Monatsh Chem (2011) 142:779–782
DOI 10.1007/s00706-011-0499-1

ORIGINAL PAPER

On the complexation of the sodium cation with beauvericin: experimental and theoretical study

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Received: 11 March 2011 / Accepted: 30 March 2011 / Published online: 21 April 2011

Abstract From extraction experiments in the two-phase water/nitrobenzene system and γ-activity measurements, the stability constant of the beauvericin·Na^+ complex species dissolved in nitrobenzene saturated with water was determined. By using quantum mechanical density functional level of theory (DFT) calculations, the most probable structure of this complex species was derived.

Keywords Antibiotics · Macrocycles · Complexation · Stability constant · DFT calculations · Complex structure

Introduction

Beauvericin (**1**; Scheme 1) is a depsipeptide with antibiotic and insecticidal effects belonging to the enniatin family. It was isolated from the fungus *Beauveria bassiana*, but it is also produced by other fungi, including several *Fusarium* species [1]; it may therefore occur in grain (such as corn, wheat, and barley) contaminated with these fungi [1–3]. Beauvericin is active against Gram-positive bacteria and mycobacteria, and it is also capable of inducing programmed cell death in mammals [1]. Chemically, beauvericin is a cyclic hexadepsipeptide with alternating methyl-phenylalanyl and hydroxy-isovaleryl residues. Its ion-complexing capability allows beauvericin to transport alkaline earth metal and alkali metal ions across cell membranes [4].

Recently, experimental evidences for a valinomycin–proton complex [5] and some unusual divalent metal cation complexes of valinomycin [6] have been reported in detail. Furthermore, the theoretical structures of the valinomycin complexes with Li^+, K^+, NH_4^+, Mg^{2+}, Ca^{2+}, and Zn^{2+} have also been solved [7–12].

In the current work, the stability constant of the beauvericin complex with the sodium cation (**1**·Na^+) is determined in the organic phase of the water/nitrobenzene extraction system. In this context it should be noted that the sodium cation was chosen for this study because it is a typical representative of the "light" univalent cations, and therefore the Na^+ ion was chosen for this study. Moreover, quantum mechanical density functional theory (DFT) calculations were used to predict the most probable structure of the **1**·Na^+ cationic complex species.

Results and discussion

Extraction experiments

Previous results [13–16] have shown that the two-phase water–NaA (A^- = picrate)/nitrobenzene extraction system can be described by the following equilibrium (1) with the corresponding extraction constant $K_{ex}(Na^+, A^-)$; aq and nb denote the presence of the species in the aqueous and nitrobenzene phases:

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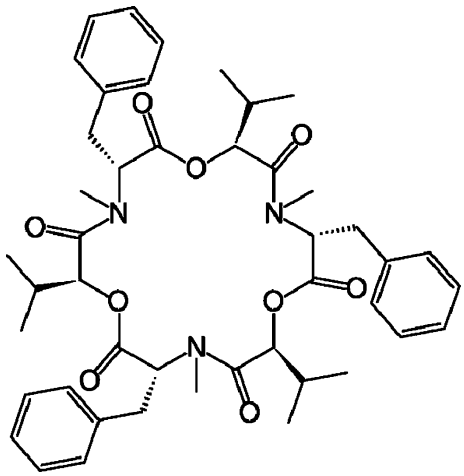

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Scheme 1

$$Na^+(aq) + A^-(aq) \leftrightarrows Na^+(nb) + A^-(nb); \quad K_{ex}(Na^+, A^-) \tag{1}$$

The constant log $K_{ex}(Na^+, A^-)$ can be written as shown in Eq. (2), where $K^i_{Na^+}$ and $K^i_{A^-}$ are the individual extraction constants for Na^+ and A^- ions in the water/nitrobenzene system [13–16].

$$\log K_{ex}(Na^+, A^-) = \log K^i_{Na^+} + \log K^i_{A^-} \tag{2}$$

Knowing $\log K^i_{Na^+} = -6.0$ [14] and $\log K^i_{A^-} = 0.8$ (A^- = picrate) [14], the extraction constant $K_{ex}(Na^+, A^-)$ was simply calculated from Eq. (2) as $\log K_{ex}(Na^+, A^-) = -5.2$.

