Synthesis and Structural Aspects of Macrocycles Composed of Two 5-Mercapto-2,3-dihydro-1,3,4-thiadiazol-2-ones and Two Xylenes

Nam Sook Cho,* Soon Il Hong, Young-Soo Park,† and Il-Hwan Suh†

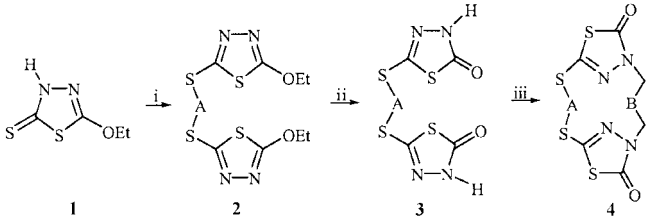
Department of Chemistry and †Department of Physics, Chungnam National University, Taejon 305-764, Korea
Received August 29, 2001

Keywords : 5-Mercapto-2,3-dihydro-1,3,4-thiadiazol-2-one, Heterocyclic macrocycle, X-Ray crystal structure, Mass spectra.

As a continuation of our studies on macrocyclic compounds containing 1,3,4-thiadiazoles,[1-6] we have turned our attention to macrocycles composed of two 5-mercapto-2,3-dihydro-1,3,4-thiadizol-2-ones and two xylenes (*para*, *meta*, and *ortho* isomers), to consider their structural aspects. A mass spectra study was also performed which it is a sensitive diagnostic tool for elucidating the structure of positional isomers, and provides the information on the electron-impact mass spectral fragmentation of 1,3,4-thiadiazoline macrocycles.[2,7]

We synthesized the macrocycles in a manner similar to that previously reported[1] for **4c** macrocycles from compound **1**, which was regioselectively *S*-alkylated in basic conditions.[1] *S*- and *N*-Bridged macrocycles were synthesized from **1** as shown in Scheme 1.

The reaction of **1** with an appropriate α,α'-dibromoxylene in the presence of Et_3N in ethanol gave the *S*-alkylated dimer **2**.[1] The yields were dependent on the geometry of xylenes (*para* 93%, *meta* 81%, *ortho* 73%[1]). The formation of **2** was confirmed by well-defined ^1H and ^{13}C NMR spectra. In the case of **2a**, the NH of compound **1** was replaced by a SCH_2 signal appearing at 4.57 and 157.0 ppm in the ^1H and ^{13}C NMR spectra, respectively.[1] The ^{13}C NMR showed that the thione carbon of **1** (184.2 ppm) typically changed to the carbon of thiadiazole of **2a** (157.0 ppm).[8] The ethoxy groups of **2** were cleanly dealkylated with HBr to give compound **3**.[1,9] The formation of **3a** was demonstrated by ^1H NMR, ^{13}C NMR, and IR. The ethoxy group was replaced by a lactam NH (12.95 ppm) in the ^1H NMR and the chemical shifts of ring carbon atoms C(2) and C(5) were shifted upwards (171.4 and 147.8 ppm, respectively) compared to **2a** (175.3 and 157.0 ppm). In addition, IR showed a strong amide carbonyl band at 1656 cm^{-1}.[9] This suggests that **3a** exists as a lactam form.[9] And, the NH of **3a** is acidic enough to be alkylated in triethylamine with α,α'-dibromoxylene. The final step is an intermolecular cyclization, through, *N,N*-bisalkylation of **3** using the corresponding α,α'-dibromoxylene. The structures of the macrocycles were firmly established by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy. The ring formation also demonstrated a geometrical effect of xylenes in yield (*para* 61%, *meta* 33%, *ortho* 51%[1]). The macrocyclization of **3a** to **4a** was through *N*-alkylation was evident with the appearance of an NCH_2 group instead of NH at 5.05 and 50.2 ppm in the ^1H and ^{13}C NMR spectra, respectively.[1] The two phenyl groups showed two peaks each, at 136.5 and 136.1, and 129.2 and 129.1 ppm, respectively in ^{13}C NMR. A strong amide carbonyl band appeared at 1671 cm^{-1} in IR and the molecular ion peak was at 472 in mass spectra.



