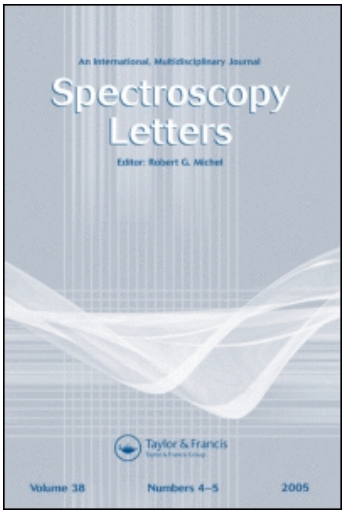


Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

Solvent Dependence of Tautomeric Equilibria of 1-(*o*-Substituted Phenyl)Barbituric and -2-Thiobarbituric Acid Derivatives

S. Funda Oğuz[a]; İlknur Doğan[a]
[a] Chemistry Department, Boğaziçi University, Bebek, Istanbul, Turkey

Online publication date: 25 October 2004

To cite this Article Oğuz, S. Funda and Doğan, İlknur(2004) 'Solvent Dependence of Tautomeric Equilibria of 1-(*o*-Substituted Phenyl)Barbituric and -2-Thiobarbituric Acid Derivatives', Spectroscopy Letters, 37: 6, 607 — 618
To link to this Article: DOI: 10.1081/SL-200037606
URL: http://dx.doi.org/10.1081/SL-200037606

SPECTROSCOPY LETTERS
Vol. 37, No. 6, pp. 607–618, 2004

Solvent Dependence of Tautomeric Equilibria of 1-(*o*-Substituted Phenyl) Barbituric and -2-Thiobarbituric Acid Derivatives

S. Funda Oğuz and İlknur Doğan*

Boğaziçi University, Chemistry Department, Bebek, Istanbul, Turkey

ABSTRACT

The enolisation tendencies of 1-(*o*-substituted phenyl)barbituric and -2-thiobarbituric acid derivatives have been studied by observing the behaviour of the compounds in different solvents by ^{1}H and ^{13}C NMR. It has been found that the enolisation tendencies of the thiobarbituric acid derivatives observed in polar solvents are greater than those of the barbituric acid derivatives. The ratio of keto–enol tautomers of thiobarbituric acid derivatives in DMSO and in DMF has been calculated.

Key Words: Barbituric acid derivatives; 2-Thiobarbituric acid derivatives; Tautomerization.

*Correspondence: İlknur Doğan, Boğaziçi University, Chemistry Department, Bebek, 34342, Istanbul, Turkey; E-mail: dogan@boun.edu.tr.

DOI: 10.1081/SL-200037606 0038-7010 (Print); 1532-2289 (Online)

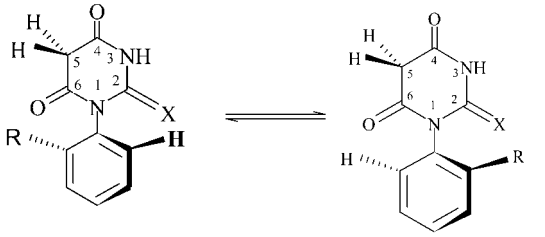
INTRODUCTION

Barbituric and thiobarbituric acid derivatives are an important class of compounds with various pharmacological activities in medicine and biological chemistry.[1,2] Their biological activity is mainly related to tautomerism, acid–base equilibria and to the nature of their substituents. The study of tautomerism in pyrimidine derivatives has been reported by many workers.[3–6] Experimental and theoretical studies of tautomerism in various barbituric acid derivatives have also been reported.[1,2,7,8] 2-Thiobarbituric acid differs from barbituric acid only in having a C═S substituted for a C═O group, but it shows some appreciable differences in the enolisation tendency.[2]

