

Analysis of Tautomerism in β -Ketobutanamides 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 ^1H NMR, 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], azetidino-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 ^1H NMR and ^{13}C NMR. 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.

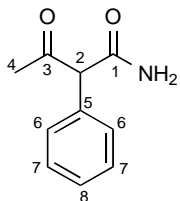
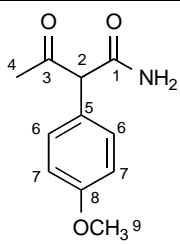
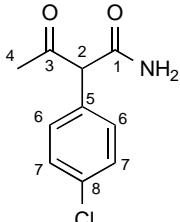
EXPERIMENTAL

Synthesis of β -Ketobutanamides

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

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

COMPOUND	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)
 <p>3-oxo-2-phenylbutanamide (I)</p>	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)
 <p>2-(4-methoxyphenyl)-3-oxobutanamide (II)</p>	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)
 <p>2-(4-chlorophenyl)-3-oxobutanamide (III)</p>	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)

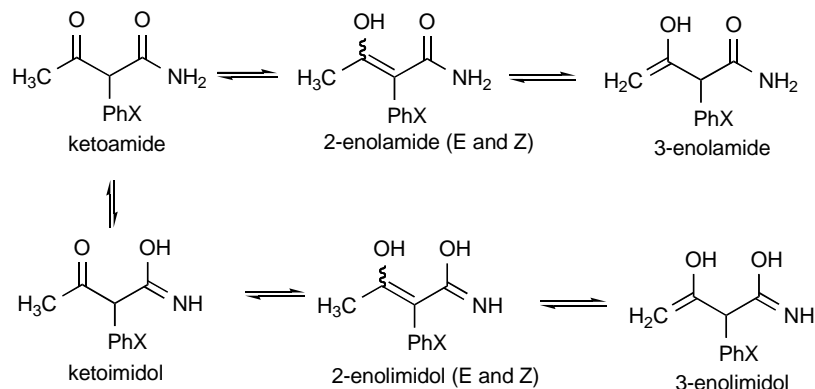
modified versions [17]. The compounds under study were identified by ^1H NMR and ^{13}C NMR in DMSO- d_6 , in which the peaks corresponding to the enol forms are depleted (Table 1).

NMR Measurements

^1H NMR 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 45°C. The content of long-lived tautomeric forms was calculated from the integrated peak intensities of hydroxyl and methine proton signals.

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



Scheme 1:

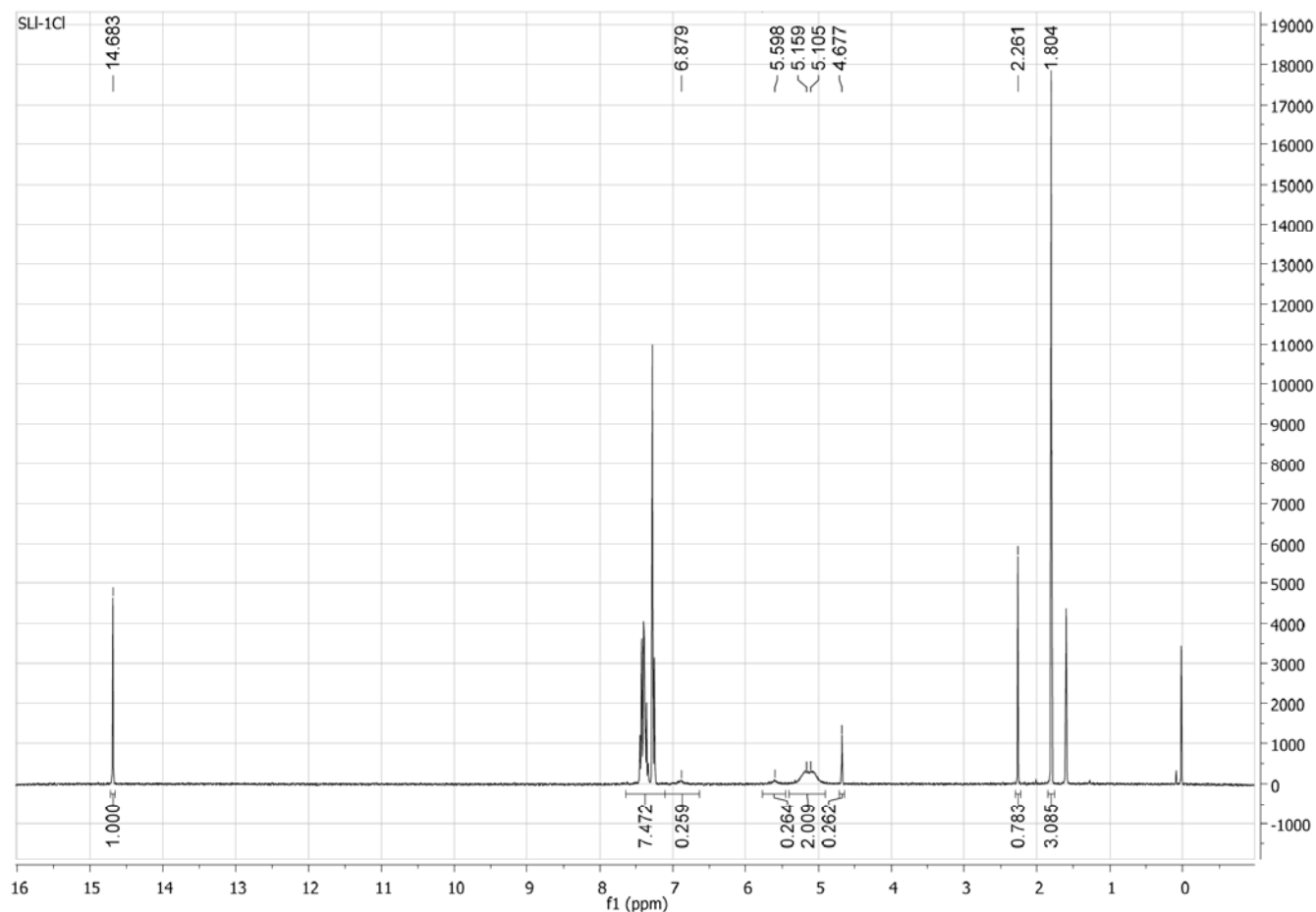


Figure 1: ^1H NMR spectrum of compound **I** in CDCl_3 at 25°C .

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

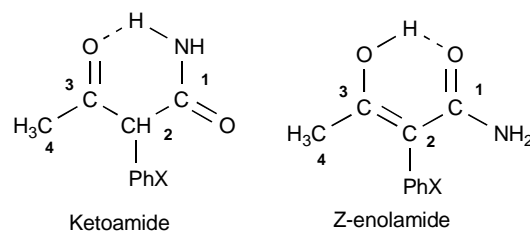
RESULTS AND DISCUSSION

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 ^1H NMR spectrum of compound **I** in CDCl_3 at 25°C . 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.



Scheme 2:

Table 2 shows the ^1H 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: ^1H NMR Chemical Shifts (in ppm) for Compounds I-III at 25°C

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 ($K_{\text{eq}} = [\text{enol}]/[\text{keto}]$) and the corresponding free energy at 25 °C ($\Delta G = -RT \ln K_{\text{eq}}$) 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.

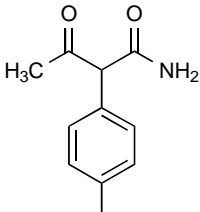
These observations can be explained regarding the influence of the substituents on the internal hydrogen bonds established in each tautomer.

- 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 solvation 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, K_{eq} and ΔG for Compounds I-III at 25°C

Compound	Solvent	% enol	% keto	K_{eq}	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 K_{eq} 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.

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

Thus, the calculated slopes and y-intercepts 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 $CDCl_3$

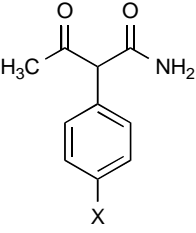
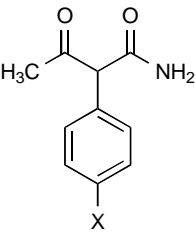
Compound	Temp	% enol	K	ΔH (kcal/mol)	ΔS (cal/mol.K)	
	I X = H	25°C	79,2	3,82	-3,0 ± 0,2	-7,4 ± 0,7
		35°C	76,1	3,18		
		45°C	73,6	2,78		
	II X = OCH ₃	25°C	75,5	3,09	-1,6 ± 0,2	-3,0 ± 0,7
		35°C	74,4	2,91		
		45°C	72,5	2,64		
	III X = Cl	25°C	79,5	3,88	-3,1 ± 0,1	-7,6 ± 0,3
		35°C	76,7	3,29		
		45°C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

