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# The High Temperature and Dilute Acid (HTDA) Procedure as a General Method of Replacing Aromatic Hydrogen by Deuterium. II<sup>1-3</sup>

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NICK H. WERSTIUK and TONY KADAI. Can. J. Chem. 52, 2169 (1974). The preparation of aniline- $d_5$ , phenol- $d_5$ , and benzoic acid- $d_5$  utilizing the conditions of high temperature and dilute acid (HTDA) is described.

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On décrit la préparation de l'aniline- $d_5$ , du phénol- $d_5$  et de l'acide benzoique- $d_5$  utilisant les conditions de haute température et d'acide dilué déjà proposées. [Traduit par le journal]

As a continuation of our studies on the development of the high temperature  $(200-300^{\circ})$  and dilute acid procedure (1, 2) as a general method for the deuteration and tritiation of aromatic compounds, we have studied H–D exchange in aniline (1), phenol (2), and benzoic acid (3). The results are listed in Tables 1, 2 and 3, respectively.



Entry l of Table l shows that under the HTDA conditions (24 h), at  $175^{\circ}$  no appreciable exchange occurs at the *meta* positions in aniline. When the temperature is increased to  $300^{\circ}$  (entry 2) aniline is converted into phenol and ammonium chloride, likely via nucleophilic aromatic substitution involving the anilinium salt. Even at  $275^{\circ}$  after 24 h (entry 3) some conversion to phenol (31%) occurs. As described in entries 4 and 6, at  $250^{\circ}$  the exchange at the *ortho* and *para* positions is rapid<sup>4</sup> followed by slow *meta* exchange with complete equilibration (95% exchange) resulting in *one* cycle after 54 h.

The HTDA procedure thus also provides a unique, likely quantitative method for the de-

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amination of aromatic amines and the conversion of aromatic oxy and thio ethers to phenols.

Thus by an appropriate choice of temperature and reaction time aniline- $d_5$  or  $-d_7^4$  and phenol- $d_5$ or  $-d_6$  can be prepared in one step directly from aniline. Thus tritiated aniline and phenol can also be prepared using the HTDA procedure. Certainly, deuterated and tritiated substituted anilines and phenols can also now be prepared via the HTDA conditions. The procedure also provides a unique route to <sup>18</sup>O labelled phenols. In a typical large-scale preparation (entries 7 and 8, Table 1) freshly recrystallized aniline hydrochloride (20 g, 0.15 mol) was stirred with  $D_2O$ (50 ml, 2.5 mol) at room temperature for several hours and the  $D_2O$  was distilled off under vacuum and recovered for use in the first cycle of subsequent exchanges. The aniline hydrochloride was dissolved in  $D_2O$  (60 ml, 2.6 mol) and the solution was sealed in a glass tube after being degassed three times via freeze-pump-thaw cycles. The tube was heated at 250° in a 21 Parr pressure apparatus containing H<sub>2</sub>O to equalize the internal pressure. After 48 h the  $D_2O$  and traces of phenol were distilled off under vacuum to yield a yellowish solid (16.4 g, 82%). The solid was heated at  $250^{\circ}$  with a fresh batch of  $D_2O$ 

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<sup>&</sup>lt;sup>3</sup>Publication delayed at authors request.

<sup>&</sup>lt;sup>4</sup>Exchange occurs readily at the *ortho* and *para* positions when aniline hydrochloride is heated at 100° in  $D_2O$  (3). Aniline- $d_7$  has been prepared in 70% yield by nitration of benzene- $d_6$  followed by reduction of the nitrobenzene- $d_5$ (4) or by treating aniline with activated platinum in  $D_2O$ at 140° for 3 days (5).

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### TABLE 1. H-D exchange in aniline hydrochloride in D<sub>2</sub>O

Entry*	Conditions		D/11	% exchange Position			% yield		
	Temp. (°C)	Time (h)	D/molecule 1†	in aromatic ring	0	m	р	1	2
1	175	24	2.85	57	1.90	0.0	0.95	86	
2	300	48	-	_				0	<u>_¶</u>
3‡	275	24	_					44	31
4	250	12	3.60	72	1.85	0.80	0.95	74	1
5	250	35	4.60	92	1.90	1.75	0.95	72	3
6	250	54	4.75	95	1.90	1.90	0.95	69	4
7§	250	48	4.15	83	1.75	1.55	0.85	82	<b>—</b> ¶
8∦	250	50	4.85	97	1.95	1.95	0.95	72	-Ÿ

\*Typically, a solution of recrystallized substrate in water was degassed three times and heated in a sealed tube. †Determined by n.m.r. integral analysis by using the back-exchanged amino group as an internal standard. ‡Run in  $H_2O$ . §The amino protons were first exchanged by washing with  $D_2O$  at room temperature. |The crude deuterated 1 from entry 7 was used in this run. ¶Not determined.

TABLE 2. H-D exchange in phenol in 4% (v/v) concentrated HCl-D<sub>2</sub>O

Entry	Conditions		D/malawia*	% exchange	Position <sup>†</sup>			
	Temp. (°C)	Time (h)	D/molecule* 2†	ring	$\overline{o+p}$	m	% recovery	
1	175	72	3.05	61	2.7	0.2	‡	
2	200	48	3.90	78	2.7	1.3	95	

\*Determined mass spectrometrically after O-D was washed out.

