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Preparation of Di- and Triamides and Their Application in Ion-Selective Electrodes

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Abstract. The synthesis of a series of non-cyclic di- and triamides each containing ether oxygen atoms is described. The ionophoric properties in an ion-selective PVC-membrane were studied. Some of these ionophores were selective for lithium ions.

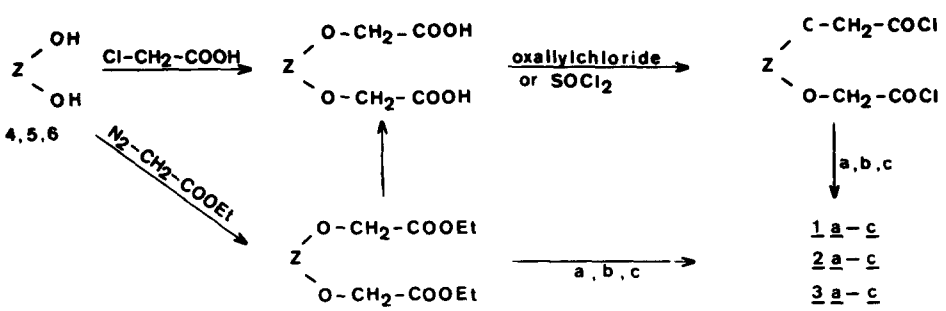
Key words. Di- and triamides, lithium ionophores, ion-selective electrodes.

1. Introduction

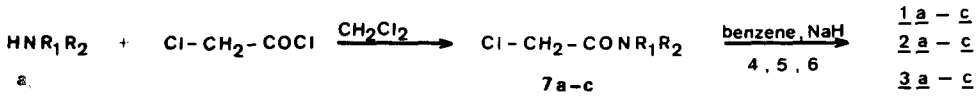
The majority of the electrically neutral ionophores for ion-selective electrodes (ISE) available from the Fluka Chemical Corp. are synthetic lipophilic non-cyclic amide complexing agents [1–3]. The sensors containing ionophores exhibit analytically useful selectivities for the direct measurement of the concentration of several cations, such as Li^+, Na^+, Mg^{2+}, Ca^{2+}, Sr^{2+} or Ba^{2+}.

We are interested in these types of ligands not only as potential ionophores for ISE, but also as compounds for selective extraction and transport of ions through artificial membranes [4], or for separation of certain cations from their mixtures on silica gel modified by carriers [5, 6].

The classical way to obtain open chain amides is shown in scheme A [7–12]. After the several steps of this synthesis, the overall yields are not very high and the final products require purification by tedious chromatographic separation. Compound **3c** may serve as an example [8].



Scheme A



Scheme B

The new compounds reported here, **1a–c**, **2a–c**, **3a–b**, as well as the known compound **3c** (ETH 227), have been prepared by a two-step synthesis in a way similar to that reported in [13] (Scheme B) and were obtained with a good yield and purity (see Figure 1 and Table 1). The amides were used in PVC-membrane electrodes and their ionophoric ability was examined. In ISE compounds **2a–c** and **3a–c** showed selectivity for lithium over other cations tested, while compounds **1a**, **1b** and **1c** exhibit selectivity for calcium. Ligands **1** and **2**, with a C=C double bond, could be modified, for example by attaching to silicagel, and used for other purposes such as for metal cation separations [5]. Further investigation of these lithium ionophores in ISE using different plasticizers confirm their outstanding behavior [14].

