

### 194. 3,7-Dioxaazelaamides as Ionophores for Lithium Ion Selective Liquid Membrane Electrodes

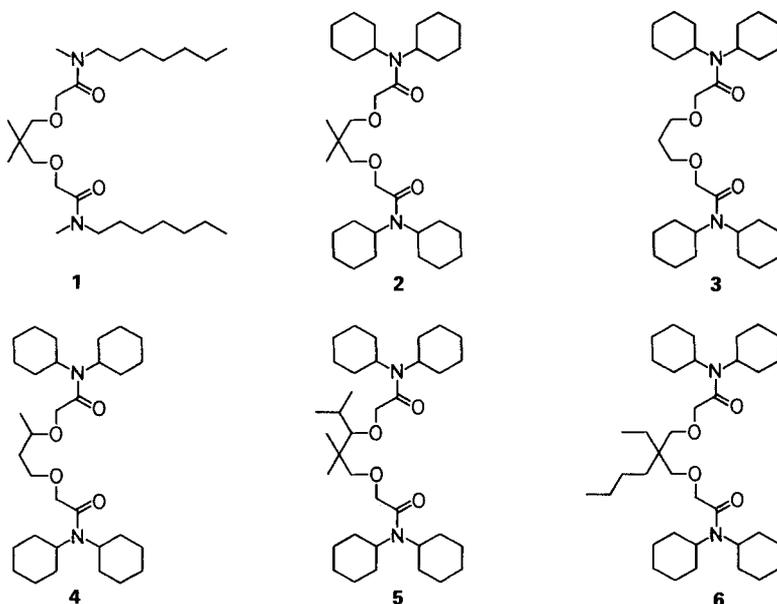
by Erich Metzger, Roland Aeschmann, Martin Egli, Gaby Suter, René Dohner, Daniel Ammann, Max Dobler, and Wilhelm Simon\*

Department of Organic Chemistry, Swiss Federal Institute of Technology (ETH), CH-8092 Zürich

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Lipophilic neutral carriers were synthesized which show  $\text{Li}^+/\text{Na}^+$  selectivities of up to *ca.* 80 in highly lipophilic liquid membranes. The sensor membranes exhibit improved response times and increased lifetimes as compared to systems described earlier. They allow reliable measurements of  $\text{Li}^+$  in blood serum within the clinical concentration range. A 1:1  $\text{Li}^+$ /ionophore complex of one representative (*N,N,N',N'*-tetracyclohexyl-5,5-dimethyl-3,7-dioxaazelaamide) has been prepared, and its structure was elucidated by X-ray analysis.

**Introduction.** – Among the different neutral carrier-based membranes recommended for  $\text{Li}^+$ -selective electrodes [1–19], only few show acceptable  $\text{Li}^+/\text{Na}^+$  selectivities for the potentiometric assay of  $\text{Li}^+$  in blood serum during therapy of manic depressive psychosis [9] [12] [15] [16] [18]. The so far highest  $\text{Li}^+/\text{Na}^+$  selectivities in analytically relevant sensors were obtained with liquid membrane electrodes based on *N,N*-dicyclohexyl-*N',N'*-diisobutyl-*cis*-cyclohexane-1,2-dicarboxamide (ETH 1810) as ionophore and



*ortho*-nitrophenyl octyl ether (*o*-NPOE) as plasticizer [12] [16]. These Li<sup>+</sup>-selective electrodes can be used successfully in the determination of Li<sup>+</sup> activities in blood serum within the clinical concentration range using an adequate fixed ion background calibration method [16].

Unfortunately, the lifetimes of such sensor membranes are rather short (few weeks) when extensively exposed to blood serum or whole blood. This is largely due to the use of a relatively polar plasticizer (*o*-NPOE) as membrane component, which is necessary to achieve a high Li<sup>+</sup>/Na<sup>+</sup> selectivity [20]. In addition, the electrode response times do not completely correspond to the requirements imposed by the practical clinical routine analysis [20].

We, therefore, searched for new Li<sup>+</sup>-selective ionophores exhibiting high Li<sup>+</sup>/Na<sup>+</sup> selectivities even in membranes with more lipophilic plasticizers, *e.g.* bis(1-butylpentyl) adipate (BBPA). The new ionophores **2–6** are structurally related to the previously described ionophore **1** [1] [2] [4]. Here, we report on the synthesis of these carriers and discuss the electromotive behaviour of highly lipophilic PVC membranes based on them, in view of Li<sup>+</sup> assays in blood serum of patients suffering from manic-depressive psychosis and being under lithium treatment. The results of an X-ray structure analysis of a 1:1 Li<sup>+</sup>/ionophore **2** complex are presented as well.

**Results and Discussion.** – The previously described ionophore *N,N'*-diheptyl-*N,N'*,5,5-tetramethyl-3,7-dioxazelaamide (ETH 149; **1**; [1] [2] [4]) induces a Li<sup>+</sup>/Na<sup>+</sup> selectivity  $\log K_{LiNa}^{Pot} = -1.2$  in BBPA/PVC membranes (membrane *a*, Column 1 in Fig. 1).

