Synthesis of Proton-Ionizable Acyclic, Macrocyclic and Macrobicyclic Compounds Containing One or Two Triazole Groups

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New acyclic, macrocyclic and macrobicyclic compounds containing one or two proton-ionizable triazole groups are prepared and characterized. The series includes six podands, a macrocycle with one triazole and one pyridine unit in the ring, a bis-triazolo macrocycle with four pentafluorobenzyl substitutents, and two bis(crown ethers) with a triazolo group connecting the two polyether rings. The solid-state structure and solubility in supercritical carbon dioxide are determined for the bis-triazolo macrocycle with pendant pentafluorobenzyl groups.

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Neutral crown ethers and cryptands are widely employed for complexation and selective extraction of alkali metal cations, alkaline earth metal cations and trivalent lanthanide ions [1]. Macrocyclic polyethers with proton-ionizable functional moieties are interesting and important complexing agents for metal ion extraction. Compared with a neutral crown ether extractant, a crown ether with a proton-ionizable group has the advantage that metal ion transport into the organic phase does not require concomitant transfer of an anion from the aqueous phase. Therefore, the extraction efficiency is independent of the identity of the aqueous phase anion. Also, the stability of the cation-macrocycle complex is increased when the macrocycle is ionized [2].

Two main strategies have evolved for incorporation of proton-ionizable functions into macrocyclic ligands, incorporation of i) proton-ionizable group(s) on the side arm(s) and ii) proton-ionizable group(s) as part of the macroring. Lariat ethers with pendant carboxylic acid [3], phosphonic acid monoethyl ester [4], hydroxamic acid [5], and, most recently, *N*-(X)sulfonylcarboxamide [6] groups as the proton-ionizable function on a pendant arm have been mostly developed in our laboratories. Also, Bradshaw and coworkers have reported a series of diaza-18-crown-6 compounds with pendant phenol and hydroxyquinoline units [7]. Macrocycles with 4-hydroxypyridine [8-13] and triazole [13-17] heterocyclic subunits within the macroring have been developed by Brandshaw, Izatt and their coworkers, de Mendoza and Torres and their coworkers [18-25] and others [26-28]. Podands [23-29] and polyaza macrobicyclic cryptands [24] with triazole subunits have been prepared, as well. Macrocycles with a single triazole unit in the macroring exhibit complexation selectivity with univalent metal ions, such as Ag^+ [30]; whereas macrocycles with two such triazole units form strong complexes with divalent metal ions [21,25]. Chiral dialkyl-substituted triazole-18-crown-6 ligands have been used for enantiomeric recognition of organic ammonium salts [31]. Acyclic ionophores containing a triazole group were found to be more efficient ligands than their macrocyclic analogues for extraction of chiral ammonium ions and their transport across supported liquid membranes due to faster dynamic complexation and decomplexation processes [23]. Macrocycles bearing proton-ionizable groups prepared up to 1990 are described in a review [32]. Also, References 1e-g contain portions that describe proton-ionizable ligands.

Previously, we reported the preparation of a series of macrocyclic compounds containing one or two proton-ionizable triazole subcyclic units [33]. These macrocycles were highly effective for the extraction of heavy metal ions, including lead(II), mercury(II), and gold(III), from aqueous solutions into chloroform. Macrocycles with two triazole subcyclic units were effective ligands for selective extraction of mercury(II) into supercritical carbon dioxide [34].

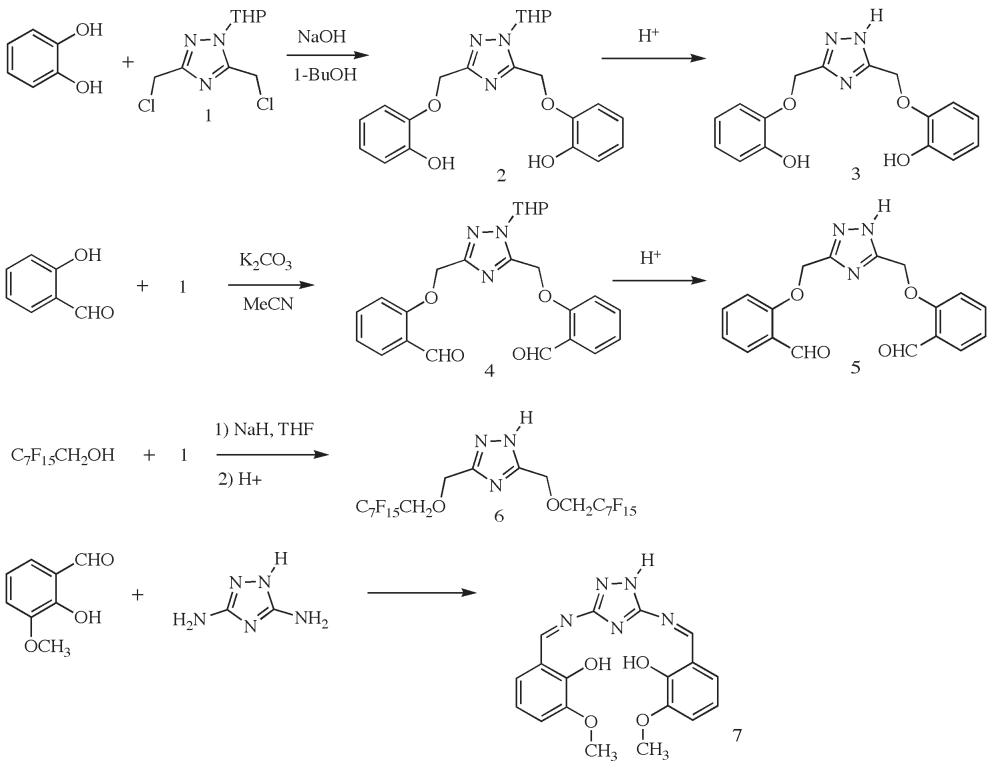
This work describes the synthesis of six triazolo podands, a pyridino-triazolo macrocycle, a bis-triazolo macrocycle with four pentafluorobenzyl groups on the ring nitrogen atoms and two bis(crown ethers) with a triazolo group as a bridge connecting two crown ether moieties. The solid-state structure for the bis-triazolo macrocycle and its solubility in supercritical carbon dioxide are reported, as well.

Results and Discussion.

Synthesis of New Triazolo-containing Compounds.

Podands **2**-**7** were synthesized as shown in Scheme 1. Podand **2** was prepared in non-maximized 25% yield by reaction of 3,5-bis(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4 triazole (**1**) with sodium hydroxide and excess catechol in 1-butanol. The tetrahydropyranyl-protecting group was removed from **2** by stirring with 15% methanolic hydrogen chloride solution for several hours to produce podand **3** in 75% yield.

