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Aza Analogs of Nucleic Acid Constituents. V. The Crystal and Molecular Structure of 8-Azaguanine Hydrochloride Monohydrate

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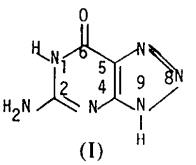
The crystal and molecular structure of 8-azaguanine hydrochloride monohydrate, $C_4H_7N_6O_2Cl.H_2O$, has been determined from three-dimensional X-ray data collected by counter methods. The material crystallizes in space group $P2_1/n$ (C_{2h}^5) of the monoclinic system with $Z=4$, $a=5{\cdot}476$ (2), $b=13{\cdot}058$ (8), $c=10{\cdot}992$ (6) Å, and $\beta=85{\cdot}11$ (2)°. A calculated density of 1·750 g cm^{-3} is in acceptable agreement with the reported value of 1·71 g cm^{-3}. The structure has been refined by least-squares methods to a final R (on F) of 0·040 for 1522 independent reflections having $F^2>3\sigma(F^2)$. The structure consists of parallel planar sheets of base-paired 8-azaguaninium cations with chloride anions located above and below the purine rings in adjacent planes. The structure is markedly different from those of guanine hydrochloride monohydrate and 8-azaguanine monohydrate in that the proton on the triazalo system is on N(8) instead of N(9), and that the additional proton is on N(3) and not, as predicted theoretically, on N(7).

Introduction

The anti-neoplastic properties of several azapurines and their nucleosides are well established (Bennett, Vail, Allan & Laster, 1973; Montgomery, Thomas & Clayton, 1970; Skipper, Montgomery, Thomson & Schabel, 1959). 8-Azaguanine (I), an analog of guanine in which C(8)–H has been replaced by N(8), is a highly effective anti-neoplastic agent (Kidder & Dewey, 1949) and also inhibits several animal tumors (Law, 1950).



(I)

The minor chemical modification of replacing a purine carbon atom by a nitrogen atom, therefore, has the effect of bringing about great changes in the biological activity of the base and nucleic acid components which contain it. Substitution at the 8-position is especially significant since this position is adjacent to the glycosidic bond in the corresponding nucleoside. Hence, this substitution can alter the relative orientation of the sugar and the base by removing the proton on the 8-position (Donohue & Trueblood, 1960; Haschemeyer & Rich, 1967) and by introducing electrostatic interactions between the base and the sugar (Schwalbe & Saenger, 1973; Prusiner, Brennan & Sundaralingam, 1973; Wood, Hruska, Mynott & Sarma, 1973). Moreover, since N(7) is known to be the most basic ring nitrogen atom in guanine (Pullman & Pullman, 1963), an examination of the structure of protonated 8-azaguanine would allow a direct examination of the electronic effects of replacement of CH by N by determining the site of protonation.

It has been shown that the structures of guanine monohydrate (Thewalt, Bugg & Marsh, 1971) and 8-azaguanine monohydrate (Macintyre, Singh & Werkema, 1965; Sletten, Sletten & Jensen, 1968) are very similar, with N(8) in the latter participating in only weak hydrogen bonding. In guanine hydrochloride monohydrate (Broomhead, 1951) and dihydrate (Iball & Wilson, 1965) the additional proton is at N(7), leaving N(3) free, but we have recently found that in 8-aza-2,6-diaminopurine sulfate monohydrate (Singh, Lewis & Hodgson, 1974) protonation is at N(3) and N(8), leaving N(7) and N(9) unprotonated.

In order to further investigate the basicity of the available sites in azapurines, we have investigated the structure of 8-azaguanine hydrochloride monohydrate; we report here the results of this investigation.

Experimental

Suitable crystals were obtained using a minor modification of the procedure of Macintyre & Zirakzadeh (1964). Examination of the crystals by precession and Weissenberg photography confirmed that they belong to the monoclinic system; the observed systematic absences of $0k0$ for k odd and $h0l$ for $h+l$ odd suggest that the space group is $P2_1/n$. The cell constants, obtained by the least-squares procedure of Busing & Levy (1967), are $a=5{\cdot}476$ (2), $b=13{\cdot}058$ (8), $c=10{\cdot}992$ (6) Å, and $\beta=85{\cdot}11$ (2)°. The observations were made at 20 °C, with the wavelength assumed as λ(Mo $K\alpha_1$)=

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0·7093 Å. A density of 1·750 g cm^{-3} calculated for four formula units per cell is in acceptable agreement with the value reported by Macintyre & Zirakzadeh.

