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Hydrogen Isotope Effect and Mechanism in the Selective Aliphatic Hydrogen Exchange in 4-Isopropylanisole

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4-Isopropylanisole has been treated with deuterated trifluoroacetic acid. In addition to the expected aromatic hydrogen exchange, the methyl hydrogens of the isopropyl group were exchanged. The kinetics and mechanism of this latter reaction have been studied. The reaction was found to follow first-order kinetics with a rate constant of $(3.3\pm0.2)\times10^{-6}s^{-1}$ at 40.0 ± 0.1 °C. When the substrate was deuterated in the methine position the rate was depressed by a factor of 4.0 at the same temperature. Isopropyl tosylate and 2-(4-methoxyphenyl)propene have been found to have catalytic effects on the exchange rate, and a hydrogen transfer between the methine positions of 4-*sec*-butylanisole and 4-isopropylanisole has also been observed under the exchange conditions. A chain mechanism with an intermolecular hydride transfer as the crucial step has been suggested.

The behaviour of 2,4,6-triisopropyltoluene on treatment with deuterated trifluoroacetic acid was reported in a previous investigation.[1] A selective aliphatic hydrogen exchange was observed in the isopropyl group in position 4 and a mechanism for the reaction was suggested. The discrimination of the isopropyl groups in the positions 2 and 6 was supposed to be due to steric hindrance. For further information about the kinetics and the mechanism in this kind of exchange reaction it was of interest to investigate some less complicated compounds. Properly substituted alkylanisoles were supposed to be the most suitable substrates. In the present investigation 4-isopropylanisole and 4-*sec*-butylanisole have been used.

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EXPERIMENTAL

Mass spectrometric determinations were performed at 70 eV either on an AEI MS 902 instrument (at the Department of Medical Biochemistry, University of Göteborg) or on a GC-MS Finnigan 4021 instrument (at the Chemistry Center, University of Lund). GLC analyses were performed on a Perkin Elmer Model 900 instrument fitted with 3 mm×2 m SE-30 columns and a flame ionization detector. For the NMR analyses a Bruker W 270 MHz instrument was used. UV analyses were carried out on a Varian, Cary 210 spectrophotometer. ESR analyses were performed on a Varian E3 ESR spectrometer (at the Department of Biophysics and Biochemistry, University of Göteborg). Deuteriotrifluoroacetic acid (TFA-*d*) with an isotopic purity >99.5 % (d_{20}=1.50) obtained from CIBA was used in the exchange experiments.

Syntheses

4-Isopropylanisole, 4-sec-butylanisole and 4-ethylanisole were prepared from the corresponding alkylphenols by ion pair alkylation according to Brändström.[2]

2,6-Dideuterio-4-(1-trideuteriomethyl-2,2,2-trideuterioethyl)anisole was prepared for characterization and identification purposes by equilibrating 4-isopropylanisole with TFA-*d* at 40 °C. The product was analyzed by GLC-MS and NMR. Ms [IP 70 eV; *m/z* (% rel. int.)] 158 (26.6), 140 (100), 139 (26.6), 110 (17.7), 109 (40). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.81 (1 H, s), 3.78 (3 H, s), 7.14 (2 H, s). The isotopic purity was better than 98.5 %.

2-(4-Methoxyphenyl)propene was prepared from 4-methoxyacetophenone by utilizing a

method of Corey and Kwiatkowski for the preparation of alkenes from carbonyl compounds,[3] Yield 20 %, m.p. 32.5–34 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.12–2.13 (3 H, m), 3.81 (3 H, s), 4.97–4.99 (1 H, m), 5.26–5.28 (1 H, m), 6.85 (2 H, d, J=9 Hz), 7.40 (2 H, d, J=9 Hz).

4-(1-Deuterio-1-methylethyl)anisole was synthesized as previously reported.[4] The isotopic purity was better than 98.5 %.

