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Quisqualic Acid

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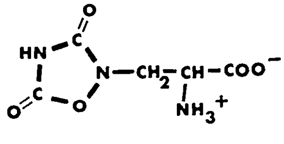
Abstract. $C_5H_7N_3O_5$, $P2_1$, $a=9{\cdot}804$ (6), $b=6{\cdot}967$ (6), $c=5{\cdot}582$ (5) Å, $\beta=94{\cdot}96$ (10)°, $Z=2$, $d_{calc}=1{\cdot}653$ g cm^{-3}. The structure was solved by the symbolic addition procedure. The high crystal density is due, in part, to an extensive hydrogen bonding network which involves all available hydrogen atoms and includes an O···(NH)···O bifurcated hydrogen bond. An extremely short C···O intermolecular approach, 2·86 Å, is also discussed.

Introduction. Quisqualic acid (QA) is a heterocyclic α-amino acid recently isolated from seeds of *Quisqualis indica* L. (Shinozaki & Shibuya, 1974).



QA may prove to be an important aid in research aimed at elucidating the role of L-glutamic acid in the central nervous system (CNS). L-glutamic acid is a neuroexcitatory substance found in the CNS, but there is still doubt as to whether it is a neurotransmitter used by the CNS. QA mimics L-Glutamic acid at glutamate-excited membranes, but is more potent by 2–3 orders of magnitude (Shinozaki & Shibuya, 1974). QA is a convulsant, and probably causes brain damage since glutamate itself and kainic acid, another glutamate agonist, reportedly produce brain lesions in convulsant or pre-convulsant doses (Olney, Rhee & Ho, 1974).

Crystals of QA were provided by Dr A. Padjen of the National Institute of Mental Health (Washington, D.C.).

The space group of the crystal and initial unit-cell parameters were obtained from precession camera photographs of several planar sections of the diffraction pattern. 676 independent reflections were collected from a small crystal (~0·12 × 0·18 × 0·39 mm) on an automatic computer-controlled diffractometer using Cu Kα radiation ($\lambda=1{\cdot}54178$ Å, Ni filter) to a $\sin\theta/\lambda$ max. of 0·579. The coordinates of 12 reflections were individually centered on the diffractometer and subjected to a least-squares refinement to obtain the reported cell dimensions. Three standard reflections, which were monitored after each 50 new reflections had been measured, gave no indication of crystal deterioration.

The structure was solved by the symbolic addition procedure for non-centrosymmetric crystals (Karle & Karle, 1966) and refined by a full-matrix least-squares program (Busing, Martin, Levy, Ellison, Hamilton, Ibers, Johnson & Thiessen, 1971) which included a correction for isotropic extinction. The full data set was used in the refinement; no reflexions were considered unobserved. Constraints were added to the least-squares program to fix the origin for space group $P2_1$ by holding the y coordinate of the geometrical centroid of the non-hydrogen atoms constant. All 7 hydrogen atoms were located in a difference map and their positional coordinates were included in the refinement. The hydrogen atoms were assigned thermal parameters

Table 1. *Fractional coordinates* (× 10^4 *for non-hydrogen and* × 10^3 *for hydrogen atoms*) *and thermal parameters with standard deviations*

The thermal parameters are of the form $T=\exp[-\frac{1}{4}(B_{11}h^2a^{*2}+B_{22}k^2b^{*2}+B_{33}l^2c^{*2}+2B_{12}hka^*b^*+2B_{13}hla^*c^*+2B_{23}klb^*c^*)]$. Standard deviations are based solely on least-squares parameters.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	3870 (4)	1927 (0)	5937 (8)	1·5 (1)	3·0 (2)	2·7 (2)	−0·0 (2)	0·5 (1)	0·1 (2)
O(1*A*)	3294 (3)	386 (6)	6370 (5)	2·7 (1)	3·3 (2)	2·8 (1)	−0·4 (1)	0·5 (1)	0·9 (1)
O(18)	4373 (4)	3066 (7)	7506 (6)	3·8 (2)	4·5 (2)	2·0 (1)	−1·2 (2)	0·1 (1)	−0·3 (1)
C(2)	3942 (4)	2512 (7)	3357 (7)	1·9 (2)	2·3 (2)	2·1 (2)	−0·1 (1)	0·3 (1)	0·0 (1)
N(2)	3648 (4)	814 (6)	1758 (6)	2·2 (2)	2·6 (2)	1·8 (1)	0·3 (1)	−0·2 (1)	−0·1 (1)
C(3)	2916 (5)	4120 (7)	2680 (7)	2·1 (2)	2·8 (2)	1·6 (1)	−0·2 (2)	−0·4 (1)	0·3 (1)
N(4)	1514 (4)	3465 (6)	2935 (6)	2·3 (2)	2·3 (2)	2·2 (1)	0·3 (1)	0·3 (1)	0·0 (1)
C(5)	607 (4)	4554 (6)	4128 (8)	2·5 (2)	2·0 (2)	2·3 (2)	0·3 (2)	0·2 (1)	−0·1 (1)
O(5)	909 (4)	5373 (7)	6017 (6)	3·6 (2)	4·1 (2)	2·8 (1)	0·3 (1)	0·2 (1)	−1·0 (1)
N(6)	−609 (4)	4440 (6)	2800 (6)	2·0 (1)	2·5 (2)	2·4 (1)	0·6 (1)	0·3 (1)	0·0 (1)
C(7)	−508 (5)	3452 (7)	728 (9)	2·6 (2)	2·2 (2)	3·0 (2)	0·3 (2)	0·4 (1)	0·1 (2)
O(7)	−1365 (3)	3088 (6)	−912 (7)	2·8 (1)	4·0 (2)	4·2 (2)	0·2 (2)	−0·7 (1)	−0·3 (2)
O(8)	821 (3)	2932 (5)	650 (6)	2·4 (1)	3·2 (2)	2·6 (1)	0·5 (1)	−0·1 (1)	−0·5 (1)

