The Molecular and Crystal Structure of the Potassium Salt of Allantoic Acid

By Hans Ringertz
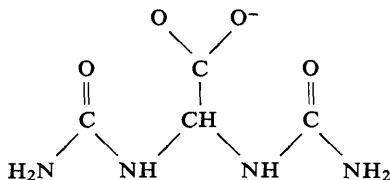
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Potassium allantoinate, $C_4H_7N_4O_4K$, crystallizes with four molecules in a monoclinic unit cell with $a=12\cdot668$, $b=8\cdot694$, $c=7\cdot101$ Å, $\beta=92\cdot39°$, space group Cc. The structure has been determined by the heavy-atom method and refined by full-matrix least-squares computations. The final R value is $4\cdot2\%$. In the allantoinate ion the carboxyl group and the two urea fractions are perfectly planar. The negative ions are held together in an intricate network of oxygen-potassium ionic contacts in sixfold coordination around each potassium ion. In addition there are five $N-H\cdots O$ hydrogen bonds from each molecule.

Introduction

As the final part of a research programme on nitrogen-containing excretory products in biological systems, the structure of allantoic acid, dicarbamido-acetic acid,

has been determined in the form of the potassium salt. An initial attempt to grow acceptably large crystals of the acid itself had failed and it was therefore decided to study potassium allantoinate.

Experimental

Commercially available allantoic acid was treated with KOH in hot ethanol. By slow cooling of the solution well shaped monoclinic domes exhibiting ortho pinacoids were formed. The cell constants were determined from photographic measurements of 15 high-angle reflexions (2θ between $110°$ and $160°$) with Cu $K\alpha$ radiation ($\lambda_{K\alpha_1}=1\cdot54051$ Å). These data were then used for a least-squares determination of the cell constants and their estimated standard deviations. The chosen monoclinic cell measured:

$$a=12\cdot668\pm0\cdot002\text{ Å}$$
$$b=8\cdot694\pm0\cdot005$$
$$c=7\cdot101\pm0\cdot001$$
$$\beta=92\cdot39\pm0\cdot01°.$$

Systematic absences were hkl with $h+k=2n+1$ and $h0l$ with $l=2n+1$, space group Cc or $C2/c$. $D_{obs}=1\cdot800$ g.cm^{-3} and $D_{calc}=1\cdot813$ g.cm^{-3}, assuming $Z=4$. Thus the centrosymmetric space group $C2/c$ having 8

general positions would have to show a twofold rotational symmetry of the molecule. The space group Cc was later established by statistical means as mentioned below.

A 0·35 mm long crystal with a cross section of 0·15 × 0·10 mm was mounted with the rotation axis parallel to the b axis. Three-dimensional data up to $\sin\theta/\lambda=0\cdot704$ were collected with a Philips automatic single crystal diffractometer, *PAILRED*, using monochromatized Mo $K\alpha$ radiation. 1000 structure amplitudes were obtained together with 329 systematic absences. The latter were used to estimate the statistics of the low intensity reflexions. The 24 amplitudes below the 70% confidence limit of the measured systematic absences were given that limiting value. Lorentz and polarization factor corrections were applied. No correction was made for absorption in the initial data treatment, but since μ was 6·3 cm^{-1}, and the crystal had been mounted normal to its long direction, this correction (Coppens, Leiserowitz & Rabinovich, 1965) was applied during the refinement. The data were placed on an absolute scale, corrected for average thermal motion, and the E values calculated in order to test the centricity. The following statistical averages were obtained:

	$\langle\lvert E\rvert\rangle$	$\langle\lvert E^2\rvert\rangle$	$\langle\lvert E^2-1\rvert\rangle$
Observed	0·870	1·000	0·752
Theoretical for centric	0·798	1·000	0·968
Theoretical for acentric	0·886	1·000	0·736 .

This favours the acentric space group Cc.

Structure determination

Initially an attempt was made to solve the $h0l$ projection which has the plane group $P1$ and the a and c axes halved. An interpretation of the Patterson projection gave an R value of 11%. This solution was, however, not consistent with the molecular geometry.

