

Effect of Increasing the Acidity on the Selective Aliphatic Hydrogen Exchange in 2,6-Dideuterio-4-(1-trideuteriomethyl-2,2,2-trideuterioethyl)anisole in Trifluoroacetic Acid

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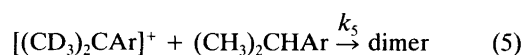
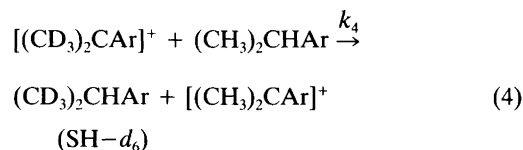
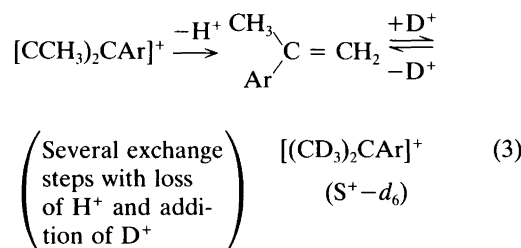
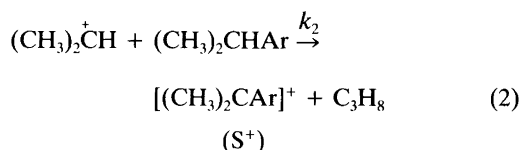
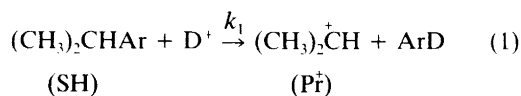
Nilsson, Å., 1987. Effect of Increasing the Acidity on the Selective Aliphatic Hydrogen Exchange in 2,6-Dideuterio-4-(1-trideuteriomethyl-2,2,2-trideuterioethyl)anisole in Trifluoroacetic Acid. – Acta Chem. Scand., Ser. B 41: 222–224.

In a recent investigation,¹ a kinetic and mechanistic study of the exchange of the methyl hydrogens in the isopropyl group of 4-isopropylanisole in trifluoroacetic acid-*d* was carried out. The reaction was found to follow first-order kinetics and the mechanism outlined in Scheme 1 was proposed. A corresponding scheme can be written for the methyl deuteriated substrate reacting in non-deuteriated acid. The formation of the isopropyl cation in step 1 ought to be dependent on the acidity of the reaction solution. By increasing the acidity, it should be possible to raise the rate of the dealkylation process and thus increase the concentration of the initiator (Pr^+) of the chain reaction. The rate of hydrogen exchange in the isopropyl group would then also increase.

The aim of the work described here was to show the correlation of the exchange rate with the Hammett acidity function, H_0 ,² as the acidity of the reaction solution is increased. Methanesulfonic acid was added to increase the acidity and the substrate used was 2,6-dideuterio-4-(1-trideuteriomethyl-2,2,2-trideuterioethyl)anisole and its methine-deuteriated analogue.

Results and discussion

The results are summarized in Table 1. A linear correlation of the exchange rate with H_0 is obtained, but the kinetics are no longer first-order as observed in the absence of methanesulfonic acid.¹ By simply plotting the fraction of remain-



(Ar denotes a *p*-methoxyphenyl group)

Scheme 1.

Table 1. Results for the selective aliphatic hydrogen exchange in 2,6-dideuterio-4-(1-trideuteriomethyl-2,2,2-trideuterioethyl)anisole and its methine-deuteriated analogue.

$-H_0$	Expt.	$-100 \cdot \text{slope of plot of } X_D \text{ vs. } t^a$
Methine- <i>h</i> compd. as substrate		
5.46	1	2.42
5.46	2	2.30
5.35	3 ^b	2.20
5.25	4	2.05
4.89	5	1.68
4.75	6	1.47
4.75	7	1.40
4.46	8	1.07
Methine- <i>d</i> analogue as substrate		
5.22	9	2.00
4.48	10	1.10

^a X_D denotes the fraction of methyl deuterons in the isopropyl group. ^bExpt. 3 is illustrated in Fig. 1.

ing methyl deuterons in the isopropyl group versus time, a straight line was obtained in every run (Fig. 1). The slopes obtained are linearly correlated with H_0 (Fig. 2).

