hand if we look at the parameters for structure **21** (just after the transition state), the two bonds C_β–H_2 and O_2–H_1 are now completely formed, while the C_α–O_1 bond remains only about 25% formed. It thus appears as if in this addition the transfer of two protons H_1 and H_2 toward O_2 and C_β, respectively, is simultaneous and occurs before the C_α–O_1 bond is complete at or just after the transition state. Thus there is no intermediate on the reaction pathway, which is thus concerted but quite asynchronous.

In conclusion, the reaction of water dimer with the ketenimine is clearly favored relative to reaction with a single water molecule and approximates closely the measured experimental parameters in aqueous solution. The calculated transition state is reached with virtually no proton transfer from water to the adjacent carbon, but the reactants enter the transition state correctly oriented for subsequent proton transfer. The reaction therefore has the characteristics of a "preassociation mechanism"[22] where although proton transfer does not contribute to the overall driving force of the reaction, the reactants are oriented in the optimal fashion to permit this in a rapid (and concerted) subsequent step.

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Lipophilic Lithium Ion Carriers

Abraham Shanzer,* David Samuel, and Rafi Korenstein

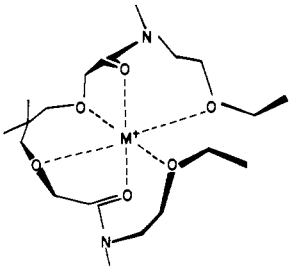
Contribution from the Departments of Organic Chemistry, Isotope Research, and Membrane Research, The Weizmann Institute of Science, Rehovot, Israel. *Received October 26, 1982*

Abstract: The design, preparation, and properties of a new series of lipophilic lithium ion carriers are described. The structure of these carriers is based on an acyclic system in which a hexafunctional lipophilic envelope is formed around the metal ion in an octahedral arrangement. The synthesis involves a series of condensation reactions using a cyclic tin–oxygen compound as an activated diol precursor. The carrier properties for lithium ions were demonstrated by in vitro experiments on liposomes using a fluorescence assay. The potential pharmacological applications of these ionophores are discussed.

Introduction

Selective ion carriers are gaining increasing interest as tools for the analysis and separation of metal ions as well as for many biological applications. Ionophores for divalent cations and some alkali ions are well known,[1] but so far, very few carriers specific for lithium ions have been described. Lithium ion carriers could have a wide range of applications. One potential pharmacological application for such carriers would be, for instance, the enhancement of the uptake of lithium into the brain and other tissues. Lithium salts have extensively and successfully been used for the treatment of manic depression and some other neurological and psychiatric disorders.[2] A major problem in lithium therapy is, however, the slow penetration of lithium through the blood brain barrier and across other membranes.[3] This results in a delayed onset of action and necessitates the administration of relatively large doses, which may be the cause of many undesirable side effects.[4] In order to examine the potential use of ionophores and in order to enhance the penetration of lithium ions into the central nervous system, we describe here the preparation and properties of a number of such lipophilic ligands.

The design of lipophilic ionophores for lithium cations is a difficult problem owing to the fact that the ions are smaller than sodium and potassium but strongly hydrated in aqueous solution.[5] It is mainly for this reason that few lithium ionophores have been synthesized. Examples of selective ligands for lithium ions relative to sodium ions are the cryptands[6] and spherands,[7] which reached remarkable binding selectivity. Some macrocyclic crown ethers[8,9] as well as acyclic polyethers[10] and acyclic dioxa diamides[11] have also been synthesized which transport lithium ions in preference to sodium ions through artificial membranes. However, the ratio of the selectivity of these carriers proved to be rather moderate and did not exceed a value of 10.[8-11] In order to improve the transport selectivity and at the same time increase the lipophilicity, we have synthesized a series of acyclic, hexafunctional dioxa diamide derivatives. These systems were expected to wrap around



the lithium ion in an octahedral arrangement using six binding sites, thus forming a lipophilic envelope of aliphatic residues. In this publication we wish to describe the preparation of such hexafunctional ionophores and to report on some of their carrier properties.

