



# Comparison of classic and microwave-assisted synthesis of benzo-thio crown ethers, and investigation of their ion pair extractions



Umit Calisir <sup>a, b</sup>, Baki Çiçek <sup>a, \*</sup>

<sup>a</sup> Balıkesir University, Faculty of Arts and Sciences, Chemistry Department, 10145 Balıkesir, Turkey

<sup>b</sup> Siirt University, Science and Technology Application and Research Center, (SIUBTAM), 56100 Siirt, Turkey

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## ABSTRACT

Macrocyclic benzo-thio crown ethers and benzo-oxo crown ethers were prepared using an esterification–ring closing method. These compounds were synthesised using 2,2'-dithiodibenzoyl chloride, and various glycols and dithiols, in the presence of pyridine base under a nitrogen atmosphere in chloroform. All reactions were performed under reflux condition with conventional heating and microwave (MW) irradiation. The synthesised macrocycles were characterised by FT-IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, LC-MS, and elemental analysis methods. Extraction studies have been performed on these original macrocycles using liquid-liquid ion-pair extraction with Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Ni<sup>2+</sup>, Ca<sup>2+</sup>, Mg<sup>2+</sup>, Zn<sup>2+</sup>, Fe<sup>2+</sup>, Fe<sup>3+</sup>, Co<sup>3+</sup>, Pb<sup>2+</sup>, Cr<sup>3+</sup>, Ag<sup>+</sup>, and Cd<sup>2+</sup>. The  $K_D$ , ext.%,  $\Delta G$  and  $\log K_{Ext}$  values were also calculated. While (**U1-U7**) ligands exhibits selectivity for Zn<sup>2+</sup>, Ag<sup>+</sup>, Ca<sup>2+</sup>, Pb<sup>2+</sup>, Fe<sup>3+</sup>, Cr<sup>3+</sup>, Co<sup>2+</sup>, Mg<sup>2+</sup>, Cd<sup>2+</sup>, and Ni<sup>2+</sup> metal salts, they showed no selectivity for Li<sup>+</sup>, K<sup>+</sup> and Na<sup>+</sup> metal salts. Furthermore, Fe<sup>3+</sup> is the most selective cation for all ligands for competitive extraction. We also observed that microwave heating can have certain benefits over conventional ovens: reaction rate acceleration, milder reaction conditions, higher chemical yield, and lower energy usage. These ligands could be used as metal sensors, enzyme inhibitors, antimicrobial/antifungal agents, and in biological applications.

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## 1. Introduction

Many synthesised macrocyclic benzo, thio and oxa crown ethers and their derivatives have shown extraordinary binding properties with metal cations [1]. Considering the reactions of thio crown ethers, their esterification–cyclisation reactions with acyl chlorides are faster than other synthetic methods. Studies of cyclisation reactions with 2,2'-dithiodibenzoic acid derivatives date back to the 1970s [2–5]. Recently, macrocyclic benzo-thio crown ethers were synthesised using condensation/esterification reactions and demonstrated quite interesting results with the carbonic anhydrase enzyme [6].

Since most organic reaction needs toxic solvents, more reaction time, and high temperature, classical methods of organic synthesis are less chosen. Microwave-assisted organic reaction is considered to be a promising green chemistry method as it reduces reaction

time from days or hours to minutes or even seconds, and has many other advantages [7].

Macrocyclic crown ethers containing sulphur atoms are considered to be more selective for elements classified as heavy and precious metals [8–16]. Furthermore, depending on modifications of the macrocyclic crown ethers, their attraction toward metal cations varies. For instance, when thiol, aryl, and thiophene moieties are used as side-arms, macrocyclic crown ethers show an increased transport rate [17,18]. Moreover, benzo crown ethers show a high affinity for Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, and Rb. Additionally, macrocyclic crowns containing a benzene ring, thiol, or pyridine ring, form a complex by binding better with Ag<sup>+</sup> than Hg<sup>2+</sup>, and with Au<sup>3+</sup> and Hg<sup>2+</sup> ions than Pd [19,20]. Mixed donor thio-oxa crown ethers coordinated Zn<sup>2+</sup> and Fe<sup>3+</sup> ions because of intermediate softness [21]. Thiadiazole substitute crown ethers present highest affinity to transition metals [22]. The metal–cation binding properties of poly (crown ethers) synthesised by cyclopolymerisation methods change with ring size, and number and electronic properties of oxygen atoms [23]. Therefore, benzo thio crown ethers can be used as potentiometric sensors due to their selectivity for metal ions in environmental systems. Crown ethers gain various abilities

