Analysis of Tautomerism in β-Ketobuanamides by Nuclear Magnetic Resonance: Substituent, Temperature and Solvent Effects

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Abstract: β-ketoamides are versatile intermediates for the synthesis of several heterocycles and they are also relevant compounds in biological systems, with their tautomeric equilibria being a crucial aspect to be studied in order to understand their chemical and biological behaviour. Tautomeric equilibria of a series of β-ketobutanamides were analyzed by means of ^{1}HNMR, determining that ketoamide and Z-enolamide are the main tautomeric species in solution, both presenting internal hydrogen bonds. Keto-enol equilibrium predominates over other possible tautomerisms (e.g. amide-imidol). The enol tautomer appears to be favoured by electron withdrawing substituents and non-protic solvents. Thermodynamic parameters ΔH and ΔS were determined in $CDCl_3$ and DMSO-d_6, showing that the keto-enol equilibria are exothermic and require a molecule order increase.

Keywords: β-ketoamides, keto-enol equilibrium, nuclear magnetic resonance spectroscopy.

INTRODUCTION

β-ketoamides are versatile intermediates for the synthesis of several heterocycles: 3-acyltetramic acids [1] (used in the total synthesis of tirandamycin and other related natural antibiotics [2]), pyrans [3], alkaloids [4], lactams and spirolactams [5], azetidin-2-ones [5], as well as several 3-hydroxyisothiazol bioisosteres of glutamic acid and analogs of the AMPA receptor agonist [6]. Moreover, some β-ketoamides have been converted into γ-ketoamides, a class of compounds related with a wide variety of biologically relevant systems [8].

The reactivity of β-ketoamides is related to their structure and their tautomeric equilibria; that is why it should be useful to determine their spectral behaviour in different conditions in order to study the tautomeric distribution. Hence, it is of practical and theoretical importance to investigate tautomeric equilibria in such systems.

Keto–enol tautomerism in β-ketoesters, β-diketones and β-ketonitriles is a topic that has been extensively studied from several points of view and by means of a variety of experimental methods [9]-[11]. However, the occurrence of this phenomenon in β-ketoamides has not been studied deeply, with exception of a few previous works [12], [13]. It is usual to describe them only as ketoamide forms [14], although some of them have been demonstrated to exist as a tautomeric mixture where the enolamide form is the major tautomer.

Keto–enol tautomerism has attracted much interest during the last few decades. The fact that the equilibrium involved is sufficiently slow to permit keto and enol tautomeric forms to be detected by nuclear magnetic resonance (NMR) spectroscopy has allowed many researches on these processes [15].

The tautomeric equilibria of some β-ketobutanamides in solution were investigated by ^{1}HNMR and ^{13}CNMR. Their chemical shifts were compared with those of related β-hydroxybutanamides. Equilibrium populations of the keto and enol forms were measured. Substituent effects on the chemical shifts and the equilibrium populations were discussed [16].

Intramolecular hydrogen bonding is the main factor that governs the kinetics and influences the structure of keto-enol tautomerism in solution. Regarding β-ketoamides, internal hydrogen bonding is possible to be established in several tautomeric forms.

In the present work, we have studied effects of substituents, solvents and temperature on the equilibria among different tautomeric forms in three substituted 3-oxo-2-phenylbutanamides.

EXPERIMENTAL

Synthesis of β-Ketobutanamides

β-ketobutanamides **I**-**III** were synthesized and purified according to literature procedures or their

*Address corresponding to this author at the Laboratorio LADECOR, División Química Orgánica, Departamento de Química, Facultad de Ciencias Exactas, UNLP, Calle 47 y 115, (1900) La Plata, Argentina; Tel: 54-221-4243104; E-mail: pallegre@quimica.unlp.edu.ar

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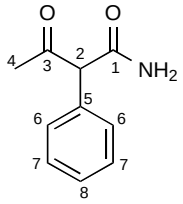
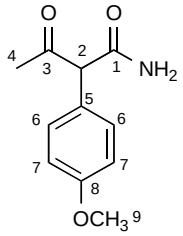
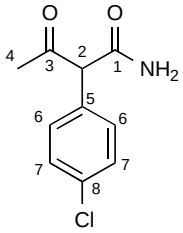
Table 1: ^{1}HNMR and ^{13}CNMR Data for the Selected β-Ketoamides (200MHz, DMSO-d_6)

