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Report

Solid-State Chemistry and Crystal Structure of Cefaclor Dihydrate[1]

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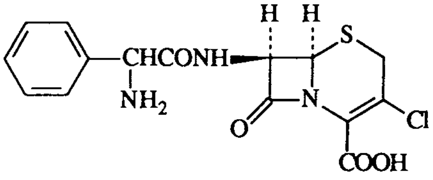
Cefaclor [7-(D-2-amino-2-phenylacetamido)-3-chloro-3-cepham-4-carboxylic acid] crystallizes as the dihydrate. Crystals belong to space group $P2_1$, with a = 10.626(3), b = 7.1288(9), c = 14.124(3), and β = 121.6(2). The structure was solved using direct methods and refined to an R of 0.0535. The bond lengths, angles, and conformation determined are as expected for cephalosporins. The two water molecules are held in the crystal differently. The ^{13}C solid-state NMR spectrum of cefaclor dihydrate is also reported and is consistent with its crystal structure.

KEY WORDS: Cefaclor; crystal structure; water of hydration; ^{13}C solid-state NMR.

INTRODUCTION

In previous papers from our laboratories, we have investigated a number of factors that can influence solid-state desolvation reactions. In general, three factors are important: (1) the atmosphere, (2) the crystal packing, and (3) the presence of nuclei and defects. Desolvation reactions are obviously greatly dependent upon the atmosphere. Dialuric acid and dihydrophenylalanine hydrate are both relatively stable in high humidities but desolvate rapidly at low humidities (1,2). The cephalosporin antibiotics are known to desolvate and resolvate (3). Crystal packing is also quite important. Previous studies have shown that both the size of the tunnel which contains the solvent molecules and the strength of the hydrogen bonds holding the solvent molecules in the tunnel can significantly influence the degree of desolvation (4,5). Finally, nuclei and defects are important for all solid-state reactions, including desolvations. For example, crystals of caffeine hydrate and dihydrophenylalanine hydrate desolvated up to five times faster when their ends were cut off with a razor blade, thereby inducing artificial nuclei and defects (2,6).

The steps in desolvation reactions are quite similar to those for other solid-state reactions (7). The dehydration of polymorphic solvates can be viewed as a four-step process. First, molecular loosening occurs so that the solvent may escape. Second, the hydrogen bonds holding the solvent in the crystal are broken. Third, a solid solution of the production crystal in the reactant crystal is formed. Finally, the product phase separates from this solid solution. The desolvation of pseudopolymorphic solvates can be viewed as a two-step process involving, first, molecular loosening, which is the process required to give the solvent molecules enough freedom to escape and, second, breaking of the host solvent hydrogen bonds or associations if they exist. Solid solutions are not formed for pseudopolymorphic solvates because the desolvated crystal has essentially the same crystal structure as the reactant crystal. In previous papers (1,2,4–6), we have reported studies of a number of model crystal solvates. In this paper, we extend our studies to the important antibiotic cefaclor.



Scheme I. Cefaclor

This paper reports the crystal structure of cefaclor dihydrate (I) X-ray powder diffraction, infrared, solid-state NMR, differential scanning calorimetry, and thermogravimetric analytical study of the dihydrate. Cefaclor monohydrate has been studied by Lorenz (8). This study shows that the crystal properties of the dihydrate are consistent with its crystal structure and with previous studies on antibiotics and other model compounds.

MATERIALS AND METHODS

Cefaclor, 7-(D-2-amino-2-phenylacetamido)-3-chloro-3-cepham-4-carboxylic acid, was a gift from Lilly Research Laboratories. Solvents used were purchased from Aldrich Chemical or other chemical houses. Solution NMR spectra were studied in D_2O or acetone d_6. The solid-state NMR

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[1] Taken from the Ph.D. thesis of Heriberto Martinez.

