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Proton–deuterium exchange of acetone catalyzed in imidazolium-based ionic liquid–D₂O mixtures

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The reaction of the proton–deuterium exchange of acetone in imidazolium-based ionic liquid (IL)–deuterium oxide mixtures was studied in detail via NMR spectroscopy. Certain ILs exhibit considerable catalytic properties and contribute to the course of reaction up to the complete deuteration. The efficiency of deuterium exchange crucially depends on the features of ILs; the type of anion and chain length of cation. The linear secondary isotope effects on the NMR chemical shifts of the ¹³C atoms in acetone were observed depending on the deuteration level of the molecule.

Introduction

Efficient deuterium labelling of organic compounds became a topic of outstanding importance in recent years because of the improved pharmacokinetic properties demonstrated by the D-labelled drugs.^{1–5} On the one hand, the properties of C–H and C–D bonds are very similar, which allows for keeping the desired biological activity of a drug molecule upon C–H/C–D replacement. On the other hand, the C–D bond is stronger than the C–H bond,⁶ which is the key characteristics to improve the drug efficiency by protecting oxidatively labile C–H bonds or *via* other mechanisms.^{1–5} The approval of the first deuterated drug on the market opened a new demand for the development of new synthetic methodologies and their mechanistic understanding.⁷

From the synthetic point of view, the replacement of C–H/C–D reactions can be carried out using transition metal catalysis. However, the application of the metal catalyst leads to the unavoidable contamination of drug molecules with metal traces and requires rigorous purification before use. Therefore, metal-free organocatalytic approaches are of considerable importance to develop new synthetic applications.^{8–14} N-Heterocyclic-carbene-based organocatalytic reactions and ionic liquids have been used actively in this area.^{15–18}

The deuterium exchange reaction of H atom in the second position in the imidazolium ring of imidazolium-based ionic liquids (ILs) mixtures with deuterium oxide is a well-known process with promising opportunities to transfer the D-label to organic functional groups. It was shown that depending on the IL the rate and overall level of deuteration can change.^{19–25}

Our studies also showed that under the same conditions, the degree of deuteration in different ILs was different ranging from complete deuteration to its absence. Of particular interest are IL/water mixtures, where micro-heterogeneous structures induce new chemical properties²⁶ and effect the biological activity.^{27,28} The H/D exchange can occur in molecules of compounds dissolved in IL–water systems as well; however, this phenomenon is less studied and its practical potential is not fully utilized. It was shown that mixtures of some ILs with CDCl₃ are active catalysts for the H/D exchange reaction of ketones and alkyne substrates.^{29,30} Recently, a dynamic nature of imidazolium systems was revealed and ambident reactivity with carbonyl compounds was shown in organocatalytic processes.³¹ Reactions involving ketones are of particular interest with challenging questions from the mechanistic point of view.³¹ Acetone, despite being a small molecule, was established as a reliable model for studying the deuteration reactions of ketones and gain mechanistic understanding.

Deuterium exchange in the keto–enol tautomeric equilibrium reactions of acetone in heavy water catalyzed by bases is being studied for a long time.³² The process can occur in deuterated solvents, having exchangeable groups, such as CDCl₃, methanol-OD, ethanol-OD or heavy water D₂O. Moreover, this reaction was used for the measurements of the ²H-labelling of water in biological fluids, which are required for determining the rates of the biochemical flux and for estimating the body composition.^{33,34} However, for such cases the base-catalyzed exchange of hydrogen (deuterium) between water and acetone is used, and the ²H-labeling of acetone is then determined *via* gas chromatography–(quadrupole) mass spectrometry. Without the catalyst, in pure CDCl₃ or D₂O solution of acetone, the H/D exchange reaction does not take place.

However, it is known that in CDCl₃ in the presence of 1,2,3-trialkylimidazolium-based ionic liquids associated with basic anions such as hydrogen carbonate, proline, and imidazolate

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the H/D exchange reaction of various substrates occurs, without the addition of any extra bases or metal.³⁰

Here, we decided to study the effect of other ILs on the H/D exchange processes of acetone, using D₂O as the D source. We report the deuteration of methyl groups in acetone, one of the simplest ketonic compounds, dissolved in IL-D₂O mixtures, with the aim of understanding if these mixtures could serve as catalysts and/or hinder the deuterium exchange in solute molecules. The ketone functional group is ubiquitously present in drugs and biologically active molecules. Gaining a mechanistic insight into the C-H/C-D replacement is an important area for the development of IL-mediated metal-free D-labelling reactions.

