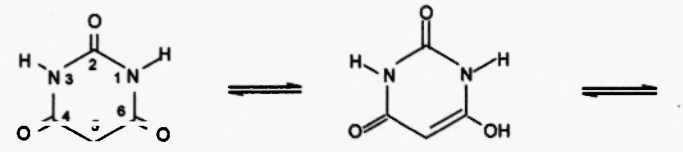
STABLE ENOL FORM OF BARBITURIC ACID

Jacek Lubczak, Ewaryst Mendyk*
Faculty of Chemistry, Rzeszów University of Technology, 6 Powstanców Warszawy Ave., 35-959 Rzeszów, Poland
*Faculty of Chemistry, Maria Curie-Skłodowska University, 2 Marii Curie- Skłodowska Sq, 20-031 Lublin, Poland
E-mail : jml@prz.rzeszow.pl

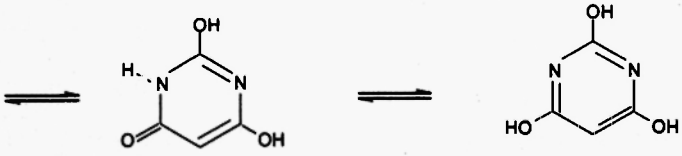
Abstract: Enol form of barbituric acid (1,3-diazine-2,4,6-triol) is formed in presence of ethylene or propylene oxides in DMF at 40 and 60°C, respectivelу, while its formation in DMF occurs in more drastic conditions. The trienol was identified and studied in water and dimethylformamide solutions with UV-VIS, IR, ^{1}H i ^{13}C-NMR, including 2-D HMBC and HMQC techniques.

Introduction

Barbituric acid (BA, 1H,3H,5H-diazine-2,4,6-trione) is non-carboxylic acid. The acidic character results from the presence of nitrogen-attached hydrogen as well as C5-H, both neighboring to carbonyl functions. These groups induce acidity of N-H and C5-H. Theoretically, four symmetry-independent tautomeric forms of BA can be considered:



(I) (II)



(III) (IV)

In the solid state BA is known as triketone form I. This has been confirmed by X-ray crystallography [1, 2] and ^{14}NQR [3]. It has also been found on the basis of ^{13}C NMR studies that BA I dominates in DMSO [4, 5]. In protophilic solvents however, the equilibrium between I and II was observed [6-9]. The keto-enol equilibrium can be established slowly, depending on the basicity of solvent [9]. Numerous data are available in literature on the keto-enol equilibria of BA depending on kind of solvent and its acid-base properties [4, 5, 8-13]. From theoretical considerations [14, 15] and spectral data [16, 17] it has been generally accepted that enol forms of BA are present only in solutions and not isolated to date. Here we report on formation of enol form of BA IV in DMF isolation of solid tautomer and some additional studies of BA in aqueous solutions.

Experimental

Formation of trienol of BA

6.4 g (0.05 mola) of BA (pure, BDH Laboratory Supplies Poole, England), 50 cm^3 DMF, 5.8 g of propylene oxide (PO; pure, Fluka, Schwitzeland) or 4.4 g ethylene oxide (EO; pure, Fluka, Schwitzeland) (0.1 mol) were placed in high-pressure 100 cm^3 reactor. The temperature of the reactor was then gradually increased to 60 or 40° C, respectively. The solution became turbid 15 to 30 minutes of heating followed by precipitation of yellow solid. The same result was observed in presence of excess of oxirane (2-10 moles per mole of BA) Formation of yellow precipitate was observed also in pure DMF in absence of alkylene oxides at 100° C after 4-5 hours (Table 1).

Table-1 : Conversion of barbituric acid in presence of oxiranes in DMF

Oxirane	Reaction conditions			Remarks
	Molar Ratio BA:oxirane	Temperature [^{0}C]	Time [h]	
PO	1:2-1:10	60	8	After 15 min solution becomes turbid and yellow solid start to precipitate
EO	1:2-1:4	40	4	After 30 min solution becomes turbid and yellow solid start to precipitate
-	-	100	1 +4 +3	No precipitation Precipitation starts Copious amount of precipitate is noted

