Synthesis and Characterization of an Eight-Membered Heterocyclic 1,3,5,7-Tetra(3-pyridyl)-1,3,5,7-tetrazacyclooctane

LI Li,a
Guo-Liang Dai,a
Xue Hua Zhu,a
Lei Yu,b
Hai Yan LiP

a School of Chemistry and Life Sciences, Suzhou University of Science and Technology, Suzhou 215009, Jiangsu, P. R. of China
b Soochow University Analysis and Testing Center, Jiangsu, P. R. of China

Corresponding Author
leeleaa@163.com

© 2023. The Author(s).

Received: 26.07.2023
Accepted after revision: 18.08.2023
Published online: 16.10.2023 (Version of Record)

License terms: (https://creativecommons.org/licenses/by/4.0/)

Abstract

N,N′-Bis(3-pyridyl)methanediamine was prepared by treating 3-aminopyridine with formaldehyde in acetonitrile. By treating it with formaldehyde, the eight-membered heterocyclic ring compound 1,3,5,7-tetra(3-pyridyl)-1,3,5,7-tetrazacyclooctane was prepared. This could occur in a two-step manner in a [3+1+3+1] cycloaddition reaction. The compounds were characterized by X-ray crystallography, 1H and 13C NMR spectroscopy, and mass spectrometry. The powder XRD pattern of 1,3,5,7-tetra(3-pyridyl)-1,3,5,7-tetrazacyclooctane was also determined and revealed an uncommon twist-crown conformation, which was further confirmed by DFT calculations.

Key words: N,N′-bis(3-pyridyl)methanediamine, 1,3,5,7-tetra(3-pyridyl)-1,3,5,7-tetrazacyclooctane, heterocycles, cyclooctanes, cycloaddition, twist-crown conformation, DFT calculations

Cyclooctane and its derivatives have been studied for decades. They have shown diverse conformations like boat–chair, crown, and boat–boat, among others. Eight-membered rings with the methylene groups replaced by oxygen, sulfur, or nitrogen moieties have received relatively little attention. There are three bidentate heterocyclic compounds containing two sulfur or nitrogen heteroatoms (1,5-di-oxadiazocine, 1,5-dithiazyclooctane, and 1,5-dithiacyclooctane-1-oxide) that have been employed as macrocyclic ligands. Kolar and Schendzielorz reported a few eight-membered heterocyclic compounds with alternate O and N atoms, namely 3,7-bis(4-trifluoromethylphenyl)-1,5,3,7-di-oxadiazocine and its derivatives, in 1985. Recently, two similar heterocyclic compounds, 3,7-bis(4-nitrophenyl)-1,5-dioxo-3,7-diazacyclooctane and 3,7-di(3-nitrophenyl)-1,5-dioxo-3,7-diazacyclooctane, have been prepared and characterized by X-ray structure determination. Two compounds with alternate S and N heteroatoms have been reported. One is 1,5-dithia-3,7-diazacyclooctane with a crown conformation, and the one is trans-5,10-bis-(methoxycarbonyl)-5,10-diphenyldipyrazolo[1,5-a:1’,5’-e]-[1,5]-diaz[3,6]dithiocine. Heterocyclic compounds with four nitrogen atoms have also been less reported; one is the energetic material 1,3,5,7-tetranitro-1,3,5,7-tetrazacyclooctane. Another one is 1,3,5,7-tetraphenyltetrazocine with a twist-chair conformation. We have previously designed and prepared the clamp-like eight-membered heterocyclic compound 3,7-di(3-pyridyl)-1,5-dioxo-3,7-diazacyclooctane (L). The two pyridyl groups in L are separated by a distorted heterococtane, which adopts a crown conformation and elicited our interest in these structures. During the synthesis of this compound, we unexpectedly obtained a 1,3,5,7-tetra(3-pyridyl)-1,3,5,7-tetrazacyclooctane by changing the reaction conditions. The molecule is centrosymmetric, being arranged around a crystallographic symmetry center. The eight-membered heterocyclic ring adopts a twist-crown conformation. The formation of the heterocyclooctane compound might occur in a two-step manner through a [3+1+3+1] cycloaddition reaction. Hence, we tried to prepare 2 in a two-step process, and the intermediate product N,N′-bis(3-pyridyl)methanediamine, which is related to two eight-membered heterocyclic compounds (Scheme 1), was isolated and characterized.

