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## The Structure of an Antihistamine: Cyproheptadine Hydrochloride Sesquihydrate

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(Received 6 July 1976; accepted 7 August 1976)

Cyproheptadine hydrochloride sesquihydrate ( $C_{21}H_{21}N \cdot HCl \cdot 1\frac{1}{2} H_2O$ ) is orthorhombic, space group *Fdd2*, with  $a = 43.53$  (1),  $b = 18.226$  (6),  $c = 9.587$  (4) Å,  $Z = 16$ . One water molecule is situated on a twofold axis. The tricyclic part of the molecule is folded and the angle between the planes of the two benzene rings is  $124.1^\circ$ . The piperidine ring has a chair and the seven-membered ring a boat conformation. The cyproheptadine molecule possesses  $C_s$  symmetry within the limits of error. The structure was refined to an  $R$  of 3.9%.

### Introduction

Several substances are known to antagonize both histamine and serotonin, among which are various phenothiazine derivatives (Gyermek, Lazar & Czák, 1956; Parratt & West, 1958). None of these compounds is, however, particularly outstanding as an antagonist of serotonin. A relatively new antihistamine, cyproheptadine hydrochloride or 4-(5*H*-dibenzo[*a,d*]-cycloheptene-5-ylidene)-1-methylpiperidine, is unique in that its antagonism towards both histamine and serotonin is of a high order. In addition cyproheptadine has some weak antrope-like activity and possesses mild central depressing properties (Stone, Wenger, Ludden, Stavorski & Ross, 1961). Clinically, cyproheptadine has been found to be effective in the treatment of various allergies. The most prominent side effect is drowsiness (Miller & Fishman, 1961).

The structure of cyproheptadine resembles in certain respects the phenothiazine antihistamines. It also bears some resemblance to lysergic acid derivatives, which are good serotonin antagonists in that they possess an *N*-substituted heterocyclic ring. In comparison with simpler indole-type serotonin antagonists, however, there is no structural resemblance. The determination of this crystal structure was undertaken as part of a general study of antihistaminic drugs.

### Crystal data

The powdered substance was obtained from Merck, Sharp & Dohme. Crystals of  $C_{21}H_{21}N \cdot HCl \cdot 1\frac{1}{2} H_2O$ ,

grown from ethanol, are colourless prisms of rhombic cross-section; space group *Fdd2*, with  $a = 43.53$  (1),  $b = 18.226$  (6),  $c = 9.587$  (4) Å,  $V = 7606$  (4) Å<sup>3</sup>,  $Z = 16$ ,  $D_m = 1.215$ ,  $D_x = 1.225$  g cm<sup>-3</sup>,  $\mu(\text{Mo } K\alpha) = 2.16$  cm<sup>-1</sup>.

### Experimental

A crystal  $0.41 \times 0.41 \times 0.37$  mm was used throughout the data collection, mounted along *c*. 2209 reflexions, including 56 with negative intensity, were measured on a paper-tape-controlled Siemens AED diffractometer by the five-value scan technique ( $\theta \leq 27^\circ$ ).  $2\theta$  values for several high-order reflexions were measured, and the cell dimensions found by least-squares calculations.

Lp corrections were applied, but absorption corrections were ignored.

Scattering factors computed from numerical Hartree-Fock wave functions (Cromer & Mann, 1968) were used for the non-hydrogen atoms; for H, the values given by Stewart, Davidson & Simpson (1965) were used.

### Structure determination and refinement

The structure was solved by direct methods with *MULTAN* 74 (Main, Woolfson, Lessinger, Germain & Declercq, 1974). Phase determination for 300 reflexions with  $E \geq 1.41$  was carried out with a weighted

tangent formula (Germain, Main & Woolfson, 1971). 2400 unique phase relations were used. A fragment of 23 peaks appeared from the best *E* map. Of these, 21 corresponded to real atoms. Outside this fragment a few peaks appeared; the highest one clearly was the Cl<sup>-</sup> ion and two smaller ones were later identified as O atoms in two molecules of water of hydration. The H atoms were found from a difference map, and their parameters included in the final cycles.