In the solid state, barbituric acid prefers the 2,4,6-triketo structure, while the 1,3-disubstituted derivative of thiobarbituric acid attains geometrical parameters suggesting strong intermolecular hydrogen bondings supported by 5,6-enolisation.[2] In most solvents, barbituric acid is present essentially in its keto form,[2] but thiobarbituric acid may be present both in keto and enol forms in comparable amounts, and the enol percentage increases with increasing the dielectric constant of the solvent.[1] In addition, the formation of an S–H isomer is considered to be more probable than the corresponding O—H isomer of the barbituric acid.[2]

The *N*-(*o*-substituted phenyl) barbituric and thiobarbituric acid derivatives studied in this work (Table 1) are axially chiral due to nonplanar

Table 1. The structures of the *N*-*o*-aryl substituted barbituric and -2-thiobarbituric acid derivatives.



M **P**

Compound	X	R
(±) − **1**	O	CH_3
(±) − **2**	O	Cl
(±) − **3**	S	CH_3
(±) − **4**	S	Cl

ground states of the molecules, the $C_{aryl}-N_{sp}2$ bond being the chiral axis and all of them exist as a pair of thermally interconvertible enantiomers M and P[9] (Table 1). When the resolution of the barbituric and 2-thiobarbituric acid derivatives were attempted on TAC and Chiralcel OD-H columns in ethanol or ethanol–hexane mixtures, many overlapping peaks have been seen which let us think about the possibility of tautomerization of these derivatives in ethanol. ^{13}C[10] and ^{1}H NMR[11] chemical shifts are known to offer a good means to distinguish between tautomeric forms of certain compounds. The purpose of the present paper is to investigate the tautomeric tendency of some axially chiral barbituric and 2-thiobarbituric acid derivatives in various solvents, using basically ^{13}C and ^{1}H NMR.

RESULTS AND DISCUSSION

In the ^{1}H NMR spectra of **1–4** (Table 1) taken in deuterated chloroform, an AB splitting at around 3.8–3.9 ppm for the diastereotopic 5-CH_2 methylene protons, a multiplet for aromatic protons (7.0–7.9 ppm), a singlet at 8.1 ppm for NH proton of barbituric and at 9.3 ppm for NH proton of thiobarbituric acid derivatives were observed [Fig. 1(a)].

Barbituric acid is known to react with carbonyl and sulfonyl compounds.[1,12–14] To investigate whether its derivatives studied here will also react with alcohols, compound **1** was refluxed in ethanol and compound **3** in methanol for 72 hr. The ^{1}H NMR spectra of the crystals obtained after the evaporation of the solvent were identical with those of the compounds showing that there is no reaction of the barbituric and 2-thiobarbituric acid derivatives with alcohols. ^{1}H NMR spectra of **1–4** taken in deuterated methanol showed the disappearance of the peaks that had been assigned to 5-CH_2 methylene protons and to the N—H proton [Fig. 1(b)]. This was interpreted in terms of an exchange process between H's on C-5 of barbituric and thiobarbituric acid derivatives and D's of deuterated methanol. The exchange of the 5-CH_2 could take place over one of the enol forms of the compound (Fig. 2). Temperature was lowered to slow down the exchange process so that the proton(s) at C-5 might be observed. However, there was not any sign of the C-5 proton signals even at $-80^{\circ}C$. On the other hand, the ^{13}C NMR spectrum of compound **3** in deuterated methanol (Fig. 3) has, in fact, shown a signal at 80 ppm, which is characteristic for the C_5 "vinyl" carbon of the enol form. The vinylic carbon signal also showed a C–D coupling which further supports the substitution of deuterium for hydrogen in the exchange process over the enol form (Fig. 3). The ^{13}C signals of **3** at 180.7, 164.5, and 39.7 ppm were assigned to the keto form (**A** in Fig. 2, Table 2), the

