New Proton-Ionizable Macrocyclic Compounds Containing One and Two Triazole Subcyclic Units - Synthesis and Complexation Properties

Sadik Elshani, Pete Apgar, Shaofen Wang and C. M. Wai*

Department of Chemistry, University of Idaho,
Moscow, Idaho 83844

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A series of new macrocyclic compounds containing one and two proton-ionizable triazole subcyclic units have been prepared and characterized. These triazolo-crowns containing benzo, *tert*-butylbenzo or cyclohexano lipophilic groups show varying solubilities in chloroform. The bistriazolo-crowns dissolved in chloroform are highly effective for extraction of lead, mercury, and gold from aqueous solutions.

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Introduction.

Macrocyclic polyethers containing proton-ionizable functional groups are interesting complexing agents for extraction of metal ions. A series of such compounds containing a carboxylic or a hydroxamic acid group on a pendant arm has been prepared recently [1-4]. These compounds have proven to be excellent chelating agents for solvent extraction of trivalent lanthanides [5,6]. One advantage of these proton-ionizable crown ethers is that the ionized group on the pendant arm provides the counteranion necessary for the transport of the cation into a nonaqueous separation layer [5-8]. In recent years, there has been a growing interest in the preparation of macrocycles containing an ionizable triazole moiety within the cavity [9-15]. Macrocycles containing one triazole subcyclic unit on the macrocyclic ring have been shown to complex selectively with univalent metal ions such as Ag^+ [16]. Chiral dialkyl-substituted triazole-18-crown-6 ligands have been used for enantiomeric recognition of organic ammonium salts [17]. So far, only a few macrocycles containing two proton-ionizable triazole subcyclic units are known in the literature and there are no data reported about their use in solvent extraction [11,14,15,18]. None of these bistriazolo-macrocycles contain benzo, *t*-butylbenzo or cyclohexano substituents. Some bistriazolo-macrocycles are quite insoluble in organic solvents, thus preventing their further study for metal extraction [14,18].

We have recently prepared a series of macrocyclic compounds containing one and two proton-ionizable triazole subcyclic units and substituted with benzo, *t*-butylbenzo or cyclohexano lipophilic groups (**1-7**, Figure 1). All these compounds except **2** are 18-membered macrocycles with six donor atoms, an appropriate size which should be suitable for interaction with heavy metal ions such as lead (Pb^{2+}) and mercury (Hg^{2+}) [19-22]. Preliminary solvent extraction and liquid membrane transport results indicate that these new triazolo-crowns are highly effective for the extraction of heavy metals, including lead, mercury, and gold, from aqueous solutions into chloroform. Of special interest is bistriazolo-crown **6**, which has a high solubility in chloroform and exhibits extremely fast kinetics for the extraction of Hg^{2+}. The extraction, similar to other proton-ionizable crown ethers, is *p*H dependent. A complete description of the solvent extraction and liquid membrane transport of cations by these new triazole-containing crown compounds will be reported elsewhere.

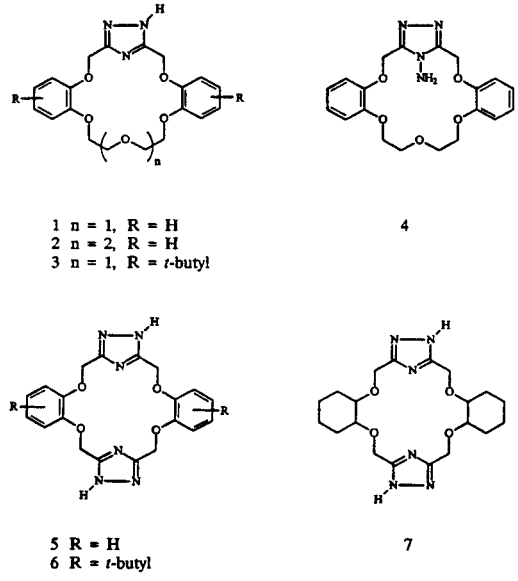


Figure 1. Structures of new triazolo-crowns.

