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

Umit Calisir [a, b], Baki Çiçek [a, *]

[a] Balıkesir University, Faculty of Arts and Sciences, Chemistry Department, 10145 Balikesir, Turkey
[b] 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, ^{1}H NMR, ^{13}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^+, Na^+, K^+, Ni^{2+}, Ca^{2+}, Mg^{2+}, Zn^{2+}, Fe^{2+},Fe^{3+}, Co^{3+}, Pb^{2+}, Cr^{3+}, Ag^+, and Cd^{2+}.The K_D, ext.%, ΔG and log K_{Ext} values were also calculated. While (**U1-U7**) ligands exhibits selectivity for Zn^{2+}, Ag^+, Ca^{2+}, Pb^{2+}, Fe^{3+}, Cr^{3+}, Co^{2+}, Mg^{2+}, Cd^{2+}, and Ni^{2+} metal salts, they showed no selectivity for Li^+, K^+ and Na^+ metal salts. Furthermore, $Fe^{3+}$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.

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′-ditihiodibenzoic 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^+, Na^+, K^+, and Rb. Additionally, macrocyclic crowns containing a benzene ring, thiol, or pyridine ring, form a complex by binding better with Ag^+ than Hg^{2+}, and with Au^{3+} and Hg^{2+} ions than Pd [19,20]. Mixed donor thio-oxa crown ethers coordinated Zn^{2+} and Fe^{3+} 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

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* Corresponding author. Department of Chemistry, Faculty of Science and Literature, Balıkesir University, 10145 Balıkesir, Turkey.
E-mail addresses: umitcalisir@siirt.edu.tr (U. Calisir), bcicek@balikesir.edu.tr (B. Çiçek).

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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, $AgNO_3$, $ZnCl_2$, $FeCl_3$, $FeCl_2$, $CrCl_3$, $CoCl_2$, $Pb(NO_3)_2$, $CdCl_2$, $MgCl_2$, $NiCl_2$, $CaCl_2$, NaCl, and KCl with **U1** (bis(1,2-dibenzo) octathio tetracarbonil-24-crown-4), **U2** (bis(1,2-dibenzo) octathio tetracarbonil-29-crown-6), **U3** (bis(1,2-dibenzo) octathio tetracarbonil-36-crown-8), **U4** (bis(1,2-dibenzo) tetrathio tetracarbonil-24-crown-4), **U5** (bis(1,2-dibenzo) tetrathio tetracarbonil-29-crown-6), **U6** (bis(1,2-dibenzo) tetrathio tetracarbonil-36-crown-8), and **U7** (bis(1,2-dibenzo) tetrathio tetracarbonil-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. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained in $CDCl_3$ or CD_3OD 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^{-1}) 746, 786, 1109, 1160, 1242, 1350, 1450, 1560, 1600, 1725, 3080; ^1HNMR ($CDCl_3$, 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^+), 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 $CaCl_2$, 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^{4,9}.0^{16,21}.0^{24,29}]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^{-1}) 1700 (O=C–S stretch), 1251 (S–C(O)–C stretch), 1053 (C–S stretch); ^1H NMR ($CDCl_3$, 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); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 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^+, CH_3CN, Error % = −0.2830). Anal. Calc. for $C_{32}H_{24}O_4S_8$ (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^{4,9}.0^{19,24}.0^{27,32}]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^{-1}) 1700 (O=C–S stretch), 1251 (S–C(O)–C stretch), 1053 (C–S stretch); ^1HNMR ($CDCl_3$, 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). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 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^+, CH_3CN, Error % = 0). Anal. Calc. for $C_{36}H_{32}O_6S_8$ (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^{4,9}.0^{2227}.0^{30,35}]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^{-1}) 1700 (O=C–S stretch), 1253 (S–C(O)–C stretch), 1053 (C–S stretch); ^1H NMR ($CDCl_3$, 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); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 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^+, CH_3CN, Error % = 0.0055). Anal. Calc. for $C_{40}H_{40}O_8S_8$ (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^{4,9}.0^{16,21}.0^{24,29}]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^{-1}) 1700 (C=O stretch), 1247 (O–C(O)–C stretch), 1054 (C–O stretch); ^1H NMR (CD_3OD, 400 MHz) δ4.15 (s, 8H), 8.49 (d, 4H, *J*=8.0 Hz), 8.80 (t, 4H, J=8.0 Hz), 9.00 (d, 4H, J=8.0 Hz). $^{13}C\{^1H\}$ NMR (CD_3OD, 100 MHz) δ 52.4122.0, 125.0, 128.2, 132.0, 133.0, 139.0, 145.0, 167.0; LC-MS *m/z* 664 (M^+, CH_3CN, Error % = 0.0060). Anal. Calc. for $C_{32}H_{24}O_8S_4$ (MW=664.79): C, 57.81; H, 3.64; S, 19.29%. Found: C, 57.70; H, 3.60; S, 19.18%.