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spectra were measured at Colorado State University on an NTC 150 using the CP/MAS technique. Infrared spectra were measured on a Beckman IR 33. Powder diffraction measurements were made on a Debye–Scherrer film camera using CuKα X rays. The single-crystal studies were conducted on a Nicolet P3 automated diffractometer using graphite monochromatized copper radiation. Thermogravimetric analyses were measured on a Perkin Elmer TGS-2 system interfaced to a Perkin Elmer System 4 microprocessor unit. The samples were usually heated at a heating rate of five degrees per minute, and a nitrogen flow rate of 10 ml/min was used.

Preparation of Cefaclor Dihydrate. Crystals of cefaclor dihydrate were prepared by weighing out 500 mg of the monohydrate and dissolving in 10 ml of 1 *N* HCl (pH approximately 1.4). The pH was raised to 4.5 by adding concentrated ammonium hydroxide dropwise. Activated charcoal was added to the solution and immediately membrane filtered (nylon 66, 0.2 μm) into a crystallization dish which was previously etched in a fine grid arrangement. The solution was then seeded, and crystals were collected after 30 min.

Crystallographic Study of Cefaclor Dihydrate. Molecular weight ($C_{15}H_{18}N_3O_6SCl \cdot 2H_2O$) = 403.85, monoclinic. Crystal parameters: a = 10.626(3), b = 7.1288(9), c = 14.124(3) Å, β = 121.6(2), V = 9.11.3(4) $Å^3$, Z = 2, D_c = 1.471 g cm^{-3}, μ(CuKα) = 30.04 cm^{-1}, space group $P2_1$.

Data Collection. Crystallographic data were collected using graphite monochromatized CuKα X rays on a Nicolet P3 automated diffractometer with the Θ–2Θ scan technique to 2Θ of 116. A variable scan rate was used with a maximum of 29.30 per minute and a minimum of 7 per minute. The scan range was from 1.2 less than $K_{\alpha1}$ to 1.2 more than $K_{\alpha2}$. Backgrounds were counted at each end of the scan range, and the length of time the background was counted was equivalent to the length of time required for the scan. Three standard reflections were measured every 50 reflections. The data were corrected for the decay of the standards (a linear rate of decay was assumed).

Structure Analysis Of the 1361 unique reflections, 1201 had F_o greater than $5\sigma F_o$, were considered "observed," and were included in the final stages of refinement. The structure was solved using the MULTAN 80 program (9). An initial E-map showed all nonhydrogen atoms except for the benzene ring and the waters of hydration. This information was recycled into a MULTAN program until the benzene ring was located. The atomic coordinates of these atoms were refined isotropically by using the SHELX 76 (10) program,

Table I. Bond Lengths (Å) and Angles for Cefaclor Dihydrate

Bond lengths (Å)

Cl(1) – C(2)	1.749(8)	C(11) – C(13)	1.55(2)
C(2) – C(3)	1.50(2)	C(13) – N(14)	1.44(2)
C(2) – C(7)	1.35(1)	N(14) – C(15)	1.34(1)
C(3) – S(4)	1.80(1)	C(15) – O(16)	1.25(1)
S(4) – C(5)	1.81(1)	C(15) – C(17)	1.47(1)
C(5) – N(6)	1.45(2)	C(17) – N(18)	1.51(1)
C(5) – C(13)	1.56(1)	C(17) – C(19)	1.52(1)
N(6) – C(7)	1.40(1)	C(19) – C(20)	1.38(2)
N(6) – C(11)	1.40(1)	C(19) – C(24)	1.41(2)
C(7) – C(8)	1.52(2)	C(20) – C(21)	1.38(2)
C(8) – O(10)	1.24(2)	C(21) – C(22)	1.37(2)
C(8) – O(9)	1.24(1)	C(22) – C(23)	1.41(2)
C(11) – O(12)	1.20(1)	C(23) – C(24)	1.40(2)

