

# Synthesis and Crystal Structure of the Hydrogen Bromide Salt of 1,4,7,10-Tetrakis(2-((4-methoxy)phenoxy)ethyl)-1,4,7,10-tetraazacyclododecane

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## Abstract

A novel molecule tetra-N-alkylation of cyclen (1,4,7,10-tetraazacyclododecane), 1,4,7,10-tetrakis(2-((4-methoxy)phenoxy)ethyl)-1,4,7,10-tetraazacyclododecane **1**, was synthesized and structurally characterized by the single-crystal X-ray diffraction. The crystals were obtained from ethanol by slow evaporation at room temperature and the four hydroquinone groups of the benzene ring formed a  $\pi$ -electron-rich cavity by C-H...Br stacking interaction. The crystal belongs to the orthorhombic system, space group Pbcn with  $a = 17.3174(15)$ ,  $b = 12.9891(11)$ ,  $c = 19.3379(17)$  Å,  $\alpha = \beta = \gamma = 90^\circ$ ,  $V = 4349.8(7)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.304$  g/cm<sup>3</sup>,  $C_{44}H_{61}BrN_4O_8$ ,  $Mr = 853.88$ ,  $F(000) = 1808$ ,  $\mu = 1.001$  mm<sup>-1</sup>, CuK $\alpha$  radiation ( $\lambda = 0.71073$ ),  $R = 0.0434$  and  $wR = 0.1091$  for 5200 observed reflections with  $I > 2\sigma(I)$ .

## Keywords

Synthesis, Crystal Structure, Cyclen Derivative

## 1. Introduction

With the high abilities in recognizing specific DNA sequence and catalyzing hydrolysis of phosphate diester bonds, chemical nucleases have rapidly become an invaluable research tool in the fields of biology, bioorganic chemistry, therapy, and molecular biology [1]-[6]. Many complexes have been designed and studied. In this used ligands, cyclen with four benzyl groups, can coordinate with most mental cations or negative ion. The successful application of several cyclen

derivative complexes for biomedical applications has stimulated interest for new cyclen-based ligands with different types of pendant arms in an attempt to find new ligands with different chemical, biological or catalytic properties [7] [8] [9] [10] [11]. Since armed cyclens have many structural and geometrical variations, they form a wide variety of metal complexes having specific sensing and signaling functions [12].

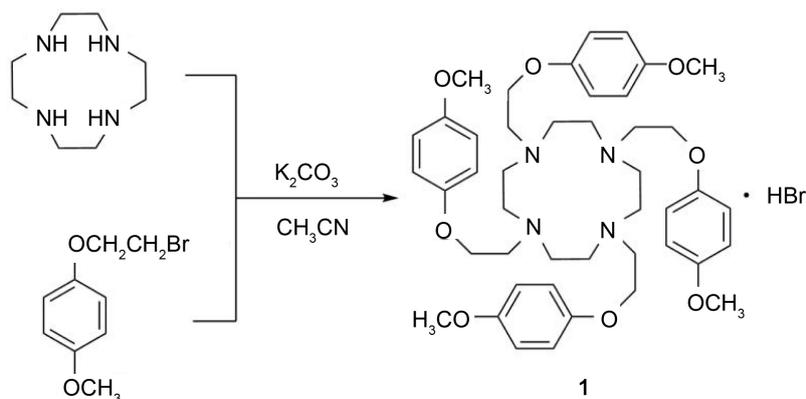
Recently, many cyclen derivatives with different types of pendant arms have been designed and reported, but only a few compounds bearing four benzyl groups. Smith C. B. and coworkers reported the preparation of the cyclen derivatives: (R)-thppc12 (L) and (S)-thph-pc12 (L'), including four benzyl or phenoxy-methyl groups, where benzyl or phoxymethyl groups project in the same direction due to the open nature of the electron-rich cavity [13]. If, in addition to bearing a donor atom, the pendant arms also have an aromatic moiety attached to them, the possibility arises of using the coordination of the ligand to a metal ion as a way of assembling a molecular receptor with a substantial cavity.

Encouraged by these considerations, we describe herein the synthesis of a new type of cyclen-base ligand with four neutral pendent groups at N residuals according to **Scheme 1**. Herein, X-ray crystal structure determination of compound 1 is undertaken to better understand the influence of structure modifications upon overall molecular geometry and conformation.