Analyses

Acidic number (AN) of BA and its enol form were determined by titration with NaOH(aq). Elemental analyses were done with Carlo-Erba Analyzer EA 1108 for C, H, N. Molar mass of enol form by cryoscopic method in DMSO has been measurement. The ^{1}H and ^{13}C NMR spectral assignments have been done by standard ^{1}H COSY, HMQC, and HMBC spectra obtained with Bruker Avance 300 MHz instrument in DMSO-d_6. IR spectra in KBr pellets were recorded on PARAGON 1000 FT spectrophotometer (Perkin-Elmer). UV spectra were obtained with SPECORD (Carl Zeis, Jena) in 1 cm cell within the 50-14x10^3 cm^{-1} region vs water reference. Thermal decomposition of BA and enol IV BA was determined with Paulik-Paulik-Erdey (MOM, Hungary) derivatograph using 200 mg initial sample mass in aerobic conditions, 20-1000°C temperature range, within 100 min. recording.

Analytical data

1H,3H,5H-diazyno-2,4,6-trion - ***triketoform of barbituric acid (I)*** m.p. = 248^{0}C; AN [mg KOH/g], Calcd.: 440, Found: 438; Elemental analysis, - % Calcd.: C 37.50; H 3.13; N 21.88; % Found: C 37,45; H 3,33; N 21,54;
IR [cm^{-1}], 3200, 3090 (NH),1724,1690 (C=O), 1420 (CH_2), 1250, 1174 (-C-O-), 806 (CH_2) 637 (C=O); ^{1}H NMR (d_6-DMSO), δ [ppm] 11.0 (2H, s, NH), 3,4 (2H, s, CH_2); ^{13}C-NMR (d_6-DMSO), δ [ppm] 167.77 ($C_{4,6}$), 151,70 (C_2), 77,33 (C_5): UV-VIS [nm] 211, ε = 4500; 256, ε = 8000 (HN-C=O).

1,3-diazyne-2,4,6-triol - ***trienol form of barbituric acid (IV)*** - m.p. 280^{0}C; Molar mass: calc. 128 g/mol, found. 129.8 g/mol; AN [mg KOH/g], Found: 160; Elemental analysis - % Found: C 37,25; H 3,10; N 21,79; IR [cm^{-1}], 3000-3150 (OH)1624 (C=C, C=N), 1440 - 1400 (CH_2), ^{1}H NMR (d_6-DMSO), δ [ppm] 9.91 (3H, s, OH), 8.2 (H, s, CH=): ^{13}C NMR (d_6-DMSO), δ [ppm] 150.93 (C_1), 148.43 (C_5), 100. 24 (C_4, C_6); UV-VIS [nm] 417, ε = 11000 (C=N, n→π*,) 233, ε=7500 (C=C and C=N).

Results and Discussion

In attempted reaction of BA with oxiranes we expected formation of N-hydroxyalkyl derivatives, similarly as it was found for other azacycles like cyanuric acid [18, 19] or parabanic acid [20]. At the process performed in DMF at 40-60^{0}C the formation of yellow precipitate was noticed. Surprisingly, the elemental analysis of yellow solid was analogous to starting BA. Absence of resonances from methylene protons of the ^{1}H NMR spectrum of the product eventually indicated that oxiranes remained unreacted in the protocol applied here. Instead, two singlet resonances at 10.0 and 8.2 ppm of 3:1 integral intensity ratio were observed (Figure-1). The resonance at 10.0 ppm was quenched upon addition of D_2O. Thus the resonances at 10.0 and 8.2 ppm were attributed to hydroxylic and methine hydrogens, respectively. ^{13}C-NMR spectrum is composed of three resonances at 100.24; 150.93; and 148.43 ppm, which were assigned to C_4 (C_6) in IV, C_1, and C_5, respectively based on HMQC and HMBC experiments (Figure-1).