Starting with the three-dimensional data it was decided to set the x and z coordinates of the potassium
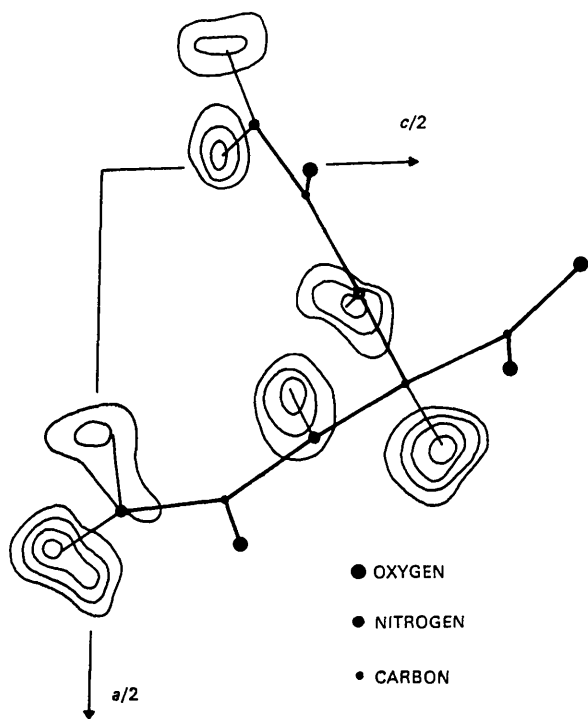
Fig. 1. Three-dimensional difference-Fourier synthesis seen along the b axis. The contours are drawn at intervals of 0.1 e.Å^{-3}, beginning at 0.2 e.Å^{-3}. Final positions of the hydrogen atoms and the rest of the molecule are superposed.
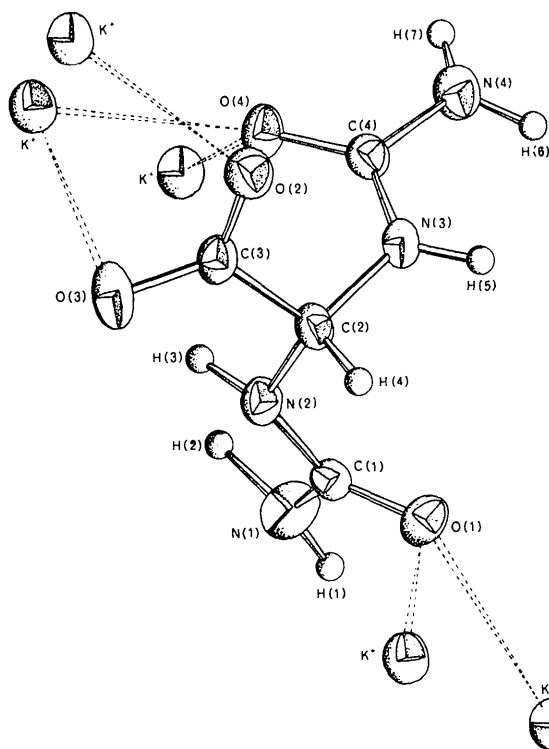

Fig. 2. Thermal ellipsoid representation of an allantoinate ion and the surrounding potassium ions showing the adopted labelling of the atoms. The ellipsoids enclose 50% probability. The hydrogen atoms are indicated by small spheres.

ion to zero throughout the calculations, while the y coordinate was easily obtained from a 3-D Patterson synthesis. Introducing the K^+ ion at this position gave an R index of 42%, and the phases were used to calculate a first 3-D electron density map. From a spherical section with a radius of 2.84 Å around the potassium position it was possible to recognize the carboxylic group of the acid ion. Introducing four atoms and the potassium ion gave another four probable atomic positions and decreased the R value to 33%. The next cycle reduced R to 26% and revealed the whole molecular configuration.

Refinement of the structure

Two cycles of full-matrix least-squares refinement brought the R value from 15 to 7.5% using one scale factor, unit weight, and isotropic temperature factors. The scattering factors for K^+ and neutral O, N, C and H were taken from *International Tables for X-ray Crystallography* (1962). A three-dimensional difference synthesis was calculated in order to distinguish the hydrogen atoms. Only 5 out of 7 were found at this first attempt. The 'heavy' atoms were then given anisotropic temperature factors and after two cycles of refinement the discrepancy index was 5.5%. A second difference synthesis indicated the positions of all the hydrogen atoms as shown in Fig. 1. The only additional peak of comparable height was one of 0.6 e.Å^{-3} less than 1 Å from the potassium position. Introduction of the hydrogen atoms and refinement of their positional parameters reduced the R value to 4.7%. The hydrogen atoms were given the same temperature factor as that of the covalently bonded 'heavy' atom. At this stage of the refinement the intensities were corrected for absorption as mentioned above. In addition the last cycles were run with a weighting scheme of the form $w = 1/(13 + F_o + F_o^2/50)$ (Cruickshank, 1965, p. 114). The final R value, excluding the 24 lowest amplitudes, was 4.2%. The average and maximum positional shifts of the non-hydrogen atoms were 9% and 48% respectively of the estimated standard deviations. Observed and calculated structure factors are listed in Table 1.

