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SYNTHESIS OF NOVEL MACROCYCLIC COMPOUNDS UTILIZING CHARACTERISTIC BONDING PROPERTIES OF HYPERVALENT SULFUR

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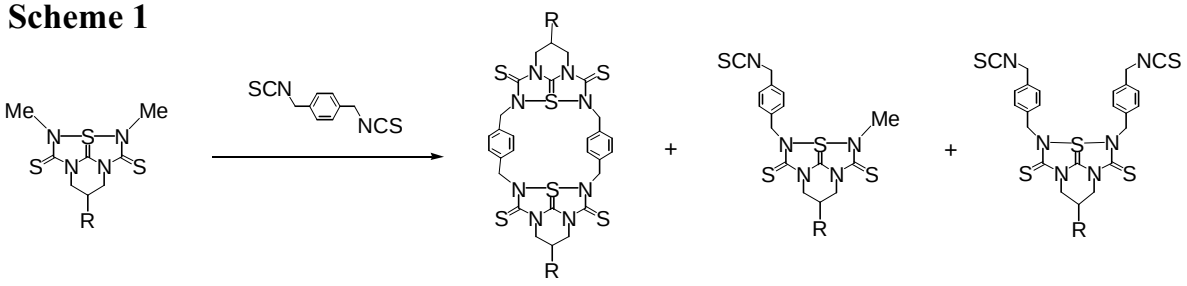
Abstract - The convenient method for the synthesis of 18-, 26-, and 30-membered macrocyclic compounds by utilizing the characteristic bonding properties of the hypervalent sulfur in the 10-S-3 tetraazathiapentalene derivatives and their chemical properties have been described. The structures were established by their spectral data and X-Ray crystallographic analysis.

Since the discovery of an unusual structure of tetraazathiapentalene derivatives,[1] the chemistry of π-hypervalent heterocyclic systems has received considerable attention from synthetic and theoretical viewpoints. A number of π-electron systems containing a 10-S-3 species have been synthesized.[2] Their structure and reactivities have also been investigated.[2,3] However, little is reported about the utility of characteristic properties of equatorial and apical bonds around the hypervalent sulfur atom in the π-electron systems toward the synthesis of macrocyclic compounds.[4] Recently, we have reported the synthesis and reactivities of 10-S-3 tetraazathiapentalene derivatives, namely 2,3-dimethyl-6,7-dihydro-*5H*-2a-thia(2a-S^{IV})-2,3,4a,7a-tetraazapent[*cd*]indene-1,4(*2H,3H*)-dithiones （ **1** ） (R=H). These compounds

exhibited unique reactivities due to the unusual bonding property of the hypervalent sulfur.[5] On the basis of these reactivities, we have planned to study the synthesis of conformationally flexible macrocyclic compounds that contain thiourea functions in the ring and also are soluble in organic solvents. This work is particularly attractive because such macrocyclic compounds are expected to serve as a predisposed ligand in bioinorganic chemistry[6] and also as a receptor of inorganic anions in molecular recognition chemistry.[7] We now report a novel and convenient method for preparing macrocyclic compounds of 18-, 26-, and 30-membered rings and also thiourea functions in the rings by utilizing the characteristic bonding property of the hypervalent sulfur.

Treatment of **1a** with 1 equiv. of *p*-xylylenediisothiocyanate in refluxing benzene for 24 h gave an 18-membered macrocyclic compound (**2a**) that bears two tetraazathiapentalene rings and two *p*-xylyl groups in a 50% isolated yield, along with a mono-substituted tetraazathiapentalene derivative (**3a**) and a disubstituted tetraazathiapentalene derivative (**4a**) in 17% and 3% yields, respectively (Scheme1).

