Catalytic Deuteration of Aromatic and Heteroaromatic Compounds

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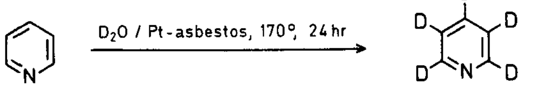
Heterogeneous deuterium-exchange reactions under neutral conditions in the liquid phase have hitherto been carried out by allowing the exchange to take place in a mixture of deuterium oxide, powdered catalyst, and the material to be deuterated[1-8]. In the most cases, these exchange reactions were not performed for preparative purposes and data concerning the degree and/or the specific site of deuteration were not generally given.

We report here a simple and efficient method for the deuteration of aromatic and heteroaromatic compounds. The procedure consists of heating a mixture of deuterium oxide, the material to be deuterated, and platinized short-fibre asbestos in a sealed tube or pressure vessel at 130–250°. A similar platinum-on-asbestos catalyst has previously been used in the vapor-phase deuteration of pyridine[9].



Some of the deuterated compounds dealt with in this study are commercially available (completely or partially deuterated), for example perdeuterophenanthrene (deuterium content >98%) and phthalazine-d_4[10]. Others, such as quinoxaline-d_6, have been individually prepared[11]. There are relatively few reports on the preparation of perdeuterated N-heteroarenes.

Table 1. Reaction Conditions and Yields of the Catalytic Deuteration of Arenes and N-Heteroarenes

Substrate	Reaction Conditions	Yield %	Total Deuterium Content (%) after: 1st cycle	2nd cycle	3rd cycle	By-products
Pyridine	170°, 24 hr	>90	>80	92.5		
Quinoline	200°, 72 hr	>80	>80	95.5		2-Hydroxyquinoline-*d*
Isoquinoline	200°, 72 hr	< 80	95.3			
Cinnoline	170°, 24 hr	>90	17.2			
	220°, 88 hr	>80	>50	88.3		
Phthalazine	170°, 90 hr	>80	64.6			
	220°, 72 hr	<45	80.4			
Quinazoline	130°, 5 hr	>80	9.0			
	150°, 12 hr	<40	38.7			2-Aminobenzaldehyde-*d*
Quinoxaline	170°, 72 hr	>85	>80	>95	98.4	2-Hydroxyquinoxaline-*d*
1,5-Naphthyridine	170°, 24 hr	>90	>80	95.7		
1,6-Naphthyridine	170°, 72 hr	>90	>80	92.4		
Acridine	200°, 72 hr	>50	>80	93.8		
Phenazine	200°, 72 hr	>65	>80	95.6		
Aniline	170°, 24 hr	>90	>80	>95[a]		
Phenanthrene	250°, 72 hr	>90	70.1			

[a] Nuclear deuteration, estimated by ^{1}H-N.M.R.

Table 2. Deuterium Content and Deuterium Distribution in the Reaction Products and Sites of Deuteration

Substrate	Total Deuterium Content (%)	Deuterium Distribution (%) in the Reaction Product d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8	d_9	d_{10}	Main *d*-products	Order of positions in the molecule which were preferably exchanged
Pyridine	92.5			1.0	9.2	16.6	73.2						D_5	(2, 6) (3, 5) (4)
Quinoline	95.5						9.4	8.4	82.2				D_7	(2) (8) (3) (4–7)
Isoquinoline	95.3					1.2	9.6	17.0	72.2				D_7	(1, 3) (4–8)
Cinnoline	17.2	9.2	78.7	12.1									H_5D	(3)
	88.3					9.9	55.6	34.5					HD_5	(3) (4, 6, 7, 8)
Phthalazine	64.6		0.1	4.8	20.8	58.7	12.9	2.7					H_2D_4	(1, 4) (6, 7)
	80.4			1.0	3.6	30.5	42.0	22.9					HD_5	(1, 4) (6, 7) (5 or 8)
Quinazoline	9.0	55.0	36.7	7.8	0.5								H_5D	(2)
	38.7	4.5	4.8	54.5	27.3	8.0	0.9						H_4D_2	(2, 4)
Quinoxaline	98.4					0.6	9.3	90.1					D_6	(2, 3) (6, 7) (5, 8)
1,5-Naphthyridine	95.7					11.6	2.4	86.0					D_6	(3, 7) (4, 8) (2, 6)
1,6-Naphthyridine	92.4					9.9	4.4	85.7					D_6	
Acridine	93.8						3.4	1.9	10.6	15.5	68.6		D_9	(3, 7) (2, 8) (1, 9) (5) (4, 6)
Phenazine	95.6						0.4	14.6	5.2	79.8			D_8	(2, 3, 7, 8) (1, 4, 6, 9)
Aniline	>95												D_5	(2, 6) (4) (3, 5)
Phenantherene	70.1		0.4	0.9	2.2	4.6	5.5	12.4	29.8	36.3	6.7	1.2	H_2D_8	(1, 2, 3, 6, 7, 8) (9, 10)

The percentages in the product mixture and the structure of the deuteration products were determined by mass spectrometry (AEI-MS 902) (except for aniline) and ^{1}H-N.M.R. (Varian HA-100). In the case of phthalazine and cinnoline, the order of preferential deuteration of the individual positions was determined by ^{1}H-N.M.R. using the Eu(FOD)$_3$ shift reagent[12].

In general and in agreement with earlier reports[3,6,7], the H-atoms in the positions ortho to the heretoatom are most readily exchanged. However, in the case of 1,5-naphthyridine the H-atom meta to the nearest N-atom was preferentially exchanged. The structures of the deuteration products of 1,6-naphthyridine could not be analyzed because of the small quantity of deuterated product available. In a number of cases, the formation of by-products was observed; some of these by-products were identified (Table 1).

Preparation of the Catalyst:

A mixture of short-fibre asbestos (9 g) and a solution of hexachloroplatinum(VI) acid ($H_2PtCl_6 \cdot 6H_2O$; 1 g) in ethanol (50 ml) was ignited while stirring[13]. In order to obtain a sufficiently homogeneous catalyst, the combustion was repeated using another portion of pure ethanol (50 ml). The catalyst was then dried exhaustively in an oven at 170° (12 hr). The platinum content in the catalyst was ~4%.

Deuteration Procedure:

The above catalyst (800 mg), the material to be deuterated (250 mg), and deuterium oxide (99.75%; 3 ml) were mixed in a pressure glass tube or in some other type of pressure reaction vessel under a nitrogen atmosphere. The tube was sealed (the vessel closed, respectively) and heated at the temperature and for the time given in Table 1. The reaction mixture was extracted with ether or chloroform, the extract dried with sodium sulfate, and evaporated. To achieve a more complete deuteration, the process was in some cases repeated once or several times. The deuteration products were purified by chromatography on alumina using benzene/pyridine (9:1) as eluent. The chemical (not the isotopic) purity of the diazanaphthalenes, quinolines, acridine, and phenazine was checked by T.L.C. on silica gel using benzene/pyridine (9:1) as eluent and U.V. light or 20% silver nitrate solution for visualization.

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