Single crystals with dimensions of 0.20 mm × 0.25 mm × 0.37 mm (1) and 0.16 mm × 0.18 mm × 0.20 mm (2) were mounted on glass fibers. Single-crystal X-ray diffraction measurements were performed on a Bruker APEX II 4K CCD area detector equipped with graphite monochromated Mo-Ka radiation (λ = 0.071073 nm) by using the ω-scan mode on all observed reflections between θ values of 2.42° to 25°.
All absorption corrections were applied by using the SADABS program. Structures were solved by direct methods and refined on $F^2$ by the full-matrix least-squares method with the SHELXTL-97 program package. All of the atoms were located from the e-maps, and hydrogen atoms were derived from the successive difference Fourier peaks. Crystallographic and structural refinement details for 1 and 2 are given in the Supporting Information.

Compound 1 crystallizes in the monoclinic space group $P_{2_1}/c$, and its asymmetric unit contains two $N,N'$-bis(3-pyridyl)methanediamine molecules. Compound 1 is Z-type in shape; the two pyridine rings are antiparallel (SI 1). Compound 2 crystallizes in the monoclinic space group $P_{2_1}/c$, and its asymmetric unit contains half of a 2 molecule. The pyridine rings are supported by an eight-membered ring in 2. The four pyridine ring are arranged mutually perpendicular in space (Figure 1). The $N_4C_4$ heterocyclic ring has a twist-crown conformation; the four symmetry-independent torsion angles are $C12–N1–C11–N3 = 110.70(12)^\circ$, $C11–N1–C12–N3A = –112.73(11)^\circ$, $C12A–N3–C11–N1 = –31.72(15)^\circ$, and $C11–N3–C12A–N1A = –36.28(15)^\circ$, respectively. These are different from those reported in 1,3,5,7-tetraphenyltetrazocine ($–38.5^\circ$, 113.8°, $–108.0^\circ$, 29.7°), which has a twist-chair conformation. This symmetry is often coincidental with a crystallographic symmetry element. Usually, as for cyclooctane, the most common and stable conformation is boat–chair, which minimizes transannular interactions and has a lower torsional strain. The predominant conformation at room temperature is boat–chair, with remaining compounds in the crown conformation. The $N$–$C$ bond lengths (1.3893(16) and 1.3877(15) Å) than those of 1.392(5) and 1.390(5) Å in 1,3,5,7-tetraphenyltetrazocine. There are intermolecular hydrogen bonds of C–H–N in compound 2; their bond lengths are 3.5629(19) and 3.5148(18) Å.

In the IR spectra, the bands at approximately 1585, 1563, and 1490 cm$^{-1}$ (1) and 1587, 1534, and 1478 cm$^{-1}$ (2) were assigned to the stretching vibrations of the pyridyl groups (SI 3). The strong peaks at around 3236 and 3156 cm$^{-1}$ (2) were attributed to the stretching vibrations of the N–H bonds. The peaks at 3035 and 2898 cm$^{-1}$ (1) and 3098 and 3037 cm$^{-1}$ (2) were attributed to the stretching vibrations of the CH$_2$ groups. The UV/visible spectra of compounds 1 and 2 were found to have similar absorption peaks (SI 6). The normalized peak heights were also equivalent to each other. Peaks at around 267 and 292 nm corresponded to $\pi–\pi^*$ and n–$\pi^*$ transitions of the pyridine ring.

