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Hydrogen-Bonding Interactions between a *cis* Peptide and a Carboxyl Group: Structure of the 1:2 2,5-Piperazinedione–Salicylic Acid Complex*

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Abstract. $C_4H_6N_2O_2.2C_7H_6O_3$, monoclinic, $P2_1/a$, $a = 18{\cdot}52\,(1)$, $b = 5{\cdot}455\,(5)$, $c = 8{\cdot}787\,(8)$ Å, $\beta = 104{\cdot}28\,(4)°$ and $Z = 2$. Final $R = 0{\cdot}041$ for 1397 observed reflections. 2,5-Piperazinedione and salicylic acid form a 1:2 complex. The COOH group of the salicylic acid forms hydrogen bonds with the amide and carbonyl groups of the *cis* peptide. There is also an internal hydrogen bond between O(1) and O(3)H of the salicylic acid.

Introduction. As a part of our study of the interactions of cyclic peptides with other molecules and ions, we carried out crystallographic investigations on the complexes of 2,5-piperazinedione (diketopiperazine, DKP) with formic acid (Kartha, Varughese & Lu, 1981) and salicylic acid and we report here the crystal structure of the latter.

DKP and salicylic acid were dissolved in a mixture of ethanol and water and gave crystals on slow evaporation. A crystal was mounted approximately about the *b* axis and the intensity data were recorded using a CAD-4 diffractometer with Ni-filtered Cu radiation. Of the 1637 unique reflections ($2\theta < 154°$) measured, 240 of them had intensities less than $2\sigma(I)$ and were excluded from the least-squares refinement.

The crystal structure was solved using multisolution techniques (Germain, Main & Woolfson, 1971) and refined by block-diagonal least-squares techniques. The quantity minimized in the refinement was $\sum w||F_o| - |F_c||^2$ where $w = 1/[\sigma(F)]^2$. The final R factor $(\sum ||F_o| - |F_c||/\sum |F_o|)$ for 1397 observed reflections was 0·041.†

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† Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36213 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional and isotropic thermal parameters with e.s.d.'s in parentheses*

	x	*y*	*z*	B_{eq}/B (Å²)
O	0·54096 (10)	0·1686 (3)	0·2298 (2)	4·26 (7)
O(1)	0·37265 (9)	−0·0699 (3)	0·1242 (2)	4·17 (7)
O(2)	0·46754 (9)	−0·1881 (3)	0·3175 (2)	4·24 (7)
O(3)	0·24010 (9)	−0·2371 (4)	0·1097 (2)	3·94 (7)
N	0·4527 (1)	0·3203 (4)	0·0268 (2)	3·50 (7)
C(*A*)	0·4256 (1)	0·4860 (5)	−0·1031 (3)	3·45 (8)
C	0·5203 (1)	0·3206 (4)	0·1230 (3)	3·16 (8)
C(1)	0·3525 (1)	−0·3920 (4)	0·2873 (2)	2·97 (7)
C(2)	0·2754 (1)	−0·3992 (4)	0·2197 (2)	3·03 (7)
C(3)	0·2320 (1)	−0·5769 (5)	0·2763 (3)	3·46 (8)
C(4)	0·2646 (1)	−0·7500 (5)	0·3736 (3)	3·81 (9)
C(5)	0·3410 (1)	−0·7472 (5)	0·4433 (3)	3·83 (9)
C(6)	0·3838 (1)	−0·5688 (5)	0·3997 (3)	3·25 (9)
C(7)	0·3979 (1)	−0·2034 (4)	0·2365 (3)	3·17 (8)
H1(C*A*)	0·412 (2)	0·403 (6)	−0·203 (3)	5·1 (7)
H2(C*A*)	0·382 (2)	0·571 (6)	−0·084 (3)	4·6 (6)
H(N)	0·420 (2)	0·202 (5)	0·046 (3)	4·8 (6)
H(C3)	0·179 (1)	−0·576 (6)	0·223 (3)	4·6 (6)
H(C4)	0·235 (2)	−0·886 (6)	0·410 (3)	5·2 (7)
H(C5)	0·364 (2)	−0·867 (5)	0·513 (3)	4·4 (6)
H(C6)	0·435 (1)	−0·562 (5)	0·444 (3)	4·9 (6)
H(O3)	0·281 (2)	−0·118 (8)	0·091 (4)	8·3 (11)
H(O2)	0·492 (2)	−0·055 (6)	0·282 (4)	6·0 (8)