11,14,17,34,37,40-hexaoxa-2,3,25,26-tetrathiapentacyclo [40.4.0.0^{4,9}.0^{19,24}.0^{27,32}]hexatetraconta-1(42),4(9),5,7,19,21,23,27,29,31,43,45-dodecaene-10,18,33,41-tetrone (U5). Prepared with diethylene glycol to the general procedure-1 (1.2138 g, 11.45 mmol; 72 h) and general procedure-2 (0.2682 g, 2.53 mmol, 1 h). Purification by column chromatography (chloroform/ethyl acetate, 4:1,*v/v*) afforded a dark-yellow-brown oily product (3.3360 g, 46%; 1.6572 g, 87%, MW). FT-IR (γ cm^{-1}) 1700 (C=O stretch), 1252 (O–C(O)–C stretch), 1055 (C–O stretch); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.75 (t, 8H, J=8.0 Hz), 4.55 (t, 8H, J=8.0 Hz), 7.22 (t, 4H, J=8.0 Hz), 7.40 (t, 4H, J=8.0 Hz), 7.72 (d, 4H, J=8.0 Hz), 8.08 (d, 4H, J=8.0 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) 70.14, 73.00, 125.80, 126.00, 127.00, 132.00, 133.00, 140.00, 166.00; LC-MS *m/z* 752 (M^+, CH_3CN, Error% = 0.0120). Anal. Calc. for $C_{36}H_{32}O_{10}S_4$ (MW=752.89): C, 57.43; H, 4.28; S, 17.04%. Found: C, 57.33; H, 4.32; S, 17.18%.

11,14,17,20,37,40,43,46-octaoxa-2,3,28,29-tetrathiapentacyclo [46.4.0.0^{4,9}.0^{2227}.0^{30,35}]dopentaconta -1(48),4(9),5,7,22,24,26,30,32,34,49,51-dodecaene-10,21,36,47-tetrone (U6). Prepared with triethylene glycol to the general procedure-1 (1.7210 g, 11.45 mmol; 72 h)and general procedure-2 (0.3803 g, 2.53 mmol, 1 h). Purification by column chromatography (chloroform/ethyl acetate, 4:1,*v/v*) afforded a dark-brown oily product (2.0648 g, 24%; 1.1277 g, 53%, MW). FT-IR (γ cm^{-1})1701 (C=O stretch), 1252 (O–C(O)–C stretch), 1054 (C–O stretch); ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.66 (s, 8H), 4.21 (t, 8H, J=8.0 Hz), 4.44 (t, 8H, J=8.0 Hz), 7.26 (t, 4H, J=8.0 Hz, 7.43 (t, 4H, J=8.0 Hz), 7.76 (d, 4H, J=8.0 Hz), 8.08 (d, 4H, J=8.0 Hz); $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 100 MHz) δ53.8, 61.8, 68.8, 126.0, 128.0, 129.0, 131.6, 131.8, 133.8, 166.0; LC-MS *m/z* 840 (M^+, CH_3CN, Error%= 0.0167). Anal. Calc. for $C_{40}H_{40}O_{12}S_4$ (MW=841.00): C, 57.13; H, 4.79; S, 15.25%. Found: C, 57.04; H, 4.75; S, 15.18%.

11,14,17,20,23,40,43,46,49,52-decaoxa-2,3,31,32-tetrathiapentacyclo[52.4.0.0^{4,9}.0^{25,30}.0^{33,38}]octapentaconta-1(54),4(9),5,7,25,27,29,33,35,37,55,57-dodecaene-10,24,39,53-tetrone (U7). Prepared with tetraethylene glycol to the general procedure-1 (2.2137 g, 11.45 mmol; 72 h) and general procedure-2 (0.4891 g, 2.53 mmol, 1 h). Purification by column chromatography (chloroform/ethyl acetate, 4:1,*v/v*) afforded a dark-brown-yellow oily product (3.8930 g, 37%; 1.8100 g, 77%, MW). FT-IR (γ cm^{-1}) 1704 (C=O stretch), 1252 (O–C(O)–C stretch), 1036 (C–O stretch); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.60 (s, 16H), 3.76 (t, 8H, J=8.0 Hz), 4.42 (t, 8H, J=8.0 Hz), 7.24 (t, 4H, J=8.0 Hz), 7.38 (t, 4H, J=8.0 Hz), 7.66 (d, 4H, J=8.0 Hz), 8.02 (d, 4H, J=8.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ62.0, 69.8, 70.0, 126.0, 128.8, 129.8, 130.0, 131.8, 132.0, 166.4; LC-MS *m/z* 928.19 (M^+, CH_3CN, Error % = 0.0979). Anal. Calc. for $C_{44}H_{48}O_{14}S_4$ (MW=929.10): C, 56.88; H, 5.21; S, 13.80%. Found: C, 56.82; H, 5.16; S, 13.72%.

2.3. *Metal extraction studies*

Liquid-liquid ion-pair extraction was performed to the synthesised novel benzo-thio crown ether derivatives. For this purpose, the solution of synthesised macrocycles in chloroform (10^{-4} mol/L) and aqueous solution of each selected metal salt (10^{-4} mol/L) were mixed separately (10 mL ligand and 10 mL salt), then agitated for 1 h at a stirring speed of 300 rpm at 25 °C. $ZnCl_2$, $CrCl_3$, $FeCl_3$, KCl, $CaCl_2$, NaCl, $MgCl_2$, $CdCl_2$, $Pb(NO_3)_2$, $NiCl_2$, $CoCl_2$, $AgNO_3$, LiCl, and $FeCl_2$, metal salts were used in this extraction. Their pH values are; 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, 8.14, 4.43, respectively. In a second part of our study, a competitive extraction was performed with an aqueous solution containing all metal ions studied herein and the solution of synthesised macrocycles in chloroform (10^{-4} mol/L). To preparing the mix solution, metal salts were combined in a volumetric flask, and mixed in water (10^{-4} mol/L). Ligand solution and mix metal solution put together in a flask and agitated for 1 h at a stirring speed of 300 rpm at 25 °C. $ZnCl_2$, $FeCl_3$, $CrCl_3$, $CoCl_2$, $Pb(NO_3)_2$, $CdCl_2$, $MgCl_2$, $NiCl_2$, $CaCl_2$, NaCl, LiCl, and KCl metal salts were used for this extraction.

