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PREPARATIVE SUPERCRITICAL DEUTERIUM EXCHANGE IN ARENES AND HETEROARENES

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Abstract: Deuterated homo– and heterocyclic aromatic substrates bearing various functionalities were prepared by isotope exchange in supercritical deuterium oxide, with little or no formation of byproducts. Equilibration was attained rapidly (1 – 24 hrs), and deuterium exchange extended to alpha positions of alkyl homologs. Nitro– and haloarenes, thioethers, telluroethers, and some heterocyclic substrates were unstable. Copyright © 1996 Elsevier Science Ltd

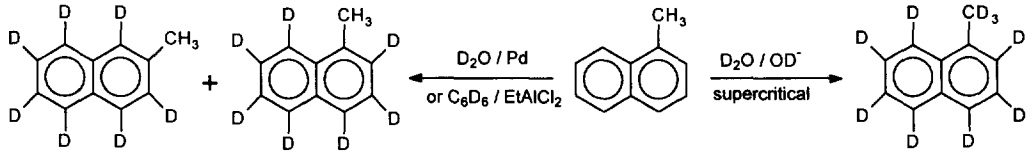
Access to deuterated organic compounds has been facilitated by the option of introducing labels post–synthetically, by isotope exchange. Common deuterium labeling methods include exchange in the presence weak[1] or strong[2,3] acids, bases,[4] organometallic reagents,[5] or noble metal catalysts under heterogeneous[6] or homogeneous[7] conditions. Limitations of these methods include skeletal rearrangements, incompatibility with specific functionalities, expensive or relatively inaccessible reagents, and sluggish or incomplete isotope exchange.[8] Supercritical deuterium exchange (SDE), which proceeds in deuterium oxide above its triple point (374°, 221 bar), offers a new, convenient approach to various deuterated organic compounds on a preparative scale. SDE has the distinct advantages of short exchange times, relatively low cost, and extended access to labeled arenes.

Supercritical water has been studied extensively as medium for chemical waste treatment through hydrolysis, oxidation, and other chemical transformations.[9–14] Few examples exist for the use of supercritical water as a reaction medium for preparative organic chemistry, even though its unique properties have long been recognized.[15–17] Protium–deuterium exchange in supercritical D_2O recently has been observed during experiments conducted to determine relative acidities of hydrocarbons in this medium, and an ionic mechanism was postulated.[18] On the other hand, products of isoquinoline[19] and 4-chlorophenol[20] in supercitical water are consistent with those expected from radical mechanisms.

During experiments, 30 mL Hastelloy–C reactors were charged with substrates (typically 1.0 g), deuterium oxide (10 g), and sodium deuteroxide solution (40%, 0.05 g), purged with nitrogen, then placed in a preheated furnace. **CAUTION:** High pressures and temperatures are encountered. After heating, the furnace was disconnected remotely and allowed to cool. Samples were diluted or extracted with dichloromethane (DCM) and removed for workup, which was accomplished by distillation for liquids, or flash chromatography (silica gel – DCM), followed by sublimation or short path distillation for solids. This process was repeated

until the desired isotopic purities (>95%) were reached. Heating and cooling times (approx. 20 min) are not included in reported reaction times. Isotopic purities and byproducts were characterized by GC–MS, by comparison between observed and calculated isotope clusters, and by ^{1}H NMR, as appropriate. Alkyl phenanthrenes employed in this study were prepared according to the literature.[21] Products not attributable to isotope exchange were not isolated, but tentatively identified by GC–MS. SDE was not influenced by addition of sulfur compounds or repeated use of autoclaves; nevertheless, the possibility of catalytic effects of metal surfaces cannot be entirely discounted at this time.

