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Benzamidine

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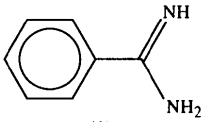
Abstract

Benzenecarboximidamide, $C_7H_8N_2$, has been prepared and its structure shows a planar molecule with distinct C=N 1.294 (3) and C—N 1.344 (3) Å distances, and a three-dimensional hydrogen-bonding network.

Comment

Amidines are of particular pharmaceutical and biological importance, and possess important bonding characteristics and ligand properties (Barker & Kilner, 1994). This widespread interest is reflected in the number of structural papers concerning amidines in the literature (Barker & Powell, 1995; Alcock, Barker & Kilner, 1988; Alcock, Blacker, Errington, Wallbridge & Barker, 1994; Dehnicke, 1990; Norrestam, Mertz & Crossland, 1983). Specifically, benzamidine, (1), has been recognized as an enzyme inhibitor in its derivative forms for many years (*e.g.* Robert & Gagnon, 1994; Beyer & Zaneveld, 1982; Jeffcoate & White, 1974; Markwardt, Landmann, & Walsmann, 1968; Diniz, Pereira, Barroso & Mares-Guia, 1965) and has been included in a number of protein structure determinations as the protonated benzamidinium ion (Bode, Turk & Stuerzebecher 1990; Perona, Tsu, McGrath, Craik & Fletterick, 1993; Banner & Hadvary, 1991; Brandstetter *et al.*, 1992; Sprang *et al.*, 1987; Marquart, Walter, Deisenhofer, Bode & Huber, 1983). This structural study was carried out to provide accurate structural data on this important amidine in its difficult-to-isolate neutral form.



(1)

The two C—N distances are different, 1.344 (3) and 1.294 (3) Å, indicating single C—N(amine) and double C=N(imine) bond character. They are similar to the values found for *N,N'*-diphenylbenzamidine, (2), (Alcock, Barker & Kilner, 1988). The small differences are attributed to the slight effect that differing substituents on the N atoms have on bonding within the N—C—N skeleton. The N—C—N angle is, however, affected by the substituents; it increases from an average of 121.5 (5)° for the two molecules in the asymmetric unit of (2) to 124.4 (2)° for (1). The other angles associated with the amidine C atom are more nearly equal in (1) than in (2) but the geometry of this atom is still essentially planar in both compounds. The C—C(amidine) distances are not greatly affected by the substitution on the N atoms and these compare well with the expected single Csp^2—Csp^2 bond length of 1.482 (11) Å (Allen *et al.*, 1987). Only one other unsubstituted parent amidine, acetamidine, has been structurally characterized, (Norrestam, Mertz, & Crossland, 1983); this shows similar amine/imine characteristics, with C—N bond lengths of 1.298 (1) and 1.344 (1) Å. The N=C—N angles and the C—C(amidine) distances show very small differences. [The structure of 2,6-diisopropyl-5,5-dimethyl-4-carboxymethoxy-1,3-dioxane phenylamidine (Marsura, Duc & Gellon, 1984; 'phenylamidine' is synonymous with 'benzamidine') has a geometry which does not correspond to the neutral localized species and the same structure is reported as the benzamidinium salt in a later paper (Le Page *et al.*, 1984).]

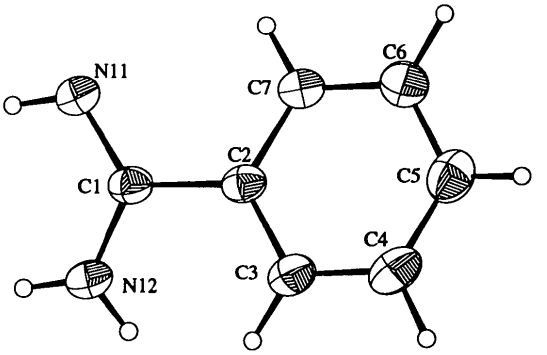


Fig. 1. Molecular structure for benzamidine with the labelling scheme for non-H atoms. Displacement ellipsoids are shown at 50% probability levels; H atoms are drawn as small circles of arbitrary radii.

