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Unleashing the potential of ^{17}O NMR using mechanochemistry

Thomas-Xavier Métro,^[a] Christel Gervais,^[b] Anthony Martinez,^[c] Christian Bonhomme,^[b] and Danielle Laurencin^{*[c]}

Abstract: ^{17}O NMR spectroscopy has been the subject of vivid interest in recent years, because there is increasing evidence that it can provide unique insight into the structure and reactivity of many molecules and materials. However, due to the very poor natural abundance of oxygen-17, ^{17}O -labelling is generally a prerequisite. This is a real obstacle for most research groups, because of the high cost and/or strong experimental constraints of the most frequently used ^{17}O -labelling schemes. Here, we demonstrate for the first time that mechanochemistry offers unique opportunities for enriching in ^{17}O a variety of organic and inorganic precursors of synthetic interest. The protocols are fast, user-friendly, and low-cost, which makes them highly attractive for a broad research community, and their suitability for ^{17}O solid state NMR applications is demonstrated.

Oxygen is an element of major importance in many molecules and materials, where it is found in a wide variety of bonding environments (covalent, ionic, coordination, hydrogen bonds, and even halogen bonds). Because of this, it is no surprise that it is one of the first elements ever to have been studied by NMR.^[1] Over the years, ^{17}O NMR spectroscopy has actually progressively emerged as a unique tool for studying the structure, properties and reactivity of many systems,^[2–4] ranging from peptides and enzyme active sites to catalysts, batteries, glasses, and molecular co-crystals, just to name a few.^[5] Indeed, the chemical shift range of ^{17}O exceeds 1500 ppm, and in the case of solids, the other ^{17}O NMR parameters (chemical shift anisotropy and quadrupolar tensors) can also provide important information concerning its local environment.^[2–4] However, despite the major advantages of ^{17}O NMR spectroscopy, this technique is still scarcely used by the community. Indeed, ^{17}O is a spin 5/2 isotope of low resonance frequency and very low natural abundance (only 0.04%), meaning that its sensitivity is extremely poor. This implies that in most cases, enriching the molecules/materials of interest is necessary prior to the NMR analyses. This is a major drawback, when considering the high cost of ^{17}O -labelled precursors (1 g of 90% ^{17}O -enriched H_2O costs ~ 2600 €, and 1 L of 70% ^{17}O -enriched O_2 ~ 5900 €),^[6] and also the lack of efficiency and/or practicality of the ^{17}O -labelling schemes which are most frequently used nowadays. Indeed, these protocols are either long and expensive

(involving excessive amounts of ^{17}O -labelled reagents and lasting several hours/days),^[7] or highly constraining (requiring strict experimental conditions due to the use of hazardous reagents, strongly acidic media and/or very high temperatures).^[8] While efficient enrichment strategies have been proposed for specific families of compounds,^[9] ^{17}O -labelling is still a major issue in most situations, and there have been vocal calls throughout the community for developing new enrichment protocols.

Mechanochemistry is a rapidly developing route for the synthesis of organic molecules, inorganic materials, and also hybrid phases.^[10] These syntheses present several advantageous features in comparison to more traditional procedures, especially because they generally enable to perform reactions in a faster and more environmentally-friendly manner. In ball-milling (BM), the reactions are induced by mechanical forces, which enable to both mix and reduce the size of different particles, and hence make them react efficiently with one another at the interfaces. Small amounts of solvent are often added, as this has been shown to significantly accelerate the reactions.^[10b] Here, we decided to investigate whether small amounts of ^{17}O -labelled water could actually be used in BM protocols, for enriching both strategic organic functions and inorganic precursors in ^{17}O .

Concerning inorganic compounds, we set our focus on metal hydroxides, because they can be readily converted into metal oxides, which are essential precursors for the synthesis of a wide range of ceramics and glasses. Here, the labelling strategy consisted in (i) treating the metal hydroxide for 30 minutes by BM in presence of 41% ^{17}O -enriched H_2O (which was introduced in less than 2 equivalents), in order to perform the isotopic scrambling of the hydroxyls; and (ii) converting the labelled intermediate into the corresponding metal oxide by heat treatment under Ar atmosphere (Scheme 1). The crystallinity of the metal (hydr)oxide phases was analyzed by powder X-ray diffraction (see supporting information), and the success of the labelling attested by ^{17}O solid state NMR.



