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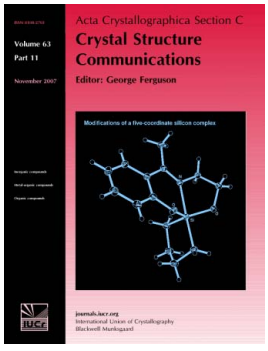

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1-(9*H*-Carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-propan-2-ol hemihydrate: a carvedilol solvatomorph

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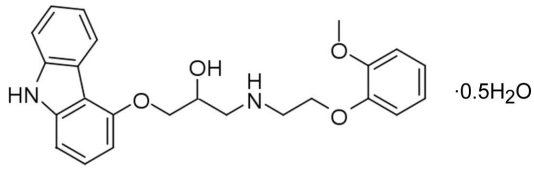
In the title racemic hemihydrated solvatomorph of carvedilol (carv), $C_{24}H_{26}N_2O_4\cdot0.5H_2O$, the asymmetric unit contains two independent organic moieties and one water molecule. Within this 2(carv)·H_2O unit, the molecular components are strongly linked by hydrogen bonds and the unit acts as the basic building block for the crystal structure. Interactions parallel to $(10\bar{1})$ generate hydrogen-bonded layers which are further linked by much weaker C—H···N/O interactions. The conformations of the organic molecules, as well as the hydrogen-bonding interactions connecting them, are compared with other related structures in the literature.

Comment

Carvedilol is a drug indicated for use in the treatment of mild-to-moderate congestive heart failure, acting both as a β_1/β_2-blocker and as an α_1-blocker. It counteracts the (sometimes undesirable) effect of natural norepinephrine, a drug/hormone produced in the human body which by binding to the β_1- and β_2-adrenergic receptors (Stafylas & Sarafidis, 2008) stimulates the nerves controlling the muscles of the heart, and by binding to the α_1-adrenergic receptors on blood vessels causes them to constrict and thus raise blood pressure (Othman *et al.*, 2007). Through a blocking action towards these receptors, carvedilol lowers blood pressure and reduces heart failure.

There are at present five reported structures containing some form of carvedilol (carv): two of them are different polymorphs of the carvedilol free base [(II) (Chen *et al.*, 1998) and (III) (Yathirajan *et al.*, 2007)], two others are phosphate salts of the protonated carvH$^+$ cation [carvH$^+$·$H_2PO_4^-$·-0.5H_2O, (IV) (Chernyshev *et al.*, 2009), and carvH$^+$·$H_2PO_4^-$·-C_3H_8O, (V) (Chernyshev *et al.*, 2010)], and the fifth structure is a copper complex with carvedilol acting as a mono-deprotonated ligand {[Cu(carv)Cl(MeOH)]$_2$·4MeOH, (VI); Zoroddu *et al.*, 2003}. We report here a hemihydrated form of the drug, namely 1-(9*H*-carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}propan-2-ol hemihydrate, (I), where two independent carvedilol molecules (labelled *A* and *B*) share a single water molecule, itself a key component in the crystal structure organization, as discussed below.



(I)

The compound crystallizes as a racemate in the centrosymmetric space group $P2_1/n$ (Fig. 1). The two independent carvedilol molecules have internal distances and angles quite similar to each other and to those of the previously reported examples. Similarities include the presence in both molecules of an O atom (O1) disordered over two sites on the host C atom (C21), with one configuration clearly dominant (see *Refinement* section for details).

In spite of their metric similarities, the conformations of molecules *A* and *B* in (I) are quite different, even though both central chains are essentially planar and the lateral aromatic side groups are structurally similar. The differences arise at the ends of the central chain, where the carbazole system and the $MeOC_6H_4$– groups are attached; it is here that the torsion angles defining the three-dimensional molecular structure show significant differences (Table 2, entries 1–2). Fig. 2(*a*)