\* Corresponding author. Department of Chemistry, Faculty of Science and Literature, Balıkesir University, 10145 Balıkesir, Turkey.

E-mail addresses: [umitalcalisir@siirt.edu.tr](mailto:umitalcalisir@siirt.edu.tr) (U. Calisir), [bcicek@balikesir.edu.tr](mailto:bcicek@balikesir.edu.tr) (B. Çiçek).

when replacing sulphur, oxygen, phenyl, and carbonyl chromosphere with each other [24].

As part of this study, novel benzo-thio crown ethers were synthesised using a high dilution method and microwave-assisted synthesis method. These synthesised ligands contain different ring cavities due to ligands and heteroatoms (S and O). Above all, their selectivity for complexation with alkaline, alkaline earth, and transition metal cations is important in determining the strength of ion-dipole interactions formed with cations, and assessing their molecular dynamic [25]. The object of the present work is to study the extractive behaviour of LiCl, AgNO<sub>3</sub>, ZnCl<sub>2</sub>, FeCl<sub>3</sub>, FeCl<sub>2</sub>, CrCl<sub>3</sub>, CoCl<sub>2</sub>, Pb(NO<sub>3</sub>)<sub>2</sub>, CdCl<sub>2</sub>, MgCl<sub>2</sub>, NiCl<sub>2</sub>, CaCl<sub>2</sub>, NaCl, and KCl with **U1** (bis(1,2-dibenzo) octathio tetracarboxyl-24-crown-4), **U2** (bis(1,2-dibenzo) octathio tetracarboxyl-29-crown-6), **U3** (bis(1,2-dibenzo) octathio tetracarboxyl-36-crown-8), **U4** (bis(1,2-dibenzo) tetrathio tetracarboxyl-24-crown-4), **U5** (bis(1,2-dibenzo) tetrathio tetracarboxyl-29-crown-6), **U6** (bis(1,2-dibenzo) tetrathio tetracarboxyl-36-crown-8), and **U7** (bis(1,2-dibenzo) tetrathio tetracarboxyl-42-crown-10) in chloroform/water (1:1) at 25 °C. The formation of 1:1 complexes of the metal-ions and electrically neutral crown ethers was indicated.

## 2. Materials and methods

All chemicals used in this study, including analytical purity solvents and reagents, were purchased from Merck, Sigma-Aldrich, and Fluka Company. The StartSYNTH-Microwave Synthesis Labstation system were used to perform some reactions. Silica gel column chromatography was applied for chromatographic purifications. FT-IR spectra were recorded on a Perkin Elmer BX 2 FTIR. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were obtained in CDCl<sub>3</sub> or CD<sub>3</sub>OD solvents using NMR spectrometer. LC-MS spectra were recorded on the 2001 AB SCIEX Mass Spectrometer using acetonitrile. Microanalysis was performed with Thermo Scientific Flash 2000 elemental analyser. 2,2'-dithiodibenzoyl chloride was prepared using a previously reported method [5]. Metal ion extraction was performed based on the work of Cicek and it is described in detail in the supporting information [20,26].

### 2.1. Synthesis of 2,2'-dithiodibenzoyl chloride

**Classic Method:** 2,2'-Dithiodibenzoic acid (1.0000 g, 3.26 mmol) was added to a 100 mL round bottom flask. A slight excess of thionyl chloride (1.5500 g, 13.05 mmol) was added into it, and the mixture stirred for 16 h at reflux to afford a brown solid (68%).

