

# Synthesis and Selectivity of sym-Hydroxydibenzo-14-crown-4 Ionophores for Protons, Alkali Metal Cations, and Alkaline Earth Cations in Polymeric Membranes

URIEL OLSHER\* and FELIX FROLOW

*Department of Chemical Services, Weizmann Institute of Science, Rehovot 76100, Israel*

GIL SHOHAM\*

*Department of Analytical and Inorganic Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel*

ELZBIETA LUBOCH, ZONG-YUAN YU, and RICHARD A. BARTSCH\*

*Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409, U.S.A.*

(Received: 7 February 1989; in final form: 29 August 1989)

**Abstract.** Six derivatives of sym-hydroxydibenzo-14-crown-4 have been prepared and incorporated into solvent-polymeric membranes. Responses of the membranes to protons, alkali metal cations, and alkaline earth cations have been determined. The preferred uptake of protons is attributed to proton complexation by stable crown ether alcohol and diol monohydrate species.

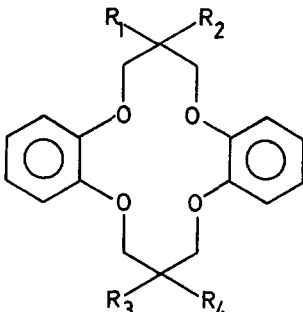
**Key words.** Crown ether alcohols and diols, solvent-polymeric membranes, selectivity for protons, alkali metal cations and alkaline earth cations.

## 1. Introduction

Crown ethers are efficient agents for solubilizing water in hydrophobic solvents such as chloroform [1]. Thus, crown ethers may be solvated by water molecules in hydrophobic media. When a macrocyclic polyether ionophore is incorporated into a hydrophobic solvent or membrane which contacts an aqueous solution, it should be solvated by water molecules. A cation probably interacts with the solvated ionophore, rather than the bare crown ether at the aqueous solution-hydrophobic membrane interface, as well as within the membrane itself [2, 3]. Binding of water molecules to cyclic polyethers is enhanced through hydrogen bonding interactions when the polyether molecule contains hydroxyl groups [2–8] or other ionizable functions [9, 10]. The hydroxyl groups in such compounds can potentially interact with a water molecule which is hydrogen bonded to the ethereal oxygens of the macrocyclic polyether.

Previously it was shown that sym-hydroxydibenzo-14-crown-4 (**1**) is a selective complexing agent for protons [6, 7] and is therefore a potential ionophore for this cation in solvent extraction and membrane transport processes. To study the effects of attaching an alkyl, aryl, or second hydroxyl group to the central carbon of the three carbon bridges in **1**, a series of derivatives **2–7** has been synthesized. Cation selectivities of these compounds in polymeric membranes for protons, alkali metal

\*Authors for correspondence.



	<u>R<sub>1</sub></u>	<u>R<sub>2</sub></u>	<u>R<sub>3</sub></u>	<u>R<sub>4</sub></u>
<u>1</u>	OH	H	H	H
<u>2</u>	OH	CH <sub>3</sub>	H	H
<u>3</u>	OH	Ph	H	H
<u>4</u>	OH	OH	H	H
<u>5</u>	CH <sub>2</sub> OH	H	H	H
<u>6</u>	OH	H	OH	H (cis)
<u>7</u>	OH	H	H	OH (trans)

cations, and alkaline earth cations has been determined by the  $\Delta$ EMF method with an ion-selective cell assembly [7, 11, 12]. We now report the syntheses and results of the cation selectivity measurements.

## 2. Experimental

Compounds 1–3 were prepared by the reported methods [6, 13].

### 2.1. PREPARATION OF SYM-GEM-DIHYDROXYDIBENZO-14-CROWN-4 (4)

To a stirred and cooled solution of crown ether alcohol 1 (1.70 g, 5.4 mmol) in 100 mL of acetone, 7 mL of Jones reagent (2.67 g of CrO<sub>3</sub>, 23 mL of conc H<sub>2</sub>SO<sub>4</sub>, and enough H<sub>2</sub>O to make 10 mL) was added dropwise during 1.5 h. After stirring for an additional 2 h at room temperature, the liquid phase was decanted and the green precipitate was washed with acetone. The combined acetone solution and washings were partially evaporated *in vacuo*, water was added to turbidity, and the mixture was placed in a refrigerator overnight. The precipitate was filtered to afford 1.18 g (66%) of 4, mp 94–96°C. <sup>1</sup>H-NMR (60 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>C(O)CH<sub>3</sub>):  $\delta$  2.00–2.65 (*m*, 2H), 2.90 (*br s*, 2H), 4.25 (*t*, 4H), 5.00 (*s*, 4H), 6.90 (*br s*, 8H). IR (Nujol): 3460, 3300 cm<sup>-1</sup> (OH). Calc.: C 65.05 H 6.07. Found: C 64.98 H 5.94.