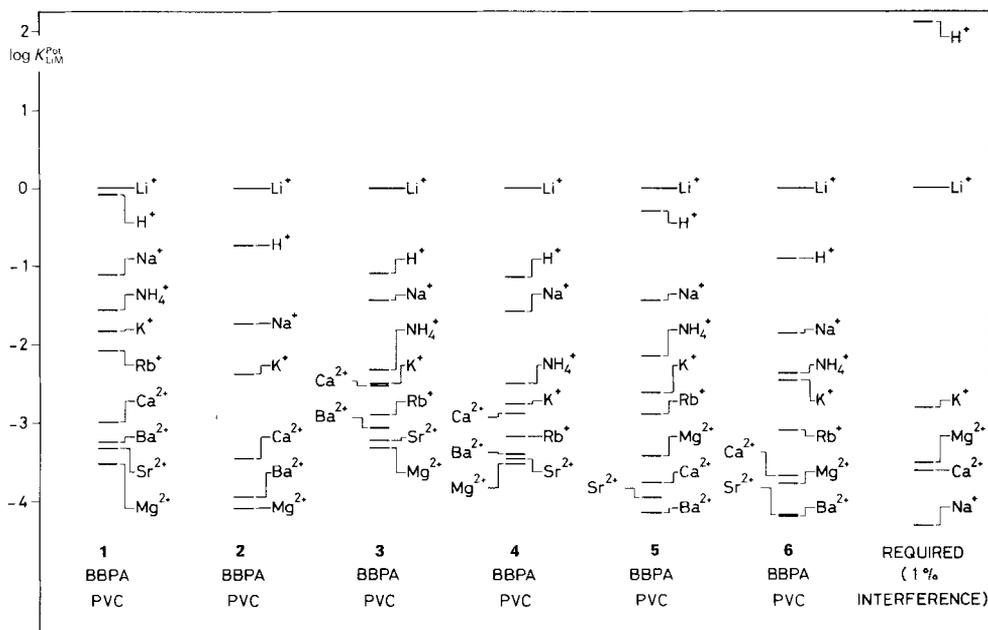


Fig. 1. Selectivities  $\log K_{LiM}^{Pot}$  of the ionophores **1–6** in BBPA/PVC membrane electrodes as obtained by the separate-solution method. Column 7: required selectivities for a 1% interference by the interfering cation to the Li<sup>+</sup> activity (worst case).

A surprisingly high improvement in the  $\text{Li}^+/\text{Na}^+$  selectivity is obtained by replacing the methyl-heptyl-amide by dicyclohexylamide groups (ETH 2015; **2**). Electrodes based on membranes containing **2** and BBPA as plasticizer (membrane *b*) exhibit a  $\log K_{\text{LiNa}}^{\text{Pot}}$  value of  $-1.7$  in separate-solution measurements [21] (Column 2 in Fig. 1).

To study the effect of amide substituents, the crystal structure of the LiNCS complex with *N,N,N',N'*-tetracyclohexyl-5,5-dimethyl-3,7-dioxazelaamide (**2**) was elucidated. The result is depicted in Fig. 2. The ligand molecule adopts a conformation with the 9 atoms from C(5) to C(101) and C(107) and from C(5) to C(901) and C(907) in two approximate planes enclosing an angle of *ca.*  $120^\circ$ . The  $\text{Li}^+$  cation coordinates the 4

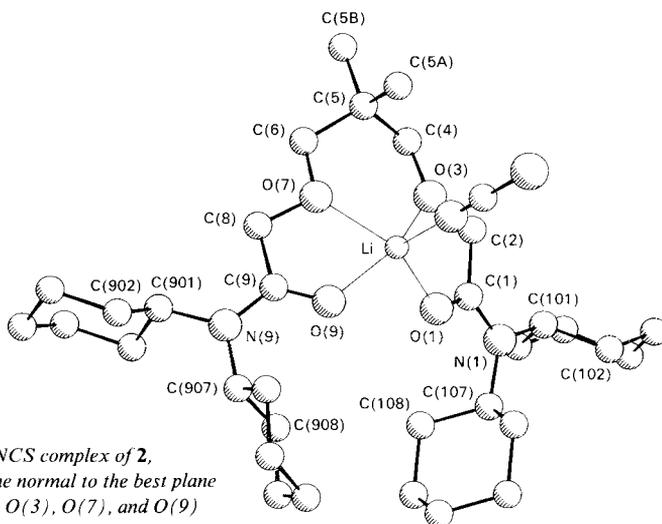


Fig. 2. The LiNCS complex of **2**, shown along the normal to the best plane through O(1), O(3), O(7), and O(9)

