

$$P_{88}^{12} = (673 - 5208C + 13398C^2 - 14168C^3 + 5313C^4)/2048.$$

$$P_{12,0}^{12} = (7 \times 13 \times 17 \times 19 \times 23)^{1/2}/2048.$$

$$P_{12,4}^{12} = 3(11 \times 17 \times 19 \times 23)^{1/2}/4096.$$

$$P_{12,8}^{12} = (21 \times 22 \times 23)^{1/2}/4096.$$

$$P_{12,12}^{12} = 1/4096.$$

The single terms $S_{\lambda m}^l$ not equal to zero are the following:

$$S_{21}^3 = -i/\sqrt{2}, \quad S_{21}^7 = -i\sqrt{39}/12,$$

$$S_{61}^7 = -i\sqrt{33}/12, \quad S_{21}^9 = -0.43301i/\sqrt{2},$$

$$S_{61}^9 = 0.90139i/\sqrt{2},$$

$$S_{01}^4 = (7/12)^{1/2}, \quad S_{41}^4 = (5/24)^{1/2},$$

$$S_{01}^6 = 1/(2\sqrt{2}), \quad S_{41}^6 = -(7)^{1/2}/4,$$

$$S_{01}^8 = (33)^{1/2}/8, \quad S_{41}^8 = (7/6)^{1/2}/4,$$

$$S_{81}^8 = (65/6)^{1/2}/8,$$

$$S_{01}^{10} = (65/6)^{1/2}/8, \quad S_{41}^{10} = -(11)^{1/2}/8,$$

$$S_{81}^{10} = -(11 \times 17/3)^{1/2}/16,$$

$$S_{01}^{12} = 0.69550266, \quad S_{41}^{12} = 0.22212032,$$

$$S_{81}^{12} = 0.24639103, \quad S_{12,1}^{12} = 0.3848273,$$

$$S_{42}^{12} = 4(5 \times 29/66)^{1/2}/15,$$

$$S_{82}^{12} = -(43 \times 449/66)^{1/2}/30,$$

$$S_{12,2}^{12} = (7 \times 53/22)^{1/2}/30.$$

If we want to carry out a ν angle rotation around a simple crystallographic axis, the corresponding Euler angles are obtained with the following formulae:

$$R(\nu)[001]: \beta = 0, \quad \alpha + \gamma = \nu,$$

$$R(\nu)[110]: \alpha = 225^\circ, \quad \beta = \nu, \quad \gamma = 135^\circ,$$

$$\text{or } \alpha = 45^\circ, \quad \beta = -\nu, \quad \gamma = -45^\circ,$$

$$R(\nu)[111]: \alpha = -\arccos \left[\frac{1 - \cos \nu + \sqrt{3} \sin \nu}{2\sqrt{(2 - \cos^2 \nu - \cos \nu)}} \right],$$

$$\beta = \arccos \left[\frac{1 + 2 \cos \nu}{3} \right],$$

$$\gamma = \alpha + \frac{\pi}{2}.$$

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On the Polymorphism of Barbituric Acid Derivatives

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Abstract

The barbituric acid derivative 5-ethyl-5-isopentyl-barbituric acid (known as amobarbital or Amytal) has

two polymorphic forms in which the hydrogen-bond systems are identical but the space group is different. Another derivative, 5,5-diethylbarbituric acid (known as barbital or Veronal), has three polymorphs with

different hydrogen-bond systems and different space groups. The present study tries to account for the different stabilities in the two cases.

1. Introduction

The pharmacologically active 5,5-dialkylbarbituric acids have molecular structures (Fig. 1) which have considerable hydrogen-bonding capability due to the presence of three O atoms attached to the ring. The most important molecular interactions in this case are N—H...O=C bonds. The different frameworks obtained with these hydrogen bonds are one-dimensional (ribbons) or two-dimensional (sheets) and in these cases the C(5) non-polar substituents project outwards from the framework.

