Communications

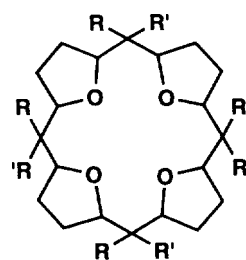## Lithium Ion-Selective Electrode Based on THF-Based 16-Crown-4 Derivatives

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Ionophore
1 : R = H, R' = CH₃
2 : R = H, R' = CH₂CH₃
3 : R = CH₃, R' = CH₂CH₃
4 : R = CH₂CH₃, R' = CH₂CH₃

Figure 1. Constitution of the synthetic Li^+ ionophores.

The concentrations of the most important cations found in biological fluids, e.g., Na^+, K^+, Ca^{2+}, and H^+, can easily be determined in clinical laboratories using ion-selective liquid membrane electrodes. In contrast, the assay of Li^+ is performed mostly by flame photometry or atomic absorption spectrometry. Since the monitoring of the Li^+ activity in blood is very important during the lithium theraphy of patients suffering from manic-depressive psychosis,[1] many research efforts are presently being focused on the design of electrically neutral carriers for Li^+-selective liquid membrane electrodes.[2,3] The main problem of the Li^+-ionophores published until now is their unsatisfying selectivity especially against Na^+ which is present in a relatively high concentration of ~140 mM in blood.[4] In the past several Li^+-selective electrodes which exhibited a Li^+/Na^+ selectivity over 10-100 were developed using a noncyclic polyether diamide,[5] a phenanthroline derivative,[6] and crown ether compounds.[7] As for Li^+, crown ethers with a 13-16-membered ring are adequate for Li^+ coordination.[8] The cavity of the 14-crown-4, especially, has the best fit for Li^+ as a 1 : 1 type ionophore-cation complex, and some 14-crown-4 derivatives have already been used for the Li^+-sensing component for ion-selective electrodes.[7]

During the search for more appropriate carriers, an interesting class of lipophilic compounds derived from 16-crown-4 derivatives containing tetrahydrofuran ring was found.[9] These ionophores were synthesized by the acid-catalyzed condensation of acetaldehyde (ionophore 1 and 2) or ketone (ionophore 3 and 4) with furan or difurylalkanes followed by catalytic hydrogenation[9] (Figure 1) in an effort to obtain highly selective ionophores for lithium ions.

The membranes consist of 2.5 wt.% ionophore, 64 wt.% plasticizer, tris (2-ethylhexyl)phosphate(TEHP), 33 wt.% poly (vinylchloride) (PVC), and 0.5 wt.% potassium tetrakis(p-chlorophenyl)borate(KTpClPB). The electrochemical cell is Ag-AgCl/1 M LiCl/membrane/measured solution/0.1 M NH₄ NO₃/4 M KCl/AgCl-Ag. The EMF measurements were performed at 25 °C with standard deviation of <0.1 mV for a single determination. Further experimental details have been described previously.[10]

The calibration curve obtained for the electrode based on ionophore 1 was linear over the activity range from 1.0×10^{-5} to 1 M with a slope of 58.2 mV for Li^+. The response time of the electrode was less than 0.5 min.

The selectivity coefficients for Li^+ relative to the interfering ion M in the PVC membrane electrodes are listed in Table 1. As shown in Table 1, electrodes based on ionophore 1 and 2 which have only methyl or ethyl groups at four bridged carbon positions exhibit excellent selectivity for Li^+ over other metal ions. On the contrary, electrodes based on ionophore 3 and 4 which have methyl and ethyl groups or diethyl groups at four bridged carbon positions exhibit less Li^+-selectivity than those based on 1 and 2. From these results, it seems to be important to introduce the small substituents such as proton and methyl on bridged carbons for the appearance of high Li^+-selectivity. This implies that the

Table 1. Selectivity Coefficients (K_{LiM}^{pot}) of Li^+-selective Electrodes Based on PVC Membranes Containing Ionophores 1-4