Previous results [17–21] indicated that the two-phase water–NaA (A^- = picrate)/nitrobenzene–**1**(beauvericin) extraction system, chosen for determination of the stability constant of the complex **1**·Na^+ in nitrobenzene saturated with water (see "Experimental"), can be characterized by the main equilibrium (3) to which the equilibrium extraction constant (4) corresponds.

$$Na^+(aq) + A^-(aq) + \mathbf{1}\,(nb) \leftrightarrows \mathbf{1}\cdot Na^+(nb) + A^-(nb); \quad K_{ex}(\mathbf{1}\cdot Na^+, A^-) \tag{3}$$

$$K_{ex}(\mathbf{1}\cdot Na^+,\ A^-) = \frac{[\mathbf{1}\cdot Na^+]_{nb}[A^-]_{nb}}{[Na^+]_{aq}[A^-]_{aq}[\mathbf{1}]_{nb}} \tag{4}$$

It is necessary to emphasize that **1** is a considerably hydrophobic ligand, practically present in the nitrobenzene phase only, where this ligand forms—with Na^+—the relatively stable **1**·Na^+ complex species.

Taking into account the conditions of electroneutrality in the organic and aqueous phases of the system under study, the mass balances of **1** and NaA at equal volumes of the nitrobenzene and aqueous phases, as well as the measured equilibrium distribution ratio of sodium, $D_{Na} = [\mathbf{1}\cdot Na^+]_{nb}/[Na^+]_{aq}$, combined with Eq. (4), we get the final expression for the above-mentioned extraction constant (Eq. 5); $C^{in,aq}_{NaA}$ is the initial concentration of NaA in the aqueous phase and $C^{in,nb}_{\mathbf{1}}$ denotes the initial concentration of **1** in the organic phase of the system under consideration.

$$K_{ex}(\mathbf{1}\cdot Na^+, A^-) = D^2_{Na} \Big/ \left\{ C^{in,nb}_1 - \frac{D_{Na}}{1 + D_{Na}} C^{in,aq}_{NaA} \right\} \tag{5}$$

In this study, from the extraction experiments and γ-activity measurements (see "Experimental"), and by using Eq. (5), the following value of the constant K_{ex} (**1**·Na^+, A^-) was determined: $\log K_{ex}$ (**1**·Na^+, A^-) = −0.8 ± 0.1.

Furthermore, with respect to Refs. [17–21], for the stability constant of the **1**·Na^+ complex in water-saturated nitrobenzene, denoted by β_{nb} (**1**·Na^+), corresponding to the equilibrium $\mathbf{1}(nb) + Na^+(nb) \rightleftarrows \mathbf{1}\cdot Na^+(nb)$, as well as for the extraction constants $K_{ex}(Na^+, A^-)$ and K_{ex}(**1**·Na^+, A^-) defined above, one can formulate Eq. (6):

$$\log \beta_{nb}(\mathbf{1}\cdot Na^+) = \log K_{ex}(\mathbf{1}\cdot Na^+, A^-) - \log K_{ex}(Na^+, A^-) \tag{6}$$

Using the constants $\log K_{ex}(Na^+, A^-)$ and $\log K_{ex}$(**1**·Na^+, A^-) defined above, and applying Eq. (6), we obtain the stability constant of the considered cationic complex species **1**·Na^+ in nitrobenzene saturated with water at 25 °C as $\log \beta_{nb}$ (**1**·Na^+) = 4.4 ± 0.1. At this point it should be noted that the stability constant of the complex species NaL^+, where L is valinomycin, in water-saturated nitrobenzene is $\log \beta_{nb}$ (NaL^+) = 6.7 [19]. This means that in the mentioned nitrobenzene medium, the stability of the **1**·Na^+ complex under study is substantially lower than that of the cationic complex species NaL^+ (L = valinomycin).

