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Ionization and Tautomerization of 2-Nitrocyclohexanone in Aqueous Solution

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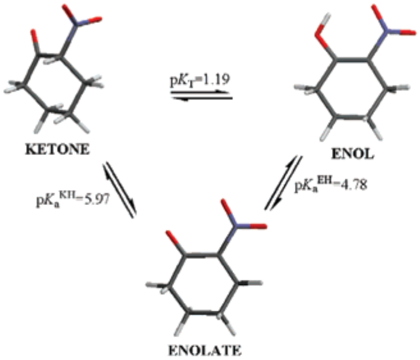

The keto−enol tautomerism of 2-nitrocyclohexanone (2-NCH) was studied in aqueous solution under different experimental conditions. Ketonization rate constants were measured spectrophotometrically at 25 °C at an ionic strength of 0.4 mol dm^{-3} (NaCl) in diluted hydrochloric acid, in diluted sodium hydroxide, and in several buffers by using $NaHSO_3$ as the scavenger of the keto form. A value of $pK_a^{EH} = 4.78$ for the enol form was obtained from the rate−pH profile of the reaction. A value of $pK_a^{KH} = 5.97$ for the keto form was directly obtained from the UV−vis spectra of 2-NCH recorded at different pHs. The equilibrium constant for the keto−enol tautomerism, $pK_T = -\log([\text{enol}]/[\text{ketone}]) = 1.19$, was obtained by combining the two pK_a values ($pK_T = pK_a^{KH} - pK_a^{EH}$). A comparison of these results with the corresponding values (Keefe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley & Sons: New York, 1990; pp 399−480) for cyclohexanone shows the dramatic effects of an α-nitro substituent on the keto−enol acidities and the tautomerization constant of alicyclic ketones. Rates and equilibria were discussed in the light of the Brønsted equation, the principle of nonperfect synchronization, and the Marcus theory. It turns out that, on passing from nitroalkanes to nitroketones, the resonance contribution to pK_a and deprotonation rate decreases, being overwhelmed by steric and inductive effects.

Introduction

In the past 20 years, many studies on rates and equilibria for keto−enol tautomerism have been performed for a wide variety of carbonyl compounds.[1−6] In sharp contrast, very little work is available for α-nitroketones.[7,8] The enol of 3-nitrobutanone (3-NB) displays an unusual stability ($pK_T = 2.34$)[8] as compared to that of the enol of butanone ($pK_T = 7.50$).[9] It was also found that both tautomers of 3-nitrobutanone are considerably acidic,

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[†] Università "G. d'Annunzio".

[‡] Università "La Sapienza".

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TABLE 1. Intercepts (k_0) and Slopes (k_B) Obtained from the Plots of the Experimental Pseudo-First-Order Rate Constants (k_e/s^{-1}) for the Ketonization of the Enol/Enolate of 2-NCH against the Concentrations of the Buffer Base B in Aqueous Solution at 25 °C and Ionic Strength 0.4 mol dm^{-3} (NaCl) (Rate Constants k_B^{EH} Refer to the Enol as the Reactant)

base	*r*	[B]/10^{-2} (mol dm^{-3})	pH^a	k_0 (s^{-1})	k_B (mol^{-1} dm^3 s^{-1})	k_B^{EH} (mol^{-1} dm^{3}s^{-1})
chloroacetate	1	1−8	3.13	0.049 (±0.002)	0.639 (±0.037)	0.56 (±0.12)
	3	0.8−8	3.28	0.048 (±0.002)	0.477 (±0.040)	
cyanoacetate	5	0.8−8	3.32	0.056 (±0.003)	0.302 (±0.062)	0.30 (±0.06)
glycolate	0.5	1−8	3.23	0.058 (±0.004)	1.59 (±0.08)	1.74 (±0.18)
	1	1−8	3.60	0.076 (±0.004)	1.69 (±0.09)	
	3	1−8	3.92	0.079 (±0.005)	1.93 (±0.11)	
acetate	0.5	0.8−8	4.08	0.110 (±0.009)	4.55 (±0.18)	4.97 (±0.61)
	1	0.6−6	4.27	0.156 (±0.008)	4.69 (±0.22)	
	3	5−50	4.76	0.348 (±0.048)	1.85 (±0.15)	
	5	10−50	4.91	0.499 (±0.015)	1.34 (±0.05)	
	10	5−40	4.96	0.527 (±0.013)	1.11 (±0.05)	
phosphate	1	2−5	5.53	0.655 (±0.025)	1.29 (±0.07)	

^{a} Potentiometrically determined soon before and after each experiment.

being the microscopic ionization constants pK_a^{KH} = 5.15 and pK_a^{EH} = 2.81. As a consequence, at moderate pHs in aqueous solution, the dominant equilibrium is that between the keto form and the enolate anion.

It is known[10] that α-substituents which are π-electron acceptors and σ-electron acceptors, such as the $-NO_2$ group, destabilize the keto and stabilize the enol tautomer by allowing extensive delocalization in the latter tautomer. A contribution to the stability of the enol might also arise from intramolecular hydrogen bonding.[11] Furthermore, the relative instability of the keto tautomers of α-nitroketones has been attributed[12] to steric hindrance and repulsive electrostatic interactions between the adjacent nitro and carbonyl groups.

With the present work, we have studied the ionization and keto−enol tautomerism of 2-nitrocyclohexanone (2-NCH) as a representative of the class of alicyclic α-nitroketones. The aci-form of 2-NCH has been ignored in the investigated equilibria due to its well-known[8] high acidity in aqueous solutions.

Results

Keto−Enol/Enolate Equilibria. It is now well-established[13−15] that for simple ketones the enol tautomer is favored in aprotic solvents while the keto tautomer, which has a higher dipole moment, is favored in polar solvents. Accordingly, the UV−vis spectrum of a 2 × 10^{-4} mol dm^{-3} aqueous solution of 2-NCH, recorded soon after the addition of the appropriate volume of a dioxane 2.5 × 10^{-2} mol dm^{-3} stock solution, shows an absorption band with a maximum at 336 nm which decreases steadily with time (within 45 min) due to the progressive conversion of the enol (or enolate) to the keto form (Figure 1). The initial absorption at 336 nm of the solution is higher at higher pHs and is lower at lower pHs, suggesting that the band at 336 nm is mainly due to the enolate of 2-NCH. The absence of one isosbestic point in Figure 1 is understandable if one considers that the spectra at the different times are not corrected for the concurrent hydration of the keto form.