Ionophore	K_{LiM}^{pot} (separate solution method)						
	Na^+	NH_4^+	K^+	Cs^+	Ca^{2+}	Mg^{2+}	Ba^{2+}
1	1.48×10^{-3}	5.89×10^{-4}	5.62×10^{-5}	2.75×10^{-5}	3.47×10^{-6}	1.66×10^{-6}	2.95×10^{-6}
2	4.20×10^{-2}	7.69×10^{-2}	4.08×10^{-3}	2.42×10^{-3}	3.24×10^{-4}	1.49×10^{-4}	1.81×10^{-4}
3	9.71×10^{-2}	3.06×10^{-1}	1.47×10^{-2}		1.75×10^{-3}	7.89×10^{-4}	7.30×10^{-4}
4	1.03×10^{-1}	3.15×10^{-1}	1.58×10^{-2}		1.96×10^{-3}	8.26×10^{-4}	9.08×10^{-4}
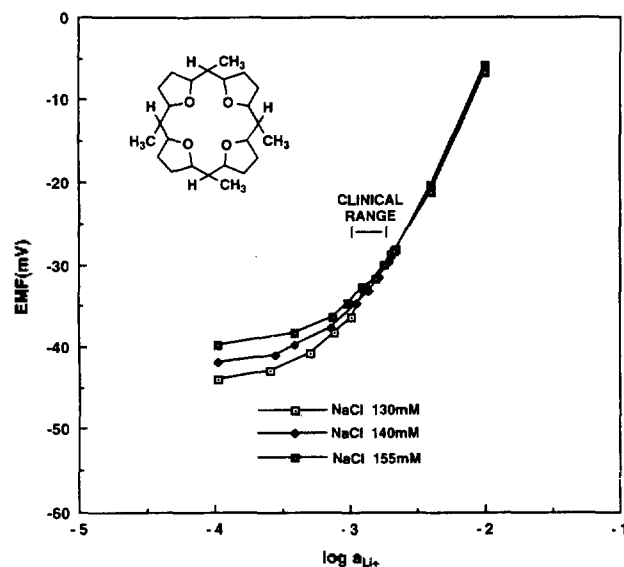
Figure 2. EMF response of Li^+-ISE based on ionophore 1 with NaCl backgrounds at average blood concentration ([NaCl] = 140 mM) and extreme physiological concentration ([NaCl] = 155 mM) levels.

bulky groups on bridged carbon cause some steric effects on complexation with Li^+ ion.

With a selectivity (K_{LiNa}^{pot}) for Li^+ against Na^+ of 1.48×10^{-3} determined by the separate solution method,[11] the membrane containing ligand 1 and KTpClPB is superior to those of previously described Li^+-selective electrodes.[2,7,12] The typical Li^+ response curves are shown in Figure 2, where the background ion concentrations of the test solutions were varied with different concentrations of Na^+ (130, 140, 150 mM). The linear Nernstian response slope was observed in the concentration range from 1 mM to 1 M when the test samples contained 140 mM Na^+. Although the theoretically required selectivities ($K_{LiNa} < 10^{-4}$) with respect to Na^+ and Ca^{2+} (1% interference) are not reached,[1,4(b)] a practical application using adequate calibration solutions seems possible with sufficient accuracy, because the blood concentrations of these ions can be expected within narrow limits (Figure 2).[1(a),13]

Kobuke and coworkers examined the lithium coordination chemistry of a tetrameric THF-based ionophore and found remarkably strong binding.[14] This strong binding probably arises in large measure from the conformationally "stiffened" nature of the ionophore. These ionophores containing THF unit lack the considerable conformational freedom that char-

acterize most crowns. The connectivity of these ionophores constrain the donor atoms to positions commensurate only with coordination of lithium. X-ray diffraction of the lithium complex reveals a square-pyramidal coordination sphere with four oxygen donor atoms disposed on one side of the mean plane of the ionophore.[15] This situation doubtless disfavors replacement of Li^+ with any larger ion. Consequently tetrameric THF-based ionophorers have not only high affinity but also high selectivity.

THF based-16-Crown-4 derivatives used in this study will be used for further applications such as Li^+-indicating or extracting agents. Further investigation on the relationship between the nature of substituents and ion selectivity is now in progress.

References

1. (a) During the lithium theraphy of manic-depressive psychosis, the clinical range of Li^+ concentration in blood is 0.7 to 1.5 mM. Amidsen, A. *Dan. Med. Bull.* **1975,** *22,* 277. (b) John, F.; Cade, J. *Med. J. Aust.* **1949,** *2,* 349. (c) Cooper, T. B. In *Psychopharmacology: The Third Generation of Progress;* Meltzer, H. Y. Ed.; Raven Press: New York, 1987; Chapt 143.

