Table 2. Calculated energies and entropies of ε-caprolactam monomer and dimer in CCl_4 at 298 K

Molecules	E_e (hartree)[a]	E_{therm}^{298} (hartree)[b]	S^{298} (J/mol K)
Monomer	−358.4426083	0.2054575	334.915
Dimer	−716.9021656	0.4158267	516.665

[a]the electronic energy. [b]the thermal energy

The solute charge distribution is represented by a single-center multipolar expansion truncated at the dipolar term. Thus, the solute-solvent interaction is treated as only the dipole-dipole interaction between the solute and the continuum. All calculation have been performed using Gaussian 92 series of program.[8] The electronic energy (E_e), and thermal energy (E_{therm}^{298}) and entropy (S_{298}) at 298 K of monomer and dimer are given in Table 2. The reaction enthalpy is obtained by the equation $\Delta H = \Delta E + \Delta(PV)$, where $\Delta E = \Delta E_e + \Delta E_{therm}$ (ΔE_e and ΔE_{therm} are the electronic energy and the thermal energy changes, respectively). Since the values of $\Delta(PV)$ is negligible in solution, $\Delta H = \Delta E = \Delta E_e + \Delta E_{therm}$. For the dimerization, ΔE_e is E_e(dimer)-2 E_e(monomer) and ΔE_{therm} is E_{therm}(dimer)-2 E_{therm}(monomer). ΔE_e and ΔE_{therm} at 298 K (ΔE_{therm}^{298}) are −0.0169397 hartree (−44.47 kJ mol^{-1}) and 0.0049117 hartree (12.89 kJ mol^{-1}), respectively. Using these values, the reaction enthalpy ΔH^{298} is calculated to be −31.58 kJ mol^{-1}, showing fairly good agreement with experimental value. The entropy change ΔS at 298 K is also calculated to be −153.17 J mol^{-1} K^{-1}.

In summary, the association of ε-caprolactam in CCl_4 solution has been investigated using near IR spectroscopy. The integrated molar absorption coefficient of the overtone band $2\nu_{NH}$ of ε-caprolactam monomer has been determined to be 73.9± 0.4. The thermodynamic parameters for the dimerization are determined to be $K = 160 \pm 8$ M^{-1} (298 K), $\Delta H° = -28.6 \pm 1.5$ kJ mol^{-1}, and $\Delta S° = -53.9 \pm 2.0$ J K^{-1} mol^{-1}. The *ab initio* calculations have been performed to obtain ΔH and ΔS at 298 K, which are −31.58 kJ/mol and −153.17 J mol^{-1} K^{-1}, respectively.

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Synthesis of Bisspiromacrocyclic Ionophores Tailor-Made for Lithium Ion

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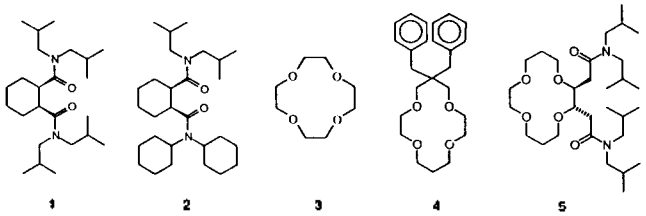
Ion-selective electrodes (ISEs) and ion-selective field effect transistors (ISFETs) are being developed for the continuous measuring cations in body fluids.[1] Many natural ionophores, for example valinomycin for potassium ion,[2] monencin for sodium ion,[3] nonactin for ammonium ion[4] and calcimycin for calcium ion,[5] selectively interact with the specific ion. Numerous synthetic diamide ionophores also display high selectivity to alkali metal ions and alkaline earth metal ions, such as N,N,N′,N′-tetracyclohexyl-3-oxapentanediamide for calcium ion,[6] N,N′-diheptyl-N,N′-dimethyl-1,4-butanediamide for magnesium ion,[7] N,N,N′,N′-tetracyclohexyl-1,2-phenylenedioxydiacetamide for sodium ion,[8] and several synthetic lithium ionophores. Ionophores with high selectivity of lithium ion over sodium ion in blood and with stability for long time usage are currently required.[9]

