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Structural Effects on Selective Aliphatic Hydrogen Exchange in Alkyl-Substituted Aromatic Compounds in Deuteriated Trifluoroacetic Acid

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A qualitative study has been carried out concerning structural effects on selective aliphatic hydrogen exchange for a variety of alkylated aromatic compounds in deuteriated trifluoroacetic acid. It has been observed that the β-hydrogen exchange in isopropyl and cyclohexyl groups is severely hindered by the presence of an *ortho* substituent, whereas this is not the case for the exchange in a cyclopentyl group. In 1-isopropylnaphthalene, hindrance from the *peri* hydrogen inhibits aliphatic hydrogen exchange in the methyl groups, while in 2-isopropylnaphthalene aliphatic exchange occurs. Also, bulky substituents, *e.g.* isopropyl groups, *ortho* to the methoxy group as in 2,4,6-triisopropylanisole, strongly retard the rate of the hydrogen exchange in the isopropyl group in position 4. Structural effects on aliphatic β-hydrogen exchange for some derivatives of indan, tetrahydronaphthalene, chroman, diphenyl ether and biphenyl have also been studied. For the indan- and tetrahydronaphthalene derivatives the presence of a methine hydrogen in the benzylic position was no longer necessary for aliphatic hydrogen exchange to occur. For 5-methoxy-1-methylindan, α-hydrogen exchange in position 1 was also observed together with the β-hydrogen exchange.

In previous work [1] the kinetics for aliphatic hydrogen exchange in the methyl groups of the isopropyl group of 4-isopropylanisole in deuteriated trifluoroacetic acid was investigated. It was also observed that 2-isopropylanisole did not undergo any measurable aliphatic hydrogen exchange under the conditions used (2.35×10^{-2} M, 40 °C). The same had been found earlier [2] for 2,4,6-triisopropyl-1,5-dimethylbenzene, whereas in 2,4,6-triisopropyltoluene [2] exchange occurred in the isopropyl group in position 4. It was therefore of interest to further investigate the influence of structural effects on aliphatic hydrogen exchange. For that purpose, a series of alkylanisoles *1–8* and suitable derivatives of naphthalene *9, 10,* indan *11, 12,* tetrahydronaphthalene *13, 14,* diphenyl ether *15, 16,* chroman *17* and biphenyl *18* have been prepared and investigated with respect to hydrogen exchange in the starred β-positions (Fig. 1).

EXPERIMENTAL

Mass spectrometric determinations were performed at 70 eV, either on an AEI MS 909 instrument (at the Department of Medical Biochemistry, University of Göteborg) or on a

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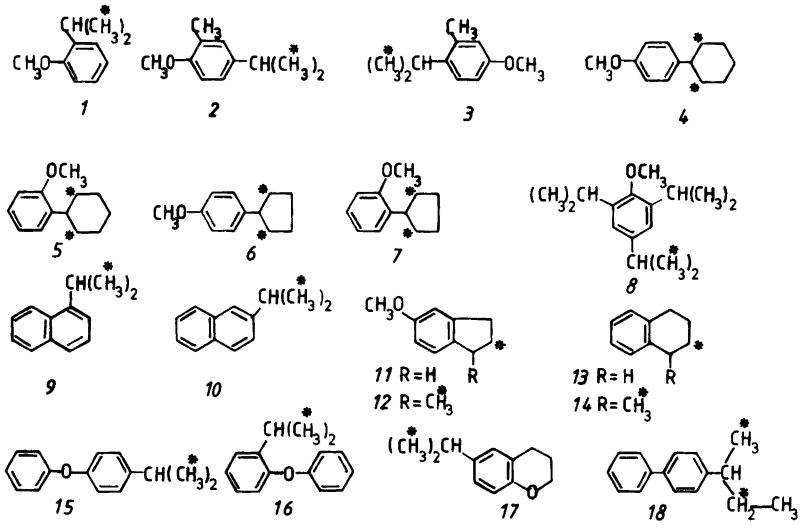

GLC–MS Finnigan 1020 instrument. GLC analyses were performed on a Perkin Elmer Model 900 instrument fitted with 3 mm×2 m SE-30 columns and a flame ionization detector. For the NMR analyses a Bruker W 270 MHz instrument was used. For HPLC separations a Waters Model 201 liquid chromatograph with a Refractive Index Detector was used. A stainless steel column, 30 cm×7.7 mm I.D., packed with Porasil A (60), was used for the preparative-scale separations. Deuteriotrifluoroacetic acid (TFA-*d*) with an isotopic purity >99.5 % (d_{20}=1.50) obtained from CIBA, was used in the exchange experiments. 1,2,3,4-Tetrahydro-6-methoxynaphthalene, obtained from Fluka, was chromatographed before use on a column of alumina with hexane as the eluent.