The $^1$H NMR spectrum, with the integral ratio, of compound 1 in methanol-d$_4$ was correct and is shown in SI 4. We also recorded the $^1$H NMR and $^{13}$C NMR spectra of compound 2 (SI 5). The hydrogen spectrum in CDCl$_3$ shows a singlet for the CH$_2$ groups at 5.30 ppm and two multiplet peaks at 6.94–7.25 ppm and 7.95–8.43 ppm, with the correct integral ratios. However, in methanol-d$_4$, the singlet was at 4.87 ppm and the multiplet peaks were at 6.99–7.02, 7.31–7.34, 7.74–7.75, and 8.12–8.13 ppm with the correct

![Scheme 1 Preparation of compounds](image-url)
Integral ratios for the pyridine groups. The chemical shifts of the carbon spectrum were different to those for 3,7-di(3-pyridyl)-1,5-dioxo-3,7-diazacyclooctane (L) that we have previously studied.\textsuperscript{15} The $^{13}$C\(^{1}H\) NMR spectrum of 2 also exhibited signals for the five different carbon atoms of the pyridyl groups at 142.30, 140.36, 137.07, 124.74, and 123.68 ppm; the methylene group peak was at 83.26 ppm. In L, these values were 140.98, 139.76, 136.92, 123.00, and 121.52 ppm for the pyridyl groups and 82.66 ppm for the methylene group.

The positive-ion electron-impact mass spectra of 1 and 2 in methanol were measured. There are obvious molecular ion peaks in the spectra. Compound 1 has a peak at $m/z$ 201 for the molecular ion. Compound 2 displays a weak but distinct peak at $m/z$ 424 for the molecular ion, as shown in Figure 2. This is similar to that reported for 1,3,5,7-tetraphenyltetrazocine.\textsuperscript{14} The phase purity of the bulk product of complex 2 was further confirmed by elemental analysis and powder X-ray diffraction; the powder XRD patterns of the synthesized samples are consistent with those simulated from the respective single-crystal structures (SI 8).

For this study, we also used DFT calculations to confirm the possible structures for compound 2 obtained in the experiment. All possible geometries of the stable configurations were optimized at the B3LYP level of theory in combination with the 6-311++G** basis set.\textsuperscript{20,21} The nature of the stationary points was verified through a vibrational analysis (no imaginary frequencies). After optimization, we identified three stable configurations, and the spatial structures of these three compounds are shown in Figure 3. They are twist-crown (A), chair–chair (B), and twist-boat–boat(C) conformations. Table 1 lists the related energy data for these three configurations. The twist-crown conformation (A) represents the most stable conformation, followed by B, and the C conformation is the most unstable among them. This further proved the rationality of the previous structural tests. The calculated geometric parameters of this compound are also listed in Table 1. In Table 2, some available experimental values are listed for comparison. The theoretical values are well in agreement with the experimental findings, so the theoretical level chosen in this work is reliable for describing the features of compound 2. Selected (left) and calculated (right) bond lengths ($\text{Å}$) and bond angles ($^{\circ}$) for 2 are listed in Table 2.
Reactions of anilines with CH₂O are complex: they may form 1,4-diazacylobutanes, cyclic trimers, tetrazocines, 1,5-dioxo-3,7-diazacyclooctanes, other oligomers, or products from more complicated reactions. During the preparation of the eight-membered heterocyclic compound, there are two factors playing key roles. One is the ratio of the substrates, and the other is temperature. This can be seen from the synthesis of heterocyclic compounds with alternate O and N atoms. In our preliminary study, we prepared a 1,5-dioxa-3,7-diazacyclooctane by treating 3-aminopyridine with aqueous formaldehyde at ambient temperature. The 3,7-bis(4-X-aryl)-1,5,3,7-dioxadiazocines (X = CF₃, COOCH₃, CN, or NO₂) were produced below zero degrees; the 3,7-di(3-nitrophenyl)-1,5-dioxa-3,7-diazacyclooctane was prepared at room temperature, and the 3,7-bis(4-nitrophenyl)-1,5-dioxa-3,7-diazacyclooctane was synthesized at ambient temperature. Randaccio et al. reported a compound of 1,3,5,7-tetraphenyltetrazocine that might provide a way to build other similar heterocycles. Convenient solvothermal method in a two-step way. This method involved rapid addition of formaldehyde (in the form of solid, dry paraformaldehyde) to a refluxing concentrated solution of freshly distilled aniline. Herein, we have built the heterocyclooctane by treatment with 3-aminopyridine in a ratio of 1:4.