Intensity data were collected at 20°C on a Picker four-circle automatic diffractometer using Mo $K\alpha$ radiation. The monoclinic crystal chosen had faces (001), (00$\bar{1}$), (010), (0$\bar{1}$0), (100), and ($\bar{1}$00), the separation of each pair of opposite faces being 0·10, 0·14, and 0·66 mm, respectively. The crystal was mounted on a glass fiber roughly normal to the (100) planes. The mosaicity of the crystal was examined by means of the narrow-source, open-counter ω-scan technique (Furnas, 1957); the widths at half-height for 12 strong reflections in various regions of reciprocal space were found to lie in the range 0·06 to 0·13°. These 12 reflections from the crystal were accurately centered through a narrow vertical slit at a takeoff angle of 1·0°. These observations formed the basis for the least-squares refinement of cell parameters and crystal orientation.

Intensity data were collected at a takeoff angle of 1·0°; at this angle the peak intensity was about 90% of the maximum value as a function of takeoff angle. The counter aperture, chosen to minimize extraneous background, was 5·8 mm high by 6·0 mm wide and was positioned 32 cm from the crystal. The data were collected by the θ–2θ scan technique at a scan rate of 0·5° min^{-1}. Allowance was made for both $K\alpha_1$ and $K\alpha_2$ radiations by using a scan range of from 0·75° below the calculated $K\alpha_1$ peak to 0·75° above the calculated $K\alpha_2$ peak position. Stationary-counter, stationary-crystal background counts of 20 s duration were taken at each end of the scan.

The Mo $K\beta$ radiation was effectively removed from the incident beam by means of a highly-oriented graphite monochromator. The pulse-height analyzer was set for approximately a 90% window. A unique data set having $2\theta(\text{Mo}) \leq 55°$ was gathered, a total of 2435 intensities being measured. As a check on crystal and electronic stability, the intensities of three standard reflections were measured every 100 reflections; the intensities of these reflections remained essentially constant throughout the run, showing only the deviations from the mean predicted from counting statistics. There were very few measureable intensities above background values of $2\theta > 55°$.

The data were processed by the method of Corfield, Doedens & Ibers (1967). A linear background correction was applied, and the intensities were assigned standard deviations according to the formula

$$\sigma(I) = [C + 0{\cdot}25\,(ts/tb)^2\,(BH + BL) + (pI)^2]^{1/2}$$

in our program *DATAPRC*. The value of p was selected as 0·045 since the crystal was of intermediate mosaicity; this term is included in the expression for the estimated standard deviation in order to prevent extremely high weight being given to very strong reflections in the least-squares refinement of the structure (Busing & Levy, 1957). The value of the linear absorption coefficient μ for this compound is 4·71 cm^{-1}, and no correction for absorption was made. Of the 2435 independent intensities measured, 1829 were greater than σ, 1656 were greater than 2σ, and 1522 were greater than 3σ.

Solution and refinement

The chlorine atom was located in a three-dimensional Patterson map; three cycles of least-squares refinement gave values of $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_2 = [\sum w(|F_o| - |F_c|)^2 - \sum w|F_o|^2]^{1/2}$ of 0·534 and 0·640, respectively. The least-squares calculations in this analysis were carried out on F, the function minimized being $\sum w(|F_o| - |F_c|)^2$ where F_o and F_c are the observed and calculated structure amplitudes, and the weights w are taken as $4F_o^2/\sigma^2(F_o^2)$. The full matrix least-squares program used

Table 1. *Positional and thermal parameters in 8-azaguanine hydrochloride monohydrate*

