A Palladium Metalloreceptor with Two 5-Amino-3*H*-1,3,4-thiadiazolin-2-one Groups

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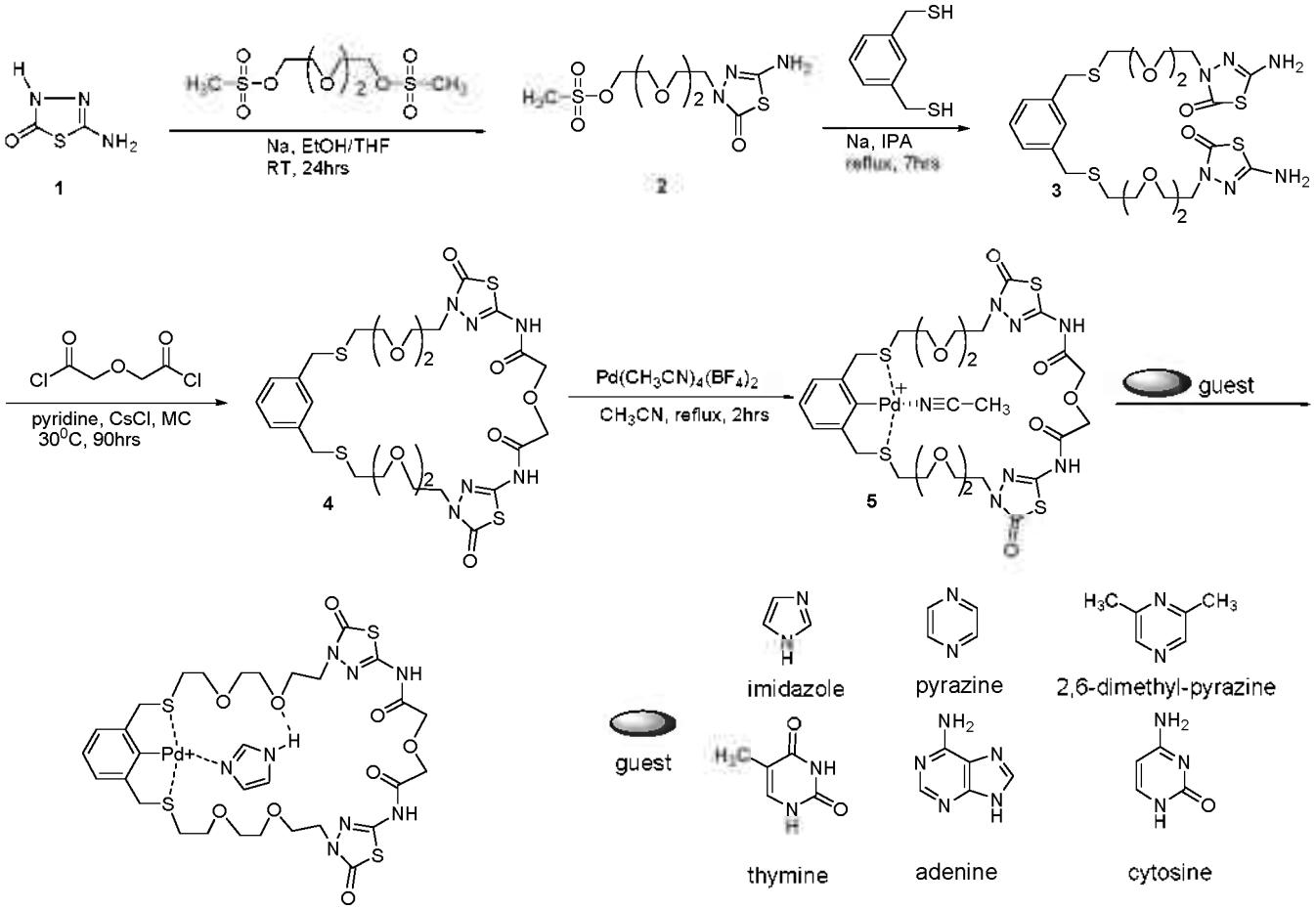
As part of an ongoing study[1-3] of metalloreceptors[1] composed of two 5-amino-3*H*-1,3,4-thiadiazolin-2-one[4] moieties and a 1,3-benzenedimethanethiol subunit, this study describes the synthesis of a metalloreceptor boasting a cavity size amenable to molecular recognition of DNA/RNA nucleobases, including cytosine, adenine, and thymine as well as imidazole, pyrazine, and 2,6-dimethylpyrazine. Both the synthesis and characteristics of molecular recognition were as described in previous reports.[1]

The synthesis of metalloreceptor **5**, which contained two 5-amino-3*H*-1,3,4-thiadiazolin-2-one groups and a 1,3-benzenedimethanethiol subunit, is shown in Scheme 1.

