

Beryllium(II) Recognition by Allosteric Effects in 1,2-Ethylenedioxybenzene Based Ditopic Receptors

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Received March 29, 2011, Accepted June 24, 2011

Efficient ditopic receptor, uranyl(II) *N,N'*-(ethylenedioxy)benzenebis(salicylideneimine) (**3**) for beryllium ion has been obtained upon functionalization of 1,2-ethylenedioxybenzene (**1**) with a uranyl-salphen (salphen = *N,N'*-phenylenebis(salicylideneimine)) unit. Binding affinities of the receptor, **3** in AN-DMSO (v/v 95:5) solution have been measured for alkali and alkaline earth metal ions by conductometry comparing **1**. The results showed that both monotopic **1** and ditopic receptor **3** were selective for Be²⁺ ions over other cations, while especially **3** that can complex both with cations (coordinated to basic oxygen of ethylenedioxybenzene) and anions (coordinated to the Lewis acidic uranyl center) results in an increase of the stability constants by a factor of 10^{2.42} with respect to **1**. Furthermore, the Be²⁺-**3** interactions are demonstrated by ¹H NMR experiments in highly polar solvent medium, DMSO-*d*₆. Higher selectivities were also observed for Be²⁺ when the ditopic receptor, **3** was incorporated into PVC membranes and tested as ion selective electrodes at neutral pH.

Key Words : Beryllium sensor, Ditopic receptors, Ion-selective electrodes, Conductance

Introduction

The search for selective ditopic receptors capable of simultaneous complexation of cationic and anionic guests is a rapidly growing area of supramolecular chemistry due to the need to develop sensors, membrane transport reagents for target metal salts of environmental and biological significance.¹⁻⁵ The selective recognition of these hydrophilic inorganic salts can thus only be achieved under conditions where their inherently high energy of hydration is overcome and selectivity-inducing interactions are used.

Beryllium is a relatively rare element in both the earth and the universe. The element is not known to be necessary or useful for either plant or animal life. However, the toxicological effects of beryllium on living systems are well known.⁶ Beryllium disease, berylliosis, is a chronic lung disease caused by inhaling dust or fumes containing beryllium. Therefore, because of its high toxicity and debated carcinogenicity, analysis of this element is necessary in the vicinity of ore processing plants and their disposal sites as well as in the industries using beryllium products.^{6,7} Notwithstanding such a framework, little is known about the biochemistry of Be²⁺, and the molecular mechanism of beryllium toxicity remains only speculative.

Unfortunately, the interest in beryllium sensor has been dampened by the fact that this ion, owing to its small size (ionic radius, 0.31 nm) and high charge density, is very strongly hydrated.⁸ In addition, due to the limits of its maximum coordination number and the high required complex stabilities, the design and synthesis of an appropriate

receptor for Be²⁺ is very difficult and there have been only few reports of Be²⁺-ion selective electrode (ISE).⁹⁻¹³

Recently, other groups and we have synthesized novel crown-ether functionalized salicylaldehyde-uranyl complexes that can serve as efficient host type compounds for hydrophilic inorganic salts.¹⁴⁻¹⁸ The presence of both cation and anion sites makes these molecules ideally suited for the recognition of inorganic salts molecules in general. The 1,2-ethylenedioxybenzene a chelating agent for Be²⁺ ion coordination has not yet been explored as a binding motif, despite of structural resemblance with other open dioxygenate ligands that may have good stable complexes with Be²⁺.¹⁹⁻²¹ In order to obtain more selective Be²⁺ receptors, we introduced uranyl-salphen substituent which contains Lewis acidic center addition to 1,2-(ethylenedioxy)benzene skeleton. The influence of the uranyl-salphen moieties that are able to form anion complex is demonstrated by allosteric effect comparing compounds **1**. In this study, what this means in practical terms is that a salphen-uranyl substituent, when connected to the ethylenedioxybenzene framework, should

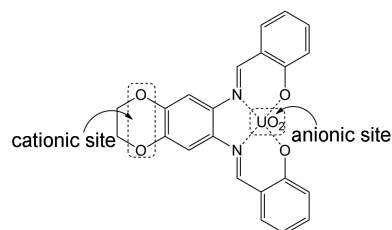


Figure 1. Both cation and anion binding site of **3**.

allow for the cooperative recognition of a complementary hydrophilic Be^{2+} salts as shown in Scheme 1.

