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The Crystal and Molecular Structure of the Monohydrate of the Rubidium Salt of 5-Fluoroorotic Acid

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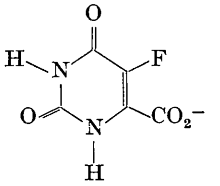
The crystal structure of the monohydrate of the rubidium salt of 5-fluoroorotic acid has been determined and refined. Bond lengths are given with a standard deviation of 0·04–0·05 Å. Bond angles are given with a standard deviation of about 2–4°. It has been shown that the pyrimidine ring is not planar, C(2) being out of the plane of the other five atoms by 0·087 Å. O(2) is out of this plane by 0·176 Å. There is significant steric hindrance between O(6), F, and one oxygen atom of the carboxyl group causing F to move out of the plane of the pyrimidine ring by 0·089 Å, and inducing a rotation of 6·9° in the plane of the carboxyl group relative to the plane of the pyrimidine ring. The hydrogen bonding in the structure is discussed. In particular, no hydrogen bond to O(2) is found.

The ion of 5-fluoroorotic acid has the structural formula:



The atom numbering scheme adopted is given in Fig. 1.

5-Fluoroorotic acid (FOA) is one of a series of synthetic purines and pyrimidines, analogous to natural purines and pyrimidines, which have been used in the treatment of certain malignant conditions. FOA is incorporated into the ribonucleic acid of animal cells *in vivo* (Chaudhuri, Montag & Heidelberger, 1958), presumably after decarboxylation to fluorouracil.

X-ray analysis of the crystal structure of FOA was undertaken to investigate the nature of the secondary bonding into which the molecule enters. A knowledge of this secondary bonding is of value in discussing the enzyme–substrate complexes formed by FOA at the various stages in its metabolism.

It was of particular interest to determine whether the fluorine atom was involved in hydrogen bonding. Fluorine has not been found to take part in hydrogen bonding in benzenoid systems. This has been interpreted as indicating that in such systems the inductive effect of fluorine is overshadowed by a very marked mesomeric effect (Baker, 1958). For example, pK_a for fluorophenol is larger than pK_a for phenol. The effect of fluorine seems to be to enrich the electron density in the π-electron system of the benzene ring, which in turn leads to an increase in electron density in the OH bond, making ionization of the hydrogen atom more difficult. The pK_a of FOA (1·2) however is less than that of orotic acid (2·8) (Duschinsky, 1959). This suggests that in this system fluorine acts as an electron withdrawing agent. Consequently there was some chance that the electron density on the fluorine atom would be high enough to permit the fluorine atom to contribute some electron density to a hydrogen bond.

FOA was found to crystallize very poorly. The crystals showed multiple twinning and conchoidal cleavage. It was decided to make the rubidium salt of the acid. This was found to crystallize as the monohydrate on cooling a hot concentrated aqueous solution.

These crystals of the monohydrate of the rubidium salt (FOA–Rb) were tiny laths, most of which were bent. The curvature was difficult to observe in the microscope since the radius of curvature was quite large. However, the defect in the crystals was immediately obvious when X-ray photographs were taken. There was a great variation in spot shape with rotation of the crystal. For some planes there was a focusing effect resulting in a very small intense spot on the film. For other planes the spot was irregular in shape or broken into two or three smaller spots.

Fortunately about five per cent of the crystals did not suffer from this defect, and gave a good single-crystal diffraction pattern. These were the crystals used in the crystal structure analysis.

Cell data

The cell dimensions were obtained from rotation and Weissenberg photographs taken about all three axes. The film measurements were corrected for absorption and crystal eccentricity by plotting the cell constants against $\cos^2\theta$ and extrapolating to $\cos^2\theta = 0$ (Buerger,

