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The 7-azanorbornane nucleus of epibatidine: 7-azabicyclo[2.2.1]heptan-7-ium chloride

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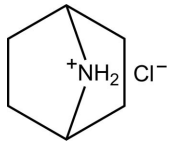
7-Azabicyclo[2.2.1]heptane (7-azanorbornane) is a bridged heterocyclic nucleus found in epibatidine, the alkaloid isolated from the skin of the tropical poison frog *Epipedobates tricolor*. Since epibatidine is known as one of the most potent acetylcholine nicotinic receptor agonists, a plethora of literature has been devoted to this alkaloid. However, there are no structural data on the unsubstituted 7-azanorbornane, the parent bicyclic ring of epibatidine and its derivatives. We herein present the structural characterization of the 7-azabicyclo[2.2.1]heptane parent ring as its hydrochloride salt, namely 7-azabicyclo[2.2.1]heptan-7-ium chloride, $C_6H_{12}N^+\cdot Cl^-$. The compete cation is generated by a crystallographic mirror plane with the N atom lying on the mirror, as does the chloride anion. In the crystal, the cations are linked to the anions by N—H···Cl hydrogen bonds, which generate [001] chains.

1. Chemical context

Since the discovery of the quinuclidine and tropane nuclei (Hamama *et al.*, 2006; Pollini *et al.*, 2006), elegant frameworks of bridged aza-heterocycles have been the focus of chemists exploring biologically active substances. One famous example in this series is epibatidine, (−)-2-(6-chloropyridin-3-yl)-7-azabicyclo[2.2.1]heptane, an active component of the skin poison extracted from the small tropical frog *Epipedobates tricolor* (Spande *et al.*, 1992; Gerzanich *et al.*, 1995; Sullivan & Bannon, 1996; Dukat & Glennon, 2003). Epibatidine comprises the first natural example of a compound incorporating an 7-azabicyclo[2.2.1]heptane (7-azanorbornane) ring system (Fletcher *et al.*, 1994). Due to the extreme binding affinity of the *exo* isomer of epibatidine towards nicotinic acetylcholine receptors, thousands of articles have been devoted to different aspects of its chemistry and biochemistry (see Carroll, 2004; Daly *et al.*, 2005; Yogeeswari *et al.*, 2006; Garraffo *et al.*, 2009). We are not aware, however, that an X-ray structure determination of the alkaloid itself has ever been reported, in spite of numerous publications related to its



synthesis. Moreover, the molecular structure of 7-azanorbornane, the functional core of epibatidine, has also not been explored, in spite of the fact that 7-azanorbornane has been known since 1930 (Braun & Schwarz, 1930; Fraser & Swingle, 1970). In continuation of our studies related to bridged aza-heterocyclic systems (Britvin *et al.*, 2015, 2016,

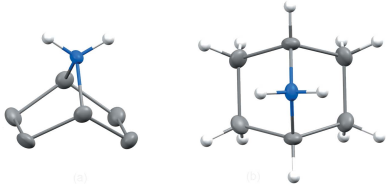


Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N7—H7B···Cl1^{i}	0.88 (3)	2.25 (3)	3.127 (2)	175 (2)
N7—H7A···Cl1	0.87 (4)	2.25 (4)	3.122 (2)	178 (3)

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

2017), we herein report on the structure of the unsubstituted 7-azabicyclo[2.2.1]heptane parent ring as its hydrochloride salt, namely 7-azabicyclo[2.2.1]heptan-7-ium chloride, **1**.

2. Structural commentary

The parent ring of 7-azabicyclo[2.2.1]heptane in **1** adopts a boat conformation (Fig. 1) resembling the molecular geometry of its nearest carbocyclic counterpart, bicyclo[2.2.1]heptane (norbornane), **2** (Fitch & Jobic, 1993). In order to achieve consistency of atomic labelling between the bicyclic cages of **1** and **2**, we herein apply the numbering scheme according to IUPAC nomenclature (Fig. 1) (Doms *et al.*, 1985). There are three unique C atoms (C1, C2 and C6) in the cation of **1**, with their clones C1^{i} [= C4 by IUPAC; symmetry code: (i) $1-x, y, z$], C2^{i} (= C3 by IUPAC) and C6^{i} (= C5 by IUPAC) generated by the mirror at $x = \frac{1}{2}$. Interatomic distances between the respective framework sites of **1** are shorter compared with the corresponding values of **2**. The distances (Å) in **1** and **2** are: C1—C2 = 1.528 (2) and 1.551 (3), C1—C6 = 1.523 (3) and 1.578 (1), and C1—N7(C7) = 1.508 (2) and 1.551 (3). The C2^{i}—C2—C1—C6 torsion angle determining the boat-like conformation is 109.4 (1)° in **1** and 108.7 (2)° in **2**. The s.u. values for **2** were generated using *PLATON* (Spek, 2009). Further details of the interatomic distances and angles of **1** can be found in the supporting information.

