

# A $D_2$ symmetric tetraamide macrocycle based on 1,1',4,4'-tetrahydro[3,3'(2*H*,2'*H*)-spirobiquinoline]-2,2'-dione: synthesis and selectivity for lithium over sodium and alkaline earth ions

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**Abstract**—Macrocyclic ionophores *d,l*-**3** and *d,l*-**4** with four amide carbonyl ligands were synthesized and investigated in lithium ion-selective electrodes. In solvent PVC membranes, ion selectivity of *d,l*-**3** and *d,l*-**4** for lithium relative to sodium was observed as  $\log K_{\text{Li,Na}}^{\text{pot}} = -1.4$  and  $-1.23$ , respectively. Spiromacrocycle *d,l*-**3** and analogue dibenzospiromacrocycle *d,l*-**4** have similar ion selectivity patterns for alkali metal ions, but *d,l*-**4** could discriminate against alkaline earth metal ions better than *d,l*-**3**. It is an example of an endopolarophilic/exolipophilic macrocyclic ionophore whose selectivity for monovalent cations over divalent cations is enhanced by thick lipophilic shells.  
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## 1. Introduction

It is well known that the amide group has high affinity for cations with high charge density. Many ionophores with amide ligands are currently employed as chemical sensors that can quantitatively and reversibly measure cationic analytes.<sup>1</sup> In particular, the development of ionophores with amide ligands has been frequently reported for achieving high selectivity for lithium over sodium in blood lithium measurement during treatment of manic depressive psychosis.<sup>2</sup> Our early reports on macrocyclic tetraamide ionophores based on the spirodi-amide building block have shown reasonable lithium selectivity over sodium in solvent PVC membrane electrodes.<sup>3</sup> Four amide carbonyl ligands in dispiromacrocylic ionophore **3** derived from 2,8-diazaspiro[5,5]undecan-1,7-dione (**1**) converge inward on the molecular cavity of the ionophore upon complexation with lithium ion.<sup>3</sup> Lithium is known to interact preferentially with four or five hard oxygen donors in complexes.<sup>4</sup> However, divalent cations such as calcium and magnesium frequently interfere in lithium ion-selective electrode ( $\text{Li}^+$ -ISE) measurements. Calcium and magnesium are both the important electrolytes in the human body, and are present in relatively high concentration in intra- and extra-

cellular fluids. Reported here is an example of an endopolarophilic/exolipophilic macrocyclic ionophore whose selectivity for monovalent cations over divalent cations is enhanced by a thick lipophilic shell. Thickness of the ligand layer influences in particular the selectivity between mono and divalent cations.<sup>5</sup> A macrocyclic tetraamide analogue based on 1,1',4,4'-tetrahydro[3,3'(2*H*,2'*H*)-spirobiquinoline]-2,2'-dione (**2**) was synthesized and its ion selectivity was studied in solvent PVC membrane electrodes.

## 2. Results and discussion

### 2.1. Synthesis

The key starting materials, spirodiamides **1** and **2**, have been recently reported as  $C_2$ -symmetric building blocks for ionophores capable of tetrahedral coordination of guest metal ions and as potential chiral auxiliaries. Spirodiamide **1** was synthesized in 60% overall yield by cyanoethylation of diethyl malonate by reaction with acrylonitrile, followed by reduction–cyclization.<sup>3a</sup> Similarly dibenzospirodiamide **2** was synthesized via reaction of malonic ester with *o*-nitrobenzyl bromide, followed by reductive cyclization in 86% yield.<sup>6</sup> Spiromacrocycle **3** was also reported in an earlier communication,<sup>3a</sup> but the detailed synthesis of **3** is given in the current paper. Spiromacrocycle **3** was synthesized by high dilution technique. Spirodiamide **1** was first converted

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to the dianion with sodium hydride in anhydrous DMSO at 70 °C. Reaction of the sodium salt of spirodiamide **1** with 1,4-bis(chloromethyl)benzene gave the desired [2+2] product, dispiromacrocyclic **3**, in 7% yield after chromatography. Similarly dibenzospirodiamide **4** was synthesized from dibenzospirodiamide **2**, which was converted to the dianion. Reaction of the sodium salt of dibenzospirodiamide **2** with 1,4-bis(chloromethyl)benzene gave a mixture of products containing the desired [2+2] products, higher oligomer, polymer, and aldehydes, which were apparently produced by reaction of benzylic chloride intermediates with hot DMSO. Two stereoisomeric macrocycles, apparently corresponding to the *meso* and *d,l* diastereomers shown in Scheme 1, were isolated from this product mixture.