SDE was shown to be well suited for the preparation of non–functionalized and functionalized aromatic substrates on a preparative scale, as indicated by the tabulated results (compounds 1 – 16). Substrates bearing methyl groups were perdeuterated, in contrast to the High Temperature Dilute Acid (HTDA) method of Werstiuk,[1] which exchanges only aromatic protons. As a result of experimental constraints, minimum reaction times required to attain equilibria could not be determined accurately, and will be subject of future work employing a flow reactor. In all cases examined in this work, SDE rates were considerably faster (e.g., two orders of magnitude) than rates observed for HTDA deuterations. SDE is particularly well suited for labeling alkylated polyaromatic hydrocarbons. SDE of 1-methylnaphthalene **3**, for example, produced 1-methylnaphthalene-d_{10} **4**, while HTDA and ethyl aluminum dichloride catalyzed exchanges produced mixtures of methylnaphthalene-d_7 isomers **1** and **2** (Scheme 1). In the presence of air, formation of oxidation products was observed during SDE. In case of 1-methylnaphthalene, reaction residues were analyzed by direct insertion probe MS, and a dimethylbinaphthyl tentatively identified as oxidation product.



1 **2** **3** **4**

Scheme 1. *Comparison of products obtained with isotopic exchange using palladium / D_2O and ethylalumium dichloride / benzene-d_6 with that obtained by SDE.*

Application of SDE to functionalized and heterocyclic substrates is limited by the harsh conditions required to attain rapid isotopic equilibration, as well as substrate pyrolysis and other chemical side reactions. In addition to the reported instability of ethers and aliphatic amines,[1] alcohols, ketals, acetals, and nitriles,[13,19] in near–critical or supercritical water, benzylic carboxylates, thioethers and telluroethers, aryl azo compounds, halogenated arenes, as well as some heterocyclic compounds appear to be too unstable to be considered as substrates for SDE (compounds 17 - 24). Some of the compounds, however, were sufficiently stable to permit partial deuteration. For instance, quinoxalines underwent considerable decomposition, which limited isotopic purities attainable as decomposition became competitive with deuteration. Nevertheless, SDE appeared to offer the only alternative to product synthesis from labeled precursors. Complete deuteration of aliphatic side chains is limited; e.g., n-butylbenzene and isobutylbenzene were deuterated in the alpha position, and the latter

Table1. Results of Supercritical Deuterium Exchange Experiments.

#	Compound	Cond's	Products (% isolated yields, % deuteration)
1	1,3,5-trimethylbenzene	c	1,3,5-trimethylbenzene-d_{12} (76, >96)
2	1-methylnaphthalene	c	1-methylnaphthalene-d_{10} (75, >97)
3	1,2-dimethylnaphthalene	c	1,2-dimethylnaphthalene-d_{12} (74, >97)
4	phenanthrene	c	phenanthrene-d_{10} (82, >98)
5	3-methylphenanthrene	b	3-methylphenanthrene-d_{12} (85, >97)
6	3,9-dimethylphenanthrene	b	3,9-dimethylphenanthrene-d_{14} (83, >96)
7	benzo[f]quinoline	c	benzo[f]quinoline-d_9 (82, >97)
8	phenanthridine	c	phenanthridine-d_9 (64, >85)
9	quinoxaline	a	quinoxaline-d_6 (42, >85)
10	2,3-dimethylquinoxaline	a	2,3-dimethylquinoxaline-d_{10} (55, >85)
11	dibenzothiophene	a	dibenzothiophene-d_8 (80, >97)
12	phenothiazine	b	phenothiazine-d_8 (71, >97)
13	isobutylbenzenebutylbenz	c	isobutylbenzene-d_8 (76, aromatic: >97, C_{prim}: 0, C_{sec}: 49, C_{tert}: 95)
14	n-butylbenzene	c	n-butylbenzene-d_7 (60, >97)
15	acetophenone	b	acetophenone-d_8 (73, >97)
16	aniline	b	aniline-d_7 (78, >97)
Substrates unsuitable for supercritical deuteration, main product assignments by GC–MS			
17	1,2-dichlorobenzene*†	b	dibenzofuran, diphenyl ether, 2-hydroxybiphenyl, dibenzo-p-dioxin
18	phenyl benzyl sulfide†	b	diphenylmethane, bibenzyl
19	diphenyl ditelluride†	a	biphenyl, terphenyl (all isomers)
20	benzothiazole†	a	aniline
21	phenazine	a	(extensive tarring)
22	azobenzene†	b	(mixture containing homo– and heterocyclic aromatics)
23	1-fluoronaphthalene†	c	naphthalene, 1-hydroxynaphthalene, hydroxyperylene
24	phenylacetic acid†	a	toluene, bibenzyl, 4,4'-dimethylbiphenyl

