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Solvent effects on tautomerics equilibria in β-ketonitriles: NMR and theoretical studies†

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Solvent effects on tautomeric equilibria in several β-ketonitriles has been investigated using nuclear magnetic resonance (NMR) spectroscopy and theoretical methods. The experimental chemical shifts were compared with theoretical values obtained by using gauge-including atomic orbital (GIAO) calculations, implemented at Density Functional Theory (DFT) level with hybrid functionals, B3LYP calculations. The solvent effect on the calculated structures has been taken into account through the polarized continuum model (PCM) for chloroform, acetone and dimethyl sulfoxide (DMSO). Also, some structural parameters were calculated in gas phase and in three different solvents. Copyright © 2010 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this paper

Keywords: β-ketonitriles; NMR spectroscopy; PCM; solvent effect; tautomeric equilibrium

INTRODUCTION

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 of these processes.[1]

Much attention has been paid to β-ketonitriles, which are useful synthetic intermediates[2] and they have been used as precursors for a wide variety of heterocyclic structures.[3–7] Recent interest in β-ketonitriles has been focused on their bioreduction[8,9] and parallel kinetic resolution[10] for the preparation of enantiopure ketones and alcohols containing a quaternary stereocenter in line with the growing importance of optically active β-hydroxy nitriles as intermediates in the preparation of γ-amino alcohols.[11]

The reactivity of β-ketonitriles is related to their structure and their tautomeric equilibria; that is why it should be useful to determine the 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.

In previous works, the presence of a tautomeric equilibrium in β-ketonitriles has been indicated between the keto form and the enol forms (E and Z).[12] However, as depicted in Scheme 1, selected β-ketonitriles could exist in four probable tautomeric forms: keto, enol E, enol Z or ketenimine.where G = H, Cl or OCH_3

In the present work, we have studied effects of substituents and solvents on the equilibria among different tautomeric forms in the **2**,**3**-diphenyl-**3**-oxopropanenitrile, **2**-(**4**-chlorophenyl)-**3**-oxo-**3**-phenylpropanenitrile and **2**-(**4**-methoxyphenyl)-**3**-oxo-**3**-phenyl propanenitrile. Differential solvation effects should shift the protomeric tautomerism. Thus, in polar solvents species with greater dipolar moment are more stabilized.

NMR measurements and quantum chemical calculations have been combined to explore the shift of established equilibria in different solvents.

Most theoretical studies of tautomeric reactions have been concerned with those occurring in the gas phase. Although some efforts have been made in the last few year to simulate tautomeric processes in solution, those were mostly in aqueous solution.[13–15]

We have undertaken a theoretical study of the molecular structure, free energy *G* and total energy of the keto–enol and nitrile–ketenimine tautomers of the selected ketonitriles with the Density Functional Theory (DFT) with the B3LYP hybrid exchange-correlation energy functional and 6-31G(d,p) basis set. The Polarizable Continuum (SCRF/PCM) solvent model was also taken into account in order to show solvent influence on electron density and electrostatic potential around the exemplary molecules. Theoretical results were compared with the experimental data.

EXPERIMENTAL

Computational methods

The molecules under study were subjected to geometry optimizations using the DFT[16,17] To this end, the B3LYP hybrid

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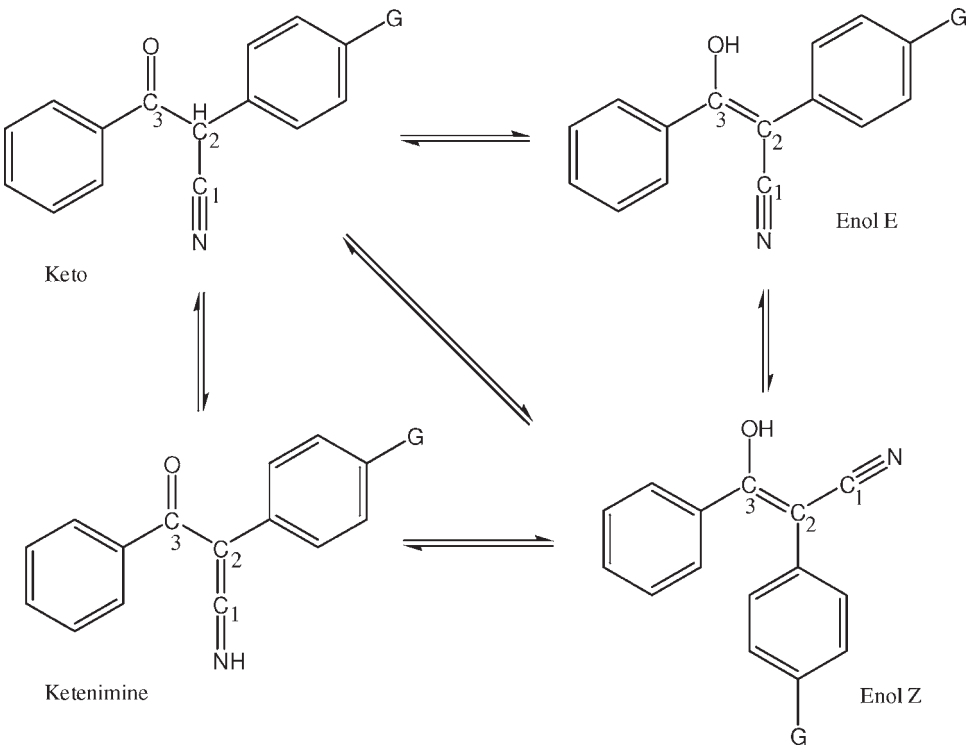