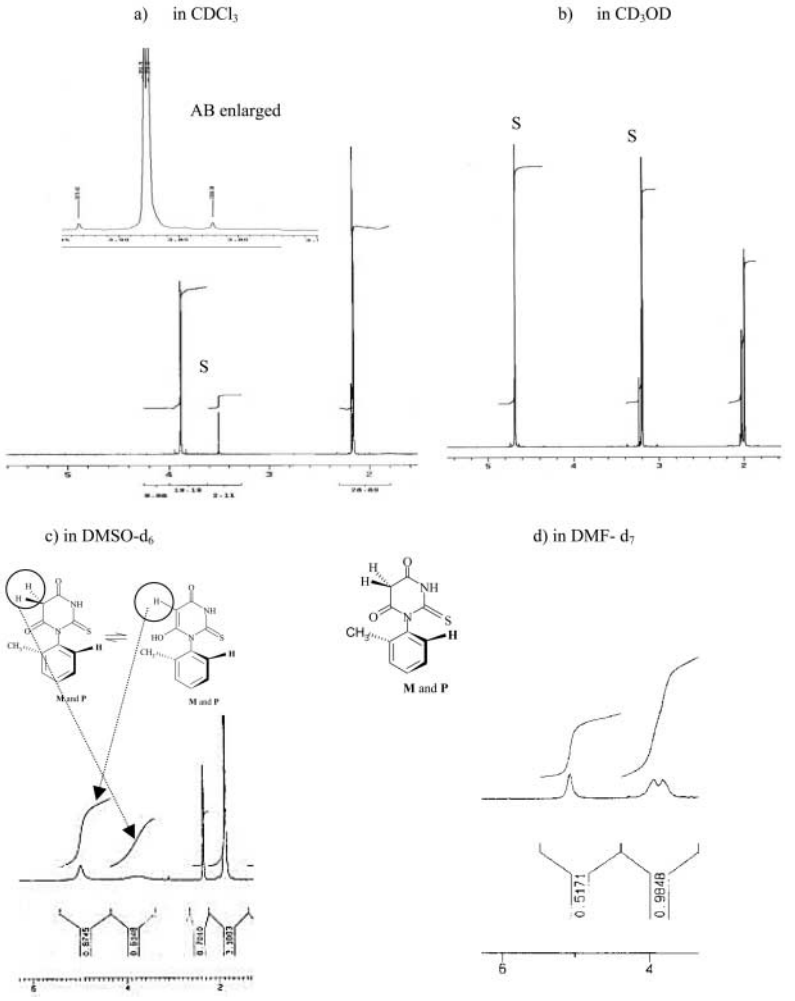


Figure 1. Partial ^{1}H NMR spectra of 1-(*o*-tolyl)-2-thiobarbituric acid, **3** in (a) $CDCL_3$, (b) methanol-d_4, (c) DMSO-d_6 and (d) DMF-d_7 showing 5-CH_2 or vinylic 5-CH proton signals. S denotes peaks from the solvent.

signals at 176.5, 161.6, and 81.6 ppm to hydroxy-keto-thione form (**B** in Fig. 2, Table 2), and the ones at 165.4, 164.2, and 81.3 ppm could be the signals of the thiol–enol–keto form (**C** in Fig. 2, Table 2).

In the ^{13}C spectrum of compound **4** in deuterated methanol, signals with chemical shifts close to signals of compound **3** have been observed, but they

