Solvent effects on the rate of the keto–enol interconversion of 2-nitrocyclohexanone†

Gabriella Siani,*[a] Guido Angelini,[a] Paolo De Maria,[a] Antonella Fontana[a] and Marco Pierini[b]

The rates of tautomerization of 2-nitrocyclohexanone (2-NCH) have been measured spectrophotometrically at 25.0 ± 0.1 °C in several organic aprotic solvents and their binary mixtures. In cyclohexane the reaction is effectively catalyzed by bases and inhibited by acids while the so-called "spontaneous reaction" appears essentially due to autocatalysis. Apparent second order rate constants (k_{app}^B) for the reaction catalyzed by triethylamine (TEA) and pyridine (Pyr) have been obtained. From the experimental k_{app}^B values rate constants for the enolization (k_1^B) and ketonization (k_{-1}^B) reactions have been calculated. A Kamlet–Taft type linear solvation energy relationship (LSER) adequately accounts for the observed solvent effects. Activation parameters for both reactions show that solvent effects are mainly entropic in origin and that there is a shift of the transition state from a ketone-like to an enol-like structure on passing from less to more polar solvents.

Introduction

The keto–enol interconversion of carbonyl compounds is one of the most investigated organic reactions in aqueous solution.[1–4] In particular the less studied α-nitroketones[2,5] represent an interesting class of derivatives due to their high acidity and relatively high enol content. They are, in principle, an equilibrium mixture of three tautomers: the keto form, the enol form and the nitronic acid form (aci form). However the aci form in most cases can be neglected in aqueous solutions[3,6] due to its high acidity and it is also hardly detectable in a number of aprotic organic solvents.[3,7] The values of the tautomeric equilibrium constants of 2-nitrocyclohexanone (2-NCH) have been recently measured[7] in organic solvents and ionic liquids and the solvent effects have been discussed in terms of multiparameter equations.

On the other hand the available data on the kinetics of keto–enol tautomerism for carbonyl compounds in aprotic solvents are very scarce. In a recent study[8] the solvent effect on the base-catalyzed tautomerization of 2-acetylcyclohexanone and 2-acetyl-1-tetralone was studied in dimethylsulfoxide (DMSO)–water mixtures of different composition. The reaction rate strongly increases at high percentages of DMSO and the author interpreted this effect in terms of solvent polarity and the molecular structure of the solvent molecules.[8] Furthermore a LC-NMR study[9] of the ketonization of the ethyl butylryl acetate enol has shown that the rate constant in three binary mixtures (D_2O–CH_3CN, D_2O–

CD$_3$OD and CD$_3$OD–CH$_3$CN) correlates well with the $E_T(30)$ parameter of the solvent.

In a previous work[10] some of us obtained kinetic data (k, $\Delta G^\#$, $\Delta H^\#$ and $\Delta S^\#$) for the enantiomer interconversion of some linear α-nitroketones by means of dynamic high-resolution gas chromatography using a β-cyclodextrin derivative chiral stationary phase. The highly negative values of $\Delta S^\#$ obtained, suggest a transition state with large charge separation in agreement with a general acid–base catalyzed mechanism for the enolization reaction.

In this work we have measured spectrophotometrically the rate constants of tautomerization of 2-NCH following the change in absorbance of the enol form at 25.0 ± 0.1 °C in some organic aprotic solvents. DFT calculations have also been performed to ascertain if the keto–enol interconversion can possibly occur with a one-step mechanism through the formation of a four-membered transition state.

Solvent effects have been discussed in terms of multiparameter equations that take into account non specific and specific solute–solvent interactions.

The separate activation parameters of enolization and ketonization, $\Delta G^\#$, $\Delta H^\#$ and $\Delta S^\#$, have been derived from rate-measurement at different temperatures in chloroform, dichloromethane and acetonitrile.

Results and discussion

Kinetics of the keto–enol interconversion of 2-NCH in cyclohexane

The rate of the keto–enol interconversion of 2-NCH has been measured in cyclohexane by UV–vis spectroscopy at 25.0 ± 0.1 °C, following the appearance of the band of the enol from a solution containing an excess of the keto form in the absence and in the presence of trifluoroacetic acid (TFA) or triethylamine (TEA).