Scheme 1.

exchange-correlation functional[18,19] together with the 6-31G(d,p) basis set as implemented in the Gaussian 03 package[20] was used. All geometrical parameters were optimized without constraints.

Dielectric solvent effects were taken into account using the SCRF-PCM version of the polarization continuum model, PCM, of Tomasi and co-workers.[21–23]

Finally, the isotropic chemical shifts for hydrogen and carbon atoms were also calculated. In this case, the isotropic magnetic shielding tensor was obtained at the B3LYP/6-31G(d,p). The reported shifts are relative to tetramethylsilane (TMS). The absolute isotropic shieldings of TMS were also calculated using B3LYP/6-31G(d,p) model.

NMR measurements

2,**3**-diphenyl-**3**-oxopropanenitrile, **2**-(**4**-chlorophenyl)-**3**-oxo-**3**-phenylpropanenitrile and **2**-(**4**-methoxyphenyl)-**3**-oxo-**3**-phenylpropanenitrile were synthesized and purified according to literature procedures.[24,25]

^{1}H NMR spectra in $CDCl_3$, acetone-d_6 and DMSO-d_6 were recorded with a Varian Mercury Plus 200 spectrometer operating at 4.5 T. The typical spectral conditions were as follows: spectral width 3201 Hz, acquisition time 4.09 s and 8–16 scans per spectrum. Digital resolution was 0.39 Hz per point. Deuterium from the solvent was used as the lock and TMS as the internal standard. Sample concentration was 0.05 M.

The content of long-lived tautomeric forms was calculated from the integrated peak intensities of the aromatics and methine proton signals.

^{13}C proton decoupled and gated decoupled spectra were recorded with the same spectrometer from $CDCl_3$, acetone-d_6 and DMSO-d_6 solutions at 25 °C. The spectral conditions were the following: spectral width 10559 Hz, acquisition times 1.303 s and 512–1000 scans per spectrum. The concentration was 30 mg/ml and digital resolution was 1.29 Hz per point.

A standard one-dimensional (1D) proton NMR spectrum and a carbon spectrum with broad-band proton decoupling were run of each sample, supplemented by 2D gradient selected correlation spectroscopy (COSY) and multiplicity-edited heteronuclear single quantum coherence (HSQC) experiments to help with the assignment of signals. All 2D spectra were recorded with the same spectrometer from solutions at 25 °C.

RESULTS AND DISCUSSION

^{1}H NMR and ^{13}C NMR spectra

Table 1 shows the ^{1}H and ^{13}C chemical shifts of the compounds studied in $CDCl_3$, acetone-d_6 and DMSO-d_6. The ketenimine form was never observed by us on the basis of ^{1}H and ^{13}C NMR spectra. For the enol forms, the assignment of E or Z was made keeping in mind the theoretical displacements.

Differential solvatation effects should shift the protomeric tautomerism. Thus, in polar solvents species with greater dipolar moment are more stabilized. This could be observed when ^{1}H-NMR spectra were recorded in solvents of different polarity.

Intramolecular hydrogen bonding is the main factor that governs the kinetics and influences the structure of keto–enol tautomerism in solution. Because of the linearity of the cyano group, a cyclic structure with an intramolecular hydrogen bond is impossible in all β-ketonitrile.