Scheme 1. Strategy used here for the ^{17}O -labelling of metal hydroxides by BM, and for their subsequent conversion to metal oxides.

Calcium hydroxide (Ca(OH)_2) was taken as a representative compound for testing the BM ^{17}O -labelling strategy, because Ca(OH)_2 and CaO are both key precursors for the elaboration of (bio)ceramics and (bio)glasses. As shown by ^{17}O Magic Angle Spinning (MAS) NMR, Ca(OH)_2 was successfully labelled in ^{17}O by BM in just 30 minutes (Figure 1). Indeed, a high resolution solid state NMR spectrum was obtained in less than 2 hours on a 600 MHz NMR spectrometer, while no signal would have been observed for this sample under these conditions in absence of enrichment. This spectrum actually confirms the high crystallinity

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Supporting information for this article is given via a link at the end of the document.

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of the labelled hydroxide, given the sharp features on the second order quadrupolar lineshape. After heat-treatment, ^{17}O -enriched CaO was isolated, and the enrichment level of this phase was estimated to $\sim 5\%$, by comparing its ^{17}O NMR signal intensity to that of a non-labelled sample prepared and analyzed under similar conditions. The same strategy was subsequently applied with success to $\text{Mg}(\text{OH})_2$ and $\text{Al}(\text{OH})_3$, which are important precursors in materials science, notably for the synthesis of heterogeneous catalysts and glasses. In both cases, ^{17}O -labelled hydroxides were obtained in 30 minutes, the efficiency of the labelling being ascertained by ^{17}O solid state NMR (Figure 1). Their conversion to metal oxides was also straightforward.

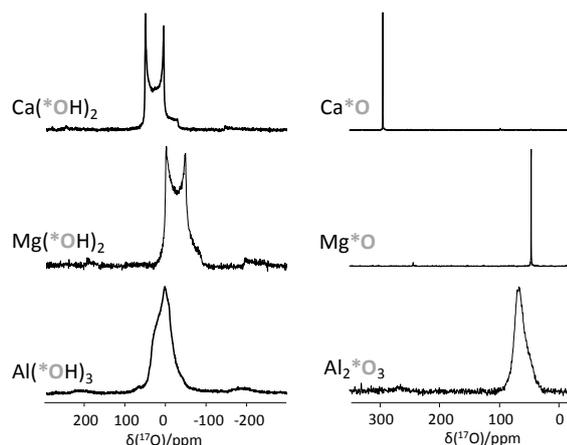
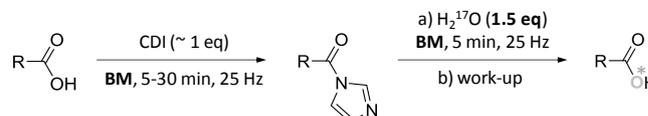


Figure 1. ^{17}O MAS NMR spectra of ^{17}O -labelled $\text{Ca}(\text{OH})_2$, CaO , $\text{Mg}(\text{OH})_2$, MgO , $\text{Al}(\text{OH})_3$, Al_2O_3 , all prepared as shown in Scheme 1. Spectra were recorded at 14.1 T (further details on the acquisition conditions are provided in supporting information, Table S1). The ^{17}O NMR spectra of these (hydr)oxides are consistent with the literature.^[4b]

The BM labelling schemes proposed here for these metal hydroxides surpass in cost, time and practicality any previously reported procedures.^[8a,11] This is best illustrated for the Ca and Mg phases. Indeed, in previous studies, $\text{Mg}(\text{OH})_2$ and $\text{Ca}(\text{OH})_2$ were prepared either by precipitation of chloride or nitrate salts in aqueous solutions,^[11a-c,11e] implying the use of excessive quantities of ^{17}O -enriched water, or by reacting reagents like Ca metal or Mg_3N_2 in presence of stoichiometric quantities of H_2^{17}O , but working under strict experimental conditions (e.g. dry solvents and/or inert atmosphere).^[8a,11e] Here, the labelling was performed in high yield ($> 85\%$) and under ambient conditions, starting directly from the commercial metal hydroxides. The cost of ^{17}O -labelling of 60 mg of $\text{M}(\text{OH})_2$ was less than 10 €, and the protocols were both fast (only 30 minutes) and user-friendly. Moreover, considering that the most common route used nowadays for the enrichment of advanced oxides consists in heating the materials at very high temperatures under $^{17}\text{O}_2$ atmosphere for several hours/days,^[5d,7c,8c] the possibility to easily label in ^{17}O some of the precursors used for the preparation of these phases (as described in Scheme 1) is a highly attractive alternative.

