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Letter

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In Situ Ultrafast 2D NMR Spectroelectrochemistry for Real-Time Monitoring of Redox Reactions

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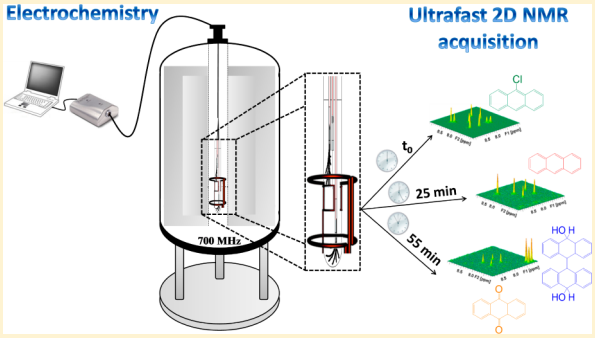
Supporting Information

ABSTRACT: The *in situ* implementation of an electrochemical cell (EC) inside a nuclear magnetic resonance (NMR) spectrometer is extremely powerful to study redox reactions in real time and identify unstable reaction intermediates. Unfortunately, the implementation of an electrochemical device near the sensitive volume of an NMR probe significantly affects the quality of the NMR signal, inducing significant line broadening resulting in peak overlap and partial loss of the multiplet structures. Two-dimensional (2D) NMR spectroscopy allows one to bypass signal overlapping by spreading the peaks along two orthogonal dimensions, while providing precious information in terms of structural elucidation. Nevertheless, the acquisition of 2D NMR data suffers from long acquisition durations which are incompatible with fast redox processes taking place in solution. Here, we present a new approach to deal with this issue, consisting of coupling EC-NMR with ultrafast 2D spectroscopy, capable of recording 2D spectra much faster than conventional 2D NMR. This approach is applied to the real-time monitoring of a model reaction. Fast correlation spectroscopy (COSY) spectra are recorded every 3 min in the course of the 80 min reaction, leading to the unambiguous identification of one reaction intermediate and two reaction products. The evolution of 2D NMR peak volumes in the course of time provides further insight into the mechanism of this reaction involving an unstable intermediate. This study demonstrates the feasibility and the relevance of coupling *in situ* spectroelectrochemistry with ultrafast 2D spectroscopy to monitor real-time electrochemical reactions in the NMR tube.



In analytical chemistry, major advances often arise from the combination of orthogonal techniques to increase the amount of information accessible in a single experiment. Among these associations, the coupling of electrochemistry to various analytical methods has been widely reported in literature.[1−4] In particular, the coupling of an electrochemical cell with nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography, or mass spectrometry is widely used to study and mimic various reactions in metabolic processes.[1,3,5−7] The present study focuses on NMR spectroelectrochemistry, a powerful tool for the structural elucidation of electrochemical reaction products. It is particularly useful not only to observe unstable intermediates but also to elucidate metabolic reaction pathways.[7,8] Many electrochemical devices have been introduced with respect to the development of *in situ* electrochemical cell (EC)-NMR.[1,9−12] Most of these studies have been supported by ^{1}H NMR detection even if some examples reported the observation of the ^{13}C nuclei.[13−15] Nevertheless, the implementation of an electrochemical device near the sensitive volume of an NMR probe significantly affects the quality of the NMR signal. Indeed, the degradation of the sample homogeneity induces significant line broadening resulting in peak overlaps and partial losses of the multiplet structures.[16] This limits the application of *in situ* EC-NMR to situations where NMR peaks are well separated. Two-dimensional (2D) NMR spectroscopy allows one to bypass signal overlapping by spreading the peaks along two orthogonal dimensions, while providing precious information in terms of structural elucidation.[17,18] Nevertheless, the acquisition of 2D NMR data suffers from long acquisition durations (from 10 min to a few hours) inherent to its time-incremental nature. Therefore, conventional 2D NMR is incompatible with fast redox processes taking place in solution. Fortunately, several NMR methods have been proposed to shorten the duration of 2D NMR experiments, among which stands ultrafast (UF) 2D NMR, a method capable of yielding 2D NMR correlations in a single scan.[19−21] Thanks to recent improvements, the UF 2D NMR approach is characterized by a high analytical performance in terms of robustness, repeatability, and resolution and is increasingly used in various applications.[22−27] In particular, recent papers have described the interest of this technique to monitor fast chemical or biochemical processes in real time,

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making it possible to follow the evolution of unstable reaction intermediates as the reaction progresses.[28−33] An additional feature of UF 2D NMR is the possibility to record several scans to increase the sensitivity, resulting in a fast and versatile multiscan approach[34] whose time-resolution and sensitivity can be adapted to the reaction time scale. Therefore, the short time scale of this 2D experiment makes it the perfect candidate for the real-time study of redox reactions involving chemical reaction intermediates.