The process was over after incubation for 60 min to equilibrate the solution at room temperature. Using the concentrations of the metal ions remaining in the aqueous solution, measured by atomic absorption spectrophotometry, inductively coupled plasma atomic emission spectrophotometry and inductively coupled plasma mass spectrophotometry methods, the extraction constants (K_D, ext%, ΔG and log K_{Ext}) and selectivity factors (S_f) were calculated [27,28].

3. Results and discussion

3.1. *Synthesis of benzo thio-oxa crown ethers*

Macrocyclic benzo-thio crown ethers and benzo-oxacrown ethers were synthesised and physical organic studies were performed. The synthetic route is given in Scheme 1. 2,2′-Dithiodibenzoyl chloride reacted with ethylene glycol dithiol or ethylene glycol derivatives (e.g., 1,2-ethane dithiol, diethylene glycol dithiol, triethylene glycol dithiol, monoethylene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol) in an esterification–cyclisation reaction. The synthesis was performed in the presence of pyridine under a nitrogen atmosphere and in chloroform solvent. Classic method and Microwave-assisted method were applied reaction mixture to display differences between methods. Classic method is that the reaction performed in an oil bath to reflux reaction system (conventional heating). Microwave-assisted method needs shorter time, lower solvent usage, and gives higher yield. To investigate the best reaction conditions some parameters were changed systematically (summarized in Table 1). Table 2 have been also arranged for yields and reaction times so as to display clearly.

FT-IR, ^1H NMR, ^{13}C NMR, and LC-MS spectra were collected for the final compounds. The FT-IR spectra showed that intense peaks for mono/di/tri-ethylene glycol dithiols (C–SH band, 2550 cm^{-1}), mono/di/tri-tetraethylene glycols (O–H stretch, 3300 cm^{-1}), and acyl chloride (C=O and C–Cl stretches, 1715 and 693 cm^{-1}, respectively) disappeared, with the new carbonyl stretch of the ester or thioester products (1700 cm^{-1}) appearing as a result of esterification–cyclisation.

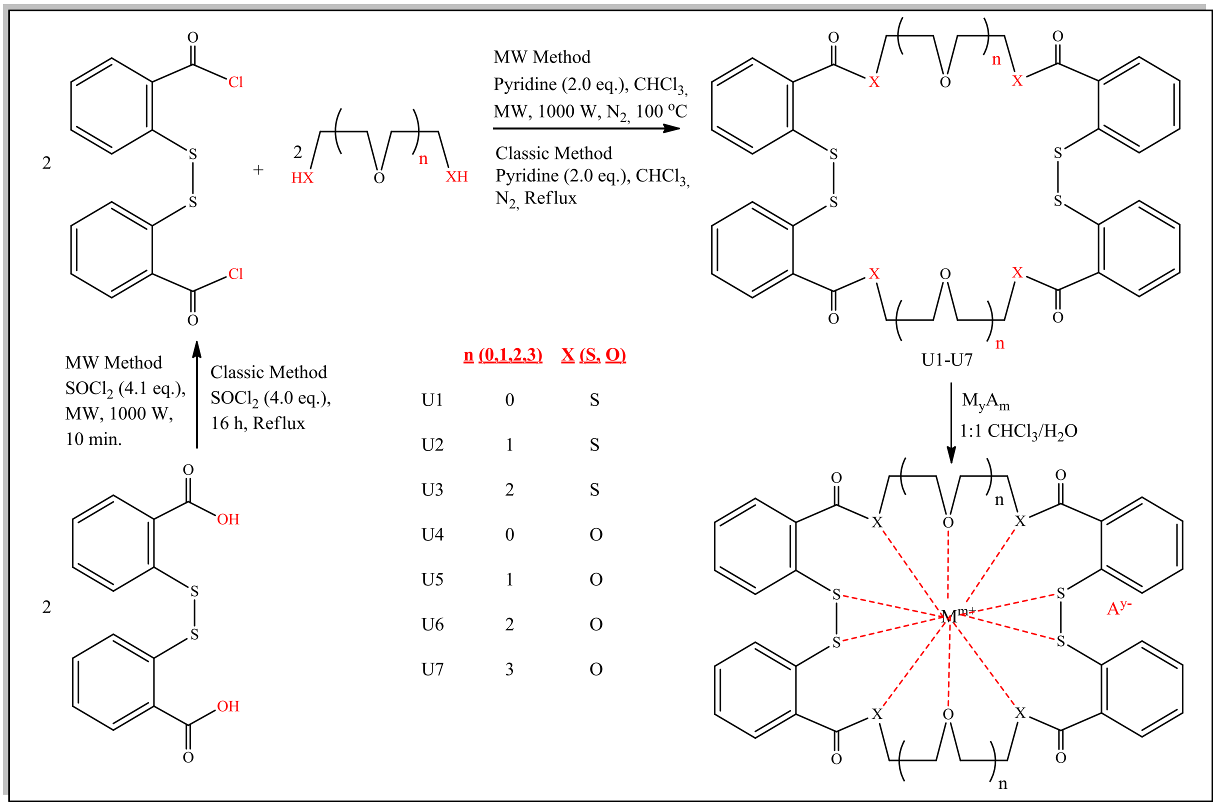
The ^1H NMR spectra of all synthesised crowns showed signals in the ranges 2.86–4.55 ppm, for aliphatic hydrogens, and 7.20–8.10 ppm for aromatic hydrogens, *except for the aromatic hydrogen atoms of compound (**U4**)*. In addition, ^{13}C NMR and LC-MS spectra aided compound verification.

