Pergamon

Tetrahedron Letters, Vol. 38, No. 35, pp. 6217-6220, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01429-9

Tetrahedrally Arranged Tetraamide Macrocycle: Synthesis and Properties of L-Tartaric acid-based Macrocyclic Tetraamide

Heung-Jin Choi*, Mi-Ok Kwak and Jong-Mok Kim†

Department of Industrial Chemistry, Kyungpook National University, Taegu 702-701, Korea
†Kumho Chemical Laboratories, P.O. Box 64 Yuseong, Taejeon 305-600, Korea

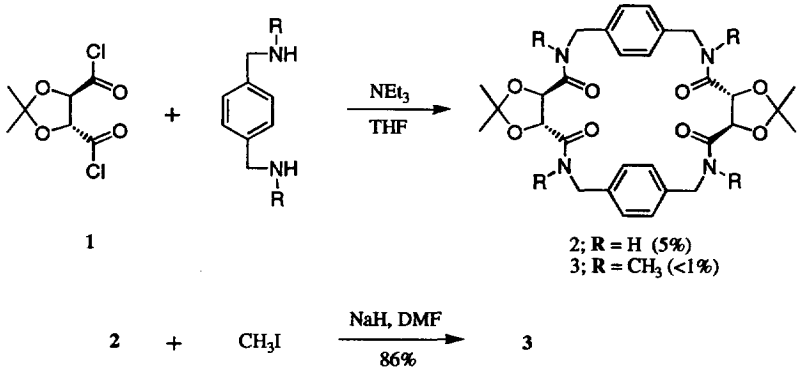
Abstract: *A first example of chiral tetraamide macrocycles 2 and 3 of which four amide oxygen ligand sites can converge inward molecular cavity upon complexation with alkali metal ion were synthesized from p-xylylenediamine and 2,3-O-isopropylidene-L-tartaryl chloride, 1 derived from L-tartaric acid.*

The ligands with amide functional groups as binding sites have been reported to show strong and also selective complexation toward alkali and alkaline earth metal ions.[1,2] Increasing interests toward lithium ion selective ionophores for the actual and potential applications in science, medicine and technology leads to design and synthesize new types of lithium ionophores.[3,4]

A few acyclic diamide ligands are known to show high ion selectivity toward lithium over sodium and other alkali metal ions.[1] Ion selectivity of specific ion over others was affected by many factors. However, a few factors, which include the size selectivity of ion toward ligand diameter, and the type of ligand atom and functionality, are considered and able to be controlled for developing new kinds of host macrocycles. The small and hard lithium ion coordinates preferentially with 4, 5 and 6 hard oxygen donors to other soft donor atoms like nitrogen and sulfur.[4,5] The dipolar amide ligands strongly complex with lithium ion in the manner of ion-dipole interaction.[6] The dipole moment is increasing from primary to secondary to tertiary amides. It is known from an electrostatic point of view that the most selective lithium ionophores exhibit 4-fold tetrahedral coordination and 5-fold square pyramidal coordination.[4]

Above considerations leads to design tetrahedrally oriented macrocyclic tetraamide ionophores, which might show better selectivity to lithium due to preorganized ligand orientation and ligand cavity size. Tetrahedral orientation of four ligands require two units of C_2-symmetrical dicarbonyl moieties, for which chiral tartaric acid was chosen. With symmetrical *p*-xylylenediamine as spacer the tetrahedrally oriented macrocyclic tetraamide ionophores **2** was designed as a model ionophore. To observe conformational behavior of tertiary amide macrocycle over secondary macrocycle **2** on the complexation toward guest ions, tertiary amide macrocycle **3**, was also designed. Reported here are the first examples of tetrahedrally arranged tetraamide chiral macrocycle based on L-tartaric acid.

The tetraamide macrocycles **2** and **3** were synthesized from 2,3-*O*-isopropylidene-L-tartaryl chloride, **1** prepared from L-tartaric acid,[7] and *p*-xylylenediamines (Scheme 1). Reaction of acid chloride **1** with



Scheme 1

p-xylylenediamine in THF at room temperature gave a mixture of polymeric products and the desired [2+2] product, tetraamide macrocycle **2** in 5% yield after column chromatography, along with trace amount of [3+3] product, hexaamide macrocycle.[8] Under same reaction conditions with *N,N'*-dimethyl-*p*-xylylenediamine **3** was only formed in trace probably due to steric repulsion upon cyclization of the corresponding [2+2] acyclic intermediate, which resulted in polymeric product. The steric hindrance in macrocycle **3** plays also in direct *N*-methylation on secondary amide macrocycle **2** with methyl iodide in presence of KOH in DMSO, that resulted in low yield 43% of **3** along with mono-, di-, and tri-methyl products. The reaction was proceeded in slow and could not be completed due to steric hindrance. Much harsher reaction conditions with sodium hydride as base in DMF afforded **3** in higher yield, 86%.[9]

