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Substituent, Temperature and Solvent Effects on the Keto-Enol EQUILIBRIUM in β-Ketoamides: A Nuclear Magnetic Resonance Study

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ABSTRACT

Substituent, temperature and solvent effects on tautomeric equilibria in several β-ketoamides have been investigated by means of nuclear magnetic resonance spectroscopy (NMR). Keto-enol equilibrium predominates over the amide-imidol one. The relative stability of the individual tautomers and the corresponding equilibrium shifts are explained considering electronic and steric effects and tautomer stabilization *via* internal hydrogen bonds. In solution, these compounds exist mainly as ketoamide and Z-enolamide tautomers, both presenting intramolecular hydrogen bonds.

Keywords: β-Ketoamides; Keto-Enol Equilibrium; Nuclear Magnetic Resonance Spectroscopy

1. Introduction

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 [1-3]. However, the occurrence of this phenomenon in β-ketoamides has not been studied deeply, with exception of a few previous works [4,5]. It is usual to describe them only as keto forms [6], although some of them have been demonstrated to exist as a tautomeric mixture where the enol form is the major tautomer.

The importance of studying β-ketoamides arises from their versatility as intermediates in the synthesis of several heterocycles: 3-acyltetramic acids [7] (used in the total synthesis of tirandamycin and other related natural antibiotics [8]), pyrans [9], alkaloids [10], lactams and spirolactams [11], azetidin-2-ones [12], as well as several 3-hydroxyisothiazol bioisosteres of glutamic acid and analogs of the AMPA receptor agonist [13]. Moreover, some β-ketoamides have been converted into γ-ketoamides, a class of compounds related with a wide variety of biologically relevant systems [14].

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 their tautomeric distribution. Hence, it is of practical and theoretical importance to investigate tautomeric equilibria in such systems.

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 investigations on these processes [15].

The tautomeric equilibria of some β-ketobutanamides in solution were investigated by means of ^{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. This point has been studied for a series of 3-oxo-2-phenylbutanamides [17].

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In the present work, effects of substituents, solvents and temperature on the equilibria among different tautomeric forms in eleven *β*-ketoamides have been studied. Differential solvation effects, electron donor and acceptor substituents and temperature variations should shift the protomeric tautomerism.

2. Experimental

2.1. Synthesis of *β*-Ketoamides

β-ketoamides were synthesized and purified according to literature procedures or their modified versions [18]. 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**).

2.2. 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˚C, 35˚C and 45˚C. 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 spectrometer operating at 4.5 T from DMSO-d_6 solutions at 25˚C. The spectral conditions were the following: spectral width 10,559 Hz, acquisition times 1.303 s and 512 - 1000 scans per spectrum.

3. Results and Discussion

Schemes 1 and **2** show the possible tautomeric structures for *β*-ketoamides **I-III** and **IV-XI** respectively.

Each NMR spectrum is the result of the superposition of the spectra of the individual tautomers, since they are altogether in equilibrium. The only two tautomeric forms that could be identified in each spectrum were ketoamide and Z-enolamide (**Scheme 3**). 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 corresponding protons was made keeping in mind the theoretical displacements.

As an example, **Figure 1** shows the ^{1}HNMR spectrum of **I** (3-oxo-2-phenylbutanamide) in $CDCl_3$ at 25˚C. Values at the top correspond to the chemical shifts and the ones at the bottom, to the integration of each peak.

In order to assign the ^{1}HNMR signals to the corresponding tautomers, the peaks can be separated into to groups whose integration values show simple ratios. Peaks A, B, C and D appear to be in 3:1:1:1 ratio, while peaks X, Y and Z show 3:2:1 ratio.

Table 2 shows the expected number of non-aromatic signals and their respective integration for each tautomer, considering that in some of them internal hydrogen bond is possible to be established.

Thus, peaks X, Y ans Z can be assigned to the Z-enolamide hydrogens (CH_3, NH_2 and OH respectively), whereas peaks A, B, C and D can assigned to the ketoamide hydrogens (CH_3, CH, NH and NH respectively). The possibility of the latter to belong to ketoimidol or 2-enolimidol tautomers is discarded regarding previous studies which include theoretical calculations on these compounds [19].

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 ketoamides, the two tautomers of major concentration are capable of establishing internal hydrogen bonds (see **Scheme 3**). This stabilizing factor explains the following observations:

1) The high relative concentration of the involved tautomers,

2) The high value of δ observed for the hydroxyl proton in the enolamide form (peak Z, **Figure 1**),

3) The two different δ values of the hydrogen atoms bonded to nitrogen in the ketoamide form (peaks C and D, **Figure 1**).

Table 3 shows the ^{1}H chemical shifts of the studied compounds in $CDCl_3$ and DMSO-d_6. In many cases, hydrogens attached to N were observed as very broad and low peaks in DMSO-d_6 (due to the fact that they establish hydrogen bonds with the solvent causing a signifycant broadening of the corresponding signals), so their chemical shift could not be stablished properly. Atom numbering is shown in **Scheme 3**.

Table 4 shows the enol content present in each compound for both solvents. The integrated spectra made possible to calculate the enol ratio considering the peaks of H linked to C-2 (ketoamide tautomer) and the OH (Z-enolamide tautomer). Thus, enolic contents were calculated as follows:

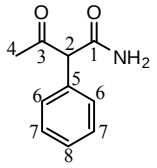
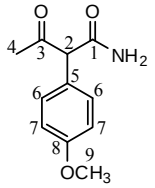
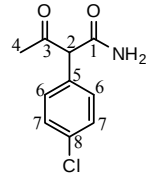
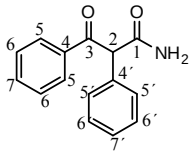
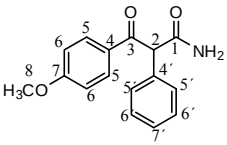
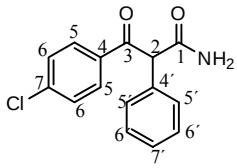
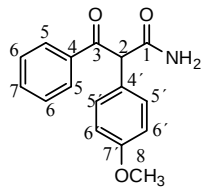
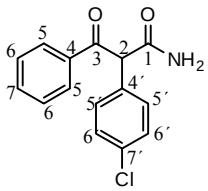
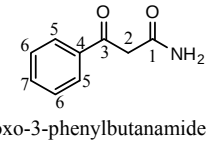
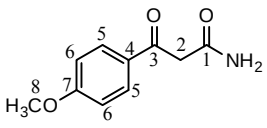
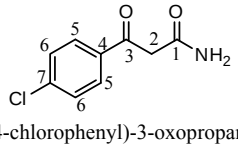
% enol = (OH integration)/(C-2 integration) Compounds **I-VIII**

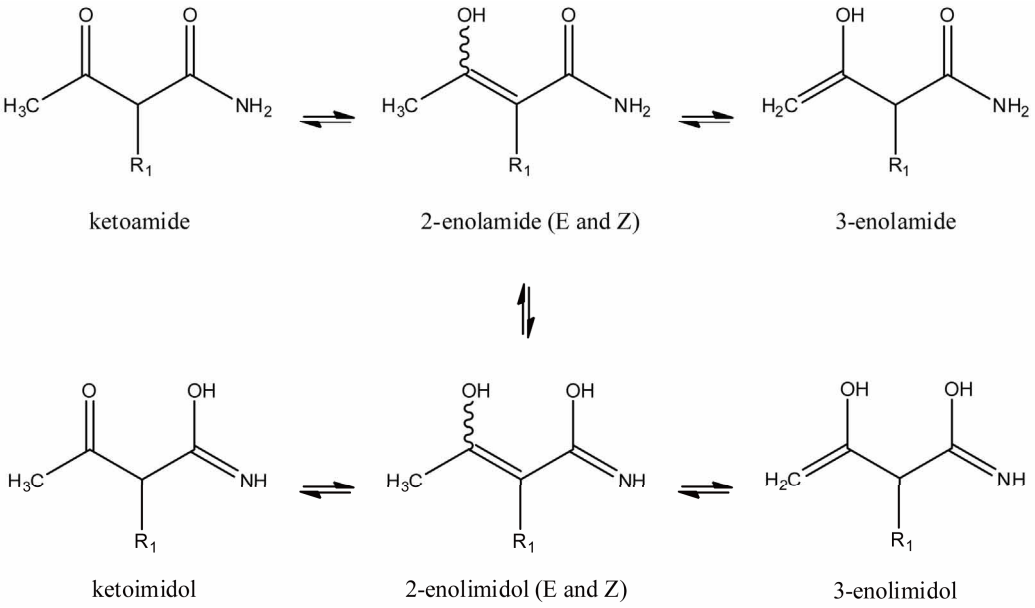
% enol = (OH integration)/((C-2 integration)/2) Compounds **IX-XI**

Then the equilibrium constant (Keq = [enol]/[keto]) and the corresponding free energy differences at 25˚C ($\Delta G^0 = -RT\ \ln Keq$) for the keto-enol equilibrium were determined (**Table 3**).

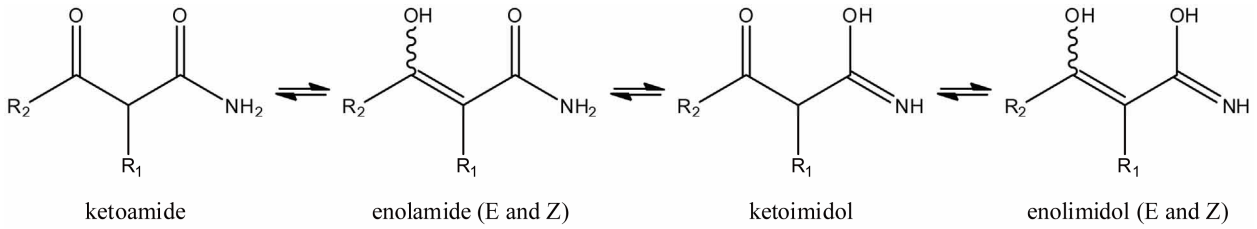
The relative stability of individual tautomers and the corresponding equilibrium shifts are explained considering several factors, such as electronic effects on the carbonyl group, stabilization by conjugation of the enol

Table 1. ^{1}HNMR and ^{13}CNMR data for the selected β-ketoamides (200MHz, DMSO-d_6).