* threefold molar excess of sodium carbonate added instead of sodium hydroxide
† reaction medium, H_2O instead of D_2O
a 380 – 385°, water density 0.3 g/cm^3, 1 hr reaction time
b 400 – 410°, water density 0.3 g/cm^3, 8 – 12 hrs reaction time
c 420 – 430°, water density 0.3 g/cm^3, 24 hrs reaction time

partially in the methylene beta position. Acidic reaction conditions were not explored in detail, but were observed to lead to extensive skeletal rearrangements (e.g., isomerization of isobutylbenzene) and rapid deterioration of the pressure cells employed in this study. The full scope of this preparative approach to perdeuterated aromatic and heteroaromatic standards remains to be explored.

REFERENCES

1. Werstiuk, N. H.; Kadai. T. *Can. J. Chem.* **1974**, *52*, 2169-2171.
2. Bean, G. P.; Johnson, C. D.; Katritzky, A. R.; Ridgewell, B. J.; White, A. M. *J. Chem. Soc. (B)* **1976**, 1219-1220.
3. Bean, G. P.; Katritzky, A. R.; Marzec, A. *Bull. Acad. Pol. Sci.* **1968**, *16(9)*, 453-457.
4. Shatenshtein, A. I. *Adv. Phys. Org. Chem.* **1963**, *72*, 154-201.
5. Long, M. A.; Garnett, J. L.; Vinig, R. F. W.; Mole, T. *J. Am. Chem. Soc.* **1972**, *94*, 8632-8633.
6. Hsiao, C. Y., Ottoway, C. A.; Wetlaufer, D. B. *Lipids* **1979**, *9(11)*, 913-915.
7. Garnett, J. L.; Hodges, R. J. *J. Am. Chem. Soc.* **1967**, *87*, 4546-4547.
8. Buncel, E.; Jones, J. R. *Isotopes in the Physical and Biomedical Sciences. Volume 1. Labelled Compounds (Part A)*, Elsvier Science Publisheing Company Inc.: NY, NY, 1987.
9. Johnson, B. J.; Hannah, R. E.; Cunningham, V. L.; Daggy, B. P.; Sturm, F. S.; Kelly, R. M. *Biotech.* **1988**, *6*, 1423-1427.
10. Reardon, P.; Metts, S.; Crittendon, C.; Daugherty, P.; Parsons, E. J. *Organometallics* **1995**, *14*, 3810-3816.
11. Siskin, M.; Ferrughelli, D. T.; Katritzky, A. R.; Rabai, J. *Energy Fuels*, **1995**, *9(2)*, 311-343.
12. Townsend, S. H.; Abraham, M. A.; Huppert, G. L.; Klein, M. T.; Paspek, S. C. *Ind. Eng. Chem. Res.* **1988**, *27*, 143-149.
13. Kuhlmann, B.; Arnett, E. M.; Siskin, M. *J. Org. Chem.* **1994**, *59*, 3098-3101.
14. Crittendon, R. C.; Parsons, E. J. *Organometallics* **1994**, *13*, 2587-2591.
15. Shaw, R. W.; Brill, T. B.; Clifford, A. A.; Eckert, C. A.; Franck, E. U. *Chem. Eng. News* **1981**, *12*, 26-39.
16. Jessop, P. G.; Ikariya, T.; Noyori, R. *Science* **1995**, *269*, 1065-1069.
17. Jerome, K. S.; Parsons, E. J. *Organometallics* **1993**, *12(8)*, 2991-2993.
18. Yao, J.; Evilia, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 11229-11233.
19. Houser, T. J.; Tiffani, D. M.; Li, Z.; McCarville, M. E.; Houghton, M. E. *Fuel* **1986**, *65(6)*, 827-832.
20. Yang, H. H.; Eckert, C. A. *Ind.Eng.Chem.Res.* **1988**, *27*, 2009-2014.
21. Sargent, M. V.; Smith, D. O. N. *J. Chem. Soc. (C)* **1970**, 329-331.

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