4-(1-Deuterio-1-methylpropyl)anisole with an isotopic purity better than 98 % was prepared from 2-(4-methoxyphenyl)-2-butanol by reduction with a mixture of aluminium chloride and lithium tetradeuteridoaluminate in diethyl ether utilizing a method of Brown and White.[5] Yield 15 % after HPLC chromatography. The product was identified by NMR and MS.

Isopropyl tosylate was prepared according to an established procedure.[6]

Kinetic runs

The kinetic experiments were run at 40.0±0.1 °C in sealed NMR tubes. In order to optimize the NMR signals and to have a deuterium content of more than 98 % in the exchangeable pool, the concentration of substrate was held at 2.35×10^{-2} M in TFA-*d*. In order to verify the first-order character of the kinetics, check experiments were carried out with 4.6×10^{-2} M and 1.23×10^{-2} M solutions. The hydrogen exchange was followed by comparing the intensities of the NMR signals from the remaining methyl protons of the isopropyl group with the intensity of the signal from the methoxy group. The exchange was followed to the extent of 70–80 %. The rate constants were calculated with a least squares program. The results are summarized in Table 1.

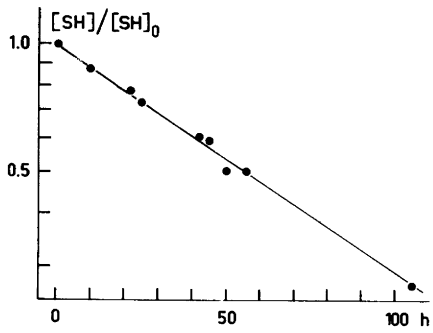

Fig. 1. Exchange in 4-isopropylanisole in TFA-*d*. Semilogarithmic plot of remaining fraction of starting material as function of time. Run 1:3.

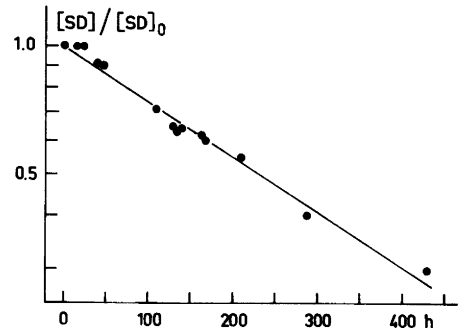

Fig. 2. Exchange in 4-(1-deuterio-1-methylethyl)anisole in TFA-*d*. Semilogarithmic plot of remaining fraction of starting material as function of time. Run. 2:2.

Typical plots of single runs are given in Figs. 1 and 2.

By means of mass spectrometry it was observed that either none or all six methyl protons of the isopropyl group of a molecule were exchanged for deuterium at any instant.

Experiments to check suggested mechanism

Experiments to reveal a radical mechanism. The exchange rate was not changed by the addition of radical inhibitors like iodine or hydroquinone, nor was it influenced by UV irradiation or the presence of oxygen. No signal could be detected by ESR spectrometry.

Intermolecular methine hydrogen exchange was observed under the kinetic conditions in a solution of equivalent amounts of 4-(1-deuterio-1-methylethyl)anisole and 4-*sec*-butylanisole in TFA. The hydrogen transfer between the two different methine positions was observed by means of NMR and MS-analyses. The experiment was repeated with 4-(1-deuterio-1-methylpropyl)anisole and 4-isopropylanisole.

Dealkylation and transalkylation experiments. A 2.4×10^{-2} M solution of 4-isopropylanisole in TFA was kept at 40 °C for two months. By GLC and GLC-MS analyses approximately 1 % anisole was detected after that time, the identity being confirmed by means of an authentic sample. Some dimeric material, mass (2×150–2) was also observed. Under the same conditions and in the presence of equivalent amounts of phenetole a transisopropylation was observed to a degree of 1 %. 4-Isopropylphenetole was identified by GLC-MS *via* an authentic sample.

