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SYNTHESIS AND BINDING PROPERTIES OF LITHIUM-SELECTIVE [14]-O_4 MACROCYCLES AND THEIR USE IN A LITHIUM ION-SELECTIVE ELECTRODE

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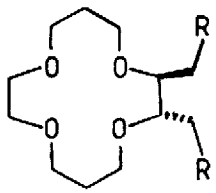
Summary: A series of chiral 14-crown-4 derivatives have been prepared and examined as selective ionophores for lithium ions by incorporation into polymeric membrane electrodes: a dibutylamide derivative exhibits good electrode characteristics with a lithium to sodium selectivity of 400:1.

The use of neutral lipophilic ion-complexing agents as sensing ionophores in ion-selective electrodes has been well-established.[1] The potentiometric selectivity of such sensors for a given ion is determined primarily by the complexation specificity of the ionophore involved. Several neutral carriers for the lithium ion have been reported which exhibit only moderate selectivity for lithium over sodium.[2-7] As sodium is the primary interferent ion for lithium assay in serum (as is required in the clinical monitoring of patients being prescribed Li_2CO_3 for manic depression) or in enriched brines, high discrimination for binding lithium is essential.

It has been established that derivatives of 1,4,8,11-tetraoxacyclotetradecane (14-crown-4) selectively bind lithium cations in the presence of competing Na^+, K^+ and Ca^{2+} cations.[2-4] The reported selectivities - in particular for Li^+ over Na^+ - are less than ideal if Li^+ is to be assayed under clinically relevant conditions i.e. monitor $[Li^+]$ in the range 3 mM to 0.3 mM, in the presence of 140 mM Na^+, 4.3 mM K^+ and 1.26 mM Ca^{2+}. Nevertheless several 14-crown-4 derivatives have been examined as neutral carriers in solvent polymeric ion selective electrodes.[5,6]

We sought to prepare a series of mono- and difunctionalised [14]-O_4 derivatives in which lithium/sodium selectivity was enhanced. To do this we incorporated strong σ-donors (e.g. amides) that favour binding to cations of high charge density.[7,8] In addition, such donors were required to be geometrically disposed so as to bind effectively to a lithium ion sitting in the plane of the O_4 ring. Accordingly the substituents were located on the two-carbon chain in the O_4 ring, with an intervening methylene group. When the donor binds to lithium, a six-ring chelate is then generated: chelate rings of this size also exhibit a preference to bind lithium with respect to sodium as noted in related work with macrocycles[9] and in enolate association with β-keto esters or β-diketones.[10] These requirements necessitated that the disubstituted crown was chiral - with the secondary donors trans-disposed and set up to bind to lithium on opposite faces of the O_4 plane.

Reaction of 1,10-dichloro-4,7-dioxadecane with (S)-1,4-benzyloxymethylbutane-2,3-diol in the presence of LiO^{t}Bu in ^{t}BuOH[11,12] afforded 1a (51%) $[\alpha]_D^{20}$ = -10.5 (c.1.0, CH_2Cl_2). Debenzylation ($Pd(OH)_2/C/H_2$; EtOH-TsOH) afforded the diol 1b (91%) $[\alpha]_D^{20}$ = -11.5 (c.1.0, CH_2Cl_2), and tosylation yielded the ditosylate 1c (48%, mp 74-5°C). Addition of cyanide (KCN/DMSO/3h/95°C) afforded the dinitrile 1d (50%, mp 78-9°C) and methanolysis (MeOH/dry HCl) afforded the dimethyl ester 1e (54%), $[\alpha]_D^{20}$ = -39.5 (c.1.0, CH_2Cl_2). Following ester hydrolysis (Me_4NOH/MeOH-H_2O) and acid chloride formation (PCl_5, CH_2Cl_2), the bis N,N-dibutylamide 1f was isolated as a colourless oil (78%) $[\alpha]_D^{20}$ = -33.7 (c.1.0, CH_2Cl_2) after reaction with Bu_2NH/Et_3N in CH_2Cl_2. In a parallel set of experiments starting from racemic 1-benzyloxymethyl-propane-2,3-diol, the monosubstituted analogues 2a-2e were prepared, culminating in the synthesis of the N,N-dimethylamide derivative, 2g. When the additional donors (either ether oxygen, amide or ester carbonyl) bind to the Li^+ cation complexed in the plane of the ring, molecular modelling experiments suggest that (with the C-substituent in a pseudo-axial site[13]) the oxygen lone-pair of the acid derivatives particularly is ideally disposed to interact with the bound cation. The difunctionalised derivatives should also tend to disfavour any competitive 2:1 (ligand:cation) binding with Na^+ and K^+, leading to enhanced discrimination in favour of Li^+.