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Table I. Spectroscopic Properties of Dioxa Diamide Derivatives

compd	mass spectrum,[a] m/e	IR spectrum,[b] (cm^{-1}) CO	IR spectrum,[b] (cm^{-1}) COC	NMR spectrum,[c] chemical shifts (ppm) $(CH_3)_2C-$	$(CH_3)_2-CCH_2-$	$-OCH_2-CO-$	$-CONCH_2-$	$-CH_3$	$-(CH_2)_5-$	others
3	614	1735 1650	1190 1100 1050	0.95 (s)	3.30 (s)	4.05 (s)	3.4 (m)	0.95 (m)	1.3 (m)	2.5 (t, J = 6 Hz) $-CH_2COO-$
4		1700 1650	1120	1.0 (s)	3.48 (s)	4.36 (s)	3.48 (m)	1.0 (m)	1.36 (m)	2.8 (t, J = 5 Hz) $-CH_2COOH$ 3.83 (t, J = 5 Hz) $-NCH_2CH_2COOH$ 8.3 (s) $-COOH$
6	414	1660 1540	1130	0.97 (s)	3.30 (s)	3.93 (s)	3.25 (t, J = 6 Hz)	0.88 (t, J = 6 Hz)	1.29 (m)	
8	558	1650 1465	1115	0.94 (s)	3.30 (s)	4.12 (s) 4.17 (s)	3.5 (t)	0.88 (m)	1.26 (m)	3.5 (m) $-CH_2OCH_2-$
9	541[d]	1640	1100	1.0 (s)	3.46 (s)	4.33 (s)	3.46 (m)	1.0 (m)	1.33 (m)	2.73 (t, J = 6 Hz) $-CH_2CO-$ 3.66 (q, J = 6 Hz) $-CONCH_2CH_3$

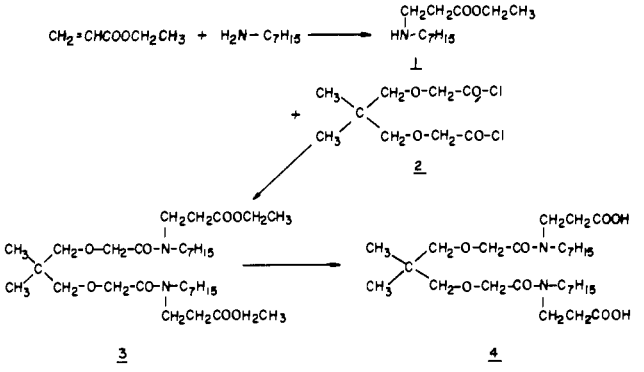
[a] The molecular ion peaks are given unless otherwise stated. [b] The IR spectra have been recorded in Nujol. [c] The NMR spectra have been recorded in $CDCl_3$ solution and the chemical shifts given are relative to internal $(CH_3)_4Si$. Only the indicative signals are quoted. [d] m/e 541 corresponds to the molecular ion peak $-CH_2CH_2CON(CH_2CH_3)_2$.

Table II. Analytical Data of Dioxa Diamide Derivative

compd	molecular formula	elemental analysis, calcd, % C	H	N	found, % C	H	N
3	$C_{33}H_{62}O_8N_2$	64.46	10.16	4.56	64.20	10.32	4.60
4	$C_{29}H_{54}O_8N_2$	62.34	9.74	5.01	62.52	10.01	4.95
6	$C_{23}H_{46}O_4N_2$	66.63	11.18	6.76	66.85	11.30	6.50
8	$C_{31}H_{62}O_6N_2$	66.63	11.18	5.01	66.42	11.02	5.22
9	$C_{37}H_{72}O_6N_4$	66.43	10.85	8.37	66.35	11.01	8.25

