Synthesis and Structural Aspects of Macrocyclic Compounds Containing 5-Amino-3*H*-1,3,4-thiadiazolin-2-one Subunits

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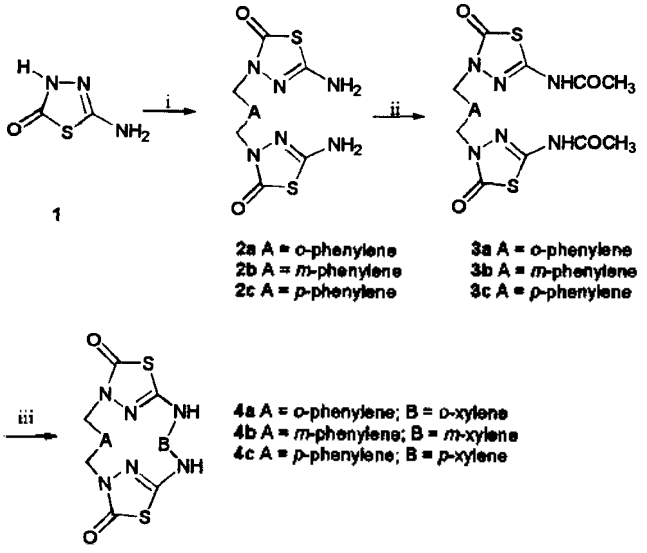
In light of the interest in the construction of polydendate macrocycles containing heterocyclic subunits,[1,2] as well as the limited examples[3-8] of the inclusion of 1,3,4-thiadiazole in a macrocyclic framework, we describe the synthesis and characterization of macrocycles containing two 5-amino-1,3,4-thiadiazolin-2-one **1** herein. The synthesis, tautomeric behavior, and selective alkylation of compound **1** have been reported as a compound of biological and analytical interests.[9] Of the four possible tautomers, **1** is believed to exist as a stable lactam form on the basis of spectroscopic results and *ab initio* calculations.[9] In natural systems, molecular recognition most commonly occurs through hydrogen bonding. The macrocycles linked to the 3 and 5-positions of subunits can form hydrogen bonds with guest molecules through their lactam groups. And also they can potentially form complexes with transition meal cations. From Scheme 1, it is readily apparent that these macrocycles were designed to form 16-, 18- and 20-membered macrocycles to produce central holes of various sizes and shapes.

Each of the three macrocycles **4** consists of four subunits; two heterocyclic subunits **1** and two *o*, *m* and *p*-xylenes, respectively. The structural characterization of macrocycles **4** has been achieved by ^{1}H and ^{13}C NMR and mass spectra. Owing to the lack of information[4,10] about the electron-impact mass spectral fragmentation of 1,3,4-thiadiazoline derivatives, mass spectra are of interest, furthermore, they



Scheme 1. Reagents and conditions: i, α,α'-dibromoxylene, KOH, EtOH, reflux; ii, CH_3COCl, pyridine; α,α'-dibromoxylene, KOH, EtOH, reflux.

can provide a sensitive diagnosis tool for structure elucidation of positional isomers. **1** is regioselectively alkylated at N(3) in basic conditions.[9b] The reaction of **1** with the corresponding α,α'-dibromoxylenes in the presence of KOH in ethanol gave the N-alkylated dimers **2**. The well-defined ^{1}H and ^{13}C NMR spectra revealed the structure of **2**. In the case of **2a**, signals corresponding to the NCH_2 group appeared at 4.92 and 46.6 ppm in the ^{1}H and ^{13}C NMR spectra, respectively, along with phenyl group, while the thiadiazoline carbon atoms C(2) and C(5) resonated at 166.6 and 151.7 ppm, respectively. All of these values are within their normal characteristic ranges. For an intermolecular cyclization, 2+2 alkylation, between **2** and the corresponding α,α'-dibromoxylenes the amino group of **2** was activated *via* acetylation.[11] The formation of **3** was conformed by ^{1}H and ^{13}C NMR. The amino group was replaced by an amide NH (11.99-11.13 ppm) in the ^{1}H NMR of **3a**. Acetyl appeared at 2.0 and 27.9 and 174.6 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. The 2+2 alkylation and deacetylation took place consecutively in KOH-EtOH, between **3** and the corresponding α,α'-dibromoxylenes to give target macrocycles. The **4** macrocycles were derived from **1** with overall yields of 1.9-11 % after recrystallization from the appropriate solvent.