3. Supramolecular features

The structural integrity of **1** is maintained *via* intermolecular hydrogen bonding between the protonated secondary site N7 and the chloride counter-ion Cl1 (Table 1). Each chloride ion is linked to the two adjacent amine centres *via* N—H···Cl hydrogen bonds so that the 7-azanorbornane cages are arranged into zigzag chains flattened on (010) and propagating along the *c*-axis direction (Fig. 2). That type of interleaved zigzag packing is known among chloride salts of secondary amines, both for alkyl- and arylamines (Adams *et al.*, 1997; Nancy *et al.*, 2003; Muller *et al.*, 2007) and heterocyclic systems (Gribkov *et al.*, 2006; Wang *et al.*, 2011; Fun *et al.*, 2011).

4. Database survey

Of more than 120 structures containing the 7-azanorbornane ring system in the Cambridge Structural Database (CSD, Version 5.38, latest update May 2017; Groom *et al.*, 2016), 17 entries represent the 7-azabicyclo[2.2.1]heptane parent ring unsubstituted at the carbon sites. All these compounds belong to *N*-substituted derivatives of 7-azanorbornane (Ohwada *et al.* 1998; Cheng *et al.* 2002; Otani *et al.* 2003; Hori *et al.* 2008; Longobardi *et al.* 2015).

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_6H_{12}N^+\cdot Cl^-$
M_r	133.62
Crystal system, space group	Orthorhombic, $Cmc2_1$
Temperature (K)	100
a, b, c (Å)	9.1532 (6), 8.7029 (8), 8.7336 (5)
V (Å^3)	695.71 (9)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.45
Crystal size (mm)	0.08 × 0.06 × 0.04
Data collection	
Diffractometer	Bruker APEXII CCD
Absorption correction	Multi-scan (*SADABS*; Sheldrick, 2015)
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	3239, 777, 769
R_{int}	0.017
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.638
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.017, 0.048, 1.15
No. of reflections	777
No. of parameters	47
No. of restraints	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.21, −0.12
Absolute structure	Refined as an inversion twin
Absolute structure parameter	0.19 (9)

Computer programs: *APEX2* (Bruker, 2015), *SAINT* (Bruker, 2015), *SHELXT* (Sheldrick, 2015a), *OLEX2* (Dolomanov *et al.*, 2009), *SHELXL2014* (Sheldrick, 2015b), *Mercury* (Macrae *et al.*, 2008) and *publCIF* (Westrip, 2010).

5. Synthesis and crystallization

7-Azabicyclo[2.2.1]heptane hydrochloride, **1**, was obtained from Sigma Aldrich. The purity of the substance has been proven by elemental analysis (analysis calculated for

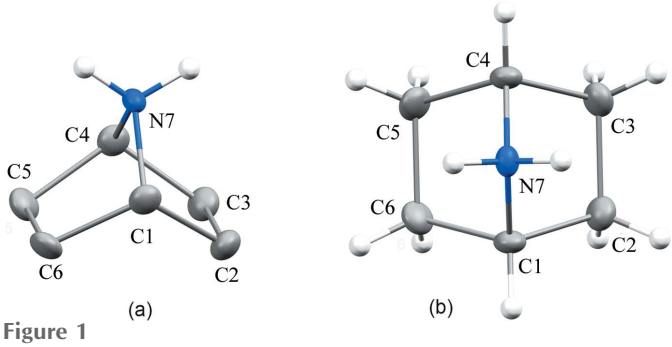


Figure 1
The molecular structure and systematic atomic numbering scheme of the 7-azabicyclo[2.2.1]heptane (7-azanorbornane) parent ring in **1**. Displacement ellipsoids are drawn at the 50% probability level. H atoms on C atoms in view (*a*) and the chloride counter-ion have been omitted for clarity. The labelling in the Figures corresponds to IUPAC notation (see text). Atoms C4, C3 and C5 are generated from C1, C2 and C6, respectively, by the symmetry operation $(1-x, y, z)$.