**Microwave-assisted Method:** 2,2'-Dithiodibenzoic acid (1.0000 g, 3.26 mmol) and thionyl chloride (1.6000 g, 13.50 mmol) was taken in a round bottom flask in StartSYNTH-Microwave Synthesis Labstation system. (MW, E=1000 W, 80 °C, 10 min, yield >> 68%). M. p. 75–76 °C; FT-IR (γ cm<sup>-1</sup>) 746, 786, 1109, 1160, 1242, 1350, 1450, 1560, 1600, 1725, 3080; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 100 MHz) δ 7.30–7.60 (m, 4H), 7.75 (d, 2H, J = 8.0 Hz), 8.40 (d, 2H, J = 8.0 Hz). LS-MS (m/z) 342 (M<sup>+</sup>), 340, 338, 303, 233, 201, 179, 169, 167, 148, 133, 118, 102, 94.

### 2.2. Synthesis of benzo-thio crown ethers, **U1–U7**

**General procedure-1 (Classic).** 2,2'-Dithiodibenzoyl chloride (11.45 mmol), pyridine (22.90 mmol), and either a dithiol or diol (11.45 mmol) in the chloroform (150 mL) were added to a reaction flask. The reaction mixture was refluxed for 3–7 days under a nitrogen atmosphere, then left to cool to room temperature.

**General procedure-2 (Microwave-assisted).** 2,2'-dithiodibenzoyl chloride (2.53 mmol), pyridine (5.06 mmol), and either a dithiol or diol (2.53 mmol) were taken in a round bottom flask, and chloroform (10 mL) was added. The reaction mixture was refluxed for 1 h

under a nitrogen atmosphere in StartSYNTH-Microwave Synthesis Labstation system. (MW, E=1000 W, 100 °C), then left to cool to room temperature.

**General Work-up Procedure:** The resultant mixture was evaporated under vacuum. Distilled water (30–40 mL) was poured onto the remaining residue, which was then extracted with organic solvent (chloroform, 3 × 10 mL). The combined extracts were dried with anhydrous CaCl<sub>2</sub>, evaporated under vacuum, and purified by silica gel column chromatography, to afford an oily solid product.

**2,3,11,14,22,23,31,34-octathiapentacyclo [34.4.0.0.0<sup>4</sup>,0<sup>16</sup>,21,0<sup>24</sup>,2<sup>9</sup>]tetraconta-1(36),4(9),5,7,16,18,20,24,26,28,37,39-dodecaene-10,15,30,35-tetrone (U1).** Prepared with 1,2-ethanedithiol to the general procedure-1 (1.0800 g, 11.45 mmol; 7 days) and general procedure-2 (0.2386 g, 2.53 mmol, 1 h). Purification by column chromatography (chloroform/ethyl acetate, 4:1, v/v) afforded a dark yellow-brown oily product (3.4500 g, 36%; 1.4018 g, 76%, MW). FT-IR (γ cm<sup>-1</sup>) 1700 (O=C–S stretch), 1251 (S–C(O)–C stretch), 1053 (C–S stretch); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 4.41 (s, 8H), 7.22 (t, 4H, J=8.0 Hz), 7.42 (t, 4H, J=8.0 Hz), 7.78 (d, 4H, J=8.0 Hz), 8.10 (d, 4H, J=8.0 Hz); <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz) δ 29.80, 131.50, 131.80, 132.20, 132.30, 132.60, 137.00, 166.20; LC-MS m/z 730 (M<sup>+</sup>, CH<sub>3</sub>CN, Error % = -0.2830). Anal. Calc. for C<sub>32</sub>H<sub>24</sub>O<sub>4</sub>S<sub>8</sub> (MW=729.05): C, 52.72; H, 3.32; S, 35.19%. Found: C, 52.65; H, 3.26; S, 35.12%.