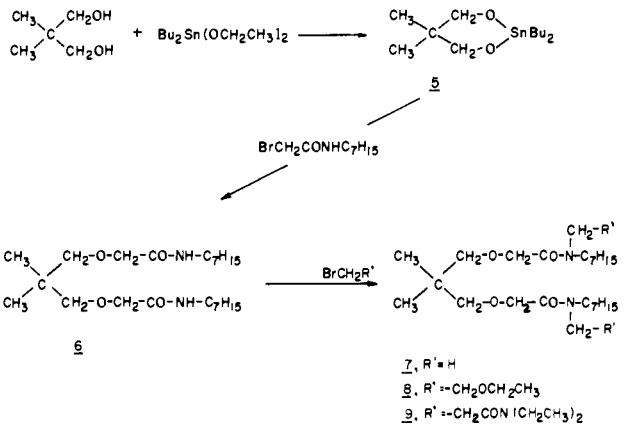
Synthesis of Lithium Ion Carriers

The preparations of dioxa diamides described previously[11] have been based on the decomposition of diazoethyl acetate in the presence of the diol followed by hydrolysis to the dicarboxylic acids. The latter are then converted to the corresponding acyl halides and condensed with amines to produce the diamides. We have used a similar reaction scheme for the preparation of the diester **3** and the related diacid **4**. In addition, the tetroxa diamide **8** and dioxa tetramide **9** have also been synthesized by a novel route in which the stannoxane **5**[12] was used as an activated diol precursor.



The diester **3** was prepared by addition of heptylamine to ethyl acrylate[13] and condensation of the resulting secondary amine **1** with 5,5-dimethyl-3,7-dioxanonanedioyl dichloride **2**.[11] Mild hydrolysis of the diester **3** with potassium carbonate[14] yielded the corresponding diacid **4** in high yield (89%).

The preparation of the tetroxa diamide **8** and the dioxa tetramide **9** was based on the use of stannoxane **5**[12] as an activated diol precursor. The cyclic stannoxane **5** was readily prepared by reacting 2,2-dimethyl-1,3-propanediol with dibutyltin diethoxide and treating it in situ with *N*-heptylbromoacetamide in order to produce *N,N'*-diheptyl-5,5-dimethyl-3,7-dioxanonane (**6**). Alkylation of **6** in the presence of sodium hydride with either 2-bromoethyl ether or 3-bromo-*N,N*-diethylpropionylamide gave the expected tetroxa diamide **8** and dioxa tetramide **9**, respectively. The same reaction scheme was also applied for preparing the known tetrafunctional parent compound **7**[11] via alkylation of the intermediate diamide **6** with methyl iodide.



Each new compound was characterized by its spectroscopic properties (summarized in Table I). The IR spectra of the compounds show absorptions characteristic of amide and ether functions. Substitution on nitrogen is evident both from the IR spectra and from the proton NMR spectra. Thus the diester **3** shows a characteristic ester frequency at 1735 cm^{-1} and the diacid **4** an absorption at 1700 cm^{-1} attributable to the carboxyl group. The methylene protons adjacent to the propionyl carbonyl in the NMR spectra of the diester **3**, diacid **4**, and tetramide **9** all appear as well-resolved triplets between 2.5 and 2.8 ppm, whereas the acidic proton of the diacid **4** absorbs at 8.3 ppm as an exchangeable singlet.

Proton NMR spectra of the tetroxa diamide **8** in chloroform solution containing lithium picrate indicates that the ionophore indeed binds to the cation. Addition of lithium picrate to a chloroform solution of the ether **8** results in a downfield shift of the protons adjacent to the ether and amide functions, whereas the other protons remain virtually unchanged. The NMR spectra of the tetroxa diamide **8** with and without lithium picrate are given

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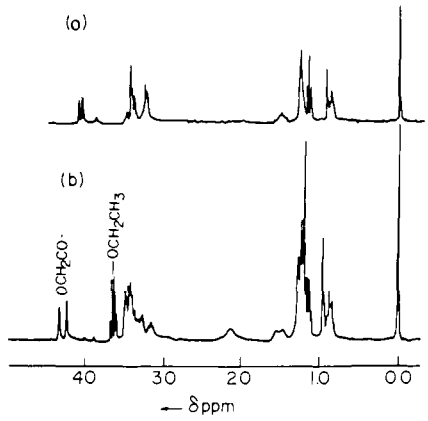

Figure 1. NMR spectra of tetroxa diamide **8** in the absence (a) and presence (b) of lithium picrate.

in Figure 1, showing a pronounced shift of the ethyl ether function upon addition of lithium ions, as the quartet moves out of a previously unresolved multiplet.

