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9-Aminoacridine Hydrochloride Monohydrate

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9-Aminoacridine hydrochloride monohydrate, $C_{13}H_{10}N_2.HCl.H_2O$ crystallizes in the triclinic space group $P\bar{1}$, $a=9{\cdot}779$ (1), $b=8{\cdot}880$ (1), $c=7{\cdot}859$ (1) Å, $\alpha=103{\cdot}61°$ (1), $\beta=96{\cdot}72°$ (1), $\gamma=111{\cdot}43°$ (1), $V=601{\cdot}66$ (7) Å^3, F.W. 248·71, $Z=2$, $D_x=1{\cdot}373$, $D_{\rm obs}=1{\cdot}374$, λ(Cu $K\alpha$) = 1·5418 Å, μ(Cu $K\alpha$) = 25·66 cm^{-1}. The salt was crystallized from ethanol. A structural determination by X-ray diffraction resulted in a final residual $R=0{\cdot}042$ for 1916 observed reflections. All hydrogen atoms were located and refined isotropically. The molecule is monoionized with the proton on the nitrogen atom of the central ring. This nitrogen atom is hydrogen bonded to a water molecule. The amino group is hydrogen bonded to two chloride ions. There is considerable vertical stacking of the ring systems of adjacent molecules in the crystalline state.

Introduction

Crystallographic studies of some analogues of acridine alkylating agents that show mutagenic and antitumor properties (Glusker, Berman & Carrell, 1972) have revealed that in some cases the acridine ring system is nearly planar (Carrell, 1972) while in others it is buckled (Glusker, Minkin & Orehowsky, 1972; Berman & Glusker, 1972; Glusker, Gallen & Carrell, 1973) with angles of 7–13° between the two outer rings. However no data, apart from those obtained for acridine itself (Phillips, 1956; Phillips, Ahmed & Barnes, 1960), are available for simpler acridines. Therefore 9-aminoacridine was studied in order to obtain accurate bond lengths and angles and to determine the degree of planarity in this simple molecule which lacks an alkylating side chain.

Experimental

Commercial 9-aminoacridine hydrochloride was recrystallized from 95% ethanol as parallelepipeds. A crystal, nearly ellipsoidal in shape and with dimensions 0·15 × 0·15 × 0·25 mm, was selected for the data collection. Three-dimensional data were collected on a Syntex automated diffractometer with monochromatic Cu $K\alpha$ radiation and the θ–2θ scan technique. The intensity data were converted to structure amplitudes by application of Lorentz and polarization factors and an ellipsoidal absorption correction μ[Cu $K\alpha$] = 25·66 cm^{-1} (Johnson, 1963), and placed on an absolute scale by means of a Wilson plot. Additional details of data collection are included in Table 1.

Table 1. *Data collection and crystal data*

Range of sin θ/λ:	0·05–0·61 Å^{-1}
Number of reflections measured:	2258
Number of theoretically accessible reflections:	2757
Number of reflections below threshold value:	346
Criterion for threshold value:	$I_{\rm obs}=2{\cdot}33\ \sigma(I)$
Criterion for $\sigma(I)$:	counting statistics
Criterion for $\sigma(F)$:	$\sigma(F)=(F/2)\ \{[\sigma^2(I)/I^2]+\delta^2\}^{1/2}$ δ = measured instrumental uncertainty = 0·0200
Intensity loss with time during data collection:	6% over 71 h
Formula:	$C_{13}H_{10}N_2.HCl.H_2O$, F.W. 248·71
Cell dimensions:	$a=9{\cdot}779$ (1), $b=8{\cdot}880$ (1), $c=7{\cdot}859$ (1) Å, $\alpha=103{\cdot}61$ (1)°, $\beta=96{\cdot}72$ (1)°, $\gamma=111{\cdot}43$ (1)°, $V=601{\cdot}66$ (7) Å^3
Space group:	$P\bar{1}$, $Z=2$
Density:	$D_{\rm obs}=1{\cdot}374$, $D_x=1{\cdot}373$ g cm^{-3}
Absorption coefficient:	μ(Cu $K\alpha$) = 25·66 cm^{-1}

Structure determination

The structure was solved in the non-centrosymmetric space group $P1$. Coordinates for one of the two molecules in the unit cell were determined from a Patterson map. The other molecule and the water and chloride ions were found from successive electron density maps with increasing numbers of atoms included in structure-factor calculations. The chloride ions, although heavier than any of the other atoms in the molecule, were detected late in these calculations. The centers of symmetry were then found and all subsequent calculations were done in the true space group $P\bar{1}$.