2a, **3a**, A = *p*-xylene **4a**, A = *p*-xylene, B= *p*-phenylene
2b, **3b**, A = *m*-xylene **4b**, A = *m*-xylene, B= *m*-phenylene
2c, **3c**, A = *o*-xylene **4c**, A = *o*-xylene, B= *o*-phenylene

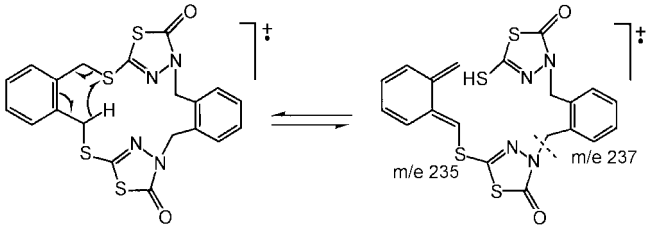
Scheme 1. Reagents and conditions: **i**, α,α'-dibromoxylene, Et_3N, EtOH, reflux, **ii**, HBr, EtOH, reflux, **iii**, α,α'-dibromoxylene, Et_3N, EtOH, reflux.

Macrocycles **4a** and **4b** were clearly characterized in a single-crystal X-ray diffraction study. Unfortunately, the X-ray study of *ortho* compound **4c** could not be carried out because we failed to obtain single-crystal from a variety of solvents. In all cases, we obtained either powder or small quantities of crystals that were unsuitable for the experiment. As shown in the X-ray crystal structure of **4a** (Figure 1), a 20-membered macrocycle and the most stable conformer, four ring units are alternatively more or less up and down. The two 1,3,4-thiadiazolone rings (26.55°) are more parallel each other than that the two benzene rings (83.15°). The structure of macrocycle **4b** (Figure 2) is twisted; the two benzene rings are anti-parallel (41.77°) and the two 1,3,4-thiadiazolone rings exist at an angle of 51.97°.

To study the structure of **4a** in solution, we tried variable low-temperature ^1H NMR at up to −75 °C in $CDCl_3$. However, there was no indication of equatorial or axial hydrogen separation in either SCH_2 or NCH_2. This implies that bond rotation occurs more or less freely under these circumstances. These phenomena suggest that it might serve as a good host molecule through self-assembly with suitable guest molecules, although the solid structures do not have a good shape as receptors. Unfortunately, variable low-temperature ^1H NMR of compounds **4b** and **4c** could not be carried out, because they are only soluble in DMSO and suitable solvents for the experiment are precluded by their low solubility.

The isomers of macrocycles are clearly identified by the number of peaks of phenyl rings on ^{13}C NMR; the *para* (**4a**), *meta* (**4b**), and *ortho* (**4c**) compounds have 2, 4, and 3 peaks for each phenyl ring, respectively. Mass spectroscopy can also differentiate the isomers by their fragmentation patterns. The fragmentation patterns of the *para* and *meta* compounds are similar, but that of the *ortho* compound is quite different. The *ortho* compound (**4c**) revealed a prominent *ortho* effect,[10] as shown in Scheme 2. The base peak is a molecular ion peak at 472 (100%), although peaks at 235 (39.75%) and 237 (49.89%) are major peaks, resulting from a 6-membered cyclic transition state *via S* benzylic hydrogen transfer to the opposite bridged sulfur atom. The other major peaks are 236 ($M^+/2$, 24.20%), 135 ($CH_2C_6H_4CH{=}S^+$, 78.58%), and 104 ($CH_2C_6H_4CH_2^+$, 59.02%). All isomers produce 104 identical fragments. The *para* compound **4a** is fragmented quite differently from **4c**. The base peak is 439 (M^+-SH, 100%); the next major peak is 104 (92.90%); and the molecular ion peak is at 472 (80.30%), with peaks at 237 ($M^+/2+1$, 9.83%), and 236 ($M^+/2$, 3.62%). The fragmentation patterns of the *meta* compound (**4c**) is similar to that of the *para* compound (**4a**), however, there are big differences in the ratios of fragments. The base peak is the molecular ion peak (472); and the next major peaks are at 439 (65.01%), 104 (40.57 %), 237 (4.60%), and 236 (2.36%).

