organic compounds

(4-Methoxy-3-nitrobenzylidene-amino)guanidinium chloride

Joshua R. Ring,[a] Sean Parkin[b] and Peter A. Crooks[a]*

[a]Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY 40536, USA, and [b]Department of Chemistry, University of Kentucky, Lexington, KY 40506, USA
Correspondence e-mail: pcrooks@uky.edu

In the title compound, $C_9H_{12}N_5O_3^+ \cdot Cl^-$, the cation is almost entirely planar. The imine double bond is exclusively in the E geometry.

Comment

N-Methyl-D-aspartate receptors (NMDARs) are highly regulated ligand-gated ionotropic glutamate receptor channels that are affected by many substrates, including the endogenous ligand, glycine. The cation channel is nonselectively permeable to Na^+, K^+ and Ca^{2+}, but is blocked by Mg^{2+} at physiological conditions. Overactivation of the NMDAR can lead to hyperexcitablility and a number of neurotoxic effects and neurological diseases, such as epilepsy (Meldrum et al., 1999), Alzheimer's disease (Dodd, 2002) and Huntington's disease (Li et al., 2003), and has also been shown to be a mechanism that leads to alcohol dependence (Lovinger et al., 1989). However, the physiological function of this channel is crucial in many neural functions, such as learning and memory, and thus a therapeutic agent that is an antagonist at NMDARs cannot be one which irreversibly inhibits channel flux.

The polyamine agmatine has been demonstrated to exhibit antagonist activity at the polyamine binding sites of NR2B subunits of the NMDAR complex, but only in the presence of pathologically high levels of the longer-chain polyamine-site agonists, such as spermine and spermidine (Gibson et al., 2002). The intriguing properties of agmatine as a potent and selective allosteric competitive inhibitor of the NMDAR complex have led to an interest in optimizing the structure of this molecule for use in drug development. As a result, conjugates of aminoguanidine and an array of arylaldehydes have been synthesized and screened as NMDAR inhibitors. Thus, the title compound, (I), was synthesized from Schiff base formation of 4-methoxy-3-nitrobenzaldehyde with aminoguanidine hydrochloride, and exhibited potent inhibition of the NMDAR complex in the presence of spermidine.

In order to establish the structure and geometry of compound (I), suitable crystals of this compound were prepared for X-ray analysis. The data obtained demonstrated an exclusive E geometry in the newly formed imine double bond. An ellipsoid plot of the product is provided in Fig. 1, and selected geometric parameters are included in Table 1.

(I)
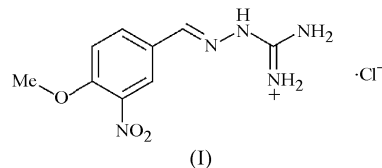
The values for the bond lengths in the guanidine group are comparable to those found in the starting material aminoguanidine hydrochloride. The bond lengths reported for aminoguanidine are 1.32 Å for the two terminal exo C—N bonds of the guanidino group and 1.35 Å for the endo C—N bond of the guanidino group, which were calculated to correspond to a weighting of roughly 40% double-bond character for each of the exo C—N bonds and 20% double-bond character for the endo C—N bond. The bond lengths observed in the X-ray structure of compound (I) for the exo C10—N11 [1.324 (2) Å] and C10—N12 [1.317 (2) Å] bonds, and the endo C10—N9 [1.350 (2) Å] bond, were in close accordance with the corresponding bond lengths in the aminoguanidine molecule. Thus, the double bond of the guanidinium group in (I) is predominantly exo, as is observed in the aminoguanidine structure, in spite of the presence of a new arylimine grouping in the molecule. In the crystal structure, the chloride counter-ion is more closely associated with N12, which may account for the slightly shorter length of this terminal C10—N12 bond compared with the length of C10—N11.