Bond angles

Cl(1) – C(2) – C(3)	114.8(6)	O(12) – C(11) – C(13)	136.8(7)
C(3) – C(2) – C(7)	127.8(8)	C(5) – C(13) – C(11)	85.5(7)
C(7) – C(2) – Cl(1)	117.4(8)	C(5) – C(13) – N(14)	120.2(9)
C(2) – C(3) – S(4)	113.1(7)	C(11) – C(13) – N(14)	113.9(9)
C(3) – S(4) – C(5)	96.0(6)	C(13) – N(14) – C(15)	122.7(9)
S(4) – C(5) – C(13)	116.1(7)	N(14) – C(15) – O(16)	120.6(9)
S(4) – C(5) – N(6)	110.4(6)	N(14) – C(15) – C(17)	117.3(8)
N(6) – C(5) – C(13)	88.1(8)	O(16) – C(15) – C(17)	122.1(8)
C(5) – N(6) – C(7)	126.1(7)	C(15) – C(17) – N(18)	107.0(7)
C(5) – N(6) – C(11)	95.6(7)	C(15) – C(17) – C(19)	116.4(7)
C(7) – N(6) – C(11)	132.1(9)	N(18) – C(17) – C(19)	110.6(9)
C(2) – C(7) – C(8)	126.9(7)	C(17) – C(19) – C(20)	120(1)
C(2) – C(7) – N(6)	117.8(9)	C(17) – C(19) – C(24)	119.2(9)
N(6) – C(7) – C(8)	115.3(7)	C(20) – C(19) – C(24)	121(1)
C(7) – C(8) – O(10)	116(1)	C(19) – C(20) – C(21)	119.2(1)
C(7) – C(8) – O(9)	116(1)	C(20) – C(21) – C(22)	122(1)
O(9) – C(8) – O(10)	128(1)	C(21) – C(22) – C(23)	120(1)
N(6) – C(11) – O(12)	132.9(9)	C(22) – C(23) – C(24)	120(1)
N(6) – C(11) – C(13)	90.3(8)	C(19) – C(24) – C(23)	118(1)

Table II. Final Atomic Parameters and Anisotropic Thermal Parameters for Cefaclor Dihydrate

Atomic parameters with estimated standard deviation in parentheses

Atom	x/a	y/b	z/c
Cl(1)	0.6491(2)	0.7251(6)	0.9475(2)
C(2)	0.4559(9)	0.723(2)	0.8730(7)
C(3)	0.388(1)	0.705(2)	0.943(8)
S(4)	0.2024(3)	0.6178(5)	0.8669(2)
C(5)	0.1388(9)	0.772(2)	0.7488(8)
N(6)	0.2308(6)	0.752(1)	0.7017(5)
C(7)	0.3854(8)	0.741(1)	0.7614(6)
C(8)	0.4559(8)	0.752(2)	0.6918(6)
O(9)	0.4704(8)	0.912(1)	0.6641(6)
O(10)	0.4838(8)	0.600(1)	0.6645(6)
C(11)	0.1221(8)	0.669(1)	0.6027(7)
O(12)	0.1240(6)	0.603(1)	0.5251(5)
C(13)	0.0065(9)	0.699(2)	0.6365(8)
N(14)	−0.0708(9)	0.531(1)	0.6334(7)
C(15)	−0.2165(9)	0.528(1)	0.5938(7)
O(16)	−0.2912(6)	0.6743(9)	0.5601(5)
C(17)	−0.2824(9)	0.346(1)	0.5937(7)
N(18)	−0.4474(7)	0.376(1)	0.5365(6)
C(19)	−0.2228(9)	0.253(2)	0.7060(7)
C(20)	−0.180(1)	0.067(1)	0.7199(9)
C(21)	−0.134(2)	−0.019(2)	0.821(1)
C(22)	−0.123(1)	0.077(2)	0.908(1)
C(23)	−0.165(1)	0.268(2)	0.8956(9)
C(24)	−0.216(1)	0.357(2)	0.7933(8)
W(1)	0.1208(8)	1.218(1)	0.6907(6)
W(2)	0.412(1)	1.249(2)	0.7476(8)