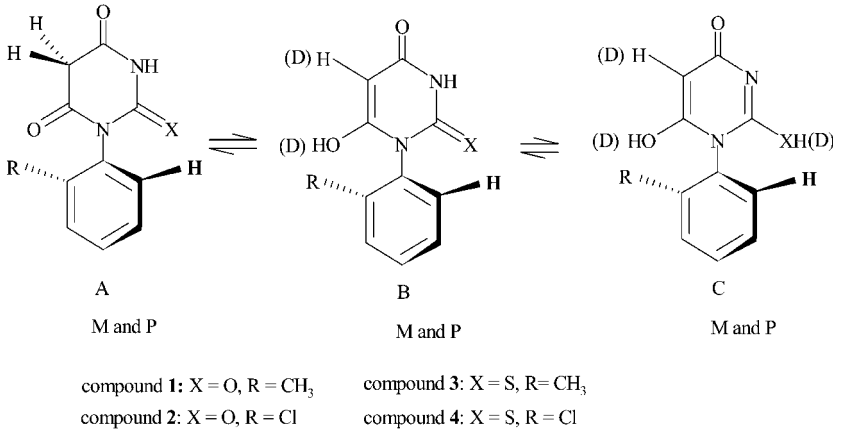


Figure 2. Some of the possible tautomers of barbituric and 2-thiobarbituric acid derivatives in CD_3OD.

were too weak to make assignments for. It may be concluded that tautomerization occurs to a slight extent in compound **4**.

Compounds **1** and **2** in methanol-d_6 showed no ^{13}C peaks at 80–90 ppm, indicating the absence of the hydroxy-keto form (**B** in Fig. 2) of compounds **1** and **2** in methanol-d_6 on the NMR time scale.

To observe the behaviour of 5,5-dimethyl-2-thiobarbituric acid derivatives in methanol, ^1H spectrum of 5,5-dimethyl-1-(*o*-fluorophenyl)-2-thiobarbituric acid was taken in deuterated methanol. Only the expected disappearance of the peak due to the exchangeable N–H was observed in the spectrum.

In the ^1H NMR spectrum of compound **3**, taken in another polar but aprotic solvent, DMSO-d_6 [Fig. 1(c)], we observed the change of the AB signal at 3.8 ppm to a broad singlet accompanied with the formation of a broad singlet at 4.97 ppm. This indicates the tautomerization of compound **3** in DMSO-d_6. The new appearing broad singlet at 4.97 ppm should belong to the vinylic hydrogen at C-5. The ratio of keto : enol tautomers of **3** in DMSO-d_6 has been found as 26% : 74% from the integral values of the 5-CH_2 AB and 5-CH vinylic protons (Fig. 1). For compound **4** the ratio of 5-CH vinylic proton to —NH proton was figured as 25–75% as well. For this compound, the signal of 5-CH_2 AB protons was masked by the broad H_2O signal of the solvent. The ^{13}C NMR spectrum of compound **3** taken in DMSO-d_6 showed a signal at 82.50 ppm, which has been assigned to the vinylic C-5 signal (Fig. 4). There are signals for carbons of enol tautomers at 161.47 ppm, 162.27 ppm (C-4 and C-6), and 176.51 ppm (C-2) indicating the presence of tautomer **B** shown in Fig. 2. Based on the ^{13}C-NMR results,