This paper describes the synthesis and preliminary extraction data for a series of macrocycles with the one and two triazole subcyclic units shown in Figure 1. With the exception of **1**, the other triazolo-crowns have not been reported in the literature. Macrocycles **5-7** contain two triazole groups with different lipophilic groups including benzo, *t*-butylbenzo, and cyclohexano as part of the macrocyclic host. Introducing *t*-butyl groups to the macrocyclic hosts tends to enhance their solubilities in organic solvents.

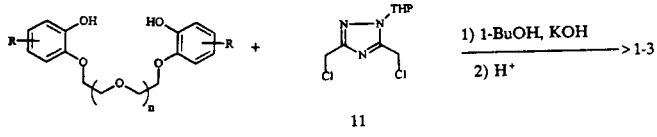
Results and Discussion.

Synthesis of the New Triazolo-Crowns.

Compounds **1-3** were prepared by the reaction of 3,5-

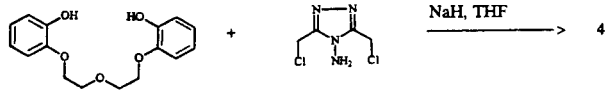
bis(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4 triazole (**11**) with appropriate bisphenols in 1-butanol and potassium hydroxide as a base followed by an acid hydrolysis as shown in Scheme I. Starting compounds **8** [23], **9** [2], **10** [24], **11** [11,25,26], **12** [13,26] were prepared as reported.

Scheme I. Preparation of Triazolo-Crowns 1-4



11

8 n = 1, R = H
9 n = 2, R = H
10 n = 1, R = *t*-butyl

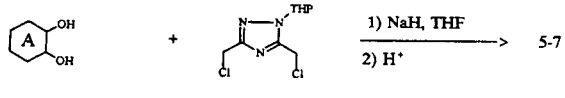


8 12

Compound **1** was prepared by Bradshaw *et al.* from bisphenol **8** and *N*-tetrahydropyranyl-protected 2,5-triazoledimethyl dichloride (**11**) in tetrahydrofuran and potassium *t*-butoxide as a base [12]. The mono triazolo-crowns **1-3** were isolated as white solids in 68-81% yields and were purified by recrystallization. The $N-NH_2$ group was acting as a protecting group during the synthesis of macrocycle **4** and was preserved in order to provide an additional pendant arm. Attempts to remove this group by nitrous acid to give compound **1** were unsuccessful due to the low solubility of **4** in diluted hydrochloric acid.

Compounds **5-7**, each containing two triazole subcyclic units, were prepared by the reaction of **11** with the appropriate catechlos and *trans*-1,2-cyclohexanediol, respectively, in tetrahydrofuran (THF) and sodium hydride as a base followed by an acid hydrolysis as shown in Scheme II. These new bistriazolo-crowns are expected to be effective for divalent cations.

Scheme II. Preparation of Bistriazolo-Crowns 5-7



11

13 A = benzo
14 A = *t*-butylbenzo
15 A = cyclohexano

The bistriazolo-crowns **5-7** were purified by chromatography and recrystallization (when possible). Desired compounds were isolated as white solids in 18-34% yields. The structures proposed for these new macrocyclic compounds are consistent with the data obtained from their ir and ^1H nmr spectra and elemental analyses.

Extraction Properties of the New Triazole-Containing Crown Ethers.

