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Organocatalytic Imidazolium Ionic Liquids H/D Exchange Catalysts

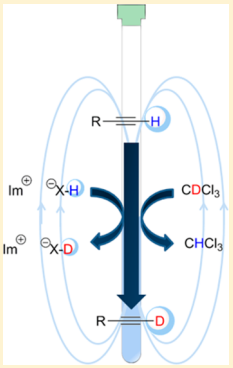
Marcileia Zanatta,[†] Francisco P. dos Santos,[*,†] Cristina Biehl,[†] Graciane Marin,[†] Gunter Ebeling,[†] Paulo A. Netz,[†] and Jairton Dupont[†,‡]

[†]Institute of Chemistry − UFRGS Av. Bento Gonçalves, 9500 Porto Alegre, RS, Agronomia 91501-970, Brazil

[‡]School of Chemistry, University of Nottingham University Park, Nottingham NG72RD, United Kingdom

Supporting Information

ABSTRACT: Simple 1,2,3-trialkylimidazolium cation associated with basic anions, such as hydrogen carbonate, prolinate, and imidazolate, is an active catalyst for the H/D exchange reaction of various substrates using $CDCl_3$ as D source, without the addition of any extra bases or metal. High deuterium incorporation (up to 49%) in acidic C−H bonds of ketone and alkyne substrates (pK_a from 18.7 to 28.8) was found at room temperature. The reaction proceeds through the fast and reversible deuteration of the 2-methyl H of the imidazolium cation followed by D transfer to the substrate. The IL acts as a neutral base catalyst in which the contact ion pair is maintained in the course of the reaction. The basic active site is due to the presence of a remote basic site in the anion namely, OH of bicarbonate, NH of prolinate, and activated water in the imidazolate anion. Detailed kinetic experiments demonstrate that the reaction is first order on the substrate and pseudozero order relative to the ionic liquid, due to the fast reversible reaction involving the deuteration of the ionic liquid by the solvent.



INTRODUCTION

Deuterium-labeled compounds have a broad range of applications in pharmaceutical, environmental, material, and chemical science, although they have not been found in nature.[1−3] Pharmaceutical companies and researchers in medicinal chemistry came up with the idea that exchanging the C−H bond with a C−D bond can create drugs with altered physiological profiles. Significant pharmacological effects on the metabolic profile, toxicity, and efficacy of pharmaceutical compounds have been discovered due to these deuterium substitutions.[4,5] Deuterated compounds are additionally required as internal standards for GC and LC-MS analysis of pesticides and environmental pollutant studies.[4,6] Moreover, they have a particular use for the development of efficient optical devices, such as optical polymer fibers and materials for organic light-emitting diodes.[7] In combination with NMR spectroscopy, they are also useful in elucidating the structure of large molecules (e.g., proteins and oligonucleotides), and for mechanistic studies of chemical and biological transformations.[8] As a consequence, the development of efficient and selective labeling methodologies through catalytic H/D exchange reactions at selected carbon centers is of keen interest.[7]

Deuterium labeling of organic compounds can be achieved using syntheses starting from suitable isotope marker precursors or via isotope exchange reactions. The second is more valuable since deuterium can be introduced postsynthetically.[8] Numerous methods for H/D exchange based on homogeneous or heterogeneous catalysis have already been described.[7] The most common involve the metal catalysts with Ir,[9,10] Pd,[11] Pt,[12] Rh,[13] Re,[14] and Cr[15] with or without carbon, including the oxidized form of metals like PtO_2.[1,4,16] In addition, D_2 gas can be used to deuterate organic molecule analogues to hydrogenation of olefins, acetylenes, and cyanides. For these types of reactions, D_2O has been studied extensively as a precursor for D_2 gas, because it is the least expensive and most readily available source of deuterium. D_2O is the most common solvent used for this type of reaction, even for metal catalysis.[6] Deuterium incorporation is harder to achieve in aprotic solvent $CDCl_3$ than in protic polar solvents, such as MeOD and D_2O. This difficulty is partly due to the limited strength of bases in this medium. The use of $CDCl_3$ as a deuterium source is favorable for deuteration of sensitive substrates and organic compounds, which are insoluble in D_2O. Furthermore, most of the H/D exchange reactions for acidic compounds reported in the literature involve drastic protic conditions that are not compatible with sensitive functional groups.[8]

There are just a few works reporting the H/D exchange in imidazolium salts where the C2 position is substituted by methyl group, normally using relatively strong bases, such as NaOD, KOH or triethylamine (Et_3N).[17,18] We have recently demonstrated that solutions of imidazolium ILs associate with basic anions such as hydrogen carbonate, prolinate, and imidazolate not only maintain their intimate ion pair structure but also behave as neutral species in apolar solvents. In particular, with anions containing remote basic sites, the ILs act as neutral bases. Indeed, the presence of intimate ion pairs in the case of BMMI·HCO_3 and BMMI·Pro (Figure 1) ILs in $CDCl_3$ and CD_3CN induces the augmentation of the remote basic sites, that is, OH and NH, respectively.[19]

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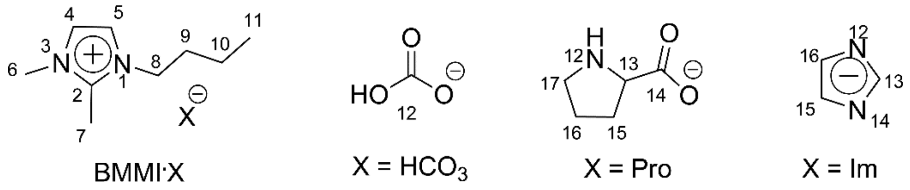
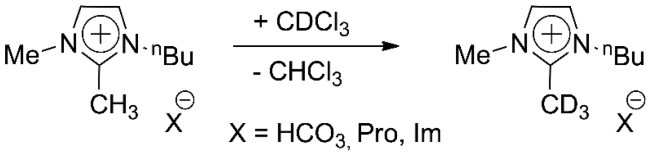


Figure 1. Imidazolium salts prepared and used in this study.