Experimental

ILs used in the study (Table 1, and Fig. 1) were obtained from ABCR, Germany, and Acros, Belgium. D₂O (99.9 atom% D) was purchased from Cambridge Isotope Laboratories. Commercially available acetone was purified before use.

Composition of all samples in D₂O is 4.0% v/v of acetone, with 1/1 v/v D₂O/IL. The composition of the sample in H₂O is 4.0% v/v of acetone-d₆, with 0.9/1 v/v H₂O/[C₄mim][OAc], so that the samples with H₂O and D₂O will have the same molar ratio of water/[C₄mim][OAc].

The ¹H and ¹³C inverse gated NMR spectra of the samples presented here were acquired at 303 K on a 400 MHz Bruker AVANCE NEO spectrometer equipped with a temperature controlled Smart probe. DEPT (Distortionless Enhancement by Polarization Transfer) and APT (Attached Proton Test) NMR techniques were used to clearly represent the level of the deuteration of methyl groups and were acquired also on a Varian Mercury 300 VX. MestreNova was used to process spectra.

Results and discussion

Acetone has seven possible H/D mass isotopomers (with masses ranging from 58.080 for unlabeled two CH₃ groups to 64.116 for fully labelled CD₃ groups), and ten isotopomers, considering the labelling positions. The distribution among them, rate and level of deuteration depend on the temperature, acetone concentration, IL-D₂O ratio, and type of IL.

¹³C NMR spectroscopy provides an excellent possibility to study the H/D exchange due to the existing large isotope effects on the chemical shifts of carbons in acetone, leading to the

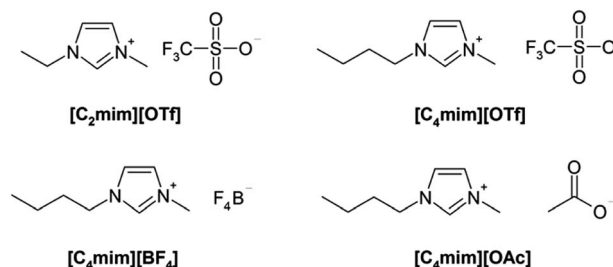


Fig. 1 Structures of the used ILs.

separation of signals, corresponding to various isotopomers. The deuteration can be easily detected due to the splitting patterns arising from the deuterons attached to the carbon atoms both in the ¹H and in ¹³C{¹H} NMR spectra (deuterium is an isotope with spin = 1). Moreover, the study can be done by monitoring the signals of both carbonyl and methyl groups. The sequential deuteration of CH₃ groups of acetone in numerous IL-D₂O mixtures is a slow process at room temperature and can be easily monitored. Deuterium enrichment (in %) will be estimated by the degree of deuteration % D.¹⁰ As an example, in Fig. 2, the H/D exchange of acetone in [C₄mim][OAc]-D₂O at various time intervals of the reaction is presented (the reaction begins directly in the NMR tube after sample preparation). After

