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(S)-(+)-Ketamine hydrochloride

Patrick Hakey, Wayne Ouellette,* Jon Zubieta and Timothy Korter

 Department of Chemistry, Syracuse University, Syracuse, New York 13244, USA
 Correspondence e-mail: wouellet@syr.edu

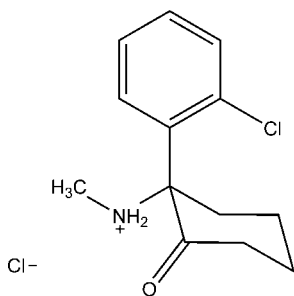
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 Key indicators: single-crystal X-ray study; $T = 90$ K; mean $\sigma(\text{C}-\text{C}) = 0.002$ Å; R factor = 0.028; wR factor = 0.066; data-to-parameter ratio = 14.6.

The crystal structure of the title compound {systematic name: (S)-(+)-N-[1-(2-chlorophenyl)-2-oxocyclohexyl]methanaminium chloride}, $\text{C}_{13}\text{H}_{17}\text{ClNO}^+\cdot\text{Cl}^-$, was determined at 90 (2) K. The (S)-(+)-ketamine hydrochloride salt is a well known anesthetic compound and is dramatically more potent than its *R* isomer. In the title compound, the cyclohexanone ring adopts a chair conformation with the oxo group in the equatorial orientation. The methylamino and 2-chlorophenyl groups at the 2-position have an equatorial and an axial orientation, respectively. The packing of ions is stabilized by an infinite one-dimensional $\cdots\text{Cl}\cdots\text{H}-\text{N}-\text{H}\cdots\text{Cl}\cdots$ hydrogen-bonding network, involving NH_2^+ groups as donors and chloride anions as acceptors.

Related literature

For related literature, see: Chankvetadze *et al.* (2002); Domino *et al.* (1965); Marhofer *et al.* (2001); Mathisen *et al.* (1995); Pees *et al.* (2003); Reich & Silvy (1989); Smirnova *et al.* (1989); White *et al.* (1985); Wolff & Winstock (2006).



Experimental

Crystal data

 $\text{C}_{13}\text{H}_{17}\text{ClNO}^+\cdot\text{Cl}^-$
 $M_r = 274.18$
 Monoclinic, $P2_1$
 $a = 8.4338$ (4) Å
 $b = 7.0715$ (4) Å

 $c = 11.3524$ (6) Å
 $\beta = 101.875$ (1)°
 $V = 662.56$ (6) Å³
 $Z = 2$
 Mo $K\alpha$ radiation

 $\mu = 0.47$ mm⁻¹
 $T = 90$ (2) K

 $0.50 \times 0.12 \times 0.10$ mm

Data collection

 Bruker APEX CCD area-detector diffractometer
 Absorption correction: multi-scan (SADABS; Sheldrick, 2008)
 $T_{\min} = 0.798$, $T_{\max} = 0.954$

 6985 measured reflections
 3251 independent reflections
 3146 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.020$

Refinement

 $R[F^2 > 2\sigma(F^2)] = 0.027$
 $wR(F^2) = 0.066$
 $S = 1.07$
 3251 reflections
 223 parameters
 1 restraint

 All H-atom parameters refined
 $\Delta\rho_{\text{max}} = 0.30$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.17$ e Å⁻³
 Absolute structure: Flack (1983),
 1472 Friedel pairs
 Flack parameter: 0.00 (5)

Table 1

Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$\text{N1}-\text{H1A}\cdots\text{Cl2}^{\ddagger}$	0.83 (3)	2.39 (3)	3.1359 (15)	151 (2)
$\text{N1}-\text{H1B}\cdots\text{Cl2}$	0.869 (19)	2.278 (19)	3.1065 (13)	159.4 (17)

 Symmetry code: (i) $-x, y - \frac{1}{2}, -z + 1$.

Data collection: SMART (Bruker, 2002); cell refinement: SAINT (Bruker, 2002); data reduction: SAINT; program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: CrystalMaker (Palmer, 2006); software used to prepare material for publication: SHELXTL (Sheldrick, 2008).

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: BH2181).

