MACROCYCLIC Li^+-SELECTIVE DIAMIDES

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Received December 12, 1990
Accepted January 7, 1991

Several macrocyclic diamides of 4,4,5,5-tetramethyl-3,6-dioxaoctanedioic acid with various N-alkyl substituents have been prepared. Selectivity of these compounds was investigated electrochemically in polymeric (PVC) membranes of ion-selective electrodes.

Some time ago we found[1] that macrocyclic diamides derived from 4,4,5,5-tetramethyl--3,6-dioxaoctanedioic acid have the ability to bind lithium ions selectively. In polyvinylchloride membranes these compounds possess very good properties as ionophores suitable for use in lithium-selective electrodes. In our earlier paper[2] we examined the optimal size of a macrocycle needed for reaching the highest selectivity. Also, we saw that, in addition to the effect of the ring size, selectivity is also affected by the character of the alkyl substituent on the amide nitrogen. This work was devoted to the preparation and study of selective properties of some other cyclic diamines bearing various substituents on amide groups.

EXPERIMENTAL

The melting points were determined using a Kofler hot stage and have been corrected. The mass spectra were recorded with an AEI MS 901 mass spectrometer. The ^{1}H NMR spectra were obtained with a Jeol PS 100 spectrometer at 20 MHz using the CW technique in deuteriochloroform and with hexamethyldisiloxane as the internal standard. Chemical shifts are given in ppm. Elemental analyses were carried out with a Perkin–Elmer 240 Elemental Analyzer. Column chromatography was performed on neutral Al_2O_3 (Merck, 70–230 mesh) or on silica gel (Kieselgel 60; Fluka, 70–230 mesh); Alugram SIL G/UV (Macherey–Nagel) plates were used in TLC with spot detection in UV light or by spraying with Dragendorff's reagent.

Starting Materials

N-(2-Aminoethyl)pyrrolidine, 5,6,7,8-tetrahydro-1-naphthylamine, diphenylamine, 1,12-dodecanediamine, 1,12-dibromododecane and cesium carbonate were commercial products (Fluka). N-Alkyl-4-toluenesulfonamides were prepared by employing the usual procedure, i.e. by reacting amines with 4-toluenesulfonyl chloride in 15% NaOH. 4,4,5,5-Tetramethyl-3,6-dioxaoctanedioyl dichloride was prepared by a reported procedure[3] before each reaction.

Diamines

Oligomethylenediamines were prepared by reacting the corresponding N-substituted 4-toluenesulfonamides with 1,12-dibromododecane in anhydrous dimethylformamide in the presence of Cs_2CO_3 (ref.[4]) with subsequent detosylation using a HBr–phenol mixture or sodium metal in isoamyl alcohol[5]. Cyclic diamine and N,N'-dibenzyl-4,4,5,5-tetramethyl-3,6-dioxa-1,8-octanediamine were prepared by reduction of the corresponding diamides with $LiAlH_4$.

N,N'-*Bis*[2-(1-*pyrrolidinyl*)*ethyl*]-1,12-*dodecanediamine*. The intermediate, N,N'-bis[2-(1-pyrrolidinyl)ethyl]-N,N'-bis(4-toluenesulfonyl)-1,12-dodecanediamine (3·5 g) was detosylated by boiling with 33 ml of freshly distilled 48% HBr and 6·5 g phenol for 8 h. After cooling and addition of ether (20 ml) the precipitated dihydrobromide was isolated by suction. The base was obtained after dissolution in hot water by alkalization with NH_4OH. The raw product was purified on Al_2O_3 by elution with a benzene–methanol mixture (5 : 1). Diamine was obtained as oil (1·25 g; 65%). For $C_{24}H_{50}N_4$ (394·6) calculated: 14·19% N; found: 13·81% N. Mass spectrum: 394 (M^+), 324, 310, 296, 281, 267, 253, 239, 225, 168.

