

Interaction of the univalent silver cation with [Gly⁶]-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 $\text{Ag}^+(\text{aq}) + \mathbf{1}\cdot\text{Na}^+(\text{nb}) \rightleftharpoons \mathbf{1}\cdot\text{Ag}^+(\text{nb}) + \text{Na}^+(\text{aq})$ occurring in the two-phase water – nitrobenzene system ($\mathbf{1}$ = [Gly⁶]-antamanide; aq = aqueous phase, nb = nitrobenzene phase) was determined as $\log K_{\text{ex}}(\text{Ag}^+, \mathbf{1}\cdot\text{Na}^+) = 1.5 \pm 0.1$. Further, the stability constant of the $\mathbf{1}\cdot\text{Ag}^+$ complex in nitrobenzene saturated with water was calculated for a temperature of 25 °C: $\log \beta_{\text{nb}}(\mathbf{1}\cdot\text{Ag}^+) = 4.5 \pm 0.2$. Finally, by using quantum chemical DFT calculations, the most probable structure of the cationic complex species $\mathbf{1}\cdot\text{Ag}^+$ was derived. In the resulting complex, the “central” cation Ag^+ is coordinated by four noncovalent interactions to the corresponding four carbonyl oxygen atoms of the parent ligand $\mathbf{1}$. Besides, the whole $\mathbf{1}\cdot\text{Ag}^+$ complex structure is stabilized by two intramolecular hydrogen bonds. The interaction energy of the considered $\mathbf{1}\cdot\text{Ag}^+$ complex was found to be -465.5 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 noted that antamanide prevents the inhibition of depolymerization of F-actin and G-actin in the liver cell membranes of mammals [4]. It was also found that antamanide inhibits tumor cell growth *in vitro* [2], displays an antitumor action in an animal model [5], and attenuates IL-2-induced multisystem organ edema [6].

In general, nearly all cyclic peptides tend to be extremely resistant to the process of digestion, enabling them to survive in the human digestive tract [7]. This trait makes cyclic peptides attractive to designers of protein-based drugs that may be used as scaffolds which, in theory, could be engineered to incorporate any arbitrary protein domain of medicinal value to allow those components to be

delivered orally. This is especially important for delivery of other proteins that would be destroyed without such implementation. Cyclic peptides are also somewhat more “rigid” compared to the corresponding linear peptides, and this attribute promotes binding by removing the “entropic penalty” [7].

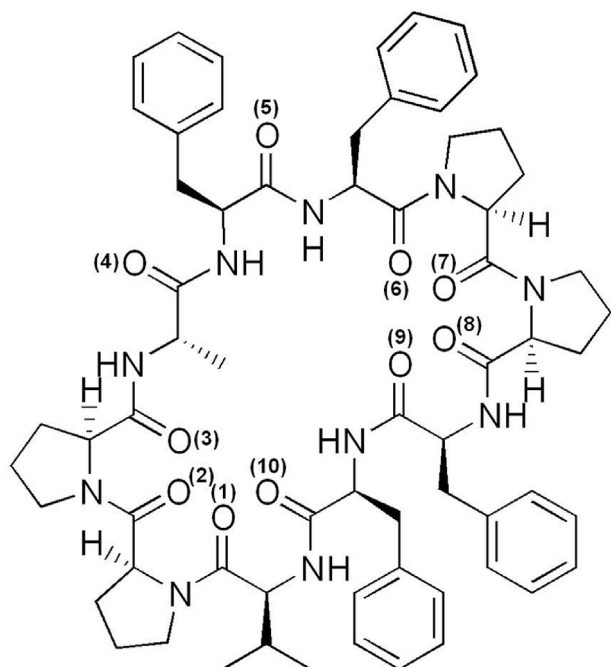
The dicarbollylcobaltate anion (DCC^-) [8] and some of its halogen derivatives have been applied very often for the extraction of various metal cations (especially Cs^+ , Sr^{2+} , Ba^{2+} , Eu^{3+} , and Am^{3+}) from aqueous solutions into a polar organic phase, both under laboratory conditions for theoretical or experimental purposes [9–16], and on the technological scale for the separation of some high-activity isotopes in the reprocessing of spent nuclear fuel and acidic radioactive waste [17,18].

Ruzza et al. [19] synthesized and tested a series of linear and cyclic antamanide analogues modified in position 6 and 9 with glycine or tyrosine residue. The corresponding experiments demonstrated a cytotoxic and/or cytostatic action for antamanide and some of its synthetic analogues. Due to the different ability of antamanide and its analogues to exhibit antitoxic and/or anticarcinogenic activity, these pharmacological effects may be ascribed to different mechanisms [19].

