



Protonation of antamanide: Experimental and theoretical study



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ABSTRACT

On the basis of extraction experiments and γ -activity measurements, the extraction constant corresponding to the equilibrium $\text{H}_3\text{O}^+(\text{aq}) + \mathbf{1} \cdot \text{Na}^+(\text{nb}) \rightleftharpoons \mathbf{1} \cdot \text{H}_3\text{O}^+(\text{nb}) + \text{Na}^+(\text{aq})$ occurring in the two-phase water–nitrobenzene system ($\mathbf{1}$ = antamanide; aq = aqueous phase, nb = nitrobenzene phase) was evaluated as $\log K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1} \cdot \text{Na}^+) = -0.4 \pm 0.1$. Further, the stability constant of the $\mathbf{1} \cdot \text{H}_3\text{O}^+$ complex in nitrobenzene saturated with water was calculated for a temperature of 25 °C: $\log \beta_{\text{nb}}(\mathbf{1} \cdot \text{H}_3\text{O}^+) = 5.7 \pm 0.2$. Finally, by using quantum mechanical DFT calculations, the most probable structure of the cationic complex species $\mathbf{1} \cdot \text{H}_3\text{O}^+$ was derived. In the resulting complex, the “central” cation H_3O^+ is bound by two linear hydrogen bonds and one bifurcated hydrogen bond to the corresponding four oxygens of the parent ligand $\mathbf{1}$. Besides, the whole $\mathbf{1} \cdot \text{H}_3\text{O}^+$ complex structure is stabilized by two intramolecular H-bonds. The interaction energy of the considered $\mathbf{1} \cdot \text{H}_3\text{O}^+$ complex was found to be -458.7 kJ/mol, confirming also the formation of this cationic species.

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1. Introduction

The cyclic decapeptide antamanide, *cycl*[–Val(1)–Pro(2)–Pro(3)–Ala(4)–Phe(5)–Phe(6)–Pro(7)–Pro(8)–Phe(9)–Phe(10)–], consisting entirely of L-amino acids (see Scheme 1), forms 1:1 complexes with a variety of metal cations [1,2]. Antamanide was isolated from the poisonous mushroom *Amanita phalloides* [3] and it has the unique property of counteracting the toxin phalloidin, produced by the mentioned mushroom. Furthermore, it should be emphasized that antamanide also prevents the inhibition of depolymerization of F-actin and G-actin in the liver cell membranes of mammals [4].

The dicarbollylcobaltate anion (DCC^-) [5] and some of its halogen derivatives have been applied very often for the solvent extraction of various metal cations (especially Cs^+ , Sr^{2+} , Ba^{2+} , Eu^{3+} , and Am^{3+}) from aqueous solutions into a polar organic phase, both under laboratory conditions for theoretical or analytical purposes [6–13], and on the technological scale for the separation of some high-activity isotopes in the reprocessing of spent nuclear fuel and acidic radioactive waste [14–16].

Recently, protonation of valinomycin, some calix[4]arenes, dibenzo-18-crown-6, a hexaarylbenzene-based receptor, and beauvericin has been investigated in detail [17–21]. On the other hand, in the current work, the solvent extraction of H_3O^+ into nitrobenzene by means of a synergistic mixture of sodium dicarbollylcobaltate (NaDCC) and antamanide (abbrev. $\mathbf{1}$; see Scheme 1) was studied. Moreover, the

stability constant of the proved $\mathbf{1} \cdot \text{H}_3\text{O}^+$ complex species in the organic phase of the water–nitrobenzene extraction system was determined. Finally, applying quantum mechanical DFT calculations, the most probable structure of this cationic complex species was predicted.

2. Experimental section

2.1. Chemicals

Compound $\mathbf{1}$ (see Scheme 1) was prepared by the method described in Ref. [22]. Cesium dicarbollylcobaltate (CsDCC) was synthesized by means of the method published by Hawthorne et al. [23]. The other chemicals used (Lachema, Brno, Czech Republic) were of reagent grade purity. A nitrobenzene solution of sodium dicarbollylcobaltate (NaDCC) was prepared from CsDCC by the procedure described elsewhere [24]. The radionuclide $^{22}\text{Na}^+$ was obtained from DuPont, Belgium; its radionuclidic purity was 99.9%.