The plot of Fig. 1 shows that the tautomerization reaction of 2-NCH is catalyzed by bases and hampered by acids. It is somewhat unexpected that the "spontaneous" tautomerization is detectable

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† Electronic supplementary information (ESI) available: UV-determined tautomeric constants, K_T, of 2-NCH in several organic solvents and their binary mixtures and selected descriptors of solvent polarity; second order rate constants, k_{app}^B, k_1^B and k_{-1}^B for the base catalyzed keto–enol interconversion of 2-NCH in aprotic solvents at different temperatures. See DOI: 10.1039/b813011f
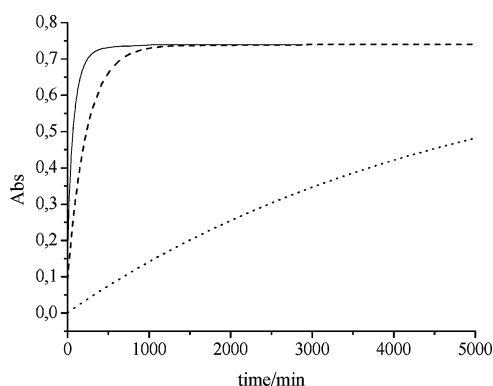
Fig. 1 Kinetic profiles for the tautomerization of 2-NCH in cyclohexane in the presence of TEA (solid line), TFA (dotted line) and in the absence of the catalyst (dashed line).

in an aprotic solvent such as cyclohexane. In this solvent the tautomerization reaction can only occur either by intramolecular proton transfer in a one-step mechanism through the formation of a four-membered transition state or by an intermolecular stepwise mechanism of autocatalysis. The two possibilities are separately analyzed as follows.

Intramolecular proton transfer

Some DFT calculations (non local density functional model BP with a 6–31G** basis set) have been performed on the most stable geometries, obtained by conformational search, of the keto form (KH), the enol form (EH) and the nitronic acid form (ACI) of 2-NCH to test if an intramolecular proton transfer mechanism is a plausible mechanism. Structures and energies of the transition states (TS) have also been optimized for the enol–aci, keto–aci and keto–enol intramolecular interconversions.

It is noteworthy that the present calculations point to a very easy interconversion between the enol and the aci form and that the enol is the most stable tautomer in the gas phase ($K_T = 19.4$) as well as in apolar solvents (see Table 1).

The results are shown in Fig. 2, in the form of an energy diagram.

The energy values obtained in the gas phase and in a highly apolar solvent like cyclohexane ($\varepsilon = 2.0$), as expected, are very similar.

The $\Delta E^\#$ values for the different forms of 2-NCH reported in Fig. 2 are too high to support a mechanism of interconversion *via* intramolecular proton transfer. This conclusion is in agreement with that previously advanced for simple carbonyl compounds[11] and some linear α-nitroketones.[10]
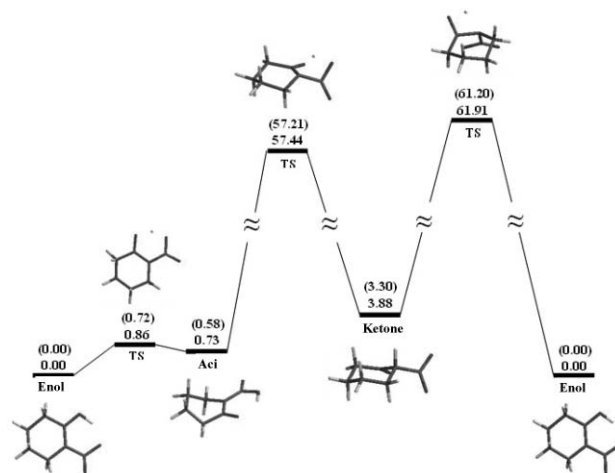

Fig. 2 Energy diagram for the keto–enol–aci interconversions of 2-NCH *via* intramolecular proton transfer. The energy values reported in the diagram are in kcal mol⁻¹ and refer to calculations performed in a vacuum (out of parentheses) and in cyclohexane (within parentheses).

Intermolecular proton transfer

An energetically more favorable mechanism may occur if a second molecule with basic functionalities can assist the proton transfer in one concerted step, as depicted in Scheme 1a, or in two steps through the formation of a more or less intimate (depending upon the particular solvent) ion paired intermediate, as depicted in Scheme 1b.
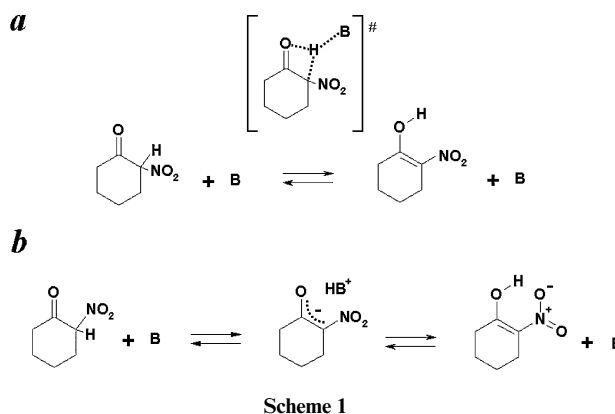
Scheme 1