In the case of the imidazolate anion (Figure 1) the water trapped inside the IL network is responsible for the basic nature of the IL.[20] Indeed, these species are active in the catalytic transfer of D from $CDCl_3$ to the C2-Me position of the imidazolium cation (Scheme 1). Moreover, we have also demonstrated the potential use of these ILs as a catalyst for D-transfer from $CDCl_3$ to substrates containing acidic sites.[19]

Scheme 1. H/D Exchange Ionic Liquids (Catalysts)



Herein we report the H/D exchange reaction of alkynes and ketones monitored by NMR using BMMI·X (X = prolinate, imidazolate, and hydrogen carbonate, Figure 1). The IL catalyzed H/D exchange reactions are metal and alkaline-free, it allows the use of $CDCl_3$ as transferring agent instead of D_2O and it can be used for both polar and nonpolar substrates. Mechanistic insights were obtained via detailed kinetic studies.

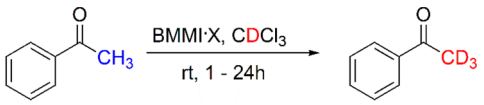
RESULTS AND DISCUSSION

The influence of the reaction conditions on the formation of deuterated acetophenone was investigated using different salts of 1-^{n}butyl-2,3-dimethylimidazolium, especially BMMI·Im. Several concentrations of substrates and catalyst quantities were tested (Table 1).

The influence of concentration was investigated first (entries 1−4 in Table 1). As can be seen (entry 3), the yield increased to 32% with 1.25 mol·L^{-1} of solvent. Further increase in the concentration had no apparent effect on the reaction (entry 4), which may indicate kinetic saturation. The catalyst quantity was also studied under this last condition (entries 4 and 5). Doubling the amount of catalyst increased the degree of deuteration to 41% after 24 h for BMMI·Im. This condition was applied to three different ILs used as the catalyst: BMMI·HCO_3 (pK_a = 3.6), BMMI·Pro (pK_a = 1.95 and 10.64), and BMMI·Im (pK_a = 18.6) (entries 5−7). In these cases, the anions have a crucial influence on the yield of the reaction. Unexpectedly, the most active catalyst was BMMI·Pro, following the order BMMI·HCO_3 < BMMI·Im < BMMI·Pro. It is clear that there is no direct relationship between the basicity of the anion and the degree of deuteration, as has already been reported.[8,19] The last test showed that no reaction occurs in the absence of the catalyst, even after 72 h (entry 8).

Deuterium labeling of ketones 1−19 (Table 2) was explored using the optimized reaction conditions (20 mol% IL, r.t., 24 h). It is interesting to observe that all deuterated products were

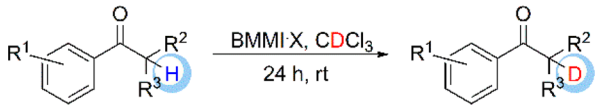
Table 1. Effects of Reaction Conditions on the Degree [%][b] of Deuteration of Acetophenone in $CDCl_3$ after 1 and 24 h[a]



entry	catalyst (mol%)	X	subst. conc. (mol L^{-1})	% D[b] (1h)	% D[b] (24h)
1	10	Im	0.2	15	21
2	10	Im	0.9	26	27
3	10	Im	1.25	30	32
4	10	Im	2	30	31
5	20	Im	2	36	41
6	20	Pro	2	47	53
7	20	HCO_3	2	0	≤5
8	–	–	2	0	0[c]

[a]Reaction conditions: r.t., BMMI·X, without stirring, 1−24 h. [b]Determined by ^{1}H NMR spectroscopy (see Figures S1−S5). [c]After 72 h.

Table 2. Deuteration of Ketones 1−19 Using 20 mol% BMMI·X as Catalyst in $CDCl_3$[a]



entry	X	R^1	R^2	R^3	% D (1h)	% D[b] (24h)
1	Pro	H	H	H	47	53
2a	HCO_3	4-CH_3	H	H	0	≤5
2b	Pro	4-CH_3	H	H	22	60
2c	Im	4-CH_3	H	H	21	22
3	Pro	4-OCH_3	H	H	7	58
4a	HCO_3	4-I	H	H	0	15
4b	Pro	4-I	H	H	19	57
4c	Im	4-I	H	H	29	38
5	Pro	4-Br	H	H	36	61
6	Pro	4-Cl	H	H	27	56
7	Pro	4-NO_2	H	H	21	39[c]
8	Pro	4-CF_3	H	H	37	59
9	Pro	2-CH_3	H	H	31	65
10	Pro	2-OCH_3	H	H	41	54
11	Pro	2-Br	H	H	30	57
12	Pro	2-CF_3	H	H	56	56
13	Pro	3-CH_3	H	H	35	53
14	Pro	3-OCH_3	H	H	47	57
15	Pro	3-Br	H	H	35	56
16	Pro	3-CF_3	H	H	53	53
17	Pro	H	H	CH_3	46	55
18	Pro	H	CH_3	CH_3	0	0
19	Pro	3-Ph-4[d]	H	H	58	59

[a]Reaction conditions: r.t., 20 mol% BMMI·X, without stirring in a concentration of 2 mol·L^{-1} (0.5 mL of solvent). [b]Determined by ^{1}H NMR spectroscopy (see Figures S6−S27). [c]Partial degradation of IL. [d]2-Acetonaphthone.