Table 1. Complex Geometry of  $\text{Li}^+$  Cation

$\text{Li} \cdots \text{O}(1)$	1.950 Å	$\text{O}(1) \cdots \text{O}(3)$	2.537 Å	$\text{O}(1) \cdots \text{Li} \cdots \text{N}(\text{NCS})$	$115.0^\circ$
$\text{Li} \cdots \text{O}(3)$	2.229 Å	$\text{O}(1) \cdots \text{O}(9)$	2.938 Å	$\text{O}(3) \cdots \text{Li} \cdots \text{N}(\text{NCS})$	$105.1^\circ$
$\text{Li} \cdots \text{O}(7)$	2.085 Å	$\text{O}(3) \cdots \text{O}(7)$	2.759 Å	$\text{O}(7) \cdots \text{Li} \cdots \text{N}(\text{NCS})$	$117.0^\circ$
$\text{Li} \cdots \text{O}(9)$	1.979 Å	$\text{O}(7) \cdots \text{O}(9)$	2.568 Å	$\text{O}(9) \cdots \text{Li} \cdots \text{N}(\text{NCS})$	$110.1^\circ$
$\text{Li} \cdots \text{N}(\text{NCS})$	2.032 Å				

O-atoms of the ligand and the N-atom of the  $\text{NCS}^-$  anion to form a slightly distorted quadratic pyramid. The 4 O-atoms form the base of the pyramid, displaced by  $\pm 0.13$  Å from their mean plane. The  $\text{Li}^+$  cation is 0.76 Å above this plane, and the thiocyanate N is at the apex. The complex geometry is given in Table 1. This 4 + 1 coordination is not typical for  $\text{Li}^+$ . A search in the CSD (Cambridge Structural Database [22]) showed that for 259 cases, the coordination number varies from 1 to 8 if ligand atoms closer than 2.5 Å are counted (coordination number 1, 7 cases; 2, 24 cases; 3, 33 cases; 4, 155 cases; 5, 28 cases; 6, 9 cases; 7, 1 case; 8, 2 cases). The distances to the carbonyl O-atoms are close to the observed mean distance (1.94 Å) in these complexes, the distances to the ether O-atoms are rather long and the  $\text{Li} \cdots \text{N}$  distance is quite short (observed 2.00–2.20 Å). Bond distances and angles and selected torsion angles are given in Tables 2, 3, and 4. They show no peculiarities. The structure of the  $\text{Li}^+$  complex of **2** (Fig. 2) does not offer an obvious

explanation for the rather large effect of the substituents of the N-atoms on the  $\text{Li}^+/\text{Na}^+$  selectivity.

Further slight changes in selectivities are induced by alkyl substituents at C(4) and especially C(5) of dioxazelaamide (see 3–6; selectivities given in Fig. 1).

The highest  $\text{Li}^+/\text{Na}^+$  selectivities in BBPA/PVC membranes are obtained with 5-butyl-*N,N,N',N'*-tetracyclohexyl-5-ethyl-3,7-dioxazelaamide (ETH 2137, 6; membrane *f*) with  $\log K_{\text{LiNa}}^{\text{Pot}} = -1.9$  (Column 6 in Fig. 1). The electrode response (*EMF* vs.  $\log a_{\text{Li}}$ ) of this sensor had a slope of  $58.7 \pm 0.5$  mV at  $\text{Li}^+$  activities in the range  $10^{-5}$ – $10^{-1}$  M ( $n = 2$ ;  $21^\circ$ ; theoretical: 58.4 mV). Ionophore 6 is reaching the required selectivities for a contribution of  $\leq 1\%$  to the  $\text{Li}^+$  activity by the interfering cations in blood (Column 7 in Fig. 1) with respect to  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{H}^+$  and almost with respect to  $\text{K}^+$  as interferents. It clearly does not meet the selectivity requirements with respect to  $\text{Na}^+$  [23]. The  $\text{Li}^+/\text{Na}^+$  selectivity is even lower than the one of an *o*-NPOE/PVC membrane with the ionophore ETH 1810 [12] [16]. Therefore, useful direct potentiometric measurements in the clinical  $\text{Li}^+$  range of 0.7–1.5 mmol/l [24–26] are possible only if a fixed  $\text{Na}^+$  background (0.14 mol/l) calibration is used. Under these conditions, the *EMF* difference between a  $\text{Li}^+$

Table 2. Bond Lengths (Å) for the  $\text{LiNCS}$  Complex of 2. Estimated standard deviations are 0.004–0.01 Å.