Anisotropic thermal parameters and standard deviations in parentheses

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl(1)	0.035(1)	0.086(2)	0.038(1)	−0.009(2)	0.011(1)	−0.011(2)
C(2)	0.033(4)	0.038(6)	0.041(5)	−0.007(5)	0.023(4)	−0.011(5)
C(3)	0.046(6)	0.078(9)	0.036(5)	−0.018(7)	0.026(5)	−0.012(7)
S(4)	0.049(1)	0.050(2)	0.044(1)	0.003(1)	0.034(1)	−0.008(1)
C(5)	0.038(5)	0.032(6)	0.053(5)	−0.000(5)	0.036(4)	−0.001(4)
N(6)	0.020(3)	0.032(4)	0.043(4)	−0.000(4)	0.022(3)	−0.002(4)
C(7)	0.031(4)	0.027(5)	0.036(4)	−0.012(5)	0.025(4)	−0.006(4)
C(8)	0.016(4)	0.054(7)	0.022(4)	−0.012(5)	0.008(3)	−0.005(5)
O(9)	0.052(5)	0.041(4)	0.051(5)	−0.002(4)	0.036(4)	−0.008(4)
O(10)	0.051(4)	0.052(5)	0.056(4)	−0.008(4)	0.041(4)	0.004(4)
C(11)	0.021(4)	0.048(7)	0.035(5)	0.011(5)	0.013(4)	0.002(5)
O(12)	0.040(4)	0.068(5)	0.034(3)	−0.001(4)	0.022(3)	−0.006(4)
C(13)	0.033(5)	0.033(6)	0.052(6)	0.003(5)	0.031(4)	−0.001(5)
N(14)	0.028(4)	0.033(5)	0.062(6)	0.018(5)	0.028(4)	0.013(4)
C(15)	0.032(5)	0.026(5)	0.031(5)	0.002(4)	0.022(4)	0.004(5)
O(16)	0.025(3)	0.031(4)	0.055(4)	0.002(3)	0.018(3)	0.002(3)
C(17)	0.026(5)	0.039(6)	0.035(5)	−0.008(4)	0.023(4)	−0.000(4)
N(18)	0.022(4)	0.037(5)	0.037(4)	−0.010(4)	0.018(3)	0.003(4)
C(19)	0.025(4)	0.037(6)	0.033(4)	−0.000(5)	0.018(4)	0.003(5)
C(20)	0.053(6)	0.032(7)	0.053(6)	0.006(5)	0.036(5)	0.008(5)
C(21)	0.11(1)	0.024(7)	0.09(1)	0.019(6)	0.066(9)	0.027(7)
C(22)	0.064(7)	0.07(1)	0.057(7)	0.022(8)	0.038(6)	0.006(7)
C(23)	0.055(6)	0.073(9)	0.041(6)	0.014(6)	0.030(5)	0.006(6)
C(24)	0.051(6)	0.040(6)	0.041(6)	−0.008(5)	0.030(5)	−0.001(5)
W(1)	0.070(4)	0.039(4)	0.083(5)	0.005(4)	0.035(4)	0.018(4)
W(2)	0.084(6)	0.064(5)	0.110(6)	−0.007(6)	0.069(5)	−0.007(6)

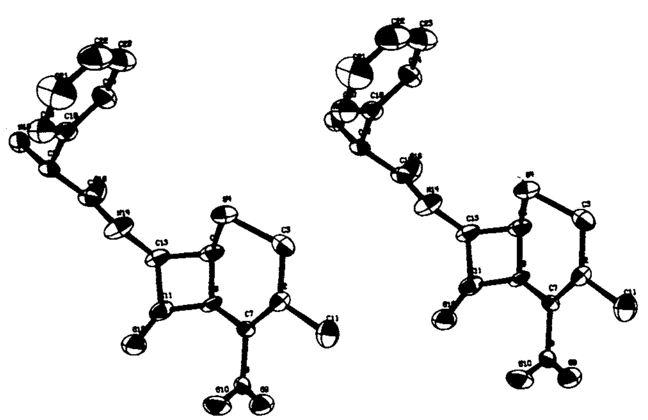


Fig. 1. Stereoscopic view of the crystal structure of cefaclor dihydrate along with the atomic numbering.

and after two cycles of refinement, a difference map showed the two water molecules. Further refinement, first with isotropic temperature factors and then with anisotropic temperature factors, gave a final R factor of 0.0654. The hydrogen atoms, which could not be located from a difference map, were placed in calculated positions. When the hydrogen atoms were included in the calculation, the R factor dropped to 0.0535.

