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Preparation of a new receptor for anions, macrocyclic polythiolactam—structure and high anion-binding ability

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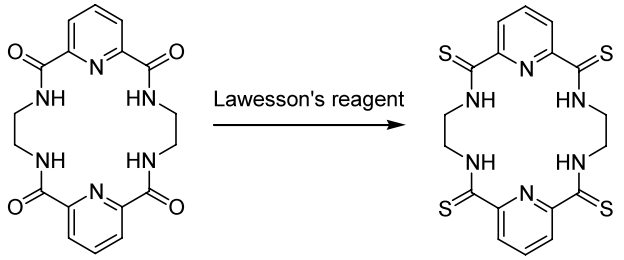
Abstract—Thiocarbonylation of a macrocyclic tetralactam gave a new macrocyclic tetrathiolactam. The chemical transformation enhances hydrogen-bonding ability of the N–H protons in the cavity of the macrocycle, and provides strong affinity toward anions. The association properties of the polythiolactam with anions was examined, and molecular structures of the macrocycle and its Cl^- complex were determined.

Recognition and sensing of anions have been a subject of intensive current interest, and hydrogen bonding is one of the important recognition elements in anion sensing.[1] Arranged binding sites in receptor structures will provide attractive hosts and tune the binding ability of the receptors. Among various studies on the anion receptors, extensive studies have especially been achieved for macrocyclic and acyclic amides as the hydrogen bond donors, because amide group forms a strong N–H···anion hydrogen bond.[1,2] It has recently been reported that a neutral macrocyclic tetralactam, **1**, exhibits pronounced affinity toward anions.[2c] The macrocyclic polylactam **1** has amide hydrogens directed to the center of the cavity, and effectively interacts with hydrogen bond acceptors. On the other hand, molecular design and investigation of binding ability of macrocyclic polythiolactams as the anion receptor have been limited.[3] Thioamides are stronger acids than amides, and the substitution of sulfur for oxygen of amide enhances ability as a hydrogen bond donor of the N–H protons, although it seems to weaken the strength as a hydrogen bond acceptor.[4] Under these circumstances, we prepared a new polythiolactam, **2**, by thiocarbonylation of **1**, and examined anion-binding ability of the polythiolactam-type neutral macrocyclic receptor.

Chemical transformation of amides to thioamides has been carried out by using 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, **3**, (so-called Lawesson's reagent).[5] The reaction of **1** with **3** smoothly proceeded and afforded the corresponding polythiolactam **2** with an isolated yield of 56%.[6] FAB-mass spectrum of **2** exhibited a protonated molecular-ion peak of $[M+H]^+$ at m/z of 447. In contrast to poor solubility of **1** in organic solvents,[2c] **2** has good solubility in polar solvents such as THF and DMSO. In the ^1H NMR spectrum of **2** (Fig. 1(a)), the signals attributed to the N–H proton in the thioamide group and the vicinal methylene protons are detected at δ 11.3 and 4.2, respectively, and no signal attributed to the N–H proton of amide group (detected at δ 9.5 for **1**) is observed. In the ^{13}C NMR spectrum of **2**, the signals attributed to thiocarbonyl and the vicinal methylene carbons are observed at δ 190.9 and 44.4, respectively, and no signal of the carbonyl carbon of **1** at δ 163.1 is detected.



1 **2**

The crystal of **2** was obtained from a DMSO solution. A crystallographic analysis of **2** (Fig. 2) reveals that **2** adopts an approximately C_{2h} conformation and solvates with two molecules of DMSO, one of which serves as hydrogen bond acceptor.[7] The macrocyclic system would be stiffened by four intramolecular hydrogen bonds between the thioamide N–H protons

Keywords: macrocycle; thioamide; thiocarbonylation; hydrogen bond; neutral anion receptor.

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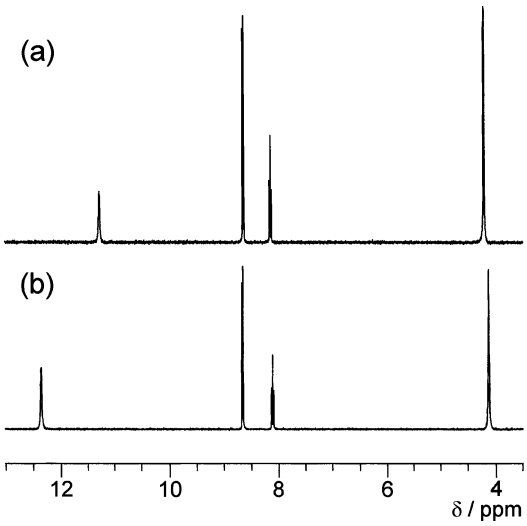

Figure 1. ^{1}H NMR spectra (400 MHz, DMSO-d_6, 298 K): (a) free **2**; (b) 4.4 equiv. of $(n\text{-Bu})_4$NOAc was added to **2**.