Four molecules are hydrogen bonded together around a $\bar{4}$ axis [N(11)···N(12)($-0.5+y$, $0.5-x$, $0.5-z$) 3.102 (3) Å] to form a tetrameric sub-unit; these sub-units are linked to their neighbours along the *c* axis [N(11)···N(12)(x, y, $1+z$) 3.032 (3) Å].

Experimental

Benzamidine hydrochloride hydrate (Ex. Aldrich; 14.4 g, 92 mmol) was added to a solution of sodium ethoxide (2.18 g sodium) in dry ethanol (50 ml). The solution was stirred for two hours before the solvent was removed under vacuum. The

benzamidine was isolated from the reaction mixture by sublimation under vacuum at 343 K yielding colourless needle crystals [yield 8.6g (78%)]. Elemental analysis, calculated for $C_7H_8N_2$; C 70.57, H 5.92, N 23.51%, found C 69.53, H 6.32, N 23.55%. ^{1}H NMR ($CDCl_3$): 7.55 (Ar-H, 2H, *d*, 7.8 Hz, 1.9 Hz), 7.40–7.31 (Ar-H, 3H, *m*), 5.80 (NH, 3H, *s*). ^{13}C NMR: 166.29 (N—C—N), 136.71, 130.20, 128.52, 125.86, (Ar) p.p.m.

Crystal data

$C_7H_8N_2$
M_r = 120.16
Tetragonal
$I\bar{4}$
a = 15.7353 (20) Å
c = 5.2803 (17) Å
V = 1307.28 Å^3
Z = 8
D_x = 1.22 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 25 reflections
θ = 58.5–59.9°
μ = 0.567 mm^{-1}
T = 293 K
Block
0.24 × 0.20 × 0.20 mm
Colourless

Data collection

Rigaku AFC-7*R* diffractometer
$\omega/2\theta$ scans
Absorption correction: empirical, ψ-scan (North, Phillips & Mathews, 1968)
T_{min} = 0.973, T_{max} = 0.998
1484 measured reflections
1279 independent reflections

911 observed reflections [$I > 3\sigma(I)$]
R_{int} = 0.0287
θ_{max} = 74.80°
$h = -19 \rightarrow 19$
$k = 0 \rightarrow 19$
$l = 0 \rightarrow 6$
3 standard reflections monitored every 100 reflections
intensity decay: 11.57%, correction applied

Refinement

Refinement on F
R = 0.034
wR = 0.029
S = 0.957
911 reflections
115 parameters
H atoms placed geometrically after each cycle
Weights: four-term polynomial (*CRYSTALS*; Watkin, Carruthers & Betteridge, 1985)

$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.189 e Å^{-3}
$\Delta\rho_{min}$ = −0.173 e Å^{-3}
Extinction correction: Larson (1970)
Extinction coefficient: 27 (4)
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2B)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
N(11)	0.6083 (1)	0.0980 (1)	0.5984 (4)	0.0493
N(12)	0.5936 (2)	0.1243 (2)	1.0312 (4)	0.0563
C(1)	0.6400 (1)	0.1131 (1)	0.8199 (4)	0.0418
C(2)	0.7339 (1)	0.1207 (1)	0.8436 (4)	0.0399
C(3)	0.7707 (2)	0.1663 (2)	1.0408 (5)	0.0518
C(4)	0.8582 (2)	0.1761 (2)	1.0517 (6)	0.0587
C(5)	0.9090 (2)	0.1400 (2)	0.8690 (5)	0.0621
C(6)	0.8729 (2)	0.0938 (2)	0.6738 (6)	0.0620
C(7)	0.7858 (2)	0.0842 (2)	0.6632 (5)	0.0508

Table 2. *Selected geometric parameters (Å, °)*

N(11)—C(1)	1.294 (3)	C(3)—C(4)	1.387 (4)
N(12)—C(1)	1.344 (3)	C(4)—C(5)	1.376 (4)
C(1)—C(2)	1.489 (3)	C(5)—C(6)	1.384 (4)
C(2)—C(3)	1.390 (3)	C(6)—C(7)	1.380 (4)
C(2)—C(7)	1.379 (3)		
N(11)—C(1)—N(12)	124.4 (2)	C(2)—C(3)—C(4)	120.1 (3)
N(11)—C(1)—C(2)	118.3 (2)	C(3)—C(4)—C(5)	120.1 (3)
N(12)—C(1)—C(2)	117.3 (2)	C(4)—C(5)—C(6)	120.0 (3)
C(1)—C(2)—C(3)	121.2 (2)	C(5)—C(6)—C(7)	119.7 (3)
C(1)—C(2)—C(7)	119.7 (2)	C(2)—C(7)—C(6)	120.9 (2)
C(3)—C(2)—C(7)	119.1 (2)		