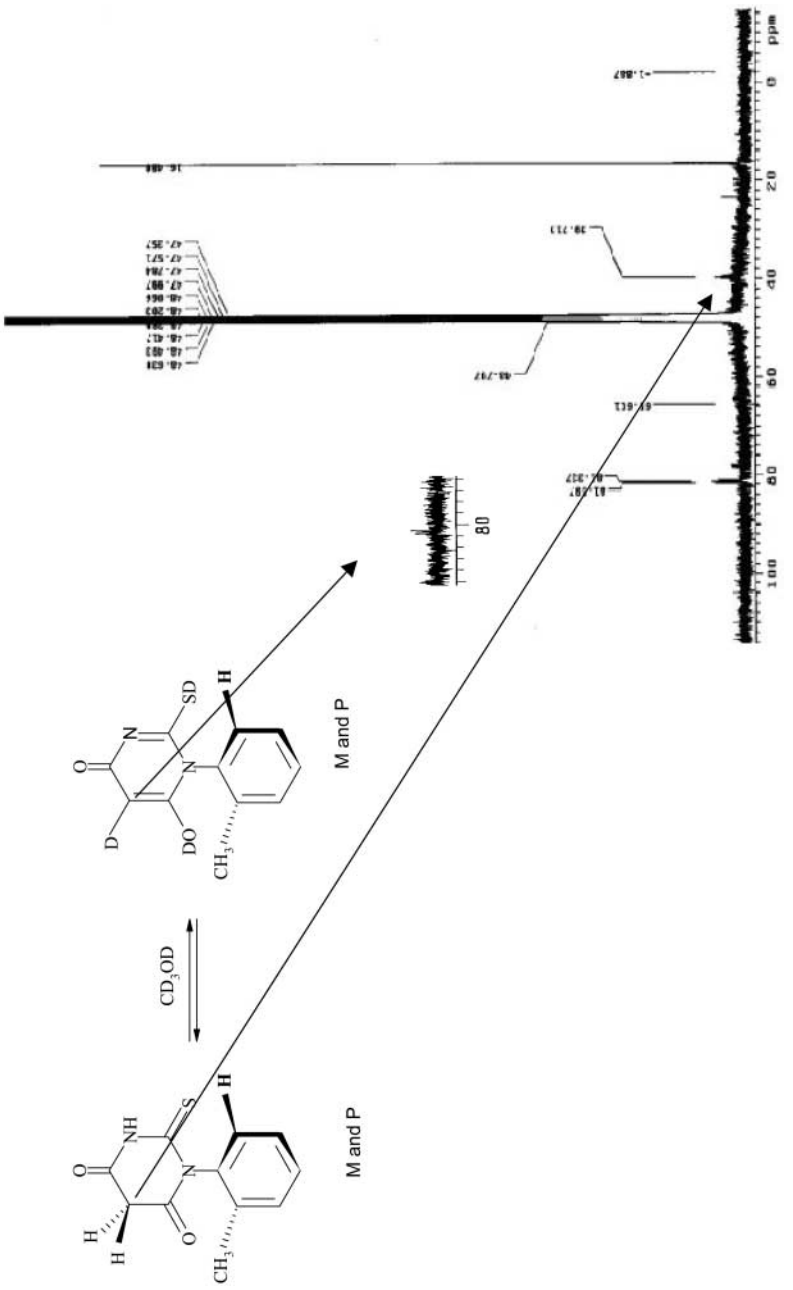
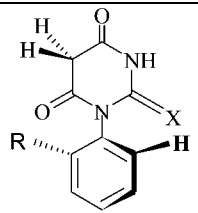


Figure 3. Partial ^{13}C NMR spectrum of 1-(*o*-tolyl)-2-thiobarbituric acid **3** in CD_3OD showing the C_5-D coupling.

Table 2. ^{1}H and ^{13}C NMR Results of thiobarbituric acid derivatives in different solvents.



M and P

	$CDCl_3$	CD_3OD	DMSO-d_6	Pyridine-d_5	DMF-d_7
(±)−**3**					
^{1}H NMR					
H signal (δ ppm)					
–NH	9.38	—	12.7	—	—
5-CH_2	3.87, 3.89 (AB)	—	3.80(broad)	—	3.9(f)
5-CH[a]	—	—	4.97(s)	—	5.1(s)
^{13}C NMR					
C number (δ ppm)					
2	178.5	165.4[b]; 176.5[a], 180.7[c]	176.51[a]	177.0	Obscured[d]
4 or 6	162.2; 163.4	161.6[a]; 164.2[b]; 164.5[c]	161.47[a]; 162.27[a]	162.4; 162.8	Obscured[d]
5	39.8	39.7[c]; 81.6[a]; 81.3[b]	82.50[a]	—	41.3[c], 82.2[a]

(*continued*)

Table 2. Continued.

