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SYNTHESIS AND EXTRACTION PROPERTIES OF NEW FUSED BENZOCROWN-HETEROCYCLE LIGANDS FOR ALKALI AND ALKALINE EARTH METAL CATIONS

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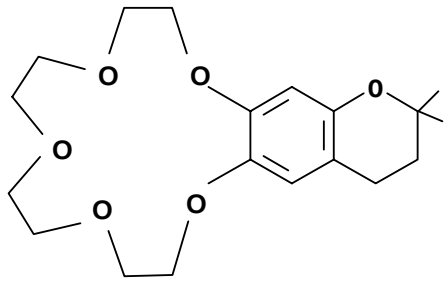
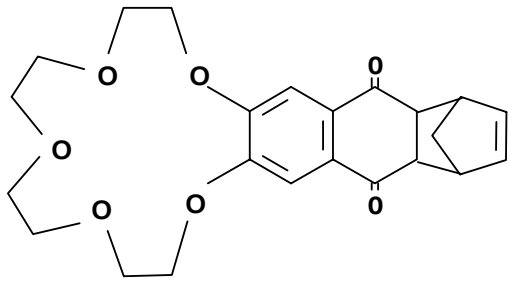
Abstract – Heterocyclic compounds **(5-9)** were synthesized and reacted with 4,5-bis (bromomethyl) benzo-15-crown-5 to afford the fused benzocrown - heterocycle ligands **(10-14)**. The complexing ability of these macrocyclic ligands toward Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Li^+/Mg^{2+} and Li^+/K^+ was measured by the solvent extraction method. The data show that extractability of the double cations enhances remarkably when compared with the extraction ability of the single cation.

INTRODUCTION

Many investigation have been carried out into macrocyclic ligands containing heterocycles in which the heterocyclic ring is either as a part of the macrocycle framework, [1-17] or as a substituent on the benzene ring of the benzocrown ethers.[18-23] However, the literature on the synthesis and extraction properties of benzocrown ether containing fused heterocycles is less extensive and only two fused benzocrown - heterocycle ligands, **(1)** and **(2)**, were reported by Caups[24] and Otsuki,[25] respectively (Figure 1).



(1)



(2)

Figure 1

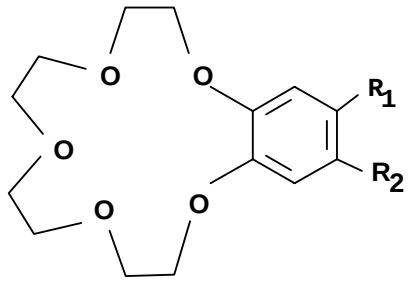
1,3-4-Oxadiazole-2-thione derivatives are reported to show a broad spectrum of biological activities.[26,27] These oxadiazoles have been shown to exhibit analgesic , muscle relaxant and tranquilizing properties.[28]

1,2,4-Triazole derivatives also find a broad application as enzyme inhibitors[29] and peptide analog inhibitors,[30] fungicidal, herbicidal and anti-inflammatory properties.[31-36]

Prompted by the above observations that the combination of two or more heterocyclic and non-heterocyclic systems enhances the biological profile many - fold than its parent nuclei, we considered to synthesize some oxadiazole and triazole derivatives fused to the benzo-15-crown-5 ether which might show extra biological activities. Also by taking these structural features into consideration, it was thought worthwhile to synthesize and investigate the extraction properties of these fused benzocrown-heterocycles for alkali and alkaline earth metal cations.

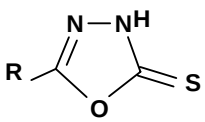
RESULTS AND DISCUSSION

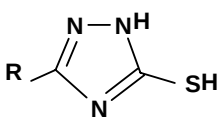
Benzo-15-Crown-5 **(3)** was prepared from catechole by Pedersen's procedure.[37] 4,5,-Bis (bromomethyl)benzo-15-crown-5 **(4)** was prepared from **(3)** by reaction with para- formaldehyde and 33% solution of HBr in acetic acid.[38] 5-(4-Chlorophenyl)-1,3,4-oxadizole-2-thione **(5)** was prepared by reaction of 4-chlorobenzoylhydrazide with potassium hydroxide and carbon disulfide under reflux in ethanol.[39] Similarly, reaction of benzoylhydrazide with potassium hydroxide and carbon disulfide afforded 5-phenyl-1,3-4-oxadiazole-2-thione **(6)** in 75% yield.[40] Refluxing of benzoylthiosemicarbazide with sodium ethoxide in ethanol gave 5-phenyl-3-mercapto-1,2,4-triazole **(7)** in 79% yield.[41] 5-Methyl-3-mercapto-1,2,4-triazole **(8)** was prepared from acetylthiosemicarbazide with formamide for 20 min.[43] 4,5-Bis(bromomethyl)benzo-15-crown-5 **(4)** was refluxed with the heterocycles, **(5)**, **(6)**, **(7)**, **(8)**, and **(9)**, in acetonitrile and a few drops of triethylamine for 6-8 h to give the fused benzocrown-heterocycles, **(10)**, **(11)**, **(12)**, **(13)**, and **(14),** respectively (Figure 2).