Full-matrix least-squares refinement was performed with *CRYLSQ* of *X-RAY 72* (Stewart, Kruger, Ammon, Dickinson & Hall, 1972), minimizing  $\sum \omega(|F_o| - |F_c|)^2$  with unit weights. With the weighting programs of *X-RAY 72*,  $\omega = 1/\sigma_{F_o}^2$  was applied to the reflexions. The final *R* was 3.9%; the average parameter shifts expressed as fractions of the estimated standard deviation were approximately 0.5.

Final atomic coordinates and temperature factors are given in Tables 1 and 2.\*

### Description and discussion of the structure

Fig. 1 is a stereo drawing of the molecule and shows the atomic numbering. The molecule consists of a

\* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32088 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

chair-formed piperidine ring double-bonded to a tricyclic system. This ring system can be roughly divided into two planes, each consisting of a benzene

Table 2. Fractional coordinates ( $\times 10^3$ ) and thermal parameters ( $\times 10^3$ ) for hydrogen atoms

Isotropic temperature factor is  $\exp(-8\pi^2 U \sin^2 \theta / \lambda^2)$ .

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i>
H(O1)	-0.3 (7)	337 (2)	302 (4)	132 (10)
H(O2)	12.9 (9)	334 (2)	187 (5)	120 (15)
H(O3)	4.1 (9)	-38 (2)	666 (4)	148 (13)
H	27.3 (5)	186 (1)	387 (3)	46 (7)
H(1)	193.0 (7)	107 (2)	748 (3)	65 (8)
H(2)	175.8 (6)	168 (2)	945 (3)	89 (9)
H(3)	136.1 (7)	254 (2)	907 (3)	69 (9)
H(4)	115.4 (5)	275 (1)	699 (3)	43 (6)
H(6)	123.5 (6)	343 (1)	316 (3)	68 (8)
H(7)	156.4 (7)	400 (2)	150 (3)	80 (8)
H(8)	198.6 (9)	327 (2)	87 (5)	109 (17)
H(9)	210.5 (7)	218 (2)	166 (3)	78 (9)
H(10)	197.8 (7)	111 (2)	294 (3)	84 (10)
H(11)	192.0 (6)	73 (1)	517 (3)	65 (8)
H(171)	89.0 (6)	154 (1)	615 (3)	56 (8)
H(172)	64.4 (5)	216 (1)	575 (3)	52 (7)
H(181)	66.1 (5)	74 (1)	445 (3)	47 (7)
H(182)	40.1 (6)	100 (1)	549 (3)	60 (8)
H(191)	70.0 (5)	123 (1)	220 (3)	45 (6)
H(192)	47.7 (6)	188 (1)	169 (3)	58 (8)
H(201)	69.2 (5)	275 (1)	315 (3)	47 (6)
H(202)	96.0 (6)	238 (1)	222 (3)	51 (7)
H(211)	2.9 (7)	113 (2)	235 (4)	80 (10)
H(212)	26.5 (7)	46 (2)	278 (3)	81 (9)
H(213)	1.3 (7)	75 (2)	378 (4)	94 (10)

Table 1. Fractional coordinates ( $\times 10^4$ ) and thermal parameters ( $\times 10^4$ ) for non-hydrogen atoms

Numbers in parentheses in this and subsequent tables are estimated standard deviations of the last digits. Anisotropic temperature factor is  $\exp[-2\pi^2(U_{11}h^2a^{*2} + \dots + 2U_{12}hka^*b^* + \dots)]$ .