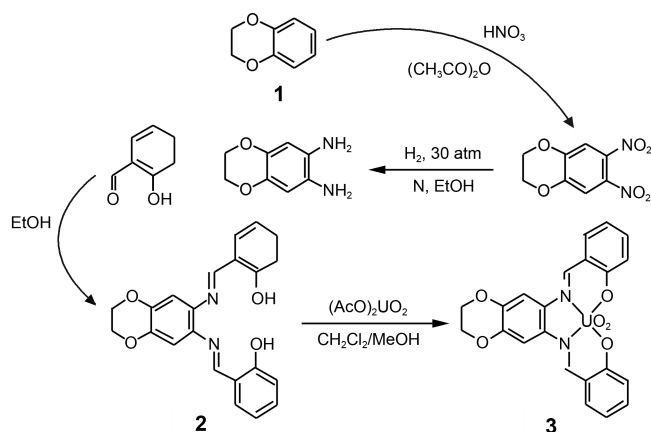
Herein we report that 1,2-ethylenedioxybenzene with uranyl-salphen unit, ditopic receptor **3** (Fig. 1) forms strong complexes with beryllium salts, in which Be^{2+} recognition is ensured by ion-dipole interaction of Be^{2+} -ethylenedioxybenzene, and counter ion binding to the Lewis acidic uranyl center of salphen complex is established through conductometric titration and ^1H NMR as well as incorporated into a PVC-based ISEs.

Experimental

Apparatus. NMR spectra were recorded with a Bruker Avance-300 spectrometer operating at 300 MHz (^1H) using $\text{DMSO}-d_6$ as solvent. FT-IR spectra were recorded with a Varian, 640-IR spectrometer. Low- and high-resolution fast atom bombardment-mass spectrometry was measured using a JEOL JMS-700 (MStation) instrument. Conductance measurements at 298.15 K were carried out using a Metrohm model 660 conductivity bridge (Swiss) at a frequency of 2 kHz. The conductance cell was a Russell-type glass-bodied electrode with a cell constant of 0.769 cm^{-1} . The potential differences between the ISEs and the reference electrode (Orion sleeve-type double junction Ag/AgCl reference electrode; model 90-02) were measured using a PC equipped with high-impedance input 16-channel analog-to-digital converter (KOSENTECH, Korea).

Reagents. Beryllium sulfate tetrahydrate was purchased from Alfa Aesar. The membrane components, PVC, tris(2-ethylhexyl) phosphate (TEHP) and oleic acid (OA) were obtained from Aldrich. Other components such as tetrahydrofuran (THF) and synthetic reagents were purchased from Junsei. All other chemicals were of analytical reagent grade. All solutions and standards were made up with double distilled water.

Synthesis of the Receptor. Commercially available **1** was purchased. The salphen H_2 derivatives, *N,N'*-(ethylenedioxy)-benzenebis(salicylideneimine) (**2**) and its uranyl complexes (**3**) were synthesized according to the following Scheme 1.



Scheme 1. Synthesis of salphen H_2 derivatives (**2**) and its uranyl complex as ionophores (**3**).

Synthesis of *N,N'*-(ethylenedioxy)benzenebis(salicylideneimine) (**2**): **2** was synthesized using nitration of 1,2-(ethylenedioxy)benzene (**1**) followed by catalytic hydrogenation and schiff-base condensation with salicylaldehyde. The product was purified by silica gel column chromatography (ethylacetate/*n*-hexane, 1:4); yield, 70%; mp 182–183 °C; mass, $m/z = 388$ (M^+ , 100); FT-IR (KBr) 3410 ($-\text{OH}$), 2962 ($=\text{C}-\text{H}$), 1586, 1542 ($-\text{N}=\text{C}-$), 1176 ($-\text{C}-\text{O}-$) cm^{-1} ; ^1H -NMR (300 MHz, CDCl_3) δ 2.13–2.19 (m, 2H, CCH_2C), 3.36–3.70 (t, 4H, $2\text{CH}_2\text{O}$), 6.76 (s, 2H, ArH), 6.84–6.85 (dd, 2H, ArH), 6.96–6.98 (t, 2H, ArH), 7.37–7.39 (t, 2H, ArH), 7.62–7.65 (dd, 2H, ArH), 8.51 (s, 2H, NCH), 13.15 (s, 2H, ArOH).