The preparation procedures have been described previously.[1] The only structural difference between metalloreceptor **5** and the previously reported molecule is the cavity size, as a result of chain length differences between the 1,3-benzenedimethanethiol and 5-amino-3*H*-1,3,4-thiadiazolin-2-one units.[1]

Regiospecific *N*-alkylation of **1** revealed that the reaction of **1** with tri(ethylene glycol) dimethanesulfonate in the presence of $NaOC_2H_5$ in ethanol gave the N-alkylated product **2**. 1,3-Benzenedimethanethiol was *S*-alkylated with **2** under basic conditions ($NaOCH(CH_3)_2$-$(CH_3)_2CHOH$) to supply the chelation sites necessary to complex palladium ion.[5-7] The syntheses of compounds **2** and **3** have been described previously.[1]

Target macrocycle **4** was obtained from **3** using Cs^+-mediated cyclization,[8] which involved high-dilution *N*, *N'*-diacylation of **3** at the NH_2 groups of the 1,3,4-thiadiazole



Scheme 1. Synthesis of metalloreceptor **5**.

rings, using diglycolyl chloride. Diglycolyl chloride was added to a CH_2Cl_2 solution of **3** over a 72 h period. The structure of the macrocycle was established by the presence of characteristic peaks in the ^1H and ^{13}C NMR, IR, and FAB-HRMS spectra. The successful *N*-acylation and subsequent macrocyclization of **3** to **4** was evidenced by the replacement of the NH_2 group of **3** by a $NHCOCH_2$ group, as indicated by peaks at δ 10.20 and 4.22 ppm in the ^1H NMR spectrum and at δ 166.7 and 68.1 ppm in the ^{13}C NMR spectrum of compound **4**. The IR spectrum of **4** exhibited a peak at 1670 cm^{-1}, corresponding to the amide carbonyl group. The FAB-HRMS spectra also supported structure **4** (*m*/*z* 731.1666).

The palladated metalloreceptor **5** was formed by refluxing compound **4** in an acetonitrile solution containing one equivalent of $[Pd(CH_3CN)_4][BF_4]_2$. This resulted in the replacement of the labile acetonitrile ligand with one equivalent of macrocyle **4** (1L). All spectroscopic and analytical data were consistent with palladation and the molecular formula $[Pd(L)(CH_3CN)][BF_4]$.[1-3] The ^1H NMR peak corresponding to the benzylic CH_2S protons was broader than that in 1L (3.74 ppm) and was shifted downfield to 4.35 ppm. The four aromatic hydrogen atoms in **4** were replaced with three hydrogen atoms in **5**. Palladation was also evident in the ^{13}C NMR spectrum, which showed a downfield peak shift from 36.5 to 46.4 ppm for benzylic carbon atoms. The peak representing the carbon atom bonded to Pd also shifted, from 129.5 ppm to 156.7 ppm. These results are very similar to those previously reported.[1-3,9-11] In addition, a strong ion peak representing $[Pd(L)]^+$ was observed at *m*/*z* 835.0543 in the FAB-HRMS spectrum. The resulting metalloreceptor **5** was a colorless, air-stable solid and was soluble in most polar organic solvents.

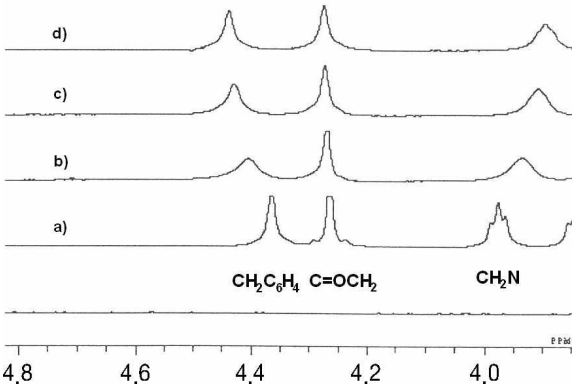


Figure 1. NMR spectra of metalloreceptor **5** upon the addition of various amount of adenine (**A**). a): metalloreceptor **5**. b): **5** : **A** = 1 : 0.6. c): **5** : **A** = 1 : 1.4. d): **5** : **A** = 1 : 2.2.

To examine the molecular recognition (coordination) properties of metalloreceptor **5**, ^1H NMR spectra were evaluated in the presence of several guest molecules consisting of the DNA/RNA nucleobases cytosine, adenine, and thymine, as well as imidazole, pyrazine, and 2,6-dimethylpyrazine. Metalloreceptor **5** acted as host molecule and was dissolved in DMSO-d_6 (0.01-0.02 M). Guest stock solutions were prepared in the same solvent at concentrations ranging from 0.04 to 0.08 M and were added in small increments to the host solution until peak shifts in the ^1H NMR spectra ceased. The ^1H NMR spectrum was recorded after each addition (as shown in Figure 1), and the calculated complexation constants are listed in Table 1.