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supporting information

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S1. Comment

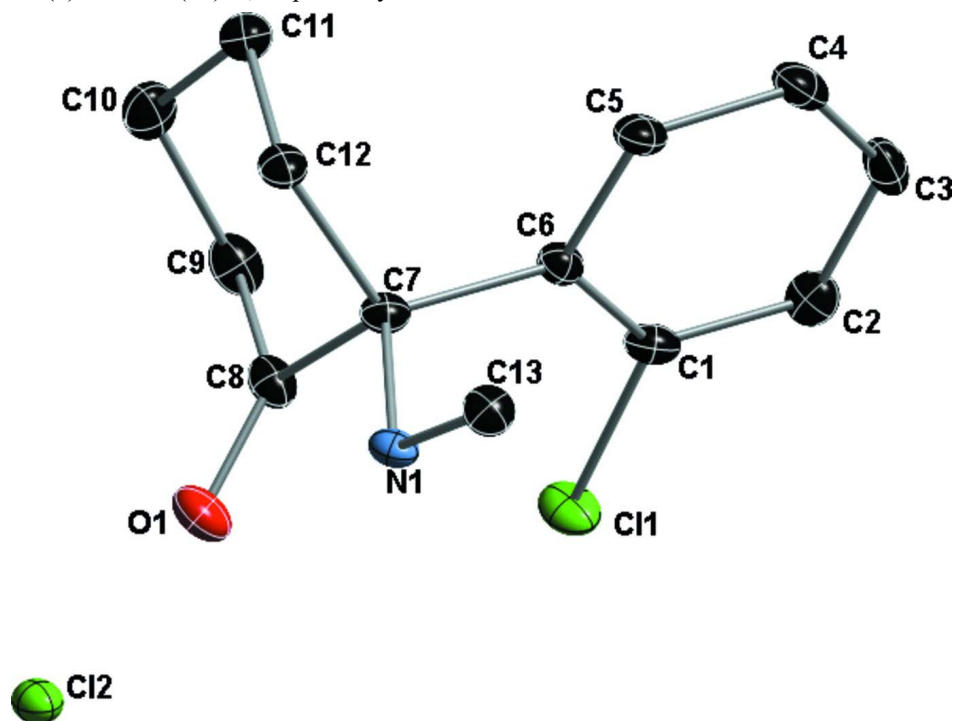
The title compound, (S)-(+)-ketamine hydrochloride, has been investigated by single-crystal X-ray diffraction at 90 (2) K (Fig. 1 and 2). The use of ketamine has been shown to lead to a state of dissociative anesthesia (Domino *et al.*, 1965). This study focuses on the *S* isomer of the well known anesthetic compound ketamine hydrochloride because it is dramatically more potent than its *R* isomer (White *et al.*, 1985). The pure *S* isomer is available commercially as Ketanest S™, while the racemic mixture, containing both *S* and *R* isomers is available under many names, including: Ketalar™, Ketanest™, and Ketaject™ (Marhofer *et al.*, 2001; Wolff & Winstock, 2006). Both the *S* and *R* isomers of neutral ketamine have been structurally characterized by X-ray diffraction in an earlier investigation (Chankvetadze *et al.*, 2002). The compound is listed as a Schedule III controlled substance by the Federal government of the United States (Wolff & Winstock, 2006). Ketamine hydrochloride was first investigated in the 1960's and is a derivative of the more dangerous psychotomimetic drug, Phencyclidine (Domino *et al.*, 1965). The chirality of Ketamine can be attributed to the C2 position, located on the cyclohexanone ring (Reich & Silvay, 1989). The potency of the drug is dependent upon its conformation, with the *S* isomer displaying analgesic effects roughly 4 times greater than those displayed by the levorotatory enantiomer *R*-(-)-Ketamine in controlling the pain of postoperative patients (Mathisen *et al.*, 1995). In comparison to the racemic mixture, the *S*-isomer produces analgesic and anesthetic effects with twice the potency of the racemic (White *et al.*, 1985). Increased potency enables the use of a much lower dosage while still producing the required effect, in turn leading to a quicker recovery time from the anesthesia (Pees *et al.*, 2003). The potential advantages of the *S* isomer over the racemic mixture have led to an increase in clinical use of the enantiomerically pure compound, particularly in Europe (Marhofer *et al.*, 2001). The potency, the increasing clinical usage, and the strong potential for abuse of (S)-(+)-Ketamine hydrochloride, provide a need for the complete characterization of this molecule, and its previously unpublished crystal structure. An unequivocal understanding of the solid-state crystal structure of the compound is a necessity for detection and identification methods such as THz vibrational spectroscopy, or solid-state NMR, among others. This study has determined that the compound crystallizes in the monoclinic space group *P*2₁, with a unit cell volume of 662.56 (6) Å³ at 90 K, and *Z* value 2. The complete atomic coordinates have also been determined.