Synthesis of Uranyl(II) *N,N'*-(ethylenedioxy)benzenebis(salicylideneimine) (**3**): **3** was dissolved in CHCl_3 . Uranyl acetate dihydrate was dissolved in methanol. This solution was slowly added to the solution of **2**. Bright red or orange powders were precipitated immediately. Stirring was continued for one hour. The precipitate was collected by filtration, washed with EtOH , and dried under vacuum overnight to yield an orange-red powder. Yield, 90%; mass, $m/z = 642$ (M^+ , 100); FT-IR (KBr) 2962 ($=\text{C}-\text{H}$), 1605, 1586 ($-\text{N}=\text{C}-$), 1176 ($-\text{C}-\text{O}-$) cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 4.4 (s, 4H, CH_2O), 6.66–6.76 (m, 2H, ArH), 7.0 (d, 2H, ArH), 7.4 (s, 2H, ArH), 7.54–7.64 (m, 2H, ArH), 7.74–7.80 (m, 2H, ArH), 9.5 (s, 2H, NCH).

Conductance Measurements. A solution of the BeSO_4 salt (concentration of $5.0 \times 10^{-5}\text{ mol/dm}^3$) was placed in the conductometric cell in 95% AN-DMSO mixed solvent (7 cm^3) and titrated with a solution of the ligand (concentration range from 5.0×10^{-4} to 2.3 of mole ratio, $[\text{Be}^{2+}]/[\text{n}]$) in the same solvent. Conductance readings at 298.15 K were recorded after each addition and the molar conductance was calculated. A plot of molar conductance versus the Be^{2+} -ligand concentration ratio, $[\text{Be}^{2+}]/[\text{n}]$ was used to determine the stoichiometry of the complex and the formation constants, $\log K_f$, calculated by fitting all conductometric curves with a non-linear least-square curve fitting program KINFIT.²²

Electrode Preparation and ISE Measurements. Ion-selective membranes were prepared in accord with the procedure used to prepare ISEs containing **1** and **3**. In the present study, 5 mL THF was used to dissolve approximately 180 mg of a mixture composed of ~1 wt % of the receptor **3**, ~33 wt % polymer matrix (PVC), ~66 wt % plasticizer (TEHP) and small amount of additive (oleic acid). The resulting membrane, obtained by following evaporation as before,^{23,24} was mounted on a home-made electrode body. The response of the sensor for Be^{2+} ions was examined by measuring electromotive force (EMF) of the following electrochemical cell:

$\text{Ag} \mid \text{AgCl} \mid \text{sat. KCl} \mid \text{sample solution} \parallel \text{PVC membrane} \parallel 10^{-2}\text{ M BeSO}_4 + 10^{-2}\text{ M NaCl solution} \mid \text{AgCl} \mid \text{Ag}$.

Dynamic response curves and calibration plots were obtained through the step addition of standard solutions to 100 mL of background electrolyte at 25 °C. The solutions were magnetically stirred during the recording of all emf

values. The selectivity coefficients ($\log K_{Be,j}^{pot}$) were determined by a separate solution method using the reduced form of the Nicolsky-Eisenman equation.²⁵

$$\log K_{Be,j}^{pot} = (E_1 E_2)/S + (1 - z_A/z_B) \log$$

Where E_1 is the potential measured in 10^{-2} M solution of the interfering ion, E_2 is the potential measured in 10^{-2} M primary ion (Be^{2+}), S is the calibration slope, z_A and z_B are electrical charges of Be^{2+} and interfering ions, respectively, and a is the activity of the primary ion (10^{-2} M). The detection limits of the electrodes were also estimated according to the method suggested in IUPAC recommendation.

Results and Discussion

Binding Studies. **3** is characterized by the availability of both an electron accepting and a donating site within the same molecule. This availability allows the ditopic receptors to recognize and interact with both cationic and anionic guest molecules. Important molecules of this type include bifunctional molecules that contain acidic cation or basic anion binding center. The effective relative-stability of 1:1 host-guest complexes is subject to cooperative coordination and is expected to be important in determining the selectivity features of host-guest interactions.