Results and discussion

Molecular arrangement

The allantoinate ion is not stretched to its maximum length but twisted around the tetrahedral bonds from the central carbon atom C(2). This brings the four oxygen atoms into ionic contact with five different potassium ions, thus forming a densely packed system in three dimensions. This is consistent with the high density of the compound, 1.8 g.cm^{-3}. These oxygen–potassium contacts can be seen in Figs. 2 and 4, where the hydrogen bonding system, including ten contacts between oxygen and nitrogen for each allantoinate ion is also demonstrated.

Table 1. *Final observed and calculated structure factors*

The sign * represents a 'less than' reflexion. The columns are h, $10F_o$, $10F_c$, $10A$ and $10B$.

Molecular structure

The labelling and the thermal displacement ellipsoids of the atoms can be seen in Fig. 2 and the final positional and vibrational parameters in Table 2. From these values the interatomic distances and angles have been calculated and they are shown in Fig. 3, and are shown together with their estimated standard deviations in Table 3. These e.s.d.'s seem rather large but are in accordance with the values calculated in advance using the formula given by Cruickshank (1965, p. 116). The root-mean-square components of thermal displacement along the three principal axes are tabulated

Table 2. *Final fractional atomic positional parameters and anisotropic temperature factor parameters, all with estimated standard errors*

The thermal parameters are in the form: $\exp(-\beta_{11}h^2 - \beta_{22}k^2 - \beta_{33}l^2 - 2\beta_{12}hk - 2\beta_{23}kl - 2\beta_{13}hl)$. All values are $\times 10^4$.

	x/a	σ	y/b	σ	z/c	σ	β_{11}	σ	β_{22}	σ	β_{33}	σ	β_{12}	σ	β_{23}	σ	β_{13}	σ
K	0		612	2	0		42	1	73	3	92	4	−2	1	−2	2	−3	2
O(1)	3435	7	4221	9	2339	13	36	4	82	10	123	16	−15	5	1	7	−12	8
O(2)	946	7	2629	10	7580	13	52	5	91	10	143	16	8	6	33	8	24	10
O(3)	1884	10	687	9	6497	14	74	7	62	10	125	17	10	6	10	8	16	9
O(4)	54	7	2168	9	3293	11	49	5	57	8	124	14	−11	5	1	7	−2	8
N(1)	3099	10	2136	13	485	16	63	7	104	15	114	18	−22	8	22	9	−18	12
N(2)	2485	8	2201	9	3475	14	46	5	50	9	132	17	−1	5	30	8	−11	10
N(3)	1177	7	4128	10	4102	13	39	5	51	9	125	18	2	5	5	8	17	9
N(4)	−372	10	4630	15	2431	20	47	7	93	13	215	28	3	7	−4	11	75	15
C(1)	3029	7	2941	10	2100	15	21	4	57	10	122	17	3	5	1	7	14	10
C(2)	1992	8	3110	11	4906	14	37	5	56	10	78	15	13	6	15	7	5	10
C(3)	1570	8	2043	11	6471	14	33	5	56	11	101	16	−7	6	−2	8	4	9
C(4)	285	7	3560	11	3253	13	32	5	62	11	94	15	8	6	6	7	2	10

	x/a	σ	y/b	σ	z/c	σ
H(1)	3454	213	2533	280	−382	406
H(2)	2473	216	1218	286	177	374
H(3)	1969	169	1358	235	3013	332
H(4)	2527	174	3782	239	5603	297
H(5)	1287	174	5197	259	3847	318
H(6)	−148	220	5546	253	2108	443
H(7)	−989	235	4333	251	1951	430

Table 3. *Distances and angles of the allantoinate ion, with estimated standard deviations*