The X-RAY 72 System of Programs (Stewart, Kruger, Ammon, Dickinson & Hall, 1972) was used to calculate all maps. The non-hydrogen atoms were refined, first with isotropic temperature factors, then with anisotropic temperature factors by a full-matrix least-squares method (Gantzel, Sparks, Long & Trueblood, 1969). Hydrogen atoms were located from a difference map. The hydrogen atoms were refined isotropically. The weights of the reflections during refinement were $1/[\sigma^2(F)]$ with zero weight for those reflections below the threshold value. The quantity minimized in the least-squares calculations was $\sum\omega\{||F_o|-$

Table 2. *Final atomic parameters*

Positional parameters are given as fractions of cell edges $\times 10^4$ ($\times 10^3$ for hydrogen). Anisotropic temperature factors are expressed as $\exp\,[-\frac{1}{4}(h^2a^{*2}B_{11}+k^2b^{*2}B_{22}+l^2c^{*2}B_{33}+2hka^*b^*B_{12}+2hla^*c^*B_{13}+2klb^*c^*B_{23})]$ and isotropic temperature factors as $\exp\,(-B\sin^2\theta/\lambda^2)$ with B values given in Å^2.

The standard deviations for each parameter, determined from the inverted full matrix, are given in parentheses and apply to the last specified digits. The numbering system of *Chemical Abstracts* is used with 4a, 8a, 9a and 10a replaced by 11–14 respectively.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	1604 (2)	−0612 (3)	0146 (3)	2·61 (7)	3·34 (8)	3·89 (10)	0·90 (7)	0·29 (7)	1·09 (8)
C(2)	1553 (3)	−1261 (3)	1556 (4)	3·29 (8)	3·71 (8)	4·43 (11)	0·97 (7)	0·90 (8)	1·64 (9)
C(3)	2843 (3)	−684 (3)	2929 (4)	4·28 (9)	4·09 (8)	3·79 (9)	1·78 (8)	0·78 (8)	1·76 (9)
C(4)	4171 (3)	521 (3)	2864 (3)	3·35 (7)	3·75 (8)	3·35 (9)	1·57 (8)	0·06 (7)	1·01 (8)
C(5)	7147 (3)	4396 (3)	63 (4)	2·40 (7)	3·43 (9)	4·28 (11)	0·68 (7)	0·31 (7)	0·64 (9)
C(6)	7316 (3)	5123 (3)	−1279 (4)	2·85 (7)	3·71 (9)	5·04 (12)	0·65 (8)	1·25 (8)	1·07 (10)
C(7)	6085 (3)	4670 (3)	−2704 (4)	3·53 (8)	3·97 (9)	4·32 (10)	1·14 (8)	1·44 (8)	1·54 (9)
C(8)	4708 (3)	3481 (3)	−2758 (3)	3·12 (7)	3·56 (8)	3·47 (9)	1·24 (7)	0·75 (7)	1·04 (8)
C(9)	3067 (2)	1403 (3)	−1403 (3)	2·42 (6)	2·58 (7)	3·27 (8)	1·00 (6)	0·31 (6)	0·61 (7)
N(10)	5579 (2)	2419 (2)	1368 (3)	2·28 (5)	3·10 (6)	3·67 (8)	0·86 (6)	−0·15 (6)	0·78 (7)
C(11)	4247 (2)	1209 (3)	1416 (3)	2·56 (6)	2·64 (7)	3·40 (9)	1·18 (6)	0·27 (6)	0·56 (7)
C(12)	4491 (2)	2688 (3)	−1386 (3)	2·40 (6)	2·63 (7)	3·21 (8)	0·99 (6)	0·48 (6)	0·57 (7)
C(13)	2959 (2)	649 (3)	29 (3)	2·44 (6)	2·63 (7)	3·21 (8)	1·06 (6)	0·34 (6)	0·68 (7)
C(14)	5731 (2)	3157 (3)	33 (3)	2·53 (6)	2·76 (7)	3·50 (9)	1·11 (7)	0·53 (6)	0·55 (7)
N(15)	1884 (2)	923 (3)	−2723 (3)	2·69 (6)	3·58 (7)	3·90 (8)	0·23 (6)	−0·39 (6)	1·64 (7)
O(16)	−1991 (2)	3339 (3)	4211 (3)	2·81 (5)	4·47 (7)	5·60 (9)	0·94 (6)	−0·43 (6)	0·98 (7)
Cl(17)	997 (1)	2674 (1)	4407 (1)	2·89 (2)	3·54 (2)	5·18 (2)	0·62 (1)	−0·22 (1)	1·77 (2)

