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Experimental and theoretical study on the complexation of the strontium cation with nonactin

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HIGHLIGHTS

- Stability constant of the Sr^{2+}. nonactin complex (abbrev. **1**·Sr^{2+}) in nitrobenzene was determined as log β_{nb} (**1**·Sr^{2+}) = 7.1 ± 0.1.
- By using DFT calculations, the structure of the **1**·Sr^{2+} complex having S_4 symmetry was predicted.
- In the resulting complex, the "central" cation Sr^{2+} is bound by eight bond interactions to eight oxygens of the nonactin ligand **1**.

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ABSTRACT

From extraction experiments and γ-activity measurements, the extraction constant corresponding to the equilibrium $Sr^{2+}(aq) + 2A^-(aq) + \mathbf{1}(nb) \Longleftrightarrow \mathbf{1} \cdot Sr^{2+}(nb) + 2A^-(nb)$ taking place in the two-phase water-nitrobenzene system (A^- = picrate, **1** = nonactin; aq = aqueous phase, nb = nitrobenzene phase) was evaluated as log K_{ex}(**1**·Sr^{2+}, $2A^-$) = −2.0 ± 0.1. Further, the stability constant of the **1**·Sr^{2+} complex in nitrobenzene saturated with water was calculated for a temperature of 25 °C: log β_{nb} (**1**·Sr^{2+}) = 7.1 ± 0.1. Finally, by using DFT calculations, the most probable structure of the cationic complex species **1**·Sr^{2+} was derived. In the resulting complex having S_4 symmetry, the "central" cation Sr^{2+} is bound by eight relatively strong bond interactions to eight oxygen atoms of the parent nonactin ligand **1**.

1. Introduction

Macrotetrolides (nonactin, monactin, dinactin, trinactin, and tetranactin) [1–6], isolated from a variety of *Streptomycetes* species, are cyclotetralactones derived from nonactic acid and homononactic acid as the building units [4] of ionophoretic character [7]. With the exception of nonactin, they exhibit, in addition to antibacterial and antifungal activity, also remarkable acaricidal, insecticidal, coccidiostatic, and anthelminthic effects [5,8,9]. Besides, the macrotetrolide antibiotics are very potent uncouplers of oxidative phosphorylation in mitochondria [10].

The stability and selectivity of complex formation of natural macrocyclic ionophores (valinomycin, nonactin, monactin, dinactin, and trinactin) with alkali metal ions and monovalent thallium cation have been studied by polarography [11]. With valinomycin, both stability constants and homogenous dissociation rate constants have been determined from polarographic kinetic currents. The macrotetrolides gave diffusion controlled currents. The stability of their complexes increases with the degree of substitution from nonactin to trinactin [11]. The very large differences in stabilities of the ammonium and the other alkali metal complexes of nonactin are the cause of the high ammonium selectivity of the nonactin-based ion-selective electrode [12]. Recently, experimental evidences for a valinomycin – proton complex and for some unusual divalent metal cation complexes of valinomycin have been reported in detail [13,14]. Furthermore, the theoretical structures of the valinomycin complexes with Li^+, K^+, NH_4^+, and Mg^{2+} have been solved as well [15–18].

In the current work, the stability constant of the complex of nonactin (abbrev. **1**; see Scheme 1) with the strontium cation (abbrev. **1**·Sr^{2+}) was determined in nitrobenzene saturated with water. Besides, applying DFT calculations, the most probable structure of the **1**·Sr^{2+} cationic complex species was predicted on the basis of the thorough conformational analysis (i.e., different mutual positions of the ligand **1** and the Sr^{2+} cation were considered during

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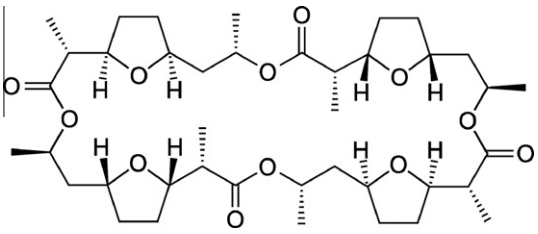


Scheme 1. Structural formula of nonactin (abbrev. **1**).

the geometry optimization) and the respective vibrational frequency calculations.

