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Piperidine-appended imidazolium ionic liquids as task-specific catalysts: computational study, synthesis, and multinuclear NMR

Kenneth K. Laali[a]*, Arezu Jamalian[a] and Gabriela L. Borosky[b]*

Imidazolium ionic liquids (IMILs) with a piperidine moiety appended via variable length methylene spacers (with *n* = 1–4) were studied computationally to assess their potential to act as internal base for *N*-heterocyclic carbene (NHC) generation. Proton transfer energies computed by B3LYP/6-311+G(2d,p) were least endothermic for the basic-IL with *n* = 3, whose optimized structure showed the shortest C_2-H----N(piperidine) distance. Inclusion of counter anion (Cl or NTf_2) caused dramatic conformational changes to enable close contact between the acidic C_2-H and the anions. To examine the prospect for internal C_2-H----N coordination, multinuclear NMR data (^{1}H, ^{15}N, and ^{13}C) were computed by gauge independent atomic orbitals–density functional theory (GIAO-DFT) in the gas phase and in several solvents by the PCM method for comparison with the experimental NMR data for the basic ILs (with *n* = 2–4) synthesized in the laboratory. These studies indicate that interactions with solvent and counter ion are dominant forces that could disrupt internal C_2-H----N coordination/proton transfer, making carbene generation from these basic-ILs unlikely without an added external base. Therefore, the piperidine-appended IMILs appear suitable for application as dual solvent/base in organic/organometallic transformations that require the use of mild base, without the necessity to alkylate at C-2 to prevent *N*-heterocyclic carbene formation. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: basic ionic liquids; C_2-H----N coordination; GIAO-DFT; multinuclear NMR; piperidine tether; structure optimization

INTRODUCTION

Because of the inherent high acidity at the C-2 position,[1] the efficacy of imidazolium ionic liquids (IMIL) to act as "inert solvent" in base-catalyzed organic transformations is intimately tied to the prospect of intervention by *N*-heterocyclic carbenes (NHCs) via an acid–base equilibrium (Fig. 1).[2]

Despite the fact that this equilibrium strongly favors the IMILs, formation of covalent side-products in the Baylis–Hilman reaction arising from deprotonation of IMILs and observation of unexpected by-products in the base-catalyzed Claisen–Schmidt condensation have pointed to the involvement of NHCs.[2] Other studies also pointing to NHCs include formation of the C_2-carboxylate zwitterion in the reaction of 1-methylimidazole with dimethylcarbonate,[3] and zwitterion formation via the reaction of 1,3-dialkyl-imidazolium acetate with CO_2.[4] The X-ray structure of 1,3-dialkylimidazolium acetate shows strong H-bonding interactions between C_2-H and the counter ion.[4] The imidazolium/counter ion interactions have also been studied computationally.[5] These and other studies provide ample evidence that IMILs are not inert in base-catalyzed reactions particularly at higher temperatures.

In comparison to butyl methyl imidazolium hydroxide [BMIM][OH], which has been extensively employed as a "task-specific" IL in a variety of base-catalyzed reactions,[6] ILs in which the base is chemically appended to the cationic core have not been studied extensively. 1,4-diazabicyclo[2.2.2]octane (DABCO) -based room temperature ionic liquids were prepared and utilized in Aza-Michael addition of α,β-unsaturated amides and secondary amines (Fig. 2a).[7] A piperidine-appended imidazolium chloride with a $–CH_2$-CH_2- tether was synthesized and employed in the Michael addition of 1,3-dicarbonyl compounds to nitroalkanes (Fig. 2b).[8]

To block the prospect of NHC formation, in a recent study we employed a C_2-methylated IL (Fig. 2c) as dual solvent-base in the Sonogashira coupling reactions.[9]

In relation to these studies, and in continuation of our work on application of ILs as solvent and catalyst in electrophilic and onium ion chemistry,[10] DFT computations were performed in the present study on basic ILs **1–4** (Fig. 3) to examine their gas-phase and solution (polarized continuum model (PCM)) structures and to obtain proton transfer energies as a way to assess the possibility for these basic-ILs to form NHCs. To examine the potential for internal C_2-H---N coordination as a function of the length of the tether, ^{1}H, ^{15}N, and ^{13}C NMR chemical shifts were computed by GIAO-DFT in the gas phase and in several solvents (by PCM method) and were compared with the experimental NMR data for ILs **2–4** prepared in the laboratory.