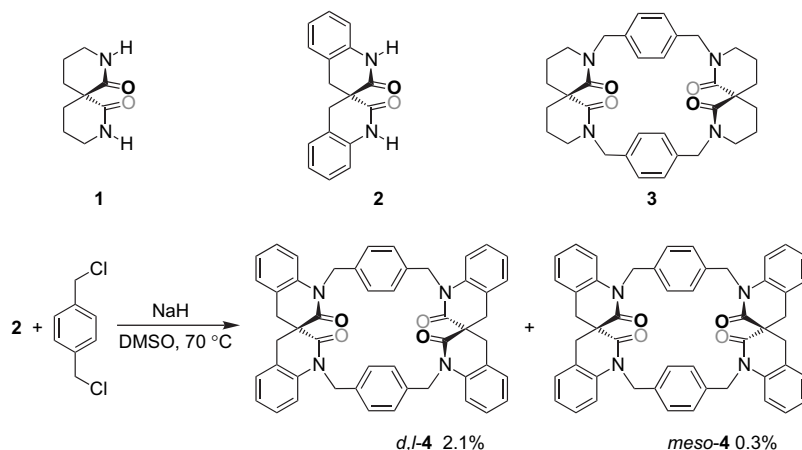
The desired [2+2] products were isolated by column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 97:3) followed by preparative HPLC (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 95:5). The isomers were further purified by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/MeOH, giving colorless needle-shaped crystals and transparent cubic crystals in 2.1% and 0.3% yield, respectively. The major needle-shaped crystals were further resolved into two components by chiral HPLC, whereas the minor transparent cubic crystals remained as a single component without further resolution. The major needle-shaped crystals were identified as a racemic mixture of chiral macrocycle *d,l*-**4** and the minor product as achiral macrocycle *meso*-**4**, without ambiguity. The [2+2] composition of macrocycles **4** were demonstrated by mass spectrometry. In each of these compounds the benzylic protons produce a pair of doublets in the proton NMR spectrum, demonstrating that these geminal protons are diastereotopic in both macrocycles.

## 2.2. Potentiometric ion selectivity of ionophores in the PVC membranes

The potentiometric response of PVC polymeric Li<sup>+</sup>-ISEs based on amide ionophores was examined for alkali metal and alkaline earth ions and ammonium ion. The selectivity of Li<sup>+</sup>-ISEs was found to be varied depending on the particular plasticizer used, whether the membrane contained a lipophilic anion additive, and whether the fixed interference method or the separate solution method was used for

measurements.<sup>7</sup> The incorporation of salts of lipophilic anions such as potassium tetrakis(*p*-chlorophenyl)borate (KTpCIPB) into the membrane phase reduces the interference by sample anions. Selectivities for a given ionophore are very sensitive to the amount of such lipophilic anions relative to the ionophore concentration. The lithium selectivity changes drastically with respect to the stoichiometry of anion additive KTpCIPB, relative to the amide ionophores. The best performance was achieved with less than 100 mol % of KTpCIPB for the 1:1 ionophores complexing with lithium ion. With excess additives the selectivities approached the sequence of classical ion-exchange membranes in which the selectivities are proportional to ion lipophilicity.<sup>8</sup> Simon's membrane composition was employed to allow comparison with previously reported results of diamide ionophore ETH 1810, *cis*-*N,N*-dicyclohexyl-*N',N'*-diisobutylcyclohexane-1,2-dicarboxamide, which has been known as a good lithium ionophore.<sup>7</sup> The membranes were composed of about 1 wt % of the ionophore, 0.4 wt % of KTpCIPB (corresponding to about 60 mol %, relative to the ionophore), about 65.6 wt % of *o*-nitrophenyloctyl ether (*o*-NPOE) as a plasticizer, and 33 wt % of PVC.<sup>8</sup>