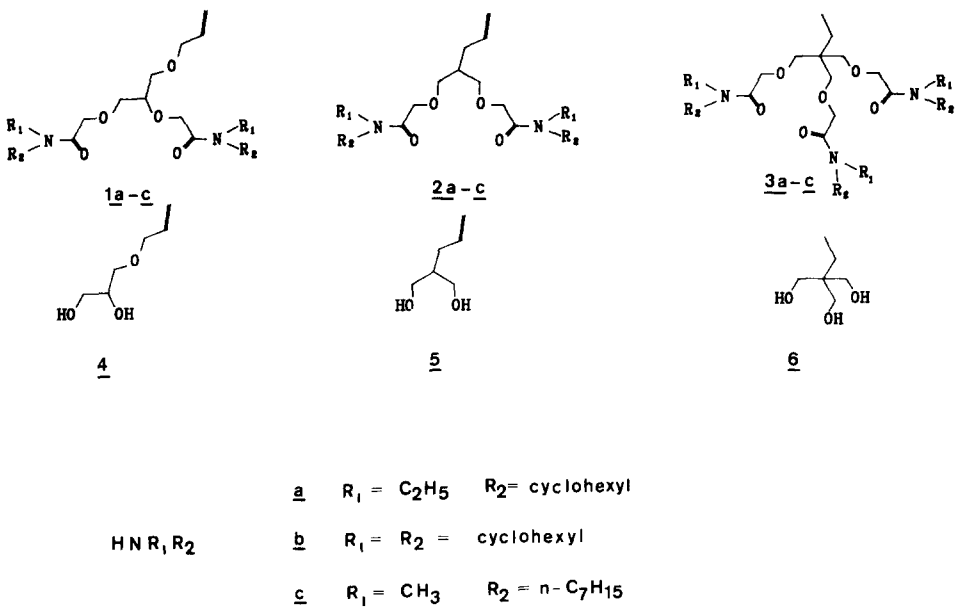


Fig. 1. Compounds used in this study.

2. Experimental

The proton NMR spectra were obtained on a JEOL FX-GOQ or on a Tesla 60 MHz spectrometer in $CDCl_3$ (Aldrich). The chemical shifts are reported in δ (ppm) using TMS as an internal standard. Infrared (IR) spectra were obtained on a SPECORD M 80 spectrometer (Carl Zeiss–Jena). The organic reagents and solvents used for the synthesis were reagent grade. Mass spectra were obtained on

Table. I. Yields and Physical Properties of Compounds **1–3**

Comp.	Formula	MS (M^+)	m.p (°C)	Yield (%)	IR(C=O) (cm^{-1})	NMR Spectra (δ)
1a	$C_{26}H_{46}O_5N_2$	466	oil	67.5	1640	1.1 (2t, 6H), 1.35 (m, 8H), 1.7 (m, 12H), 3.2 (m, 4H), 3.5 (m, 2H), 3.65 (m, 5H), 4.0 (s, 2H), 4.2 (s, 2H), 4.4 (s, 2H), 5.2 (m, 2H), 5.85 (m, 1H).
1b	$C_{34}H_{58}O_5N_2$	574	108	85	1652	1.0–2.0 (br m, 40H), 2.8 (m 4H), 3.5 (m, 5H), 3.9 (d, 2H), 4.0 (s, 2H), 4.2 (s, 2H), 5.1 (m, 2H), 5.75 (m, 1H).
1c	$C_{26}H_{50}O_5N_2$	470	oil	75	1652	0.85 (t, 6H), 1.23 (b s, 20H), 2.93 (s, 6H), 3.2 (m, 4H), 3.66 (m, 5H), 3.93 (d, 2H), 4.1 (s, 2H), 4.33 (s, 2H), 5.2 (m, 2H), 5.85 (m, 1H).
2a	$C_{26}H_{46}O_4N_2$	450	oil	73.5	1636	1.15 (m, 6H), 1.4 (m, 8H), 1.75 (m, 12H) 2.1 (m, 3H), 3.15 (m, 6H), 3.45 (d, 4H), 4.05 (s, 4H), 5.0 (m, 2H), 5.8 (m, 1H).
2b	$C_{34}H_{58}O_4N_2$	558	oil	80	1652	1–2 (br m, 40H), 2.1 (m, 3H), 2.7 (m, 4H), 3.45 (d, 4H) 4.0 (s, 2H), 5.0 (m, 2H), 5.7 (m, 1H).
2c	$C_{26}H_{50}O_4N_2$	454	oil	85	1652	0.85 (t, 6H), 1.23 (br s, 20H), 2.1 (m, 3H), 2.9 (s, 6H), 3.15 (m, 4H), 3.45 (d, 4H), 4.05 (s, 4H).
3a	$C_{36}H_{65}O_6N_3$	635	oil	84.5	1656	0.9 (t, 3H), 1.1 (m, 11H), 1.4 (m, 12H), 1.75 (m, 18H), 2.7 (m, 3H), 3.2 (m, 6H), 3.45 (s, 6H), 4.05 (s, 6H).
3b	$C_{48}H_{83}O_6N_3$	797	125	60	1644	0.9 (t, 3H), 1.0–2.2 (br m, 62H), 2.7 (m, 6H). 3.4 (s, 6H), 4.0 (s, 6H).
3c	$C_{36}H_{83}O_6N_3$	642	oil	76	1656	0.85 (t, 12H), 2.26 (br s, 32H), 2.9 (d, 9H), 3.3 (m, 6H), 3.4 (s, 6H), 4.05 (s, 6H).

a Varian MAT 711 mass spectrometer using the field desorption (FD) technique. The ^{1}H NMR spectra and mass spectra of all compounds confirmed their structure and purity.