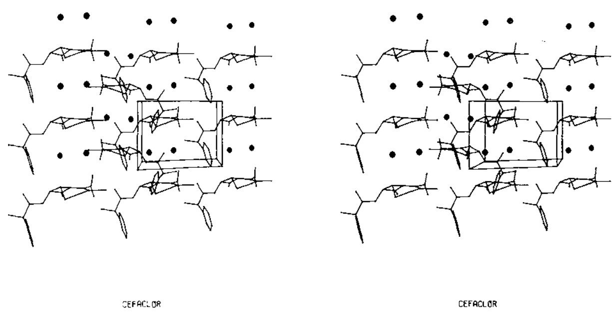


Fig. 2. Stereoscopic view of the crystal packing of cefaclor dihydrate. The directions of the axis are (a) across, (b) vertical, and (c) out of the plane of the paper.

RESULTS AND DISCUSSION

Crystal Structure Cefaclor Dihydrate. Table I lists the bond lengths and angles, and Table II lists the atom parameters for cefaclor dihydrate. A stereoscopic drawing of the cefaclor molecule is shown in Fig. 1. Table III lists the intermolecular contacts not involving hydrogen atoms which are less than 3.50 Å. All bond lengths were, as expected, within experimental error. The bond lengths and angles for the β-lactam ring were within two standard deviations of those reported for the phenoxymethyl-Δ2-desacetoxyl ceph-

Table III. Intermolecular Contacts <3.5 Å for Cefaclor Dihydrate Not Involving Hydrogen Atoms

O(10)· · ·O(16)	3.45(4) I	C(8)· · ·N(18)	3.30(3) VI
O(10)· · ·N(18)	2.78(4) I	W(1)· · ·O(12)	2.90(1) VI
O(10)· · ·C(24)	3.23(9) I	O(12)· · ·C(17)	3.40(5) VI
W(2)· · ·O(10)	3.03(4) II	O(10)· · ·N(18)	3.31(5) VI
O(16)· · ·C(20)	3.40(7) II	O(9)· · ·O(16)	3.29(9) VI
W(1)· · ·C(11)	3.45(4) II	O(9)· · ·C(17)	3.14(9) VI
W(1)· · ·N(14)	2.84(6) II	O(9)· · ·N(18)	2.72(2) VI
O(16)· · ·C(20)	3.40(7) II	N(18)· · ·C(8)	3.30(3) VII
W(2)· · ·O(9)	2.88(4) III	N(18)· · ·O(10)	3.30(5) VII
W(2)· · ·W(1)	2.77(4) III	C(17)· · ·O(9)	3.14(9) VII
C(20)· · ·O(16)	3.40(7) IV	C(17)· · ·O(12)	3.40(5) VII
O(10)· · ·W(2)	3.03(4) IV	O(16)· · ·O(9)	3.29(9) VII
C(11)· · ·W(1)	3.45(4) IV	N(18)· · ·O(9)	2.72(2) VII
N(14)· · ·W(1)	2.84(6) IV	O(12)· · ·C(13)	3.47(8) VII
O(16)· · ·O(10)	3.45(4) V	C(15)· · ·O(9)	3.3(1) VII
N(18)· · ·O(10)	2.78(4) V	O(12)· · ·W(1)	2.9(1) VII
C(24)· · ·O(10)	3.23(9) V	O(16)· · ·N(18)	2.77(7) VIII
C(13)· · ·O(12)	3.47(8) VI	N(18)· · ·O(16)	2.77(7) IX
O(9)· · ·C(15)	3.3(1) VI		

Roman numerals denote the following positions relative to the reference molecule at x,y,z

