oxygens on each sulfate interact with the metal atoms. Assuming the metal atoms are molybdenum(V), the whole group has a total charge of 4 −. The analogous phosphate anion, $[Mo_5P_2O_{23}]^{6-}$, is known (Strandberg, 1973); the two ions are isostructural. However, in the phosphate case, the counterion is sodium, and that structure contains 13 water molecules which interact with the heavy ion; thus the crystals are not isostructural.

Intensity data measured by the Laue method have again allowed solution of the structure of a crystal too small for conventional diffractometer intensity measurements. Its power has been more dramatically demonstrated because the chemical constitution was quite unknown. Although the R factor and e.s.d.'s of bond lengths and angles are higher than usual, there is in this case no ambiguity about the chemistry (although reliable location of H atoms would not have been practicable). Solution by direct methods was possible here, despite the absence of axial and low-resolution reflection data. The question of sample absorption has been addressed and a satisfactory technique for its correction has been designed, implemented and demonstrated. However, the final R factor of 0.107 is still not as low was one would wish, or as low as has been achieved with Laue data for organic compounds (e.g. R = 0.082, Gomez de Anderez et al., 1989; R = 0.053, Helliwell, Gomez de Anderez et al., 1989; R = 0.076, Maginn, 1989). The variation of atomic scattering factors with wavelength, through the anomalous-dispersion terms f' and f'', has still not been taken into account in the structure-factor calculations. This is likely to be significant and will be addressed shortly.

Furthermore, although for this compound, measurements with monochromatic radiation were used initially to determine the unit-cell dimensions, procedures have now been developed for determining the axial ratios and cell angles (Carr, Cruickshank & Harding, 1992) and even absolute values of cell lengths (Carr, Dodd & Harding, 1993) from Laue diffraction patterns.

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Experimental Charge Density and Electrostatic Potential in Adenine Hydrochloride Hemihydrate at 123 K

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Abstract

The charge-density distribution in adenine hydrochloride hemihydrate has been determined from X-ray diffraction data collected to $(\sin\theta/\lambda) = 1.32\,\text{Å}^{-1}$ at 123 K. Some significant differences in molecular geometry are observed when compared with the earlier room-temperature study by Kistenmacher & Shigematsu [Acta Cryst. (1974), B30, 166–168]. Several multipole refinement strategies were evaluated. The electrostatic potential, isolated from the crystal lattice, and the deformation density in the nucleobase have been calculated following multipole refinements based on the rigid pseudoatom model of Stewart; they show features similar to those observed in

the charge-density study of 9-methyladenine by Craven & Benci [*Acta Cryst.* (1981), **B37**, 1584-1591], and to theoretical calculations on adenine. Lone-pair electron density is clearly revealed and the acidic nature of the H atom bound to C(8) is confirmed.

Introduction

The room-temperature X-ray crystal structure of adenine hydrochloride hemihydrate, $C_5H_6N_5^+.Cl^-.0.5H_2O$, has been previously reported by Broomhead (1948), Cochran (1951) and Kistenmacher & Shigematsu (1974). Cochran's paper, with the intriguing subtitle 'The Electron Distribution in Adenine Hydrochloride', represented the then state of the art. It was the first time that H atoms had been located in an electron-density map (Glusker, 1981), making it possible to distinguish tautomeric forms of the adenine molecule.

The determination of the detailed electron-density distribution and accurate molecular geometry in adenine hydrochloride was the object of the research reported here, which is part of an investigation into the effects of protonation, substitution and metal binding on nucleic-acid bases. The results of this study will later be compared with those for a complex of protonated adenine, $1H^+$-adeniniumtrichlorozinc(II), with a view to examining any differences induced in the nucleobase by coordination to zinc.

Experimental

Crystals of adenine hydrochloride are monoclinic, space group $P2/c$. The unit-cell parameters at room temperature, obtained by Kistenmacher & Shigematsu, were a = 8.779 (4), b = 4.831 (2), c = 19.459 (12) Å, β = 114.32 (1)° and Z = 4. The asymmetric unit contains one adenine moiety, protonated at N(1), one chloride ion and one half of a water molecule, the O atom being located on a twofold rotation axis.