Concerning organic molecules, carboxylic acids were selected as representative functions for the development of new ^{17}O -labelling schemes, because they are present in many important molecules of biological relevance (e.g. amino acids, metabolites, drugs), and also in key building blocks like ligands and monomers. Here, the labelling strategy we employed was adapted from a recently reported BM protocol.^[12] It consisted in (i) activating the carboxylic group using CDI (1,1'-carbonyl-diimidazole) (see supporting information Figure S7), and (ii) hydrolyzing the

intermediate with 41%- ^{17}O enriched H_2O , which was introduced in less than 2 equivalents per $-\text{COOH}$ function (Scheme 2). The purity of the final molecule was verified by ^1H solution NMR and its crystallinity by powder X-ray diffraction (see supporting information). The efficiency of the ^{17}O labelling was determined by mass spectrometry and ^{17}O solid state NMR.



Scheme 2. Strategy used here for the ^{17}O -enrichment of carboxylic groups. In this scheme, the oxygen label (*) has been put on the $\text{C}-^*\text{OH}$ only (to indicate that only one of the 2 carboxylic oxygens is enriched in the reaction), but in the isolated crystalline ibuprofen phase, both the $\text{C}=\text{O}$ and $\text{C}-\text{OH}$ are equally labelled in ^{17}O .

We started our study with ibuprofen, because this molecule is the most common anti-inflammatory drug on the market and is often used as a standard for testing new drug formulations, and yet, to the best of our knowledge, it had never been labelled in ^{17}O . Ibuprofen was treated with 1.0 eq. of CDI for 5 min in a ball-mill, followed by the addition of 1.5 eq. of H_2^{17}O and 5 min ball-mill mixing. After work-up, the pure molecule was isolated in 75% yield. Mass spectrometry analyses demonstrated that the labelling was successful (Figure 2a), with an average ^{17}O -enrichment $\sim 8\%$ per carboxylic oxygen in the crystalline phase, and ^{17}O MAS NMR spectra were recorded in less than 2 hours (Figure 2b).

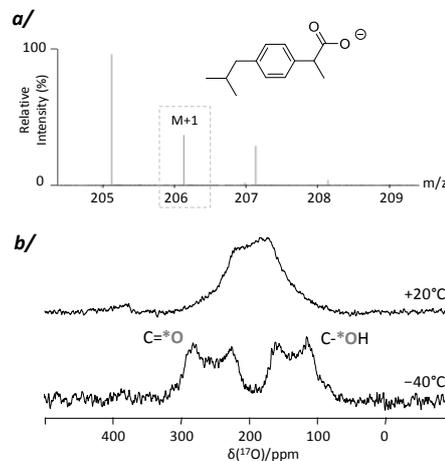


Figure 2. ^{17}O labelling of ibuprofen. a/ Mass spectrometry analysis (TOF, MS ES); the relative intensity at "M+1" (dashed box) demonstrates the success of the ^{17}O -enrichment; b/ ^{17}O MAS solid state NMR spectra recorded at 14.1 T; measurements were performed at different temperatures showing that the $\text{C}=\text{O}$ and $\text{C}-\text{OH}$ resonances are resolved at -40°C (see supporting information, Table S1 and Figures S9 and S10 for further details).

