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Benzamidine

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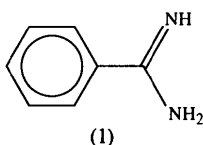
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Abstract

Benzenecarboximidamide, C₇H₈N₂, 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 benzamidine 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.



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 Csp²—Csp² 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 benzamidine salt in a later paper (Le Page *et al.*, 1984).]

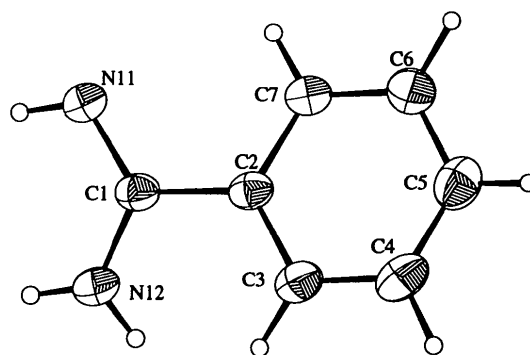


Fig. 1. Molecular structure for benzamidine with the labelling scheme for non-H atoms. Displacement ellipsoids are shown at 50% probability levels; H atoms are drawn as small circles of arbitrary radii.

Four molecules are hydrogen bonded together around a 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 C₇H₈N₂: C 70.57, H 5.92, N 23.51%, found C 69.53, H 6.32, N 23.55%. ¹H NMR (CDCl₃): 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*). ¹³C NMR: 166.29 (N—C—N), 136.71, 130.20, 128.52, 125.86, (Ar) p.p.m.

Crystal data

C ₇ H ₈ N ₂	Cu Kα radiation
<i>M_r</i> = 120.16	λ = 1.5418 Å
Tetragonal	Cell parameters from 25 reflections
<i>I</i> 4	θ = 58.5–59.9°
<i>a</i> = 15.7353 (20) Å	μ = 0.567 mm ^{−1}
<i>c</i> = 5.2803 (17) Å	<i>T</i> = 293 K
<i>V</i> = 1307.28 Å ³	Block
<i>Z</i> = 8	0.24 × 0.20 × 0.20 mm
<i>D_x</i> = 1.22 Mg m ^{−3}	Colourless
<i>D_m</i> not measured	

Data collection

Rigaku AFC-7R diffractometer	911 observed reflections
ω/2-θ scans	[<i>I</i> > 3σ(<i>I</i>)]
Absorption correction:	<i>R</i> _{int} = 0.0287
empirical, ψ-scan (North, Phillips & Mathews, 1968)	θ _{max} = 74.80°
<i>T</i> _{min} = 0.973, <i>T</i> _{max} = 0.998	<i>h</i> = −19 → 19
1484 measured reflections	<i>k</i> = 0 → 19
1279 independent reflections	<i>l</i> = 0 → 6
	3 standard reflections monitored every 100 reflections
	intensity decay: 11.57%, correction applied

Refinement

Refinement on <i>F</i>	(Δ/σ) _{max} = 0.003
<i>R</i> = 0.034	Δρ _{max} = 0.189 e Å ^{−3}
<i>wR</i> = 0.029	Δρ _{min} = −0.173 e Å ^{−3}
<i>S</i> = 0.957	Extinction correction: Larson (1970)
911 reflections	Extinction coefficient: 27 (4)
115 parameters	Atomic scattering factors from <i>International Tables for X-ray Crystallography</i> (1974, Vol. IV, Table 2.2B)
H atoms placed geometrically after each cycle	
Weights: four-term polynomial (CRYSTALS; Watkin, Carruthers & Betteridge, 1985)	

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

	$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$			
	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{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: *SIR92* (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*.

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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.

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

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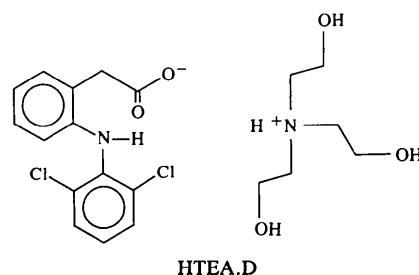
Abstract

The structure of the salt of 2-(2,6-dichlorophenylamino)-phenylacetic acid (HD) with tris(2-hydroxyethyl)amine (TEA), $C_6H_{16}NO_3^+ \cdot C_{14}H_{10}Cl_2NO_2^-$, 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 $O-H \cdots N \leftrightarrow O^- \cdots H-N^+$ system.



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 [$O3 \cdots O2$ 2.633 (3) and $O4 \cdots O1(\frac{3}{2} - x, \frac{1}{2} + y, -z)$ 2.613 (3) Å], while the O5 atom of one HTEA molecule is bonded to the O4 atom of another [$O5 \cdots O4(\frac{1}{2} + x, \frac{3}{2} - y, z)$ 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

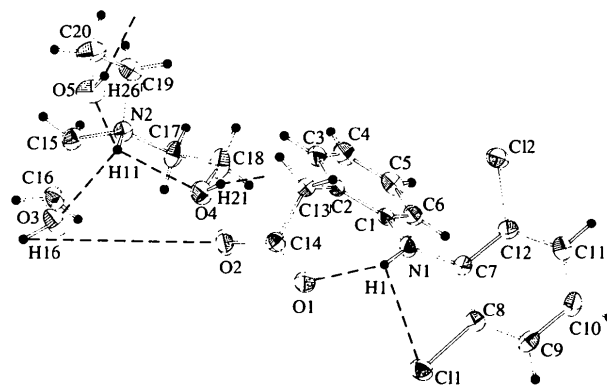


Fig. 1. The molecular conformation of the 1:1 adduct HTEA.D showing the atomic labelling and hydrogen bonds (50% probability displacement ellipsoids and H atoms as spheres of arbitrary size). For clarity, only the main conformer of HTEA is given.