2. (a) Tsukube, H.; Hori, K.; Inoue, T. *Tetrahedron Lett.* **1993,** *34,* 6749. (b) Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L.-H. *J. Org. Chem.* **1993,** *58,* 5411. (c) Shanzer, A.; Samuel, D.; Korenstein, R. *J. Am. Chem. Soc.* **1983,** *105,* 3815.

3. (a) Hiratani, K.; Okada, T.; Sugihara, H. *Anal. Chem.* **1987,** *59,* 766. (b) Metzer, E.; Aeschimann, R.; Egli, M.; Suter, G.; Dohner, R.; Ammann, D.; Dobler, M.; Simon, W. *Helv. Chim. Acta* **1986,** *69,* 1821.

4. (a) Bowen, H. J. M. *Environmental Chemistry of the Elements;* Academic Press: 1979; pp 105-106. (b) Metzger, E.; Ammann, D.; Simon, W. *Anal. Chem.* **1986,** *56,* 132.

5. Godzekpo, V. P. Y.; Hungerford, J. M.; Ibrahim, A. M.; Xie, R. Y.; Christian, G. D. *Anal. Chem.* **1986,** *58,* 1948.

6. (a) Sugihara, H.; Okada, T.; Hiratani, K. *Chem. Lett.* **1987,** 2391. (b) Metzger, E.; Ammann, D.; Asper, R.; Simon, W. *Anal. Chem.* **1986,** *58,* 132.

7. (a) Suzuki, K.; Yamada, H.; Sato, K.; Watanabe, K.; Hisamoto, H.; Tobe, Y.; Kobiro, K. *Anal. Chem.* **1993,** *65,* 3404. (b) Olsher, U. *J. Am. Chem. Soc.* **1982,** *104,* 4006. (c) Kitazawa, S.; Kimura, K.; Yano, H.; Shono, T. *J. Am. Chem. Soc.* **1984,** *106,* 6978.

8. It is suggested by CPK molecular model examination that Li$^+$ fit into the 15-crown-4 ring and more favorably into the 14-crown-4 one. Kimura, K.; Oishi, H.; Miura, T.; Shono, T. *Anal. Chem.* **1987**, *59*, 2331.

9. Although the yield of this reaction is substantially improved by addition of lithium salts, the definite work of Healy and Rest shows that this is not a template but rather a pH effect. Healy, M. de S.; Rest, A. S. *J. Chem. Soc. Perkin I* **1985**, 973.

10. (a) Kim, J. S.; Jung, S. O.; Lee, S. S.; Kim, S-J. *Bull. Kor. Chem. Soc.* **1993**, *14*, 123. (b) Kim, S. M.; Jung, S. U.; Kim, J.; Lee, S. S.; Kim, J. S. *J. Kor. Chem. Soc.* **1993**, *37*, 773.

11. IUPAC Recommendation for Nomenclature of Ion-Selective Electrodes. *Pure Appl. Chem.* **1976**, *48*, 127.

12. Kim, J. S.; Lee, B. Y. The 5th Symposium on Biofunctional Chemistry, Hiroshima, Japan, June 5-6, 1990, abstract p 13.

13. Amdisen, A. D. *Hand book of Lithium Theraphy*; MTP Press: Lancaster, U. K., 1986.

14. Kobuke, Y.; Hanji, K.; Horiguchi, K.; Asada, M.; Nakayama, Y.; Furukawa, J. *J. Am. Chem. Soc.* **1976**, *98*, 7414.

15. Van Beylen, M. B.; Roland, B.; King, G. S. D.; Aerts, J. *J. Chem. Res., Synop.* **1985**, 388.

## Synthesis of Substituted 1,3-Butadienes Via Cyanocuprate-Mediated Transmetalations of Vinylstannanes

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Vinylstannanes have been widely used as masked vinyl anion equivalents in organic synthesis.[1] Transmetalation of vinylstannanes with Me$_2$Cu(CN)Li$_2$ or Me(2-Th)Cu(CN)Li$_2$(2-Th=2-Thienyl) gives in situ generated vinyl mixed higher order(HO)cyanocuprate reagent, which is utilized for the conjugate addition of enone[2] and epoxide opening reaction[3] in regiospecific manner. Palladium-catalyzed cross-coupling reaction of vinylstannanes with vinyl triflates[4] or vinyl iodides[5] is effective for the stereospecific synthesis of conjugated dienes. However, there has been no report on the cyanocuprate-mediated transmetalations of trimethylstannyl alkenes and their synthetic applications except 1,4-*bis*-trimethylstannyl-1,3-butadiene.[6] Furthermore, coupling reaction[7] of vinyl triflates with lithium dialkylcuprates affords to give the corresponding olefin, but it fails to prepare the substituted 1,3-butadienes.