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> <sub>11</sub>	<i>U</i> <sub>22</sub>	<i>U</i> <sub>33</sub>	<i>U</i> <sub>12</sub>	<i>U</i> <sub>13</sub>	<i>U</i> <sub>23</sub>
Cl <sup>-</sup>	34.0 (2)	2403.4 (4)	0 (0)	652 (4)	591 (4)	681 (4)	139 (3)	-228 (4)	8 (4)
O(1)	112.9 (6)	3606.1 (11)	2436 (3)	1364 (20)	639 (12)	763 (14)	-126 (13)	196 (16)	28 (13)
O(2)	0 (0)	0 (0)	6210 (4)	1077 (25)	735 (20)	687 (21)	-7 (16)	0	0
C(1)	1783.9 (6)	1409.9 (15)	7411 (4)	494 (14)	605 (15)	850 (21)	-48 (12)	-262 (15)	162 (16)
C(2)	1676.4 (7)	1780.5 (17)	8528 (3)	674 (18)	816 (20)	589 (18)	-234 (16)	-266 (16)	222 (17)
C(3)	1444.4 (7)	2284.0 (17)	8375 (3)	638 (17)	706 (17)	512 (16)	-261 (14)	-64 (13)	-1 (15)
C(4)	1320.4 (5)	2405.1 (13)	7066 (3)	434 (12)	515 (14)	500 (14)	-101 (10)	-42 (11)	-4 (11)
C(5)	1279.0 (4)	2166.1 (11)	4522 (2)	315 (10)	409 (11)	431 (12)	20 (9)	-31 (9)	-7 (10)
C(6)	1422.9 (5)	3171.1 (14)	2875 (3)	433 (12)	668 (16)	514 (15)	-69 (11)	-67 (11)	91 (12)
C(7)	1614.8 (6)	3489.1 (17)	1889 (3)	605 (16)	888 (20)	549 (17)	-153 (15)	-95 (14)	192 (16)
C(8)	1875.5 (7)	3119.7 (21)	1466 (3)	577 (17)	1224 (29)	468 (15)	-190 (18)	56 (13)	29 (16)
C(9)	1941.8 (6)	2448.6 (18)	2019 (3)	477 (13)	1046 (23)	514 (15)	-33 (14)	46 (13)	-127 (16)
C(10)	1855.4 (5)	1414.3 (16)	3608 (4)	398 (12)	610 (16)	841 (21)	52 (11)	-21 (14)	-223 (16)
C(11)	1820.4 (5)	1169.5 (13)	4900 (4)	372 (12)	508 (14)	901 (19)	56 (10)	-135 (14)	-71 (15)
C(12)	1671.9 (5)	1534.8 (13)	6064 (3)	373 (11)	459 (12)	673 (17)	-45 (9)	-165 (12)	58 (12)
C(13)	1423.7 (5)	2033.6 (12)	5905 (3)	342 (10)	421 (11)	485 (13)	-63 (9)	-91 (10)	37 (11)
C(14)	1486.6 (5)	2492.2 (12)	3455 (3)	325 (10)	567 (13)	411 (12)	-62 (10)	-49 (10)	-44 (12)
C(15)	1755.5 (5)	2116.8 (15)	3036 (3)	379 (12)	697 (16)	512 (14)	-68 (11)	-21 (11)	-178 (12)
C(16)	975.8 (4)	2060.6 (11)	4309 (2)	318 (10)	449 (12)	427 (12)	19 (9)	-43 (9)	2 (10)
C(17)	764.1 (5)	1741.9 (13)	5387 (3)	352 (10)	539 (13)	459 (14)	-40 (9)	-57 (10)	13 (11)
C(18)	549.7 (5)	1162.4 (12)	4805 (3)	363 (11)	506 (12)	563 (13)	-15 (10)	-46 (10)	66 (11)
C(19)	590.7 (5)	1683.9 (13)	2480 (3)	346 (10)	660 (14)	447 (13)	43 (10)	-93 (11)	-13 (13)
C(20)	811.2 (5)	2268.7 (14)	2981 (3)	334 (10)	665 (15)	484 (14)	-15 (10)	-73 (10)	110 (12)
C(21)	151.2 (6)	898.9 (14)	3055 (3)	440 (12)	646 (16)	815 (19)	-96 (11)	-123 (14)	-104 (15)
N	375.1 (4)	1448.0 (10)	3591 (2)	293 (8)	432 (10)	531 (12)	44 (8)	-58 (8)	-69 (9)

ring, C(5) and C(10) or C(11). The bond distances and angles are listed in Tables 3 and 4. The mean  $C(sp^2)$ -H distance is 0.94 Å, compared with 0.98 Å for  $C(sp^3)$ -H. All individual C-H distances have a standard deviation of 0.03 Å.