Quantum mechanical calculations

The quantum mechanical calculations were carried out at the density functional level of theory (DFT, B3LYP functional) [22, 23] using the Gaussian 03 suite of programs [24]. The 6-31G(d) 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 03 keyword "Int = UltraFine."

Although a possible influence of a polar solvent on the detailed structures of **1** and its complex with Na^+ could be imagined, our quantum mechanical calculations in similar cases, performed in an analogous way, showed very good agreement of experiment with theory [25–31].

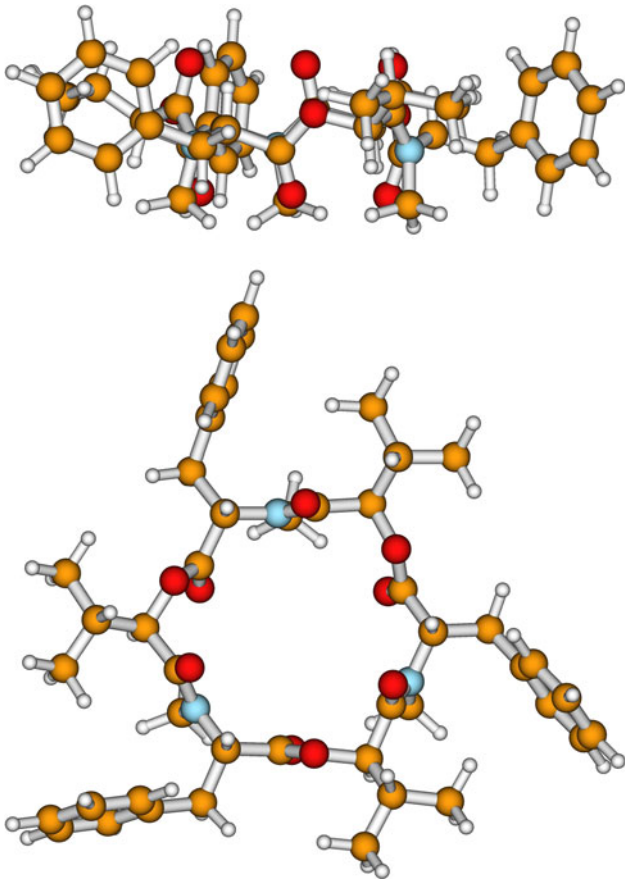

Fig. 1 Two projections of the DFT-optimized structure of free ligand **1** [B3LYP/6-31G(d)]

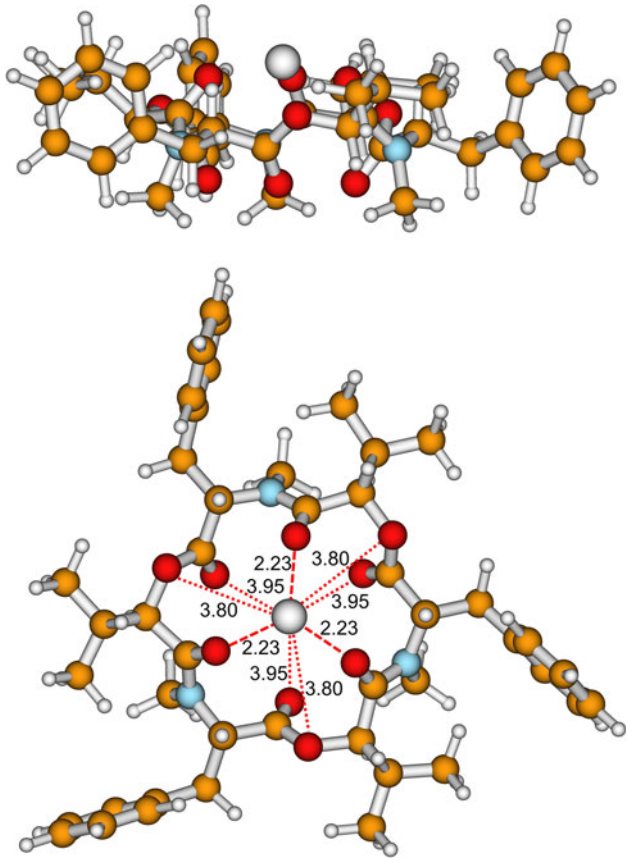

Fig. 2 Two projections of the DFT-optimized structure of the **1**·Na^+ complex [B3LYP/6-31G(d)]

In the model calculations, we optimized the molecular geometries of the parent beauvericin ligand **1** and its complex with the sodium cation. The optimized structure of the free ligand **1** with C_3 symmetry is illustrated in Fig. 1.