When dried in a vacuum oven at 50°C for 8 h, 4 was dehydrated to form sym-ketodibenzo-14-crown-4 as an extremely hygroscopic oil. <sup>1</sup>H-NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  2.33 (*p*, 2H), 4.20 (*t*, 4H), 5.03, (*s* 4H), 6.60–7.20 (*m*, 8H). IR (neat): 1730 cm<sup>-1</sup> (C=O).

### 2.2. PREPARATION OF SYM-(HYDROXYMETHYL)DIBENZO-14-CROWN-4 (5)

Under nitrogen, 1,3-bis(2-hydroxyphenoxy)propane (8.10 g, 30 mmol) [14, 15], 420 mL of 1-butanol and 18 mL of water was heated to 90–95°C and 2.40 g (60 mmol) of sodium hydroxide was added. After stirring for 1 h, a solution of 3.75 g (30 mmol) of 3-chloro-2-chloromethyl-1-propene in 30 mL of 1-butanol was added dropwise and the mixture was stirred at 90–95°C for 24 h. The solvent was evaporated *in vacuo* and 200 mL of water was added to the residue. After acidifica-

tion to pH = 1 with 6N HCl, the aqueous solution was extracted with chloroform (3 × 200 mL). The combined extracts were washed with water (2 × 200 mL), dried over magnesium sulfate, and evaporated *in vacuo*. The crude product was purified by chromatography on alumina with dichloromethane as eluent to give 7.0 g (72%) of sym-methylenedibenzo-14-crown-4, mp 94–95°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.23 (*p*, 2H), 4.20 (*t*, 4H), 4.70 (*s*, 4H), 5.37 (*s*, 2H), 6.90 (*s*, 8H). MS: *m/z* 312.15 (M<sup>+</sup>). Calc.: C 73.09 H 6.41. Found C: 72.94 H 6.29.

To a solution of 6.24 g (20 mmol) of sym-methylenedibenzo-14-crown-4 in 30 mL of tetrahydrofuran under nitrogen at 0°C was added dropwise 10 mL (70 mmol) of 10 M borane–dimethyl sulfide complex. The mixture was stirred at 0°C for 2 h and then at room temperature for 2 h. Water (10 mL) was added and residual dimethyl sulfide was removed by evaporation *in vacuo*. Aqueous sodium hydroxide (3N, 70 ml) and 5 mL of 30% hydrogen peroxide were successively added, the mixture was stirred at 50°C for 5 h, and the organic layer was separated. The aqueous layer was saturated with sodium chloride and extracted with chloroform. The combined layer and chloroform solution were dried over magnesium sulfate and evaporated *in vacuo*. The crude product was chromatographed on silica gel with chloroform as eluent to give 5.28 g (80%) of **5**, mp 168–169°C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 2.27 (*p*, 2H), 2.48 (*s*, 1H), 3.95 (*d*, 2H), 4.10–4.40 (*m*, 8H), 6.92 (*br s*, 8H). IR (KBr): 3528 cm<sup>-1</sup>(OH). MS: *m/z* 330.20 (M<sup>+</sup>). Calc.: C 69.07 H 6.71. Found: C 69.08 H 6.64.

### 2.3. PREPARATION OF SYM-*CIS*-DIHYDROXYDIBENZO-14-CROWN-4 (**6**) AND SYM-*TRANS*-DIHYDROXYDIBENZO-14-CROWN-4 (**7**)

To a solution of catechol (7.70 g, 70 mmol) and lithium hydroxide (1.68 g, 70 mmol) in 450 mL of 2-methyl-2-propanol at reflux under nitrogen was added 11.2 g (50 mmol) of 1,1-(*o*-phenylenedioxy)bis(2,3-epoxypropane) [16, 17] and the reaction mixture was stirred for 6 h. After a second portion of lithium hydroxide (1.68 g, 70 mmol) was added, the reaction mixture was stirred and refluxed for an additional 48 h. The solvent was evaporated *in vacuo* and the residue was dissolved in chloroform (500 mL). The chloroform solution was washed with water (2x) and the water layers were back-extracted with chloroform. The chloroform layers were combined, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was dissolved in 100 mL of methanol and chromatographed on a column of alumina (150 g on top) and silica gel (250 g on bottom) with methanol and then methanol–water (7:3) containing 1% lithium perchlorate as eluents to give 13.20 g (75%) of a mixture of the *cis* and *trans* isomers.

To separate **6** and **7** [18], 10 g of the mixture dissolved in 10 mL of methanol was chromatographed on Florisil and eluted with methanol to give **7**, followed by a mixture of **6** and **7**. When no more **7** was detected, the eluent was changed to methanol–water (7:3) containing 1% lithium perchlorate which gave pure **6**. Crystallization from dichloromethane gave **7** as the monohydrate with mp 167–168°C (lit.[18] mp 164°C). The *cis*-diol **6** precipitated when methanol was evaporated from the aqueous methanol eluent to give the monohydrate with mp 132–133°C (lit.[18] mp 133°C) which could be dehydrated by heating in a vacuum oven to give **6** with mp 160–161°C (lit.[18] mp 160°C).