The former mechanism is more likely in less polar solvents, while the latter mechanism should be prevalent in more polar solvents. In Scheme 1, B can be a molecule of an external general base (triethylamine or pyridine) or a second molecule of 2-NCH. The presence of TFA, which can reduce the basicity of 2-NCH, makes

Table 1 Second order rate constants, k_{app}^{TEA}, k_1^{TEA} and k_{-1}^{TEA} for the base catalyzed keto–enol interconversion of 2-NCH in some aprotic solvents

Solvent	$k_{app}^{TEA}/M^{-1}s^{-1}$	$k_1^{TEA}/M^{-1}s^{-1}$	$k_{-1}^{TEA}/M^{-1}s^{-1}$	$K_T{}^a$	λ_{max}^{EH}
Cyclohexane	0.194 (±0.005)	0.168	0.026	6.46	319
CCl$_4$	2.50 (±0.16)	2.14	0.359	5.97	323
CHCl$_3$	32.7 (±0.2)	21.5	11.2	1.92	330
CH$_2$Cl$_2$	74.4 (±0.8)	32.6	41.8	0.78	330
CH$_3$CN	522 (±21)	55.9	466	0.12	330

^{a} Values determined by UV–vis spectroscopy from ref. 7.

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the process much slower (Fig. 1). The mechanism of autocatalysis is also supported by some experiments carried out in cyclohexane carefully purified through chromatographic columns containing basic and acid aluminium oxide to remove possible acidic and/or basic impurities. The "spontaneous" rate constant, k_{app}^0, increased from 6.38×10^{-5} to 1.51×10^{-4} s^{-1} as the concentration of 2-NCH increased from 2.0×10^{-5} to 1.0×10^{-4} mol dm^{-3}.

Docking experiments between 2-NCH molecules in their keto form have been performed, taking into account both homochiral (R-KH : R-KH) and heterochiral (R-KH : S-KH) associations. The most stable and most populated homo and hetero chiral adducts have at least one of the basic functionalities of a molecule of 2-NCH facing the acidic hydrogen of the other molecule (see Fig. 3). This result suggests transition states in which one molecule of 2-NCH assists the transfer of the acidic hydrogen from the other molecule.
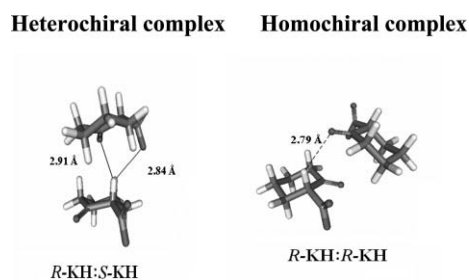

Fig. 3 Hetero and homo KH : KH adducts obtained by docking procedures based on molecular mechanics calculations.

General base catalysis

The rate of the base-catalyzed tautomerization of 2-NCH has been measured in different solvents, following the increase (in cyclohexane and carbon tetrachloride) or the decrease (in the more polar solvents where the keto tautomer is more stable than the enol tautomer) of the absorbance at the λ_{max} of the enol form (see typical examples in Fig. 4).

Triethylamine, TEA, or pyridine, Pyr, have been used as the catalysts. In most solvents the concentration of the catalyst was varied over a range of a factor of ten. Under the adopted experimental conditions, all the kinetic profiles were consistent with a pseudo-first order process according to eqn 1.
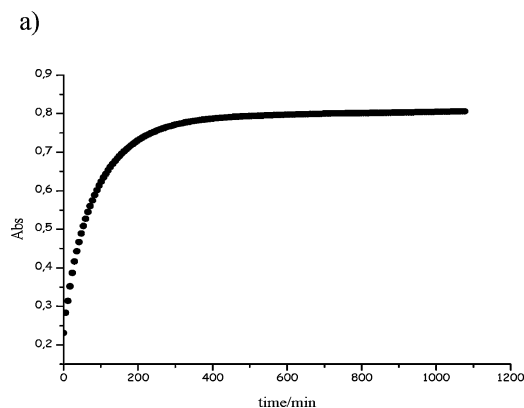
$$\text{rate} = k_{app}\,[\text{2-NCH}] \tag{1}$$

