

The Crystalline Complex (1:1) of Salicylamide and 5-Ethyl-5-isoamylbarbituric Acid (Amobarbital)

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[C₇H₇NO₂]. [C₁₁H₁₈N₂O₃], m.p. 124°, is monoclinic, space group *P*2₁/*c*, with *a* = 13·028 (5), *b* = 12·558 (5), *c* = 12·719 (5) Å, β = 107·60 (1)°; *D*_{meas} = 1·216 g cm⁻³ and *D*_{calc} = 1·217 g cm⁻³ for *Z* = 4. The crystal structure was determined by direct methods from 4089 integrated intensities measured with a computer-controlled four-circle diffractometer and graphite-monochromated Cu *K*α radiation. Refinement gave a final *R* index of 0·072. The crystal structure of the complex resembles the crystal structures of the components in many respects, including some apparent disorder in the isoamyl group of amobarbital, a strong O–H···O intramolecular hydrogen bond (2·49 Å) in salicylamide, and the nature of the intermolecular NH···O hydrogen bonding.

Introduction

The drug-active barbiturates form crystal complexes with a number of amides (Gartland & Craven, 1973). A comparison of the mode of hydrogen bonding in these complexes and in the crystal structures of the component molecules is of interest since it may suggest differences in the hydrogen-bonding affinity of the donor and acceptor groups involved.

Experimental

The 1:1 complex of salicylamide and amobarbital (Fig. 1) was first prepared by Kuroyanagi (1956). Our crystals were grown by cooling a solution consisting of ethanol and cyclohexane (5:1, v/v) supersaturated with respect to both salicylamide and amobarbital. Crystal data were measured on a computer-controlled four-circle diffractometer, using graphite-monochromated Cu *K*α radiation (λ = 1·5418 Å). The crystal, which measured approximately 0·32 × 0·16 × 0·16 mm was mounted with its long dimension (*a*) along the diffractometer φ axis. Integrated intensities for 4089 non-symmetry-related reflections were collected with the

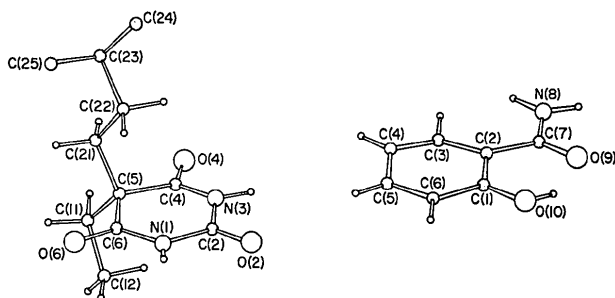


Fig. 1. Molecular structures and atomic nomenclature for 5-ethyl-5-isoamylbarbituric acid or amobarbital (left) and salicylamide (right).

θ/2θ scan method. There were 868 reflections with integrated intensity (*I*) less than 2σ(*I*). These were assigned intensities *I* = σ(*I*)/2.

The crystal structure was determined by direct methods with the computer-programmed procedure of Germain, Main & Woolfson (1971), applied to the 389 reflections with normalized structure factors |*E*| ≥ 1·5. A set of phases was obtained which correctly revealed all but three atoms when used to calculate an *E* synthesis.

Refinement of the atomic parameters (Table 1) was by least-squares methods, minimizing the function $\sum_w \Delta^2$ where $\Delta = |F_{\text{meas}}| - |F_{\text{calc}}|$, and $w^{-1} = 0\cdot54 + \frac{1}{h} 0\cdot0017 |F_{\text{meas}}|^2$. The atomic form factors which were used were those of Cromer & Waber (1965) for carbon, nitrogen and oxygen, and of Stewart, Davidson & Simpson (1965) for hydrogen. Because of computer limitations, parameters were refined alternately in two blocks. The first block consisted of all 235 non-hydrogen atom parameters. The second block consisted of 208 parameters for the hydrogen atoms together with parameters of heavier atoms to which they are bonded. The latter parameters were included so as to have overlapping of the two blocks. The refinement was terminated when the largest change in a non-hydrogen atom positional parameter was 0·5σ. In the final cycles, reflections with *I* < 2σ(*I*) and 15 low-angle reflections for which |*F*_{calc}| was significantly less than |*F*_{meas}|, were assigned zero weight. The final *R* values* were 0·072 for all reflections and 0·055 for reflections with non-zero weight.†

$$* R = \left(\frac{\sum_h |\Delta|}{\sum_h |F_{\text{meas}}|} \right).$$

† The table of observed and calculated structure amplitudes has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30291 (25 pp., 1 microfiche). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