2.1. PREPARATION OF CHLOROACETAMIDES **7a–c**

Preparation of Chloracetamide **7a**

A solution of 11.3 g (0.1 mole) of chloroacetyl chloride in 40 mL of methylene chloride was added portionwise into an ice cooled solution of 12.7 g (0.1 mole) of cyclohexylethylamine and 12 g (0.12 mole) of triethylamine in 50 mL of methylene chloride. The reaction mixture was stirred overnight at room temperature and then washed successively with water, 1 M HCl, water, sodium carbonate solution and again water and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the product was distilled under vacuum (85–87°C 0.09 mmHg). The yield of pure compound **7a** was 11.2 g (60%); IR (film) 1650 cm^{-1}; NMR: δ 1.1 (*t*, 3 H), 1.4 (*m*, 6 H), 1.75 (*m*, 4 H), 3.25 (*q*, 2 H), 3.5 (*m*, 1 H), 4.0 (*s*, 2 H).

Preparation of Chloroacetamide **7b**

A solution of 11.3 g (0.1 mole) of chloroacetyl chloride in 40 mL of methylene chloride was added portionwise to an ice cold solution of 36.2 g (0.2 mole) of dicyclohexylamine (Fluka, purum). The reaction mixture was treated as above for **7a**. After evaporation of the solvent the product precipitated. Crystallization from ethanol gave 15.5 g (65%) of amide **7b**; mp 106–108°C (it was not previously obtained in crystalline form [15]); Ir (nujol) 1636 cm^{-1}; NMR δ 0.9–2.7 (*bm*, 20 H), 3.0 (*bm*, 1 H), 3.3 (*bm*, 1 H), 3.96 (*s*, 2 H).

Preparation of Chloroacetamide **7c**

Compound **7c** was prepared in the same manner as **7a** to give 17.0 g (85%). The product was purified by molecular distillation, bp 120–130°C/0.1 mm; IR (film) 1656 cm^{-1}; NMR: δ 0.8 (*t*, 3 H), 1.23 (*br*, 10 H), 2.87 and 3.0 (2*s*, 3 H), 3.3 (*m*, 2 H), 4.0 (*s*, 2 H).

2.2. GENERAL PROCEDURE FOR THE PREPARATION OF AMIDES **1a–c** (Scheme B).

Preparation of Podand **1a**

Diol **4** (Aldrich) 0.66 g, (0.5 mmole) and 240 mg (10 mmole) of NaH in 15 mL of benzene were refluxed for about 1 h. Then a benzene solution of 10 mmole (2.03 g) of freshly distilled chloroacetamide **7a** was added portionwise. The mixture was refluxed for 48 h and 1 mL of ethanol was added to the cooled reaction mixture. The mixture was washed several times with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give 1.5 g (64.5%) of **1a** as a pale yellow oil. The crude product was chromatographed on Silica gel using chloroform–ethyl acetate (3 : 1) as eluant. Podand **1b** was prepared in a similar manner. The yields and physical properties for **1a–c** are given in Table I.

2.3. GENERAL PROCEDURE FOR THE SYNTHESIS OF AMIDES **2a–c** (Scheme B)

Preparation of Podand **2a**

Diglycol **5** (prepared from diethyl allylmalonate, Aldrich) 1.15 g (10 mmole) and 480 mg (20 mmole) of NaH in 25 mL of benzene were refluxed for 1 h and cooled. A solution of 20 mmole (4.06 g) of freshly distilled chloroacetamide **7a** in benzene was added portionwise to the above solution. After stirring for 5 h at room temperature, the mixture was refluxed for an additional 24 h. Ethanol (1 mL) was added to decompose the excess NaH and the solution was washed several times with water and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product (3.07 g, 74%) was obtained as a pale yellow oil. Podands **2b** and **2c** were prepared in similar manner. The yields and physical properties for **2a–c** are given in Table I.

