The Base-Catalyzed Keto−Enol Interconversion of 2-Nitrocyclohexanone in Ionic Liquids
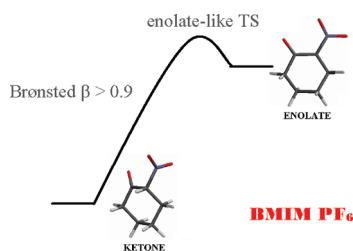
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While the solvent effect on the rate of tautomerization of 2-nitrocyclohexanone in several organic solvents appears to depend essentially on the permittivity of the solvent, a different behavior is observed in some ionic liquids. In particular the rate of the reaction in ionic liquids (ILs) is much faster than expected solely on the basis of the permittivity of the studied ILs. However, if more solvent parameters are taken into consideration (namely the polarizability, H-bond acidity, and cohesive pressure of the solvent) one comprehensive linear solvation energy relationship (LSER) for both organic and IL media can be obtained and no special "ionic liquid effect" can be highlighted. The kinetic results have also been discussed in terms of the Brønsted equation. It turns out that on passing from molecular solvents to ILs the transition state structure of the enolization reaction becomes markedly enolate-like (Brønsted β value close to 1).

Introduction

Ionic liquids (ILs) are substances that are composed solely of anions and cations and that are liquid at around (and often below) room temperature. Although ILs have recently gained wide attention mainly as alternative solvents in "green chemistry", probably their most important feature is the ability to act as "designer solvents".[1] The great variety of cations and anions, which can be used in the preparation of ILs, offers to the chemist an incredible number of opportunities (the evaluated number of potential ILs is higher than 10^{18}),

thus making the selection of the best IL for a specific application quite difficult. The study of how the modification of the IL structure affects the properties and the reactivity of dissolved species is an important area of research.[2] Kinetic and mechanistic studies have been recently performed on nucleophilic and electrophilic substitutions, electrophilic addition, and other common organic reactions.[3] These studies have given, in some cases, detailed information on the

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interaction of ILs with substrates, transition states, intermediates, and products. This information should help the chemists to choose, or design, the "best" IL for a given reaction. Recently we have been investigating the solvent effect of ILs on the keto−enol tautomerism of α-nitroketones.[4,5] In a previous work,[4] the keto−enol equilibrium constants of 2-nitrocyclohexanone (2-NCH) in several organic solvents and ILs at 25.0 ± 0.1 °C have been analyzed in terms of multiparameter equations. Permittivity (unavailable by direct measurements) and cohesive pressure values of the investigated ILs have been derived.

The tautomeric equilibrium of 2-NCH is in favor of the enol form (EH) in the gas phase and in apolar solvents while it is displaced toward the keto form (KH) upon transfer to water, aprotic polar organic solvents, and ILs. This displacement has been attributed[4] to the fact that cavitational and nonspecific electrostatic contributions, which strongly stabilize KH, more than compensate for the specific electrostatic contributions which stabilize EH. Thus the keto−enol interconversion of 2-NCH appears a suitable probe reaction to obtain information on the solvent properties of ILs. This interconversion is a general base catalyzed reaction that can be conveniently investigated[5] by UV−vis spectroscopy. In this work we have studied the kinetics of the tautomerization reaction using different pyridines as the catalysts in some ILs. The obtained results have been compared with those previously obtained[5] in conventional organic solvents.

Results and Discussion

Keto−Enol Equilibria. The UV−vis spectrum of a 1×10^{-4} M solution of 2-NCH in cyclohexane, registered immediately after dissolution, is characterized by two absorption maxima, at 319 (weaker) and 205 nm (stronger), which can be attributed respectively to the enol and keto forms. As time passes the band at 319 nm increases whereas the band at 205 nm decreases until the equilibrium position is reached. The attainment of the equilibrium is accelerated by bases (triethylamine, pyridines, etc.), whereas acids slow down the process.[5] One isosbestic point at 217 nm characterizes the collected spectra (Figure 1).

Solvent Effects on the Kinetics of the Keto−Enol Interconversion. The kinetics of the tautomeric interconversion of 2-NCH was studied at 25.0(±0.1) °C in the six ILs of Scheme 1, following by UV/vis spectroscopy the decrease of the absorbance at the λ_{max} of the enol form as previously described.[5]

The mechanism of the base-catalyzed enolization reaction of 2-NCH is reported in Scheme 2, where B is the catalyst.