Data collection: *AFC-7R Software* (Molecular Structure Corporation, 1993). Data reduction: *TEXSAN* (Molecular Structure Corporation, 1992). Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin, Carruthers & Betteridge, 1985). Molecular graphics: *CAMERON* (Pearce & Watkin, 1993). Software used to prepare material for publication: *CRYSTALS*.

HRP wishes to thank the CCDC and the University Chemical Laboratories, Cambridge, for the use of X-ray diffraction and computing facilities.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: HA1142). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Alcock, N. W., Barker, J. & Kilner, M. (1988). *Acta Cryst.* C**44**, 712–715.

Alcock, N. W., Blacker, N. C., Errington, W., Wallbridge, M. G. H. & Barker, J. (1994). *Acta Cryst.* C**50**, 456–458.

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–19.

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435–436.

Banner, D. W. & Hadvary, P. J. (1991). *Biol. Chem.* **266**, 20085–20093.

Barker, J. & Kilner, M. (1994). *Coord. Chem. Rev.* **133**, 219–300.

Barker, J. & Powell, H. R. (1995). *Acta Cryst.* C**51**, 1714–1716.

Beyer, S. A. & Zaneveld, L. J. D. (1982). *J. Reprod. Fertil.* **66**, 425–431.

Bode, W., Turk, D. & Stuerzebecher, J. (1990). *Eur. J. Biochem.* **193**, 175–182.

Brandstetter, H., Turk, D., Hoeffken, H. W., Grosse, D., Stuerzebecher, J., Martin, P. D. & Dehnicke, K. (1992). *J. Mol. Biol.* **226**, 1085–1099.

Dehnicke, K. (1990). *Chem. Ztg*, **114**, 295–304.

Diniz, C. R., Pereira, A. A., Barroso, J. & Mares-Guia, M. (1965). *Biochem. Biophys. Res. Commun.* **21**, 448–453.

Jeffcoate, S. L. & White, N. J. (1974). *Clin. Endocrinol. Metab.* **38**, 155–157.

Larson, A. C. (1970). *Crystallographic Computing*, edited by F. R. Ahmed, S. R. Hall & C. P. Huber, pp. 291–294. Copenhagen: Munksgaard.

Le Page, Y., Tran Qui, D., Marsura, A., Duc, C. L., Gellon, G. & Gey, C. (1984). *Acta Cryst.* A**40**, C-81.

Markwardt, F., Landmann, H. & Walsmann, P. (1968). *Eur. J. Biochem.* **6**, 502–506.

Marquart, M., Walter, J., Deisenhofer, J., Bode, W. & Huber, R. (1983). *Acta Cryst.* B**39**, 480–490.

Marsura, A., Duc, C. L. & Gellon, G. (1984). *Tetrahedron Lett.* **25**, 4509–4510.

Molecular Structure Corporation (1992). *TEXSAN. Single Crystal Analysis Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Molecular Structure Corporation (1993). *Rigaku AFC-7R Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Norrestam, R., Mertz, S. & Crossland, I. (1983). *Acta Cryst.* C**39**, 1554–1556.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Pearce, L. J. & Watkin, D. J. (1993). *CAMERON*. Chemical Crystallography Laboratory, University of Oxford, England.
Perona, J. J., Tsu, C. A., McGrath, M. E., Craik, C. S. & Fletterick, R. J. (1993). *J. Mol. Biol.* **230**, 934–949.
Robert, M. & Gagnon, C. (1994). *Int. J. Androl.* **17**, 232–240.
Sprang, S., Standing, T., Fletterick, R. J., Stroud, R. M., Finer-Moore, J., Xuong, N.-H., Hamlin, R., Rutter, W. J. & Craik, C. S. (1987). *Science*, **237**, 905–909.
Watkin, D. J., Carruthers, J. R. & Betteridge, P. W. (1985). *CRYSTALS User Guide*. Chemical Crystallography Laboratory, University of Oxford, England.

