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L-Lysine Sulphate, $C_6H_{16}N_2O_2^{2+}.SO_4^{2-}$: A Novel Conformation of the L-Lysine Side Chain

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Abstract. $M_r = 244{\cdot}27$, orthorhombic, $P2_12_12_1$, $a = 5{\cdot}573$ (1), $b = 11{\cdot}536$ (1), $c = 16{\cdot}594$ (2) Å, $V = 1066{\cdot}8$ (3) Å^3, $Z = 4$, $D_x = 1{\cdot}52$, $D_m = 1{\cdot}52$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ(Cu $K\alpha$) = 2·82 mm^{-1}, final $R = 0{\cdot}056$ for 1110 observed data. The side chain of the L-lysine molecule adopts an unusual folded conformation, which allows specific ion-pair interactions between the sulphate anion and the α- and ε-NH_3^+ groups of the same molecule. This conformation might be found in proteins with an N-terminal lysine crystallized from ammonium sulphate solutions.

Introduction. With the development of protein crystallography the organization of the solvent on the surface of the protein molecule is receiving increasing attention. Ions present in the crystallization medium often interact with the protein, stabilizing specific conformations of polar side chains. In this context the sulphate ion is of particular interest since a large number of proteins are crystallized from concentrated ammonium sulphate solutions. In this paper we present the structure of L-lysine sulphate, where the side chain of the amino acid adopts an unusual conformation which allows an interaction of the sulphate anion with the charged α- and ε-amino groups of the same molecule.

Experimental. Crystals obtained from an aqueous alcoholic solution of L-lysine and sulphuric acid, 0·5 × 0·2 × 0·5 mm, Enraf–Nonius CAD-4F diffractometer, Ni-filtered Cu $K\alpha$, two standard reflections, 1310 independent with $\theta \leq 75°$, 1110 with $I > 3\sigma(I)$, Lp correction, absorption ignored; S atom by Patterson synthesis, structure by heavy-atom method, anisotropic block matrix followed by full matrix; H (from ΔF synthesis and geometrical considerations) not refined, final $R_w = 0{\cdot}073$, $w = 1/\sigma^2(F_o)$, $F(000) = 520$, atomic scattering factors from *International Tables for X-ray Crystallography* (1974), Enraf–Nonius SDP software and PDP 11/34 computer of the Centro di Metodologie Chimico-Fisiche dell'Università di Napoli.

Discussion. The atomic parameters are given in Table 1,* and the crystal structure is shown in Fig. 1.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38205 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional atomic coordinates and thermal parameters with e.s.d.'s in parentheses*

Equivalent B's are defined as $(B_{11} \times B_{22} \times B_{33})^{1/3}$.

	x	y	z	B_{eq}(Å^2)
S	0·0795 (2)	0·6619 (1)	0·6658 (1)	2·2 (1)
O(1)	−0·1835 (6)	0·6534 (4)	0·6672 (2)	3·0 (2)
O(2)	0·1583 (6)	0·6490 (3)	0·5816 (2)	3·0 (1)
O(3)	0·1854 (7)	0·5678 (3)	0·7152 (2)	3·2 (1)
O(4)	0·1510 (9)	0·7739 (3)	0·6974 (3)	4·5 (2)
O(5)	0·5898 (9)	0·4632 (4)	0·3424 (2)	4·4 (2)
O(6)	0·3028 (7)	0·5692 (4)	0·4030 (2)	3·3 (2)
N	0·6126 (7)	0·6492 (3)	0·5148 (2)	2·3 (1)
NZ	0·4031 (8)	0·3428 (4)	0·7454 (3)	3·2 (2)
C	0·5040 (10)	0·5289 (4)	0·3991 (3)	2·9 (2)
CA	0·6969 (9)	0·5524 (4)	0·4627 (3)	2·3 (2)
CB	0·7516 (9)	0·4455 (4)	0·5127 (3)	2·6 (2)
CG	0·5457 (10)	0·4063 (5)	0·5670 (3)	3·0 (2)
CD	0·6106 (10)	0·2996 (5)	0·6161 (3)	3·1 (2)
CE	0·4183 (11)	0·2624 (5)	0·6745 (3)	3·4 (2)