The bistriazolo-crowns show high extraction efficiencies for heavy metal ions Pb^{2+}, Hg^{2+}, and Au^{3+}. Due to its high extraction efficiency and solubility in chloroform, bistriazolo-crown **6** appears to be the best extractant among the group of ionizable crown ethers reported in this paper. In our extraction experiments, the concentration of crown ether in the organic phase (chloroform) was fixed at 1×10^{-4} *M* and the concentration of each metal in the aqueous phase was 5×10^{-6} *M*. The extraction efficiency of crown ether **6** for mercury (Hg^{2+}) exceeds 96% in the *p*H range 2.5-8.0. The distribution coefficient (D) of Hg^{2+} in this system is greater than 20. The extraction of Hg^{2+} by bistriazolo-crown **6** is extremely fast, requiring only one to two minutes of shaking to reach the equilibrium value. No specific counteranions are needed for the extraction. A surprising result is the extraction of gold (Au^{3+}) by crown ether **6** in acidic solutions. Gold can be extracted (>95%) by this crown ether even in 1 *M* nitric acid solutions. The rate of extraction of Au^{3+} is much slower, relative to that of Hg^{2+}, requiring 15-20 minutes to complete the extraction. Lead (Pb^{2+}) can be extracted (>95%) in the *p*H range 6.5-8.5. Mercury and gold extracted in the organic phase can be quantitatively stripped with 2 *M* and 5 *M* nitric acid, respectively. Lead extracted in the organic phase can be stripped with a dilute acid solution such as 0.1 *M* nitric acid.

The solubilities of bistriazolo-crowns **5**, **6**, and **7** in chloroform at 22 ±1° are 3.0×10^{-4} *M*, 6.7×10^{-1} *M*, and 3.2×10^{-4} *M*, respectively, according to our experiments. These crown ethers are water insoluble but can be dissolved in chloroform readily for liquid-liquid extraction of metal ions. Crowns ether **6**, which has a *t*-butyl group attached to each benzene ring, has a solubility in chloroform almost 3 orders of magnitude greater than those of **5** and **7**. Because of their small solubilities in chloroform, bistriazolo-crowns **5** and **7** probably have limited applications for extracting metal ions with relatively high concentrations in aqueous solutions. The ability of these new ionizable crown ethers containing two triazole groups to extract mercury and gold in acidic solution is highly significant. They may have important applications for mercury and gold recovery from waste water and other environmental samples.

EXPERIMENTAL

Commericial reagents were obtained from Aldrich and Fluka (thionyl chloride) and were used as purchased. Tetrahydrofuran

(THF) was distilled from sodium and benzophenone. The proton nuclear magnetic resonance (nmr) spectra were obtained on a Bruker AF 200 Instrument (200 MHz). Infrared (ir) spectra were obtained on a Digilab Qualimatic FTIS-80. Mass spectra were obtained on VG Micro mass 70/70 HS Mass spectrometer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Starting compounds **8** [23], **9** [2], **10** [24], **11** [11,25,26], and **12** [13,26] were prepared as reported. Elemental analyses were performed by Desert Analytics, Tucson, AZ. All new compounds were confirmed as pure materials by tlc analysis.

General Procedure for the Preparation of Macrocycles **1-3**.

Under nitrogen, 10 mmoles of the appropriate bisphenol was dissolved in 120 ml of 1-butanol. To this mixture, 21 mmoles of potassium hydroxide pellets were added and the reaction mixture was heated. After refluxing for 30 minutes, 3,5-*bis*(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole (**11**) (10 mmoles) dissolved in 50 ml of 1-butanol was added dropwise for 3 hours. After the addition was completed, the reaction mixture was refluxed for 24 hours. After cooling to room temperature, the 1-butanol was evaporated *in vacuo* and the residue dissolved in dichloromethane. The dichloromethane layer was washed with water and evaporated. The white solids obtained were purified by column chromatography on silica gel with dichloromethane and dichloromethane/methanol (95:5) as eluents. The tetrahydropyranyl-blocking group was removed from the product by stirring in 75 ml of 15% methanolic hydrogen chloride for several hours at room temperature. The methanol was evaporated and the residue was neutralized with saturated aqueous sodium bicarbonate solution. The product was extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and evaporated to give **1-3** as white solids. Compounds **1** and **2** were further purified by recrystallization from methanol and **3** by recrystallization from dichloromethane/*n*-pentane.

Compound **1** (70%), mp 206-207° (lit [12] 203.5-204.5) was prepared from **8** and **11**; ^{1}H nmr (deuteriochloroform): δ 3.90 (s, 4H), 4.19 (s, 4H), 5.25 (s, 4H), 6.86-6.98 (m, 8H), NH proton was not observed; ms: 384 (M^+).