Excess pyridine, Pyr, was used as the catalyst and Pyr concentration was varied over a range of a factor of 10. The absorbances at the λ_{max} of EH were followed as a function of time. Under the adopted experimental conditions the reaction follows the pseudo-first-order rate law reported in eq 1.

$$\text{rate} = k_{app}[\text{2-NCH}] \qquad (1)$$

k_{app} values were obtained by using a least-squares fitting of the experimental data. A plot of k_{app} vs. [Pyr] gives a straight line whose slope represents the second-order rate constant
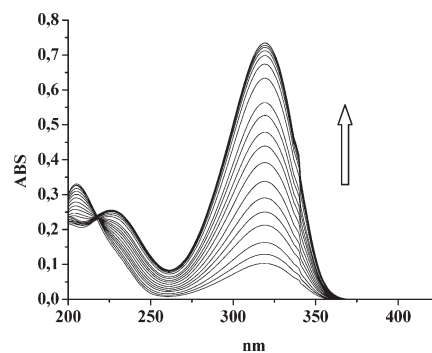

FIGURE 1. Absorption spectra of a 1×10^{-4} M solution of 2-NCH in cyclohexane, registered at different times. The increase of the absorption band at 319 nm is due to the enolization reaction of the keto form.
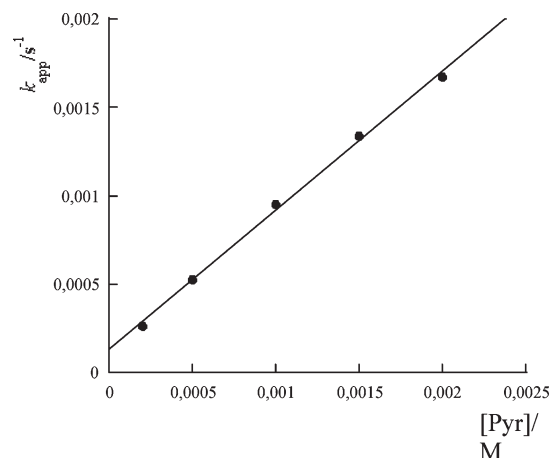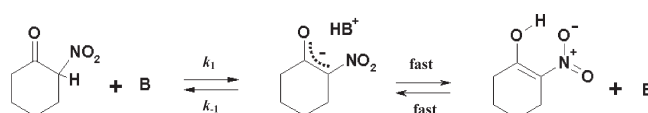

FIGURE 2. Plot of the pseudo-first-order rate constant, k_{app}, against [Pyr] in IL **3**.

SCHEME 1. **Structures of the Investigated ILs**

|			
1	$R^1 = C_4H_9$	$R^2 = H$	$X^- = PF_6^-$
2	$R^1 = C_2H_5$	$R^2 = H$	$X^- = TF_2N^-$
3	$R^1 = C_4H_9$	$R^2 = CH_3$	$X^- = TF_2N^-$
4	$R^1 = C_4H_9$	$R^2 = H$	$X^- = TF_2N^-$
5	$R^1 = C_6H_{13}$	$R^2 = H$	$X^- = TF_2N^-$
6	$R^1 = C_4H_9$		$X^- = TF_2N^-$

SCHEME 2

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TABLE 1. Kinetic Data for the Keto−Enol Interconversion of 2-NCH in the Six ILs of Scheme 1 in Some Molecular Solvents and Their Binary Mixtures