3.2. *Liquid-liquid ion-pair extraction*

The principle of the liquid-liquid ion-pair extraction method is to transfer an inorganic reagent from one phase (especially water) to anorganic phase that does not mix with water (e.g., chloroform, dichloromethane) selectively (see Supporting material, Fig. S1). The extraction process causes ion-pair formation between a cationic crown complex and a counter ion (Eq. (1)).

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

where $M^{m+}$is the metal ion, A^- is the counter ion, *L* is the crown



	n (0,1,2,3)	X (S, O)
U1	0	S
U2	1	S
U3	2	S
U4	0	O
U5	1	O
U6	2	O
U7	3	O

Scheme 1. Synthesis of benzo-thiocrown ethers (**U1**–**U7**) with classic and microwave-assisted method and investigation of their complexation with metals. (M^{m+}: Na^+, Li^+, K^+, Ca^{2+}, Zn^{2+}, Mg^{2+}, Fe^{3+}, Fe^{2+}, Co^{2+},Cr^{3+}, Pb^{2+}, Ag^+, Ni^{2+}, Cd^{2+}; A^{y-}:Cl^-, NO_3^-; m: 1,2,3 and y: 1).

Table 1
Microwave-assisted reaction conditions of benzo-thio crown ethers.

Ligand	Temp. (°C)	Time (min)	Energy (W)	Reaction
U3	25	10	1000	Not detected
U3	80	10	1000	Not completed
U3	80	20	1000	Not completed
U3	80	40	1000	Not completed
U3	100	20	1000	Not completed
U3	100	40	1000	Not completed
U3	100	60	1000	Completed

Table 2
Microwave-assisted reaction and ordinary reaction conditions-yields of benzo-thio crown ethers.

Ligand	Classic Synthesis Method		Microwave-assisted Synthesis Method	
	Reaction Time (h)	Yield (%)	Reaction Time (h)	Yield (%)
U1	168	36	1	76
U2	168	18	1	36
U3	168	28	1	58
U4	72	52	1	83
U5	72	46	1	87
U6	72	24	1	53
U7	72	37	1	77

ether, and MLA_m is the ion pair containing M^{m+}, A^-, and L.

$$K_{ex,\ w} = \frac{[MLA_m]_{Org.}}{M^{m+}{}_w A^m{}_w L_w} \tag{2}$$

$$L_{(w)}L_{(Org)} \tag{3}$$

$$S_{f\ (Metal1)} = \left(\frac{K_{D\ (Metal\ 1)}}{K_{D\ \ (Metal\ 2)}}\right) \tag{4}$$

$$Log\ S_{f\ (Metal1)} = Log\left(\frac{K_{D\ (Metal\ 1)}}{K_{D\ \ (Metal\ 2)}}\right) \tag{5}$$

The bare metal ion radii of the metal cations used in this study are shown in Table 3. Using the synthesised crowns, Table 3 indicates the **U1**–**U7** benzo thio-oxa crown ether extraction percentages for Li^+, Zn^{2+}, Mg^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Fe^{2+}, Fe^{3+}, Cd^{2+}, Cr^{3+}, Na^+, Ca^{2+} and K^+ ions relative to the ion radii. According to Table 3, in terms of metal ion, the highest extraction percentage was for Fe^{3+} and Cr^{3+} ions. Pb^{2+}, Cd^{2+}, Ag^+, Fe^{2+} and Ca^{2+} had moderate extraction percentages. Furthermore, the Fe^{3+} ion extraction ability of the ligands was in the order **U6**>**U3**>**U1**>**U7**>**U2**>**U5**>**U4**. From these results, the ring cavities of the synthesised crowns can be estimated. All synthesised ligands also showed no binding against the small metal ions in the order of Na^+, K^+, and Li^+.

From these results, for almost all of the ligands in chloroform, Fe^{3+} and Cr^{3+} resulted in a higher extraction percentage than other metal ions. For instance, ligand **U1** wasextractedbyFe^{3+}better than any other metal ions. There was a connection between heteroatom rate (S/O) and extraction percentage, as shown in Table 3. Heteroatom ratio is related to the fact that crown ethers are relatively hard base and soft base character. The increase in the number of oxygen

Table 3
Percentage extraction values for ligands **U1**–**U7** with Li^{+}, Zn^{2+}, Mg^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Fe^{2+}, Fe^{3+}, Cd^{2+}, Ag^{+}, Cr^{3+}, Na^{+}, Ca^{2+}, and K^{+} metal salts in chloroform, and S/O (sulphur/oxygen) heteroatom rate for ligands.