2.4. GENERAL PROCEDURE FOR THE SYNTHESIS OF PODANDS **3a–c** (Scheme B).

Preparation of Podand **3a**

Triol **6** (Fluka, purum) 1.34 g (10 mmole) and 720 mg (30 mmole) of NaH in 30 mL of benzene were refluxed for about 1 h. Freshly distilled chloroacetamide **7a** 6.12 g (30 mmole) in benzene was added portionwise. The mixture was refluxed for 72 h and then it was washed several times with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give 5.36 g (85%) of **3a** as a pale yellow oil. The crude product was purified by column chromatography on Silica gel (elution with chloroform). Podands **3b** and **3c** were prepared in similar manner. The yields and physical properties for **3a–c** are given in Table I.

2.5. PREPARATION OF PODAND **1c** (Scheme A)

Preparation of 3-(2-oxa-4-pentenyl)-3,6-dioxaoctanedioic acid (Scheme A)

Diol **4**, 26.4 g (0.2 mole) in 200 mL of *t*-butyl alcohol, was added to a stirred solution of 100 g (0.88 mole) of *t*-BuOK in 500 mL of *t*-butyl alcohol. Chloroacetic acid 41.58 g (0.44 mmole) was added over a 1-h period to the above solution at reflux temperature and the mixture was further refluxed for 3 days. The *t*-butyl alcohol was removed under reduced pressure and the residue was mixed with 700 mL of water. The aqueous phase was washed twice with 300 mL portions of ethyl acetate. The pH of the aqueous phase was adjusted to 2.0 with HCl and it was saturated with NaCl and then extracted with 3 portions of 200 mL of ethyl acetate. The combined organic extracts were washed twice with 300 mL of brine and dried over anhydrous $MgSO_4$. The solvent was removed and 33.44 g (47%) of the crude product was obtained as an oil. The diacid was purified on a column filled with Dowex Macroporous Basic Anionite-OH (16–50 mesh) to give 25 g (35%) of 3-(2-oxa-4-pentenyl)-3,6-dioxaoctanedioic acid; NMR δ 3.55 (*m*, 2 H), 3.75 (*m*, 3 H), 4.05 (*d*, 2 H), 4.2 (*s*, 2 H), 4.35 (*s*, 2 H), 5.3 (*m*, 2 H), 5.9 (*m*, 1 H), 8.45 (6*s*, 2 H).

Preparation of 3-(2-oxa-4-pentenyl)-3,6-dioxaoctanedioic acid chloride (Scheme A)

3-(2-oxa-4-pentenyl)-3,6-dioxaoctanedioic acid, 1.3 g (5 mmole), and 2.54 g (0.02 mole) of oxallyl chloride was added portionwise to 15 mL of dry benzene containing 2 drops of pyridine during a period of 20 min. The mixture was stirred at room temperature for 20 h and then the solvent was evaporated under reduced pressure to yield 100% of acid chloride; NMR δ 3.6 (*m*, 2 H), 3.75 (*m*, 3 H), 4 (*m*, 2 H), 4.5 (*s*, 2 H), 4.65 (*s*, 2 H), 5.25 (*m*, 2 H), 5.9 (*m*, 1 H). The brown oil was used in the next step without further purification.

Preparation of **1c** *(Scheme A)*

A solution of 3-(2-oxa-4-pentenyl)-3,6-dioxaoctanedioic acid chloride in 5 mL of benzene was added to a solution of 10 mmole (1.29 g) of ethylheptylamine (Fluka) and 10 mmole (790 mg) of pyridine in 10 mL of benzene. The mixture was stirred at room temperature for 20 h and then refluxed for 1 h. The solution was washed successively with water, 1 M HCl, water, sodium carbonate and water, dried over anhydrous $MgSO_4$ and evaporated to dryness to give 1.91 g (75%) of **1c** as a dark oil. Product **1c** was purified on silica gel (chloroform). The physical properties for **1c** are listed in Table I.

2.6. ELECTRODE SYSTEM

The poly(vinyl chloride) (PVC) membranes were prepared as described in [11] using *o*-nitrophenyloctyl ether (NPOE) as the plasticizer (65%), PVC high molecular S-72 (32%) and ionophore (3%). The membranes were incorporated into Ag/AgCl electrode bodies, with 0.01 M NaCl as internal electrolyte. A double-junction reference electrode of the Radelkis OP0820P type was used with tetramethylammonium nitrate in the bridge cell.