Transport Properties of Lithium Carriers

In order to evaluate the potential of these compounds as ion carriers for various biological applications, their ability to transfer lithium ions through vesicular lipid bilayers (liposomes) was tested. Liposomes are generally regarded as appropriate models for biological membranes,[15] and the carrier capability of new ligands through such vesicles is a good indication of their ability to penetrate into regions of biological tissues surrounded by lipophilic membranes. Equilibrium constants are of little predictive value for this purpose since the efficiency of a carrier molecule to transport a specific ion across a membrane depends on several factors, including rate of uptake and of release as well as equilibrium constants.[16]

The efficiency of the carrier was studied by using the release of a highly fluorescent internal probe as a measure of lithium ion transport through the lipid bilayer. The highly water-soluble fluorescent probe 6-carboxyfluorescein was encapsulated in multilamellar vesicles (liposomes) prepared from soybean lipids. When the liposomes were loaded with a high concentration of dye, the fluorescence due to the self-quenching process was reduced.[17] When various ionophores were added to a suspension of these liposomes in the presence of lithium salts, a gradual increase in fluorescence was observed owing to the release of dye out of the liposomes into the surrounding solution with concurrent dilution. The large dilution of the dye on the outside of the liposomes diminishes self-quenching, causing an increase in the intensity of the fluorescence.

Kinetic analysis of carrier-induced fluorescence increase fits a pseudo-first-order reaction (Figure 2). Direct comparison of the relative efficiencies of the studied carriers is obtained from the rates of the transmembrane dye transport shown in Figure 2. It is evident that the most efficient carrier for lithium ions is the tetroxa derivative **8**. The tetramide **9** and the diester **3** are less efficient, and the secondary amide **6** is almost ineffective. The tetroxa derivative **8** carries lithium ions as efficiently as valinomycin carries potassium ions. It should be stressed that the rates of permeation through the first layer of the multilayered vesicles gave similar rates to those obtained from the single bilayer vesicles, demonstrating the independence of the release on the radius of the membrane curvature.

In order to obtain an estimate for the carrier selectivity of the most potent carrier, the tetroxa derivative **8**, equilibrium partition experiments were performed in a water/methylene chloride system

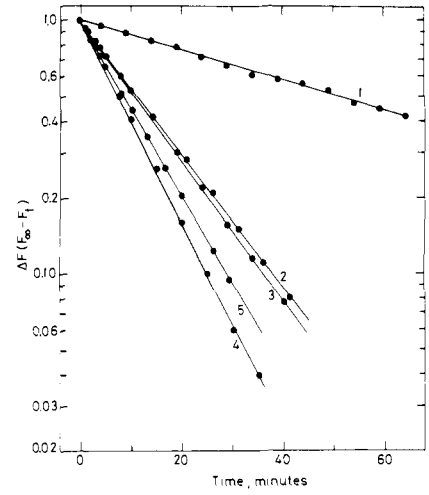

Figure 2. Kinetics of carrier-induced fluorescence change (ΔF) from multilamellar liposomes. The amplitudes of fluorescence change were normalized: excitation, 492 nm; emission, 520 nm. F_∞ is fluorescence at steady state: (1) amide **6**, $k = 2.2 \times 10^{-4}$ s^{-1}; (2) ester **3**, $k = 1.02 \times 10^{-3}$ s^{-1}; (3) amide **9**, $k = 1.07 \times 10^{-3}$ s^{-1}; (4) ether **8**, $k = 1.52 \times 10^{-3}$ s^{-1}; (5), valinomycin, $k = 1.34 \times 10^{-3}$ s^{-1}. Curves 1–4 were obtained in the presence of 200 mM Li_2SO_4 whereas curve 5 was obtained in the presence of 200 mM K_2SO_4.

with lithium chloride and sodium chloride. Analyses of these experiments were in agreement with a 1:1 carrier/ion complex[18] and provided equilibrium partition constants K of 0.05 for the lithium salt, and of 0.0012 for the sodium salt.[19] These results demonstrate a selectivity factor of carrier **8** for lithium ions over sodium ions of more than 40 and thereby exceeds the selectivity of any lithium carrier obtained so far.[8-11]

The same ionophore (ionophore **8**) has also been shown to render planar lipid bilayers (consisting of phospholipids) permeable to lithium cations,[20] the selectivity being Li^+ (1) > ClO_4^- (0.7) > Na^+ (0.07) > K^+ (0.016) > Rb^+ (0.0095) > Cs^+ (0.0083) > Cl^- (0.001). Magnesium and sulfate were unpermeable.