Crystals, grown from acidic aqueous solution, were mounted on 2 mm-long glass fibres attached to copper pins. Diffraction data were collected on a CAD-4 diffractometer, with graphite-monochromated Mo $K\alpha$ X-radiation (λ = 0.71069 Å), from a crystal cooled in a liquid nitrogen stream, held at 123 (1) K. Several crystals were screened for quality, and the best specimen, measuring 0.250 × 0.250 × 0.115 mm, mounted on the diffractometer with b^* tilted at a few degrees from the φ axis, was used for data collection. Unit-cell parameters at 123 K obtained from a least-squares fit of 25 reflections, measured at four symmetry-equivalent positions, in the range $13.1 \leq \theta \leq 27.5°$, were a = 8.709 (1), b = 4.826 (1), c = 19.286 (1) Å and β = 113.45 (1)°, V = 742.69 (1) Å^3. A total of 13 011 reflections to $(\sin\theta/\lambda)$ = 1.32 Å^{-1} were measured in the range $-17 \leq h \leq 17$, $-9 \leq k \leq 9$, $-48 \leq l \leq 45$; ω/θ scans, variable scan range $(1.0 + 0.35\tan\theta)°$, aperture size $(1.6 + \tan\theta)$ mm. A full sphere of data was collected to $(\sin\theta/\lambda)$ = 0.77 Å^{-1}. This was supplemented by higher-

order data collected from the $k \geq 0$ hemisphere selected on the basis of E-value calculations from a preliminary refinement and experimental tests so that $I(hkl)$ was expected to be $\geq 2\sigma(I)$. Three intensity control reflections (006, 211 and 6$\bar{1}$9) showed no long-term trends but there were short-term variations of $\pm 2\%$; data were corrected for this effect. The final data set, after omitting 826 reflections that had not been remeasured at the slow scan speed because they had a negative net peak count after the fast scan, comprised 12 185 reflections. Absorption corrections were applied (μ = 4.64 cm^{-1}), Gaussian integration, transmission factors 1.107 (max.) and 1.047 (min.). Unique set of 3404 reflections, $R_{int}(F^2)$ = 2.7%. The *XTAL* system of crystallographic programs (Hall & Stewart, 1989) was used for all conventional calculations, and the *POP* procedure of Craven, Weber & He (1987), which assumes the rigid pseudoatom model of Stewart (1976), was used for charge-density calculations.

Conventional refinements

Starting coordinates for the non-H atoms were taken from the room-temperature study of adenine hydrochloride by Kistenmacher & Shigematsu (1974); the H atoms were located in a difference map and were initially assigned isotropic temperature factors 1.5 times that of their parent atoms. Using the full data set, the positional and anisotropic thermal parameters of the non-H atoms and the scale and extinction factors were refined [final g = 1.4 (3) × 10^3], and anomalous-dispersion corrections applied. Extinction correction factors less than 0.99 for F_{obs} were 0.95 (21$\bar{3}$) and 0.98 (002, 006, 012, 10$\bar{6}$). Refinements were performed with the program *SFLSX* (Hall, Spadaccini, Olthof-Hazekamp & Dreissig, 1989); scattering factors for neutral atoms and dispersion corrections were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). All conventional refinements minimized $\Sigma w|F_{obs} - F_{calc}|^2_H$ with 106 variables and $(\Delta/\rho)_{max} \leq 0.001$. $R(F)$ = 3.3, wR = 3.1% and S = 3.038, where w = $1/\sigma^2(F)$, with $\sigma(F)$ from a combination of counting statistics and mean deviations from equivalent reflections as detailed in *SORTRF*, merge 1 option (Hall, Spadaccini & Stewart, 1989). A high-order refinement of a data set of 1709 reflections, with $\sin\theta/\lambda \geq 0.65$ Å^{-1}, converged at $R(F)$ = 3.0, wR = 1.7% and S = 1.195.

A zinc complex of protonated adenine has been investigated by neutron diffraction at room temperature by McCall (1980); the bond lengths to H atoms obtained in that study have been used to estimate more accurate H-atom coordinates in adenine hydrochloride. The positions of the H atoms were extended along their bond vectors to the neutron bond lengths of the zinc complex; the revised H-atom positions were then included in the refinements, $R(F)$ = 3.5, wR = 3.5%, S = 3.357 (full data set), and R = 3.0, wR = 1.7% and S = 1.192 (high-order data only). Difference maps calculated after these refinements gave residual densities of $\Delta\rho_{max}$ = 0.7 and $\Delta\rho_{min}$ = -0.5 e Å^{-3},

