Synthesis of Heteromacrocycles as Ligands of a Palladium-Artificial Enzyme and Crystal Structure

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Molecular recognition is a general principle in nature, and the design of artificial receptors (enzymes) for specific target molecules based on molecular recognition is an important theme in bioorganic chemistry. Enzymes are often surrounded by a hydrophobic sheath of amino acids that shields them from undesirable hydrolysis and polymerization reactions, and facilitates their normal functions. The mimicking of metalloenzyme active sites are of particular interest.1-3 Artificial metalloenzymes possessing molecular-recognition properties have attracted attention since the 1980s. Some compounds have been utilized for enantioselective sulfoxidation,4,5 hydrogenation,6,7 or asymmetric allylic alkylation reactions.8

In the present work, we have prepared ligands of a palladium-artificial enzyme as amino acid substitutes. 5-Amino-3H-1,3,4-thiadiazolin-2-one (1)9 and 5-amino-3H-1,3,4-thiadiazolin-2-thione (2)10-derived mimics of a metalloenzyme active sites were designed. To provide potential chelation sites to allow the formation of palladium ion complexes, 1,3-benzenedimethanethiol was introduced.11-13 In order to form a hydrogen bond and control the size of the macrocycle cavity, an ether linkage was inserted and compounds 1 and 2 were acylated with acyl halide.

Results and Discussion

The synthesis of ligands containing two units of 5-amino-3H-1,3,4-thiadiazolin-2-one (1) were accomplished according to Scheme 1. The difference between 3a and 3b is the length of the chain, which influences the size of the macrocycle cavity. According to the regiospecific N-alkylation of 1, the reaction of 1 with tri(ethyleneglycol) dimethanesulfonate in the presence of NaOC2H5 in ethanol gave the N-alkylated product (3b). The formation of 3b was confirmed by 1H and 13C NMR spectra. The NH signal of compound (1) was replaced by that of NCH2 at δ 3.90 and 46.0 in the 1H and 13C NMR spectra, respectively. To introduce 1,3-bezenedimethanethiol, the compound was S-alkylated with 3b under basic conditions (NaOCH(CH3)2- (CH3)2CHOH. The formation of 4b was also confirmed by 1H and 13C NMR spectra. The SH signal of 1,3-bezene-
Table 1. Crystal data and structure refinement for macrocycle, 8b, [C_{29}H_{40}N_{6}O_{6}S_{6}].

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{29}H_{40}N_{6}O_{6}S_{6}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>761.03</td>
</tr>
<tr>
<td>Temperature</td>
<td>295(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Triclinic, P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.9202(11) Å, b = 9.9488(12) Å, c = 21.220(2) Å</td>
</tr>
<tr>
<td></td>
<td>α = 76.545(8)°, β = 84.623(8)°, γ = 83.502(7)°</td>
</tr>
<tr>
<td>Volume</td>
<td>1815.3(4) Å²</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>2, 1.392 Mg/m³</td>
</tr>
<tr>
<td>F(000)</td>
<td>800</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.50 × 0.32 × 0.23 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.98 to 26.00 °</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>11350/7088 [R_{int} = 0.0227]</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.034</td>
</tr>
<tr>
<td>Final R indices [I &gt; 2σ(I)]</td>
<td>Ri = 0.0675, wR₂ = 0.1864</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>Ri = 0.1144, wR₂ = 0.2201</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>1.146 and -0.588 e Å³</td>
</tr>
</tbody>
</table>

dimethanethiol was replaced by a SCH₂ at δ 2.61 and 30.8 in the ¹H and ¹³C NMR spectra, respectively. 1,3-Benzenedimethanethiol supplies the chelation sites to form complexes with palladium ions.

To obtain the target macrocycle containing two 5-amino-3H-1,3,4-thiadiazoline-2-ones and one 1,3-benzenedimethanethiol from 4b, we attempted Cs⁺-mediated cyclization,¹¹ which involves N,N'-diacylation of 4b at the NH₂ group of the 1,3,4-thiadiazole rings using diglycolyl chloride with a high-dilution technique. Glutaryl chloride was added to a CH₂Cl₂ solution of 4b over a 72 h period. The structure of the macrocycle was established using ¹H and ¹³C NMR, IR, and FAB-HRMS spectra. The successful macrocyclization of 4b to 5b was supported by evidence of N-acylation, which indicated that a NHCOCH₂ group replaced the NH₂ functional group at δ 11.88 and 3.84 in the ¹H NMR spectrum, and at δ 166.7 and 45.6 ppm in the ¹³C NMR spectrum. The IR spectrum also displays the carbonyl group of the amide at 1653 cm⁻¹. FAB-HRMS spectra clearly supported structure 5b (729.1869).