Discussion

In a search for selective lithium ion carriers for possible pharmacological applications, we have proposed a series of acyclic, hexafuncional ligands. Using liposomes as models of biological membranes and a fluorescence assay, these compounds have been found to transport lithium ions through lipophilic membranes. In addition, equilibrium partition experiments on the most potent ligand demonstrated its high carrier selectivity for lithium ions over sodium ions. Our results also lend support to the suggestion that lithium can be coordinated both tetrahedrally and octahedrally.[21] The octahedral coordination of lithium has been inferred from the crystal structure of aluminum silicates and other minerals. The lithium ionophores described here are likely to be also octahedrally coordinated which accounts for their high transport capability. Preliminary experiments with the most potent of the ligands, the ether **8**, on experimental animals (rats), have indicated that this ligand can enhance lithium uptake into the brain when administered intraveneously or intraventricularly.[22]

Theses results taken together are, we believe, the first indication of the specific lithium ion carrying properties of a new series of ionophores which could have extremely interesting pharmacological applications in lithium therapy for manic depression and in the treatment of lithium toxicity. Other applications are in the

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manufacture of ion selective electrodes and lithium batteries and in the extraction of lithium from sea water and waste brines.

Experimental Section

6-Carboxyfluorescein Assay. Soybean lipids (Sigma) (15 mg) were dissolved in chloroform which was later evaporated, producing a thin film of lipid. A solution (0.5 mL) containing 200 mM of lithium 6-carboxyfluorescein salt (6-carboxyfluorescein from Eastman pH 7) was added. The solution was vortexed thoroughly, producing multilamellar vesicles. The preparation was frozen and thawed twice; 25 mL of 200 mM Li_2SO_4 was added, and the suspension was passed through a Sephadex G-50 column (eluting with 200 mM Li_2SO_4) to remove untrapped carboxyfluorescein. The first elution band was collected. The multilayer vesicles were centrifuged down (17 000*g*, 15 min) and used as such. A characteristic assay consisted of 0.003 mL of bangosomes in 3 mL of 200 mM Li_2SO_4. The concentration of the ionophores studied was 10 μM. In the case of preparing single bilayer vesicles additional sonication was performed after the vortex step and before passage on the G-50 column. The vesicles were spinned down at 75000*g* for several hours. The emission of the 6-carboxyfluorescein-loaded vesicles was measured at 520 nm (excitation 492 nm). To a 3 mL suspension of vesicles 10 μM of ionophore as added. The ionophore induced increase of fluorescence was monitored continuously on a Perkin-Elmer MPF-44A fluorescence spectrophotometer.

Equilibrium Partition Experiments. Aqueous solutions of picric acid (2.10^{-4} M) and either LiCl (0.3 M) or NaCl (0.5 M) were prepared and adjusted to a pH value of 7.0 with the corresponding hydroxides. Volumes of 3 mL of each were allowed to equilibrate with equal volumes of methylene chloride and the concentrations of each salt in each phase (methylene chloride and water) determined by measuring the concentrations of the picrate through its UV absorption at 377 nm (ϵ 13 700) and at 356 nm (ϵ 19 200), respectively. The experimental data were analyzed according to Eisenman[18] by inputing the observed values and varying the two-phase concentration equilibrium constant K for the formation of the ion–ionophore complex and the equilibrium constant K_{IP} for the ion pairing in the organic phase to obtain the best fit with experimental parameters.

Preparation of Ionophores. Ethyl *N*-Heptyl-3-aminopropionate (1). Ethyl acrylate (25 g, 0.25 mol) was dissolved in 50 mL of ethanol. The reaction mixture was cooled to −60 °C, treated dropwise with 37 mL (0.25 mol) of heptylamine, and then allowed to warm up slowly to room temperature; stirring was continued for 2 days. Subsequent concentration of the mixture and distillation in vacuo provided the amino ester **1** as a colorless oil: 29.7 g (0.21 mol, 84%), bp 81–83 °C (17 mmHg); NMR ($CDCl_3$) δ 4.0 (q, 2 H, –OCH–), 2.6 (m, 6 H, $-NCH_2CH_2CO$ and $-NCH_2-$) and 0.8–1.4 ppm (m, 16 H, aliphatic hydrogens).