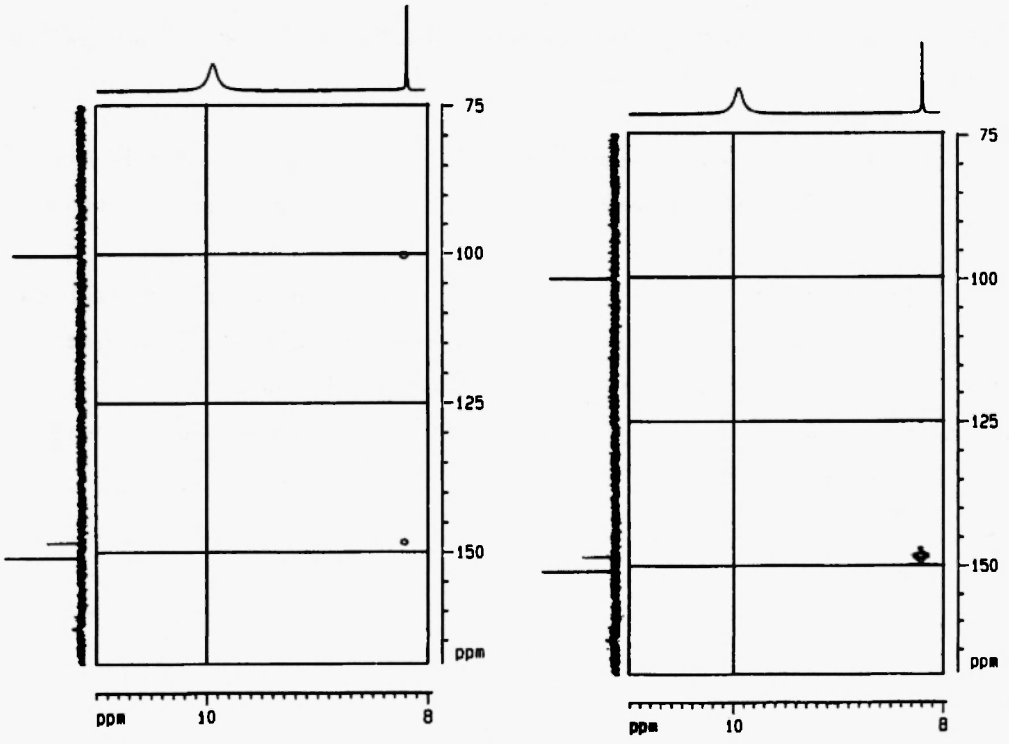


Figure-1 : 2-D ^{1}H- ^{13}C correlation spectra of enol form of BA; a) HMBC b) HMQC

IR spectrum of IV differs considerably from that of I. The ν(C=O) band at 1650 cm^{-1} and δ(NH) band at 1370-1340 cm^{-1} of I disappear, instead broad absorption from valence C=C and C=N and δ(OH) appear. The most characteristic features of the spectrum of IV are the absence of the bands from CH_2 centered at 810 cm^{-1} and deformation mode of C=O at 640 cm^{-1} in I. Instead new band at 1480 cm^{-1} attributed to ring stretching appears in the spectrum of IV. Acidic number of IV is much lower in comparison with that of I (see Analytical data).

UV-Vis spectrum of I is composed of two bands in UV region, attributed to n $\rightarrow\pi^*$ transitions centered at 211 and 256 nm (Figure-2a), while they are replaced with broad absorption centered at 233 nm in the spectrum of IV, which contains only one band at 408 nm attributed to $\pi\rightarrow\pi^*$ of coupled C=C i C=N chromophores (Figure-2b). Yellow IV slowly rearranges into colorless I within 10 days, which corroborates with UV-Vis spectral assignments (Figure-2c).