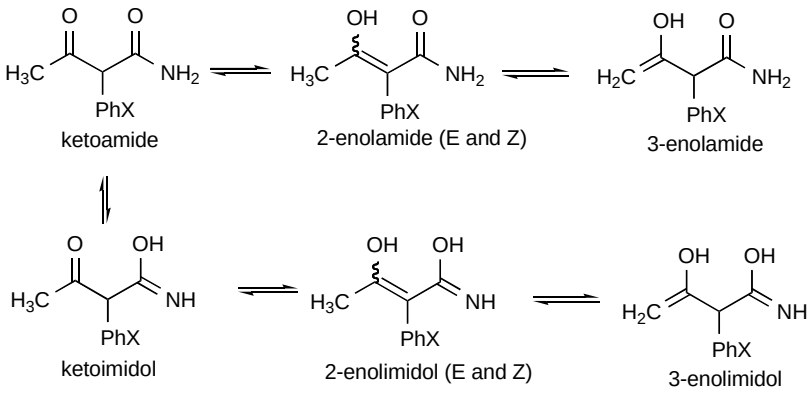
COMPOUND	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
 3-oxo-2-phenylbutanamide (I)	2.13 (s, 3H (4)); 4.58 (s, 1H (2)); 7.2-7.4 (m, 5H (6,7,8)).	27.3 (4); 65.3 (2); 127.1 (8); 127.8 (6); 128.8 (7); 138.8 (5); 172.7 (1); 206.0 (3)
 2-(4-methoxyphenyl)-3-oxobutanamide (II)	2.10 (s, 3H (4)); 3.85 (s, 3H (9)); 4.51 (s, 1H (2)); 6.87 (d, 2H (7)); 7.12 (d, 2H (6)).	27.1 (4); 56.5 (9); 62.1 (2); 114.4 (7); 130.1 (6); 131.1 (5); 159.1 (8); 171.0 (1); 205.5 (3)
 2-(4-chlorophenyl)-3-oxobutanamide (III)	2.16 (s, 3H (4)); 4.65 (s, 1H (2)); 7.17 (d, 2H (6)); 7.37 (d, 2H (7)).	27.8 (4); 66.3 (2); 128.9 (7); 130.5 (6); 132.7 (8); 136.9 (5); 173.1 (1); 206.2 (3)

modified versions [17]. The compounds under study were identified by ^{1}HNMR and ^{13}CNMR in DMSO-d_6, in which the peaks corresponding to the enol forms are depleted (Table **1**).

NMR Measurements

^{1}HNMR spectra in $CDCl_3$ and DMSO-d_6 were recorded with a Bruker 300 spectrometer, 300,13 MHz, grad Z and temperature control. The typical spectral conditions were as follows: spectral width 4000 Hz, acquisition time 2 s and 8–16 scans per spectrum. Digital resolution was 0.39 Hz per point, TMS was used as internal standard. Sample concentrations were 0.05 M. Spectra were taken at 25, 35 and 45ºC. The content of long-lived tautomeric forms was calculated from the integrated peak intensities of hydoxyl and methine proton signals.

^{13}C proton decoupled and gated decoupled spectra were recorded with a Varian Mercury Plus 200



Scheme 1:

