

Baki Çiçek* and Zekai Onbaşıoğlu

Synthesis and characterization of 1,3,4-thiadiazole-2,5-dithio crown ethers

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Abstract: Hetero-crown ethers (ligands **I–IV**) containing 1,3,4-thiadiazole-2,5-dithiol (bismuthiol) were synthesized and fully characterized. The ligands were prepared by a nucleophilic substitution (S_N2) reaction of the appropriate ethylene glycol dihalide derivatives with 1,3,4-thiadiazole-2,5-dithiol dipotassium salt under highly diluted conditions, and subsequent ring closure. Complexation constants and selectivity factors for these heterocyclic ligands in dichloromethane or chloroform were determined by ion-pair extraction from an aqueous solution containing Ag^+ , Ca^{2+} , Zn^{2+} , Fe^{3+} , Cr^{3+} , Co^{2+} , Cd^{2+} , Mg^{2+} , Pb^{2+} , Ni^{2+} , Cu^{2+} , Mn^{2+} , Na^+ and K^+ . These ligands could be applied as metal sensors and used to separate metals from various mixtures.

Keywords: bismuthiol; crown ether; cyclization; ion-pair extraction; selectivity factor.

Introduction

Synthetic macrocyclic crown ethers were first synthesized in 1967 by Pedersen, who also studied their selectivity for binding alkali and earth alkaline metal cations [1, 2]. Because crown ethers are usually selective for different metals [3], they can be used for separation of specific metals from mixtures. Macrocyclic crown ethers containing sulfur atoms are more selective for heavy metals and precious metals than their oxygenated analog [4–7]. Because of their selective binding, hetero-crown ethers could be used as active components in selective ion membranes for use in electrodes and as molecular receptors [8]. For these applications, the synthesis of crown ethers focuses on their construction from heterocyclic subunits, which have unique chemical and biological properties.

1,3,4-thiadiazoles and their derivatives are important heterocyclic building blocks that have been used as metal binding agents and corrosion inhibitors, in organic and analytical chemistry, and in industrial applications and medicine. Biological activity typically increases with complexation to a thiadiazole [9, 10]. Thiadiazoles can bind heavy metals, such as $Hg(II)$, and transition metals with high selectivity [11]. A 2,5-thiadiazole macrocycle can be synthesized by reaction of polyethylene glycol dihalide with 2,5-dimercapto-1,3,4-thiadiazole dipotassium salt at high dilution. The product formed by nucleophilic displacement by the halide with an alkoxide reagent has a polyethylene glycol in the ring [12]. 1,3,4-Thiadiazole-2,5-dithiol compounds, such as dithiolane, have been used as ligands for binding transition metal cations [13]. Lindoy and Busch synthesized the unsaturated aza-thia crown ethers and studied their nickel complexes [14]. 1,3,4-Thiadiazole-2,5-dithiol compounds exhibit high nucleophilicity because the thiadiazole ring contains three donor atoms (one S and two N) [15]. A steric center in the crown ether is important in determining the selectivity of the hetero-crown ether for complexation of alkaline, alkaline earth and transition metal cations.

The aim of the present research was to investigate the performance of bismuthiol crown ethers for the extraction of various metal ions (Zn^{2+} , Mg^{2+} , Ni^{2+} , Co^{2+} , Pb^{2+} , Fe^{3+} , Cd^{2+} , Ag^+ , Cr^{3+} , Na^+ , Ca^{2+} , Cu^{2+} , Mn^{2+} and K^+) from aqueous solutions at 25°C. The hetero-crown ethers **I–IV** (Figure 1 and Scheme 1) were prepared using a high-dilution method. These heterocyclic ligands contain a ring cavity and the heteroatoms, S and O.

Results and discussion

Synthesis

1,3,4-thiadiazole-2,5-dithio crown ethers **I–IV** were synthesized by the reactions shown in Scheme 1. The complexation studies performed with these compounds are also shown.