The dispiromacrocyclic **3** and **4** have been tested as ionophores in PVC membranes of Li<sup>+</sup>-ISEs. The selectivities of the resulting electrodes were determined by the separate solution method.<sup>9</sup> From the prior communication, the dispiromacrocyclic ionophore **3** displayed significant selectivity for lithium relative to sodium ( $\log K_{\text{Li,Na}}^{\text{pot}} = -1.4$ ). This level of selectivity is consistent with the tentative structural assignment of **3** as the *D*<sub>2</sub>-symmetric chiral isomer, *d,l*-**3**. In the *C*<sub>2h</sub>-symmetric achiral *meso* isomer, *meso*-**3**, which was not isolated from the product mixture, the four-carbonyl ligands are not oriented to enable coordination of guest metal ions efficiently according to molecular models. The four amide carbonyl ligands in *d,l*-**3** are structurally pre-organized to converge on the molecular cavity and to coordinate small metal ions such as lithium in a distorted tetrahedral geometry. For comparison of ion selectivity of these structurally similar ionophores, *d,l*-**3** and *d,l*-**4** were tested under the same conditions. The *meso* isomer of the dibenzospirodiamide macrocycle, *meso*-**4** has not been tested as an ionophore, because a comparable PVC membrane containing *meso*-**4** could not be prepared due to its insolubility in



Scheme 1.

THF, which is a standard solvent for preparing PVC membranes for ISEs.

Selectivity coefficients for PVC membranes containing ionophores ETH 1810, *d,l*-3, and *d,l*-4 are listed in Table 1. Ionophore ETH 1810 gave results that are comparable to the selectivity coefficients reported by Simon and co-workers.<sup>8</sup> The control membrane containing lipophilic anion additive, KTpCIPB shows higher selectivity for more lipophilic metal cations. This is a common phenomenon for ion-exchange membranes. Membranes containing the additive tetrakis(*p*-chlorophenyl)borate behave like ion-exchange resins in the absence of ionophores. Lipophilic solvent PVC membranes containing the spiromacrocyclic ionophores *d,l*-3 and *d,l*-4 gave good potentiometric responses, and also displayed significant selectivities for lithium relative to sodium ( $\log K_{\text{Li,Na}}^{\text{pot}} = -1.40$  and  $-1.23$ , respectively), even though these selectivities are moderate compared to structurally optimized ionophore ETH 1810 ( $\log K_{\text{Li,Na}}^{\text{pot}} = -2.22$ ). The selectivity patterns of the isomorphous ionophores *d,l*-3 and *d,l*-4 are fairly similar to each other for alkali metal ions. The dibenzo analogue *d,l*-4 with thicker lipophilic benzene moiety shows slightly higher affinity toward lipophilic ions, such as rubidium and cesium. However, the dibenzo analogue *d,l*-4 could better discriminate against alkaline earth metal ions such as magnesium, calcium, and barium than the analogue *d,l*-3. The selectivity coefficient differences

( $\Delta \log K_{\text{Li,M}}^{\text{pot}}$ ) between analogous ionophores *d,l*-3 and *d,l*-4 are 0.68 for magnesium, 1.32 for calcium, and 1.33 for barium, which means that *d,l*-4 excludes these divalent cations by factors of 5, 20, and 21, respectively. A preference for divalent relative to monovalent cations of the same size are observed with ligand *d,l*-3, which has a small thickness of the ligand layer around the central atom and high dipole moments, apparently increasing the stability of the complex.<sup>10</sup> In contrast, modifying the skeleton of ionophore from *d,l*-3 to *d,l*-4 by adding much thicker lipophilic benzene shell, gives higher lipophilicity and greater selectivity for monovalent cations relative to divalent cations.