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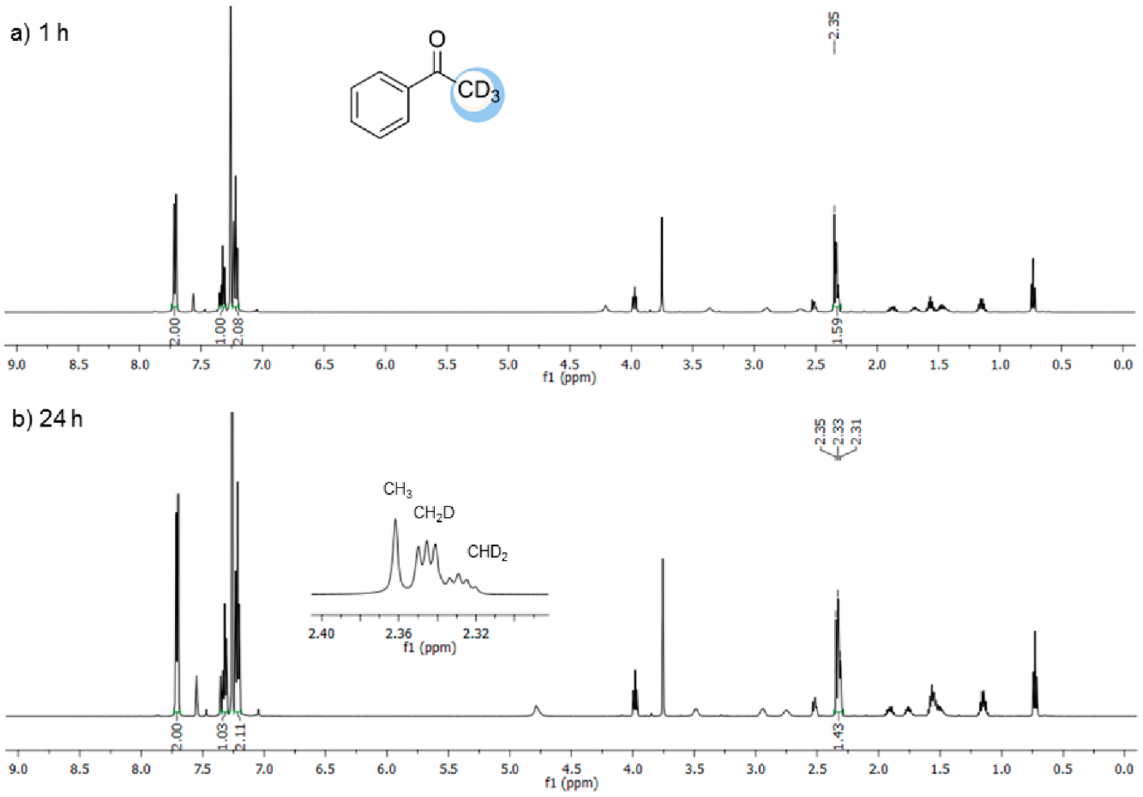
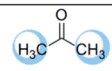
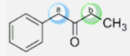
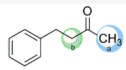
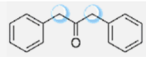


Figure 2. ^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) spectrum of deuterated acetophenone with BMMI·Pro, 1 h (a) and 24 h (b), (Table 2, entry 1b), (for more details see Figure S2).

Table 3. Deuteration of Ketones (with Two Possible Positions) Using BMMI·X as Catalyst[b]

Entry	X	Substrate	% D[a] (1h)	% D[a] (24h)
1a	HCO_3		0	0
1b	Pro		24	50
1c	Im		28	34
2a	HCO_3		8[c]	66[c]
2b	Pro		18[c]	49[c](40[d])
2c	Im		13[c]	23[c]
3a	HCO_3		0	0
3b	Pro		17[c]	53[c] (37[d])
3c	Im		8[c] (10[d])	9[c] (11[d])
4	Pro		0	0

[a]Determined by ^{1}H NMR spectroscopy (see Figure S28–S37). [b]Reaction conditions: rt, 20 mol% BMMI·X, without stirring, concentration of 2 mol·L^{-1} (0.5 mL of solvent). [c]Deuteration degree at a position. [d]Deuteration degree at b position.

obtained cleanly in good yield after workup without further purification. The deuterium incorporation has been evaluated by ^{1}H NMR spectroscopy, as exemplified by Figure 2. We proceeded to investigate the reaction between acetophenone and BMMI·Pro in $CDCl_3$ by the decrease in the intensity of the CH_3 (Cα) hydrogen signals (formerly singlet at 2.35 ppm), and the appearance of a triplet and a quintet signal corresponding to CH_2D and CHD_2 (2.33 and 2.31 ppm) (Figure 2). Furthermore, by ^{2}H NMR three different signals were observed suggesting that there are three distinct deuterated species CH_2D, CHD_2, and CD_3 (2.39, 2.36, and 2.33 ppm) (Figure S3). Finally, the ^{13}C NMR spectrum allowed to identify a singlet at 77.4 ppm corresponding to $CHCl_3$, which appears after the deuterium transfer (see Figure S4).