The obtained values of k_{app} were linearly related to [B] according to eqn 2

$$k_{app} = k_{app}^0 + k_{app}^B[\text{B}] \tag{2}$$

where B is Pyr or TEA. The second order rate constants, k_{app}^B, can be calculated from the slopes of the plots of k_{app} against [B] (see a typical example in Fig. 5).
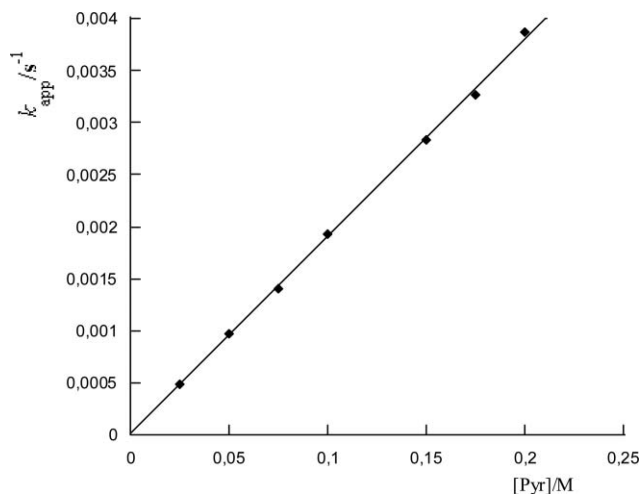

Fig. 5 Plot of the pseudo-first order rate constant, k_{app}, *vs.* [Pyr] in CH$_2$Cl$_2$. The slope corresponds to the second order rate constant for the Pyr-catalyzed keto–enol interconversion, k_{app}^{Pyr}.

As expected the contribution of k_{app}^0 is not detectable in the presence of Pyr or TEA.

Since the tautomerization reaction is a reversible reaction (Scheme 1), k_{app}^B includes both contributions from the enolization, k_1^B, and the ketonization, k_{-1}^B, reaction. k_1^B and k_{-1}^B have been calculated in the five aprotic solvents from eqn 3 and 4 by using previously determined[7] $K_T = [\text{EH}]/[\text{KH}]$ values.

$$k_1^B = k_{app}^B[K_T/(K_T + 1)] \tag{3}$$
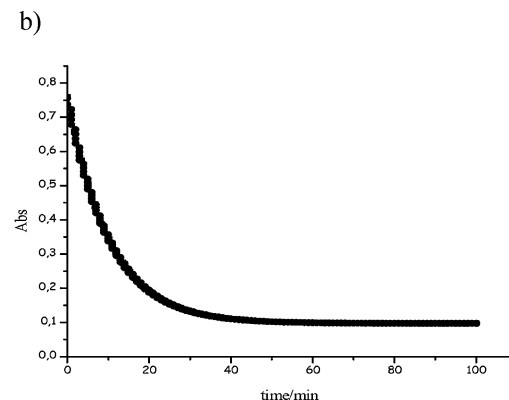
$$k_{-1}^B = k_{app}^B - k_1^B \tag{4}$$

Fig. 4 Kinetic profiles for the keto–enol interconversion of 2-NCH catalyzed by pyridine (a) in cyclohexane and (b) in acetonitrile.

Table 2 Second order rate constants, k_{app}^{Pyr}, k_1^{Pyr} and k_{-1}^{Pyr} for the base catalyzed keto–enol interconversion of 2-NCH in some aprotic solvents and binary mixtures, listed in order of increasing permittivity, ε

Solvent	$10^{-2} k_{app}^{Pyr}/M^{-1}s^{-1}$	$10^{-2} k_1^{Pyr}/M^{-1}s^{-1}$	$10^{-2} k_{-1}^{Pyr}/M^{-1}s^{-1}$	$K_T{}^a$	ε
Cyclohexane	0.0256 (±0.0010)	0.0222	0.00342	6.46[b]	2.0
CCl₄	0.0643 (±0.0013)	0.0551	0.00923	5.97[b]	2.2
CHCl₃	1.30 (±0.01)	0.855	0.445	1.92[b]	4.8
CH₂Cl₂	1.89 (±0.01)	0.828	1.062	0.78[b]	8.9
CH₃CN–CH₂Cl₂ (20 : 80)	3.88 (±0.16)	1.08	2.80	0.39	13.7
CH₃CN–CH₂Cl₂ (50 : 50)	6.43 (±0.10)	1.16	5.27	0.22	21.7
CH₃CN–CHCl₃ (80 : 20)	8.82 (±0.10)	1.06	7.76	0.14	28.8
CH₃CN–CH₂Cl₂ (80 : 20)	8.98 (±0.11)	1.08	7.90	0.14	30.7
CH₃CN	9.60 (±0.16)	1.03	8.57	0.12[b]	35.9

[a] Values determined by UV–vis spectroscopy as in ref. 7. [b] From ref. 7.