The properties of novel ionophore *d,l*-4 were further investigated by varying the kind of the plasticizer and amount of the lipophilic anion additive, KTpCIPB. The plasticizer, bis(1-butylpentyl)adipate (BBPA), is known as less lipophilic than *o*-NPOE, and has been used as a plasticizer for PVC polymeric NH<sub>4</sub><sup>+</sup>-ISEs containing the ionophore nonactin.<sup>11</sup> Five PVC membranes containing the plasticizer *o*-NPOE and varying amount of KTpCIPB, 0–120 mol % with respect to the ionophore *d,l*-4, were prepared to determine the optimum amount of the lipophilic anion additive. The lithium ion selectivity coefficients of the resulting electrodes were determined and are listed in Table 2. The control membrane containing no lipophilic anion additive shows high affinity for more lipophilic alkali metal ions, in the order of cation lipophilicity, Cs<sup>+</sup>>Rb<sup>+</sup>>K<sup>+</sup>>Na<sup>+</sup> but discriminates against the more hydrophilic alkaline earth metal dications such as Ba<sup>2+</sup>, Mg<sup>2+</sup>, and Ca<sup>2+</sup>. This phenomenon is commonly observed for solvent PVC membrane containing lipophilic plasticizers, such as *o*-NPOE. Such phenomena of ion-exchange membranes are enhanced when an excess of a lipophilic anion is added, with respect to the amount of ionophore. All cations examined had higher affinities to the membrane, hence poorer lithium ion selectivities when the Li<sup>+</sup>-ISE contained 120 mol % KTpCIPB. The optimum amount of the lipophilic anion additive was examined for lithium selectivity. Theoretically, 100 mol % of the anion additive is required for the best sensitivity and selectivity for ionophores forming 1:1 complexes. With the addition of suitable amount of lipophilic anion additive KTpCIPB, lipophilic cations such as Cs<sup>+</sup> and Rb<sup>+</sup> have higher affinity to the membranes, but hydrophilic alkaline earth metal dications such as Ba<sup>2+</sup>, Mg<sup>2+</sup>, and Ca<sup>2+</sup> have lower affinity. Response to K<sup>+</sup> and NH<sub>4</sub><sup>+</sup> ions was not affected strongly by the amount

**Table 1.** Selectivity coefficients,  $\log K_{\text{Li,M}}^{\text{pot}}$ , for solvent polymeric membranes containing ionophores, ETH 1810, *d,l*-3 or *d,l*-4; plasticizer, *o*-NPOE, and lipophilic anion additive, KTpCIPB, and for control membrane lacking ionophore, and required selectivity coefficients,  $\log K_{\text{Li,M}_{\text{max}}}^{\text{pot}}$

Interfering ion	Control	ETH 1810	<i>d,l</i> -3	<i>d,l</i> -4	$\log K_{\text{Li,M}_{\text{max}}}^{\text{pot}}$ <sup>a</sup>	
					Intra	Extra
Na <sup>+</sup>	0.37	-2.22	-1.40	-1.23	-3.2	-4.3
K <sup>+</sup>	1.97	-2.58	0.67	0.35	-4.2	-2.8
Rb <sup>+</sup>	2.59	-2.73	1.29	1.47		
Cs <sup>+</sup>	3.24	-2.65	1.38	2.16		
NH <sub>4</sub> <sup>+</sup>	1.62	-2.60	0.91	0.46		
Mg <sup>2+</sup>	-0.48	-4.02	-1.61	-2.29	-3.7	-3.5
Ca <sup>2+</sup>	-0.29	-2.75	-0.83	-2.15	-2.1	-3.6
Ba <sup>2+</sup>	-0.29	-2.93	-0.79	-2.12		

Selectivity coefficients determined by the separate solution method with 0.1 M solutions of the chlorides.

<sup>a</sup> Selectivity factors required for 1% interference, based on intra- and extra-cellular ion activities.

**Table 2.** Selectivity coefficients,  $\log K_{\text{Li,M}}^{\text{pot}}$ , for solvent polymeric membranes based on ionophore *d,l*-4 containing *o*-NPOE or BBPA as plasticizer and varying amounts of lipophilic anion additive, KTpCIPB

Interfering ion	<i>o</i> -NPOE					BBPA	
	KTpCIPB (mol %) <sup>a</sup>					KTpCIPB (mol %) <sup>a</sup>	
	0	30	60	90	120	0	60
Na <sup>+</sup>	-0.07	-0.92	-1.23	-0.50	0.41	0.02	-0.75
K <sup>+</sup>	1.22	0.85	0.35	1.21	2.06	1.03	0.17
Rb <sup>+</sup>	1.90	1.97	1.47	2.10	2.66	1.87	1.19
Cs <sup>+</sup>	2.45	2.61	2.16	2.74	3.32	2.64	1.97
NH <sub>4</sub> <sup>+</sup>	1.03	0.95	0.46	1.05	1.65	1.01	0.31
Mg <sup>2+</sup>	-1.84	-2.30	-2.29	-1.47	-0.66	-1.85	-2.44
Ca <sup>2+</sup>	-1.45	-1.75	-2.15	-1.42	-0.29	-1.95	-2.39
Ba <sup>2+</sup>	-0.14	-1.63	-2.12	-1.23	0.02	-1.84	-1.36