As was observed in the crystal structure determinations of amobarbital I and amobarbital II [see Fig. 2 in Craven & Vizzini (1969)] the calculated electron density peaks are diffuse for the terminal atoms C(23), C(24), and C(25) of the isoamyl group. The largest principal values for the r.m.s. amplitudes of thermal vibration of these atoms is 0.59 Å for C(25). In amobarbital I the corresponding value is 0.60 Å. In all three of these crystal structures, the hydrogen atoms bonded to C(23), C(24) and C(25) could not be found in electron density difference maps. However, in the final stages of the present refinement, a diffuse hydrogen-atom-like peak ($0.5 \text{ e } \text{Å}^{-3}$) was observed at the expected tetrahedral

bond angle, and at a distance of 1.4 Å from atom C(23). This peak may be the result of a partial conformational disordering with respect to rotation about the C(22)–C(23) bond. No attempt was made to incorporate such disordering into the assumed model of the crystal structure.

Discussion

The amobarbital bond lengths and angles (Fig. 2) and conformation agree well with those reported for the two crystalline forms of amobarbital itself (Craven & Vizzini, 1969). The geometry of the salicylamide molecule (Fig. 3) has been determined with greater accuracy

Table 1. Atomic parameters

Positional parameters are given as fractions of the lattice translations. Anisotropic temperature factors correspond to the expression $T = \exp [-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$, and isotropic temperature factors to the expression $\exp(-B \sin^2 \theta/\lambda^2)$. E.s.d.'s given in parentheses refer to the least significant figures in parameter values. Atom labels are consistent with those of Craven & Vizzini (1969) and Sasada *et al.* (1964).

(a) Carbon, nitrogen and oxygen atom parameters ($\times 10^4$)

(i) Amobarbital										
	<i>x</i>	<i>y</i>	<i>z</i>	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	
N(1)	-314 (1)	1597 (1)	2058 (1)	53 (1)	92 (1)	87 (1)	-18 (1)	38 (1)	-31 (1)	
C(2)	-211 (1)	1038 (2)	1175 (2)	48 (1)	72 (1)	67 (1)	-5 (1)	22 (1)	-13 (1)	
O(2)	-917 (1)	454 (1)	634 (1)	55 (1)	95 (1)	89 (1)	-17 (1)	24 (1)	35 (1)	
N(3)	740 (1)	1179 (1)	934 (1)	53 (1)	84 (1)	66 (1)	-9 (1)	27 (1)	-22 (1)	
C(4)	1583 (1)	1813 (2)	1493 (1)	49 (1)	69 (1)	65 (1)	-5 (1)	22 (1)	-8 (1)	
O(4)	2378 (1)	1880 (1)	1189 (1)	54 (1)	101 (1)	87 (1)	-8 (1)	35 (1)	-16 (1)	
C(5)	1508 (1)	2385 (2)	2515 (2)	52 (1)	80 (1)	73 (1)	-15 (1)	25 (1)	-23 (1)	
C(6)	444 (2)	2229 (2)	2763 (2)	60 (1)	96 (2)	80 (2)	-16 (1)	34 (1)	-33 (1)	
O(6)	262 (1)	2645 (2)	3541 (1)	89 (1)	166 (2)	118 (2)	-40 (1)	61 (1)	-80 (1)	
C(11)	1647 (2)	3589 (2)	2369 (2)	86 (2)	78 (2)	113 (2)	-18 (1)	41 (2)	-25 (1)	
C(12)	775 (3)	4069 (2)	1412 (3)	128 (3)	86 (2)	169 (3)	10 (2)	41 (2)	-2 (2)	
C(21)	2415 (2)	1947 (2)	3510 (2)	65 (1)	112 (2)	70 (1)	-15 (1)	18 (1)	-17 (1)	
C(22)	2361 (3)	730 (2)	3655 (2)	131 (3)	114 (2)	88 (2)	-12 (2)	12 (2)	-1 (2)	
C(23)	3351 (3)	229 (3)	4478 (2)	161 (3)	135 (3)	101 (2)	42 (3)	34 (2)	8 (2)	
C(24)	3215 (5)	-993 (4)	4429 (4)	401 (10)	112 (3)	167 (5)	37 (4)	21 (5)	9 (3)	
C(25)	3501 (5)	581 (4)	5630 (3)	260 (6)	212 (5)	122 (3)	89 (5)	-15 (4)	-42 (3)	
(ii) Salicylamide										
	<i>x</i>	<i>y</i>	<i>z</i>	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	
C(1)	6972 (1)	1954 (2)	2681 (2)	50 (1)	70 (1)	78 (1)	-1 (1)	27 (1)	-9 (1)	
C(2)	5852 (1)	1862 (1)	2208 (1)	48 (1)	59 (1)	69 (1)	-1 (1)	24 (1)	-5 (1)	
C(3)	5195 (1)	2535 (2)	2593 (2)	56 (1)	80 (1)	91 (2)	8 (1)	25 (1)	-18 (1)	
C(4)	5624 (2)	3280 (2)	3399 (2)	74 (2)	101 (2)	111 (2)	9 (1)	32 (1)	-43 (2)	
C(5)	6730 (2)	3378 (2)	3830 (2)	80 (2)	101 (2)	105 (2)	-5 (1)	23 (2)	-45 (2)	
C(6)	7402 (2)	2723 (2)	3478 (2)	58 (1)	98 (2)	93 (2)	-7 (1)	20 (1)	-30 (1)	
C(7)	5428 (1)	1078 (1)	1314 (1)	49 (1)	57 (1)	69 (1)	-2 (1)	23 (1)	-3 (1)	
N(8)	4381 (1)	1030 (1)	797 (1)	49 (1)	75 (1)	89 (1)	-1 (1)	20 (1)	-21 (1)	
O(9)	6062 (1)	465 (1)	1040 (1)	54 (1)	75 (1)	95 (1)	2 (1)	25 (1)	-27 (1)	
O(10)	7660 (1)	1303 (1)	2376 (1)	47 (1)	96 (1)	111 (1)	-4 (1)	29 (1)	-37 (1)	

