Keto–Enol Tautomerism

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# The Thermodynamically Stable Form of Solid Barbituric Acid: The Enol Tautomer**

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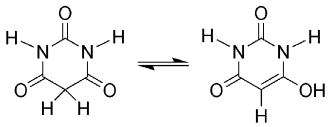
Barbituric acid, which has been known since 1863,[1] is drawn in textbooks always as the keto tautomeric form **1** (Scheme 1). Indeed, this is the most stable form in the gas phase[2] and in solution.[3] Also in the solid state, the keto tautomer is observed in the metastable phase I,[4] the commercial phase II,[4b] and a high-temperature phase III,[5] as well as in its dihydrates.[6] In contrast, we now observe that the recently discovered tautomeric polymorph IV[7] consists of molecules in the enol form **2**, and that this polymorph is actually the thermodynamically stable phase at ambient conditions. The preference for the enol form in the solid state is explained by the formation of an additional strong hydrogen bond in the crystal, leading to a more favorable lattice energy.



**1** **2**

***Scheme 1.*** Barbituric acid in the keto (**1**) and enol (**2**) tautomeric forms.

Polymorph IV is obtained from phase II by grinding or milling. Solid-state NMR (SSNMR), IR, and Raman experiments revealed this to be a tautomeric polymorph, which does not consist of the keto tautomer **1**, but of one of the enol forms.[7a] The spectroscopic data suggested the trienol tautomer, but other enol tautomers could not be ruled out.[8]

All attempts to obtain single crystals of phase IV by recrystallization failed, and dehydration of the dihydrate yielded only phase II.[5c] The grinding or milling processes resulted in powders of poor crystallinity. However, it was possible to index the laboratory X-ray powder data and to solve the crystal structure by simulated annealing,[9] while refinement was carried out by the Rietveld method from synchrotron data (Figure 1).[10] The bond lengths in the OCN framework revealed phase IV to consist of molecules in the enol form **2**.

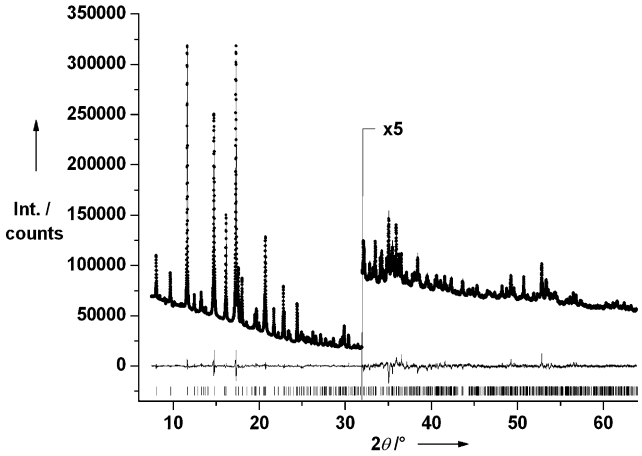



***Figure 1.*** Rietveld refinement from synchrotron X-ray powder data ($\lambda = 1.0012$ Å). Experimental intensities (dots), calculated intensities (solid line), difference diagram (below). Tick marks (bottom) indicate positions of possible reflections.

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Reliable positions of the hydrogen atoms were determined by Rietveld refinement on neutron powder data.[11] All refinements converged to the enol tautomer **2** (Figure 2). In an additional Rietveld run, the occupancies of all possible

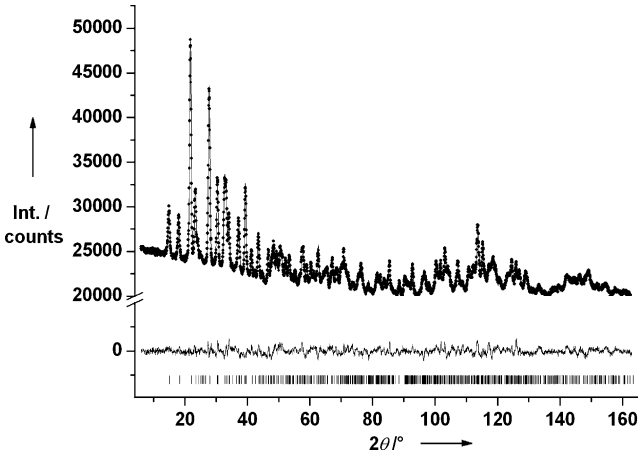


***Figure 2.*** Rietveld refinement from neutron powder data ($\lambda = 1.8857$ Å).

hydrogen positions were refined as well. For the H atoms of the enol form **2**, the occupancies were close to 1, whereas all other possible hydrogen positions refined to occupancies close to 0, thereby confirming the enol form.

The crystal structure is made up of planar molecules forming zigzag chains through two N–H···O hydrogen bonds. The presence of the hydroxy group allows the interconnection of the chains through two resonance-assisted[12] O–H···O hydrogen bonds, leading to a three-dimensional hydrogen-bonding network (Figure 3).