Table 1. Non-H-atom coordinates from conventional high-order refinement

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i{}^*a_j{}^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq} (Å^2)
C(2)	0.69007 (08)	0.23446 (13)	0.55826 (3)	0.0128 (1)
C(4)	0.65878 (07)	0.44469 (13)	0.45157 (3)	0.0110 (1)
C(5)	0.79302 (07)	0.62452 (12)	0.48596 (3)	0.0103 (1)
C(6)	0.88224 (07)	0.60338 (12)	0.56475 (3)	0.0104 (1)
C(8)	0.68907 (08)	0.72529 (15)	0.36881 (3)	0.0142 (1)
N(1)	0.82390 (07)	0.40164 (07)	0.59751 (3)	0.0121 (1)
N(3)	0.60260 (07)	0.24651 (13)	0.48529 (3)	0.0131 (1)
N(6)	1.01048 (08)	0.76010 (14)	0.60581 (3)	0.0140 (1)
N(7)	0.81106 (07)	0.80010 (12)	0.43321 (3)	0.0122 (1)
N(9)	0.59445 (07)	0.51213 (13)	0.37686 (3)	0.0141 (1)
Cl	0.28125 (02)	0.17999 (04)	0.27435 (1)	0.01718 (5)
O(w)	0.00000	0.75694 (18)	0.25000	0.0153 (2)

and $\Delta\rho_{max}$ = 0.2 and $\Delta\rho_{min}$ = −0.2 e Å^{-3}, for the full and high-order refinements respectively. Coordinates used to calculate bond lengths and angles came from this last high-order refinement and are presented in Table 1.

Multipole refinements

The invariant cores of the non-H atoms were described by isolated neutral Hartree-Fock scattering curves, except for the Cl atom which was assigned the scattering factor for Cl$^-$ and was not assigned multipole parameters. [Experience from another charge-density study (Cunane & Taylor, 1993) has shown that the use of an ionic scattering factor has little effect on the outcome of refinement error values and on the calculated charge-density distribution and its derived properties, particularly those of interest herein, even though, in this case, a total of four additional electrons per unit cell are included in the model. This procedure also gave a value of ΣP_v closer to zero.] H atoms were from the spherically averaged bonded model of Stewart, Davidson & Simpson (1965). All X-ray scattering factors were taken from International Tables for X-ray Crystallography (1974, Vol. IV). Refinements on F^2 minimized $\Sigma w|F_{obs}^2 - F_{calc}^2|_H^2$.

Many refinements were attempted using various strategies with a view to testing the robustness of the method. Of the set of eight multipole refinements reported here, the first four were with H atoms found in the difference map and extended to neutron bond lengths; positional parameters and isotropic temperature factors of the H atoms were held invariant. Two weighting schemes were used: scheme 1, with σ as for the conventional refinements above; scheme 2, with σ modified to $[\sigma^2_{scheme\ 1} + (0.01F_{obs})^2]^{1/2}$. Refinements I (weighting scheme 1) and II (weighting scheme 2) used the complete data set; the scale, type I extinction, and the coordinates, anisotropic harmonic and anharmonic thermal parameters for the non-H atoms were included in the refinement, together with multipole population coefficients to octopole level for non-H and dipole level for H atoms. Refinements III (weighting scheme 1) and IV (weighting scheme 2) used high-order data to refine the coordinates and thermal parameters of the non-H atoms, and these were then held fixed, while all

Table 2. Results of multipole refinements

QME is the quadratic mean error defined in the text. S is the scale factor.

No.	$R(F^2)$	$wR(F^2)$	QME(F^3)	$S(F^2)$	$R(F)$	$wR(F)$	QME(F)	$S(F)$
I	0.020	0.024	1.23	0.0965	0.020	0.012	1.19	0.3106
II	0.020	0.027	1.10	0.0968	0.020	0.014	1.07	0.3111
III	0.025	0.030	1.47	0.0987	0.023	0.015	1.47	0.3142
IV	0.025	0.032	1.23	0.0988	0.022	0.016	1.24	0.3143
V	0.021	0.025	1.28	0.0965	0.021	0.013	1.24	0.3106
VI	0.021	0.028	1.13	0.0968	0.021	0.014	1.10	0.3111
VII	0.025	0.030	1.48	0.0988	0.023	0.015	1.49	0.3140
VIII	0.025	0.032	1.25	0.0987	0.023	0.016	1.26	0.3142

the data were used to refine the multipole parameters of all the atoms; such a high-order refinement should effectively deconvolute thermal motion from deformation density.