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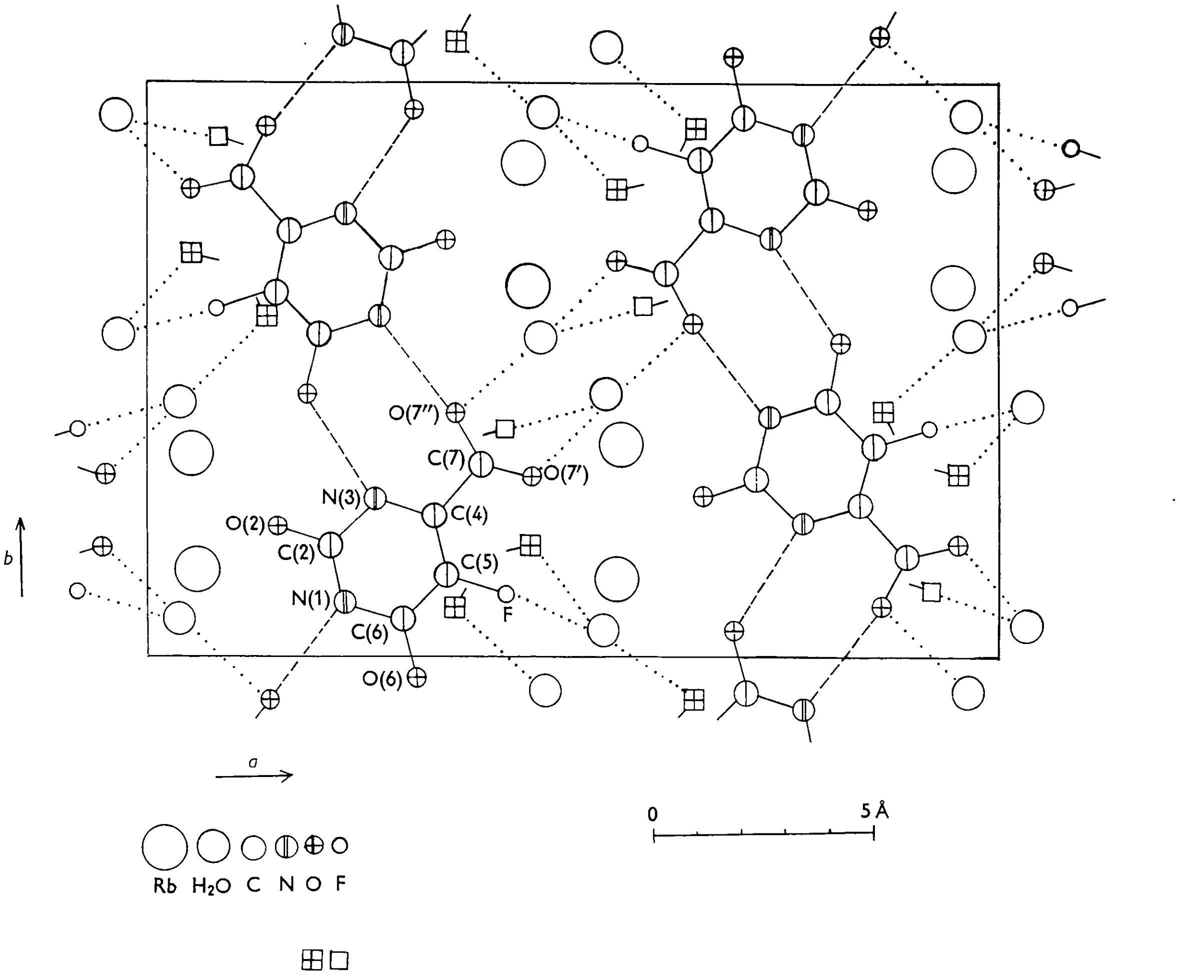

Fig. 1. Projection of the structure of FOA–Rb on to (001). Only one of the two overlapping layers of anions is shown in full. Some of the oxygen and fluorine atoms from the lower layer are included where necessary to complete the hydrogen bonding pattern of the water molecules. These atoms are represented by square symbols.

1942). The resulting cell dimensions were checked by direct measurement of 2θ for a number of reflections on the G. E. Single Crystal Orienter (Furnas, 1957). The cell data found are:

$$a = 19\cdot14 \pm 0\cdot02,\ b = 12\cdot72 \pm 0\cdot01,\ c = 6\cdot62 \pm 0\cdot01\ \text{Å}.$$

System: orthorhombic. $D_m = 2\cdot257$, $D_c = 2\cdot282$ g.cm^{-3}. $Z = 8$.

Systematic extinctions:

$hk0$ absent for h odd.
$0kl$ absent for k odd.
$h0l$ absent for l odd.

On the basis of these absences the space group was deduced to be *Pbca*. This space group has a multiplicity of eight and so the asymmetric unit contains only one FOA ion, one rubidium ion and one water molecule.