#### 2.4. PREPARATION OF SOLVENT-POLYMERIC MEMBRANES AND CATION SELECTIVITY MEASUREMENTS

The solvent-polymeric membranes were prepared with 2 weight % of the crown ether alcohol, 33 weight % of poly(vinyl chloride) (PVC), and 65 weight % of the membrane solvent *o*-nitrophenyl octyl ether (NPOE). The membrane preparation and measuring technique have been described in detail elsewhere [7, 11, 12]. The EMF measurements were performed at 25°C with a standard deviation of <0.1 mV in a single measurement using 0.1M solutions of the respective chlorides.

### 3. Results

Synthetic routes to the dibenzo-14-crown-4 (DB14C4) alcohols and diols 1–7 are summarized in Figure 1. Compounds 1–3 were prepared by reported methods [6, 13]. Compounds 4 and 5 are new and an original synthetic route was utilized to prepare 6 and 7.

The potentiometrically-determined selectivity factors induced in solvent-polymeric membranes by the seven DB14C4 alcohols and diols 1–7 are presented in Figures 2 and 3. The selectivity factors, given as  $\log K_{Na,M}^{pot}$  values, represent the membrane preference for cation M relative to cation  $Na^+$ , the reference cation. The membrane solvent was *o*-nitrophenyl octyl ether (NPOE).

The results presented in Figures 2 and 3 may be summarized briefly as follows: (1) Proton uptake is highly significant with respect to uptake of other cations for membranes containing all of the compounds 1–7. (2) For the metal cations, membranes containing 1–4, 6, 7 are selective for  $K^+$ , and the membrane containing 5 prefers  $Li^+$ . (3) For all of the membranes containing the DB14C4 alcohols and diols 1–7, there is strong preference for uptake of monovalent cations over the divalent cations, with a somewhat lower favoring for 1–3 than with 4–7. (4) Substitution of the geminal hydrogen in 1 by methyl, phenyl, or hydroxyl groups in 2, 3, and 4, respectively, does not affect the membrane selectivity pattern. (5) Replacement of a methylene group hydrogen on the central carbon of the transannular three-carbon bridge of 1 does not alter the membrane selectivity pattern in compounds 6 and 7.

### 4. Discussion

#### 4.1. SYNTHESIS OF NEW DB14C4 DERIVATIVES

Sym-*gem*-dihydroxydibenzo-14-crown-4 (4) was the unexpected product of Jones oxidation of sym-hydroxydibenzo-14-crown-4 (1). Diol 4 was isolated rather than the anticipated sym-ketodibenzo-14-crown-4. Although 4 could be dehydrated by heating in a vacuum oven to give the keto form, the latter readily reabsorbed water to form the *gem*-diol.

sym-(Hydroxymethyl)dibenzo-14-crown-4 (5) was prepared by hydroboration–oxidation of sym-methylenedibenzo-14-crown-4 which had been synthesized by the reaction of 3-chloro-2-chloromethyl-1-propene and 1,3-bis(2-hydroxyphenoxy)-propane.