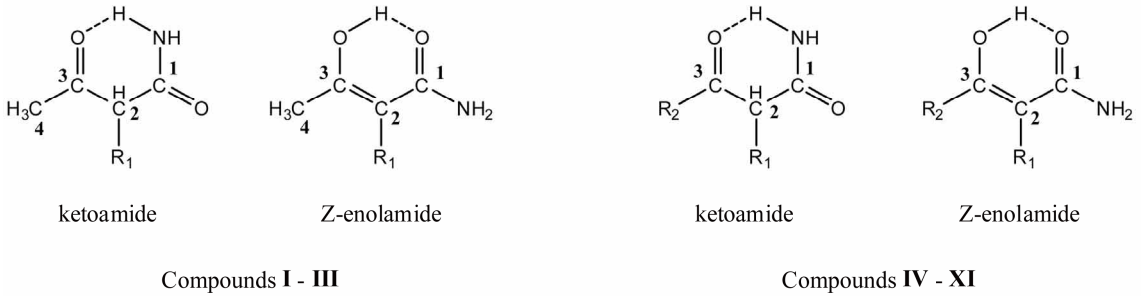
COMPOUND	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)	COMPOUND	^{1}H NMR δ (ppm)	^{13}C NMR δ (ppm)
 3-oxo-2-phenylbutanamide (**I**)	2.13 (s, 3H, 4) 4.58 (s, 1H, 2) 7.2-7.4 (m,5H, 6-7-8)	27.3 (4) 65.3 (2) 127.1 (8) 127.8 (6) 128.8 (7) 138.8 (5) 172.7 (1) 206.0 (3)	 2-(4-methoxyphenyl)-3-oxobutanamide (**II**)	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)	 3-oxo-2,3-diphenylpropanamide (**IV**)	5.75 (s, 1H, 2) 7.2-7.9 (m, 10H, 5-5′-6-6′-7-7′)	60.3 (2) 127.5 (7′) 129.4 (6′) 128.0 (5′) 141.0 (4′) 128.2 (6) 128.9 (5) 132.7 (7) 172.1 (1) 195.6 (3)
 3-(4-methoxyphenyl)-3-oxo-2-phenylpropanamide (**V**)	3.83 (s, 3H, 8) 5.69 (s, 1H, 2) 7.1-7.9 (m, 10H, 5-5′-6-6′-7-7′)	60.9 (2) 55.6 (8) 114.3 (6) 127.2 (7′) 128.4 (5′) 129.0 (4) 129.3 (6′) 129.8 (5) 140.4 (4′) 165.2 (7) 172.5 (1) 194.1 (3)	 3-(4-chlorophenyl)-3-oxo-2-phenylpropanamide (**VI**)	5.74 (s, 1H, 2) 7.2-8.0 (m, 10H, 5-5′-6-6′-7-7′)	61.5 (2) 127.5 (7′) 128.1 (5′) 128.7 (6) 129.2 (6′) 130.4 (5) 135.0 (4) 138.3 (7) 140.5 (4′) 173.2 (1) 195.3 (3)
 2-(4-methoxyphenyl)-3-oxo-3-phenylpropanamide (**VII**)	3.73 (s, 3H, 8) 5.68 (s, 1H, 2) 7.1-7.9 (m, 10H, 5-5′-6-6′-7-7′)	60.5 (2) 55.3 (8) 114.8 (6′) 128.4 (6) 128.8 (5) 130.6 (5′) 132.7 (4′) 133.1 (7) 136.7 (4) 159.5 (7′) 171.1 (1) 193.2 (3)	 2-(4-chlorophenyl)-3-oxo-3-phenylpropanamide (**VIII**)	5.79 (s, 1H, 2) 7.3-7.9 (m, 10H, 5-5′-6-6′-7-7′)	61.7 (2) 128.2 (6) 128.7 (5) 129.3 (6′) 131.0 (5′) 133.0 (7′) 133.5 (7) 136.9 (4) 138.5 (4′) 173.0 (1) 195.3 (3)
 3-oxo-3-phenylbutanamide (**IX**)	3.44 (s, 2H, 2) 7.16 (s, 2H, N) 7.5-7.9 (m, 5H, 5-6-7)	45.3 (2) 128.9 (5) 128.5 (6) 133.1 (7) 136.7 (4) 171.3 (1) 194.2 (3)	 3-(4-methoxyphenyl)-3-oxopropanamide (**X**)	3.41 (s, 2H, 2) 3.83 (s, 3H, 8) 7.02 (s, 2H, N) 7.21 (d, 2H, 6) 7.83 (d, 2H, 5)	44.8 (2) 55.8 (8) 114.2 (6) 129.0 (4) 129.8 (5) 165.0 (7) 171.2 (1) 193.5 (3)
 3-(4-chlorophenyl)-3-oxopropanamide (**XI**)	3.55 (s, 2H, 2) 7.20 (s, 2H, N) 7.60 (d, 2H, 6) 7.88 (d, 2H, 5)	46.2 (2) 128.7 (6) 130.2 (5) 134.8 (4) 138.7 (7) 171.8 (1) 195.1 (3)			



Scheme 1. Possible tautomeric structures for compounds I-III.



Scheme 2. Possible tautomeric structures for compounds IV-XI.



Scheme 3. Internal hydrogen bonds occurring in Z-enolamide and ketoamide tautomers.

Table 2. Expected signal integration for non-aromatic hydrogens in compund I tautomers.

Tautomer	ketoamide	2-enolamide	3-enolamide	ketoimidol	2-enolimidol	3-enolimidol
Expected signal integration	3:1:1:1	3:2:1	2:1:1:1:1	3:1:1:1	3:1:1:1	1:1:1:1:1:1

double bond, steric effects introduced by bulky groups and tautomer stabilization *via* internal hydrogen bonds.

Steric effects: The structure of Z-enolamide tautomers of compounds presenting two phenyl groups (compounds **IV-VIII**) exhibit greater steric repulsion than compounds having a phenyl and a methyl groups (compounds **I-III**), reducing the enol content in the former ones. In the case of ketoamide tautomer, this steric repulsion is reduced because of the rotation in the C-2 - C-3 bond, letting the two phenyl groups to get further from each other.

On the other hand, bulky phenyl groups in C-2 position increase the enolic content (compare compounds **IX-XI** with **I-III** and **IV-VIII**). This fact is in concordance with previous studies [20,21].