	$CDCl_3$	CD_3OD	DMSO-d_6	Pyridine-d_5	DMF-d_7
(±) − **4**					
^{1}H NMR					
H signal (δ ppm)					
–NH	9.31	—	12.7	—	—
5-CH_2	3.88, 3.91 (AB)	—	Mask[e]	—	—
5-CH[a]	—	—	5.19(s)	—	
^{13}C NMR					—
C number (δ ppm)					—
2	177.9	176.5	179.2[a]	178.6	—
4 or 6	161.3; 163	161.7; 163.8	168.9[a], 169.5[a]	163.9; 164.2	—
5	40.3	Too weak	80[a]	—	—

[a]Vinylic tautomer B in Fig. 2.
[b]Tautomer C in Fig. 2.
[c]Tautomer A in Fig. 2.
[d]Obscured by the solvent peak.
[e]Signal is masked by the broad H_2O signal of the solvent.
[f]Distorted. See Fig. 5.

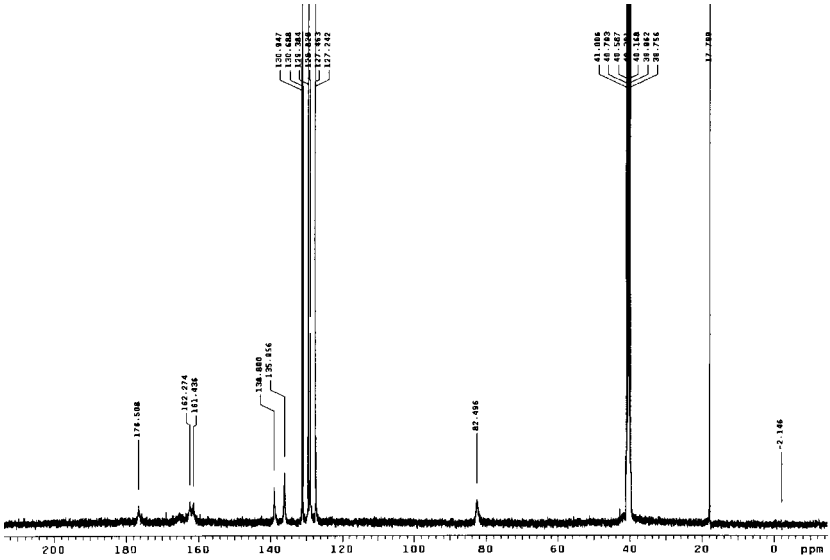


Figure 4. ^{13}C NMR spectrum of 1-(*o*-tolyl)-2-thiobarbituric acid **3** in DMSO-d_6.

the predominating tautomers in DMSO-d_6 has been assigned as **B** and **C** out of the other possible tautomers.

In order to gain further evidence for the tautomer structures, HMQC spectrum of compound **3** was also taken. The broad H_2O signal of the solvent DMSO-d_6 masks the 5-CH_2 methylene protons in longer time interval, therefore the HMQC NMR spectrum of compound **3** was taken in dimethylformamide-d_7, DMF-d_7 (Fig. 5). In the ^{1}H NMR spectrum of compound, **3** in DMF-d_7, a distorted AB spectrum for 5-CH_2 methylene protons was seen at 3.9 ppm and a singlet for 5-CH vinylic proton was observed at 5.1 ppm in the ratio of 50% : 50%. In the ^{13}C NMR spectrum of this compound, the peak for 5-CH_2 was observed at 41.3 ppm and that for 5-CH was seen at 82.2 ppm. From the HMQC spectrum (Fig. 5), correlation between peaks at 82.2 ppm and at 5.1 ppm could be seen, which further proves the keto–enol tautomerization with possible structures **B** and **C** shown in Fig. 2. Increase of the temperature in ^{1}H NMR probe increases the rate of the keto–enol tautomerization, and the peaks for methylene and vinylic protons almost disappeared at 60°C. The methylene and vinylic proton peaks reappeared upon cooling to ordinary probe temperature (30°C). This also supports our explanation for the disappearance of the 5-CH_2 methylene peaks in deuterated methanol due to fast exchange of D for H.