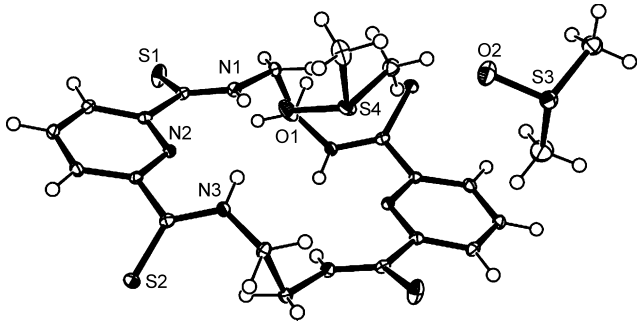

Figure 2. X-Ray crystal structure of **2** (obtained as **2**·2DMSO) with thermal ellipsoids drawn at the 50% probability level.

and pyridine imine nitrogens, which is also observed with **1**.[2c]

^{1}H NMR spectroscopy was adopted to study the anion-binding ability of **2** in DMSO-d_6.[2,3,8] Addition of tetrabutylammonium salts ($(n\text{-Bu})_4$NX; $X^- = F^-$, Cl^-, Br^-, I^-, AcO^-, and $H_2PO_4^-$) led to drastic downfield shifts in the N–H resonance as shown in Figure 1(b). The large downfield shift of the N–H signal is consistent with the presence of a hydrogen-bonding interaction between the inner thioamide protons and the anions.[2,3] Table 1 summarizes changes of the chemical shift of the N–H protons in **2** ($\Delta\delta_{max}$) and association constants (K), $K = [\mathbf{2}\cdot Cl^-]/[\mathbf{2}][X^-]$, which is estimated from titration by assuming a 1:1 binding stoichiometry.[2,8] The curve fitting for the NMR titration data supported the 1:1 binding ratio, and Job's analysis also verified the 1:1 stoichiometry for formation of the all complexes. As expected, **2** shows large association constants for anions; **2** interacts with anions more tightly than **1**.[2c] Among the halide anions, the highest interaction was observed with fluoride anion. The association constant for **2** with fluoride anion could only be determined at higher temperatures because of the line broadening of the N–H proton signal in the ^{1}H NMR spectrum at room temperature, presumably due to the high stability of the complex.[2h] This reflects the hydrogen bond acceptor strength of the halide anions[9] as well as size complementarity between anions and the cavity of receptor; the smallest fluoride anion seems to tightly bind with the thioamide protons in the cavity.

Table 1. Changes of chemical shift ($\Delta\delta_{max}$) of the N–H protons in **2** and association constants (K) of **2** with tetrabutylammonium salts[a]

X^-	K (M^{-1})[b]	$\Delta\delta_{max}$
AcO^-	1.4×10^4	1.08
$H_2PO_4^-$	3.9×10^3	1.08
F^-	(9.6×10^3)[c]	2.79 (3.19)[c]
Cl^-	1.1×10^3	0.62
Br^-	1.5×10^2	0.14
I^-	<2	0.03

[a] Estimated from ^{1}H NMR titration (in DMSO-d_6, $T = 298$ K).
[b] Errors estimated to be <±10%.
[c] Slow equilibrium between free **2** and complex was observed at room temperature. The numbers in parentheses are data at 373 K.

The crystal of the 1:1 complex of **2** with chloride anion [**2**·Cl^-] was obtained from a mixture of **2** with PPh_4Cl in CH_2Cl_2. The molecular structure of the complex is presented in Figure 3.[10] Complexation of **2** with chloride anion led to a conformational change of **2**. The chloride anion is surrounded by four thioamide N–H protons and by PPh_4^+, and lies above the plane determined by the four nitrogen atoms of the cyclic thioamide. The complex [**2**·Cl^-] is slightly distorted, but all four thioamide hydrogen atoms would take part in the interaction (Table 2). The molecular structure in Figure 3 also indicates that Cl^- seems to be somewhat too large to fit inside the cavity of **2**.

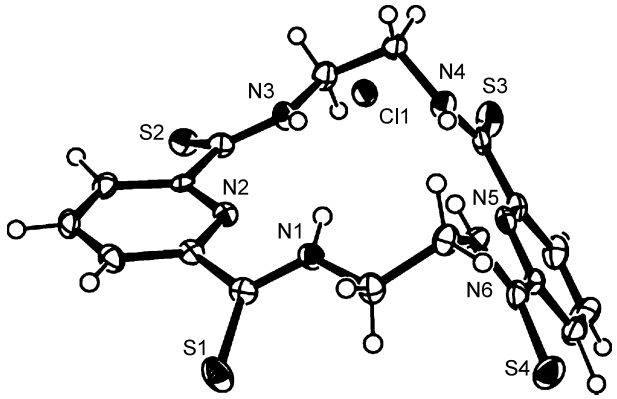

Figure 3. X-Ray crystal structure of [**2**·Cl^-] complex (obtained as [**2**·Cl]PPh_4) with thermal ellipsoids drawn at the 50% probability level. PPh_4^+ cation is omitted for clarity.