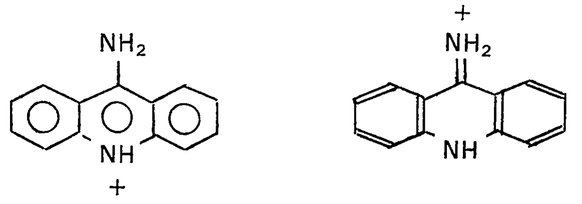
Table 2 (*cont.*)

	x	y	z	B
H(1)	074 (3)	−100 (4)	−074 (4)	4·3 (6)
H(2)	058 (3)	−199 (4)	162 (4)	5·8 (8)
H(3)	283 (3)	−118 (4)	383 (4)	5·1 (7)
H(4)	507 (3)	086 (4)	372 (4)	4·7 (7)
H(5)	789 (3)	458 (4)	098 (5)	5·6 (8)
H(6)	825 (3)	595 (4)	−128 (4)	4·9 (7)
H(7)	622 (3)	521 (4)	−361 (4)	5·0 (7)
H(8)	390 (3)	318 (3)	−377 (4)	4·1 (6)
H(10)	628 (4)	260 (4)	208 (5)	4·2 (9)
H(15)	188 (3)	138 (4)	−352 (4)	4·1 (7)
H(15′)	116 (4)	020 (5)	−280 (5)	5·1 (8)
H(16)	−122 (4)	321 (5)	435 (5)	8·0 (10)
H(16′)	−176 (4)	382 (5)	377 (5)	5·6 (12)

$|F_c||\}^2$. The final residual R was 0·042 with a weighted value of R=0·057. Parameters obtained from the refinement are listed in Table 2. The atomic scattering factors for chloride, oxygen, nitrogen and carbon are those in *International Tables for X-ray Crystallography* (1962) and for hydrogen from Stewart, Davidson & Simpson (1965). The anomalous dispersion corrections for the chloride ion are those given by Cromer & Liberman (1970).*

Discussion of structure

The bond lengths and interbond angles are shown in Fig. 1. The molecule is monoionized with the one proton residing on the nitrogen atom, N(10), of the central ring. The amino group [N(15)] does not readily add a proton even in highly acid solutions [pK_a=9·99 for the central ring nitrogen atom and <−2 for the amino group, Albert (1966)]. The state of ionization is confirmed by both the hydrogen-atom position (located from the difference map) and by the hydrogen bonding as shown in Table 3. The C–NH$_2$ bond, C(9)–N(15), is approximately a double bond as a result of resonance in the cation as shown below:



The hydrogen atom H(10), attached to N(10) in the central ring system, forms a hydrogen bond to a water oxygen atom, O(16), at 2·790 Å. The non-protonated

Table 3. *Hydrogen-bond system*

Donor (D)	Acceptor (A)	$D\cdots A$ (Å)	H–D (Å)	H$\cdots A$ (Å)	$\angle A\cdots$H–D (°)
N(15)–H(15)····	Cl(17$^{\text{i}}$)	3·230 (2)	0·83 (3)	2·45 (3)	159 (1)
N(15)–H(15^1)···	Cl(17$^{\text{ii}}$)	3·233 (2)	0·74 (2)	2·55 (3)	154 (3)
N(10)–H(10)····	O(16$^{\text{iii}}$)	2·790 (2)	0·77 (3)	2·03 (3)	170 (3)
O(16)–H(16)····	Cl(17)	3·180 (1)	0·80 (2)	2·39 (2)	174 (4)
O(16)–H(16^1)···	Cl(17$^{\text{iv}}$)*	3·180 (1)	0·61 (2)	2·87 (3)	115 (4)

* Not a hydrogen bond.