2.7. E.M.F. MEASUREMENTS

All potentials were measured at 20 ± 1°C using an N 517 (MERA ELWRO) pH-meter equipped with a V541 digital voltmeter, which allowed a reading accuracy up to ± 0.1 mV. All selectivity coefficients ($\log K^{\text{Pot}}_{\text{Li,M}}$) were determined by the separate solution method (SSM) and were calculated by the matched potential method [16, 17].

3. Discussion

The procedure shown in Scheme B seems to be especially useful for the preparation of triamides **3a–c**, where steric hindrance could cause low yields in each step of the usual synthetic method (Scheme A) and the separation of pure amide from by-products is not simple. This method has a special advantage in the synthesis of *N,N*-dicyclohexylamides, which are difficult to obtain with good yield because of the bulky cyclohexyl groups. Dicyclohexylchloroamide **7b** can be easily purified by crystallization from ethanol. The last step in Scheme B with both substrates in the

Table II. The characteristics of ionophores.

Electrode ionophore	ion preference	Slope mV	Detection limit mol/dm^3	Lipophilicity of ligand[a] log $P = \Sigma\pi$
1a	Ca^{2+}	27	3.1×10^{-6}	6.78
1b	Ca^{2+}	29	4.2×10^{-7}	8.52
1c	Ca^{2+}	28	3.1×10^{-6}	5.54
2a	Ca^{2+}	26	3.0×10^{-6}	5:28
	Li^+	54	3.1×10^{-4}	
2b	Ca^{2+}	29	3.0×10^{-7}	8.46
	Li^+	58	1.0×10^{-4}	
2c	Ca^{2+}	25	3.1×10^{-6}	5.60
	Li^+	51	2.5×10^{-4}	
3a	Li^+	56	1.4×10^{-4}	9.57
3b	Li^+	58	1.0×10^{-5}	12.18
3c	Li^+	57	6.3×10^{-5}	7.71

[a]for a more detailed explanation see the text.

pure state gave nearly pure products **1–2b**. Prolongation of the reaction time up to several days resulted in a better yield and purity of product **3b**. Table I lists all amides and their physical and spectral properties.

Table II presents the characteristics of the electrodes containing ligands **1a–c**, **2a–c** and **3a–c**. The potentiometrically determined ion selectivities of the synthesized compounds are presented in Figure 2. The selectivity coefficient (log $K^{Pot}_{Li,M}$)

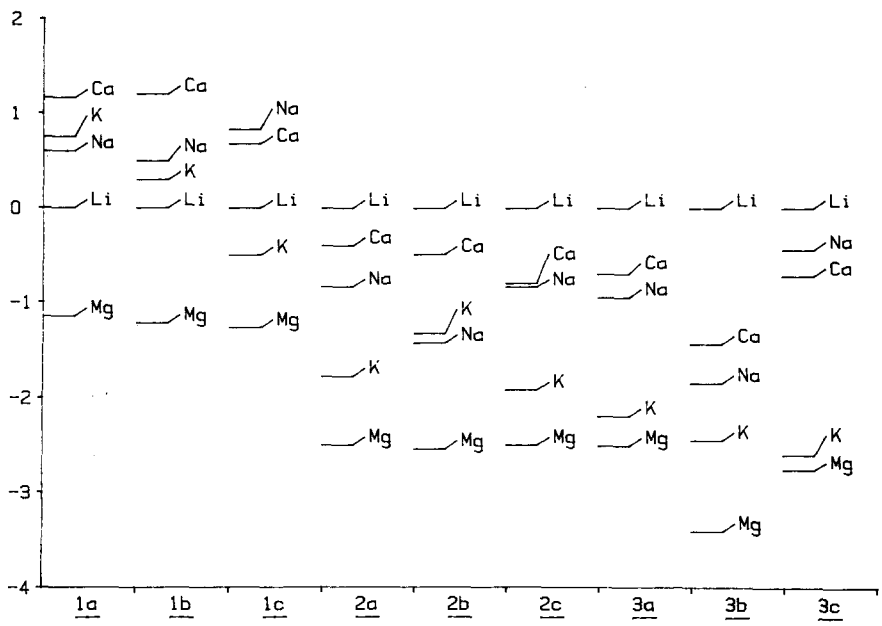


Fig. 2. The selectivity coefficients (log $K_{Li,M}$) for electrodes **1a–c**. **2a–c** and **3a–c**.