***N*,*N*′-Diheptyl-5,5-dimethyl-*N*,*N*′-bis[3-(ethyl propionato)]-3,7-dioxanonanediamide (3).** Diacyl dichloride **2** (2 mL, 0.0093 mol) as dissolved in dry methylene chloride and treated dropwise at -5 °C with 2.52 g (0.018 mol) of the amino ester **1**. The mixture was then allowed to warm up to room temperature, and stirring was continued for 24 h. Concentration of the reaction mixture in vacuo and chromatography of the residue on silica gel provided the diester **3**, 4.56 g (0.0074 mol, 79.5%).

***N*,*N*-Diphenyl-5,5-dimethyl-*N*,*N*′-di[3-propionato]-3,7-dioxanonanediamide (4).** Diester **3**, (13.05 g, 0.0212 mol) as dissolved in 150 mL of ethanol and treated with 50 mL of a saturated aqeous solution of potassium carbonate under reflux over night. The two phases separated; the water layer was removed, acidified with dilute HCl, and extracted with ether and the ether phase was washed with water. Concentration in vacuo and chromatography of the residue on silica gel provided the diacid **4**, 10.54 g (0.0189 mol, 89.1%).

***N*,*N*′-Diheptyl-5,5-dimethyl-*N*,*N*′-di[3-(2-oxapentyl)]-3,7-dioxanonanediamide (8), *N*,*N*′-Diheptyl-5,5-dimethyl-*N*,*N*′-bis[3-(*N*,*N*′-diethylpropionylamido)]-3,7-dioxanonanediamide (9), and *N*,*N*′-Diheptyl-*N*,*N*′,5,5-tetramethyl-3,7-dioxanonanediamide (7).** To a solution of 4 mL (0.0148 mol) of dibutyltin diethoxide in 60 mL of toluene was added 1.54 g (0.0148 mol) of 2,2-dimethyl-1,3-proanediol; the reaction mixture was heated under reflux overnight under concurrent removal of ethanol as a binary azeotrope. Then 6.95 g (0.0298 mol) of *N*-heptylbromoacetamide and 0.8 mol pyridine were added and reflux wax continued for 2 h. The crude reaction mixture was filtered, concentrated, and chromatographed on silica gel to provide 3.69 g (0.0086 mol, 58.1%) of the diamide **6**. An amount of 502 mg (0.0012 mol) of diamide **6** in 25 mL of benzene was then treated with 170 mg of sodium hydride; the mixture was heated to reflux under nitrogen 0.405 mL (0.0036 mol) of 1-bromo ether added and heating continued for 7 h. Excess sodium hydride was subsequently destroyed by addition of 95% ethanol–water; the organic layer was separated, washed, dried, and concentrated in vacuo to give an oil residue. Chromatography of the residue on silica gel provided pure tetra ether **8** as an oil, 400 mg (0.00078 mol, 65%). Alkylation of the diamide **6** with 3-bromo-*N*,*N*′-diethylpropionylamide under analogous reaction conditions afforded the dioxa tetramide **9**, in 40% yield, with methyl iodide the diamide **7** in 65% yield.

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Registry No. 1, 85553-27-1; **2**, 65115-09-5; **3**, 84031-86-7; **4**, 85553-28-2; **5**, 36887-65-7; **6**, 85553-29-3; **7**, 58821-96-8; **8**, 80712-94-3; **9**, 84031-87-8; CH_2=$CHCOOCH_2CH_3$, 140-88-5; H_2N-C_7H_{15}, 111-68-2; $Bu_2Sn(OCH_2CH_3)_2$, 1067-41-0; $BrCH_2CONHC_7H_{15}$, 5463-16-1; $BrCH_2CH_2OCH_2CH_3$, 592-55-2; $BrCH_2CH_2CON(CH_2CH_3)_2$, 5437-82-1; Li^+, 17341-24-1; 2,2-dimethyl-1,3-propanediol, 126-30-7; methyl iodide, 74-88-4.