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* The table of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30313 (15 pp., 1 microfiche). Copies may be obtained from the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3 (*cont.*)

Table of superscripts

None	x	y	z
i	x	y	$z-1$
ii	$-x$	$-y$	$-z$
iii	$1+x$	y	z
iv	$-x$	$1-y$	$1-z$
v	$1-x$	$-y$	$-z$
vi	$1-x$	$1-y$	$-z$

amino group, N(15)H(15)H(15′), is hydrogen bonded to two chloride ions, both at 3·18 Å. In addition to the hydrogen bond from N(10), the water oxygen atom, O(16), is hydrogen bonded to one chloride ion and has a weak interaction with a second.

The 9-aminoacridine molecule is almost planar and each of the three fused rings taken individually is planar within experimental error (Table 4). The calculated angle between the two outer fused rings is only 1·0°, a value comparable with that found for acridine of 1·2° (Phillips, 1956; Phillips, Ahmed & Barnes, 1960).

Table 4. *Deviations of atoms from planes through parts of the molecule*

Plane	1	2	3	4
C(1)	0·015*	0·000*	−0·005	0·062
C(2)	0·003*	0·003*	−0·027	0·053
C(3)	−0·016*	−0·004*	−0·049	0·023
C(4)	−0·008*	0·003*	−0·032	0·018
C(5)	0·004*	−0·016	0·022	−0·003*
C(6)	0·014*	−0·020	0·043	0·003*
C(7)	−0·001*	−0·048	0·032	−0·001*
C(8)	−0·013*	−0·060	0·011	0·000*
C(9)	−0·003*	−0·035	−0·001*	0·027
N(10)	0·005*	−0·000	0·003*	0·015
C(11)	0·004*	0·000*	−0·008*	0·027
C(12)	−0·016*	−0·049	−0·004*	0·000*
C(13)	0·017*	−0·001*	0·007*	0·050
C(14)	−0·005*	−0·024	0·004*	0·001*
N(15)	−0·001	−0·046	0·004	0·040

* included in the calculation of the plane
e.s.d. (N) = 0·003 Å, e.s.d. (C) = 0·004 Å.

Equations of planes

1. $6{\cdot}14499\,x-6{\cdot}87265\,y-3{\cdot}02285\,z=1{\cdot}34738$
2. $6{\cdot}18176\,x-6{\cdot}92179\,y-2{\cdot}94265\,z=1{\cdot}3726$
3. $6{\cdot}16636\,x-6{\cdot}82269\,y-3{\cdot}07915\,z=1{\cdot}36641$
4. $6{\cdot}06906\,x-6{\cdot}89741\,y-3{\cdot}02030\,z=1{\cdot}28961$

where x, y and z are fractional coordinates.

The packing of the molecules in the crystal is illustrated in Fig. 2. Each water molecule is surrounded by two chloride ions and the ionized nitrogen atom of the central ring of a 9-aminoacridine molecule. Each chloride ion is surrounded by two amino nitrogen atoms [N(15)] and two water molecules.

The vertical stacking of ring systems is shown in Fig. 3. The amino group is not involved in this overlap but each molecule has another above and below it at planes 3·4 Å apart, molecules in adjacent layers being related by a center of symmetry. The closest approaches are for the atoms C(8), C(12) and C(14) of the molecule at $1-x, 1-y, -z$.

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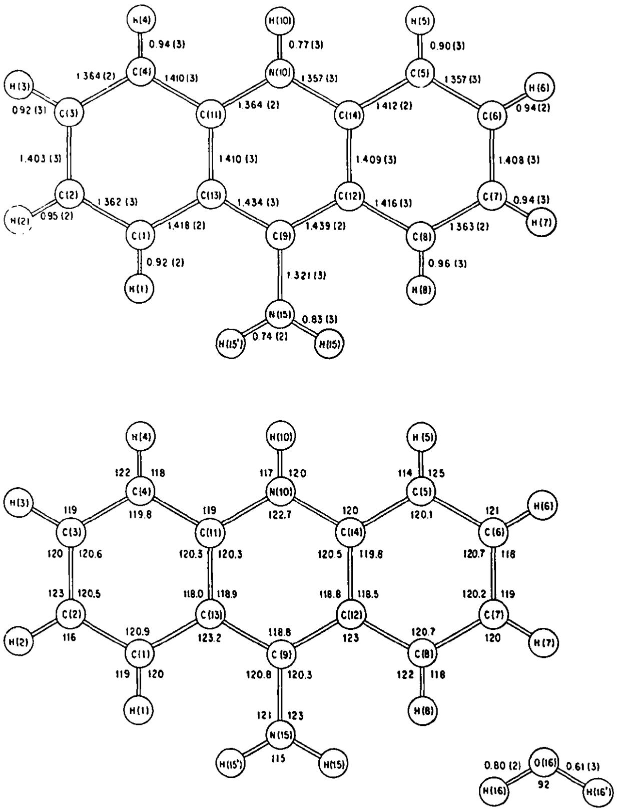

Fig. 1. Bond lengths and interbond angles in 9-aminoacridine. Estimated standard deviations for bond lengths are given in parentheses.

