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The Crystal and Molecular Structure of Dimethylglyoxal Bisguanylhydrazone Dihydrochloride Dihydrate, $C_6H_{14}N_8.2HCl.2H_2O$[*]

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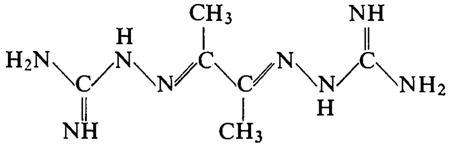
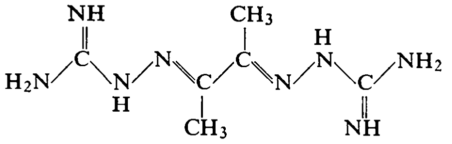
The compound dimethylglyoxal bisguanylhydrazone,



has, in contrast to the monomethyl compound, no activity toward human acute myelocytic leukemia. The crystal and molecular structure of the crystalline dihydrochloride dihydrate, $C_6H_{14}N_8.2HCl.2H_2O$, has been determined by X-ray diffraction. The salt crystallizes in the monoclinic space group $P2_1/c$ (C_{2h}^5); $a=5{\cdot}799$ (4), $b=9{\cdot}239$ (8), $c=14{\cdot}447$ (12) Å, $\beta=113{\cdot}98$ (3)°; $Z=2$; $D_x=1{\cdot}432$ and $D_m=1{\cdot}44$ (1) g.cm^{-3}. Data were collected on a Picker automated four-circle diffractometer, employing θ–2θ scans with a scintillation counter and crystal-monochromated Mo $K\alpha$ radiation ($\lambda=0{\cdot}71069$ Å). A combination of Patterson and direct-method techniques revealed the positions of all nonhydrogen atoms; the final structure (including hydrogen atoms) was refined by full-matrix least-squares analysis to an R of 0·055 ($R_w=0{\cdot}045$). The structure consists of planar dipositive $C_6H_{16}N_8^{2+}$ ions hydrogen-bonded to both Cl^- and H_2O. The dominant interaction found in the monomethyl compound, an interaction involving π-orbitals on adjacent parallel molecules, is less pronounced in the dimethyl structure. The mean interplanar spacing for the latter is 3·40 Å compared with 3·19 Å in the monomethyl structure.

Introduction

Dimethylglyoxal bisguanylhydrazone (dimethyl GAG),



possesses no activity towards human acute myelocytic leukemia in contrast to the activity of the monomethyl compound. It seemed desirable to determine the molecular structure of dimethyl GAG so that it could be compared with the known structure of methyl GAG (Hamilton & La Placa, 1968).

Although there are some interesting differences between the two structures, any possible biological implications can only be inferred from additional data, and discussion of this aspect of the problem is deferred to a later paper.

Experimental

Crystal data

Dimethylglyoxal bisguanylhydrazone dihydrochloride dihydrate: $C_6H_{14}N_8.2HCl.2H_2O$. Water-clear, monoclinic prismatic crystals. The lattice constants were determined by centering of 18 reflections and subsequent least-squares refinement: $a=5{\cdot}799$ (4), $b=9{\cdot}239$ (8), $c=14{\cdot}447$(12) Å, $\beta=113{\cdot}98$ (3)°, $T=298$(4)°K, λ(Mo $K\alpha$) = 0·71069 Å, $Z=2$, $D_x=1{\cdot}432$ and $D_m=1{\cdot}44$(1) g.cm^{-3} by flotation, $\mu=4{\cdot}735$ cm^{-1} (Mo $K\alpha$). The systematic absences $h0l$, $l=2n+1$, $0k0$, $k=2n+1$ imply space group $P2_1/c$.