To the best of our knowledge, there is no literature report on the stability of the **3** complexes with metal ions. Thus, in preliminary experiments, the complexation of **3** with a wide variety of cations including alkali, alkaline earth was investigated in 95% AN-DMSO mixed solvent at 25 °C. In order to investigate the interactions between Be^{2+} and ligands, **1** and **3**, we employed conductometry which can determine the stoichiometry and stability constants for the complexes formed between ionophores and Be^{2+} salts. Figure 2 shows the plots of molar conductance, Λ_m , against the ionophores **1** and **3** vs. Be^{2+} salts concentration ratio, $[n]/[\text{Be}^{2+}]$. As shown in Fig. 2, the Be^{2+} binding curve for ditopic receptor, **3** possesses a sharp plateau at 1:1 mole ratio indicative of a

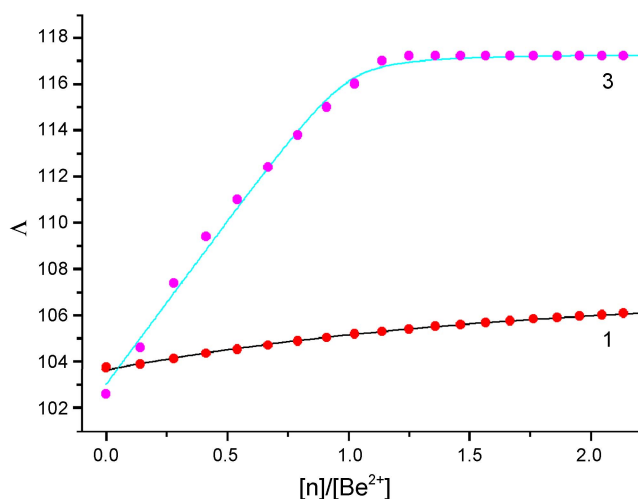


Figure 2. Λ ($\text{S}^{-1}\text{cm}^2\text{mol}^{-1}$) vs. $[3]/[\text{Be}^{2+}]$ in 95% AN-DMSO solution.

Table 1. $\log K_f$ values of **1** and **3** complexes in 95% AN-DMSO binary mixtures at different cations

| | LiNO_3 | NaNO_3 | KNO_3 | $\text{Be}(\text{NO}_3)_2$ | $\text{Mg}(\text{NO}_3)_2$ |
|----------|-----------------|-----------------|----------------|----------------------------|----------------------------|
| 1 | 3.24 | 3.97 | 3.15 | 3.97 | 3.64 |
| 3 | 4.37 | 4.71 | 4.34 | 6.39 | 4.44 |

strong Be^{2+} binding, whereas the curve for monotopic receptor **1** without salphen unit a gentler slope. A likely explanation for this phenomenon is that uranyl(II) center forms an anion complex with ditopic receptor **3**, which creates a cooperative coordination allosteric effect for both cation and anion binding. While, this *allosteric effect* is not possible for the **1**.

The stability constants of the complexation between the ionophores and Be^{2+} can be determined by analysis of the molar conductance data using the KINFIT program. A best fitting curve for $n\text{-Be}^{2+}$ was obtained by a nonlinear least-square fitting procedure and the results are shown in Table 1. It is clear from data in Table 1 that all the receptors (**1** and **3**) form quite strong complexes with Be^{2+} ion than any other cations studied. Especially, the results show that ditopic receptor **3** exhibits an enhancement of stability constant ($\log K_f = 6.39$) for Be^{2+} binding when anion is bound at the salphen-uranyl center in comparison with monotopic receptor **1** ($\log K_f = 3.97$). The order of formation constants is as follows; $\text{Be}^{2+} \gg \text{Na}^+ > \text{Mg}^{2+} > \text{Li}^+ > \text{K}^+$, where ditopic receptor **3** showed an excellent selectivity for Be^{2+} over other cations.