2.2. Extraction

The extraction experiments were carried out in 10 mL polypropylene test-tubes with polypropylene stoppers: 2 mL of an aqueous solution of HCl of a concentration in the range from 1×10^{-3} to 3×10^{-3} mol/L and 10 kBq of $^{22}\text{Na}^+$ were added to 2 mL of a nitrobenzene solution of $\mathbf{1}$ and NaDCC, whose initial concentrations varied also from 1×10^{-3} to 3×10^{-3} mol/L (in all experiments, the initial concentration of $\mathbf{1}$ in nitrobenzene, $C_{\mathbf{1}}^{\text{in,nb}}$, was equal to the initial concentration of NaDCC in this medium, $C_{\text{NaDCC}}^{\text{in,nb}}$). The

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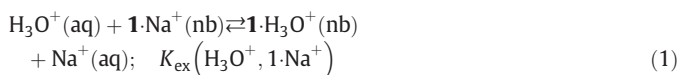
test-tubes filled with the solutions were shaken for 3 h at $25 \pm 1^\circ\text{C}$, using a laboratory shaker. Then the phases were separated by centrifugation. Finally, 1 mL samples were taken from each phase and their γ -activities were measured by means of a well-type NaI(Tl) scintillation detector connected to a γ -analyzer Triathler (Hidex, Turku, Finland).

The equilibrium distribution ratios of sodium, D_{Na} , were determined as the ratios of the corresponding measured radioactivities of $^{22}\text{Na}^+$ in the nitrobenzene and aqueous samples.

3. Results and discussion

3.1. Extraction experiments

Previous results [5,17,25–27] indicated that the two-phase water–HCl–nitrobenzene–**1** (antamanide)–sodium dicarbollylcobaltate (NaDCC) extraction system (see Experimental section), chosen for determination of the stability constant of the $\mathbf{1}\cdot\text{H}_3\text{O}^+$ complex in nitrobenzene saturated with water, can be characterized by the main chemical equilibrium



with the respective extraction constant $K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+)$:

$$K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+) = \frac{[\mathbf{1}\cdot\text{H}_3\text{O}^+]_{\text{nb}} [\text{Na}^+]_{\text{aq}}}{[\text{H}_3\text{O}^+]_{\text{aq}} [\mathbf{1}\cdot\text{Na}^+]_{\text{nb}}} \quad (2)$$

where aq and nb denote the presence of the species in the aqueous and nitrobenzene phases, respectively. At this point it should be noted that **1** is a considerably lipophilic ligand, practically present in the nitrobenzene phase only, where this ligand forms – with H_3O^+ and Na^+ – the relatively stable complexes $\mathbf{1}\cdot\text{H}_3\text{O}^+$ and $\mathbf{1}\cdot\text{Na}^+$, as given below.

Employing the conditions of electroneutrality in the organic and aqueous phases of the system under study, the mass balances of the univalent cations studied at equal volumes of the nitrobenzene and aqueous phases, as well as the measured equilibrium distribution

ratio of sodium, $D_{\text{Na}} = [\mathbf{1}\cdot\text{Na}^+]_{\text{nb}}/[\text{Na}^+]_{\text{aq}}$, combined with Eq. (2), we gain the final expression for $K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+)$ in the form

$$K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+) = \frac{1}{D_{\text{Na}}} \frac{C_{\text{NaDCC}}^{\text{in,nb}}}{(1 + D_{\text{Na}}) C_{\text{HCl}}^{\text{in,aq}} - C_{\text{NaDCC}}^{\text{in,nb}}} \quad (3)$$

where $C_{\text{HCl}}^{\text{in,aq}}$ is the initial concentration of HCl in the aqueous phase and $C_{\text{NaDCC}}^{\text{in,nb}}$ denotes the initial concentration of NaDCC in the nitrobenzene phase of the system under consideration.

In this work, from the extraction experiments and γ -activity measurements (see Experimental section) by means of Eq. (3), the following value of the constant $K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+)$ was determined as $\log K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+) = -0.4 \pm 0.1$ (see Table 1). This constant experimentally proves the justifying of the extraction mechanism and the presentation of the corresponding species, expressed by the two-phase chemical equilibrium (1).