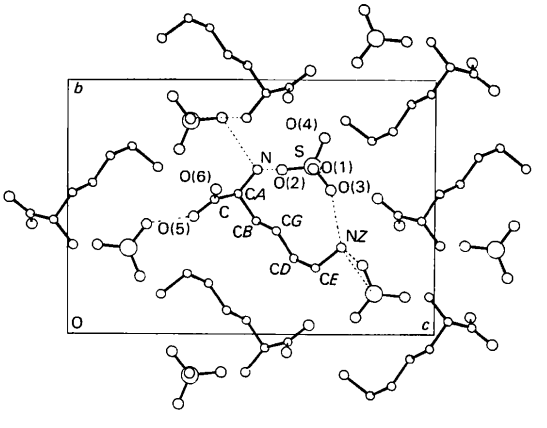

Fig. 1. The crystal structure of L-lysine sulphate as viewed perpendicular to the *yz* plane. Contacts indicative of hydrogen bonding (see Table 4 and the text) are shown by broken lines.

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Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

S–O(1)	1·469 (3)	S–O(2)	1·472 (4)
S–O(3)	1·482 (4)	S–O(4)	1·450 (4)
C–O(5)	1·299 (6)	C–O(6)	1·216 (7)
C–*CA*	1·530 (7)	*CA*–N	1·488 (6)
CA–*CB*	1·518 (7)	*CB*–*CG*	1·527 (7)
CG–*CD*	1·520 (7)	*CD*–*CE*	1·507 (8)
CE–NZ	1·500 (7)		
O(1)–S–O(2)	107·8 (4)	O(6)–C–*CA*	122·9 (8)
O(1)–S–O(3)	109·9 (4)	C–*CA*–N	108·2 (6)
O(1)–S–O(4)	109·1 (4)	C–*CA*–*CB*	111·9 (7)
O(2)–S–O(3)	109·4 (4)	N–*CA*–*CB*	110·9 (6)
O(2)–S–O(4)	110·5 (4)	*CA*–*CB*–*CG*	114·3 (7)
O(3)–S–O(4)	110·1 (4)	*CB*–*CG*–*CD*	112·1 (7)
O(5)–C–O(6)	127·0 (9)	*CG*–*CD*–*CE*	114·0 (8)
O(5)–C–*CA*	110·1 (7)	*CD*–*CE*–*NZ*	111·6 (8)

Molecular dimensions. The non-hydrogen bond distances and angles presented in Table 2 are in agreement with data obtained from X-ray and neutron crystallographic studies of L-lysine monohydrochloride dihydrate (Wright & Marsh, 1962; Koetzle, Lehmann, Verbist & Hamilton, 1972; Bugayong, Sequeira & Chidambaram, 1972). The largest differences are found in the carboxylic group which is unprotonated in the L-lysine monohydrochloride dihydrate structure. In the present structure the L-lysine molecule carries two positive charges at the α- and ε-amino groups, balanced by the two negative charges of the sulphate anion. The difference Fourier map clearly indicates the presence of the H atom attached to O(5) of the carboxylic group, hydrogen-bonded to O(3) of the sulphate anion. This result is confirmed by the interatomic distances and angles of the two groups. For the carboxylic group the C–O(6) distance of 1·216 (7) Å corresponds to a double bond (C=O) and the C–O(5) distance of 1·299 (6) Å corresponds to a single bond (C–OH). The values of the two bond lengths are similar to those of a protonated carboxylic group. The values of the bond angles *CA*–C–O(5), 110·1 (7)°, and *CA*–C–O(6), 122·9 (8)°, give the same indication. The orientation of the group is such that the –C=O bond is synperiplanar with respect to the *CA*–N bond, the torsion angle N–*CA*–C–O(6) being −12·6 (8)°. The SO_4^{2-} tetrahedron is regular and the small differences in the S–O bond lengths can be explained by the different environments of the O atoms: O(4), which participates in only one N–H···O hydrogen bond, has the shortest S–O distance of 1·450 (4) Å; O(1) and O(2), with S–O bond distances of 1·469 (3) and 1·472 (4) Å, respectively, participate in two N–H···O hydrogen bonds; finally O(3) is involved in two different hydrogen bonds of types N–H···O and O–H···O the last being the strongest hydrogen bond in the structure; the corresponding S–O distance is 1·482 (4) Å. The high sensitivity of the S–O bond distances to the strength and the number of the hydrogen bonds which may be formed has also been noted in other crystal structures (Vilminot, Philippot & Lehmann, 1976).