Starting from the integrated spectra, the proportion of the present tautomeric species can be considered and then the equilibrium constant (K_{eq} = [enol]/[keto]) and the corresponding free energy at 25 °C ($\Delta G = -RT \ln K_{eq}$) for the keto–enol equilibrium are determined. (Table 2).

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Table 1. ^{1}H and ^{13}C Chemical shifts (δ/ppm) for **2**,**3**-diphenyl-**3**-oxopropanenitrile, **2**-(**4**-chlorophenyl)-**3**-oxo-**3**-phenylpropanenitrile and **2**-(**4**-methoxyphenyl)-**3**-oxo-**3**-phenyl-propanenitrile (atom numbering is depicted in Scheme 1)

Compound	Solvent	δ_H	δ_C
	$CDCl_3$	5.67 (1*H*, s, CH keto); 7.26–8.00 (11.3*H*, m, aromatic)	47.1 (C-2 keto); 89.9 (C-2 enol E); 114.8 (C-1 enol E); 116.9 (C-1 keto); 128.5–134.7 (Aromatics C); 164.9 (C-3 enol E); 188.2 (C-3 keto)
G = H	Acetone-d_6	5.88 (1*H*, s, CH keto); 7.03–8.05 (23.8*H*, m, aromatic)	46.9 (C-2 keto); 89.5 (C-2 enol); 115.5 (C-1 enol Z); 116.0 (C-1 enol E); 116.8 (C-1 keto); 128.1–135.2 (Aromatics C); 166.1 (C-3 enol E), 166.9 (C-3 enol Z); 188.9 (C-3 keto)
	DMSO-d_6	7.46–8.10 (m, aromatic)	88.5 (C-2 enol Z); 88.9 (C-2 enol E); 119.9 (C-1 enol Z); 121.5 (C-1 enol E); 127.5–136.3 (Aromatics C); 168.6 (C-3 enol); 168.7 (C-3 enol)
	$CDCl_3$	5.72 (1*H*, s, CH keto); 7.03–7.98 (11.7*H*, m, aromatic)	46.4 (C-2 keto); 90.5 (C-2 enol E); 116.4 (C-1 ceto); 117.1(C-1 enol E); 128.9–135.7 (Aromatics C); 166.0 (C-3 enol E); 188.8 (C-3 keto)
G = Cl	Acetone-d_6	5.73 (1*H*, s, CH keto); 6.85–7.86 (39.3*H*, m, aromatic)	46.1 (C-2 keto); 87.5 (C-2 enol Z); 88.1 (C-2 enol E); 113.9 (C-1 ceto); 114.3 (C-1 enol Z); 115.5 (C-1 enol E); 128.7–135.6 (Aromatics C); 166.5 (C-3 enol E); 167.2 (C-3 enol Z); 187.6 (C-3 keto)
	DMSO-d_6	7.49–8.17 (m, aromatic)	87.4 (C-2 enol Z); 87.9 (C-2 enol E); 119.6 (C-1 enol Z); 121.1 (C-1 enol E); 129.1–136.1 (Aromatics C); 169.3 (C-3 enol E); 169.5 (C-3 enol Z)
	$CDCl_3$	3.78 (3*H*, s, Methoxy H keto); 5.60 (1*H*, s, CH keto) 6.88–7.98 (9.2*H*, m, aromatic)	45.9 (C-2 keto form); 116.8 (C-1 keto form); 118.8–134.6 (Aromatics C); 189.1 (C-3 keto form)
G = OCH_3	Acetone-d_6	3.75 (3.1*H*, s, Methoxy H keto); 3.79 (1.5*H*, s, Methoxy H Enol E); 3.84 (0.6*H*, s, Methoxy H Enol Z); 5.70 (1*H*, s, CH keto); 6.87–8.00 (14.9*H*, m, aromatic)	45.9 (C-2 keto form); 89.2 (C-2 enol form); 113.8 (C-1 enol Z); 115.1(C-1 enol E); 117.1 (C-1 keto form); 122.8–136.7 (Aromatics C); 165.8 (C-3 enol E); 166 (C-3 enol Z); 189.6 (C-3 keto form)
	DMSO-d_6	3.81 (s, Methoxy H Enol E); 3.88 (s, Methoxy H Enol Z); 7.16–8.10 (m, aromatic)	87.1 (C-2 enol Z); 87.7 (C-2 enol E); 119.9 (C-1 enol Z); 121.7 (C-1 enol E); 127.7–138.1 (Aromatics C); 169.8 (C-3 enol E); 170.0 (C-3 enol Z)