No changes in the ^1H NMR spectrum of **5** were observed with the addition of up to 10 equivalents of thymine, which indicated no interaction between **5** and thymine. In contrast, significant changes in proton chemical shifts of **5** were observed upon the addition of cytosine, imidazole, and 2,6-dimethylpyrazine. In these instances, one equivalent of guest molecule was sufficient to produce a baseline-resolved shift in the ^1H NMR peak positions. Therefore, the estimated complexation constants (K) were larger than 10^4 ($K = [HG]/([H][G])$, where H = host, G = guest, and HG = host-guest complex). The K-values for adenine and pyrazine were $1.4 \times 10^3 \pm 0.1 \times 10^3$ and $1.1 \times 10^2 \pm 0.1 \times 10^2$, respectively. The ability of guest molecules to complex with metalloreceptor **5** increased in the order thymine < pyrazine < adenine < imidazole/cytosine/2,6-dimethylpyrazine.

This trend is the same as that observed for the previously reported metalloreceptor, where complexation ability increased as uracil/thymine (K < 1) < adenine (K = 6000) < cytosine/imidazole ($K > 10^4$).[1] The only difference between **5** and the previously reported macrocycle is the length of the chain between the thiadiazoline ring and *m*-xylenedithiol, which significantly increases the size of the macrocycle cavity.

The possible intermolecular interactions responsible for generating host-guest complexes in this system include hydrogen bonding, σ-bonding to Pd, and π-π stacking. However, no changes were observed in the ^1H NMR spectrum of cytosine, which exhibited the greatest complexation constant with **5**, when it was added to a solution of **4** in DMSO-d_6 solution. This confirms that as the same as the previously reported system, the interactions responsible for molecular recognition in **5** primarily consisted of σ-bonding to Pd rather than hydrogen bonding or π-π stacking.

Although it does not completely explain the results in Table 1, the basic nature of the guest molecule appears to be the most important factor in forming complexes with **5**. There are

Table 1. The calculated complexation constants (K)[a] with associated changes in the ^1H NMR chemical shift (Δδ) of $ArCH_2S$ in metalloreceptor **5** upon the addition of guest molecules

Guest	Thymine	Pyrazine	Adenine	2,6-Dimethylpyrazine	Imidazole	Cytosine
K (M^{-1})	$< 1^{b,d}$	$1.1 \pm 0.1 \times 10^2$	$1.4 \pm 0.1 \times 10^3$	$> 1 \times 10^{4c,d}$	$> 1 \times 10^{4c,d}$	$> 1 \times 10^{4c,d}$

[a]K was obtained from the slope of the plot ([HG]/[H] vs. [G]) obtained from ^1H NMR titration of **5** with a guest molecule. [b]No chemical shift changes were observed upon the addition of up to 10 equivalents of guest molecule. [c]One equivalent of guest molecule was sufficient to produce a baseline-resolved change in peak position. [d]These values were estimated from the approximation that peaks less than 1/10 of the major peak intensity usually cannot be resolved by NMR. Thus, under these experimental conditions, $K = (0.001\ M)/(0.01\ M \times 0.1\ M) = 1\ M^{-1}$ and $K = (0.01\ M)/(0.001\ M \times 0.001\ M) = 10000\ M^{-1}$.

many possible binding sites on nucleic acid bases. However, metal ion binding occurs predominantly at N3 in pyrimidine bases and at N1 or N7 in purine bases.[12-13] The acidities (pK_a) of protonated forms in aqueous solution were reported as 4.5 and 4.1 for the N3 of cytosine and the N1 of adenine, respectively.[13] In methanol solution, the basicity of bases also increased as thymine (pK_b = 17.5)[14] < adenine (pK_b = 13.0)[14] < cytosine (pK_b = 11.3).[14] which is in good agreement with the order of complexation constant in Table 1. 2,6-Dimethylpyrazine (pK_a = 2.5)[15] is a stronger base than pyrazine (pK_a = 1.1)[15] and imidazole (pK_a = 6.95)[16] is the strongest base among the bases in Table 1. The results show that there is a robust correlation between the complexation constant and the basicity of guest molecules. In conclusion, the complex formation is influenced more strongly by basicity than by steric effect in the case of a macrocyclic host and small DNA/RNA bases.

Experimental

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 the internal reference. Elemental analyses were carried out on an EA 1110 (CE Instrument). FAB-HRMS spectra were obtained on a JEOL-JMS HX-100/110A spectrometer at Korea Basic Science Institute, Taeduk, Taejon. The molecular recognition study was done using a JEOL JNM-AL400 NMR spectrometer.