N(1)–C(1)	1.349	O(3)–C(4)	1.425	N(NCS)–C(NCS)	1.150
N(1)–C(101)	1.480	C(4)–C(5)	1.514	C(NCS)–S(NCS)	1.654
N(1)–C(107)	1.489	C(5)–C(5a)	1.532		
O(1)–C(1)	1.230	C(5)–C(5b)	1.544	cyclohexyl rings:	
C(1)–C(2)	1.525	C(5)–C(6)	1.509	range	1.512–1.540
N(9)–C(9)	1.346	C(6)–O(7)	1.439	mean value	1.526±0.007
N(9)–C(901)	1.485	O(7)–C(8)	1.421		
N(9)–C(907)	1.480	C(8)–C(9)	1.512		
C(2)–O(3)	1.411	O(9)–C(9)	1.228		

Table 3. Bond Angles ( $^\circ$ ) for the  $\text{LiNCS}$  Complex of 2. Estimated standard deviations are 0.3–0.4 $^\circ$ .

C(1)–N(1)–C(101)	122.3	C(5a)–C(5)–C(5b)	108.9	N(NCS)–C(NCS)–S(NCS)	179.5
C(1)–N(1)–C(107)	120.2	C(5a)–C(5)–C(6)	112.1		
C(101)–N(1)–C(107)	117.5	C(5b)–C(5)–C(6)	105.7	cyclohexyl groups:	
N(1)–C(1)–O(1)	122.5	C(5)–C(6)–O(7)	111.7	range	108.8–112.1
N(1)–C(1)–C(2)	118.8	C(6)–O(7)–C(8)	109.3	mean value	110.6± 0.9
O(1)–C(1)–C(2)	118.7	O(7)–C(8)–C(9)	107.2		
C(1)–C(2)–O(3)	106.6	N(9)–C(9)–C(8)	117.3		
C(2)–O(3)–C(4)	113.1	N(9)–C(9)–O(9)	122.5		
O(3)–C(4)–C(5)	111.0	C(8)–C(9)–O(9)	120.2		
C(4)–C(5)–C(5a)	111.0	C(9)–N(9)–C(901)	122.1		
C(4)–C(5)–C(5b)	106.5	C(9)–N(9)–C(907)	120.4		
C(4)–C(5)–C(6)	112.4	C(901)–N(9)–C(907)	117.3		

Table 4. Selected Torsion Angles ( $^\circ$ ) for the  $\text{LiNCS}$  Complex of 2

C(101)–N(1)–C(1)–C(2)	8.0	C(4)–C(5)–C(6)–O(7)	65.3
C(107)–N(1)–C(1)–C(2)	–170.3	C(5)–C(6)–O(7)–C(8)	176.8
N(1)–C(1)–C(2)–O(3)	173.1	C(6)–O(7)–C(8)–C(9)	172.8
C(1)–C(2)–O(3)–C(4)	–154.8	O(7)–C(8)–C(9)–N(9)	–175.0
C(2)–O(3)–C(4)–C(5)	–178.6	C(8)–C(9)–N(9)–C(901)	0.3
O(3)–C(4)–C(5)–C(6)	–65.4	C(8)–C(9)–N(9)–C(907)	174.4

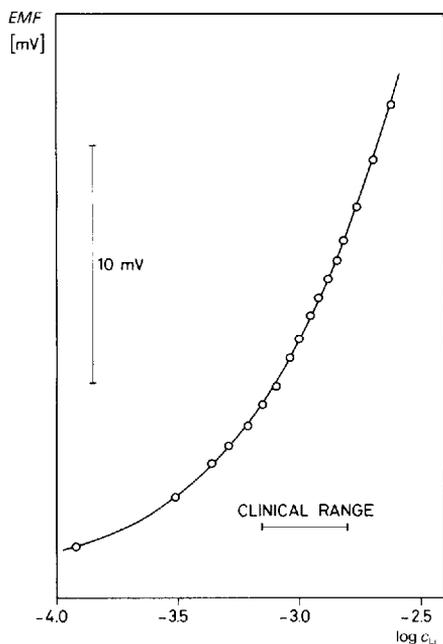


Fig. 3. Electrode response of a  $\text{Li}^+$ -selective electrode in blood serum below, in, and above the clinical  $\text{Li}^+$ -concentration range. Membrane with ionophore **6** in BBPA/PVC (membrane *f*).

concentration of 0.7 mmol/l and 1.5 mmol/l is only 7.2 mV (Fig. 3) due to the relatively low  $\text{Li}^+/\text{Na}^+$  selectivity (with the required  $\log K_{\text{LiNa}}^{\text{Pot}}$  value for less than 1% interference by  $\text{Na}^+$  of  $-4.3$  (see Column 7 in Fig. 1) an EMF range of 19.3 mV would result). As a consequence, high requirements with respect to the standard deviation in the signal measured have to be met. For a 5-fold subdivision of the clinically relevant  $\text{Li}^+$  range (7.2 mV) with a 95% confidence limit [27], a standard deviation in the signals measured of  $\leq 0.36$  mV is required. Sensors with membranes based on ionophore **6** show standard deviations in the measured EMF of less than 0.1 mV for aqueous sample solutions and undiluted serum. These high signal stabilities and the short response times (*ca.* 20–30 seconds to reach the final EMF value to within 0.36 mV) make the sensor in this respect superior to the previously described membrane electrodes based on the ionophore ETH 1810 and *o*-NPOE as plasticizer [12] [16]. No lifetime restrictions could be observed during a measuring period of 7 weeks.