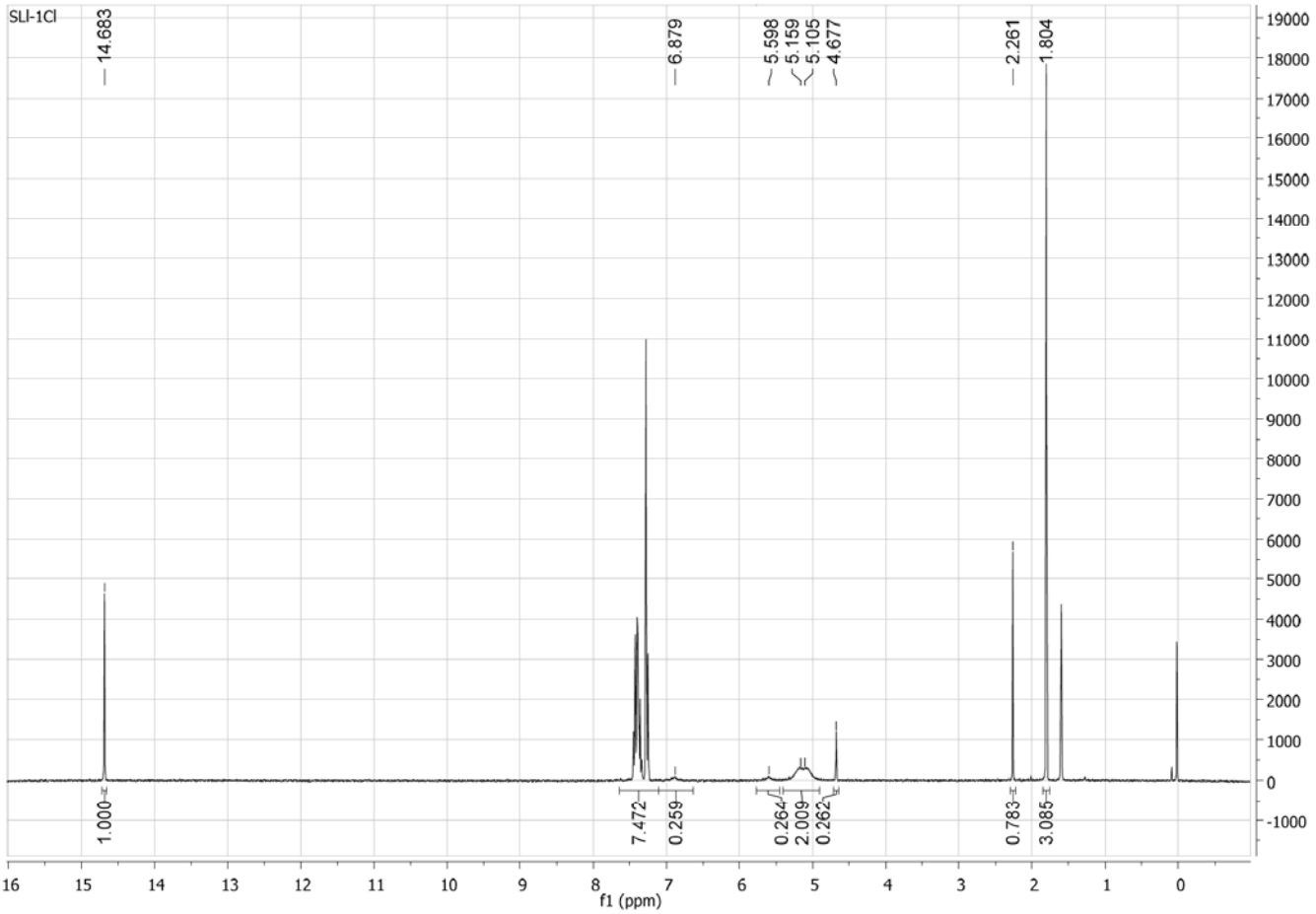


Figure 1: ^{1}HNMR spectrum of compound **I** in $CDCl_3$ at 25ºC.

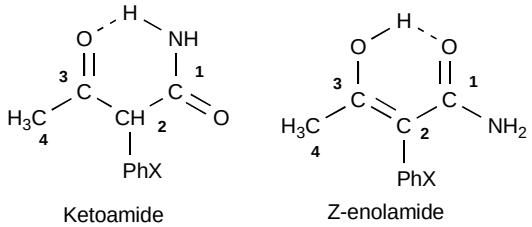
spectrometer operating at 4.5 T from DMSO-d_6 solutions at 25 ºC. The spectral conditions were the following: spectral width 10559 Hz, acquisition time 1.303 s and 512–1000 scans per spectrum.

RESULTS AND DISCUSSION

Scheme **1** shows the possible tautomeric structures for β-ketoamides **I**-**III**.