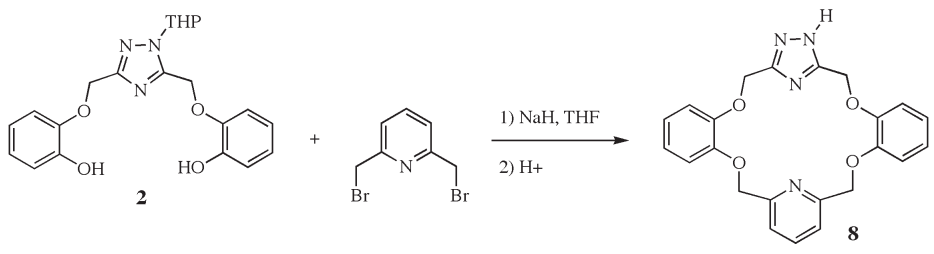
Scheme 1



Podand **4** was prepared in 95% yield by reaction of **1** with salicylaldyde and potassium carbonate in acetonitrile. The tetrahydropyranyl-protecting group was removed as above to provide podand **5** in 71% yield. Podand **6**, which contains two partially fluorinated alkyl groups, was prepared in 80% yield by reaction of **1** with 1-(1*H*,1*H*)perfluorooctanol and sodium hydride in tetrahydrofuran followed by acid hydrolysis of the tetrahydropyranyl-protecting group. Due to its high fluorine content and the strong metal ion complexation propensity of the triazole group, this ligand is expected to have applications in metal ion separations involving a fluorous phase [35] or supercritical carbon dioxide [36]. The Schiff-base podand **7** was prepared in 70% yield by reaction of 3,5-diamino-1,2,4-triazole (guanazole) with 2-hydroxy-3-methoxy-benzaldehyde (*o*-vanillin) in ethanol. In addition to a proton-ionizable triazolo unit, podands **3** and **7** contain two proton-ionizable phenolic groups.

Podands **2**, **4**, and **5** are potential intermediates for the formation of the other new triazole-containing compounds. The synthesis of such a compound that contains one pyridino and one triazolo group is shown in Scheme 2. Thus, reaction of *N*-tetrahydropyranyl-protected podand **2** with 2,6-bis(bromomethyl)pyridine and sodium hydride in tetrahydrofuran followed by acid hydrolysis of the tetrahydropyranyl-protecting group produced macrocycle **8** in 55% yield. In a similar fashion, other macrocyclic compounds containing different subcyclic units could be prepared.

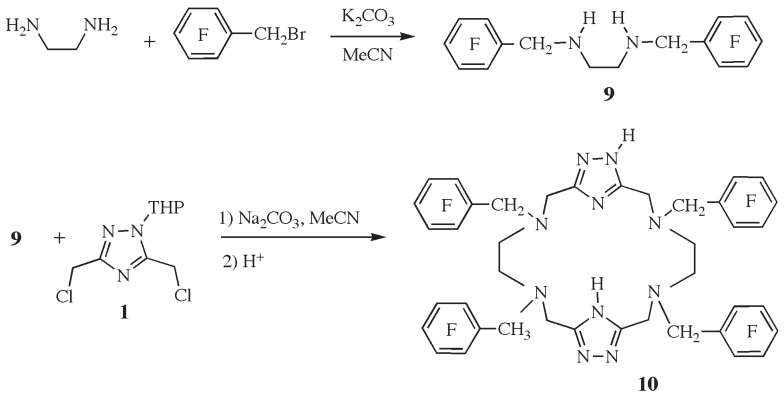
Scheme 2



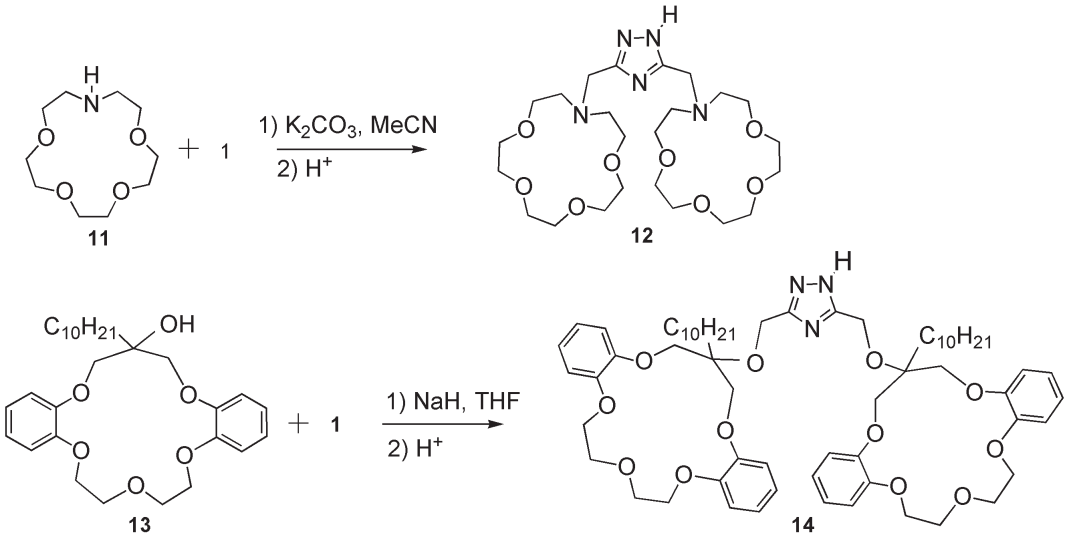
The synthetic route to *N*,*N*',*N*'',*N*'''-tetra(pentafluorobenzyl) tetraazabistriazolo-18-crown-6 (**10**) is presented in Scheme 3. First, *N*,*N*'-di(pentafluorobenzyl) 1,2-ethylenediamine (**9**) was prepared in 72% yield by reaction of pentafluorobenzyl bromide, 1,2-ethylenediamine, and potassium carbonate in acetonitrile. Subsequently, reaction of **9** with **1** and sodium carbonate in acetonitrile followed by acid hydrolysis of the tetrahydropyranyl-protecting group provided macrocycle **10** in 5% overall yield from the 2 + 2 cyclization reaction. (Low yields for such 2 + 2 cyclization reactions have been reported previously by others [13].) The solid-state structure of **10•1.5Methanol** is described in the next section. Macrocyclic ligands with one or more fluorine-containing side arms have potential applications in metal ion separations involving a fluorous phase [35] or supercritical carbon dioxide [36]. Therefore, the solubility of **10** was measured in supercritical carbon dioxide. At 60 °C and 300 atmospheres pressure, the solubility of **10** in neat supercritical carbon dioxide was 0.86 X 10^{-4} *M* with an estimated error of ±20% of the stated value.

