Ab initio structure determination of the form II of phenobarbital by powder X-ray diffraction.

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Phenobarbital (C\textsubscript{12}H\textsubscript{12}O\textsubscript{3}N\textsubscript{2}, also called 5-ethyl-5-phenylbarbituric acid or phenobar-bitone), is a derivative of uracil and is physiologically used as a sedative hypnotic agent. It exhibits a high degree of polymorphism with around twelve anhydrous modifications (Mesley et al., 1968) and, at least, a monohydrate one. The reason of such number of polymorphs is the possibility of a variety of intermolecular H-bonding schemes in the barbituric acid family (Craven et al., 1969; Craven & Vizzini, 1971). Williams (1973) has reported cell parameters and space groups of four polymorphs and he solved also the structure of the monohydrate form (called form XIII). The structure of an anhydrous form (form III), obtained from X-ray diffraction by a single crystal, has been also published (Williams, 1974). To our knowledge, since this date, any structural resolution of other forms of this compound has been done.

The aim of this experiment is to determine the crystal structure of the commercially available phenobarbital (Aldrich Chemical Company, purity rate : 98%) which is, according to Mesley et al. (1968), the form II. Taking into account possible changes of the form by dissolving and recrystallisation to obtain single crystals, the X-ray diffraction experiment was done with a powder sample of commercial chemical. The ab initio structure determination was performed with a simulated-annealing method in order to get a starting model, followed by Rietveld refinements using soft constraints on bond lengths and bond angles.

The X-ray diffraction pattern was recorded at room temperature with the B2 diffractometer located on the synchrotron radiation source of HASYLAB (DESY, Hamburg, Germany). The wavelength was 1.119862 Å and the recorded 2\(\theta\) range ran from 4.5 to 40\(^\circ\) with a step width of 0.003\(^\circ\). A scintillation counter with a Ge (111) analysing crystal was used in order to get high resolution. Powder was introduced in a Lindemann glass capillary of 1 mm in diameter. To determine the cell, the position of the Bragg peaks between 4.5 to 18\(^\circ\), 20, was extracted with WINPLOTR (Roisnel and Rodriguez-Carvajal, 2002). The 20 most intense reflections were introduced in TREOR (Werner et al., 1985) and a triclinic cell was found with a volume of 1706.4 Å\(^3\). With the usual rule of 18 Å\(^3\) per non-H atom, this volume corresponds to 6 molecules on the unit cell. To refine these parameters and the parameters of the width of the reflections, the Profile Matching option of FULLPROF (Rodriguez-Carvajal, 2001) was used and some reflections with a low intensity were not indexed. These reflections are due to an impurity contained in the commercial compound. This impurity has not been identified.

To get a starting structural model, Monte-Carlo simulated annealing calculations were performed with FOX (Favre-Nicolin and Cerny, 2002). Calculations have been started with the space group P –1 and 3 molecules per asymmetric unit. The molecule without H atoms introduced in FOX was the mean molecule obtained with those of the two forms where the structure is solved. During the simulated annealing simulations, the molecules can translate and rotate randomly, some torsion angles can also change. After about 20 millions trials, a solution for a starting structural model seems to be obtained with the space group P –1.
The H atoms are introduced geometrically with DEBVIN (Brückner and Immirzi, 1997). The next step is the Rietveld refinements with the program FULLPROF. Attempts have first been done with rigid bodies, but these refinements always failed. Then reduced coordinates of all non-H atoms have been fitted with soft restraints on all bond lengths and bond angles of the molecules. During these refinements, the H atoms are correctly replaced with DEBVIN. Crystallographic data are as follow: \( a = 10.7376 \ (1), \ \ b = 23.5444 \ (1), \ \ c = 6.7875 \ (1) \ \text{Å}, \ \alpha = 90.982 \ (1), \ \beta = 94.479 \ (1), \ \gamma = 88.128 \ (1) \ ^\circ, \ \ V = 1709.6 \ (1) \ \text{Å}^3 \). The final reliability factors are: \( R_p = 0.142, \ R_{wp} = 0.167, \ R_{exp} = 0.131, \chi^2 = 1.61, \ R_u = 0.0341 \) and \( R_F = 0.0472 \).

The structure of the form II of phenobarbital can be described as follow: the first molecule of the asymmetric unit and its equivalent are located approximately in the \((a, c)\) plane at \( y = 0.5 \); the second molecule and its equivalent are also located in the \((a, c)\) plane, but at \( y = 0.0 \). The third molecule is placed between the two first molecules (Figure 1). The crystalline cohesion is assumed by H bonds of N–H···O type. For the 3 molecules, each N atom is a donor atom. For the first and the second molecules, the H bonds connect a N atom to an O atom of an equivalent molecule. They form chains in the \((a+c)\) direction at \( y = 0.0 \) for the second molecule and at \( y = 0.5 \) for the first molecule. The N atoms of the third molecule are connected to the O atoms Oa4 and Oa6 of the first molecule. As a consequence, these two atoms are acceptor twice.

\[\text{Figure 1:} \ \text{Projection in the} \ (a, b) \ \text{plane of the unit cell of form II of phenobarbital. Black dashed lines show the H-bonding network between the 1}^{\text{st}} \ \text{molecule of the unit cell; blue ones are for the 2}^{\text{nd}} \ \text{molecule and red ones are for the H bonds between the 3}^{\text{rd}} \ \text{and 1}^{\text{st}} \ \text{molecules of the asymmetric unit.}\]

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\text{References:}

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