An alternative means of dealing with H atoms when there are no neutron data available is to subject the non-H-atom framework of the molecule to a rigid-body thermal analysis and to subsequently derive effective anisotropic temperature factors for the H atoms. Using programs developed by Craven & He (1983), following the method of He & Craven (1985), internal librational axes were chosen across the C(4)—C(5) and N(1)—C(5) vectors, with resultant mean-square librational amplitudes of 16 (4) and 7 (2) deg^2; corrections for internal vibration modes in the C—H and N—H bonds were estimated from low-temperature neutron diffraction studies of adenosine (Klooster, Ruble, Craven & McMullan, 1991) and 1-methyluracil (McMullan & Craven, 1989), which provided accurate information on the anisotropic behaviour of the H atoms. Dipole parameters were imposed upon the C—H and N—H bonds, to compensate for the bond shortening which occurs when H-atom positions are refined with X-ray data; the components of the dipole moments along local atomic axes were estimated from a charge-density study of 9-methyladenine (Craven & Benci, 1981). When the coordinates of the H atoms, with fixed anisotropic thermal parameters derived from the rigid-body analysis and with fixed dipole parameters are subsequently refined, the resultant bond lengths should be similar to those from a refinement of neutron data. Refinements V to VIII are analogous to refinements I to IV, but with the 'new' anisotropic H atoms. In V and VI, the positional parameters and monopoles of H were refined along with the usual parameters on the non-H atoms. In the high-order refinements, VII and VIII, the H-atom coordinates were held at the values obtained in V and VI.

The results of refinements I-VIII are given in Table 2.* QME is the quadratic mean error, defined by

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*Lists of structure factors, thermal parameters, H-atom coordinates and least-squares-planes data from the conventional refinements together with monopole parameters from refinements I-VIII, multipole population parameters (VIII), refined H-atom coordinates (V and VI), bond lengths to H atoms (VI) and final difference map, $[\Delta\rho = 1/V\Sigma(F_o - F_{c_{multipole}})\exp(-2\pi i\mathbf{H}\cdot\mathbf{r})]$, where $F_{c_{multipole}}$ was calculated from a multipole model of the electron density, have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55707 (15 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, Abbey Square, Chester CH1 2HU, England.

Table 3. *Bond lengths* (Å) *and bond angles* (°) *in adenine hydrochloride hemihydrate from low-temperature high-order conventional refinement*

N(1)—C(2)	1.371 (1)	C(5)—C(6)	1.408 (1)
N(1)—C(6)	1.364 (1)	C(5)—N(7)	1.380 (1)
C(2)—N(3)	1.308 (1)	C(6)—N(6)	1.320 (1)
N(3)—C(4)	1.353 (1)	N(7)—C(8)	1.323 (1)
C(4)—C(5)	1.394 (1)	C(8)—N(9)	1.365 (1)
C(4)—N(9)	1.361 (1)		
C(2)—N(1)—C(6)	123.77 (5)	C(6)—C(5)—N(7)	131.61 (5)
N(1)—C(2)—N(3)	124.80 (7)	N(1)—C(6)—C(5)	113.83 (5)
C(2)—N(3)—C(4)	112.42 (5)	N(1)—C(6)—N(6)	120.89 (5)
N(3)—C(4)—C(5)	127.35 (5)	C(5)—C(6)—N(6)	125.28 (6)
N(3)—C(4)—N(9)	127.05 (5)	C(5)—N(7)—C(8)	103.88 (5)
C(5)—C(4)—N(9)	105.59 (6)	N(7)—C(8)—N(9)	113.23 (6)
C(4)—C(5)—C(6)	117.81 (6)	C(4)—N(9)—C(8)	106.72 (5)
C(4)—C(5)—N(7)	110.57 (4)		

$[\Sigma w_H \Delta_H^2/(n_{obs} - n_{param})]^{1/2}$, where $\Delta_H = |F_o - F_c|_H$ or $|F_o^2 - F_c^2|_H$. There are no significant differences in R, and only minor differences in QME, when set I-IV, with isotropic H atoms, and set V-VIII, with anisotropic H atoms, are compared (*i.e.* I with V, II with VI *etc.*), indicating that the multipole refinements are not model-dependent with respect to the H atoms. R values from refinements with weighting scheme 2 show insignificant differences when compared with those with weighting scheme 1; the QME values are lowered appreciably with the second weighting scheme. The high-order refinements result in R values and QME's which are slightly larger than those from the analogous all-data refinements. This was not considered to be serious, and the coordinates and charge parameters from refinement VIII were used in the charge density and electrostatic potential calculations which are presented here; refinement VIII was chosen because it was expected that a high-order refinement would result in better deconvolution of thermal parameters from deformation density, and the 'derived' anisotropic H atoms should be the best model available in the absence of neutron diffraction data. Difference maps, calculated in the least-squares plane through the adenine ring after each of these refinements, showed similar features, the largest residual densities being -0.16 and $+0.20 \, e \, \text{Å}^{-3}$.