Bis(crown ethers) are macrobicyclic polyethers with two cyclic polyether units connected by a spacer. These ligands can have higher cation-binding properties than the single macrocycles due to their ability to form intramolecular sandwich complexes in which the adjacent crown ether units cooperate [37-42]. As a result of sandwich complex formation, they may exhibit remarkable selectivity toward some metal ions in crown ether-based, ion-selective electrodes [38]. Zavada and coworkers prepared a series of bis(monoazacrown ethers) and studied the effects of the spacer length and ring size on the stability and selectivity in their formation of sandwich complexes with alkali metal cations [40]. They noted that not only the macrocyclic polyether ring size, but also the spacer length, had a remarkable influence on the ligand selectivities toward alkali metal cations [40a].

Scheme 3



Scheme 4



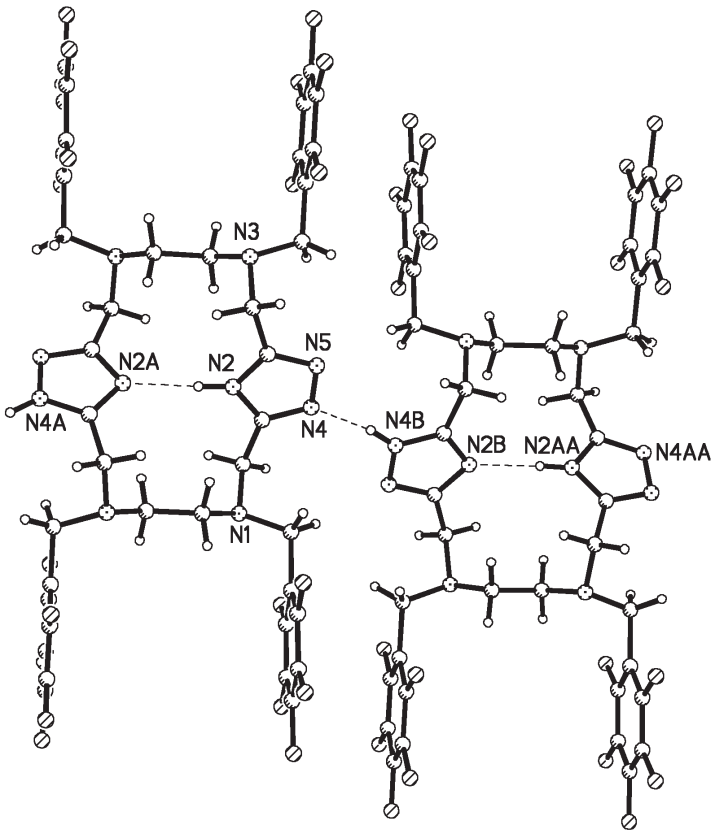


Figure 1. Ball-and-stick model and numbering scheme for solid-state structure of macrocycle **10•1.5Methanol**.

Unlike most of the bis(crown ethers) reported to date, bis(crown ethers) **12** and **14** (Scheme 4) utilized a proton-ionizable bridging unit to connect the two crown ether moities. This arrangement may lead to stronger complex formation of these bicyclic ligands with metal ions. Bis(monoazacrown ether) **12** was prepared in 70% yield by reaction of **1** with aza-15-crown-5 (**11**) and potassium carbonate in acetonitrile followed by an acid hydrolysis to remove the tetrahydropyranyl-protecting group. Reaction of **1** with *sym*-(decyl)(hydroxy)dibenzo-16-crown-5 (**13**) and sodium hydride in tetrahydrofuran followed by acid hydrolysis to remove the tetrahydropyranyl-protecting group provided an 81% yield of bis(crown ether) **14**. The scope of these reactions could be broadened to include the preparation of new triazole-containing bis(crown ethers) starting from a variety of azacrown ethers and lariat ether alcohols.

Identities of these new acyclic, macrocyclic and macrobicyclic triazole-containing compounds were confirmed by ir, nmr and mass spectroscopic data, combustion analyses and, in the case of **10**, a crystal-structure determination.

Solid-state Structure of Bis-triazolo Macrocycle **10**.

A suitable crystal of **10•1.5Methanol** was grown from deuteriochloroform-methanol and its solid-state structure was determined by X-ray diffraction. Details of the structure determination and refinement are given in the Experimental section.

The molecular numbering scheme and solid-state structure are shown in Figure 1. The hydrogen atoms on N2 and N4 are disordered at 50%. These hydrogen atoms are responsible for a series of inter- and intramolecular hydrogen bonds, which result in a hydrogen-bonded linear chain of macrocycles along the ac diagonal (unit cell plot presented *vide supra*). The fluorinated aromatic rings, although aligned in a parallel fashion, neither π-stack nor interdigitate (Figure 2). Instead the linear hydrogen bonded chains of macrocycles align to create a F-rich region with F•••F contacts as close as 2.797 Å (Figure 3). This seems to be the main driver in the crystal packing and may even be the source of the twist in the macrocycle itself. The packing of the molecules to form linear hydrogen-bonded chains of macrocycles and tightly packed F-rich regions creates large channels in the unit cell in which disordered solvent molecules reside (Figure 3).

Cyclic polyether compounds with an unsubstituted triazole unit have a tautomerizable NH proton that may be located on any of the three triazole nitrogen atoms. It may be bonded to one of the nitrogen atoms oriented outside the

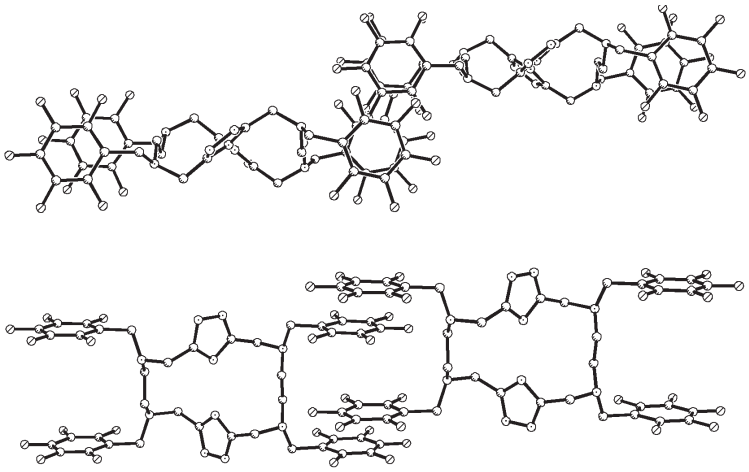


Figure 2. Ball-and-stick model for solid-state structure of macrocycle **10•1.5Methanol** showing positions of *N*-pentafluorobenzyl groups in adjacent molecules.