The form of the anisotropic ellipsoid is exp $[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl	0·54873 (9)	0·35257 (4)	0·50257 (2)	0·0161 (2)	0·00375 (3)	0·00683 (5)	0·0001 (1)	0·00294 (6)	0·00004 (3)
O(6)	0·0895 (3)	0·1955 (1)	0·3217 (2)	0·0208 (5)	0·0022 (1)	0·0069 (1)	0·0005 (2)	0·0022 (2)	0·0002 (1)
N(1)	0·0107 (3)	0·3657 (1)	0·3352 (2)	0·0147 (5)	0·0026 (1)	0·0059 (1)	−0·0003 (2)	0·0019 (2)	0·0001 (1)
N(2)	−0·0960 (4)	0·5345 (1)	0·3631 (2)	0·0193 (6)	0·0026 (1)	0·0076 (2)	0·0005 (2)	0·0029 (3)	−0·0001 (1)
N(3)	0·2569 (4)	0·4951 (1)	0·2438 (2)	0·0183 (6)	0·0021 (1)	0·0065 (2)	−0·0003 (2)	0·0025 (3)	0·0002 (1)
N(7)	0·5372 (3)	0·2615 (1)	0·1555 (2)	0·0176 (6)	0·0034 (1)	0·0057 (1)	0·0006 (2)	0·0011 (2)	−0·0006 (1)
N(8)	0·6763 (4)	0·3324 (1)	0·1025 (2)	0·0143 (6)	0·0039 (1)	0·0059 (2)	−0·0001 (2)	0·0021 (3)	−0·0007 (1)
N(9)	0·6081 (3)	0·4303 (1)	0·1219 (2)	0·0162 (6)	0·0034 (1)	0·0060 (2)	−0·0004 (2)	0·0019 (2)	0·0001 (1)
C(2)	0·0575 (4)	0·4671 (1)	0·3142 (2)	0·0131 (6)	0·0026 (1)	0·0047 (2)	0·0002 (2)	0·0003 (3)	0·0001 (1)
C(4)	0·4055 (4)	0·4193 (1)	0·1942 (2)	0·0138 (6)	0·0025 (1)	0·0044 (1)	−0·0003 (2)	0·0001 (3)	−0·0001 (1)
C(5)	0·3605 (4)	0·3158 (2)	0·2154 (2)	0·0136 (6)	0·0023 (1)	0·0045 (2)	0·0001 (2)	0·0004 (3)	−0·0001 (1)
C(6)	0·1504 (4)	0·2827 (1)	0·2931 (2)	0·0138 (6)	0·0025 (1)	0·0044 (2)	0·0003 (2)	0·0002 (3)	0·0001 (1)
O(W)	−0·4136 (4)	0·1112 (2)	0·4485 (2)	0·0230 (7)	0·0037 (1)	0·0135 (3)	0·0007 (2)	0·0073 (3)	−0·0007 (1)
H(O2)	−0·338 (8)	0·063 (3)	0·439 (4)	4·78 (17)					
H(O1)	−0·342 (9)	0·163 (4)	0·431 (4)	5·89 (5)					
H(N22)	−0·227 (6)	0·511 (2)	0·409 (3)	3·14 (5)					
H(N21)	−0·073 (6)	0·603 (3)	0·355 (3)	3·00 (8)					
H(8)	0·788 (6)	0·320 (2)	0·059 (3)	2·55 (3)					
H(3)	0·296 (6)	0·554 (3)	0·228 (3)	3·45 (12)					
H(1)	−0·125 (7)	0·353 (2)	0·383 (3)	3·53 (1)					

in this analysis was a local modification of J. A. Ibers's *NUCLS*. In calculations of F_c the atomic scattering factors for Cl were taken from Cromer & Waber (1965), those for H from Stewart, Davidson & Simpson (1965), and those for O, N, and C from the tabulations of Ibers (1962). The effects of the anomalous dispersion of chlorine were included in calculations of F_c (Ibers & Hamilton, 1964), the values of $\Delta f'$ and $\Delta f''$ for Cl being taken from Cromer (1965). Only the 1522 data which were greater than three times their estimated standard deviations were used in the refinement of the structure. The O, N and C atoms of the azapurine and the water oxygen atom were located in subsequent difference Fourier syntheses, and isotropic least-squares refinement yielded values of 0·139 and 0·180 for R_1 and R_2. Anisotropic least-squares refinement then gave $R_1=0{\cdot}058$ and $R_2=0{\cdot}079$. All of the hydrogen atoms were successfully located in a subsequent difference Fourier map, and two cycles of least-squares refinement with hydrogen atoms refined isotropically and the non-hydrogen atoms refined anisotropically gave $R_1=0{\cdot}042$ and $R_2=0{\cdot}053$. Examination of the value of R_2 as a function of $\sin\theta$ suggested that the weighting scheme was inappropriate, with the weights for low-order data too large; the weights for data with $0\leq 2\theta<20°$ were divided by 3·45 and those for data with $20°\leq 2\theta<30°$ were divided by 2·00. Reflection 103 flooded the counter and was eliminated. A subsequent least-squares calculation gave $R_1=0{\cdot}040$ and $R_2=0{\cdot}048$.