Each RMN spectrum is the result of superposition of the spectra of the individual tautomers, since they are altogether in equilibrium. Figure **1** shows the ^{1}HNMR spectrum of compound **I** in $CDCl_3$ at 25ºC. The only two tautomeric forms that could be identified in each spectrum were ketoamide and Z-enolamide (Scheme **2**). The rest of the tautomeric forms could not be detected, and this fact indicates that they are absent or in very low concentration. The assignment of the peaks to their correspondent proton was made keeping in mind the theoretical displacements.

Intramolecular hydrogen bonding is the main factor that governs the kinetics and influences the structure of keto–enol tautomerism in solution. In the case of β-ketoamides, the two tautomers of major concentration are capable of establishing internal hydrogen bonds. This stabilizing factor explains the high concentration of the involved tautomers, the high chemical shift (δ) value observed for the hydroxyl proton in the Z-enolamide form and the two different (δ) values of the hydrogen bonded to nitrogen in the ketoamide form.



Ketoamide Z-enolamide

Scheme 2:

Table **2** shows the ^{1}H chemical shifts of the compounds studied in $CDCl_3$ and DMSO-d_6. Atom numbering is shown in Scheme **2**.

Table **3** shows the enol content present in each compound for both solvents. The integrated spectra

Table 2: ^{1}HNMR Chemical Shifts (in ppm) for Compounds I-III at 25ºC

Compound	Solvent	δ_H
I	$CDCl_3$	1.80 (C-4 enol); 2.26 (C-4 keto); 4.68 (C-2 keto); 5.10/5.16 (NH_2 enol); 5.60/6.88 (NH_2 keto); 7.2-7.5 (aromatics); 14.68 (OH enol).
	DMSO-d_6	1.66 (C-4 enol); 2.13 (C-4 keto); 4.58 (C-2 keto); 7.2-7.4 (aromatics); 15.7 (OH enol).
II	$CDCl_3$	1.79 (C-4 enol); 2.24 (C-4 keto); 3.82 (OCH_3 keto); 3.84 (OCH_3 enol); 4.61 (C-2 keto); 5.10/5.31 (NH_2 enol); 5.73/6.81 (NH_2 keto); 6.9-7.4 (aromatics); 14.63 (OH enol).
	DMSO-d_6	1.71 (C-4 enol); 2.10 (C-4 keto); 3.85 (OCH_3 keto); 3.89 (OCH_3 enol); 4.51 (C-2 keto); 6.8-7.2 (aromatics) 15.67 (OH enol).
III	$CDCl_3$	1.80 (C-4 enol); 2.26 (C-4 keto); 4.63 (C-2 keto); 5.02/5.21 (NH_2 enol); 5.63/6.89 (NH_2 keto); 7.2-7.5 (aromatics); 14.72 (OH enol).
	DMSO-d_6	1.66 (C-4 enol); 2.16 (C-4 keto); 4.65 (C-2 enol); 7.3-7.5 (aromatics); 15.79 (OH enol).

make possible to calculate the enol ratio considering the peaks of H linked to C-2 (ketoamide tautomer) and the hydroxylic H (Z-enolamide tautomer). Thus, enolic contents are calculated as follows:

$$\% \text{ enol} = (\text{OH integration})/(\text{C-2 integration})$$

Then the equilibrium constant (Keq = [enol]/[keto]) and the corresponding free energy at 25 ºC (ΔG = -RT ln Keq) for keto–enol equilibrium are determined (Table **3**).

The relative stability of individual tautomers and the corresponding equilibrium shifts are explained considering several factors, such as electronic effects on the carbonyl group, stabilization by conjugation of the enol double bond and tautomer stabilization *via* internal hydrogen bonds.

Substituent Effect

The substituents may push or pull electrons inductively or by resonance. The effects of an electron releasing methoxy group and an electron withdrawing chlorine atom attached at the para-position of phenyl rings are opposite to each other: chlorine atom (compound **III**) increases the enol content, whereas methoxy group (compound **II**) shifts the equilibrium towards the keto tautomer.