S2. Experimental

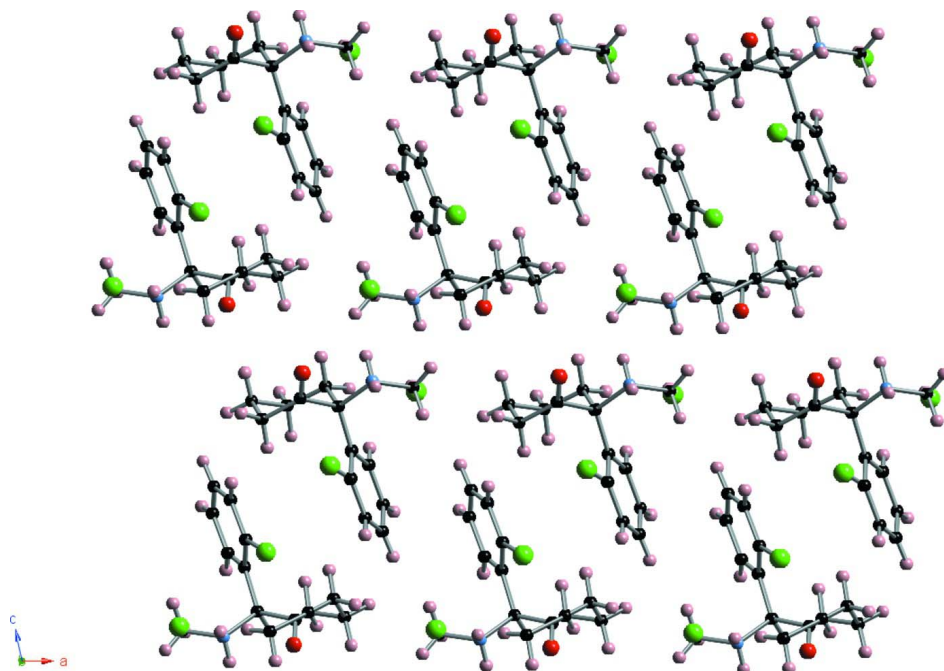
All material used for this work was purchased from Sigma-Aldrich (minimum 99% pure) and used without further purification. The absolute configuration of the enantiomer was verified by measuring the optical rotation of the material using a Jasco DIP-1000 digital polarimeter. The absolute configuration determined from anomalous dispersion-effects is consistent with the expected enantiomer.

S3. Refinement

H atoms were located in a difference map and refined freely. The C—H and N—H bond lengths range from 0.91 (2) to 1.014 (17) and 0.83 (3) to 0.869 (18) Å, respectively.

**Figure 1**

Perspective view of the title salt, with the atom numbering scheme and thermal ellipsoids drawn at 50% probability level. H atoms have been omitted for clarity

**Figure 2**

The crystal packing of the title compound viewed along the *b* axis.

(S)-(+)-N-[1-(2-chlorophenyl)-2-oxocyclohexyl]methanaminium chloride

Crystal data

$C_{13}H_{17}ClNO \cdot Cl$

$M_r = 274.18$

Monoclinic, $P2_1$

Hall symbol: P 2yb

$a = 8.4338 (4) \text{ \AA}$

$b = 7.0715 (4) \text{ \AA}$

$c = 11.3524 (6) \text{ \AA}$

$\beta = 101.875 (1)^\circ$

$V = 662.56 (6) \text{ \AA}^3$

$Z = 2$

$F(000) = 288$

$D_x = 1.374 \text{ Mg m}^{-3}$

Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$

Cell parameters from 3471 reflections

$\theta = 2.5\text{--}28.2^\circ$

$\mu = 0.47 \text{ mm}^{-1}$

$T = 90 \text{ K}$

Rod, colourless

$0.50 \times 0.12 \times 0.10 \text{ mm}$

Data collection

Bruker APEX CCD area-detector
diffractometer

Radiation source: fine-focus sealed tube

Graphite monochromator

Detector resolution: $512 \text{ pixels mm}^{-1}$

φ and ω scans

Absorption correction: multi-scan

(*SADABS*; Sheldrick, 2008)