In the final least-squares cycle no parameter exhibited a shift greater than 0·5 times its e.s.d., which was taken as evidence of convergence. Examination of the values of F_o and F_c suggested to us that no correction for secondary extinction was necessary, and none was applied. A final difference Fourier map was virtually featureless, with no peak in excess of 0·63 e Å^{-3}. The highest peak was roughly in the middle of the C(4)–C(5) bond of the base. Other workers (*e.g.* Hodgson & Ibers, 1969) have observed similar peaks and have interpreted them as possibly indicating the presence of bonding electrons in C–C bonds; a similar interpretation is not unreasonable in the present case, especially since the next highest peak in the map was only 0·39 e Å^{-3}.

The positional and thermal parameters obtained from the final least-squares cycle are presented in Table 1.*

Description of the structure

The structure consists of 8-azaguaninium cations which are hydrogen bonded to chloride anions and to water molecules; the structure of the cation is shown in Fig. 1. The bond lengths in the cation are also shown in Fig. 1, while the bond angles are listed in Table 2. As can be seen in Fig. 1, the site of protonation in the triazolo system is N(8), while the extra proton due to the cationic nature of the molecule is at N(3); this is in marked contrast to the structures of other reported guanine analogs and derivatives. Thus, in 8-azaguanine monohydrate (Macintyre *et al.*, 1965; Sletten *et al.* 1968) and in guanine monohydrate (Thewalt *et al.*, 1971) protonation is at N(9), and in guanine hydrochloride monohydrate (Broomhead, 1951) protonation

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30574 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

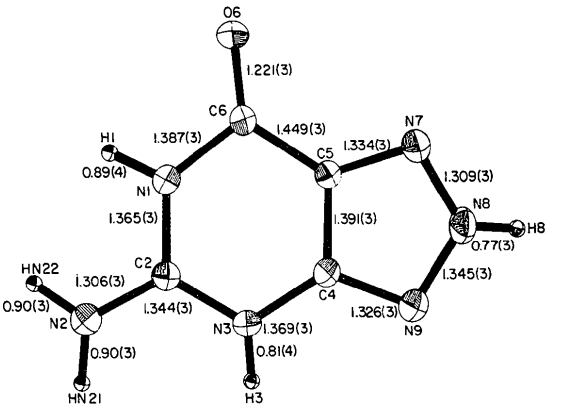

Fig. 1. View of the 8-azaguaninium cation in 8-azaguanine hydrochloride monohydrate. The thermal ellipsoids of the hydrogen atoms have been artificially reduced for clarity.

Table 2. *Bond angles in* 8-*azaguanine hydrochloride monohydrate* (°)

C(6)——N(1)–C(2)	127·5 (2)	N(3)—C(4)—N(9)	127·5 (2)
C(6)——N(1)–H(1)	118 (2)	C(4)—C(5)—C(6)	120·8 (2)
H(1)——N(1)–C(2)	114 (2)	N(7)—C(5)—C(6)	130·5 (2)
N(1)——C(2)–N(3)	119·8 (2)	C(4)—C(5)—N(7)	108·6 (2)
N(1)——C(2)–N(2)	118·5 (2)	C(5)—C(6)—N(1)	111·1 (2)
N(2)——C(2)–N(3)	121·7 (2)	C(5)—C(6)—O(6)	128·3 (2)
C(2)——N(2)–H(N21)	122 (2)	N(1)—C(6)—O(6)	120·6 (2)
C(2)——N(2)–H(N22)	117 (2)	C(5)—N(7)—N(8)	102·9 (2)
H(N21)–N(2)–H(N22)	119 (3)	N(7)—N(8)—N(9)	117·1 (2)
C(2)——N(3)–C(4)	117·9 (2)	N(7)—N(8)—H(8)	123 (2)
C(2)——N(3)–H(3)	125 (2)	N(9)—N(8)—H(8)	119 (2)
H(3)——N(3)–C(4)	117 (2)	C(4)—N(9)—N(8)	101·7 (2)
N(3)——C(4)–C(5)	122·9 (2)	H(O1)–O(*W*)–H(O2)	114 (4)
N(9)——C(4)–C(5)	109·6 (2)		