solvent	$k_{app}^{Pyr}/10^{-2}$ ($M^{-1}s^{-1}$)	$k_{app}^{0}/10^{-2}$ (s^{-1})	$k_1^{Pyr}/10^{-2}$ ($M^{-1}s^{-1}$)	$k_{-1}^{Pyr}/10^{-2}$ ($M^{-1}s^{-1}$)
1	162(±8)	0.040(±0.008)	13.5	149
2	199(±9)	0.16(±0.01)	24.1	175
3	78.4(±2.4)	0.013(±0.003)	8.40	70.0
4	74.5(±2.9)	0.034(±0.003)	10.1	64.4
5	215(±4)	0.028(±0.004)	29.1	186
6	54.7(±1.7)	0.039(±0.010)	7.70	47.0
C_6H_{12}	0.026(±0.001)[a]		0.0222[a]	0.00342[a]
CCl_4	0.064(±0.001)[a]		0.0551[a]	0.00923[a]
$CHCl_3$	1.30(±0.01)[a]		0.855[a]	0.445[a]
CH_2Cl_2	1.89(±0.01)[a]		0.828[a]	1.062[a]
CH_3CN	9.60(±0.16)[a]		1.03[a]	8.57[a]
$CH_3CN−CH_2Cl_2$ (20:80)	3.88(±0.16)[a]		1.08[a]	2.80[a]
$CH_3CN−CH_2Cl_2$ (50:50)	6.43(±0.10)[a]		1.16[a]	5.27[a]
$CH_3CN−CH_2Cl_2$ (80:20)	8.98(±0.11)[a]		1.08[a]	7.90[a]
$CH_3CN−CHCl_3$ (80:20)	8.82(±0.10)[a]		1.06[a]	7.76[a]

[a]From ref 5.
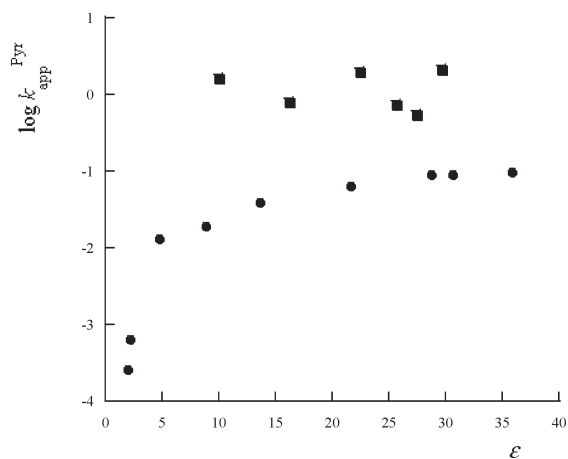
FIGURE 3. Plot of $\log k_{app}^{Pyr}$ vs. ε for the tautomerization reaction of 2-NCH in organic solvents (●) and in ILs (■). The values of ε are from refs 4 and 5.

FIGURE 4. Comparison between $\ln k_{app}^{Pyr}$ calculated from eq 5 [$\ln k_{app}^{Pyr}$(calc)] and the experimental values.

for the reversible pyridine-catalyzed reaction, k_{app}^{Pyr}, and the intercept represents the first-order rate constant, k_{app}^{0}, for the so-called spontaneous reaction (eq 2).

$$k_{app} = k_{app}^{0} + k_{app}^{Pyr}[Pyr] \qquad (2)$$

A typical example is reported in Figure 2.

Since the tautomerization reaction is a reversible process, k_{app}^{Pyr} is actually the sum of the two rate constants of enolization, k_1^{Pyr}, and ketonization, k_{-1}^{Pyr}.

k_1^{Pyr} and k_{-1}^{Pyr} have been calculated in the six ionic liquids from eqs 3 and 4 by using previously determined[4] $K_T = [EH]/[KH]$ values.
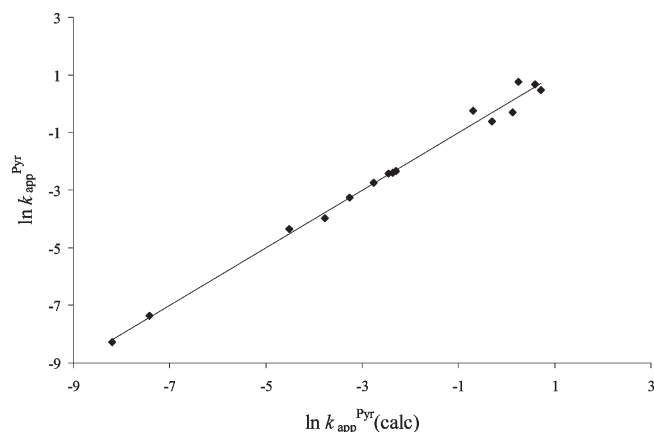
$$k_1^{Pyr} = k_{app}^{Pyr}[K_T/(K_T + 1)] \qquad (3)$$

$$k_{-1}^{Pyr} = k_{app}^{Pyr} - k_1^{Pyr} \qquad (4)$$

A K_T value of 0.164 in IL **6** has been obtained by following the reported procedure.[4]

The values of the different rate constants are listed in Table 1. The corresponding values previously obtained[5] in five aprotic solvents and their binary mixtures are also reported in Table 1 for the sake of comparison.