N,N'-*Bis*(*diphenylmethyl*)-1,12-*dodecanediamine* was prepared from N-(diphenylmethyl)-4-toluenesulfonamide and 1,12-dibromododecane through N,N'-bis(diphenylmethyl)-N,N'-bis(4-toluenesulfonyl)-1,12-dodecanediamine in the yield 69%, m.p. 138–140°C (ethanol). For $C_{52}H_{60}N_2O_4S_2$ (841·1) calculated: 74·25% C, 7·19% H, 3·33% N, 7·50% S; found: 74·23% C, 7·26% H, 3·10% N, 7·5% S. Reduction of this intermediate with sodium in isoamyl alcohol gave the diamine (yield 43%), m.p. 55°C (aqueous ethanol). For $C_{38}H_{48}N_2$ (532·8) calculated: 85·66% C, 9·08% H, 5·26% N; found: 85·30% C, 9·36% H, 5·08% N. Mass spectrum: 532 (M^+), 455, 365, 288, 211, 182, 168.

N,N'-*Bis*(5,6,7,8-*tetrahydro*-1-*naphthyl*)-1,12-*dodecanediamine* was prepared from N-(4-toluenesulfonyl)-5,6,7,8-tetrahydro-1-naphthylamine through N,N'-bis(5,6,7,8-tetrahydro-1-naphthyl)-N,N'-bis(4-toluenesulfonyl)-1,12-dodecanediamine, glass. For $C_{46}H_{60}N_2O_4S_2$ (769·1) calculated: 71·84% C, 7·86% H, 3·64% N, 8·34% S; found: 72·14% C, 8·03% H, 3·35% N, 8·44% S. The product was detosylated with sodium in isoamyl alcohol, yield 50%, m.p. 69°C (ethanol). For $C_{32}H_{48}N_2$ (460·7) calculated: 83·42% C, 10·50% H, 6·08% N; found: 83·45% C, 10·82% H, 6·02% N. Mass spectrum: 460 (M^+), 301, 300, 160.

1,16-*Diazacyclooctacosane*. By reacting tetradecanedioyl dichloride with 1,12-dodecanediamine in anhydrous benzene in the presence of triethylamine using high dilution techniques[6] cyclic diamide was prepared. The raw product was extracted with tetrahydrofuran several times, the solvent was distilled off, and pure 1,16-diaza-2,15-dioxocyclooctacosane was obtained, m.p. 159–162°C (30%). For $C_{26}H_{50}N_2O_2$ (422·7) calculated: 6·62% N; found: 6·49% N. The diamide (1·6 g) was reduced in tetrahydrofuran (60 ml) by boiling with $LiAlH_4$ (2·4 g) for 30 h. After decomposition with water the diamine was extracted with ether. The waxy raw product (0·9 g) obtained after evaporation of ether was used without isolation in the preparation of macrocyclic diamide.

N,N'-*Dibenzyl*-4,4,5,5-*tetramethyl*-3,6-*dioxa*-1,8-*octanediamine*. To 3·4 g of 4,4,5,5-tetramethyl-3,6-dioxaoctanedioyl dichloride in 100 ml benzene, a solution of 2·5 g benzylamine and 3·2 ml triethylamine in 100 ml benzene was added dropwise. After standing for 3 h triethylamine hydrochloride was removed by filtration, benzene was distilled off, and the the product was recrystallized from aqueous ethanol. The yield was 3·1 g (63%) of the dibenzyldiamide, m.p. 140–142°C. For $C_{24}H_{32}N_2O_4$ (412·5) calculated: 69·88% C, 7·82% H, 6·79% N; found: 69·34% C, 7·54% H, 6·79% N. Diamide (2 g) was added in parts to 3 g $LiAlH_4$ in 20 ml ether and 10 ml benzene and the reaction mixture was refluxed 18 h. After the remaining $LiAlH_4$ was decomposed, 10 m

water and 4 ml 15% NaOH was added. The organic layer was separated and dried with $MgSO_4$. The oily residue that remained after the solvents had been distilled off was dissolved in ether, diamine dihydrochloride was precipitated with a solution of hydrogen chloride in ether and isolated by suction. For $C_{24}H_{38}N_2O_2Cl_2$ (457·4) calculated: 63·01% C, 8·37% H, 15·5% Cl, 6·12% N; found: 62·80% C, 8·54% H, 15·67% Cl, 6·10% N. The base used in the preparation of cyclic diamide was obtained from an equivalent amount of hydrochloride dissolved in a small amount of water by alkalizing with NH_4OH, extracted with benzene and used directly.