Comparing the different substituents at position 4 (entries 2–8), it becomes evident that the percentage of deuteration increases (entry 1). There are high similarities of deuterium incorporation (56–61%), except for 4-nitroacetophenone due to visible catalyst (IL) degradation observed by fast color changing from yellow to brown and by gas evolution. By comparing the same substituents (CH_3, Br, and CF_3) in positions 2, 3, or 4, positions 2 and 4 possess high and similar deuteration (60–65% to CH_3, 61–57% to Br, and 59–56% to CF_3), whereas substitution at position 3 results in a lower percentage of deuteration (53, 56, 53%, respectively). This can be explained by the equivalence of positions 2 and 4 regarding electron delocalization in the aromatic system. For all acetophenone derivatives, it appeared that the nature of the

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substituent on the aromatic ring or methyl group does not significantly affect the global deuterium incorporation, as has been reported in literature.[8]

It is also apparent from the data in Table 2 that there is no direct relationship between the acidity of the α-H and the degree of deuteration. A small difference of deuteration level observed when comparing electron-withdrawing CF_3-substituted acetophenone (pK_a =22.7 and 22.8; entries 8 and 16) and the derivatives with electron-donating groups, such as CH_3 and OCH_3 (pK_a =25.2, 25.7, and 24.5; entries 2, 3, and 14).

For orto-acetophenone derivatives, the highest percentage of deuteration occurs for R with positive inductive effects (entries 9−12). For meta-acetophenone derivatives, it appears that the nature of the substituent on the aromatic ring or on the methyl group does not have a significant effect on global deuterium incorporation, with yields between 53 and 57% (entries 13−16).[8]

Comparing deuteration of a primary, secondary, and tertiary Cα (entries 1b, 17−18), the percentage of the deuteration of the primary and secondary carbon are almost the same (53 and 55%, respectively), whereas the tertiary carbon is not deuterated. This result is due to steric hindrance in the last compound, as has already been shown.[8]

Finally, concerning the influence of aromatic substituents, the percentage of deuteration with a phenyl group is lower than that of a naphthyl group (entries 1 and 19, respectively). In fact, the naphthyl group can interact more efficiently with ionic liquid contact ion pairs to form a clathrate-like intermediate akin to the already observed interaction of aromatics with imidazolium-based ionic liquids.[21] Acetophenone and naphthyl ketone present 53 and 59% of deuteration, respectively.

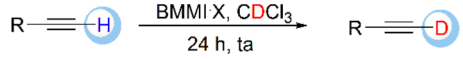
Next, ketones with two possible deuterations were studied to examine the acidity of the carbonyl Cα atoms (Table 3).

For propanone, (Table 3, entry 1) the deuteration percentage increased in the following order: HCO_3 < Im < Pro, preserving the behavior previously observed. When comparing a carbonyl Cα neighbor with a phenyl group and a carbonyl Cα neighbor with a methyl group, deuteration (entries 2a−c) occurs preferentially at the carbon next to the phenyl. Another trend concerns the fact that deuteration occurs preferentially at primary and secondary carbons compared with tertiary carbons. The methyl group (position a) presents a higher percentage of deuteration than position b (entries 3a−c). When a symmetric ketone with carbon atoms bonded to phenyl groups was used, deuteration was not observed (entry 4). This can be due to steric hindrance, which has already been shown to inhibit deuteration.

These results prompted us to investigate the scope of our methodology to other acidic molecules, the alkynes (Table 4). Unlike ketones, the most efficient catalyst for all alkyne substrates was the IL-containing the Im anion, followed by Pro and finally, HCO_3 (Im> Pro> HCO_3). Since alkynes have a single acidic H, catalytic activity is enhanced in the IL-containing a more basic anion and forms a less ionic contact ion pair.[22] Therefore, the higher lipophilicity of BMMI·Im that forms a stronger contact ion pair than the other ILs may facilitate the interaction with the relative low polar substrates and hence to promote more efficiently the H/D exchange reaction.

The effect of a single substituent on an alkyne was also considered, the percentage of deuteration increasing in the order: Me < Cl < OH (Table 4, entries 2−4). The deuteration upon exchanging the substituent to an amine remained satisfactory, being ≥49% even when using BMMI·HCO_3 as a catalyst.

Table 4. Deuteration of Alkynes Using BMMI·X as Catalyst[a]

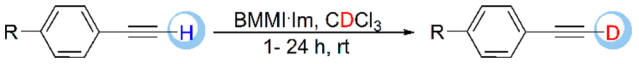


entry	X	R	% D[b] (1h)	% D[b] (24h)
1a	HCO_3	Ph	23	60
1b	Pro	Ph	31	71
1c	Im	Ph	82	84
2	Pro	$(CH_2)_3CH_3$	14	23
3	Pro	$(CH_2)_3Cl$	14	33
4a	HCO_3	$(CH_2)_3OH$	24	29
4b	Pro	$(CH_2)_3OH$	24	35
4c	Im	$(CH_2)_3OH$	76	76
5a	HCO_3	CH_2NH_2	18	49
5b	Pro	CH_2NH_2	6	49
5c	Im	CH_2NH_2	49	63

[a]Reaction conditions: r.t., 20 mol% of BMMI·X, without stirring in a concentration of 0.9 mol·L^{-1} (0.8 mL of solvent). [b]Determined by ^{1}H NMR spectroscopy (see Figure S38−S50).