Analyzing some known lithium ionophores such as N,N,N′,N′-tetraisobutyl-*cis*-cyclohexane-1,2-dicarboxamide **1**,[10] N,N-dicyclohexyl-N′,N′-diisobutyl-*cis*-cyclohexane-1,2-dicarboxamide **2**,[11] 12-Crown-4 **3**,[12] 6,6-dibenzyl-1,4,8,11-tetraoxacyclotetradecane **4**[13] and 14-crown-4 derivatives **5**,[14] we modeled



principles to design new types of lithium ionophores playing for the high selectivity toward to lithium ion over interfering ions in blood: (1) As binding sites four or five oxygen atoms in amide functionality play important role to interact with hard and small lithium ion based on 'hard and soft acid-base' principle.[15] Furthermore the binding sites spherically arrange to interact with spherical lithium ion to form stable and selective complexes based on preorganization theory. In case of four binding sites tetrahedral arrangement will be favored. (2) Cyclic hosts interact with ions more strongly than acyclic their counterparts based on preorganization and size selectivity of host-guest chemistry. (3) Selectivity of ionophores in membrane in ISEs and ISFETs also depends

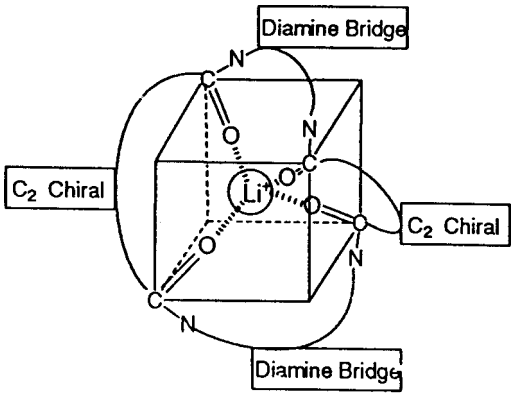


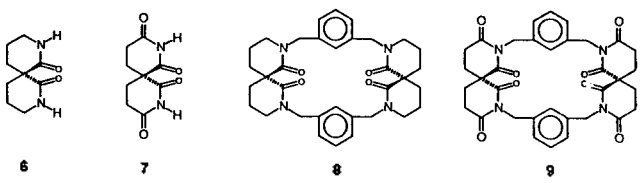
Figure 1. Tetrahedrally arranged tetraamide macrocycle model for Li^+ Ionophore.

on abilities are much the reversibility of formation and decomplexation of host-guest complex. Flexible, conformationally labile ionophores can form reversible complex, which is essential for measuring ions in aqueous medium by ISEs and ISFETs.[16] (4) Bulkiness of substituents can control the stoichiometries of the specific ions and other interfering ions by forming one-to-one, two-to-one, three-to-one complexes, etc. Also lipophilicity *i.e.*, endopolarophilic/exolipophilic, of ionophores in lipophilic membrane are also required to transport ions from hydrophilc aqueous medium to lipophilic membrane.[17] Variable liphophilic substituents can affect selectivity of ionophores.

Careful consideration of these principles and molecular modeling calculations led to the model of a new class of ionophores shown in Figure 1. Four ligand oxygen atoms of amide groups converge and arrange tetrahedrally on the molecular cavity by the incorporation of two chiral subunits with C_2 symmetry. Spacer groups regulate to achieve the correct cavity size, flexibility to form complex reversibly and some degree of steric hindrance to form 1 : 1 complex with lithium ion.

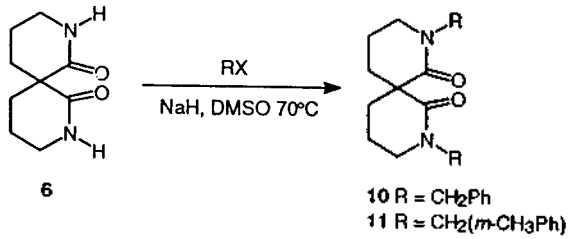
Results and Discussion

2,8-Diazaspiro[5,5]undecane-1,7-dione **6** or 2,8-diazaspiro-[5,5]undecane-1,3,7,9-tetraone **7** is chosen for synthetic feasibility and for the chiral subunits with C_2 symmetry required for tetrahedral arrangement. With two chiral units of spirodiamide **6** or spirodiimide *1*, two *m*-xylidene spacer units for optimum cavity size led to [2+2] macrocycles **8** and **9** respectively.