The same strategy was subsequently applied with success to a protected amino acid (Boc-phenylalanine; Boc = *t*-butoxycarbonyl) and two ligands of major importance in the field of metal-organic frameworks (MOFs), namely terephthalic and trimesic acids. In all cases, the average enrichment levels achieved for the carboxylic oxygen atoms in the crystalline phases ranged between ~ 3 and 10 % (see supporting information, Figures S13, S17 and S20). This allowed the 1-dimensional ^{17}O MAS NMR spectra of all these crystalline phases to be easily

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recorded in just a few hours (Figure 3), and a high-resolution 2-dimensional multiple-quantum MAS spectrum of terephthalic acid to be obtained overnight (see supporting information, Figure S14). Most interestingly, the comparison of the ^{17}O spectra of ibuprofen, Boc-phenylalanine, terephthalic acid, and trimesic acid highlights differences in the dynamics around the O atoms within the crystal structures. Indeed, while the spectrum of Boc-phenylalanine depicts the expected resonances of distinct C=O and C-OH groups, as expected from the crystal structure and in agreement with DFT calculations (density functional theory, see supporting information, Figure S21), those of the three other compounds show average features at room temperature. In the case of ibuprofen, this can be explained by dynamic phenomena occurring between the H-bonded carboxylic functions, in line with previous observations made in the literature.^[13] As a matter of fact, it was possible to “freeze” these movements by performing ^{17}O NMR analyses at different temperatures: at -40°C , the resonances of the C=O and C-OH groups are resolved (Figure 2b). For terephthalic and trimesic acids, the ^{17}O NMR spectra are still under study to interpret the lineshapes, which is beyond the scope of the present article.

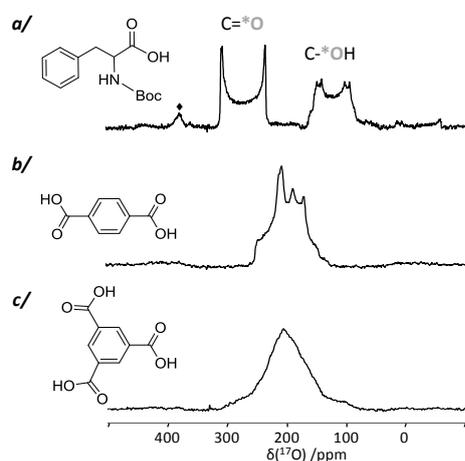


Figure 3. ^{17}O MAS solid state NMR spectra of ^{17}O -labelled a/ Boc-phenylalanine; b/ terephthalic acid and c/ trimesic acid. All spectra were recorded at 14.1 T (for further details on NMR conditions, see supporting information, Table S1). The (♦) signal comes from the rotor (ZrO_2).

The labelling scheme proposed here for carboxylic acids outstands previously published procedures in terms of time and practicality. Indeed, most previous protocols required more than 16 hours (when not several days),^[5b,7b,13b,14-16] while here experiments were over in just 2 hours. Moreover, all four carboxylic acids were enriched starting directly from the commercial compounds under ambient conditions *and* in absence strong acids during the labelling step, which is highly advantageous in comparison to other protocols.^[7b,13b,14-16] Last but not least, the *total* amount of 41% ^{17}O labelled water engaged here to label 60 mg of each of the four molecules was less than 70 μL (*i.e.* less than 50 €), while several procedures actually use *at least* this quantity for enriching the equivalent of 60 mg of a single carboxylic acid containing molecule.^[7b,16,17]

The potential of mechanochemistry is not limited to carboxylic acids and metal hydroxides. Indeed, we found that other strategic reagents like $\text{B}(\text{OH})_3$ (used for the synthesis of glasses, ceramics and hybrid materials) and boronic acids (used for the synthesis of covalent-organic frameworks – COFs – and coordination polymers) can also be successfully labelled in ^{17}O by BM in less

than 1 hour, by engaging stoichiometric quantities of H_2^{17}O and applying a protocol similar to the one described in Scheme 1 (see supporting information). For $\text{B}(\text{OH})_3$, this is all the more noteworthy because previous protocols used to enrich related boron precursors in ^{17}O started from BCl_3 ,^[5e,17] which is highly toxic and delicate to manipulate, because its hydrolysis is exothermic and leads to the release of HCl. The BM procedure is by far much safer, quicker and more user-friendly.

