Polymorphism in 2-(4-hydroxy-2,6-dimethylanilino)-5,6-dihydro-4H-1,3-thiazin-3-ium chloride

Julio Gutierrez,[a] Rodney Eisenberg,[b] Gabrielle Herrensmith,[a] Thomas Tobin,[a] Tonglei Li[c] and Sihui Long[c]*

[a]Maxwell H. Gluck Equine Center, University of Kentucky, Lexington, KY 40546, USA, [b]Frontier Biopharm, PO Box 614, Richmond, Kentucky 40475, USA, and [c]Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY 40536, USA

Correspondence e-mail: slong0@email.uky.edu

Details of the structures of two conformational polymorphs of the title compound, $C_{12}H_{17}N_2OS^+ \cdot Cl^-$, are reported. In form (I) (space group $P\bar{1}$), the two N—H groups of the cation are in a *trans* conformation, while in form (II) (space group $P2_1/c$), they are in a *cis* arrangement. This results in different packing and hydrogen-bond arrangements in the two forms, both of which have extended chains lying along the a direction. In form (I), these chains are composed of centrosymmetric $R_4^2(18)$ (N—H···Cl and O—H···Cl) hydrogen-bonded rings and $R_2^2(18)$ (N—H···O) hydrogen-bonded rings. In form (II), the chains are formed by centrosymmetric $R_4^2(18)$ (N—H···Cl and O—H···Cl) hydrogen-bonded rings and by $R_4^2(12)$ (N—H···Cl) hydrogen-bonded rings.

Comment

Polymorphism, the phenomenon of a given molecule existing in more than one crystal structure, is a normal observation for organics (McCrone, 1965). Polymorphism is of great importance in pharmaceuticals, as well as in materials science, because individual forms may have different physicochemical properties which can potentially lead to new formulations or new materials. Conformational polymorphism, a branch of polymorphism, is particularly interesting since it provides ideal cases for structure–property relationship studies (Bernstein, 2002, 1987). Conformational polymorphism arises from intrinsic molecular flexibility and is the result of a compromise between inter- and intramolecular interactions.

The free base of the title compound, (1), is the principal metabolite fragment recovered from equine urine after enzymatic hydrolysis of xylazine [N-(2,6-dimethylphenyl)-5,6-dihydro-4H-1,3-thiazin-2-amine], which is a relatively short-acting α-2 agonist tranquilizer widely used in equine medicine. Optimal regulatory control of the use of xylazine is dependent

on the detection and quantification of urinary metabolites or metabolite fragments such as the free base of (1) (Mutlib *et al.*, 1992). We report here the conformational polymorphism of (1), which occurs in two crystalline forms, *viz.* (I) and (II).
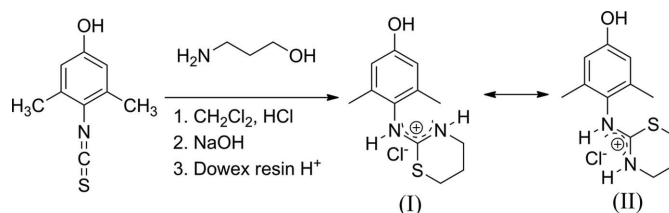
Our analysis establishes that form (I) is triclinic (space group $P\bar{1}$) and form (II) monoclinic (space group $P2_1/c$), with one formula unit in the asymmetric unit in each case. Views of forms (I) and (II) are given in Figs. 1 and 2, respectively. In both forms, imine atom N3 is protonated, and in both forms the six-membered heterocyclic ring has a half-chair conformation, with atom C5 0.704 (2) Å from the S1/C2/N3/C4/C6 plane in form (I) and 0.699 (2) Å from the same plane in form (II). The C2—N2 and C2—N3 bond lengths in (I) are 1.3296 (16) and 1.3180 (16) Å, respectively, and the corresponding values in (II) are 1.328 (2) and 1.322 (2) Å. These dimensions are entirely consistent with delocalization of the
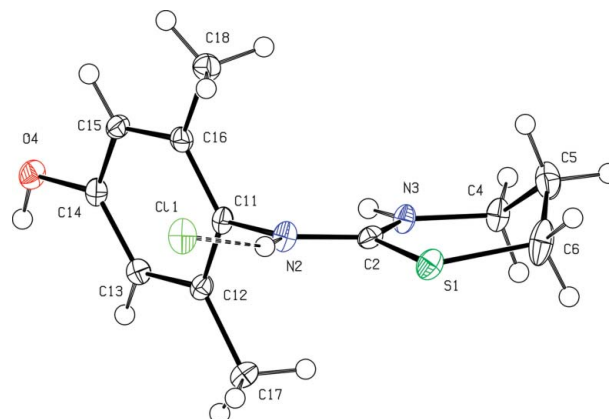