$T_{\min} = 0.798$, $T_{\max} = 0.954$

6985 measured reflections

3251 independent reflections

3146 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.020$

$\theta_{\max} = 28.3^\circ$, $\theta_{\min} = 1.8^\circ$

$h = -11 \rightarrow 11$

$k = -9 \rightarrow 9$

$l = -15 \rightarrow 15$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.027$

$wR(F^2) = 0.066$

$S = 1.07$

3251 reflections

223 parameters

1 restraint

0 constraints

Primary atom site location: structure-invariant
direct methods

Secondary atom site location: difference Fourier
map

Hydrogen site location: inferred from
neighbouring sites

All H-atom parameters refined

$w = 1/[\sigma^2(F_o^2) + (0.0378P)^2 + 0.0273P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} = 0.001$

$\Delta\rho_{\max} = 0.31 \text{ e } \text{\AA}^{-3}$

$\Delta\rho_{\min} = -0.17 \text{ e } \text{\AA}^{-3}$

Absolute structure: Flack (1983), 1472 Friedel
pairs

Absolute structure parameter: 0.00 (5)

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
Cl2	0.05227 (4)	0.23769 (5)	0.35081 (3)	0.01627 (9)
Cl1	0.34238 (5)	-0.13679 (5)	0.87212 (4)	0.02248 (10)
O1	0.38001 (14)	-0.03746 (17)	0.60012 (10)	0.0205 (2)
N1	0.11098 (16)	0.1291 (2)	0.62148 (11)	0.0132 (3)
C1	0.27185 (19)	0.0822 (2)	0.90899 (14)	0.0157 (3)
C2	0.2437 (2)	0.0998 (3)	1.02456 (15)	0.0212 (3)
C3	0.1889 (2)	0.2691 (3)	1.06202 (16)	0.0239 (4)
C4	0.1635 (2)	0.4199 (3)	0.98344 (15)	0.0218 (4)
C5	0.19088 (19)	0.4012 (2)	0.86757 (15)	0.0175 (3)
C6	0.24628 (16)	0.2315 (3)	0.82673 (13)	0.0140 (3)
C7	0.26395 (16)	0.2136 (2)	0.69555 (12)	0.0124 (3)
C8	0.40443 (19)	0.0878 (2)	0.67428 (13)	0.0155 (3)
C9	0.57016 (19)	0.1543 (2)	0.73576 (15)	0.0176 (3)
C10	0.59821 (19)	0.3492 (3)	0.68330 (14)	0.0175 (3)
C11	0.46277 (19)	0.4860 (2)	0.69619 (15)	0.0166 (3)
C12	0.29711 (19)	0.4052 (2)	0.63815 (14)	0.0142 (3)
C13	-0.04410 (18)	0.2160 (3)	0.63712 (14)	0.0170 (3)
H11B	0.471 (2)	0.511 (3)	0.7848 (19)	0.024 (5)*
H12A	0.294 (2)	0.378 (3)	0.5499 (16)	0.014 (4)*
H13A	-0.060 (2)	0.181 (3)	0.7166 (17)	0.015 (5)*
H10B	0.603 (2)	0.334 (3)	0.6003 (17)	0.016 (5)*
H9A	0.649 (2)	0.055 (3)	0.7199 (18)	0.024 (5)*
H1B	0.116 (2)	0.140 (3)	0.5461 (17)	0.008 (4)*
H10A	0.703 (3)	0.397 (3)	0.7211 (17)	0.021 (5)*
H13B	-0.126 (2)	0.167 (3)	0.5775 (18)	0.021 (5)*
H9B	0.574 (2)	0.167 (3)	0.8215 (18)	0.018 (5)*
H5	0.174 (2)	0.503 (3)	0.8174 (19)	0.023 (5)*
H12B	0.209 (2)	0.490 (3)	0.6419 (16)	0.018 (5)*
H3	0.166 (2)	0.278 (3)	1.1373 (19)	0.026 (6)*
H2	0.259 (2)	-0.003 (3)	1.0735 (17)	0.015 (5)*
H4	0.128 (2)	0.542 (3)	1.0038 (18)	0.022 (5)*
H13C	-0.038 (2)	0.351 (3)	0.6318 (16)	0.018 (5)*

