applied using SAINT and SADABS programs within the APEX2 program package [7].

The structures were solved by a direct method. Positions of non-hydrogen atoms were refined in the anisotropic approximation by the full-matrix least-squares technique. Hydrogen atoms of amino groups and hydrate water were revealed from the Difference Fourier maps and their positions were refined in the isotropic approximation. The other hydrogen atoms were placed in the geometrically calculated positions and refined in the isotropic approximation with fixed positional and thermal parameters (riding model). The structures were solved and refined using SHELXS [8] and SHELXL-2018/3 [9]. In salt **3** oxygen atoms of the nitrate anion were disordered over two positions with weights of 0.54% and 0.46%. Crystallographic data and characteristics of the experiment for structures **2** are **3** are summarized in Table 1. CIF files containing full information on the studied structures have been deposited with the Cambridge Crystallography Data Center (for **2** CCDC 1937269, for **3** CCDC 1937270), where from they can be freely obtained upon request at the site www.ccdc.cam.ac.uk/data_request/cif.

TABLE 1. Crystallographic Data and Characteristics of the Single Crystal X-Ray Diffraction Experiment for Compounds **2** and **3**

Parameter	**2**	**3**
Chemical formula	$C_{17}H_{26}NO_3^+\cdot Cl^-\cdot H_2O$	$C_{17}H_{26}NO_3^+\cdot NO_3^-\cdot H_2O$
M	345.85	372.41
Crystal system	Monoclinic	
Space group	$P2_1$	$P2_1$
a, *b*, *c*, Å	9.3627(5), 7.8674(3), 12.6695(7)	9.470(1), 8.061(1), 12.913(2)
β, deg	106.628(2)	106.96(1)
V, $Å^3$	894.21(8)	942.9(2)
Z	2	2
D_{calc}, g/cm^3	1.284	1.312
μ, mm^{-1}	0.233	0.102
Number of measured / independent / observed reflections	4020 / 2415 / 2319	1898 / 1785 / 1647
Number of refined parameters	225	279
R_{int}	0.0240	0.0175
θ range, deg	1.68-25.67	2.40-25.0
Sacnning type	φ, ω	ω/2θ
GOOF	1.114	1.050
R_1; wR_2 ($I \geq 2\sigma(I)$)	0.0272; 0.0677	0.0385; 0.0996
R_1; wR_2 (entire array)	0.0290; 0.0702	0.0420; 0.1033
$\Delta\rho_{max}$; $\Delta\rho_{min}$, e/Å^3	0.184; –0.159	0.198; –0.217
Absolute structural parameter	0.01(3)	0.1(2)

RESULTS AND DISCUSSION

In continuation of studying the stereochemistray of sesquiterpene lactones we carried out the single crystal X-ray diffraction analysis of crystal hydrates of dimethylamino arglabine hydrochloride (**2**) and dimethylamino arglabine hydronitrata (**3**). The total views of crystal hydrates **2** and **3** are shown in Figs. 1 and 2 respectively.

From the data obtained it follows that bond lengths and bond angles in crystal hydrates **2** and **3** are close to usual ones [10].

Five- (A) and seven-member (B) carbocycles, B cycle, and lactone cycles (C) are *trans*-linked (torsion angles O3C1C5H4 = –138(–136)° and H6C6C7H7 = –170(–172)°) (hereinafter, values for the cation of 3 are given in parentheses).

The conformation of the five-member cycle A is an almost ideal 1β-*envelope* (ΔC_S^1 = 0.6(1.2)°) [11]; the C2, C3, C4, and C5 atoms are coplanar within ±0.003(±0.005) Å, and the C1 atom is out-of-plane by 0.342(0.361) Å to the β-side. The seven-member cycle B adopts the conformation of a slightly distorted 7α,1,10β-*chair* (ΔC_S^7 = 3.7(3.6)°). The C5, C6, C8, and C9 atoms are coplanar within ±0.02(±0.02) Å, and the C1, C10 atoms are out-of-plane by 0.95(0.93) Å and 0.97(0.96) Å in β-, and the C7 atom is out-of-plane by –0.70(–0.72) Å to the α-side respectively. The conformation of the lactoneo cycle is a slightly distorted 7α-*envelope* (ΔC_S^7 = 3.7(4.0)°). The C6, C11, C12, and O1 atoms are coplanar within ±0.01(±0.01) Å, and the C7 atom is out-of-plane by –0.65(–0.64) Å to the α-side. Methyl(dimethylamino group) adopts a pseudo-equatorial orientation; the C11 atom is practically in the above plane (–0.008(–0.008) Å). In general, the cycle conformations are similar in the cations of compounds **1**, **2**, and **3**.