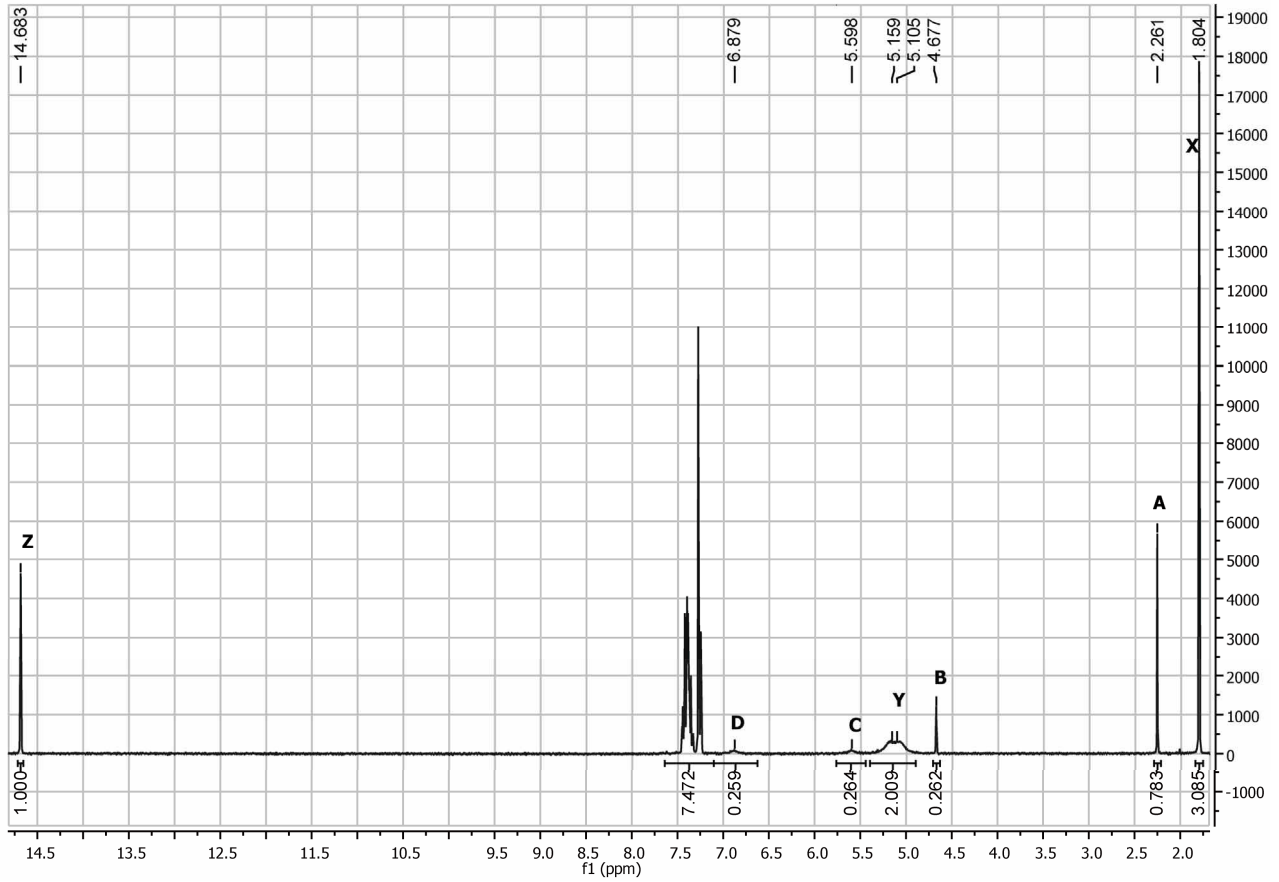


Figure 1. ^{1}HNMR spectrum of compound I in $CDCl_3$ at 25°C.

Substituent effects: 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 atoms (compounds **III**, **VI**, **VIII** and **XI**) increase the enol content, whereas methoxy groups (compounds **II**, **V**, **VII** and **X**) shift the equilibrium towards the keto tautomer. These effects are more pronounced if the substituent is in C-3 (compare **V-VII/VI-VIII**).

These observations could be explained taking into account the influence of the substituents on the internal hydrogen bonds established in each tautomer:

An electron donor in C-2 position (compounds **II**, 2-(4-methoxyphenyl)-3-oxobutanamide, and **VII**, 2-(4-methoxyphenyl)-3-oxo-3-phenylpropanamide) weakens the enol hydrogen bond destabilizing it, and, at the same time, stabilizes the keto form. These facts decrease the enolic content.

An electron acceptor in C-2 position (compounds **III**, 2-(4-chlorophenyl)-3-oxobutanamide, and **VIII**, 2-(4-chlorophenyl)-3-oxo-3-phenylpropanamide) strengthens the enol hydrogen bond stabilizing it, and, at the same time, destabilizes the keto form. These facts increase the enolic content.

An electron donor in C-3 position (compounds **V**, 3-(4-methoxyphenyl)-3-oxo-2-phenylpropanamide, and **X**, 3-(4-methoxyphenyl)-3-oxopropanamide) strengthens the enol hydrogen bond stabilizing it, but it stabilizes the keto form even more. These facts decrease the enolic content.

An electron acceptor in C-3 position (compounds **VI**, 3-(4-chlorophenyl)-3-oxo-2-phenylpropanamide, and **XI**, 3-(4-chlorophenyl)-3-oxopropanamide) strengthens the enol hydrogen bond stabilizing it, and, at the same time, destabilizes the keto form. These facts increase the enolic content.

In C-2 position, the stabilizing effects in keto and enol form would be, ultimately, inductive. That is why in this position the effects are weaker than in C-3, were inductive and mesomeric effects are affecting the keto and enol form. These assumptions are supported by previous works in the gas phase [19] (where the same behaviour was observed and supported by theoretical calculations) and the analysis of the dependence of δ with temperature in the next section.

Temperature effects: Enol contents and equilibrium constants Keq were determined for compounds **I-XI** in

Table 3. ^{1}H chemical shifts (δ, ppm) for compounds I-XI (atom numbering depicted in Scheme 3).