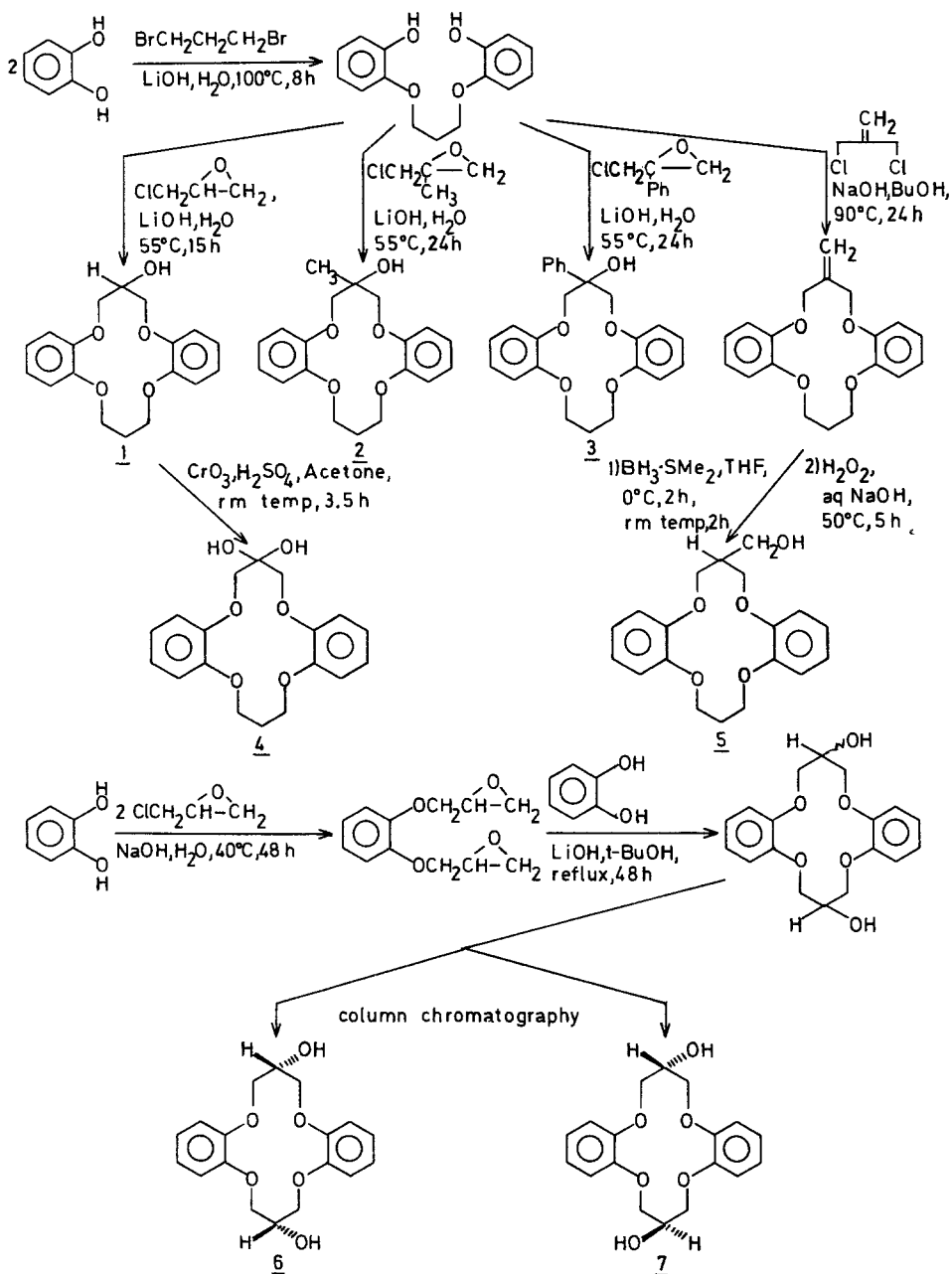


Fig. 1. Synthetic routes to dibenzo-14-crown-4 alcohol derivatives.

Although the synthesis of *cis*-diol **6** and *trans*-diol **7** had been described earlier [18], a new route was devised which involved the ring closure of catechol with the diepoxide formed from reaction of catechol with two moles of epichlorohydrin. Diols **6** and **7** were separated by chromatography.

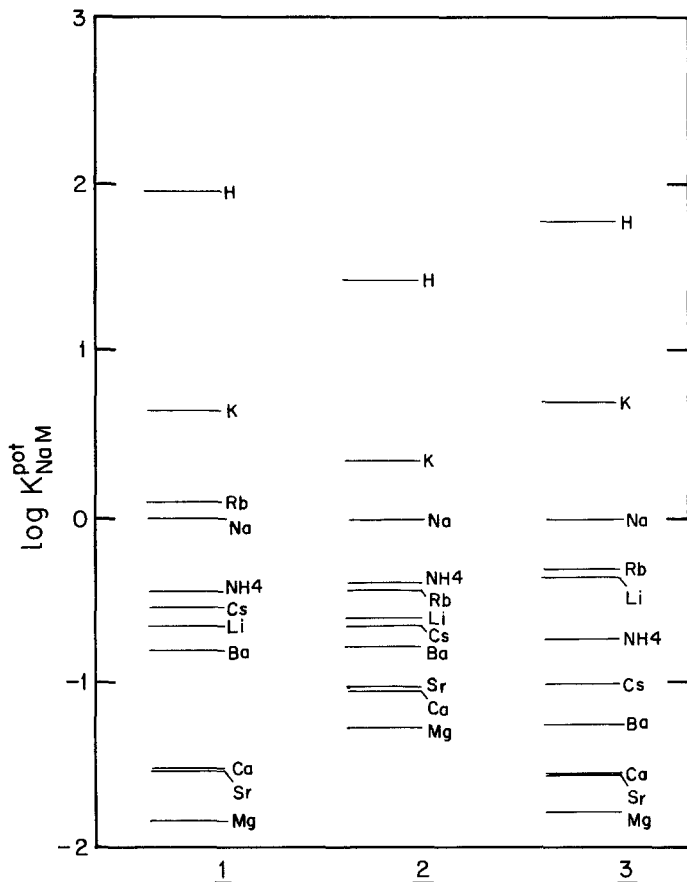


Fig. 2. Selectivity factors  $\log K_{Na,M}^{pot}$  for solvent-polymeric membranes containing crown ether alcohols 1-3. (Membrane composition: 2 weight % ionophore, 33 weight % PVC, 65 weight % NPOE.)