## 2. Experimental Section

### 2.1. Materials and Instruments

All chemicals were of reagent grade and used without further purification. All aqueous solutions were prepared from deionized or distilled water. Reaction and the resultant products were monitored by thin-layer chromatography (TLC) on Merck pre-coated silica gel F254 plates with separated compounds visualized at 254 nm under a UV lamp. Melting point (uncorrected) was determined on a XT4 MP: apparatus (Taikē Corp, Beijing, China). NMR was recorded in  $\text{CDCl}_3$  on a Varian Mercury 300 spectrometer and resonance was given in ppm ( $\delta$ ) relative to TMS.



**Scheme 1.** Synthetic route to compound 1.

## 2.2. Synthesis of the Title Compound (1)

Compound **1** was synthesized based on literature method (**Scheme 1**) [14]. To a solution of cyclen (0.2 g, 1.16 mmol), 1-(2-bromoethoxy)-4-methoxybenzene (1.34 g, 5.8 mmol) in 30 mL CH<sub>3</sub>CN was added K<sub>2</sub>CO<sub>3</sub> (0.83 g, 6.0 mmol). The resulting solution was heated under reflux and the progress of the reaction was monitored by TLC (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 7:1 silica gel). After disappearance of the starting material (ca. 8 h), the remaining solids were removed by filtration, and the filtrate was cooled to give compound **1**, white solid, yield: 89.5%. Melting point: 128°C - 129°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 6.79 - 6.69 (16H, dd, C<sub>6</sub>H<sub>4</sub>), 4.02 (8H, s, cyclen-CH<sub>2</sub>CH<sub>2</sub>O), 3.75 (12H, s, OCH<sub>3</sub>), 3.27 (8H, s, cyclen-CH<sub>2</sub>CH<sub>2</sub>O), 3.13 (16H, s, NCH<sub>2</sub>CH<sub>2</sub>N).

## 3. X-Ray Crystal Structure Determination

Crystallographic characteristics and X-ray-data collection and structure refinement parameters are presented in **Table 1**. Selected bond lengths are provided in **Table 2**. Selected bond angles are provided in **Table S1**. The crystal of **1** (0.2 mm ×

**Table 1.** Crystal data and structure refinement parameters of C<sub>44</sub>H<sub>61</sub>BrN<sub>4</sub>O<sub>8</sub> (**1**).

System, sp. gr., Z	Orthorhombic, Pbcn, 4
a, b, c Å	17.3174(15), 12.9891(11), 19.3379(17)
$\alpha, \beta, \gamma$ deg	90, 90, 90
V, Å <sup>3</sup>	4349.8(7)
D <sub>x</sub> g·cm <sup>-3</sup>	1.304
Radiation, $\lambda$ , Å	CuK $\alpha$ , 0.71073
$\mu$ , mm <sup>-1</sup>	1.001
T, K	293(2)
Sample size, mm	0.2 × 0.2 × 0.2
Diffractometer	Apex II
Scan mode	$\omega/\phi$
Absorption correction, T <sub>min</sub> , T <sub>max</sub>	Multi-scan, 0.819, 0.819
$\theta_{max}$ , deg	28.08
h, k, l ranges	-22 ≤ h ≤ 22, -16 ≤ k ≤ 6, -25 ≤ l ≤ 24
Number of reflections: measured/unique (N1), Rint/with I > 2 $\sigma$ (I) (N2)	24759/5200, 0.0434/2982
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Number of refined parameters	260
R1/wR2 relative to N1	0.0434/0.1091
R1/wR2 relative to N2	0.0771/0.1189
S	0.89
$\Delta\rho_{max}/\Delta\rho_{min}$ , e/Å <sup>3</sup>	0.624/-0.498
Program package	Sadabs [10], SHELXTL [11]