Macrocyclic Diamides

Cyclic oligomethylenediamides were prepared by reacting the corresponding chlorides of dicarboxylic acids with dialkyldiamines in benzene in the presence of triethylamine by using high dilution technique. The products were purified by column chromatography on neutral aluminium oxide or silica gel.

7,20-*Bis*[2-(1-*pyrrolidinyl*)*ethyl*]-2,2,3,3-*tetramethyl*-7,20-*diaza*-1,4-*dioxacyclodocosane*-6,21--*dione* (I). Chromatographic isolation was performed on Al_2O_3 by elution with benzene–-methanol (5 : 1); yield 50%, oil. For $C_{34}H_{64}N_4O_4$ (592·8) calculated: 68·90% C, 10·88% H, 9·45% N; found: 69·31% C, 11·05% H, 8·94% N. Mass spectrum: 592 (M^+), 577, 508, 507, 496. 149, 97, 84. ^{1}H NMR spectrum: 1·16—1·23 m, 32 H (4 CH_3, 10 CH_2); 1·73 m, 4 H (2 NCH_2, $(CH_2)_{10}$); 2·57 m, 8 H (2 $NCH_2CH_2CH_2$); 2·62 m, 8 H (2 $NCH_2CH_2CH_2CH_2$); 3·38 t, 4 H (2 CH_2N); 3·44 t, 4 H (2 NCH_2CH_2N); 4·05 m, 4 H (2 OCH_2CO).

7,20-*Bis*(*diphenylmethyl*)-2,2,3,3-*tetramethyl*-7,20-*diaza*-1,4-*dioxacyclodocosane*-6,21-*dione* (II) was isolated chromatographically on Al_2O_3 by elution with a benzene–acetone mixture (5 : 0·8); yield 68%, oil. For $C_{48}H_{62}N_2O_4$ (731·0) calculated: 78·86% C, 8·55% H, 3·83% N; found: 78·21% C, 8·86% H, 3·48% N. Mass spectrum: 730 (M^+) 672, 563, 463, 398, 168. ^{1}H NMR spectrum: 0·82—1·18 m, 32 H (4 CH_3, 10 CH_2); 2·10 s, 2 H (2 NCH); 3·35 m, 4 H (2 NCH_2); 4·13 s, 4 H (2 OCH_2CO); 7·18—7·23 m, 20 H (4 C_6H_5).

5,5,6,6-*Tetramethyl*-2,9-*dioxo*-1,10-*diaza*-4,7-*dioxa*-*bicyclo*[14,12,8]*hexatriacontane* (III). Chromatographic isolation of the product was performed on silica gel by elution with a benzene–-acetone mixture (5 : 4); yield 20%, glass. For $C_{36}H_{68}N_2O_4$ (592·9) calculated: 72·92% C, 11·56% H, 4·72% N; found: 72·41% C, 11·49% H, 4·31% N. Mass spectrum: 592 (M^+), 577. 562, 534, 508, 490, 478, 462, 448, 438. ^{1}H NMR spectrum: 1·22 m, 56 H (4 CH_3, 22 CH_2), 1·52 m, 8 H (4 NCH_2); 4·12 m, 4 H (2 OCH_2CO).

7,20-*Bis*(5,6,7,8-*tetrahydro*-1-*naphthyl*)-2,2,3,3-*tetramethyl*-7,20-*diaza*-1,4-*dioxacyclodocosane*-6,21-*dione* (IV) was isolated on silica gel using a benzene–acetone system (5 : 0·5); yield 42%, m.p. 146—148°C. For $C_{42}H_{62}N_2O_4$ (658·9) calculated: 76·55% C, 9·48% H, 4·25% N; found 76·65% C, 9·72% H, 4·09% N. Mass spectrum: 658 (M^+), 600, 575, 557, 455, 160. ^{1}H NMR spectrum: 0·88—1·35 m, 40 H (4 CH_3, 10 CH_2, 4 CH_2 5,6,7,8-tetrahydronaphthyl); 1·70 m, 8 H (4 CH_2 5,6,7,8-tetrahydronaphthyl); 2·75 m, 4 H (NCH_2); 4·39 m, 4 H (OCH_2CO); 7·07 to 7·08 m, 6 H (2 C_6H_3).

