Synthesis and Lithium Ion-Selectivity of 2-Phenylcyclohexano- and 2,3-Diphenylcyclohexano-14-crown-4 Derivatives

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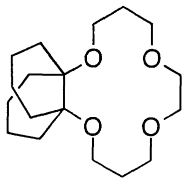
Cis- and *trans*-2-phenylcyclohexano-14-crown-4 and *cis*- and *trans*-2,3-diphenylcyclohexano-14-crown-4 were prepared and their ion selectivity was determined by means of extraction of alkali metal picrates, stability constants, and ion-selective electrodes. Cis diphenyl derivative exhibits the highest lithium ion-selectivity of the four ionophores examined, which is as high as that of decalino-14-crown-4, one of the best Li^+-selective ionophores.

Much interest has been focused on a highly lithium ion-selective electrode in connection with the medical and clinical use of lithium carbonate for the therapy of manic-depressive psychosis.[1] However, little ionophores have been synthesized which possess sufficient Li^+/Na^+ selectivity for the practical use.[2] We reported previously that 14-crown-4 derivatives such as decalino-14-crown-4 (**1**) bearing a bulky substituent on one side of the ethano bridge exhibited excellent Li^+/Na^+ selectivity.[3] Our design is based on the steric hindrance which prevents the formation of 2:1 (crown ether : cation) complex with larger Na^+, leading to high selectivity toward Li^+. The major drawback in **1** is its scarce availability due to the low yield in the final cylization step of the synthesis.[3a] In order to find an alternative and readily available substituent which provides effective steric hindrance in complexation, we prepared *cis*- and *trans*-2-phenylcyclohexano-14-crown-4 (**2**) and (**3**) and *cis*- and *trans*-2,3-diphenylcyclohexano-14-crown-4 (**4**) and (**5**), and investigated their ion selectivity by means of extraction of alkali metal picrates, stability constants with alkali metal perchlorates, and ion-selective electrodes.[4]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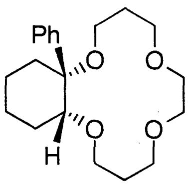
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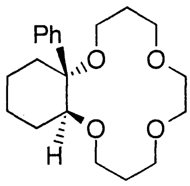
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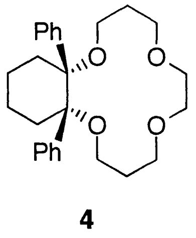
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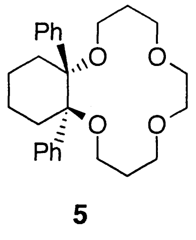
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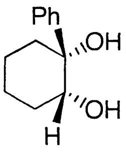
The cyclohexanediol units **6**, **7**, and **9** were prepared according to the procedures previously reported.[4,5] Since stereoselective synthesis of cis diphenyl diol **8** was not reported, it was prepared in 24% yield by the pinacol coupling of 1,6-diphenylhexane-1,6-dione[6] using titanium reagents prepared from $TiCl_4$ and Mg(Hg).[7] Condensation of **6**-**9** with bis-*p*-toluenesulfonate of 4,7-dioxadecane-1,10-diol was carried out in tetrahydrofuran in the presence of NaH and $LiClO_4$ under high dilution conditions. While crown ethers **2**-**4** were obtained in satisfactory yields of 50, 27, and 35%, respectively, the yield of **5** was low (3%).[8]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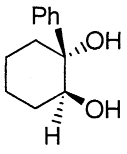
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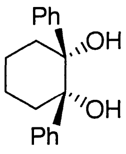
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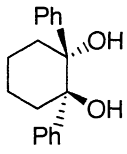
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In order to estimate the ion selectivity of **2**-**5**, extraction of alkali metal picrates was undertaken in the water/dichloromethane system. As shown in Table 1, trans derivatives **3** and **5** exhibit low extractability in every case, leading to the low ion selectivity. By contrast, while Li^+/Na^+ selectivity of cis monophenyl derivative **2** is only moderate, cis diphenyl **4** exhibits large extractability for Li^+ as well as high Li^+/Na^+ selectivity, which are as large as those of decalino-**1**. The stability constants (*Ka*) of the complexes between **2**-**5** with $LiClO_4$ were determined in cyclohexanone at 80 °C by the ^7Li NMR titration method.[9] The *Ka* values for **2**-**5** are 5.1×10^3, 4.0×10^2, 7.0×10^3, and 1.3×10^2 $dm^3\ mol^{-1}$, respectively.[10] The low extractability of trans isomers **3** and **5** is, therefore, ascribed to their low complexation ability, which is probably due to the conformational rigidity of the phenyl-substituted *trans*-cyclohexane units.[11]