A portion of the ^1H NMR spectrum of **3** in $\text{DMSO-}d_6$ is shown in Fig. 3(a). Addition of *ca.* 1.0 molar equivalent of solid BeSO_4 caused the appearance of a second species (Fig. 3(b)), whose ethylene proton ($-\text{OCH}_2\text{-CH}_2\text{O}-$) of 1,2-ethylenedioxybenzene was downfield shifted from δ 4.2 (free **3**) to δ 5.0 (complexed **3**), respectively. The presence of separate signals of free and Be^{2+} -complexed receptor indicates slow equilibrium on the ^1H NMR time scale at room temperature. Fig. 3, which indicate ditopic receptor **3** form a very strong complex with beryllium salts.

Whereas the proton signal of **1** (not shown) undergoes negligible variations upon addition of BeSO_4 . This means that Be^{2+} -**1** interactions are significantly weakened in DMSO such as polar solvent.

A definite confirmation that the uranyl-salphen unit plays

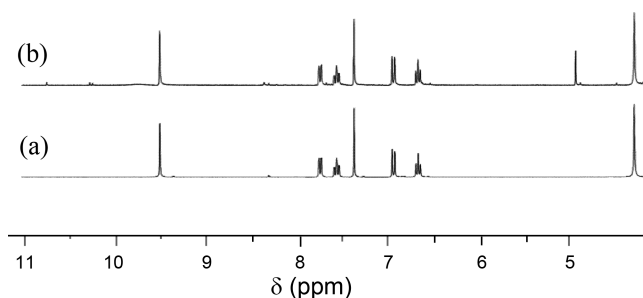


Figure 3. Portions of the ^1H NMR spectra in $\text{DMSO-}d_6$ of: (a) **3** only, (b) **3** + 1 equiv. BeSO_4 .

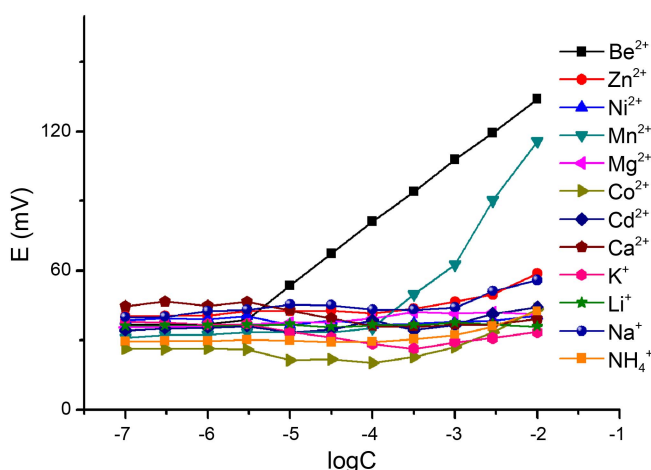


Figure 4. Response curves of the membrane (3/TEHP/PVC/OA) towards various cations.

an important role in the complexation of the **3**-BeSO₄ was obtained in DMSO-*d*₆ solution. This implies that BeSO₄ is complexed by ditopic receptor, **3** in a ditopic fashion. Therefore, the influence of the anionic site on the complexing behavior of **3** can be regarded as an *allosteric effect*.

Ion-Selective Electrode Studies. Receptor-based ISEs provide another means of testing whether a given receptor displays selectivity for targeted ions. Like the bulk extraction studies described above, this method can provide insight into recognition events that take place at an aqueous-organic interface. Potential measurements of the PVC-membrane electrode include response, sensitivity, selectivity, and are often expressed in relative terms as a selectivity coefficient K_{ij}^{Pot} , where *i* and *j* represent the two competing analytes, and the linear range over which the response, Nernstian or otherwise, is seen. The polymeric membrane was composed of compounds **1** and **2** as the ionophore, PVC, TEHP and OA for the purpose of reducing the membrane resistance and suppressing the permeation of counter anions from the aqueous phase into the membrane phase.

The best electrode (3/TEHP/PVC/OA) exhibited a near Nernstian slope of 29.1 mV/decade for the Be²⁺ ion concentration in the range of 3.0×10^{-6} - 1.0×10^{-2} M with detection limits of approx. 1.6×10^{-6} M. The potentiometric responses of the electrode are independent of pH over the range of 5.0-8.0 with satisfactory reproducibility.