is at N(7) and N(9). Protonation at N(8) and N(3), however, has been observed in 8-azaxanthine (Nowacki & Bürki, 1955; Mez & Donohue, 1969) and in the 8-aza-2,6-diaminopurine cation (Singh *et al.*, 1974). Hence, it appears possible that the replacement of C(8) by N(8) can bring about a reduction in the basicity of N(7) and an enhancement of that of N(3) in purines and related species. This may be of biological significance since it is well established that the carcinogenic activity of nitrogen and sulphur mustards is due to their alkylation of N(7) in guanine in DNA and RNA (Pullman & Pullman, 1963); the present study suggests that since N(3) is more basic than N(7) in 8-azaguanine, alkylation of 8-azaguanine in the nucleic acids in which it has been incorporated may not occur at N(7). It should be noted that the most basic site in 8-azaguanine predicted by quantum mechanics is N(7) (Pullman & Pullman, 1963), which is apparently in disagreement with our result.

A comparison of the geometry of the cation with that of neutral 8-azaguanine (Sletten *et al.*, 1968) suggests that the effect of protonation at N(3) is to lengthen the bonds involving N(3) [*i.e.* C(2)–N(3) and N(3)–C(4)] while shortening the adjacent bond N(1)–C(2) and the exocyclic bond C(2)–N(2). Similar effects were observed in copper–guanine hydrochloride complex where both N(3) and N(7) were protonated and N(9) was coordinated to the metal. The effect of the protonation at N(8) on the bond lengths, however, is less easy to discern, presumably because this involves only a tautomeric change.

Singh (1965) has noted that the bond angles at nitrogen in pyrimidines are markedly altered by hydrogen attachment, and Ringertz (1972) has generalized this concept to predict the angular dependence of all purine bond angles on extra-annular substitution. As can be seen in Table 3, the bond angles observed here for 8-azaguaninium are in good agreement with the tabulation of Ringertz, with the bond angles at N(7) and N(9) of 102·9 (2) and 101·7 (2)° reflecting the lack of protonation at those sites while the angle of 117·9 (2)° at N(3) is very similar to that found in other N(3)-protonated purines.

A variety of least-squares planes is tabulated in Table 4. As can be seen from an examination of plane 1, the nine atoms of the ring are roughly coplanar, with no atom deviating from the best least-squares plane by more than 0·014 Å; the attached atoms N(2) and O(6) deviate only slightly from this plane. Moreover, an examination of planes 2 and 3 (Table 4) suggests that the triazole portion of the ring lies approximately in the best least-squares plane of the pyrimidine moiety, and *vice versa*; the angle between the pyrimidine plane and the triazole plane is only 0·36°.

Table 3. *Predicted and observed intra-ring angles in 8-azaguanine hydrochloride monohydrate* (°)

	Obs.	Calc.[a]	Range[b]
N(1)	127·5	125·1	122–129
C(2)	119·8	123·3	122–127
N(3)	117·9	118·4	118–119
C(6)	111·1	111·7	108–116
N(7)	102·9	101·8	102–109
N(9)	101·7	103·4	102–105

(*a*) Ringertz (1972). (*b*) The range of experimentally observed intra-ring angles at the atom indicated for a number of purines in which the substitution at the atom is the same as in the present case. Data from Ringertz (1972).