Non-hydrogen intraionic distances

	(Å) (σ)		(Å) (σ)
C(1)–O(1)	1·236 (12)	C(3)–O(2)	1·246 (14)
C(1)–N(1)	1·349 (15)	C(3)–O(3)	1·245 (13)
C(1)–N(2)	1·377 (14)	C(4)–O(4)	1·246 (12)
C(2)–N(2)	1·449 (14)	C(4)–N(3)	1·351 (13)
C(2)–N(3)	1·458 (13)	C(4)–N(4)	1·363 (16)
C(2)–C(3)	1·559 (14)		

Distances to hydrogen atoms

	(Å) (σ)
N(1)–H(1)	0·85 (28)
N(1)–H(2)	1·14 (26)
N(2)–H(3)	1·03 (21)
C(2)–H(4)	1·01 (21)
N(3)–H(5)	0·96 (23)
N(4)–H(6)	0·88 (24)
N(4)–H(7)	0·88 (29)

Angles involving non-hydrogen atoms

Apex	(°) (σ)
O(1)–C(1)–N(1)	122·9 (1·0)
O(1)–C(1)–N(2)	122·7 (1·0)
N(1)–C(1)–N(2)	114·4 (0·9)
C(1)–N(2)–C(2)	119·0 (0·8)
N(2)–C(2)–N(3)	112·0 (0·8)
N(2)–C(2)–C(3)	110·2 (0·8)
N(3)–C(2)–C(3)	112·5 (0·8)
O(2)–C(3)–O(3)	126·1 (1·1)
O(2)–C(3)–C(2)	116·8 (0·9)
O(3)–C(3)–C(2)	117·1 (0·9)
C(2)–N(3)–C(4)	121·1 (0·8)
O(4)–C(4)–N(3)	122·6 (0·9)
O(4)–C(4)–N(4)	122·3 (1·0)
N(3)–C(4)–N(4)	115·1 (0·9)

Angles involving hydrogen atoms

Apex	(°) (σ)
C(1)–N(1)–H(1)	117 (18)
C(1)–N(1)–H(2)	117 (14)
H(1)–N(1)–H(2)	122 (22)
C(1)–N(2)–H(3)	116 (13)
C(2)–N(2)–H(3)	109 (13)
N(2)–C(2)–H(4)	111 (12)
N(3)–C(2)–H(4)	107 (12)
C(3)–C(2)–H(4)	104 (12)
C(2)–N(3)–H(5)	124 (13)
C(4)–N(3)–H(5)	113 (13)
C(4)–N(4)–H(6)	122 (18)
C(4)–N(4)–H(7)	119 (15)
H(6)–N(4)–H(7)	117 (24)

in Table 4 together with the angles between these principal axes and those of an orthogonal system with X along the a axis and Y along the b axis.

Table 4. *Principal axes* (i) *of anisotropic temperature factors, referred to orthogonal axes XYZ*

X is along the crystallographic a axis and Y along the b axis. The r.m.s. displacements $\bar{\mu}_i$ are in Å and the direction angles, V, are in degrees.

	i	$\bar{\mu}_i$ (σ)	V_x (σ)	V_y (σ)	V_z (σ)
K	1	0·151 (3)	101 (3)	79 (8)	16 (7)
	2	0·167 (3)	83 (6)	166 (7)	77 (8)
	3	0·186 (3)	167 (4)	99 (6)	100 (4)
O(1)	1	0·146 (11)	134 (11)	48 (9)	73 (15)
	2	0·177 (11)	114 (17)	91 (20)	156 (17)
	3	0·198 (10)	127 (13)	138 (9)	73 (21)
O(2)	1	0·155 (11)	123 (12)	72 (17)	141 (6)
	2	0·180 (11)	119 (13)	151 (14)	91 (15)
	3	0·235 (11)	133 (7)	68 (8)	51 (6)
O(3)	1	0·145 (12)	84 (5)	24 (12)	113 (13)
	2	0·183 (12)	101 (8)	112 (13)	155 (13)
	3	0·247 (11)	168 (7)	81 (5)	82 (8)
O(4)	1	0·142 (11)	107 (7)	17 (8)	86 (12)
	2	0·178 (10)	88 (18)	85 (13)	174 (15)
	3	0·203 (10)	163 (7)	107 (7)	94 (19)
N(1)	1	0·161 (14)	75 (20)	81 (29)	18 (7)
	2	0·179 (13)	57 (13)	147 (12)	90 (33)
	3	0·247 (14)	143 (8)	122 (8)	72 (7)
N(2)	1	0·134 (13)	77 (19)	26 (28)	68 (20)
	2	0·154 (13)	50 (12)	115 (28)	50 (16)
	3	0·217 (11)	137 (8)	95 (7)	47 (8)
N(3)	1	0·133 (12)	88 (13)	20 (10)	110 (11)
	2	0·176 (12)	22 (58)	84 (24)	69 (54)
	3	0·185 (13)	112 (58)	70 (12)	30 (43)
N(4)	1	0·139 (14)	81 (11)	35 (6)	124 (5)
	2	0·195 (13)	11 (11)	100 (11)	89 (9)
	3	0·266 (15)	85 (9)	57 (5)	34 (5)