The curvature of the electrode response in Fig. 3 is mainly dictated by the interference of  $\text{Na}^+$  (serum background concentration of  $\text{Na}^+$ : 0.139 mol/l;  $K_{\text{LiNa}}^{\text{Pot}} = 0.012$ ). A variation of  $\text{Na}^+$  over the physiological range in blood (0.135–0.150 mol/l) produces uncertainties in the measured EMF of  $-0.7$  to  $+1.3$  mV relative to an average  $\text{Na}^+$  concentration of 0.140 mol/l (worst case). This is well above the tolerated signal uncertainty of 0.36 mV (see above). A sufficiently reliable  $\text{Li}^+$  assay is, therefore, possible only if the  $\text{Na}^+$  activity is measured simultaneously and if corrections of the  $\text{Li}^+$  activity for  $\text{Na}^+$  interference are made.

#### Experimental Part

**1. Syntheses.** – 1.1. *Instruments.* IR: Perkin-Elmer PE 125; in  $\text{CHCl}_3$ ;  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$ : Bruker WM-300; in  $\text{CDCl}_3$ ; 300.14 MHz; TMS internal reference, chemical shifts in ppm with  $\delta(\text{TMS}) = 0$ .  $^{13}\text{C-NMR}$ : Bruker WM-300; in  $\text{CDCl}_3$ ; 75.74 MHz. MS: Kratos AEI MS-50;  $m/z$  (relative intensities).

1.2. *5-Butyl-N,N,N',N'-tetracyclohexyl-5-ethyl-3,7-dioxazelaamide* (**6**; Ionophore ETH 2137). *Diethyl 5-butyl-5-ethyl-3,7-dioxazelaate*. Successively, 5.0 g (31.2 mmol) of 2-butyl-2-ethyl-1,3-propanediol (*purum*; *Fluka AG*, Buchs, Switzerland) and 6.5 ml (62.4 mmol) of ethyl diazoacetate (*purum*; *Fluka AG*) were added to 50 ml of dried  $\text{CH}_2\text{Cl}_2$ . The soln. was purged with  $\text{N}_2$  and cooled to 0–5° in an ice-bath. One ml of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (*pract.*; *Fluka AG*) was slowly added by an injection syringe. A violent reaction with  $\text{N}_2$  formation was observed. After the addition, the soln. was stirred at r.t. for 1 h and then refluxed at 45° for 1½ h. The solvent was evaporated and the crude product purified by flash chromatography on silica gel (**60**; *Fluka AG*) with hexane/AcOEt 8:2 yielding 6.08 g (58.6%) of the product. IR (liquid): 1755.

*5-Butyl-5-ethyl-3,7-dioxazelaic Acid*. To a soln. of 6.08 g (18.3 mmol) of diethyl 5-butyl-5-ethyl-3,7-dioxazelaate in 100 ml of  $\text{MeOH}/\text{H}_2\text{O}$  4:1, 3.6 g (64 mmol) of KOH (*purum*; *Siegfried AG*, Zofingen, Switzerland) were added, and the mixture was refluxed at 80° for 19 h. After cooling to r.t., it was acidified with 6M HCl to ca. pH 1. The solvents were evaporated, and the residue was extracted with acetone. The acetone soln. was dried over  $\text{MgSO}_4$  and evaporated. Yield ca. 5 g (> 95%). IR ( $\text{CHCl}_3$ ): 3500–2500 (br.), 1720.

*5-Butyl-5-ethyl-3,7-dioxazelaoyl Dichloride*. A soln. of 5.0 g (18.1 mmol) of 5-butyl-5-ethyl-3,7-dioxazelaic acid, 5.2 ml (72.4 mmol) of  $\text{SOCl}_2$  (*purum*; *Fluka AG*), and 3 drops of DMF (*puriss. p.a.*; *Fluka AG*) in 100 ml of toluene was refluxed at 100–120° for 1 h. After evaporation, the crude product was distilled under vacuum (205°/0.08 Torr). Yield 4.06 g (71.6%). IR (liquid): 1805, 1750.