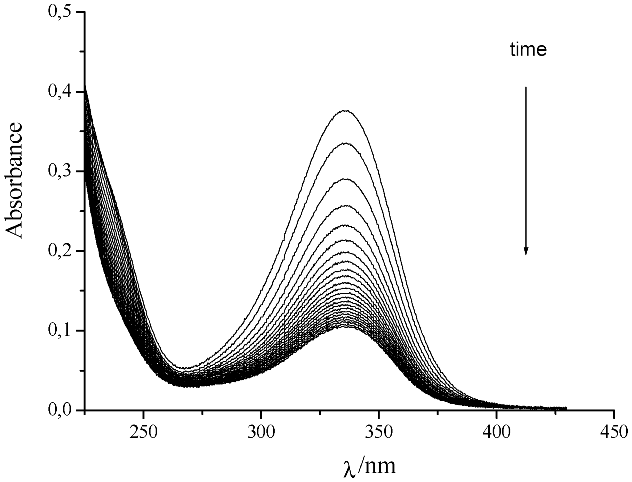

FIGURE 1. Absorption spectra of an aqueous 2 × 10^{-4} mol dm^{-3} solution of 2-NCH, registered at different times, showing the decrease of the absorption band at 336 nm due to the ketonization reaction of the enol (enolate) form.

Kinetics of the Ketonization Reaction. The rate of ketonization of the enol/enolate of 2-NCH has been measured spectrophotometrically in cyanoacetate, chloroacetate, acetate, glycolate, and phosphate buffers at different buffer ratios, r = [B]/[A], by following the decrease of the absorbance of the enolate at λ_{max} = 336 nm. In most experiments, the concentration of the conjugate base B of the buffer acid A, at constant r, was varied over a range of ca. a factor of 10 (see Table 1). Sodium bisulfite was used as the scavenger of the keto form following a previously reported procedure.[8,16,17] The concentration of $NaHSO_3$ was varied over the range of 0.5−50 × 10^{-2} mol dm^{-3}. The observed pseudo-first-order rate constant, k_e, increases upon increasing [$NaHSO_3$] at relatively low concentrations of $NaHSO_3$, but levels off to a limiting value at higher bisulfite concentrations (see a typical example in Figure 2).

The reaction is zero order, with respect to $NaHSO_3$, at [$NaHSO_3$] ≥ 0.1 mol dm^{-3}, where the ketonization step becomes rate determining. Under this condition, the ketonization reaction is irreversible and the potentially competitive hydration

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[17] Harcourt, M. P.; More O’Ferrall, R. A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1415−1425.

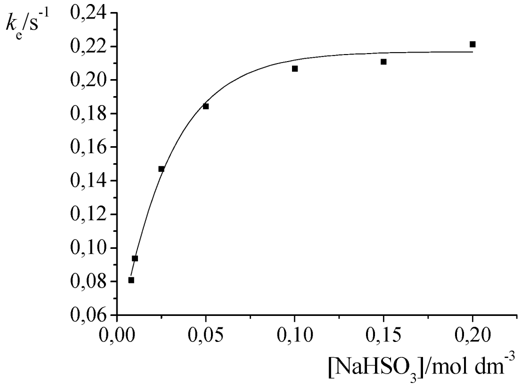

FIGURE 2. Plot of the observed rate constants for the ketonization reaction of 2-NCH, k_e/s^{-1}, against [NaHSO$_3$] in glycolate buffer with $r = 5$, [B] = 0.06 mol dm^{-3}, initial [2-NCH] = 1 × 10^{-3} mol dm^{-3}, $\lambda = 336$ nm, ionic strength = 0.4 mol dm^{-3} (NaCl).

TABLE 2. Pseudo-First-Order Rate Constants (k_e/s^{-1}) for the Ketonization of the Enol/Enolate of 2-NCH in HCl and NaOH at 25 °C and an Ionic Strength 0.4 mol dm^{-3} (NaCl)

pH	k_e/s^{-1}	pH	k_e/s^{-1}
1.30	0.030 (±0.001)	3.27	0.052 (±0.002)
1.54	0.026 (±0.001)	3.40	0.053 (±0.003)
2.02	0.027 (±0.001)	3.55	0.059 (±0.002)
2.89	0.035 (±0.002)	6.00	0.649 (±0.018)
3.14	0.042 (±0.002)	6.60	0.655 (±0.022)

reaction is suppressed as the keto tautomer is instantaneously trapped by the scavenger as it forms. The k_e is linearly related to [B] according to eq 1:

$$k_e = k_0 + k_B[\mathrm{B}] \tag{1}$$

where k_0 and k_B represent the pseudo-first-order rate constant (including the contribution of [OH$^-$]) for the buffer independent ketonization and the second-order rate constant for general base catalysis, respectively. On the other hand, a contribution of acid catalysis was not detected (see Table 2). The values of k_B for the different buffer bases, B, can be obtained from the slopes of the plots of k_e against [B].

The pH values of the acetate buffer solutions are close to the pK_a^{EH} of the enol, and rate constants, k_B, are related to pH by eq 2, where k_B^{EH} is the corresponding rate constant for the ketonization of the enol.[5,6,18]

$$k_B = k_B^{EH}/(1 + K_a^{EH}/[\mathrm{H}^+]) \tag{2}$$

A best fit of eq 2 by using K_a^{EH} obtained from the pH profile (see the following section) gave for acetate catalysis a value of $k_B^{EH} = 4.97(\pm 0.61)$ dm^3 mol^{-1} s^{-1}. An analogous treatment in terms of eq 2 for the other buffers of Table 1 was not attempted due to the paucity of experimental data, and the values of k_B^{EH} for chloroacetate and glycolate buffers have been calculated by averaging the k_B values obtained at different r.

The ketonization reaction was similarly followed in dilute HCl and NaOH solutions. The obtained pseudo-first-order rate constants (k_e) are reported in Table 2.