Table 2. Keto–enol content in solvents of different polarity

Compounds	Solvent	Diel. const. (D)	% Keto	% Enol (E or Z)	K_{eq}	ΔG (kcal/mol)
	$CDCl_3$	4.8	91	9	0.099	1.369
G = H	Acetone-d_6	20.7	43	57	1.326	−0.167
	DMSO-d_6	46.7	0	100	—	—
	$CDCl_3$	4.8	77	23	0.299	0.715
G = Cl	Acetone-d_6	20.7	23	77	3.348	−0.716
	DMSO-d_6	46.7	0	100	—	—
	$CDCl_3$	4.8	100	0	0	—
G = OCH_3	Acetone-d_6	20.7	60	40	0.667	0.240
	DMSO-d_6	46.7	0	100	—	—

Table 3. Relative energy magnitudes in gas phase by the B3LYP/6–31G(d,p) method (with energies in kcal/mol)*

	Gas phase			
	Keto	Ketenimine	Enol E	Enol Z
G = H	0	11.80	3.30	4.73
G = Cl	0	11.72	2.44	4.14
G = OCH_3	0	12.28	3.16	4.86

Data from Table 2 clearly demonstrate that an increase in the solvent polarity increases the proportions of more polar enol forms.

The relative stability of individual tautomers is explained by electronic effects on the carbonyl group, conformational effects on the keto structure, stabilization by conjugation of the enol double bond and steric effects introduced by bulky groups.

The substituents may push or pull electrons inductively or by resonance.

The keto form was found to be the most stable in $CDCl_3$, while in DMSO-d_6 the enol is more stable. The effects of a methoxy group and a chlorine atom attached at the *para*-position of the two phenyl rings (Table 2) are opposite to each other, but this effect is not relevant in DMSO-d_6 and $CDCl_3$. In the acetone-d_6 solution, the electron-releasing methoxy group favours the keto form (60%), whereas the electron-attracting chlorine atom shifts the equilibrium towards enol forms (77%). In the same way, in $CDCl_3$ the quantity of enol increases 23% when replacing methoxy group by chlorine atom.

The ^{1}H NMR spectra taken in dry DMSO-d_6 solutions did not contain signals corresponding to the CH proton.

The hydroxyl signal was not observed in any solvent.

B3LYP calculations

The geometries of the ketonitriles were optimized at the B3LYP/6–31G(d,p) level of theory in order to investigate the stability of ketenimine, keto and enol forms in the gas phase and in the three different solvents: chloroform, acetone and dimethyl sulfoxide (DMSO) (refer to supporting information). The values of the relative energies (kcal/mol) of all the tautomeric forms of compounds studied are reported in Tables 3 and 4. Some geometrical parameters calculated are shown in Tables 5–7.

As expected, the first evidence from theoretical calculations, performed with the PCM solvent model, was that the keto and the enol forms are the only relevant tautomers of ketonitriles.

Other authors have applied the PCM model successful to predict the conduct of a tautomeric equilibrium in solution.[26–30]

The results show that there are no great variations among the geometric parameters when considering molecules in vacuum and in solvents. But an enlargement in the distance O—H in the enol can be observed when the solvent polarity increases. This could be due to the principal interaction between the solute and the solvent that is produced between these atoms. But the PCM method is not able to take into account this interaction explicitly, so the resulting energies show that the keto form is the most stable, although the energy difference between the keto form and the enol form decreases remarkably in all cases compared with the same energy difference in vacuum.

It is important to stress that the PCM model does not consider the presence of explicit solvent molecules; hence specific solute–solvent interactions are not described and the calculated solvation effects arise only from mutual solute–solvent electrostatic polarization. For this reason, the solvent was explicitly included in the calculations. So a molecule of the considered solvent was placed near the solute and a geometry optimization calculation at B3LYP/6-31G(d,p) level in vacuum. The results are shown in Table 8.

When analysing the structures, the solvent molecules are found on the OH groups in the enol case. The distance between the H of the enols and the O of the solvent is 1.79 Å approximately, and the angle formed by H···O—H atoms is in the interval 153–163°. In these structures, the enlargement of the OH bond is also observed, as in the model PCM. But, no preferential position is found in the case of the keto forms.