*Diamide 6*. To a soln. of 4.94 g (27.2 mmol) of dicyclohexylamine (*puriss. p.a.*; *Fluka AG*) and 2.73 g (27.0 mmol) of anh.  $\text{Et}_3\text{N}$  (*Siegfried AG*) in ca. 150 ml of  $\text{CH}_2\text{Cl}_2$ , 4.06 g (13.0 mmol) of 5-butyl-5-ethyl-3,7-dioxazelaoyl dichloride in 20 ml of  $\text{CH}_2\text{Cl}_2$  were slowly added under stirring. The mixture was stirred at r.t. for 18 h and then washed several times with  $\text{H}_2\text{O}$ . The  $\text{CH}_2\text{Cl}_2$  phase was dried over  $\text{MgSO}_4$  and the solvent evaporated. The product (5.6 g, 71.5%) was purified on a silica-gel column (240 g of silica gel **60**; *Fluka AG*). Yield 0.11 g (1.4%). IR ( $\text{CHCl}_3$ ): 3000, 2930, 1630.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 0.81 (t,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$ ); 0.88 (t,  $\text{CH}_3\text{CH}_2$ ); 1.06–1.83 (m, 44 H,  $\text{CH}_2$  of 4 cyclohexyl and aliph. chains); 2.40–2.47 (m, 2 NCH $\text{CH}_2$ ); 2.87–2.93 (m, 2 NCH); 3.32 (s, 2  $\text{CH}_2\text{OCH}_2\text{CO}$ ); 3.50–3.57 (m, 2 NCH); 4.02 (s, 2  $\text{CH}_2\text{OCH}_2\text{CO}$ ).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ): 7.7 (q,  $\text{CH}_3$ ); 14.2 (q,  $\text{CH}_3$ ); 23.6–31.4 (m, 24  $\text{CH}_2$  of Bu, Et, and cyclohexyl); 41.2 (s,  $\text{C}(\text{CH}_2)_4$ ); 56.0 (d, 2 NCH( $\text{C}_5\text{H}_{10}$ )); 57.3 (d, 2 NCH( $\text{C}_5\text{H}_{10}$ )); 73.4 (t, 2  $\text{CH}_2\text{OCH}_2\text{CO}$ ); 74.2 (t, 2  $\text{CH}_2\text{OCH}_2\text{CO}$ ); 168.5 (s, 2 CO). MS: 602 (4,  $M^+$ ), 381 (10), 380 (37,  $M^+ - (\text{CH}_2\text{CON}(\text{C}_6\text{H}_{11})_2)$ ), 365 (6), 364 (4,  $M^+ - (\text{OCH}_2\text{CON}(\text{C}_6\text{H}_{11})_2)$ ), 180 (5,  $\text{N}(\text{C}_6\text{H}_{11})_2$ ), 160 (24), 57 (100,  $(\text{CH}_2)_3\text{CH}_3$ ), 29 (31,  $\text{CH}_2\text{CH}_3$ ). Calc. for  $\text{C}_{37}\text{H}_{66}\text{N}_2\text{O}_4$ : C 73.71, H 11.03, N 4.65; found: C 73.71, H 10.84, N 4.56.

1.3. The carriers **2–5** were synthesized similarly, starting from the corresponding diols obtainable from *Fluka AG* (**2**, **3**, **5**) and from *Aldrich*, Steinheim, FRG (**4**).

*N,N,N',N'-Tetracyclohexyl-5,5-dimethyl-3,7-dioxazelaamide* (**2**). Calc. for  $\text{C}_{33}\text{H}_{58}\text{N}_2\text{O}_4$ : C 72.53, H 10.70, N 5.13; found: C 72.61, H 10.61, N 4.95.

*N,N,N',N'-Tetracyclohexyl-3,7-dioxazelaamide* (**3**). Calc. for  $\text{C}_{31}\text{H}_{54}\text{N}_2\text{O}_4$ : C 71.77, H 10.49, N 5.40; found: C 71.74, H 10.55, N 5.31.

*N,N,N',N'-Tetracyclohexyl-4-methyl-3,7-dioxazelaamide* (**4**). Calc. for  $\text{C}_{32}\text{H}_{56}\text{N}_2\text{O}_4$ : C 72.14, H 10.59, N 5.26; found: C 72.08, H 10.62, N 5.14.

*N,N,N',N'-Tetracyclohexyl-4-isopropyl-3,7-dioxazelaamide* (**5**). Calc. for  $\text{C}_{36}\text{H}_{64}\text{N}_2\text{O}_4$ : C 73.42, H 10.95, N 4.76; found: C 73.09, H 10.76, N 4.70.

*Isothiocyanatof* [*N,N,N',N'-tetracyclohexyl-5,5-dimethyl-3,7-dioxazelaamide-O,O',O''lithium* (*ETH 2015-LiNCS*)]. A soln. of 300 mg (0.55 mmol) of **2** and 17.8 mg (0.27 mmol) of LiSCN (*pract.*; *Fluka AG*; high-vacuum dried for 24 h) in 4 ml of AcOEt (*puriss.*; *Fluka AG*) was allowed to stand in a flask with partly opened cap. After crystallization, the needles were filtered off (100 mg, 29.7%). IR ( $\text{CHCl}_3$ ): 2080, 1630. Calc. for  $\text{C}_{33}\text{H}_{58}\text{N}_2\text{O}_4 \cdot \text{LiNCS}$ : C 66.74, H 9.56, N 6.87; found: C 66.89, H 9.64, N 6.95.