Intensity data

The intensities were collected on CASCADE, our automatic single-crystal diffractometer (Cowan, Macintyre & Werkema, 1963). 1155 planes were observed out of a total of 1706 within the Cu $K\alpha$ range; *i.e.* 68%. These intensities however are not completely satisfactory owing to the extremely small size of the crystals available, and therefore low counting rates for the reflections. The crystal used for measuring intensities had dimensions 0·68 × 0·048 × 0·038 mm. Many of the intensities measured were only just distinguishable from the background, and these have relatively large errors.

In view of the potentially very low quality of the data it is gratifying that the final agreement between observed and calculated structure factors is as close as it is.

When preparing the input tape for CASCADE it is not known which reflections will be accidentally absent. Therefore all reflections permitted by the space group and accessible to the radiation used are included on the tape and are examined. The 1706 intensities within the Cu $K\alpha$ range were measured by CASCADE in just under two weeks. The intensity of the diffracted beam was measured for 100 sec. For each reflection the background intensity was measured twice. Both background counts were for 100 sec, and the measurements were made with the counter set at 1·5° above and below the calculated 2θ setting of the reflection.

A list of the final observed and calculated structure factors is available from one of us (W. M. M.) on request.

Determination of the structure

The rubidium atom is sufficiently heavy that its contribution determines the relative phase of most of the structure factors. Thus solution of the phase problem involved only locating the rubidium atom in the asymmetric unit.

Three lines in the three-dimensional Patterson function for FOA–Rb were found which contained vector density peaks of height appropriate to a Rb–Rb vector. These lines were the Harker lines $P(u\frac{1}{2}0)$, $P(0v\frac{1}{2})$ and $P(\frac{1}{2}0w)$. The coordinates of the rubidium atom were calculated from the positions of the vector peaks on these lines.

A three-dimensional Fourier synthesis was computed using only those structure factors whose phase angles seemed to be determined by the rubidium atom contribution. This synthesis gave the positions of five of the six ring atoms and the carbon atom and one oxygen atom of the carboxyl group. A structure factor calculation made with the coordinates of these seven atoms and the rubidium atom gave an R value of 0·36, $[R = (\Sigma||F_o|-|F_c||)/\Sigma|F_o|]$. Several more Fourier syntheses gave the positions of the remaining atoms. After the last Fourier synthesis it was possible to assign phases to all 1155 observed structure factors and R had the value 0·22. In these structure factor calculations the rubidium atom was given an arbitrary isotropic temperature factor of 2 Å^{-2}, and the light atoms were all assigned the arbitrary isotropic temperature factor of 3 Å^{-2}.

Refinement of the structure

The atomic coordinates and individual isotropic thermal parameters were refined first by a diagonal least-squares procedure. The refinement converged at $R=0{\cdot}16$. The atomic coordinates and individual anisotropic thermal parameters were then refined with a block diagonal least-squares procedure. In this calculation the weighting function, $1/\sqrt{w} = 0{\cdot}185|F_o|+3{\cdot}13$ was used. The constants in this expression were obtained by plotting $\Sigma w(\Delta F)^2$ against $|F_o|$ for various ranges of $|F_o|$. The procedure is one developed by Dr F. M. Lovell of this laboratory to satisfy the condition given by Cruickshank (Cruickshank *et al.*, 1961) that the averages of $w(\Delta F)^2$ should be constant over the range of $|F_o|$. The refinement of atomic coordinates and anisotropic thermal parameters converged at a value of the reliability index $R=0{\cdot}14$ over 1155 planes. The final atomic coordinates and

Table 1. *Atomic coordinates of* FOA–Rb *and their e.s.d.*

All quantities are given as fractions of the unit cell edges × 10^4

	x	$\sigma(x)$	y	$\sigma(y)$	z	$\sigma(z)$
Rb	4485	1	1397	2	3651	4
F	836	6	3962	9	4562	19
N(1)	2700	8	914	14	1	40
N(3)	2355	10	2720	15	49	32
C(2)	2892	11	1963	17	237	37
C(4)	1647	10	2572	18	4839	36
C(5)	1501	11	3612	18	4708	33
C(6)	2026	10	4433	16	4793	33
C(7)	1112	10	1617	15	4791	32
O(2)	3492	8	2239	11	583	23
O(6)	3121	7	364	11	4690	30
O(7′)	507	7	1904	10	4846	21
O(7″)	1394	6	768	12	4835	30
O(w)	4639	8	4409	12	2779	26