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 keto); 7.2 - 7.5 (aromatics); 15.79 (OH enol).
IV	$CDCl_3$	5.30 (NH_2 enol); 5.61 (C-2 keto); 5.53/6.98 (NH_2 keto); 7.1 - 8.0 (aromatics); 15.25 (OH enol).
	DMSO-d_6	5.75 (C-2 keto); 7.2 - 7.9 (aromatics)
V	$CDCl_3$	3.90 (OCH_3 keto); 3.93 (OCH_3 enol); 5.31 (NH_2 enol); 5.49 (C-2 keto); 5.63/7.18 (NH_2 keto); 6.9 - 8.0 (aromatics); 14.31 (OH enol).
	DMSO-d_6	3.83 (OCH_3 keto); 5.69 (C-2 keto); 7.1 - 7.9 (aromatics)
VI	$CDCl_3$	5.37/5.46 (NH_2 enol); 5.54 (C-2 keto); 5.72/6.93 (NH_2 keto); 7.0 - 8.0 (aromatics); 15.30 (OH enol).
	DMSO-d_6	5.74 (C-2 keto); 7.2 - 8.0 (aromatics)
VII	$CDCl_3$	3.76 (OCH_3 keto); 3.76 (OCH_3 enol); 5.38 (NH_2 enol); 5.54 (C-2 keto); 5.66/6.9[1] (NH_2 keto); 6.8 - 8.0 (aromatics); 15.22 (OH enol).
	DMSO-d_6	3.73 (OCH_3 keto); 5.68 (C-2 keto); 7.1 - 7.9 (aromatics)
VIII	$CDCl_3$	5.33 (NH_2 enol); 5.58 (C-2 keto); 5.62/7.2[1] (NH_2 keto); 7.0 - 8.0 (aromatics); 15.32 (OH enol).
	DMSO-d_6	5.79 (C-2 keto); 7.3 - 7.9 (aromatics)
IX	$CDCl_3$	3.99 (C-2 keto); 5.26 (NH_2 enol); 5.57 (C-2 enol); 5.55/7.02 (NH_2 keto); 7.2 - 8.1 (aromatics); 14.22 (OH enol).
	DMSO-d_6	3.90 (C-2 keto); 7.15 (NH_2 enol); 5.78 (C-2 enol); 7.36 (NH_2 keto); 7.4 - 8.1 (aromatics); 15.31 (OH enol).
X	$CDCl_3$	3.86 (OCH_3 enol); 3.90 (OCH_3 keto); 3.93 (C-2 keto); 5.49 (C-2 enol); 5.64/7.2[1] (NH_2 keto); 6.9 - 8.0 (aromatics); 14.31 (OH enol).
	DMSO-d_6	3.78 (C-2 keto); 3.80 (OCH_3 enol); 3.84 (OCH_3 keto); 5.63 (C-2 enol); 7.0 - 8.0 (aromatics); 15.27 (OH enol).
XI	$CDCl_3$	3.96 (C-2 keto); 5.34 (NH_2 enol); 5.54 (C-2 enol); 5.68/7.00 (NH_2 keto); 7.2 - 8.0 (aromatics); 14.28 (OH enol).
	DMSO-d_6	3.86 (C-2 keto); 5.74 (C-2 enol); 7.1 - 8.0 (aromatics); 15.31 (OH enol).

[1]In compounds **VII**, **VIII** and **X**, the peak corresponding to the ketoamide NH_2 overlaps the aromatic signals and its value could not be determined precisely.

$CDCl_3$ and DMSO-d_6 at five different temperatures between 25˚C and 45˚C. Equation 1 provides a simple method to determine ΔH and ΔS in keto-enol tautomerization for the studied compounds.

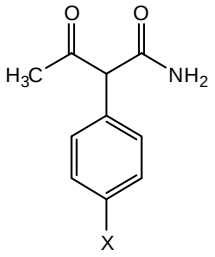
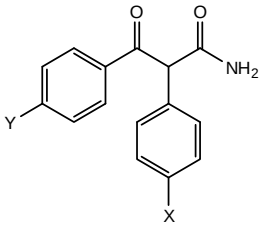
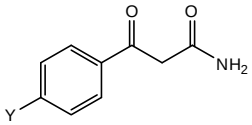
$$\ln\left(\frac{[\text{enol}]}{[\text{keto}]}\right) = \ln k = -\frac{\Delta G}{RT} = -\frac{\Delta H}{R}\cdot\frac{1}{T} + \frac{\Delta S}{R} \qquad (1)$$

Figures 2 and **3** show the ln$K$ *vs* 1/T plot for β-ketoamides **I-XI** in both solvents. The calculated slopes and y-intercepts from these graphics can be used to determine the enthalpy and entropy changes. Results are shown in **Table 5**.

As it is expected, compounds bearing an electron releasing group (compounds **II**, **V**, **VII** and **X**), which have lower enolic contents (**Table 3**), show higher values of ΔH. Compounds attached to electron withdrawing groups (compounds **III**, **VI, VIII** and **XI**) have higher enolic contents and lower ΔH values.

Solvent effects: Differential solvatation effects should shift the protomeric tautomerism. Data from **Table 4** clearly demonstrate that an increase in the solvent polarity increases the proportions of keto forms for compounds **I-VIII**. In the case of compounds **IX-XI**, the effect is the opposite. This effect can be explained considering the values of ΔH and ΔS of each compound.

Table 4. Keto-enol content, equilibrium constant (Keq) and ΔG^0 in $CDCl_3$ and DMSO-d_6 at 25˚C for compounds I-XI.

Compound		Solvent	% enol	% keto	Keq	ΔG^0 (kcal·mol^{-1})
	**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
	IV X = Y = H	$CDCl_3$	28.0	72.0	0.389	0.56 ± 0.06
		DMSO-d_6	0.0	100.0	0.0	-
	**V** X = H/Y = OCH_3	$CDCl_3$	9.0	91.0	0.099	1.79 ± 0.06
		DMSO-d_6	0.0	100.0	0.0	-
	VI X = H/Y = Cl	$CDCl_3$	40.6	59.4	0.684	0.22 ± 0.06
		DMSO-d_6	0.0	100.0	0.0	-
	VII X = OCH_3/Y = H	$CDCl_3$	25.0	75.0	0.333	0.65 ± 0.06
		DMSO-d_6	0.0	100.0	0.0	-
	VIII X = Cl/Y = H	$CDCl_3$	28.8	71.2	0.404	0.54 ± 0.06
		DMSO-d_6	0.0	100.0	0.0	-
	**IX** Y = H	$CDCl_3$	12.2	87.8	0.139	1.17 ± 0.06
		DMSO-d_6	29.1	70.9	0.411	0.53 ± 0.06
	X Y = OCH_3	$CDCl_3$	3.8	96.2	0.0393	1.94 ± 0.06
		DMSO-d_6	14.7	85.3	0.173	1.58 ± 0.06
	XI Y = Cl	$CDCl_3$	16.7	83.3	0.200	0.95 ± 0.06
		DMSO-d_6	39.4	60.6	0.650	0.26 ± 0.06

