

Electrolytically Initiated Selective Aliphatic Hydrogen Exchange in 4-Isopropylanisole

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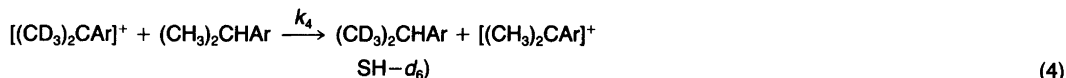
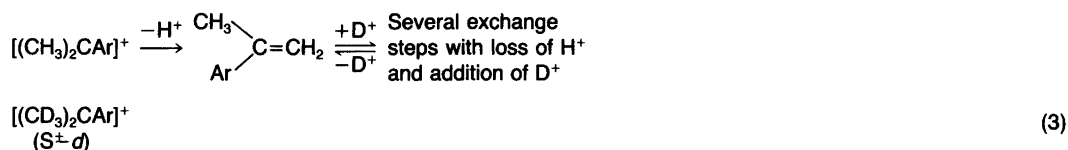
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Anodic oxidation of 4-isopropylanisole in trifluoroacetic acid-*d* has been observed to promote the exchange of the methyl hydrogens of the isopropyl group. No aliphatic hydrogen exchange was detected when 2-isopropylanisole and 4-ethylanisole were treated in the same way. Oxidation products from constant potential electrolyses of 4-isopropylanisole and 2-isopropylanisole have been identified.

For a variety of alkylated aromatic compounds a selective aliphatic hydrogen exchange has been reported to occur on treatment with trifluoroacetic acid-*d*,^{1,2,3} and for 4-isopropylanisole the result of a kinetic and mechanistic study of the exchange of the methyl hydrogens in the isopropyl group has been reported.³ For the aliphatic

hydrogen exchange in 4-isopropylanisole a chain reaction mechanism as shown in Scheme 1 has been outlined.³ It is suggested that oxidation of the substrate to a benzylic carbocation is an important step in the reaction mechanism. If the benzylic cation could be produced by an independent oxidizing agent in the reaction vessel,



Scheme 1. Ar denotes a *p*-methoxyphenyl group.

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the rate of the aliphatic hydrogen exchange would be increased. It therefore became of interest to investigate whether anodic oxidation could have any effect on the exchange rate and also whether the oxidation products could be related to the exchange reaction. As no aliphatic hydrogen exchange had been detected in a previous experiment for 2-isopropylanisole² and 4-ethylanisole³ under ordinary conditions, it was of interest, for comparison, to investigate also these two compounds under electrolytic conditions.

Experimental

Mass spectrometric determinations were performed at 70 eV on either an AEI MS 909 instrument (at the Department of Medical Biochemistry, University of Göteborg) or a GLC-MS Finnigan 1020 instrument. For the NMR analyses a Bruker WH 270 MHz instrument was used. For HPLC separations and analyses a Varian 5000 liquid Chromatograph fitted with a Varian UV-100 detector was used. Trifluoroacetic acid with an isotopic purity of >99.5%

($d_{20} = 1.50$) obtained from CIBA was used in the exchange experiments. Trifluoroacetic acid from FLUKA was distilled twice before use for preparative anodic oxidation. Tetrabutylammonium tetrafluoroborate was prepared according to standard procedures. Other chemicals were of commercial grade and used without further purification. A three-electrode system was used for voltammetry and electrolysis. During electrolysis the counter electrode was separated from the anode compartment by a glass frit. A platinum electrode of large area (approx. 55 cm²) was used as an anode for electrolysis, while a small glassy carbon disc electrode (3 mm in diameter) was used for voltammetric characterization. The potentiostat was a PAR model 173/276 controlled by an HP 85B desk computer. The reference electrode was Ag/Ag⁺ (0.1 M Bu₄NBF₄, 0.01 M AgNO₃ in acetonitrile).

Syntheses

4-Isopropylanisole, 2-isopropylanisole and 4-ethylanisole were prepared from the corre-