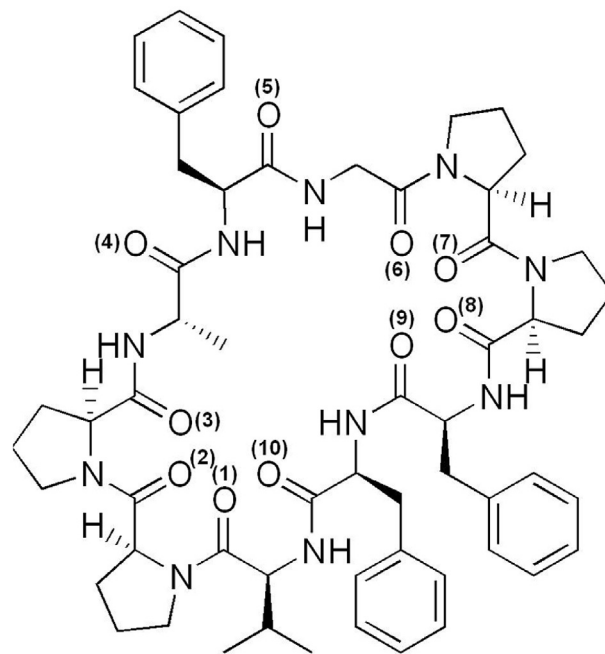
In acetonitrile medium, interactions of the cations Na^+ , K^+ , Ca^{2+} , and Tb^{3+} with glycine⁶ antamanide analogue have been also

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Scheme 1. Structural formula of antamanide.



Scheme 2. Structural formula of [Gly⁶]-antamanide (abbrev. **1**).

studied [2]. However, up to now, interaction between the Ag⁺ ion and antamanide (or its analogue, respectively) has not been reported. Therefore, in the current work, the solvent extraction of Ag⁺ into nitrobenzene by means of a mixture of sodium dicarbollylcobaltate (NaDCC) [7] and the mentioned glycine⁶ antamanide analogue, *cycl*[-Val(1)-Pro(2)-Pro(3)-Ala(4)-Phe(5)-Gly(6)-Pro(7)-Pro(8)-Phe(9)-Phe(10)-], denoted by [Gly⁶]-antamanide (abbrev. **1**; see Scheme 2), was investigated. In this context it is necessary to note that Ag⁺ is a typical representative of the “soft” univalent cations; thus, this cation was chosen for the present study. Besides, we must add that the applied experimental method is very simple and quite unambiguous. Moreover, the stability constant of the proven **1**·Ag⁺ complex species in the organic phase of the water–nitrobenzene extraction system was evaluated. Finally, applying quantum chemical DFT calculations, the most probable structure of this cationic complex species was predicted.

2. Experimental

Synthesis of [Gly⁶]-antamanide (**1**; see Scheme 2) was described elsewhere [19]. Cesium dicarbollylcobaltate (CsDCC) [8] was synthesized by means of the method published by Hawthorne et al. [20]. The other chemicals used (Lachema, Brno, Czech Republic) were of reagent grade purity. A nitrobenzene solution of hydrogen dicarbollylcobaltate (HDCC) [8] was prepared from CsDCC by the procedure described in Ref. [21]. The equilibration of the nitrobenzene solution of HDCC with stoichiometric NaOH, which was dissolved in an aqueous solution of NaCl (0.20 M), yielded the corresponding NaDCC solution in nitrobenzene. The carrier-free radionuclide ²²Na⁺ was obtained from DuPont, Belgium; its radionuclidic purity was 99.9%.

The extraction experiments were carried out in 10 mL polypropylene test-tubes with polypropylene stoppers: 2 mL of an aqueous solution of AgNO₃ of a concentration in the range from 1 × 10⁻³ to 3 × 10⁻³ M and 10 kBq of ²²Na⁺ were added to 2 mL of a nitrobenzene solution of **1** and NaDCC, whose initial concentrations varied also from 1 × 10⁻³ to 3 × 10⁻³ M. In all these experiments,

the initial concentration of **1** in nitrobenzene, C₁^{in,nb}, was equal to the initial concentration of NaDCC in this medium, C_{NaDCC}^{in,nb}. The test-tubes filled with the solutions were shaken for 3 h at 25 ± 1 °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 ²²Na⁺ in the nitrobenzene and aqueous samples (the uncertainties of these distribution ratios were always lower than 3%).

3. Computational details

The theoretical calculations were carried out at the density functional level of theory (DFT, B3LYP functional) [22,23], employing the Gaussian 09 suite of programs [24]. The LanL2DZ 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. This was ensured by means of the Gaussian 09 keyword “integral(ultrafinegrid)”.

The most probable structure of the cationic complex **1**·Ag⁺ was predicted on the basis of the thorough conformational analysis (i. e., eight very different initial mutual positions of the ligand **1** and the Ag⁺ cation were considered during the geometry optimization) and the respective vibrational frequency analysis.

Localized molecular orbitals were computed using Firefly QC package [25], which is partially based on the GAMESS (US) [26]

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