I	$1+x,y,z$
II	$x,1+y,z$
III	x,y,z
IV	$x,-1+y,z$
V	$-1+x,y,z$
VI	$-x,0.5+y,1-z$
VII	$-x,-0.5+y,1-z$
VIII	$-1-x,0.5+y,+1-z$
IX	$-1-x,-0.5+y,1-z$

alosporin and those reported for cephaloglycine (11). The aromatic benzene ring bond lengths and angles were within experimental error of the expected value of 1.4 Å. The length of the carbon oxygen bond for the carboxyl group is 1.24(1) Å, indicating that it is slightly distorted. The bond angle in this functionality is 128°, indicating that the electron density is distributed nearly evenly between the two oxygens. It is important to note that we attempted to determine the crystal structure of cefaclor monohydrate for comparison but were unable to do so.

The crystal packing of the dihydrate is shown in Fig. 2. An enlarged view of the hydrogen bonding network involving the water molecules is shown in Fig. 3. It is clear from this figure that the two water molecules are held in the crystal structure differently. One of the water molecules, W(1), is hydrogen bonded to three other atoms, while the other water molecule, W(2), is hydrogen bonded to only two other atoms. Water molecule W(1) is hydrogen bonded to water mol-

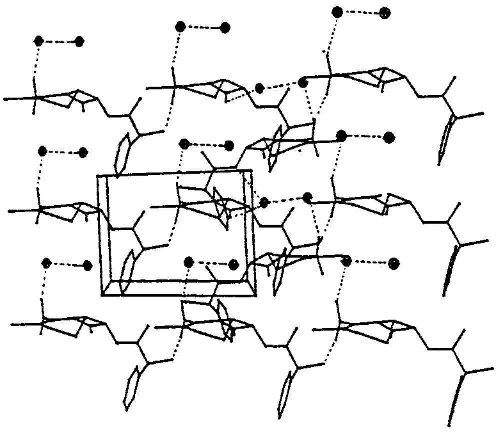


Fig. 3. Crystal packing of cefaclor dihydrate showing hydrogen bonding network. The directions of the axis are (a) across, (b) vertical, and (c) out of the plane of the paper.

Table IV. Powder Pattern of Cefaclor Dihydrate Up to 2Θ of 40°

2Θ	*d* (Å)	*hkl*[a]	Relative intensity from powder pattern	Relative intensity × 10^{-3a}	*d* (Å), monohydrate[b]	Relative intensity monohydrate[b]
7.38	11.98	$00\bar{1}$	100	115	12.90	75
8.75	10.10		18		10.05	17
12.77	6.93		7		6.58	13
14.41	6.15	011	70	189	6.08	13
14.70	6.03		30			
14.8	5.99		37			
15.08	5.87		17			
15.13	5.86		16			
15.78	5.61	110	33	181	5.42	96
17.8	4.98	112	27	209	5.01	100
18.92	4.69		14		4.75	4
18.99	4.67		12			
19.58	4.53		19			
21.1	4.21		44			
22.2	4.00		23		4.06	54
22.78	3.90		29			
23.3	3.82	210	21	162	3.86	4
24.1	3.69		29	106	3.69	29
25.0–25.2	3.55	$30\bar{2}$	33	335	3.53	58
		020		290		
25.3–25.4	3.51	013,$01\bar{3}$	31	203		
26.05	3.42		17		3.41	4
26.6	3.35	$12\bar{1}$	24	222		
26.76	3.33		12		3.29	17
28.2	3.16		9		3.23	13
28.76	3.10	103	51	116	3.13	4
28.83	3.096	$11\bar{4}$	51	158		
29.6	3.02	300	35	159	2.99	21
32.62	2.66		11		2.81	25
33.6	2.67		10		2.67	8
34.1	2.83		9		2.52	8
35.74	2.51		21		2.48	4
37.18	2.42		16		2.35	17
38.41	2.34		9			
38.84	2.32		23			
39.15	2.30		10			

[a] From crystal structure.
[b] From ref. 8.