6 **7** **8** **9**

The chiral spirodiamide **6** was synthesized from catalytic hydrogenation of diethyl bis(2-cyanoethyl) malonate, which was afforded by cyanoethylation of acrylonitrile to diethylmalonate.[18] The analogous spirodiimide **7** was similarly synthesized from acid catalyzed hydrolysis of bis(2-cyanoethyl) malonitrile obtained by cyanoethylation of acrylonitrile to malonitrile.[18]



6

10 R = CH_2Ph
11 R = $CH_2(m\text{-}CH_3Ph)$

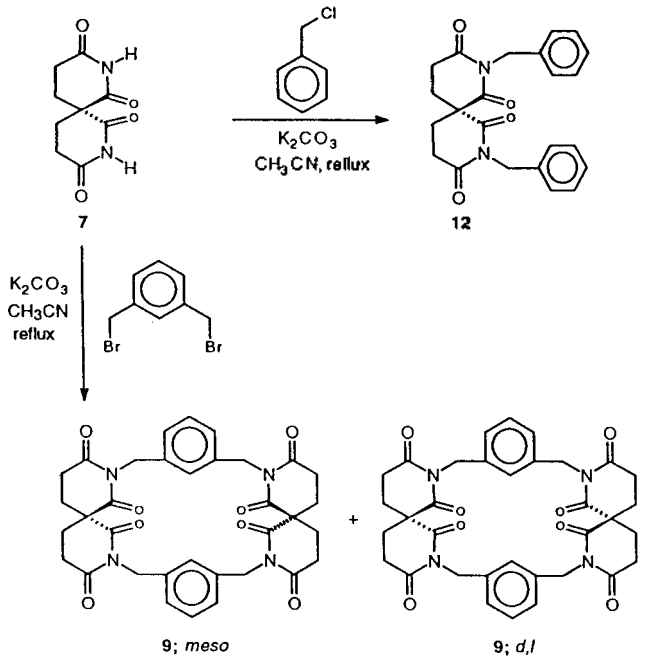
Scheme 1.

N-alkylation reaction on spirodiamide **6** was examined with several benzylic halides. For example, dianion of spirodiamide **6** generated by treating with sodium hydride in anhydrous DMSO at 65-70 ℃ was reacted with excess benzyl chloride yielding N,N'-dibenzylspirodiamide **10** in 80-93% (Scheme 1). Under such reaction condition, some portion of benzylic halides were oxidized to the corresponding aldehydes. In spite of its oxidative property, DMSO was chosen as reaction medium because spirodiamide **6** has very low solubility in most organic solvents but it is soluble enough in DMSO for high dilution cyclization. Reaction of the sodium salt of spirodiamide with 1,3-bis(bromomethyl) benzene in high dilution gave a mixture of products containing higher oligomers polymers and several aldehydes which were oxidized from the expected reaction intermediates. The desired [2+2] macrocycle product **8** could not be isolated in spite of changing several reaction factors.

N-Alkylation of spirodiimde **7**, which was considerably more acidic than analogous diamide **6**, with benzyl chloride in refluxing acetonitrile gave dibenzylspirodiimide **12** in 97% yield. Reaction of **7** with stoichiometric amount of 1,3-bis-(bromomethyl) benzene and potassium carbonate in refluxing acetonitrile gave a mixture of two stereoisomeric [2+2] macrocycles, apparently corresponding to the *meso* and *d, l* diastereomers shown in Scheme 2. These isomers are observed in the crude product mixture in about 1 : 1 ratio, by ^1H NMR analysis.

Two stereoisomeric macrocycles, **9a** and **9b** were isolated in 26% and 22% yield, respectively by column chromatography (silica gel, 1 : 9 hexane/ethyl acetate), and could be further purified by recrystallization from CH_2Cl_2-CH_3OH and CH_2Cl_2-EtOAc, respectively. The composition of [2+2] macrocycles, **9a** and **9b** were demonstrated by mass spectrometry. The benzylic protons of both *meso* and *d, l* diastereomeric macrocycles produce a pair of doublets in the proton NMR spectrum, demonstarating that these geminal protons are diastereotopic in the macrocycles.

New dispirodiimide macrocycles **9a** and **9b** were tested as ionophores for lithium in poly(vinyl chloride) membrane containing the plasticizer *o*-nitrophenyloctyl ether.[11] The resulting electrodes from **9a** and **9b** response sluggishly and unstably towards alkali and alkaline earth metal ions. By contrast the analogous dispirodiamide macrocycle exhibited fast response and significant selectivity of about 25 for lithium over sodium.[18] The potentiometric response of ionophores to ions is dictated largely by the complexation properties of the ionophores involved. For a molecule to act as



Scheme 2.

an ionophore, complexation and decomplexation between host molecules and ions are at a relatively fast rate. This requires that the ionophore molecule be flexible enough to undergo rapid conformational rearrangements.[16] Slow and unstable responses of spirodiimide-based macrocycles **9** are probably due to its rigid conformations and electronic properties of imide functionality.

