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## RESEARCH ARTICLE

## Chemical-Reductant-Free Electrochemical Deuteration Reaction using Deuterium Oxide

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Dedicated to the 100th anniversary of the School of Chemistry and Chemical Engineering, Nanjing University

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Abstract: Herein, we report a protocol for electrochemical deuteration of a, β-unsaturated carbonyl compounds under catalyst- and externalreductant-free conditions with deuteration rates as high as 99% and yields up to 91% in 2 h. The use of graphite felt for both the cathode and the anode was key to ensuring chemoselectivity and high deuterium incorporation under neutral conditions without the need for an external reductant. This protocol has a number of advantages over previously reported deuteration reactions that use stoichiometric metallic reductants. Mechanistic experiments showed that O2 evolution at the anode not only eliminated the need for an external reductant but also regulated the pH of the reaction mixture, keeping it approximately neutral.

#### Introduction

Replacement of hydrogen atom with deuteron brings additional property and function to molecules. For example, the  $\alpha$ deuterated amino acid (Scheme 1a) was applied as label in protein for NMR,<sup>[1]</sup> HDX-MS,<sup>[2]</sup> X-ray crystallography,<sup>[3]</sup> and Raman scattering microscopy.<sup>[4]</sup> Also, *a*-deuterated amino acid has minimum derivation from its natural counterpart and could provide enhanced metabolism profile in pharmaceutical compounds.<sup>[5]</sup> Recently, a number of innovative deuteration protocols have been established with various deuterium reagents, such as D<sub>2</sub>,<sup>[6]</sup> d6-DMSO,<sup>[7]</sup> d6-ethanol,<sup>[8]</sup> d3-acetonitrile,<sup>[9]</sup> and d6benzene.  $^{\left[ 10\right] }$  As  $D_{2}O$  is the most readily available deuterium source, the development of deuteration methods using D<sub>2</sub>O directly would be highly desirable.

A number of arts of direct deuteration of organic molecules with H<sub>2</sub>O/D<sub>2</sub>O have been achieved. [11] In these cases, external reductants, for example Mg,<sup>[11b]</sup> Sml<sub>2</sub>,<sup>[11e]</sup> Zn,<sup>[11k]</sup> Mn,<sup>[11m]</sup> or 304 stainless steel,<sup>[11f]</sup> were required as electron donor (Scheme 1b). However, another essential function of these reductants was underrepresented. As water is the most stable storage of hydrogen species, utilizing the deuterium in D<sub>2</sub>O need large amount energy input. So, it is necessary to couple a highly energetic reductant to make the reaction happen, which will produce unwanted basic species and limit functional compatibility. As the nature uses photosynthesis to produce organic compounds with only water and carbon dioxide, it is possible and important to develop a protocol could fulfil the deuteration with D<sub>2</sub>O in the absence of any external reductants.

Organic electrosynthesis recently underwent a dramatic development and challenge transformations are achieved with novel mechanism.<sup>[12]</sup> In these transformations, cathodic hydrogen evolution is a highly efficient strategy to build molecules without external oxidant.<sup>[13]</sup> Inspired by these hydrogen evolution arts and recently advances in electrochemical reduction reactions,<sup>[14]</sup> we presumed that an electrochemical deuteration reaction using deuterium oxide could be achieved without additional reductant. In this approach, the oxygen could be released by an anodic oxidation of basic species to fulfil the task as the reductant alternative under neutral condition (Scheme 1c).

a) Example of deuterated compounds



Scheme 1. Deuterated compounds and deuteration with D<sub>2</sub>O as the deuterium source. EWG: electron withdrawing group.

#### **Results and Discussion**

On the onset of our study, compound 1a bearing a terminal epoxide was chosen as the model substrate (Table 1). With a series of optimizations, we could achieve the deuteration of 1a to saturated ester 2a in 71% yield and 95/97 ( $\alpha/\beta$ %) D incorporation

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ratio. The epoxide remained intact (entry 1). Next, several reported metal/D<sub>2</sub>O combinations were evaluated with 1a under respective optimized conditions. It was found by using Pd(OAc)<sub>2</sub> as catalyst and 2.0 equiv Mn as terminal reductant (entry 2), 2a was obtained in MeCN in 61% NMR yield and the deuterium incorporation ratio was 22% and 77% respectively. [11m] If DMF was used instead, Pd(OAc)<sub>2</sub>/Mn/D<sub>2</sub>O combination failed to give the desired transformation and the substrate 1a decomposed completely (entry 3). Other known protocols, such as NiCl<sub>2</sub>/Zn/D<sub>2</sub>O (entry 4) <sup>[11k]</sup> and Sml<sub>2</sub>/D<sub>2</sub>O (entry 5), <sup>[11e]</sup> decomposed 1a and the reaction mixture turn quite basic. A reaction using ZnCl<sub>2</sub>/Mg/D<sub>2</sub>O did not lead to the conversion. [11b] A SUS304 ball milling protocol was also evaluated and no conversion was observed (entry 7). [11f] We also evaluated the other electrode materials. It is unexpected that Pt cathode did not give conversion with other conditions remained unchanged (entry 8). When graphite rod was used both anode, the reaction only gave trance conversion (entry 9). Such unusual anode effect in a cathodic reduction was also observed recently by Waldvogel and Rodrigo in their work of electrochemical reduction of nitrones. <sup>[14g]</sup>.



