Communications to the Editor

Novel Organometallic Ionophore with Specificity toward Li^+

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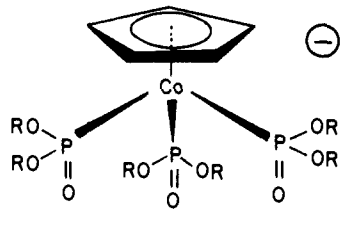
The preparation of synthetic ionophores has been the subject of intensive study ever since the discovery of naturally occurring ionophoric antibotics.[1-4] Ionophores selective to Li^+ ions[5-13] have received special interest in view of the importance of Li^+ in the treatment of manic depressive patients.[14,15] The presently known ionophores for alkali metal ions may be classified into two main groups: crown ethers[1,6-8,10] and open-chain ligands with etheric and carbonylic oxygens[5,9,11,16] to which the metal is probably bound. We report here a new class of ionophores for alkali metal ions: the organometallic ligands $[(C_5H_5)Co[P(O)(OR)_2]_3]^-$ (**1**).[17] The



ligand with R = C_2H_5 (L^- hereafter) has specific ionophoric properties toward Li^+.

Organometallic ligands **1** form compelxes with a variety of transition- and rare-earth-metal ions[18-21] in which the metal ion is bound to the three P=O oxygens. Recently, L^- was found to bind to alkali metal ions in methanol[22] as well as in water.[23] The association constants in these two solvents follow the trend $H^+ > Li^+ > Na^+ > K^+$, with those in methanol about 3 orders of magnitudes greater than those in water.

We studied the ionophoric properties of L^- by following its effect on the rate of transport of Na^+ and Li^+ across artificial phospholipid vesicles using ^{23}Na and ^7Li NMR. The intravesicular and extravesicular Na^+ and Li^+ signals were separated by adding the shift reagent $Dy(TPP)_2^{7-}$ (TPP = tripolyphosphate) to the extravesicular solution.[24] This shift reagent, which has been used

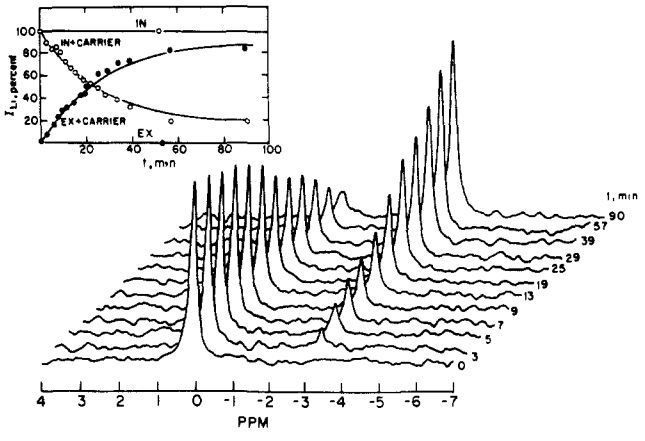


Figure 1. Time course of Li^+ efflux measured by ^7Li NMR. Vesicles were loaded with 75 mM NaCl and 75 mM LiCl; the extravesicular solution contained 150 mM KCl and 3.5 mM $K_7Dy(TPP)_2$. At time zero 100 μM of the sodium salt of L^- was added. The solid lines in the insert are the result of a fitting procedure, assuming an exponential decay.

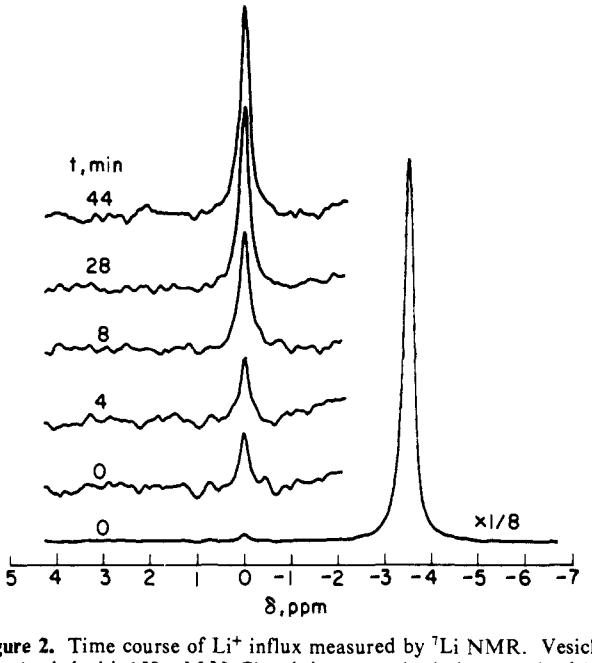


Figure 2. Time course of Li^+ influx measured by ^7Li NMR. Vesicles were loaded with 150 mM NaCl and the external solution contained 150 mM LiCl and 3.5 mM $K_7Dy(TPP)_2$. At time zero 200 μM of the sodium salt of L^- was added.

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to shift the resonances of ^{23}Na and ^{39}K,[25-31] proved to be an efficient shift reagent for ^{7}Li as well.

