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Cephalexin: a channel hydrate

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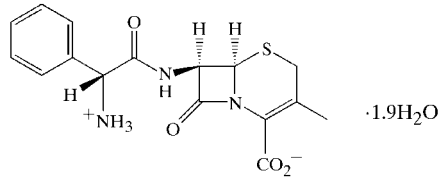
The antibiotic cephalexin [systematic name: D-7-(2-amino-2-phenylacetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid] forms a range of isomorphic solvates, with the maximum hydration state of two water molecules formed only at high relative humidities. The water content of the structure reported here ($C_{16}H_{17}N_3O_4S\cdot1.9H_2O$) falls just short of this configuration, having three independent cephalexin molecules, one of which is disordered, and 5.72 observed water molecules in the asymmetric unit. The facile nature of the cephalexin solvation/desolvation process is found to be facilitated by a complex channel structure, which allows free movement of solvent in the crystallographic *a* and *b* directions.

Comment

The cephalosporin derivative cephalexin (CEX) is an antibiotic useful for treating a variety of infections, including those of the respiratory tract, of the skin and of other soft tissues. The characterization of the solid-state properties of CEX has, however, been hampered by uncertainty over the exact nature of its hydration behaviour. CEX can form a range of hydrates in the solid state, all with essentially identical unit cells, and has thus been identified as part of the class of compounds known as isomorphic desolvates (Stephenson *et al.*, 1998). Indeed, CEX is known to go further and reversibly replaces water with other small, polar, solvent molecules (Pfeiffer *et al.*, 1970). Powder diffraction studies show that the isomorphic solvates have similar unit-cell dimensions but, despite their crystallographic similarities, their commercially important physical properties (such as their solubilities and dehydration behaviour) vary considerably. Despite considerable interest in CEX, no single-crystal structure determination had previously been achieved, and so the structural basis of its ready solvation/desolvation process remained unknown. However, we have overcome the problems of small crystal size and loss of (single) crystallinity upon facile dehydration by utilizing careful sample preparation methods (see *Experimental*) and the extra intensity of synchrotron radiation to report here the first crystal structure of any CEX hydrate, that of $CEX\cdot1.9H_2O$, (I).



(I)

The asymmetic unit of (I) was found to contain three CEX molecules and, spread over ten sites, 5.72 water molecules. The three crystallographically independent molecules of CEX (Fig. 1) were found to exist in the zwitterionic form, with no significant differences in their bond lengths or angles. One CEX molecule is disordered. There is some flexibility in the amide backbone, with the O—C—C—N(H_3) torsion angles ranging from 27.3 (6) to 44.5 (6)°. The geometry of the related species cefadroxil (Shin & Cho, 1992) has a similar conformation, fitting within the range found here for CEX, as does CEX complexed with β-napthol (Kemperman *et al.*, 1999), although here the amide backbone is more eclipsed (equivalent angle = 16.2°).

That the stochiometrically exact dihydrate is not found is unsurprising, given the steep gradient observed by Stephenson *et al.* (1998) in the moisture adsorption isotherms of CEX. Only above 70% relative humidity does CEX begin to approach a genuine dihydrate. The structural basis of the ready transportation of water is seen in Fig. 2. The water molecules lie in a distinct channel, which zigzags along the *a* direction. The channel displays distinct and repeating narrow and wide sections along its length, with the narrower section (containing atoms O17 and O19) centred about $a = 0$ and 0.5, and the wider section about $a = 0.25$ and 0.75. These wide and narrow sections extend separately along the *b* direction, creating a grid of channels extending throughout the *ab* plane.