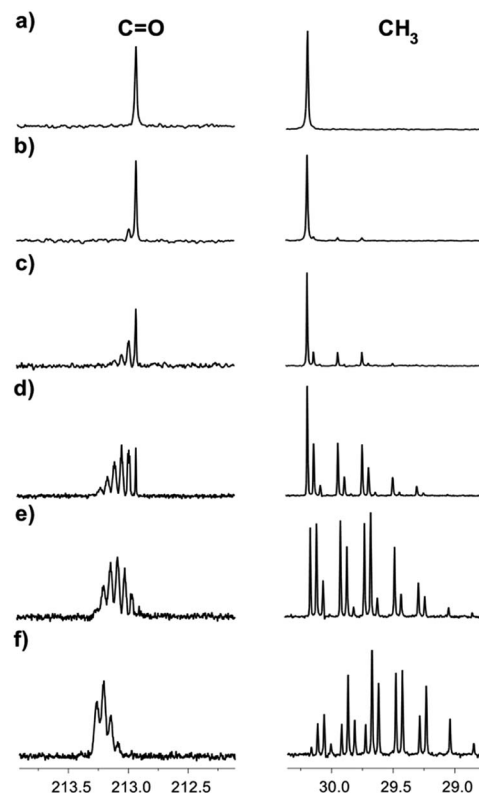


Fig. 2 ¹³C NMR spectra of acetone in the binary mixtures of D₂O in the IL [C₄mim][OAc] after a certain reaction time: (a) one hour; (b) 1 day, % D = 1.5; (c) 1 week, % D = 7.5; (d) 3 weeks, % D = 20; (e) 5 weeks, % D = 34; (f) 4 months, % D = 81.

Table 1 Summary of the ILs used in this study

Abbreviation	Name
[C ₄ mim][BF ₄]	1-Butyl-3-methylimidazolium tetrafluoroborate
[C ₄ mim][OAc]	1-Butyl-3-methylimidazolium acetate
[C ₄ mim][OTf]	1-Butyl-3-methylimidazolium trifluoromethanesulfonate
[C ₂ mim][OTf]	1-Ethyl-3-methylimidazolium trifluoromethanesulfonate



one hour of reaction, there is no visible deuteration and the spectrum of acetone is seen, consisting of two singlets, corresponding to carbonyl and methyl carbons (Fig. 2a). The deuteration was evident in the NMR spectra in this sample even after one day (Fig. 2b). As time passes, the isotopomer signals begin to appear as a result of sequential deuterium-exchange (Fig. 2b–f).

The signals of the carbonyl group of the mixture of acetone isotopomers appear in the region of 212.5–213.5 ppm. Theoretically, there could be seven multiplets, corresponding to seven mass isotopomers with a different deuterium content in the molecule of acetone. On the $^{13}\text{C}\{^1\text{H}\}$ 400 MHz NMR spectra the signals of the isotopomers moved downfield from the singlet signal corresponding to the unlabelled acetone (Fig. 3). They are ordered by the number of labelled deuterium atoms in each isotopomer and separated from each other by $\Delta\delta = 0.0588$ ppm. The first multiplet is a 1:1:1 triplet and corresponds to acetone- d_1 , the second multiplet is a 1:2:3:2:1 quintet and corresponds to acetone- d_2 , followed by 1:3:6:7:6:3:1 septet (acetone- d_3), then 1:4:10:16:19:16:10:4:1 nonet (acetone- d_4), then 1:5:15:20:45:51:45:20:15:5:1 undecet (acetone- d_5), and finally 1:6:21:40:80:116:141:116:80:40:21:6:1 tredecet (acetone- d_6).

Signals of most of the isotopomers with their fine structures are shown in Fig. 3. Each of the d_2 , d_3 and d_4 signals corresponds to two isotopomers with differently labelled methyl groups, but since they have very close chemical shifts and small spin–spin coupling constants over two bonds $^2J_{\text{CD}} = 0.8$ Hz, the spin system can be considered as AX_n , where n is a number of labeled deuteriums. Due to the above-mentioned, not all lines in all of these multiplets are well resolved. Obviously, the further the H/D reaction goes, the more intensive are the d_5 and d_6 signals, and the d_0 – d_2 disappear (Fig. 2f).

The $^{13}\text{C}\{^1\text{H}\}$ spectral patterns of the methyl groups in the acetone isotopomers appear in the region of 29.0–31.0 ppm and also allow to distinguish the isotopomers by the number of deuterons attached to the carbon ($\text{CD} = 1:1:1$ triplet, $\text{CD}_2 = 1:2:3:2:1$ quintet, $\text{CD}_3 = 1:3:6:7:6:3:1$ septet). As the deuteration progresses, the triplet corresponding to the CH_2D group appears (Fig. 2b) in addition to the singlet line corresponding to the non-deuterated CH_3 group (Fig. 2a). After a week of the H/D

exchange reaction, the quintet with low intensity, corresponding to the CHD_2 group becomes also visible (Fig. 2c). After three weeks of the reaction, the intensities of the CH_2D triplet and CHD_2 quintet has grown significantly, while the intensity of the CH_3 singlet has decreased. After five weeks of reaction, the signals of the CD_3 septet have started also to appear (Fig. 2e–f).