Figure 1
The molecular structure of form (I) of (1), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.
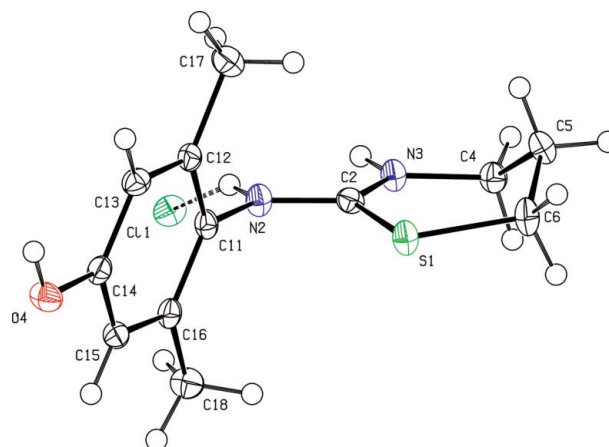

Figure 2
The molecular structure of form (II) of (1), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.
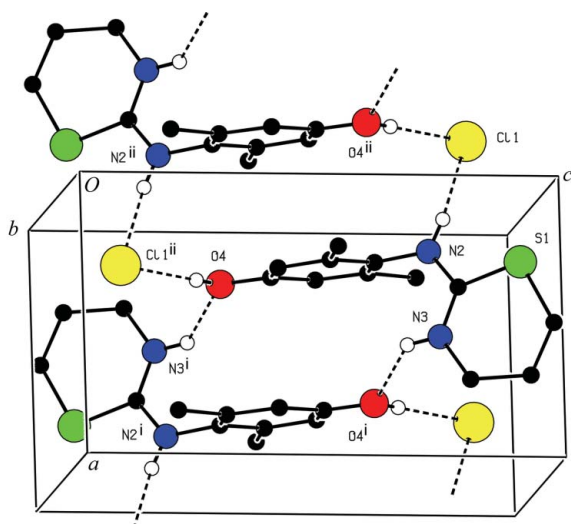
Figure 3
The crystal packing of form (I). (For details of symmetry codes, see Table 1.)

C2=N2 double bond over the N2—C2—N3 moiety, as shown in structures (1*a*) and (1*b*) in the scheme below. Thus, the two cations could either be considered as configurational isomers (with C2—N2 considered as the double bond), with form (I) the *E* isomer and form (II) the *Z* isomer, or as conformational isomers (with C2—N3 considered as the double bond). As seen in Figs. 1 and 2 (which have been drawn to have similar orientations of the six-membered heterocyclic rings), the principal difference between the two forms is in the orientation of the 4-hydroxy-2,6-dimethylanilino moiety with respect to the heterocyclic ring. In form (I), the S1—C2—N2—C11 torsion angle is −176.54 (9)°, while in form (II) the corresponding value is 3.0 (2)°.

(1*a*)   (1*b*)
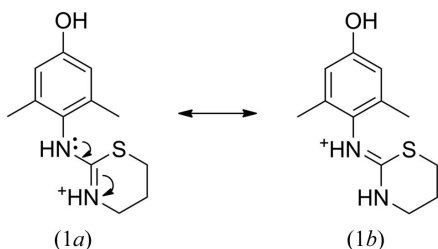
Due to the conformational difference between the cations in the two polymorphs, the packing patterns are dissimilar. In polymorph (I) (Fig. 3), hydrogen bonds between the protonated imine NH group and the phenol O atom (N3—H3···O4^i; see Table 1 for details) link two cations to form an 18-membered ring dimer centred at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$, with the hydrogen-bonded ring graph-set descriptor $R_2^2(18)$ (Bernstein *et al.*, 1995). This dimer is further connected through hydrogen bonds between the chloride ion and the hydroxy O4—H4 and secondary N2–H2 groups of neighbouring cations (details in Table 1) to form a second set of 18-membered rings, but this time with hydrogen-bond descriptor $R_4^2(18)$, lying about inversion centres at $(0, \frac{1}{2}, \frac{1}{2})$, $(1, \frac{1}{2}, \frac{1}{2})$, *etc.* This gives rise to a one-dimensional chain along the *a* axis of the triclinic cell.