Results and discussion

Bond lengths and angles, calculated after the high-order conventional refinement (Table 3), when compared with those obtained in the room-temperature study of adenine hydrochloride by Kistenmacher & Shigematsu (1974), show some significant differences: for C(2)—N(3), C(4)—C(5) and C(8)—N(9) Kistenmacher & Shigematsu found 1.289 (4), 1.377 (4) and 1.351 (4) Å respectively, compared with 1.308 (1), 1.394 (1) and 1.365 (1) Å in this study. These differences can probably be attributed to the effects of thermal motion at room temperature. Bond angles are equivalent within experimental error in the two studies, except for C(5)—N(7)—C(8) and C(4)—C(5)—N(7), 103.1 (2) and 111.3 (2)° at room temperature, 103.88 (5) and 110.57 (4)° at 123 K. The H—O—H angle is 108.1 (1)° (the O—H bond length was set at 1.00 Å).

The multipole refinements resulted in differences in bond lengths and angles that are not significant when compared with those from the conventional refinements. The refined coordinates of atoms H(1), H(62) and H(9) are in good agreement with those found in the difference map and extended to neutron lengths, whereas H(2), H(61) and H(8) differ in at least one coordinate by more than 3 e.s.d.'s. The bond lengths to H atoms, particularly the C—H bonds, refined to lengths which are greater than expected, C(2)—H(2), 1.13 (1) and C(8)—H(8), 1.17 (1) Å. Bond angles involving the refined H atoms compared with those determined from the conventional all-data refinement and with the results of Kistenmacher & Shigematsu, using their standard deviations, show no significant differences.

The calculation of least-squares planes through the non-H atoms of the pyrimidine and imidazole rings reveals that the adenine moiety is very nearly planar; a fold across C(4)—C(5) between the six- and five-membered rings makes an angle of only 0.79 (3)°. The H atoms are not quite coplanar with the ring framework, the small deviations probably resulting from intermolecular hydrogen-bonding interactions. A thermal ellipsoid plot of adenine hydrochloride at 123 K is depicted in Fig. 1, including the ellipsoids for H atoms with derived anisotropic thermal parameters.

The difference density $(X - X_{HO})$, based on the expression

$$\Delta\rho = 1/V \sum(F_o - F_{c_{HO}})\exp(-2\pi i \mathbf{H}\cdot\mathbf{r}),$$

was calculated using coordinates and thermal parameters from the conventional high-order refinement, and structure factors calculated with free spherical atoms, to match the all-data refinement. The maximum and minimum densities obtained were 0.39 and $-0.40 \, e \, \text{Å}^{-3}$. The map of the difference density in the adenine least-squares plane ap-
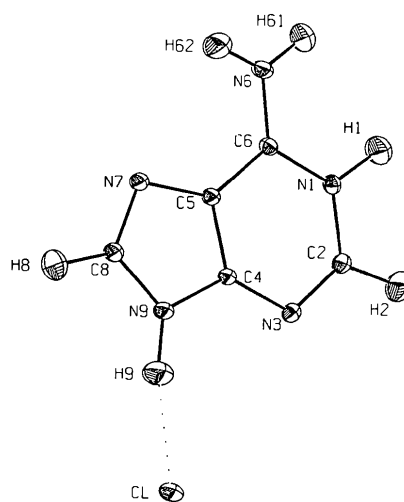

Fig. 1. Atomic labelling and thermal ellipsoids in adenine hydrochloride hemihydrate at 50% probability level, at 123 K.

pears in Fig. 2 (g = 1.4 × 10³ and scale factor = 0.3130); bonding density and lone-pair density at N(3) and N(7) are clearly revealed. A section plotted perpendicular to the plane of the adenine base at N(7) (Fig. 3) shows that the lone-pair electron density lies well off the plane of the base, its maximum lying somewhat below the vector N(7)—H(62)'. The atom H(62)' is involved in an intermolecular hydrogen bond to N(7), with H···N distance 1.945 Å, and lies 0.3 Å above the plane of the page in Fig. 3. The internal angle at C(5)—N(7)—C(8) suggests a degree of hybridization somewhere between p^3 and sp^3; the location of the lone-pair density supports this notion.