(3) $R_1 = R_2 = H$

(4) $R_1 = R_2 = -CH_2Br$





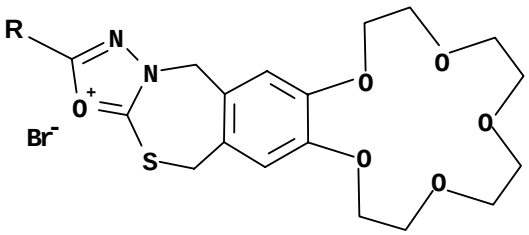
(5) R = *p*-Cl C_4H_4

(6) R = C_6H_5

(7) R = $-C_6H_5$

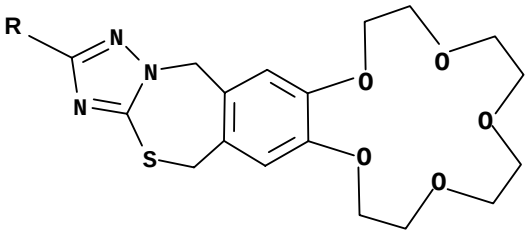
(8) R = CH_3

(9) R =H



(10) R = *P*-ClC_6H_4

(11) R = -C_6H_5



(12) R = -C_6H_5

(13) R = -CH_3

(14) R = H

Figure 2

Alkali and Alkaline Earth Metal Picrate Extractions. The complexing abilities of compounds **(10-14)** and two model compounds **(3)** and **(4)** were assessed by solvent extraction of alkali and alkaline earth metal picrate from aqueous solution into dichloromethane according to Haines's procedure.[22] The procedure was repeated four times to ensure complete extraction. The extraction efficiency was determined by measuring the absorbance of picrate salt in the aqueous phase at 354 nm using UV spectrophotometer. The results are presented in Table1. Whereas selective extraction of Na^+ normally would be anticipated on the basis of the 15-crown-5 ring size,[44,45] the data in Table 1 indicate that the observed extraction selectivity order for compound **(10-14)** is $K^+>Na^+>Li^+$.[45] When the alkali metal picrate extraction capability of **(10)** and **(11)** is compared with **(12-14)**, it is observed that **(10)** and **(11)** extract all three alkali metal picrate less efficiently than **(12-14)**. This could be duo to the electron withdrawing effect of the heterocyclic part in **(10)** and **(11)** which is absent is **(12-14)**. The data obtained for alkaline earth metal picrate extractions show that the extraction efficiencies are lower than alkali metals. Compounds **(10)** and **(11)** exhibit stronger complexation, and compounds **(13)** and **(14)** show lower complexation ability toward Ca^{2+} when compared with Mg^{2+}. Compound **(12)** shows the same complexation ability for both Mg^{2+} and Ca^{2+}.

When complexation property was examined with a double cation experiment, these fused macrocycles showed unique cation complexing properties. In spite of the consistency of the crown ring size, compounds **(10-14)** exhibit much higher extraction efficiency for both Li^++Mg^{2+} and Li^++K^+ cations when compared with the single cation, and the model compounds **(3)** and **(4)** (Table1).

X-Rray crystallography shows that the five memberd ring in compounds **(10-14)** is planar[46] and the seven memberd ring is in chair form[47] which makes the whole molecule to be bended.[45,48] The observed higher picrate extraction selectivity for much bulky guests, *i.e.* Li^{+}+Mg^{2+} and Li^{+}+K^{+}, strongly suggests the existence of "sandwich" complexes which result from this bending and therefore much cooperativity between fused crown ring-heterocycle ligands.[45,49] This complexation ability is much less for a single cation which is small and therefore cannot be kept as strongly as the bulky double cation guests.