Thus, the proportions of isotopomers with different ratios of deuterated groups coexist in one sample, which can be clearly visualized by the DEPT experiment. DEPT is an experimental NMR technique, which allows to determine the number of hydrogens bound to each carbon. The DEPT spectrum consists of three separate spectra, corresponding to the carbon atoms of CH_3 , CH_2 , and CH groups, or, in our case, to the CH_3 , CH_2D , and CHD_2 groups (Fig. 4a–c). Signals from the CD_3 group with no attached protons are absent in the DEPT spectra. The spectrum in Fig. 4d is the proton decoupled ^{13}C spectrum, in which signals of all carbons are visible including the septet arising from the CD_3 group.

Analogously, the composition of the reaction mixture can be monitored by the APT NMR experiment (Fig. 5), which was acquired in this work using Bruker Avance NEO spectrometer.

In the APT spectrum, signals from the carbons with an odd number of protons are in antiphase with those containing even number of protons. After 1.5 weeks in $[\text{C}_2\text{mim}][\text{OTf}]\text{-D}_2\text{O}$, the singlet and quintet corresponding to the CH_3 and CHD_2 groups and the triplet from the CH_2D group can be seen as positive and negative signals, respectively (Fig. 5a). Finally, after 5 months of reaction, singlet and triplets signals corresponding to the CH_3 and CH_2D groups fully disappear from the NMR spectra, and only signals corresponding to the CHD_2 and CD_3 groups are

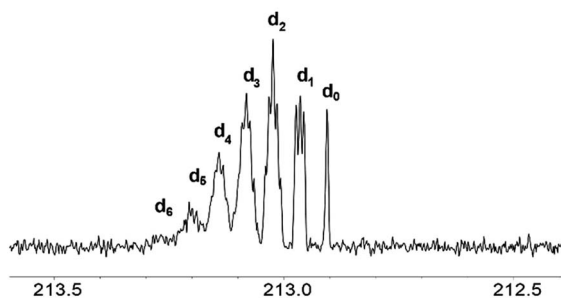


Fig. 3 ^{13}C NMR spectra of the CO region of acetone in the binary mixtures of D_2O with IL $[\text{C}_4\text{mim}][\text{OAc}]$ after 3 weeks of reaction (% D = 28).

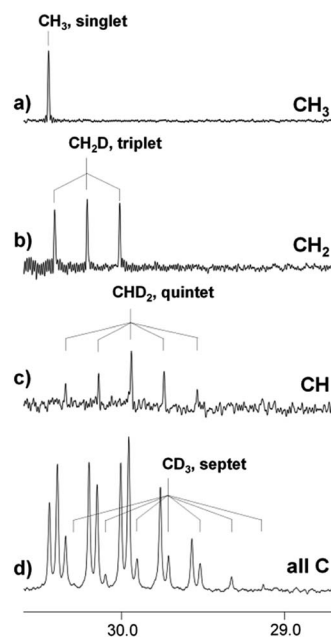


Fig. 4 ^{13}C NMR DEPT (a–c) spectrum and $^{13}\text{C}\{^1\text{H}\}$ (d) spectra of acetone in the $[\text{C}_4\text{mim}][\text{BF}_4]\text{-D}_2\text{O}$ binary mixture after 5 months of reaction (% D = 40).



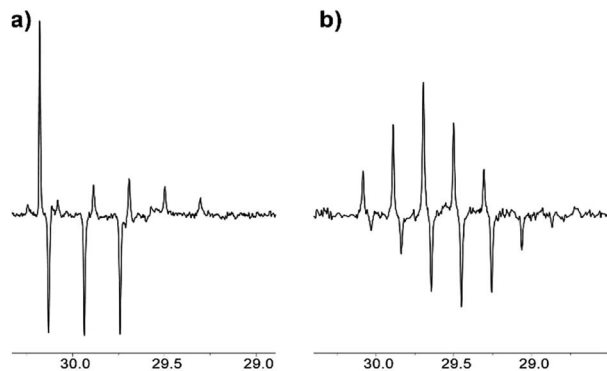


Fig. 5 ^{13}C NMR APT spectrum of acetone in $[\text{C}_2\text{mim}][\text{OTf}]-\text{D}_2\text{O}$ binary mixture after (a) 1.5 weeks, % D = 23; (b) 5 months of reaction, % D = 90.

visible in the spectrum, with a quintet appearing upfield (*i.e.* positive), and a septet appearing downfield (Fig. 5b).