**2. Potentiometric Measurements.** – 2.1. *Reagents*. The electrolyte solns. for the potentiometric measurements were prepared with doubly quartz distilled  $\text{H}_2\text{O}$  and chloride salts of high purity (*purum p.a.* or *puriss. p.a.* (*Fluka AG*, Buchs, Switzerland) and *pro analysis* (*E. Merck*, Darmstadt, FRG)). The blood serum (ca. 100 ml) was obtained from the Medico-Chemical Central Laboratory, University Hospital, Zurich, Switzerland, where the  $\text{Na}^+$ ,  $\text{K}^+$ , total  $\text{Ca}^{2+}$ , and the  $\text{Li}^+$  concentrations were determined by flame photometry or atomic-absorption spectrometry. Thus, a  $\text{Li}^+$  concentration of 0.12 mmol/l was measured in the serum. Further samples were prepared for the EMF studies (*Fig. 3*) by multiple addition of small volumes of 0.05M LiCl/0.135M NaCl to the serum sample. After each addition and a short mixing period, volumes of 0.1 ml were taken for EMF measurements. Poly(vinyl chloride) (PVC S704 'hochmolekular') originated from *Lonza AG*, Visp, Switzerland (now available from *Fluka AG*); bis(1-butylpentyl) adipate (BBPA, *purum p.a.*) was supplied by *Fluka AG*.

2.2. *Cell Assemblies and EMF Measurements. Macroelectrodes*. The EMF studies for the characterization of

the membranes with respect to selectivity and electrode response were performed with the following type of cell: Hg; Hg<sub>2</sub>Cl<sub>2</sub>, KCl(sat.) | 3M KCl | sample soln. || ion-selective membrane || internal-filling soln., AgCl; Ag. The reference electrode was a double junction saturated calomel electrode (as already used in [16]). Aq. 0.001M LiCl was employed as internal-filling soln. of the ion-selective electrodes. The measurements were carried out with 6 different membranes of the following approximate compositions (wt.-%): (a) 1.2% carrier 1, 66.9 % BBPA; 31.9% PVC; (b) 1.6% carrier 2, 65.3 % BBPA; 33.1% PVC; (c) 1.7% carrier 3, 65.3 % BBPA; 33.0% PVC; (d) 1.8% carrier 4, 65.6 % BBPA; 32.6% PVC; (e) 1.8% carrier 5, 65.7 % BBPA; 32.5% PVC; (f) 2.0% carrier 6, 65.6 % BBPA; 32.4% PVC. The membranes were prepared as previously described [28] and were mounted in Philips macro-electrode bodies IS 560 (N.V. Philips, Eindhoven, NL). The electrodes were conditioned overnight in ca. 2 ml of the internal-filling soln. before use. The EMF measurements with the macroelectrodes including the mathematical evaluation of the data were performed as described in [16] (aq. solns.). Further references concerning theoretical aspects can also be found there.

*Small Channel Flow through Electrode.* Fixed ion background and blood-serum studies (Fig.3) were carried out with the following cell type: Hg; Hg<sub>2</sub>Cl<sub>2</sub>, KCl(sat.)|1M NH<sub>4</sub>NO<sub>3</sub>||sample soln.||ion-selective membrane||internal-filling soln., AgCl; Ag. The ion-selective electrode was a small poly(methyl methacrylate) body with a vertical channel (0.8 mm i.d.) into which the sample solution (0.1 ml) could be injected from above. The sample channel was contacted with the ion-selective membrane *f*. The other membrane side was in contact with the internal-filling soln. (LiCl 0.001M/NaCl 0.14M/Agar 0.5%) and a AgCl/Ag wire as internal reference electrode. The external reference electrode was a conventional macroelectrode as used in [16] but equipped with a thin glass tip. It was dipped from above into the sample channel of the ion selective electrode body. The sample solns. were injected into the channel by a small glass syringe and were removed downwards by applying vacuum. The flow-through system was cleaned with two sample injections. The sample injected afterwards was measured for 4 min by taking an EMF value in 20-s intervals. The mean of the last 6 values was taken for further evaluation. No corrections were made for liquid-junction potentials. Due to the relatively constant ionic strength, concentrations were not converted into activities.

**3. X-Ray Crystal Structure.** – 3.1. *Crystal Data.* The complex formed from LiNCS and 2 (C<sub>33</sub>H<sub>58</sub>N<sub>2</sub>O<sub>4</sub> · LiNCS) has a mol. wt. of 611.9. Monoclinic, *a* = 27.369(9), *b* = 25.886(4), *c* = 10.849(4) Å, β = 107.78(3)°, *V* = 7319 Å<sup>3</sup>, *Z* = 8, space group *C2/c*, *D*<sub>m</sub> = 1.107, *D*<sub>x</sub> = 1.110 g/cm<sup>3</sup>.