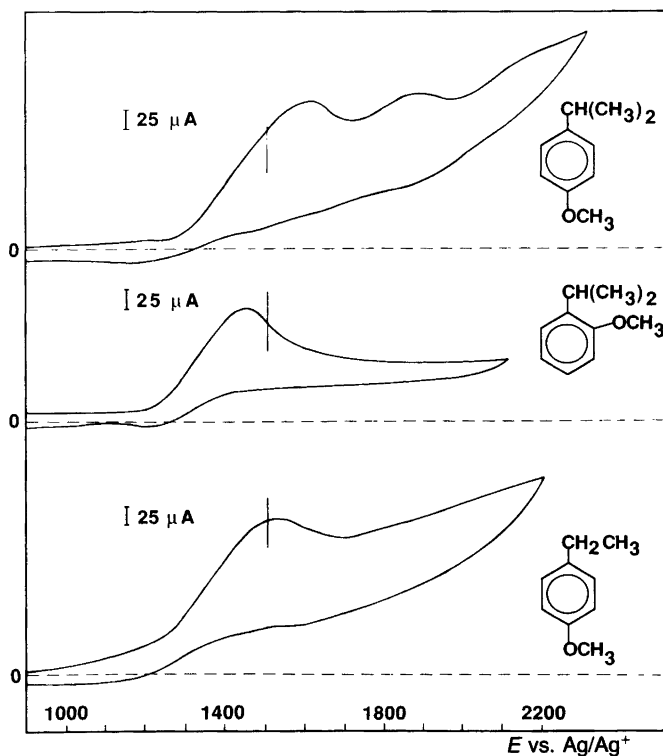


Fig. 1. Cyclic voltammograms of the three starting materials. The potential of each electrolysis is marked in the figure. Working electrode: Glassy carbon. Sweep rate: 50 mV/s.

sponding alkylphenols by ion-pair alkylation according to Brändström.⁴

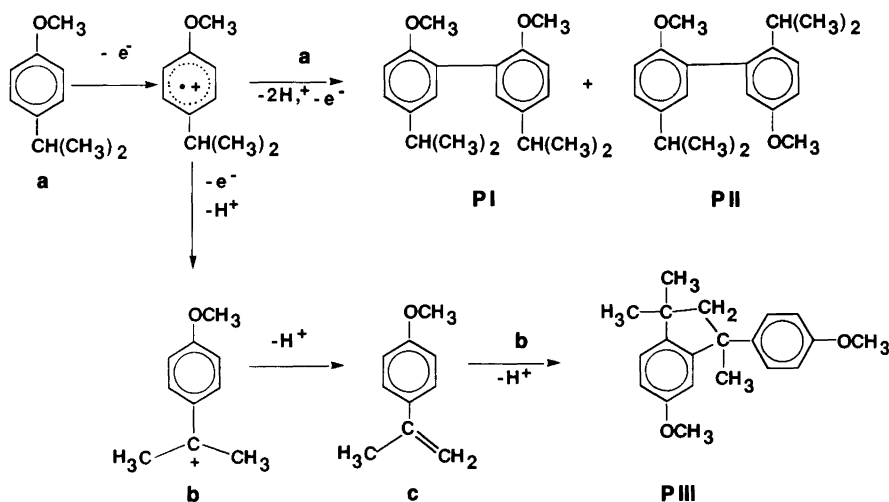
Preparative anodic oxidation of 4-isopropylanisole (30 mg, $2 \cdot 10^{-4}$ mol) was performed under constant potential conditions. In Fig. 1, typical voltammograms for 4-isopropylanisole, 2-isopropylanisole and 4-ethylanisole are shown. In order to avoid interference from product oxidation, the potentials were held in the vicinity of the first oxidation peak. A detailed description of the voltammetric behaviour of these compounds and of some of their oxidation products will be given elsewhere.⁵ After electrolysis, the trifluoroacetic acid was distilled off and sodium hydrogen carbonate was added to the residue until no more carbon dioxide was evolved. The resulting mixture was then agitated for four hours with hexane and then for another two hours with diethyl ether. The ether solution was filtered through a short column of alumina in order to get rid of small amounts of supporting electrolyte. After evaporation of the solvents a total amount of 28 mg of mixed products was obtained. NMR and GLC-MS analyses of the crude extracts revealed that the ether extract consisted mainly of polymeric material. In the hexane extract only a minor amount of polymeric material was observed. The components of the hexane extract were separated by semi-preparative HPLC. A combina-

tion of straight phase and reversed phase chromatography was used. Structures of the identified main products **P II**–**P III** in the hexane extract are shown in Scheme 2. Products having a molecular weight higher than 500 were not identified.