The exchange experiments were carried out as previously described,[1] in separate experiments for each substrate except for substrates *9* and *10* which were not separated before use. Where isomers elsewhere were available, experiments were also carried out with isomeric mixtures. The extent of exchange was checked by NMR after 16 h. If no exchange could be detected after 16 h, the experiment was continued for another 56 h. The NMR observations in each experiment were confirmed by GLC–MS. The results are summarized in Table 1.

Table 1. Summary of the aliphatic β-hydrogen exchange for substrates *1–18* in deuteriated trifluoroacetic acid at 40.0(1) °C, 16 h. Concentration of substrate: 2.35×10^{-3} M.

Substrate	Extent of exchange %	Substrate	Extent of exchange
1	0[a]	*10*	15
2	37	*11*	24
3	0[a]	*12*	>98
4	28	*13*	12
5	0*a*	*14*	24
6	90	*15*	15
7	81	*16*	0*a*
8	0*b*	*17*	21
9	0*a*	*18*	0*a*

[a] No exchange could be detected after another 56 h. [b] An exchange of ≈1 % could be detected after another 56 h.

Syntheses

2-Isopropylanisole 1 was prepared from 2-isopropylphenol by ion-pair alkylation.[3]

5-Isopropyl-2-methoxytoluene 2 was synthesized *via* chloromethylation [4] of 4-isopropylanisole and subsequent reduction of the product by lithium tetrahydridoaluminate.[2] ^{1}H NMR ($CDCl_3$): δ 1.21 (6H, d, J=6.5 Hz), 2.22 (3H, s), 2.81 (1H, h, J=6.5 Hz), 3.78 (3H, s), 6.74 (1H, d, J=10 Hz), 6.96–7.04 (2H, m). MS [IP 70 eV: *m/e* (% rel. int.)]: 164 (28), 150 (11), 149 (100), 119 (10), 91 (21), 77 (12).

2-Isopropyl-5-methoxytoluene 3 was prepared by reduction of 2-(5-methoxy-2-toluyl)-2-propanol,[5] prepared *via* a Grignard synthesis on the methoxy derivative obtained from 2-methyl-4-hydroxyacetophenone. This in turn was prepared by a Fries rearrangement [6] at low temperature from *m*-cresyl acetate. The methylation of the phenol function was carried out with methyl iodide in acetonitrile in the presence of an equivalent amount of sodium carbonate at room temperature.

For the desired 2-isopropyl-5-methoxytoluene *3* the following data were obtained. ^{1}H NMR ($CDCl_3$): δ 1.11 (6H, d, J=6.9 Hz), 2.22 (3H, s), 2.98 (1H, h, J=6.9 Hz), 3.68 (3H, s), 6.59–6.64 (2H, m), 7.05 (1H, d, J=7.7 Hz). MS [IP 70 eV: *m/e* (% rel. int.)]: 164 (31), 150 (29), 149 (100), 134 (81), 91 (10).

4-Cyclohexylanisole 4 *and 2-cyclohexylanisole* 5 were prepared in a mixture by Friedel-Crafts alkylation of anisole with cyclohexylbromide according to a reported method.[7] Separation and purification were performed *via* a combination of column chromatography on silica gel and preparative TLC.

4-Cyclopentylanisole 6 *and 2-cyclopentylanisole* 7 were prepared and purified as described above for the cyclohexyl derivatives (*cf.* Ref. 8).

2,4,6-Triisopropylanisole 8 was prepared from anisole and diisopropyl ether according to a reported method.[9]

1-Isopropylnaphthalene 9 *and 2-isopropylnaphthalene* 10 were prepared according to a reported method.[10] The two isomers were not separated before use in exchange experiments.

5-Methoxyindan 11 was prepared by reduction of 5-methoxy-1-indanone [5] (*cf.* Ref. 11).

5-Methoxy-1-methylindan 12 was synthesized by hydrogenation of 5-methoxy-1-methyl-1-indene obtained from the spontaneous dehydration of 5-methoxy-1-methyl-1-indanol, which was prepared by a Grignard synthesis on 5-methoxy-1-indanone (*cf.* Ref. 12).

1,2,3,4-Tetrahydro-6-methoxy-1-methylnaphthalene 14 was prepared *via* 6-methoxytetralone as described above for 5-methoxy-1-methylindan (*cf.* Ref. 13).