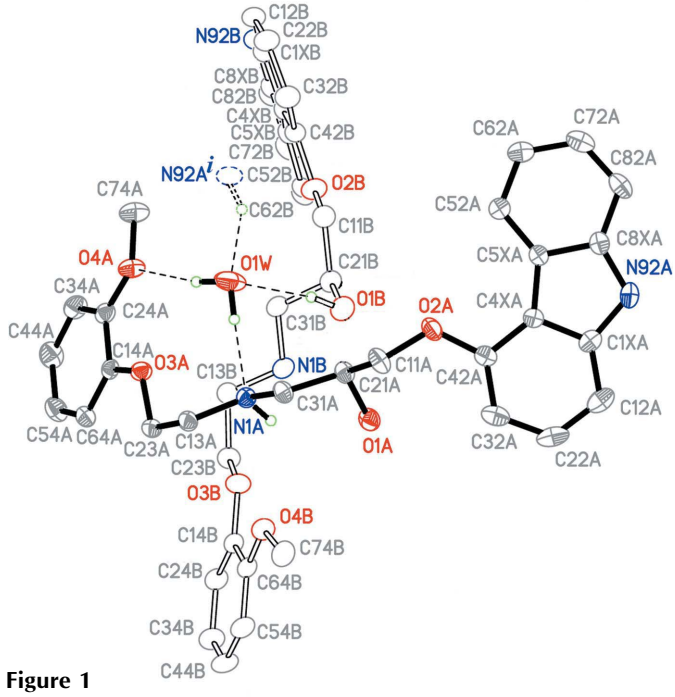


Figure 1
The molecular structure of (I), showing the atom-labelling scheme and with displacement ellipsoids drawn at the 30% probability level. Only the major component of disordered atoms O1*A*/*B* and the H atoms involved in hydrogen bonds are shown. Hydrogen bonds are indicated by dashed lines. [Symmetry code: (i) $-x+\frac{1}{2}, y-\frac{1}{2}, -z+\frac{1}{2}$.]

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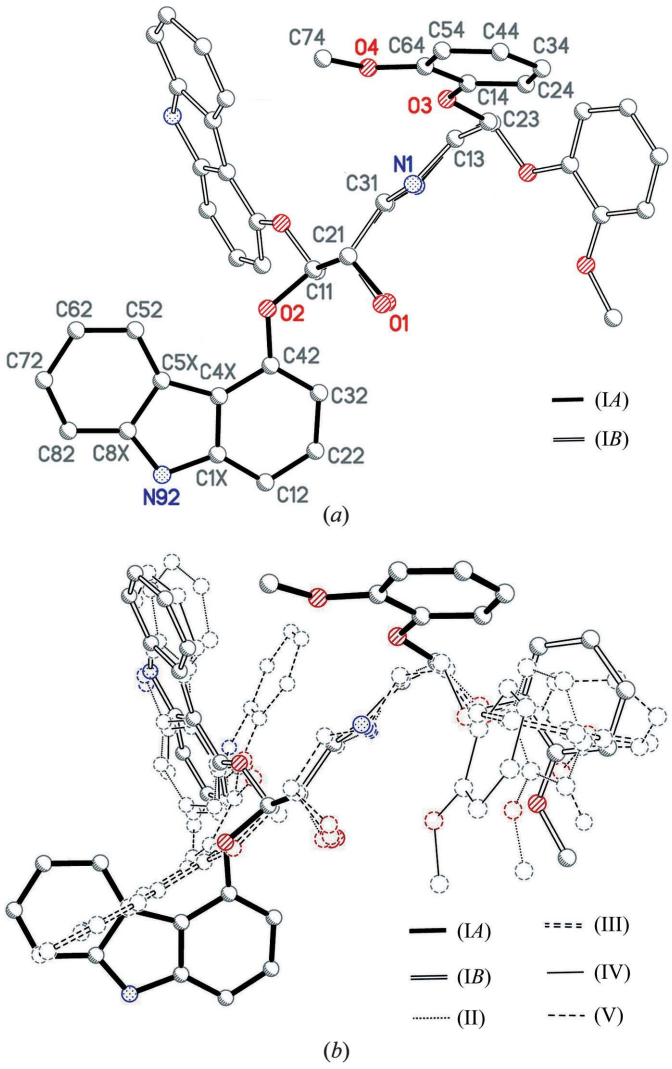


Figure 2
(*a*) The overlap of the two independent molecules (*A* and *B*) in (I), after a least-squares fit of their 'skeletal spine', *viz.* C11—C21(O1)—C31—N2—C13—C23. (*b*) The same as for (*a*) but performed with the remaining carvedilol structures available in the literature. [See *Comment* for definitions of structures (II), (III), (IV) and (V).]

presents a combined view of both molecules after a least-squares fit of their 'skeletal spine' [atoms C11—C21(O1)—C31—N2—C13—C23]; the way in which the side wings depart from each other is apparent.