It has been suggested that the H of the chloroform can form hydrogen bonds with electronegative atoms. This implies that these kinds of unions could be formed in the O of the keto form, in the nitrogen of the nitrile group or in the OH group of the enols. It was found that the major interaction was produced

Table 4. Relative energy magnitudes in solutions by the B3LYP/6–31G(d,p) method using PCM model (with energies in kcal/mol)[a]

Compound	Tautomer	In chloroform	In acetone	In DMSO
G = H	Keto	0	0	0
	Ketenimine	12.57	12.81	12.82
	Enol E	2.55	2.16	2.08
	Enol Z	3.13	2.56	2.76
G = Cl	Keto	0	0	0
	Ketenimine	11.83	11.57	11.53
	Enol E	1.82	1.27	1.24
	Enol Z	2.51	1.87	1.93
G = OCH_3	Keto	0	0	0
	Ketenimine	13.05	12.94	12.96
	Enol E	2.89	2.18	2.19
	Enol Z	12.66	2.79	2.68

[a] The energy of the most stable tautomer for each entry is taken as reference.

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Table 5. Optimized geometrical parameters at B3LYP/6–31G(d,p) theory level: Bond lengths (Å)

Compound	Bond lengths [Å]	Tautomer	Gas phase	Chloroform	Acetone	DMSO
	CN	Keto	1.16019	1.16056	1.16069	1.16076
		Ketenimine	1.22085	1.21624	1.21396	1.21395
		Enol E	1.16527	1.16652	1.16711	1.16728
		Enol Z	1.16489	1.16620	1.16679	1.16690
G = H	CO	Keto	1.21786	1.22133	1.22299	1.22361
		Ketenimine	1.22599	1.23073	1.23321	1.23326
		Enol E	1.36241	1.35313	1.34917	1.34841
		Enol Z	1.36287	1.35680	1.35385	1.22380
	OH	Enol E	0.96744	0.97683	0.98283	0.98421
		Enol Z	0.96767	0.97760	0.98498	0.98420
	NH	Ketenimine	1.02156	1.03192	1.03711	1.03820
	CN	Keto	1.16014	1.16020	1.16056	1.16064
		Ketenimine	1.21960	1.21505	1.21322	1.21266
		Enol E	1.16512	1.16630	1.16694	1.16698
		Enol Z	1.16479	1.16597	1.16666	1.16689
G = Cl	CO	Keto	1.21779	1.22080	1.22283	1.22303
		Ketenimine	1.22496	1.22986	1.23209	1.23261
		Enol E	1.36155	1.35179	1.34736	1.34619
		Enol Z	1.36155	1.35401	1.35138	1.35123
	OH	Enol E	0.96761	0.97758	0.98354	0.98529
		Enol Z	0.96775	0.97912	0.98467	0.98568
	NH	Ketenimine	1.02117	1.03150	1.03699	1.03829
	CN	Keto	1.16026	1.16026	1.16086	1.16089
		Ketenimine	1.22198	1.21534	1.21534	1.21470
		Enol E	1.16531	1.16718	1.16718	1.16718
		Enol Z	1.16496	1.16634	1.16697	1.16715
$G = OCH_3$	CO	Keto	1.21812	1.21812	1.22336	1.22380
		Ketenimine	1.22627	1.23311	1.23311	1.23360
		Enol E	1.36445	1.35053	1.35053	1.34914
		Enol Z	1.36450	1.35787	1.35510	1.35481
	OH	Enol E	0.96734	0.98233	0.98233	0.98429
		Enol Z	0.96760	0.97775	0.98343	0.98555
	NH	Ketenimine	1.02183	1.03704	1.03704	1.03790
		Enol Z	1.36473	1.36808	1.36973	1.37003

Table 6. Optimized geometrical parameters at B3LYP/6–31G(d,p) theory level: Bond angle (°) C(1)—C(2)—C(3)

		Bond angle (°) C(1)—C(2)—C(3)			
Compound	Tautomer	Gas phase	Chloroform	Acetone	DMSO
G = H	Keto	110.066	109.681	109.667	109.712
	Ketenimine	119.008	119.595	119.635	120.012
	Enol E	117.794	118.606	118.743	118.877
	Enol Z	117.756	117.543	117.225	117.305
G = Cl	Keto	109.968	109.671	109.676	109.672
	Ketenimine	118.933	119.367	119.511	119.630
	Enol E	117.568	118.497	118.944	118.710
	Enol Z	117.755	117.484	117.300	117.535
$G = OCH_3$	Keto	110.078	110.078	109.624	109.676
	Ketenimine	119.424	120.268	120.268	120.222
	Enol E	117.550	118.658	118.658	118.402
	Enol Z	117.805	117.426	117.343	117.362