As mentioned, macrocycles have the potential to coordinate with a suitable acid through self-assembly using the basic nitrogen atoms. A study on host-guest interaction is in progress.



Scheme 2. Fragmentation of Macrocycle **4c**.

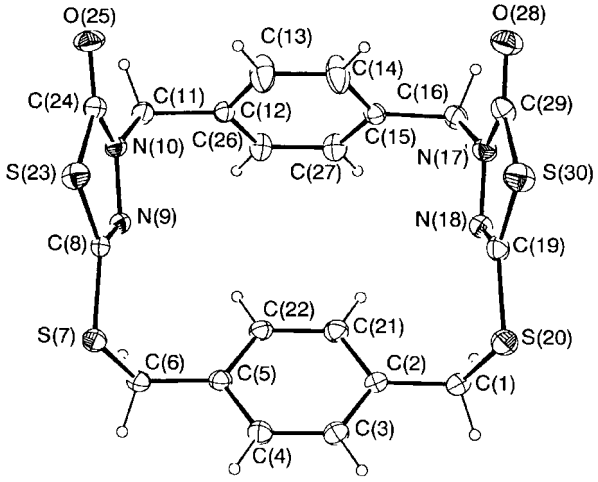


Figure 1. The molecular structure of macrocyle **4a**, showing the atomic numbering used for the crystallographic analysis.

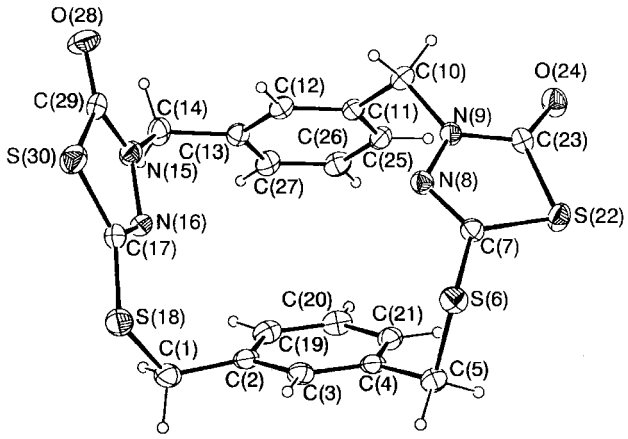


Figure 2. The molecular structure of macrocycle **4b**, showing the atomic numbering used for the crystallographic analysis.

Experimental Section

The IR spectra were recorded on a Jasco Report-100 spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained using a Bruker ARX-400 spectrophotometer at 400 MHz and 100 MHz respectively with tetramethylsilane as the internal reference. Electron impact mass spectra were performed with a JEOL JMS-SX 102A spectrophotometer (70 eV) at the Korea Basic Science Institute, Taejon, Korea. 5-Ethoxy-2,3-dihydro-1,3,4-thiadiazole-2-thione **1** was prepared as previously reported.[9] The syntheses of α,α'-bis[(5-ethoxy-1,3,4-thiazole-2-yl)thio]xylene (**2**) and α,α'-bis[(5-oxo-1,3,4-thiadiazoline-2-yl)thio]xylene (**3**) and macrocycles (**4**) generally followed the procedures previously reported for the synthesis of macrocycle **4c**.[1]

***α,α'*-Bis[(5-ethoxy-1,3,4-thiazol-2-yl)thio]-*p*-xylene (2a)**. Yield 93% (recrystallization from EtOH), mp: 109-111 °C; R_f: 0.50 (*n*-hexane : EA = 7 : 3); IR (KBr pellet, cm^{-1}): 2982 (CH), 1512, 1470, 1260; ^1H NMR ($CDCl_3$, δ): 7.34 (4H, s, C_6H_4), 4.57 (4H, q, J = 7.2 Hz, $2OCH_2$), 4.38 (4H, s, $2SCH_2$), 1.47 (6H, t, J = 7.2 Hz, $2CH_3$); ^{13}C NMR ($CDCl_3$, δ): 175.3 (C-O), 157.0 (C-S), 135.8, 129.5 (C_6H_4), 69.3 (OCH_2), 37.6 (SCH_2), 14.3 (Me).