Anal. Calcd. for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52. Found: C, 62.31; H, 5.22.

Compound **2** (68%), mp 167-168°, was prepared from **9** and **11**; ^{1}H nmr (deuteriochloroform): δ 3.55 (s, 4H), 3.87 (s, 4H), 4.16 (s, 4H), 5.23 (s, 4H), 6.86 (s, 8H), NH proton was not observed; ms: 428 (M^+).

Anal. Calcd. for $C_{22}H_{25}N_3O_6$: C, 61.81; H, 5.89. Found: C, 61.61; H, 5.85.

Compound **3** (81%), mp 198-200°, was prepared from **10** and **11**; ^{1}H nmr (deuteriochloroform): δ 1.27 (s, 18H), 3.89 (s, 4H), 4.17 (s, 4H), 5.23 (s, 4H), 6.79-7.04 (m, 6H), NH proton was not observed; ms: 496 (M^+).

Anal. Calcd. for $C_{28}H_{37}N_3O_5$: C, 67.85; H, 7.52. Found: C, 67.65; H, 7.79.

Preparation of Macrocycle **4**.

Bisphenol **8** (10 mmoles) in 50 ml of tetrahydrofuran was added dropwise to a suspension of 30 mmole (0.72 g) of sodium hydride in 50 ml of tetrahydrofuran at room temperature under nitrogen. After addition was completed, the reaction mixture was stirred for 30 minutes at room temperature and then heated under reflux. Then, 10 mmoles of 4-amino-3,5-*bis*(chloromethyl)-1,2,4-triazole (**12**) dissolved in 50 ml of tetrahydrofuran was added dropwise for 3 hours, and heating and stirring were continued for 24 hours. After the reaction mixture was cooled to room temperature, water was added to destroy unconsumed sodium hydride. Tetrahydrofuran was evaporated and the aqueous solution was extracted with chloroform. The chloroform layer was washed with water, dried over anhydrous magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel with dichloromethane/methanol (9:1) as eluant to give 1 g (25%) of white solid; mp 161-163°; ir (potassium bromide): 3356, 3290 cm^{-1} (NH); ^{1}H nmr (deuteriochloroform): δ 3.80-3.84 (m, 4H), 4.00-4.04 (m, 4H), 5.08 (s, 4H), 5.91 (s, 2H), 6.68-7.00 (m, 8H); ms: 399 (M^+).

Anal. Calcd. for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.56. Found: C, 60.08; H, 5.64.

General Procedure for the Preparation of Bistriazole-Containing Macrocycles **5** and **6**.

The appropriate catechol **13** or **14** (30 mmoles) in 100 ml of tetrahydrofuran was added dropwise to a suspension of 80 mmoles of sodium hydride in 60 ml of dry tetrahydrofuran at room temperature under nitrogen. After addition was completed, the reaction mixture was stirred for 30 minutes at room temperature and then heated under reflux. Then, 30 mmoles of 3,5-*bis*-(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole (**11**) dissolved in 70 ml of tetrahydrofuran was added dropwise for 3 hours, and heating and stirring were continued for 48 hours.

After the reaction mixture was cooled to room temperature, water was added to destroy unconsumed sodium hydride. Tetrahydrofuran was evaporated and an aqueous solution was extracted with dichloromethane. Dichloromethane was evaporated and the residue was purified by column chromatography on silica gel with dichloromethane and dichloromethane/methanol (96:4) as eluants. The tetrahydropyranyl-blocking group was removed from the crude product by stirring in about 200 ml of 15% methanolic hydrogen chloride overnight at room temperature. The methanol was evaporated and the residue was neutralized with saturated aqueous sodium bicarbonate solution. The product was extracted with chloroform, dried over anhydrous magnesium sulfate and evaporated to give **5** and **6** as solids.

Compound **5** was isolated in 20-24% yields after recrystallization from methanol, mp 240-242°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 5.14 (s, 8H), 6.70-7.18 (m, 8H); ms: 407 (M^+).