Intensity measurement

A prismatic crystal of dimensions $0{\cdot}163\times0{\cdot}124\times0{\cdot}194$ mm (the latter dimension along b) was mounted on a four-circle computer-controlled diffractometer, equipped with a pyrolytic graphite monochromator set for the 002 reflection with Mo $K\alpha$ radiation. A scintillation counter with aperture 4 × 5 mm was set 26 cm from the crystal. Pulse height and shape discrimination was used in the counting circuitry. A coupled θ–2θ step scan was used, with a scan range of $\Delta2\theta=2(1+1{\cdot}5\tan\theta)$ and a step size of $\delta2\theta=0{\cdot}05°$. The background was taken as the average of 10 points at each end of the scan. The 300 and 006 reflections were scanned every 30 reflections. There was no systematic trend in the intensity of these reflections with time. The maximum variation of these intensities was consistent with Poisson counting statistics (about 5%). Four octants $\pm h$, $\pm k$, $+l$ of reciprocal space were examined. The total number of observations obtained was 4803. Of these, five were rejected for known malfunctions in

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equipment. Of the 2016 independent reflections, 1898 had been observed more than once; the average discrepancy between the intensities of these reflections was about 2%. Only the 1997 reflections with a measured intensity greater than $2\sigma_{\text{count}}$ (the Poisson counting statistical error) were used in the subsequent analysis. Structure amplitudes were derived by the application of Lorentz and polarization corrections. An absorption

Table 1. *Observed (FO) and calculated (FC) structure factors and e.s.d.'s of observed FOSIG*

The observed values have been corrected for extinction using the value of $g = 0{\cdot}3734 \times 10^{-4}$ obtained in the least-squares refinement. All values are in electrons and have been multiplied by 10. $10^{*}F(000) = 3240$.

correction was calculated, using a Gaussian grid integration; the transmission coefficients ranged from 0·8717 to 0·9137.

Structure determination and refinement

The Patterson synthesis revealed the chlorine atom positions; subsequent refinement of these positions, using data restricted to $\sin\theta/\lambda \leq 0{\cdot}364$, yielded an observed Fourier map which, when compared with an E map generated from phased E's obtained from Dewar's symbolic-addition programs *FAME* and *MAGIC* (Dewar, 1970), revealed the position of all nonhydrogen atoms. Each chosen atom was among the highest 30 peaks in both of the above maps. Full-matrix least-squares refinement of these positions and anisotropic thermal parameters led to an unweighted R of 0·07, at which time a difference Fourier map (data restricted as above) revealed clearly the positions of the 12 independent hydrogen atoms, which were included in the final refinement with isotropic thermal parameters. The final measures of agreement are

$$R = \frac{\sum|F_o - F_c|}{\sum|F_o|} = 0{\cdot}048\,,$$

$$R_w = \left[\frac{\sum w|F_o - F_c|^2}{\sum|F_o|^2}\right]^{1/2} = 0{\cdot}055\,,$$

and

$$S = \left[\frac{\sum w|F_o - F_c|^2}{N_o - N_v}\right]^{1/2} = 1{\cdot}31$$

for $N_o = 1997$ nonzero intensities measured to $\sin\theta/\lambda = 0{\cdot}66$. The weights, w, were defined as $1/\sigma^2(F)$ with $\sigma(F) = (1/2F)\,[\sigma^2_{\text{count}} + (0{\cdot}03\,F^2)^2]^{1/2}$. Final observed and calculated structure factors and $\sigma(F)$ values are given in Table 1. Spherical atomic scattering factors for H, C, N, O, and Cl^- were obtained from Cromer & Waber (1972). Anomalous scattering for Cl was included: $\Delta f' = 0{\cdot}15$, and $\Delta f'' = 0{\cdot}19$ (Cromer, 1965). An isotropic extinction parameter (Zachariasen, 1967) was included in the least-squares program *LINUS*; anisotropic extinction was not significant (Coppens & Hamilton, 1970). Maximum corrections were, for $(hkl) = (12\bar{2})$, $E = (F^2_{\text{obs}}/F^2_{\text{calc}}) = 0{\cdot}77$; $(12\bar{3})$, $E = 0{\cdot}80$; (006), $E = 0{\cdot}93$; and (013), $E = 0{\cdot}92$. The function minimized was $\sum w|F_o - F_c|^2$. Only F's greater than $2\sigma(F)$ were admitted to the refinement.

Tables 2 and 3 give the final positional and thermal motion parameters. Fig. 1 shows the bond distances corrected for rigid-body thermal motion (see below) and bond angles.