Table 2. *Anisotropic thermal parameters of* FOA–Rb

The b_{ij} are defined by the expression $T=\exp[-(h^2b_{11}+k^2b_{22}+l^2b_{33}+hkb_{12}+klb_{23}+hlb_{13})]$, which is the factor by which the atomic scattering factor is multiplied to correct for anisotropic thermal vibration. The b_{ij} are multiplied by 10^4

	b_{11}	b_{22}	b_{33}	b_{12}	b_{23}	b_{13}
Rb	13	51	200	1	10	1
F	16	38	150	0	−1	1
N(1)	7	34	350	−12	19	−20
N(3)	12	43	170	0	−3	−2
C(2)	12	46	150	−8	−11	−6
C(4)	18	32	130	11	−5	−2
C(5)	10	43	180	−11	2	9
C(6)	17	30	150	−2	17	8
C(7)	12	40	82	−6	35	−1
O(2)	17	41	190	−8	−7	−10
O(6)	11	39	300	−9	9	−29
O(7′)	12	34	160	0	4	2
O(7″)	5	39	380	−15	−31	3
O(w)	17	58	170	10	28	2

Table 3. *Intramolecular bond lengths in the fluoroorotate ion and their estimated standard deviations*

Bond	Length	Estimated standard deviation
N(1)–C(2)	1·39 Å	0·05 Å
C(2)–O(2)	1·22	0·05
C(2)–N(3)	1·41	0·05
N(3)–C(4)	1·41	0·05
C(4)–C(7)	1·58	0·05
C(7)–O(7′)	1·22	0·04
C(7)–O(7″)	1·21	0·04
C(4)–C(5)	1·36	0·05
C(5)–F	1·35	0·04
C(5)–C(6)	1·45	0·05
C(6)–O(6)	1·22	0·05
C(6)–N(1)	1·37	0·05

their estimated standard deviations (e.s.d.) are given in Table 1. The final anisotropic thermal parameters are given in Table 2. The bond lengths with their r.m.s. standard deviations are given in Table 3. The bond angles are given in Table 4 with their r.m.s. standard deviations.

Table 4. *Intramolecular bond angles in the fluoroorotate ion and their estimated standard deviations*

Angle	Magnitude	e.s.d.
C(6)–N(1)–C(2)	124·6°	3·5°
N(1)–C(2)–N(3)	116·8	3·3
N(1)–C(2)–O(2)	122·9	3·6
O(2)–C(2)–N(3)	120·3	3·5
C(2)–N(3)–C(4)	121·8	3·3
N(3)–C(4)–C(5)	117·4	3·5
N(3)–C(4)–C(7)	114·8	3·1
C(7)–C(4)–C(5)	127·9	3·3
C(4)–C(5)–C(6)	124·0	3·5
C(4)–C(5)–F	121·3	3·3
F–C(5)–C(6)	114·7	3·1
C(5)–C(6)–N(1)	115·1	3·3
C(5)–C(6)–O(6)	122·6	3·5
O(6)–C(6)–N(1)	122·3	3·5
C(4)–C(7)–O(7′)	112·5	2·9
C(4)–C(7)–O(7″)	113·4	2·9
O(7′)–C(7)–O(7″)	133·9	3·3

After the last cycle of least-squares refinement a three-dimensional difference Fourier synthesis was computed. This showed a zero gradient at all the atomic positions, and no large corrections to the thermal parameters were indicated. Unfortunately the hydrogen atoms could not be located with certainty from this synthesis. Therefore, no further refinement was carried out.

Computing methods

The computations were carried out partly on an IBM 1620 computer and partly on an IBM 709. The three-dimensional Fourier syntheses were carried out on the IBM 1620 with a program written by D. Van der Helm (Van der Helm, Johnson & Patterson, 1961). The corresponding structure factor calculations were performed on the IBM 1620 computer with a program written in this laboratory (Macintyre *et al.*, 1961). The diagonal isotropic refinement program was an IBM 709 program supplied by J. H. Van den Hende (Van den Hende, 1962). The block diagonal anisotropic refinement program was one for the IBM 709 computer originally written by P. K. Gantzel and K. N. Trueblood of U. C. L. A. and later modified by R. Deverill of this laboratory. This program was used to calculate the e.s.d. of the final atomic parameters, using the usual procedure for least squares. The final difference Fourier synthesis was calculated on the IBM 709 computer with the Van den Hende modification of the Shoemaker–Sly Fourier program (Van den Hende, 1962). The equations of the best planes were evaluated on the IBM 709 computer with a program written by D. R. Harris (Harris, 1963).