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Diclofenac Salts. IV. Tris(2-hydroxyethyl)-ammonium 2-(2,6-Dichlorophenylamino)-phenylacetate

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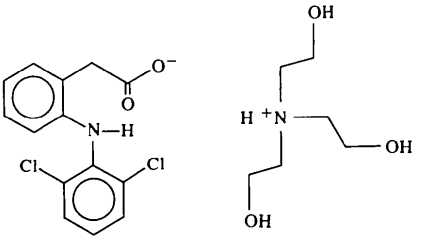
Abstract

The structure of the salt of 2-(2,6-dichlorophenylamino)-phenylacetic acid (HD) with tris(2-hydroxyethyl)amine (TEA), $C_6H_{16}NO_3^+.C_{14}H_{10}Cl_2NO_2^-$, consists of hydrogen-bonded $HTEA^+$ cations and D^- anions, as found in similar acid–base adducts of HTEA. There are no intermolecular hydrogen bonds between the ammonium H atom and the phenylacetate group; this may be attributed to the presence of a weak trifurcated intramolecular N—H···$(O)_3$ hydrogen bond within the cation. Inter-ion hydrogen bonds are established through the OH groups of the cations leading to a two-dimensional network.

Comment

The crystal structure determination of the title compound was carried out as part of a study on acid–base adducts derived from diclofenac (HD), a potent non-steroidal drug widely used in rheumatology as its sodium salt. The aim of this structural study was to look for a relationship between the conformational features of these salts and their solubility. The solid-state structure of HTEA.D contains a sequence of $HTEA^+$ cations and D^- anions linked by hydrogen bonds (Fig. 1). The presence of ionic moieties agrees with the model of Huyskens & Zeegers-Huyskens (1964) which predicts that a difference of about four orders of magnitude between the acid dissociation constants of the base (TEA, pK_a = 7.8; van Mier, Kanters & Poonia, 1988) and the acid (HD, pK_a = 3.80; Fini, Zecchi & Tartarini, 1985) leads to an almost complete shift of the proton-transfer equilibrium of the O—H···N ↔ O^-···H—N^+ system.



HTEA.D

The interionic linkage can be described as follows: the carboxyl O2 and O1 atoms of D accept two hydrogen bonds from the hydroxyl O3 and O4 atoms of HTEA [O3···O2 2.633 (3) and O4···O1($\frac{3}{2}-x$, $\frac{1}{2}+y$, $-z$) 2.613 (3) Å], while the O5 atom of one HTEA molecule is bonded to the O4 atom of another [O5···O4($\frac{1}{2}+x$, $\frac{3}{2}-y$, z) 2.744 (3) Å]. The former two cation–anion hydrogen bonds generate an infinite two-dimensional network along the [010] and [100] base vectors, respectively. We note that this network of hydrogen bonds can persist in solvents of low dielectric

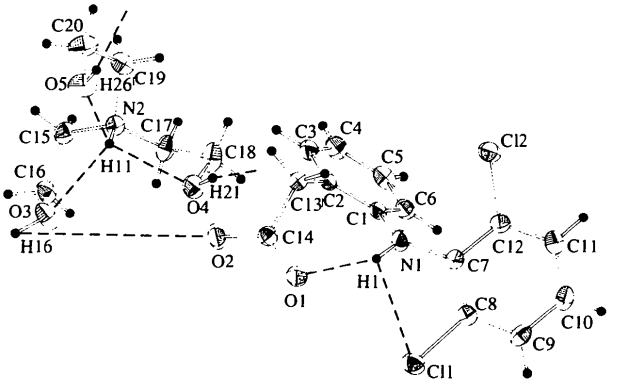


Fig. 1. The molecular conformation of the 1:1 adduct HTEA.D showing the atomic labelling and hydrogen bonds (50% probability displacement ellipsoids and H atoms as spheres of arbitrary size). For clarity, only the main conformer of HTEA is given.