* *Correspondence to: Kenneth K. Laali, Department of Chemistry, University of North Florida, 1, UNF Drive, Jacksonville, FL, 32224, USA.*
E-mail: Kenneth.Laali@UNF.edu

Gabriela L. Borosky, INFIQC, CONICET and Departamento de Matemática y Física, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, Córdoba 5000, Argentina
E-mail: gborosky@fcq.unc.edu.ar

a *K. K. Laali, A. Jamalian*
Department of Chemistry, University of North Florida, 1, UNF Drive, Jacksonville, FL, 32224, USA

b *G. L. Borosky*
INFIQC, CONICET and Departamento de Matemática y Física, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, Córdoba 5000, Argentina

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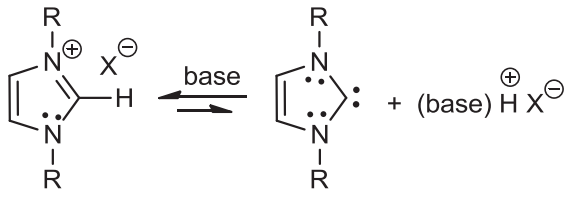
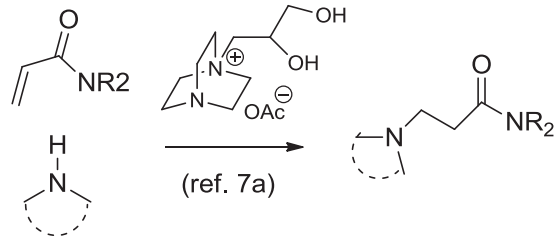
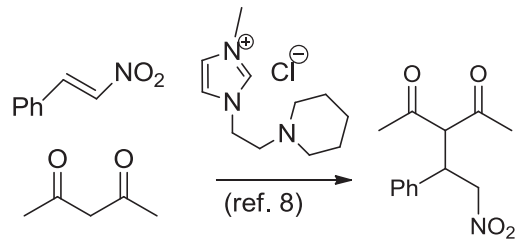


Figure 1. Imidazolium–NHC equilibrium



a.



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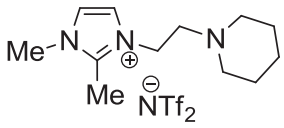
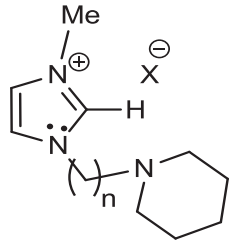


c.

Figure 2. (a) Application of a DABCO-based IL. (b) Application of a piperidine-appended IL. (c) The C_2-methylated basic IL



1; n = 1; X = Cl
2: n = 2; X = Cl
2a: n = 2; X = NTf2
3: n = 3; X = Br,Cl
4; n = 4; X = Br,Cl

Figure 3. Piperidine-appended IMILs

COMPUTATIONAL METHODS

Quantum mechanical calculations were performed with the Gaussian 09 suite of programs.[11] Molecular structures were fully optimized at the B3LYP/6-311+G(2d,p) density functional theory (DFT) level.[12–14] Stationary points were characterized as minima by harmonic vibrational frequency calculations (no imaginary frequencies). NMR chemical shifts were calculated by the GIAO (gauge independent atomic orbitals) method.[15,16] The ^{1}H and ^{13}C NMR chemical shifts were referenced to tetramethylsilane, and ^{15}N chemical shifts were referenced to nitromethane (GIAO magnetic shielding tensors were 31.9 ppm for ^{1}H, 182.5 ppm for ^{13}C, and −153.2 ppm for ^{15}N, values related to the GIAO isotropic magnetic susceptibility). Solvation effects were considered by performing polarized continuum model (polarizable continuum model using the integral equation formalism variant)[17–20] energy minimizations in various solvents: chloroform (dielectric constant $\varepsilon = 4.71$), acetone ($\varepsilon = 20.49$), methanol ($\varepsilon = 32.61$), acetonitrile ($\varepsilon = 35.69$), dimethylsulfoxide ($\varepsilon = 46.83$), and water ($\varepsilon = 78.36$).