#### 4.2. SELECTIVITY STUDIES

Compounds **1-7** appear to meet all the general requirements of a ligand to be used for ionophoric purposes [7]. Except for **5**, these compounds share the same sym-hydroxydibenzo-14-crown-4 structural unit. It is therefore not surprising that their selectivities for protons, alkali metal cations, and alkaline earth cations are very similar.

The basic sym-hydroxydibenzo-14-crown-4 unit in **1-4**, **6** and **7** is found to be the dominant structural feature which determines the cation selectivity. Hence replacement of the geminal hydrogen atom in **1** by a methyl group in **2** or by a phenyl group in **3** or attachment of a second hydroxyl group in **4**, **6** and **7** does not change the cation binding selectivities of the ligands.

The crystal structure of the monohydrate **1** [6] shows two important features: (1) The observed mean intramolecular distance of the hydroxyl oxygen with its two neighboring ethereal oxygens (2.80 Å) is consistent with a fairly strong hydrogen-bonding system (see Figure 4a). It seems reasonable therefore that in nonpolar

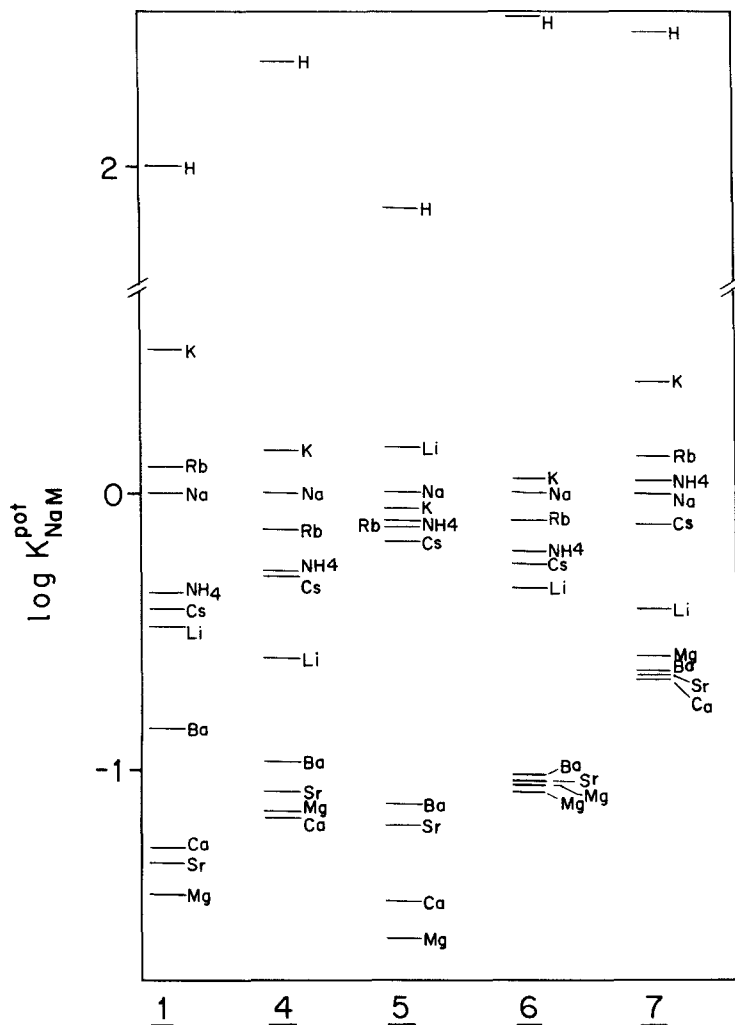
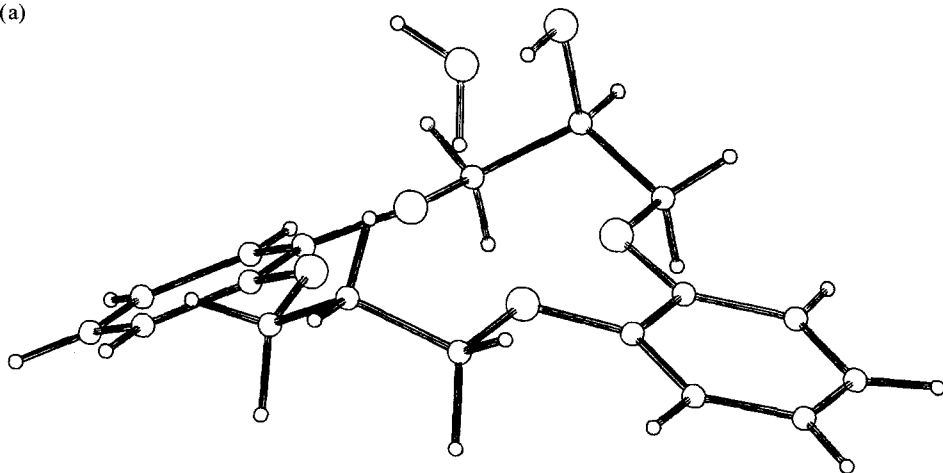


