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Hydrogen-bonding interactions in the 4-aminobenzoic acid salt of atenolol monohydrate

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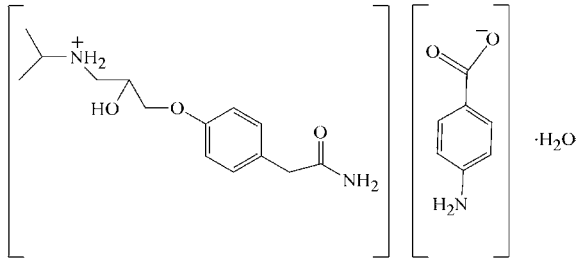
Atenolol {or 4-[2-hydroxy-3-(isopropylamino)propoxy]phenylacetamide} crystallizes with 4-aminobenzoic acid to give the salt {3-[4-(aminocarbonylmethyl)phenoxy]-2-hydroxypropyl}isopropylammonium 4-aminobenzoate monohydrate, $C_{14}H_{23}N_2O_3^+\cdot C_7H_6NO_2^-\cdot H_2O$. In the crystal structure, the water molecule, the carboxylate group of 4-aminobenzoate, and the hydroxy and ether O atoms of atenolol form a supramolecular $R_3^3(11)$ heterosynthon. Three other types of supramolecular synthons link the asymmetric unit into a two-dimensional structure.

Comment

Multicomponent crystals of active pharmaceutical ingredients (APIs) may offer advantages over the corresponding APIs in terms of physical properties such as crystallinity, solubility and dissolution rate (Black *et al.*, 2007; Childs *et al.*, 2007). Hydrogen-bonded supramolecular synthons are commonly used as a reliable method in the formation of these crystals (Wenger & Bernstein, 2006). Recently, the hierarchy of synthons in a competitive environment has been studied intensively (Bis *et al.*, 2007). Atenolol, 4-[2-hydroxy-(3-isopropylamino)propoxy]phenylacetamide, is a drug belonging to the group of beta blockers used primarily in cardiovascular diseases. From the viewpoint of crystal engineering, atenolol can provide various hydrogen-bonding interactions since it contains multiple typical hydrogen-bonding groups. Recently, Cai *et al.* (2006) reported its hydrated succinate and fumarate salts, in which various hydrogen bonds result in three-dimensional structures. In the present study, we chose 4-aminobenzoic acid as a second component containing both amino and carboxylic acid groups in the structure and prepared the monohydrous molecular salt, (I), of atenolol, in which versatile hydrogen-bonding interactions result in a two-dimensional structure.

The crystal structure of (I) contains one atenolol, one 4-aminobenzoic acid and one water molecule in the asymmetric unit. Difference Fourier maps show that 4-aminobenzoic acid transfers the carboxyl H atom to the secondary amine of atenolol. The C—O distances in the carboxylate



(I)

group are equal within error margins [1.264 (2) and 1.263 (2) Å]. The water molecule is simultaneously hydrogen bonded to the carboxylate group and the ether O atom of atenolol (O6—H6*B*···O4 and O6—H6*A* ···O2; Table 1). The hydroxy group of atenolol is also hydrogen bonded to the carboxylate group of the anion (O3—H3···O5), forming a supramolecular $R_3^3(11)$ heterosynthon (Fig. 1). The amide group of atenolol is hydrogen bonded to the amine group of another 4-aminobenzoate anion [N3—H3*A*···O1($1-x, 2-y, 1-z$)], which generates a centrosymmetric tetramer based on the $R_6^6(38)$ synthon. Moreover, N2—H8···O6($1-x, 2-y, 1-z$) hydrogen bonds between the water molecule and the protonated secondary amine of atenolol participate in the formation of the tetramer. The tetramer is further linked into a one-dimensional chain structure along the *b* axis by N2—H9···O3($1-x, 1-y, 1-z$) hydrogen bonds between the hydroxy group and the secondary amine from an adjacent atenolol molecule, generating a self-complementary $R_2^2(10)$ synthon (Fig. 2). The amide group of atenolol is also involved in hydrogen-bonding interactions with the carboxylate group of the anion [N1—H1*B*···O4($1-x, y, \frac{3}{2}-z$)], giving a centrosymmetric $R_6^4(26)$ ring which connects the one-dimensional chain into a two-dimensional structure (Fig. 3).

Atenolol contains an amide group, a secondary amine, and hydroxy and ether O atoms. For such a complicated system, it is difficult to predict reliable supramolecular synthons. In the structure of its succinate salt (Cai *et al.*, 2006), the carboxylate group of succinate is simultaneously hydrogen bonded to the hydroxy and secondary amine groups of atenolol, generating a centrosymmetric three-component adduct. There exists a

Figure 1
A displacement ellipsoid plot of (I), shown with 50% probability displacement ellipsoids. The dashed lines indicate hydrogen bonds.