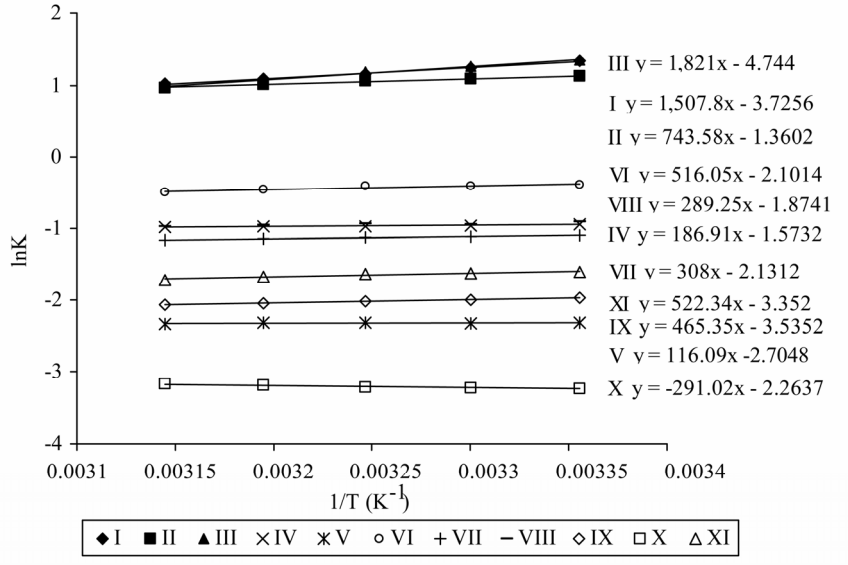


Figure 2. ln*K vs* 1/*T* plot for compounds I-XI in $CDCl_3$.

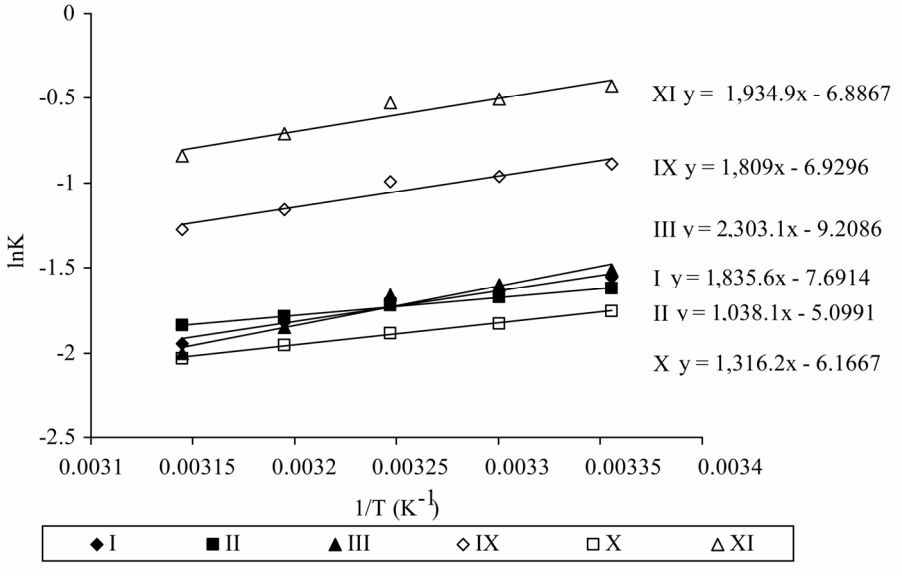
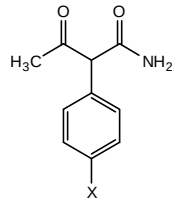
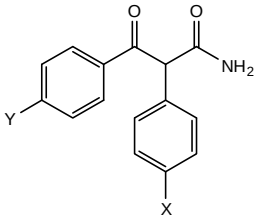
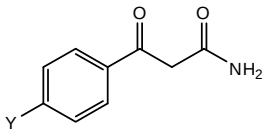


Figure 3. ln*K vs* 1/*T* plot for compounds I-III and IX-XI in DMSO-d_6.

Table 5. Thermodinamic parameters in $CDCl_3$ and in DMSO-d_6 for compounds I-XI.

Compound		$CDCl_3$		DMSO-d_6	
		ΔH (kcal·mol^{-1})	ΔS (cal·mol·K^{-1})	ΔH (kcal·mol^{-1})	ΔS (cal·mol·K^{-1})
	**I** X = H	−3.0 ± 0.2	−7.4 ± 0.7	−3.6 ± 0.8	−15 ± 3
	II X = OCH_3	−1.6 ± 0.2	−3.0 ± 0.7	−2.0 ± 0.2	−10.0 ± 0.5
	III X = Cl	−3.1 ± 0.1	−7.6 ± 0.3	−5 ± 1	−18 ± 4
	**IV** X = Y = H	−0.40 ± 0.02	−3.20 ± 0.05	-	-
	V X = H/Y = OCH_3	−0.23 ± 0.08	−6.7 ± 0.3	-	-
	VI X = H/Y = Cl	−1.0 ± 0.3	−4 ± 1	-	-
	VII X = OCH_3/Y = H	−0.32 ± 0.07	−3.3 ± 0.3	-	-
	VIII X = Cl/Y = H	−0.58 ± 0.08	−3.7 ± 0.5	-	-
	**IX** Y = H	−0.92 ± 0.01	−7.02 ± 0.04	−3.6 ± 0.9	−14 ± 3
	X Y = OCH_3	+0.5 ± 0.3	−4.9 ± 0.9	−2.7 ± 0.2	−14.4 ± 0.5
	XI Y = Cl	−1.1 ± 0.3	−7 ± 1	−4 ± 1	−14 ± 4

As it can be seen from **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 of establishing two intermolecular hydrogen bonds per molecule, while in the ketoamide tautomer only one intermolecular hydrogen bond is possible (**Scheme 4**).