EXPERIMENTAL

General

The reagents and solvents employed in the synthetic effort were highest purity commercial samples and were used without further purification. NMR spectra were recorded on Varian 500 MHz instrument in different NMR solvents ($CDCl_3$, CD_3OD, acetone-d_6, MeCN-d_3, and DMSO-d_6) (Tables 3–6). The ^{15}N NMR spectra were externally referenced relative to neat $MeNO_2$ (0 ppm). The data are embedded in Tables 3–6.

General procedure for synthesis of 1-methyl-3-(2-(piperidin-1-yl)ethyl)-1H-imidazol-3-ium-chloride (IL-2)

The basic IL-2 ($n = 2$) was prepared by a slight modification of the literature method by reacting 1-(2-chloroethyl)piperidine with *N*-methyl imidazole.[8] In the work-up stage, the white solid was dissolved in water and EtOH (1:1) and basified to pH = 9. After removal of water and EtOH under vacuum, the ionic liquid was extracted with dichloromethane (DCM) and dried. For further purification, the product was washed with toluene and dried at 70 °C under vacuum overnight. The IL-2 was obtained in 93% yield as yellow oil. The basic IL-2a was synthesized by standard metathesis with $LiNTf_2$.

Synthesis of IL-3 (n = 3) and IL-4 (n = 4).

Initial studies

Our initial goal was to follow the same approach as described previously (as in Fig. 4). The 1-(3-chloropropyl) piperidine **5** was commercially available (Aldrich) as monohydrochloride salt, but its price was prohibitive (~$140 for 10 g), and a suitable commercial source for 1-(4-chlorobutyl) piperidine **6** could not be found. Therefore, synthesis of these compounds was attempted.

According to a procedure reported by Buchanan *et al.*,[21] piperidine was reacted with 1-bromo-4-chlorobutane (1:1) in tetrahydrofuran at room temperature, but the isolated product was the piperidinium hydrobromide rather than the desired **7** (Fig. 5) . Dropwise addition of the piperidine or increasing the amount of piperidine to 1.5 equivalents did not change the outcome.

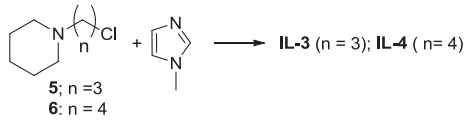


Figure 4. Initial plan of synthesis

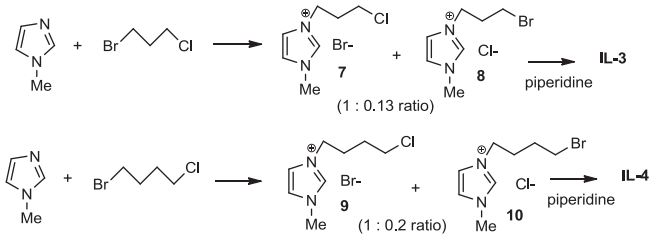


Figure 5. Synthesis of Basic ILs

Applying different bases and solvents such as K_2CO_3 in acetone or in tetrahydrofuran,[22] or NaOH under phase transfer catalysis conditions[23] and under reflux, similarly did not produce the desired piperidine derivative.

Subsequent studies

(i) *N*-methyl imidazole (1.0 equiv.) was added dropwise to 1.3 equiv. of 1-bromo-3-chloropropane in acetonitrile, and the reaction was stirred at room temperature and monitored by ^{1}H-NMR. After 60 h a 45% conversion was observed by NMR. When the reaction mixture was refluxed, in order to increase conversion, a white solid was formed whose ^{1}H-NMR was consistent with a bis-imidazole derivative. (ii) In the next run, to a solution of 12.3 g (1.3 equiv.) of 1-bromo-3-chloropropane in 40 mL of MeCN was added dropwise *N*-methyl imidazole (5.0 g, 0.06 mol, 1.0 equiv.) dissolved in MeCN (40 mL). The reaction was continued at room temperature for 5 days and monitored with ^{1}H-NMR, at which point the solvent was evaporated under vacuum and the residue was washed with toluene and dried in vacuo. A mixture of 1-methyl-3-(3-chloropropyl) imidazolium **7** and 1-methyl-3-(bromopropyl) imidazolium salts **8** were obtained (67% combined yield; 1.0 to 0.13 ratio by NMR). (iii) A solution of *N*-methyl imidazole (5.0 g, 0.06 mol, 1.0 equiv.) in MeCN was added dropwise to 1-bromo-4-chlorobutane (13.4 g, 1.3 equiv.) dissolved in 40 mL of acetonitrile. The reaction mixture was stirred at room temperature for 5 days and the progress of the reaction was monitored by ^{1}H-NMR. The solvent was then removed under vacuum, and the residue was washed with toluene and dried in vacuo to give a mixture of 1-methyl-3-(4-chlorobutyl) imidazolium **9** and 1-methyl-3-(4-bromobutyl) imidazolium salts **10** (85% combined yield; 1.0 to 0.2 ratio by NMR).