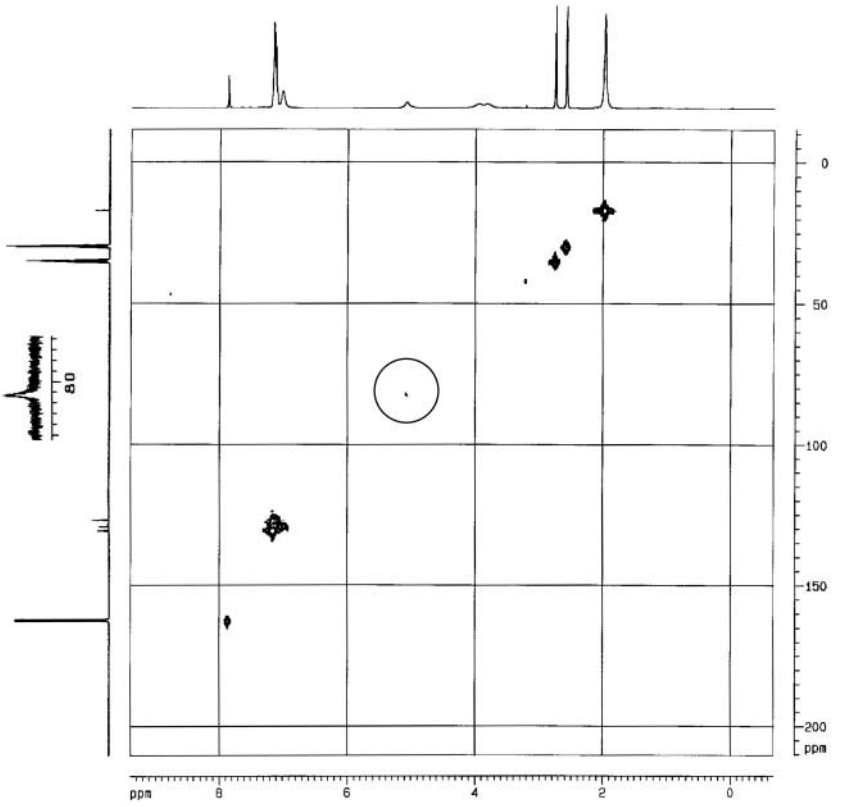


Figure 5. The HMQC spectrum of compound **3** in DMF-d_7. The correlation between peaks at 4.5 and 82 ppm could be seen very clearly.

The ^{1}H NMR spectrum of compound **1** in DMSO-d_6 did not show the presence of any peak around 5 ppm, which means that in NMR time scale no tautomerization has been seen for compound **1**. In the ^{13}C NMR spectrum of this compound in DMSO-d_6, no signal appeared at around 80–90 ppm, which would have indicated the enol formation. So compound **1** stays predominantly in keto form (Fig. 2, structure **A**) in DMSO-d_6.

It has been seen that the enolisation rate of the thiobarbituric acid derivatives in DMSO-d_6 is greater compared to that in DMF-d_7 when the ratio of vinylic protons to aromatic protons taken into consideration.

To observe the behaviour of barbituric and thiobarbituric acid derivatives in another polar solvent, their spectra were taken in deuterated pyridine, which is as well basic. In the ^{1}H NMR spectrum of **1**–**4**, the disappearance of peaks

of 5-CH_2 methylene protons and —NH proton were observed, which could be considered as an exchange process between H of –NH and H's on C-5 of barbituric and thiobarbituric acid derivatives and D's of D_2O after deprotonation of the compound by the deuterated pyridine. In the ^{13}C NMR spectra of compounds **1**–**4**, the peaks of 5-CH_2 methylene carbon at 40 ppm disappeared and no additional peaks were observed, again probably due to the fast exchange, since no reaction was observed, when the barbiturate **1** was refluxed with pyridine for 24 hr.

The ^1H NMR spectrum of compound **3** in the mixture of deuterated aprotic and protic solvents, $CDCl_3$ and methanol-d_6 (1 : 1) did not show any sign of the peaks of 5-CH_2 methylene and 5-CH vinyl protons.