**14,37-dioxa-2,3,11,17,25,26,34,40-octathiapentacyclo [40.4.0.0.0<sup>4</sup>,0<sup>19</sup>,24,0<sup>27</sup>,32]hexatetraconta-1(42),4(9),5,7,19,21,23,27,29,31,43,45-dodecaene-10,18,33,41-tetrone (U2).** Prepared with diethylene glycol dithiol to the general procedure-1 (1.7456 g, 11.45 mmol; 7 days) and general procedure-2 (0.3857 g, 2.53 mmol, 1 h). Purification by column chromatography (chloroform/hexane, 10:1, v/v) afforded a dark-brown oily solid (1.6895 g, 18%; 0.7443 g, 36%, MW). FT-IR (γ cm<sup>-1</sup>) 1700 (O=C–S stretch), 1251 (S–C(O)–C stretch), 1053 (C–S stretch); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.86 (s, 8H), 4.28 (s, 8H), 7.24 (t, 4H, J=8.0 Hz), 7.40 (t, 4H, J=8.0 Hz), 7.70 (d, 4H, J=8.0 Hz), 8.08 (d, 4H, J=8.0 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz) δ 28.6, 68.0, 128.4, 131.0, 131.4, 133.0, 134.0, 134.4, 167.8. LC-MS m/z 816 (M<sup>+</sup>, CH<sub>3</sub>CN, Error % = 0). Anal. Calc. for C<sub>36</sub>H<sub>32</sub>O<sub>6</sub>S<sub>8</sub> (MW=817.16): C, 52.91; H, 3.95; S, 31.39%. Found: C, 52.87; H, 3.92; S, 31.35%.

**14,17,40,43-tetraoxa-2,3,11,20,28,29,37,46-octathiapentacyclo [46.4.0.0.0<sup>4</sup>,0<sup>22</sup>,27,0<sup>30</sup>,35]dopentaconta-1(48),4(9),5,7,22,24,26,30,32,34,49,51-dodecaene-10,21,36,47-tetrone (U3).** Prepared with triethylene glycol dithiol to the general procedure-1 (2.0872 g, 11.45 mmol; 7 days) and general procedure-2 (0.4612 g, 2.53 mmol, 1 h). Purification by column chromatography (chloroform/ethyl acetate, 4:1, v/v) afforded a dark-yellow-brown oily product (2.8911 g, 28%; 1.3284 g, 58%, MW). FT-IR (γ cm<sup>-1</sup>) 1700 (O=C–S stretch), 1253 (S–C(O)–C stretch), 1053 (C–S stretch); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.86 (t, 8H, J=8.0 Hz), 3.72 (s, 8H), 4.42 (t, 4H, J=8.0 Hz), 7.20 (t, 4H, J=8.0 Hz), 7.36 (t, 4H, J=8.0 Hz), 7.76 (d, 4H, J=8.0 Hz), 8.04 (d, 4H, J=8.0 Hz); <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 100 MHz) δ 29.22, 69.60, 69.80, 125.60, 126.00, 128.00, 130.40, 131.80, 132.60, 166.00. LC-MS m/z 904 (M<sup>+</sup>, CH<sub>3</sub>CN, Error % = 0.0055). Anal. Calc. for C<sub>40</sub>H<sub>40</sub>O<sub>8</sub>S<sub>8</sub> (MW=905.26): C, 53.07; H, 4.45; S, 28.34%. Found: C, 53.10; H, 4.49; S, 28.18%.

**2,3,11,14,22,23,31,34-octathiapentacyclo [34.4.0.0.0<sup>4</sup>,0<sup>16</sup>,21,0<sup>24</sup>,2<sup>9</sup>]tetraconta-1(36),4(9),5,7,16,18,20,24,26,28,37,39-dodecaene-10,15,30,35-tetrone (U4).** Prepared with ethylene glycol to the general procedure-1 (0.7099 g, 11.45 mmol; 72 h) and general procedure-2 (0.1569 g, 2.53 mmol, 1 h). Purification by column chromatography (chloroform/ethyl acetate, 4:1, v/v) afforded a dark-yellow oily product (2.8911 g, 52%; 1.3960 g, 83%, MW). FT-IR (γ cm<sup>-1</sup>) 1700 (C=O stretch), 1247 (O–C(O)–C stretch), 1054 (C–O stretch); <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 4.15 (s, 8H), 8.49 (d, 4H, J=8.0 Hz), 8.80 (t,

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