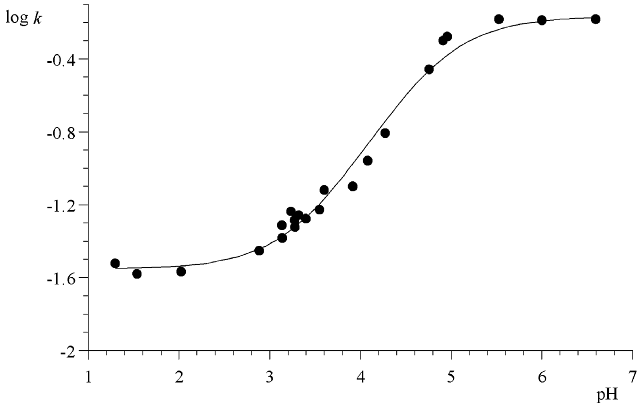

FIGURE 3. Rate−pH profile for the ketonization reaction of the enol of 2-NCH.

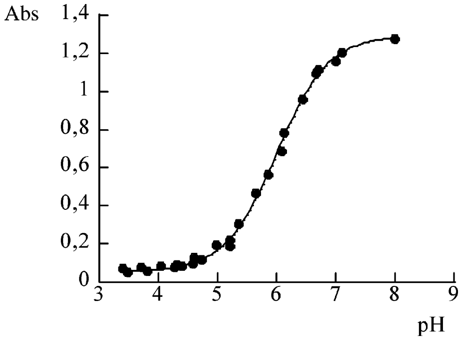

FIGURE 4. Plot of the absorbance, Abs, at $\lambda = 336$ nm against pH of a 1 × 10^{-3} mol dm^{-3} solution of 2-NCH.

Rate−pH Profile and Determination of the Ionization Constant, pK_a^{EH}, of the Enol. A rate−pH profile for the ketonization reaction can be obtained by plotting log k_0 and log k_e values from Tables 1 and 2 (reported as "log k" in Figure 3) against the corresponding experimental pHs.

The data fit eq 3:

$$k = \{k_W^{E} K_a^{EH}/[\mathrm{H}^+] + k_W^{EH}\}/\{1 + K_a^{EH}/[\mathrm{H}^+]\} \tag{3}$$

where k_W^E and k_W^{EH} are the rate constants for the "water" reaction for the enolate, E, and the enol, EH, respectively.

A value of p$K_a^{EH} = 4.78(\pm 0.03)$ can be obtained from eq 3, while a value of $k_{OH}^{EH} = 1.08 \times 10^9$ mol^{-1} dm^3 s^{-1} for the OH$^-$-catalyzed ketonization of the enol can be obtained from eq 4, where K_W is the ionic product of water.

$$k_{OH}^{EH} = k_W^{E} K_a^{EH}/K_W \tag{4}$$

Determination of the Ionization Constant, pK_a^{KH}, of the Keto Tautomer. The apparent acid dissociation constant, K_a^{app}, of 2-NCH in aqueous solution, that is, the experimental acid ionization constant for the deprotonation of the mixture of the two tautomers, was measured spectrophotometrically by monitoring the absorbance at $\lambda_{max} = 336$ nm of a 1 × 10^{-3} mol/dm^3 solution of 2-NCH after equilibrium had been established at each pH. The pHs of the different solutions were set by using glycolate, acetate, cacodilate, phosphate, and borate buffers at appropriate buffer ratios. The experimental results are reported in Figure 4.

The total absorbance, Abs, of the solution is given by eq 5:

$$\mathrm{Abs} = \epsilon_{KH}[\mathrm{KH}] + \epsilon_{EH}[\mathrm{EH}] + \epsilon_{E}[\mathrm{E}] \tag{5}$$

Taking into account that [2-NCH] = [KH] + [EH] + [E], and that the keto form does not absorb at 336 nm, eq 5 reduces to

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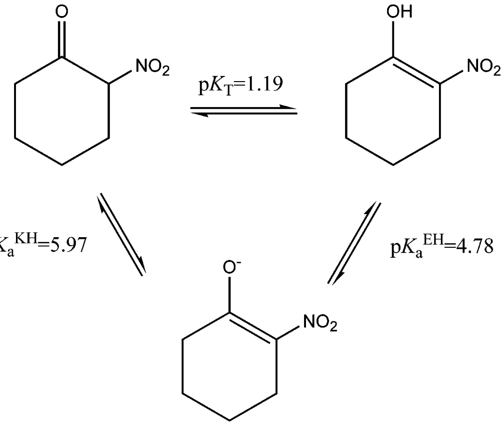
[18] Carey, A. R. E.; Fukata, G.; More O'Ferrall, R. A.; Murphy, M. G. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1711−1722.

SCHEME 1



eq 6:

$$\text{Abs} = (\text{Abs}_{\text{min}}[\text{H}^+] + \text{Abs}_{\text{max}}K_a^{\text{app}})/(K_a^{\text{app}} + [\text{H}^+]) \quad (6)$$

where Abs_{min} (0.055) and Abs_{max} (1.295) are the limiting absorbances at the lowest and the highest pHs, respectively. A pK_a^{app} = 6.00(±0.02) could be obtained from a best fit of experimental data to eq 6.

The ionization constant of the keto tautomer, K_a^{KH}, can be calculated from eq 7:

$$1/K_a^{\text{app}} = \{[\text{EH}] + [\text{KH}]\}/\{[\text{E}][\text{H}^+]\} = 1/K_a^{EH} + 1/K_a^{KH} \quad (7)$$

by using the above pK_a^{app} and the pK_a^{EH} = 4.78 from the rate−pH profile of Figure 3. A value of pK_a^{KH} = 5.97 was obtained.

We conclude that the values of K_a^{app} and K_a^{KH} are equal within the experimental error.

Determination of the Tautomeric Constant, pK_T. The values of pK_a^{EH} and of pK_a^{KH} can be combined to obtain the tautomeric constant pK_T= −log([enol]/[ketone]) = pK_a^{KH} − pK_a^{EH} = 1.19 in aqueous solution at 25 °C according to the thermodynamic cycle of Scheme 1.

The rate constants for the ionization of the keto form of 2-NCH by hydroxide, k_{OH}^{KH}, and water, k_W^{KH}, can be calculated by fitting k_{OH}^{EH} and k_W^{EH} to eqs 8 and 9, respectively.

$$k_{OH}^{KH} = k_{OH}^{EH}K_T \quad (8)$$

$$k_W^{KH} = k_W^{EH}K_T \quad (9)$$

The obtained values are reported in Tables 3 and 4.