Discussion of the structure

The FOA–Rb structure can be described as a layer structure. There are two different layers which alternate with one another. One layer consists of strings of FOA anions which are hydrogen-bonded together. The second layer contains the rubidium ions and the water molecules. The layers then appear to be held together by the ionic attraction between the positive rubidium ions and the negative anions.

The FOA anions are approximately parallel to the *ab* plane. The layer in which these anions lie can be considered to be parallel to the *ab* plane. There is one such layer at $z \simeq 0$ and another at $z \simeq \frac{1}{2}$.

The mean plane of the rubidium ions and water molecules is likewise parallel to the *ab* plane. The mean planes have $z = \frac{1}{4}$ and $z = \frac{3}{4}$. Neither the rubidium ions nor the water molecules lie exactly on these planes, successive rubidium ions being above and below the planes by 0·12z and successive water molecules likewise lying above the plane and below it by about 0·03z.

The projection of the crystal structure on (001) is given in Fig. 1. The cell contains two layers of anions normal to the *c* axis. For clarity only one of these layers is completely represented in the diagram. Atoms from the lower layer which are necessary to demonstrate the hydrogen bonding are included and represented by square symbols.

The rubidium atom does not show simple coordination. There are nine atoms within a distance of 3·2 Å from the rubidium atom, distributed in an irregular fashion around the rubidium ion. Thus the packing in the crystal seems to be controlled by the packing of the anions, the rubidium ion fitting into holes of minimum potential energy left after the anion layers were formed.

Molecular dimensions

The corresponding bond lengths and angles in FOA and 5-fluoro-2′-deoxy-β-uridine (Harris & Macintyre, 1964) (FUDR) are equal to within experimental error. A comparison of corresponding bond lengths and angles in FOA with those of thymine (Gerdil, 1961) and calcium thymidylate (Trueblood, Horn & Luzzati, 1961) gives a similar result.

However, the large standard deviations of the bond-lengths in the FOA–Rb analysis make these comparisons of doubtful value.

Hydrogen bonding between anions

Fluoroörotate anions

Within each layer of anions in the crystal, strings of anions are held together by hydrogen bonds. There are two such hydrogen bonds. One is a bond between N(1) and O(7″); the other is formed between N(3) and O(6). In each case the nitrogen atom acts as the proton donor in the bond.

The lengths of these bonds and the angles involving them are given in Table 5. The length of the bond N(3)–H ··· O(6) (2·85 Å) is within the range of hydrogen bond lengths (2·93 Å ± 0·1 Å) given by Pimentel & McClellan (1960) for N–H ··· O bonds involving amido nitrogen atoms. Also it is equal to the length of the hydrogen bond found in FUDR involving a pyrimidine NH group (2·861 Å) (Harris & Macintyre, 1964).

Table 5. *Lengths and angles of hydrogen bonds between* FOA *anions, and their estimated standard deviations*

Bond	Length	e.s.d.
N(1)–H ··· O(7″)	2·76 Å	0·04 Å
N(3)–H ··· O(6)	2·85	0·04

Angle	Magnitude	e.s.d.
N(3)–O(6)–C(6)	134·7°	2·6°
N(1)–O(7″)–C(7)	165·0	2·6

The bond N(1)–H ··· O(7″) is shorter, being 2·76 Å in length. O(7″) is one of the oxygen atoms of the carboxyl group. It carries a partial negative charge. Therefore, more electron density is available on this atom than on a neutral oxygen atom to interact with the hydrogen atom in forming a hydrogen bond. Thus it might be expected that the hydrogen bond formed by a charged carboxylate oxygen atom will be stronger, and therefore shorter than one formed by a neutral oxygen atom.

It is interesting to note that no hydrogen bond is formed to O(2) in FOA–Rb. Nor does O(2) take part in the hydrogen bonding scheme of uracil (Parry, 1954), FUDR (Harris & Macintyre, 1964), or 5-iodo-2-deoxy-β-uridine (Macintyre & Werkema, 1964). In both thymine (Gerdil, 1961) and calcium thymidylate (Trueblood *et al.*, 1961) O(2) does form a hydrogen bond. The reason for such a difference in the behavior of O(2) is not clear. Both oxygen atoms should carry a partial negative charge arising from withdrawal of charge from the neighboring nitrogen atoms. However, O(2) adjoins two nitrogen atoms and O(6) adjoins only one. One might expect a higher partial charge on O(2) than on O(6), and O(2) might be expected to form a stronger hydrogen bond. Thus, the observed absence of hydrogen bonding to O(2) cannot be explained on simple electronic grounds.