When bismuthiol (1,3,4-thiadiazole-2,5-dithiol) dipotassium salt was allowed to react with a dichloride derivative (1,2-dibromoethane, diethylene glycol dichloride,

*Corresponding author: Baki Çiçek, Department of Chemistry, Faculty of Science and Literature, University of Balıkesir, 10145 Balıkesir, Turkey, e-mail: bcicek@balikesir.edu.tr

Zekai Onbaşıoğlu: Department of Chemistry, Faculty of Science and Literature, University of Balıkesir, 10145 Balıkesir, Turkey

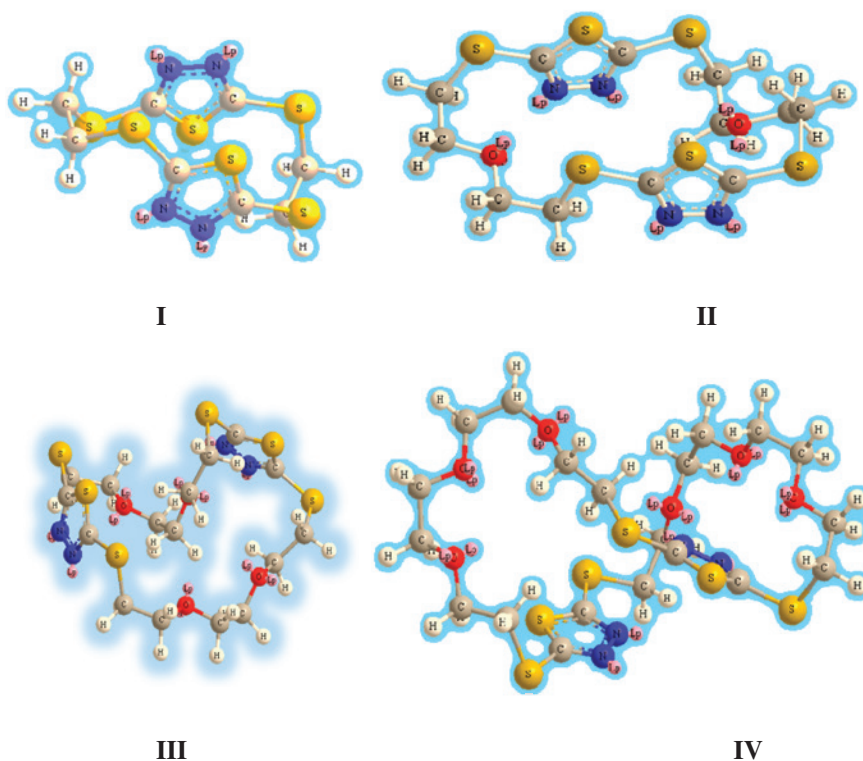
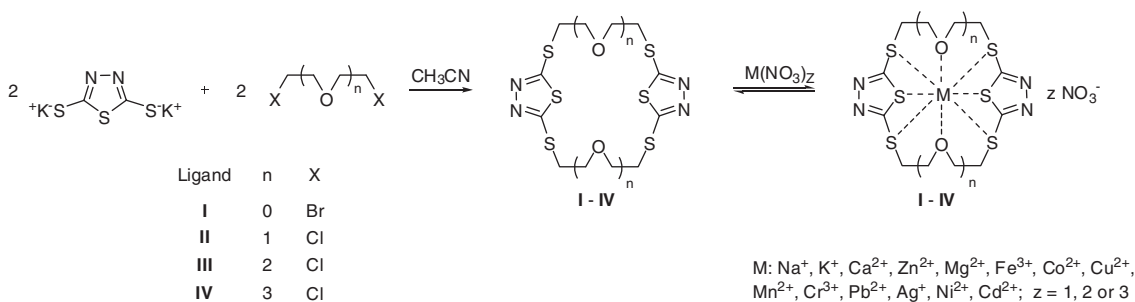


Figure 1 Three-dimensional representations of the synthesized macroheterocyclic crown ethers I–IV.



Scheme 1

triethylene glycol dichloride, or tetraethylene glycol dichloride) under a nitrogen atmosphere in acetonitrile, the product of a heterocyclization was obtained.

Ion-pair extraction

Ion-pair extraction involves selective transfer of an inorganic reagent from one phase (e.g. water) to an immiscible phase (e.g. chloroform or dichloromethane). With crown ethers, this type of extraction involves the formation of an ion pair between the cation complexed in the crown ether and the counter ion. The extraction equilibrium constant

(K_{ex}) can be calculated using the following equations 1–3 [16–19]:

$$M^{+m}_{(w)} + mA^{-}_{(w)} + L_{(w)} \rightleftharpoons MLA_{m(\text{Org.})} \quad (1)$$

where M^{+m} is the metal ion ($m=1-3$), A^{-} is the counter ion, L is the crown ether, and MLA_m is the ion pair that contains M^{+m} , A^{-} and L .

$$K_{(\text{ex},w)} = [MLA_m]_{\text{Org.}} / [M^{+m}]_w \cdot [A^{-}]_w^m \cdot [L]_w \quad (2)$$

$$L_{(w)} \rightleftharpoons L_{(\text{Org.})} \quad (3)$$

$$S_{\text{f}(\text{Metal 1})} = \text{Log}(K_{\text{D}(\text{Metal 1})} / K_{\text{D}(\text{Metal 2})}). \quad (4)$$