The influence of the reaction conditions on the formation of D_1-phenylacetylene using BMMI·Im was investigated in more detail. Different concentrations and catalyst quantities were tested. (Table 5). First, the influence of concentration was examined (entries 1−5).

Table 5. Effect of Reaction Conditions on the Degree [%][a] of Deuteration of Alkynes in $CDCl_3$ after 1 and 24 h[b]



entry	R	catalyst (mol%)	subst. conc. (mol L^{-1})	% D[a] 1h	% D[a] 24h
1	H	10	0.2	27	67
2	H(4-Me)	10	0.9	81 (32)	85 (47)
3	H(4-Me)	20	0.9	82 (65)	84 (72)
4	H	10	1.25	79	81
5	H	10	2	73	76
6	H	20	2	73	76
7	H	–	0.9	0[c]	0[c]

[a]Determined by ^{1}H NMR spectroscopy. [b]Reaction conditions: r.t., BMMI·Im, without stirring, 1−24 h. [c]After 72 h.

As can be seen, the yield in 24 h increased with the concentration until a maximum point was reached. Increasing further the concentration had no apparent effect on the reaction (entries 4 and 5), which may indicate a saturation point, as was observed for the ketone reactions. The catalyst quantity was also studied (entries 2−3 and 5−6). As a consequence of doubling the amount of catalyst, the degree of deuteration increased to 72% after 24 h when 4-methyl phenylacetylene as a substrate was used. Once again, the last test showed that no reaction occurs in the absence of catalyst even after 72 h (entry 7).

The first step involves the formation of "catalytic active species" in which the IL is activated by the solvent. In this stage, it is vital to have ion pair contact for the reaction to occur. Indeed, treatment of BMMI·Pro with D_2O affords exclusively BMMI·Pro(D) resulting from the selectively H/D exchange reaction between the NH of prolinate with D_2O. Evaporation of the D_2O and dissolution of the thus isolated BMMI·Pro(D)

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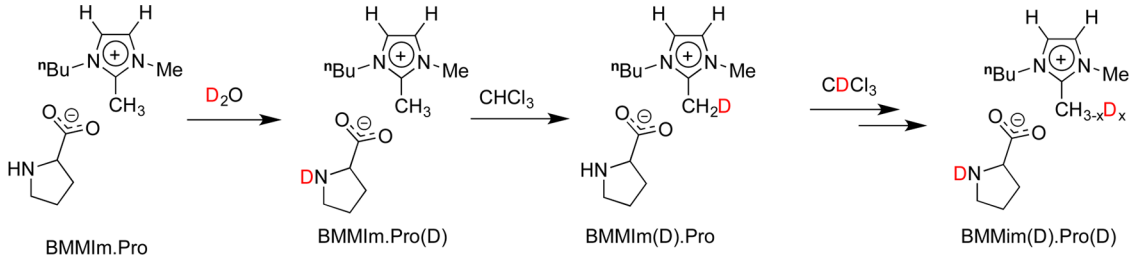
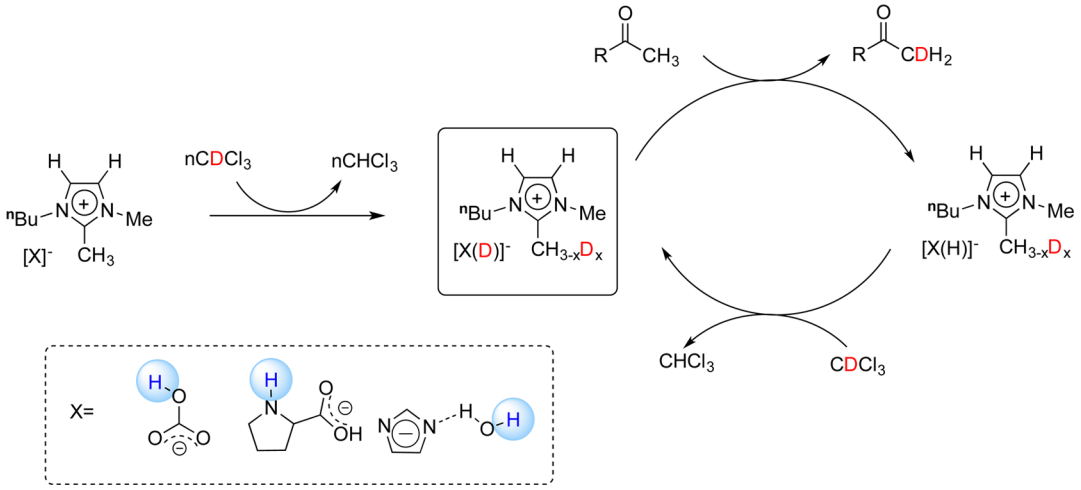
Scheme 2. Reaction Paths Involved in the Formation of the Catalytic Active Species BMMI(D)·Pro(D)