Table 1. First-order rate constants for the selective aliphatic hydrogen exchange reaction in 4-isopropylanisole and its methine-deuterated analogue when dissolved in deuterated trifluoroacetic acid. Temperature 40.0(1) °C.

Kinetic run	Substrate conc×10^2/M	Number of points	Time interval h	$k\times10^6/s^{-1}$	Mean value
Methine-*h* as substrate					
1:1	2.35	13	0.3–110	3.1(1)	
1:2	2.35	10	0.5–115	3.4(1)	
1:3	2.35	9	0.5–105	3.5(1)	
1:4	2.35	8	0.5–140	3.3(1)	
1:5	4.6	8	0.5–108	3.3(1)	
1:6	1.23	8	0.5–115	3.4(1)	3.3(2)
Mehine-*d* as substrate					
2:1	2.35	14	48–432	0.83(3)	
2:2	2.35	14	0.5–430	0.82(3)	
2:3	2.35	11	0.3–430	0.87(3)	
2:4	2.35	9	16–432	0.81(3)	0.83(4)

Kinetic runs 1:3 and 2:2 are illustrated in Figs. 1 and 2.

The catalytic effects of 2-(4-methoxyphenyl)-propene and of isopropyl tosylate were observed under ordinary conditions in the presence of the alkene in a molar concentration of 5 % of that of the substrate and of the tosylate in a molar concentration of 10 % of that of the substrate in separate experiments. Addition of the alkene caused a dramatic change. The degree of exchange was raised by a factor of 20 after the first 2 h (*cf.* also Fig. 3) in the presence of the alkene, whereas the presence of isopropyl tosylate raised the degree of exchange by a factor of 1.2–1.3 after 24 h.

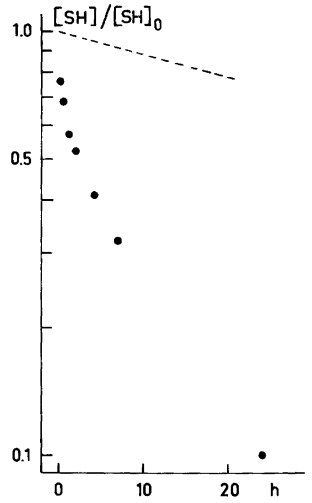

Fig. 3. Selective aliphatic hydrogen exchange in 4-isopropylanisole, 2.35×10^{-2} M, in TFA-*d*, in the presence of 1.2×10^{-3} M 2-(4-methoxyphenyl)propene. Temperature 40.0±0.1 °C. The dashed line represents the uncatalyzed exchange.

Salt effects on the exchange rate were examined by the addition in separate experiments of lithium perchlorate and of sodium iodide in molar concentrations equal to that of the substrate. Lithium perchlorate increased the degree of exchange by a factor of 2 after 24 h whereas addition of sodium iodide had a retarding effect. In the presence of iodide ions small amounts of both iodinated and trifluoroacetylated material could be identified by GLC–MS analysis together with 4-isopropylphenol. After hydrolysis the two first-mentioned products could not be detected. Instead an alcohol was detected, probably 4-methoxyphenyl-2-propanol. In the presence of iodide ions, iodine was also formed. Iodine itself however, had no retarding effect on the exchange rate, as was also observed in the previous investigation on 2,4,6-triisopropyltoluene.[1]

UV analyses were performed in the region of 500–240 nm in order to detect the presence of a possible intermediate 2-(4-methoxyphenyl)-propene under the exchange conditions. No alkene absorption was observed but in addition

$$(CH_3)_2CHAr + D^+ \xrightarrow{k_1} (CH_3)_2\overset{+}{C}H + ArD \quad (1)$$

(SH) (Pr^+)

$$(CH_3)_2\overset{+}{C}H + (CH_3)_2CHAr \xrightarrow{k_2} [(CH_3)_2CAr]^+ + C_3H_8 \quad (2)$$