Hydrogen bonds involving water

The nature of the hydrogen bonding involving the water molecule cannot be definitely established from the results of this analysis. From a consideration of interatomic distances there appear to be three atoms close enough to the oxygen atom of the water molecule (O(w)) to form hydrogen bonds. These are F, O(7′) and O(7″). The distances of these atoms from O(2) are given in Table 6, together with the sum of their van der Waals radii. For each possible pair of hydrogen bonds the angle formed by the two bonds is given in Table 7.

In each case the observed distance between O(w) and one of the three atoms is close to but greater than the sum of the van der Waals radii of the atoms. Thus in each case the observed distance can correspond to a hydrogen bond or to a non-bonded interatomic contact. The distance of 2·96 Å between O(7″) and O(w) seems to be long for a hydrogen bond. However, in potassium sodium DL-tartrate.4H_2O there was found a distance of 2·92 Å, between a carboxyl oxygen atom and a water oxygen atom, which was described as a hydrogen bond (Sadanaga, 1950). Furthermore, Pimentel & McClellan (1960) list several hydrogen bonds of length 2·90–2·95 Å, between oxygen atoms and water molecules in hydrated crystals. Thus, it is perfectly possible that a long hydrogen bond exists between O(w) and O(7″).

Table 6. *Lengths of possible hydrogen bonds formed by the water molecule*

Van der Waals radii are from Pauling (1960)

Bond	Length	e.s.d.	Sum of van der Waals radii ($r_A + r_O$) in A ··· H–O
F ··· H–O	2·82 Å	0·03 Å	2·75 Å
O(7′) ··· H–O	2·83	0·04	2·80
O(7″) ··· H–O	2·96	0·04	2·80

Table 7. *Angles formed at* O(w) *by the three possible pairs of hydrogen bonds formed by water molecule*

Angle	Magnitude	e.s.d.
F ··· H–O–H ··· O(7′)	71·8°	0·9°
O(7′) ··· H–O–H ··· O(7″)	118·8	1·2
O(7″) ··· H–O–H ··· F	151·4	1·4

The information provided by the angles of the three possible hydrogen bonding schemes of the water molecule is more illuminating but also inconclusive. Pimentel & McClellan (1960) give a list of bond angles in hydrogen bonded water as found in twelve hydrated crystals. The angles quoted are the angles $B(1)\hat{O}B(2)$ in the structure B(1) ··· H–O–H ··· B(2). The values of these angles range from 83° to 120° with an average value of 101°. It is reasonable to assume that the value of the angle in FOA–Rb will probably lie within these limits. On this basis the hydrogen bonding schemes F · · · H–O–H · · · O(7′) (angle 71·8°) and O(7″) · · · H–O–H · · · F (angle 151·8°) are probably excluded. Therefore, it is likely that the water molecule is hydrogen-bonded to O(7′) and O(7″).

It must be emphasized that this assignment of the water hydrogen bonds is not certain in the absence of positive location of the hydrogen atoms. It is seldom that location of the hydrogen atom is essential for unambiguous identification of a hydrogen bond but unfortunately this is the case in FOA–Rb.

It will be observed from Fig. 1 that the atoms O(7′) and O(7″), presumably connected by hydrogen bonding through the water molecule, are on different anions, at approximately the same *z* coordinate and on different hydrogen-bonded strings of anions. Such hydrogen bonds will connect together those strings of hydrogen-bonded anions to form the layers of anions discussed above.

Planarity of the FOA anion

Significant deviations from planarity of the pyrimidine ring have been found in other systems (Harris & Macintyre, 1964). Therefore, it is of some interest to examine the planarity of the pyrimidine ring in FOA–Rb.

The equation of the best plane through the six atoms of the pyrimidine ring was found to be:

$$-0\cdot1271X+0\cdot0522Y+0\cdot9905Z-2\cdot947=0\ , \quad (1)$$

where X, Y, Z are the coordinates in Å of points on the plane with respect to the a, b and c crystallographic axes. The distances of some of the atoms in the FOA anion from this plane are given in Table 8.