Values of K_T in CH₃CN–CH₂Cl₂ and CH₃CN–CHCl₃ binary mixtures of various composition have been determined by following the previously described procedure.[7]

Comparison of the rate constants for TEA (pK_a in water = 10.8[12]) and Pyr (pK_a in water = 5.17[13]) catalysis in the different solvents, collected in Tables 1 and 2, clearly shows that the stronger base acts as the most efficient catalyst.

Tables 1 and 2 show that rate constants increase on passing from apolar to polar solvents. To evaluate the solvent effect on the rate of tautomerization a correlation analysis was performed as follows. A good correlation was found simply by plotting k_{app}^B against solvent permittivity, ε, both for TEA ($R^2 = 0.996$) and Pyr catalysis ($R^2 = 0.990$; Fig. 6—solid line). In the case of binary mixtures the values of ε calculated as previously reported.[14] An analogous satisfactory correlation was obtained for the ketonization rate constant k_{-1}^B both for TEA ($R^2 = 0.993$) and Pyr catalysis ($R^2 = 0.990$; Fig. 6—dotted line), while the correlation for the enolization rate constant k_1^B was not linear (Fig. 6—dashed line) and it seems scarcely affected by the solvent permittivity.
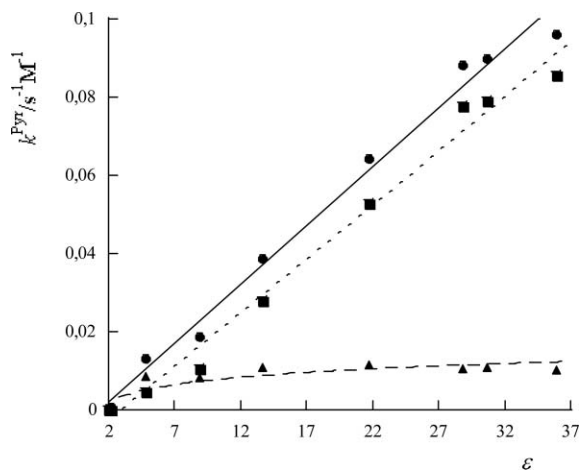

Fig. 6 Plots of k_{app} (●—solid line), k_1 (▲—dashed line) and k_{-1} (■—dotted line) against solvent permittivity, ε, for the Pyr catalyzed tautomerization of 2-NCH.

A multiparameter treatment[15] of the data obtained for Pyr catalysis was performed according to the Kamlet–Taft type eqn 5:

$$\ln k^B = C + \sum_i f_i D_i \qquad (5)$$

where D_i represents the i selected descriptors of solvent polarity, f_i the corresponding regression coefficients and C is the regression constant.

The best correlations were obtained from the equation that uses the cohesive pressure, δ^2, the previously described[7] normalized polarity index, T_N (analogous to the well known[16–18] indexes π^*, π^*_{azo} and E_T) and the Kirkwood's function, $F(\varepsilon) = (\varepsilon - 1)/(2\varepsilon + 1)$ (eqn 6). These parameters express different and complementary properties of the solvent, namely the electrostatic shielding of partial or full charges [$F(\varepsilon)$], the cavitational energy (δ^2) and the aspecific as well as donor–acceptor and hydrogen bonding interactions (T_N).

$$\ln k^{Pyr} = C + aF(\varepsilon) + b\delta^2 + cT_N \qquad (6)$$

For binary mixtures the values of δ were calculated from eqn 7:

$$\delta = [(\%)_{V/V1}\delta_1 + (\%)_{V/V2}\delta_2]/100 \qquad (7)$$

where 1 and 2 refer to the two different solvents. The results are collected in Table 3.

Poorer correlations were observed for LSERs that use other classical solvent parameters (the results are available upon request).

The values of $\ln k^{Pyr}$ calculated from eqn 6 have been plotted against the corresponding experimental values. Fig. 7 shows, as an example, the good validation of the correlation of eqn 6 applied to k_{app}^{Pyr} values ($R^2 = 0.998$).