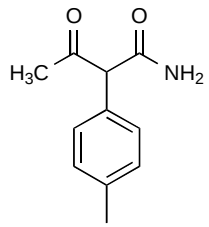
These observations can be explained regarding the influence of the substituents on the internal hydrogen bonds established in each tautomer.

- An electron donor in C-2 position (compound **II**) weakens the enol hydrogen bond destabilizing it, and, at the same time, stabilizes the keto form. These facts make the enolic content decrease.
- An electron acceptor in C-2 position (compound **III**) strengthens the enol hydrogen bond stabilizing it, and, at the same time, destabilizes the keto form. These facts make the enolic content increase.

Solvent Effect

Differential solvatation effects should shift the protomeric tautomerism. Data from Table **3** clearly demonstrate that an increase in the solvent polarity increases the proportions of keto forms. This effect can be explained considering that DMSO-d_6 is a hydrogen bond acceptor solvent (while $CDCl_3$ is not) and it competes with carbonyl groups for establishing

Table 3: Enol and Keto Populations, Keq and ΔG for Compounds I-III at 25ºC

Compound		Solvent	% enol	% keto	Keq	ΔG (kcal/mol)
	I X = H	$CDCl_3$	79,2	20,8	3,82	-0,79 ± 0,06
		DMSO-d_6	17,3	82,7	0,210	0,97 ± 0,06
	II X = OCH_3	$CDCl_3$	75,5	24,5	3,09	-0,67 ± 0,06
		DMSO-d_6	16,5	83,5	0,198	0,96 ± 0,06
	III X = Cl	$CDCl_3$	79,5	20,5	3,88	-0,80 ± 0,06
		DMSO-d_6	18,0	82,0	0,220	0,90 ± 0,06

hydrogen bonds. This factor make both internal bonds weaker (in keto and enol tautomers), destabilizing the tautomeric forms in solution. Apparently, this destabilization should be greater in the enol tautomer, shifting the equilibrium towards the keto tautomer in DMSO-d_6.

Temperature Effect

Tables **4** and **5** show the enol content and the equilibrium constant Keq for compounds **I-III** in $CDCl_3$ and DMSO-d_6, respectively, at three different temperatures. Equation 1 provides a simple method to determine ΔH and ΔS of keto-enol tautomerization for the studied compounds.

$$\ln\left(\frac{[\text{enol}]}{[\text{keto}]}\right) = \ln K = -\frac{\Delta G}{RT} = -\frac{\Delta H}{R}\cdot\frac{1}{T} + \frac{\Delta S}{R} \qquad \text{Equation 1}$$

Thus, the calculated slopes and y-intecepts from ln K vs 1/T graphics can be used directly to determine the enthalpy and entropy changes. Figures **2** and **3** show the graphics of ln K vs 1/T for β-ketoamides **I-III** in both solvents.

As it can be seen in Tables **4** and **5**, the values of ΔH are more negative in DMSO-d_6, indicating that the enol form would be favored in this solvent. This effect can be explained considering that the enolamide form is capable to establish two hydrogen bonds per molecule, while in the ketoamide tautomer only one hydrogen bond is possible (Scheme **3**).

On the other hand, ΔS values are more negative in DMSO-d_6, what would shift the equilibrium towards the keto tautomer. This can be explained from the different molecular arrangements that are set when the tautomers establish hydrogen bonds, showing different degrees of molecular order (Scheme **3**).

The result of these two contrary effects is experimental and the overall equilibrium shift (which depends ultimately on ΔG, Table **2**) indicates that, in

Table 4: Enol Content, K, ΔH and ΔS for Compounds I-III in $CDCl_3$

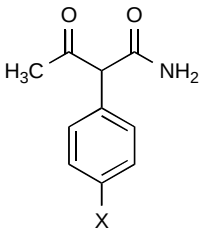
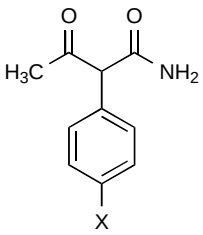
Compound		Temp	% enol	K	ΔH (kcal/mol)	ΔS (cal/mol.K)
	I X = H	25°C	79,2	3,82	-3,0 ± 0,2	-7,4 ± 0,7
		35°C	76,1	3,18		
		45°C	73,6	2,78		
	II X = OCH_3	25°C	75,5	3,09	-1,6 ± 0,2	-3,0 ± 0,7
		35°C	74,4	2,91		
		45°C	72,5	2,64		
	III X = Cl	25°C	79,5	3,88	-3,1 ± 0,1	-7,6 ± 0,3
		35°C	76,7	3,29		
		45°C	72,5	2,64		