The charge-density distribution, defined by

$$\Delta\rho = 1/V \sum(F_{c_{multipole}} - F_{c_{free\ atom}})\exp(-2\pi i\mathbf{H}\cdot\mathbf{r}),$$

was calculated using the electron-population parameters obtained from the multipole refinements, and plotted in the least-squares plane through the adenine moiety (Fig. 4); the maximum bonding density is 0.82 e Å⁻³. Cross-

sections of deformation density, plotted through the midpoints of bonds in the purine ring, are all elliptical to varying extents, indicating π-electron delocalization; the degree of ellipticity correlates with bond lengths as expected, those bonds with more π-character being shorter. Charge density in the water molecule is shown in Fig. 5, revealing the shape of the lone-pair electron density on the O atom; these plots show features similar to those of the water molecule in potassium oxalate monohydrate, studied at low temperature by Jovanovski, Thomas & Olovsson (1987). Net atomic charges, which are the negatives of the monopole population parameters, are given in Table 4. While their magnitudes are of limited physical significance, their relative values reveal interesting features. It was found that all the H atoms carry a positive charge, H(1) and H(9), bound to N(1) and N(9), having a somewhat larger magnitude than the two amino-group H atoms and those bound to C. The N atoms are negatively charged, C(2) and C(6) are neutral, whereas a small negative charge resides on C(4), C(5) and C(8). The C(8)—H(8) bond has a rather large dipole moment for a C—H bond, indicating that H(8) has a notable acidity.

The experimental charge density in 9-methyladenine determined by Craven & Benci (1981) provides a useful comparison for adenine hydrochloride. The deformation density in the adenine least-squares plane of both compounds exhibits similar general features; however, the net atomic charges are significantly different, as is to be expected when comparing a protonated with a neutral base. In 9-methyladenine the H atoms bound to N are also charged more positively than those bound to C, consistent with electrostatic models of hydrogen bonding; there is also a large dipole deformation on the H atom bound to C(8) as observed in the hydrochloride, which is further evidence that this may be a characteristic of
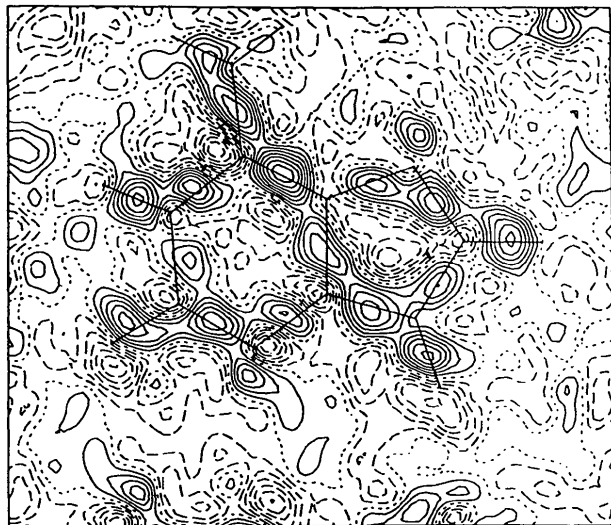

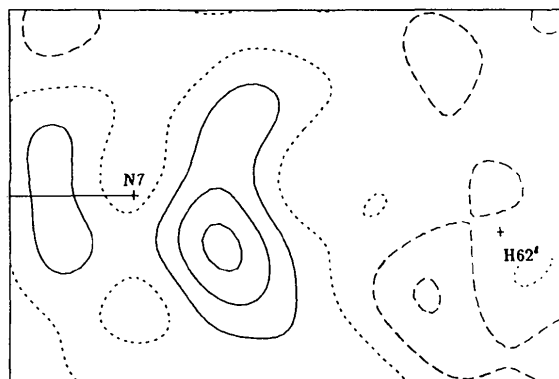Fig. 2. Difference density, $X - X_{HO}$, in the adenine least-squares plane; contours at 0.05 e Å⁻³.

Fig. 3. Section of $X - X_{HO}$ difference density, perpendicular to the plane of the base and containing the C(5)—N(7)—C(8) bisector; the base plane is drawn at left; contours at 0.1 e Å⁻³.
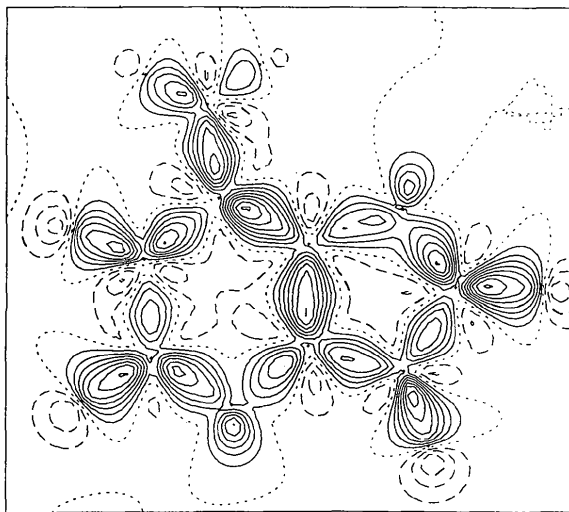