The best planes for the benzene rings were calculated (Schomaker, Waser, Marsh & Bergman, 1959) and the results are summarized in Table 5. The angle between planes I and II is  $124.1^\circ$ . The benzene rings are planar within the limits of error. We cannot, however, describe the tricyclic system as consisting of two planar halves folded along an axis from C(5) to halfway between C(10) and C(11). C(5), C(10) and C(11) deviate significantly from the planes of the two aromatic rings (Table 5). Similar non-planarity is found in phenothiazine and its derivatives (McDowell, 1975 and references given therein). These compounds have a similar unsaturated ring system, except that the vinylene [C(10)-C(11)] is replaced by a S atom. The very close analogy between the biological actions of these compounds constitutes an example of bioisosterism between S and vinylene in condensed aromatic ring systems (Schatz, 1960). Another example of this bioisosterism is found in the biological actions of cyproheptadine and the S analogue. Here the antiserotonin and antihistaminic properties are almost identical (Engelhardt *et al.*, 1965).

Cycloheptene (Fig. 2) has the boat conformation,  $\theta_1 = 153.1$ ,  $\theta_2 = 129.4^\circ$ , and possesses  $C_s$  symmetry within experimental error. A microwave spectrum analysis of 1,3,5-cycloheptatriene (Butcher, 1965) gives an analogous conformation with  $\theta_1 = 151 \pm 4$ ,  $\theta_2 = 130 \pm 5^\circ$ . Another investigation (Trætteberg, 1964) also gives a boat conformation with  $\theta_1 = 140 \pm 2$ ,  $\theta_2 = 144 \pm 2^\circ$ .

The methyl group on the piperidine N is important for both antihistaminic and antiserotonin properties. Larger alkyl and substituted alkyl groups, with the exception of ethyl, lead to a decrease in both activities (Engelhardt *et al.*, 1965).

Table 3. *Interatomic distances* (Å)

C(1)-C(2)	1.349 (5)	C(8)-C(9)	1.364 (5)
C(2)-C(3)	1.372 (4)	C(7)-C(8)	1.381 (4)
C(3)-C(4)	1.383 (4)	C(6)-C(7)	1.388 (4)
C(4)-C(13)	1.378 (3)	C(6)-C(14)	1.385 (3)
C(12)-C(13)	1.402 (3)	C(14)-C(15)	1.414 (3)
C(1)-C(12)	1.399 (4)	C(9)-C(15)	1.405 (4)
C(10)-C(15)	1.460 (4)	C(11)-C(12)	1.452 (4)
C(5)-C(13)	1.488 (3)	C(5)-C(14)	1.488 (3)
C(16)-C(17)	1.502 (3)	C(16)-C(20)	1.509 (3)
C(17)-C(18)	1.513 (3)	C(19)-C(20)	1.516 (3)
C(18)-N	1.484 (3)	C(19)-N	1.483 (3)
C(10)-C(11)	1.325 (5)		
C(5)-C(16)	1.349 (3)	H(O1)-O(1)	0.86 (3)
C(21)-N	1.489 (3)	H(O2)-O(1)	0.74 (5)
		H(O3)-O(2)	0.84 (4)
N-H	0.91 (2)		

Table 4. *Bond angles* ( $^\circ$ )

C(2)-C(1)-C(12)	122.0 (3)	C(8)-C(9)-C(15)	122.2 (3)
C(1)-C(2)-C(3)	120.3 (3)	C(7)-C(8)-C(9)	119.8 (3)
C(2)-C(3)-C(4)	119.4 (3)	C(6)-C(7)-C(8)	119.4 (3)
C(3)-C(4)-C(13)	121.8 (2)	C(14)-C(6)-C(7)	121.7 (2)
C(4)-C(13)-C(12)	118.4 (2)	C(6)-C(14)-C(15)	118.9 (2)
C(1)-C(12)-C(13)	117.9 (2)	C(9)-C(15)-C(14)	117.8 (2)
C(1)-C(12)-C(11)	118.7 (2)	C(9)-C(15)-C(10)	117.8 (2)
C(11)-C(12)-C(13)	123.4 (2)	C(10)-C(15)-C(14)	124.4 (2)
C(5)-C(13)-C(12)	121.4 (2)	C(5)-C(14)-C(15)	120.3 (2)
C(4)-C(13)-C(5)	120.1 (2)	C(5)-C(14)-C(6)	120.8 (2)
C(10)-C(11)-C(12)	128.0 (2)	C(11)-C(10)-C(15)	127.8 (3)
C(13)-C(5)-C(14)	114.9 (2)		
C(13)-C(5)-C(16)	121.7 (2)	C(14)-C(5)-C(16)	123.1 (2)
C(5)-C(16)-C(17)	123.4 (2)	C(5)-C(16)-C(20)	123.8 (2)
C(17)-C(16)-C(20)	112.7 (2)		
C(16)-C(17)-C(18)	113.2 (2)	C(16)-C(20)-C(19)	113.1 (2)
C(17)-C(18)-N	111.1 (2)	C(20)-C(19)-N	112.2 (2)
C(18)-N-C(19)	109.9 (2)		
C(18)-N-C(21)	117.7 (2)	C(19)-N-C(21)	111.2 (2)
C(18)-N-H	108 (2)		
C(19)-N-H	107 (2)	H(O1)-O(1)-H(O2)	101 (4)
C(21)-N-H	109 (2)	H(O3)-O(2)-H(O3)	118 (4)