Table 7. Optimized geometrical parameters at B3LYP/6–31G(d,p) theory level: Dihedral angle $_{Ar}C—C(2)—C(3)-c_{ar}$

		Dihedral angle [°] $_{Ar}C—C(2)—C(3)—C_{Ar}$			
Compound	Tautomer	Gas phase	Chloroform	Acetone	DMSO
G = H	Keto	84.582	82.168	76.853	77.242
	Ketenimine	160.573	164.789	166.568	167.082
	Enol E	−178.150	−176.730	−176.328	−176.003
	Enol Z	10.823	10.566	11.819	11.154
G = Cl	Keto	86.584	78.700	79.765	78.560
	Ketenimine	164.987	166.378	166.828	167.753
	Enol E	−178.070	−176.855	−176.106	−175.927
	Enol Z	10.775	10.529	10.709	10.007
G = OCH_3	Keto	83.859	83.859	80.517	77.996
	Ketenimine	162.033	167.749	167.749	167.957
	Enol E	−177.983	−176.404	−176.404	−176.196
	Enol Z	10.932	10.491	10.414	9.790

between the chloroform molecule and the carbonyl group, then with the nitrile group and finally with the hydroxyl group.

The relative energies show that in DMSO the most stable tautomer is enol as it is also found experimentally. This would indicate that its stability is due to the H bond interaction between the solute and the solvent. But in acetone this interaction is not strong enough to stabilize the enol, except when the substituent group is Cl, and keto form is the most stable. In chloroform only the keto form is stable.

Then, with the optimized geometry of the solute–solvent complex, both calculations of single point and the PCM method were used. The results are shown in Table 9.

The enol relative stability, which also agrees with the experimental results, is most stable in DMSO; in acetone and in chloroform, the most stable is the keto form. This is due to the formation of intermolecular hydrogen bonds between the solvent and the solute.

In acetone and in DMSO, enol E is the most stable, except when the substituent is the OCH_3 group; in this case the more stable tautomer is the enol Z. In these cases, there exists a great difference in the dipolar moments between the E and Z forms. The solvent represented by a polarizable continuum shows a significant effect on the dipolar moments of the individual tautomers. The dipolar moments (μ) increase by changing the gas phase to the solution as well as by increasing the solvent polarity (Table 10). This would explain the relative energy decrease in the PCM calculations.

Tables 11–14 show the calculated ^{1}H Chemical shifts of methine, aromatics, hydroxyl and NH protons in three compounds in the gas phase and in chloroform, acetone and DMSO solutions.

Table 8. Relative energy in solutions by the B3LYP/6–31G(d,p) method considering the explicit solvent (with energies in kcal/mol)

	Explicit solvent		
	Acetone	Chloroform	DMSO
Cl			
Keto	3.46	0.00	5.77
Enol E	0.00	2.02	0.00
Enol Z	0.48	3.05	0.12
H			
keto	0.00	0.00	2.42
Enol E	0.71	4.11	0.07
Enol Z	1.02	5.01	0.00
OCH_3			
Keto	0.00	0.00	9.22
Enol E	8.67	4.07	7.00
Enol Z	7.32	4.92	0.00

Table 9. Relative energy in solutions by the B3LYP/6–31G(d,p) method considering the explicit solvent and PCM model (with energies in kcal/mol)

	Explicit solvent + PCM		
	Acetone	Chloroform	DMSO
Cl			
Keto	4.12	0.00	6.04
Enol E	0.00	1.11	0.00
Enol Z	0.29	0.55	0.53
H			
Keto	0.70	0.00	1.38
Enol E	0.00	3.16	0.00
Enol Z	0.21	3.90	0.52
OCH_3			
Keto	6.67	0.00	7.18
Enol E	0.29	3.31	0.92
Enol Z	0.00	3.92	0.00

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Table 10. Calculated dipole moments of optimized tautomers (Debye)

Compound	Tautomer	Gas (1.0)	Chloroform (4.8)	Acetone (20.7)	DMSO (46.7)
G = H	Keto	2.590	3.280	3.567	3.616
	Ketenimine	1.170	1.700	1.945	1.979
	Enol E	1.781	2.600	2.858	2.917
	Enol Z	2.707	3.381	3.617	3.649
G = Cl	Keto	2.447	3.090	3.316	3.366
	Ketenimine	2.054	2.698	2.961	3.017
	Enol E	2.407	3.092	3.348	3.403
	Enol Z	2.728	3.432	3.667	3.694
$G = OCH_3$	Keto	2.969	3.653	4.001	4.090
	Ketenimine	1.335	1.936	2.155	2.220
	Enol E	1.349	2.049	2.251	2.279
	Enol Z	3.034	3.743	3.998	4.248