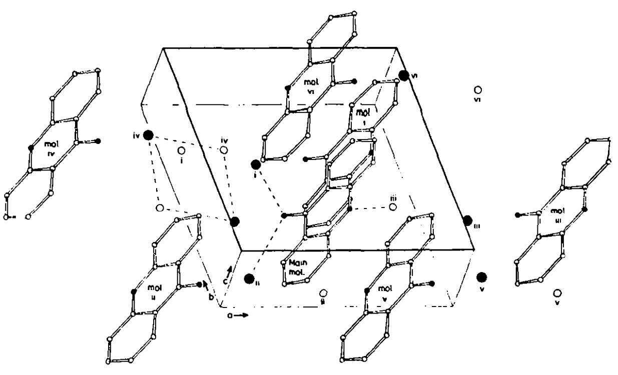

Fig. 2. Packing of molecules in the crystal. This is a view down −**c***. Nitrogen and chloride ions are black. The superscripts, defined in Table 3, are shown.

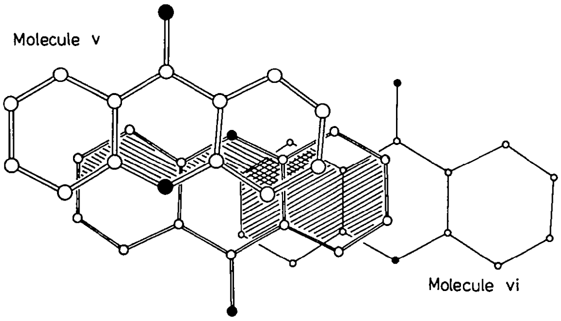

Fig. 3. Overlap of ring systems. Three molecules in parallel planes 3·4 Å apart are shown. The vertical stacking is indicated by the shading.

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The Crystal and Molecular Structures of Tetranactin*

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The structure of macrotetrolide antibiotic tetranactin, $C_{44}H_{72}O_{12}$, has been determined by the direct method with reflexion data collected on a 4-circle diffractometer. The crystals are monoclinic, space group $C2/c$ with four molecules in the unit cell of dimensions $a=25·44$ (3), $b=9·46$ (1), $c=24·52$ (3) Å and $\beta=129·83$ (8)°. The final R value for 3496 observed reflexions, obtained by the least-squares method with the block-matrix approximation, is 0·059, including anisotropic temperature factors for non-hydrogen atoms. The tetranactin molecule has a crystallographic twofold symmetry, and the molecular shape is fairly elongated and twisted. The outline of the molecule resembles that of a propeller which is remarkably different from that of nonactin. The intra- and intermolecular van der Waals contacts observed for tetranactin serve to stabilize the molecular and crystal structures.

Introduction

Tetranactin, $C_{44}H_{72}O_{12}$, is a macrotetrolide antibiotic (Ando *et al.*, 1971) and is one of the homologous compounds of nonactin (Dominguez, Dunitz, Gerlach & Prelog, 1962), which exhibit high K^+ selectivity for the alkali metal ion transport through the biological membranes. Physicochemical properties of the macrocyclic antibiotics (nonactin, valinomysin, eniatin, gramicidin and others) as the alkali metal ion carriers have been investigated extensively (Ogata & Rasmussen, 1966; Graven, Lardy & Estrada-O, 1967; Mueller & Rudin, 1967). A correlation between the hydration energy of the cation and the origin of the cation specificity of the macrocyclic molecules on the formation of the alkali metal ion complexes in acetone-d_6($+D_2O$) solution has been examined by proton magnetic resonance (p.m.r.) (Prestegard & Chan, 1970). However, the conformational changes of the molecules during the complex formation have remained unknown, except for those

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* Part of this work was presented at the 9th International Congress of Crystallography (31 August 1972, Kyoto) by Iitaka, Sakamaki & Nawata (1972*a*).