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Ranitidine hydrochloride, a polymorphic crystal form

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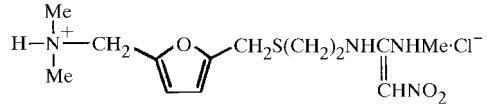
In the title compound, dimethyl({5-[2-(1-methylamino-2-nitroethenylamino)ethylthiomethyl]-2-furyl}methyl)ammonium chloride, $C_{13}H_{23}N_4O_3S^+\cdot Cl^-$, protonation occurs at the dimethylamino N atom. The ranitidine molecule adopts an eclipsed conformation. Bond lengths indicate extensive electron delocalization in the *N*,*N*′-dimethyl-2-nitro-1,1-ethenediamine system of the molecule. The nitro and methylamino groups are *trans* across the side chain C=C double bond, while the ethylamino and nitro groups are *cis*. The Cl^- ions link molecules through hydrogen bonds.

Comment

Ranitidine, an H_2 receptor antagonist, is a high potency inhibitor of gastric acid secretion, and is used in the treatment of peptic ulcers and related gastrointestinal disorders (Brogden *et al.*, 1982). The crystal structure of ranitidine hydrogen oxalate (Kojić-Prodić *et al.*, 1982) and ranitidine hydrochloride (Ishida *et al.*, 1990) have been reported previously. Here, we report the crystal structure of ranitidine hydrochloride, (I), in a different and as yet unpublished crystal form, and compare it with the published structures.



(I)

The molecular structure of (I) is presented in Fig. 1. The enamine portion of the molecule can exist in two possible configurations with respect to the C15=C18 double bond: *E* and *Z* arrangements, in which the methylamino and nitro substituents are *cis* and *trans* to each other, respectively. The *Z* configuration is adopted in this structure, as opposed to the *E* arrangement in the crystal structure of ranitidine hydrogen oxalate and both forms, disordered, in the previous structure determination of ranitidine hydrochloride. An equimolar mixture of *E*/*Z* enamine isomers has been reported in solution (Cholerton *et al.*, 1984); interconversion presumably is facilitated by π-electron delocalization over the enamine system. Thus, the C15=C18 bond in this structure is lengthened to 1.425 (3) Å, and the single bonds C15—N14, C15—N16 and C18—N19 are shortened to 1.335 (3), 1.332 (3) and 1.349 (3) Å, respectively. Similarly, the two N—O distances in the nitro group, 1.270 (2) and 1.284 (2) Å, indicate electron delocalization, even though O20 takes part in a strong hydrogen bond and O21 is involved in a weak C—H···O interaction. The same phenomena were observed in ranitidine hydrogen oxalate, whereas in the other crystal form of ranitidine hydrochloride, the disordered structure was interpreted in terms of electronically localized *E* and *Z* forms with distinct double- and single-bond lengths. Bond distances and angles in the rest of the molecule agree well with commonly accepted values. The least-squares plane through the nine atoms involved in the enamine moiety (C13 to O21) indicate that they are planar, the r.m.s. deviation of the atoms being 0.035 (2) Å with a maximum of 0.069 (2) Å for O20 and a minimum of 0.001 (1) Å for C13. The ranitidine molecule, as a whole, adopts an eclipsed conformation (*i.e.* neither fully folded nor fully extended) similar to that of disordered ranitidine hydrochloride. Rotation of the group of atoms C13 through O21 by 114° about the C12—C13 bond results in

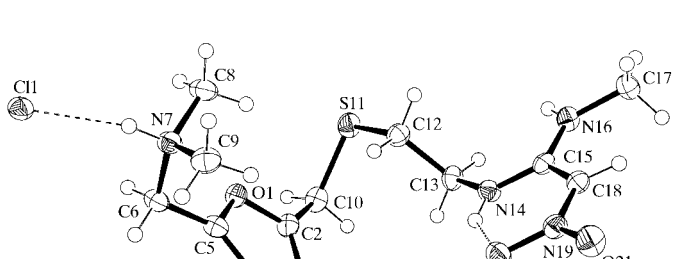


Figure 1
ORTEP-3 (Farrugia, 1997) view of the title molecule showing 50% probability displacement ellipsoids. H atoms are drawn as small circles of arbitrary radii.