Scheme 3. Proposed Catalytic Cycle for Deuteration of Substrates



in $CHCl_3$ yields the BMMI(D)·Pro derivative resulting from the H/D exchange intraionic reaction between the Pro(D) anion and the BMMI cation (Scheme 2, and Figures S52 – S55). The proton transfer from the cation to the anion has already been proven to be energetically possible according to DFT calculations.[23]

It is probable that IL anions act as D transfer catalysts between $CDCl_3$ and the IL pair, due to the presence of a labile proton in its structure.[8] For the imidazolate anion, the H_2O present in the structure acts as the acid, donating the hydrogen and forming an H-bonded with the anion. The H/D exchange reaction of the 2-Me position of BMMIm cation probably occurs via the deoxy-Breslow-like intermediate arising from the fast deprotonation of 2-Me group leading to a 2-methylene-imidazole species followed by D^+ addition that generates the deuterated 2-Me BMMIm cation.[24−26]

Deuteration of the substrate occurs in the second step (Scheme 3). There is a deuterium transfer of deuterated IL to the substrate. At the same time, $CDCl_3$ reacts again with the catalyst maintaining the deuterated form. In this step, competition between substrate and the C7 (CH_3) on the IL may also occur.[19,20]

To prove the proposed reaction mechanism, two experiments were performed. First, a test using only the substrate (S) (acetophenone and phenylacetylene) with the deuterated solvent, even after 72 h, does not deuterate the substrates. This result confirm that the ILs are required in the reaction medium

In the second test, only the catalyst (IL) and the deuterated solvent were used. After 24 h of reaction, the $CDCl_3$ was evaporated to obtain the pure deuterated ionic liquid (DIL). The substrate (phenylacetylene) was then added to the catalyst without the addition of any solvent. It was possible to observe the deuteration of the substrate (25%), using ^1H NMR, by the decrease of the integral about the peak of the alkyne acidic H, even in the absence of solvent (Figure 3a). This result was also confirmed by ^2H and ^{13}C NMR, where a triplet corresponding to the deuterated form of the carbon atom with a triple bond was observed (Figure S51 and 3b). The lower percentage of deuteration in the absence of solvent is because less D is available, unlike in the presence of a solvent where an "infinite" source of deuterium exists. These results demonstrate that deuteration occurs by the transfer of D from the IL to the substrate (Scheme 4).

Scheme 4. Deuteration Reaction Steps

$$\text{DSolv} + \text{IL} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Solv} + \text{DIL} \qquad \text{(a)}$$

$$\text{DIL} + \text{S} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{DS} + \text{IL} \qquad \text{(b)}$$

The deuterated solvent (DSolv) reacts with the catalyst (IL) producing the deuterated form of the catalyst (DIL). This reaction is fast and reversible. Next, the substrate (S) interacts with the activated catalyst that undergoes reaction to form the final product (DS = substrate deuterated), according to Scheme 4.[27]

Monitoring the kinetics of the reaction was first carried out by varying the substrate concentration while keeping the IL concentration constant. Then the IL concentration was varied with the substrate kept constant. Data were collected every 30 s

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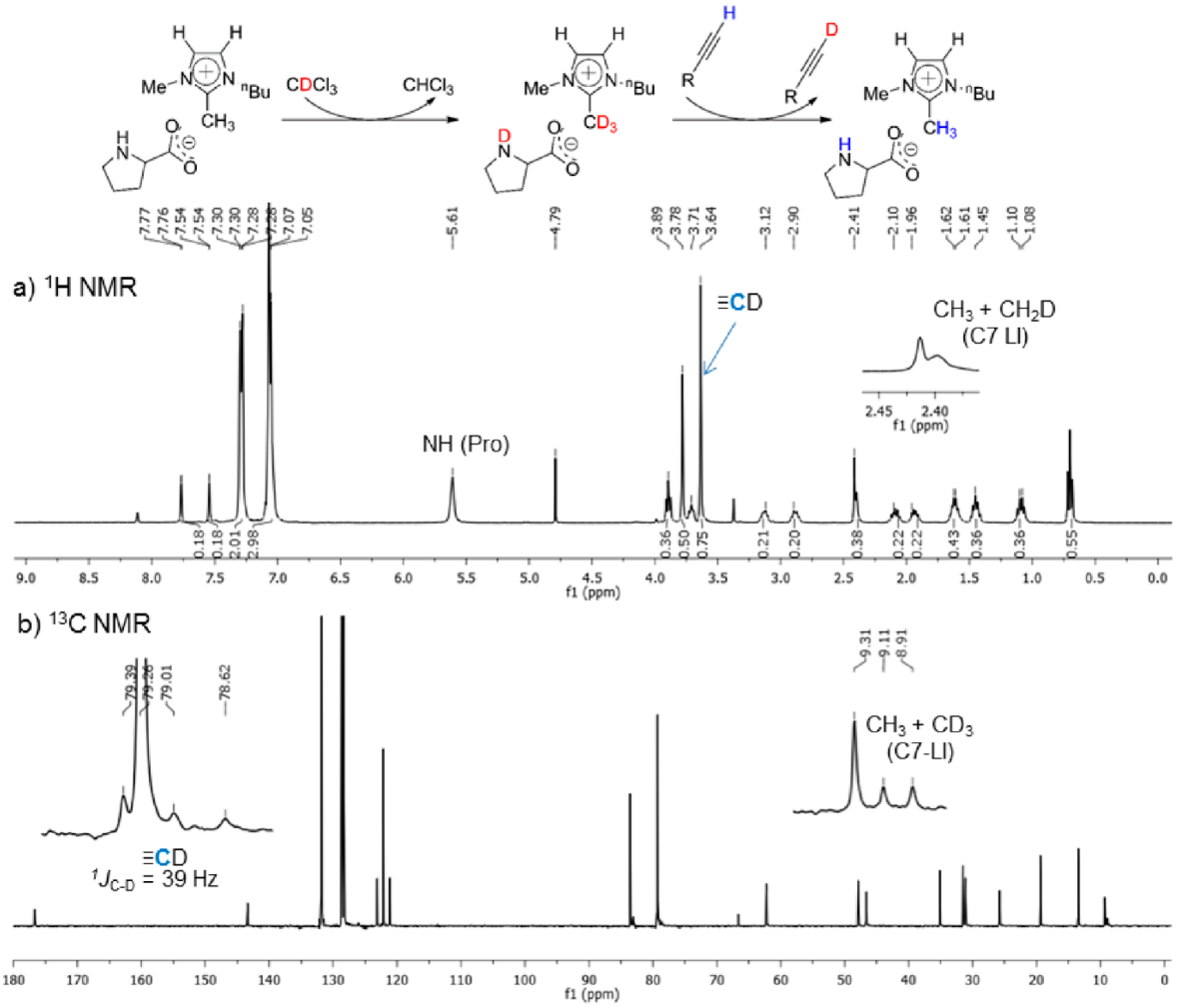