Fig. 3. Selectivity factors  $\log K_{Na,M}$  for solvent-polymeric membranes containing crown ether alcohols and diols 1 and 4-7. (Membrane composition: 2 weight % ionophore, 33 weight % PVC, 65 weight % NPOE.)

aprotic organic solvents, the hydroxyl group of the free compound **1**, would be hydrogen-bonded at the ethereal oxygens of the macrocyclic ring via intramolecular hydrogen bonds. Thus, the hydroxyl group should prefer the axial position (see Figure 5a) rather than the equatorial one (see Figure 5b). Hence the molecule should be preorganized for water binding to form a stable monohydrate complex. (2) The molecular structure of the monohydrate complex offers a favorable ligand for proton binding via hydronium ion formation [7, 19-24] which explains the preferred proton uptake by compounds **1-7**.

As might be expected from the crystal structure of the **1** monohydrate complex, *cis*-diol **6** forms a monohydrate complex as well [8]. In this complex, the water

(a)



(b)

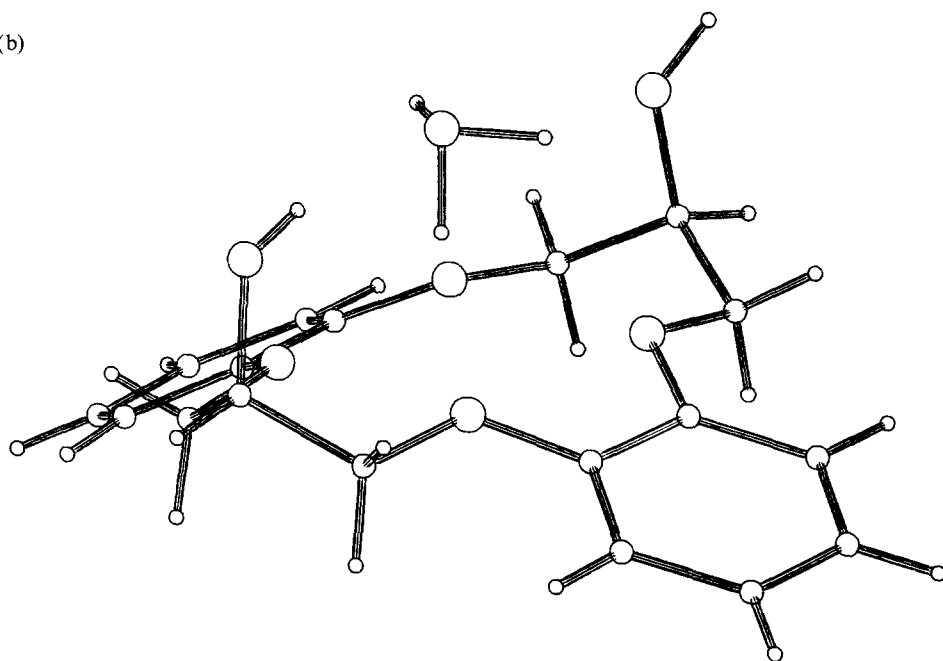


Fig. 4. (a) Crystal structure for the *sym*-hydroxydibenzo-14-crown-4 · H<sub>2</sub>O complex. (b) Crystal structure for the *sym-cis*-dihydroxydibenzo-14-crown-4 · H<sub>2</sub>O complex. (One hydrogen atom of the H<sub>2</sub>O is disordered over two sites by two-fold symmetry. Both possible positions are shown.)

molecule is hydrogen bonded by both hydroxyl groups and the ethereal oxygens (see Figure 4b). It might be anticipated that this monohydrate complex would be more stable than that of **1** due to the additional intramolecular hydrogen bond with a second hydroxyl group. Quantum chemical calculations reveal that chain-like hydrogen bonding in the crystal structure is energetically favored over individual interactions. This is due to a cooperative effect which leads to increased hydrogen-