EXPERIMENTAL

Solvents, reagents, and chemical materials were obtained from Merck and Fluka Company. Melting point was measured on digital electrothermal melting point apparatus model 9100. TLC were performed on Kieselgel PG60 with l: 4 (v/v) methanol-chloroform. IR spectra were recorded on a Shimadzu Fourier transform infrared spectrophotometer model 4300. Proton NMR spectra were obtained by using a Bruker AC 100 Fourier transform spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS) as an internal standard. A Shimadzu model A120 UV-visible spectro photometer was used to measure absorbance at 354 nm in connection with the picrate extraction experiments described below. MS were recorded on Massens Puktrometer CH-VA spectrometer at 70 ev. Elemental analysis was performed on Termofinnigan Flash EA micro analyzer. Benzo-15-crown-5 **(3)**,[37] 4,5-bis(bromomethyl)benzo-15-crown-5 **(4)**,[38] 5-(4-chlorophenyl)-2-thione **(6)**,[40] 5-phenyl-3-mercapto-1,2,4-triazole **(7)**,[41] 5-methyl-3-mercapto-1,2,4-triazole **(8)**,[42] 3-mercapto-1,2,4-triazole **(9)**,[43] were prepared by literature procedure. All of these compounds showed satisfactory TLC, mp, MS, ^{1}HNMR and IR spectral data.

General procedure for synthesis of fused benzocrown-heterocycle ligands (10-14). To a stirred solution of the required heterocyclic compound (5 mmol) in boiling acetonitril (50 mL) containing a few drops of triethylamine, was added bis (bromomethyl) benzo-15-crown-5 **(4)** (5 mmol, dissolved in 5 mL acetonitril) dropwise and the mixture refluxed for 6-8 h after which time it was concentrated in vacuo. The residue was disoled in chloroform (6 mL) and washed with 2% sodium hydroxide (3×5 mL) and water (3×5 mL). The combined organic extracts were dried over sodium sulfate and then concentrated to give the product. A small amount of compounds **(10-14)** were purified by column chromatography (methanol-chloroform) for elemental analysis. The following macrocyclic ligands were prepared.

2-(4-Chlorophenyl)-5, 8, 9, 11, 12, 14, 15, 17, 18, 21-decahydro[1,3,4]oxadiazolo[3,2-c] [1,4,7,10,13]-pentaoxacyclopentadecino[3,2-h][2,4]benzothiazepin-1-ium bromide (10). Yield 53%, mp 151-152°C,

IR (KBr cm^{-1}) 1690 (C=N), 1500 (C=C), 1120 (COC). ^{1}HNMR ($CDCl_3$) δ3.5-4.3 (18H, m, C*H*$_2$ crown, S-C*H*$_2$) 6.9-7.1 (2H, s, Ar-*H* crown), 7.4 (2H, s, N- C*H*$_2$), 7.5-8.0 (4H, dd, Ar-*H*). MS (m/z): M^+ = 506. *Anal.* Calcd for $C_{24}H_{26}N_2O_6SClBr$: C, 49.2; H, 4.5; N,4.8; S, 5.5. Found; C,48.9; H, 4.6; N, 5.2; S, 5.1.

2-Phenyl-5, 8, 9, 11, 12, 14, 15, 17, 18, 21-decahydro[1, 3, 4]oxadiazolo [3, 2-h] [1, 4, 7, 10, 13]-pentaoxacyclopentadecino[3, 2-h] [2, 4]benzothiazepin-1-ium bromide (11). Yield 69%, mp 147-148°C. IR (KBr cm^{-1}) 1690 (C=N), 1500 (C=C), 1120 (COC). ^{1}HNMR ($CDCl_3$) δ3.5-4.3 (18H, m, C*H*$_2$ crown, S-C*H*$_2$) 6.7-6.9 (2H, s, Ar- *H* crown), 7.2 (2H, s, N- C*H*$_2$) 7.4-8.0 (5H, m, Ar-*H*). MS (m/z): M^+ = 471. *Anal.* Calcd for $C_{24}H_{27}N_2O_6SBr$: C, 52.3; H, 4.9; N,5.1; S, 5.8. Found; C, 52.8; H, 4.8; N, 5.6; S, 6.3.