Brønsted Plots. The rate constants, k_B^{KH}, for the ionization of 2-NCH by the buffer bases, B, of Table 1 can be calculated by fitting k_B^{EH} of Table 1 to eq 10:

$$k_B^{KH} = k_B^{EH}K_T \quad (10)$$

Figure 5 is a Brønsted plot of k_B^{KH}, k_{OH}^{KH}, and k_W^{KH} against the corresponding pK_a values. Rate constants and acid dissociation constants have been statistically corrected for the number *p* of acidic proton and for the number *q* of basic sites.[19] From the obtained straight line, a Brønsted β of 0.63(±0.02) can be calculated.

TABLE 3. Dissociation and Rate Constants for the Ionization by OH⁻ in Water at 25 °C of the Monocarbonyl Compounds of Scheme 2 (The Data in Bold Have Been Used for the Brønsted Plot of Figure 6b)

compound	pK_a^{KH}	−log(*K*/p)	log(k_{OH}^{KH}/p)	log(k_{OH}^{KH}/p) calcd[a]	intrinsic barriers (kcal/mol)
1	25.60	10.3	-3.40		
2	**21.48**	**5.74**	**-2.98**	-2.55	16.8
3	21.00	5.74	-2.18		
4	**20.33**	**4.59**	**-2.43**	-1.91	16.9
5	**19.30**	**4.04**	**-1.46**	-1.61	17.0
6	**19.27**	**4.01**	**-1.14**	-1.60	17.0
7	**18.90**	**3.64**	**-1.83**	-1.40	17.0
8	18.41	3.15	-1.17		
9	**18.30**	**3.04**	**-1.08**		
10	**18.27**	**3.01**	**-1.13**	-1.06	17.0
11	**18.26**	**2.52**	**-2.62**		
12	16.70	1.44	-0.41		
13	**16.60**	**1.34**	**-0.85**	-0.19	17.0
14	**15.91**	**0.47**	**0.20**	0.25	16.9
15	**15.76**	**0.32**	**0.25**	0.33	16.9
16	15.49	-0.25	-0.85		
17	**13.27**	**-2.17**	**1.91**	1.55	16.6
18	13.10	-2.34	1.00		
19	**12.20**	**-3.24**	**2.05**	2.06	16.4
20	**11.00**	**-4.74**	**3.24**	2.75	16.1
21	10.40	-5.34	2.40		
2-NCH	**5.97**	**-9.77**	**7.84**	4.89	14.4
3-NB	**5.15**	**-10.6**	**7.51**	5.22	14.0

[a] Calculated according to the Marcus equation.

TABLE 4. Dissociation and Rate Constants for the Ionization by H_2O at 25 °C of the Monocarbonyl Compounds of Scheme 2 (The Data in Bold Have Been Used for the Brønsted Plot of Figure 7b)

compound	log(*K'*/p)	log(k_W^{KH}/p)
6	**-21.5**	**-9.82**
9	**-20.5**	**-9.21**
11	**-20.0**	**-9.78**
12	-18.9	-8.10
15	**-17.8**	**-7.36**
16	-17.5	-7.56
17	**-15.3**	**-5.85**
18	-14.9	-6.33
20	**-12.8**	**-6.36**
2-NCH	**-7.71**	**-2.74**
3-NB	**-6.90**	**-3.19**

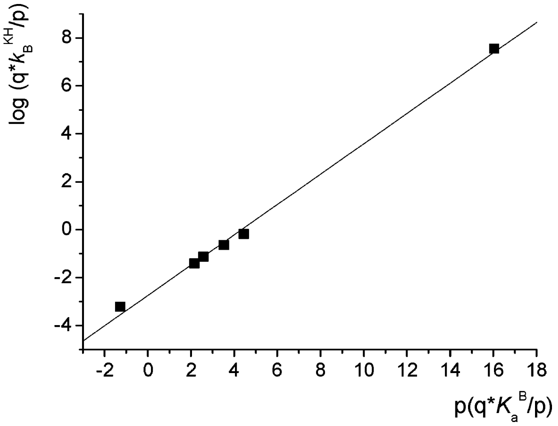


FIGURE 5. Brønsted plot for the ionization reaction of 2-NCH.

The values of k_{OH}^{KH} for 2-NCH and a number of simple monocarbonyl compounds[1] (Scheme 2) have been used for the Brønsted plots of Figure 6, where abscissa values, p*K*, refer to the equilibrium of Scheme 3.

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[19] Bell, R. P.; Evans, P. G. *Proc. R. Soc. London, Ser. A* **1966**, *291*, 297−323.

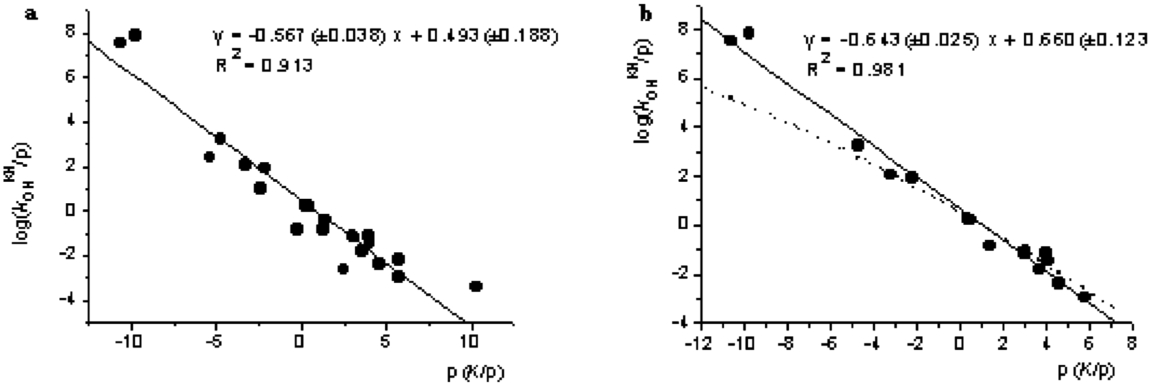


FIGURE 6. Brønsted plots for the ionization by OH^- (a) of all the monocarbonyl compounds of Table 3 and (b) of only the ketones of Table 3 (for the dotted line of Figure 6b, see the text under the Discussion section).