In form (II) (Fig. 4), the cations are interconnected through hydrogen bonds between the chloride ion and all three
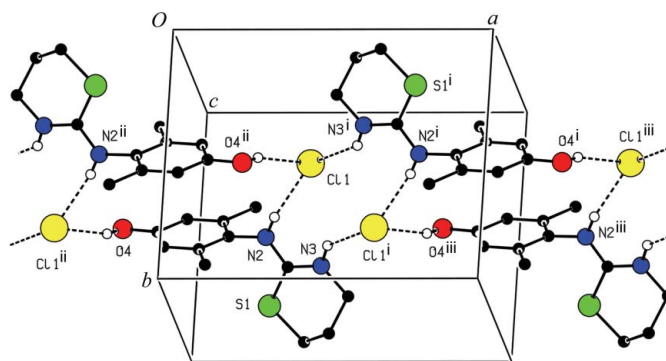

Figure 4
The crystal packing of form (II). [For details of symmetry codes, see Table 2; additionally, (iii) $1 + x, y, z$.]

hydrogen-bond donors from different neighbouring cations, *viz.* O4—H4, imine N3—H3 and amino N2—H2 (details in Table 2). There is a 12-membered ring [centred at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$] involving the N2—H2 and N3—H3 groups and the chloride ion, with descriptor $R_4^2(12)$ (details in Table 2). This dimer is then connected *via* N2—H2···Cl1 and O4—H4···Cl1^{ii} hydrogen bonds (Table 2) to generate 18-membered rings [centred at $(0, \frac{1}{2}, \frac{1}{2})$, $(1, \frac{1}{2}, \frac{1}{2})$, *etc.*] with descriptor $R_4^2(18)$, the same as in form (I). In this way, a one-dimensional chain is developed along the *a* axis of this monoclinic cell.

Our work has thus shown that the two crystalline forms discovered for (1) can be considered as either configurational or conformational isomers, due to the delocalization of the amine lone-pair of electrons over three atoms. The configurational/conformational variation in the two forms gives rise to differences in packing and hydrogen-bond arrangements in the crystal structures.

Experimental

3,5-Dimethyl-4-isothiocyanatophenol (1.70 g, 9.50 mmol) was dissolved in dry dichloromethane (20 ml) and 3-aminopropanol (1.70 ml, 22.18 mmol) was added. The reaction mixture was refluxed overnight with stirring. The solution was then cooled to room temperature and the solvent removed under reduced pressure to give the crude product. Concentrated hydrochloric acid solution (8 ml) was added to the crude product and the resulting solution was refluxed overnight with stirring. The solution was poured into 10% NaOH (50 ml) and stirred for 3 h. The final product (yield 2.0 g, 90.9%) was precipitated using Dowex resin H$^+$ form (pH = 1) (Kai *et al.*, 2007). Crystals (m.p. 503 K, from differential scanning calorimetry) from methanol and ethanol were found to be the same and were designated as form (I), and those from propan-2-ol were form (II).

Polymorph (I)

Crystal data

C$_{12}$H$_{17}$N$_2$OS$^+$·Cl$^-$	$\gamma = 70.8388\,(6)°$
$M_r = 272.79$	$V = 658.17\,(2)$ Å^3
Triclinic, $P\bar{1}$	$Z = 2$
$a = 6.9961\,(1)$ Å	Mo $K\alpha$ radiation
$b = 7.9421\,(1)$ Å	$\mu = 0.44$ mm^{-1}
$c = 13.0864\,(2)$ Å	$T = 90$ K
$\alpha = 73.3925\,(6)°$	$0.30 \times 0.20 \times 0.10$ mm
$\beta = 84.1579\,(6)°$	

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N2—H2$\cdots$Cl1	0.88	2.28	3.1244 (11)	161
N3—H3$\cdots$O4[i]	0.88	2.12	2.8143 (13)	136
O4—H4$\cdots$Cl1[ii]	0.84	2.17	2.9913 (10)	165

Symmetry codes: (i) $-x + 1, -y + 1, -z + 1$; (ii) $-x, -y + 1, -z + 1$.