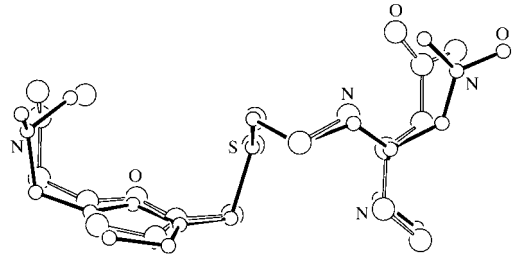


Figure 2
Superposition of ranitidine hydrochloride (small circles) and the *Z* isomer in the disordered structure of ranitidine hydrochloride (large circles) after 114° rotation of the present structure about the C12—C13 bond.

conformational coincidence of this structure with the *Z* isomer in the disordered ranitidine HCl structure (Fig. 2) [primed set of atoms in Ishida *et al.* (1990)]. In contrast, ranitidine hydrogen oxalate was found to have a folded conformation. An open conformation is reportedly the one most likely to exist in solution (Sega *et al.*, 1982; Gaggelli *et al.*, 1988).

An intramolecular hydrogen bond from N14 to O20 (see Table 1) helps to stabilize the planarity of the 2-ethylamino-2-methylamino-1-nitroethylene moiety. Such an interaction is present in all of the ranitidine crystal structures and is the reason for *E*/*Z* configurations being favored in the solid state; in aqueous solution, with water available as a hydrogen-bond donor, rotation about the C15—C18 bond occurs readily (Cholerton *et al.*, 1984). Rotation also occurs in other solvents; attempted crystallization of the present material in acetonitrile, the crystallization solvent used in the previous ranitidine hydrochloride structure determination, resulted in our getting crystals of that crystal form.

The furyl ring is almost perfectly planar and forms an angle of 69.5 (1)° with the plane through the atoms of the 2-ethylamino-2-methylamino-1-nitroethylene moiety (C13 through O21), which is close to the value 63.4 (1)° in disordered ranitidine hydrochloride and 75.2 (1)° in ranitidine hydrogen oxalate. In (I), the molecules are held together through hydrogen bonds from N7 and N16 to two different Cl anions (Table 1), forming one-dimensional infinite chains of molecules running perpendicular to the *b* axis along the base vector (101) in a head-to-tail fashion. The chains of molecules are held together by van der Waals interactions and weak hydrogen bonds of the C—H···O type (Steiner, 1997; Desiraju, 1996). The existence of this type of C—H bond is facilitated by the presence of the adjacent activating groups NO_2 and N^+, and Cl^- ions. The Cl^- ion is coordinated by four H atoms (H7, H16, H6*B* and H8*A*), forming a tetrahedron with almost perfect geometry.

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N7—H7···Cl1	0.94 (3)	2.13 (3)	3.070 (2)	172 (3)
N14—H14···O20	0.86	1.93	2.612 (3)	135
N16—H16···Cl1^{i}	0.86	2.37	3.166 (2)	155
C6—H6*A*···O20^{ii}	0.97	2.33	3.263 (3)	160
C6—H6*B*···Cl1^{iii}	0.97	2.80	3.712 (2)	158
C8—H8*A*···Cl1^{iv}	0.98	2.66	3.568 (3)	153
C9—H9*B*···O21^{ii}	0.96	2.47	3.424 (3)	171
C18—H18···O21^{v}	0.93	2.47	3.399 (3)	173

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

Experimental

Crystals of (I) were obtained as colorless prisms by solvent evaporation from a methanol–ethyl acetate mixture.

Crystal data

$C_{13}H_{23}N_4O_3S^+\cdot Cl^-$
M_r = 350.86
Monoclinic, $P2_1/n$
a = 12.1918 (6) Å
b = 6.5318 (3) Å
c = 22.0382 (8) Å
β = 93.985 (3)°
V = 1750.76 (13) Å^3
Z = 4
D_x = 1.331 Mg m^{-3}
Mo *K*α radiation
Cell parameters from all reflections
μ = 0.354 mm^{-1}
T = 100 (2) K
Prism, colorless
0.45 × 0.25 × 0.23 mm

Data collection

Nonius KappaCCD diffractometer
ω rotation scans
3994 measured reflections
3994 independent reflections
2680 reflections with $I > 2\sigma(I)$
θ_{max} = 27.48°
h = 0 → 15
k = 0 → 8
l = −28 → 28

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.130
S = 0.802
3994 reflections
210 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0488P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Ranitidine hydrochloride crystallized in the monoclinic system; space group $P2_1/n$ from the systematic absences. All H atoms, except for H7 at N7 which was found from a difference map, were calculated geometrically. During the refinement, H atoms were treated isotropically and were riding on their parent atoms (at distances 0.93 to 0.98 Å), except for H7 which had its positional and isotropic displacement parameters refined independently.

Data collection: *KappaCCD Server Software* (Nonius, 1997); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1581). Services for accessing these data are described at the back of the journal.

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