Moreover, these drugs often have several polymorphic forms. These different crystalline structures have different melting points which can serve as measures of the stabilities of the crystals.

The aim of this work is to study the relative stabilities of different polymorphs of one molecule considering also the stabilization or destabilization due to the geometry of the molecule.

In the present work we have studied two important barbiturates: barbital or 5,5-diethylbarbituric acid, also known as Veronal (Craven & Vizzini, 1969, 1971), and amobarbital or 5-ethyl-5-isopentylbarbituric acid (Amytal) (Craven, Vizzini & Rodrigues, 1969).

The former, barbital, exists as three different polymorphs and three different frameworks of hydrogen bonding are observed. In amobarbital the hydrogen-bonding framework is identical in the two polymorphs but the crystalline arrangement of the ribbons is different in the two crystals.

2. Method

The method of computation of the crystal-lattice energy has been described (Caillaet & Claverie, 1974, 1975; Caillaet, Claverie & Pullman, 1976, 1977, 1978*a,b*).

We only recall the main features of the method; the interaction energy is considered as the sum of three long-range contributions (electrostatic, polarization

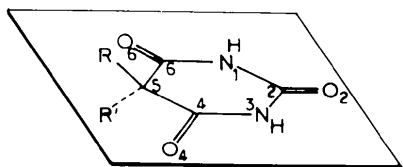


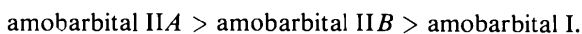
Fig. 1. Molecule of 5,5-dialkylbarbituric acid. R = ethyl, R' = ethyl: barbital; R = ethyl, R' = isoamyl: amobarbital.

and dispersion) and a short-range repulsive contribution. The usual simplified formulae (dipole approximation) are used instead of the short-range ones at large intermolecular distances. The different contributions to the total energy are obtained as a sum of atom-atom terms except the polarization energy which is not pair-wise additive; this last energy is obtained as the sum of the polarization energies of each molecule polarized by the electric field due to the other molecules.

The net atomic charges used in these calculations are obtained by the CNDO method with the Pople & Segal (1965, 1966) parametrization for the repulsion integrals. This method of calculation gives also the total energy of the molecule; the results obtained for amobarbital are in Table 1(*a*). According to this parametrization, the most stable molecular geometry is that of amobarbital I and the least stable that of amobarbital IIB:



We have tried to take into account the slight differences of geometry of the molecules. For this purpose, we have used Ohno's parametrization (Sichel & Whitehead, 1967, 1968) for the repulsion integrals. In this case, the most stable molecule is amobarbital IIA and the order of the stabilities is different from the preceding one; we obtain



With both parametrizations the energy differences are rather large. It is, nevertheless, encouraging that with the second parametrization (which aims at a better reproduction of bonding energies) the configurations IIA and IIB are found to be more stable than configuration I, in agreement with the greater experimental stability of amobarbital II (as inferred from its higher melting point). However, in the present work, we shall discuss the relative stabilities by considering essentially the lattice energies, without taking into account the internal energies of the molecules, since their differences appear unrealistically large in the framework of the methods used so far.

Table 1. Total energies of the different geometries of amobarbital

	Total energy (a.u.)	Energy differences: molecule - amobarbital I (a.u.)	Energy differences (kJ mol ⁻¹)
(a) Parametrization of Pople & Segal			
Amobarbital I	-169.990	0	0
IIA	-169.459	+0.531	+1421.000
IIB	-169.242	+0.748	+1964.708
(b) Parametrization of Ohno			
Amobarbital I	-127.129	0	0
IIA	-127.678	-0.549	-1442.011
IIB	-127.289	-0.160	-420.258

3. Results and discussion

(A) Amobarbital

Amobarbital exists as two polymorphs with the same hydrogen-bonded structural unit (a double ribbon), but the crystal structure differs in the way in which the double ribbons are assembled. In amobarbital I the ribbons are parallel and in polymorph II they are cross-linked. The crystal data for the polymorphs are given in Table 2.