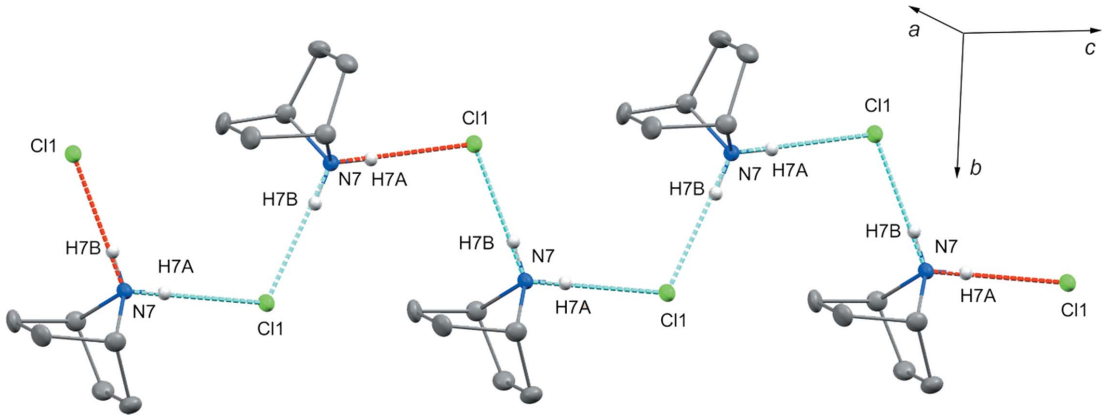


Figure 2
Hydrogen bonding in the crystal structure of **1**. Protonated molecules of 7-azanorbornane are linked *via* N—H···Cl hydrogen bonds to form infinite zigzag chains propagated along the *c* axis. Displacement ellipsoids are drawn at the 50% probability level. H atoms not involved in hydrogen bonding have been omitted for clarity.

$C_6H_{12}ClN$: C 53.93, H 9.05, N 10.48%; found: C 53.89, H 9.08, N 10.44%). ^{1}H NMR (400 MHz) spectrum (Bruker Avance 400, $SiMe_4$ external standard, D_2O solution): δ 4.21–4.19 (*m*, 2H, 2 × C*H* at C1 and C4; the atom-numbering scheme is according to IUPAC nomenclature, see Fig. 1), 1.92–1.84 (*m*, 4H, 4 × *endo-H*CH at C2, C3, C5, C6), 1.78–1.71 (*m*, 4H, 4 × *exo-H*CH at C2, C3, C5, C6). ^{13}C{^{1}H} NMR (101 MHz): δ 58.9 (*s*, C1 and C4), 26.7 (*s*, C2, C3, C5, C6). Crystals of **1** suitable for structural studies were obtained by slow evaporation of its aqueous solution.

6. Refinement

H atoms at the protonated N7 atom were refined freely, whereas H atoms on C atoms were refined based on a riding model. Crystal data, data collection and structure refinement details are summarized in Table 2.

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supporting information

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The 7-azanorbornane nucleus of epibatidine: 7-azabicyclo[2.2.1]heptan-7-ium chloride

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Computing details

Data collection: *APEX2* (Bruker, 2015); cell refinement: *SAINT* (Bruker, 2015); program(s) used to solve structure: SHELXT (Sheldrick, 2015a) and *OLEX2* (Dolomanov *et al.*, 2009); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015b) and *OLEX2* (Dolomanov *et al.*, 2009); molecular graphics: *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *publCIF* (Westrip, 2010).

7-Azabicyclo[2.2.1]heptan-7-ium chloride

Crystal data

$C_6H_{12}N^+\cdot Cl^-$
M_r = 133.62
Orthorhombic, $Cmc2_1$
a = 9.1532 (6) Å
b = 8.7029 (8) Å
c = 8.7336 (5) Å
V = 695.71 (9) Å^3
Z = 4
$F(000)$ = 288
D_x = 1.276 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 2988 reflections
θ = 3.2–30.7°
μ = 0.45 mm^{-1}
T = 100 K
Block, colourless
0.08 × 0.06 × 0.04 mm

Data collection

Bruker APEX-II CCD diffractometer
Radiation source: fine focus sealed tube
Graphite monochromator
φ and ω scans
Absorption correction: multi-scan (SADABS; Sheldrick, 2015)
3239 measured reflections
777 independent reflections
769 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 27.0°, θ_{min} = 3.2°
h = −11→11
k = −4→11
l = −11→10