The ^1H and ^{13}C NMR spectral data for thiobarbituric acid derivatives in different solvents are summarized in Table 2.

EXPERIMENTAL

Apparatus

^1H and ^{13}C NMR spectra were recorded on a Varian 400 MHz or Bruker 400 MHz NMR spectrometers.

Synthesis

1-(*o*-Substituted phenyl) barbituric and 1-(*o*-substituted phenyl)-2-thiobarbituric acid derivatives were synthesized by the reaction of diethylmalonate with the appropriate arylurea or arylthiourea in sodium ethoxide solution. The crude products were purified by recrystallization from ethanol.[3]

ACKNOWLEDGMENTS

This project has been supported by Boğaziçi University research fund, Project Numbers: B.A.P. 03B503 and 04B505. We thank Ayla Türkekul for recording the NMR spectra.

REFERENCES

1. Jovanovic, M.V.; Biehl, E. Substituent and solvent effects on tautomeric equilibria of barbituric acid derivatives and isosterically related compounds. J. Heterocycl. Chem. **1987**, *24*, 191–204.

2. Zuccarello, F.; Buemi, G.; Gandolfo, C.; Contino, A. Barbituric and thiobarbituric acids: a Conformational and Spectroscopic Study. Spectrochim. Acta Part A **2003**, *59*, 139–151.
3. Zhang, X.M.; Malick, D.; Petersson, G.A. Enolization enthalpies for aliphatic and thiocarbonyl compounds. J. Org. Chem. **1998**, *63* (16), 5314–5317.
4. Das, S.; Dogra, S.K. Ground and excited state prototropic reactions in 2-(2′-methoxyphenyl)-3H-imidazo[4,5-6]pyridine. J. Chem. Soc., Faraday Trans. **1998**, *12*, 2765–2771.
5. Rubin, Y.V.; Morozov, Y.; Venkateswarlu, D.; Leszczynski, J. Prototropic equlibria in 4-thiouracil: a combined spectroscopic and ab initio SCF-MO investigation. J. Phys. Chem. A **1998**, *102* (12), 2194–2200.
6. Luyten, I.; Pankiewicz, K.W.; Watanabe, K.A.; Chattopadhyaya, J. Determination of the tautomeric equilibria of psi-uridine in basic solution. J. Org. Chem. **1998**, *63* (4), 1033–1040.
7. Ralhan, S.; Ray, N.K. Density functional study of barbituric acid and its tautomers. THEOCHEM **2003**, *634*, 83–88.
8. Kakkar, R.; Katoch, V. Theoretical study of the excited state intramolecular proton transfer in barbituric acid. THEOCHEM **2002**, *578*, 169–175.
9. Oğuz, F.; Doğan, İ. Determination of energy barriers and racemization mechanisms for thermally interconvertable barbituric and thiobarbituric acid enantiomers. Tetrahedron: Asymmetry **2003**, *14*, 1857–1863.
10. Pihlaja, K.; Kleinpeter, E. *Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis*; Wiley-VCH: New York, 1994; 188.
11. Friebolin, H. *Basic One- and Two-dimensional NMR Spectroscopy*, 3rd Ed.; Wiley-VCH: Weinheim, New York, 1998; 322.
12. Kosugi, H.; Kato, T.; Kikugawa, K. Formation of yellow, orange and red pigments in the reaction of alk-2-enals with 2-thiobarbituric acid. Anal. Biochem. **1987**, 456–464.
13. Oğuz, F.; Doğan, İ. Reactions of barbituric and 2-thiobarbituric acid derivatives with acetone. Spectrosc. Lett. **1998**, *31* (2), 469–482.
14. Doğan, İ.; Yaman, A. The reaction of 5-methyl-3-(*o*-tolyl)rhodanine with acetone-d_6 and methanol. Spectrosc. Lett. **2001**, *34* (3), 365–370.

Received May 7, 2003
Accepted August 20, 2004