Ligand	Ext. % (Chloroform)	S/O rate
U1	$Fe^{3+} > Pb^{2+} > Ag^{+} > Cr^{3+} > Ca^{2+} > Fe^{2+} > Cd^{2+} > Mg^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Na^{+} = K^{+} = Li^{+}$	2.00
U2	$Cr^{3+} > Pb^{2+} > Cd^{2+} > Fe^{3+} > Ca^{2+} > Fe^{2+} > Zn^{2+} > Mg^{2+} > Ni^{2+} > Co^{2+} > Ag^{+} > Na^{+} = K^{+} = Li^{+}$	1.33
U3	$Fe^{3+} > Cd^{2+} > Fe^{2+} > Cr^{3+} > Ca^{2+} > Pb^{2+} > Ag^{+} > Mg^{2+} > Ni^{2+} > Zn^{2+} > Co^{2+} > Na^{+} = K^{+} = Li^{+}$	1.00
U4	$Cr^{3+} > Pb^{2+} > Ca^{2+} > Cd^{2+} > Ag^{+} > Fe^{3+} > Ni^{2+} > Zn^{2+} > Mg^{2+} > Co^{2+} > Fe^{2+} > Na^{+} = K^{+} = Li^{+}$	0.50
U5	$Cr^{3+} > Cd^{2+} > Fe^{3+} > Ca^{2+} > Pb^{2+} > Mg^{2+} > Ni^{2+} > Co^{2+} > Zn^{2+} > Fe^{2+} > Ag^{+} > Na^{+} = K^{+} = Li^{+}$	0.40
U6	$Fe^{3+} > Cr^{3+} > Ag^{+} > Ca^{2+} > Cd^{2+} > Pb^{2+} > Zn^{2+} > Ni^{2+} > Fe^{2+} > Co^{2+} > Mg^{2+} > Na^{+} = K^{+} = Li^{+}$	0.33
U7	$Fe^{3+} > Ag^{+} > Cr^{3+} > Ca^{2+} > Cd^{2+} > Mg^{2+} > Fe^{2+} > Pb^{2+} > Zn^{2+} > Ni^{2+} > Co^{2+} > Na^{+} = K^{+} = Li^{+}$	0.29

on the molecule elevates the hard base character and the increase in the sulphur number raises the soft base character. Hard bases are sensitive to hard acids, soft bases like mild acids [21,22]. The highest heteroatom rate was 2.00, belonging to **U1**. This ligand had a higher extraction percentage with Fe^{3+} than any other metal salts. Normally, a complex is expected to form with soft acids. However, the Fe^{3+}ion is a hard acid, and shows the highest affinity for hard bases. As opposed to the normal situation, where hard acid and hard base react with each other, the ligand cavity, ion radius and solvent effect also played an important role in this work. When the S/O ratio of decreases for **U1** and **U4; U2** and **U5** ligand-pairs having similar cavities, the percentage of extraction decreases. The effect S/O factor replaces with the effect of cavity as **U3** and **U6** pair is examined. Because of the steric effect between sulphur and oxygen, the cavity of U6 is relatively higher than that of **U3**. Ligand **U1** had too small a ring cavity, such why it could not form a complex with large-diameter metal ions. Almost all ligands showed similar extraction percentages for Fe^{3+} and Cr^{3+} ions, which were the highest among the metal ions.

As expected, **U2, U3, U4, U5, and U6** had S/O rates of 1.33, 1.00, 0.50, 0.40, 0.33, 0.29, respectively, and had higher extraction percentages for Cr^{3+} and Fe^{3+} ions because complex formation with iron and chromium ions (hard acids) and the ligands (hardest bases) were possible. In addition, the increase in the ring cavity supports this finding. Raising ring cavities between **U2** and **U3** enhances the binding ratio (Table 3, see Supporting information). The same is true for the ligands **U4, U5** and **U6**, of which ring cavities increase, and S/O ratios decrease, respectively. The binding percentage of Fe^{3+} ions in these ligands is inversely proportional with the S/O ratio, and directly proportional to the cavity. The percentages of binding with the Cr^{3+} ion in **U2, U3, U4, U5, and U6** have generally constant values (see Supporting informationTables 3 and 4). In the Fe^{+2} extraction works, each ligands show moderate selectivity. It is explained that the cavity of Fe^{3+} is larger than that of Fe^{2+}.