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hydrogen-bonded chain of amide groups linking the adduct into a two-dimensional structure, which is further linked into a three-dimensional structure by hydrogen bonds between amide and carboxylate groups, together with hydrogen bonds between hydroxy and secondary amine groups. By contrast, in (I), no hydrogen bonding is formed between the carboxylate group of the anion and the secondary amine of atenolol, although 4-aminobenzoic acid transfers its carboxylic acid H atom to the secondary amine. Moreover, the ether O atom of atenolol also participates in hydrogen-bonding interactions, resulting in the $R_3^3(11)$ synthon. The hydrogen-bonding pattern of the amide group in (I) is also different from that in the succinate salt. The amide group generates two rings, *viz*. $R_6^6(38)$ and $R_6^4(26)$, with amine and carboxylate groups of the anion, respectively. Thus, atenolol interacts with 4-aminobenzoate through three types of featured synthons.

In conclusion, in the crystal structure of (I), the water molecule, the carboxylate group of the anion, and the hydroxy and ether O atoms of atenolol form a supramolecular $R_3^3(11)$ heterosynthon, while three other types of self-complementary supramolecular synthons, *viz*. $R_6^6(38)$, $R_6^4(26)$ and $R_2^2(10)$, link the asymmetric unit into a two-dimensional structure.

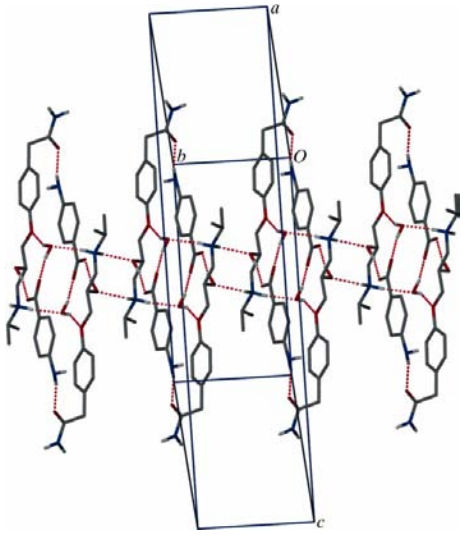

Figure 2
The one-dimensional structure of (I), viewed along the *b* axis. Dashed lines indicate hydrogen bonds.

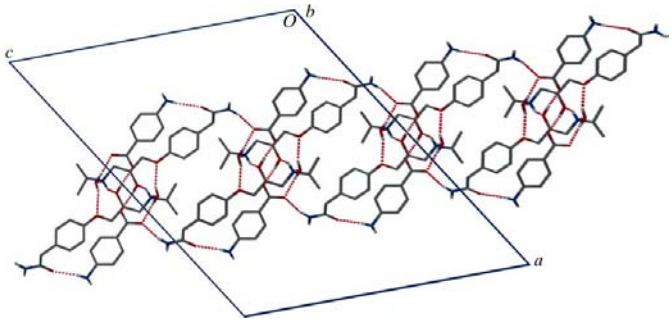

Figure 3
The two-dimensional structure of (I), viewed along the *b* axis. Dashed lines indicate hydrogen bonds.

Experimental

A mixture of atenolol (0.067 g, 0.25 mmol) and 4-aminobenzoic acid (0.034 g, 0.25 mmol) was dissolved in ethanol (95%, 15 ml). The solution was kept in air and after several days colorless crystals were obtained. Differential scanning calorimetry showed two endothermic peaks at 395 and 434 K.

Crystal data

$C_{14}H_{23}N_2O_3^+\cdot C_7H_6NO_2^-\cdot H_2O$
M_r = 421.49
Monoclinic, $C2/c$
a = 28.547 (6) Å
b = 7.4223 (15) Å
c = 23.822 (5) Å
β = 122.34 (3)°
V = 4265 (2) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 150 (2) K
0.48 × 0.20 × 0.16 mm

Data collection

Nonius KappaCCD diffractometer
8459 measured reflections
4897 independent reflections
3926 reflections with $I > 2\sigma(I)$
R_{int} = 0.021

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.138
S = 1.08
4897 reflections
309 parameters
9 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.66 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O6—H6A···O2	0.86 (2)	2.22 (2)	3.042 (2)	161 (2)
O6—H6B···O4	0.87 (2)	1.89 (2)	2.744 (2)	171 (2)
O3—H3···O5	0.89 (2)	1.71 (2)	2.594 (2)	172 (3)
N1—H1B···O4^{i}	0.87 (2)	2.15 (2)	3.008 (2)	171 (2)
N3—H3A···O1^{ii}	0.87 (2)	2.02 (2)	2.880 (2)	171 (2)
N2—H8···O6^{ii}	0.87 (2)	1.92 (2)	2.773 (2)	166 (2)
N2—H9···O3^{iii}	0.87 (2)	2.15 (2)	2.812 (2)	133 (2)

Symmetry codes: (i) $-x+1, y, -z+\frac{3}{2}$; (ii) $-x+1, -y+2, -z+1$; (iii) $-x+1, -y+1, -z+1$.

H atoms bonded to C atoms were positioned geometrically and treated as riding [C—H = 0.95–1.00 Å and U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(C)]. H atoms bonded to N and O atoms were located in difference maps and were refined with a distance restraint of O—H = N—H = 0.86 (1) Å; the displacement parameters were freely refined. The maximum residual electron density is larger than normally expected. The nearest atom to this maximum is atom C10 at a distance of 1.15 Å.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *X-SEED* (Barbour, 2001); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ3104). Services for accessing these data are described at the back of the journal.

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