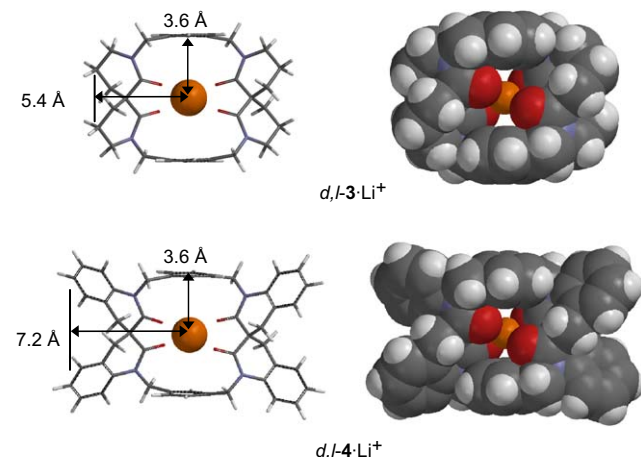
<sup>a</sup> mol % of the anion additive KTpCIPB with respect to ionophore *d,l*-4 in PVC membranes, which were composed of about 1 wt % of the ionophore *d,l*-4, 66 wt % of *o*-NPOE plasticizer and 33 wt % of PVC.

of the lipophilic anion additive, but the common interfering dications could be better discriminated. Specially the membrane containing 60 mol % of KTpCIPB with respect to the ionophore *d,l*-4 shows good lithium ion selectivity over sodium, which is the most important interfering ion in blood serum during lithium measurement.

Membranes containing the plasticizer BBPA instead of *o*-NPOE could better discriminate between alkaline earth and alkali metal ions. For example, the selectivity coefficient differences ( $\log K_{\text{Li,Cs}}^{\text{pot}} - \log K_{\text{Li,Ca}}^{\text{pot}}$ ) between relatively lipophilic Cs<sup>+</sup> and highly hydrophilic Ca<sup>2+</sup> are 3.90 for the control membrane with *o*-NPOE and 4.59 for the control membrane with BBPA. However, with the addition of KTpCIPB to the membrane composed of BBPA, the lithium ion selectivities against all metal ions examined were enhanced, but practical lithium ion selectivity over sodium ion was not obtained.

### 2.3. Molecular modeling

Energy-minimized structures of *d,l*-3·Li<sup>+</sup> and *d,l*-4·Li<sup>+</sup> complexes are shown in Figure 1. The distances between ligand O and Li<sup>+</sup> are all the same in each complex: 2.196 Å for *d,l*-3·Li<sup>+</sup> and 2.118 Å for *d,l*-4·Li<sup>+</sup>. Bond angles,  $\angle \text{O-Li-O}$ , are measured as 75° and 137° in *d,l*-3·Li<sup>+</sup>, and 76° and 136° in *d,l*-4·Li<sup>+</sup> for angles formed by two ligand oxygens of the same dibenzospirodiamide moiety and by oxygens of two different spirodiamide moieties, respectively. The complexing geometry of Li<sup>+</sup> to the ionophores *d,l*-3 and *d,l*-4 is very similar. Fusion of benzene rings of *d,l*-4 onto the *d,l*-3 skeleton does not significantly affect complex geometry. The distance from the molecular center to the *para*-xylyl moieties was unchanged, but the thickness of molecular shell is enlarged to 7.2 Å from 5.4 Å. The thicker lipophilic shell of ionophore *d,l*-4 apparently enhances ion selectivities for monovalent cations over divalent cations.



**Figure 1.** Energy-minimized structures of pseudo-tetrahedral complexes of *d,l*-3·Li<sup>+</sup> and *d,l*-4·Li<sup>+</sup> (Spartan'04 V1.0.1 PM3 semiempirical). In *d,l*-3·Li<sup>+</sup> the distances 5.4 and 3.6 Å are measured from the lithium atom to the center of the line connecting the two gamma carbons of the spirodiamide moiety, and to the center of the benzene ring in the *para*-xylyl moiety, respectively. The distance 7.2 Å in *d,l*-4·Li<sup>+</sup> is measured from the lithium atom to the center of the line connecting the two *para* carbons of the benzene rings in dibenzospirodiamide moiety.