Table 1 (*cont.*)

	x	y	z
H(C2)	491 (6)	282 (11)	325 (10)
H(N2)	286 (8)	50 (13)	187 (11)
H(N2)	444 (7)	−5 (12)	218 (11)
H(N2)	373 (6)	103 (12)	17 (11)
H(C3)	291 (6)	533 (12)	374 (11)
H(C3)	258 (6)	451 (11)	45 (10)
H(N6)	−143 (7)	470 (12)	390 (11)

equal to the final isotropic value for the atom to which they were bonded. The function minimized was $\sum w(|F_o|-|F_c|)^2$ where the weight (w) was calculated according to the procedure outlined by Gilardi (1973). Final R values were $R=4{\cdot}0\%$ and $R_w=7{\cdot}6\%$. Table 1 lists the refined coordinates for all the atoms and the thermal parameters for the non-hydrogen atoms.*

Discussion. The results of the structure determination are illustrated in Fig. 1. Fig. 2 shows the bond lengths and angles. Three hydrogen atoms were found bonded to N(2) and no hydrogen atoms were found in the vicinity of either O(1*A*) or O(1*B*). Therefore, N(2) must carry a positive charge and the negative charge is distributed over the carboxyl group. In accord with this conclusion, the carboxyl bond distances are almost equal (1·247 and 1·251 Å, respectively) and lie between normal C–OH and C–O values. The five-membered ring is essentially planar, with all ring torsion angles less than 10° (see Table 3). The NH_3^+–CH–COO^- group is non-planar [the O(1*A*)–C(1)–C(2)–N(2) torsion angle is −16·5°] which is probably a distortion caused by strong intermolecular (hydrogen-bond) forces. There are 4 independent hydrogen bonds, involving all the hydrogens covalently bonded to nitrogen atoms. The hydrogen bond which links N(2)–H to a neighboring carboxyl group is bifurcated; *i.e.* the N(2)–H bond is not preferentially directed at either of the carboxyl oxygen atoms, but points toward a position approximately midway between them. The bifurcated system is essentially planar; the calculated displacement of the hydrogen atom from a plane passing through N(2), O(1*A*) and O(1*B*) is 0·046 Å (e.s.d. ~0·06 Å). Table 2 lists the distances and angles which describe the hydrogen bonding network and the network is illustrated in the packing diagram (Fig. 3). One of the carboxyl oxygens [O(5)] does not participate in a hydrogen bond, although it is involved in a close intermolecular approach to N(6). However, the H···O distances and the N(6)H···O angles (see Table 2) clearly indicate that

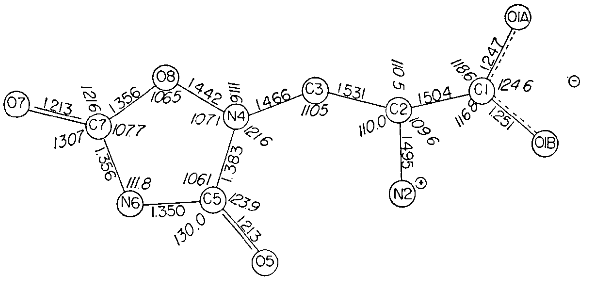


Fig. 2. Bond distances and angles for quisqualic acid. Standard deviations, based solely on least-squares parameters, are of the order of 0·006 Å for the bonds and 0·4° for the angles.

Fig. 1. Results of the structure analysis. The atoms are shown at their final refined positions.