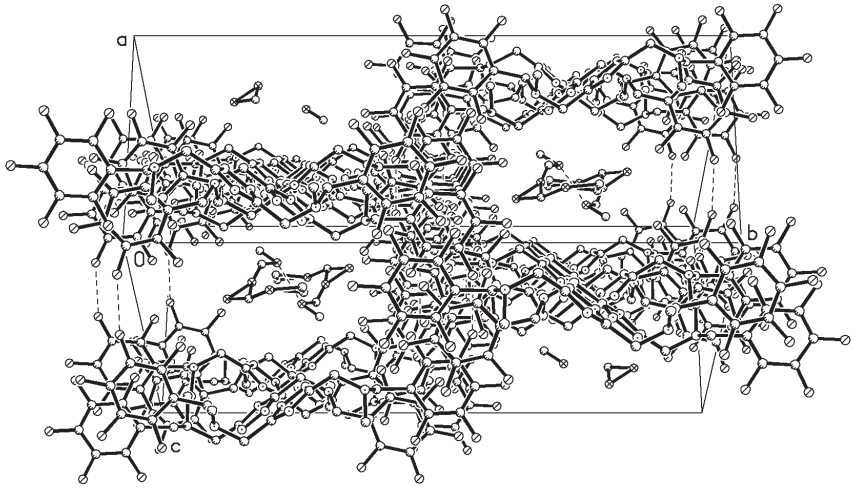


Figure 3. Unit cell for solid-state structure of macrocycle **10•1.5Methanol** showing large channels in which the disordered solvent molecules reside.

polyether ring or to the nitrogen atom that is common to both rings. As mentioned previously, this NH proton is ionizable. The location of this hydrogen atom will play an important role in the complexation properties of these ligands. The crystal structures for several polyether macrocycles with such a NH triazole group have been determined [15-17]. In macrocycles that are relatively rigid near the triazole ring, the NH proton is located inside the cavity, linked to a water molecule [15]; while in more flexible macrocycles, it is outside the cavity [16,17]. In the case of macrocycle **10**, the NH proton of one triazole group is located inside the cavity, while the NH proton of the second triazole group projects outside the cavity. To the best of our knowledge, this is the first crystal-structure determination for a macrocycle that contains two triazole subcyclic units.

EXPERIMENTAL

Reagents and solvents were purchased from commercial sources and used without further purification, unless otherwise noted. Tetrahydrofuran was distilled from sodium under nitrogen with benzophenone ketyl as indicator. Acetonitrile was distilled from calcium hydride. Starting materials **1** [16,43,44], **11** [45], and **13** [5] were prepared by reported procedures. Infrared (ir) spectra were recorded with a Perkin Elmer Model 1600 FT-IR spectrophotometer. Proton magnetic resonance (nmr) spectra were obtained with a Bruker AF-200 (200 MHz) spectrometer. Fluorine magnetic resonance spectra were recorded at 282.4 MHz with a Bruker AF-300 spectrometer. Mass spectra were obtained with a VG Micromass 70/70 HS mass spectrometer. Elemental analyses were performed by Desert Analytics Laboratory of Tucson, Arizona.

Table 1

Crystal Data and Structure Refinement for **10•1.5Methanol**

Formula	$C_{40}H_{26}F_{20}N_{10}$•1.5(CH_4O)
Formula weight	1074.77
Temperature, K	173(2)
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	
a, Å	10.5981(4)
b, Å	28.3821(13)
c, Å	17.5793(8)
b, deg	99.353(1)
Volume	5217.5(4)
Z	4
D_{calc}, Mg/m^3	1.368
m, mm^{-1}	0.136
F(000)	2172
θ range, deg	1.85-26.36
Reflections collected	14872
Independent/observed refls.	5302 (Rint = 0.0799) 3045 ([I>2s(I)])
Data/restraints/parameters	5302/0/347
Goodness-of-fit on F^2	1.132
SHELX-93 weight parameters	0.1330, 20.9023
Final R indices [I>2s(I)])	
R1	0.1060
wR2	0.2642
Final R indices (all data)	
R1	0.1735
wR2	0.3120

3.5-Bis[2-(*o*-hydroxyphenoxy)-1-(tetrahydro-2-pyranyl)]-1,2,4-triazole (**2**).

Under nitrogen, 19.80 g (180 mmol) of catechol was dissolved in 200 mL of 1-butanol and 2.60 g (65 mmol) of sodium hydroxide pellets was added. The stirred solution was heated to reflux and 7.47 g (30 mmol) of 3,5-bis(chloromethyl)-1-(tetrahydro-2-pyranyl)-1*H*-1,2,4-triazole (**1**) in 100 ml of 1-butanol was added dropwise over a 3-h period. The reaction mixture was refluxed for 48 h, allowed to cool to room temperature and evaporated *in vacuo*. The residue was dissolved in dichloromethane and the solution was washed with water, dried over sodium sulfate and evaporated *in vacuo* to give the crude product, which was chromatographed on silica gel with dichlormethane and then dichloromethane-methanol (19:1) as eluents collecting only the purest fractions to afford a 25% yield of tan solid with mp 105-107°. ir (deposit from dichloromethane solution on a sodium chloride plate): 3330 (OH), 1207, 1111 (C-O) cm^{-1}. ^1H nmr (deuteriochlroroform): δ 1.57 (s, 3H), 1.94-2.17 (m, 3H), 3.51-3.64 (m, 1H), 3.83-3.91 (m, 1H), 5.12 (s, 2H), 5.24 (s, 2H), 5.39-5.45 (m, 1H), 6.77-7.00 (m, 8H), 8.06 (br s, 1H), 9.23 (br s, 1H). MS: 397 (M^+).

Anal. Calcd for $C_{21}H_{23}N_3O_5$: C, 63.46; H, 5.83; N, 10.57. Found: C, 63.79; H, 6.06; N, 10.60.

3,5-Bis[2-(*o*-hydroxyphenoxy)]-1,2,4-triazole (**3**).

The tetrahydropyranyl-protecting group was removed from **2** (1.99 g, 5.0 mmol) by stirring in 50 mL of 15% methanolic hydrochloric acid for several hours at room temperature. The methanol was evaporated *in vacuo* and the residue was neutralized with saturated aqueous sodium bicarbonate. Extraction with dichloromethane was attempted. However, a solid formed at the interface of the aqueous and organic layers. The solid was collected by filtration, washed with water, air dried and recrystallized from ethanol to give a 1.24 g (75%) of white solid with mp 200-202°. ir (potassium bromide): 3365 (NH, OH), 1275, 1210, 1112 (C-O) cm^{-1}. ^1H nmr (deuteriodimethyl sulfoxide): δ 5.18 (s, 4H), 6.69-7.09 (m, 8H), 7.69 (br s, 2H), (NH proton was not observed). MS: 313 (M^+) (anhydrous).