Table 4. *Least-squares planes*

	In-plane-atoms*	Δ(Å)	Out-of-plane atoms†	Δ(Å)
Plane 1	N(1)	0·012	O(6)	−0·037
	C(2)	0·050	O*W*	0·022
	N(3)	−0·010	Cl	3·071
	C(4)	−0·001		
	C(5)	0·001		
	C(6)	−0·014		
	N(7)	0·003		
	N(8)	0·004		
	N(9)	0·001		
Plane 2	N(1)	0·010	N(7)	0·013
	C(2)	0·002	N(8)	0·016
	N(3)	−0·010	N(9)	0·010
	C(4)	0·005	O(6)	−0·036
	C(5)	0·006	N(2)	0·015
	C(6)	−0·013	Cl	3·079
Plane 3	C(5)	0·000	N(1)	0·016
	C(4)	0·000	N(2)	0·029
	N(7)	0·000	N(3)	−0·006
	N(8)	0·001	C(2)	0·010
	N(9)	−0·001	C(6)	−0·014
			O(6)	−0·038

* Atoms included in the calculation of the least-squares plane.

† Atoms excluded from the calculation of the least-squares plane.

The intermolecular base pairing in 8-azaguanine hydrochloride monohydrate is very interesting, and is depicted in Fig. 2. Every available donor or acceptor atom is involved in hydrogen-bonding. The base pairing shown in Fig. 2 involves N(2)–H···N(7) and N(3)–H···O(6) hydrogen bonds, while there are probably N(1)–H(1)···Cl, N(8)–H(8)···Cl, N(8)–H(8)···O*W*, N(2)–H···Cl, and N(9)···H–O*W* hydrogen bonds between the base and the anion or solvent molecule. It appears that H(8) may be involved in bifurcated hydrogen bonding, with N(8)···O*W* and N(8)···Cl distances of 2·81 and 3·30 Å, respectively, and angles at H(8) of 144 and 134°, respectively. The probable hydrogen bonds in the structure are summarized in Table 5. This hydrogen-bonding scheme is in contrast to that in 9-methylguanine hydrobromide (Sobell & Tomita, 1964) in which there are no interpurine hydrogen bonds, and to that in guanine hydrochloride monohydrate (Broomhead, 1951), in which the base pairing is through centrosymmetrically related pairs of N(7)–H···O(6) hydrogen bonds. This latter

mode of pairing is not available in 8-azaguanine hydrochloride monohydrate since N(7) is not protonated.

The molecular plane is roughly the crystallographic (103) plane; a view of the system perpendicular to this direction is shown in Fig. 3. As is evident from an examination of Fig. 3, although the interplanar separation is only 3·11 Å there is little stacking interaction between the bases. This is in contrast to the structures of guanine monohydrate (Thewalt *et al.*, 1971) and 8-azaguanine monohydrate (Macintyre *et al.*, 1965; Sletten *et al.*, 1968), in which there is considerable stacking, but is consistent with the observation (Bugg, 1972) that only weak interactions are expected for protonated bases; it should be noted, however, that the structures of the charged purines isoguanine sulphate (Subramanian & Marsh, 1971) and 8-aza-2,6-diaminopurine sulphate (Singh *et al.*, 1974) contain considerable base stacking.

As is seen in Fig. 3 there are significant interactions between the chloride ions in one plane and the bases in the adjacent planes. Thus, as is shown in Fig. 3, the chloride in one plane lies 3·29 Å above the pyrimidine moiety of the base in the plane below, while another chloride sits 3·07 Å below the triazole portion of the same base. The interactions are each localized over two bonds of the ring rather than being delocalized over the entire ring system. Hence, while the halogen–purine interaction is reminiscent of that found in one of the two independent molecules of guanosine hydrobromide (Tougard, 1972), it is entirely different from that found in 9-methylguanine hydrobromide (Sobell & Tomita, 1964).

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Table 5. *Probable A–H···B hydrogen bonds*

A–H···*B*	*A*–H···*B* angle (°)	*A*–H(Å)	H···*B*(Å)	*A*···*B*(Å)
N(1)—H(1)·····Cl	169	0·89	2·14	3·02
N(3)—H(3)·····O(6)	176	0·81	2·01	2·83
N(8)—H(8)·····Cl	134	0·77	2·72	3·30
N(2)—HN(21)···N(7)	176	0·90	2·09	2·99
N(8)—H(8)·····O(*W*)	144	0·77	2·16	2·81
N(2)—HN(22)···Cl	146	0·90	2·57	3·37
O(*W*)–HO(1)····Cl	128	0·79	2·66	3·21
O(*W*)–HO(2)····N(9)	171	0·75	2·22	2·97