The synthesis of ligands containing two 5-amino-3H-1,3,4-thiadiazolin-2-thione (2) units was accomplished according to Scheme 2. The difference between 6a and 6b is the length of the chain. As a,α'-m-xylenedithiol is a palladation chelation site,¹¹ an α,a'-m-xylenedithiol moiety was introduced to the macrocyclic compounds to chelate palladium.

According to the regiospecific S-alkylation, compound 2 with the appropriate chloride (6a or 6b) in the presence of NaOEt in ethanol gave an (S)-alkylated dimer (7a or 7b), as shown in the previous method.¹⁵ Again, the difference between 7a and 7b is the length of the chain, which influences the size of the macrocycle cavity. To obtain target macrocycles containing two 2-amino-5-alkylthio-1,3,4-thiadiazole and one 1,3-benzenedimethanethiol from 2, we attempted Cs⁺-mediated¹¹⁺ cyclization involving N,N'-diacylation of 7b at the NH₂ of the 1,3,4-thiadiazole rings using glutaryl chloride with a high-dilution technique to synthesize ligands of 8a and 8b. Glutaryl chloride was added to a CH₂Cl₂ solution of 7b over a 20 h period. The structure of the macrocycle was established using ¹H and ¹³C NMR, IR, and FAB-HRMS. The successful macrocyclization of 7b to 8b was supported by evidence of N-acylation, which indicated that an NHCOCH₂ group replaced

Scheme 2. Synthesis of heteromacrocycles containing two units of 5-amino-3H-1,3,4-thiadiazolin-2-thione (2).
CH3. 13C NMR (100 MHz, CDCl3) (400 MHz, CDCl3-dimethanethiol) were followed the previous procedures. 

1H NMR (400 MHz, CDCl3-d6, δ): 7.24-7.15 (4H, m, C6H4), 5.24 (4H, br, 2NH2), 3.86 (4H, t, 2CH2N, J = 5.2 Hz), 3.71-3.68 (8H, m, 2OCH2 + 2CH2S), 3.57-3.54 (12H, m, 3 (CHOH)2), 2.58 (4H, t, 2CH2S, J = 6.4 Hz). 13C NMR (400 MHz, CDCl3-d6, δ): 167.4 (C=O), 150.9 (C=N), 135.8, 129.4, 128.6, 127.6 (C6H4), 70.7, 70.23, 70.15, 68.2 (4OCH), 46.1 (NCH3), 36.5 (C6H4CH2), 30.8 (SCH2). Anal. Calcd for C29H40N6O6S4: C 45.55; H 5.73; S 20.27. Found: C 45.54; H 5.72; S 20.28.

9.19, 13, 19, 23, 36, 37-Hexaaza-6,16-dioxo-3,11,21,29-tetra-thiotetracyclo-[29,3,1,13,15](37,40), 20(37), 31(32), 33(34)-pentaene-10,14,18,22-tetraene (5a). To a solution of 3a (3.5 g, 6.4 mmol) in methylene chloride (300 mL), pyridine (1.0 mL, 12.9 mmol) and cesium chloride (1.1 g, 6.5 mmol) were added. Solution of glutar chloride (1.7 g, 9.8 mmol) in methylene chloride (250 mL) was added for 72 h using syringe pump. After addition of glutar 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 MgSO4. The solvent was distilled off to give oily product. First precipitation induced by addition of acetone (5 mL). And then methylene chloride was added to afford crude precipitate product. The crude product was recrystallized from C6H12OH to afford pure product (0.3 g, 97%). mp: 218-220 °C. Rf: 0.33 (CHCl3 : MeOH = 9 : 1). IR (KBr, cm⁻¹): 3434 (C=ONH), 1671 (C=O), 1628 (C=ONH). 1H NMR (DMSO-d6, 400 MHz, δ): 11.94 (2H, br, 2NH), 7.20-7.04 (4H, m, C6H4), 3.90 (4H, t, 2CH2N, J = 5.2 Hz), 3.67 (8H, m, 2OCH2 + 2CH2S, J = 6.0 Hz). 13C NMR (DMSO-d6, 100 MHz, δ): 171.2 (C=O), 166.7 (C=O), 142.4 (C=O), 138.6, 129.1, 127.8, 127.1 (C6H4), 70.3, 45.7 (2OCH2), 45.7 (CH3), 35.4 (NCH2), 33.6 (C6H4CH2), 30.1 (SCH2), 19.8 (CH2CH2CH3). FABHRMS calcld. for C29H40N6O6S4: 641.1344, found 641.1340.