Structures of the macrocycles were firmly established by ^{1}H and ^{13}C NMR, mass and elemental analysis. The successful macrocyclization of **2a** to **4a** was supported by the evidence of N-alkylation, which was provided with the appearance of an $NHCH_2$ group instead of NH_2 at 4.43 and 42.5 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. And two phenyl groups show three peaks respectively, at 137.1, 135.1, 128.8, 128.3, 127.6, and 127.3 ppm. Further structural proofs were afforded by their mass spectra (the molecular ion peak, 438). It was strongly affected by a prominent ortho effect.[12] The base peak was 218, which might proceed *via* a 6-membered cyclic transition state by a benzylic hydrogen transfer to the opposing nitrogen bridged atom as shown Figure 1.

However, in different positional isomer **4b** and **4c**, the base peaks are the molecular ion peaks respectively. In addi-

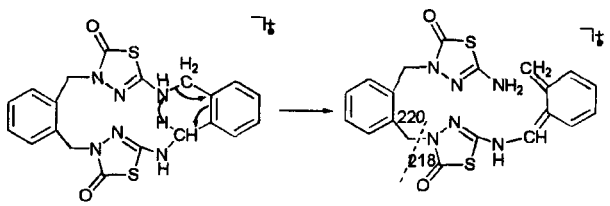


Figure 1

tion, the next main peaks are observed at 104 ($[CH_2C_6H_4CH_2]^+$) in **4b** and **4c**, in contrary, the peak is relatively small in **4a** because of ortho effect fragmentation. Different opening mechanism can be envisaged for **4b** and **4c**, which may involve a 5-membered cyclic transition state by a benzylic hydrogen transfer to either the nitrogen atom or carbonyl oxygen of the adjacent 1,3,4-thiadizoline ring. As a consequence, different intensities of the [M/2 +1], 220 are shown and it is absent in **4a**. All three isomers show [M/2] 219. Surprisingly, only in **4c**, 73 fragment (CHN_2S^+) was arisen by a decomposition of 1,3,4-thiadiazoline ring. The ^{13}C NMR clearly differentiate three macrocycle isomer structures, though the mass fragmentation can also allow it. The *ortho*, *meta* and *para* macrocycles of ^{13}C NMR demonstrated 6, 8 and 4 peaks of phenyl groups respectively. In addition, and microanalytical data clearly support the molecular formula $C_{20}H_{18}N_6S_2O_2$.

The shape and size of central holes and coordination sites of host molecules are significant factors to show their functions. Thus the deduction of the most stable conformer is very useful for host-guest study. Macrocycles **4** may adopt *syn* (up-up) conformation as well as *anti* conformation (up-down). The variable temperature NMR study was tried to draw the conformer structure. This experiment should be done at low temperature. They are only soluble in DMSO and unfortunately suitable solvent should be precluded by its scarce solubility.

Thus, we attempted another method, singlecrystal x-ray diffraction study. It also failed to obtain single-crystals of macrocycles from a variety of solvents, but in all cases we obtained either powders or small quantities of crystals unsuitable for the experiment.

Macrocycles can potentially coordinate transition metal cations, thus, the complexation reaction of **4a** with a silver salt was carried out. It formed as white crystal. It is hard to speculate the structure of the complex without clear evidence because the coordination number of Ag(I) is very irregular[13,14] such as two, four, five and six co-ordination. To prove its structure we are attempting to obtain single crystal of this complex for x-ray diffraction study. And the study of complexation with transition metals or organic carboxylic acids is in progress.