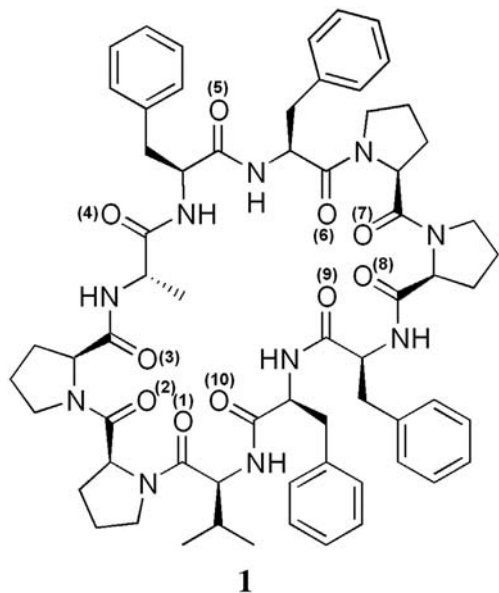
Furthermore, with respect to our previous results [5,17,27], for the extraction constant $K_{\text{ex}}(\text{H}_3\text{O}^+, \text{Na}^+)$ corresponding to the equilibrium $\text{H}_3\text{O}^+(\text{aq}) + \text{Na}^+(\text{nb}) \rightleftharpoons \text{H}_3\text{O}^+(\text{nb}) + \text{Na}^+(\text{aq})$ and for the extraction constant $K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+)$ defined above, as well as for the stability constants of the complexes $\mathbf{1}\cdot\text{H}_3\text{O}^+$ and $\mathbf{1}\cdot\text{Na}^+$ in nitrobenzene saturated with water, denoted by $\beta_{\text{nb}}(\mathbf{1}\cdot\text{H}_3\text{O}^+)$ and $\beta_{\text{nb}}(\mathbf{1}\cdot\text{Na}^+)$, respectively, one gets

$$\log \beta_{\text{nb}}(\mathbf{1}\cdot\text{H}_3\text{O}^+) = \log \beta_{\text{nb}}(\mathbf{1}\cdot\text{Na}^+) + \log K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+) - \log K_{\text{ex}}(\text{H}_3\text{O}^+, \text{Na}^+). \quad (4)$$

Using the value $\log K_{\text{ex}}(\text{H}_3\text{O}^+, \text{Na}^+) = 0.3$ inferred from Ref. [25], the constant $\log K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+)$ given above, $\log \beta_{\text{nb}}(\mathbf{1}\cdot\text{Na}^+) = 6.4 \pm 0.1$ [28], determined from the distribution of sodium picrate in the water–nitrobenzene extraction system containing the ligand **1**, and applying Eq. (4), we obtain the stability constant of the $\mathbf{1}\cdot\text{H}_3\text{O}^+$ complex in water-saturated nitrobenzene at 25°C as $\log \beta_{\text{nb}}(\mathbf{1}\cdot\text{H}_3\text{O}^+) = 5.7 \pm 0.2$. This means that in the mentioned nitrobenzene medium, the stability of the $\mathbf{1}\cdot\text{H}_3\text{O}^+$ complex under study is somewhat lower than that of the cationic complex species $\mathbf{1}\cdot\text{Na}^+$. In this context it is necessary to note that the stability constant of the complex species $\mathbf{2}\cdot\text{H}_3\text{O}^+$, where **2** denotes valinomycin (see Scheme 2), in nitrobenzene saturated with water is $\log \beta_{\text{nb}}(\mathbf{2}\cdot\text{H}_3\text{O}^+) = 5.3 \pm 0.1$ [17]. Thus, in this medium, the stabilities of the complexes $\mathbf{1}\cdot\text{H}_3\text{O}^+$ and $\mathbf{2}\cdot\text{H}_3\text{O}^+$ under consideration are nearly comparable.

3.2. DFT calculations

The theoretical calculations were performed at the density functional level of theory (DFT, B3LYP functional) [29,30], employing the Gaussian 09 suite of programs [31]. The 6-31G(d,p) basis set was used and the optimizations were unconstrained. In order to increase the numerical accuracy and to reduce oscillations during the molecular geometry optimization, two-electron integrals and their derivatives were calculated by using the pruned (99,590) integration grid, having 99 radial shells and 590 angular points per shell, which was requested by means of the Gaussian 09 keyword “Int = UltraFine”. The most probable structure of the $\mathbf{1}\cdot\text{H}_3\text{O}^+$ cationic complex was predicted on the basis of the thorough conformational analysis (i. e., different initial mutual positions of the ligand **1** and the hydroxonium cation H_3O^+ were considered



Scheme 1. Structural formula of antamanide (abbrev. **1**).

Table 1
Experimental data concerning determination of $\log K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+)$ on the basis of Eq. (3).

$C_{\text{HCl}}^{\text{in,aq}}$ (mol/L)	$C_{\text{NaDCC}}^{\text{in,nb}}$ (mol/L)	D_{Na}	$\log K_{\text{ex}}(\text{H}_3\text{O}^+, \mathbf{1}\cdot\text{Na}^+)$
1.0×10^{-3}	1.0×10^{-3}	1.49	−0.3
1.5×10^{-3}	1.5×10^{-3}	1.60	−0.4
2.0×10^{-3}	2.0×10^{-3}	1.48	−0.3
2.5×10^{-3}	2.5×10^{-3}	1.66	−0.4
3.0×10^{-3}	3.0×10^{-3}	1.72	−0.5

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