(b) Hydrogen atom positional parameters ($\times 10^3$)

(i) Amobarbital					(ii) Salicylamide				
	<i>x</i>	<i>y</i>	<i>z</i>	$B(\text{Å}^2)$		<i>x</i>	<i>y</i>	<i>z</i>	$B(\text{Å}^2)$
H(1)	-92 (1)	150 (2)	218 (2)	5.0 (5)	H(3)	440 (2)	247 (2)	229 (2)	4.0 (4)
H(3)	89 (2)	80 (2)	39 (2)	5.7 (5)	H(4)	510 (2)	373 (2)	365 (2)	7.4 (7)
H(111)	238 (2)	371 (2)	228 (2)	5.5 (5)	H(5)	701 (2)	391 (2)	446 (2)	5.8 (5)
H(112)	173 (2)	397 (2)	307 (2)	6.5 (6)	H(6)	819 (2)	273 (2)	373 (2)	5.4 (5)
H(121)	73 (3)	371 (3)	73 (3)	8.6 (9)	H(81)	417 (2)	52 (2)	30 (2)	5.3 (5)
H(122)	14 (3)	393 (3)	153 (3)	9.4 (10)	H(82)	390 (2)	142 (2)	99 (2)	5.6 (6)
H(123)	88 (3)	480 (3)	137 (3)	10.2 (10)	H(10)	725 (2)	91 (2)	186 (2)	7.0 (7)
H(211)	309 (2)	212 (2)	339 (2)	5.2 (5)					
H(212)	240 (2)	235 (2)	421 (2)	6.9 (6)					
H(221)	224 (3)	33 (3)	295 (4)	10.7 (10)					
H(222)	174 (3)	60 (3)	389 (3)	9.6 (10)					

than in the crystal structure of salicylamide itself (Sasada, Takano & Kakudo, 1964). The atoms of the benzene ring are coplanar within ± 0.01 Å, with the amide carbon atom C(7) and the phenolic oxygen atom O(10) displaced 0.07 Å and 0.05 Å from the ring plane in opposite senses. There is a dihedral angle of 5.4° between the planes of the benzene ring and the amide group C(7), O(9), N(8). The internal hydrogen bond involving the phenolic group and the amide oxygen atom has an O...O distance (2.49 Å) shorter than the corresponding hydrogen bond in salicylic acid (2.62 Å, Sundaralingam & Jensen, 1965). The shorter O...O distance occurs together with a longer carbonyl bond length (1.253 vs. 1.234 Å) suggesting that the internal hydrogen bond in salicylamide is stronger because the