But this behaviour is not exclusive to molecules *A* and *B* in (I); a very similar behaviour can be observed in the remaining noncoordinated carvedilol molecules/ions [(II)–(V)] mentioned above. All of them present a rather planar aliphatic central chain, as shown by the torsion angles involving the constituent atoms (Table 1, entries 3–5), differing by just a few degrees from a perfect antiperiplanar local conformation [with the sole exception of C11—C21—C31—N1 for compound (V)]. This can be seen in Fig. 2(*b*), where a similar fit as in Fig. 2(*a*) is shown, but performed on all six molecular units. Fig. 2(*a*) clearly shows the variety of conformations attainable through the combination of the rather low energy barrier to rotation in the aliphatic chain and the highly interactive character of both aromatic ends (the carbazole group, *via* its donor N92—H92 group, and the $MeOC_6H_4$– unit through its O1 acceptor). In the case of (I), this latter tendency is enhanced by the presence of a highly active water molecule, which is a determinant in the final packing of the structure.

Table 2 presents numerical values for the most significant hydrogen bonds in the structure and Fig. 1 displays all those in which O1*W* takes part. The water molecule acts as a double donor–double acceptor (Table 2, entries 1–2 and 3–4, respectively). The water molecule is attached to carvedilol molecule *A* through hydrogen bonds 1 and 2, giving rise to an $R_2^2(10)$ ring (Bernstein *et al.*, 1995). The third hydrogen bond links independent carvedilol molecules *A* and *B* into a strongly bound 2(carv)·H_2O unit. Finally, the remaining hydrogen bond accepted by O1*W* (Table 2, entry 4, and Fig. 1) links these three-component units into zigzag chains parallel to [010] (Fig. 3).

There are two further conventional hydrogen bonds in the structure of (I) (Table 2, entries 5–6), which link ribbons together along [101] and define broad planes parallel to $(10\bar{1})$. Strikingly, neither of the N1*A*—H1*A*N or N92*B*—H92*B* groups is involved in hydrogen-bonding interactions: interplanar linkage is achieved through much weaker C—H···N/O contacts and no significant π–π interactions could be detected in the structure. The resulting packing scheme is schematically depicted in Fig. 3, where some of these planes (in different shading) are seen down *b*, with their projected image running along [101].

As a final remark about which are the leading sites for hydrogen bonding in carvedilol, in unsolvated polymorphs (II) and (III) there are two direct contacts joining adjacent molecules with each other and giving rise to characteristic two-dimensional structures. These interactions, of the hydroxy–amine O—H···N and carbazole–methoxy N—H···O types, are quite similar in both unsolvated structures, in spite of circumstancial differences in the unit cell, the atomic confor-

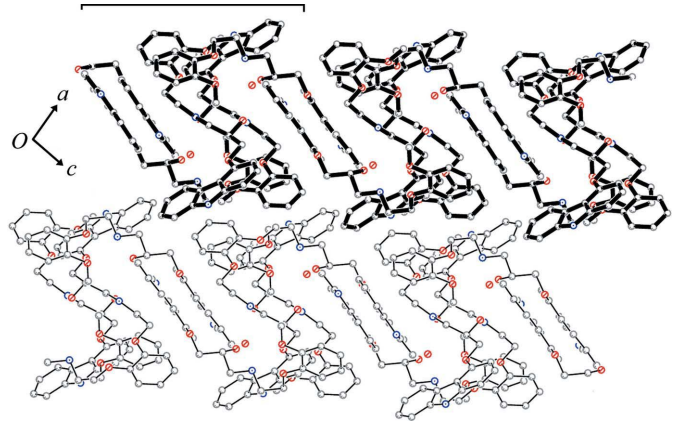
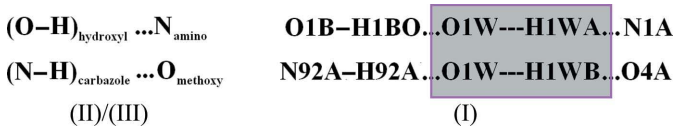


Figure 3
A packing diagram for (I), viewed down the [010] chains (coming out of the plane, and marked with a square bracket), showing in projection the broad hydrogen-bonded $(10\bar{1})$ planes (drawn in alternate shading). H atoms bonded to C atoms have been omitted for clarity.

mation and the packing disposition, as shown in Yathirajan *et al.* (2007).

In the present hemihydrated form, (I), there are instead four hydrogen bonds connecting adjacent *A* and *B* molecules, but this is a deceiving difference: a closer look shows that, in fact, the single hydration water molecule can be considered as only an intermediate step in a more complex set-up of the same type of interactions. The scheme below shows the way in which this is achieved, and how the same bonding scheme can be envisioned by just thinking of the interactions involving O1*W*—H1*WA*/*B* as 'transparent'. Thus, the water molecule would not play any genuine interacting role but 'propagates' instead the leading interactions, generated by the same participants as in (II) and (III). This is only one of the many roles that hydration water molecules can play in crystal structures; a very detailed analysis (for the particular case of inorganic/geological compounds, but readily extendable to any general case) can be found in Hawthorne (1992).