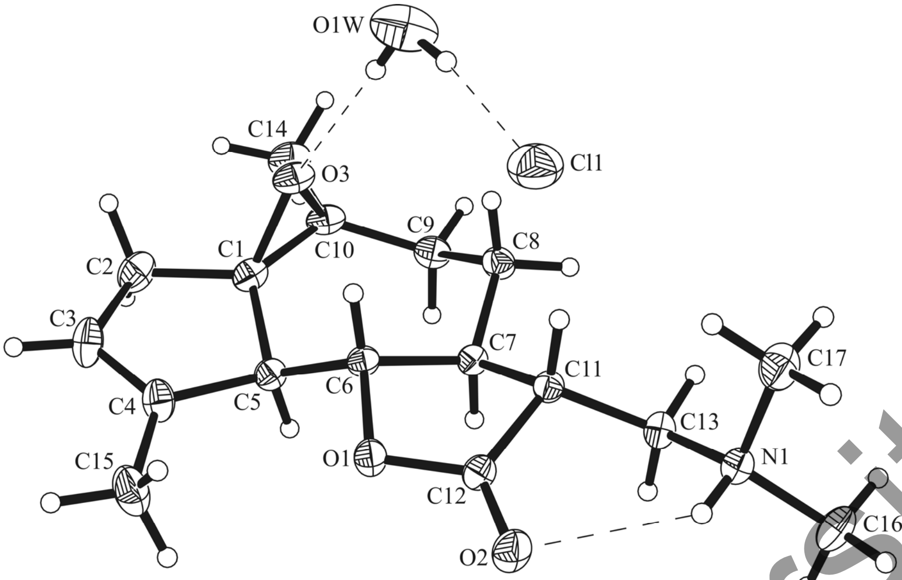

Fig. 1. Structure of the crystal hydrate of dimethylamino arglabine hydrochloride (**2**) (thermal vibrational ellipsoids are shown with a 30% probability; hydrogen bonds are depicted by the dashed line).

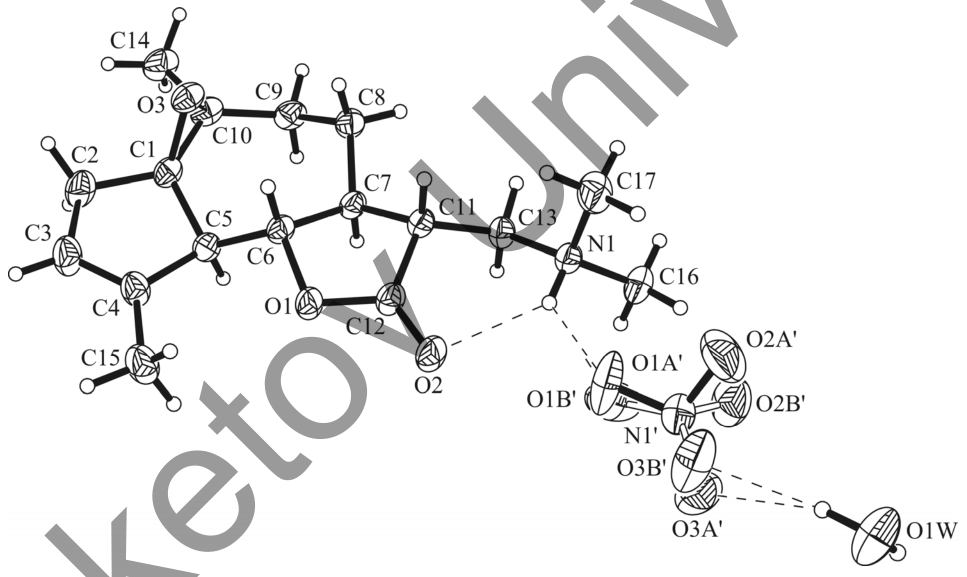

Fig. 2. Structure of the crystal hydrate of dimethylamino arglabine hydronitrate (**3**) (thermal vibrational ellipsoids are shown with a 30% probability; hydrogen bonds are depicted by the dashed line).

As mentioned above, in the crystal structure of salt **1** there is a strong hydrogen bond N1–H (x, y, z)…Cl1 (x, y, z) between the cation and the anion (distances N1–H 1.02 Å, N1…Cl1 2.95 Å, H…Cl1 1.96 Å, angle N1–H…Cl1 165°). The conformation along the C13–N1 bond becomes the least favorable among all possible *gauche*-conformations (C11–C13–N1–H 175°, C11–C13–N1–C16 –68.5°, C11–C13–N1–C17 58.2°) (Fig. 3).