Figure 1 presents the experimental setup of the *in situ* UF 2D NMR spectroelectrochemistry experiment. The electrochemical

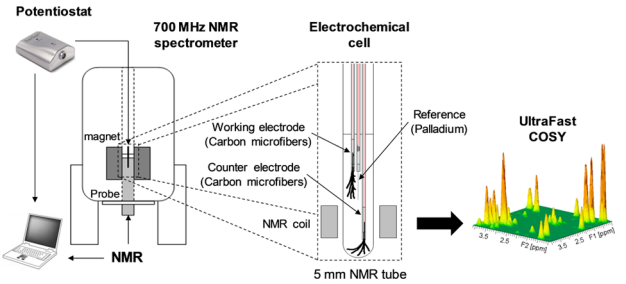

Figure 1. Schematization of an *in situ* EC-2D ultrafast NMR experiment.

device was used as described by Bussy et al.[8] Particular efforts were made to design an experimental setting minimizing the effects of inhomogeneities, i.e., line broadening leading to sensitivity losses. In the most favorable case, the sensitivity was divided by two compared to the tube without electrodes. More detailed information is given in the Supporting Information. With respect to the development of *in situ* UF 2D NMR spectroelectrochemistry, the reduction of 9-chloroanthracene was chosen as a model of redox reaction. The EC-UF 2D NMR experiments described below were recorded on a 700 MHz spectrometer with a cryogenically cooled probe. Three electrodes were introduced in a 5 mm NMR tube containing 800 μL of solution made in acetonitrile-d_3/D_2O 95:5 (v/v). The initial solution concentrations were 25 mM of 9-chloroanthracene and 50 mM of Bu_4NPF_6 as a supporting electrolyte. Chronoamperometry was performed for 80 min at a potential −1.2 V versus the palladium pseudoreference electrode. 2D UF correlation spectroscopy (COSY) spectra were acquired along the electrochemical reduction every 3 min. The sampling period of 3 min was defined as the best compromise between sensitivity and reaction kinetics, making it possible to accumulate 32 scans for each spectrum. A noticeable feature of UF 2D NMR is the need to compromise between the resolution and the accessible spectral width, particularly at high fields. Here, a small spectral width of 2.5 ppm was chosen, which was sufficient to observe all the aromatic ^{1}H peaks involved in the reaction. Still, the spectral width can be increased if needed by means of interleaved acquisitions or peak folding.[35,36]

The electrochemical reduction of 9-chloroantracene proceeds through a reactive intermediate whose aromatic signals overlap with those of the reactant. Figure 2A presents real-time UF 2D COSY spectra recorded at different times during the electrochemical reduction of 9-chloroanthracene. These spectra show characteristic correlation peaks of the reactant and of two reaction products, as well as the peak from an intermediate which increases at the beginning of the reaction and disappears for t > 30 min.

The first step of this oxidation is the loss of one electron and the formation of a cationic radical. This intermediate is directly attacked by a water molecule to obtain a radical intermediate. This compound, which was not observed on the NMR spectra, would not persist in the solution because it is easily dimerized to form 10,10′-dihydroxy-9,9′,10,10′-tetrahydro-9,9′-bianthryl, **c**, which is the major reaction product. The second reaction product, anthraquinone, **d**, can be obtained by the oxidation of the radical intermediate. The formation of this minor product is highly dependent on the amount of water present in the solvent. This mechanism is coherent with those previously described in the literature.[37,38] Moreover, the structure of compounds **a**, **b**, and **d** was further confirmed by spiking the