The calculated selectivity factors, S_i (equation 4), of the heterocyclic ligands show that ligand II is selective toward Ag^+ , Cd^{2+} and Pb^{2+} among the investigated metals in the competitive extraction solution. Ligands I, III and IV are selective toward Ag^+ , Cd^{2+} , Cu^{2+} and Pb^{2+} . When the metal ion concentration is reduced to 10^{-4} mol/L, ligand I becomes selective toward Ag^+ and Fe^{3+} , ligand II toward Cd^{2+} , Pb^{2+} , Fe^{3+} and Na^+ , ligand III toward Fe^{3+} and Cd^{2+} and ligand IV toward Fe^{3+} . The proportions of the metal ions extracted by each ligand were also calculated. For all ligands, the proportion extracted for each metal ion increases with increasing radius of the ion in the following order: Mg^{2+} , Ni^{2+} , Co^{2+} , Pb^{2+} , Fe^{3+} , Cd^{2+} , Ag^+ , Cr^{3+} , Na^+ , Ca^{2+} , Mn^{2+} , Cu^{2+} and K^+ [20, 21]. These results show that the ligands are more selective toward Cu^{2+} , Fe^{3+} , Cd^{2+} and Ag^+ at 10^{-3} mol/L and Fe^{3+} , Cd^{2+} and toward Ag^+ at 10^{-4} mol/L (see Tables in Supporting Information).

Conclusions

Bismuthiol crown ethers were synthesized in high yields. After characterization, they were used for extraction studies. All compounds efficiently form complexes with the studied metal ions. The calculated selectivity factors S_i for the extractions are related to the radii of the metal cations. Among the metal ions tested, most of the ligands were selective toward Pb^{2+} , Fe^{3+} , Cu^{2+} , Cd^{2+} and Ag^+ . For the competitive extractions at two different concentrations, the ligands are selective toward Cr^{3+} , Cu^{2+} , Fe^{3+} , Cd^{2+} and Ag^+ at 10^{-3} mol/L and Cr^{3+} , Fe^{3+} , Cd^{2+} and Ag^+ at 10^{-4} mol/L. The complexation strength of the S, O and N atoms of the ligands depends on the relative softness/hardness of the ligand and metal ion [22, 23]. The extraction results show that the synthesized heterocyclic ligands could be used for complexation of biologically important metal ions, applied as metal sensors and used to separate metals from various mixtures.

Experimental

All aqueous solutions were prepared with ultradistilled water. Stock solutions (10^{-3} M and 10^{-4} M) of crown ethers were prepared in dichloromethane for ligand I and chloroform for ligands II–IV. Fourier transform infrared (FT-IR) spectra were recorded on a Perkin Elmer BX 2 FTIR. Mass spectra were recorded on a 2001 AB SCIEX mass spectrometer using electrospray ionization (ESI). ^1H -NMR (400 MHz) and ^{13}C -NMR (100 MHz) spectra were obtained for DMSO- d_6 solution for ligand I and in CDCl_3 for ligands II–IV. Melting points were measured on an Electrothermal melting point apparatus and are not corrected. After extraction of the metal ion, the concentration

was measured using ICP-AES and ICP-Perkin Elmer Optima 3100 XL instruments. Microanalyses were performed with a Perkin–Elmer 2400II elemental analyzer. All measurements were performed at room temperature. The metal-ion extraction work was performed as previously described [17, 19].

Synthesis of 1,3,4-thiadiazole-2,5-dithio crown ethers I–IV

Bismuthiol dipotassium salt (2.26 g; 10 mmol) was added to acetonitrile (400 mL) and the mixture was heated under reflux for 2 h in order to ensure a homogeneous solution. This solution was treated dropwise under reflux for 7 h with a solution of 1,2-dibromoethane, diethylene glycol dichloride, triethylene glycol dichloride, or tetraethylene glycol dichloride (10 mmol) in acetonitrile (100 mL). After the addition was completed, the mixture was heated under reflux under a nitrogen atmosphere for an additional 5 days and then cooled. The resultant precipitate of I–IV was filtered. The mother liquor was concentrated under reduced pressure, treated with distilled water (40 mL) and the mixture was extracted with chloroform (3×10 mL). The extract was dried with anhydrous K_2SO_4 , filtered and concentrated under reduced pressure. An additional amount of I–IV crystallized after the solution was cooled in the refrigerator for 2 days. The combined product was crystallized from ethanol.

