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Efficient H-D Exchange of Aromatic Compounds in Near-Critical D_2O Catalysed by a Polymer-Supported Sulphonic Acid

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Abstract

Hydrogen atom exchange of aromatic compounds in neutral near-critical D_2O has been improved by using a polymer-supported sulphonic acid catalyst. Phenol, aniline, quinoline, and substituted aromatic hydrocarbons are selectively ring-perdeuterated in high yields with insignificant by-product formation at 325 °C for 24 h in D_2O/Deloxan.® © 1999 Elsevier Science Ltd. All rights reserved.

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Acid catalyzed H-D exchange of aromatic and heteroaromatic substrates has been studied since the 1960s.[1] The most commonly employed catalysts are concentrated mineral acids and highly reactive Lewis acids, such as organoaluminium halides or fluorinated carboxylic acids. However, all those reagents suffer inconveniences and H-D exchange is still an active field of research. For example, current research on H-D/T exchange in aromatic compounds involves the use of polymer-supported sulphonic acids as catalysts[2] in D_2O in near-critical or supercritical conditions. D_2O at high temperature and pressures has demonstrated its potential for H-D exchange in organic compounds, displaying different reactivity and selectivity depending on the pH.

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Neutral D_2O induces only partial deuteration of activated aromatic compounds towards electrophilic substitition (*eg. ortho-para* deuteration of anilines and phenols),[3,4] being not efficient in the promotion of H-D exchange in weakly activated compounds like aromatic hydrocarbons. The addition of acid[5,6] (*eg.* DCl 2 %) or base[7,8] (*eg.* NaOD 2 %) catalyses the H-D exchange even in hydrocarbons and deactivated compounds like benzoic acid, producing the corresponding perdeuterated compounds. However, the high temperature-dilute acid procedure (HTDA) requires an acid resistant vessel[9] and the alkaline D_2O procedure requires temperatures of 380-430 °C. The use of a polymer-supported acid catalyst for H-D exchange has many advantages, but so far only partial deuteration of activated aromatic compounds has been achieved.[2]

In this communication we report the efficient and selective ring-perdeuteration of a range of aromatic compounds using a polymer-supported sulphonic acid, Deloxan®, as a catalyst in near-critical D_2O. Several aromatic compounds (Table 1) were reacted in D_2O/Deloxan® at 325 °C for 24 h.[1]

Aniline, phenol, quinoline and aromatic hydrocarbons were perlabelled on the aromatic ring under the reaction conditions. In a single reaction, D-incorporations > 90 % were achieved with no significant by-product formation (GC > 90 %) and excellent yields. The reaction is performed in a neutral medium with a non-deuterated polymeric catalyst which is easy to recover. Furthermore, no corrosion of the vessel was observed. Therefore, it is a procedure suitable for the preparation of aromatic substrates on a preparative scale.

D_2O/Deloxan® does not induce H-D exchange in benzylic positions, providing different selectivity from HTDA[5,6] or alkaline D_2O[7,8] procedures. Thus, D-incorporation in the benzylic position of ethylbenzene was less than 10 %, allowing the preparation of ethylbenzene-d_5 with selective perdeuteration of the aromatic ring. The procedure is not efficient for labelling strongly deactivated aromatic compounds; *p*-toluic acid and acetophenone gave only 10 % D-exchange on aromatic ring. Moreover, acetophenone was

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[1] In a general procedure, an aromatic compound (0.4 g; 13 %w), D_2O (3.0 ml) and Deloxan® (0.4 g) were heated in a high pressure and temperature stainless steel vessel (5.2 ml, internal volume) (see Ref [10] for a detailed description of the system). The reaction was performed under Ar (10 bar at 20 °C) and D_2O was degassed before use. Products were isolated after extraction (CH_2Cl_2 or diethyl ether) and analyzed by GC, NMR and MS. Deuterium content was determined by mass spectrometry at low ionizing voltage (15-20 e.v.). All samples that contained NH_2 and OH groups were back-exchanged in H_2O before analysis.

labelled on the CH_3 position (90 %) rather than the ring, exchange that also takes place in neutral D_2O at 250 °C.[11]

D_2O/Deloxan® is a milder reaction system than HTDA or alkaline D_2O. Thus, aniline was perdeuterated in D_2O/Deloxan® whilst it decomposed to phenol in HTDA due to protonation of amino group. D_2O/Deloxan® requires lower temperatures than alkaline D_2O, limiting the formation of oxidation products. In fact, the only substrate that underwent slight oxidation (< 5 %) under our reaction conditions was ethylbenzene. Furthermore, the thermal stability of Deloxan® in near-critical D_2O has improved the procedure carried out originally with other polysulphonic acids (e.g. Nafion) of limited thermostability (T < 200 °C).

Table 1. H-D exchange of aromatic compounds in D_2O/Deloxan® at 325 °C for 24 h[a]

Entry	Substrate	Product[c,d,e]	% H-D exchange[f]
1	phenol	phenol-d_7	90
2	phenol (no cat.)[b]	phenol-d_3	*o,p*; 89; *m*: 16
3	aniline	aniline-d_7	81
4	aniline (250 °C, 2h, no cat.)	aniline-d_3	*o,p*: 92; *m*: 1
5	quinoline	quinoline-d_7	76
6	ethylbenzene	ethylbenzene-d_5	*ring*: 95, *Me*: 9
7	ethylbenzene (no cat.)	ethylbenzene-d_5	*ring*: 22, *Me*: 1
8	naphthalene	naphthalene-d_8	91
9	anthracene	anthracene-d_{10}	94
10	phenanthrene	phenanthrene-d_{10}	95
11	pyrene	pyrene-d_{10}	94
12	fluorene	fluorene-d_{10}	92
13	acenaphthene	acenaphthene-d_{10}	86
14	*4*-toluic acid	*4*-toluic acid-d_4	*ring*: 58, *Me*: 8
15	acetophenone	acetophenone-d_3	*ring*: 10, *Me*: 90

[a]Reactions performed in a high T/p batch reactor. [b]The same results were obtained in the reaction at 250 °C in: *i)* D_2O/Deloxan® for 24 h or *ii)* D_2O for 2h. [c]Yields > 90%. [d]GC purity > 90 %. [e]Product recovery > 90 %..[f]Determined by mass spectrometry.

Finally, control experiments were performed to assess the effect of the catalyst and temperature. The reaction of phenol at 325 °C with no catalyst, or at 250 °C with catalyst, for 24 h promoted the H-exchange in *o,p*-positions only, with insignificant exchange of *m*-positions. Ethylbenzene similarly underwent insignificant D-H exchange after 24 h at 325 °C without catalyst.

As a corollary, phenol-d_3, aniline-d_3 and quinoline-d_1 (*o,p*-D-exchange >90 %) were prepared in our batch reactor in neutral D_2O at 250 °C in only 2 h. This contrasts with previous reports[3] suggesting slower equilibration with phenol and aniline requiring 25 h to achieve partial D-incorporation in *o,p*-positions (< 55 %). This procedure can be also applicable to the selective tritiation of organic compounds.

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