In additional work to determine which metal cations were more selective for the synthesised macrocyclic crown ethers, we used a competitive extraction. For this purpose, 13 metal salts and our ligands were mixed in a 1:1 concentration ratio in chloroform/water at 25 °C. From these extractions, selectivity factors (S_f) were calculated. Considering the selectivity factor values towards the Li^{+}, Zn^{2+}, Mg^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Fe^{3+}, Cd^{2+}, Cr^{3+}, Na^{+}, Ca^{2+}, and K^{+}

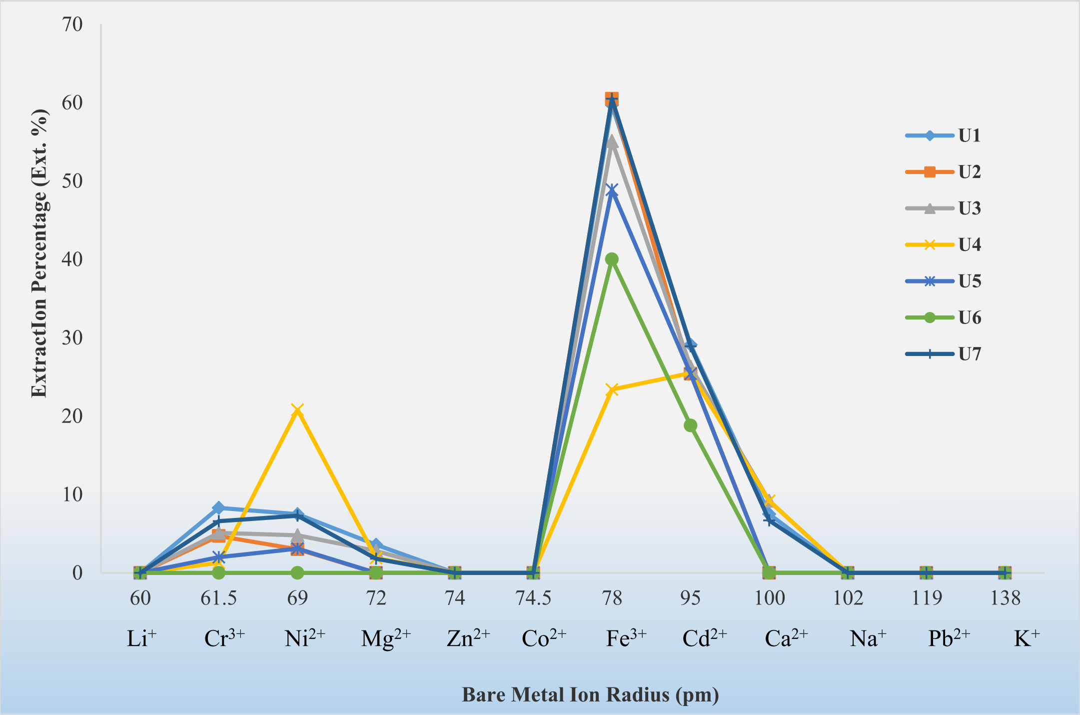


Fig. 1. Competitive extraction change of benzo thio-oxa crown ethers**U1**–**U7** towards Li^{+}, Zn^{2+}, Mg^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Fe^{3+}, Cd^{2+}, Cr^{3+}, Na^{+}, Ca^{2+}, and K^{+} ions relative to ion radii in chloroform/water at 25 °C.

mixture, ligand U1 was selective for Fe^{3+}, Cr^{3+}, and Cd^{2+}, **U2** was selective for Fe^{3+}, **U6**, **U5**, and **U3** were generally selective for Fe^{3+} and Cd^{2+}, and, finally, **U4** and **U7** ligands were selective for Fe^{3+}, Cd^{2+} and Ni^{2+} in that order (see in Supporting information Tables 5 and 6). These results were also compatible with the values in Fig. 1, which contains extraction percentages and ionic radii. Approximately all synthesised compounds had high selectivity for Fe^{3+} due to its the syngeneic effects of ion charge and cavity. The amount of percentage rate for Cr^{3+} also decreased when the mixture of metals with all synthesised ligands were applied to the extraction process. It could be explained again with the syngeneic effects of ion charge and cavity. In the competitive extraction, each ligands show no selectivity against Li^{+}, Zn^{+2}, Co^{+2}, Na^{+}, Pb^{+2}, and K^{+} metals for the mixture of studied metals (Fig. 1).

Additionally, wavelength scanning was carried out using UV/visible (UV/vis) spectrophotometry of the synthesised compounds to explore their chromophore properties in chloroform (see in Supporting information Scheme 1). The synthesised compounds absorbed UV–visible light (detailed in the supporting information, Table 1). The influence of solvent and protonation on the photophysical properties of the compounds was studied using this UV/Vis method. Based on the UV/VIS wavelength scanning results, various compounds showed chromophore characteristics that could potentially be applied in new studies.

4. Conclusions

In this paper, novel macrocyclic benzo-thio crown ethers were synthesised in high yields, and utilised in extraction studies. Pyridine was used as a catalyst and high dilution procedure, classified as esterification-cyclisation reaction, was applied in classical method. The synthesis of benzo-thio crown ethers under microwave irradiation can have certain benefits over conventional heating. Microwave assisted synthesis has higher yields, shorter reaction times, simpler reaction conditions, and low rate of by-product. The synthesised benzo-thio crown ethers U1–U7 were characterised using FT-IR, ^{1}H NMR, ^{13}C NMR, LC-MS spectra, and microanalyses. As the synthesised molecules have many advantages in terms of functionality (e.g., substituted benzene, thioester, ether), they could be used as complexion agents for metal ions. That's why, the metal ions used in this study are very important in the human body. Generally, all of these compounds showed a strong affinity for metal ions. These novel crown ethers also displayed reasonably high binding properties and extraction percentages. Furthermore, the synthesised molecules could be very important in the separation of metals from mixtures as a metal sensor. Finally, they could have future uses in metal complexation, biological activity, antimicrobial and antifungal studies, and more.