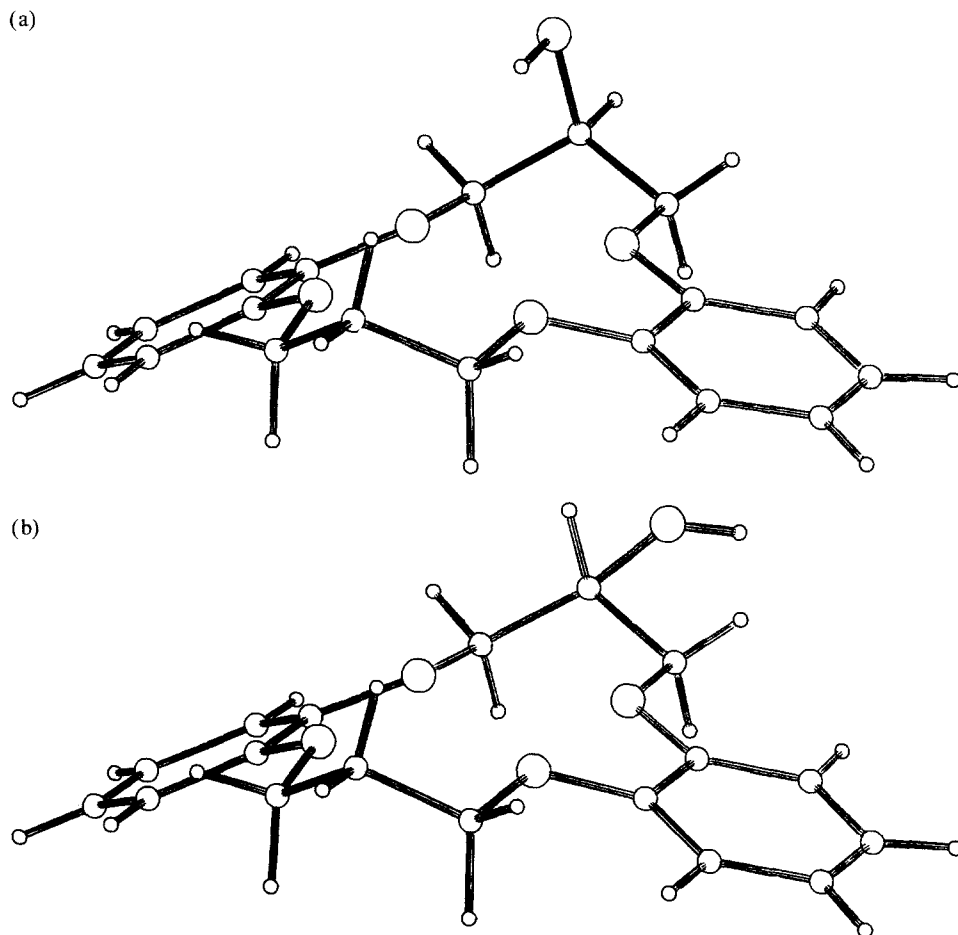


Fig. 5. (a) Conformation for sym-hydroxydibenzo-14-crown-4 with an axial hydroxyl group. (b) Conformation for sym-hydroxydibenzo-14-crown-4 with an equatorial hydroxyl group.

bonding activity of a hydroxyl group if it is already accepting or donating a hydrogen bond [25, 26].

Additional evidence for the stability of the monohydrate complexes comes from the unsuccessful attempts to grow crystals of alkali metal cation salt ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ) · sym-hydroxydibenzo-14-crown-4 complexes. In all cases, the alkali metal cations were rejected and **1** crystallized as the monohydrate complex. Hence, the preorganized ligand **1** prefers water binding via a hydrogen bond network over complexation with alkali metal cations.

Compound **5** does not have the sym-hydroxydibenzo-14-crown-4 unit which is common to all of the other DB14C4 derivatives. The  $-\text{OH}$  group in **1** is replaced by  $-\text{CH}_2\text{OH}$  and the additional methylene group prevents formation of a stable monohydrate complex. Ligand **5** has a macrocyclic cavity which resembles that of DB14C4 itself. Since DB14C4 is selective for  $\text{Li}^+$ , this explains the preference for complexation of  $\text{Li}^+$  by **5** over the other alkali metal cations and the alkaline earth

cations. The uptake of protons by membranes containing **5** may be attributed to protonation of the hydroxyl group or of a less stable hydrate complex.

In general, the divalent cations are strongly rejected by all seven DB14C4 alcohols and diols due to a special structural property of the DB14C4 framework whose preferred V-shaped conformation allows direct or close contact with the counterion(s) on only one side of the complex. Therefore, complexation of divalent cations is disfavored due to a lack of room for the charge-balancing counterion(s), especially if they are monovalent [27, 28].

## 5. Conclusions

The cation selectivity pattern for compounds **1–4**, **6** and **7** is controlled by the sym-hydroxydibenzo-14-crown-4 unit. The molecules are preorganized for water binding via intramolecular hydrogen bonds of the hydroxyl groups with the neighboring ethereal oxygens. Preference for proton uptake by solvent-polymeric membranes is most easily understood in terms of proton complexation by stable monohydrate complexes of the crown ether alcohols and diols.