Synthesis of IL-3(a) and IL-4 (b).

(*a*) To the imidazolium salt 7 + 8 (2.0 g) in EtOH was added 0.72 g of piperidine in EtOH (20.0 mL), and the reaction mixture was refluxed for 48 h. The solvent was removed under vacuum, and the residue was extracted with DCM, filtered and subsequently dried in vacuo. (*b*) Piperidine (0.68 g, 0.008 mol, 1.0 equiv.) was added to a mixture of 1-methyl-3-(3-chloropropyl) imidazolium **9** and 1-methyl-3-(bromopropyl) imidazolium salts **10** (2.0 g) in 20 mL of EtOH, and the reaction mixture was stirred under reflux for 48 h. The solvent was evaporated, and the residue was extracted with DCM, filtered (to remove any insoluble impurities), and dried in vacuo overnight. *For* (*a*) *and* (*b*) *both* the white solid residue was dissolved in H_2O and EtOH (1:1) and neutralized with NaOH. The solvent mixture was removed, and the residue was extracted with DCM. The solvent was then evaporated, and the basic was dried under vacuum at 70 °C. Further purification was achieved by washing with toluene and vacuum drying (yield: 85% for IL-3 and 93% for IL-4).

RESULTS AND DISCUSSION

Synthesis of piperidine-appended ILs

Synthesis of IL-2 ($n = 2$) had already been reported,[8] and in the present study it was synthesized with slight modifications. In an effort to use the same general approach for the synthesis of IL-3 and IL-4, several methods were tested for the preparation of the needed 1-(3-chloropropyl) piperidine **5** and 1-(4-chlorobutyl) piperidine **6**, but these were unsuccessful (experimental). Taking a different approach, imidazolium salts 7 + 8 and 9 + 10 were prepared and were subsequently allowed to react with piperidine to furnish ILs-3 and IL-4 respectively (Fig. 5).

Computational studies

The basic-ILs **1–4** ($n = 1$ to 4) were studied computationally. The difference in energy between the imidazolium and carbene forms was initially evaluated in the gas phase by proton transfer from the acidic C_2-H of the imidazolium moiety to the basic nitrogen atom of piperidine (Reaction 1, Table 1). Conformational flexibility of the studied basic-ILs increases with the length of the tether. Considering this, the most stable conformation exhibiting the shortest C_2-H---N(piperidine) distance (strongest interaction) was selected for each basic-IL.

Endothermicity of Reaction 1 decreased with the length of the spacer. In case of $n = 3$ it was not possible to characterize the carbene, as this species collapsed to the imidazolium ion. This fact indicated that in the gas-phase potential energy surface of this system, the stationary point corresponding to the carbene species would be separated from the more stable imidazolium minimum by a very small energy barrier.

Calculations were then carried out in various solvents (Table 1). The counter ions considered were chloride and bis (trifluoromethylsulfonyl)amide (NTf_2^-) anions. Reaction 1 was also endothermic, and differences in the relative energy of both spe-

Table 1. ΔE_r values (kcal/mol) for carbene formation at the B3LYP/6-311+G(2d,p) level

Solvent	$n = 1$	$n = 2$	$n = 3$	$n = 4$
Gas phase	25.44	15.82	—	11.06
$CHCl_3$[a]	—	24.03	—	—
	—	21.75[b]	—	—
Acetone[a]	28.45	21.10	14.20	20.15
CH_3OH[a]	—	20.68	—	—
CH_3CN[a]	27.76	20.62	13.64	19.62
DMSO[a]	27.59	20.46	13.49	19.46
H_2O[a]	27.25	20.26	13.29	19.25