Potentiometric responses based on **3** towards Be²⁺ and various interfering ions are shown in Fig. 4. All of the ions under investigation show negligible responses except for Mn²⁺. This is likely due to the high selectivity of the ionophore for beryllium ions over other metal ions as well as the rapid exchange kinetics of the resulting Be²⁺-**3** complex in membrane interface.

The logarithmic values of the selectivity coefficients calculated for Be²⁺ as the primary cation ($\log K_{ij}^{Pot}$) are presented in Fig. 5. The proposed Be²⁺-ISEs based on 1,2-ethylene dioxybenzene and its functionalized salphen-uranyl complex showed an excellent selectivity over all other cations tested. Moreover, the membrane of **3** that contains a

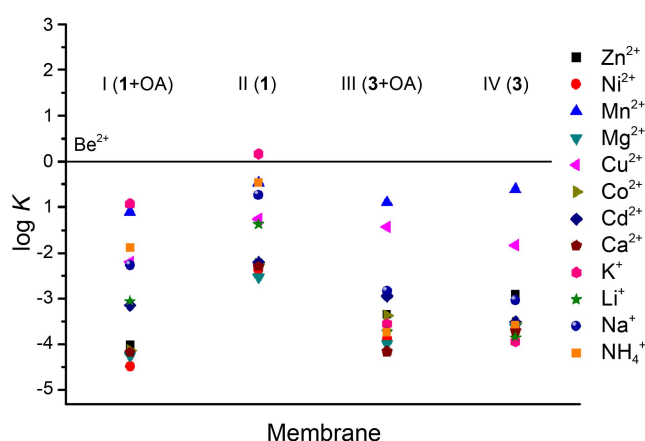


Figure 5. Selectivity coefficients for electrodes prepared with PVC/TEHP (1:2 by weight) membranes containing **1** or **3** and oleic acid as a lipophilic additive with Be²⁺ as the primary cation.

ditopic site with additive OA provided an increased sensitivity and selectivity towards Be²⁺ in comparison with the membranes doped with only receptors (II and IV).

In our previous work, we demonstrated that salphen-uranyl complex showed near-Nernstian negative responses to a range of anionic analytes, including phosphates, when incorporated into PVC/*o*-NPOE membranes and tested as ISEs.²⁶ This observation displays a response process that is dominated by anion chelation and leads to the negative response under the interfacial conditions of the ISE experiment.

Functionalized **3** mediates their observed ISE response (positive) for Be²⁺ by acting more as specific, while sulfate recognition of sulfate-salphen-uranyl interaction is comparatively weak, as shown to the effect of this binding being most apparent under the ¹H NMR experiments.

These results are consistent with a picture wherein **3** is capable of acting as a ditopic receptor, binding concurrently both the Be²⁺ and SO₄²⁻ ions coordinate to the ethylene oxygens and salphen-uranyl core, respectively. While not fully determined by the present experiments, presumably these observations reflect the greater importance of cooperative sulfate ion ligation, as opposed to Be²⁺ binding, in terms of determining both the extent of the ISE response and the inherent Be²⁺ selectivities.

Conclusions

In this study we describe the synthesis and characterization of ditopic and monotopic systems, **1** and **3** acting as a moderately selective receptor for beryllium salts which was tested with conductance and ¹H NMR as well as incorporated into a PVC-based ion-selective electrode (ISE).

These new neutral receptors for beryllium salts contain an immobilized 1,2-ethylenedioxybenzene (Lewis basic binding site) and uranyl-salphen unit (Lewis acidic binding site). Ditopic receptor, **3** is an excellent receptors for the complexation of Be²⁺ due to the coordination of beryllium ion to the 1,2-ethylenedioxybenzene in addition to cooperative

anion (salphen-uranyl) interactions. The conductometric measurements in 95% AN-DMSO show for the ligand, **3** the formation of the 1:1 adducts, with the stability constants in the order of $\text{Be}^{2+} \gg \text{Na}^+ > \text{Mg}^{2+} > \text{Li}^+ > \text{K}^+$. The specificity of a PVC-derived ISE altered by the use of functionalized 1,2-ethylenedioxybenzene augurs well for the generation of electrodes that can recognize and sense selectively a range of targeted analytes.

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