Table 11. B3LYP/6–31G(d,p) PCM ^{1}H isotropic chemical shifts of different groups (ppm) relative to TMS in the gas phase

^{1}H isotropic chemical shifts in gas phase					
	Tautomer	CH	H aromatics	OH	NH
G = H	Keto	5.10	7.35–8.53	—	—
	Ketenimine	—	7.29–8.13	—	8.02
	Enol E	—	7.24–8.28	4.23	—
	Enol Z	—	7.01–7.78	4.04	—
G = Cl	Keto	5.05	7.27–8.53	—	—
	Ketenimine	—	7.12–8.00	—	8.38
	Enol E	—	7.18–8.24	4.36	—
	Enol Z	—	7.11–8.25	4.11	—
$G = OCH_3$	Keto	5.25	6.84–8.70	—	—
	Ketenimine	—	6.81–8.30	—	8.12
	Enol E	—	6.86–8.45	4.29	—
	Enol Z	—	6.46–7.88	4.06	—

Table 12. B3LYP/6–31G(d,p) PCM ^{1}H isotropic chemical shifts of different groups (ppm) relative to TMS in chloroform solution

^{1}H isotropic chemical shifts in chloroform					
	Tautomer	CH	H aromatics	OH	NH
G = H	Keto	5.65	7.65–8.59	—	—
	Ketenimine	—	7.54–8.47	—	9.11
	Enol E	—	7.50–8.20	5.73	—
	Enol Z	—	7.18–7.89	5.79	—
G = Cl	Keto	5.67	7.66–8.59	—	—
	Ketenimine	—	7.55–8.48	—	9.45
	Enol E	—	7.44–8.17	5.89	—
	Enol Z	—	6.72–7.88	6.00	—
$G = OCH_3$	Keto	4.94	6.22–7.87	—	—
	Ketenimine	—	6.92–8.11	—	9.13
	Enol E	—	6.94–8.13	5.82	—
	Enol Z	—	6.54–7.87	5.67	—

Table 13. B3LYP/6–31G(d,p) PCM ^{1}H isotropic chemical shifts of different groups (ppm) relative to TMS in acetone solution

^{1}H isotropic chemical shifts in acetone					
	Tautomer	CH	H aromatics	OH	NH
G = H	Keto	5.97	7.71–8.57	—	—
	Ketenimine	—	7.63–8.34	—	9.57
	Enol E	—	7.59–8.21	6.54	—
	Enol Z	—	7.59–7.99	6.74	—
G = Cl	Keto	5.98	7.63–8.58	—	—
	Ketenimine	—	7.45–8.03	—	9.93
	Enol E	—	7.56–8.19	6.67	—
	Enol Z	—	7.23–7.91	6.80	—
G = OCH_3	Keto	5.95	7.17–8.58	—	—
	Ketenimine	—	7.03–8.26	—	9.48
	Enol E	—	7.01–8.03	6.43	—
	Enol Z	—	6.64–7.89	6.46	—

Table 14. B3LYP/6–31G(d,p) PCM ^{1}H isotropic chemical shifts of different groups (ppm) relative to TMS in DMSO solution

^{1}H isotropic chemical shifts in DMSO					
	Tautomer	CH	H aromatics	OH	NH
G = H	Keto	6.05	7.73–8.56	—	—
	Ketenimine	—	7.69–8.29	—	9.67
	Enol E	—	7.62–8.23	6.71	—
	Enol Z	—			—
G = Cl	Keto	6.03	7.79–8.59	—	—
	Ketenimine	—	7.61–8.07	—	10.05
	Enol E	—	7.58–8.20	6.91	—
	Enol Z	—	6.86–7.99	6.87	—
G = OCH_3	Keto	6.05	7.07–8.55	—	—
	Ketenimine	—	7.06–8.26	—	9.58
	Enol E	—	7.04–8.17	6.66	—
	Enol Z	—	6.66–7.98	6.71	—

Table 15. B3LYP/6–31G(d,p) PCM ^{13}C isotropic chemical shifts (ppm) of relevant carbon atoms in the three compounds relative to TMS in the gas phase. (Atom numbering is depicted in Scheme 1.)