On the other hand, ΔS values are more negative in this solvent, 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 with DMSO-d_6, with different degrees of molecular coordination order (**Scheme 4**).

The result of these two contrary effects is explained by experimental determinations, and the overall equilibrium shift (which depends ultimately on ΔG, **Table 4**) indicates that in compounds **I-VIII** the entropic effect predominates over the enthalpic effect. On the other hand, in compounds **IX-XI** the entropic effect is the one that rules the situation.

The difference between these two opposite behaviors can be explained considering that in compounds **I-VIII** (in which R_1 = Ar) the solvation of one NH hydrogen is sterically hindered by the phenyl group in C-2 position. In the case of compounds **IX-XI** (in which $R_1 = H$) both NH hydrogens are easily solvated. These assumptions are supported by the different decrease in ΔH in DMSO-d_6 respecting to $CDCl_3$ (approximately a decrease of 1 Kcal/mol in compounds **I-VIII** and 3 Kcal/mol in compounds **IX-XI**).

Data obtained from these experiments suggest an enthalpy-entropy compensation (since ΔH and ΔS seem to be lineally correlated $\Delta H = a \cdot \Delta S + b$), but, at first sight, this correlation would not be strictly valid since ΔS and ΔH values were obtained from the same experiment [22]. However, linearity between ln$K$ at two different temperatures (25˚C and 45˚C) is observed, as shown in **Figure 4**. From the equation ln$K$(45˚C) = m·ln$K$(25˚C) + n, a simple deduction can be made to obtain $\Delta H = a \cdot \Delta S + b$ (*i.e.* an enthalpy-entropy compensation), as follows:

$$\ln K_2 = m \cdot \ln K_1 + n$$

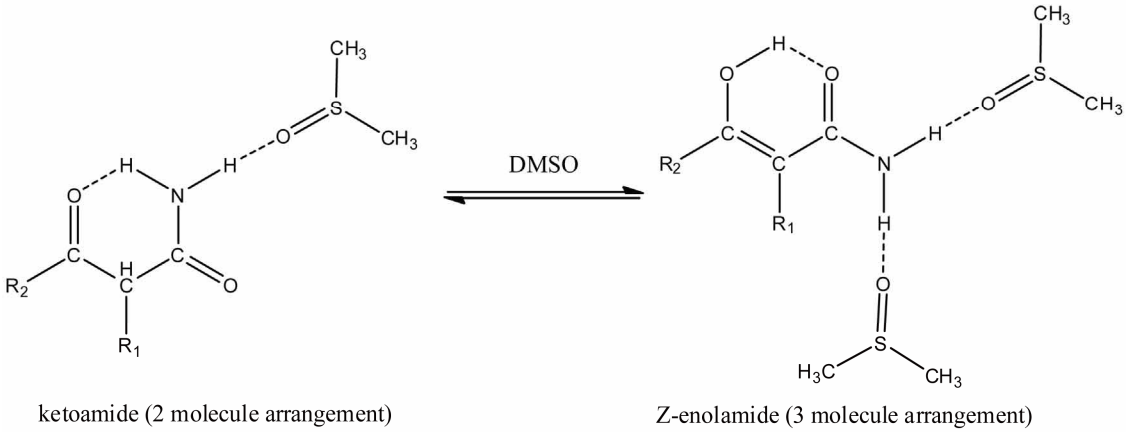
$$-\Delta G_2 / (RT_2) = -m \cdot \Delta G_1 / (RT_1) + n$$

$$-\Delta H / (RT_2) + \Delta S / R = -m \cdot \Delta H / (RT_1) + m \cdot \Delta S / R + n$$

$$\Delta H = (m-1) T_1 T_2 / (mT_2 - T_1) \cdot \Delta S + nRT_1 T_2 / (mT_2 - T_1)$$

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

where T_1 = 25˚C (298 K), T_2 = 45˚C (318 K), K_1 and K_2 are the equilibrium constants at T_1 and T_2 respectively, and ΔH and ΔS are supposed to be constant within the



Scheme 4. Tautomer-solvent interactions via hydrogen bond in DMSO-d_6.

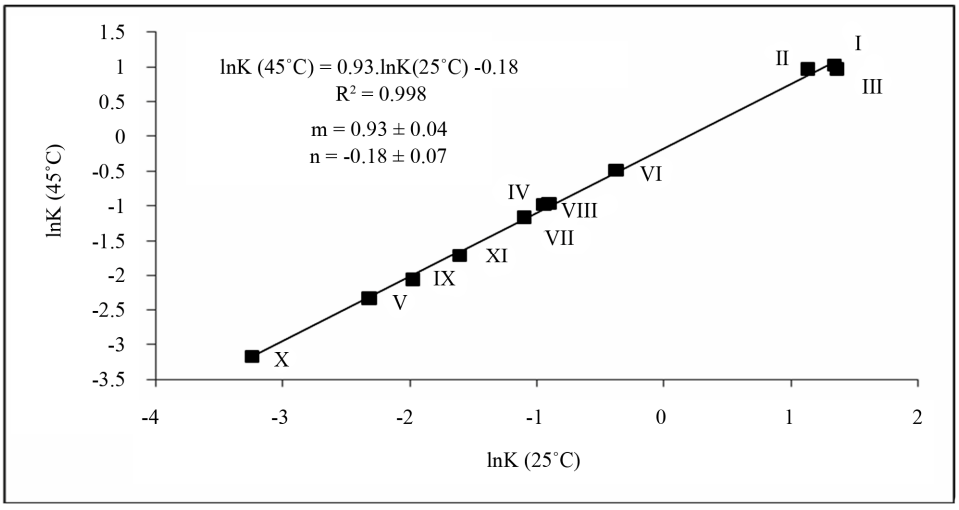


Figure 4. ln$K$ (45˚C) *vs* ln$K$ (25˚C) plot for compounds I-XI in $CDCl_3$.

temperature interval. This enthalpy-entropy compensation suggests a common mechanism underlying all of the studied equilibria [22].