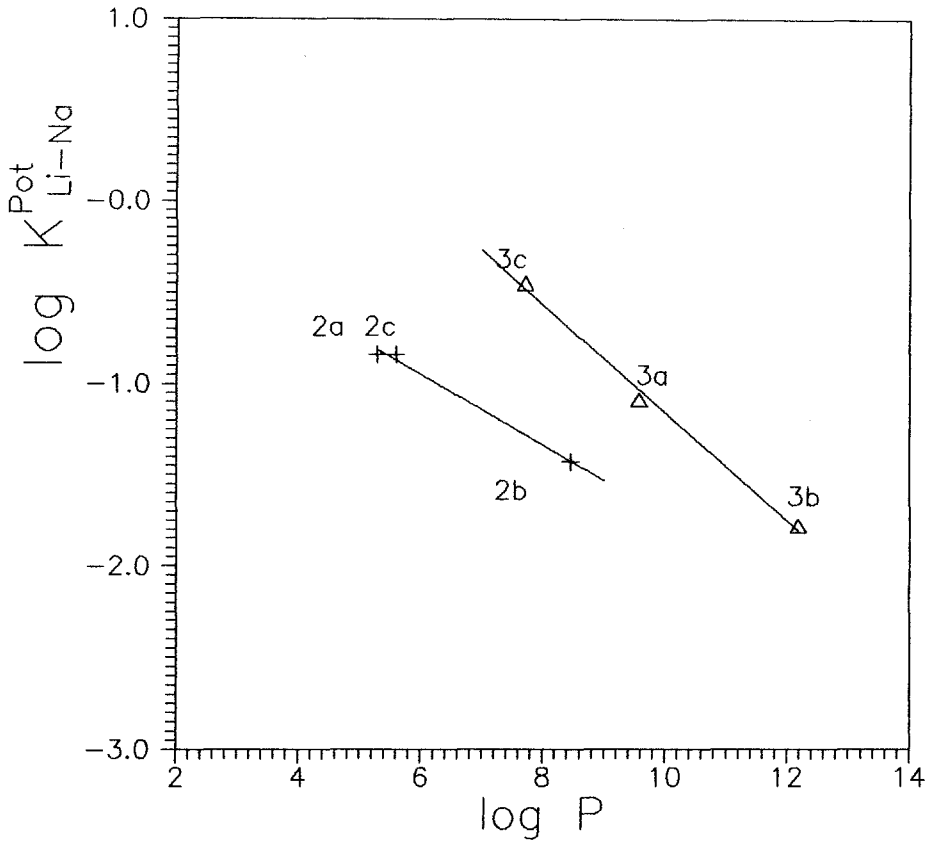


Fig. 3. The plot of log P vs. log $K^{Pot}_{Li,Na}$ for compounds **2a–c** and **3a–c**.

indicates preference of the membrane system for the M ions, such as K^+, Na^+, Ca^{2+}, Mg^{2+} in relation to Li^+.

The most lipophilic ligands are dicyclohexylamides **2b** and **3b** and they were found to be the best ionophores in ion-selective electrodes, considering the stability, the life time characteristic and the selectivity for Li over Na. The lipophilicity was calculated according to the method of Hansch [18–19]. It was found that for the known compound **3c** (ETH 227) this value ($\log P = 7.7$) correlates well with the value determined by thin layer chromatography by Oesch *et al.* ($\log P_{TLC} = 7.8$) [21].

In Figure 3 are shown plots of calculated $\log P$ values in relation to the $\log K^{Pot}_{Li,Na}$ values for two series of compounds **2a–c** and **3a–c**. A similar relation found between lipophilicity and selectivity of the crown ethers was interpreted by Cygan *et al.* [20] as the result of different complex stoichiometry.

The highly lipophilic compound **3b** ($\log P = 12.1$) works as a very good lithium ionophore in PVC-NPOE ion-selective electrodes (see Figure 2), with the selectivity for Li over Na as high as $\log K = -1.85$. The electrode based on **3b** has outstanding stability and life time characteristics.

Compound **3b** has three carbons between the two ether oxygen atoms. Such an arrangement of atoms seems to be most suitable for Li cation complexation [10, 22–24]. Thus, our results confirm some factors emphasized by Christian *et al.* [24] to have an effect on the selectivity for lithium. They are: the size of the pseudocavity or cavity, the type and number of coordinating atoms and the lipophilicity of bulky substituents, which hinders the formation of complexes with larger cations of different complex stoichiometry.

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