H1A	0.105 (3)	0.015 (4)	0.6352 (18)	0.024 (5)*
H11A	0.483 (3)	0.601 (4)	0.6570 (18)	0.029 (6)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C12	0.02035 (17)	0.01438 (16)	0.01376 (16)	0.00042 (14)	0.00279 (12)	-0.00059 (13)
C11	0.0302 (2)	0.01408 (17)	0.02266 (19)	0.00260 (16)	0.00414 (15)	0.00452 (14)
O1	0.0253 (6)	0.0180 (6)	0.0188 (6)	0.0042 (5)	0.0059 (5)	-0.0035 (5)
N1	0.0159 (6)	0.0117 (6)	0.0117 (6)	0.0003 (5)	0.0019 (5)	-0.0008 (5)
C1	0.0155 (7)	0.0150 (7)	0.0163 (7)	-0.0006 (6)	0.0020 (6)	0.0008 (6)
C2	0.0197 (8)	0.0285 (9)	0.0145 (7)	-0.0054 (7)	0.0016 (6)	0.0048 (7)
C3	0.0211 (8)	0.0358 (11)	0.0159 (8)	-0.0058 (7)	0.0064 (6)	-0.0049 (7)
C4	0.0192 (8)	0.0261 (9)	0.0203 (8)	-0.0013 (6)	0.0048 (6)	-0.0092 (7)
C5	0.0170 (7)	0.0169 (8)	0.0180 (7)	0.0013 (6)	0.0022 (6)	-0.0013 (6)
C6	0.0129 (6)	0.0164 (7)	0.0126 (6)	-0.0008 (6)	0.0026 (5)	-0.0003 (6)
C7	0.0130 (6)	0.0126 (7)	0.0113 (6)	0.0003 (6)	0.0015 (5)	0.0006 (6)
C8	0.0192 (8)	0.0145 (7)	0.0135 (7)	0.0044 (6)	0.0053 (6)	0.0035 (6)
C9	0.0148 (7)	0.0197 (8)	0.0183 (8)	0.0046 (6)	0.0038 (6)	0.0024 (6)
C10	0.0159 (7)	0.0200 (8)	0.0171 (7)	-0.0001 (6)	0.0044 (6)	0.0002 (6)
C11	0.0171 (7)	0.0143 (7)	0.0186 (8)	-0.0001 (6)	0.0042 (6)	0.0012 (6)
C12	0.0153 (7)	0.0127 (7)	0.0146 (7)	0.0003 (5)	0.0028 (5)	0.0013 (5)
C13	0.0149 (7)	0.0163 (8)	0.0197 (7)	-0.0001 (6)	0.0033 (5)	-0.0022 (7)

Geometric parameters (Å, °)

C11—C1	1.7403 (16)	C7—C8	1.540 (2)
O1—C8	1.210 (2)	C7—C12	1.553 (2)
N1—C13	1.488 (2)	C8—C9	1.503 (2)
N1—C7	1.5108 (19)	C9—C10	1.539 (2)
N1—H1B	0.869 (18)	C9—H9A	1.01 (2)
N1—H1A	0.83 (3)	C9—H9B	0.97 (2)
C1—C2	1.386 (2)	C10—C11	1.527 (2)
C1—C6	1.397 (2)	C10—H10B	0.957 (18)
C2—C3	1.382 (3)	C10—H10A	0.96 (2)
C2—H2	0.91 (2)	C11—C12	1.528 (2)
C3—C4	1.378 (3)	C11—H11B	1.01 (2)
C3—H3	0.92 (2)	C11—H11A	0.96 (2)
C4—C5	1.388 (2)	C12—H12A	1.014 (17)
C4—H4	0.96 (2)	C12—H12B	0.96 (2)
C5—C6	1.401 (2)	C13—H13A	0.971 (19)
C5—H5	0.91 (2)	C13—H13B	0.93 (2)
C6—C7	1.5321 (19)	C13—H13C	0.96 (2)
C13—N1—C7	116.17 (12)	C9—C8—C7	114.74 (13)
C13—N1—H1B	107.8 (12)	C8—C9—C10	107.60 (13)
C7—N1—H1B	107.7 (12)	C8—C9—H9A	106.5 (12)
C13—N1—H1A	106.8 (15)	C10—C9—H9A	113.3 (12)