Macrocycles **2** and **3** were identified by IR, NMR, elemental analysis and mass spectrometry. The [2+2] compositions of macrocycles **2** and **3** were demonstrated by mass spectrometry. The expected C_2 symmetry of **2** was observed by ^1H and ^{13}C NMR spectra, and diastereotopic benzylic protons produce a pair, at 4.71 and 4.20 ppm, of doublet-doublet coupled with proton on nitrogen in the proton NMR spectrum. However, tetramethyl macrocycle **3** lost the expected C_2 symmetry. The proton NMR spectrum of **3** revealed complex pattern of peaks. The diastereotopic benzylic protons were shown as many multiplets over 3.4 to 5.6 ppm; some of them are shielded and some deshielded. Cautious examination of the multiplets suggest a mixture of the many conformers of **3**. This unusual conformational rigidity might be related with the limited conformational freedom of macrocycle **3** due to the steric hindrance of extra four methyl groups. To demonstrate the conformational rigidity, dynamic proton NMR spectra of **3** in $CDCl_3$ were taken at many different high temperatures. At higher temperatures the peaks of benzylic protons are getting broader and simpler, but remained the pattern over 3.4 to 5.7 ppm. The conformational mobility of **3** could not be observed up to 60°C.

By FABMS (NBA) mass spectrometry complexes of lithium and sodium ions with **2** were observed at m/e 587 and 603, respectively. A sample of **2** prepared from 1:1 molar mixture of sodium chloride and lithium chloride has shown mass peaks at m/e 580 (5.6%, $[M]^+$), 587 (2.2%, $[M+Li]^+$) and 603 (4.5%, $[M+Na]^+$). Apparently macrocycle **2** has strong complexation ability toward to alkali metals. A possible structure of these complexes are tetrahedral configuration of amide oxygen ligand sites converged toward to metal ion at molecular cavity from an electrostatic view point shown in Figure 1. Recently M. Bhattacharjee and R. Datta

have firstly reported that macrobicycle **4** with six amide ligand sites able to arrange in octahedral environment forms 1:1 complexes towards transition metal ions, such as Fe^{3+} and Cu^{2+} ions in ethanol.[10]

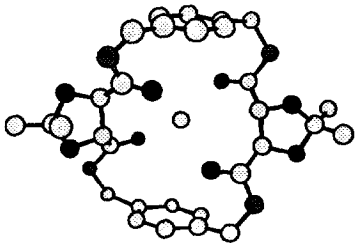
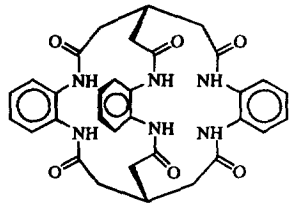


Figure 1. A proposed structure of metal complex with **2**.



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The ligand **2** was treated with $NiCl_2$, $FeCl_3$ or $CuCl_2$ in ethanol. However, the complexes with transition metal ions are not demonstrated by spectrometric analysis. It is not clear yet whether the multivalent metal complexes of **2** are not formed, or its behavior is different from monovalent ion complexes, which was detected by FAB mass spectrometry.

The tetraamide macrocycles **2** and **3** have been tested as ionophores in PVC membranes containing the plasticizer *o*-nitrophenyloctyl ether and the liphophilic anion, tetrakis(*p*-chlorophenyl) borate.[1] The selectivities of the ion selective electrodes towards Li^+, Na^+, K^+ and NH_4^+ ions were determined by the separate solution method.[11] In these membranes the macrocyle **2** and **3** both gave some potentiometric responses up to 10^{-3} M ion solution. The selectivity trends of these membranes were $K^+ > NH_4^+ > Na^+ > Li^+$. The selectivity coefficients of lithium to sodium (log $K_{Li,Na}$) were 0.4 and 0.6 for **2** and **3**, respectively. No appreciable selectivity for lithium was observed.

The chiroptical property changes due to the complexational behavior of **2** with metal ions were studied by CD. The CD spectrum of free macrocycle **2** shows a negative Cotton effect; CD (C, 0.23mM; CH_2Cl_2-EtOH (10:1), deg cm^2 $dmol^{-1}$), 25 °C; $[\theta]_{262}$ 0; $[\theta]_{234}$ -8500; $[\theta]_{225}$ 0.[12] The negative maxima were slightly enhanced for a solution of **2** with one equivalent of lithium or sodium perchlorates; $[\theta]_{232}$ -9600. The optical activity of the chiral macrocycle **2** and its complexational phenomena with lithium and sodium were observed by CD study. However, any chiral recognition was not observed when a mixture of **2** and 2-aminobutane in $CDCl_3$ measured by ^1H NMR.

Currently any strong evidence of complextional behavior of **2** in solution, except by FABMS, was not observed. However, this first example of tetraamide macrocycle **2** was readily synthesized from optically active L-tartaric acid. Systematic variation of the structure of **2** may result superior complexational properties.

Acknowledgment. We wish to thank professors Geun Sig Cha and Hak Hyun Nam, Kwangwoon University, South Korea for ion selectivity measurement. We appreciate the financial support of this work by the Korea Science and Engineering Foundation (941-1100-020-2).