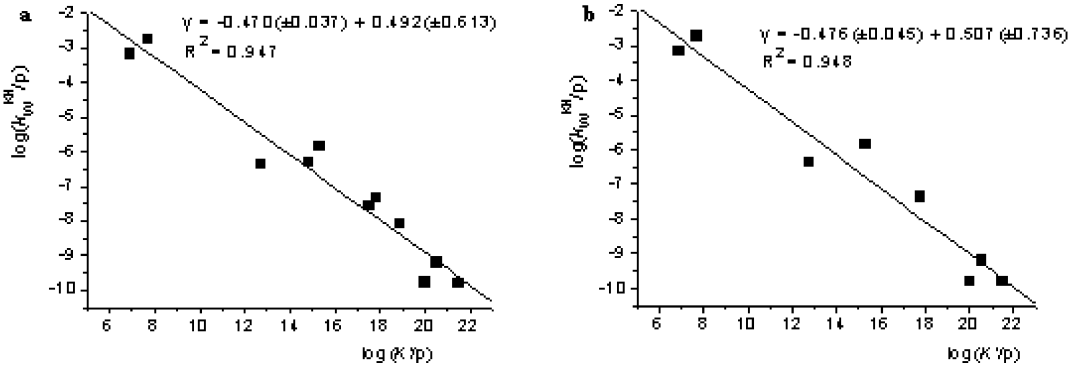
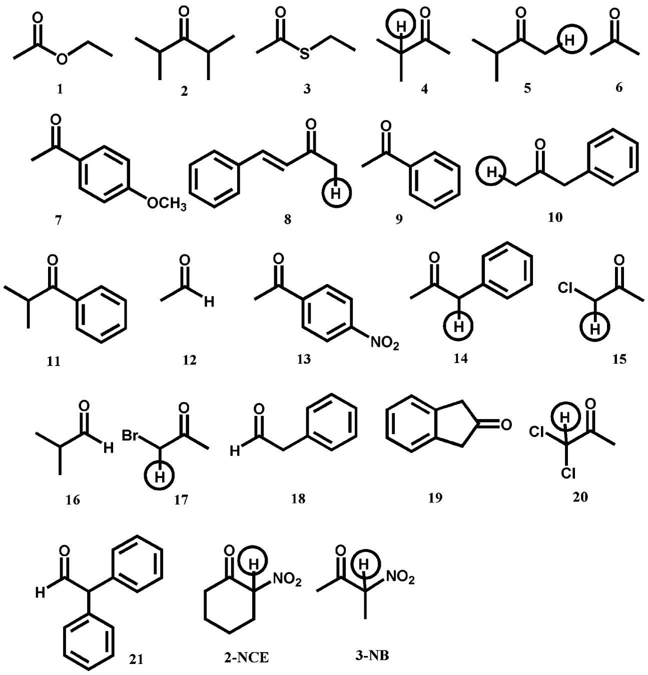


FIGURE 7. Brønsted plots for the ionization by H_2O (a) of all the monocarbonyl compounds of Table 4 and (b) of only the ketones of Table 4.

SCHEME 2



The Brønsted plots of k_W^{KH} for 2-NCH and the same monocarbonyl compounds (Scheme 2) against pK' of Scheme 4 are reported in Figure 7.

Rate and equilibrium constant values used for the Brønsted plots of Figures 6 and 7 are reported in Tables 3 and 4, respectively.

SCHEME 3

$$OH^- + KH \overset{K}{\rightleftharpoons} E^- + H_2O$$

$$K = K_a^{KH}\frac{[H_2O]}{K_W}$$

SCHEME 4

$$H_2O + KH \overset{K'}{\rightleftharpoons} E^- + H_3O^+$$

$$K' = \frac{K_a^{KH}}{[H_2O]}$$

Molecular Modeling.[20] An exhaustive conformational analysis has been carried out by molecular mechanic calculations with the MM2* force field in order to obtain the geometries of lowest energy for the two tautomeric forms as well as the enolate anion of 2-NCH. Each geometry has been further minimized by semiempirical calculations with the AM1 Hamiltonian as well as the Hartree−Fock ab initio method at the SCF level, employing the 6-31G* basis set. For the selected conformations, the corresponding hydration energies, based on the SM5,4 model of Cramer and Truhlar, were estimated. For sake of comparison,

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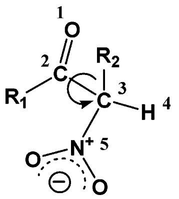
(20) Conformational searches were carried out by Batchmin and Macromodel version 4.5 (Columbia University, NY) using the following options: MM2* force field, Monte Carlo stochastic algorithm with 3000 generated structures, minimization by PR conjugate gradient. All of the rotatable bonds were explored. The aqueous solvation energies by the SM5,4 model and all of the semiempirical calculations were performed by using the computer program SPARTAN '02, Wavefunction Inc., 18401 Von Karman Avenue, Suite 370 Irvine, CA 92612.

TABLE 5. Estimated Hydration Energies, Values of $^{+}\delta$(H), and Steric Entropy Contributions for the Selected Conformations of NP, 3-NB, and 2-NCH

	Ab initio calculations					Semiempirical calculations			
	conformations of species X	energy of species X in vacuum (au)	hydration energy (kcal/mol)	dipole moment (debye)	steric entropy (eu)	$^{+}\delta$(H) (AM1)	pK_a (calcd)	dihedral angle of O═C−C−NO$_2$	dihedral angle of O═C−C−H
NP	1KH	-395.424757	-4.641	1.03	0.77	0.167	3.7	-169	-48.0
	2KH	-395.423126	-8.655	6.30		0.157	6.2	-8.06	112
3-NB	1KH	-434.464325	-3.543	2.01	0.55	0.166	3.9	-146	-30.1
	2KH	-434.463475	-4.235	1.44		0.164	4.4	-116	-1.38
	3KH	-434.461599	-7.358	4.82		0.147	8.7	38.4	153
	$1EH_Z$	-434.449888	-4.548	4.54	0.00	0.272	3.0	−	−
	$2EH_Z$	-434.426606	-11.181	7.42		0.226	9.4	−	−
	$3EH_E$	-434.437298	-6.522	4.56	0.25	0.233	8.4	−	−
	$4EH_E$	-434.436839	-8.921	5.64		0.234	8.3	−	−
	$1E^{-}_{Z}$	-433.886893	-60.743	9.85	0.01	−		−	−
	$2E^{-}_{E}$	-433.902280	-55.53	2.98		−		−	−
2-NCH	1KH	-511.371880	-7.172	6.83	0.11	0.155	6.7	-2.24	113
	2KH	-511.371440	-4.724	4.27		0.161	5.2	-105	10.5
	$1EH_Z$	-511.364827	-4.185	4.63	0.00	0.272	3.0	−	−
	$2EH_Z$	-511.343648	-9.484	7.28		0.224	9.6	−	−
	$1E^{-}_{Z}$	-510.800207	-59.312	12.05	0.00	−		−	−