7,20-*Dibenzyl*-2,2,3,3-*tetramethyl*-7,20-*diaza*-1,4-*dioxacyclodocosane*-6,21-*dione* (V) was a compound described in ref.[2].

7,20-*Dibenzyl*-2,2,3,3-*tetramethyl*-7,20-*diaza*-1,4-*dioxacyclodocosane*-8,19-*dione* (VI). The compound was isolated on silica gel by elution with a mixture benzene–hexane–methanol (3 : 1 : 0·5) and the product was recrystallized from a benzene–hexane mixture, white needles, m.p. 107 to 109°C (yield 63%). For $C_{36}H_{54}N_2O_4$ (578·8) calculated: 74·70% C, 9·40% H, 4·84% N;

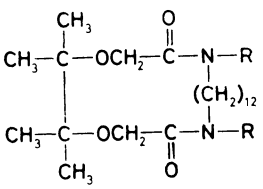
found: 74·84% C, 9·60% H, 4·87% N. Mass spectrum: 578 (M^+), 563, 433, 328, 300, 286, 256, 244, 150. ^{1}H NMR spectrum: 1·04—1·17 m, 28 H (8 CH_2, 4 CH_3); 2·3 t, 4 H (2 CH_2CO); 3·3—3·7 m, 8 H (2 OCH_2CH_2N); 4·6 s, 4 H (2 CH_2Ph); 7·25 m, 10 H (2 C_6H_5).

Preparation of Membrane Electrodes and EMF Measurements

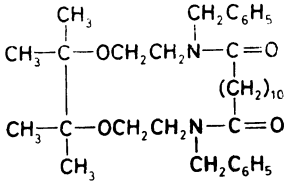
The membranes were prepared by casting a solution of high-molecular weight PVC in cyclohexanone containing dipentyl phthalate as the plasticizer and ionophore by employing a procedure reported earlier[7]. From a membrane c. 0·15 mm thick a disc was cut out and welded to a PVC tube, i.d. 5 mm. The electrode was completed by inserting an internal wire Ag/AgCl electrode and filled with a 0·1M-LiCl solution. EMF of the cell was measured at 25°C with an Ionalyzer (Orion) electrometer. In all cases the following cell was used: Hg; Hg_2Cl_2/KCl_{sat}/0·1M-NH_4NO_3/ measured solution/polymeric membrane/internal solution 0·1M-LiCl/AgCl; Ag. The selectivity coefficients, K^{pot}_{LiM}, were determined by employing the separate solution method in 0·1M chloride solutions of the respective cations.

RESULTS AND DISCUSSION

This work continues our attempts to elucidate the influence of the structure of macrocyclic diamide on the preference complexation of lithium ions. We therefore prepared several macrocyclic diamides of tetramethyldioxaoctanedioic acid (*I*—*V*)



I, R = $CH_2CH_2\overline{N(CH_2)_3CH_2}$
II, R = $CH(C_6H_5)_2$
III, R_2 = $(CH_2)_{14}$
IV, R = 5,6,7,8-tetrahydro-1-naphthyl
V, R = $CH_2C_6H_5$



VI

with various types of substituents of the amide nitrogen atom differing in their steric requirements. As has been found earlier[2], the optimal ring size in this type of ligands is 22 atoms with the joining link of amide nitrogen atoms containing 12 methylene groups. This is why, in order to assess the effect of alkyl groups attached to these nitrogen atoms, the same macrocyclic ring was preserved in all compounds. Cyclic diamide *VI* is then a compound with an altered structure of the ring in which amide carbonyls have been shifted towards the aliphatic chain joining amide nitrogen atoms in the macrocycle. Ion selective properties of new ionophores (ligands) were studied electrochemically after they had been incorporated into the membranes from high-molecular weight polyvinylchloride plastified with dipentyl phthalate.