The root mean square standard deviation of position of the ring atoms is 0·04 Å. This figure may be regarded as the radius of the sphere within which the atom has a 65% probability of being found. Thus if an atom deviates from the mean plane by 0·04 Å or less the deviation is probably not significant. On this basis C(2) has some probability of being out of the plane of the other five atoms of the ring. A second plane was found by fitting a plane through the positions of N(1), N(3), C(4), C(5) and C(6). This plane has the equation:

$$-0\cdot1072X+0\cdot0449Y+0\cdot9932Z-2\cdot990=0\ . \quad (2)$$

Distances of some of the atoms in the FOA anion from this plane are given also in Table 8.

It is clear from the data in Table 8 that atoms N(1), N(3), C(4), C(5) and C(6) are accurately coplanar. It is also clear that C(2) is very probably not in the plane of these five ring atoms since it is 0·087 Å or over two standard deviations from the plane.

Table 8. *Distances of atoms of the* FOA *anion from the two planes through the pyrimidine ring represented by equations* (1) *and* (2)

Atom	Distance from (1)	Distance from (2)
N(1)	−0·026 Å	+0·001 Å
C(2)	+0·048	+0·087
N(3)	−0·032	−0·001
C(4)	+0·004	+0·001
C(5)	+0·016	+0·004
C(6)	−0·002	−0·001
O(2)	+0·091	+0·176
O(6)	+0·027	+0·048
F	+0·103	+0·089
C(7)	+0·031	+0·034
O(7′)	+0·187	+0·169

Presumably C(2) is in sp^2 hybridization and so O(2), C(2), N(1) and N(3) should be in the same plane. The best plane through these four atoms was found to have the equation:

$$-0\cdot1922X+0\cdot0674Y+0\cdot9790Z-2\cdot646=0\ . \quad (3)$$

O(2), C(2), N(1), N(3) are less than one standard deviation from the plane and so these four atoms probably are coplanar.

The normal of plane (3) makes an angle of 6·8° with the normal of plane (2).

A similar effect was observed in FUDR (Harris & Macintyre, 1964) and calcium thymidylate (Trueblood *et al.*, 1961) where it was ascribed to steric hindrance between O(2) and the CH group of the glycosidic bond. However, no such explanation is available here. Furthermore, as O(2) forms no hydrogen bond it is not being pulled out of the mean plane of the pyrimidine ring by such forces.

This effect could be explained if the three bonds formed by the nitrogen atoms of the ring were not coplanar.

F and O(7′) are significantly out of the mean plane, O(7′) being almost twice as far from the mean plane as F. These departures from the mean plane of the pyrimidine ring are explainable in terms of steric hindrance between F and O(6), and between F and O(7′).

The sum of the van der Waals distances of F and O is 2·75 Å (Pauling, 1960). Thus, it is expected that an unstrained separation between F and O would be at least 2·75 Å. The distance observed between F and O(6) in the FOA anion is 2·68 Å, and the distance between F and O(7′) is 2·70 Å. Forcing F and O(7′) into the plane of the ring would shorten these distances still more, giving a structure with even more strain.

The interaction between F and O(7′) leads to a rotation of the plane of the carboxyl group relative to the pyrimidine ring. The atoms of the carboxyl group and C(4) are coplanar with the following equation for their mean plane:

$$0{\cdot}0027X-0{\cdot}0029Y+1{\cdot}0000Z-3{\cdot}1960=0\ .$$

The angle between the normal to this plane and the normal to equation (2) for the pyrimidine ring is 6·9°.

The C(4)-C(7) bond

In FOA the bond C(4)–C(7) is of unusual length. The value expected for the bond connecting a carboxyl carbon atom to an aromatic ring system is about 1·50 Å (see, for example, Skinner, Stewart & Speakman, 1954). The bond length observed in FOA is almost two standard deviations longer, 1·58 Å. The difference may be accounted for in a number of ways.

The deviation of the pyrimidine ring from planarity indicates that the ring is not a truly aromatic ring. Furthermore, the shortness of the C(4)–C(5) bond indicates a large amount of double bond character in that bond and so other bonds formed by C(4) will have a total bond order close to unity. Thus, the bond C(4)–C(7) may be expected to be longer in FOA than in a benzenoid molecule.

Rotation of the plane of the carboxyl group out of the plane of the pyrimidine ring will reduce the lateral overlap between p_z orbitals on C(4) and C(7). This effect is small in FOA, since the dihedral angle is only about 7°, but it will lengthen the C(4)–C(7) bond slightly.

These two effects, together with the large standard deviation of 0·05 Å for the bond, probably account for the extreme length of the bond.

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