The data in Table 1 show that k_{app}^{Pyr}, k_1^{Pyr}, and k_{-1}^{Pyr} values are considerably higher in the six ionic liquids than

in the studied molecular solvents and their binary mixtures. A correlation analysis of the kinetic data was then performed to evaluate the solvent effects on the tautomerization process. In the case of molecular solvents a good correlation was found by simply plotting k_{app}^{Pyr} values against the solvent permittivity, ε.[5] An attempt to include the studied ILs in the same correlation fails as clearly appears in Figure 3.

However a good correlation ($R^2 = 0.991$) for all of the investigated solvents was obtained from the Kamlet−Taft type LSER of eq 5, which also takes into account the dipolarity/polarizability (π^*), the H-bond acidity (α), and the cohesive pressure (δ^2) of the solvent. The values of ε (27.5) and δ (11.4) for IL **6** have been obtained as previously described.[4] Figure 4 reports the corresponding validation curve ($R = 0.996$).

$$\ln k_{app}^{Pyr} = cost + s\pi^* + a\alpha + cF\varepsilon + d\delta^2 \qquad (5)$$

The same four parameters can account for the solvent effect on the ketonization rate constant, k_{-1}^{Pyr}, whereas only two parameters (α and π^*) are sufficient in the case of the enolization rate constant, k_1^{Pyr} (eq 6).

$$\ln k_1^{Pyr} = cost + s\pi^* + a\alpha \qquad (6)$$

Table 2 summarizes the results obtained by applying the Kamlet−Taft type LSERs of eqs 5 and 6 to the kinetic data.

TABLE 2. Correlation Coefficients, R^2, for LSERs 5 and 6 for the Rate Constants of Keto−Enol Interconversion of 2-NCH

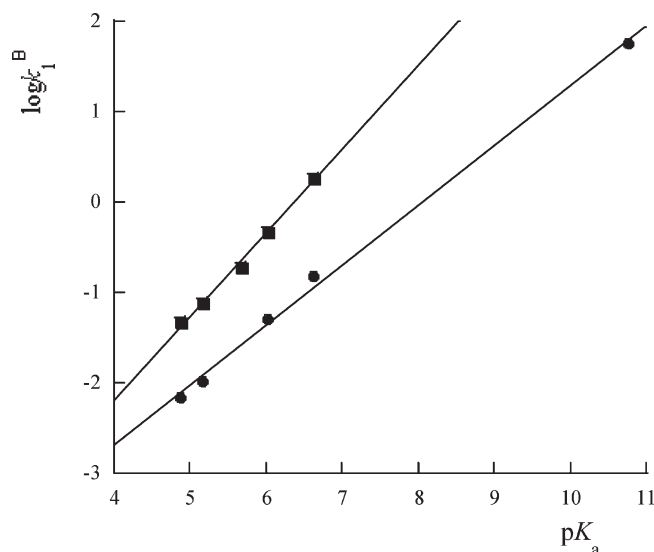| rate constant	R^2	LSER
k_{app}^{Pyr}	0.991	$\ln k_{app}^{Pyr} = -11.3 + 1.86\pi^* + 4.73\alpha + 8.18F(\varepsilon) + 0.021\delta^2$ SD = 0.316; $F = 264$
k_{-1}^{Pyr}	0.994	$\ln k_{-1}^{Pyr} = -14.78 + 2.06\pi^* + 4.60\alpha + 13.56F(\varepsilon) + 0.026\delta^2$ SD = 0.314; $F = 398$
k_1^{Pyr}	0.978	$\ln k_1^{Pyr} = -8.36 + 4.03\pi^* + 4.04\alpha$ SD = 0.330; $F = 269$
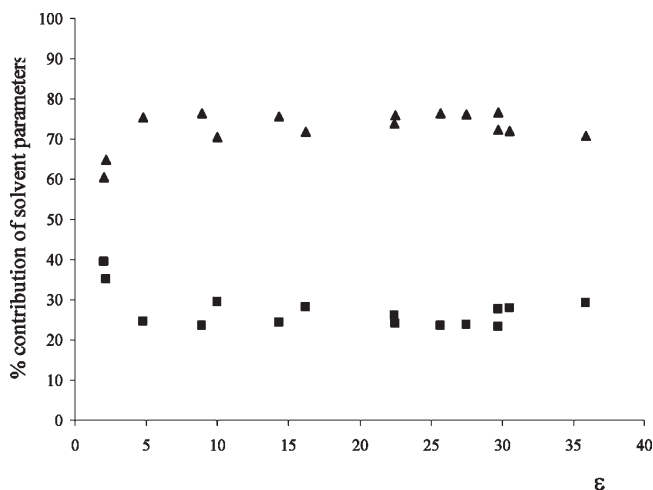
FIGURE 5. Percent contribution of electrostatic (▲) and cavitational energy interactions (■) on the ketonization rate constant, k_{-1}^{Pyr}, in solvents of different permittivity, ε.