Conformation of the L-*lysine molecule.* As can be seen from the dihedral angles reported in Table 3, considerable differences exist between the conformation of the L-lysine molecule found in the present structure and those found in other crystal structures. The differences in the conformation arise mainly from the different values of the dihedral angles χ_1 and χ_4 of the side chain. The χ_1 angle of 53·6 (7)° is unusual and places the γ-C atom *trans* to the H atom attached to the α-C atom (g^+ position). This position of the γ atom is less favourable than the *t* and g^- position *trans* to the more bulky amino and carboxyl groups respectively. Experimental data on dihedral angles derived from X-ray studies of protein structures (Janin, Wodak, Levitt & Maigret, 1978) also indicate that, for residues with no branching at the β-C atom, the g^- and, to a lesser extent, the *t* position are strongly preferred. The fraction of residues in the g^+ conformation is very small. A similar analysis performed on small-molecule crystal structures (Benedetti, Morelli, Nemethy & Scheraga, 1982), where the side chains are more severely involved in intermolecular contacts, indicates a somewhat higher population for the g^+ position. This conformation, however, has never been found previously for the L-lysine side chain. The dihedral angles χ_2 and χ_3 assume values close to 180° whereas χ_4 is −73·3 (8)°. The combined values of χ_1, χ_2, χ_3 and χ_4 give rise to a folded conformation of the molecule which allows specific interactions between the sulphate anion and the two α- and ε-amino groups of the same molecule. The specific interaction which is the most important feature of the structure is illustrated in Fig. 2. It involves the electrostatic attraction between the two positively charged $-NH_3^+$ groups and the negatively charged SO_4^{2-} and also two N–H···O hydrogen bonds. This interaction might be found in proteins with an N-terminal lysine crystallized from ammonium sulphate solutions. It is interesting that in the structure

Table 3. *Torsion angles* (°) [*defined as in IUPAC–IUB Commission on Biochemical Nomenclature* (1970)]

	ψ	χ_1	χ_2	χ_3	χ_4	Reference
L-Lysine monohydrochloride dihydrate	−19·2 (3)	−56·4 (2)	−176·0 (1)	−171·1 (2)	179·2 (2)	(*a*)
L-Lysine L-aspartate	−29·5 (7)	−67·7 (7)	179·6 (6)	165·5 (7)	161·2 (6)	(*b*)
$PtCl_6$–L-lysine	−28·7 (16)	−179·1 (20)	168·1 (20)	172·2 (22)	−73·1 (18)	(*c*)
L-Lysine sulphate	−12·6 (8)	53·6 (7)	−179·6 (9)	176·3 (9)	73·3 (8)	(*d*)

References: (*a*) Koetzle, Lehmann, Verbist & Hamilton (1972); (*b*) Bhat & Vijayan (1976); (*c*) L'Haridon, Lang, Pastuszak & Dobrowolski (1978); (*d*) present paper.

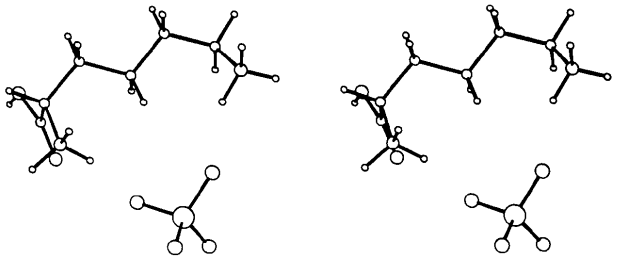

Fig. 2. Stereoscopic view of L-lysine sulphate.