### 3. Conclusion

In summary, macrocyclic tetraamide ionophores *d,l*-3 and *d,l*-4 in which four amide carbonyl ligands are structurally preorganized to converge on the molecular cavity and to coordinate tetrahedrally to small metal ions such as lithium were synthesized and tested as possible lithium ionophores in solvent PVC membranes. These PVC membranes containing the plasticizer *o*-NPOE and the lipophilic anion additive KTpCIPB gave good potentiometric responses to alkali metal ions and alkaline earth metal ions. Significant selectivities for lithium relative to sodium were observed as  $\log K_{\text{Li,Na}}^{\text{pot}} = -1.4$  for *d,l*-3 and  $-1.23$  for *d,l*-4. Both isomeric ionophores *d,l*-3 and *d,l*-4 show similar ion selectivity patterns for cations such as Na<sup>+</sup>, K<sup>+</sup>, and NH<sub>4</sub><sup>+</sup>, but the dibenzo analogue *d,l*-4 with lipophilic benzene moiety shows slightly higher affinity toward more lipophilic ions such as Rb<sup>+</sup> and Cs<sup>+</sup>. However, the dibenzo ionophore *d,l*-4 could discriminate against alkaline earth metal ions better than the analogue *d,l*-3 by factors of 5 for Mg<sup>2+</sup>, 20 for Ca<sup>2+</sup>, and 21 for Ba<sup>2+</sup>. Modifying the skeleton of ionophore *d,l*-3 to *d,l*-4, by adding a much thicker lipophilic benzene shell, gives higher lipophilicity and greater selectivity for monovalent cations relative to divalent cations. This is an example of an endopolarophilic/exolipophilic macrocyclic ionophore whose selectivity for monovalent cations over divalent cations is enhanced by thick lipophilic shells.

### 4. Experimental

#### 4.1. Reagents

*cis*-*N,N*-Dicyclohexyl-*N,N'*-diisobutylcyclohexane-1,2-dicarboxamide (ETH 1810) was synthesized.<sup>12</sup> High molecular weight poly(vinyl chloride) (PVC), 2-nitrophenyl octyl ether (*o*-NPOE), bis(1-butylpentyl)adipate (BBPA), and potassium tetrakis(*p*-chlorophenyl)borate (KTpCIPB) were obtained from Fluka. Analytical grade chloride salts of cesium, rubidium, potassium, sodium, lithium, barium, calcium, magnesium, and ammonium were obtained from Fluka. Doubly distilled water was used to prepare all aqueous electrolyte solutions. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use, and dimethyl sulfoxide (DMSO) was distilled from CaH<sub>2</sub> under reduced pressure.

#### 4.2. Preparation of polymeric ion-selective electrodes

The typical composition of solvent polymeric membranes for Li<sup>+</sup>-ion-selective electrodes was 33 mg PVC, 66 mg plasticizer, 1 mg ionophore, and various amounts of KTpCIPB (about 30 mol % in respect to the divalent carriers and 60 mol % to the tetravalent ligands). The mixture was then completely dissolved in 2 mL of THF. All membrane cocktails were cast into glass rings (1 inch i.d.) placed on glass plates for conventional ion-selective electrodes. Solvent was allowed to evaporate for 24 h at room temperature in a closed container. The thickness of the resulting membrane was about 0.3 mm.

A membrane disk (7 mm diameter) cut out with a punch was mounted in a Philips electrode body (IS-561). The electrode was filled with internal filling solution (0.1 M LiCl) and conditioned for 24 h by soaking in a 0.1 M LiCl solution. A silver/silver chloride coated wire was used as an internal reference electrode.

### 4.3. Potentiometric measurements

All emf measurements were performed at  $24 \pm 1$  °C by means of a Mettler Delta 350 meter with an Orion sleeve-type double-junction Ag/AgCl reference electrode (Model 900200). The emf readings were referenced to zero with a 0.1 M LiCl sample solution. The emf readings for interfering metal ions were used directly for selectivity coefficient calculations. The selectivity coefficients ( $\log K_{Li,M}^{pot}$ ) were determined by the separate solution method<sup>8</sup> (SSM, 0.1 M chloride). Activities were calculated according to the Debye–Hückel procedure.