Table 1. The comparison of deuteration protocols of substrate 1a			
Entry <sup>[a]</sup>	Conditions <sup>[a]</sup>	Yield <sup>[b]</sup>	D content (α/β%) <sup>[c]</sup>
1	GF(+)/GF(-), D <sub>2</sub> O (20 equiv), <i>n</i> Bu <sub>4</sub> NBF <sub>4</sub> (0.5 equiv), DMF (5 mL), 6 V, rt	71%	95/97
2	D <sub>2</sub> O (80 equiv), Pd(OAc) <sub>2</sub> (5 mol%), Mn (2.0 equiv), MeCN (2 mL), rt	52%	22/77
3	D <sub>2</sub> O (80 equiv), Pd(OAc) <sub>2</sub> (5 mol%), Mn (2.0 equiv), DMF (2 mL), rt	decomposed	
4	NiCl <sub>2</sub> 6H <sub>2</sub> O (10 mol%), Zn (2.0 equiv), Dioxane/D <sub>2</sub> O (3:1), 80 °C	decomposed	
5	SmI <sub>2,</sub> THF/D <sub>2</sub> O (2.0 equiv), rt	decomposed	
6	$ZnCl_2$ (1.5 equiv), Mg (1.5 equiv), $D_2O$ (2 mL)	no reaction	
7	SUS304 ball-milling	no reaction	
8	Entry 1 with GF(+)/Pt(-)	no reaction	
9	Entry 1 with graphite rod(+)/GF(-)	trace	

[a] conditions: **1a** (0.2 mmol), GF: graphite felt, DMF: N,N-dimethyl formamide, THF: tetrahydrofuran. [b] isolated yield. [c] content of 100% indicates one D atom on one carbon of **2a**.

With the optimized conditions in hand, we explored the substrate scope of the reaction by testing a number of unsaturated alkenes and alkynes (Scheme 2). Alkyl cinnamates **2b–2i** were obtained in good yields with high deuterium incorporation. We were pleased to find that phenyl **2j**, which is

labile under basic hydrolysis conditions, could be obtained in good yield. A variety of cinnamate-ester-containing natural products were also subjected to this electrochemical deuteration transformation. Specifically, L-menthol (2k), borneol (2l), diacetone-D-glucose (2m), pregnenolone (2n), estrone (2o), cholesterol (2p), diosgenin (2q), hydroxyl proline (2r), and stavudine derivatives (2s) were prepared in moderate to good yields and good deuterium incorporations. Cinnamates with electron-withdrawing or electron-donating groups on the phenyl rings gave good yields of the corresponding products (2t-2z) along with good deuterium ratios. Naphthalene and heterocyclic moieties were tolerated; good yields of desired compounds 2aa-**2ae** were obtained. To our delight, aliphatic  $\alpha,\beta$ -unsaturated compounds were also compatible with this protocol, furnishing deuterated esters 2af-2ah, respectively. Trisubstituted esters could be converted to desired products 2ai-2ak, respectively, in good yields with high deuterium incorporation. Unsaturated amides were also compatible substrates, affording 2al-2ap in good vields with good deuterium incorporation. Substrates with amine-protecting groups were examined. As expected, a Boc group in product 2aq was tolerated, and we were pleased to find that Cbz and alloc groups, which are readily removed under Pdcatalyzed hydrogenation conditions, remained intact during this electrochemical reaction (2ar and 2as). Deuterated amides bearing a variety of functional groups (2at-2ay) were produced in moderate to good yields with high deuterium incorporation. Because acids might undergo Kolbe decarboxylation under basic conditions, we thought it would be informative to test the behaviour of some unsaturated acids under these conditions, and we were pleased to find that deuterated acids were stable throughout the reaction, affording 2az-2bb. No decarboxylative side products were detected by GC-MS for any of the tested acids. Three alkyne substrates were tested and found to afford fully deuterated products 2bc -2be, respectively. A nitrile substrate 1bf was converted to 2bf with moderate yield and more than one deuterium was detected at  $\alpha$ -position.