4-Isopropyldiphenyl ether 15 *and 2-isopropyldiphenyl ether* 16 were prepared by alkylation of diphenyl ether in nitrobenzene.[14] The two isomers were isolated and purified *via* HPLC using hexane as the eluent.

4-Isopropyldiphenyl ether *15*: ^{1}H NMR ($CDCl_3$): δ 1.24 (6H, d, J=7.3 Hz), 2.89 (1H, h, J=7.3 Hz), 6.9–7.3 (9H, m). MS [IP 70 eV: *m/e* (% rel. int.)]: 212 (48), 198 (15), 197 (100), 119 (14), 104 (19), 19 (42), 77 (39), 65 (21), 51 (22).

2-Isopropyldiphenyl ether *16*: ^{1}H NMR ($CDCl_3$): δ 1.22 (6H, d, J=7.2 Hz), 3.21 (1H, h, J=7.2 Hz), 6.9–7.3 (9H, m). MS [IP 70 eV: *m/e* (% rel. int.)]: 212 (50), 197 (100), 181 (25), 119 (39), 115 (15), 103 (38), 91 (95), 77 (57), 65 (18), 51 (30), 41 (12).

6-Isopropylchroman 17 was prepared in low yield by heating 1 g of 3-(4-isopropylphenoxy)-1-propanol (obtained by ion-pair alkylation [3] of 4-isopropylphenol with 3-iodopropanol) in conc. sulphuric acid at 80–90 °C for 10 h (*cf.* Ref. 15). From the crude product, 75 mg of the desired product was obtained, using a combination of column chromatography on alumina and preparative TLC, with hexane as the eluent. ^{1}H NMR ($CDCl_3$): δ 1.22 (6H, d, J=7.6 Hz), 1.92–2.02 (2H, m), 2.73–2.87 (3H, m), 4.12–4.18 (2H, t, distorted, J=6.1 Hz), 6.70 (1H, d, J=8 Hz), 6.87 (1H, s), 6.95 (1H, d, J=8 Hz). MS [IP 70 eV: *m/e* (% rel. int.)]: 176 (63), 161 (100), 133 (65), 115 (19), 106 (22), 105 (36), 91 (32), 77 (41), 65 (19), 51 (27), 41 (36).

4-sec-Butylbiphenyl 18 was prepared by reduction [5] of 2-(p-biphenyl)-2-butanol, obtained by a Grignard synthesis on 4-phenylacetophenone with ethyl bromide. ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, t, J=7.4 Hz), 1.26 (3H, d, J=6.9 Hz), 1.51–1.66 (2H, m), 2.59–2.71 (1H, m), 7.21–7.58 (9H, m). MS [IP 70 eV: *m/e* (% rel. int.)]: 210 (27), 182 (15), 181 (100), 166 (100), 166 (22), 165 (25), 152 (10).

RESULTS AND DISCUSSION

The results of the exchange experiments are summarized in Table 1. Reactions on isomeric mixtures gave the same result as in separate runs. For 5-methoxy-1-methylindan *12* an α-hydrogen exchange was also observed in position 1.

In a previous kinetic investigation the chain mechanism given in Scheme 1 was suggested for the selective aliphatic hydrogen exchange reaction in 4-isopropylanisole.[1]

$$(CH_3)_2CHAr + D^+ \longrightarrow (CH_3)_2C^+H + ArD \quad (1)$$

$$(CH_3)_2C^+H + (CH_3)_2CHAr \longrightarrow [(CH_3)_2CAr]^+ + C_3H_8 \quad (2)$$

$$[(CH_3)_2CAr]^+ \xrightarrow{-H^+} CH_3-\underset{\displaystyle Ar}{\overset{\displaystyle |}{C}}=CH_2 \overset{+D^+}{\underset{-D^+}{\rightleftarrows}}$$

several exchange steps with loss of H^+ and addition of D^+ $\rightleftarrows$ (3)

$$[(CD_3)_2CAr]^+$$

$$[(CD_3)_2CAr]^+ + (CH_3)_2CHAr \longrightarrow (CD_3)_2CHAr + [(CH_3)_2CAr]^+ \quad (4)$$

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

Scheme 1. Ar denotes a 4-methoxyphenyl group.