***α,α'*-Bis[(5-ethoxy-1,3,4-thiazol-2-yl)thio]-*m*-xylene (2b)**. Yield 81% (from SiO_2 column *n*-hexane : EA = 7 : 3), mp: 54-55.8 °C; R_f: 0.41 (*n*-hexane : EA = 7 : 3); IR (KBr pellet, cm^{-1}): 2978 (CH), 1511, 1256; ^1H NMR ($CDCl_3$, δ): 7.38 (1H, s, *m*-(CH) of C_6H_4), 7.31-7.24 (3H, m, $(CH)_3$ of C_6H_4), 4.51 (4H, q, J = 7.1 Hz, $2OCH_2$), 4.38 (4H, s, $2SCH_2$), 1.44 (6H, t, J = 7.1 Hz, $2CH_3$); ^{13}C NMR ($CDCl_3$, δ): 175.3 (C-O), 156.9 (C-S), 136.7, 129.8, 129.0, 128.7 (C_6H_4), 69.3 (OCH_2), 37.8 (SCH_2), 14.4 (Me).

***α,α'*-Bis[(5-ethoxy-1,3,4-thiazol-2-yl)thio]-*o*-xylene (2c)**.[1] Yield 73% (recrystallization from EtOH), mp: 73-74 °C; R_f: 0.42 (*n*-hexane : EA = 7 : 3); IR (KBr pellet, cm^{-1}): 3000 (CH), 1500, 1260; ^1H NMR (DMSO-d_6, δ): 7.41-7.37 (2H, m, $(CH)_2$ of C_6H_4), 7.29-7.26 (2H, m, $(CH)_2$ of C_6H_4), 4.59 (4H, s, $2SCH_2$), 4.48 (4H, q, J = 7.0 Hz, $2OCH_2$), 1.37 (6H, t, J = 7.0 Hz, $2CH_3$); ^{13}C NMR (DMSO-d_6, δ): 175.0 (C-O), 156.3 (C-S), 134.8, 130.7, 128.2 (C_6H_4), 69.7 (OCH_2), 35.0

(SCH_2), 14.1 (Me).

***α,α'*-Bis[(4,5-dihydro-5-oxo-1,3,4-thiazol-2-yl)thio]-*p*-xylene (3a)**. Yield 92% (recrystallization from EtOH : THF = 3 : 1), mp: 208-210 °C; R_f: 0.63 (*n*-hexane : EA = 5 : 5); IR (KBr pellet, cm^{-1}): 3120 (NH), 3062, 2950 (CH), 1656 (C=O), 1500, 1200; ^{1}H NMR (DMSO-d_6, δ): 12.95 (2H, s, NH), 7.35 (4H, s, C_6H_4), 4.32 (4H, s, SCH_2); ^{13}C NMR (DMSO-d_6, δ): 171.4 (C=O), 147.8 (C-S), 135.9, 129.2 (C_6H_4), 36.2 (SCH_2).

***α,α'*-Bis[(4,5-dihydro-5-oxo-1,3,4-thiadizol-2-yl)thio]-*m*-xylene (3b)**. Yield 87% (recrystallization from EtOH : THF = 3 : 2), mp: 147-149 °C; R_f: 0.24 (*n*-hexane : EA = 5 : 5); IR (KBr pellet, cm^{-1}): 3180 (NH), 2960 (CH), 1695 (C=O), 1500; ^{1}H NMR (DMSO-d_6, δ): 12.95 (2H, s, NH), 7.40 (1H, s, *m*-(CH) of C_6H_4), 7.31-7.29 (3H, m, $(CH)_3$ of C_6H_4) 4.32 (4H, s, SCH_2); ^{13}C NMR (DMSO-d_6, δ): 171.5 (C=O), 147.7 (C-S), 136.9, 129.5, 128.8, 128.3 (C_6H_4), 36.4 (SCH_2).