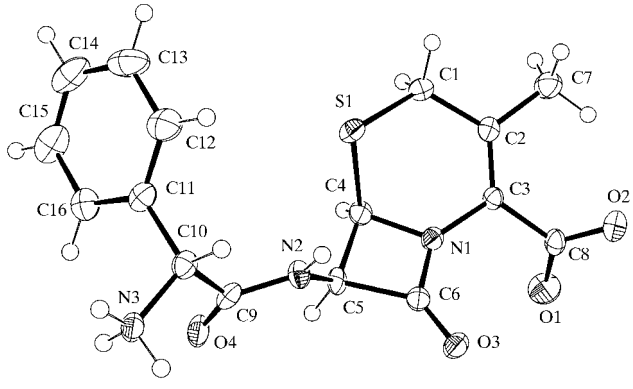


Figure 1
A displacement ellipsoid plot of one of the three unique molecules of CEX in the asymmetric unit. Non-H atoms are shown as 50% probability ellipsoids and H atoms as small spheres of arbitrary size.

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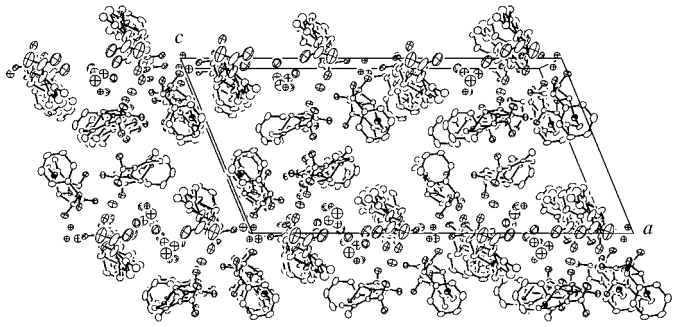

Figure 2
The crystal packing of (I), viewed along the *b* axis.

Only atom O15 appears to lie outside the channels running along *b*. With solvent transport blocked only in the *c* direction, it can easily be seen how different CEX hydrates can have similar unit cells. The water sites exist as pairs with a total occupancy of 1, except for atom O13 in the wide section, which is the only fully occupied site, and the uniquely positioned atom O15. This complex arrangement with fluctuating void spaces must have a considerable effect on the dehydration behaviour of CEX. Interpreting the hydrogen-bonding behaviour is difficult, as the H atoms of the water molecules could not be reliably placed. Table 1 shows only hydrogen bonding involving N—H donors, but it should be remembered that there must be considerable bonding *via* O—H donors as well. Within these limitations, some interesting points can be raised. Firstly, only those water sites already highlighted (the narrow channel sites O15, O17 and O19, and the wholly occupied site O13) form hydrogen bonds with amine units. It is tempting to suggest that loss of the other water molecules should be favoured, leaving, as is in fact found under ambient conditions, a compound that is approximately a monohydrate. There is also a sharp change in the gradient of Stephenson's moisture adsorption isotherm, corresponding to a psuedo-stable partial hydrate ($CEX{\cdot}nH_2O$, with $n = 0.25$–0.35). This behaviour could be explained by further site-selective stripping of water to leave perhaps only the completely occupied site O13 (giving $CEX{\cdot}0.33H_2O$) or the unique site O15 (giving $CEX{\cdot}0.24H_2O$).

Experimental

Crystalline CEX was obtained by suspending small amounts of technical grade CEX powder in a saturated aqueous solution and allowing slow evaporation to take place at room temperature. The crystals were isolated from solution, blotted free of liquid, packed in well sealed containers, with a minimum of void space, and stored at 277 K in a refrigerator to maintain their stoichiometry for the purpose of analysis. Thermogravimetric analysis showed the presence of 9.0% (*w*/*w*) water (*cf.* 9.4% required for $CEX{\cdot}2H_2O$) and microanalytical data also suggested the presence of approximately two water molecules. Exposure to ambient laboratory conditions led to rapid loss of water (giving $CEX{\cdot}H_2O$). Samples were transported to the SRS in sealed containers packed with dry ice. Prior to data collection, the samples were exposed to a humidity of more than 75% for 2 h to ensure maximum hydration.