Table 2. Selected hydrogen bonds in [**2**·Cl^-] complex

D–H···A	d(H···Cl) (Å)	d(N···Cl) (Å)	(N–H···Cl) (°)
N(1)–H···Cl(1)	2.37(2)	3.197(4)	160.4(5)
N(3)–H···Cl(1)	2.412(9)	3.222(4)	157.8(5)
N(4)–H···Cl(1)	2.69(2)	3.280(4)	130.9(5)
N(6)–H···Cl(1)	2.53(2)	3.285(4)	157.9(5)

As described above, new neutral macrocyclic polythiolactam **2** has been prepared by thiocarbonylation of the corresponding polylactam **1**. Thiocarbonylation of **1** easily improves hydrogen bond donor ability of the N–H protons, thus, **2** exhibits strong affinity toward anions. This new synthetic procedure seems to be important and be able to be expanded, because there has been extensive studies on the amide-type receptors. Further studies on preparation of other thioamide-type receptors as well as applications of the polythiolactam are in progress.

Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center; publication numbers CCDC 207146 (**2**) and 207147 ([**2**·Cl^-]PPh_4).

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6. 3,6,14,17,23,24-Hexaazatricyclo[17.3.1.$1^{8,12}$]tetracosa-1(23),8(24),9,11,19,21-haxaene-2,17,13,18-tetrathione, **2**: **1** (830 mg, 2 mmol) and **3** (4.05 g, 10 mmol) were suspended in THF (150 mL), and the mixture was refluxed for 48 h under N_2. The reaction mixture was filtered and the solvent in the filtrate was removed by evaporation. The crude product was thoroughly washed with methanol and purified by column chromatography on silica gel (518 mg, 56% yield). FAB-MS: m/z 447 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 11.29 (br. s, 4H), 8.64 (d, 4H), 8.15 (t, 2H), 4.21 (br. s, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 190.9, 150.2, 138.6, 126.7, 44.4. Anal. calcd for $C_{18}H_{18}N_6S_4$: C, 48.40; H, 4.06; N, 18.82; S, 28.72. Found: C, 48.10; H, 4.22; N, 17.98; S, 28.14%.
7. Crystallographic data for **2**: $C_{22}H_{30}N_6O_2S_6$, $M=602.88$, monoclinic, space group $P2_1/c$, $a=10.50(4)$, $b=9.84(3)$, $c=17.77(6)$ Å, $\beta=99.26(4)°$, $V=1810.9(10)$ Å^3, $Z=2$, $D_{calcd}=1.106$ g cm^{-3}, μ(Mo Kα)$=4.03$ cm^{-1}, $T=113$ K, $F(000)=632$. A total of 13800 reflections were measured, 4087 unique. The structure was solved by direct method (SIR-88) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotoropically. The hydrogen atoms were refined using a riding model. The final cycle of full-matrix least squares refinement on F was based on 3697 observed reflections ($I>3\sigma(I)$, 220 valuable parameters) with factors of $R=0.043$, $Rw=0.070$, GOF$=0.85$.
8. Association constants (K) are determined by titrating a DMSO-d_6 solution of **2** (5.7 mM) with aliquots of salt solution. We used non-linear least-squares regression for curve fitting. Although we obtained good fit of 1:1 binding isotherms to the titration experimental data in all most of all cases, the possibility of 2:1 (**2**:anion) complex formation could also be considered. See: Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311–312.
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10. Crystallographic data for [**2**·Cl](PPh$_4$): $C_{42}H_{38}ClN_6PS_4$, $M=821.47$, triclinic, space group $P\bar{1}$, $a=11.0025(12)$, $b=13.4310(6)$, $c=14.7175(2)$ Å, $\alpha=70.05(2)$, $\beta=79.21(2)$, $\gamma=88.16(2)°$, $V=2007.0(2)$ Å^3, $Z=2$, $D_{calcd}=1.359$ g cm^{-3}, μ(Mo Kα)$=3.82$ cm^{-1}, $T=113$ K, $F(000)=856$. A total of 39203 reflections were measured, 8342 unique. The structure was solved by direct method (SIR-92) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotoropically. The hydrogen atoms were refined using a riding model. The final cycle of full-matrix least squares refinement on F was based on 5306 observed reflections ($I>3\sigma(I)$, 525 valuable parameters) with factors of $R=0.056$, $Rw=0.079$, GOF$=0.95$.