2. Experimental

Nonactin (purum, ⩾98%; abbrev. **1**; see Scheme 1) was purchased from Aldrich. The other chemicals used (Lachema, Brno, Czech Republic) were of reagent grade purity. A solution of strontium picrate (abbrev. SrA_2) in water was prepared by dissolving stoichiometric amount of picric acid in an aqueous solution of $Sr(OH)_2$. The radionuclide $^{85}Sr^{2+}$ was supplied by DuPont, Belgium.The extraction experiments were carried out in 10 mL polypropylene test-tubes with polypropylene stoppers: 2 mL of an aqueous solution of SrA_2 (1×10^{-4} to 3×10^{-4} M) and micro amounts of $^{85}Sr^{2+}$ were added to 2 mL of a nitrobenzene solution of **1**, the initial concentration of which varied from 1×10^{-2} to 3×10^{-2} M (in all experiments, the initial concentration of **1** in nitrobenzene, $C_1^{in,nb}$, was always higher than the initial concentration of SrA_2 in water, $C_{SrA_2}^{in,aq}$). 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 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 NK 350 (Gamma, Budapest, Hungary).

The equilibrium distribution ratios of strontium, D_{Sr}, were determined as the ratios of the corresponding measured radioactivities of $^{85}Sr^{2+}$ in the nitrobenzene and aqueous samples.

3. Results and discussion

3.1. Extraction experiments

Regarding the results of previous papers [19–21], the two-phase water-SrA_2 (A^- = picrate) – nitrobenzene extraction system can be described by the following equilibrium

$$Sr^{2+}(aq) + 2A^-(aq) \Longleftrightarrow Sr^{2+}(nb) + 2A^-(nb); \quad K_{ex}(Sr^{2+}, 2A^-) \quad (1)$$

with the corresponding extraction constant $K_{ex}(Sr^{2+}, 2A^-)$; aq and nb denote the presence of the species in the aqueous and nitrobenzene phases, respectively. For the constant $K_{ex}(Sr^{2+}, 2A^-)$ one can write [19,21]

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

where $K^i_{Sr^{2+}}$ and K^i_A are the individual extraction constants for Sr^{2+} and A^-, respectively, in the water–nitrobenzene system [19,21]. Knowing the values $\log K^i_{Sr^{2+}} = -10.7$ [21] and $\log K^i_{A^-} = 0.8$ (A^- = picrate) [19], the extraction constant $K_{ex}(Sr^{2+}, 2A^-)$ was simply calculated from Eq. (2) as $\log K_{ex}(Sr^{2+}, 2A^-) = -9.1$.

Previous results [22,23] indicated that the two-phase water-SrA_2 (A^- = picrate)-nitrobenzene-**1** (nonactin) extraction system, chosen for determination of the stability constant of the complex $\mathbf{1}\cdot Sr^{2+}$ in nitrobenzene saturated with water (see Experimental), can be characterized by the main chemical equilibrium

$$Sr^{2+}(aq) + 2A^-(aq) + \mathbf{1}(nb) \Longleftrightarrow \mathbf{1}\cdot Sr^{2+}(nb) + 2A^-(nb); \quad K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-) \quad (3)$$

to which the equilibrium extraction constant

$$K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-) = \frac{[\mathbf{1}\cdot Sr^{2+}]_{nb}[A^-]^2_{nb}}{[Sr^{2+}]_{aq}[A^-]^2_{aq}[\mathbf{1}]_{nb}} \quad (4)$$

corresponds. It is necessary to emphasize that **1** is a considerably hydrophobic ligand, practically present in the nitrobenzene phase only, where this ligand forms – with the Sr^{2+} cation – the relatively stable complex $\mathbf{1}\cdot Sr^{2+}$, as given below.