Table 4 (*cont.*)

	i	$\bar{\mu}_i$ (σ)	V_x (σ)	V_y (σ)	V_z (σ)
C(1)	1	0·128 (13)	165 (34)	81 (15)	113 (31)
	2	0·145 (13)	65 (33)	148 (26)	72 (17)
	3	0·181 (13)	89 (12)	69 (15)	21 (15)
C(2)	1	0·126 (14)	123 (11)	122 (46)	130 (48)
	2	0·138 (13)	95 (31)	137 (42)	47 (47)
	3	0·190 (13)	146 (9)	64 (10)	69 (9)
C(3)	1	0·141 (13)	120 (25)	30 (26)	89 (34)
	2	0·156 (14)	66 (35)	75 (38)	151 (33)
	3	0·173 (13)	140 (24)	116 (20)	119 (33)
C(4)	1	0·142 (13)	130 (20)	139 (30)	100 (49)
	2	0·153 (13)	99 (40)	70 (44)	158 (35)
	3	0·172 (13)	139 (19)	55 (21)	71 (29)

The configuration of the ionized carboxylic group is in agreement with earlier structure determinations of potassium salts of organic acids (*e.g.* Larsson & Nahringbauer, 1968). The perfect symmetry in both bond lengths and angles of the carboxylic group indicates that it is fully ionized. The only aberrant feature is the long C(2)–C(3) distance, which however has been reported for 'central' carboxylic groups. (For references see Glusker, van der Helm, Love, Dornberg, Minkin, Johnson & Patterson, 1965).

Compared with the configuration of triuret (Ringertz, 1966 and Carlström & Ringertz, 1965), the two urea fractions are slightly changed. The differences in the two C–N bonds in each fraction have been significantly equalized probably because of the changed hybridization state of the central carbon C(2). The remaining insignificant difference between C(1)–N(1)
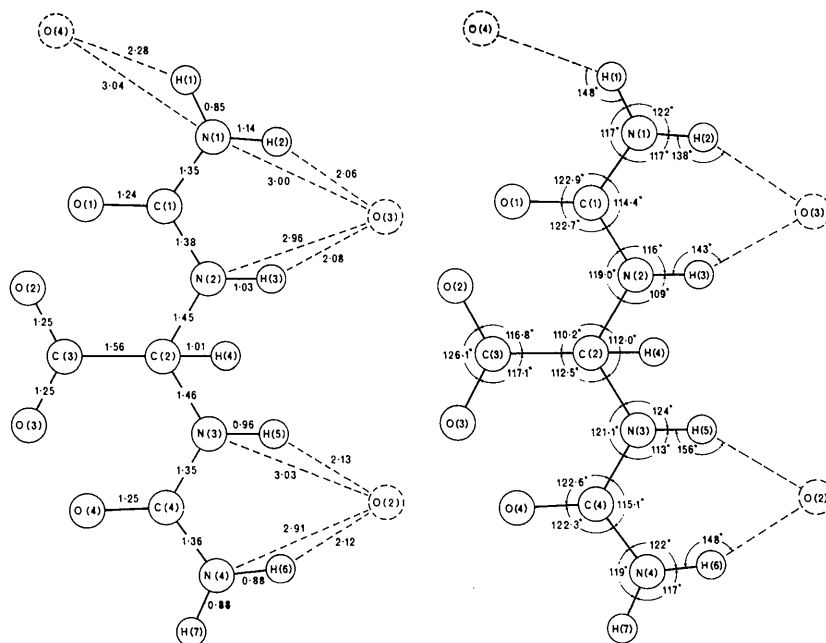

Fig. 3. Diagrams showing bond lengths and most of the bond angles of the allantoinate ion, including the hydrogen bonds to neighbouring ions.

and C(1)–N(2) might be due to the hydrogen bonding system.