Fig. 4. Deformation density, calculated from a multipole model of the electron density, in the adenine least-squares plane; contour interval 0.1 e Å⁻³.

purines as noted by Craven & Benci. Eisenstein (1988) has used the results of the 9-methyladenine experiment to make a comparison with the deformation density obtained from theoretical calculations on neutral adenine; sections through the deformation density perpendicular to the plane of the base in both adenine and 9-methyladenine show features similar to those obtained for the protonated adenine base in this study.

The electrostatic potential in adenine hydrochloride isolated from the crystal lattice was calculated from the experimental charge-density distribution, and mapped in the adenine least-squares plane (Fig. 6a); it features prominent negative potential extending from the N(3) and N(7) atoms and compact positive contours near the H atoms. Maps calculated at distances of 1 and 2 Å above and below the plane (Figs. 6b–e) indicate that negative potential has strong influence in the region surrounding the adenine base. The electrostatic potential in the least-squares plane of adenine hydrochloride closely resembles that in 9-methyladenine, as calculated by Stewart (1982). A study of adenine by Pullman & Pullman (1981), where ab initio wavefunctions were used to calculate electrostatic potential, also resulted in a map of similar appearance to that of the hydrochloride.

Table 4. *Atomic charges* $(-P_v \times 10^2)$ *averaged over eight multipole refinements*

C(2)	− 5 (3)	N(9)	− 12 (2)
C(4)	− 14 (2)	O(w)	− 14 (2)
C(5)	− 14 (2)	H(1)	22 (1)
C(6)	− 1 (2)	H(2)	14 (2)
C(8)	− 14 (2)	H(61)	16 (2)
N(1)	− 14 (2)	H(62)	18 (2)
N(3)	− 9 (2)	H(8)	17 (2)
N(6)	− 18 (2)	H(9)	25 (1)
N(7)	10 (2)	H(w)	18 (1)

(a)

(b)   (c)