Figure 3. NMR spectrum of phenylacetylene with deuterated BMMI·Pro without deuterated solvent, using a D_2O capillary: ^1H NMR (a), ^{13}C NMR (b).

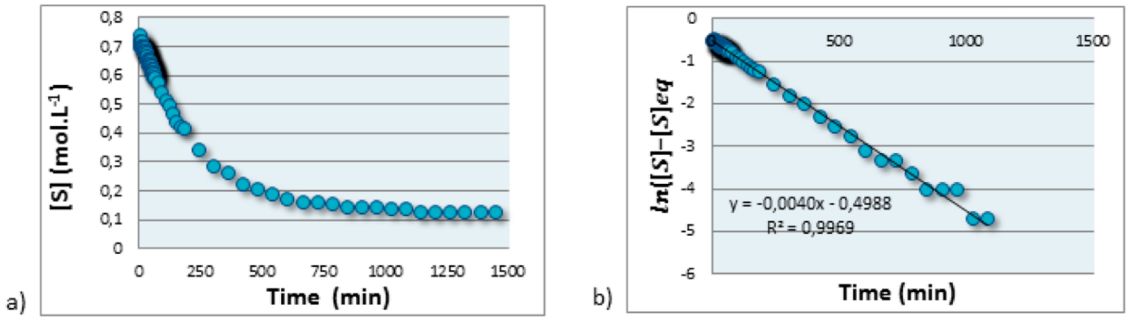

Figure 4. (a) Reaction monitoring ($[S] \times t$), (b) Kinetic plot ($\ln([S] - [S]_{eq}) \times t$). Kinetics of the reaction between phenylacetylene (0.9 mol·L^{-1}), BMMI·Pro (0.18 mol·L^{-1}), and $CDCl_3$. (See more graphs in Supporting Information.)

during the first hour, after that the data have been gathered in longer intervals until the reactions achieve the equilibrium (see Figure S56). Plots of the substrate concentration versus time were prepared (Figure 4a).

Clearly, the kinetics of the catalytic process shows two coupled steps, presented in Scheme 3. Both steps are reversible allowing the reaction to achieve the equilibrium state. We assume that the first reversible reaction (a) is faster than the second (b), because the DIL can be observed at the beginning of the reaction (time shorter than 3 min). As a result, it can be considered that IL and DIL concentrations are constant. Another interesting point to be considered is the excess of the substrate about the IL. Thus, the kinetic mechanism could be solved using a modified reversible pseudo first order eq (eqs 1−16):

Assuming the equilibrium reaction as (a) and (b):

$$\frac{d[\mathrm{IL}]}{dt} = -k_1[\mathrm{IL}][\mathrm{DSolv}] + k_{-1}[\mathrm{DIL}][\mathrm{Solv}] + k_2[\mathrm{DIL}][S] - k_{-2}[\mathrm{IL}][\mathrm{DS}] \quad (1)$$

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$$\frac{d[S]}{dt} = -k_2[S][\mathrm{DIL}] + k_{-2}[\mathrm{IL}][\mathrm{DS}] \quad (2)$$

S_o is the initial substrate concentration. It is clear that (eq 3):

$$S_o = [S] + [\mathrm{DS}] \text{ and therefore } [\mathrm{DS}] = S_o - [S] \quad (3)$$

Assuming that the first step is faster, we can postulate that (eqs 4 and 5):

$$[\mathrm{DIL}] \cong \text{Constant, therefore: } k_2' = k_2[\mathrm{DIL}] \quad (4)$$

$$[\mathrm{IL}] \cong \text{Constant, therefore: } k_{-2}' = k_{-2}[\mathrm{IL}] \quad (5)$$