C7—N1—H1A	111.3 (15)	C8—C9—H9B	109.6 (12)
H1B—N1—H1A	106.7 (19)	C10—C9—H9B	109.0 (12)
C2—C1—C6	122.11 (15)	H9A—C9—H9B	110.8 (16)
C2—C1—C11	116.19 (13)	C11—C10—C9	110.66 (13)
C6—C1—C11	121.69 (12)	C11—C10—H10B	110.3 (11)
C3—C2—C1	120.18 (16)	C9—C10—H10B	108.8 (12)
C3—C2—H2	121.6 (12)	C11—C10—H10A	111.8 (13)
C1—C2—H2	118.2 (12)	C9—C10—H10A	110.1 (13)
C4—C3—C2	119.23 (15)	H10B—C10—H10A	105.0 (16)
C4—C3—H3	121.0 (14)	C10—C11—C12	110.94 (14)
C2—C3—H3	119.7 (14)	C10—C11—H11B	108.0 (12)
C3—C4—C5	120.40 (16)	C12—C11—H11B	111.3 (12)
C3—C4—H4	123.7 (13)	C10—C11—H11A	106.8 (14)
C5—C4—H4	115.9 (13)	C12—C11—H11A	110.4 (13)
C4—C5—C6	121.81 (16)	H11B—C11—H11A	109.3 (17)
C4—C5—H5	118.8 (13)	C11—C12—C7	111.90 (12)
C6—C5—H5	119.4 (13)	C11—C12—H12A	109.5 (10)
C1—C6—C5	116.27 (13)	C7—C12—H12A	106.2 (12)
C1—C6—C7	123.69 (15)	C11—C12—H12B	113.2 (13)
C5—C6—C7	119.89 (14)	C7—C12—H12B	108.5 (12)
N1—C7—C6	109.33 (11)	H12A—C12—H12B	107.2 (15)
N1—C7—C8	106.29 (12)	N1—C13—H13A	107.3 (11)
C6—C7—C8	115.60 (12)	N1—C13—H13B	107.4 (12)
N1—C7—C12	108.57 (11)	H13A—C13—H13B	111.0 (17)
C6—C7—C12	113.44 (13)	N1—C13—H13C	110.3 (11)
C8—C7—C12	103.13 (11)	H13A—C13—H13C	109.3 (16)
O1—C8—C9	124.09 (15)	H13B—C13—H13C	111.5 (17)
O1—C8—C7	120.38 (14)		
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C6—C1—C2—C3	-0.2 (2)	C5—C6—C7—C8	146.41 (14)
C11—C1—C2—C3	179.44 (13)	C1—C6—C7—C12	-157.03 (14)
C1—C2—C3—C4	-0.3 (3)	C5—C6—C7—C12	27.58 (18)
C2—C3—C4—C5	0.7 (3)	N1—C7—C8—O1	6.73 (18)
C3—C4—C5—C6	-0.7 (3)	C6—C7—C8—O1	128.23 (15)
C2—C1—C6—C5	0.2 (2)	C12—C7—C8—O1	-107.40 (16)
C11—C1—C6—C5	-179.37 (11)	N1—C7—C8—C9	177.01 (12)
C2—C1—C6—C7	-175.34 (14)	C6—C7—C8—C9	-61.50 (17)
C11—C1—C6—C7	5.1 (2)	C12—C7—C8—C9	62.88 (15)
C4—C5—C6—C1	0.2 (2)	O1—C8—C9—C10	107.30 (17)
C4—C5—C6—C7	175.93 (14)	C7—C8—C9—C10	-62.57 (16)
C13—N1—C7—C6	48.63 (18)	C8—C9—C10—C11	55.38 (17)
C13—N1—C7—C8	174.05 (13)	C9—C10—C11—C12	-55.57 (17)
C13—N1—C7—C12	-75.59 (16)	C10—C11—C12—C7	59.27 (17)
C1—C6—C7—N1	81.64 (16)	N1—C7—C12—C11	-171.44 (12)
C5—C6—C7—N1	-93.75 (17)	C6—C7—C12—C11	66.81 (16)
C1—C6—C7—C8	-38.2 (2)	C8—C7—C12—C11	-58.97 (15)

Hydrogen-bond geometry (Å, °)

<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
N1—H1A \cdots Cl2 ⁱ	0.83 (3)	2.39 (3)	3.1359 (15)	151 (2)
N1—H1B \cdots Cl2	0.869 (19)	2.278 (19)	3.1065 (13)	159.4 (17)

Symmetry code: (i) $-x, y-1/2, -z+1$.