(d)   (e)
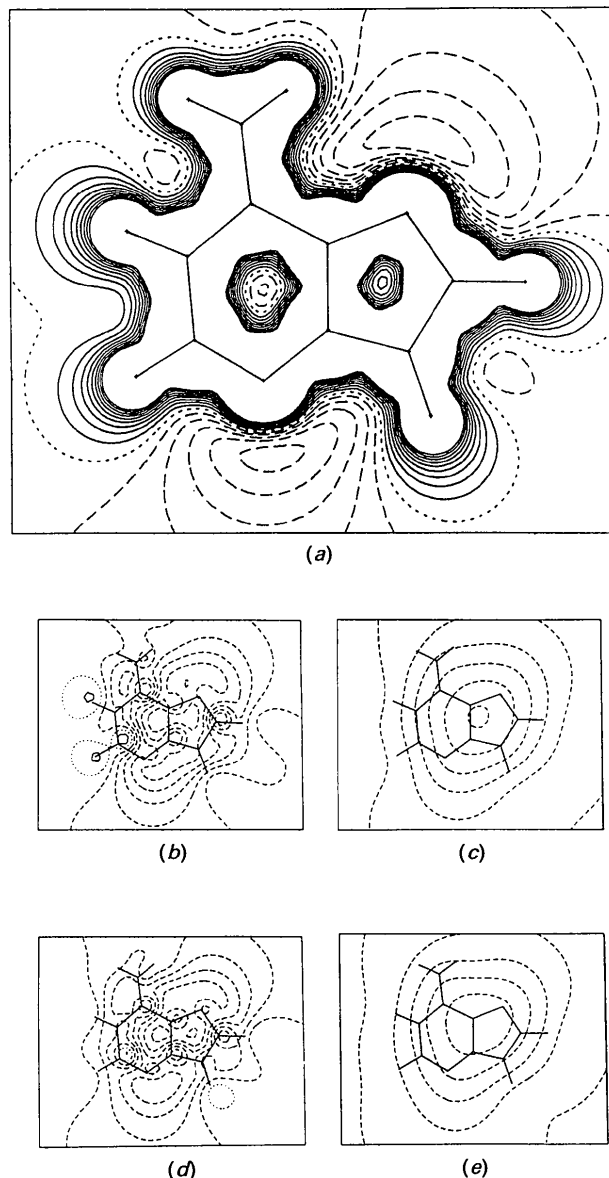
Fig. 6. Electrostatic potential in adenine hydrochloride, isolated from the crystal lattice, calculated from the multipolar model of the charge-density distribution; contours at 0.05 e Å^{-1}, the zero contour is dotted and negative contours dashed. The maximum positive contour drawn is +0.45 e Å^{-1}. (a) In the adenine plane, (b) 1 Å above, (c) 2 Å above, (d) 1 Å below and (e) 2 Å below the adenine plane.
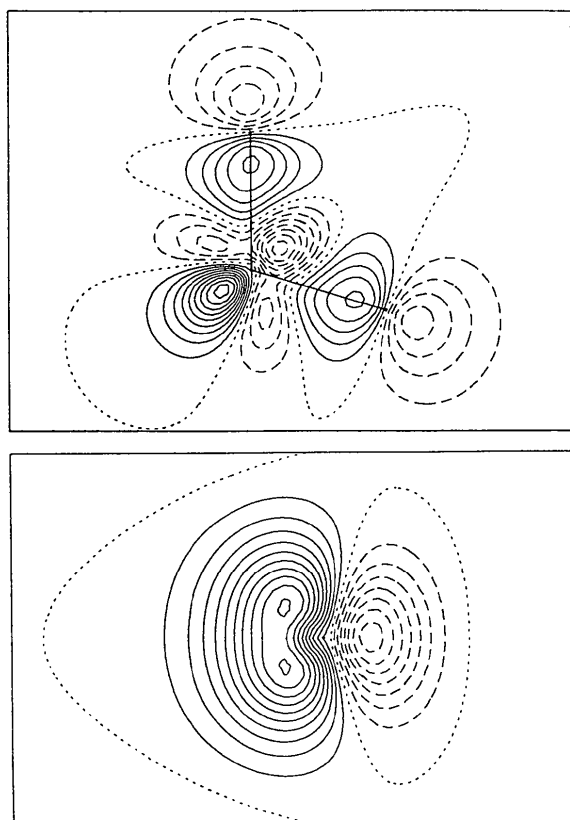

Fig. 5. Deformation density, from the multipole model, in the water molecule: (above) in the H—O—H least-squares plane, and (below) in the plane bisecting the H—O—H angle; contour interval 0.1 e Å^{-3}.

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Salt-Bridge Formation by *Cinchona* Alkaloids: Quininium Salicylate Monohydrate

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Abstract

$C_{20}H_{25}N_2O_2^+ \cdot C_7H_5O_3^- \cdot H_2O$, $M_r = 480.56$, orthorhombic, $P2_12_12_1$, $a = 6.957$ (2), $b = 17.108$ (1), $c = 20.477$ (6) Å, $V = 2437$ (1) Å^3, $Z = 4$, $D_m = 1.30$ (1), $D_x = 1.31$ g cm^{-3}, λ(Cu $K\alpha$) $= 1.5418$ Å, $\mu = 7.194$ cm^{-1}, $F(000) = 1024$, $T = 293$ K, $R = 0.0341$ for 2507 reflections. Hydrogen bonds link the quininium cation, salicylate anion and water molecule to form an eleven-membered ring which can be compared to salt-bridge clusters observed in myoglobin. The effect of protonation on the quinuclidine geometry is discussed.

Introduction

Quinine (I) is an important antimalarial drug which occurs in the bark of the *Cinchona* tree together with other *Cinchona* alkaloids, such as quinidine (II), cinchonidine (III) and cinchonine (IV).
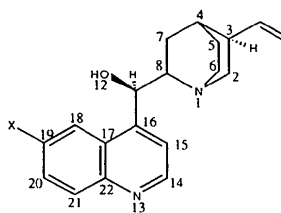
	X	Absolute configuration	
		C8	C9
(I)	—OCH₃	*S*	*R*
(II)	—OCH₃	*R*	*S*
(III)	—H	*S*	*R*
(IV)	—H	*R*	*S*

The similarity of the molecular structures of the free bases, (I)–(IV), in the crystalline state (Pniewska & Suszko-Purzycka, 1989; Kashino & Haisa, 1983; Oleksyn, 1982; Oleksyn, Lebioda & Ciechanowicz-Rutkowska, 1979) suggests that differences, if any, in