That was attempted to discuss the selectivity factors for all synthesised compounds. Hence, the metal salts used in this work exhibited results corresponding with compound cyclic cavity. From these results, it can be stated that the synthesised compounds were selective for metals with ion radii between 78 and 100 p.m. (e.g., Fe^{3+}, Cd^{2+}, and Ca^{2+}). If the ion radius was too high (e.g., Na^{+}, Pb^{2+}, and K^{+}), or between 74.0 and 74.5 p.m. (e.g., Zn^{2+}, Mg^{2+}, and Co^{2+}), ligands showed no selectivity (bare ion radii are given in the supporting information, Table 2). However, an interesting result occurred with Ca^{2+}, which has a huge ion radius. That can be explained by the stability of the complex formed via ion-dipole interactions between the calcium ions and ligands. Another interesting result was that Ni^{2+} ions are attracted to ligand **U4**, which was explained byU4being the smallest compound synthesised. Moreover, whole ligands, as noted previously, did not generally show large differentials, except for Fe^{3+}, Cd^{2+}, and Ni^{2+}. This situation for Fe^{3+} ions changes with the sulphur/oxygen rate of the ligand forming the complex. When this rate increased, the attraction to Fe^{3+} increased.

As a result, reported microwave-assisted synthesis benefits include decreased reaction times, reduced energy consumption, improved yield and selectivity, and decreased solvent amounts, which helps to develop the green chemistry reactions.

Conflict of interest

The authors declare no competing financial interests. This work has been supported by Balikesir University Scientific Research Projects Unit with project number BAP: 2012/69.

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In this study, both Baki Çiçek and Umit Calisir designed the study, performed all experiments/analysis, and evaluated the results and prepared the manuscript. Baki Çiçek was the supervisor of Umit Calisir during this work, which is presented as a Master's thesis.

List of abbreviations

K_D	The ratio of the metal concentration in the organic phase to the metal concentration in the aqueous phase
Ext%	Extraction percentage
ΔG	Gibbs energy
K_{Ext}	Extraction equilibrium constant
Sf	Selectivity factor
$M^{m+}{}_{(w)}$	Free metal concentration in the water phase at equilibrium
$A^{-}{}_{(w)}$	Free anion concentration in the water phase at equilibrium
$L_{(w)}$	Free ligand concentration in the water phase at equilibrium.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.molstruc.2017.07.081.

References

[1] R. Ostaszewski, L. Prodi, M. Montalti, The synthesis and complexation studies of thia-anthracene receptors, Tetrahedron 55 (1999) 11553–11562, http://dx.doi.org/10.1016/S0040-4020(99)00654-7.

[2] B.S.E. Drewes, P.C. Coleman, Synthesis of New Macrocycles. Part 1. Monomeric and Dimeric O-Phthalate Esters, J.C.S. Perkin I, 1967, pp. 2148–2153.

[3] B.G.R. Siegfried, E. Drewes, Synthesis of new macrocycles. Part 5.l cyclization of 2,2'-dithiodibenzoic acid derivatives 6 (1976) 2574–2576.

[4] A.K.F. Arndt, Über einige Derivate der Thio-salicylsäure und des Oxy-3-thionaphthens, Berichte Der Dtsch. Chem. Ges. (A B Ser. 59 (1926) 1074–1081, http://dx.doi.org/10.1002/cber.19260590603.

[5] S.M. Seyedi, M. Shadkam, a. Ziafati, A convenient synthesis of new macrocyclic thioether-esters and ether-esters: extraction properties of these esters for alkali, alkaline earth, and transition metal cations, Phosphorus. Sulfur. Silicon Relat. Elem. 180 (2005) 1953–1960, http://dx.doi.org/10.1080/104265090902714.

[6] B. Çiçek, A. Ergun, N. Gençer, Synthesis and evaluation in vitro effects of some macrocyclic thiacrown ethers on erythrocyte carbonic anhydrase I and II, Asian J. Chem. 24 (2012) 1–3.

[7] J.S. Yadav, B.V.S. Reddy, CsF-Al2O3 mediated rapid condensation of phenols with aryl halides: comparative study of conventional heating vs. microwave irradiation, New J. Chem. 24 (2010) 489–491, http://dx.doi.org/10.1039/b001824o.

[8] A.T. Yordanov, D.M. Roundhill, Solution extraction of transition and post-transition heavy and precious metals by chelate and macrocyclic ligands, Coord. Chem. Rev. 170 (1998) 93–124, http://dx.doi.org/10.1016/S0010-8545(97)00074-X.