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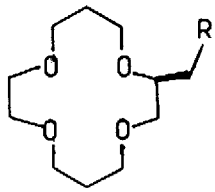

2

R = a) X=Y=OCH_2Ph
b) X=Y=OH
c) X=Y=OTs
d) X=Y=CN
e) X=Y=CO_2Me
f) X=$CONBu_2$
g) Y=$CONMe_2$

Titration of the derivatives 1 and 2 with LiCl in d^4-methanol was monitored by ^{13}C NMR and sharp curve bends were obtained at 1:1 stoichiometries. That the amide group was bound to Li^+ in 2g was confirmed by the observed ^{13}C NMR coordination shift ($\Delta\delta_c$ = 0.64 ppm for amide resonance) and by i r. spectroscopy ($\Delta\nu_{CO}$ = 20 cm^{-1}, in a Nujol matrix). Polymeric membranes were prepared under standardised conditions with 1.2% crown ether, 0.4% potassium tetrakis (4-chlorophenyl)borate, 65.6% ortho-nitrophenyl octyl ether and 32.8% PVC.[14] Potentiometric measurements were carried out in a flow system using the fixed interference method evaluating response to Li^+ in the activity range 10^{-5} to 0.1 mol

dm^{-3}, in the presence and absence of interfering cations (K^+, Na^+, Ca^{2+}). Electrodes based on 1a, 2a, 1e and 1f showed a near-Nernstian response in the range 0.1 - 10^{-5} mol dm^{-3} Li^+ (310 K, 60 mV per decade) in the absence of interfering ions with 1f exhibiting a detection limit of $10^{-5.4}$. Addition of trioctylphosphine oxide to the cocktail tended to diminish the sensitivity but marginally improved the response as shown by a marginally improved slope of emf response versus cation concentration. In all cases, response times were good (<30 sec) and electrode stabilities were excellent (reproducible results after 3 months). In the presence of background interfering ions which mimic serum conditions, the electrode based on 1f behaved best. It showed a detection limit of $10^{-3.5}$ ($10^{-3.8}$ in the presence of 150 mM Na^+ only) - superior to previously reported systems - with a slope in the clinical range of 58 mV and a selectivity coefficient log $K^{pot}_{Li^+,Na^+}$ = -2.6. Its behaviour is compared to the commercial Li^+ ion-selective electrode (Philips 561-Li^+) in Figure 1. These electrode characteristics are not optimised, yet it is clear that electrodes based on 1f - or its congeners - offer considerable promise for the determination of Li^+ activities in biological systems. Moreover as 1f is chiral (and C-2 symmetric), it may prove a good candidate as a chiral auxiliary in enantioselective lithiations of prochiral substrates.

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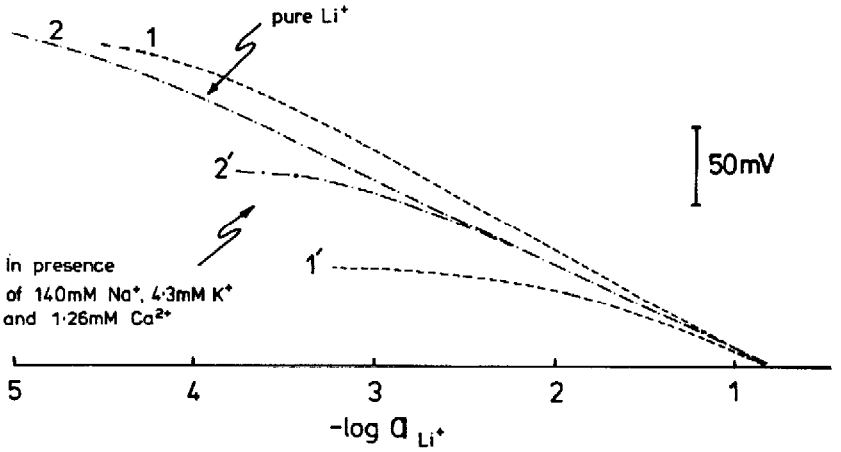

Figure 1. Response of ion-selective electrodes to varying lithium activities : 1,1'-Philips Li^+ISE (561), 2,2'-ISE based on 1f at 310 K in absence (1,2) and presence (1',2') of Na^+ (140 mM), K^+ (4.3 mM), Ca^{2+} (1.26 mM).

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