Thus, the dispirodiimide macrocycles **9** have been examined to be converted to the corresponding dispirodiamide macrocycles **8** by reducing to the amide functionality from four exo- carbonyl groups of **9** which are sterically exposed relatively to four endo carbonyl groups. Various reducing reagents, $LiAlH_4$, $NaBH_4$, BH_3-THF, BH_3-Me_2S and DIBAL-H were employed for this reduction. None of them gives selective reduction. Easy preparation of **9** stimulates its use to various metal ion complexations with its partially reduced tetraamide macrocycle **8** and with its fully reduced tetraamine ligand, which can form tetrahedral complexes with transition metals including nickel and copper.

Experimental

Reagents and Instruments. All commercially obtained solvents and reagents were used without further purification except for DMSO. ^1H and ^{13}C NMR spectra were obtained with Varian Unity Plus-300 (300 MHz) using TMS as an internal standard. Mass spectra were determined on a Shimadzu QP-1000 spectrometer at 70 eV. IR spectra were obtained using a Perkin-Elmer 1600 series FT IR. Melting points were measured using a Buchi capillary melting point apparatus, and were not corrected. Analytical TLC was performed using Kieselgel $60F_{254}$ silica gel plates. For column chromatography, Merck silica gel (70-230 mesh) was used as absorbents.

Preparation of N,N'-Bisbenzyl-2,8-diazaspiro[5,5]undecane-1,7-dion (10). Sodium methylsulfinylcarbanion in DMSO was prepared from the reaction of powdered sodium hydride (900 mg) washed with hexane with freshly distilled DMSO (50 mL) at 70 ℃ for 40 minutes under nitrogen with stirring until evolution of hydrogen was completed. To a clear solution was added dried solid spirodiamide **6**[18] (1.82 g) and the reaction mixture was stirred for 30 minutes to form a viscous emulsion-like solution. To this spirodiamide dianion solution, benzyl chloride (2.66 g) was added by a syringe, and the reation mixture was further of stirred for additional 5 hours to complete the reaction. To a cooled reaction mixture 50 mL brine was added, the product was extracted with diethyl ether (3×100 mL). The combined ether layer was washed with 50 mL of brine and dried over $MgSO_4$. After removing solvent *in vacuo*, it afforded the crude product, which was recrystallized from ethyl acetate (3.4 g, 93%).

N,N'-Bis(*m*-methylbenzyl)-2,8-diazaspiro[5,5]undecane-1,7-dion **11** was prepared by the same method as described above with α-bromo-*m*-xylene.

N,N'-Bisbenzyl-2,8-diazaspiro[5,5]undecane-1,7-dion (10). mp 122-123.5 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 10H), 4.74 (d, J=14.9 Hz, 2H), 4.56 (d, J=14.9 Hz, 2H), 3.37 (m, 2H), 3.21 (m, 2H), 2.50 (m, 2H), 2.00 (m, 2H), 1.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.19, 137.12, 128.49, 127.67, 127.05, 51.01, 50.58, 47.25, 33.01, 19.33; IR (KBr) 3059, 3026, 2938, 2866, 1625, 1486, 1452, 1431, 1350, 1333, 1284, 1195, 732 cm^{-1}; mass spectrum, m/z (rel intensity) 362 (1.4, M^+), 271 (4.1), 186 (12.7), 181 (1.4), 133 (22.3), 132 (17.7), 91 (100); Anal. Calcd for $C_{23}H_{26}N_2O_2$; C, 76.21; H, 7.23; N, 7.73. Found: C, 76.45; H, 7.28; N, 7.74.

N,N'-Bis(*m*-methylbenzyl)-2,8-diazaspiro[5,5]undecane-1,7-dion (11). yield 85%; mp 104-105 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 2H), 7.08 (m, 6H), 4.81 (d, J=14.7 Hz, 2H), 4.42 (d, J=14.7 Hz, 2H), 3.38 (m, 2H), 3.20 (m, 2H), 2.50 (m, 2H), 2.34 (s, 6H), 2.00 (m, 2H), 1.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 138.1, 137.1, 128.6, 128.5, 127.9, 124.7, 51.1, 50.5, 47.2, 32.9, 21.4, 19.4; mass spectrum, m/z (rel intensity) 391 (0.9), 390 (1.2, M^+), 364 (1.2), 363 (10.0), 105 (100).