Scheme 1



1 **2** **3** **4**

a: R=$(CH_2)_7Me$; **b**: R=$(CH_2)_{11}Me$

Table 1. Reaction of **1a,b** with *p*-xylylenediisothiocyanate[a]

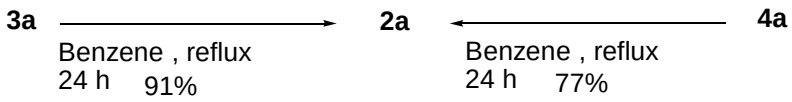
Entry	Compound	Solvent	Concn x10^2 (mol/dm^3)	Product (Yield/%)[b] **2**	**3**	**4**
1	**1a**	Benzene	2.68	**2a**(50)	**3a**(17)	**4a**(3)
2	**1a**	Benzene	6.70	**2a**(53)	**3a**(14)	**4a**(3)
3	**1a**	Benzene	13.40	**2a**(55)	**3a**(11)	**4a**(3)
4	**1a**	Toluene	2.68	**2a**(43)	**3a**(13)	**4a**(5)
5	**1a**	Benzene/Hexane[c]	10.00	**2a**(77)	**3a**(6)	**4a**(1)
6	**1b**	Benzene	10.00	**2b**(46)	**3b**(17)	**4b**(4)

[a] Reactions were carried out under reflux in benzene or toluene. Reaction time ;24 h.
[b] Isolated yields based on **1a** used. [c] Benzene : Hexane = 3 : 2.

The other tetraazathiapentalene derivative (**1b**) reacted similarly with *p*-xylylenediisothiocyanate to give **2b**, **3b**, and **4b**, respectively. The results are summarized in Table 1.

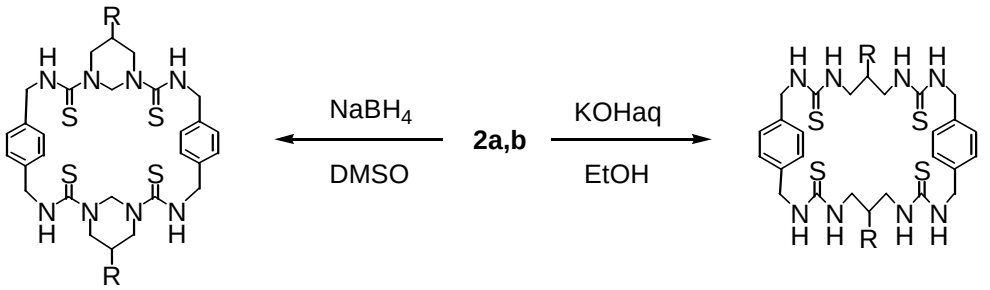
The change in concentration of **1a** did not affect the yield of **2a** (Entries 1-3), but the yield of **2a** slightly decreased with increasing the reaction temperature (Entry 4). When a benzene/hexane mixed solvent was used instead of benzene, the yield of **2a** increased markedly (Entry 5). Compounds (**3a)** and (**4a)** were converted into **2a** upon refluxing in benzene for 24 h in 91% and 77% yields, respectively (Scheme 2). This result clearly suggests that **2a** is formed *via* **3a** and **4a**.

Scheme 2



The reaction of **2a** with $NaBH_4$ in DMSO at room temperature for 24 h gave the 26-membered macrocyclic compound (**5a**) containing four thiourea moieties in a 67% yield, after the usual work-up of the reaction mixture and then column chromatography of the residue on silica gel with CH_2Cl_2/AcOEt (19 : 1). Compound (**2b**) reacted similarly with $NaBH_4$ to give the macrocyclic compound (**5b**) in a moderate yield (Scheme 3).

Scheme 3



5a ; R=$(CH_2)_7Me$ (67%)
5b ; R=$(CH_2)_{11}Me$ (44%)

6a ; R=$(CH_2)_7Me$ (44%)

The structures of **5a**,**b** were determined by their IR, ^{1}H-NMR and MS spectra, and elemental

analyses.[8] The structure of **5a** was further confirmed by X-ray crystallographic analysis.[9] Figure 1 shows an ORTEP drawing of **5a**.[10]