[9] T. Lu, X. Wang, M. Tan, Y. Liu, Y. Inoue, T. Hakushi, Studies on rare-earth complexes with Crown Ethers. Part XXV. Synthesis, characterization, and

structure of the complexes of lanthanite nitrates with 13-crown-4, Helv. Chim. Acta 76 (1993) 241–247, http://dx.doi.org/10.1002/hlca.19930760117.
[10] R.L. Bruening, B.J. Tarbet, K.E. Krakowiak, M.L. Bruening, R.M. Izatt, J.S. Bradshaw, Quantitation of cation binding by silica gel bound thiamacrocycles and the design of highly selective concentration and purification columns for Palladium(I I), Gold(I I I), Silver(I), and Mercury(I I), Anal. Chem. 63 (1991) 1014–1017.
[11] T. Nabeshima, N. Tsukada, K. Nishijima, H. Ohshiro, Y. Yano, Remarkably selective Ag(+) extraction and transport by thiolariat ethers, J. Org. Chem. 61 (1996) 4342–4350. http://www.ncbi.nlm.nih.gov/pubmed/11667335.
[12] B. Çiçek, Ü. Çakir, A. Azizoglu, The associations of macrocyclic ethers with cations in 1,4-dioxane/water mixtures; Potentiometric Na + and K + binding measurements and computational study, J. Incl. Phenom. Macrocycl. Chem. 72 (2012) 121–125, http://dx.doi.org/10.1007/s10847-011-9949-y.
[13] P. Hendry, L.F. Lindoy, D. Yellowlees, The kinetics and mechanism of Zn(II) dissociation from human carbonic anhydrase B in the presence of chelating agents, Inorganica Chim. Acta 65 (1982) 237–239.
[14] L.F. Lindoy, D.H. Bush, Nickel complexes of two new quadridentate macrocycles, Inorg. Nucl. Chem. Lett. 5 (1969) 525–528.
[15] L.F. Lindoy, Reactions involving metal complexes of sulphur ligands, Coord. Chem. Rev. 43210 (1969) 41–71, http://dx.doi.org/10.1016/s0010-8545(00)80092-2.
[16] L.G. Armstrong, L.F. Lindoy, Nickel complexes of macrocyclic ligands derived from salicylaldehyde, Inorg. Nucl. Chem. Lett. 10 (1974) 349–352.
[17] H. Tsukube, K. Takagi, T. Higashiyama, T. Iwachido, N. Hayama, “Armed thiacrown ether”: a specific carrier for soft metal cation, Tetrahedron Lett. 26 (1985) 881–882, http://dx.doi.org/10.1016/S0040-4039(00)61954-8.
[18] T. Nabeshima, N. Tsukada, H. Furusawa, T. Hosoya, Remarkably selective binding of silver ion by thiolariat ether with a 15-crown-5 ring, J. Chem. Soc. Chem. Commun. (1992) 1092–1094.
[19] T. Krueger, K. Gloe, H. Stephan, B. Habermann, K. Hollmann, E. Weber, Molecular modeling studies on novel open-chain and cyclic thia compounds and their Ag(I) and Hg(II) complexes, J. Mol. Model. 2 (1996) 386–389.
[20] B. Çiçek, A. Yıldız, Synthesis, metal ion complexation and computational studies of thio oxocrown ethers, Molecules 16 (2011) 8670–8683, http://dx.doi.org/10.3390/molecules16108670.
[21] B. Çiçek, Ü. Çalışır, The investigation of complexation properties and hard-soft acid-base relationship between thiacrown ethers and metal ions, Lett. Org. Chem. 13 (2016) 572–577, http://dx.doi.org/10.2174/1570178613666-1609061053.
[22] B. Çiçek, Z. Onbaşıoğlu, Synthesis and characterization of 1,3,4-thiadiazole-2,5-dithio crown ethers, Heterocycl. Commun. 22 (2016) 329–332, http://dx.doi.org/10.1515/hc-2016-0097.
[23] T. Kakuchi, O. Haba, K. Yokota, Cyclopolymerization of divinyl ethers. Synthesis and the cation-binding property of poly (crown ethers), Macromolecules 25 (1992) 4854–4858.
[24] E. Lukovskaya, Y. Glazova, Y. Fedorov, A. Bobylyova, A. Mizerev, A. Moiseeva, A. Anisimov, A. Peregudov, O. Fedorova, Effect of the chromophoric unit on the complex formation properties in the crown ether containing styryl dyes, Dye. Pigment. 104 (2014) 151–159, http://dx.doi.org/10.1016/j.dyepig.2013.12.027.
[25] V. Lamare, J.-F. Dozol, S. Fuangswasdi, F. Arnaud-Neu, P. Thuéry, M. Nierlich, Z. Asfari, J. Vicens, A new calix[4]arene-bis(crown ether) derivative displaying an improved caesium over sodium selectivity: molecular dynamics and experimental investigation of alkali-metal ion complexation, J. Chem. Soc. Perkin Trans. 2 (1999) 271–284, http://dx.doi.org/10.1039/a806714g.
[26] Ü. Çakir, B. Çiçek, Y.K. Yildiz, M. Alkan, Solvent effect upon ion-pair extraction of different sodium dyes using some crown ethers, J. Incl. Phenom. Macrocycl. Chem. 34 (1999) 153–165.
[27] Ü. Çakir, B. Çiçek, Extraction-ability and -selectivity of tetra-aza-crown ethers for transition metal cations, Transit. Met. Chem. 29 (2004) 263–268.
[28] C. Erk, U. Cakir, B. Cicek, Estimation of Li+, K+ and Ca2+ complexation with 12 crown-4, 15 crown-5 and 18 crown-6 using a Na+ISE in dioxane-water, part IV - cation equilibrium constants of macrocyclic ethers with ion selective electrodes, Mikrochim. Acta 132 (1999) 79–82.