This crystal structure is in agreement with $^{1}$H-$^{1}$H and $^{1}$H-$^{13}$C proximities obtained from $^{1}$H DQ MAS and $^{1}$H-$^{13}$C off-resonance CP (LGCP) FSLG-HETCOR SS NMR experiments (see the Supporting Information). These techniques also allowed a complete $^{1}$H and $^{13}$C peak assignment, which attributes the short resonance-assisted O–H···O hydrogen bond to the $^{1}$H signal at $\delta = 15.0$ ppm thus to a strong interaction.[13]

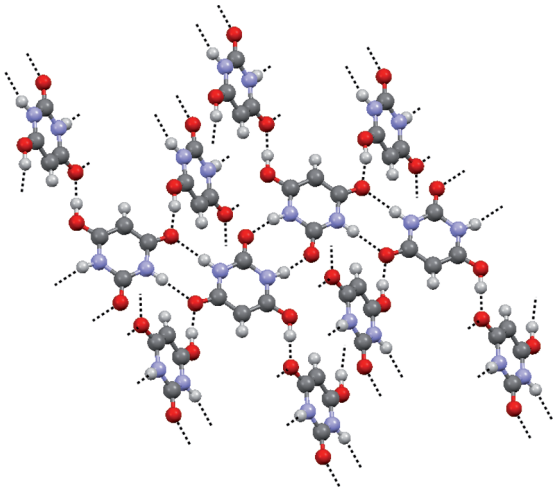

***Figure 3.*** Hydrogen-bond pattern in polymorph IV with molecules in the enol tautomeric form.

Furthermore, a careful analysis of $^{15}$N LGCP build-up curves on an $^{15}$N natural-abundance sample provided a N–H distance of (1.04 ± 0.02) Å for both $^{15}$N signals ($\delta = 110.7$ and 122.6 ppm). These SS NMR and also IR data (see the Supporting Information) are in agreement with the enol structure **2** revealed by neutron powder data.

According to the differential scanning calorimetry (DSC), phase IV converts at 172 °C into phase II in an endothermic transformation (see the Supporting Information). This indicates that the two phases are enantiotropically related and phase IV is the stable polymorph at room temperature. On cooling, the reverse transition is not observed, because phase II is kinetically stable.

The thermodynamic stability of phase IV at room temperature was confirmed by slurry experiments, i.e. by stirring a suspension of barbituric acid in a weakly dissolving solvent (e.g. ethanol or butanone) for one week. In the presence of seed crystals of phase IV, a complete conversion of phase II (or phase I) into phase IV was observed. In the absence of seed crystals, phase II is kinetically stable and no conversion to phase IV occurs.[5c] Clearly, the nucleation of phase IV is controlled kinetically, and seeding seems to play an important role. This may explain why polymorph IV had not been observed before.

Energies of all possible tautomers of barbituric acid in the gas phase were calculated by ab initio methods at the CCSD-T/cc-pvtz level. The keto tautomer **1** has the lowest energy, followed by the enol tautomer **2** with an energy difference of 53.7 kJ mol$^{-1}$. All other tautomers are less stable by at least 90 kJ mol$^{-1}$.

In the solid state, the energy difference between tautomers **1** and **2** is more than compensated by the lattice energy. According to periodic-boundary dispersion-corrected DFT calculations,[14] the lattice energy (intermolecular energy) of phase IV is more favorable than that of phase II by 58.5 kJ mol$^{-1}$. Apparently the extraordinary lattice energy of phase IV is caused by the additional strong hydrogen bonds.

All the experimental and the computational evidence are in agreement with the presence of the enol form **2** in the thermodynamically stable form at room temperature. Correspondingly, in textbooks of organic chemistry the following sentences should be added: "In the solid state, barbituric acid can exist either in the keto form or in the enol form (depending on the crystal structure). At room temperature, the enol form is thermodynamically preferred, because of the higher number of hydrogen bonds in the crystal".

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[8] In an earlier article, the identification of the trienol tautomer was mainly based on $^{15}$N NQS (nonquaternary suppression) NMR data. However, upon repeating the measurements using different spectral editing techniques (two types of NQS and the dipolar dephasing pulse sequence all from the standard Bruker library with several dephasing periods), we obtained puzzling results. This prompted us to perform new NMR experiments and extract the N–H distances from heteronuclear dipolar coupling (see the Supporting Information).

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[11] Barbituric acid, phase IV. Colorless powder, $C_4H_4N_2O_3$, $M_r = 128.09\ g\,mol^{-1}$; a) Rietveld refinement from synchrotron powder data, recorded at SLS (PSI, Villigen, Switzerland), transmission mode, sample in capillary, $\lambda = 1.0012$ Å, $2\theta = 6.49$–$63.86°$, room temperature. Monoclinic, space group $P2_1/n$ (no. 14), $Z = 4$. Lattice parameters $a = 11.87614(6)$ Å, $b = 8.91533(4)$ Å, $c = 4.83457(3)$ Å, $\beta = 95.0854(4)°$. $V = 509.868(5)$ Å$^3$, $\rho_{calc} = 1.669\ g\,cm^{-3}$. $R_{exp} = 0.433/1.889$, $R_{wp} = 1.716/7.484$, $R_p = 1.192/8.675$ (without/with background correction), GoF = 3.968. Restraints for the H atoms, overall planar restraint; b) Rietveld refinement from neutron powder data recorded at HRPT (PSI, Villigen, Switzerland), $\lambda = 1.8857$ Å, $2\theta = 6.0°$ to $163.0°$, room temperature. $R_{exp} = 0.643/5.267$, $R_{wp} = 1.327/10.871$, $R_p = 1.033/10.265$, GoF = 2.064. No restraints. CCDC 794120 and 794121 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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