(S^+)

$$[(CH_3)_2CAr]^+ \xrightarrow{-H^+} CH_3-\underset{\underset{Ar}{|}}{C}=CH_2 \underset{-D^+}{\overset{+D^+}{\rightleftharpoons}} \text{several exchange steps with loss of } H^+ \text{ and addition of } D^+ \rightleftharpoons \quad (3)$$

$[(CD_3)_2CAr]^+$

($S^{\pm}d_6$)

$$[(CD_3)_2CAr]^+ + (CH_3)_2CHAr \xrightarrow{k_4} (CD_3)_2CHAr + [(CH_3)_2CAr]^+ \quad (4)$$

(SH-d_6)

$$[(CD_3)_2CAr]^+ + (CH_3)_2CHAr \xrightarrow{k_5} \text{dimer} \quad (5)$$

Scheme 1. Ar denotes a 4-methoxyphenyl group.

to the isopropylanisole pattern at 270 and 276 nm a weak but broad absorption was observed at 356 nm. This latter absorption was also recorded for a solution of 2-(4-methoxyphenyl)propene in TFA together with a signal at 272 nm from an indane derivative formed via dimerisation of the alkane. (The indane derivative was identified by NMR and MS). No typical alkene absorption was observed from the alkene in TFA, however. No signals were recorded for the alkene or the 4-isopropylanisole at 356 nm in ethanol or in acetic acid. The absorption at 356 nm in TFA is therefore supposed to be due to an intermediate carbenium ion in a concentration of about 10^{-6} M or less.

An exchange experiment with 4-ethylanisole was carried out under conditions similar to those in the kinetic runs above. No aliphatic hydrogen exchange could be detected.

SUGGESTED MECHANISM AND KINETICS

The experimental results may be explained by the chain mechanism for the aliphatic exchange reaction given in Scheme 1.

Eqn. (1) shows the formation of the initiator (Pr^+). The rate constant k_1 contains the dependence on the solvent TFA-*d* which is present in constant concentration during the reaction. Eqn. (2) represents the chain initiation step. Eqn. (3) illustrates a rapid reaction sequence. From product studies it is found that the deuteriation is completed before the next step, formulated as in eqn. (4), takes place. Eqn. (4) is the propagation step in which SH is irreversibly consumed [see eqn. (3)]. Eqn. (5) illustrates the chain-terminating step.

In the following the concentrations irrespective of the kind of isotope in the methyl positions will be denoted

$[SH_{tot}]=[SH]+[SH-d_6]$,
$[S^+_{tot}]=[S^+]+[S^{\pm}d_6]$ and $[Pr^+_{tot}]=[Pr^+]+[Pr^{\pm}d_6]$

Neglecting possible secondary isotope effects and assuming that the carbonium ions are present in steady-state concentrations, it is possible to write the following equations:

$$\frac{d[Pr^+_{tot}]}{dt}=k_1[SH_{tot}]-k_2[SH_{tot}][Pr^+_{tot}]=0 \quad (6)$$

giving

$$[Pr^+_{tot}]=k_1/k_2 \quad (7)$$

$$\frac{d[S^+_{tot}]}{dt}=k_2[SH_{tot}][Pr^+_{tot}]-k_5[SH_{tot}][S^+_{tot}]=0 \quad (8)$$

which leads to

$$[S^+_{tot}]=(k_2/k_5)[Pr^+_{tot}]=k_1/k_5 \quad (9)$$

In eqn. (9) $[S^+_{tot}]=[S^+]+[S^{\pm}d_6]$, but according to reaction (3) (S^+) will momentarily be transformed into $(S^{\pm}d_6)$ which implies that (S^+_{tot}) is identical with $(S^{\pm}d_6)$ and so $[S^{\pm}d_6]=k_1k_5$.