In order to correlate enol contents and thermodynamical functions (ΔH and ΔS) with the stability of the intramolecular hydrogen bonds, the dependence of δ of OH and NH hydrogens with temperature were studied for compounds **I-III** and **IX-XI** in $CDCl_3$. Previous works have established that $\Delta\delta/\Delta T$ values can be correlated with the stability of hydrogen bonds (the lower the value of $\Delta\delta/\Delta T$, the greater the stability of the bond) [23,24]. The data are presented in **Tables 6** and **7**.

This analysis was not made for compounds **IV-VIII**, since the signals corresponding to NH hydrogen are overlapped with the aromatic ones, not allowing a precise determination of their δ.

Table 6. Temperature dependence of δ for compounds I-III in $CDCl_3$.

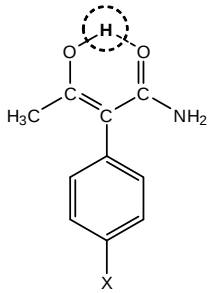
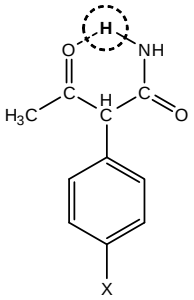
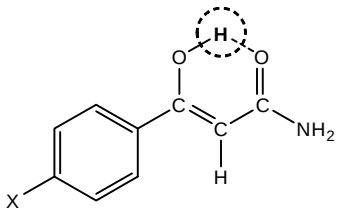
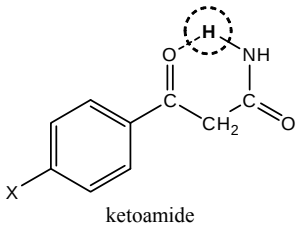
Tautomeric form	Compound	Temp.	δ (ppm)	$\Delta\delta/\Delta T$ (ppb·K^{-1})
 enolamide Z	**I** X = H	25˚C 35˚C 45˚C	14.665 14.650 14.632	−1.6 ± 0.1
	II X = OCH_3	25˚C 35˚C 45˚C	14.612 14.597 14.577	−1.8 ± 0.2
	III X = Cl	25˚C 35˚C 45˚C	14.700 14.689 14.675	−1.2 ± 0.1
 ketamide	**I** X = H	25˚C 35˚C 45˚C	6.867 6.798 6.731	−6.80 ± 0.06
	II X = OCH_3	25˚C 35˚C 45˚C	6.805 6.750 6.675	−6.5 ± 0.6
	III X = Cl	25˚C 35˚C 45˚C	6.860 6.773 6.715	−7.3 ± 0.8

Table 7. Temperature dependence of δ for compounds IX-XI in $CDCl_3$.

Tautomeric form	Compound	Temp.	δ (ppm)	$\Delta\delta/\Delta T$ (ppb·K^{-1})
 enolamide Z	**IX** X = H	25˚C 35˚C 45˚C	14.223 14.208 14.192	−1.7 ± 0.2
	X X = OCH_3	25˚C 35˚C 45˚C	14.228 14.205 14.198	−1.5 ± 0.5
	XI X = Cl	25˚C 35˚C 45˚C	14.260 14.248 24.237	−1.15 ± 0.03
 ketoamide	**IX** X = H	25˚C 35˚C 45˚C	7.152 7.095 7.043	−5.80 ± 0.06
	X X = OCH_3	25˚C 35˚C 45˚C	7.116 7.051 7.012	−5.2 ± 0.8
	XI X = Cl	25˚C 35˚C 45˚C	6.976 6.925 6.856	−6.0 ± 0.6

The calculated $\Delta\delta/\Delta T$ values agree with the ones obtained in previous works for similar compounds ($\Delta\delta/\Delta T < 4$ ppb·K^{-1} for O—H•••O and $\Delta\delta/\Delta T < 9$ ppb·K^{-1} for N—H•••O) [23,24], corroborating that the hydrogen bonds are, indeed, intramolecular.

Taking into account data from **Tables 6** and **7**, it can be concluded that they are consistent with the previous assumption regarding the effect of the internal hydrogen bonds on the stability of the tautomers. In other words, compounds showing lower values of $\Delta\delta/\Delta T_{\text{OH enol}}$ and higher values of $\Delta\delta/\Delta T_{\text{NH keto}}$ are also the ones that have higher enolic content and *vice versa*.

4. Conclusions

It has been demonstrated that keto-enol tautomerism in *β*-ketoamides (studied by NMR spectroscopy, a very useful technique for the determination of tautomeric species in solution) is strongly dependent on the solvents, temperature and substituents. Intramolecular hydrogen bond seems to be the main factor in stabilizing the different tautomeric forms.

In solution, these compounds exist mainly as ketoamide and Z-enolamide tautomers, both presenting internal hydrogen bonds. The rest of the possible tautomers (ketoimidol, E-enolamide, 3-enolamide, enolimidol) show very low concentration (at least lower than the detection limit) or probably do not exist in neutral solution.

In all cases, the equilibrium is shifted to the Z-enolamide form by several factors:

1) Electron withdrawing substituents attached to aromatic rings (e.g. chlorine).

2) A temperature decrease, since the equilibria are exothermic (except for compound **X**).

3) Bulky groups in C-2 position. This effect is less important when two phenyl groups in C-2 and C-3 positions are present, because of the steric hindrance.

4) The presence of hydrogen bond acceptor solvents (e.g. DMSO), but only when there are no bulky groups in C-2. Otherwise, hydrogen bond acceptor solvents decrease the enol content.

All these factors increase the enolamide content apparently by stabilizing the Z-enolamide tautomers (strengthening the internal O—H•••O = C hydrogen bond) and/or destabilizing the ketoamide tautomer (weakening the internal C = O•••H—N hydrogen bond).

5. Acknowledgements

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rahydroquinazolines," *Tetrahedron*, Vol. 58, No. 5, 2002, pp. 1011-1016. http://dx.doi.org/10.1016/S0040-4020(01)01196-6

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