Experimental Section

All melting points were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and were uncorrected. 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 spectrometer at 400 MHz and 100 MHz respectively with tetramethylsilane as internal reference at 28 °C. Electron impact mass spectra were performed with a JEOL JMS-SX 102A spectrometer (70 eV) at the Korea Basic Science Institute, Taejon, Korea. Elemental analyses were run on an Elementar Analysensysteme GmbH Vario EL at the Korea Basic Science Institute, Seoul, Korea. The progress of reaction and purity of products were traced with TLC. 5-Amino-1,3,4-thiadiazolin-2-one was prepared as previously reported.[9a]

General procedure for the synthesis of α,α'-bis(5-amino-1,3,4-thiadiazolin-3-yl)xylenes 2a-c. The compound **1**, (25.7 mmol) was dissolved in KOH (1.7 g, 30.7 mmol)-EtOH (30 mL) solution. Corresponding α,α'-dibromoxylene (12.8 mmol) was added to the solution. The reaction mixture was heated under reflux until the compound **1** was disappeared on TLC. The solvent was evaporated under reduced pressure to leave a solid residue, which was washed with water. The crude product was recrystalized from the appropriate solvent.

α,α'-Bis(5-amino-1,3,4-thiadiazolin-3-yl)-*o*-xylene 2a. The product (yield, 29.8%) was obtained as white precipitate, mp: 201-203 °C (from H_2O : DMF = 1 : 1); R_f 0.45 (THF : *n*-hexane = 10 : 9); IR (KBr, υ_{max}, cm^{-1}) 3394, 3308, 3190 (NH), 3033 (CH), 1677 (C=O), 1618 (NH), 1567 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ_H) 7.32-7.14 (4H, m, Ph), 6.74 (4H, br, 2 x NH_2), 4.92 (4H, s, 2 x CH_2); ^{13}C NMR (100 MHz; DMSO-d_6, δ_C) 166.6 (C=O), 151.7 (C=N), 134.7, 128.9, 128.0 (Ph), 46.6 (CH_2).

α,α'-Bis(5-amino-1,3,4-thiadiazolin-3-yl)-*m*-xylene 2b. The product (yield, 59%) was obtained as white precipitate mp: 326-328 °C (from H_2O : DMF = 1 : 1); R_f 0.14 (THF : *n*-hexane = 10 : 9); IR (KBr, υ_{max}, cm^{-1}) 3420, 3330, 3210 (NH), 3050, 2950 (CH), 1690 (C=O), 1640 (NH), 1580 (C=N); ^1H NMR (400 MHz; DMSO-d_6, δ_H) 7.35-7.13 (4H, m, Ph), 6.69 (4H, br, 2 x NH_2), 4.77 (4H, s, 2 x CH_2); ^{13}C NMR (100 MHz; DMSO-d_6, δ_C) 166.4 (C=O), 151.3 (C=N), 137.1, 128.8, 126.9, 126.8 (Ph), 48.9 (CH_2).

α,α'-Bis(5-amino-1,3,4-thiadiazolin-3-yl)-*p*-xylene 2c. The product (yield, 64.3%) was obtained as white precipitate, mp 282.4-287.3 °C (from H_2O : DMF = 1 : 1); R_f 0.32 (THF : *n*-hexane = 10 : 9); IR (KBr, υ_{max}, cm^{-1}) 3383, 3299, 3189 (NH), 2942 (CH), 1689 (C=O), 1626 (NH), 1561 (C=N); ^1H NMR (400 MHz; DMSO-d_6, δ_H) 7.22 (4H, s, Ph), 6.69 (4H, br, 2 x NH_2), 4.77 (4H, s, 2 x CH_2); ^{13}C NMR (100 MHz; DMSO-d_6, δ_C) 167.6 (C=O), 152.5 (C=N), 137.2, 129.0 (Ph), 49.2 (CH_2).