The errors associated with each parameter were appraised in terms of the F-test and the deviation associated with the equation. Unnecessary terms in the correlation were eliminated.

The relative contributions of the solvent parameters to the ketonization rate constant, k_{-1}^{Pyr}, have been calculated, on a percentage basis, from the absolute values of the regression coefficients of Table 2. It turns out that the electrostatic interactions [π^*, α, and $F(\varepsilon)$] overwhelm cavitational energy interactions in each investigated solvent (see Figure 5).

As expected, the contribution of the electrostatic interactions significantly increases with ε up to a ε value of about 8. On the other hand, the contribution of the cavitational energy decreases in the same range of ε values. This is consistent with a more efficient solvation of a charge-separated transition state by more polar solvents. In the case of the enolization rate constant, k_1^{Pyr}, it appears that only electrostatic interactions have a role in the observed solvent effect (see the last row of Table 2).

On the basis of the above LSER treatment no special "ionic liquid effect" exists for the keto−enol interconversion of 2-NCH in agreement with the results obtained for other recently investigated reactions.[6] However, other solvent parameters, in addition to ε, should be taken into account when comparing ILs with molecular solvents.

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FIGURE 6. Brønsted plots for the base-catalyzed enolization reaction of 2-NCH in acetonitrile (●) and in IL **6** (■).

Brønsted Correlations. An IL consists of cations and anions and the strong interaction between oppositely charged species may result in a medium that, taken as a whole, behaves as a moderately polar solvent. In fact the values of ε calculated for the ILs of Scheme 1 from the keto−enol equilibrium constants[4] of 2-NCH (as well as those measured by microwave spectroscopy[8] for similar ILs) span an interval that is typical of molecular solvents of moderate polarity such as CH_3OH or CH_3CN. Nevertheless, positively or negatively charged species (reagents, intermediates, or transition states) might well interact with ILs, efficiently competing with a counterion of the IL. These interactions can strongly affect the reactivity in ILs by stabilizing charged reagents and/or transition states.

Linear free energy relationships between rate and equilibrium constants provide an important tool for the study of reaction mechanisms.[9] In particular, the Brønsted relation correlates the effectiveness of acids and bases as catalysts in proton transfer reactions with their acid or base strength.[9] An interesting aspect of the Brønsted relation is that the Brønsted coefficients (α and/or β) may provide information on the extent of proton transfer at the reaction's transition state. The kinetics of the keto−enol interconversion of 2-NCH was followed in three molecular solvents ($CHCl_3$, CH_2Cl_2, and CH_3CN) and ILs **1** and **6**, using different bases,

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(9) (a) Bell R. P. In *The proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973; Chapter 10. (b) Bronsted, J. N.; Pedersen, K. *Z. Phys. Chem.* **1924**, *108*, 185–285.