Applying the conditions of electroneutrality in the organic and aqueous phases of the system under study, the mass balances of **1** and SrA_2 at equal volumes of the nitrobenzene and aqueous phases, as well as the measured equilibrium distribution ratio of strontium, $D_{Sr} = [\mathbf{1}\cdot Sr^{2+}]_{nb}/[Sr^{2+}]_{aq}$, combined with Eq. (4), we gain the final expression for the extraction constant $K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-)$:

$$K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-) = D^3_{Sr}/\left\{C^{in,nb}_{\mathbf{1}} - \frac{D_{Sr}}{1+D_{Sr}}C^{in,aq}_{SrA_2}\right\} \quad (5)$$

where $C^{in,aq}_{SrA_2}$ is the initial concentration of SrA_2 in the aqueous phase and $C^{in,nb}_1$ denotes the initial concentration of **1** in the organic phase of the system under consideration.

In this study, from the extraction experiments and γ-activity measurements (see Experimental) by means of Eq. (5), the following value of the constant $K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-)$ was determined: $\log K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-) = -2.0 \pm 0.1$ (see Table 1).

Moreover, with respect to previous results [22,23], for the extraction constants $K_{ex}(Sr^{2+}, 2A^-)$ and $K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-)$ defined above, as well as for the stability constant of the complex $\mathbf{1}\cdot Sr^{2+}$ in nitrobenzene saturated with water, denoted by β_{nb} ($\mathbf{1}\cdot Sr^{2+}$), one gets

$$\log \beta_{nb}\,(\mathbf{1}\cdot Sr^{2+}) = \log K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-) - \log K_{ex}(Sr^{2+}, 2A^-) \quad (6)$$

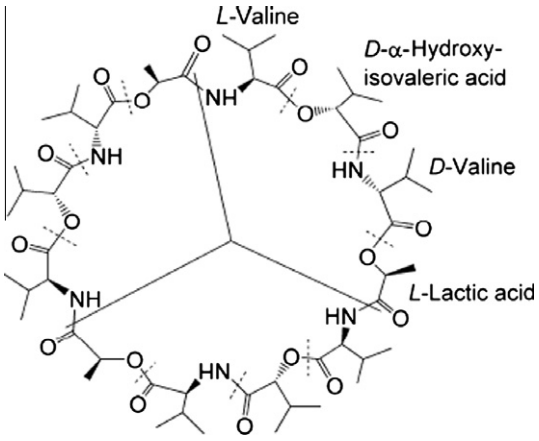
Using the constants $\log K_{ex}(Sr^{2+}, 2A^-)$ and $\log K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-)$ given above, and employing Eq. (6), we obtain the stability constant of the $\mathbf{1}\cdot Sr^{2+}$ complex in water-saturated nitrobenzene at 25 °C as $\log \beta_{nb}\,(\mathbf{1}\cdot Sr^{2+}) = 7.1 \pm 0.1$. In this context it should be noted that the stability constant of the complex species $\mathbf{2}\cdot Sr^{2+}$, where **2** denotes valinomycin (see Scheme 2), in nitrobenzene saturated with water is $\log \beta_{nb}\,(\mathbf{2}\cdot Sr^{2+}) = 5.4$ [24]. This means that in the mentioned nitrobenzene medium, the stability of the $\mathbf{1}\cdot Sr^{2+}$ complex under study is somewhat higher than that of the cationic complex species $\mathbf{2}\cdot Sr^{2+}$ (**2** = valinomycin).

3.2. DFT calculations

The theoretical calculations were carried out at the density functional level of theory (DFT, B3LYP) [25,26], using the Gaussian 03 suite of programs [27], analogously as in our previous papers [28–35]. The LanL2DZ basis set was used in the same way as in our recent article [35], studying interaction of the cesium cations with an electroneutral ligand, and the optimizations were unconstrained. In order to increase the numerical accuracy and to reduce

Table 1
Experimental data concerning determination of $\log K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-)$ on the basis of Eq. (5).