### 4.4. Synthesis

**4.4.1. 3,11,18,26-Tetraazaheptacyclo[26.2.2.2<sup>13,16</sup>.1<sup>3,7</sup>.1<sup>7,11</sup>.1<sup>18,22</sup>.1<sup>22,26</sup>]-octatriaconta-13,15,28,30,31,35-hexaene-33,34,37,38-tetrone, 3.** To sodium hydride (60% dispersion in mineral oil, 180 mg, 4.4 mmol) washed with hexane was added dry DMSO (20 mL) and the resulting mixture was stirred at 70 °C for 30 min under nitrogen. To a clear solution was added 2,8-diazaspiro[5,5]undecane-1,7-dione, **1** (364 mg, 2 mmol) and the mixture was stirred for additional 30 min. This solution was transferred to a 50-mL syringe and the volume was adjusted to 35 mL by adding extra DMSO. A solution of 1,4-bis(chloromethyl)benzene (350 mg, 2 mmol) in DMSO (35 mL) was prepared in another 50-mL syringe. These two solutions were simultaneously added dropwise by a syringe pump to 250 mL of anhydrous DMSO containing anhydrous MgSO<sub>4</sub> (480 mg) at 70 °C for a period of 2 h, and the resulting reaction mixture was heated for additional 2 h under nitrogen. The solvent was removed in vacuo and the residue was dissolved in chloroform (100 mL). The mixture was washed with brine (100 mL). The chloroform layer was separated and the brine layer was further extracted with chloroform (2 × 50 mL). The combined chloroform solutions were dried over anhydrous MgSO<sub>4</sub> and evaporated under reduced pressure. The product was isolated by a column chromatography (silica gel, EtOAc/MeOH 8:2) and further purified by a preparative TLC to yield a solid product (27 mg, 7%). Mp 324–326 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.21 (s, 8H), 5.44 (d,  $J=14.7$  Hz, 4H), 3.41 (d,  $J=14.7$  Hz, 4H), 3.6 (m, 4H), 3.3 (m, 4H), 2.4 (m, 8H), 1.7 (m, 8H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  170.2, 135.9, 127.8, 51.9, 48.6, 48.5, 33.9, 20.5; IR (film) 2930, 1627, 1513, 1484, 1440, 1416, 1285, 1204, 728 cm<sup>-1</sup>; FAB MS (NOBA)  $m/z$  586 ([M+H<sub>2</sub>O]<sup>+</sup>, 58%), 569 ([M+1]<sup>+</sup>, 100%), 568 ([M]<sup>+</sup>, 11%), 284 ([M]<sup>+/2</sup>, 13%).

**4.4.2. 3,19,26,42-Tetraazaundecacyclo[42.2.2.2<sup>21,24</sup>.1<sup>3,11</sup>.1<sup>11,19</sup>.1<sup>26,34</sup>.1<sup>34,42</sup>.0<sup>4,9</sup>.0<sup>13,18</sup>.0<sup>27,32</sup>.0<sup>36,41</sup>]-tetrapentaconta-4,6,8,13,15,17,21,23,27,29,31,36,38,40,44,46,47,51-octadecene-49,50,53,54-tetrone, 4.** To sodium hydride (60% dispersion in mineral oil, 120 mg, 3 mmol) washed with hexane was added dry DMSO (10 mL) and the mixture