[a] Cl^- as the counter ion.
[b] NTf_2^- as the counter ion.

cies were more pronounced than in the gas phase. Although solvation increased the endothermicity, comparisons between reaction energies in the diverse solvents exhibited almost no variations with the different solvent polarities. The least favored proton transfer was for the structure with one methylene as spacer ($n = 1$), while reaction energies only differed by about 1 kcal/mol between $n = 2$ and $n = 4$. Interestingly, the least endothermic reaction process took place in the case of $n = 3$.

Inspection of bond lengths in the optimized geometries indicated that the basic-IL with $n = 3$ has the shortest C_2-H----N(piperidine) distance (1.99 Å in the gas phase/3.56 Å in solvent; Table 2; the corresponding structures are displayed in Fig. 6). This geometrical feature is in concert with the computed reaction energy for proton transfer from the imidazolium cation to carbene, which was the most favored with $n = 3$. Hence, this derivative appeared most susceptible to carbene generation. Interestingly, incorporation of Cl^- as counter ion had a dramatic effect on the optimized geometries by modifying the relative orientation of both rings in order to enable close contact between the acidic C_2-H and Cl^- (Fig. 6b). These H----Cl^- computed distances were on average 2.40–2.47 Å (Table 2) and did not vary noticeably with increasing the length of the spacer. Even though the main interaction of C_2-H in solvents was with the counter ion, the tether length in IL-3 allowed attainment of the shortest C_2-H----N(piperidine) distance (Table 2), thus assisting the proton transfer.

There was also little change in the computed geometries as a function of solvent polarity. Therefore, interaction of the acidic C_2-H with the counter ion appears to be a dominant factor in determining the structure of the basic-ILs in these piperidine-appended imidazoliun salts. The larger NTf_2^- anion did not induced significant changes in the structures of both the imidazolium and the carbene forms. The optimized structure of IL-2 with NTf_2 counter ion shows preferential C_2-H----NTf_2 interactions despite the rather inert nature of this counter ion (Fig. 7).

The GIAO-NMR shifts were computed from the optimized structures with inclusion of counter ion (Cl^- and NTf_2^-). Close correspondence between the computed and experimental ^{15}N and ^{13}C NMR chemical shifts were observed. Chemical shift variations for ^{15}N and ^{13}C were rather insensitive to solvent effects (Tables 3 and 4).

The GIAO-NMR signal of the piperidine nitrogen for IL-3 appeared at higher fields than in the other analogs (Table 3); however, this effect was not observed in the experimental chemical shifts.

Minor changes in the chemical shift of the acidic C_2-H proton were observed in different solvents. This signal was most deshielded in acetone-d_6 for all three basic-ILs ($n = 2$–4), suggesting attractive hydrogen bond interactions. Observation of a relatively less deshielded C_2-H in CD_3OD as solvent may be because of its preferential interaction with the piperidine nitrogen. The computed ^1H NMR values for C_2-H were most deshielded in acetone and in chloroform and showed no variations in the other solvents (Table 5). In contrast to the generally good correspondence observed between ^{15}N and ^{13}C GIAO-DFT shifts and experimental chemical shifts, the computed ^1H NMR values were generally more deshielded compared with experimental values. Computed shifts were not scaled, as our main purpose was to compare relative chemical shifts for the different basic ILs rather than to reproduce the experimental values. However, no clear correlation was observed between ^1H NMR shifts and C_2-H----N (piperidine) distances or proton transfer reaction energies.