SCHEME 5



the same search was performed for 3-nitrobutanone, 3-NB, and the keto form of nitropropanone, NP. The semiempirical atomic charges on the α-hydrogens, $^{+}\delta$(H), have been used as the descriptors of their acidity in order to predict pK_a values (Table 5) of the corresponding conformations, according to the procedure of ref 8. The $^{+}\delta$(H) values have been considered as a function of the O═C−C−H and O═C−C−NO$_2$ torsional angles shown in Scheme 5, within each keto conformation. Ab initio energies of the different conformations together with the corresponding hydration energies are reported in Table 5. The steric entropy contributions, S, were evaluated by eq 11where

$$S^{X} = -Rp_i^{X} \ln p_i^{X} \qquad (11)$$

R is the gas constant and p_i is the Boltzmann population of each conformation of species X (where X = KH, EH, or E) obtained from the total energy of X, including the hydration energy. S^{EH} for the enol of 3-NB was evaluated assuming that free *E/Z* interconversion is unattainable. The data obtained are collected in Table 5.

Discussion

The rate−pH profile of Figure 3 shows a region, at intermediate pHs, for apparent OH$^-$ catalysis and two regions where the reaction is pH-independent. The plateau at lower pH values ($1.3 \leq \text{pH} \leq 3$) corresponds[21] to the "water" ketonization of the enol, $k_W^{EH} = 0.028(\pm 0.002)\ \text{s}^{-1}$. The mechanism of this reaction involves ionization of the enol to the enolate ion followed by the rate-determining protonation of the enolate by hydronium ion. Thus a hydronium ion is produced in the first step which is then consumed in the second step. Accordingly, the rate of the process should be independent of hydronium ion concentration. In fact, H_3O^+ catalysis for the ketonization reaction of the undissociated enol is detectable[1] only for relatively basic ketones, and it is not surprising that it is not detectable for nitroketones.[8] The positive limb (in the range $3.0 \leq \text{pH} \leq 4.9$) probably represents the water ketonization of increasing amounts of enolate upon increasing the pH, k_W^{E}, rather than the kinetically indistinguishable OH$^-$-catalyzed ketonization of the enol, k_{OH}^{EH}. The plateau at higher pH values corresponds to the reaction after full conversion to the enolate anion, $k_W^{E} = 0.652(\pm 0.003)\ \text{s}^{-1}$. The point of inflection corresponds to the pK_a^{EH} of the enol, and a value of pK_a^{EH} 4.78(±0.03) can be obtained from a best fit of experimental data to eq 3.

The effectiveness of acids and bases as catalysts in proton-transfer reactions is generally related linearly[22] to their acid or basic strengths. However, if a sufficiently large range of pK_a values is investigated, a curvature is often observed in the plot of log k against pK_a. This curvature is usually in the direction of a smaller slope (α or β) at higher velocities.[22] An interpretation of such a curvature is offered by the Marcus theory[23] in terms of constant intrinsic barriers. In the case of the enolization reaction, the intrinsic barrier for a given catalyst (e.g., OH$^-$ or H_2O) depends only of the type of carbonyl compound (e.g., monocarbonyl, dicarbonyl, etc.).[21,23,24] Nevertheless a good linear Brønsted plot, extending over 14 pK units and 5 log k units, was evidenced by Amyes and Richard[25] for the proton abstraction by OH$^-$ from a number of monocarbonyl compounds. The authors explained this extended linearity in terms of non-constant intrinsic barriers.[25] An interesting occasion for testing this explanation is offered by the present and previous[8] results on 2-NCH and 3-NB. The Brønsted plots of log k_{OH}^{KH}

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(Table 3) and log k_W^{KH} (Table 4) against pK (Figure 6a) and pK' (Figure 7a) are linear over 20 and 16 pK units, respectively. The correlation coefficient, R^2, of the plot of Figure 6a increases up to 0.98 if only the ketones of Table 3 are considered (Figure 6b). The Brønsted plot of Figure 6b extends to 16 pK units with an α of 0.64, a value considerably higher than that (α = 0.38) found by Amyes and Richard.[25] It should be noticed, however, that the reported[25] α value refers also to aldehydes, esters, and thioesters and refers to a lower number of considered structures.[25] The unusual linearity of the correlation of Figure 6b is apparently against the prediction of the Marcus theory. For the ketones of Table 3, a constant intrinsic barrier $\Lambda = 16.8$ kcal mol^{-1} can be calculated by a linear interpolation of the data to p$K = 0$. This Λ value can be inserted into the Marcus equation (eq 12 derived at 298 K without the inclusion of a work term, $w_r = 0$)[25] in order to obtain a set of "calculated" log k_{OH}^{KH}.

$$\log k_{OH}{}^{KH} = 1/1.36\{17.44 - w_r - \Lambda[1 + (1.36\mathrm{p}K - w_r)/(4\Lambda)]^2\} \quad (12)$$

The calculated values of log k_{OH}^{KH} have then been plotted against pK, and as expected, a curve is obtained (dotted line in Figure 6b).

Individual intrinsic barriers, Λ′, can vice versa be calculated from the experimental values of log k_{OH}^{KH} by using eq 12. We note that the obtained values (Table 3) are lower for more reactive compounds, in agreement with the "reactivity−selectivity principle".