A similar mechanism is probably operating for the aliphatic hydrogen exchange in the alkyl derivatives *2, 4, 6–8, 10, 15,* and *17.* From the results for substrates *1, 3, 9* and *16* in this work and from a previous investigation on 2,4,6-triisopropyl-1,3-dimethylbenzene and 2,4,6-triisopropyltoluene,[2] the conclusion might be drawn that aliphatic hydrogen exchange in an isopropyl group is strongly retarded by the presence of an *ortho* substituent. This also seems to be true for a cyclohexyl group with a methoxy substituent in the *ortho* position *5,* whereas the exchange in a cyclopentyl group seems to be very little affected by an *ortho* substituent *7.* For an isopropyl group, the *peri* hydrogen in α-isopropylnaphthalene *9* seems to cause steric hindrance enough to inhibit hydrogen exchange, although substrate *9* should be the more reactive one of *9* and *10* as far as stabilization of a benzylic cation is concerned, if no steric hindrance were involved.

Since no aliphatic hydrogen exchange is observed for compounds *1,3,5,9* and *16* even in the presence of the corresponding reactive isomer, steric hindrance in forming a benzylic cation can explain the fact that these compounds are non-reactive.

For the cyclopentyl derivatives *6* and *7* the extent of exchange is remarkably higher than for the cyclohexyl and isopropyl derivatives *4* and *2*, respectively. An explanation of this could be that it is easier to form a benzylic intermediate cation in the five-membered ring than in the six-membered ring or in an isopropyl group. This explanation is also in accordance with what has been observed in connection with solvolysis of 1-chloro-1-methylcycloalkanes[16,17] and 1-phenyl-substituted cycloalkyl *p*-nitrobenzoates.[18,19] From studies of molecular models, it is found that an *ortho* substituent causes less disturbance by

steric hindrance to the coplanarity between the aromatic ring and the bonds to the benzylic carbon in the suggested intermediate cation of the cyclopentyl derivative, than in the cations of the cyclohexyl- and isopropyl derivatives. Then the steric hindrance from an *ortho* substituent probably will be of similar importance in the hydride removal step.

Bulky substituents in positions *ortho* to the methoxy group, as in 2,4,6-triisopropylanisole *8*, also have a retarding effect on the exchange rate in the isopropyl group in position 4. Steric hindrance to conjugation between the methoxy group and the benzylic carbon in the intermediate cation can possibly explain the observed slow hydrogen exchange. Steric hindrance to conjugation between the methoxy group and the aromatic ring has also been observed from UV spectroscopy for this compound.[9]

Compound *17* was investigated in order to find out whether the ring strain in the oxygen-containing ring would cause an insufficient conjugation between the oxygen atom and the benzylic carbocation center, and thus retard or prevent the hydrogen exchange. This does not seem to be the case, however.

For compound *15*, a lower extent of exchange than that previously observed for 4-isopropylanisole[1] was expected due to the phenyl group on oxygen. The extent of exchange for compound *15*, however, is of comparable size to that observed for 4-isopropylanisole.

Previously, it has been observed that the presence of a methine hydrogen in the benzylic position is a necessary condition for an aliphatic hydrogen exchange to occur in alkylanisoles. This requirement no longer seems to be true for 5-methoxyindan *11* and 1,2,3,4-tetrahydro-6-methoxynaphthalene *13*. The reactivity in these bicyclic substrates, in spite of the absence of a methine hydrogen in the benzylic position might be due to ring strain.

It also seems, from the extent of hydrogen exchange, as if the steric crowding around the reactive benzylic position of substrates *12* and *14* is of no importance, since in these cases the extent of hydrogen exchange is even greater than that for 4-isopropylanisole (given in Table 1). For the indan and tetrahydronaphthalene derivatives, the hydrogen exchange might be initiated *via* a carbonium ion formed by a ring-opening protiodealkylation process at the activated position *para* to the methoxy group. It is observed that 5-methoxy-1-methylindan *12* undergoes the exchange reaction much more rapidly than the corresponding tetrahydronaphthalene derivative *14*. This might be due to a greater ease of formation of a planar benzylic cation in the five-membered ring of the indan derivative than in the corresponding six-membered part of the tetrahydronaphthalene derivative. This suggestion is also in accordance with what has been reported from alcoholysis of 3-chloro-1,2-benzocycloalkenes [20] and with the results of molecular mechanics calculations on the same systems and on the corresponding benzyl cations.[21]

It is also possible that the higher degree of hydrogen exchange in the indan derivative *12* is due to a different kind of mechanism, since the benzylic proton in position 1 is also exchanged. Preliminary kinetic measurements also indicate that the half life of conversion is substrate dependent, which was not the case for 4-isopropylanisole. This observation will be further investigated.

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