Finally, BM-labelling was also found to be beneficial for the study of water molecules within crystal structures. Water is known to be of major importance in the structure of many organic and inorganic salts, including MOFs, and their study by ^{17}O NMR has been the subject of much interest.^[18] Here, we successfully enriched in ^{17}O the crystalline commercial $\text{Sr}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ phase, by ball milling it for just 15 minutes in presence of stoichiometric quantities of H_2O . The resonances of the H_2O molecules were resolved from the hydroxyl ones by MQMAS (Figure 4), and the NMR parameters for these water molecules were found to be consistent with those calculated by DFT (see supporting information, Figure S28). Alternatively, another way of studying water environments within crystal structures is to synthesize the phases directly by BM, in presence of H_2^{17}O . This is what we performed for a Zn-terephthalate coordination polymer (see supporting information, Figure S30). In this case, the characteristic features of a second-order quadrupolar lineshape were easily observed by ^{17}O MAS NMR for the Zn^{2+} -coordinated water molecules. The small discrepancies between the experimental and DFT-calculated NMR parameters show that ^{17}O NMR could actually be used to help refine the crystal structure, through “NMR-crystallography” types of approaches.^[19] Once more, it is worth noting that both protocols described here for preparing ^{17}O -enriched hydrated phases are very fast and cost-efficient.

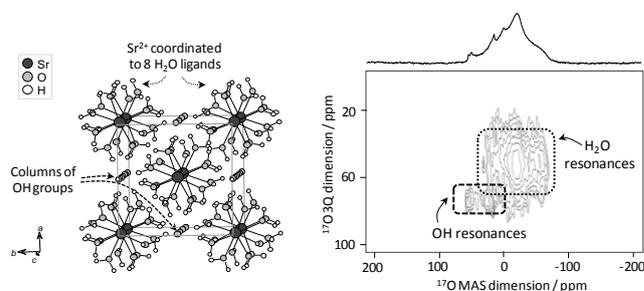


Figure 4. Representation of the crystal structure of $\text{Sr}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (top), and ^{17}O MQMAS NMR spectrum (bottom); the projection in the direct dimension corresponds to the MAS spectrum (see supporting information, Table S1 for acquisition conditions and Figure S28 for comparisons with DFT calculations).

In summary, we have shown that mechanochemistry is perfectly suited for the ^{17}O labelling of both organic and inorganic compounds, and notably of precursors which are of major importance in materials science for the elaboration of MOFs, COFs, and advanced functional oxides. The enrichment of the 11 samples mentioned herein (3 metal hydroxides, 4 carboxylic acids, 2 boron compounds and 2 crystalline phases with coordinated water ligands), all of which were characterized by ^{17}O MAS NMR, required only $\sim 220 \mu\text{L}$ of H_2^{17}O , which represents a cost of just ~ 135 €. Moreover, each BM synthesis took less than 2 hours. It is the first time that such a wide range and diversity of ^{17}O enriched compounds is synthesized at such low cost and in such a short

period of time for solid state NMR. Moreover, the protocols were very easy to perform. This implies that further optimization of each of these syntheses will be possible and affordable, which is a major advantage in comparison to several of the other routes proposed so far, for which the ^{17}O -enrichment level is not optimized due to the prohibitively high costs of the experiments and/or the strong experimental constraints. For the metal hydroxides described here, even higher enrichments will be accessible by adapting the amount of ^{17}O -enriched water added and the milling time, while for molecules containing carboxylic acid functions, this will also be possible by monitoring and then maximizing the enrichment-level after each synthetic step. Moreover, it will be possible to further increase the labelling by repeating these reactions and/or using > 80% ^{17}O -labelled water as a precursor, or, alternatively, developing other BM-based protocols, and this is a point we are currently looking into.

Based on all the above characteristics, it is expected that BM procedures will find numerous applications in the future in ^{17}O NMR, and this study actually already opens up many interesting perspectives, because 8 new compounds were characterized. More generally, we foresee that by rendering the ^{17}O labelling more accessible, ^{17}O NMR will finally become a more routine analytical technique used by a much broader range of researchers. Moreover, new NMR developments are also expected to emerge, such as unprecedented $^{17}\text{O}\dots\text{X}$ correlation experiments using doubly-labelled phases prepared by BM, which will be beneficial not only to conventional ^{17}O NMR spectroscopy but also to DNP (dynamic nuclear polarization).^[20]

Experimental Section

All experimental details are provided in the supplementary information.

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Keywords: ^{17}O NMR • mechanochemistry • isotopic labelling • solid state NMR

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