Thus, in the IL- D_2O mixture it is possible to find many (up to all possible) isotopomers of acetone with a certain distribution by the level of deuterium labelling after a certain period of reaction time.

Interestingly, we have observed that the rate of the deuteration process is essentially different for various ILs (Fig. 6). The reaction in the $[\text{C}_4\text{mim}][\text{OAc}]$ and $[\text{C}_2\text{mim}][\text{OTf}]$ systems occurred relatively faster, with almost complete deuteration of acetone in the latter observed in 5 months (Fig. 6c). The slowest process takes place in the mixture of $[\text{C}_4\text{mim}][\text{OTf}]$, where even after 5 months the deuteration did not go further than the CH_2D group (Fig. 6a). Such different deuteration efficiencies in the $[\text{C}_2\text{mim}][\text{OTf}]$ and $[\text{C}_4\text{mim}][\text{OTf}]$ samples imply that the addition of only one CH_2 group to the alkyl chain of the imidazolium ring changes drastically the effect of IL on the deuterium exchange processes. On the other hand, the exchange in the $[\text{C}_4\text{mim}][\text{BF}_4]$ sample (Fig. 6b) is greater than that in $[\text{C}_4\text{mim}][\text{OTf}]$,

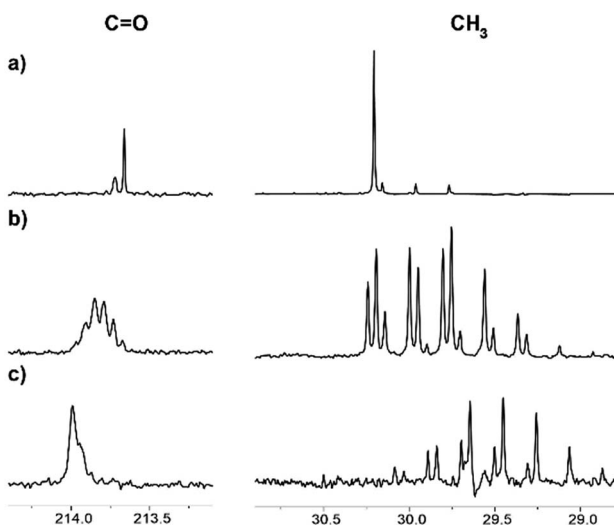


Fig. 6 ^{13}C NMR spectra of acetone in the binary mixtures of D_2O with ILs after 5 months of reaction: (a) $[\text{C}_4\text{mim}][\text{OTf}]$, % D = 4; (b) $[\text{C}_4\text{mim}][\text{BF}_4]$, % D = 40; (c) $[\text{C}_2\text{mim}][\text{OTf}]$, % D = 95.

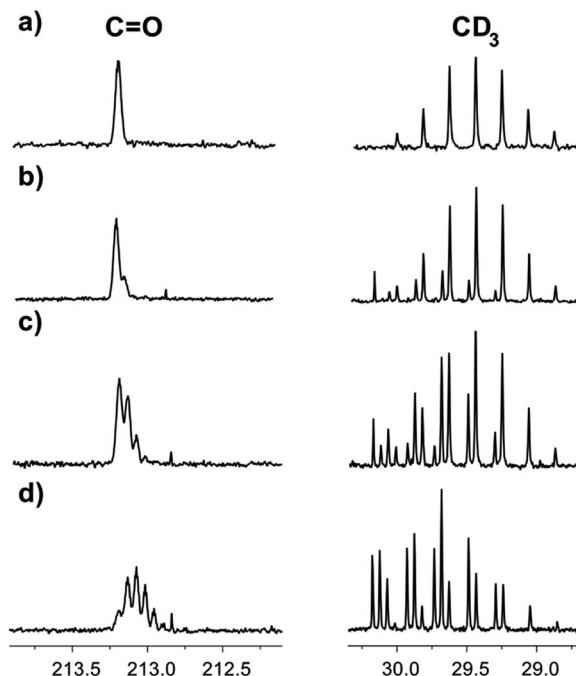


Fig. 7 ^{13}C NMR spectra of acetone- d_6 in binary mixtures of H_2O with IL $[\text{C}_4\text{mim}][\text{OAc}]$ (a) the same day, % D = 100; (b) 2 days later, % D = 96; (c) 5 days later, % D = 88; (d) 16 days later, % D = 67.