Table 5: Enol Content, K, ΔH and ΔS for Compounds I-III in DMSO-d_6

Compound		Temp	% enol	K	ΔH (kcal/mol)	ΔS (cal/mol.K)
	I X = H	25°C	17,3	0,211	-3,6 ± 0,8	-15 ± 3
		35°C	15,7	0,186		
		45°C	12,5	0,143		
	II X = OCH_3	25°C	16,5	0,198	-2,0 ± 0,2	-10,0 ± 0,5
		35°C	15,2	0,179		
		45°C	13,7	0,159		
	III X = Cl	25°C	18,0	0,220	-5 ± 1	-18 ± 4
		35°C	16,0	0,190		
		45°C	11,9	0,135		

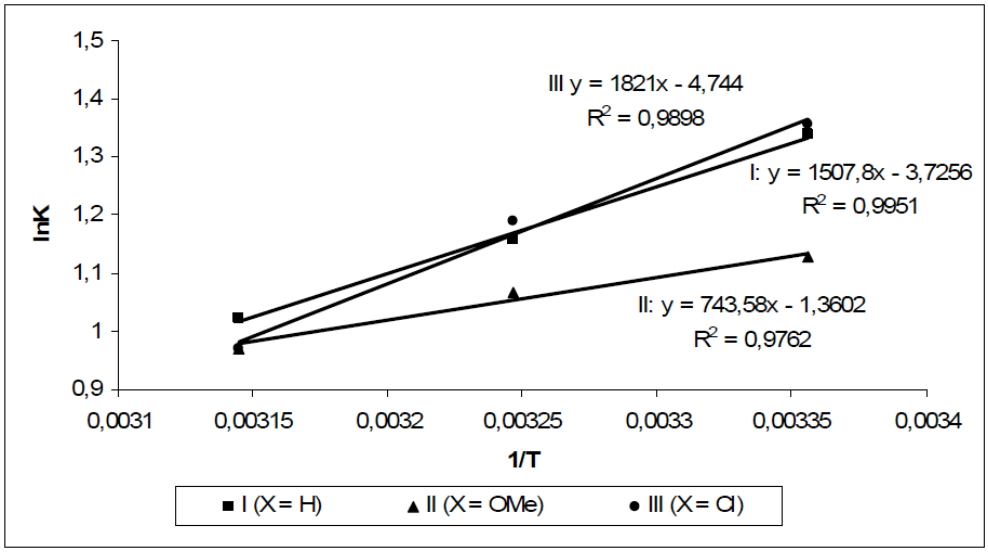


Figure 2: lnK vs 1/T plot for compounds **I-III** in $CDCl_3$.