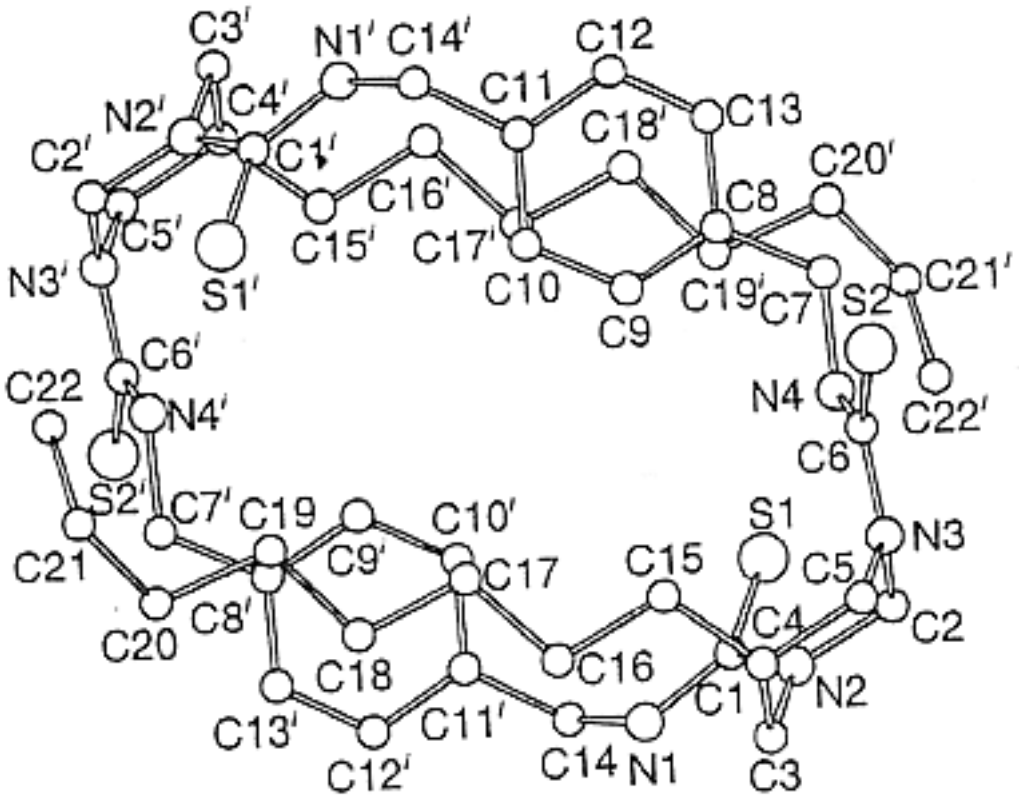
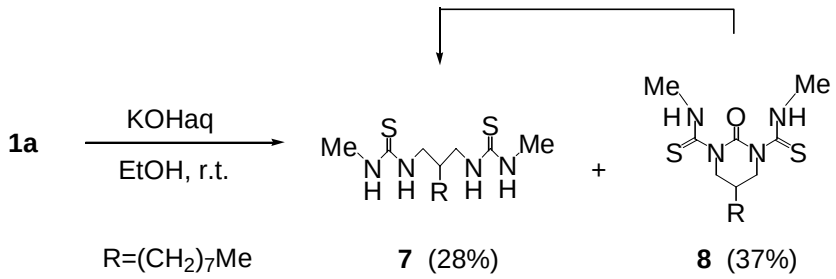


Figure 1. ORTEP drawing of **5a**.[10] H atoms and solvent molecules are omitted. The molecule has a crystallographic center of symmetry at the center of the macrocycle. Symmetry code: *i* (1-x, -y, 2-z). Selected bond lengths (Å) and angles (degrees): S1-C1=1.70(2), N1-C1=1.36(2), N1-C14=1.43(2), N2-C1=1.38(2), N2-C2=1.43(2), N2-C3=1.49(2), C1-N1-C14=124(2), C1-N2-C2=125(2), N1-C1-N2=117.4(14), C2-N2-C3= 110(2).

Treatment of **2a** with an aqueous EtOH-KOH solution gave the 30-membered macrocyclic compound (**6a**) having four thiourea moieties in a 44% yield with elimination of $C=S^{IV}$ moiety of the tetraazathiapentalene framework. The structure of **6a** was determined by comparison of its spectral data with those of **5a**, and elemental analysis. We have also found that the reaction of **1a** with an aqueous KOH solution gives the ring-opened compound (**7**) and the cyclic urea derivative (**8**) in 28% and 37% yields, respectively. Treatment of **8** with an aqueous KOH solution under similar conditions for a while gave **7** in a 69% yield (Scheme 4).

These results suggest that the conversion of **2a** into **6a** proceeds *via* a carbonyl intermediate such as **8**.