Formation of the Schiff base at the C7—N8 bond also affects the length of the N8—N9 bond in (I). This corresponding N—N bond length in the aminoguanidine starting material was reported as 1.42 Å, but in (I), this bond was observed to have a length of 1.381 (2) Å, indicating slight double-bond character. The C1—C7 bond [1.459 (2) Å] is also shorter than a standard C—C σ bond, and it is clear that some
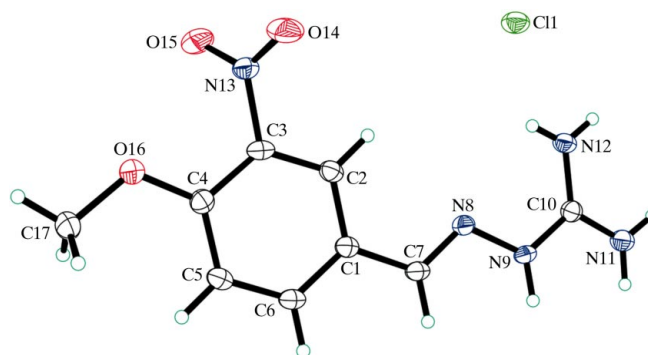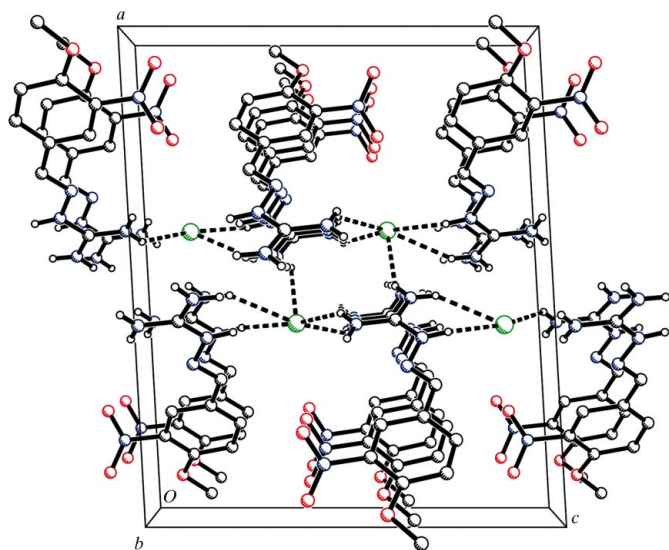

Figure 1
A view of the planar compound (I). Displacement ellipsoids are drawn at the 50% probability level and H atoms are included as small spheres of arbitrary radii.

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double-bond character is distributed to some extent along the C1—C7—N8—N9—C10 bond series. The bond angles along this series of atoms (C1—C7—N8, C7—N8—N9 and N8—N9—C10; Table 1) are closer to the ideal value of 120° for angles between sp^2 atoms than to the value of 109.5° observed for sp^3 atoms.

The assumption of an extended double-bond characteristic throughout the molecule is also supported by the planarity of the entire molecule, as is seen in the torsion angle values (Table 1). None of the torsion angles deviate by more than 10° from the plane of the molecule, except for the O atoms of the nitro group and the H atoms of the methyl group. Along the C6—C1—C7—N8—N9—C10 chain of atoms, the torsion angles are a tight 176.38 (16), 178.78 (14) and 176.16 (15)° for C6—C1—C7—N8, C1—C7—N8—N9 and C7—N8—N9—C10, respectively. Planarity of the molecule also extends through atoms O16 to C17, and thus includes the 4-methoxy group, as indicated by the C4—O16—C17 bond angle of 117.53 (13)°. The partial double-bond character of the C4—O16 bond results in C3 and C17 possessing an *E* geometry, which is probably a result of the steric hindrance of the nitro substituent at position 3 of the benzene ring (C3). With the extended conjugation throughout the molecule, and the *E geometry* of the C7—N8 bond, there is no possibility of intramolecular hydrogen-bond formation between the O atoms of the nitro group and the H atoms attached to N atoms of the guanidine group.