Anal. Calcd. for $C_{20}H_{18}N_6O_4$: C, 59.11; H, 4.46. Found: C, 59.07; H, 4.67.

Compound **6** was isolated in a 20% yield after column chromatography on silica gel with dichloromethane and dichloromethane/methanol (95:5) as eluants and recrystallization from dichloromethane-*n*-hexane. A white solid was obtained, mp 178-180°; ^{1}H nmr (deuteriochloroform): δ 1.24 (s, 18H), 5.15 (s, 8H), 6.91 (s, 6H), NH protons were not observed; ms: 519 (M^+) (anhydrous).

Anal. Calcd. for $C_{26}H_{34}N_6O_4 \cdot 0.25H_2O$: C, 64.29; H, 6.55. Found: C, 64.36; H, 6.61.

Preparation of Bistriazole-Containing Macrocycle **7**.

Trans-1,2-cyclohexanediol (1.97 g, 17 mmoles) in 120 ml of tetrahydrofuran was added dropwise to a suspension of 1.44 g (60 mmoles) of sodium hydride in 30 ml of dry tetrahydrofuran at room temperature under nitrogen. The mixture was stirred at room temperature for 30 minutes and at reflux temperature for 2-3 hours. Then, 17 mmoles (4.23 g) of **11** dissolved in 50 ml of

tetrahydrofuran were added dropwise for 3-4 hours. After the addition was completed, heating and stirring were continued for 48 hours. After cooling to room temperature, unconsumed sodium hydride was carefully destroyed with cold water. Tetrahydrofuran was evaporated and the water layer was extracted with dichloromethane. The dichloromethane layer was evaporated and the residue was chromatographed on silica gel with dichloromethane/methanol (90:10) as eluant. The tetrahydropyranyl-blocking group was removed as above. The product was purified by column chromatography on silica gel with dichloromethane/methanol (90:10) as eluant to give 0.66 g (18%) of **7** as a white solid, mp 258-260°; ^{1}H nmr (deuteriochloroform): δ 1.22 (s, 8H), 1.69 (s, 4H), 2.07 (s, 4H), 3.28 (s, 4H), 4.68-4.94 (m, 8H), 9.43 (broad s, 2H); ms: 419 (M^+).

Anal. Calcd. for $C_{20}H_{30}N_6O_4$: C, 57.41; H, 7.21. Found: C, 57.18; H, 7.15.

Solvent Extraction Procedure.

An aqueous sodium acetate buffer solution (10 ml, 0.01 *M*) containing the radioisotopes ^{203}Hg and ^{198}Au in trace quantities was mixed with equal volumes of the extraction solution (triazolocrown **6** at 1 x 10^{-4} *M* in chloroform) for the experiments. The *p*H adjustments were made by nitric acid and sodium hydroxide. An Orion Model 701 *p*H meter with an Orion Model 91 semi-microelectrode was used for the *p*H measurements. The samples were shaken vigorously in 30 ml high density polyethylene bottles at room temperature (25 ± 1°) using a Burrell Model 75 wrist action shaker until equilibrium was attained. After shaking, the mixture was allowed to stand for several minutes for phase separation. The distribution coefficients were determined by gamma counting, *i.e.* 5 ml each of the aqueous and organic phases were transferred to 2 dram polyvials from the system for radioactivity measurements. Lead (Pb^{2+}) concentrations were determined by atomic absorption spectrophotometry (AAS) using an IL VIDEO 12 AA Spectrophotometer.

Radioactivity Measurement.

The radioisotopes ^{203}Hg and ^{198}Au were produced in a 1-MW TRIGA nuclear reactor located near our campus at a steady flux of 6 x 10^{12} n cm^{-2} s^{-1}. The activities of ^{203}Hg($t_{1/2}$ = 46.8 d) and ^{198}Au($t_{1/2}$ = 2.7 d), at 279.2 and 411.8 keV gamma peaks, respectively, were counted using an Ortec Ge(Li) detector. The detector had a resolution of 2.3 keV at 1336-keV radiation from ^{60}Co and an efficiency of 15% relative to a 3 x 3 sodium iodide crystal.

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