The relative contributions of the solvent parameters of eqn 6 to the different rate constants have been calculated, on a percentage basis, from the absolute values of the regression coefficients (see Table 3). It turns out that total specific and non-specific electrostatic interactions prevail over cavitational energy interactions in each solvent investigated (see Fig. 8). As expected, while the contribution of the former interactions increases in solvents with an ε value lower than about 8, the contribution of the latter interactions decreases in the same range of ε values. This is

Table 3 LSER of eqn. 6 applied to the different rate constants of the Pyr-catalyzed tautomerization of 2-NCH

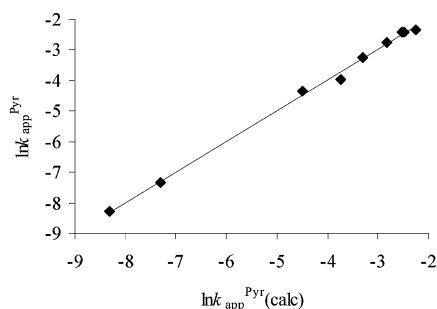| Kinetic constant (k^B)	R^2	LSER
k_{app}^{Pyr}	0.997	$\ln k_{app}^{Pyr} = -11.7 + 9.36F(\varepsilon) + 0.021\delta^2 + 3.05T_N$
k_1^{Pyr}	0.997	$\ln k_1^{Pyr} = -9.26 + 4.62F(\varepsilon) - 0.004\delta^2 + 4.60T_N$
k_{-1}^{Pyr}	0.998	$\ln k_{-1}^{Pyr} = -15.3 + 17.4F(\varepsilon) + 0.021\delta^2 + 2.53T_N$

Fig. 7 Plot of experimental $\ln k_{app}^{Pyr}$ values against values calculated from eqn 6.

consistent with the more efficient solvation of a charge-separated transition state by more polar solvents (Scheme 1).

Determination of the activation parameters $\Delta G^{\#}$, $\Delta H^{\#}$ and $\Delta S^{\#}$, for the enolization and ketonization reactions

The kinetics of the tautomerization reaction of 2-NCH have been also investigated in the temperature range 283.15–323.15 K in CHCl$_3$, CH$_2$Cl$_2$ and CH$_3$CN. $\Delta G^{\#}$ values for the enolization and ketonization reactions have been calculated from k_1^B and k_{-1}^B values at different temperatures (see ESI†) according to the Eyring eqn 8

$$\Delta G^{\#}(T) = RT(\ln T/k^B + \ln k_B/h) \qquad (8)$$

where R is the gas constant, T is temperature, h is the Planck constant and k_B is the Boltzmann constant. The values of $\Delta H^{\#}$ and $-\Delta S^{\#}$ can be determined as the slope and the intercept of a plot of $\Delta G^{\#}/T$ vs. $1/T$. The obtained results are collected in Table 4.

The data of Table 4 show that $\Delta G^{\#}$ values of enolization and ketonization, for a given catalyst, significantly decrease on passing from the less polar (cyclohexane) to the more polar (CH$_3$CN) solvent. This effect is due to a more efficient stabilization, by more polar solvents, of the polar transition state where the acidic proton of the reactant is somewhat transferred to the neutral base catalyst. The relative values of $\Delta G_1^{\#}$ and $\Delta G_{-1}^{\#}$ suggest that there is a shift from a ketone-like to an enol-like structure of the TS of the tautomerization reaction (according to the Hammond postulate) on passing from the less to the more polar solvents.

The contribution of the term $T\Delta S^{\#}$ to $\Delta G^{\#}$, for both reactions, is higher than that of $\Delta H^{\#}$, particularly in CHCl$_3$, the only exception being the Pyr-catalyzed reaction in CH$_3$CN. This fact suggests that the solvent effect on the rate of tautomerization is mainly entropic in origin and that there is a tendency for $\Delta H^{\#}$ and $\Delta S^{\#}$ to compensate each other. The entropy decrease ($\Delta S^{\#} < 0$) observed in the investigated solvents depends on the combination of two different molecules (substrate and catalyst) to form one unstable geometry (transition state) with loss of six (roto-translational) degrees of freedom.

Conclusions

(i) The tautomerization reaction of 2-NCH occurs in aprotic solvents at 25.0 °C. The reaction is effectively catalyzed by bases and inhibited by acids, while the so-called "spontaneous" reaction is probably due to autocatalysis.
(ii) The rate of proton transfer is faster when the basic strength of the catalyst is higher.
(iii) The overall solvent effect can be accounted for by a Kamlet–Taft type multiparameter equation.
(iv) The ketonization reaction of the enol is faster in the more polar solvents and the solvent effect appears to be prevalently entropic in origin.
(v) According to the Hammond postulate there is a shift from a ketone-like to an enol-like structure of the transition state on passing from less polar to more polar solvents.