The dimensions of the unit cells are very similar, but the space groups are different and in crystal II a remarkable feature is observed, namely one half of the amobarbital molecules exhibit one geometry (denoted IIA) and the other half a *different* geometry (denoted IIB). Both geometries IIA and IIB are different from the geometry observed in amobarbital I, form IIB being the closer to form I.

As in the previous papers, we proceed by calculating the minimum energy of the crystals with different structures. First, we have calculated the minimum energy for the two polymorphs. In amobarbital I, there is a minimum at $-115.14 \text{ kJ mol}^{-1}$; for amobarbital II the minimum value obtained is $-279.52 \text{ kJ mol}^{-1}$ for the complex amobarbital IIA-amobarbital IIB (*i.e.* $-279.52/2 = -139.76 \text{ kJ mol}^{-1}$ for one molecule of the compound). These results are collected in Table 3. Since we are considering the same molecule in two different crystals, the melting points may serve as a measure of the stabilities of the crystals studied. It can be seen that amobarbital II has a melting point higher than that of amobarbital I; similarly, the crystal energy of amobarbital II is higher (in absolute values) than that of amobarbital I.

Table 2. *Crystal data for amobarbital*

Polymorph I	
m.p. = 427–429 K	$a = 21.480 \text{ \AA}$
Crystal system: monoclinic	$b = 11.590$
Space group: $C2/c$	$c = 10.370$
$Z = 8$	$\beta = 97.07^\circ$
Polymorph II	
m.p. = 433–435 K	$a = 10.281 \text{ \AA}$
Crystal system: monoclinic	$b = 22.601$
Space group: $P2_1/c$	$c = 11.679$
$Z = 8$	$\beta = 109.1^\circ$

Table 3. *Lattice energies of the polymorphic crystals of amobarbital*

Crystal	Crystalline structure	Lattice energy (kJ mol^{-1})
Amobarbital I m.p. 427–429 K	Experimental $C2/c$ $Z = 8$	-115.14
Amobarbital II m.p. 433–435 K	Experimental $P2_1/c$ $Z = 2 \times 4$	-139.76 ($-279.52/2 = -139.76$)

To verify that the geometry of the molecule in each crystal is the best one, we have introduced the geometry of amobarbital IIA in the unit cell of amobarbital I and conversely the geometry of amobarbital I in the unit cell of amobarbital II. The results are given in Table 4.

In the first case, we use only one of the different molecules (*i.e.* amobarbital IIA) and as before we translate the molecule to obtain the correct position in the crystal structure of amobarbital I.

In the other case the crystalline cell is obtained by translating the molecule of amobarbital I in the two different molecular positions in the crystal of amobarbital II.

The results have been referred to one molecule of the compound in order to make the comparison easier. We observe that the experimental crystals are more stable than the hypothetical ones.

(B) Barbital

5,5-Diethylbarbituric acid exists in many polymorphic forms, three of which have been studied in detail. They are obtained from the same ethanol solution by slow evaporation. Their different characteristics are given in Table 5.

In polymorph II, the molecule possesses a symmetry axis passing through C(2) and C(5), which is also a symmetry axis of the space group. Thus, the number of molecules is reduced to $Z = 4$ instead of $Z = 8$.