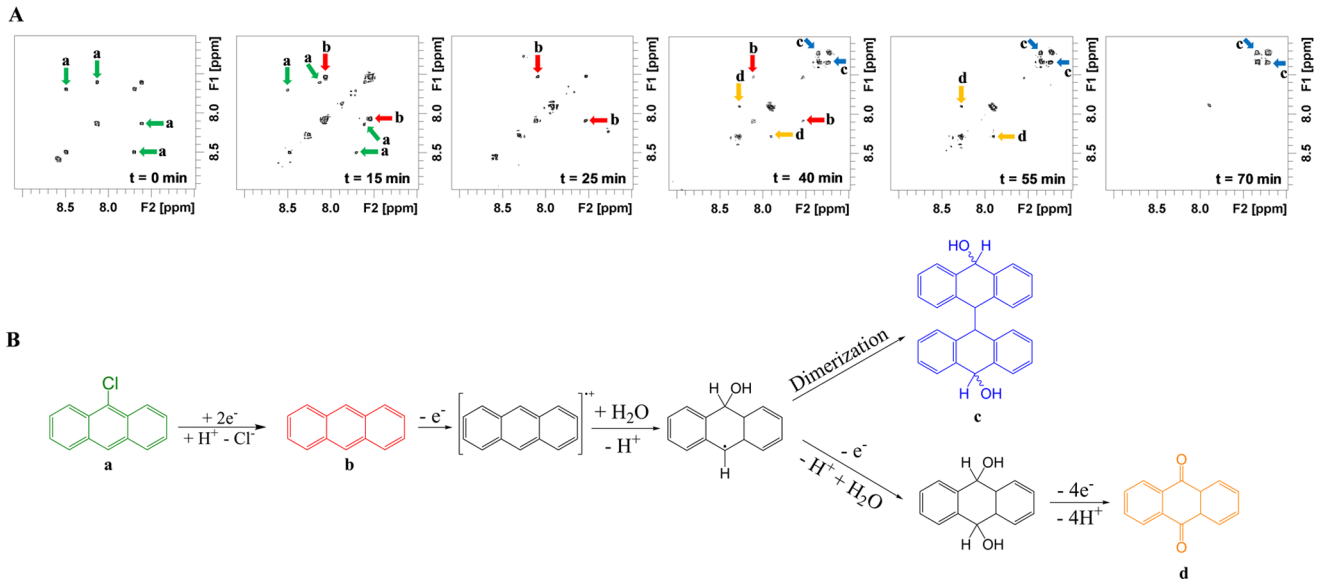

Figure 2. (A) Real-time 2D COSY NMR spectra recorded *in situ* during the electrochemical reduction of 9-chloroanthracene. The spectra were recorded in 3 min each, with the experimental setting of Figure 1. The correlation peaks of each compound are marked by arrows. Experimental details are given in the Supporting Information. (B) Redox behavior of 9-chloroanthracene based on these spectra.

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tube with commercial standards, while the structure of **d** was confirmed by additional mass spectrometry analysis.

Further insight into the reaction mechanism can be provided by plotting the 2D peak volumes as a function of time during the redox process (Figure 3). Even if 2D NMR is not directly

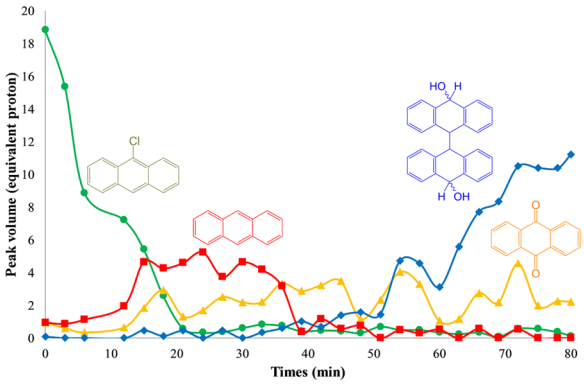

Figure 3. Evolution of the 2D peak volumes on COSY spectra recorded in real time during the electrochemical oxidation of 9-chloroanthracene, for the precursor (green circles), instable intermediate (red squares), and reaction products (blue rhombuses, orange triangles). For each compound, the volumes correspond to the average of the peaks marked by arrows in Figure 2, normalized to the number of equivalent protons.

quantitative, as 2D peak volumes depend on J-couplings and relaxation times,[39] all the compounds involved in this reaction have similar structures. Therefore, the evolution of 2D NMR peak volumes brings reliable qualitative information on the evolution of the concentration in the course of time. Future investigations could consider the use of appropriate analytical procedures to obtain accurate quantitative information, such as the use of calibration procedures or the correction of 2D peak volumes based on theoretical calculations.[39] Moreover, previous studies have demonstrated the high repeatability of UF experiments,[40,41] ensuring that the peak volume variations reflect the actual evolution of chemical species during the reaction. Here, this information is extremely interesting to observe the disappearance of the precursor and the instability of the electrochemical intermediate. Still, the interpretation of Figure 3 is further complicated by the formation of polymers in the NMR tube, which were not detected in NMR due to their low concentration and large line widths but which could be observed by a color change in the tube after the reaction.

In order to further confirm the potential of coupling *in situ* electrochemistry with ultrafast NMR, we also attempted to monitor the 80 min reaction by means of conventional 2D NMR experiments recorded under routine conditions, using conventional COSY experiments recorded every 10 min. However, the spectra did not lead to any observable correlation peak after the start of the reaction; only major diagonal peaks were observed with poor signal-to-noise ratio. While the quality of these spectra might be improved by relying on nonlinear processing strategies,[42,43] this result is explained by the intrinsic nature of conventional 2D NMR experiments: the lines of the $s(t_1,t_2)$ 2D matrix are recorded at different times, and the sample composition evolves during the acquisition, leading to incoherent chemical information between the different lines of the 2D matrix. On the contrary, in UF 2D NMR, the whole 2D matrix is acquired in a fraction of a second, and even if NS scans are averaged, the final data set is the sum of NS full 2D matrices. This highlights the relevance of ultrafast-based acquisition methods for the real-time study of samples whose composition evolves in the course of time. Still, it should be noted that UF experiments are more sensitive to concentration gradients and diffusion phenomena than their conventional counterpart. Such phenomena, which are likely to affect the EC-NMR experiment, may generate sensitivity losses and line shape modifications.[44]

CONCLUSIONS

This study demonstrates the feasibility and relevance of coupling *in situ* spectroelectrochemistry with ultrafast 2D spectroscopy to monitor real-time electrochemical reactions in the NMR tube. This powerful coupling is essential to circumvent peak overlaps and line-broadening effects arising from the introduction of the electrochemical device in the tube and to follow the evolution of instable reaction intermediates. The promising results obtained with this EC-UF 2D NMR approach open a number of promising perspectives for the structural elucidation of electrochemical reactions.

ASSOCIATED CONTENT

Supporting Information

Additional information as noted in the text. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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