The crystal packing for (I) is illustrated in Fig. 2, viewed along the *b* direction. The flat molecules form parallel stacks along the *b* axis, as do the chloride ions. Each chloride ion forms five hydrogen bonds with each of the five guanidine H atoms, with H⋯*A* distances in the range 2.44–2.70 Å (see Table 2). This arrangement forms stable chains of intermolecular connectivity in the *c* direction.

Figure 2
The stacking arrangement in the crystal structure of the title compound, viewed along the *b* axis.

Experimental

Crystal data

$C_9H_{12}N_5O_3{}^+ \cdot Cl^-$	$V = 1201.76$ (6) Å^3
$M_r = 273.69$	$Z = 4$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 16.7260$ (4) Å	$\mu = 0.33$ mm^{-1}
$b = 5.1384$ (1) Å	$T = 90.0$ (2) K
$c = 14.0045$ (5) Å	$0.25 \times 0.16 \times 0.08$ mm
$\beta = 93.1793$ (13)°	

Data collection

Nonius KappaCCD diffractometer	4859 measured reflections
Absorption correction: multi-scan	2744 independent reflections
(*SCALEPACK*; Otwinowski &	2220 reflections with $I > 2\sigma(I)$
Minor, 1997)	$R_{\text{int}} = 0.024$
$T_{\min} = 0.923$, $T_{\max} = 0.976$	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.041$	H atoms treated by a mixture of
$wR(F^2) = 0.111$	independent and constrained
$S = 1.07$	refinement
2744 reflections	$\Delta\rho_{\max} = 0.35$ e Å^{-3}
166 parameters	$\Delta\rho_{\min} = -0.44$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C1—C7	1.459 (2)	N9—C10	1.350 (2)
C3—N13	1.469 (2)	C10—N12	1.317 (2)
C4—O16	1.352 (2)	C10—N11	1.324 (2)
C7—N8	1.279 (2)	N13—O14	1.221 (2)
N8—N9	1.381 (2)	O16—C17	1.436 (2)
C2—C1—C7	121.52 (15)	N8—C7—C1	120.63 (15)
C4—C3—N13	118.30 (16)	C7—N8—N9	115.00 (14)
O16—C4—C5	125.77 (16)	C10—N9—N8	118.48 (14)
O16—C4—C3	117.04 (15)	N11—C10—N9	117.05 (15)
C2—C1—C7—N8	−5.7 (3)	C2—C3—N13—O14	−57.4 (2)
N8—N9—C10—N12	9.3 (2)	C4—C3—N13—O15	−61.5 (2)
N8—N9—C10—N11	−172.09 (14)	C3—C4—O16—C17	179.29 (16)

The flat NH$_2$ groups were allowed to refine along the N—H vector to distances of 0.856 (17) and 0.813 (18) Å. H atoms were found in difference Fourier maps and subsequently placed in idealized positions with constrained C—H distances of 0.95 (aromatic) and 0.98 Å (methyl), and an N—H distance of 0.88 Å. U_{iso}(H) values were set at either 1.5U_{eq} or 1.2U_{eq} of the attached atom.

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Table 2
Hydrogen-bond geometry (Å, °).

$D—H\cdots A$	$D—H$	$H\cdots A$	$D\cdots A$	$D—H\cdots A$
N9—H9$\cdots$Cl1[i]	0.88	2.44	3.1961 (14)	144
N11—H11$A\cdots$Cl1[ii]	0.86	2.51	3.2524 (16)	146
N11—H11$B\cdots$Cl1[i]	0.86	2.52	3.2787 (16)	149
N12—H12$A\cdots$Cl1[iii]	0.81	2.53	3.2223 (16)	144
N12—H12$B\cdots$Cl1	0.81	2.70	3.3315 (16)	136

Symmetry codes: (i) $x, -y - \frac{1}{2}, z - \frac{1}{2}$; (ii) $-x + 1, -y - 1, -z + 2$; (iii) $x, y - 1, z$.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL/PC* (Sheldrick, 1995); software used to prepare material for publication: *SHELXL97* and local procedures.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3076). Services for accessing these data are described at the back of the journal.

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