Figure 2 shows the structure obtained by the full DFT optimization of the **1**·Na^+ complex, which also has C_3 symmetry, together with the lengths of the corresponding bonds (in Å; 1 Å = 0.1 nm). As follows from this figure, the complexation with the Na^+ cation changes the overall shape of the parent ligand **1** only slightly. In the resulting **1**·Na^+ cationic complex species, which is most energetically favored, the "central" cation Na^+ is bound by nine bond interactions to nine oxygen atoms (2.23, 3.80, 3.95, 2.23, 3.80, 3.95, 2.23, 3.80, and 3.95 Å) of the parent beauvericin ligand **1**.

Finally, the interaction energy, E(int), of the **1**·Na^+ complex (calculated as the difference between electronic energies of the complex **1**·Na^+ and isolated **1** and Na^+ species: $E(\text{int}) = E(\mathbf{1}\cdot Na^+) - E(\mathbf{1}) - E(Na^+)$) was found to be -419.4 kJ mol^{-1}, which confirms the formation of the considered cationic complex **1**·Na^+.

Conclusions

In conclusion, we have demonstrated that a complementary theoretical and experimental approach can provide important information on the beauvericin ligand (**1**) complexation with the sodium cation. From the experimental investigation of the resulting complex **1**·Na^+ in the two-phase water/nitrobenzene system, the strength of the considered **1**·Na^+ cationic complex species in nitrobenzene saturated with water was characterized quantitatively by the stability constant, $\log \beta_{nb}$ (**1**·Na^+) = 4.4 ± 0.1 (for a temperature of 25 °C). By using the theoretical quantum mechanical DFT calculations, the structural details of the **1**·Na^+ complex, such as position of the Na^+ ion in the parent beauvericin ligand **1** as well as the interatomic distances within the complex species under study, were obtained.

Experimental

Beauvericin (**1**; Scheme 1) was purchased from Aldrich. The other chemicals used (Lachema, Brno, Czech

Republic) were of reagent grade purity. A solution of sodium picrate (NaA) in water was prepared by dissolving a stoichiometric amount of picric acid in an aqueous solution of NaOH. The radionuclide $^{22}Na^{+}$ (DuPont, Belgium) was of standard radiochemical purity.

The extraction experiments were carried out in 10-cm^3 glass test tubes with polyethylene stoppers: 2 cm^3 of an aqueous solution of NaA (concentration in the range from 1×10^{-3} to 5×10^{-3} M) and microamounts of $^{22}Na^{+}$ were added to 2 cm^3 of a nitrobenzene solution of **1**, the concentration of which varied from 2×10^{-3} to 1×10^{-2} M (in all experiments, the initial concentration of **1** in nitrobenzene, $C_1^{in,nb}$, was always higher than the initial concentration of NaA in water, $C_{NaA}^{in,aq}$). The test tubes filled with the solutions were shaken for 2 h at 25 ± 1 °C, using a laboratory shaker. Then the phases were separated by centrifugation. Afterwards, 1-cm^3 samples were taken from each phase and their γ-activities were measured using a well-type NaI(Tl) scintillation detector connected to a γ-analyzer NK 350 (Gamma, Budapest, Hungary).

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

Acknowledgments This work was supported by the Czech Ministry of Education, Youth and Sports (projects MSM 4977751303 and MSM 6046137307) and by the Czech Science Foundation (project P205/10/2280). The computer time at the MetaCentrum (project MSM 6383917201), as well as at the Institute of Physics (computer Luna/Apollo), Academy of Sciences of the Czech Republic, is gratefully acknowledged.

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