3-Aminopyridine was purchased from the Aldrich reagents company. Formaldehyde (in solid form) and acetonitrile were purchased from commercial sources and used as received without further purification. Melting points were recorded by using an electrothermal melting point apparatus. Carbon, hydrogen, and nitrogen analyses were carried out by direct combustion on an EA1110-CHNSO elemental analyzer. FT-IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer. Powder X-ray diffraction determination was performed using a Brucker AVANCE III 400MHz spectrometer by adopting atmospheric pressure chemical ionization mode. The samples were dissolved in the methanol before testing.

CDCC 855709 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

### Table 2

<table>
<thead>
<tr>
<th>Bond lengths</th>
<th>Selected (Left) and Calculated (Right) Bond Lengths (Å) and Bond Angles (°) for 2²</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₁–C₁</td>
<td>1.3889 (16) 1.3993</td>
</tr>
<tr>
<td>N₁–C₁₂</td>
<td>1.4457 (15) 1.4478</td>
</tr>
<tr>
<td>N₃–C₁₁</td>
<td>1.4651 (15) 1.4673</td>
</tr>
<tr>
<td>C₁₂–N₃A</td>
<td>1.4616 (15) 1.4643</td>
</tr>
<tr>
<td>C₁–C₅</td>
<td>1.4033 (18) 1.4120</td>
</tr>
<tr>
<td>C₆–C₁₀</td>
<td>1.3993 (18) 1.4069</td>
</tr>
<tr>
<td>Bond angles</td>
<td></td>
</tr>
<tr>
<td>C₁–N₁–C₁₁</td>
<td>121.10 (10) 120.77</td>
</tr>
<tr>
<td>C₁₁–N₁–C₁₂</td>
<td>117.54 (10) 118.14</td>
</tr>
<tr>
<td>C₆–N₃–C₁₁</td>
<td>120.01 (10) 120.25</td>
</tr>
<tr>
<td>N₁–C₁₁–N₃</td>
<td>113.37 (10) 114.18</td>
</tr>
</tbody>
</table>

* Symmetry code for 2: x, –y, –z.

---

L. Li et al. SynOpen 2023, 7, 486–490

THIEME OPEN ACCESS

Paper
maintained at that temperature for 10 h. After the sample had cooled to room temperature and was filtered, the desired product was afforded as white rectangular crystals. Compound 2 could also be prepared in 70% yield by treating 1 with formaldehyde in a ratio of 1:5.

White rectangular crystals; yield: 0.620 g (36%); mp 225 °C. FT-IR (KBr): 3430 (m), 3036 (w), 2898 (w), 1585 (vs), 1563 (s), 1490 (vs), 1438 (s), 1404 (m), 1377 (s), 1364 (s), 1351 (vs), 1302 (vs), 1275 (s), 1249 (s), 1189 (m), 1166 (s), 1133 (m), 1029 (m), 1008 (m), 970 (m), 937 (m), 798 (s), 777 (m), 709 (s), 617 (w), 536 (w), 518 (w), 458 (w).

1H NMR (400 MHz, CD 3OD): δ = 8.13 (d, J = 2.8 Hz, 4 H), 7.74 (dd, J = 1.2, 0.8 Hz, 4 H), 7.31–7.34 (dq, 4 H), 6.99–7.02 (q, 4 H), 4.87 (s, 8 H).

1H NMR (400 MHz, CDCl3): δ = 7.95–8.43 (m, 8 H), 6.94–7.25 (m, 8 H), 5.30 (s, 8 H).

13C{1H} NMR (400 MHz, CD 3OD): δ = 142.30, 140.36, 137.07, 124.74, 123.68, 83.26.


Conflict of Interest
The authors declare no conflict of interest.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0042-1751494.

References
(17) Brucker APEX2, SAINT, and SADABS; Brucker AXS Inc: Madison (WI), 2009.