The incorporation of a water molecule into the crystal lattice of salt **1** causes the redistribution of hydrogen bonds. The hydrogen bond between the anion and the cation becomes broken. A hydrogen bond of the anion and the cation with a water molecule is formed (O1W–H1W…Cl1 and O1W–H2W…O3) along with the intramolecular N1–H…O2 bond in

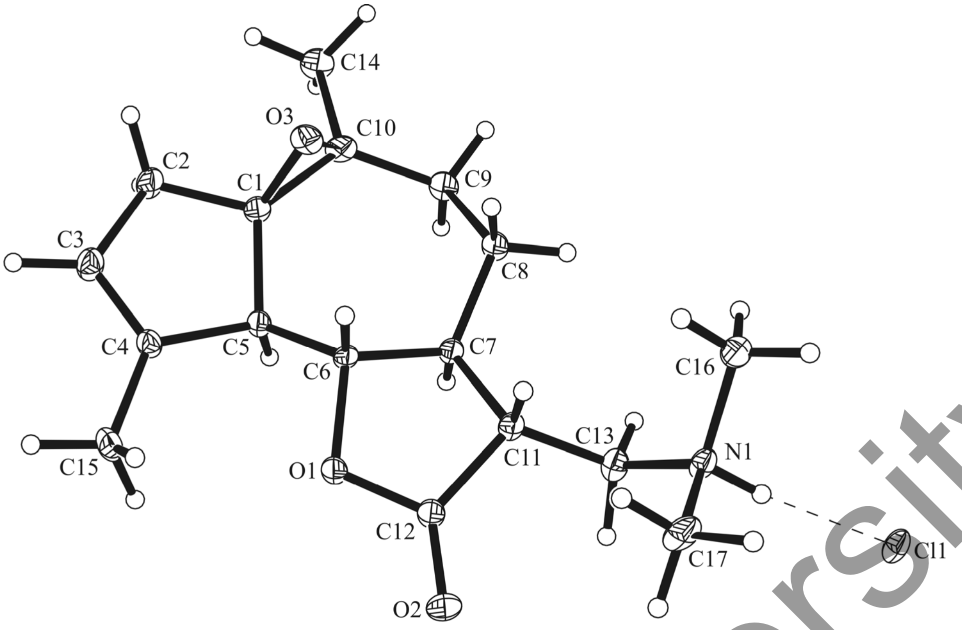

Fig. 3. Structure of dimethylamino arglabine hydrochloride (**1**) (thermal vibrational ellipsoids are shown with a 30% probability; hydrogen bonds are depicted by the dashed line).

TABLE 2. Hydrogen Bonds in Compounds **2** and **3** (d, Å; φ, deg)

D–H…A	*d*(D–H)	*d*(H…A)	*d*(D…A)	φ(D–H…A)
		Compound **2**		
N1–H…O2 (*x*, *y*, *z*)	0.85(3)	2.24(3)	2.898(3)	135(2)
O1W–H1…Cl1 (*x*, *y*, *z*)	0.88(5)	2.37(6)	3.235(4)	170(5)
O1W–H2···O3	0.73(5)	2.36(6)	3.082(5)	171(5)
		Compound **3**		
N1–H…O2 (*x*, *y*, *z*)	0.92(3)	2.13(3)	2.870(3)	137(3)
N1–H…O1A′ (–1+*x*, *y*, *z*)	0.92(3)	2.28(3)	2.969(13)	131(3)
N1–H…O1B′ (–1+*x*, *y*, *z*)	0.92(3)	2.25(3)	2.949(14)	133(3)
O1W–H1…O3A′ (*x*, *y*, *z*)	0.83(5)	2.04(5)	2.856(8)	170(5)
O1W–H1…O3B′ (*x*, *y*, *z*)	0.83(5)	2.02(5)	2.786(9)	154(6)
O1W–H2···O3 (1–*x*, –1/2+*y*, 1–*z*)	0.88(6)	2.09(6)	2.964(4)	179(5)

the cation (Table 2). The conformation along the C13–N1 bond adopts a more favorable *gauche*-form (C11–C13–N1–H 53(2)°, C11–C13–N1–C16 168.9(2)°, and C11–C13–N1–C17 67.2(3)°) (Fig. 1).

In compound **3**, the nitrate anion, unlike the chlorine ion in **2**, has three oxygen atoms as potential donors of the hydrogen bond. Nitrate anion substitution for the chlorine anion allows the NO$_3$ group to form hydrogen bonds with water (O1W–H…O3A(O3B)) and the cation (N1–H…O3A(O3B)). The water molecule also forms a hydrogen bond O1W–H2W…O3 with the cation O3 atom. At the same time, the cation retains the intramolecular N1–H…O2 hydrogen bond (Table 2). The conformation along the C13–N1 bond is also retained (C11–C13–N1–H 50(2)°, C11–C13–N1–C16 166.2(3)°, and C11–C13–N1–C17 –70.3(3)°) (Fig. 2).

In the crystal packing of compound **3** the presence of three donor centers in the anion enables the formation of infinite cation–anion–water–cation ribbons along the *b* axis via the hydrogen bonds. On the contrary, in the crystal structure of compound **2** only the anion–water–cation associate is formed.

Thus, the incorporation of the water molecule into the crystal lattice of dimethylamino arglabine hydrochloride and hydronitrate salts leads to a change in the conformation along the C13–N1 bond of the dimethylamino arglabine cation, and consequently, the formation of the intramolecular N1–H…O2 hydrogen bond in compounds **2** and **3**.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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