In this paper we wish to report (i) in situ vinyl HO cyanocuprate formation from transmetalation of trimethylstannyl alkenes and (ii) stereospecific synthesis of substituted 1,3-
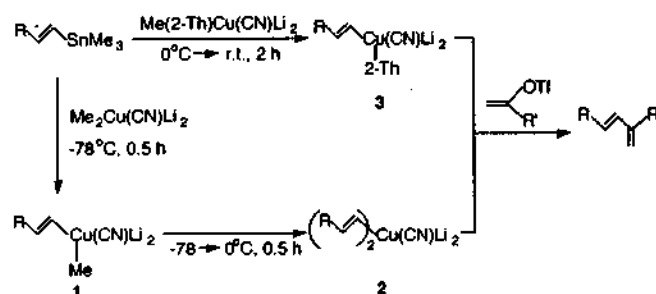
Scheme 1.

butadienes *via* coupling reaction of the vinyl HO cyanocuprates with vinyl triflates. Treatment of trimethylstannyl alkene[8] with Me$_2$Cu(CN)Li$_2$ in THF at −78 ℃ for 0.5 h led to Cu/Sn exchange to give in situ generated mixed HO reagent 1 as shown in Scheme 1. Reaction of 1 with vinyl triflate at −78 ℃ appeared to be proceeded with virtually completely selective substitution of methyl residue, whereas addition of an enone[9] smoothly effected 1,4-addition of vinyl residue. For example, reaction of in situ [Ph(C=CH$_2$)](Me)Cu(CN)Li$_2$, generated from transmetalation of 1-phenyl-1-trimethylstannyl ethene and 1 equiv of Me$_2$Cu(CN)Li$_2$ at −78 ℃, with 1-trifluoromethanesulfonyloxy-3,3,4,4-tetrahydronaphthalene gave 1-methyl-3,3,4,4-tetrahydronaphthalene in 81% yield with trace amount of the corresponding 1,3-butadiene.

Thus, it was necessary to produce in situ HO mixed cyanocuprate without methyl ligand for the exclusive vinyl substitution with vinyl triflates. Fortunately, treatment of trimethylstannyl alkenes with 0.55 equiv of Me$_2$Cu(CN)Li$_2$ at −78° ~0 ℃ for 0.5 h gave reddish divinylcyanocuprate 2 in contrast with tributylstannyl alkenes and no interference was observed with tetramethyltin in the second transmetalation. Reaction of 2 with vinyl triflates smoothly proceeded with disappearing of red color and 0.75 equiv of the reagent was required for the completion of the reaction.

Anticipating the formation of in situ HO cyanocuprate not having methyl ligand, was also examined transmetalation of trimethylstannyl alkenes using Me(2-Th)Cu(CN)Li$_2$. In spite of somewhat slower process, Me(2-Th)Cu(CN)Li$_2$ was also found to undergo in situ ligand exchange with trimethylstannyl alkenes, and the resultant greenish vinyl HO cyanocuprate 3 coupled with vinyl triflates to give substituted 1,3-butadienes.

As shown in Table 1, various structurally different 1,3-butadienes could be prepared by this method without appreciable side products. The reaction worked well with 1 or 2-trimethylstannyl alkenes and aliphatic or cyclic vinyl triflates. Divinyl HO cyanocuprate generated in situ was more reactive than the corresponding (vinyl)(2-Th)Cu(CN)Li$_2$ and tetramethyltin didn't interfere with the substitution of vinyl group during coupling reaction. Significantly, it has been shown that the transmetalation of trimethylstannyl alkenes and the coupling reaction with vinyl triflates occurred stereospecifically with respect to the double bond. Treatment of 2-trifluoromethanesulfonyloxy-1-heptene with (PhCH=CH)(L)Cu(CN)Li$_2$(L=PhCH=CH or 2-Th) gave (1*E*)-1-phenyl-3-pentyl-1,3-butadiene with none of the (1*Z*)-isomer detected by ^{1}H NMR. Similar treatment of 4-*tert*-butyl-1-trifluoromethanesulfonyloxy-1-cyclohexene with (PhCH=CH)$_2$Cu(CN)Li$_2$ gave