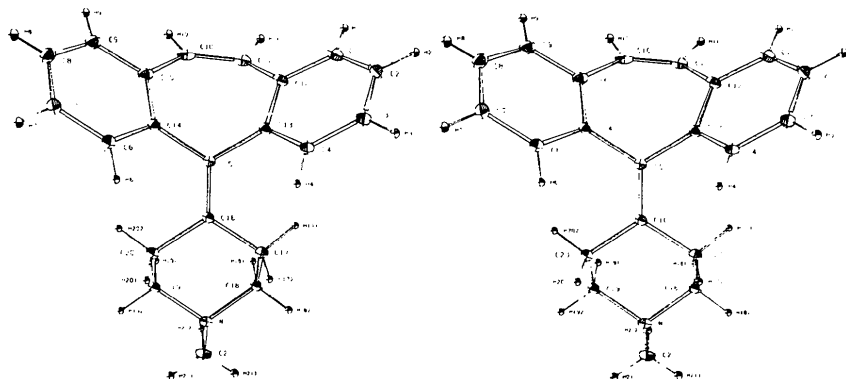


Fig. 1. Stereoscopic drawing of the cyproheptadine molecule  $C_{21}H_{21}N$  showing the thermal ellipsoids and atomic numbering. Figs. 1 and 4 were drawn with *ORTEP* (Johnson, 1965).

Table 5. Deviations ( $\text{\AA}$ ) of atoms from least-squares planes through the two benzene rings

The standard deviation of the atoms from the planes is 0.0154 for plane I and 0.0041 for plane II.  $\chi^2$  is 72.79 (5 degrees of freedom) for plane I and 5.57 (5 degrees of freedom) for plane II.

Atoms defining the plane		Atoms not defining the plane	
<b>Plane I</b>			
C(1)	-0.0151	H(1)	-0.0413
C(2)	-0.0018	H(2)	-0.0417
C(3)	0.0092	H(3)	-0.0086
C(4)	0.0008	H(4)	-0.0216
C(12)	0.0240	C(5)	-0.0611
C(13)	-0.0171	C(11)	0.1456
<b>Plane II</b>			
C(6)	-0.0008	H(6)	-0.0258
C(7)	0.0024	H(7)	0.0295
C(8)	0.0005	H(8)	-0.0271
C(9)	-0.0050	H(9)	-0.1013
C(14)	-0.0035	C(5)	0.0052
C(15)	0.0063	C(10)	0.0606

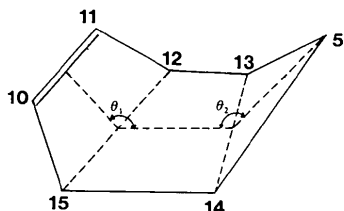


Fig. 2. Configuration of the seven-membered ring.

Packing of the molecules is determined primarily by hydrogen bonding. A suggested pattern is shown in Fig. 3 viewed along *a*. The hydrogen-bond distances are listed in Table 6. The two water molecules are linked with the  $\text{Cl}^-$  ion to form 12-membered rings. Each ring contains four  $\text{Cl}^-$  ions which individually are hydrogen-bonded to piperidine N atoms. In addition to the hydrogen bonds, there also exist some intermolecular contacts involving the methyl group (Table 6).

Fig. 4 shows the molecular packing viewed along *c*.