Experimental

Materials

The organic solvents (cyclohexane, carbon tetrachloride, dichloromethane, chloroform and acetonitrile), 2-nitrocyclohexanone and trifluoroacetic acid were commercial samples of AnalaR grade and were used without further purification. Triethylamine and pyridine were distilled in the presence of NaOH before each experiment.

Instruments

The kinetic runs were carried out with a UV–vis spectrophotometer provided with a thermostatted (±0.1 °C) cell holder.
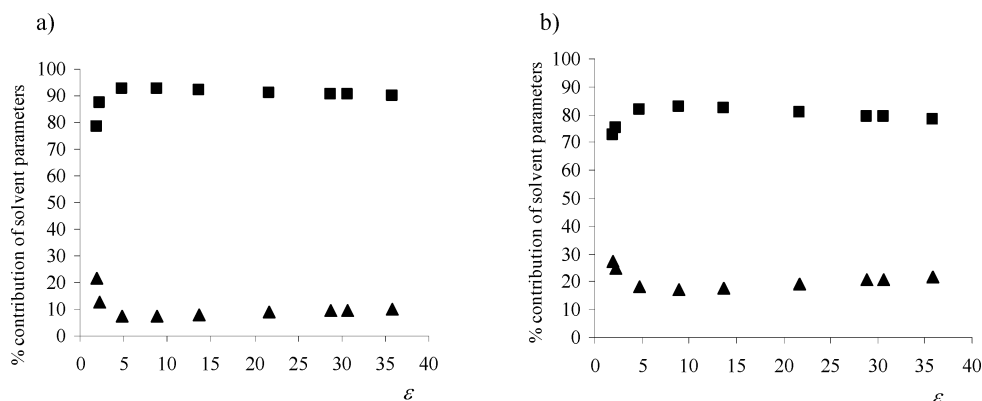

Fig. 8 Percent contribution of electrostatic (■) and cavitational energy interactions (▲) on the enolization (a) and ketonization (b) reaction of 2-NCH in solvents of different permittivity, ε.

Table 4 Activation parameters, $\Delta G^{\#}$ (kcal mol^{-1} at 298.15 K), $\Delta H^{\#}$ (kcal mol^{-1}) and $\Delta S^{\#}$ (e.u.), for the enolization and ketonization reactions of 2-NCH in CHCl$_3$, CH$_2$Cl$_2$ and CH$_3$CN

	Enolization				Ketonization			
	$\Delta G_1^{\#}$	$\Delta H_1^{\#}$	$\Delta S_1^{\#}$	$-T\Delta S_1^{\#}$	$\Delta G_{-1}^{\#}$	$\Delta H_{-1}^{\#}$	$\Delta S_{-1}^{\#}$	$-T\Delta S_{-1}^{\#}$
Catalysis by TEA								
Cyclohexane	18.5	—	—	—	19.6	—	—	—
CCl$_4$	17.0	—	—	—	18.1	—	—	—
CHCl$_3$	15.6	2.54	−44	13.1	16.0	4.20	−40	11.8
CH$_2$Cl$_2$	15.3	5.17	−40	11.9	15.2	5.53	−32	9.59
CH$_3$CN	15.1	7.00	−27	8.05	13.8	5.88	−27	8.05
Catalysis by Pyr								
Cyclohexane	22.4	—	—	—	23.5	—	—	—
CCl$_4$	21.9	—	—	—	23.0	—	—	—
CHCl$_3$	20.3	7.29	−43	12.8	20.7	9.02	−39	11.6
CH$_2$Cl$_2$	20.3	8.82	−38	11.3	20.1	9.19	−37	11.0
CH$_3$CN–CH$_2$Cl$_2$ 20 : 80	20.1	—	—	—	19.6	—	—	—
CH$_3$CN–CH$_2$Cl$_2$ 50 : 50	20.1	—	—	—	19.2	—	—	—
CH$_3$CN–CHCl$_3$ 80 : 20	20.1	—	—	—	19.0	—	—	—
CH$_3$CN–CH$_2$Cl$_2$ 80 : 20	20.1	—	—	—	19.0	—	—	—
CH$_3$CN	20.2	10.4	−33	9.82	18.9	9.32	−32	9.54

Kinetic measurements

The keto–enol interconversion of 2-NCH was followed spectrophotometrically by monitoring the variation of the absorbance at $\lambda_{\max}^{EH}$ of the enol form of 2-NCH at different temperatures. A small aliquot of a stock solution of 2-NCH in CCl$_4$ was added immediately before each kinetic run to a cuvette containing Pyr or TEA dissolved in the appropriate organic solvent. The initial concentration of 2-NCH was *ca.* 1×10^{-3} mol dm^{-3} in all experiments.