**Table 2.** Selected bond angles for C<sub>44</sub>H<sub>61</sub>BrN<sub>4</sub>O<sub>8</sub> (**1**).

Bond	d	Bond	d	Bond	d	Bond	d
O1-C7	1.377(2)	C7-C12	1.369(3)	C1-H1A	0.9700	C15-C20	1.372(3)
O1-C6	1.417(2)	C7-C8	1.374(3)	C1-H1B	0.9700	C16-C17	1.376(3)
O2-C10	1.367(2)	C8-C9	1.369(3)	C2-C3	1.508(3)	C16-H16A	0.9300
O2-C22	1.402(3)	C8-H8A	0.9300	C2-H2A	0.9700	C17-C18	1.378(3)
O3-C15	1.378(2)	C9-C10	1.381(3)	C2-H2B	0.9700	C17-H17A	0.9300
O3-C14	1.409(3)	C9-H9A	0.9300	C3-H3A	0.9700	C18-C19	1.364(3)
O4-C18	1.374(2)	C10-C11	1.367(3)	C3-H3B	0.9700	C19-C20	1.391(3)
O4-C21	1.409(3)	C11-C12	1.389(3)	C4-N2i	1.465(2)	C19-H19A	0.9300
N1-C2	1.475(2)	C11-H11A	0.9300	C4-H4A	0.9700	C20-H20A	0.9300
N1-C1	1.476(2)	C12-H12A	0.9300	C4-H4B	0.9700	C21-H21A	0.9600
N1-C5	1.478(3)	C13-C14	1.510(3)	C5-C6	1.501(3)	C21-H21B	0.9600
N1-H33	0.9178	C13-H13A	0.9700	C5-H5A	0.9700	C21-H21C	0.9600
N2-C3	1.448(3)	C13-H13B	0.9700	C5-H5B	0.9700	C22-H22A	0.9600
N2-C4 <sup>i</sup>	1.465(2)	C14-H14A	0.9700	C6-H6A	0.9700	C22-H22B	0.9600
N2-C13	1.467(2)	C14-H14B	0.9700	C6-H6B	0.9700	C22-H22C	0.9600

Symmetry transformations used to generate equivalent atoms:  $-x + 1, y, -z + 3/2$ .

0.2 mm × 0.2 mm) was selected for data collection which was performed on a Bruker Apex II CCD diffractometer equipped with a graphite-monochromatic CuK $\alpha$  radiation ( $\lambda = 0.71073$  nm) at 293(2) K. A total of 24,759 reflections were collected in the range of  $1.96 \leq \theta \leq 28.08^\circ$  ( $-22 \leq h \leq 22, -16 \leq k \leq 6$  and  $-25 \leq l \leq 24$ ), of which 24,759 were unique with  $R_{\text{int}} = 0.1233$  and 5200 were observed with  $I > 2\sigma(I)$ . Corrections for LP factors and semi-empirical absorption were applied based on Sadabs [15]. Unique data ( $R_{\text{int}} = 0.1233$ ) were used to solve the structure by direct methods with SHELXS-97 program [16]. Most non-hydrogen atoms were determined with an E-map and the others were located in successive difference Fourier syntheses. Then, the final refinement was carried out by full-matrix least-squares methods with anisotropic thermal parameters for the non-hydrogen atoms on  $F^2$ . The hydrogen atoms were located theoretically and refined with riding model position parameters and fixed isotropic thermal parameters. A full-matrix least-squares refinement gave the final  $R = 0.0434$ ,  $wR = 0.1091$  ( $w = 1/[\sigma^2(\text{Fo}^2) + (0.20P)^2 + 0.00P]$ , where  $P = (\text{Fo}^2 + 2\text{Fc}^2)/3$ ),  $S = 0.89$ ,  $(\Delta/\sigma)_{\text{max}} = 0.00$ ,  $(\Delta\rho)_{\text{max}} = 0.624$  and  $(\Delta\rho)_{\text{min}} = -0.498$  e/Å<sup>3</sup>. The CIF file containing complete information on the studied structure was deposited with CCDC, deposition number 1,403,270, and is freely available upon request from the following web site: [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), and also available from the authors.

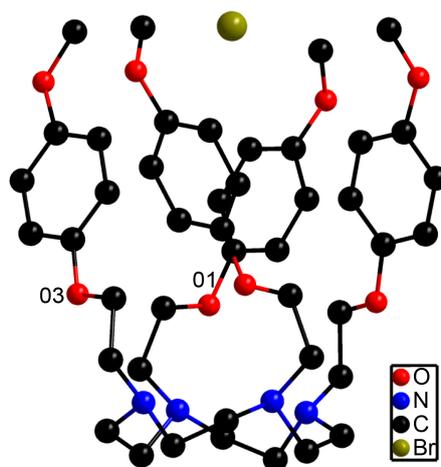
#### 4. Results and Discussion

We describe herein the structure of the title compound **1** which is stable in air at room temperature. It is soluble in methanol and ethanol at higher temperature

and soluble in  $\text{CH}_2\text{Cl}_2$  and  $\text{CHCl}_3$ . X-ray quality crystals of **1** were grown from ethanol by slow evaporation at room temperature for several days. The molecular structure of **1** crystallizes in orthorhombic space group Pbcn. Molecular structure of **1** is shown in **Figure 1**.