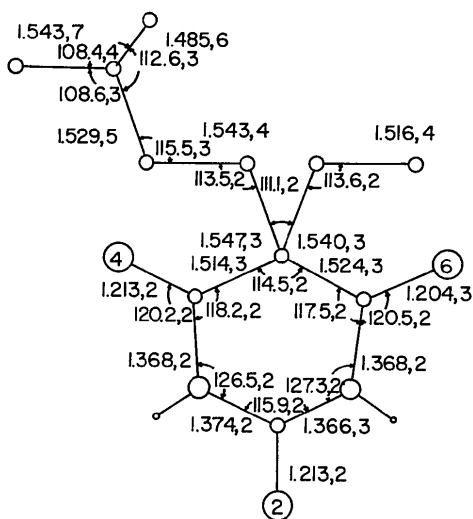


Fig. 2. Bond lengths (Å) and angles ($^\circ$) with e.s.d.'s for amobarbital. Each parameter is separated from its e.s.d. by a comma. The e.s.d. refers to the least significant digit in the parameter.

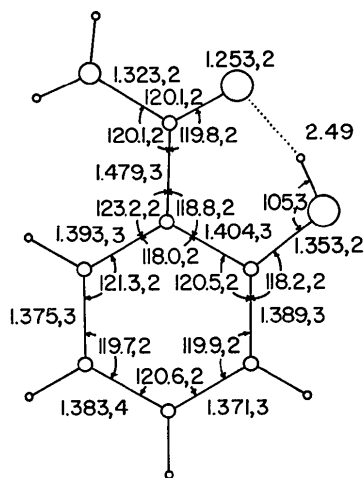


Fig. 3. Bond distances (Å) and angles ($^\circ$) for salicylamide. Each parameter is separated from its e.s.d. by a comma. The e.s.d. refers to the least significant digit in the parameter.

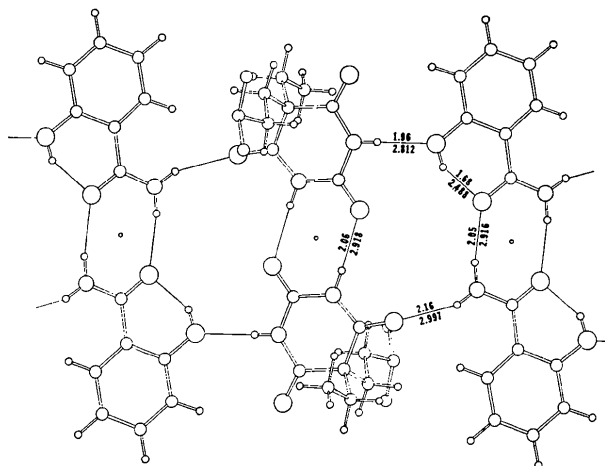


Fig. 4. Hydrogen bonding in the crystal structure. A single hydrogen-bonded chain is viewed normal to (110).

carbonyl oxygen is more electronegative than in salicylic acid.

The crystal structure consists of hydrogen-bonded chains made up of alternating hydrogen-bonded dimers of amobarbital and salicylamide (Fig. 4). The planes of adjacent dimers are at an angle of 29° . The chains run parallel to *a*, which is the direction of fastest crystal growth, and are oriented parallel to (110) and (1 $\bar{1}$ 0). The chains are packed so that in the view down *a* there are tunnels with minimum cross-sectional dimensions of about 6×7 Å, into which project the ethyl and isoamyl groups. The terminal isoamyl atoms are enclosed by four benzene rings. However, there are no short intermolecular distances, so that the arrangement is consistent with the observed large apparent amplitudes of thermal vibration, and possible conformational disorder of atoms C(24) and C(25).

Our principal aim in determining this crystal structure was to compare the hydrogen-bonding arrangements in the molecular complex with those in the crystal structures of the individual components. In the crystal structure of salicylamide (Sasada *et al.*, 1964), there are hydrogen-bonded chains similar to those of the complex (Fig. 4). The N...O hydrogen-bond distance between molecules of salicylamide within a dimer is 2.94 Å, which is very similar to the corresponding distance in the complex with amobarbital (2.92 Å). Both amobarbital I and II (Craven & Vizzini, 1969) contain hydrogen-bonded chains in which there can be recognized the same kind of amobarbital dimers as in the complex with salicylamide. The N...O distances (2.92, 2.92, 2.88 Å) in these dimers are also very similar to the corresponding distance in the complex (2.92 Å).