The selectivity coefficients with respect to Li^+ obtained by EMF measurements are given in Fig. 1. Compound *I* with pyrrolidinylethyl groups is a ligand which similarly to macrocyclic diamides containing ester N-substituents (cf. ref.[2]) has other possible binding sites in the molecule. The strongly basic pyrrolidinylethyl substituent has completely eliminated the original Li^+ selectivity, however. A similar absence of selectivity with respect to Li^+ shows cyclic diamide *VI* with an isomeric ring, where the carbonyl group is situated on the opposite side of the nitrogen atom compared with ligand *V* which has a high Li^+ selectivity. This demonstrates that the complexation of ligands with lithium ions requires the presence of $-OCH_2CON-$ sequences in the macrocycle of the ligand. Ligand II with diphenylmethyl substituents of amide nitrogen atoms already shows a certain preference for Li^+. Compared with benzyl substituents[2], however, the presence of another phenyl group results in a drastic decrease in selectivity. The lower complexation of Li^+ may e.g. be a consequence of an unfavourable influence of electron systems of further benzene rings. Bicyclic ligand *III* has a medium selectivity. Here we have a favourable effect of aliphatic chains on lipophilicity of the molecule. On the other hand, however, bridging of amide nitrogen atoms and the bicyclic structure of the ligand thus formed

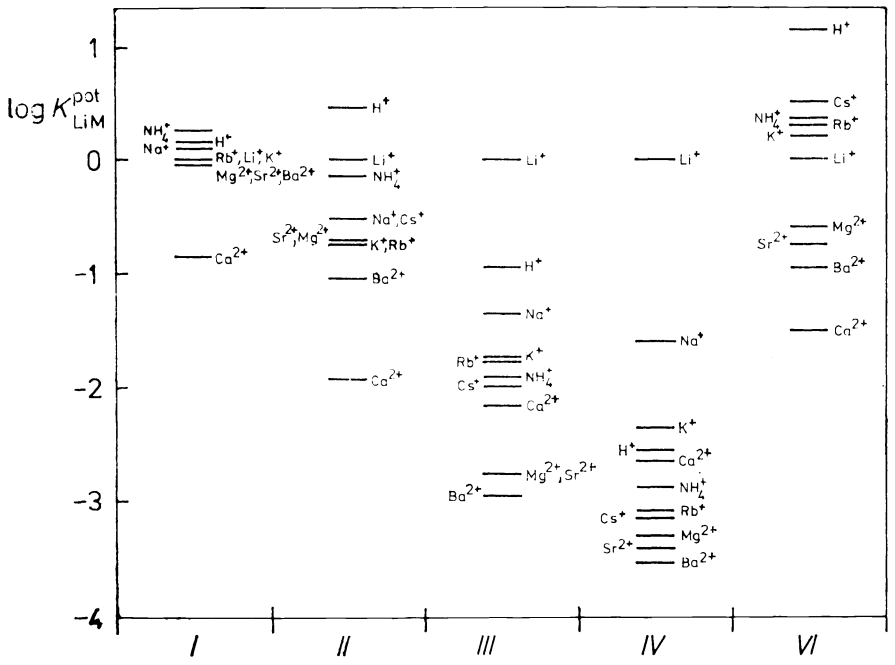


FIG. 1

Selectivity coefficients K^{pot}_{LiM} of PVC membranes containing macrocyclic diamides *I*—*VI*

obviously impedes reaching an optimal conformation for the complexation of lithium cations.

The highest selectivity is found with derivative *IV* with tetrahydronaphthyl substituents of amide nitrogen atoms. The preference for Li^+ observed with this ligand can be compared with the best ionophores of the same type reported earlier which contain benzyl or cyclohexyl groups[2]. Moreover, sensitivity of ligand *IV* towards H ions is lower by an order of magnitude.

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Translated by L. Kopecká.