Computational methods

Optimized geometries of the tautomeric forms of 2-NCH were obtained by performing molecular modeling calculations with the computer program SPARTAN 04 (Wavefunction Inc. 18401 Von Karman Avenue, Suite 370 Irvine, CA 92612) running on a PC equipped with Intel Pentium 4, CPU 3.40 GHz, 2 GB of RAM and OS Windows 2000 Professional. As the first step, conformational searches on the keto, enol and aci forms of 2-NCH were carried out by setting the options as follow: MMFF force field; search by the Montecarlo stochastic algorithm (all rotatable bonds explored); maximum number of conformers = 100; window energy cut = 5 kcal mol^{-1}. As the second step, the most stable conformer obtained of each tautomeric form was further optimized at the SCF level by the non local density functional model BP with the 6–31G** basis set. Transition state geometries for the enol–aci, keto–aci and keto–enol intramolecular interconversions were also achieved by the same quantistic model, again optimized at the SCF level. The solvation energies of the tautomers and the transition states of 2-NCH in cyclohexane were obtained by performing single-point calculations on the BP optimized geometries by the conductor like screening model (COSMO), as implemented in the Amsterdam density functional (ADF) package v. 2007.01.

A rigid docking experiment between the most stable conformations of 2-NCH within the (*R*) configuration was performed by the home made computer program MolInE,[19] carrying out molecular mechanics calculations based on the mm2* force field. The same procedure was repeated after inverting the configuration of one of the two molecules. All the adducts obtained were finally optimized, relaxing all their degrees of freedom by the molecular mechanics method based on the mm2* force field, as implemented in the computer program MacroModel v.4.0.

References

1 R. P. Bell, *The Proton in Chemistry*, Chapman and Hall, London 1973.
2 J. R. Keefe and A. J. Kresge, in *The Chemistry of Enols*, ed. Z. Rappoport, Wiley & Sons, New York, 1990, 399.
3 J. Toullec, in *The Chemistry of Enols*. ed. Z. Rappoport, Wiley & Sons, New York, 1990, 323.
4 A. J. Kresge, *Acc. Chem. Res.*, 1990, **23**, 43.
5 A. Fontana, P. De Maria, G. Siani, M. Pierini, S. Cerritelli and R. Ballini, *Eur. J. Org. Chem.*, 2000, 1641.
6 G. Angelini, P. De Maria, A. Fontana, M. Pierini and G. Siani, *J. Org. Chem.*, 2007, **72**, 4039.
7 G. Angelini, C. Chiappe, P. De Maria, A. Fontana, F. Gasparrini, D. Pieraccini, M. Pierini and G. Siani, *J. Org. Chem.*, 2005, **70**, 8193.
8 E. Iglesias, *New J. Chem.*, 2005, **29**, 625.
9 Chun C. Zhou and D. R. Hill, *Magn. Reson. Chem.*, 2007, **45**, 128.
10 F. Gasparrini, M. Pierini, C. Villani, P. De Maria, A. Fontana and R. Ballini, *J. Org. Chem.*, 2003, **68**, 3173.
11 D. Lee, C. K. Kim, B. S. Lee and I. Lee, *J. Comput. Chem.*, 1997, **18**, 56.
12 S. Bergstrom and G. Olofsson, *J. Solution Chem.*, 1975, **4**, 535.
13 H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, 1955, **77**, 1723.
14 P. Wang and A. Anderko, *Fluid Phase Equilib.*, 2001, **186**, 103.
15 A. R. Katritzky, D. C. Fara, H. Yang, K. Tamm, T. Tamm and M. Karelson, *Chem. Rev.*, 2004, **104**, 175.
16 C. Laurence, P. Nicolet, M. T. Dalati, J.-L. M. Abboud and R. J. Notario, *J. Phys. Chem.*, 1994, **98**, 5807.
17 C. Reichardt, *Chem. Rev.*, 1994, **94**, 2319.
18 E. Buncel and S. Rajagopal, *J. Org. Chem.*, 1989, **54**, 798.
19 (*a*) S. Alcaro, F. Gasparrini, O. Iucani, S. Mecucci, D. Misiti, M. Pierini and C. Villani, *J. Comput. Chem.*, 2000, **21**, 515; (*b*) S. Alcaro, F. Gasparrini, O. Incani, L. Caglioti, M. Pierini and C. Villani, *J. Comput. Chem.*, 2007, **28**, 1119.

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Org. Biomol. Chem., 2008, **6**, 4236–4241 | 4241