$[\text{OTf}]$, and less than that in $[\text{C}_4\text{mim}][\text{OAc}]$ in the same time interval, which means that the nature of the anion also has a significant effect and should be taken into account.

Correspondingly, the opposite process of the D/H exchange is also possible, if a mixture of acetone- d_6 and H_2O is prepared.¹³ We have studied acetone- d_6 in H_2O and in the $[\text{C}_4\text{mim}][\text{OAc}]-\text{H}_2\text{O}$ mixture. In pure H_2O , there was no hydrogen replacement by deuterium after at least five weeks, as opposed to the $[\text{C}_4\text{mim}][\text{OAc}]-\text{H}_2\text{O}$ mixture, where the D/H exchange becomes visible the next day and the rate of hydrogen transfer is quite high (Fig. 7). As expected, the appearance of consecutive multiplets is in the reverse order compared to the H/D exchange pattern.

It is known that there are deuterium isotope effects on the NMR chemical shifts and spin-spin coupling constants (see, for

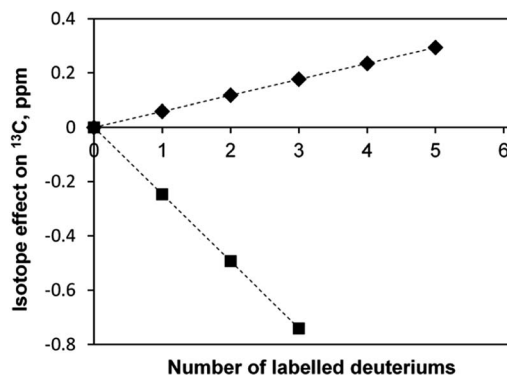


Fig. 8 Deuterium isotope effects on the chemical shifts of ^{13}C carbons of acetone in $[\text{C}_4\text{mim}][\text{BF}_4]$; \blacklozenge – carbonyl group, \blacksquare – methyl group.



instance, the case of dichloromethane³⁵). We have also observed such isotope effects. For instance, in the sample [C₄mim][BF₄]-D₂O the secondary linear upfield deuterium isotope effects on the chemical shifts (in ppm) of the ¹³C-methyl atoms of acetone depending on the deuteration level *n*, equals to $-0.2469 \times n$, and the downfield linear isotope effect on the ¹³C-carbonyl atom, equals to $0.0587 \times n$ (Fig. 8). A primary isotopic effect of $-0.068 \times n$ (in Hz) on the ¹J_{CD} spin-spin coupling constants of methyl carbon is also observed.

Conclusions

Here, we described a unique phenomenon of the catalytic H/D-exchange reaction in acetone mediated by imidazolium-based ILs. We have studied the deuteration of the methyl groups of acetone in D₂O aqueous mixtures of several imidazolium based ILs via NMR spectroscopy. Depending on the type of anion and/or alkyl chain length of the cation, the effectiveness of the H/D exchange differs significantly. The shorter the chain the more effective is the exchange. An almost complete deuteration was observed in the presence of [C₄mim][OAc] and [C₂mim][OTf].

The linear deuterium isotope effects on the NMR chemical shifts of ¹³C atoms of acetone were observed depending on the deuteration level of the molecule (upfield for methyl carbon, and downfield for carbonyl).

Obviously, the observed phenomenon opens several new directions for further studies. Here, we focused our investigation on the room temperature reaction to reveal the process in complete details and to detect all the possible isotopomers with their interconversions. Increasing the temperature to speed up the process and enlarging the scope to involve different ketones will be a subject for our future studies.

Conflicts of interest

There are no conflicts to declare.

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