Data collection

Nonius KappaCCD area-detector diffractometer	5923 measured reflections
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)	2981 independent reflections
	2762 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.017$
$T_{min} = 0.881$, $T_{max} = 0.958$	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.028$	156 parameters
$wR(F^2) = 0.072$	H-atom parameters constrained
$S = 1.03$	$\Delta\rho_{max} = 0.32$ e Å^{-3}
2981 reflections	$\Delta\rho_{min} = -0.28$ e Å^{-3}

Polymorph (II)

Crystal data

$C_{12}H_{17}N_2OS^+\cdot Cl^-$	$V = 1370.02$ (5) Å^3
$M_r = 272.79$	$Z = 4$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 11.8877$ (2) Å	$\mu = 0.42$ mm^{-1}
$b = 9.2120$ (2) Å	$T = 90$ K
$c = 12.6673$ (3) Å	$0.50 \times 0.20 \times 0.10$ mm
$\beta = 99.0242$ (10)°	

Data collection

Nonius KappaCCD area-detector diffractometer	6046 measured reflections
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)	3141 independent reflections
	2389 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.031$
$T_{min} = 0.818$, $T_{max} = 0.959$	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.042$	157 parameters
$wR(F^2) = 0.112$	H-atom parameters constrained
$S = 1.10$	$\Delta\rho_{max} = 0.50$ e Å^{-3}
3141 reflections	$\Delta\rho_{min} = -0.31$ e Å^{-3}

All H atoms were found in difference Fourier maps and were subsequently placed in idealized positions, with O—H = 0.82 Å, N—H = 0.86 Å, Csp^2—H = 0.93 Å, and Csp^3—H = 0.97 Å for CH$_2$ H atoms and 0.96 Å for methyl H atoms. All H atoms were allowed for as riding, with U_{iso}(H) = 1.5U_{eq}(parent atom) for hydroxy and methyl H atoms, and 1.2U_{eq}(parent atom) for all others.

For both compounds, data collection: *COLLECT* (Nonius, 2002); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *XP* in *SHELXTL*

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N2—H2$\cdots$Cl1	0.86	2.33	3.1245 (17)	154
N3—H3$\cdots$Cl1[i]	0.86	2.57	3.2437 (17)	136
O4—H4$\cdots$Cl1[ii]	0.82	2.28	3.0579 (14)	159

Symmetry codes: (i) $-x + 1, -y + 1, -z + 1$; (ii) $-x, -y + 1, -z + 1$.

(Sheldrick, 2008); software used to prepare material for publication: *SHELXL97* and local procedures.

References

Bernstein, J. (1987). *Organic Solid State Chemistry*, Vol. 32, edited by G. R. Desiraju, pp. 471–518. Amsterdam: Elsevier.
Bernstein, J. (2002). *Polymorphism in Molecular Crystals*. New York: Oxford University Press.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Kai, H., Morioka, Y., Tomida, M., Takahashi, T., Hattori, M., Hanasaki, K., Koike, K., Chiba, H., Shinohara, S., Kanemasa, T., Iwamoto, Y., Takahashi, K., Yamaguchi, Y., Baba, T., Yoshikawa, T. & Takenaka, H. (2007). *Bioorg. Med. Chem. Lett.*, **17**, 3925–3929.
McCrone, W. C. (1965). *Physics and Chemistry of the Organic Solid State*, Vol. 2, edited by D. Fox, M. M. Labes & A. Weissberge, pp. 725–767. New York: Interscience.
Mutlib, A. E., Chui, Y. C., Young, L. M. & Abbott, F. S. (1992). *Drug Metab. Dispos.* **20**, 840–848.
Nonius (2002). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.