The angular configuration around the central C(2) atom is normal for an sp^3 hybridized carbon atom bonded to three approximatively equal-weight radicals
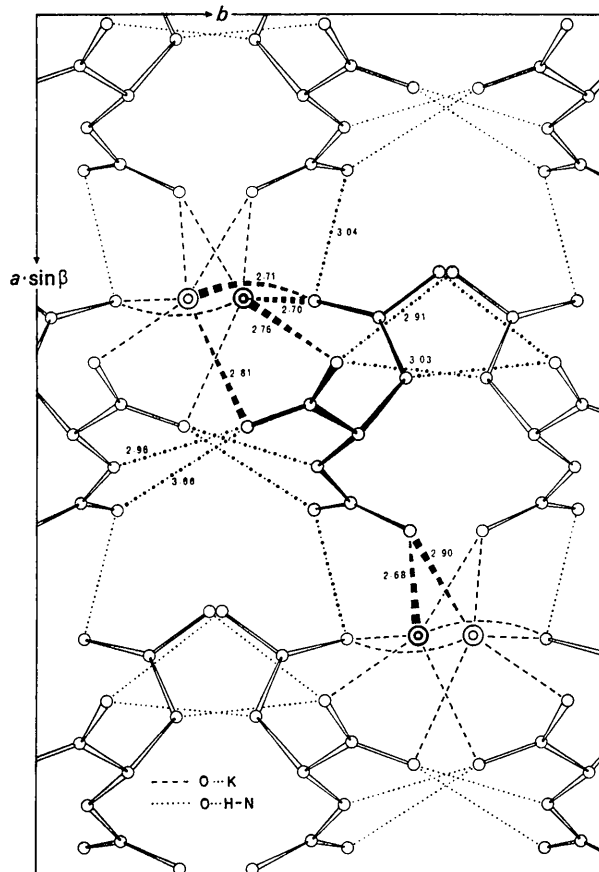

Fig. 4. A stereographic drawing of the crystal structure projected along the c axis showing the ionic contacts between potassium and oxygen and also the hydrogen bonding system.

and one hydrogen atom. (See e.g. van der Helm, Glusker, Johnson, Minkin, Burow & Patterson, 1968.)

The least-squares planes of the structure

Table 5 shows some least-squares planes calculated through the allantoinate ion including only non-hydrogen atoms given equal weight. In the carboxylic group and in the two urea fractions none of the atoms deviated more than 0·016 Å from the corresponding plane. Thus they are perfectly planar within the experimental error. The two different urea parts are twisted in opposite directions with respect to the central plane (II), by 61° for (III) and by 84° for (IV). The carboxylic part is twisted 20° with respect to plane (II) and 14° and 40° to planes (V) and (VI) respectively.

The potassium ion environment

The potassium ion is surrounded by six oxygen atoms at the vertices of a distorted octahedron. As can be seen in Fig. 4, the K–O distances vary between 2·68 and 2·90 Å. The lower limit for this distance for six-fold coordination, given in International Tables for X-ray Crystallography (1962), is 2·72 Å but Okaya (1965) states 2·63 Å as quite normal under the same circumstances. The closest potassium–potassium contact is approximately equal to half the c axis or 3·71 Å, which is rather short.

Hydrogen bonding

Five of the six available nitrogen-bonded hydrogen atoms are involved in hydrogen bonds to oxygen atoms. This is demonstrated in Figs. 3 and 4, and the angles and distances involved are tabulated in Table 6. Both of the carboxylic oxygen atoms are bonded to the corresponding two nitrogen atoms in the urea fractions of the neighbouring ions in each direction along the b axis. In addition the 'terminal' O(4) atom is bonded in the a direction to the 'terminal' N(1) atom of $(x-\frac{1}{2}; \frac{1}{2}-y; z-\frac{1}{2})$. The lengths of the N–H$\cdots$O bonds are between 2·91 and 3·04 Å, indicating fairly weak hydrogen bonds.

Table 5. Equations of some least-squares planes in the allantoinate ion and the distances of the atoms from these planes

Equations are expressed in the form $lX + mY + nZ = D$ where D, X, Y and Z are in Å in an orthogonal system with X along the a axis and Y along the b axis.