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8. A solution of 2,3-*O*-isopropylidene-L-tartaryl chloride, **1** (1.0 g, 4.4 mmol) in 35 mL of THF and a solution of *p*-xylylenediamine (0.61 g, 4.4 mmol) and triethyl amine (2.5 mL) in 35 mL of THF were simultaneously added to 300 mL of THF *via* syringe pump over 5 h at room temperature under a nitrogen atmosphere. The reaction mixture was further stirred overnight, and then concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 97:3 methylene chloride/methanol). The mixture of [2+2] macrocycle **2** and [3+3] macrocycle separated from chromatography was recrystallized from methanol to yield 102 mg (5%) of **2** as white solid. From the combined filtrate from three reactions, successive recrystallization afforded 10 mg of [3+3] macrocycle as white solid.

   [2+2] Macrocycle **2**: TLC (R_f, 0.31; 9:1 methylene chloride/methanol); IR (KBr) 3339, 3102, 2991, 2936, 1690, 1656, 1534, 1432, 1831, 1237, 1168, 1115, 1081, 1023, 877 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.61 (br t, 4H, N*H*), 7.20 (s, 8H, Ar-*H*), 4.71 (dd, J = 15.2, 7.5 Hz, 4H, benzylic H_a), 4.47 (s, 4H, -C*H*-), 4.20 (dd, J = 15.2, 4.5 Hz, 4H, benzylic H_b), 1.52 ppm (s, 12H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 169.4, 137.2, 127.6, 112.3, 77.4, 42.7, 25.7 ppm; MS (EI, 70eV) *m/z* 581 (49), 580 (56.9) $[M]^+$, 290 (39.9). 119 (100); Anal. Calcd for $C_{30}H_{36}N_4O_8$: C, 62.06; H, 6.24; N, 9.64. Found: C, 62.11; H, 6.19; N, 9.69.

   [3+3] Macrocycle: TLC (R_f, 0.27; 9:1 methylene chloride/methanol); ^1H NMR (500 MHz, $CDCl_3$) 7.46 (t, J = 12.0 Hz, 6H, N*H*), 7.24 (s, 12H, Ar-*H*), 4.56 (s, 6H, -C*H*-), 4.51 (dd. J = 15.0, 6.3 Hz, 6H, benzylic H_a), 4.45 (dd, J = 15.0, 6.0 Hz, 6H, benzylic H_b), 1.47 ppm (s, 18H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 169.4, 137.1, 127.8, 112.4, 77.4, 42.7, 26.0 ppm; FABMS (NBA) *m/z* 893 (20) $[M+Na]^+$, 871 (3.1), 870 (1) $[M]^+$, 136 (38). 55 (100).
9. A round-bottomed flask containing sodium hydride (20 mg) washed with hexane was charged with a solution of **2** (50 mg) in 10 mL of DMF under nitrogen atmosphere. To the resulting solution at 90 °C was added methyl iodide (0.2 mL). The reaction mixture was further heated for 4 h. After removing solvent under high vacuum, the residue was purified by flash chromatography (silica gel, 97:3 methylene chloride/methanol) to give 47 mg (86 %) of the product as a white solid: IR (KBr) 2987, 2934, 1650, 1489, 1415, 1253, 1214, 1160, 1060, 863, 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.2 -7.1 (m, 8H, Ar-*H*), 5.7-5.2 (m, J = 14.5 Hz, 4H, benzylic H_a), 4.2-3.4, (m, J = 14.5 Hz, 4H, benzylic H_b), 3.18-3.12 (m, 12H, N-CH_3), 3.1-2.8 (m, 4H, -C*H*-), 1.7-1.4 ppm (m, 12H, CH_3, a major at 1.454 ppm (82% intensity); ^{13}C NMR (75 MHz, $CDCl_3$) 169-167 (5 major set of peaks), 137-135 (4 major set of peaks), 129-127 (5 major set of peaks), 113-112 (3 major set of peaks), 76-75.5 (4 major set of peaks), 53-51 (3 major set of peaks), 35-33 (4 major set of peaks), 26.5-26 (4 major set of peaks); MS (EI, 20eV) *m/z* 640 (3.7), 639 (4.0), 638 (3.4), 637 (1.2) $[M+1]^+$, 579 (12). 133 (100).
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12. The macrocycle **2** is very insoluble in many organic solvents. The rough solubilities of **2** in 10 mL of solvent are as follows: DMSO, very soluble; DMF, 8-9 mg; CH_2Cl_2, 6-8 mg; CH_3OH, 4-5 mg; THF, 2-3 mg; CH_3CN, 2-3 mg; Dioxane ~1 mg. To dissolve the metal perchlorate salts mixed solvent, CH_2Cl_2-EtOH (10:1) was used. In this solvent system the CD measurement was successful.

(*Received in Japan* 5 *March* 1997; *revised* 7 *July* 1997; *accepted* 11 *July* 1997)