Where k_2' and k_{-2}' are pseudo first order kinetic constants. Eq 2 becomes

$$\frac{d[S]}{dt} = -k_2'[S] + k_{-2}'(S_o - [S]) = k_{-2}'S_o - (k_2' + k_{-2}')[S] \quad (6)$$

Defining an auxiliary variable (eqs 7 and 8):

$$W \equiv k_{-2}'S_o - (k_2' + k_{-2}')[S] \quad (7)$$

$$dW \equiv -(k_2' + k_{-2}')d[S] \quad (8)$$

The kinetic equation can be written as (eq 9):

$$-\frac{1}{(k_2' + k_{-2}')}\frac{dW}{dt} = W \quad (9)$$

And its solution is (eqs 10−12):

$$W = W_o e^{-(k_2' + k_{-2}')t} \quad (10)$$

$$W_o = k_{-2}'S_o - (k_2' + k_{-2}')S_o = -k_2'S_o \quad (11)$$

$$W = k_{-2}'S_o - (k_2' + k_{-2}')[S] = -k_2'S_o e^{-(k_2' + k_{-2}')t} \quad (12)$$

Rearranging the equation, we have (eq 13):

$$[S] = \frac{k_{-2}'S_o + k_2'S_o e^{-(k_2' + k_{-2}')t}}{k_2' + k_{-2}'} \quad (13)$$

Considering that, when $t \to \infty$: $[S] \to [S]_{eq}$ (eq 14):

$$[S]_{eq} = \frac{k_{-2}'S_o}{k_2' + k_{-2}'} \quad (14)$$

Then:

$$[S] = [S]_{eq} + \left(\frac{k_2'}{k_2' + k_{-2}'}\right)S_o e^{-(k_2' + k_{-2}')t} \quad (15)$$

Linearizing the eq (eq 16):

$$\ln([S] - [S]_{eq}) = \ln\left[\left(\frac{k_2'}{k_2' + k_{-2}'}\right)S_o\right] - (k_2' + k_{-2}')t \quad (16)$$

The kinetic eq (eq 16) based on the proposed mechanism should yield a linear plot of $\ln([S] - [S]_{eq})$ against t. This is indeed true for all the experiments (details in the Supporting Information).

The reaction is first order with respect to the substrate and also with respect to the ionic liquid, but due to the coupled deuteration equilibrium (first step in Scheme 3) the deuterated ionic liquid concentration is maintained constant, yielding a pseudozero order kinetics with respect to the ionic liquid (Figures 4 and S57−S62).

As expected, we found a linear equation with a correlation coefficient of 0.9969, proving the reaction order. Moreover the value of $(k_2' + k_{-2}')$ could be obtained by the slope. Calculating k_2' and k_2'we obtain $k_2' = 3.4 \times 10^{-3}$ min^{-1} and $k_{-2}' = 5.6 \times 10^{-4}$ min^{-1}. Graphics and data in other concentrations can be seen in the Supporting Information.

CONCLUSIONS

In summary, BMMI·X especially Pro and Im are efficient isotope exchange catalysts in $CDCl_3$ at room temperature for a broad range of substrates. The ability of this ILs for deuteration could be ascribed to both, its high pK_a value and the presence of a labile proton in its structure. Indeed, the fact that deuteration of both, cation and anion of the ILs without any base addition, clearly demonstrates the highly noninert nature of ionic liquids even containing C2 substituted cations (C7).

EXPERIMENTAL SECTION

Materials and Instruments. All NMR experiments were obtained spectrometers operating at 400 MHz for ^{1}H and 500 MHz for ^{1}H. Spectra have been achieved with a probe temperature of 298 K under conditions for ^{1}H (spectral width 6400 Hz with 32 K data points and zero filled to 128 K to give a digital resolution of 0.05 Hz/pt). Chemical shifts were reported in parts per million (ppm, δ) and referenced to solvent pick: $CDCl_3$ (δ 7.26 in ^{1}H and 77.0 in ^{13}C). Commercial $CDCl_3$ was dried by distillation. All NMR (^{1}H, ^{2}H, ^{13}C) spectra are provided in the Supporting Information.

Preparation of Imidazolium Salts and Reactions. BMMI·HCO_3, BMMI·Im, and BMMI·Pro were prepared according to known procedures.[19,20,28−30]

Synthesis of Deuterated Ketones. Catalysts (0.2 mmol) and ketones substrates (1 mmol) were charged in an Eppendorf without stirring. $CDCl_3$ (0.5 mL) was added and the reaction solution transferred to a NMR tube kept at room temperature (298 K). The ^{1}H NMR analysis were performed after 1 and 24 h. The deuterium incorporation was calculated using a substrate signal as the internal standard.

Synthesis of Deuterated Alkynes. Catalysts (0.144 mmol) and alkynes substrates (0.72 mmol) were charged in an Eppendorf without stirring. $CDCl_3$ (0.8 mL) was added and the reaction solution transferred to a NMR tube kept at room temperature (298 K). The ^{1}H NMR analysis was performed after 1 and 24 h. The deuterium incorporation was calculated using a substrate signal as the internal standard.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03029.

Spectra for all compounds and kinetic data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: fpsantos@ufrgs.br

ORCID

Francisco P. dos Santos: 0000-0003-1530-9505

Jairton Dupont: 0000-0003-3237-0770

Notes

The authors declare no competing financial interest.

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