Ion selectivity of **2**-**5** was also measured by potentiometric PVC-membrane electrodes containing the crown ethers.[12] As shown in Figure 1, cis diphenyl derivative **4** exhibits high

Table 1. Extractability of alkali metal picrates in water/dichloromethane system by ionophores **1**-**5** [a]

Crown ether	Extractability / %					Selectivity
	Li^+	Na^+	K^+	Rb^+	Cs^+	Li^+/Na^+
2	42.8	7.7	1.4	0.7	0.6	5.6
3	3.1	0.8	0.7	0.8	0.9	3.9
4	74.1	4.8	1.1	1.0	1.1	15.4
5	1.6	0.6	0.6	0.5	0.6	2.7
1[b]	80.6	5.0	1.2	1.2	0.7	16.1

[a] [ionophore]=7.0×10^{-4} M, [picric acid]=7.0×10^{-5} M, [alkali metal hydroxide]=1.0×10^{-1} M, 25.0±0.1 °C. [b] Ref. 3a.

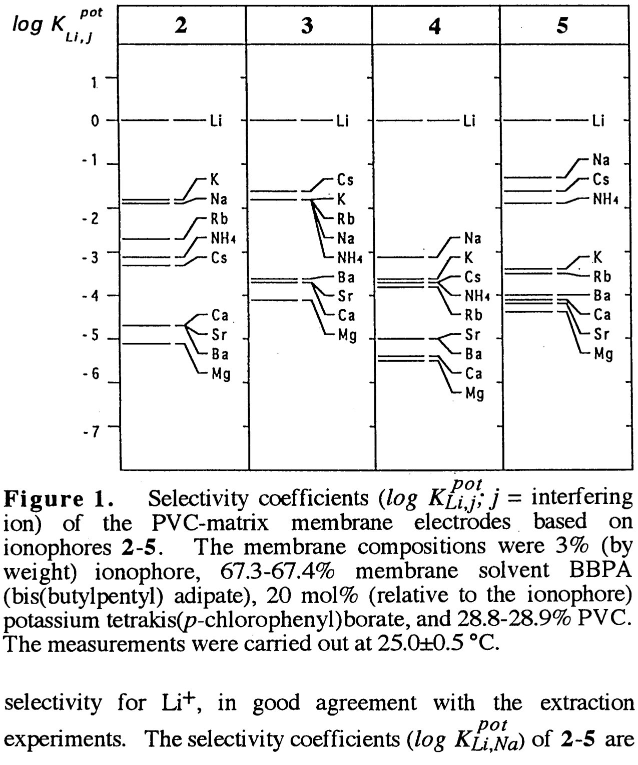

Figure 1. Selectivity coefficients ($log\ K^{pot}_{Li,j}$; j = interfering ion) of the PVC-matrix membrane electrodes based on ionophores **2**-**5**. The membrane compositions were 3% (by weight) ionophore, 67.3-67.4% membrane solvent BBPA (bis(butylpentyl) adipate), 20 mol% (relative to the ionophore) potassium tetrakis(*p*-chlorophenyl)borate, and 28.8-28.9% PVC. The measurements were carried out at 25.0±0.5 °C.

selectivity for Li^+, in good agreement with the extraction experiments. The selectivity coefficients ($log\ K^{pot}_{Li,Na}$) of **2**-**5** are -1.9, -1.8, -3.1, and -1.3, respectively. The selectivity of **4** well compares that of **1** (-3.3).[3b]

In summary, cis diphenyl derivative **4** exhibits Li^+-selectivity as high as that of decalino-**1**, one of the best Li^+-selective ionophores for ion-selective electrodes so far known. Since the phenyl groups in **4** allows introduction of functional groups, the ion selectivity may be tunable using the electronic and coordinative properties of the additional substituents.