Table 3. *Fractional coordinates and isotropic U values* × 10⁴ *for hydrogen atoms* (*numbered according to the atoms to which they are bonded*

	x	y	z	U
N2H	−3291 (35)	2435 (19)	594 (15)	75
N3H(1)	−6722 (39)	3879 (23)	279 (17)	203
N3H(2)	−8754 (48)	3778 (28)	−695 (18)	343
N4H(1)	−6603 (43)	1195 (23)	−1736 (16)	165
N4H(2)	−8888 (45)	2051 (23)	−1874 (18)	228
C3H(1)	38 (44)	946 (24)	1632 (17)	241
C3H(2)	2474 (50)	933 (28)	1444 (18)	355
C3H(3)	760 (42)	2248 (24)	1197 (17)	241
OH(1)	−3635 (50)	3667 (30)	2034 (19)	342
OH(2)	−3266 (49)	2263 (26)	2354 (21)	405

Thermal motion

The thermal motion, represented by 50% probability ellipsoids, is shown in Fig. 1. A least-squares fit of the rigid-body translation (**T**) and libration (**L**) tensors to the observed U's was obtained by use of a computer program (*TLS*6) described by Schomaker & Trueblood (1968). The results are presented in Table 4. Bond distances before and after correction for the librational motion are given in Table 5. The axis of maximum librational amplitude lies very close to the $C_2 - C_2^1$ axis of the ion.

Table 4. *Results of rigid-body analysis of thermal parameters*

	Eigenvalues **T** and **L**	Direction cosines of eigenvectors†		
Librational tensor, **L**	22·13 (°)²	0·8044	−0·4943	0·3296
	3·49	0·2769	−0·1788	−0·9441
	0·65	0·5256	0·8507	−0·0069
Translational tensor, **T**	0·0275 Å²	0·6998	−0·3377	−0·6295
	0·0234	0·2129	0·9398	−0·2674
	0·0182	0·6819	0·0531	0·7295

† Direction cosines relative to orthogonal axes **a**, **b**, **c***. The origin is at the molecular symmetry center; hence **S**, the screw tensor, is identically zero. $\sigma(\Delta U_{ij}) = 0{\cdot}0027$.

Table 2. *Fractional coordinates* × 10⁵ *for heavy atoms*

Thermal parameters, U^{ij} (Å²) × 10⁴, are as they appear in the Debye–Waller expression: $\exp\,[-2\pi^2\sum a_i{}^* a_j{}^* h_i h_j U^{ij}]$. Here, and elsewhere in this paper, e.s.d.'s in the last significant figure are in parentheses.

	x	y	z	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl	29196 (8)	53293 (5)	16990 (3)	200 (2)	244 (3)	196 (5)	29 (1)	34 (2)	14 (4)
N(1)	−28084 (24)	9585 (14)	−3817 (9)	129 (4)	170 (5)	135 (5)	25 (3)	34 (2)	0 (4)
N(2)	−39322 (25)	20127 (15)	−288 (10)	133 (4)	216 (5)	125 (5)	44 (3)	20 (2)	−14 (4)
N(3)	−73815 (30)	34534 (19)	−3298 (12)	175 (5)	43 (5)	175 (5)	93 (4)	28 (4)	−28 (4)
N(4)	−73873 (29)	18118 (17)	−15297 (10)	134 (4)	274 (5)	140 (5)	38 (4)	8 (2)	−7 (4)
C(1)	−5561 (28)	5703 (16)	2037 (11)	115 (4)	153 (5)	130 (5)	1 (3)	22 (2)	7 (4)
C(2)	−62691 (29)	24324 (17)	−6417 (11)	121 (4)	200 (5)	130 (5)	19 (3)	36 (4)	22 (4)
C(3)	8707 (34)	11948 (20)	12279 (13)	141 (5)	222 (5)	160 (5)	19 (4)	12 (4)	−40 (4)
O	−27934 (26)	30243 (16)	20322 (10)	191 (4)	274 (5)	226 (5)	22 (3)	62 (4)	−18 (4)

Table 5. *Bond distances before and after rigid-body thermal motion corrections*

	Uncorrected	Corrected
C(1)–C(1′)	1·473 (3) Å	1·478 Å
C(1)–C(3)	1·500 (2)	1·503
C(1)–N(1)	1·298 (2)	1·300
N(1)–N(2)	1·376 (2)	1·381
N(2)–C(2)	1·354 (2)	1·356
C(2)–N(3)	1·318 (2)	1·323
C(2)–N(4)	1·321 (2)	1·324

Discussion of the structure

There is a remarkable similarity between the two hydrogen-bonding schemes and overall crystal packing in methyl GAG and dimethyl GAG.