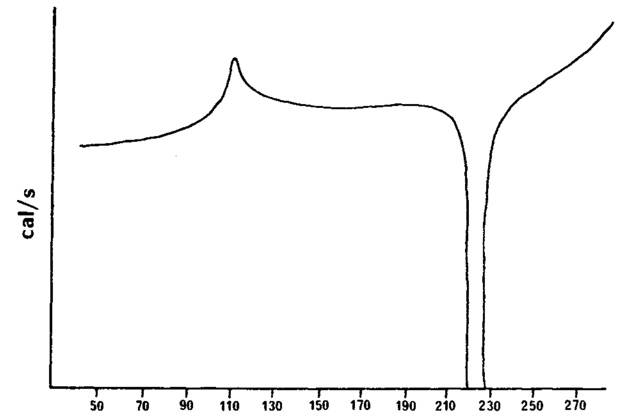


Fig. 4. DSC of cefaclor dihydrate. A heating rate (*dT*/*dt*) of 5°C/min was used.

ecule W(2) with a contact distance of 2.77(4) Å. It is also hydrogen bonded to O(12), which is the carbonyl of the β-lactam molecule 2 (generated by twofold screw axis) with the contact distance of 2.90(1) Å and to the amide nitrogen N(14) of molecule 1 [contact distance, 2.84(6) Å]. The other water molecule, W(2), is hydrogen bonded to W(1) and to O(9) (which is the oxygen of the carboxylate group) with a contact distance of 2.88(4) Å and is related to the molecule at *x*, *y*, *z* by a translation of −1 in the *y* direction.

The powder diffraction data for cefaclor dihydrate are shown in Table IV along with the published data for the monohydrate (8). It is clear that powder diffraction is a good method for distinguishing the dihydrate from the monohydrate.

The thermogravimetric analysis of cefaclor dihydrate shows that it undergoes smooth desolvation beginning at 64°C. Half of the water was lost at 74°C and the total water was lost at 110°C at a heating rate of 5°C/min. The observed total weight loss for water was 9% (calculated for loss 8.91%). The DSC of the dihydrate showed two transitions (see Fig. 4). The first was an exothermic transition at 108°C with the ΔH of 2.03 × 10^{12} erg/mol (0.12 cal/g), and the second was observed at 216°C and corresponds to melting followed by an exothermic transition. The transition at 108°C is most likely exothermic due to a combination of water loss (endothermic) and resolidification (exothermic). Analysis of the solid formed from desolvation shows that it is amorphous, thus this is a polymorphic desolvation.

The infrared spectrum of the dihydrate shows a broad–OH absorption attributable to water at 3250 to 3500 cm^{-1}, an NH amide stretching band at 3200 cm^{-1}, a β-lactam stretching at about 1760 cm^{-1}, and an amide carbonyl band at 1690 cm^{-1}. The IR spectrum of the dihydrate is similar to that

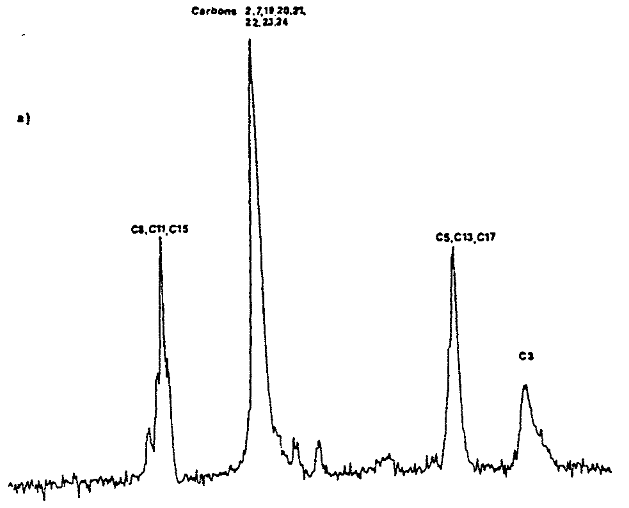
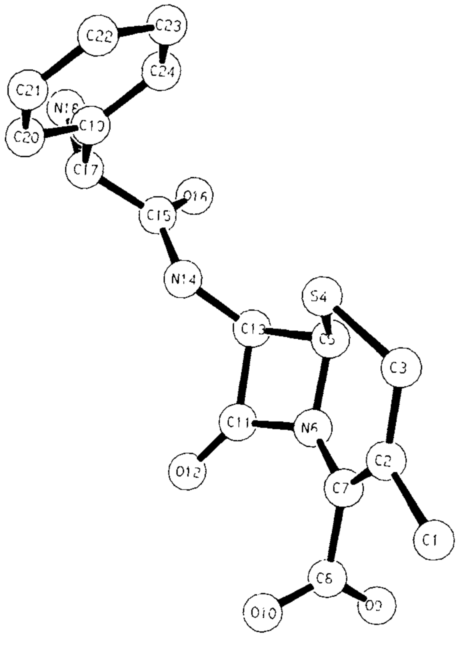