***α,α'*-Bis[(4,5-dihydro-5-oxo-1,3,4-thiadizol-2-yl)thio]-*o*-xylene (3c)[1]**. Yield 73% (recrystallization from EtOH : toluene = 1 : 1), mp: 160-162 °C; R_f: 0.14 (*n*-hexane : EA = 7 : 3); IR (KBr pellet, cm^{-1}): 3200 (NH), 2960 (CH), 1680 (C=O), 1050; ^{1}H NMR (DMSO-d_6, δ): 13.00 (2H, s, NH), 7.46-7.50 (2H, m, $(CH)_2$ of C_6H_4), 7.40-7.36 (2H, m, $(CH)_2$ of C_6H_4), 4.56 (4H, s, SCH_2); ^{13}C NMR (DMSO-d_6, δ): 171.5 (C=O), 147.5 (C-S), 134.7, 130.8, 128.3 (C_6H_4), 34.1 (SCH_2).

Macrocycle (4a). Yield 61% (recrystallization from EtOH), mp: 252-255 °C; R_f: 0.48 (*n*-hexane : EA = 5 : 5); IR (KBr pellet, cm^{-1}): 2975 (CH), 1671 (C=O), 1423, 1277; ^{1}H NMR (DMSO-d_6, δ): 7.35 (4H, s, C_6H_4), 6.99 (4H, s, C_6H_4), 5.05 (4H, s, NCH_2), 4.15 (4H, s, SCH_2); ^{13}C NMR (DMSO-d_6, δ): 169.8 (C=O), 147.2 (C-S), 136.5, 136.1, 129.2, 129.1 (C_6H_4), 50.2 (NCH_2), 34.2 (SCH_2); MS (EI), *m*/*z*: 472 (M^+, 80.30%), 439 (100), 383 (5.37), 237 (9.83), 236 (3.62), 205 (4.87), 170 (4.21), 147 (7.27), 118 (5.74), 104 (92.90), 91 (10.97), 78 (6.76).

Macrocycle (4b). Yield 32.8% (recrystallization from MeOH), mp: 187.5-189 °C; R_f: 0.14 (*n*-hexane : EA : EtOH = 5 : 3 : 1); IR (KBr pellet, cm^{-1}): 2930 (CH), 1672 (C=O), 1655, 1421, 1050; ^{1}H NMR (DMSO-d_6, δ): 7.39-7.23 (4H, m, C_6H_4), 7.10-6.95 (4H, m, C_6H_4), 4.94 (4H, s, NCH_2), 4.23 (4H, s, SCH_2); ^{13}C NMR (DMSO-d_6, δ): 168.9 (C=O), 146.5 (C-S), 137.3, 136.3, 129.0, 128.3, 128.1, 128.0, 127. 9, 126.5 (C_6H_4), 49.9 (NCH_2), 36.3 (SCH_2); MS (EI), *m*/*z*: 472 (M^+, 100%), 439 (65.1), 339 (9.01), 249 (8.95), 237 (4.60), 236 (2.36), 245 (8.10), 179 (7.18), 170 (14.73), 147 (10.17), 135 (7.24), 104 (40.17), 105 (21.04), 103 (18.57), 91 (6.72), 78 (7.34).

Macrocycle (4c).[1] Yield 51% (from THF : EtOH = 4 : 1), mp: 248-250 °C; R_f: 0.16 (*n*-hexane : EA = 7 : 3); IR (KBr pellet, cm^{-1}): 2950 (CH), 1700 (C=O), 1500, 1057; ^{1}H NMR (DMSO-d_6, δ): 7.40-7.35 (4H, m, C_6H_4), 7.26-7.22 (4H, m, C_6H_4), 5.44 (4H, s, NCH_2), 4.49 (4H, s, SCH_2); ^{13}C NMR (DMSO-d_6, δ): 168.7 (C=O), 146.5 (C-S), 134.4, 134.1, 130.8, 129.4, 128.5, 128.3 (C_6H_4), 47.3 (NCH_2), 32.4 (SCH_2); MS (EI), *m*/*z*: 472 (M^+, 100), 237 (49.89), 236 (24.20), 235 (39.73), 203 (12.63), 176 (9.12), 175 (49.12), 159 (14.32), 136 (18.18), 135 (78.58), 118 (21.64), 117 (40.07), 104 (59.02).