The synthesis of 5-amino-3*H*-1,3,4-thiadiazolin-2-one (1)[4], tri(ethyleneglycol) dimethanesulfonate,[1] 1-(5-amino-2,3-dihydro-2-oxo-1,3,4-thiadiazol-3-yl)-3,6-dioxaoctyl-8-methanesulfonate (**2**),[1] 1,3-benzenedimethanethiol,[13] and α,α'-bis-[8-(5-amino-2,3-dihydro-2-oxo-1,3,4-thiadiazol-3-yl)-3,6-dioxaoctylthio]-*m*-xylene (**3**)[1] were followed the previous procedures.

12,16,22,26,42,43-Hexaaza-6,9,19,29,32-pentaoxa-3,14,24,35-tetrathiotetracyclo-[35,3,1,1,^{12,15}1^{23,26}]-tritetraconta-1(41),15(42),23(43),37(38),39(40)-pentaene-13,17,-21,25-tetraone (4). To a solution of **3** (3.5 g, 6.4 mmol) in methylene chloride (300 mL), pyridine (1.04 mL, 12.88 mmol) and cesium chloride (1.1 g, 6.5 mmol) were added. Solution of diglycolyl chloride (1.7 g, 9.7 mmole) in methylene chloride (250 mL) was added for 72 h using syringe pump. After addition of diglycolyl chloride solution, the reaction mixture was stirred for additional 24 h. The end point of reaction was checked by TLC. The salt was filtered off and the solution was washed with saturated NaCl solution and dried with $MgSO_4$. The solvent was distilled off to give product residue. Methylene chloride (5 mL) was added to afford crude precipitate product. The crude product was recrystallized from C_2H_5OH to afford pure product (0.4 g, 10%). mp: 149-150 °C. R_f: 0.55 (chloroform: methanol = 9 : 1). IR (KBr, cm^{-1}): 3185 (C=ONH), 1670 (C=O), 1574 (C=ONH). ^1H NMR (DMSO-d_6, 400 MHz, δ): 10.20 (2H, br, NH), 7.27-7.18 (4H, m, C_6H_4), 4.22 (4H, s, C=OCH_2), 4.10 (4H, t, 2CH_2N, J = 4.8 Hz), 3.77-3.74 (8H, m, 2OCH_2+ 2C$H_2C_6H_4$), 3.58 (12H, m, 3(CH_2O)$_2$), 2.59 (4H, t, 2CH_2S, J = 6.4 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 167.6 (C=O), 166.7 (CH_2C=O), 142.2 (C=N), 138.5, 129.5, 128.7, 127.6 (C_6H_4), 70.9, 70.3, 70.2 (3OCH_2), 68.1 (C=OCH_2), 46.3 (NCH_2), 36.5 ($C_6H_4CH_2$S), 30.7 (SCH_2). FABHRMS calcd. for $C_{28}H_{39}N_6O_9S_4$ 731.1661, found 731.1666.

Metalloreceptor (5). To a solution macrocycle (**4**) (0.3 g, 0.3 mmol) in CH_3CN (10 mL), $[Pd(CH_3CN)_4]$ $[BF_4]_2$ (0.2 g, 0.3 mmol) in CH_3CN (5 mL) was added once under a nitrogen atmosphere. The reaction mixture was stirred at rt for 1 h. The color of reaction solution was turned from brown to yellow. Then, it was stirred at reflux for additional 3 h. The end point of reaction was checked by TLC. The solvent was distilled off to give crude product. The yellow product washed with *n*-hexane to afford yellow product (0.28 g, 85%). R_f: 0.63 (chloroform : methanol = 9 : 1). IR (KBr, cm^{-1}): 1653 (C=O), 1576 (C=ONH). ^1H NMR (CD_3CN-d_3, 400 MHz, δ): 9.99 (2H, br, 2NH), 6.99-6.90 (3H, m, C_6H_4), 4.35 (4H, s, 2CH_2 C_6H_4), 4.24 (4H, s, 2C=OCH_2), 3.96 (4H, br, 2CH_2N), 3.70 (4H, t, 2CH_2O, J = 5.2Hz), 3.80 (4H, t, 2CH_2O, J = 5.2Hz), 3.53 (8H, m, 4CH_2O), 3.24 (4H, t, 2CH_2S, J = 5.2Hz). ^{13}C NMR (CD_3CN-d_3, 100 MHz, δ): 169.7 (N-C=O), 168.3 (CH_2C=O), 156.7, 151.7 (C_6H_4), 142.4 (C=N), 126.5, 123.9 (C_6H_4), 71.7, 71.01, 71.0, 68.4 (4OCH_2), 70.3 (C=OCH_2), 47.3(NCH_2), 46.4 ($C_6H_4CH_2$S), 40.0 (SCH_2). FABHRMS calcd. for $C_{28}H_{37}N_6O_9PdS_4^+$ 835.0548, found 835.0543.

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