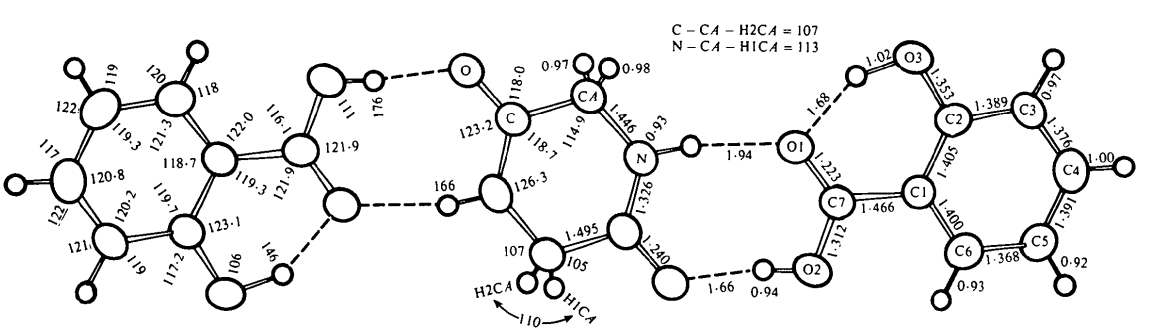

Fig. 1. Bond lengths (Å) and angles (°); e.s.d.'s for those involving non-H atoms are 0·002 Å and 0·1°, for those involving H atoms 0·04 Å and 0·9°. Hydrogen-bond parameters are also marked.

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Table 2. *Hydrogen-bond parameters*

D and *A* denote the donor and acceptor atoms.

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N–H···O(1)	0·93 (4) Å	1·94 (4) Å	2·844 (2) Å	166 (0·9)°
O(3)–H···O(1)	1·02 (4)	1·68 (4)	2·592 (2)	146 (0·9)
O(2)–H···O	0·94 (4)	1·66 (4)	2·597 (2)	176 (0·9)

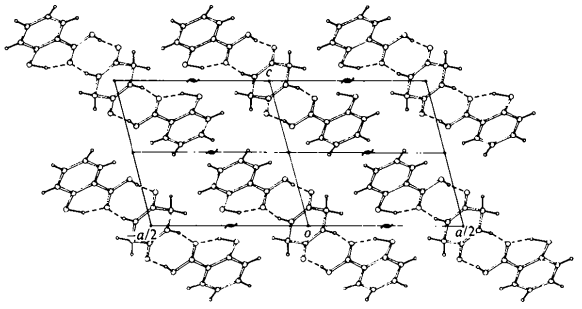

Fig. 2. Packing of the structure; projection along **b**.

Discussion. The final positional parameters are listed in Table 1, and the bond lengths and angles are shown in Fig. 1. The dimensions of the DKP are in good agreement with those in the crystal structure of the uncomplexed DKP (Degeilh & Marsh, 1959). In salicylic acid, C(1)–C(6) and C(1)–C(2) are longer than other bonds in the six-membered ring as observed in the crystal structure of salicylic acid (Sundaralingam & Jensen, 1965; Cochran, 1953).

The six-membered ring of the DKP is nearly planar with φ, ψ and ω values of $-2{\cdot}2$, $2{\cdot}4$ and $2{\cdot}5°$ respectively. As there are no side-chain substitutions at the α-carbon atoms, the DKP ring is expected to be planar (Kartha & Varughese, 1980). However, slight deviation from planarity could occur at a very modest cost of energy, and in this case there are strong hydrogen bonds between the peptide and the carboxyl group of the salicylic acid.

In salicylic acid, the plane of the carboxyl group is tilted by 9° with respect to the plane of the six-membered ring and makes an angle of 4° with respect to the plane containing C(*A*), C, O and N atoms.

The complex is formed by the hydrogen-bonding interactions between the *cis* peptide and carboxyl group of the salicylic acid. The amide group is hydrogen bonded to O(1) with an O–H distance of 1·94 Å. The OH of the carboxyl group takes part in a strong hydrogen-bonding interaction with the carbonyl of the peptide with an O···H distance of 1·66 Å. The internal hydrogen bond between O(3) and O(1) observed in salicylic acid is retained here with an O···H distance of 1·68 Å. O(1) thus accepts two protons. All the protons capable of taking part in hydrogen bonding do so within the complex itself (Table 2) and there is no intercomplex hydrogen bonding. Fig. 2 gives the projection of the structure down the *b* axis.

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