X-ray single-crystal structural analysis revealed that all the bond lengths and bond angles in the compound are within normal ranges and comparable to those corresponding in other similar compounds (**Table 2** and **Table S1**). As shown in **Figure 1**, the asymmetric unit of **1** contains one half of organic cation, because it is situated on twofold axis. All the four hydroquinone groups of the benzene ring deviate in the same direction. They converge to form the resemblance of a binding  $\pi$ -electron-rich cavity. The depth of the cavity measured from the plane of O(1) and O(3) to the uppermost aromatic oxygen atom is 5.7 Å. The diameter of the cavity, defined as the shortest separation between the ring centroids of the three phenyl rings, is calculated to be 4.5 Å. There is no evidence for  $\pi\cdots\pi$  interactions between the phenyl ring and another phenyl ring with their shortest separation larger than 4 Å. Similarly, Timothy S. R. *et al.* [17] also reported the defined boundaries of the  $\pi$ -electron-rich cavity *via* C-H $\cdots\pi$  stacking interactions, and commented on the cyclen derivatives, including four phenoxyethyl groups.

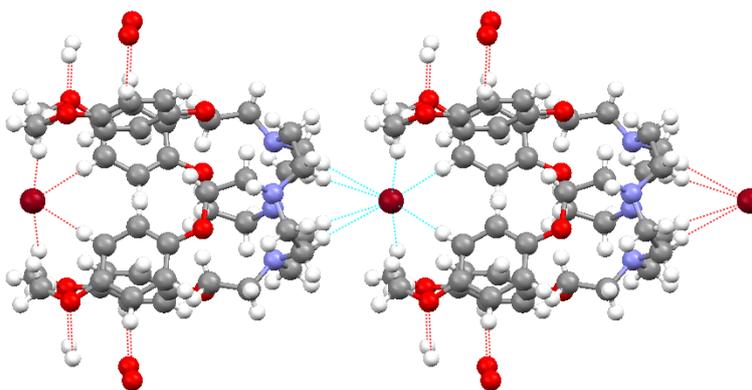
Hydrogen bonding interactions are usually important in the synthesis of supramolecular architecture [18]. In addition to the aromatic interactions, there are intermolecular C-H $\cdots$ O hydrogen bonding interactions between the C(9)-H(9A) and C(17)-H(17A) groups from benzyl groups carbon atoms (C(7) to C(12) and C(15) to C(20)) and O(2) and O(4) from methoxyl, resulting in an extended two-dimensional structure. But there are not intermolecular C-H $\cdots$ O hydrogen bonding interactions between (O(1) and O(3)) and benzyl groups carbon atoms (**Figure 2**). As shown in **Figure 2**, there are intramolecular C-H $\cdots$ Br hydrogen bonding interactions between the (C(2)-H(2A)), and



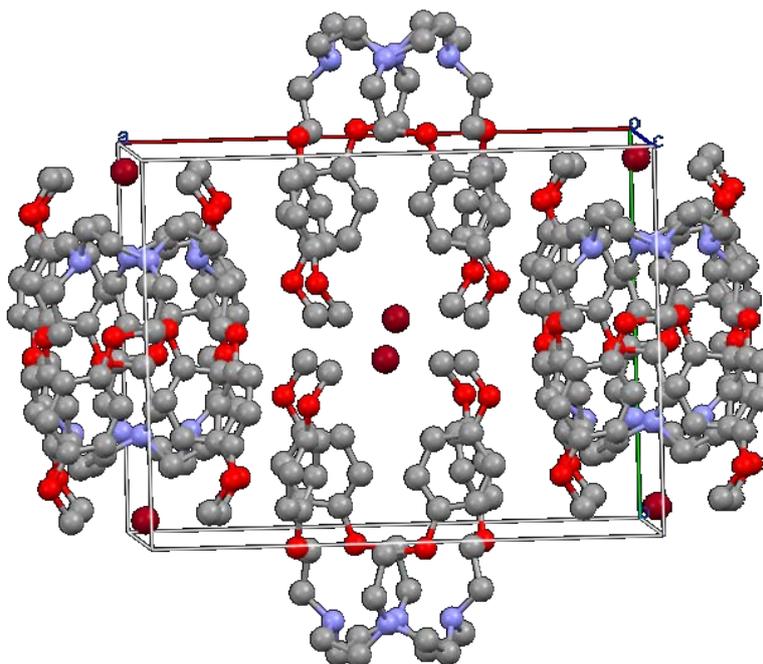
**Figure 1.** Molecular structure of **1**. All hydrogen atoms are omitted from the figure for clarity.