Table 4. *Lattice energies of hypothetical crystals built with different molecular geometries*

Geometry of the molecule	Crystalline structure	Lattice energy (kJ mol^{-1})
Amobarbital IIA	Amobarbital I $C2/c$ $Z = 8$	-110.07
Amobarbital I	Amobarbital II $Z = 2 \times 4$	-73.27 ($-146.54/2 = -73.27$)

Table 5. *Crystal data for barbital*

Polymorph I	
m.p. 463 K	$a = 26.921 \text{ \AA}$
Crystal system: hexagonal	$b = c = 6.828$
Space group: $R\bar{3}$	
$Z = 8$	
Polymorph II	
m.p. 456 K	$a = 7.120 \text{ \AA}$
Crystal system: monoclinic	$b = 14.162$
Space group: $C2/c$	$c = 9.810$
$Z = 4$	$\beta = 89.25^\circ$
Polymorph IV	
m.p. 449 K	$a = 12.585 \text{ \AA}$
Crystal system: monoclinic	$b = 22.083$
Space group: $P2_1$	$c = 6.788$
$Z = 8$	$\beta = 90.90^\circ$

In this case, the three $\text{NH}\cdots\text{O}=\text{C}$ hydrogen-bonded frameworks are different; in barbital I and barbital II there are ribbon-type frameworks, with different crystal structures, and in barbital IV the framework is of the sheet type with four different molecules. We have calculated the different minimum energies for these three crystals. The results are given in Table 6; it can be seen that the stabilities follow the same order as the melting points. If we compare the crystals of barbital II and barbital IV we observe that only one oxygen atom, O(4), is linked by a hydrogen bond in barbital IV, whereas two oxygen atoms, O(4) and O(6), are hydrogen-bonded in barbital II. The symmetry is more important in barbital II for both the crystal lattice and the molecule itself, and the melting point is higher, indicating a greater stability (with respect to barbital IV).

Considering now barbital I and barbital II, we observe that the number of hydrogen bonds (per molecule) is the same for barbital I and barbital II; thus, the higher interaction energy of the former should be attributed to a better 'gearing' of the hydrogen-bonded complexes, resulting in higher values of the interaction energies other than those associated with hydrogen bonding.

Indeed, in barbital I, the crystal type (hexagonal) possesses higher symmetry. In this case, the molecules linked by hydrogen bonds form complexes which are arranged to form a network with the hydrogen-bonded complexes 'gearing' one with the other.

This may explain the higher stability of the crystal of barbital I.

In barbital IV, when we consider the four different molecules, their positions in the crystal resemble those of the four molecules of barbital II obtained by symmetry operations. It is possible to imagine a transition from barbital IV to barbital II: the procedure of crystallization may begin with the coupling of four molecules of barbital into two pairs followed by a slight geometrical deformation so as to obtain symmetrical molecules with equivalent atoms; it is possible after this intramolecular transformation that the different molecules move to change the space group and form a new, more symmetrical crystal of barbital II with a greater stability. The $\text{NH}\cdots\text{C}=\text{O}$ bond framework is more stable in barbital II because it involves more hydrogen bonds than that in the crystal of barbital IV.

Table 6. *Lattice energies of the polymorphic crystals of barbital*

	Space group	Minimum energy (kJ mol ⁻¹ complex)	m.p. (K)
Barbital I	<i>R</i> 3, <i>Z</i> = 8	-105.68	463
Barbital II	<i>C</i> 2/ <i>c</i> , <i>Z</i> = 4	-95.13	456
Barbital IV	<i>P</i> 2 ₁ , <i>Z</i> = 8 (4 × 2)	-87.67 -350.68/4 = -87.67	449

Conclusion

The problem of the different stabilities of the polymorphs of barbituric acid derivatives is difficult to solve completely. Direct comparison of the melting point, as a measure of the stability of the crystal, with the lattice energy such as we have calculated is very delicate because we do not take into account the geometrical peculiarities of the molecules in the crystal; it would be necessary to calculate the internal energy of the molecule in order to introduce the variation of the energy due to a variation of geometry; but, the methods of calculation are not precise enough to take account of slight variations of geometry. The agreement that we observe between the experimental ordering of the melting points and our calculated lattice energies would suggest that the differences of internal energy between the various molecular geometries are small enough not to modify the relative ordering of the lattice energies. It would obviously be better to calculate realistic values of these internal energy differences in order to confirm this hypothesis.

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