$C^{in,aq}_{SrA_2}$ (M)	$C^{in,nb}_1$ (M)	D_{Sr}	$\log K_{ex}(\mathbf{1}\cdot Sr^{2+}, 2A^-)$
1.0×10^{-4}	1.0×10^{-2}	0.050	−1.9
1.5×10^{-4}	1.5×10^{-2}	0.055	−2.0
2.0×10^{-4}	2.0×10^{-2}	0.062	−1.9
2.5×10^{-4}	2.5×10^{-2}	0.065	−2.0
3.0×10^{-4}	3.0×10^{-2}	0.059	−2.2



Scheme 2. Structural formula of valinomycin (abbrev. **2**).

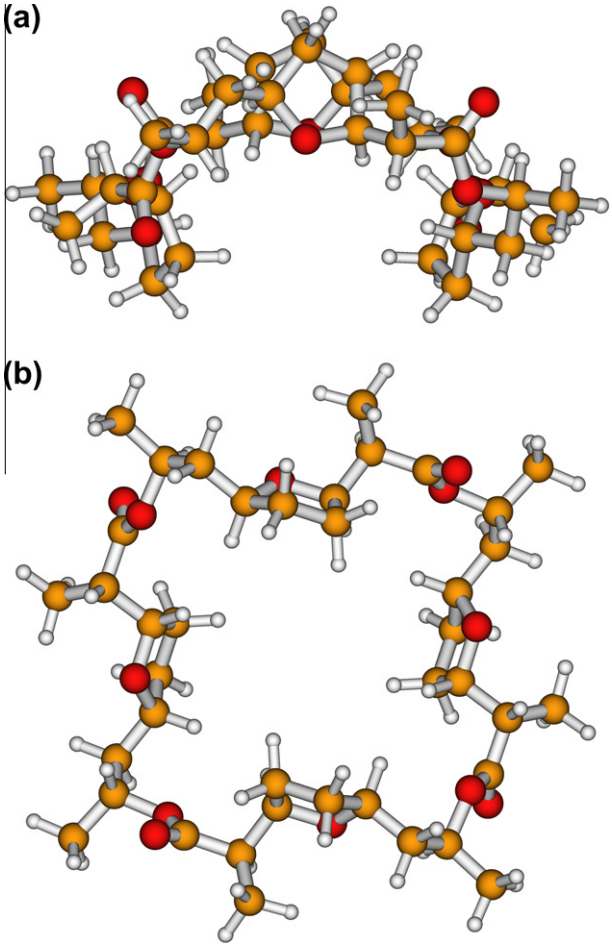


Fig. 1. Two projections of the DFT optimized structure of free ligand **1** (B3LYP/LanL2DZ): (a) side view and (b) top view.

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". Further, it was found that the most probable structures of the free ligand **1** and the considered complex **1**·Sr^{2+} have 4-fold rotation-reflectional symmetry