Table 4. *Hydrogen bonds*

D is the donor and *A* is the acceptor atom. The following superscripts distinguish atoms related, by symmetry operations, to those in Table 1: none, *x,y,z*; (i) $1+x,y,z$; (ii) $\frac{1}{2}+x,\frac{3}{2}-y,1-z$; (iii) $-x,-\frac{1}{2}+y,\frac{3}{2}-z$; (iv) $1-x,-\frac{1}{2}+y,\frac{3}{2}-z$; (v) $\frac{1}{2}-x,1-y,\frac{1}{2}+z$.

C–*D*···*A*	*D*···*A*	C–*D*···*A*
C*A*–N···O(1^{i})	2·774 (5) Å	114·4 (5)°
C*A*–N···O(2)	2·764 (5)	121·4 (5)
C*A*–N···O(2^{ii})	2·835 (5)	105·1 (5)
C*E*–N*Z*···O(1^{iii})	2·894 (6)	87·1 (5)
C*E*–N*Z*···O(3)	2·909 (6)	116·2 (5)
C*E*–N*Z*···O(4^{iv})	2·777 (7)	92·3 (5)
C–O(5)···O(3^{v})	2·634 (5)	116·4 (6)

of L-lysine–$PtCl_6$, a favourable interaction of the ε-NH_3^+ group with the Cl atoms of the $PtCl_6^{2-}$ octahedron is achieved through a similar value of the dihedral angle χ_4.

Crystal packing and hydrogen bonds. The crystal structure is stabilized by ionic interactions and hydrogen bonds which are given in Table 4. There are seven hydrogen bonds in the asymmetric unit of the crystal structure, one involving each H atom covalently bonded to N or O. The three H atoms of the α-amino group are donated to O(1) and to two O(2) of three different sulphate ions. A similar situation occurs for the ε-NH_3^+ group. The strongest hydrogen bond connects the carboxylic –OH group to O(3). The only potential acceptor atom not participating in hydrogen bonding is O(6).

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Dithiin Tautomers: Dimethyl 2,4-Diphenyl-2*H*,4*H*-1,3-dithiin-5,6-dicarboxylate(I), $C_{20}H_{18}O_4S_2$, and Dimethyl 2,6-Diphenyl-2*H*,4*H*-1,3-dithiin-4,5-dicarboxylate (II), $C_{20}H_{18}O_4S_2$

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Abstract. (I) $M_r = 386{\cdot}46$, triclinic, $P\bar{1}$, $a = 10{\cdot}886$ (2), $b = 11{\cdot}392$ (2), $c = 16{\cdot}475$ (3) Å, $\alpha = 106{\cdot}09$ (1), $\beta = 82{\cdot}70$ (1), $\gamma = 101{\cdot}69$ (1), $V = 1916{\cdot}8$ (12) Å^3, $Z = 4$, $D_c = 1{\cdot}340$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å, $\mu = 26{\cdot}2$ cm^{-1}, $F(000) = 808$, $R = 6{\cdot}1\%$ for 5007 unique reflections. (II) $M_r = 386{\cdot}46$, triclinic, $P\bar{1}$, $a = 9{\cdot}528$ (3), $b = 9{\cdot}834$ (3), $c = 11{\cdot}303$ (4) Å, $\alpha = 94{\cdot}80$ (3), $\beta = 86{\cdot}57$ (3), $\gamma = 114{\cdot}74$ (2)°, $V = 958{\cdot}1$ (10) Å^3, $Z = 2$, $D_c = 1{\cdot}341$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å, $\mu = 26{\cdot}2$ cm^{-1}, $F(000) = 404$, $R = 5{\cdot}3\%$ for 2501 unique reflections. Crystal structure analyses have established that dimethyl 2,4-diphenyl-2*H*,4*H*-1,3-dithiin-5,6-dicarboxylate (I) undergoes tautomerization in a basic solution with a migration of a proton and a double bond in the dithiin ring to produce dimethyl 2,6-diphenyl-2*H*,4*H*-1,3-dithiin-4,5-dicarbox-

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