^{13}C isotropic chemical shifts (ppm) in gas phase				
	Tautomer	C-1	C-2	C-3
G = H	Keto	107.73	49.07	184.66
	Ketenimine	191.03	74.89	185.02
	Enol E	111.88	93.17	130.26
	Enol Z	109.05	93.77	159.77
G = Cl	Keto	107.41	48.02	184.65
	Ketenimine	190.07	77.19	186.10
	Enol E	111.51	92.05	128.78
	Enol Z	108.73	92.50	160.36
G = OCH_3	Keto	115.26	48.50	184.67
	Ketenimine	184.89	74.67	192.08
	Enol E	119.39	92.95	157.58
	Enol Z	114.19	93.57	158.46

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Table 16. B3LYP/6–31G(d,p) PCM ^{13}C isotropic chemical shifts (ppm) of relevant carbon atoms in the three compounds relative to TMS in chloroform solution. (atom numbering is depicted in Scheme 1.)

^{13}C isotropic chemical shifts (ppm) in chloroform				
	Tautomer	C-1	C-2	C-3
G = H	Keto	111.11	48.98	186.22
	Ketenimine	185.46	74.90	187.13
	Enol E	114.39	90.35	164.11
	Enol Z	112.45	90.17	164.87
G = Cl	Keto	110.64	48.55	185.81
	Ketenimine	183.76	76.63	188.49
	Enol E	113.90	89.19	164.95
	Enol Z	111.98	88.87	166.05
$G = OCH_3$	Keto	110.95	48.39	185.57
	Ketenimine	185.02	74.64	187.62
	Enol E	114.55	90.40	163.25
	Enol Z	112.56	89.91	163.67

Table 17. B3LYP/6–31G(d,p) PCM ^{13}C isotropic chemical shifts (ppm) of relevant carbon atoms in the three compounds relative to TMS in the acetone. (Atom numbering is depicted in Scheme 1.)

^{13}C isotropic chemical shifts (ppm) in acetone				
	Tautomer	C-1	C-2	C-3
G = H	Keto	112.57	49.42	187.49
	Ketenimine	183.37	75.22	188.51
	Enol E	115.65	89.60	166.29
	Enol Z	114.01	88.84	167.37
G = Cl	Keto	112.08	48.16	187.25
	Ketenimine	181.65	76.70	189.64
	Enol E	115.19	88.31	167.09
	Enol Z	113.53	87.85	168.15
$G = OCH_3$	Keto	112.71	48.38	187.41
	Ketenimine	184.01	74.80	188.33
	Enol E	115.69	89.20	165.04
	Enol Z	114.03	88.71	166.09

Table 18. B3LYP/6–31G(d,p) PCM ^{13}C isotropic chemical shifts (ppm) of relevant carbon atoms in the three compounds relative to TMS in the DMSO solution. (Atom numbering is depicted in Scheme 1.)

^{13}C isotropic chemical shifts (ppm) in DMSO				
	Tautomer	C-1	C-2	C-3
G = H	Keto	112.92	49.37	187.89
	Ketenimine	182.85	75.29	188.39
	Enol E	115.94	89.45	166.68
	Enol Z	114.27	88.86	167.38
G = Cl	Keto	112.36	48.43	187.39
	Ketenimine	181.14	76.65	189.71
	Enol E	115.40	88.19	167.63
	Enol Z	113.79	87.69	168.44
$G = OCH_3$	Keto	113.06	48.44	188.01
	Ketenimine	183.55	74.83	188.61
	Enol E	115.94	89.12	165.56
	Enol Z	114.33	88.34	166.56

Tables 15–18 show the calculated ^{13}C chemical shifts of relevant carbon atoms in the three compounds in the gas phase and in chloroform, acetone and DMSO solutions.

CONCLUSIONS

It has been demonstrated that the keto–enol tautomerism in the β-ketonitriles studied by theoretical calculations and NMR spectroscopy, a very useful technique for the determination of tautomeric species in solution, is strongly dependent on the solvents and substituents.

Because of the linearity of the cyano group, a cyclic structure with an intramolecular hydrogen bond is impossible. As predicted, it is found that the enol content is greater in polar than in apolar solvents.

These compounds can exist in only one keto and one enol form (exclusive of E–Z isomers of the enol) since the ketenimine form probably does not exist in neutral solution.

Comparison of the experimental data with the calculated chemical shift to GIAO-B3LYP level of theory has permitted to determine the nature of the tautomer present in a highly polar medium.

The DFT results indicate that the major enol stability in the polar solvents is due to two factors:

(1) the interaction by hydrogen bonds between the solute and solvent molecules,
(2) the molecule polarization due to the solvent.

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