In the previous investigation,¹ in the absence of a strong acid, it was observed that the hydrogen-exchange step [eqn. (3), Scheme 1] was completed before the next step, formulated as in eqn. (4), took place. From product studies, it is observed, however, that this is not the case in the presence of methanesulfonic acid. This would be

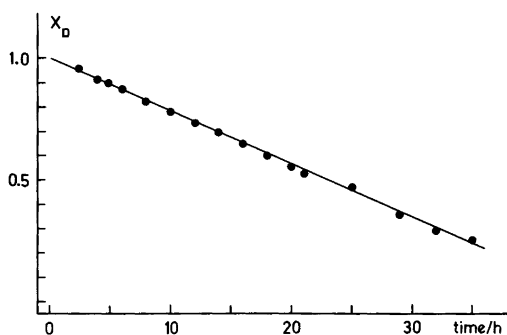


Fig. 1. Exchange in 2,6-dideuterio-4-(1-trideuterio-methyl-2,2,2-trideuterioethyl)anisole in TFA/CH₃SO₃H. $H_0 = -5.35$, expt. 3. Plot of fraction of deuterons, X_D , in the isopropyl group versus t .

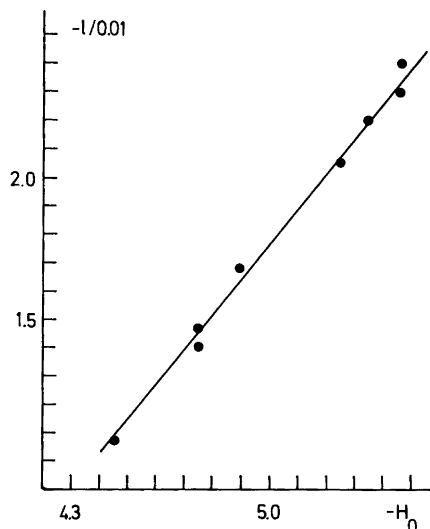


Fig. 2. Plot of the slopes obtained (l) from plots of X_D versus t as a function of H_0 for the exchange experiments 1–8. X_D denotes the fraction of methyl deuterons in the isopropyl group.

the result if the proton-removal step in eqn. (3) had become the rate-limiting step in the exchange sequence instead of the hydride-transfer step [eqn. (4)]. It is likely that such a change has occurred, since the methanesulfonate anion is a weaker base than the trifluoroacetate anion and thus gives less assistance in the proton-removal step. Another experimental support for such a shift of the rate-limiting step is the observation that no isotope effect on the exchange rate was observed when the methine-deuteriated substrate was used.

There is thus experimental evidence for an acidity dependence of the exchange which favours the previously suggested exchange mechanism. However, there is also evidence that could be interpreted in favour of a shift in the rate-limiting step of the exchange reaction sequence.

Experimental

Trifluoroacetic acid obtained from Fluka was distilled before use. Methanesulfonic acid, also from Fluka, was freed from oxidizing agents and distilled *in vacuo* before use. Mass spectrometric analyses were performed on a Finnigan 1020 GC-MS instrument. For the NMR measurements, a Bruker WH 270 MHz instrument was

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used. 2,6-Dideuterio-4-(1-trideuteriomethyl-2,2,2-trideuterioethyl)anisole and its methine-deuteriated analogue were prepared as reported.^{1,3} The kinetic measurements were performed in sealed NMR tubes at 40.0 ± 0.1 °C, using D₂O in an coaxial tube as lock solvent. The concentration of the substrate was held at 2.35×10^{-2} M in a mixture of trifluoroacetic acid and methanesulfonic acid. H_0 was varied in the range -5.5 to -4.5 . The values of H_0 were calculated from the indicator p*K*-values obtained for the methanesulfonic acid/trifluoroacetic acid system by Bessière.⁴

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