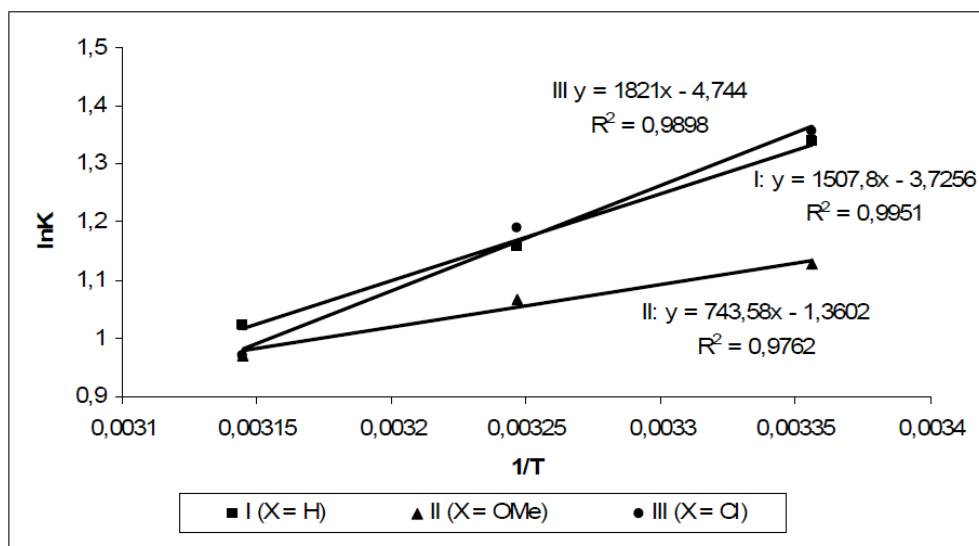


Figure 2: $\ln K$ vs $1/T$ plot for compounds I-III in CDCl_3 .

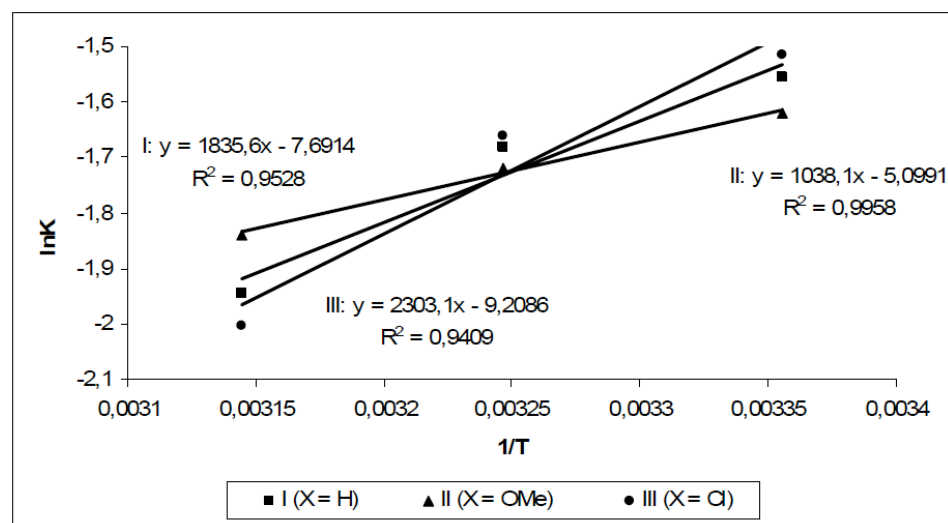
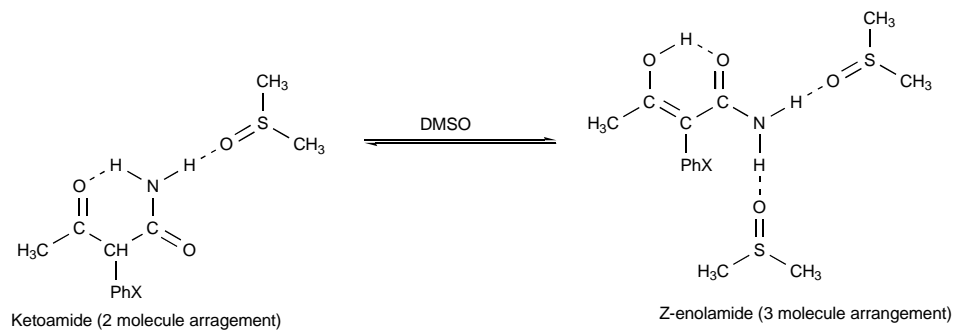


Figure 3: $\ln K$ vs $1/T$ plot for compounds I-III in DMSO-d_6 .



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 $\Delta H = a \cdot \Delta S + b$).

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 ^1H NMR 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.

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