Scheme 4



The macrocyclic compounds (**2a**,**b**, **5a**,**b** and **6a**) are highly soluble in organic solvents and stable under atmospheric conditions. The synthetic methodology reported in this paper is expected to serve as a useful tool for the synthesis of macrocyclic compounds containing thiourea functions with various spacers.

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8 **2a:** mp 223.5-224.5 °C(decomp); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 0.89 (6H, t, J = 6.7 Hz), 1.27 (28H, m), 2.16 (2H, m), 3.47 (4H, dd, J = 13.4 and 10.4 Hz), 4.89 (4H, dd, J = 13.4 and 10.4 Hz), 5.00 (8H, s), and 7.29 (8H, s); IR (KBr) 2922, 2853, 1575, 1528, 1477, 1417, 1235, 1198, 1163, 1144, 1132, and 1106 cm^{-1}; Anal. Calcd for $C_{44}H_{60}N_8S_6$: C, 59.15; H, 6.77; N, 12.54; Found: C, 58.98; H, 6.82; N,12.65.

5a: mp 209.5-211 °C(decomp); ^{1}H-NMR (acetone-d_6, 270 MHz) δ 0.86 (6H, t, J = 6.7 Hz), 1.22 (28H, m), 1.73 (2H, m), 3.40 (4H, br), 4.26 (4H, br), 4.93 (12H, br), 7.26 (8H, m), and 8.64 (4H, br); IR (KBr) 3216, 3049, 2924, 2854, 1560, 1537, 1488, 1418, 1382, 1337, 1308, 1259, 1237, 1171, 1140, 1094, 961, 933, 901, 878, 827, and 754 cm^{-1}; Anal. Calcd for $C_{44}H_{68}N_8S_4$: C, 63.11; H, 8.19; N, 13.38; Found: C, 63.25; H, 8.19; N,13.15.

6a: mp 199-200.5 °C(decomp); ^{1}H-NMR (acetone-d_6, 270 MHz) δ 0.88 (6H, t, J = 6.7 Hz), 1.29 (28H, m), 3.39 (4H, m), 3.70 (4H, m), 4.70 (8H, m), 7.27 (8H, s), and 7.36 (8H, s), {2H signal was overlapped with acetone's one.}, ^{1}H-NMR (methanol-d_4, 270 MHz) δ 0.90 (6H, t, J = 6.7 Hz), 1.25 (28H, m), 1.90 (2H, m), 3.56 (4H, m), 4.59 (8H, m), and 7.24 (8H, s), {4H signal was overlapped with methanol's one.}; IR (KBr) 3362, 3299, 3057, 2923, 2852, 1457, 1467, 1412, 1383, 1337, 1291, 1223, 970, 687, and 754 cm^{-1}; Anal. Calcd for $C_{42}H_{68}N_8S_4$: C, 62.02; H, 8.43; N, 13.78; Found: C, 61.75; H, 8.52; N,13.59.

9 Crystal data for **5a**. $C_{44}H_{68}N_8S_4 \cdot 2.14CHCl_3$, trigonal, space group R3(hexagonal setting), a = 30.380(8), c = 16.704(5) Å, V = 13351(5) Å^3, Z = 9, d_{calc} = 1.223g cm^{-3}. A colorless crystal with dimensions of 0.2x0.3x0.2 mm was sealed in a glass capillary with immersed in a minimum amount of solvent soon after picked up from the $CHCl_3$ / hexane solution, because the crystals were immediately deteriorated in the air. The specimen was cooled at 253k during the data collection to reduce the deterioration. The intensity data were collected on a MAC Sceience DIP-3000 diffractometer using the imaging plate as a detector with Mo-Kα radiation. Whole data were collected within about 12 hours. 11828 reflections measured, 6715 unique, 1760 with $|Fo| > 2.5\sigma(F)$, R = 0.148, Rw_2 = 0.393 (315 variables). The terminal three atoms of alkyl chain and solvent molecules are disordered,

so that R factors were not sufficientry reduced. The backbone structure, however, was obtained from the direct method followed by successive Fourier syntheses. Details of X-Ray structure will be published elsewhere by F. Iwasaki, M. Yasui, and N. Matsumura.

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