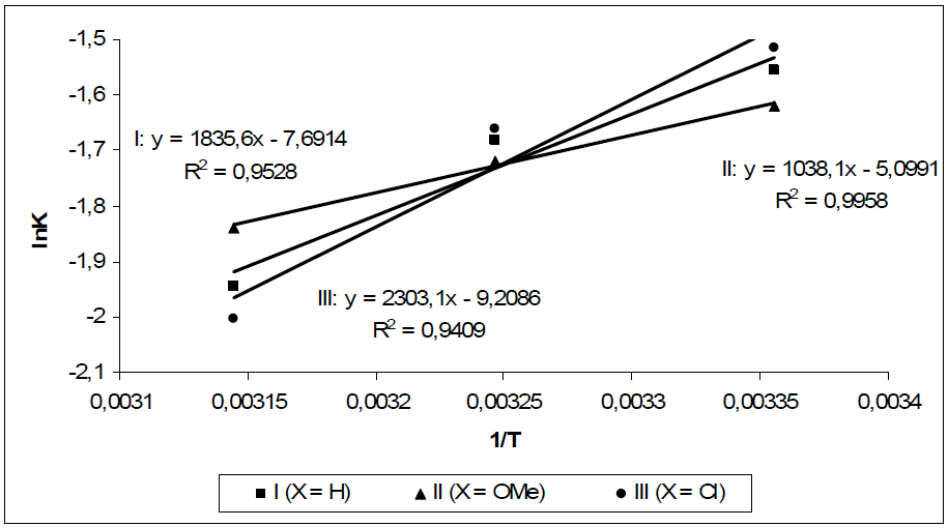
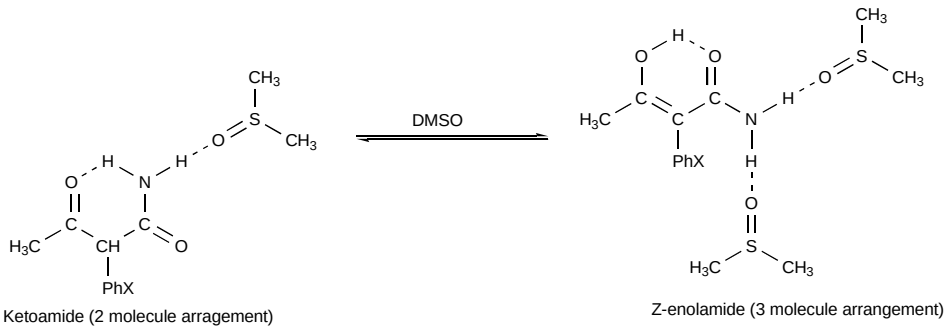


Figure 3: lnK vs 1/T plot for compounds **I-III** in DMSO-d_6.



Scheme 3:

these compounds, the entropic effect predominates over the enthalpic effect.

Data obtained from these experiments suggest an enthalpy-entropy compensation (since ΔH and ΔS seem to be linearly correlated $\Delta H = a.\ \Delta S + b$). However, this correlation is not strictly valid since ΔS and ΔH values were obtained from the same experiment, and, if an acceptable enthalpy-entropy compensation is required, they should be determined from independent experiences [18].

CONCLUSIONS

Analysis of ^{1}HNMR spectra of three substituted β-ketobutanamides made possible to study their tautomeric equilibria in solution. The most abundant tautomers appear to be ketoamide and Z-enolamide, both of them presenting internal hydrogen bonds. Several factors that affect the equilibrium have been studied: 1) Electron withdrawing substituents (e.g. chlorine atom) stabilize the enolamide tautomer, while electron donors (e.g. methoxy group) shift the equilibrium towards the ketoamide tautomer. 2) Ketoamide tautomer is favoured in proton accepting solvents (e.g. DMSO), while enolamide is stabilized in less polar solvents (e.g. $CDCl_3$). 3) The equilibrium has negative ΔH and ΔS values in both solvents, being the two of them more negative in DMSO than in $CDCl_3$. This fact can be explained considering interactions between the tautomers and the solvents.

REFERENCES

[1] Valters RE, Fülöp F, Korbonits D. Recent developments in ring-chain tautomerism. II. Intramolecular reversible addition reactions to the C=N, C=N, C=C, and C=C groups. Adv Heterocycl Chem 1996; 66: 1. http://dx.doi.org/10.1016/S0065-2725(08)60304-9

[2] Lázár L, Fülöp F. Recent Developments in the Ring-Chain Tautomerism of 1,3-Heterocycles. Eur J Org Chem 2003; 3025. http://dx.doi.org/10.1002/ejoc.200300142

[3] Lázár L, Göblyös A, Evanics F, Bernáth G, Fülöp F. Ring-Chain tautomerism of 2-aryl-substituted imidazolidines. Tetrahedron 1998; 54: 13639. http://dx.doi.org/10.1016/S0040-4020(98)00840-0