Anal. Calcd for $C_{16}H_{15}N_3O_4$•H_2O: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.63; H, 5.04; N, 12.61.

3,5-Bis[2-(*o*-formylphenoxy)-1-(tetrahydro-2-pyranyl)]-1,2,4-triazole (**4**).

Under nitrogen, a mixture of salicylaldehyde (2.44 g, 20.0 mmol) and 2.76 g (20.0 mmol) of potassium carbonate in 50 mL of acetonitrile was refluxed for 30 min. Then, 2.50 g (10.0 mmol) of **1** in 30 mL of acetonitrile was added dropwise over a 1-h period. The mixture was refluxed for 24 h, allowed to cool to room temperature and filtered. The solid was washed with dichlormethane. The combined filtrate and washings were evaporated *in vacuo* and the residue was dissolved in dichloromethane. The solution was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel with dichlormethane and then dichloromethane-ethyl acetate (9:1) as eluents to give 4.00 g (95%) of **4** as a white solid with mp 102-104°. ir (deposit from dichloromethane solution on a sodium chloride plate): 1686 (C=O), 1219, 1162 (C-O) cm^{-1}. ^1H nmr (deuteriochloroform): δ 1.60-1.74 (m, 3H), 1.80-2.12 (m, 2H), 2.23-2.41 (m, 1H), 3.57-3.69 (m, 1H), 4.02-4.13 (m, 1H), 5.44 (s, 2H), 5.60 (s, 2H), 5.63-5.69 (m, 1H), 7.01-7.28 (m, 4H), 7.50-7.60 (m, 2H), 7.81-7.87 (m, 2H), 10.44 (s, 1H), 10.52 (s, 1H).

Anal. Calcd for $C_{23}H_{23}N_3O_5$: C, 65.55; H, 5.50; N, 9.97. Found: C, 65.36; H, 5.60; N, 10.01.

3,5-Bis[2-(*o*-formylphpenoxy)]-1,2,4 triazole (**5**).

The tetrahydropyranyl-protecting group was removed from **4** (3.69 g, 8.75 mmol) as described above for the preparation of **3**. The residue was chromatographed on silica gel with dichloromethane and then dichloromethane-ethyl acetate (9:1) as eluents to give 2.10 g (71%) of **5** as a white solid with mp 140-142°. ir (deposit from dichloromethane solution on a sodium chloride plate): 3315 (NH), 1686 (C=O), 1239, 1163 (C-O) cm^{-1}. ^1H nmr (deuteriochloroform): δ 5.33 (s, 4H), 7.01-7.21 (m, 4H), 7.41-7.56 (m, 2H), 7.76-7.81 (m, 2H), 10.34 (s, 2H), (NH was not observed); MS: 337 (M^+).

Anal. Calcd for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46. Found: C, 63.96; H, 4.68; N, 12.30.

3,5-Bis[methyloxy-1(1*H*,1*H*-perfluorooctyl)]-1,2,4-triazole (**6**).

To sodium hydride (0.86 g, 36 mmol) and 30 mL of tetrahydrofuran under nitrogen, a solution of 4.00 g (10.0 mmol) of 1-(1*H*,1*H*)-perfluorooctanol in 30 mL of tetrahydrofuran was added dropwise over a 30-min period. The mixture was brought to reflux and a solution of 1.25 g (5.0 mmol) of **1** in 30 mL of tetrahydrofuran was added dropwise over a 1-h period. The reaction mixture was refluxed for 24 h and allowed to cool to room temperature. The excess of sodium hydride was destroyed by careful addition of water. The tetrahydrofuran was evaporated *in vacuo* and 50 ml of water was added. The mixture was extracted with dichloromethane

and the organic layer was evaporated *in vacuo*. The tetrahydropyranyl-protecting group was removed from the crude product by stirring in 75 mL of 15% methanolic hydrochloric acid at room temperature for several hours. The methanol was evaporated *in vacuo* and the residue was neutralized with saturated aqueous sodium bicarbonate. After addition of dichloromethane, the organic layer was separated, dried over sodium sulfate and evaporated *in vacuo* to give 3.57 g (80%) of **6** as a white solid with mp 62-64°. ir (deposit from dichloromethane solution on a sodium chloride plate): 3315 (NH), 1144 (C-O) cm^{-1}. ^1H nmr (deuteriochloroform): δ 4.02-4.16 (t, 4H, J = 13.8 Hz), 4.67 (s, 2H), 4.86 (s, 2H), (NH proton was not observed). MS: 894 (M^+).

Anal. Calcd for $C_{20}H_9F_{30}N_3O_2$: C, 26.89; H, 1.02. Found: C, 27.10; H, 1.13.

3,5-Bis(aldimino-2-hydroxy-3-methoxyphenyl)-1,2,4-triazole (**7**).

A solution of 0.20 g (2.0 mmol) of 3,5-diamino-1,2,4-triazole and 0.61 g (4.0 mmol) of 2-hydroxy-3-methoxybenzaldehyde in 50 mL of ethanol was stirred at 40-45 °C for 24 h. Upon cooling to room temperature, a yellow solid formed. The solid was filtered and recrystallized from ethanol to give 0.51 g (70%) of **7** as a yellow solid with mp 260-262°. ir (deposit from dichloromethane solution on a sodium chloride plate): 3291 (NH, OH), 1611 (C=N), 1257, 1223, 1106 (C-O) cm^{-1}. ^1H nmr (deuteriodimethyl sulfoxide): δ 3.36 (s, 3H), 3.85 (s, 3H), 6.92-6.97 (t, 2H, J = 9 Hz), 7.19-7.22 (d, 2H, J = 9 Hz), 7.44-7.47 (d, 2H, J = 9 Hz), 9.49 (s, 2H), 14.21 (s, 2H), (NH proton was not observed).

Anal. Calcd for $C_{18}H_{17}N_5O_4$: C, 58.85; H, 4.66; N, 19.06. Found: C, 58.92; H, 4.83; N, 18.84.

Macrocycle **8**.