It is of interest to compare the inter-dimer NH...O hydrogen bonds, which occur between unlike molecules in the complex, and between like molecules in the crystal structures of the separate components. The N...O distance in NH_{barb}...O(10)_{sal} is shorter

(2.81 Å) than in the corresponding $\text{NH}_{\text{sal}} \cdots \text{O}(10)_{\text{sal}}$ (3.05 Å) hydrogen bond and the distance in $\text{NH}_{\text{sal}} \cdots \text{O}(4)_{\text{barb}}$ is longer (3.00 Å) than in the corresponding $\text{NH}_{\text{barb}} \cdots \text{O}(4)_{\text{barb}}$ hydrogen bond; (2.89, 2.91, 2.86 Å), in amobarbital I and II, and other hydrogen bonds of this type involving barbiturate as both donor and acceptor (Gartland & Craven, 1974). These distances are thus compatible with the conclusion that the barbiturates are more effective hydrogen-bonding donors than acceptors.

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Lithium Nuclear-Magnetic-Resonance in Lithium Acetate Dihydrate, $\text{Li}(\text{CH}_3\text{COO}) \cdot 2\text{H}_2\text{O}$

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^7Li n.m.r. in single crystals of lithium acetate dihydrate is used to determine the quadrupole coupling parameters: (e^2qQ/h) and η . The orientations of the principal z , y and x components of the electric field gradient tensor are determined to be along the crystallographic b , a and c axes respectively. The parameters experimentally determined are $(e^2qQ/h) = 154.6$ kHz; and $\eta = 0.9$. This study indicates a tetrahedral configuration around the Li ion, confirming the recent X-ray and p.m.r. results.

Introduction

The interaction between the quadrupole moment of a nucleus and the gradient of the electric field at the nuclear site perturbs the nuclear magnetic transitions between the Zeeman levels. The electric field gradient (e.f.g.) at a site thus reflects the local structural symmetry. It is possible, therefore, to obtain information regarding structural details around the resonating nucleus from a study of the quadrupole splitting of the nuclear-magnetic-resonance lines. With this objective a study of ^7Li n.m.r. in $\text{Li}(\text{CH}_3\text{COO}) \cdot 2\text{H}_2\text{O}$ is described.

Amirthalingam & Padmanabhan (1958) first studied the structure of $\text{Li}(\text{CH}_3\text{COO}) \cdot 2\text{H}_2\text{O}$ and fixed the space group as $Cmm2$. Clark (1964) however, after a calculation of the various bond lengths, drew attention to certain inconsistencies, and Galigné, Mouvet & Falgueirettes (1970), after a redetermination of the structure, concluded that the space group is $Cmmm$ rather than $Cmm2$ and further that the Li coordination is four-fold and not sixfold. The results of a proton-magnetic-resonance study in our laboratory by Padmanabhan & Srinivasan (1972) confirmed the results of Galigné *et al.* (1970) and indicated more probable locations for the water protons. It was therefore thought worth

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while to look at the structure of this crystal from the point of view of the quadrupolar interaction at the Li sites.

According to Galigné *et al.* (1970), $\text{Li}(\text{CH}_3\text{COO}) \cdot 2\text{H}_2\text{O}$ crystals are orthorhombic with $Z=4$. Two mirror symmetry elements, one in the ac plane and a second in the bc plane, pass through the Li sites, thus fixing the directions of the principal components of the e.f.g. tensor along the three crystallographic axes. The four Li ions in the unit cell are identical from the point of view of e.f.g. because of the mirror in the ab plane and the screw axis along a . So the structure predicts a spectrum characteristic of a single nucleus in each of the crystallographic planes: a central signal and a pair of satellites. Our n.m.r. study confirms this prediction.

Experimental

Single crystals of sufficient size ($3 \times 2 \times 1.5$ cm) were grown by slow evaporation of a saturated solution of AnalaR grade lithium acetate in distilled water, over calcium chloride in a desiccator. A Robinson oscillator working at 8.7 MHz was used with a 6 inch electromagnet. A magnetic field sweep calibrated by the ^7Li signal in