Subsequently, we explored the synthetic applications of this electrochemical deuteration reaction (Scheme 3). A series of deuterium substituted amino acids were prepared (Scheme 3a), like  $\alpha$ -amino acid derivative **2bg**,  $\beta$ -amino acid derivative **2bh**, d2-DOPA precursor 2bi. A deuterated building block of CCR3 antagonist **2bj** was synthesized. <sup>[15]</sup> With  $\alpha$ , $\beta$ -unsaturated acid as starting material, a d2-isobuprofen 2bk was prepared for the first time. A single step deuteration protocol with D<sub>2</sub>O was applied to prepare 2bl, a pharmacore in pain treatment with metabolic stability enhanced by isotope effect, instead of original patent protocol requiring a D<sub>2</sub>O/EtOH/NaBD<sub>4</sub> deuteration sequence. <sup>[16]</sup> Scaled-up syntheses were carried out with  $\alpha$ -methyl cinnamic acid (1ba) as the substrate (Scheme 3b). Reactions in which 1ba was more concentrated than that in Scheme 2 worked well at 15 g scale, giving carboxylic acid 2ba in 60% yield and deuterium rate was almost identical to that obtained in 0.2 mmol scale. Subsequently, 2ba was converted to borane 3 (70%), <sup>[17]</sup> alkyne 4 (65%), <sup>[18]</sup> azide 5 (65%), <sup>[19]</sup> alkyl benzothiazole 6 (47%), <sup>[20]</sup> and alkyl caffeine 7 (35%). [21] In all these transformations, the loss of deuterium was not observed.

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**Scheme 3.** Synthetic applications of the electrochemical deuteration protocol. BI: benziodoxolone, B<sub>2</sub>pin<sub>2</sub>: bis(pinacolate)diboron, DMSO: dimethylsulfoxide.

Finally, we carried out some mechanistic experiments. First, cathodic cyclic voltammetry (CV) of a mixture of D<sub>2</sub>O and ethyl cinnamate (1c) (Scheme 4a) revealed that with a carbon cathode, D<sub>2</sub>O was inert until -2.5 V (vs saturated calomel electrode, SCE), whereas a peak for reduction of 1c was observed at -2.1 V (vs SCE), suggesting that the reaction is initiated by electron transfer to the substrate to yield an anionic radical, rather than by reduction of a proton species, such as D<sup>+</sup>. A square wave voltammetry (SWV) experiment of 1c showed two separated peaks, supporting an ECEC pathway. [14f] This possibility was confirmed by the fact the no trace of hydrogen was detected when H<sub>2</sub>O was subjected to a 6 V cell potential in the absence of 1c (see SI, section 7). In addition, because epoxide, a base-labile group remained intact during the reaction (Table 1, entry 1), we measured the pH of the reaction mixture, which did not vary significantly from neutral (Scheme 4b). Lastly, we examined the oxygen species generated in this electrochemical reaction using <sup>18</sup>O-labelled water. By subjecting the gaseous effluent of a reaction between 1c and H<sub>2</sub><sup>18</sup>O to a downstream reaction with PPh<sub>3</sub> as a trapping reagent and Et<sub>3</sub>B as a catalyst, we could capture <sup>18</sup>O<sub>2</sub> as triphenylphosphine oxide (Scheme 4c). This experiment revealed that the amount of captured <sup>18</sup>O was about 77% of the amount of 2c generated in the reaction; in contrast, if substrate 1c was omitted from this electrolysis experiment, no <sup>18</sup>O species were detected.







On the basis of these findings, a plausible pathway was proposed in Scheme 5, for example, with 1c as substrate. First, electron transfer from the cathode converts 1c to anionic radical A, which immediately undergoes deuteration with D<sub>2</sub>O to give neutral radical B. A second cathodic reduction converts B to anion C, and a second deuteration generates final product 2c. Because of the large area and porous structure of the graphite felt cathode, electron transfer and deuteration are highly concerted, and therefore the lifetimes of intermediates A, B and C are so short that side reactions, for example dimerization, do not occur. In solution, the OD anions is in steady state and undergoes oxidation to release oxygen and D<sub>2</sub>O at anode (path 1). Alternatively, the D<sub>2</sub>O might be oxidized directly at anode, giving oxygen, protonic species and neutralized the basic species forming at cathode (path 2), a process proposed in the production of adiponitrile in divided cell. The overall effect on cathode and anode regulates the pH not varying significantly.



Scheme 5. Plausible pathway for electrochemical deuteration.

#### Conclusion

In summary, we have developed a protocol for mild electrochemical deuteration reactions on graphite felt electrodes. The reaction used  $D_2O$  as the deuterium source and did not require either a transition-metal catalyst or a stoichiometric reductant. At cathode, there was a selective reduction of substrate, other than a hydrogen evolution process; At anode, the oxygen evolution could not only avoid using of reactive reductant but also consume the  $OD^-$  anion and regulate the pH level. Moderate to excellent yields and good to excellent deuterium incorporation

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were achieved with this protocol. This deuteration reaction could be scaled up to 15 g with good reproducibility. A number of deuterated pharmaceutical compounds were prepared by means of this protocol, and deuterated acid could serve as d2-synthon to prepare a variety of compounds with no loss of deuterium.

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**Keywords:** electrochemistry • deuteration • reductant free • oxygen evolution • graphite felt

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## **RESEARCH ARTICLE**

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The first catalyst-free and chemical-reductant-free deuteration of alkene and alkynes is achieved with electrochemical approach with graphite felt electrodes and deuterated water in undivided cell under neutral conditions. Up to 99% D incorporation and 91% yield can be obtained at neutral condition and compatible with electron-rich alkene, heterocycles, epoxide, and protecting groups. A series of d2- or d4 pharmaceutical compounds are prepared with this protocol.