Crystal data

$C_{16}H_{17}N_3O_4S{\cdot}1.9H_2O$
$M_r = 381.88$
Monoclinic, *C*2
$a = 31.548$ (2) Å
$b = 11.8574$ (9) Å
$c = 15.6654$ (11) Å
$\beta = 112.364$ (2)°
$V = 5419.3$ (7) Å^3
$Z = 12$
$D_x = 1.404$ Mg m^{-3}
Synchrotron radiation
$\lambda = 0.6891$ Å
Cell parameters from 14 822 reflections
$\theta = 2.1$–$27.5°$
$\mu = 0.22$ mm^{-1}
$T = 150$ (2) K
Needle, colourless
0.20 × 0.05 × 0.01 mm

Data collection

Bruker AXS SMART CCD diffractometer
ω rotation with narrow-frame scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2001)
$T_{min} = 0.96$, $T_{max} = 1.00$
14 822 measured reflections
10 703 independent reflections
8136 reflections with $I > 2\sigma(I)$
$R_{int} = 0.047$
$\theta_{max} = 26.0°$
$h = -21 \rightarrow 40$
$k = -14 \rightarrow 15$
$l = -19 \rightarrow 19$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.074$
$wR(F^2) = 0.193$
$S = 1.01$
10 703 reflections
717 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1215P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.58$ e Å^{-3}
$\Delta\rho_{min} = -0.47$ e Å^{-3}
Absolute structure: Flack (1983), 4610 Friedel pairs
Flack parameter = 0.21 (10)

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···O2^{i}	0.88	2.22	3.077 (5)	165
N3—H3*A*···O2^{ii}	0.91	1.89	2.780 (6)	165
N3—H3*B*···O5^{iii}	0.91	1.81	2.711 (5)	173
N3—H3*C*···O15	0.91	1.91	2.811 (7)	171
N5—H5*A*···O3^{ii}	0.88	2.03	2.883 (5)	164
N6—H6*A*···O6^{iii}	0.91	1.90	2.781 (6)	161
N6—H6*B*···O15	0.91	2.18	2.874 (8)	133
N6—H6*B*···O11^{iv}	0.91	2.39	2.995 (6)	124
N6—H6*B*···O10^{iv}	0.91	2.39	3.134 (8)	139
N6—H6*C*···O19^{v}	0.91	1.99	2.794 (10)	146
N6—H6*C*···O8	0.91	2.21	2.683 (6)	112
N6—H6*C*···O19^{iv}	0.91	2.27	2.912 (10)	128
N8—H8···O13	0.88	1.96	2.827 (6)	167
N9—H9*A*···O17^{iv}	0.91	1.89	2.779 (8)	166
N9—H9*A*···O17^{vi}	0.91	2.47	3.346 (8)	162
N9—H9*B*···O10^{ii}	0.91	1.93	2.799 (7)	160
N9—H9*C*···O7^{vii}	0.91	2.22	2.824 (5)	124
N9—H9*C*···O4^{iv}	0.91	2.28	3.061 (6)	144

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

Disorder in one molecule of CEX was modelled using isotropic C atoms split over two sites, with a total occupancy of 1. The H atoms of the water molecules could not be positioned reliably and were omitted from the final model. All other H atoms were placed in idealized positions and refined in riding mode. Methyl and NH_3 H-atom orientations were obtained by refining a torsion angle, and these H atoms were given U_{iso} values of $1.5U_{eq}$ of the parent atom; for other H atoms, U_{iso}(H) was taken to be $1.2U_{eq}$(parent atom) [N—H = 0.91 Å (NH_3), N—H = 0.88 Å (NH), C—H = 0.98 Å (CH_3), C—H = 0.99 Å (CH_2), C—H = 1.00 Å (CH) and C—H = 0.95 Å (sp^2-CH)]. The absolute configuration could not be determined from the intensity data and is therefore based on the known geometry of cephalosporins (Kemperman *et al.*, 1999).

Data collection: *SMART* (Bruker, 1995); cell refinement: *SAINT* (Bruker, 2000); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1543). Services for accessing these data are described at the back of the journal.

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