C(4)-H(4A)) from cyclen ring carbon atom (C(1) to C(8)) and (C(11)-H(11A) and C(21)-H(21A)) and Br(1). A three-dimensional structure is formed through these weak interactions among molecules. The molecules hydrogen bromides serve as the donor to carbon atoms, giving a total of crystallographically unique hydrogen bonds for **1**.

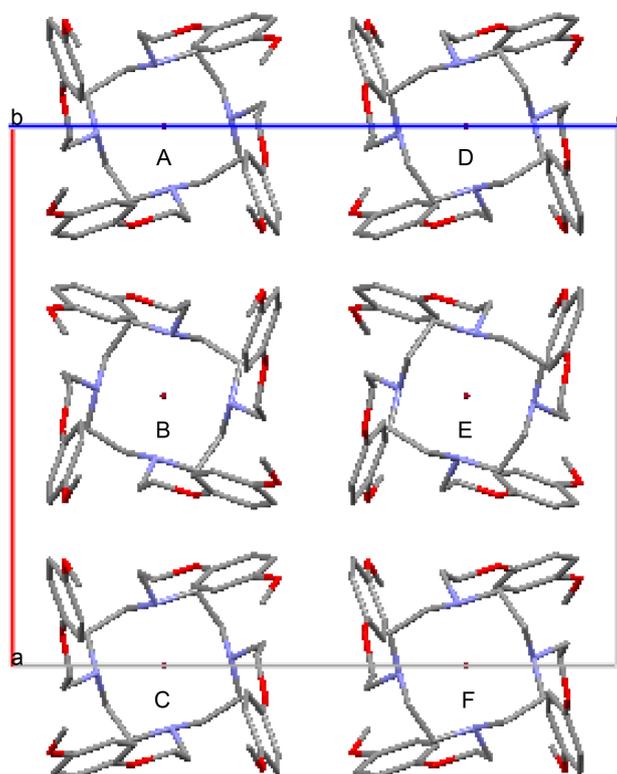
The packing diagram is shown in **Figure 3**, where four molecules exist in the unit cell. The four molecules have a centrosymmetric distribution with the centroid of the unit cell. This assignment is favorable to crystal packing. There are two enantiomorphism crystals in the crystal packing diagram of **1**. (A and D), (B and E) and (C and F) are mirror-related with each other (**Figure 4**).



**Figure 2.** Dimolecular graph of **1**. All hydrogen atoms are omitted for clarity. Intramolecular C-H...Br and C-H...O hydrogen bonds are shown as dashed lines.



**Figure 3.** Crystal packing diagram of **1**. Hydrogen atoms are omitted for clarity.



**Figure 4.** Crystal packing diagram of **1** in the unit cell along *b*.

## 5. Conclusion

In summary, this efficient one-step synthesis has yielded a novel molecule 1,4,7,10-tetrakis(2-((4-methoxy)phenoxy)ethyl)-1,4,7,10-tetraazacyclododecane **1**. The cyclen derivatives contain four hydroquinone units carrying ethylene chains. All the four hydroquinone groups form a  $\pi$ -electron-rich cavity. This cavity-like structure of cyclen derivatives is expected to present interesting properties. Indeed, the reported cyclen derivatives bearing four hydroquinone moieties may play a significant role towards the improvement in metal coordination or small molecule induced by the reinforced cycles, due to the formation of the cavity-like structure. However, this work is poor in coordinating with metal ion or small molecule. These features are currently underway.