Departure from Brønsted linearity has also been interpreted in terms of the principle of nonperfect synchronization (PNS).[26] An elementary reaction generally involves more than one concurrent and unequally developing molecular processes at the imbalanced transition state. According to the PNS,[26] "a product (reagent)-stabilizing factor whose development at the transition state is late lowers (enhances) the rate constant, whereas a product (reagent)-stabilizing factor whose development at the transition state is early enhances (lowers) the rate constant". Product-stabilizing factors that typically develop late and hence lower the rate constant are[26a,b,27] resonance, solvation, intramolecular hydrogen bonding, and specific electrostatic effects. Resonance effects are considered particularly important in enhancing the intrinsic barrier of reactions wherein the deprotonation of a carbon acid is activated by a π-acceptor substituent, as the nitro or the phenyl groups.[25,26d] Therefore, the absence of significant departures from the linearity of the Brønsted plot of Figure 6b could mean that resonance does not play a major role as a product-stabilizing factor in the ionization reaction of the investigated ketones. We have tested this possibility by means of a correlation analysis of log K or log k_{OH}^{KH} for some α-substituted ketones with different substituent parameters[28] (σ_m,σ_I,σ_R,E_s). The results of Table 6 clearly show that steric effects play the major role both for the equilibrium and for the kinetic deprotonation processes, whereas resonance effect plays a minor role.

TABLE 6. Correlation Analysis for the Rates [log(k_{OH}^{KH}/p)] and Equilibria [−log(K/p)] of Ionization of Some Ketones (compounds 6, 14, 15, 17, 20, and 3-NB of Scheme 2) with Selected Substituent Parameters (R^2 = Correlation Coefficient)

parameters	R^2 log(k_{OH}^{EH}/p)	R^2 − log(K/p)
Es	0.886	0.948
σ_I	0.491	0.573
σ_R	0.109	0.053
σ_m	0.626	0.697

A similar conclusion can be arrived at by the use of $\Delta = \alpha - \beta$ as a measure of the imbalance at the transition state,[26d] where α is the Brønsted coefficient determined by varying the substituent in the ionization reaction of a series of selected carbon acids by a given base, and β is the Brønsted coefficient determined by varying the substituent in the protonation reaction of a series of bases by a given carbon acid. Several Δ values have been calculated by using the α value (0.64) of the plot of Figure 6b and the β values for the deprotonation of acetone (0.72),[29] acetophenone (0.68),[21] isobutirophenone (0.63),[24c] 2- and 3-acetylthiophenes (0.53),[30] and 2-NCH (β = 0.63, see Results) by different bases. In all cases, Δ values are small ($-0.08 \leq \Delta \leq +0.11$), suggesting that the imbalance in the TS is either low or absent. This conclusion is also supported by a comparison of the α value (0.64) of Figure 6b with that (1.54)[31] for the ionization of arylnitroalkanes by OH$^-$, a reaction with a strongly imbalanced transition state.[26d,32]

Further evidence of a minor contribution by resonance as the product-stabilizing effect in the ionization of nitroketones by OH$^-$ may come from the application to 2-NCH and 3-NB of a treatment previously proposed by Bernasconi[26d] in terms of eq 13

$$\delta \log K_R = \delta \log k_R/(\beta n - \beta) \quad (13)$$

where δ log K_R (=log K_R − log K^{ref}) and δ log k_R (=log k_R − log k^{ref}) represent the change in the equilibrium constant and in the rate constant, respectively, induced by the resonance effect, with reference to a proton-transfer reaction (log K^{ref} and log k^{ref}) unaffected by resonance.[26d] Taking into account that the overall effect of the nitro group on the acidity of an α hydrogen of a ketone can be taken as 14.9 pK units from the ΔpK_a of propanone and nitropropanone,[33] the resonance contribution to this effect can be estimated as 3.0 (20%) pK units for 2-NCH and 3.9 (26%) pK units for 3-NB (if $n = 3$ and $\beta = 0.63$). Thus, it appears that the resonance contribution to the overall acidifying effect of the nitro group of α-nitroketones is smaller than that found[26d] for nitroalkanes (53%).

A possible reason for the unexpectedly overwhelming role played by steric and inductive effects on the deprotonation of nitroketones comes also from our molecular modeling study. From the conformational search, several representative geometries were found (Figure 8) for the keto form of 2-NCH (two

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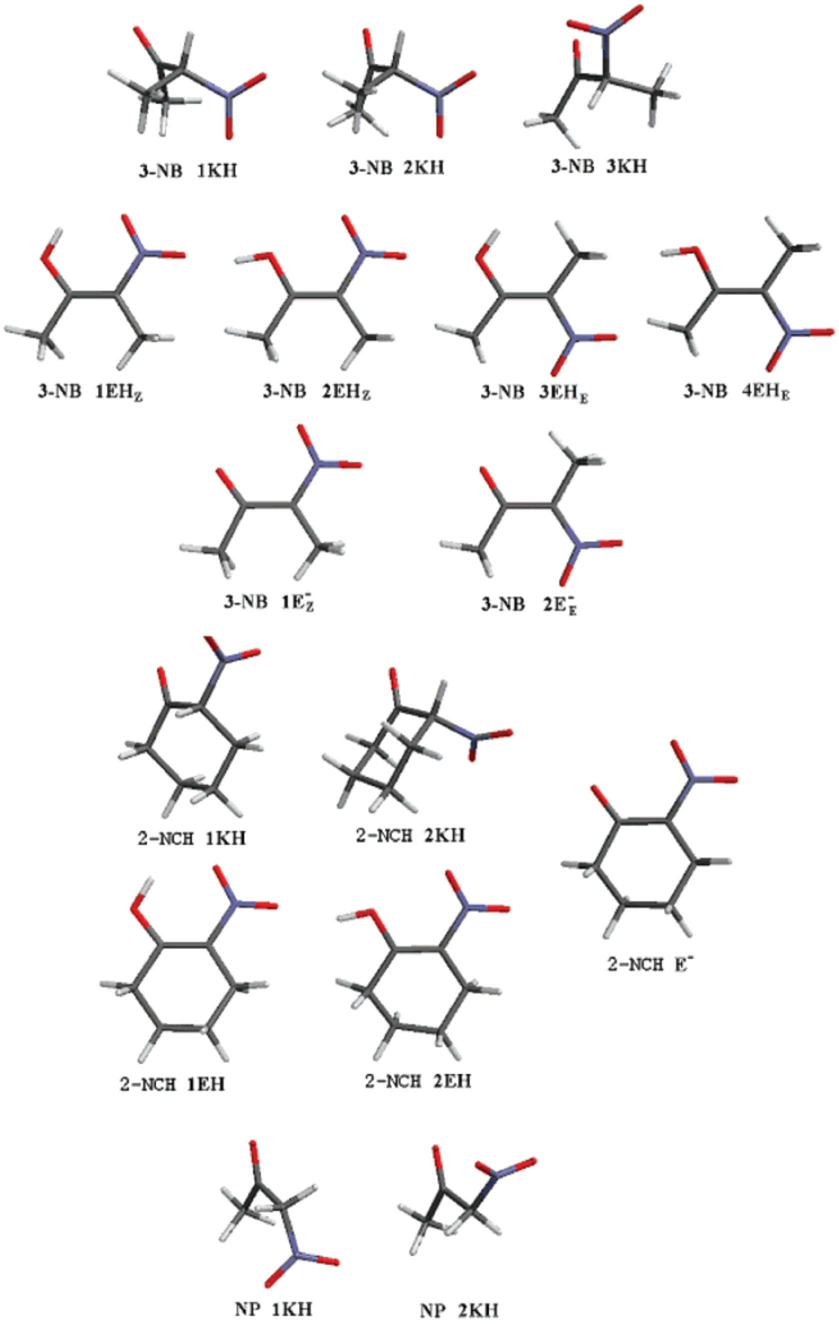