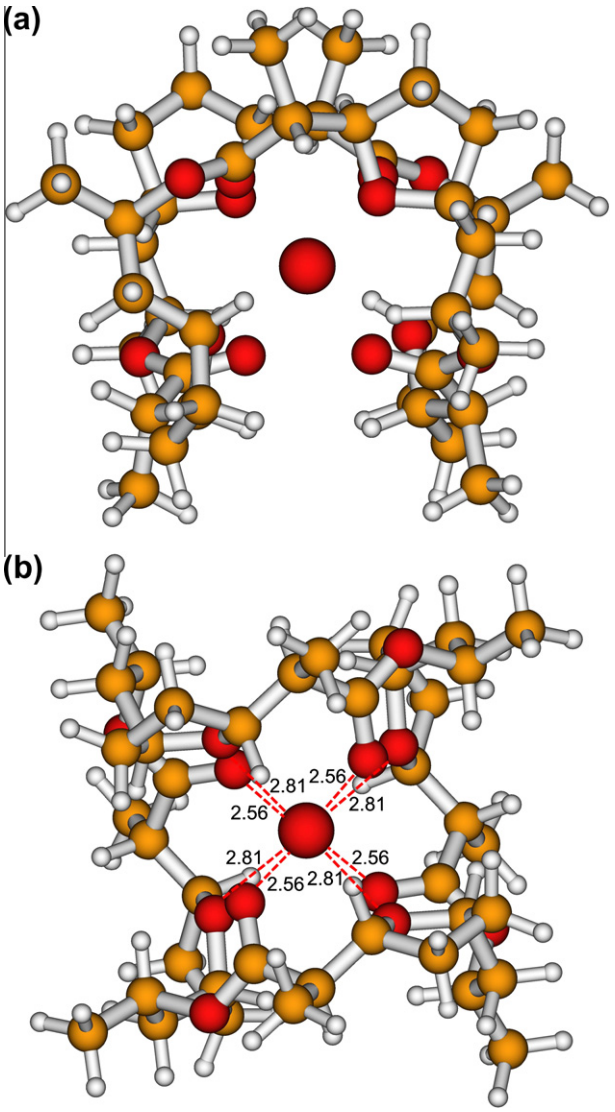


Fig. 2. Two projections of the DFT optimized structure of the **1**·Sr^{2+} complex (B3LYP/LanL2DZ): (a) side view and (b) top view.

S_4. These findings were confirmed by the respective vibrational frequency calculations.

Although a possible influence of a polar solvent on the detailed structures of **1** and the **1**·Sr^{2+} complex species could be imagined, our theoretical calculations in similar cases, performed in an analogous way, showed very good agreement of experiment with theory [28–35].

In the model calculations, we optimized the molecular geometries of the parent nonactin ligand **1** and its complex with Sr^{2+}. The optimized structure of the free ligand **1** with S_4 symmetry is illustrated in Fig. 1.

In Fig. 2, the S_4 symetric structure obtained by the full DFT optimization of the **1**·Sr^{2+} complex having a tennis-ball-seam conformation is depicted, together with the lengths of the corresponding bonds (in Å; 1 Å = 0.1 nm). In the **1**·Sr^{2+} cationic complex species, which is most energetically favoured, the "central" cation Sr^{2+} is bound by eight relatively strong bond interactions to four carbonyl oxygen atoms from ester groups (2.56, 2.56, 2.56, and 2.56 Å) and to four oxygens from tetrahydrofuran rings (2.81, 2.81, 2.81, and 2.81 Å) of the parent nonactin ligand **1** (see Fig 2.).

Finally, the interaction energy, $E(\mathrm{int})$, of the $\mathbf{1}\cdot Sr^{2+}$ complex (calculated on the basis of the respective difference of the pure electronic energies), involving the Boys-Bernardi counterpoise corrections [36–38] of the basis set superposition error, was found to be −1125.5 kJ/mol, which confirms the formation of the considered complex $\mathbf{1}\cdot Sr^{2+}$.

4. Conclusions

In summary, we have demonstrated that a complementary experimental and theoretical approach can provide important information on the nonactin (**1**) ligand complexation with the strontium cation. From the experimental investigation of the resulting complex $\mathbf{1}\cdot Sr^{2+}$ in the two-phase water-nitrobenzene extraction system, the strength of the considered $\mathbf{1}\cdot Sr^{2+}$ cationic complex species in nitrobenzene saturated with water was characterized quantitatively by the stability constant, $\log \beta_{nb}(\mathbf{1}\cdot Sr^{2+}) = 7.1 \pm 0.1$ (for a temperature of 25 °C). By using theoretical DFT calculations, the structural details of the $\mathbf{1}\cdot Sr^{2+}$ complex, such as position of the Sr^{2+} cation with regard to the parent nonactin ligand **1** as well as the significant interatomic distances within the complex species under study, were obtained.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2012.07.058.

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