Preparation of N,N'-Bisbenzyl-2,8-diazaspiro[5,5]-undecane-1,3,7,9-tetraone (12). The suspension of spirodiimide **7**[18] (210 mg) in acetonitrile (40 mL) was refluxed under nitrogen. To a clear solution were added anhydrous potassium carbonate (0.7 g) and benzyl chloride (300 mg). After refluxing for 4 hours the solvent was removed. The residue was charged with 50 mL methylene chloride, stirred briefly, and filtered to remove insolubles. The filtrate was evaporated and dried *in vacuo* for 2 days to give white glassy solid. This crude product was stirred with 10 mL hexane for a day. The white powder was obtained after filtration and dried *in vacuo* (379 mg, 97% yield).

mp 119-120 ℃; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 10H), 5.02 (d, J=14.7 Hz, 2H), 4.94 (d, J=14.7 Hz, 2H), 2.78 (m, 4H), 2.57 (m, 2H), 1.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 171.0, 137.0, 128.9, 128.7, 127.9, 50.93, 43.99, 28.93, 25.72; IR (KBr) 3436, 3048, 3025, 2391, 2860, 1960, 1954, 1890, 1819, 1619, 1484, 1455, 1425, 1343, 1284, 1261, 1196, 1173, 1079, 1020, 961, 944, 747, 734, 702 cm^{-1}; mass spectrum, m/z (rel intensity) 391 (0.40), 390 (1.2, M^+), 362 (2.6), 334 (7.9), 257 (15.3), 229 (4.7), 119 (6.7), 118 (9.9), 106 (63.6), 91 (100); Anal. Calcd for $C_{23}H_{22}N_2O_4$; C, 70.75; H, 5.68; N, 7.11. Found: C, 70.48; H, 5.56; N, 7.11.

Preparation of Bisspirodiimide [2+2] macrocycle (9). Diazaspiro[5.5]undecane-1,3,7,9-tetraone (210 mg) in acetonitrile (150 mL) was refluxed under nitrogen. To a clear solution was added anhydrous potassium carbonate (0.7 g) and α,α′-dibromo-*m*-xylene (264 mg) and this reaction mixture was refluxed for 2 days. The solvent was removed by evaporation. The residue was dissolved in methylene chloride (100 mL) and filtered to remove insolubles. After the filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The residue (325 mg) was loaded on column chromatography (silica gel, 1 : 9 hexnane/ethyl acetate). Two products, **9a** and **9b** were isolated.

9a: 81 mg (26%); mp 367-368.5 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, Ar, 2H), 7.27 (m, Ar, 6H), 5.05 (d, J=14 Hz, 4H), 4.94 (d, J=14 Hz, 4H), 2.67 (m, αCH_2 to C=O, 8H, and βCH_2 to C=O, 4H), 1.85 (m, βCH_2 to C=O, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.72, 170.66, 137.0, 128.5, 127.8, 125.9, 50.7, 49.6, 28.5, 25.7; mass spectrum, m/z (rel intensity) 627 (2.4), 626 (3.6), 625 (14.3), 624 (32.8, M^+), 568 (100); Anal. Calcd for $C_{34}H_{28}N_4O_8$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.23; H, 5.02; N, 8.72.

9b: 69 mg (22%); mp >370 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, Ar, 8H), 5.05 (d, J=14 Hz, 4H), 4.90 (d, J=14 Hz, 4H), 2.8 (m, αCH_2 to C=O, 8H, and βCH_2 to C=O, 4H), 1.90 (m, βCH_2 to C=O, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) (170.64, 170.58, 137.1, 128.1, 127.8, 50.4, 43.5, 28.4, 25.7; mass spectrum, m/z (rel intensity) 626 (5.4), 625 (8.5), 624 (19.0, M^+), 568 (100).

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Thermodynamic Parameters on Complexation of Trivalent Yttrium and Lanthanide Ions by L-thioproline

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Recently we have reported the thermodynamic parameters for lanthanide(III) complexation with L-proline[1] and *trans*-4-hydroxy-L-proline[2] in aqueous solution. It was noted that the heterocyclic nitrogen atom in proline ring and the carboxylate were involved in chelate formation and that the complexes were stabilized by the excess entropy effect. Moreover, *trans*-4-hydroxy-L-prolinate complex was more stable than L-prolinate complex. This increased stability was associated with more positive value of enthalpy change on complex formation. The data were interpreted in terms of the hydration sphere structure of the polarizable lanthanide(III)-*trans*-4-hydroxy-L-proline complex in aqueous solutions.

In this study, we have investigated the thermodynamic parameters on the L-thioprolinate complexation with yttrium (III) and lanthanide(III) cations. L-thioproline ligand is similar to L-proline, but 4-carbon atom of proline ring is replaced by sulfur atom in L-thioproline. Therfore, we have focused our interest on the role of 4-sulfur atom in thioproline ring