X-Ray crystal structure of 4a. Compound **4a** was crystallized from the slow evaporation of a solution of $CHCl_3$. Crystal data for **4a**, $C_{20}H_{16}N_4O_2S_4$: M.W. 472.61, triclinic, space group P-I, a = 9.395(2), b = 9.445(2), c = 13.299 Å, α = 76.22 (2), β = 76.79(2), γ = 68.82(1)°, V = 1055.4(4) $Å^3$, Z = 2, D_c = 1.487 g/cm^3, μ = 0.476 mm^{-1}, F(000) = 488, T = 289 (2) K. The data were collected CAD-4 diffractometer (Enraf-Nonius, 1994) using graphite-monochromated Mo-Kα radiation (0.71073 Å). The structure was solved by direct method (SHELX 86)[11] (all non-H atoms), followed by full-matrix least-squares refinement (SHELX97)[12] on F^2. Hydrogen atoms were located from ΔF synthesis and positionally refined. All non-hydrogen atoms were anisotropically refined, leading to a final R_1 and wR_2, 0.0510 and 0.1379 respectively, for 3695 unique reflections and 271 parameters. S[F^2], 0.809 and $(\Delta/\sigma)_{max}$ was 0.000. Maximum and minimum features in ΔF synthesis are 0.397 and –0.286 $eÅ^{-3}$, respectively.

X-Ray crystal structure of 4b. Compound **4b** was crystallized from the slow evaporation of a solution of $CHCl_3$. Crystal data for **4b**, $C_{20}H_{16}N_4O_2S_4$: M.W. 472.61, monoclinic, space group $P2_1/a$, a = 14.943(2), b = 15.392(2), c = 9.298(4) Å, α = 90.00, β = 90.00, γ = 99.87(2)°, V = 2106.9(9) $Å^3$, Z = 4, Dc = 1.490 g/cm^3, μ = 0.477 mm^{-1}, F(000) = 976, T = 293(2) K. The structure was determined by the same procedure previously applied for the structure determination of **4a**. Final R_1 and wR_2 were 0.0647 and 0.1419 respectively, for 2050 unique reflections and 271 refined parameters. S[F^2], 1.028, and $(\Delta/\sigma)_{max}$ was 0.000. Maximum and minimum features in ΔF synthesis are 0.418 and –0.296 $eÅ^{-3}$, respectively.

Acknowledgment. This work was supported by Korea Research Foundation Grant (KRF-2000-015-DP0279).

References

1. Cho, N. S.; Park, C. K.; Kim, H. S.; Oh, J. G.; Suh, I-H.; Oh, M. R. *Heterocycles* **1999**, *51*, 2739.
2. Cho, N. S.; Park, H. S.; Hwang, H. J. *Bull. Korean Chem. Soc*. **1999**, *22*, 611.
3. Cho, N. S.; Park, C. K.; Hwang, H. J.; Hong, S. I.; Kim, J-G.; Suh, I-H. *J. Chem. Research (S)* **1999**, 730.
4. Cho, N. S.; Hong, S. I.; Kim, J-G.; Suh, I-H. *Acta Cryst*. **2000**, *C56*, 229.
5. Cho, N. S.; Hong, S. I.; Choo, G-H.; Kim, J-G.; Suh, I-H. *Acta Cryst*. **2001**, *E57*, 368.
6. Cho, N. S.; Hong, S. I.; Kim, J-G.; Suh, I-H. *Acta Cryst*. **2001**, *E57*, 434.
7. Bottino, F.; Papparlardo, S. *Tetrahedron* **1982**, *38*, 665.
8. Papparlardo, S.; Bottino, F.; Tringalli, C. *J. Org. Chem*. **1987**, *52*, 405.
9. Cho, N. S.; Park, C. K.; Kim, H. S.; Choi, E. S.; Kang, S. K. *Bull. Korean Chem. Soc*. **1998**, *19*, 103.
10. Schwarz, H. *Top. Curr. Chem*. **1978**, *73*, 232.
11. Scheldrick, G. M. SHELXL-86, *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
12. Scheldrick, G. M. *SHELXL-97*; University of Göttingen: Germany, 1997.