Both crystal structures are ionic and are stabilized by a series of hydrogen bonds to both H_2O and Cl^-, as indicated in Fig. 2 for dimethyl GAG. The planar stacking of molecules is nearly identical and is shown in Fig. 3 for dimethyl GAG. The replacement of the C–H group in methyl GAG by C–CH_3 to form dimethyl GAG, results primarily in less skewness along the main ionic axis, a higher degree of planarity, and a significant alteration of both bond and hydrogen bond strengths in the $C(NH_2)^+$ groups forming the ion termini.

The most significant difference between the two structures is the decreased interaction between parallel molecules, as observed in the larger interionic separation of 3·40 Å (distance between mean ionic planes) in dimethyl GAG as compared with 3·19 Å in methyl GAG.

The short intermolecular interactions, indicative of pronounced charge separation, may indeed be coupled to the biological activity of methyl GAG. A similar short interaction (3·33 Å) between parallel stacked molecules has been observed in the anti-leukemia agent: 6-mercaptopurine (Sletten, Sletten & Jensen, 1969; Brown, 1969).

In dimethyl GAG, the C–N bonds within the $C(NH_2)^+$ groups are equal at 1·323 (2) and 1·324 (2) Å, while these distances ranged from 1·304(11) to 1·336(11) Å in methyl GAG, although these differences are probably not significant. Insignificant differences are found in the guanidinium group bond lengths in L-arginine

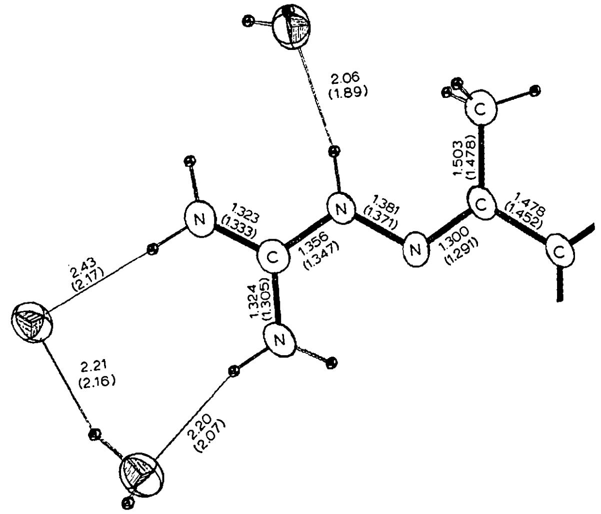

Fig. 2. Hydrogen bonding in dimethyl GAG and methyl GAG, and comparison of bond distances (Å) in local hydrogen bonding schemes, which are topologically identical. The methyl GAG distances are in parentheses and are the average of the X-ray and neutron values. E.s.d. = 3.