TABLE 3. Values of $k_1{}^B$ (M^{-1} s^{-1}) for the Base-Catalyzed Enolization Reaction of 2-NCH in Different Solvents

base, B	$k_1{}^B/10^{-2}$				
	$CHCl_3$	CH_2Cl_2	CH_3CN	IL **1**	IL **6**
4-methoxypyridine	17.4	17.6	15.0	314	186
4- methylpyridine	5.71	5.71	5.03	76.3	47.5
3- methoxypyridine	1.27	0.793	0.691		4.70
3- methylpyridine	3.33	3.18		28.4	18.9
triethylamine	2115[a]	3260[a]	5590[a]		

[a]From ref 5.

TABLE 4. Brønsted β Values for the Base-Catalyzed Enolization Reaction of 2-NCH in the Considered Solvents[a]

solvent	β	ε
$CHCl_3$	0.57 ± 0.04	4.8
CH_2Cl_2	0.62 ± 0.04	8.9
CH_3CN	0.66 ± 0.02	35.9
1	0.96 ± 0.08	10
6	0.92 ± 0.04	27.5

[a]In the last column the permittivity value, ε, of the solvent is reported.

B, as the catalysts. Linear Brønsted correlations have been obtained by plotting the second-order rate constant for enolization, log $k_1{}^B$, in the molecular solvents and ILs against the pK_a values (in water) of the conjugate acids of B. The plots obtained in CH_3CN and in IL **6** are reported, as typical examples, in Figure 6.

The values of $k_1{}^B$ for the enolization reaction of 2-NCH catalyzed by the considered bases in the different solvents are listed in Table 3 and the corresponding Brønsted β values are reported in Table 4.

Although pK_a values in water may not adequately describe the acid−base strength of the catalyst in an ionic liquid,[10] the Brønsted β values for the enolization reaction, close to unity ($\beta > 0.9$), suggest that the structure of the transition state for the enolization process is shifted toward the enolate intermediate in ILs.

Conclusions

The rates of tautomerization of 2-nitrocyclohexanone have been measured in six room temperature ionic liquids. The values of the second-order rate constants of enolization, $k_1{}^{Pyr}$, and of ketonization, $k_{-1}{}^{Pyr}$, are much higher in the studied ionic liquids than in conventional organic solvents. However, it appears that there is not a special "ionic liquid

(10) D'Anna, F.; Noto, R. *Tetrahedron* **2007**, *63*, 11681−11685.

effect" if enough solvent parameters are considered when comparing conventional organic solvents and ILs.

The increased reactivity in ILs is probably due to the stabilization of the enolate-like transition state of the reaction.

Experimental Section

Materials. 2-Nitrocyclohexanone, CH_3CN, and trifluoroacetic acid were commercial samples of AnalaR grade and were used without further purification. Triethylamine, pyridine, 3-methylpyridine, 4-methylpiridine, 3-methoxypyridine, and 4-methoxypyridine have been distilled in the presence of NaOH before each experiment. ILs of Scheme 1 were prepared from the corresponding halides, following reported procedures.[3d,11,12] The purity of imidazolium salts was checked by ESI-MS and UV spectrophotometry (purified [bmim]$^+$ salts containing [Cl]$^-$ or [Br]$^-$ < 0.1 ppm have no absorption band in the 250−300 nm region).[13] After drying (2 h at 80 °C under vacuo) the water amount in ILs was determined by the Karl Fisher technique by using an apparatus composed of a stand titrator and a coulometer. A water content within 120−150 ppm was found for ionic liquids **2−5**, whereas a water content of 348 ± 25 ppm was found for **1**.

Instruments. The kinetic experiments and spectrophotometric titrations were carried out with a UV/vis spectrophotometer provided with a thermostated cell holder.

Kinetic Measurements. The keto−enol interconversion of 2-NCH was followed spectrophotometrically by monitoring the decrease of the absorbance at $\lambda_{max}{}^{EH}$ of the enol form of 2-NCH at 25.0 ± 0.1 °C. A small aliquot of a stock solution 0.01 mol dm^{-3} of 2-NCH in CCl_4 was added to the cuvette containing Pyr or the substituted pyridines dissolved in the appropriate solvent immediately before each kinetic run. The initial concentration of 2-NCH was ca. 1×10^{-3} mol dm^{-3} in all experiments.

Supporting Information Available: Kinetic data for the base-catalyzed keto−enol interconversion of 2-NCH in CH_3CN, in CH_2Cl_2, in $CHCl_3$, in IL **1**, and in IL **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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