Table 5. Atomic Coordinates and Equivalent Temperature Factors (*U*<sub>eq</sub>[Å<sup>2</sup>])<sup>a</sup> with Estimated Standard Deviations in Parentheses for the LiNCS Complex of 2

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> <sub>eq</sub>		<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> <sub>eq</sub>
Li	0.2209(2)	0.1320(2)	0.5103(6)	0.047	C(107)	0.1956(1)	-0.0465(1)	0.5532(3)	0.045
N(1)	0.1555(1)	-0.0073(1)	0.5506(3)	0.043	C(108)	0.2430(1)	-0.0403(2)	0.6704(4)	0.056
O(1)	0.2060(1)	0.0594(1)	0.5310(3)	0.057	C(109)	0.2813(2)	-0.0833(2)	0.6720(5)	0.074
C(1)	0.1660(1)	0.0435(1)	0.5469(3)	0.044	C(110)	0.2949(2)	-0.0850(2)	0.5458(5)	0.085
C(2)	0.1274(1)	0.0827(1)	0.5662(4)	0.046	C(111)	0.2469(2)	-0.0910(2)	0.4304(5)	0.080
O(3)	0.1506(1)	0.1317(1)	0.5733(2)	0.054	C(112)	0.2094(2)	-0.0474(2)	0.4266(4)	0.063
C(4)	0.1309(1)	0.1685(1)	0.6436(4)	0.055	C(901)	0.4002(1)	0.1731(1)	0.8419(4)	0.047
C(5)	0.1561(1)	0.2207(1)	0.6456(4)	0.047	C(902)	0.4462(2)	0.2012(2)	0.8230(4)	0.062
C(5a)	0.1458(2)	0.2419(2)	0.5082(4)	0.071	C(903)	0.4722(2)	0.2340(2)	0.9435(5)	0.076
C(5b)	0.1315(2)	0.2573(2)	0.7222(4)	0.064	C(904)	0.4880(2)	0.2006(2)	1.0646(4)	0.078
C(6)	0.2126(1)	0.2197(1)	0.7193(4)	0.053	C(905)	0.4427(2)	0.1712(2)	1.0813(4)	0.087
O(7)	0.2407(1)	0.1874(1)	0.6568(2)	0.047	C(906)	0.4168(2)	0.1381(2)	0.9613(4)	0.062
C(8)	0.2939(1)	0.1901(1)	0.7261(3)	0.045	C(907)	0.3994(1)	0.1023(1)	0.6804(3)	0.046
N(9)	0.3714(1)	0.1436(1)	0.7249(3)	0.043	C(908)	0.3789(1)	0.0485(2)	0.6905(4)	0.058
O(9)	0.2966(1)	0.1259(1)	0.5714(2)	0.047	C(909)	0.4144(2)	0.0082(2)	0.6611(5)	0.074
C(9)	0.3208(1)	0.1505(1)	0.6673(3)	0.041	C(910)	0.4198(2)	0.0171(2)	0.5266(5)	0.087
C(101)	0.1052(1)	-0.0263(1)	0.5560(4)	0.046	C(911)	0.4385(2)	0.0716(2)	0.5139(5)	0.081
C(102)	0.0797(2)	-0.0613(2)	0.4411(4)	0.062	C(912)	0.4037(2)	0.1126(2)	0.5443(4)	0.060
C(103)	0.0272(2)	-0.0800(2)	0.4472(4)	0.075	N(NCS)	0.1972(1)	0.1583(1)	0.3250(3)	0.065
C(104)	0.0328(2)	-0.1078(2)	0.5742(5)	0.073	C(NCS)	0.1823(2)	0.1733(1)	0.2204(4)	0.052
C(105)	0.0571(2)	-0.0719(2)	0.6875(4)	0.075	S(NCS)	0.1609(1)	0.1943(1)	0.0694(1)	0.069
C(106)	0.1097(1)	-0.0528(2)	0.6848(4)	0.054					

<sup>a</sup>  $U_{eq} = 1/3 \sum_{ij} a^*_i \cdot a^*_j \cdot a_i \cdot a_j \cdot U_{ij}$

*Structure Analysis and Refinement.* The space group was determined from precession photographs and the cell constants from diffractometer measurements with  $\text{MoK}_\alpha$  radiation. Reflection intensities were obtained from an automatic diffractometer (*Enraf-Nonius CAD 4*, graphite-monochromatized  $\text{MoK}_\alpha$  radiation). In the range  $\theta = 0\text{--}23^\circ$  a total of 5063 reflections were recorded. Of these, only 2527 had  $I > 3\sigma(I)$  and were used in the structure analysis. The structure was solved by direct methods (SHELX84 [29]) and refined by least-squares analysis. Refinement progress was checked by difference *Fourier* syntheses. The final *R* factor was 0.036. Atomic coordinates are given in *Table 5*<sup>1)</sup>.

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<sup>1)</sup> Tables with structure factors, anisotropic vibration parameters, and calculated H-atom coordinates are available from the authors. Part of this structure analysis was done by *Rolf Bänтели* as practical work in chemical crystallography.