[4] Göblyös A, Lázár L, Evanics F, Fülöp F. Substituent effects in the ring-chain tautomerism of 1,2-diarylimidazolidines. Heterocycles 1999; 51: 2431. http://dx.doi.org/10.3987/COM-99-8624

[5] Zelenin KN, Alekseyev V V, Ukraintsev IV, Tselinsky IV. 2-Substituted Hexahydropyrimidines and Their Tautomerism. Org Prep Proc Int 1998; 30: 53. http://dx.doi.org/10.1080/00304949809355259

[6] Göblyös A, Lázár L, Fülöp F. Ring-chain tautomerism of 2-aryl-substituted-hexahydropyrimidines and tetrahydroquinazolines. Tetrahedron 2002; 58: 1011. http://dx.doi.org/10.1016/S0040-4020(01)01196-6

[7] Maloshitskaya O, Sinkkonen J, Ovcharenko VV, Zelenin KN, Pihlaja K. Chain-ring-chain tautomerism in 2-aryl-substituted hexahydropyrimidines and 1*H*-2,3-dihydroperimidines. Does it appear? Tetrahedron 2004; 60: 6913. http://dx.doi.org/10.1016/j.tet.2004.05.092

[8] Sinkkonen J, Zelenin KN, Potapov AK, Lagoda IV, Alekseyev VV, Pihlaja K. Ring-chain tautomerism in 2-substituted 1,2,3,4-tetrahydroquinazolines A ^{1}H, ^{13}C and ^{15}N NMR study. Tetrahedron 2003; 59: 1939. http://dx.doi.org/10.1016/S0040-4020(03)00148-0

[9] Bunting JW, Kanter JP. Acidity and tautomerism of β-keto-esters and amides in aqueous-solution. J Am Chem Soc 1993; 115: 11705. http://dx.doi.org/10.1021/ja00078a008

[10] Yamasaki K, Kajimoto O. Solvent effect in supercritical fluids: keto—enol equilibria of acetylacetone and ethyl acetoacetate. Chem Phys Lett 1990; 172: 271. http://dx.doi.org/10.1016/0009-2614(90)85401-W

[11] Ruiz DL, Albesa AG, Ponzinibbio A, Allegretti PE, Schiavoni MM, Solvent effects on tautomerics equilibria in *β*-ketonitriles: NMR and theoretical studies. J Phys Org Chem 2010; 23(10): 985. http://dx.doi.org/10.1002/poc.1764

[12] Hynes MJ, Clarke EM. Kinetics of enolisation of β-ketoamides. J Chem Soc Perkin Trans 1 1994; 901. http://dx.doi.org/10.1039/p29940000901

[13] Wengenroth H, Meier H. (*E*)- und (*Z*)-Enole von β-Ketocarbonsäureamiden. Chem Ber 1990; 123: 1403. http://dx.doi.org/10.1002/cber.19901230633

[14] Naoum MM, Saad GR. Solvent effect on tautomeric equilibria and dipole moments of some alpha substituted benzoylacetanilides. J Solution Chem 1998; 17: 67. http://dx.doi.org/10.1007/BF00651854

[15] Claramunt RM, López C, Santa María MD, Sanz D, Elguero J. The use of NMR spectroscopy to study tautomerism. Prog Nucl Magn Reson Spectrosc 2006; 49: 169. http://dx.doi.org/10.1016/j.pnmrs.2006.07.001

[16] Barros MT, Geraldes CFGC, Mavcock CD, Silva MI. A proton and 13C NMR study of keto-enol tautomerism of some β-ketoamides. J Mol Struct 1986; 142: 345. http://dx.doi.org/10.1016/0022-2860(86)85150-X

[17] Hauser CR, Eby CJ. Cyclization of β-Ketonitriles or β-Ketoamides with Ketones by Polyphosphoric Acid to Form Substituted 2-Pyridones. J Am Chem Soc 1957; 79(3): 725. http://dx.doi.org/10.1021/ja01560a061

[18] Starikov EB, Nordén B. Entropy–enthalpy compensation as a fundamental concept and analysis tool for systematical experimental data. Chem Phys Lett 2012; 538: 118. http://dx.doi.org/10.1016/j.cplett.2012.04.028

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