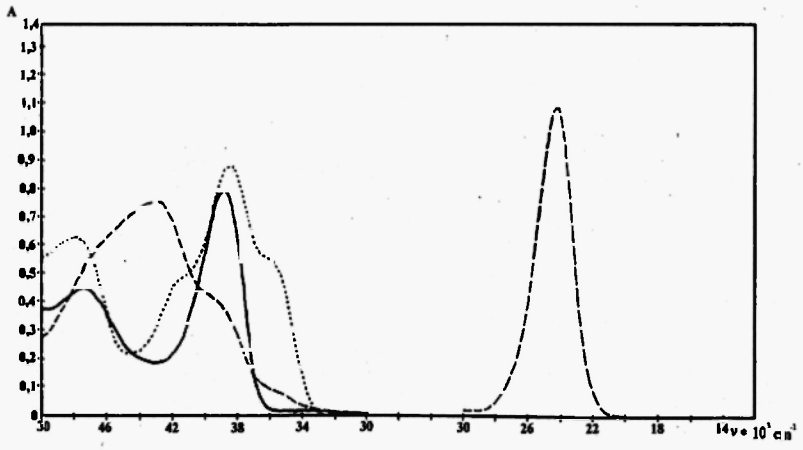
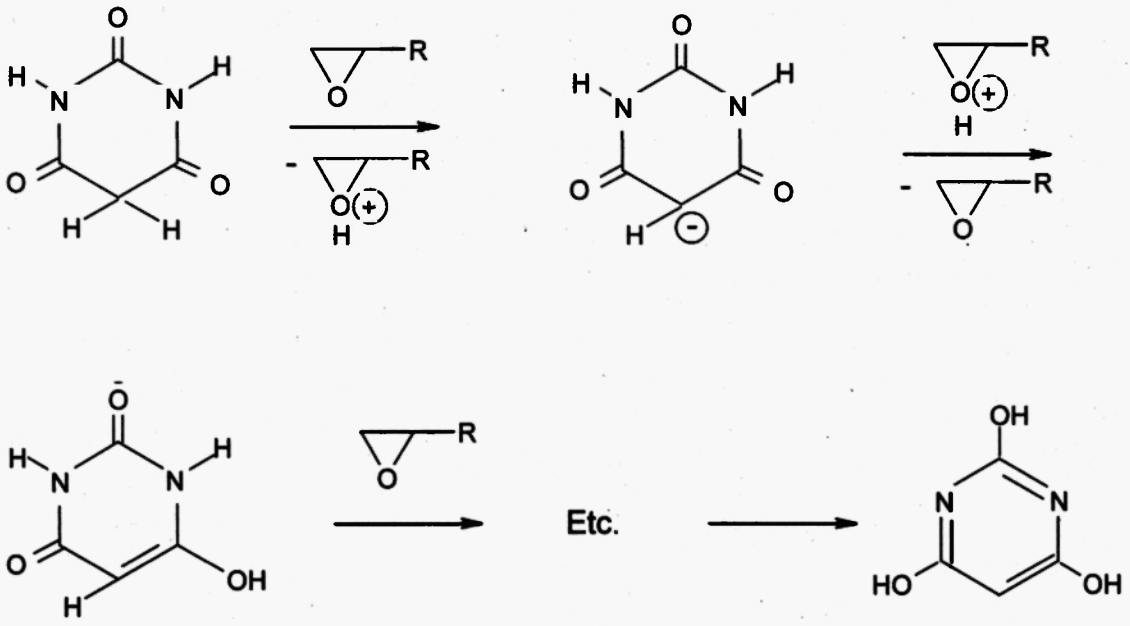


Figure-2 : UV-VIS spectrum of a) keto form (-), b) enol form (---) barbituric acid immediately after solving in water c) enol form after 5 days from moment solving in water (· · ·)

Comparison of thermogravimetrogram pattern (Figure-3) and melting points indicate that enol IV melts at higher temperature (280^{0}C) than I (248^{0}C). DTG analysis of IV indicates that simultaneous decomposition takes place, while I is more stable (decomposition starts at 380^{0}C)

Heating of BA I in DMF at 100^{0}C results in formation of IV within 4 hours. Thus, the enol form IV is thermodynamically stable in these conditions. However, the enolization is faster in presence of oxiranes and can be performed at lower temperatures. Catalytic role of oxiranes is consistent with our previous studies [22] on the reaction of other cyclic imides with oxiranes in which the crucial step of reaction was rebound of protons from acids by oxirane oxygen according to the scheme:



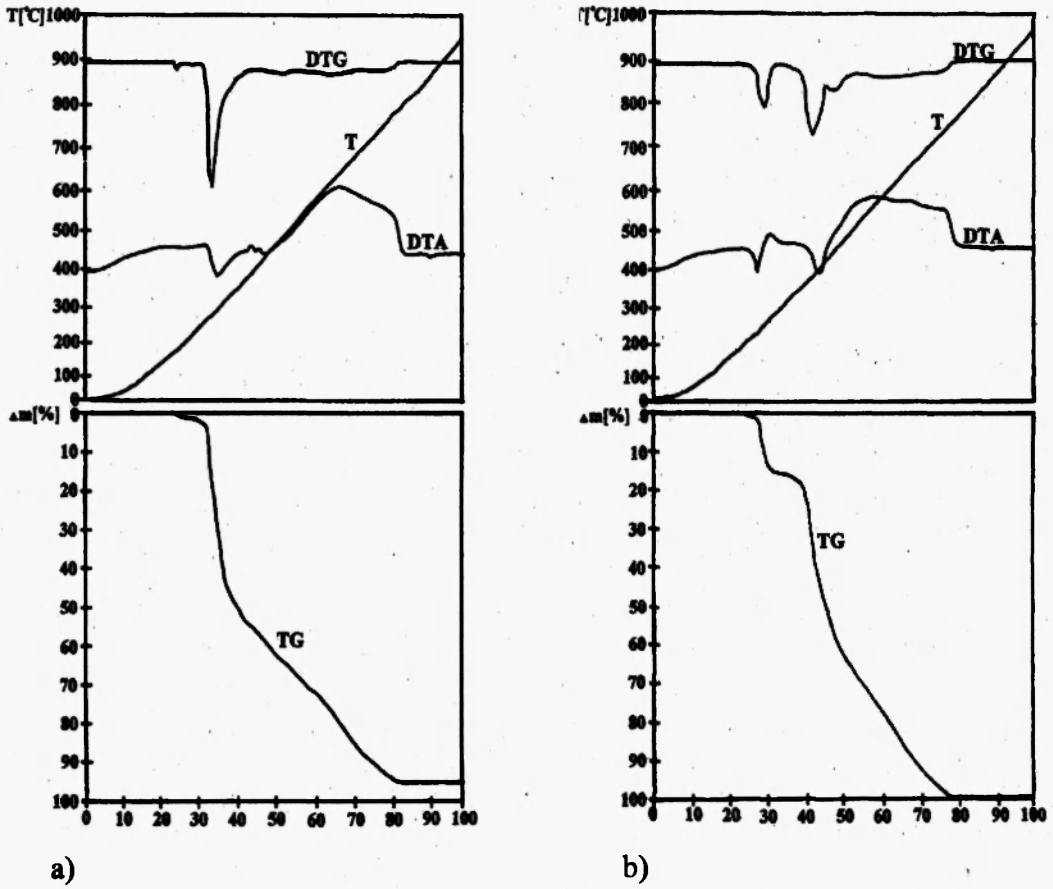


Figure-3 : Thermal analysis of BA: (a) keto form I; (b) enol form IV

References

1. G. Jeffrey, S. Ghose and J. Warwicker, *Acta Cryst.* **14,** 881 (1961).
2. W. Bolton, *Acta Cryst.* **16,** 166 (1963).
3. T. Maruizumi, Y. Hiyama and E. Niki, *Bull. Chem. Soc. Japan*, **53** 1443 (1980).
4. J. Okada, T. Esaki and Yakugaku Zasshi, **93** 1014 (1973).
5. J. Okada, T. Esaki and Yakugaku Zasshi, **56** 95 (1975).
6. O. Rosen and F. Sandberg, *Acta Chem. Scand.* 4 666 (1950).
7. J. Fox and D. Shugar, *Bull. Soc. Chim. Belg.* **61** 44 (1952).
8. W. Slesarev and B. Ivin, *Zh. Organ. Khim.* **10** 113 (1974).
9. J. Bojarski, J. Mokrosz, H. Barton and M. Paluchowska "Advances in Heterocyclic Chemistry", Vol. 38, A.R. Katritzky ed., Academic Press, N. York, 1985, p.231.
10. F. Carrrol and C. Moreland, *J. Chem. Soc. Perkin Trans.II*, 374 (1974).
11. J. Okada and T. Esaki, *Chem. Pharm, Bull.* **22,** 1580 (1974).
12. M. Jovanocic and E. Biehl, *J. Heterocyclic Chem.* **24,** 191 (1987).
13. S. Millefiori and A. Millefiori, *J. Heterocyclic Chem.* **26,** 639 (1989).
14. R. Kakkar and V. Katoch, *J. Mol. Struct.* **578,** 169 (2002).
15. S. Ralhan and N. Ray, *J. Mol. Struct.* **634,** 83 (2003).

16. F. Zuccarello, G. Buemi, C. Gandolfo and A. Contino, *Spectrochim. Acta*, Part A **59**, 139 (2003).
17. M. Rezende, P. Flores, J. Guerrero and L. Villarroel, *Spectrochim. Acta*, Part A **60**, 1637 (2004).
18. I. Hisao and K. Toshinari, *Jpn Pat.* 10158252 (1998).
19. K. Frisch, D. Tummers and A. Nijenhuis, U.S. Pat. 4198505 (1980).
20. I. Zarzyka-Niemiec, J. Lubczak, Z. Ciunik, S. Wołowiec and T. Ruman, *Heterocycl. Comm.*, **6**, 559 (2002).
21. I. Poplewska, E. Węglowska and J. Lubczak, *J. Appl. Polym Sci.*, **91**, 2750 (2004).
22. I. Cisek-Cicirko and J. Lubczak, *Inter. J. Chem. Kinetics*, **37**, 464 (2005).

Received on December 10, 2007.