was stirred at 70 °C for 30 min under nitrogen. To the resulting clear solution was added a solution of 1,1',4,4'-tetrahydro[3,3'(2*H*,2'*H*)-spirobiquinoline]-2,2'-dione, **2** (278 mg, 1 mmol) in DMSO (10 mL) and the reaction mixture was stirred for additional 30 min. This solution was transferred to a 50-mL syringe. A solution of 1,4-bis(chloromethyl)benzene (175 mg, 1 mmol) in DMSO (20 mL) was prepared in another 50-mL syringe. These two solutions were simultaneously added dropwise by a syringe pump to 150 mL of anhydrous DMSO at 70 °C for a period of 2 h, and the resulting reaction mixture was heated additionally for an hour under nitrogen. The solvent was removed in vacuo and the residue was dissolved in methylene chloride (50 mL). The mixture was washed with brine (50 mL). The methylene chloride layer was separated and the brine layer was further extracted with methylene chloride (2 × 50 mL). The combined methylene chloride layers were dried over anhydrous MgSO<sub>4</sub> and evaporated under reduced pressure. The product was isolated by a column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 97:3) and further purified by a preparative HPLC (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 95:5) to yield two diastereomeric solid products, colorless needle-shaped crystals *d,l*-**4** (8 mg, 2.1%, from CH<sub>2</sub>Cl<sub>2</sub>/MeOH) and colorless transparent cubic crystals *meso*-**4** (1 mg, 0.3%, from CH<sub>2</sub>Cl<sub>2</sub>/MeOH). By a chiral HPLC column (Regis (R,R)-Whelk-O2 100, 250 nm length, 4.6 mm ID, 10  $\mu$ m, 100 Å, normal phase, 280 nm UV detection, 1 mL/min flow rate, hexane/CH<sub>2</sub>Cl<sub>2</sub>/isopropanol 49:50:1), the needle-shaped crystals could be further resolved into two components ( $t_R$  4.9 and 7.2 min), whereas the transparent cubic crystals remained as a component without further resolution ( $t_R$  15.6 min). *d,l*-**4**:  $R_f$  (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 97:3) 0.47; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.19 (d,  $J=7.7$  Hz, 4H), 7.14 (s, 8H), 7.11 (t,  $J=7.7$  Hz, 4H), 7.00 (t,  $J=7.7$  Hz, 4H), 6.83 (d,  $J=7.7$  Hz, 4H), 5.60 (d,  $J=16$  Hz, 4H), 4.37 (d,  $J=16$  Hz, 4H), 3.41 (d,  $J=16$  Hz, 4H), 3.08 (d,  $J=16$  Hz, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  167.5, 139.7, 135.8, 127.5, 127.4, 126.5, 124.9, 123.4, 115.2, 48.6, 47.6, 35.9; IR (KBr) 3069, 2939, 1667, 1602, 1497, 1462, 1377, 1265, 1186, 751 cm<sup>-1</sup>; MS (API-ES)  $m/z$  785.3 ([M+2+Na]<sup>+</sup>, 10%), 784.3 ([M+1+Na]<sup>+</sup>, 38%), 783.3 ([M+Na]<sup>+</sup>, 65%), 780.3 ([M+2+H<sub>2</sub>O]<sup>+</sup>, 18%), 779.3 ([M+1+H<sub>2</sub>O]<sup>+</sup>, 74%), 778.3 ([M+H<sub>2</sub>O]<sup>+</sup>, 100%), 760.3 ([M]<sup>+</sup>, 5%); Anal. Calcd for C<sub>50</sub>H<sub>40</sub>N<sub>4</sub>O<sub>4</sub>: C, 78.93; H, 5.30; N, 7.36. Found: C, 78.81; H, 5.47; N, 7.02. *meso*-**4**:  $R_f$  (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 97:3) 0.45; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.25 (d,  $J=7.6$  Hz, 4H), 7.07 (t,  $J=7.6$  Hz, 4H), 7.02 (s, 8H), 7.02 (t,  $J=7.6$  Hz, 4H), 6.69 (d,  $J=7.6$  Hz, 4H), 5.72 (d,  $J=16.6$  Hz, 4H), 4.33 (d,  $J=16.6$  Hz, 4H), 3.35 (d,  $J=16$  Hz, 4H), 3.26 (d,  $J=16$  Hz, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  167.4, 139.3, 135.5, 127.1, 127.0, 125.9, 125.5, 123.7, 115.5, 49.0, 47.3, 37.3; IR (KBr) 3035, 2921, 1670, 1603, 1499, 1461, 1377, 1231, 758 cm<sup>-1</sup>; MS (API-ES)  $m/z$  785.3 ([M+2+Na]<sup>+</sup>, 18%), 784.3 ([M+1+Na]<sup>+</sup>, 60%), 783.3 ([M+Na]<sup>+</sup>, 100%), 778.3 ([M+H<sub>2</sub>O]<sup>+</sup>, 5%), 760.3 ([M]<sup>+</sup>, 10%).

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