Table 2. *Hydrogen bonds*

Donor	Acceptor	Symmetry of acceptor	N–H (Å)	N···O (Å)	H···O (Å)	N–H···O (°)	H–N···O (°)	
N(2)	O(1*B*)	$x \quad y \quad -1+z$	0·91	2·98	2·19	145·5	24·6	} bifurcated
N(2)	O(1*A*)	$x \quad y \quad -1+z$	0·91	3·01	2·18	153·1	19·1	
N(2)	O(1*B*)	$1-x \quad -\frac{1}{2}+y \quad 1-z$	0·98	2·73	1·75	167·2		
N(2)	O(7)	$-x \quad -\frac{1}{2}+y \quad -z$	0·81	2·94	2·26	141·8		
N(6)	O(1*A*)	$-x \quad \frac{1}{2}+y \quad 1-z$	0·84	2·79	1·95	176·6		
Closest intermolecular approaches								
O(5)	C(7)	$-x \quad \frac{1}{2}+y \quad 1-z$		2·86				
O(5)	N(6)	$-x \quad \frac{1}{2}+y \quad 1-z$		2·93	3·09	71·5		
O(8)	N(6)	$-x \quad -\frac{1}{2}+y \quad -z$		3·10	3·16	77·9		

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31485 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

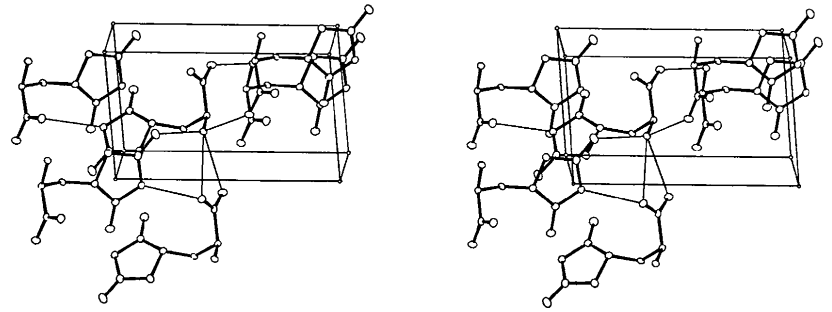

Fig. 3. Packing diagram for quisqualic acid showing the 4 independent hydrogen bonds. The figure is drawn with *a* horizontal, *c* vertical and *b* going down into the paper.

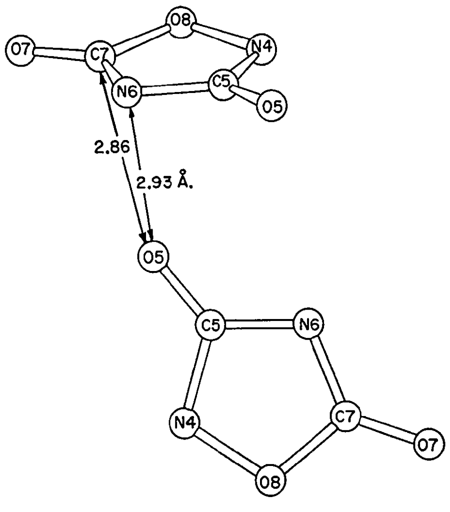

Fig. 4. Close approach of heterocyclic rings from neighboring molecules.

the hydrogen bond is between N(6) and O(1*A*). The carboxyl oxygen, O(5), is also extraordinarily close to C(7) in the adjacent molecule. The approach distance, 2·860 (± 6), is at least 0·2 Å shorter than that expected from van der Waals radii. The angle of approach is illustrated in Fig. 4. The planarity of the heterocyclic ring, and the shortened single bond distances, indicate that the π-electrons of the carboxyls interact with lone-pair electron orbitals on the nitrogen and oxygen atoms to form delocalized electron orbitals. This would provide a hypothetical mechanism for withdrawal of electrons from the carbon, C(7), to its three electronegative neighbors. This withdrawal may, in itself, reduce the effective radius of the carbon atom, and also add an attractive electrostatic component to the intermolecular interaction. Structural data pertaining to similar O···C=O short contacts have been summarized in an article by Bûrgi, Dunitz & Shefter (1974). Six of the intermolecular distances reported there are equal to or shorter than the short contact in quisqualic acid.

Table 3. *Torsion angles* (°) *in five-membered ring*

N(4)–C(5)–N(6)–C(7)	−4·5
C(5)–N(6)–C(7)–O(8)	−1·4
N(6)–C(7)–O(8)–N(4)	6·5
C(7)–O(8)–N(4)–C(5)	−9·2
O(8)–N(4)–C(5)–N(6)	8·3

References

Bürgi, H. B., Dunitz, J. D. & Shefter, E. (1974). *Acta Cryst.* **B30**, 1517–1527.

Busing, W. R., Martin, K. O., Levy, H. A., Ellison, R. D., Hamilton, W. C., Ibers, J. A., Johnson, C. K. & Thiessen, W. E. (1971). *ORXFLS*3. Oak Ridge National Laboratory Report ORNL-TM-305.

Gilardi, R. D. (1973). *Acta Cryst.* **B29**, 2089–2095.

Karle, J. & Karle, I. L. (1966). *Acta Cryst.* **22**, 849–859.

Olney, J. W., Rhee, V. & Ho, O. L. (1974). *Brain Res.* **77**, 507–512.

Shinozaki, H. & Shibuya, I. (1974). *Neuropharmacology*, **13**, 665–672.