A typical experiment was performed as follows. Large unilamellar egg phosphatidylcholine vesicles (LUV)[32] were loaded with NaCl, LiCl, or a mixture of the two. The external medium was changed to KCl by dialysis. In the presence of the shift reagent, the residual extravesicular signals of ^{23}Na or ^{7}Li shifted to higher field. Following the addition of L^-, the transport of Li^+ and Na^+ was clearly seen by the simultaneous decrease in intravesicular signals and increase in extravesicular ones (Figure 1). The unfacilitated transport of Na^+ and Li^+ was negligible in the timescale of the experiment. The fact that the shift between the intra- and extravesicular signals remained constant throughout the experiment indicated that the $Dy(TPP)_2^{7-}$ shift reagent did not penetrate the vesicles. In order to eliminate the possibility that the changes in signal intensities were the result of rupture of the vesicles caused by L^-, we followed the inward transport of ^{7}Li. The observed increase of the intravesicular ^{7}Li signal indicated that we were observing a genuine transport (Figure 2).

The time course of the process measured by the integrated areas in each experiment was phenomenologically fitted to an exponential function giving an apparent rate constant, k. The values of k calculated from the intravesicular signal intensities and those calculated from the extravesicular signals, for each experiment, were the same within the experimental error. The apparent rate constant was found to be proportional to the concentration of the carrier L^-. For example, in an experiment with vesicles loaded with 150 mM NaCl the k values for the transport of Na^+ were 3.2, 6.2, 8.7, 13.8, 17.9, and 26.7 $\times 10^{-3}$ min^{-1} for L^- concentrations 0.091, 0.182, 0.30, 0.40, 0.60, and 0.80 mM, respectively, giving $k/[L^-] = 33 \pm 3$ M^{-1} min^{-1}. In similar experiments with vesicles loaded with 150 mM LiCl, the k values for the transport of Li^+ were 2.6, 4.2, and 38.6 $\times 10^{-3}$ min^{-1} for L^- concentration of 0.01, 0.025, and 0.2 mM, respectively, giving $k/[L^-] = 208 \pm 50$ M^{-1} min^{-1}. These results are consistent with a 1:1 ligand to metal complex as the active species in the transport. Preliminary results indicated that the rate of transport of Li^+ is inversely proportional to Li^+ concentration and increases with H^+ concentration, pointing at LiL-HL exchange as a possible mechanism for the facilitated transport of Li^+. The selectivity in the rates of transport in favor of Li^+ over Na^+ was further demonstrated by competition experiments using vesicles loaded with mixtures of NaCl and LiCl. For vesicles loaded with 75 mM NaCl and 75 mM LiCl, the ratio of the rates of transport of Li^+ and Na^+ was 22 ± 6. In vesicles loaded with 110 mM NaCl and 40 mM LiCl, this ratio was about 40. The relative Li^+/Na^+ selectivity may further increase at lower $[Li^+]/[Na^+]$ ratios, as the rate of Li^+ transport is inversly proportional to the Li^+ concentration, while that of Na^+ is less sensitive to the $[Li^+]/[Na^+]$ ratio. The selectivity of L^- in favor of the Li^+ ions by a factor greater than 40 compares favorably with other Li^+ ionophores.[5-12]

The efficiency of L^- as a carrier compared to a known ionophore was determined by measuring the values of the apparent rate constants for the transport of Li^+ and Na^+ induced by monensin.[33] For vesicles loaded with 75 mM LiCl and 75 mM NaCl, the values $k/[\text{ionophore}]$ obtained for monensin were 1.4 $\times 10^3$ and 2.6 $\times 10^4$ M^{-1} min^{-1} for Li^+ and Na^+, respectively. For comparison, $k/[\text{ionophore}]$ values for L^- were 750 and 27 M^{-1} min^{-1} for the same two cations under identical conditions. It is hoped that chemical modification of the ligand will yield other ionophores with improved properties.

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Epoxidation of Olefins by Iodosylbenzene Catalyzed by Binuclear Copper(II) Complexes

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The enzyme tyrosinase catalyzes the oxygenation of phenolic derivatives by dioxygen to give catechols. The active site of the enyzme consists of a binuclear cuprous center which binds O_2 to give a peroxo-bridged dicupric center analogous to that found in oxyhemocyanin.[1] Recent studies by Karlin and co-workers on reactions of binuclear cuprous complexes with dioxygen have been dramatically successful both in mimicking the enzymatic reaction by causing the hydroxylation of an aromatic group in the ligand by dioxygen[2] and in synthesizing analogues of the peroxo-bridged binuclear cupric species.[3] However, these synthetic binuclear copper systems have not been reported to catalyze the oxygenation of externally added substrates by dioxygen or by other sources of oxygen atoms.

We have reported our observations that simple metal salts, including those of copper, are capable of catalyzing the epoxidation of olefins by iodosylbenzene in acetonitrile.[4,5] In the case of cupric nitrate, we observed a marked catalyst concentration effect and our preliminary evidence indicated that iodosylbenzene complexes were formed in a ratio of one OIPh per two cupric ions.[4] This result prompted us to investigate binuclear cupric complexes as potential catalysts for our system. We report here that **1** and **2**, binuclear cupric complexes of ligands synthesized by Karlin and co-workers,[2,6] and **3**, a binuclear cupric complex synthesized by Lippard and co-workers,[7] catalyze the epoxidation of olefins by iodosylbenzene. The mononuclear analogue of **1**,[8] i.e. **4**, is not an effective catalyst under the same reaction conditions, and **1**-**3** are also considerably better catalysts than cupric triflate (**5**).

Complexes **1** and **2** were prepared and isolated by reacting the ligands with cupric triflate in acetonitrile. Complex **3** was prepared in solution by reaction of the ligand with cupric triflate in methanol. In a typical oxygenation experiment, 0.040 g (0.18 mmol) of iodosylbenzene was added all at once to a solution of

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