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.017
$wR(F^2)$ = 0.048
S = 1.15
777 reflections
47 parameters
1 restraint
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0282P)^2 + 0.1322P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}
Absolute structure: Refined as an inversion twin
Absolute structure parameter: 0.19 (9)

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Single-crystal data collection was performed using a Bruker Kappa APEX II DUO diffractometer equipped with microfocus optics. Refinement of lattice parameters and subsequent data reduction was carried out with the Bruker *SAINT* software. The crystal structure of **1** was solved and refined using *SHELXT* and *SHELXL*-2014 (Sheldrick, 2015) via the *OLEX2* v.1.2 graphical user interface (Dolomanov *et al.*, 2009).
Refined as a 2-component inversion twin.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.62232 (18)	0.2599 (3)	0.5813 (2)	0.0174 (4)
H1	0.7205	0.2960	0.5547	0.021*
C2	0.5850 (2)	0.2715 (3)	0.75142 (19)	0.0202 (4)
H2B	0.6233	0.3655	0.7956	0.024*
H2A	0.6233	0.1843	0.8078	0.024*
C6	0.5848 (2)	0.10083 (19)	0.5202 (2)	0.0209 (4)
H6A	0.6231	0.0210	0.5864	0.025*
H6B	0.6231	0.0863	0.4176	0.025*
N7	0.5000	0.3539 (2)	0.5134 (2)	0.0139 (4)
H7B	0.5000	0.449 (4)	0.548 (3)	0.014 (7)*
H7A	0.5000	0.347 (4)	0.414 (5)	0.030 (9)*
Cl1	0.5000	0.31735 (5)	0.15788 (7)	0.01568 (15)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0107 (7)	0.0188 (10)	0.0226 (9)	0.0012 (7)	−0.0009 (6)	0.0003 (7)
C2	0.0227 (10)	0.0240 (10)	0.0140 (8)	0.0018 (8)	−0.0063 (7)	0.0029 (7)
C6	0.0239 (9)	0.0157 (9)	0.0232 (9)	0.0046 (6)	−0.0001 (7)	−0.0022 (8)
N7	0.0199 (10)	0.0119 (9)	0.0100 (9)	0.000	0.000	0.0007 (8)
Cl1	0.0213 (2)	0.0142 (2)	0.0116 (2)	0.000	0.000	0.0005 (2)

Geometric parameters (Å, º)

C1—H1	0.9800	C6—C6^{i}	1.553 (4)
C1—C2	1.528 (2)	C6—H6A	0.9700
C1—C6	1.523 (3)	C6—H6B	0.9700
C1—N7	1.508 (2)	N7—C1^{i}	1.508 (2)
C2—C2^{i}	1.556 (4)	N7—H7B	0.88 (3)
C2—H2B	0.9700	N7—H7A	0.87 (4)
C2—H2A	0.9700		
C2—C1—H1	114.5	C1—C6—C6^{i}	103.03 (9)
C6—C1—H1	114.5	C1—C6—H6A	111.2
C6—C1—C2	110.50 (19)	C1—C6—H6B	111.2

N7—C1—H1	114.5	C6^{i}—C6—H6A	111.2
N7—C1—C2	100.39 (16)	C6^{i}—C6—H6B	111.2
N7—C1—C6	100.82 (15)	H6A—C6—H6B	109.1
C1—C2—C2^{i}	102.93 (9)	C1—N7—C1^{i}	95.91 (18)
C1—C2—H2B	111.2	C1—N7—H7B	111.8 (11)
C1—C2—H2A	111.2	C1^{i}—N7—H7B	111.8 (11)
C2^{i}—C2—H2B	111.2	C1—N7—H7A	110.6 (14)
C2^{i}—C2—H2A	111.2	C1^{i}—N7—H7A	110.6 (14)
H2B—C2—H2A	109.1	H7B—N7—H7A	115 (3)
C2—C1—C6—C6^{i}	70.63 (12)	C6—C1—N7—C1^{i}	56.31 (19)
C2—C1—N7—C1^{i}	−57.1 (2)	N7—C1—C2—C2^{i}	35.24 (15)
C6—C1—C2—C2^{i}	−70.56 (14)	N7—C1—C6—C6^{i}	−34.89 (12)

Symmetry code: (i) −*x*+1, *y*, *z*.

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N7—H7*B*···Cl1^{ii}	0.88 (3)	2.25 (3)	3.127 (2)	175 (2)
N7—H7*A*···Cl1	0.87 (4)	2.25 (4)	3.122 (2)	178 (3)

Symmetry code: (ii) −*x*+1, −*y*+1, *z*+1/2.