12, 16, 22, 26, 42, 43-Hexaaza-6,9,29,32-tetraoxa-3,14,24,35-tetra-thiotetracyclo-[35,3,1,13,15](23,26)-heptatriaconta-1(41),15(42),23(43),37(38),39(40)-pentaene-13,17,21,25-tetraene (5b). The synthesis of 5b followed the same procedure of the preparation of 4a. Yield 5%, mp: 228-230 °C. Rf: 0.36 (CHCl3 : MeOH = 9 : 1). IR (KBr, cm⁻¹): 3206 (C=ONH), 1653 (C=O), 1576 (C=ONH). 1H NMR (DMSO-d6, 400 MHz, δ): 11.88 (2H, br, 2NH), 7.18-7.07 (4H, m, C6H4), 4.03 (4H, t, 2CH2N, J = 5.2 Hz), 3.84 (4H, t, C=OCH2), 3.76-3.70 (8H, m, 2OCH2 + 2CH2S, J = 6.4 Hz). 13C NMR (DMSO-d6, 100 MHz, δ): 171.2 (C=O), 166.7 (C=O), 142.4 (C=O), 138.6, 129.2, 128.1, 127.3 (C6H4), 70.1, 69.6, 69.3, 67.0 (4OCH), 45.6 (C=OCH2), 35.3 (NCH2), 33.7 (C6H4CH2), 30.1 (SCH2), 19.7 (CH2CH2CH3). FABHRMS calcld. for C29H46N6O6S4: 729.1869, found 729.1870.

The synthesis of 5-amino-3H-1,3,4-thiadiazolin-2-thione

| Experimental Section |

The synthesis of 5-amino-3H-1,3,4-thiadiazolin-2-one (1), 5-(5-amino-2,3-dihydro-2-oxo-1,3,4-thiadiazol-3-yl)-3-oxopentyl methanesulfonate (3a), a,a’-bis-[5-(5-amino-2,3-dihydro-2-oxo-1,3,4-thiazol-3-yl)-3-oxopentylmethanesulfonate (3b). The synthesis of 3b followed the same procedure of the preparation of 3a. Yield 24.2%. Oil. Rf: 0.18 (CHCl3 : MeOH = 15 : 1). IR (cm⁻¹): 3320 (NH3), 1613 (C=O), 1611 (NH), 1348, 1178 (S=O), 1131 (C=N). 1H NMR (400 MHz, CDCl3-d6, δ): 4.70 (2H, br, NH), 4.37 (2H, t, CH2N, J = 5.2 Hz), 3.90 (2H, t, CH2OMs, J = 5.6 Hz), 3.75 (4H, m, NCH2(CH2O), 3.64 (4H, m, MSOCH2(CH2O), 3.09 (3H, s, CH3). 13CNMR (100 MHz, CDCl3-d6, δ): 167.5 (C=O), 150.6 (C=N), 70.5, 70.2, 69.4, 68.9, 68.0 (SOCH2), 46.0 (NCH2), 37.7 (CH3). Anal. Calcd for C14H16N6O6S: C 33.02; H 5.23; S 19.59.


Figure 1. ORTEP diagram of macrocyle, 8b, showing the atom numbering scheme.

The NH2 at 13.64 and 3.84 ppm in the 1H spectrum, and at 160.0 and 36.6 ppm in the 13C NMR spectrum. The IR spectrum also showed the carbonyl group of the amide at 1653 cm⁻¹. FABHRMS clearly supported structure 8b (761.1414). Moreover, the structure of the macrocyle 8b was verified using X-ray crystallography. The crystallographic data and structure refinement parameters for 8b are summarized in Table 1. The selected bond distances and angles are summarized in Table 2. An ORTEP view including the atomic numbering scheme is depicted in Figure 1.
X-ray data of macrocycle (8b). X-ray intensity data were collected on a Bruker SMART APEX-II CCD diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). Structure was solved by applying the direct method using a SHELXS-97 and refined by a full-matrix least-squares calculation on F² using SHELXL-97. All non-hydrogen atoms were refined anisotropically. The amine H atoms, H7 and H15, were located in a difference map and refined freely. The other hydrogen atoms were placed in ideal positions and were riding on their respective carbon atoms (Biso = 1.2 Ueq).

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Center (Deposition No. CCDC-720138). The data can be obtained free of charge via www.ccdc.cam.ac.uk/deposit (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-01223 336033; E-mail: deposit@ccdc.cam.ac.uk).

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References