## Acknowledgements

Preparation of the solvent-polymeric membranes and the EMF measurements were conducted in the laboratories of Professor Dr. W. Simon at ETH-Zentrum in Zürich, Switzerland. One of us (G. S.) thanks the Bat-Sheva Foundation of Israel for financial support. Research conducted at Texas Tech University was supported by a grant from the Robert A. Welch Foundation.

## References

1. F. De Jong, D. N. Reinhoudt, and C. J. Smit: *Tetrahedron Lett.* 1371 (1976).
2. D. J. Cram and K. W. Trueblood: *Top. Curr. Chem.* **98**, 43 (1981).
3. J. De Villepin, A. Lautie, and M. L. Josien: *Annales Chim.* 365 (1966).
4. T. L. Tarnowski and D. J. Cran: *J. Chem. Soc., Chem. Commun.* **661**, (1976).
5. I. Goldberg: *Acta Crystallogr.* **B34**, 3387 (1978).
6. U. Olsher, F. Frolow, R. A. Bartsch, M. J. Pugia, and G. Shoham: *J. Am. Chem. Soc.*, **111**, 9217 (1989).
7. U. Olsher, F. Frolow, G. Shoham, W. Simon, G. S. Heo, and R. A. Bartsch: *Anal. Chem.*, **61**, 1618 (1989).
8. U. Olsher, F. Frolow, G. Shoham, and R. A. Bartsch, unpublished results.
9. J. S. Bradshaw, D. A. Chamberlin, P. E. Harrison, B. E. Wilson, G. Arena, N. K. Dalley, J. D. Lamb, and R. M. Izatt: *J. Org. Chem.* **50**, 3065 (1985).
10. J. S. Bradshaw, P. Huszthy, H. Koyama, S. A. Wood, G. C. LindH, S. A. Srobel, R. B. Davidson, R. M. Izatt, N. K. Dalley, J. M. Lamb, and J. J. Christensen: *J. Heterocycl. Chem.* **23**, 1837 (1986).
11. D. Ammann, W. E. Morf, P. Anker, P. C. Meier, E. Pretsch, and W. Simon: *Ion-Selective Electrode Rev.* **5**, 3 (1983).
12. W. Simon, W. E. Morf, and P. C. Meier: *Struct. Bond.* **16**, 113 (1973).
13. M. J. Pugia, B. E. Knudsen, C. V. Cason, and R. A. Bartsch: *J. Org. Chem.* **52**, 541 (1987).
14. R. W. Kierstead, A. Faraone, F. Mennona, J. Mullin, R. W. Guthrie, H. Crowley, B. Simko, and L. C. Blaber: *J. Med. Chem.* **26**, 1561 (1983).
15. R. A. Bartsch, Y. Liu, S. I. Kang, B. Son, G. S. Heo, P. G. Hipes, and L. J. Bills: *J. Org. Chem.* **48**, 4864 (1983).
16. O. Stephenson: *J. Chem. Soc.*, 1571 (1954).

17. J. Zaagzma and W. T. Nauta: *J. Med. Chem.* **17**, 507 (1974).
18. D. G. Parsons: *J. Chem. Soc., Perkin Trans 1*, 451 (1978).
19. G. S. Heo and R. A. Bartsch: *J. Org. Chem.* **47**, 3557 (1982).
20. I. M. Koltoff, W. Ji-Wang, and M. K. Chantooni, Jr.: *Anal. Chem.* **55**, 1202 (1983).
21. (a) J. O. Lundgren and J. Olovsson: *Acta Crystallogr.* **23**, 966 (1967).  
(b) J. O. Lundgren: *Acta Crystallogr.* **B26**, 1893 (1970).  
(c) R. G. Delaplane and J. A. Ibers: *Acta Crystallogr.* **25**, 2423 (1969).  
(d) T Kjällman and J. Olovsson: *Acta Crystallogr.* **B28**, 1692 (1972).
22. J. P. Behr, P. Dumas, and D. Morass: *J. Am. Chem. Soc.* **104**, 4540 (1982).
23. C. S. Shoemaker, L. B. McAfee, D. P. Shoemaker, and C. W. DeKock: *Acta Crystallogr.* **C42**, 1310 (1986).
24. J. L. Atwood, S. G. Bott, A. W. Coleman, K. D. Robinson, S. B. Whetstone, and C. M. Means: *J. Am. Chem. Soc.* **109**, 8100 (1987).
25. G. A. Jeffery and S. Takagi: *Acc. Chem. Res.* **11**, 264 (1978).
26. J. E. Del Bene and J. A. Pople: *J. Chem. Phys.* **52**, 4858 (1970); **58**, 3605 (1973); J. E. Del Bene: *J. Chem. Phys.* **55**, 4633 (1971).
27. U. Olsher: *J. Am. Chem. Soc.* **104**, 4006 (1982).
28. G. Shoham, W. N. Lipscomb, and U. Olsher: *J. Chem. Soc., Chem. Commun.*, 208 (1983).