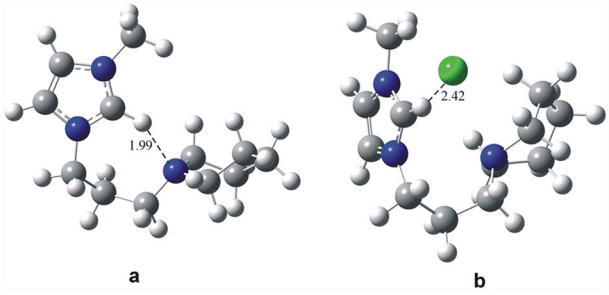


Figure 6. Imidazolium form for the compound with $n = 3$, distances in Angstroms. (a) Structure in the gas phase. (b) Solvated structure in presence of Cl^-

Table 2. Some relevant geometrical parameters at the B3LYP/6-311+G(2d,p) level

Solvent/ anion	C_2-H-----N / C_2-H-----Cl^- distance (Å)			
	$n = 1$	$n = 2$	$n = 3$	$n = 4$
Gas phase	2.62/-	2.47/ -	1.99/ -	2.18/ -
$CHCl_3/Cl^-$	—	3.69 / 2.31	—	—
$CHCl_3/NTf_2^-$	—	3.65 / 2.30[a]	—	—
Acetone/Cl^-	2.96/2.46	3.65/2.42	3.56/2.40	4.81/2.42
CH_3OH/Cl^-	—	3.63 / 2.44	—	—
CH_3CN/Cl^-	2.96/2.46	3.63/2.44	3.56/2.42	4.77/2.44
DMSO/Cl^-	2.96/2.46	3.61/2.45	3.56/2.43	4.76/2.45
H_2O/Cl^-	2.96/2.47	3.59/2.43	3.57/2.44	4.74/2.46

[a]H----N^- (NTf_2^-) distance (Å).

SUMMARY

The optimized structure of basic IL-3 showed the shortest C_2-H----N(piperidine) distance and computed energies for proton

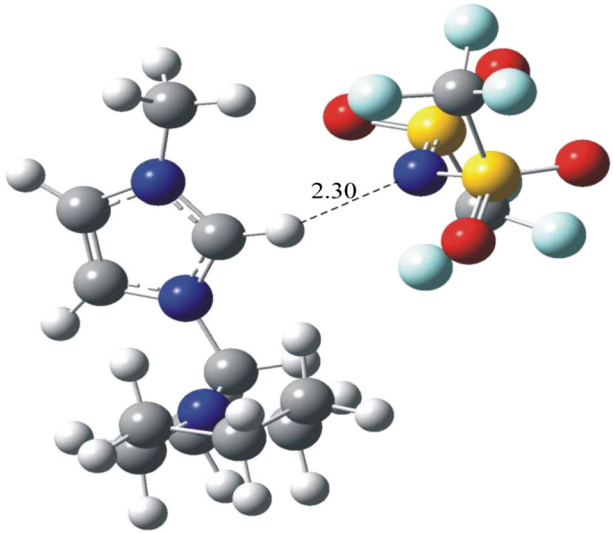


Figure 7. Imidazolium form for the compound with $n = 2$. Solvated structure in presence of NTf_2^-, distance in angstroms

Table 3. Computed (GIAO-DFT)[a] and Experimental[b] ^{15}N NMR data for the ILs

Solvent	$n=1$	$n=2$	$n=2$[c]	$n=3$	$n=4$
Gas phase	−185.3 (N_1)[d]	−196.6	—	−194.7	−189.3
	−211.0 (N_3)[d]	−209.8	—	−209.7	−210.8
	−355.6 (piperidine)[d]	−342.8	—	−355.8	−338.8
$CHCl_3$[e]	—	−205.4 (−201.9)	−202.7	—	—
	—	−210.6 (−211.5)	−211.5	—	—
	—	−346.6 (−337.8)	−346.2	—	—
Acetone[e]	−194.9	−203.6 (−201.9)	—	−199.2 (−198.3)	−196.6 (−198.7)
	−204.8	−210.5 (−210.9)		−211.6 (−209.9)	−209.5 (−211.1)
	−346.4	−346.3 (−336.8)		−364.4 (−333.4)	−336.2 (−332.8)
CH_3OH[e]	—	−203.3 (−198.4)	—	—	—
	—	−210.6 (−208.3)	—	—	—
	—	−346.3 (−335.2)	—	—	—
CH_3CN[e]	−194.7	−203.3 (−202.1)	—	−198.9	−196.6
	−204.9	−210.6 (−211.2)	—	−211.6	−209.3
	−346.2	−346.3	—	−364.4	−336.3
DMSO[e]	−194.7	−203.2 (−202.0)	—	−198.9 (−198.3)	−196.6 (−198.7)
	−204.9	−210.6 (−210.9)	—	−211.6 (−209.9)	−209.3 (−209.5)
	−346.2	−346.2	—	−364.4 (−333.2)	−336.6
H_2O[e]	−194.7	−203.0	—	−198.8	−196.5
	−204.9	−211.0	—	−211.6	−209.3
	−346.2	−346.2	—	−364.4	−336.3