Crown ether I This compound was obtained from 1,2-dibromoethane as a white solid; yield 1.34 g (24%); mp 261.2–264.0°C; ^1H NMR (DMSO- d_6): δ 3.40 (s); ^{13}C NMR (DMSO- d_6): δ 36.6, 166.9; LC-MS: m/z 352 (M^+ , 71%). Anal. Calcd for $\text{C}_8\text{H}_8\text{N}_4\text{S}_6$ (352.57): C, 27.25; H, 2.29; N, 15.89; S, 54.57. Found: C, 27.21; H, 2.30; N, 15.81; S, 54.55.

Crown ether II This compound was obtained from diethylene glycol dichloride (1.17 mL, 10 mmol) as a dark red solid; yield 1.44 g (33%); mp 98.0–99.2°C; ^1H NMR (CDCl_3): δ 3.42 (8H, t, $J=6$ Hz), 3.86 (8H, t, $J=6$ Hz); ^{13}C NMR (CDCl_3): δ 34.5, 71.1, 164.6; and LC-MS: m/z 440.7 (M^+ , 26%). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_2\text{S}_6$ (440.67): C, 32.71; H, 3.66; N, 12.71; S, 43.66. Found: C, 32.70; H, 3.65; N, 12.71; S, 43.62.

Crown ether III This compound was obtained from triethylene glycol dichloride as a brick red solid; yield 3.06 g (58%); mp 95.3–97.4°C; ^1H NMR (CDCl_3): δ 3.25 (8H, t, $J=4.5$ Hz), 3.66 (8H, br s), 3.80 (8H, t, $J=4.5$ Hz); ^{13}C NMR (CDCl_3): δ 37.6, 69.6, 73.3, 167.7; LC-MS: m/z 528.8 (M^+ , 35%). Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_4\text{O}_4\text{S}_6$ (528.78): C, 36.34; H, 4.57; N, 10.60; S, 36.38. Found: C, 36.34; H, 4.55; N, 10.60; S, 36.35.

Crown ether IV This compound was obtained from tetraethylene glycol dichloride as a light red solid; yield 2.45 g (40%); mp 90.6–93.7°C; ^1H NMR (CDCl_3): δ 3.30 (8H, t, $J=5$ Hz), 3.56 (8H, t, $J=4$ Hz), 3.62 (8H, t, $J=4.0$ Hz), 3.83 (8H, t, $J=5$ Hz); ^{13}C NMR (CDCl_3): δ 36.1, 70.4, 70.9, 71.1, 167.6; LC-MS: m/z 616.8 (M^+ , 55%). Anal. Calcd for $\text{C}_{20}\text{H}_{32}\text{N}_4\text{O}_6\text{S}_6$ (616.88): C, 38.94; H, 5.23; N, 9.08; S, 31.19. Found: C, 38.83; H, 5.19; N, 9.00; S, 31.10.

Metal extraction studies

Ion-pair extraction was performed to evaluate the selectivity of the bismuthiol crown ethers for various metal ions. Solutions of the ligands were prepared in organic solvents (I in CH_2Cl_2 , and

II–IV in CHCl_3). In the first experiment, a metal salt, $(\text{Mn}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}, \text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}, \text{Cr}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}, \text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}, \text{KNO}_3, \text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}, \text{NaNO}_3, \text{Cu}(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}, \text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}, \text{Cd}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}, \text{Pb}(\text{NO}_3)_2, \text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}, \text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}, \text{AgNO}_3, \text{pH} = 4.57, 4.30, 3.00, 3.60, 3.95, 4.40, 4.90, 4.10, 4.75, 4.40, 3.60, 4.60, 3.95, 4.00, \text{ respectively, in the aqueous solution}), and the synthesized crown ether were put together in a chloroform/water (1:1) or dichloromethane/water (1:1) mixture at 25°C . In the second experiment, a competitive extraction was performed with an aqueous solution containing all 14 metal ions ($\text{pH} = 4.20\text{--}4.30$). The prepared mixtures were shaken at 25°C for 1 h. The process was stopped after incubation for 30 min to equilibrate the solution at 25°C . After each extraction, the concentration of the metal ion remaining in the aqueous solution was measured by atomic absorption spectrophotometry and inductively coupled plasma atomic emission spectrophotometry. Relative selectivity factors ($\log S_p$) were calculated from the data. The results for competitive metal extractions with the 10^{-3} and 10^{-6} mol/L metal ion solutions and synthesized bismuthiol crown ethers are tabulated in Supporting Information.$

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