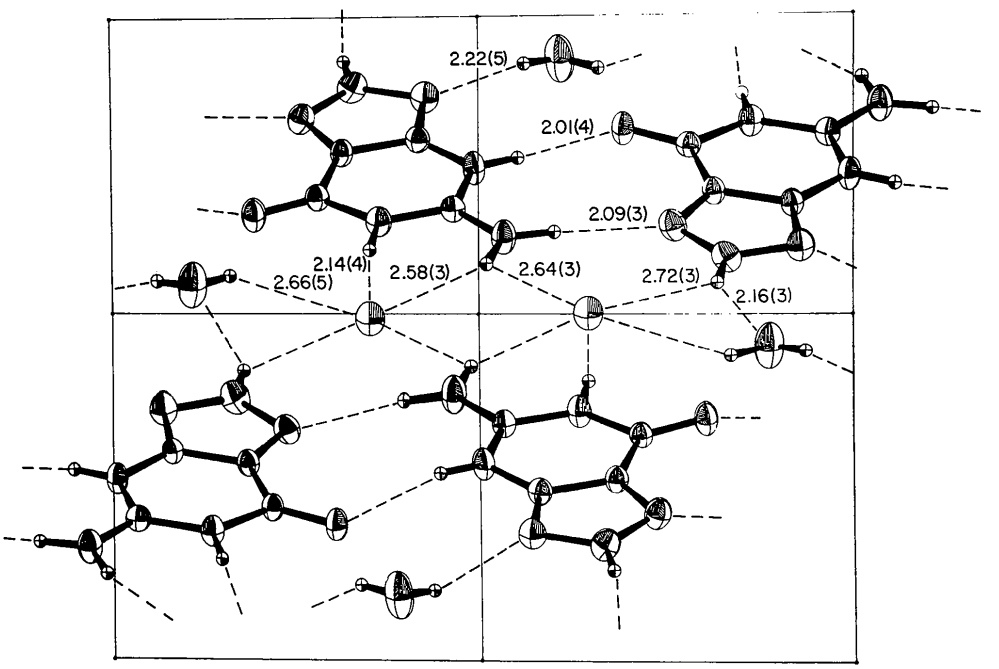

Fig. 2. Projection on the *bc* plane in 8-azaguanine hydrochloride monohydrate, showing the intermolecular base pairing and hydrogen bonding. The origin of the cell is in the center of the figure, **b** is horizontal, and **c** vertical.

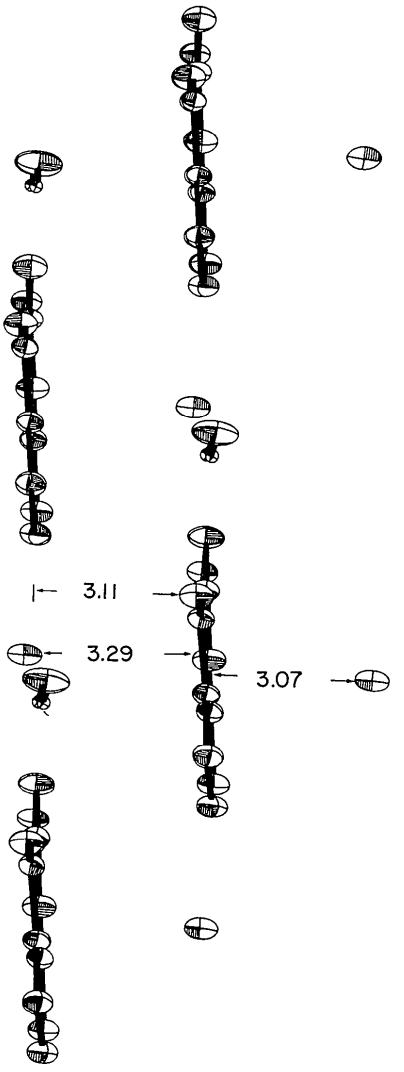

Fig. 3. View normal to the molecular (103) plane showing the interplanar stacking in 8-azaguanine hydrochloride monohydrate.

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