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## Appendix

**Table S1.** Selected bond angles for C<sub>44</sub>H<sub>61</sub>BrN<sub>4</sub>O<sub>8</sub> (1).

C7—O1—C6	116.70(16)	C8—C9—C10	120.41(19)
C10—O2—C22	117.31(18)	C8—C9—H9A	119.800
C15—O3—C14	116.58(15)	C10—C9—H9A	119.800
C18—O4—C21	116.75(17)	C11—C10—O2	124.91(19)
C2—N1—C1	111.25(16)	C11—C10—C9	119.5(2)
C2—N1—C5	110.35(16)	O2—C10—C9	115.61(19)
C1—N1—C5	111.67(16)	C10—C11—C12	119.94(19)
C2—N1—H33	109.400	C10—C11—H11A	120.000
C1—N1—H33	100.600	C12—C11—H11A	120.000
C5—N1—H33	113.200	C7—C12—C11	120.29(18)
C3—N2—C4 <sup>i</sup>	111.30(16)	C7—C12—H12A	119.900
C3—N2—C13	112.46(17)	C11—C12—H12A	119.900
C4 <sup>i</sup> —N2—C13	110.85(16)	N2—C13—C14	113.04(18)
N1—C1—C4	113.15(16)	N2—C13—H13A	109.000
N1—C1—H1A	108.900	C14—C13—H13A	109.000
C4—C1—H1A	108.900	N2—C13—H13B	109.000
N1—C1—H1B	108.900	C14—C13—H13B	109.000
C4—C1—H1B	108.900	H13A—C13—H13B	107.800
H1A—C1—H1B	107.800	O3—C14—C13	109.86(19)
N1—C2—C3	112.38(17)	O3—C14—H14A	109.700
N1—C2—H2A	109.100	C13—C14—H14A	109.700
C3—C2—H2A	109.100	O3—C14—H14B	109.700
N1—C2—H2B	109.100	C13—C14—H14B	109.700
C3—C2—H2B	109.100	H14A—C14—H14B	108.200
H2A—C2—H2B	107.900	C16—C15—C20	119.48(18)
N2—C3—C2	113.48(16)	C16—C15—O3	116.04(17)
N2—C3—H3A	108.900	C20—C15—O3	124.47(18)
C2—C3—H3A	108.900	C15—C16—C17	120.64(18)
N2—C3—H3B	108.900	C15—C16—H16A	119.700
C2—C3—H3B	108.900	C17—C16—H16A	119.700
H3A—C3—H3B	107.700	C16—C17—C18	119.86(18)
N2 <sup>i</sup> —C4—C1	112.45(16)	C16—C17—H17A	120.100
N2 <sup>i</sup> —C4—H4A	109.100	C18—C17—H17A	120.100
C1—C4—H4A	109.100	C19—C18—O4	124.42(18)
N2 <sup>i</sup> —C4—H4B	109.100	C19—C18—C17	119.97(19)
C1—C4—H4B	109.100	O4—C18—C17	115.61(17)
H4A—C4—H4B	107.800	C18—C19—C20	119.82(18)
N1—C5—C6	113.9(2)	C18—C19—H19A	120.100
N1—C5—H5A	108.800	C20—C19—H19A	120.100

**Continued**

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C6—C5—H5A	108.800	C15—C20—C19	120.20(19)
N1—C5—H5B	108.800	C15—C20—H20A	119.900
C6—C5—H5B	108.800	C19—C20—H20A	119.900
H5A—C5—H5B	107.700	O4—C21—H21A	109.500
O1—C6—C5	109.71(19)	O4—C21—H21B	109.500
O1—C6—H6A	109.700	H21A—C21—H21B	109.500
C5—C6—H6A	109.700	O4—C21—H21C	109.500
O1—C6—H6B	109.700	H21A—C21—H21C	109.500
C5—C6—H6B	109.700	H21B—C21—H21C	109.500
H6A—C6—H6B	108.200	O2—C22—H22A	109.500
C12—C7—C8	119.56(18)	O2—C22—H22B	109.500
C12—C7—O1	125.43(18)	H22A—C22—H22B	109.500
C8—C7—O1	114.98(17)	O2—C22—H22C	109.500
C9—C8—C7	120.32(19)	H22A—C22—H22C	109.500
C9—C8—H8A	119.800	H22B—C22—H22C	109.500
C7—C8—H8A	119.800		

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