Experimental

The original material, kindly provided by Laboratorios Quesada Farmacéutica, was dissolved in chloroform and the solution was left to slowly concentrate at ambient temperature in air. After one week, well developed single crystals in the form of rhomboidal plates, suitable for X-ray diffraction, were obtained. Since no particular effort was made to have a water-free solvent nor to inhibit air/moisture from getting into the solution, the reasons for the presence of a solvation water molecule may be multiple. A thermogravimetric experiment in the temperature range 300–600 K showed a diffuse mass loss in the range 340–370 K (mass loss found = 2.26%; expected mass loss for $0.5H_2O$ = 2.17%).

Crystal data

$C_{24}H_{26}N_2O_4\cdot0.5H_2O$
M_r = 415.48
Monoclinic, $P2_1/n$
a = 13.550 (3) Å
b = 16.780 (3) Å
c = 19.150 (4) Å
β = 94.36 (3)°
V = 4341.5 (15) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 291 K
0.28 × 0.18 × 0.08 mm

Data collection

Oxford Diffraction Gemini CCD S Ultra diffractometer
Absorption correction: multi-scan (*CrysAlis PRO*; Oxford Diffraction, 2009)
T_{min} = 0.98, T_{max} = 0.99
34926 measured reflections
8928 independent reflections
5209 reflections with $I > 2\sigma(I)$
R_{int} = 0.035

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.147
S = 1.05
8928 reflections
558 parameters
6 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.44 e Å^{-3}
$\Delta\rho_{min}$ = −0.39 e Å^{-3}

Table 1
Comparison of torsion angles (°) for the 'skeletal spine', *viz.* C11—C21(O1)—C31—N1—C13—C23, in (I*A*), (I*B*), (II), (III), (IV) and (V).

Torsion angle	(I*A*)	(I*B*)	(II)	(III)	(IV)	(V)
O2—C11—C21—C31	−165.6 (2)	−59.5 (3)				
N1—C13—C23—O3	−64.4 (2)	66.5 (3)				
C11—C21—C31—N1	173.5 (2)	176.8 (2)	175.0 (2)	178.19 (15)	168.5 (2)	−143.9 (4)
C21—C31—N1—C13	174.9 (2)	170.4 (2)	167.3 (2)	178.21 (13)	176.3 (2)	−176.5 (9)
C31—N1—C13—C23	−178.0 (2)	−172.4 (2)	177.8 (2)	174.43 (17)	179.3 (2)	−178.4 (6)

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

D—H···A	D—H	H···A	D···A	D—H···A
O1*W*—H1*WA*···N1*A*	0.90	1.88	2.775 (3)	178
O1*W*—H1*WB*···O4*A*	0.90	2.04	2.920 (3)	165
O1*B*—H1*BO*···O1*W*	0.90	2.24	3.131 (4)	173
N92*A*—H92*A*···O1*W*^{i}	0.90	2.01	2.862 (3)	158
N1*B*—H1*BN*···O1*B*^{ii}	0.90	2.40	3.043 (3)	129
O1*A*—H1*AO*···N1*B*^{ii}	0.90	1.98	2.863 (3)	167

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

In both independent molecules, atom O1 attached to C21 appears split over two sites, but with different occupancies, *viz.* 0.873 (3): 0.127 (3) in molecule *A* and 0.821 (3):0.179 (3) in molecule *B*. This disorder is thus configurational, with both moieties in the selected asymmetric unit having the *S* configuration for the major fraction. The split O atoms were restrained to have similar C—O distances within a tolerance of 0.001 Å and constrained to have the same anisotropic displacement parameters [SADI and EADP instructions in *SHELXL97* (Sheldrick, 2008)]. All the H atoms (except those attached to O1*A*′ and O1*B*′, which consequently were not included in the model) were found in a difference Fourier map. Those attached to C atoms were placed at calculated positions (aromatic C—H = 0.93 Å, methine and methylene C—H = 0.97 Å and methyl C—H = 0.96 Å) and were allowed to ride on their parent atom. Those attached to O and N atoms were refined for a further few cycles with restrained O—H = N—H = 0.90 (1) Å distances, and left to ride afterwards. In all cases, displacement parameters were taken as U_{iso}(H) = kU_{eq}(carrier), where k = 1.5 for the methyl groups and 1.2 for all other H atoms.

Data collection: *CrysAlis PRO* (Oxford Diffraction, 2009); cell refinement: *CrysAlis PRO*; data reduction: *CrysAlis PRO*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXL97* and *PLATON* (Spek, 2009).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3393). Services for accessing these data are described at the back of the journal.

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