2-Phenyl-5, 8, 9, 11, 12, 14, 15, 17, 18, 21-decahydro[1, 4, 7, 10, 13]pentaoxacyclopentadecino[3, 2-h] [1, 2, 4]triazolo[5, 1-c] [2, 4]benzothiazepine (12). Yield 45%, mp 88-89°C. IR (KBr cm^{-1}) 1700 (C=N), 1600, 1490, (C=C), 1150 (COC), ^{1}HNMR ($CDCl_3$) δ3.3-4.2 (18H, m, C*H*$_2$ crown, S-C*H*$_2$), 7.0-7.1 (4H, s, Ar- *H* crown, N- C*H*$_2$), 7.4-8.1 (5H, m, Ar-*H*). MS (m/z): M^+ = 469. *Anal.* Calcd for $C_{24}H_{27}N_3O_5S$: C, 61.4; H, 5.7; N, 8.9; S, 6.8. Found; C, 60.9; H, 5.4; N, 9.4; S, 7.2.

2-Methyl-5, 8, 9, 11, 12, 14, 15, 17, 18, 21-decahydro[1, 4, 7, 10, 13]pentaoxacyclopentadecino [3, 2-h] [1, 2, 4]triazolo[5, 1-c] [2, 4]benzothiazepine (13). Oil, yield 51%. IR (cm^{-1}) 1690 (C=N), 1500 (C=C), 1125 (COC). ^{1}HNMR ($CDCl_3$) δ 2.7 (3H, s, C*H*$_3$), 3.5-4.3 (18H, m, C*H*$_2$ crown, S-C*H*$_2$), 6.7-6.9 (4H, s, Ar- *H* crown, N- C*H*$_2$). MS (m/z): M^+ = 407. *Anal.* Calcd for $C_{19}H_{25}N_3O_5S$: C, 56.0; H, 6.1; N, 10.3; S, 7.9. Found; C, 55.7; H, 6.0; N, 9.8; S, 7.4.

5, 8, 9, 11, 12, 14, 15, 17, 18, 21-Decahydro[1, 4, 7, 10, 13]penta- oxacyclopentadecino[3, 2-h] [1, 2, 4]triazolo[5, 1-c] [2, 4]benzothiazepine (14). Oil, yield 46%. IR (cm^{-1}) 1700 (C=N), 1500 (C=C), 1150 (COC). ^{1}HNMR ($CDCl_3$) δ3.5-4.1 (18H, m, C*H*$_2$ crown, S-C*H*$_2$), 6.8 (4H, s, Ar- *H* crown, N- C*H*$_2$), 8.5 (1H, s, C-*H*). MS (m/z): M^+ = 393. *Anal.* Calcd for $C_{18}H_{23}N_3O_5S$: C, 54.9; H, 5.9; N, 10.7; S, 8.1. Found; C, 54.4; H, 6.3; N, 10.2; S, 7.7.

Extraction Measurement. Aqueous solution (15 mL) containing picric acid (7×10^{-7} M), alkali and alkaline earth metal chloride (0.1 M) was vigorously shaken with equal volume of dichloromethane containing benzocrown ligands **(3-14)** (7×10^{-7} M) for 15 min. The absorbance, A, of the aqueous layer

before and after the extraction experiment, Ao and Ae, respectively, was measured at the position of maximum absorption band at 354 nm and the percentage of extraction of alkali and alkaline earth metal picrates into the organic layer was calculated by the expression 100 (Ao-Ae)/Ao. Results are given in Table1.

Table1. Alkali and alkaline earth metal picrate extraction data from aqueous solution into dichloromethane by using compounds **(3), (4)** and **(10-14).**

Cation / Crown[b]	Percent of picrate extraction (%)[a]						
	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Li^+/Mg^{2+}	Li^+/K^+
3	5.4	14.6	16.3	7.9	9.8	3.3	0
4	0	10.8	7.8	3.1	6.5	4.9	0
10	0	5.1	5.4	3.1	3.6	6.6	8.5
11	0	3.8	5.2	1.6	3.3	6.6	7.4
12	0.7	5.7	10.3	3.9	3.9	8.2	9.6
13	0	5.7	7.8	3.2	2.4	7.4	10.7
14	4.3	10.3	13.9	3.9	2.7	9	12.4

a. average for four samples.

b. Organic phase (dichloromethane): (10, 11, 18-21 macrocycles) = 7×10^{-7} M.

Aqueous phase (picric acid) = 7.0×10^{-7} M.

Alkali and alkaline earth metal chloride = 1.00×10^{-3} M

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