The next equation could then be written:

$$\frac{d[SH]}{dt}=-k_4[S^{\pm}d_6][SH]=$$

$$-(k_1k_4/k_5)[SH]=-k_H[SH] \quad (10)$$

which gives

$$\ln\frac{[SH]}{[SH]_0}=-k_Ht \quad (11)$$

For the methine-deuteriated material the corresponding equation is obtained:

$$\ln\frac{[SD]}{[SD]_0}=-k_Dt \quad (12)$$

For the methine-deuterated material there should be no primary isotope effects involved with the rate constants k_1 and k_5. There should be a primary isotope effect on the rate constant k_4, however. The observable rate constant for the methine-deuterated substrate could then be written

$$k_D=k_1k_4{}^Dk_5 \quad (13)$$

leading to

$$k_H/k_D=k_4{}^H/k_4{}^D \quad (14)$$

Eqn. (8) leads to a steady-state concentration of (S^+_{tot}) which is independent of $[SH_{tot}]$ because the terminating species was assumed to be the substrate itself. The result would have been similar with any other species, the concentration of which is proportional to $[SH_{tot}]$. With a terminating species A in general,

$$[S^+_{tot}]=[S^{\pm}d_6]=k_1[SH_{tot}]/k_5[A] \quad (15)$$

From the kinetic experiments it is found that k_H is independent of $[SH_{tot}]$. It is therefore most likely that the reaction chain will terminate as in reaction (5), probably an electrophilic aromatic substitution.

DISCUSSION

There is no experimental evidence in support of a radical mechanism for the selective aliphatic hydrogen exchange observed in the present investigation. The salt effect in the presence of lithium perchlorate indicates an ionic mechanism, and there are several experimental reasons for writing the mechanism as suggested above. A dealkylation is observed and confirmed by a transalkylation reaction. The isopropyl cation formed could abstract a hydride ion and in that way initiate the exchange reaction. This is supported by the catalytic action of isopropyl tosylate which undergoes solvolysis in TFA. It also seems very probable that 2-(4-methoxyphenyl)-propene is involved in the reaction sequence as addition of this alkene has a pronounced catalytic effect. Addition of propene has no influence, however. Support of the intermolecular hydride transfer is obtained in the mixed exchange experiments, involving both 4-*sec*-butylanisole and 4-isopropylanisole in the same reaction vessel. A transfer of hydrogen between the two different methine positions is observed. The observed isotope effect strongly indicates that the methine hydrogen is involved in the ratelimiting step, probably an intermolecular hydride transfer. The formation of a dimeric product also supports a termination as suggested in eqn. (5).

The magnitude of the isotope effect is rather small for a primary one. This could be an effect of a nonlinear transition state.[7,8] Hydride transfer reactions tend to have small primary isotope effects [8,9] and different types of mechanisms may be operating in reactions for which the net result seems to be a hydride transfer. Apart from a direct hydride abstraction, which is considered to be most likely in many cases,[10,11] a multistep mechanism involving an electron-proton-electron-transfer mechanism appears to be consistent with the results in some other situations, as for instance in the reduction of substituted trifluoroacetophenone by a model of NAD(P)H.[12] In the present work no experimental evidence has been obtained that suggests such a multistep mechanism operating in the hydride-transfer step.

As has been observed earlier [1] and in this work, it is necessary to have a sufficiently powerful electron-donating substituent in the aromatic ring for the exchange to occur. *p*-

Cymene, for instance, does not undergo any aliphatic hydrogen exchange.[1] The 4-methyl group is obviously insufficient for the stabilization of the intermediate cation. It also seems that a necessary condition for an exchange to occur in this kind of system is the presence of a methine hydrogen in the benzylic position. In 4-ethylanisole, for instance, no aliphatic hydrogen exchange occurs.

Preliminary experiments with 2-isopropylanisole indicate that steric hindrance might cause drastic effects on the exchange rate. Steric hindrance and other structural effects will be further studied.

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