Fig. 5. Solid-state ^{13}C NMR spectrum of cefaclor dihydrate.

Table V. Solid-State and Solution ^{13}C NMR Chemical Shifts of Cefaclor Monohydrate and Dihydrate from 0 to 200 ppm[a]



Carbon number	Chemical shift (δ), ppm Solution ^{13}C	Dihydrate
C3	31.12	32.0–31.2
C17	57.04	57.7
C5	57.85	57.7(b)
C13	59.36	57.7
C7	127.67	132.1
C20	128.64	132.1(b)
C21	130.16	132.1
C22	130.16	132.1
C23	130.16	132.1
C24	130.16	132.1
C2	131.0	132.1
C19	131.93	132.1
C8	163.64	165.7
C11	164.55	169.4
C15	169.55	173.1

[a] The peaks observed at 210 and 232 ppm were spinning side bands for the monohydrate and dihydrate, respectively.

reported for the monohydrate (8), with the largest difference being the difference between the β-lactam stretching frequencies of about 15 cm^{-1}.

The solid-state NMR spectrum of the dihydrate is shown in Fig. 5 and is compared to the solution spectrum in Table V. The broad peaks are probably due to the presence of Cl in the molecule. There are a few large (>4-ppm) differences between the chemical shifts in the solid state and those in the solution. These include those for C7 and C11. The difference for C11 may reflect differences in hydrogen bonding to the C11 carbonyl oxygen atom.

In conclusion, these studies show that the crystal structure of cefaclor dihydrate is consistent with its solid-state chemistry, in that the water molecules are held in the crystal by defined hydrogen bonds and are lost upon heating in a way similar to that of other hydrates (4–6).

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REFERENCES

1. R. J. Clay, A. M. Knevel, and S. R. Byrn. *J. Pharm. Sci.* 71:1289–1291 (1982).
2. C. T. Lin and S. R. Byrn. *J. Am. Chem. Soc.* 98:4004 (1976).
3. R. R. Pfeiffer, K. S. Yang, and M. A. Tucker. *J. Pharm. Sci.* 59:1809–1814 (1970).
4. P. R. Perrier and S. R. Byrn. *J. Org. Chem.* 47:4671–4676 (1982).
5. S. R. Byrn. *Solid State Chemistry of Drugs,* 1st ed., Academic Press, New York, 1982.
6. C. T. Lin and S. R. Byrn. *Mol. Cryst. Liq. Cryst.* 50:99–104 (1979).
7. I. C. Paul and D. Y. Curtin. *Acc. Chem. Res.* 9:217–225 (1973).
8. L. Lorenz. *Anal. Profiles Drug Subst.* 9:107–123 (1980).
9. P. Main. *Multan 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data,* University of New York, England, 1980.
10. G. Sheldrick. *SHELX 76. Program for Crystal Structure Determination,* University Chemical Laboratory, Cambridge, 1976.
11. R. M. Sweet and L. F. Dahl. *J. Am. Chem. Soc.* 92:5489–5507 (1970).