FIGURE 8. Conformations of the keto, enol, and enolate form of 3-NB and 2-NCH and conformations of the keto form of NP obtained by molecular modeling study.

conformations), 3-NB (three conformations), and NP (two conformations), whose energies are reported in Table 5. Considering the charge value [estimated by semiempirical calculations on the acidic hydrogen, $^{+}\delta(\mathrm{H})$], the tendency of each geometry of the keto form to act as an acid can be evaluated, as it is known[8] that $^{+}\delta(\mathrm{H})$ is a meaningful descriptor of acidity. By analyzing the variations of $^{+}\delta(\mathrm{H})$ as a function of the rotation about the OC−CNO$_2$ bond (see Scheme 5), it turns out that there is a clear dependence of the polarity of the C−H bond on the reciprocal disposition of the C═O and C−NO$_2$ dipoles. Thus, the highest charge value [$^{+}\delta(\mathrm{H})_{\max}$] is attained when the O═C−C−NO$_2$ dihedral angle approaches to 150° and the O═C−C−H dihedral angle is about 30° inmodule, that is, when the C═O and C−NO$_2$ dipoles assume the most favorable alignment for the polarization of the C−H bond.

To very similar $^{+}\delta(\mathrm{H})_{\max}$ values for 3-NB and NP (0.166 and 0.167, respectively) correspond very similar experimental pK_a^{KH} values (5.15 and 5.1, respectively). The calculated pK_a values are 3.9 and 3.7, respectively. These pK_a^{KH} values are considerably lower than that of 2-NCH [$^{+}\delta(\mathrm{H})_{\max} = 0.161$; p$K_a^{\mathrm{KH}} = 5.97$ (exp), 5.2 (calcd)] where the ring decreases the degrees of freedom and does not allow the O═C−C−NO$_2$ dihedral angle to be greater than 112°. Since the most acidic conformations of the three considered nitroketones display the lowest molecular dipoles, for those conformations, a less favorable hydration is expected (see values in Table 5). Thus, the more populated and less acidic conformations of 2-NCH, 3-NB, and NP have to interconvert to the more acidic and more reactive ones in order to react with a base. If this is the case, the relevant role played by steric and inductive effects of the nitro group on the thermodynamics and kinetics of the enolization process can be easily understood. The smaller acidity observed for the enol of 2-NCH than that of the enol of 3-NB may be rationalized by considering that the internal energy difference between the enolate ion and the enol is more positive for 2-NCH than for 3-NB (see Table 5). On the contrary, the steric entropy does not play a relevant role ($\Delta S^{E-EH} = 0.00$ u.e. for 2-NCH and 0.01 u.e. for 3-NB).

Conclusions

It has been shown that 2-NCH is 5×10^{13} times more acidic than cyclohexanone,[1] while the enol of 2-NCH is about 10^7 times more acidic than that of cyclohexanone.[1] This remarkable acidity of 2-NCH is attributable to the dramatic effect of the α-nitro group. The value of $pK_T = 1.19$, for 2-NCH, is in sharp contrast with the values for simple ketones such as acetone ($pK_T = 8.33$),[33] acetophenone ($pK_T = 7.96$),[34] and cyclohexanone ($pK_T = 6.39$)[1] for which the keto−enol equilibrium is largely in favor of the more stable keto form. The keto−enol equilibria and acidities of 2-NCH could more closely resemble those of 1,3-dicarbonyl compounds such as 2-acetylcyclohexanone.[35] However, the two systems appear quite different in terms of both acidity of KH ($pK_a = 5.94$ for 2-NCH and 9.62 for 2-acetylcyclohexanone[35]) and tautomeric constants ($pK_T = 1.19$ for 2-NCH and 0.14 for 2-acetylcyclohexanone[35]). A comparison between open chain and alicyclic α-nitroketones highlights that the enol content at equilibrium is higher for 2-NCH than for 3-NB ($pK_T = 2.34$).[8] This result can be understood by remembering that alicyclic α-nitroketones can be better stabilized by intramolecular hydrogen bonds.[10]

Experimental Section

Materials. 2-Nitrocyclohexanone, inorganic salts (NaCl, $NaHSO_3$, KH_2PO_4, Na_2HPO_4), and acids ($CNCH_2COOH$, $ClCH_2COOH$, $HOCH_2COOH$, CH_3COOH) were commercial samples of AnalaR grade and were used without further purification. Aqueous solutions were prepared using deionized water.

Instruments. The kinetic experiments were carried out with a UV/vis spectrophotometer equipped with a rapid kinetic accessory for the faster reactions. The spectrophotometer was provided with a thermostated cell holder.

Kinetic Measurements. The ketonization reaction of the enolate of 2-NCH was followed spectrophotometrically by using $NaHSO_3$ as the scavenger of the ketone.[8,16,17] The decrease of the absorbanceat $\lambda = 336$ nm of the enolate was followed at 25.0 ± 0.1 °C and at a constant ionic strength of 0.4 mol dm^{-3} (NaCl). A small aliquot of a stock solution of 2-NCH in anhydrous dioxane was added to the cuvette immediately before each kinetic run, in order to minimize the hydration of the carbonyl group. The initial concentration of 2-NCH was ca. 1×10^{-3} mol dm^{-3} in all experiments. The pH of the solution was tested before and after each experiment.

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