General procedure for the synthesis of α,α'-bis(5-acetylamino-1,3,4-thiadiazolin-3-yl) xylenes 3a-c. To a solution of compound **2** (8.3 mmol) in pyridine (30 mL), was added acetyl chloride (1.8 mL, 24.8 mmol), in one portion. The mixture was stirred for 3 h. The solvent evaporated under reduced pressure to leave a solid residue, which was washed with acetone and water. The crude product was recrystallized from the appropriate solvents.

α,α'-Bis(5-acetylamino-1,3,4-thiadiazolin-3-yl)-*o*-xylene 3a. The product (yield, 92%) was obtained as white precipitate, mp: 337-339 °C (from H_2O : DMF = 1 : 1); R_f 0.50 (*n*-hexane : AcOEt : EtOH = 5 : 3 :); IR (υ_{max}, KBr, cm^{-1}) 3180, 3110 (NH), 3025 2940 (CH), 1672 (C=O), 1580 (C=N); ^1H NMR (400 MHz; DMSO-d_6, δ_H) 11.13 (2H, br, 2 x NH), 7.31-7.19 (4H, m, Ph), 5.09 (4H, s, 2 x CH_2), 2.05 (6H, s, 2 x Me); ^{13}C NMR (100 MHz; DMSO-d_6, δ_C) 174.6 (C=O), 172.2 (C=O), 148.6 (C=N), 139.6, 134.5, 133.7 (Ph), 52.0 (CH_2), 27.9 (Me).

α,α′-Bis(5-acetylamino-1,3,4-thiadiazolin-3-yl)-*m*-xylene 3b. The product (yield, 97%) was obtained as white precipitate mp: 328 °C (from EtOH); R_f 0.35 (*n*-Hexane : AcOEt = 4 : 1); IR (υ_{max}, KBr, cm^{-1}) 3192, 3116 (NH), 3030 (CH), 1673 (C=O), 1584 (C=N); ^1H NMR (400 MHz; DMSO-d_6, δ_H) 11.99 (2H, br, 2 x NH), 7.36-7.06 (4H, m, Ph), 4.93 (4H, s, 2 x CH_2), 2.03 (6H, s, 2 x Me); ^{13}C NMR (100 MHz; DMSO-d_6, δ_C) 169.0 (C=O), 166.8 (C=O), 142.9 (C=N), 136.7, 128.9, 126.9, 126.4 (Ph), 48.9 (CH_2), 22.3 (Me).

α,α′-Bis(5-acetylamino-1,3,4-thiadiazolin-3-yl)-*p*-xylene 3c. The product (yield, 69.7 %) was obtained as white precipitate, mp 330 °C (from H_2O : DMF = 7 : 15); R_f 0.73 (*n*-Hexane : AcOEt = 4 : 1); IR (υ_{max}, KBr, cm^{-1}) 3191, 3120, 3035 (NH), 2961 (CH), 1662 (C=O), 1591 (C=N); ^1H NMR (400 MHz; DMSO-d_6, δ_H) 11.90 (2H, br, 2 xNH), 7.25 (4H, s, Ph), 4.93 (4H, s, 2 x CH_2), 2.04 (6H, s, 2 x Me); ^{13}C NMR (100 MHz; DMSO-d_6, δ_C) 169.1 (C=O), 166.8 (C=O), 143.0 (C=N), 135.8, 128.1 (Ph), 48.9 (CH_2), 22.4 (Me).

General procedure for the synthesis of macrocycles 4a-c. The compound **3**, (1.4 mmol) was dissolved in KOH (0.2 g, 3.4 mmol)-EtOH (30 mL) solution. Corresponding α,α′-dibromoxylene (1.7 mmol) was added to the solution. The reaction mixture was heated under reflux until the compound **3** was disappeared on TLC. The solvent was evaporated under reduced pressure to leave a solid residue, which was washed with water. The crude product was recrystallized from the appropriate solvent mixture.