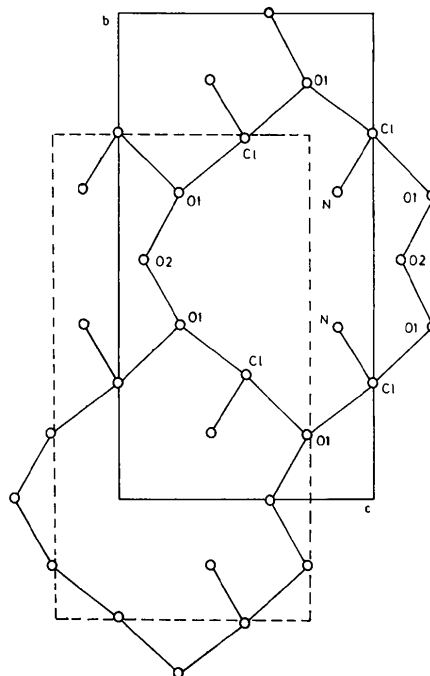


Fig. 3. Two *bc* projections showing the hydrogen-bonding pattern. The complete cell edges correspond to  $x = 0$  and  $x = 0.5$ , the broken cell edges correspond to  $x = 0.25$  and  $x = 0.75$ .

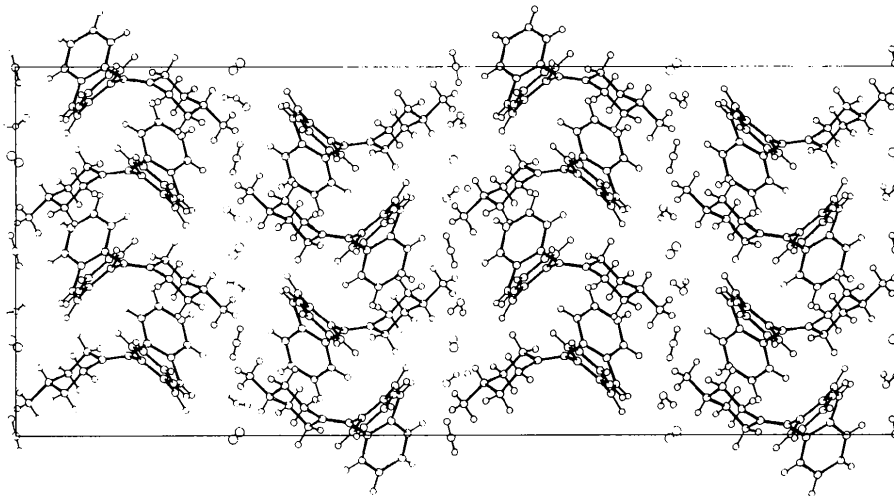


Fig. 4. The *ab* projection of the unit cell. *a* runs horizontally, left to right, and *b* vertically, bottom to top.

Table 6. *Hydrogen-bond distances and angles and some other intermolecular contacts*

$D-H \cdots A$	Position of acceptor atom	Distances (Å)		Angle (°)
		$D \cdots A$	$H \cdots A$	$D-H \cdots A$
O(1)—H(O2) $\cdots$ Cl <sup>-</sup>	$x, y, z$	3.222 (3)	2.50 (5)	165 (5)
O(1)—H(O1) $\cdots$ Cl <sup>-</sup>	$x, y + \frac{1}{2}, z + \frac{1}{2}$	3.136 (3)	2.37 (3)	149 (3)
O(2)—H(O3) $\cdots$ O(1)	$x, y - \frac{1}{2}, z + \frac{1}{2}$	2.842 (3)	2.01 (4)	170 (5)
O(2)—H(O3) $\cdots$ O(1)	$x, y + \frac{1}{2}, z + \frac{1}{2}$	2.842 (3)	2.01 (4)	170 (5)
N—H $\cdots$ Cl <sup>-</sup>	$x, y + \frac{1}{2}, z + \frac{1}{2}$	3.063 (2)	2.19 (2)	161 (3)
C(21) $\cdots$ C(21)	$\bar{x}, \bar{y}, z$	3.531 (4)		
Cl <sup>-</sup> $\cdots$ C(21)	$\bar{x}, \bar{y} + \frac{1}{2}, z - \frac{1}{2}$	3.702 (3)		

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