\*Determined by n.m.r. integral analysis. ‡Not determined.

TABLE 5. II -D CACHAIIGE III DEIZOIC ACIU III $\frac{4}{6}$ ( $\frac{1}{7}$ ) concentrated HCI-D <sub>2</sub>	TABLE 3.	H-D exchange in	benzoic acid	in 4% (v/v)	concentrated	HCl-D <sub>2</sub>
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	Condit	ions	D/malanula*	% exchange	
Entry	Temp. (°C)	Time (h)	3	ring	% recovery
1	175	72	0	0	> 95
2	250	65	3.40	68	> 95
3	275	75	4.70	94	>95

\*Determined by n.m.r. integral analysis using the back exchanged O-H as internal standard.

(60 ml) for 50 h and the  $D_2O$  was reclaimed by vacuum distillation.  $H_2O(80 \text{ ml})$  was added to the remaining solid and the solution was basified with concentrated aqueous NaOH and extracted with ether (5  $\times$  20 ml). The ether extract was washed with 5% HCl (5  $\times$  20 ml). The aqueous HCl phase was basified with concentrated NaOH, saturated with solid NaCl, and extracted with ether (5  $\times$  30 ml). The ether extract was washed with water and dried. Vacuum distillation (b.p. 43-44°, 2 mm) gave 10.3 g (72%) of aniline- $d_5$ . Nuclear magnetic resonance area intergral analysis showed that all aromatic positions had been equilibrated with 97% overall exchange.

Table 2 lists the preliminary results obtained

with phenol which establish that phenol and therefore certainly substituted phenols may be deuterated and therefore also tritiated using the HTDA conditions.

In order to establish the complete generality of the HTDA exchange procedure, benzoic acid (3) which is deactivated to electrophilic aromatic substitution was examined. The results are listed in Table 3. The data in entries 1, 2, and 3 establish that a one cycle HTDA exchange can be used successfully to deuterate and therefore tritiate in high yield aromatic nuclei which contain electron withdrawing groups.

With regard to the mechanism of exchange, protonation-deprotonation of the aromatic nu-

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cleus is likely involved. In the case of phenol, exchange may occur both through protonation of phenol or the phenoxide anion.

We are presently continuing our studies on other aromatic and polyaromatic systems with emphasis on the preparation of labelled biologically active materials.

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## Methyl Radicals in Solid Acetonitrile: Decay or No Decay<sup>1</sup>

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A comparison of both the e.s.r. spectra and the thermal stability of the radicals produced in  $\gamma$  radiolysis and 185 nm photolysis of acetonitrile shows that the former are not free methyl radicals. The initial species formed by  $\gamma$  radiolysis can be converted by photobleaching into a methyl radical weakly associated with a cyanide ion. The methyl radical of this CH<sub>3</sub>---CN<sup>-</sup> pair decays via hydrogen abstraction, whereas the free methyl radicals produced by 185 nm photolysis of acetonitrile are quite stable at 77 K. We ascribe the low energy of activation for the hydrogen abstraction in the  $\gamma$  irradiated samples not primarily to quantum mechanical tunnelling but to perturbation by the cyanide ion.

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On montre, par comparaison des spectres r.p.e. et de la stabilité thermique des radicaux produits par radiolyse  $\gamma$  et photolyse à 185 nm de l'acétonitrile, que les produits formés dans le premier cas ne sont pas des radicaux méthyles libres. Les premières espèces formées par radiolyse  $\gamma$  peuvent être transformées par photodécoloration en un radical méthyle faiblement associé avec un ion cyanure. Le radical méthyle de cette paire CH<sub>3</sub>---CN<sup>-</sup> est détruit par abstraction d'hydrogène, tandis que les radicaux méthyles libres produits par photolyse à 185 nm de l'acétonitrile sont assez stables à 77 K. La faible énergie d'activation pour la réaction d'abstraction d'hydrogène dans les échantillons irradiés par les rayons  $\gamma$  ne dépend pas principalement d'un franchissement de tunnel relevant de la mécanique quantique, mais plutôt d'une perturbation par l'ion cyanure. [Traduit par le journal]

[1]

 $\gamma$ -Radiolysis of solid acetonitrile at low temperatures yields methyl and  $\cdot$ CH<sub>2</sub>CN radicals together with a light sensitive species (1, 2). The latter has been shown to be an electron trapped on two acetonitrile molecules (3). It is destroyed on exposure of the irradiated sample to visible light but a corresponding increase in the number of methyl radicals is observed (1, 2). These

<sup>1</sup>AECL No. 4477.

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decay exponentially and irreversibly by hydrogen atom abstraction to give  $\cdot CH_2CN$  as in reaction 1

$$\cdot CH_3 + CH_3CN \rightarrow CH_4 + \cdot CH_2CN$$

The energy of activation for this reaction derived from the decay rates at 77 and 87 K was 6 kJ/mol (1, 2). This is in marked contrast to the value of 42 kJ found in the gas phase at high temperatures (373-573 K) (4).

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