Bisphenol **2** (1.23 g, 3.5 mmol) in 40 ml of tetrahydrofuran was added dropwise to a stirred suspension of 0.72 g (30.0 mol) of sodium hydride in 50 mL of tetrahydrofuran at room temperature under nitrogen. The mixture was stirred at room temperature for 30 min and then at reflux for 10-15 min. Then 0.87 g (3.5 mmol) of 2,6-bis(bromomethyl)pyridine in 40 mL of tetrahydrofuran was added dropwise over a 3-h period. Reflux with stirring was continued for 24 h, after which the mixture was allowed to cool to room temperature. The unconsumed sodium hydride was carefully destroyed by addition of cold water. The tetrahydrofuran was evaporated *in vacuo* and the aqueous layer was extracted with dichloromethane. The organic layer was evaporated *in vacuo* and the residue was chromatographed on silica gel with dichloromethane-ethyl acetate (9:1) as eluent. The tetrahydropyranyl-protecting group was removed as described previously. The crude product was chromatographed on silica gel with dichloromethane-ethyl acetate (9:1) as eluent to give 0.80 g (55%) of **8** as a white solid with mp 88-90°. ir (deposit from dichloromethane solution on a sodium chloride plate): 3328 (NH), 1253, 1123 (C-O) cm^{-1}. ^1H nmr (deuteriochlrorform): δ 5.15-5.21 (d, 8H, J = 11.8 Hz), 6.95-7.08 (m, 8H), 7.34-7.38 (d, 2H, J = 7.8 Hz), 7.69-7.77 (q, 1H, J = 7.6 Hz), (NH proton was not observed). MS: 417 (M^+).

Anal. Calcd for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45. Found: C, 66.48; H, 5.08; N, 13.12.

N,*N*′-Dipentafluorobenzyl 1,2-ethylenediamine (**9**).

To a cooled mixture (ice bath) of 1,2-ethylenediamine (0.42 g, 7.0 mmol), 0.96 g (7.0 mmol) of potassium carbonate and 40 mL of acetonitrile, 3.65 g (14.0 mmol) of pentafluorobenzyl bromide was added dropwise over a 30-min period. The mixture was stirred at room temperature for 24 h and filtered. The filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel with dichloromethane and then dichloromethane-methanol (19:1) as eluents to give 2.10 g (72%) of **9** as a white solid with mp 38-40°. ir (deposit from dichloromethane solution on a sodium chloride plate): 3327 (NH) cm^{-1}. ^1H nmr (deuteriochloroform): δ 1.59 (s, 2H), 2.66 (s, 4H), 3.87 (s, 4H). ^{19}F nmr (deuteriochloroform): δ -144.49 to –144.66 (m, 4F), -155.72 to -155.95 (t, 2F, J = 20.9Hz), -162.21 to -162.49 (m, 4F).

Anal. Calcd for $C_{16}H_{10}F_{10}N_2$: C, 45.73; H, 2.40; N, 6.66. Found: C, 45.88; H, 2.38; N, 6.66.

N,*N*′,*N*″,*N*‴-Tetra(pentafluorobenzyl) tetraazabistriazolo-18-crown-6 (**10**).

A mixture of *N*,*N*′-di(pentafluorobenzyl) 1,2-ethylenediamine (**9**) (2.10 g, 5.0 mmol) and 10.00 g of sodium carbonate in 150 mL of acetonitrile was refluxed for 30 min. Then, 1.25 g (5.0 mmole) of **1** dissolved in 30 ml of acetonitrile was added dropwise over a 3-h period. The mixture was stirred under reflux for 48 h, allowed to cool to room temperature, and filtered. The filtrate was evaporated *in vacuo* and the residue was chromatographed on silica gel with dichloromethane and then dichloromethane-methanol (19:1) as eluents. The tetrahydropyranyl-protecting groups were removed as described above. The crude product was chromatographed on silica gel with dichloromethane-methanol (19:1) as eluent followed by recrystallization from dichloromethane to produce 0.27 g (5%) of **10** as a white solid with mp 95-97°. ir (deposit from dichloromethane solution on a sodium chloride plate): 3320 (NH) cm^{-1}. ^1H nmr (deuteriochloroform): δ 2.66 (s, 8H), 3.61 (s, 8H), 3.83 (s, 8H), (NH protons were not observed). ^{19}F nmr (deuteriochloroform): δ -143.36 to -143.53 (m, 8F), -154.27 to -154.49 (t, 4F, J = 20.9 Hz), -161.94 to -162.61 (m, 8F); MS: 1027 (M^+).

Anal. Calcd for $C_{40}H_{26}F_{20}N_{10}$: C, 46.79; H, 2.55; N, 13.64. Found: C, 46.57; H, 2.58; N, 13.65.

3,5-Bis(methyl-aza-15-crown-5)-1,2,4-triazole (**12**).

A mixture of aza-15-crown-5 (0.87 g, 4.0 mmol), 0.50 g (2.0 mmol) of **1** and 0.55 g (4.0 mmol) of potassium carbonate in 20 mL of acetonitrile was stirred under reflux for 12 h, allowed to cool to room temperature and filtered. The filtrate was evaporated *in vacuo* and the residue was dissolved in dichloromethane. The organic solution was washed with water and evaporated *in vacuo*. The tetrahydropyranyl-protecting group was removed as described above. The crude product was chromatographed on silica gel with dichloromethane and then dichloromethane-methanol (9:1) as eluents to give 0.74 g (70%) of **12** as an oil. ir (deposit from dichloromethane solution on a sodium chloride plate): 3280 (NH), 1249, 1124 (C-O) cm^{-1}. ^1H nmr (deuteriochloroform): δ 2.82-2.89 (m, 8H), 3.52-3.90 (m, 32H), 4.01 (s, 4H), (NH proton was not observed).

Anal. Calcd for $C_{24}H_{45}N_5O_8$: C, 54.22; H, 8.53; N, 13.17. Found: C, 53.96; H, 8.57; N, 12.98.

3,5-Bis[oxymethyl-*sym*-(decyl)dibenzo-16-crown-5]-1,2,4-triazole (**14**).

To a mixture of sodium hydride (0.43 g, 18 mmol) in 20 mL of tetrahydrofuran under nitrogen, a solution of 1.46 g (3.0 mmol) of *sym*-(decyl)(hydroxy)dibenzo-16-crown-5 (**13**) in 20 mL of

tetrahydrofuran was added dropwise over a 15-min period. The mixture was brought to reflux and a solution of 0.38 g (1.5 mmol) of **1** in 10 ml of tetrahydrofuran was added dropwise over a 15-min period. The mixture was stirred under reflux for 15 h and allowed to cool to room temperature. The excess of sodium hydride was destroyed by careful addition of water and the tetrahydrofuran was evaporated *in vacuo.* The aqueous residue was extracted with dichloro-methane. The organic layer was evaporated *in vacuo* and the residue was stirred with 30 ml of 15% methanolic hydrogen chloride to remove the tetrahydropyranyl-protecting group as described above. The crude product was chromatographed on silica gel with dichloromethane and then dichloromethane-ethyl acetate (9:1) as eluents to produce 1.30 g (81%) of **14** as a white solid with mp 49-51°. ir (deposit from dichloromethane solution on a sodium chlroide plate): 3328 (NH), 1256, 1123 (C-O) cm^{-1}. ^1H nmr (deuteriochloroform): δ 0.88-0.91 (t, 6H, J = 3.2 Hz), 1.26 (s, 32H), 1.87-2.03 (m, 4H), 3.75-3.95 (m, 8H), 4.08-4.14 (m, 12H), 4.44-4.49 (d, 4H, J = 10 Hz), 5.14 (s, 4H), 6.74-6.97 (m, 16H), (NH proton was not observed).