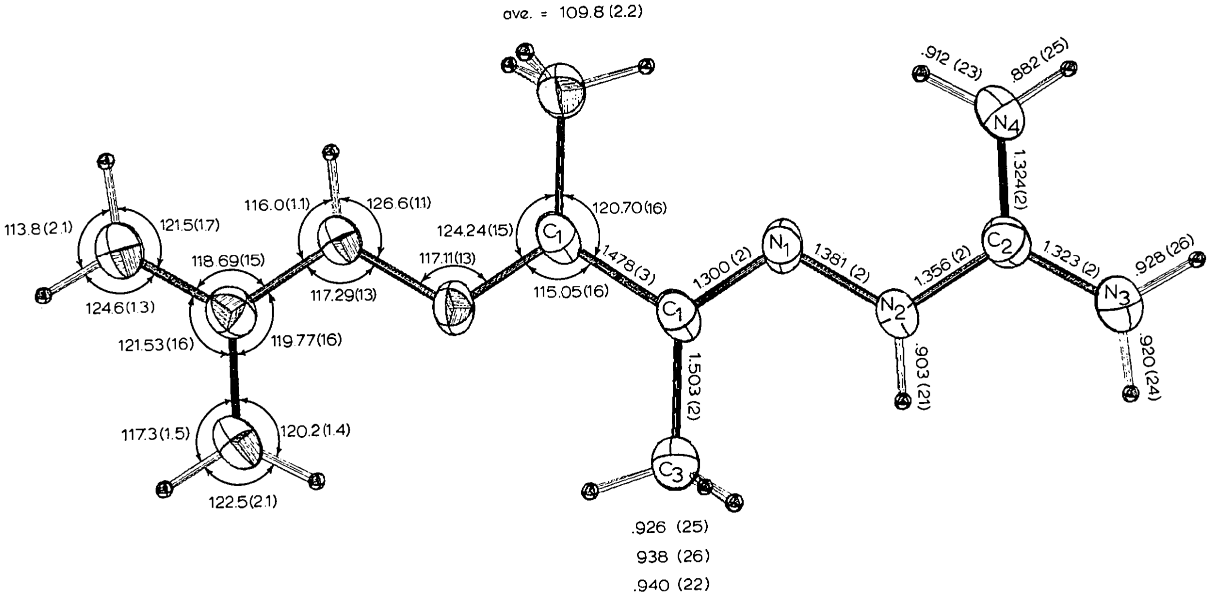

Fig. 1. Bond distances and angles in dimethyl GAG. All distances, except those involving hydrogen, have been corrected for rigid-body thermal motion.

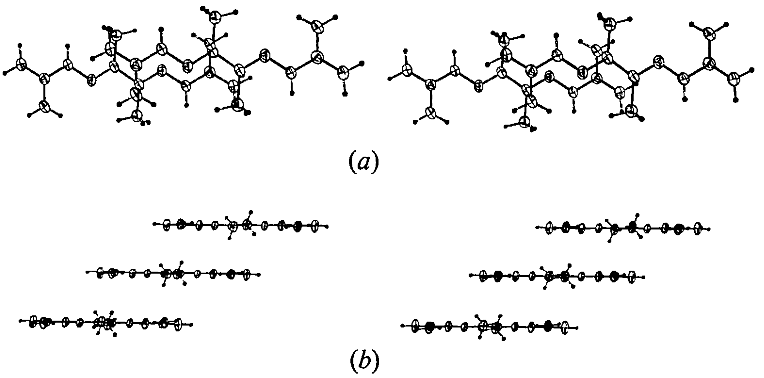

Fig. 3. Two stereoscopic views of the parallel planar packing of adjacent molecules in dimethyl GAG. The interplanar distance is 3·4 Å. The corresponding distance in methyl GAG is 3·2 Å.

hydrochloride (Mazumdar, Venkatesan, Mez & Donohue, 1969), in L-arginine dihydrate (Karle & Karle, 1964; Verbist, Lehmann, Koetzle & Hamilton, 1972). The mean values for C–N distances are 1·334 and 1·332 in these two structures of arginine. A detailed comparison of bond lengths and strengths in methyl GAG and dimethyl GAG would require a better set of data for methyl GAG.

Compared with dimethyl GAG, methyl GAG exhibits distortions from the expected planarity (Table 6). The largest nonhydrogen atom deviation from a mean plane in dimethyl GAG is for N(2) (−0·011 Å) in the ion body, and for N(3) (+0·0101 Å) at the terminus. Contrasted with this is the 0·20 Å deviation of the terminal nitrogen atoms in methyl GAG (Hamilton & La Placa, 1968). The largest nonmethyl hydrogen deviation from the dimethyl GAG plane is +0·072 Å, indicative of a well delocalized π-electron system in the compound. We hope in the future to obtain both experimental (by accurate low-temperature X-ray work) and theoretical charge distributions for this series of compounds.

Table 6. *Least-squares plane for nonhydrogen atoms (x, y, z in fractional coordinates)*

$$3{\cdot}401x+6{\cdot}465y-8{\cdot}736z=0{\cdot}0\ \text{Å}$$

The mean error in heavy-atom positions is about 0·002 Å and in hydrogen-atom positions about 0·02 Å. The deviations of the atoms from the plane in Å are as follows:

C(1), +0·002; C(3), −0·004; N(1), −0·002; N(2), −0·011; C(2), +0·001; N(3), +0·010; N(4), −0·005; N2H, −0·06; N4H(1), 0·04; N4H(2), −0·06; N3H(1), −0·02; N3H(2), +0·07.

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