4a. The product (yield, 36%) was obtained as white precipitate, mp: 329-333 °C (from AcOEt : DMF = 5:1); R_f 0.54 (*n* -hexane : AcOEt : EtOH = 5 : 3 :1); IR (KBr, υ_{max}, cm^{-1}) 3327 (NH), 3033 (CH), 1659 (C=O), 1577 (C=N); ^1H NMR (400 MHz; DMSO-d_6, δ_H) 7.71 (2H, t, 2 x NH), 7.29-7.12 (8H, m, 2 x Ph), 5.00 (4H, s, 2 x CH_2), 4.43 (4H, d, 2 x NHC$\underline{H_2}$); ^{13}C NMR (100 MHz; DMSO-d_6, δ_C) 166.6 (C=O), 150.4 (C=N), 137.1, 135.1, 128.8, 128.3, 127.6, 127.3 (Ph), 46.5 (CH_2), 42.5 (CH_2); Anal. Calcd. for $C_{20}H_{18}N_6S_2O_2$: C, 54.8; H, 4.1; N, 19.2; S, 14.6. Found: C, 54.8; H, 4.3; N, 19.1; S, 13.5. MS (EI) m/z (relative intensity) 438 (M^+, 12), 219 (16), 218 (100), 104 (17), 78 (5),77 (6).

4b. The product (yield, 3.3%) was obtained as white precipitate, mp: 297.6 °C (from AcOEt : hexane = 1 : 1); R_f 0.57 (*n*-hexane : AcOEt = 4 : 1); IR (KBr, υ_{max}, cm^{-1}) 3552, 3478, 3415 (NH), 1638 (C=O), 1575 (C=N); ^1H NMR (400 MHz; DMSO-d_6, δ_H) 7.91 (2H, t, 2 x NH), 7.29-7.03 (8H, m, 2 x Ph), 4.76 (4H, s, 2 x CH_2), 4.30 (4H, d, 2 x NHC$\underline{H_2}$); ^{13}C NMR (100 MHz; DMSO-d_6, δ_C) 165.7 (C=O), 150.7 (C=N), 139.2, 136.6, 128.6, 128.1, 126.6, 125.1, 123.9, 123.1 (Ph), 48.9 (CH_2), 44.8 (CH_2)); Anal. Calcd. for $C_{20}H_{18}N_6S_2O_2$: C, 54.8; H, 4.1; N, 19.2; S, 14.6. Found: C, 54.4; H, 4.4; N, 18.6; S, 14.2. MS (EI) m/z (relative intensity) 438 (M^+, 110), 220 (6), 219 (4), 104 (48), 78 (4) 77 (2).

4c. The product (yield, 24.6%) was obtained as white precipitate, mp 330 °C (from AcOEt : hexane = 1 : 1); R_f 0.66 (*n*-hexane : AcOEt = 4 : 1) IR (KBr, υ_{max}, cm^{-1}) 3200 (NH), 3000, 2920 (CH), 1662 (C=O), 1583 (C=N); ^1H NMR (400 MHz; DMSO-d_6, δ_H) 7.82 (2H, t, 2 x NH), 7.24-7.06 (8H, dd, 2 x Ph), 4.74 (4H, s, 2 x CH_2), 4.20 (4H, d, 2 x NHC$\underline{H_2}$); ^{13}C NMR (100 MHz; DMSO-d_6, δ_C) 166.1 (C=O), 149.8 (C=N), 136.9, 135.6, 128.6, 127.7 (Ph), 48.6 (CH_2), 45.2 (CH_2); Anal. Calcd. for $C_{20}H_{18}N_6S_2O_2$: C, 54.8; H, 4.1; N, 19.2; S, 14.6. Found: C, 54.3; H, 4.3; N, 18.6; S, 14.3. MS (EI) m/z (relative intensity) 438 (M^+, 110), 220 (4), 219 (3), 104 (65), 78 (4) 77 (3), 73 (44).

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