References and Notes

1 A. D. Amdisen, *"Handbook of Lithium Therapy,"* MTP Press, Lancaster (1986).

2 E. Metzger, D. Ammann, D. Asper, and W. Simon, *Anal. Chem.*, **58**, 132 (1986); K. Kimura, O. Oishi, T. Murata,, and T. Shono, *Anal. Chem.*, **59**, 2331 (1987); T. Tohda, H. Sasakura, K. Suzuki, and T. Shirai, *Proc. the 54th Chem. Soc. Japan Annual Meeting*, Tokyo, p 473 (1987); H. Sugihara, T. Okada, and K. Hitatani, *Chem. Lett.*, 2391 (1987); A. S. Attiyat, G. D. Christian, R. Y. Xie, X. Wen, and R. A. Bartsch, *Anal. Chem.*, **60**, 2561 (1988); K. Suzuki, K. Hayashi, K. Tohda, K. Watanabe, M. Ouchi, T. Hakushi, and Y. Inoue, *Anal. Lett.*, **24**, 1085 (1991); R. Kataky, P. E. Nicholson, D. Parker, A. K. Covington, *Analyst*, **116**, 135 (1991).

3 a) K. Kobiro, T. Hiro, T. Matsuoka, K. Kakiuchi, Y. Tobe, and Y. Odaira, *Bull. Chem. Soc. Jpn.*, **61**, 4164 (1988); b) K. Kobiro, Y. Tobe, K. Watanabe, H. Yamada, and K. Suzuki, *Anal. Lett.*, **26**, 49 (1993); c) K. Suzuki, H. Yamada, K. Sato, K. Watanabe, H. Hisamoto, Y. Tobe, and K. Kobiro, *Anal. Chem.*, **65**, 3404 (1993).

4 For the use of three of these units as the chiral centers of 18-crown-6 derivatives; K. Naemura, H. Miyabe, and Y. Shingai, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 957.

5 G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **21**, 3277 (1965); G. Berti and F. Macchia, *Tetrahedron Lett.*, **1965**, 3421.

6 R. C. Fuson and J. T. Walker, *Org. Syn., Coll. Vol., II*, 169 (1943).

7 E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, **41**, 260 (1976).

8 The low yield of **5** can be attributed to the strain developed in the transition state of cyclization in which both of the phenyl groups adopt axial position. Indeed, MM2 calculations for **4** and **5** indicate that the latter is less stable by 10.3 kcal/mol.

9 For every host-guest systems examined, the complexed and uncomplexed metal ions can equilibrate on the NMR time scale under these conditions.

10 The stability constants of **2** and **4** with $NaClO_4$ were determined to be 2.8x10 and 2.3x10 $dm^3\ mol^{-1}$, respectively, under the similar conditions using ^{23}Na NMR, from which the Li^+/Na^+ selectivities of 180 and 300 were estimated, respectively. The corresponding *Ka* with Na^+ for **3** and **5** were too small to be determined.

11 The ^{13}C NMR spectra of cis derivatives **2** and **4** are temperature-dependent; at a low temperature (-80°C), the peaks appear as sets of those due to two conformers (for **2**, 1:3 ratio and for **4**, inevitably 1:1). On the other hand, the ^{13}C NMR of trans isomers **3** and **5** are temperature-independent, indicating that the cyclohexane rings are fixed in conformations in which the phenyl groups adopt axial positions.

12 Measurements were carried out according to the procedures previously described: K. Suzuki, K. Tohda, H. Aruga, M. Matsuzoe, H. Inoue, and T. Shirai, *Anal. Chem.*, **60**, 1714 (1988).