Anal. Calcd for $C_{62}H_{87}N_3O_{12}$: C, 69.83; H, 8.22; N, 3.94. Found: C, 69.88; H, 8.27; N, 4.00.

Supercritical Carbon Dioxide Solubility Determination for Macrocycle **10**.

The supercritical carbon dioxide solubility measurement was performed with an ISCO (Lincoln, NE) supercritical fluid extractor (SFE) unit. An excess amount of **10** was placed inside a glass tube and the ends were plugged with a small amount of glass wool. The weight was determined on a four decimal digital balance and the tube was placed into a 10-mL cell in the SFE unit and held at 60° and 300 atm for 20 min. The inlet valve was then closed and the system was depressurized through a fused silica restrictor. The analyte was collected in a glass vial containing 10 mL of chloroform. After depressurizing the system, the tube was removed from the extraction cell and reweighed on the same balance. The empty cell was reinstalled into the oven and flushed with supercritical carbon dioxide for 20 min to remove any residual solute that remained in the system. The solubility was determined by taking the weight difference and the known volume of the cell.

X-ray Data Collection, Structure Determination and Refinement for **10•1.5Methanol**.

Suitable crystals of **10•1.5Methanol** were grown from deuteriochloroform and methanol. The transparent single crystal of **10•1.5Methanol** was mounted on a fiber and transferred to the goniometer. The crystal was cooled to -100 °C during data collection with a stream of cold nitrogen gas. The choice of the centric alternative for **10•1.5Methanol** was confirmed by subsequent solution and successful refinement of the structure, despite the presence of disordered solvent. A summary of data collection parameters is given in Table 1 [46].

The hydrogen atoms for the macrocycle were placed in calculated positions and allowed to ride on the bonded atom with B = 1.2*Ueqv. The macrocycle sits on a two-fold axis and as a result the hydrogen atoms bonded to N2 (internal) and N4 (external) are disordered at 50%. Thus one hydrogen atom at any one position in the unit cell may reside on N2 and is hydrogen bonded in an intramolecular fashion to N2 related by the two-fold axis. Similarly, the hydrogen atom bonded to N4 may reside on one N4 position in the macrocycle and is hydrogen bonded in an intermolecular fashion to N4 on another macrocycle related by a symmetry element.

Refinement of non-hydrogen atoms was carried out with anisotropic temperature factors (except for the disordered solvent). After location of all of the macrocycle atomic positions, it was evident that disordered solvent existed in large cavities within the unit cell. The locations and positions of the solvent peaks suggested the presence of methanol (one of the crystallization solvents). No evidence for the other crystallization solvent (deuteriochloroform) was observed.

The diffuse peaks associated with the solvent molecules and the large cavities within the unit cell, suggest that the solvent is only very weakly entrapped and may indeed be easily lost. This may account for the difficulty in obtaining suitable single crystals and the high R values obtained in the final refinement. Despite these difficulties, the overall structure and packing are quite clear.

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REFERENCES AND NOTES

[1] For recent reviews: [a] G. W. Gokel, *Chem. Soc. Rev.*, 39 (1992); [b] Y. Inoue and G. W. Gokel, Cation Binding by Macrocycles, Marcel Dekker, New York, 1990; [c] R. D. Hancock and A. E. Martell, *Chem. Rev.*, **89**, 1875 (1989); [d] R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, *Chem. Rev.*, **91**, 1721 (1991); [e] R. M. Izatt, J. S. Bradshaw, K. Pawlak, R. L. Bruening and B. J. Tarbet, *Chem. Rev.*, **92**, 1261 (1992); [f] R. M. Izatt, K. Pawlak and J. S. Bradshaw, *Chem. Rev.*. **95**, 2529 (1995); [g] J. S. Bradshaw, R. M. Izatt, A. V. Bordunov, C. Y. Zhu and J. K. Hathaway, Comprehensive Supramolecular Chemistry, Vol. **1**, G. W. Gokel, ed., Pergamon, New York, 1996, p 35.

[2] R. A. Bartsch, W. A. Charewicz, S. I. Kang and W. Walkowiak, Liquid Membranes: Theory and Applications, ACS Symposium Series 347, R. D. Noble and J. D. Way, eds., American Chemical Society, Washington, DC, 1987, p. 86.

[3] R. A. Bartsch, C. L. Cowey, S. Elshani, M. J. Goo, V. J. Huber, S. N. Ivy, R. J. Johnson, J. S. Kim, E. Luboch, J. A. McDonough, M. J. Pugia, B. Son and Q. Zhao, *J. Heterocyclic Chem.*, **38**, 311 (2001) and references cited therein.

[4a] M. J. Pugia, G. Ndip, H. K. Lee, I.-W. Yang, R. A. Bartsch, *Anal. Chem*., **58**, 2723 (1986), [b] S. Elshani, M. X. B. Xia, C. M. Wai, N. R. Natale, R. W. Widner, R. A. Bartsch, *J. Heterocyclic Chem*., **35**, 1381 (1998).

[5] S. Elshani, R. Noriuki, C. M. Wai, N. R. Natale, R. A. Bartsch, *J. Heterocyclic Chem*. **35**, 875 (1998).

[6] V. J. Huber, S. N. Ivy, J. Lu and R. A. Bartsch, *J. Chem. Soc., Chem. Commun*., 1499 **(**1997).

[7a] J. S. Bradshaw, *J. Inclusion Phenom. Mol. Recogn. Chem*., **29**, 221 (1997) and references cited therein; [b] J. S. Bradshaw and R. M. Izatt, *Acc. Chem. Res.*, **30**, 338 (1997) and references cited therein.

[8] J. S. Bradshaw, N. O. Spencer, G. R. Hansen, R. M. Izatt and

J. J. Christensen, *J. Heterocyclic Chem.*, **20**, 353 (1983).

[9] Y. Nakatsuji, J. S. Bradshaw, P. Tse, G. Arena, B. E. Wilson, N. K. Dalley and R. M. Izatt, *J. Chem. Soc., Chem. Commun*., 749 (1985).

[10] R. M. Izatt, G. C. LindH, G. A. Clark, J. S. Bradshaw, Y. Nakatsuji, J. D. Lamb and J. J. Christensen, *J. Chem. Soc., Chem. Commun*., 1676 (1985).