[a] ^{15}N-GIAO-NMR at the B3LYP/6-311+G(2d,p)-PCM level.
[b] Experimental chemical shifts in the corresponding deuterated solvents in parenthesis.
[c] NTf_2^- as the counter ion.
[d] Same assignment order for the rest of the entries.
[e] Cl^- as the counter ion.

Table 4. Computed (GIAO-DFT)[a] and Experimental[b] ^{13}C NMR data for the Imidazolium-C_2

Solvent	$n=1$	$n=2$	$n=2$[c]	$n=3$	$n=4$
Gas phase	137.4	140.4	—	148.5	143.1
$CHCl_3$[d]	—	146.1 (137.4)	144.4 (136.4)	—	—
Acetone[d]	143.8	144.0 (138.6)	—	144.2	143.0
CH_3OH[d]	—	143.7 (137.0)	—	—	—
CH_3CN[d]	143.5	143.7 (138.1)	—	143.8	142.6
DMSO[d]	143.4	143.6 (137.8)	—	143.7	142.5
H_2O[d]	143.3	143.6	—	143.6	142.4

[a] ^{13}C GIAO-NMR at the B3LYP/6-311+G(2d,p)-PCM level.
[b] Experimental chemical shifts in the corresponding deuterated solvents in parenthesis.
[c] NTf_2^- as the counter ion.
[d] Cl^- as the counter ion.

transfer to piperidine to form NHCs was comparatively less endothermic, suggesting that this IL is most prone to NHC formation. Inclusion of the counter ion caused dramatic conformational changes because of strong interactions with the chloride anion. This ion interaction with C_2-H was also dominant with the more "inert" NTf_2 anion. Nevertheless, the tether length in IL-3 allowed attainment of the shortest C_2-H----N(piperidine) distance (Table 3), thus assisting the proton transfer. To examine the prospect for internal C_2-H----N coordination, multinuclear NMR data (^1H, ^{15}N, and ^{13}C) were computed by GIAO-DFT in the gas phase and in several solvents by the PCM method for comparison with the experimental NMR data for the basic ILs (with $n=2$–4) synthesized in the laboratory. Whereas the ^{15}N and ^{13}C chemical shifts were rather insensitive to changes in solvent, a minor solvent dependency of the C_2-H was observed in ^1H NMR, whereby this signal was most deshielded in acetone-d_6. The present studies underscore the importance of solvent and counter ion as dominant forces that could disrupt internal C_2-H----N coordination/proton transfer, and this greatly diminishes the prospect of intervention by NHCs without the addition of external base. Because the prospect for NHC-derived side-products appears unlikely, these base-appended ILs have the potential for wider application in base-catalyzed organic/organometallic transformations.

Table 5. Computed (GIAO-DFT)[a] and Experimental[b] ^{1}H NMR data for the Imidazolium C_2-H

Solvent	$n=1$	$n=2$	$n=2$[c]	$n=3$	$n=4$
Gas phase	(8.4)	(9.6)	—	(12.2)	(11.3)
$CHCl_3$[d]	—	9.66 (12.4)	8.73 (9.5)	9.47	9.71
Acetone[d]	(11.2)	10.34 (11.1)	—	10.03 (11.3)	10.02 (11.2)
CH_3OH[d]	—	9.09 (10.9)	—	—	—
CH_3CN[d]	(11.1)	9.48 (10.9)	—	9.41 (11.1)	9.69 (11.0)
DMSO[d]	(11.1)	9.36 (10.9)	—	9.41 (11.0)	8.81 (11.0)
H_2O[d]	(11.0)	(11.0)	—	(10.9)	(10.9)

[a]GIAO-NMR chemical shifts at the B3LYP/6-311+G(2d,p)-PCM level in parenthesis.
[b]Experimental chemical shifts in the corresponding deuterated solvents.
[c]NTf_2^- as the counter ion.
[d]Cl^- as the counter ion.

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