Plane	Atoms in plane	l	m	n	D
I	C(2), C(3), O(2), O(3)	0·7468	0·2619	0·6113	4·6100
II	C(2), C(3), N(2), N(3)	0·6899	0·5700	0·4462	4·4026
III	C(1), N(1), N(2), O(1)	0·8344	−0·4247	0·3513	2·5879
IV	C(4), N(3), N(4), O(4)	0·5036	−0·1230	−0·8551	−2·2375
V	C(2), C(3), N(2)	0·8582	0·0700	0·5085	3·9974
VI	C(2), C(3), N(3)	0·2166	0·6905	0·6901	4·7844

Atom	Δ(I)	Atom	Δ(II)	Atom	Δ(III)	Atom	Δ(IV)
C(2)	0·000	C(2)	−0·331	C(1)	0·006	C(4)	−0·016
C(3)	−0·001	C(3)	0·103	N(1)	−0·002	N(3)	0·005
O(2)	0·000	N(2)	0·113	N(2)	−0·002	N(4)	0·005
O(3)	0·000	N(3)	0·115	O(1)	−0·002	O(4)	0·006

Table 6. (a) *Some distances and angles involved in hydrogen bonds and* (b) *the shortest potassium–oxygen distances*

(a)

Nitrogen	Oxygen	Hydrogen	N–O (Å)	(σ)	H–O (Å)	(σ)	$\angle$N–H–O(°)	(σ)
N(1)	O(4) $(x+\frac{1}{2}; \frac{1}{2}-y; z-\frac{1}{2})$	H(1)	3·038	(14)	2·28	(28)	148	(25)
N(1)	O(3) (x; $-y$; $z-\frac{1}{2}$)	H(2)	3·000	(14)	2·06	(25)	138	(20)
N(2)	O(3) (x; $-y$; $z-\frac{1}{2}$)	H(3)	2·962	(12)	2·08	(21)	142	(16)
N(3)	O(2) (x; $1-y$; $z-\frac{1}{2}$)	H(5)	3·031	(13)	2·13	(22)	156	(19)
N(4)	O(2) (x; $1-y$; $z-\frac{1}{2}$)	H(6)	2·909	(15)	2·12	(26)	148	(25)

(b)

	Oxygen	K–O (Å)	(σ)
K — — —	O(1) $(x-\frac{1}{2}; \frac{1}{2}-y; z-\frac{1}{2})$	2·684	(9)
	O(1) $(x-\frac{1}{2}; y-\frac{1}{2}; z)$	2·901	(8)
	O(2) (x; y; $z-1$)	2·764	(8)
	O(3) (x; $-y$; $z-\frac{1}{2}$)	2·806	(12)
	O(4) (x; y; z)	2·700	(8)
	O(4) (x; $-y$; $z-\frac{1}{2}$)	2·707	(8)

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A Reinvestigation of 8-Azaguanine Monohydrate

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The crystal structure of 8-azaguanine monohydrate, $C_4H_6N_6O_2$ has been refined by full-matrix least squares to an R index of 0·053. Standard deviations in the bond lengths involving only nonhydrogen atoms are in the range 0·0014–0·0018 Å and for C–H and N–H bonds about 0·02 Å. The corresponding standard deviations in angles are 0·1 and 1·0° respectively. The main difference from the previous investigation involves the water molecule which is found to be disordered. This gives rise to a hydrogen bonding scheme in which N(8) also participates. The ability of N(8) to form a hydrogen bond may be responsible for the anticarcinogenic action of 8-azaguanine.

Introduction

An X-ray crystallographic investigation of 8-azaguanine monohydrate was undertaken as part of a program in this laboratory to establish accurate molecular dimensions of purine and pyrimidine derivatives. The structure of this compound has already been reported

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(Macintyre, Singh & Werkema, 1965). The structure did not refine, however, to an R value less than 0·12 for the full set of data, presumably because the crystal used in that work was very small, 0·34 mm × 0·04 mm × 0·04 mm. In the present work a considerably larger crystal with dimensions 0·35 mm × 0·20 mm × 0·15 mm was used so that precision of the data, at least as far as counting statistics is concerned, is much improved. Furthermore, we have observed approximately twice the number of reflections used in the previous refine-