[11] J. S. Bradshaw, M. L. Colter, Y. Nakatsuji, N. O. Spencer, M. F. Brown, R. M. Izatt, G. Arena, P. Tse, B. E. Wilson, J. D. Lamb and N. K. Dalley, *J. Org. Chem*., **50**, 4865 (1985).

[12] J. S. Bradshaw, Y. Nakatsuji, P. Huszthy, B. E. Wilson, N. K. Dalley and R. M. Izatt, *J. Heterocyclic Chem*., **23**, 353 (1986).

[13] J. S. Bradshaw, K. E. Krakowiak, P. Huszthy and R. M. Izatt, *J. Heterocyclic Chem*., **28**, 773 (1991).

[14] J. S. Bradshaw, B. A. Jones, R. B. Nielsen, N. O. Spencer and P. K. Thompson, *J. Heterocyclic Chem.*, **20**, 957 (1983).

[15] J. S. Bradshaw, D. A. Chamberlin, P. E. Harrison, B. E. Wilson, G. Arena, N. K. Dalley, J. D. Lamb, R. M. Izatt, F. G. Morin and D. M. Grant, *J. Org. Chem*., **50**, 3065 (1985).

[16] J. S. Bradshaw, R. B. Nielsen, P. K. Tse, G. Arena, B. E. Wilson, N. K. Dalley, J. D. Lamb, J. J. Christensen and R. M. Izatt, *J. Heterocyclic Chem*., **23**, 361 (1986).

[17] J. S. Bradshaw, C. W. McDaniel, B. D. Skidmore, R. B. Nielsen, B. E. Wilson, N. K. Dalley and R. M. Izatt, *J. Heterocyclic Chem*., **24**, 1085 (1987).

[18] J. M. Alonso, M. R. Martin, J. de Mendoza, T. Torres and J. Elguero, *Heterocycles* **26**, 989 (1987).

[19] F. Fernandez-Lazaro, J. de Mendoza, O. Mo, S. Rodriguez-Morgade, T. Torres and M. Yanez, *J. Chem. Soc., Perkin Trans. II*, 797 (1989).

[20] J. de Mendoza, J. M. Ontaria, M. C. Ortega and T. Torres, *Synthesis*, 398 (1992).

[21] J. A. Duro, J. M. Ontaria, A. Sastre, W. Schafer and T. Torres, *J. Chem. Soc., Dalton Trans*., 2595 (1993).

[22] M. V. Martinez-Diaz, J. de Mendoza and T. Torres, *Synthesis*, 1091 (1994).

[23] M. V. Martinez-Diaz, J. de Mendoza and T. Torres, *Tetrahedron Lett.*, **35**, 7669 (1994).

[24] B. Cabezon, M. Irurzun, T. Torres and P. Vazquez, *Tetrahedron Lett.*, **39**, 1067 (1998).

[25] M. Nicolau, S. Esperanza and T. Torres, *J. Org. Chem*., **67**, 1392 (2002).

[26] G. Tarrago, C. Marzin, O. Najimi and V. Pellegrin, *J. Org. Chem*., **55**, 420 (1990).

[27] A. H. M. Elwahy and A. A. Abbas, *Tetrahedron*, **56**, 885 (2000).

[28] A. H. M. Elwahy, A. A. Abbas and R. M. Kassab, *Synthesis*, 260 (2002).

[29] E. Alcalde, C. Ayala, I. Dinares and N. Mesquida, *J. Org. Chem*., **66**, 2291 (2001).

[30] R. M. Izatt, G. C. LindH, R. L. Bruening, P. Huszthy, C. W. McDaniel, J. S. Bradshaw and J. J. Christensen, *Anal. Chem*., **60**, 1694 (1988).

[31] Y. Li, L. Echegoyen, M. V. Martinez-Diaz, J. de Mendoza and T. Torres, *J. Org. Chem*., **56**, 4193 (1991).

[32] C. W. McDaniel, J. S. Bradshaw and R. M. Izatt, *Heterocycles*, **30**, 665 (1990).

[33] S. Elshani, P. Apgar, S. Wang and C. M. Wai, *J. Heterocyclic Chem*., **31**, 1271 (1994).

[34] S. Wang, S. Elshani and C. M. Wai, *Anal. Chem*., **67**, 919 (1995).

[35a] J. A. Gladysz, *Science*, **266**, 55 (1994); [b] I. T. Horwath and J. Rabai, *Science*, **266**, 72 (1994); [c] D.-W. Zhu, *Synthesis*, 953 (1993); [d] G. Pozzi, M. Cavazzini, S. Quici and S. Fontana, *Tetrahedron Lett.*, **38**, 7605 (1997).

[36] *Chem. Eng. News*, April 15, 1996, p. 27.

[37] Y. Takeda, *Top. Curr. Chem.*, **121**, 1 (1984).

[38] K. Kimura and T. Shono, Cation Binding by Macrocycles, Y. Inoue and G. W. Gokel, eds., Marcel Dekker, New York, 1990, p. 429 and references cited therein.

[39] M. J. Pugia, B. E. Knudsen and R. A. Bartsch, *J. Org. Chem.*. **52**, 2617 (1987).

[40a] P. Holy, J. Koudelka, M. Belohradsky, I. Stibor and J. Zavada, *Collect. Czech. Chem. Commun.*, **56**, 1482 (1991); [b] M. Belohradsky, P. Holy, J. Koudelka, and J. Zavada, *Collect. Czech. Chem. Commun.*, **58**, 153 (1993).

[41] A. S. Craig, R. Kataky, R. C. Matthews, D. Parker, G. Ferguson, A. Lough, H. Adams, N. Bailey and H. Schneider, *J. Chem. Soc., Perkins Trans. 2*, 1523 (1990).

[42] R. A. Bissell, E. Calle, A. P. de Silva, S. A. de Silva, H. Q. N. Gunaratne, J. L. Habib-Jiwan, S. L. A. Peiris, R. A. D. D. Rupasinghe, T. K. S. D. Samarasinghe, K. R. A. S. Sandanayake and J. P. Soumillion, *J. Chem. Soc., Perkin Trans. 2*, 1559 (1992).

[43] M. Adamek, *Collect. Czech. Chem. Commun*., **25**, 1964 (1960).

[44] S. S. Novikov, V. M. Brusnikinia and V. A. Rudenko, *Khim. Geterotsikl. Soedin*. **5**, 157 (1969).

[45] M. J. Johnson, I. O. Sutherland and R. F. Newton, *J. Chem. Soc., Perkin Trans. I*, 357 (1979).

[46] A CIF file with data for **10•1.5Methanol** has been deposited. CCDC reference code: 260642.