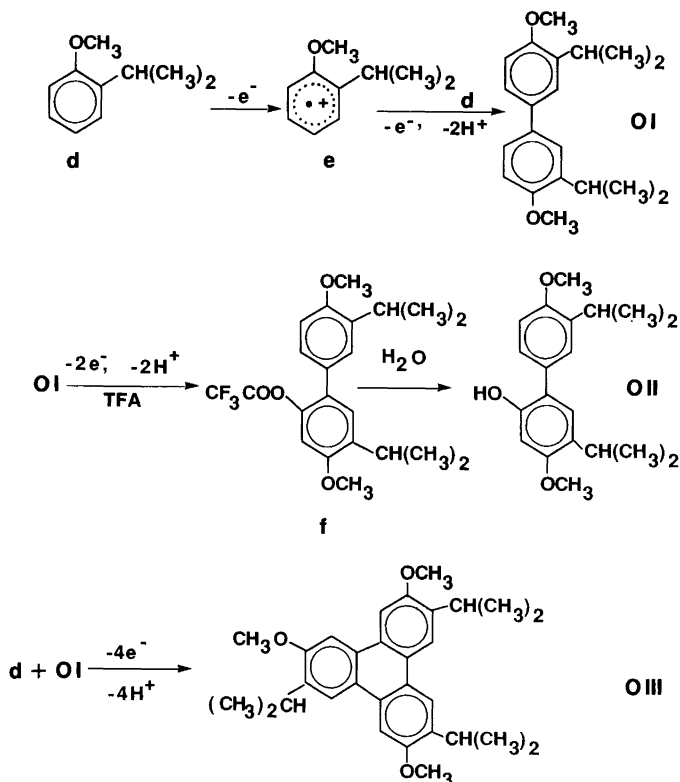
P I: Analyses by GLC-MS and NMR: MS [IP 70 eV; *m/e* (% rel. int.)]: 298 (32.7), 283 (100), 134 (66.0), 165 (10); ¹H NMR (270 MHz, CDCl₃): δ 1.25 (12H, d, *J* = 7.25 Hz), 2.88 (2H, h, *J* = 7.25 Hz), 3.73 (6H, s), 6.91 (2H, d, *J* = 9.0 Hz), 7.12 (2H, d, *J* = 2.5 Hz), 7.17 (2H, ³*J* = 9.0 Hz, ⁴*J* = 2.5 Hz).

P II: Analyses by GLC-MS and NMR: MS [IP 70 eV; *m/e* (% rel. int.)]: 298 (100), 283 (83), 255 (22.3), 241 (33.3), 225 (22.3), 209 (19.9), 195 (15.1), 178 (15.1), 165 (34.9), 152 (18.6), 142 (18.6), 134 (60.0), 119 (22.3), 91 (18.6); ¹H NMR (270 MHz, C₂D₂Cl₄): δ 1.06 and δ 1.22 [(6H, two d, *J* = 6.5 Hz (at 150°C. 1.14 6H, d, *J* = 6.5 Hz)], 1.26 (6H, d, *J* = 7.0 Hz), 2.75 (1H, h, distorted, *J* = 6.5 Hz), 2.88 (1H, h, distorted, *J* = 7.0 Hz), 3.73 (3H, s), 3.86 (3H, s), 6.74 (1H, ³*J* = 8.0 Hz, ⁴*J* = 2.6 Hz), 6.85 (1H, d, *J* = 8.3 Hz), 6.88 (1H, d, *J* = 2.5 Hz), 6.98 (1H, d, *J* = 2.0 Hz), 7.07 (1H, d, *J* = 8.0 Hz), 7.15 (1H, ³*J* = 8.3 Hz, ⁴*J* = 2.0 Hz).

P III: Analyses by GLC-MS and NMR: MS [IP 70



Scheme 2. Product formation on anodic electrolysis of 4-isopropylanisole. Only identified products are included in the scheme.



Scheme 2. Product formation on anodic electrolysis of 2-isopropylanisole. Only identified products are included in the scheme.

eV; *m/e* (% rel. int.): 296 (12.2), 231 (100), 173 (83.0), 158 (10.8), 133 (66.2), 121 (33.8), 91 (16.2), 77 (10.4); ¹H NMR (270 MHz, CDCl₃): δ 1.02 (3H, s), 1.28 (3H, s), 1.62 (3H, s), 2.14 (1H, d, *J* = 12.4 Hz), 2.31 (1H, d, *J* = 12.4 Hz), 3.63 (3H, s), 3.71 (3H, s), 6.50 (1H, d, *J* = 2.5 Hz), 6.65 (2H, d, *J* = 8.60 Hz), 6.71 (1H, ³*J* = 8.25 Hz, ⁴*J* = 2.5 Hz), 6.95 (1H, d, *J* = 8.25 Hz), 5.96 (2H, d, *J* = 8.60 Hz).

Preparative anodic oxidation of 2-isopropylanisole (30 mg, 2 · 10⁻⁴ mol) was carried out as for 4-isopropylanisole. During the electrolysis at 1.5 volt vs. Ag/Ag⁺ the reaction solution turned blue-green coloured. The crude product, amounting to 27 mg, was isolated as described above. The ether extract contained only a small amount of the supporting electrolyte, as could be observed by NMR spectroscopy. The hexane extract was analyzed by HPLC, NMR and

GLC-MS. From GLC-MS, two dominant products of molecular weights 298 and 314 were detected. HPLC analyses revealed another three products. All five products were separated by means of semi-preparative HPLC for identification purposes. Three products were identified as having the structures OI–OIII shown in Scheme 3. Two minor products of molecular weights 284 and 548, corresponding to the molecular formulas C₁₉H₂₄O₂ and C₃₈H₄₄O₃ were isolated but not identified. The molecular formula C₁₉H₂₄O₂ may correspond to a diphenyl ether derivative. Among the products from electrolysis of 2-isopropylanisole, no indane derivative or other products arising from a styrene derivative could be identified.

For the identified products the following data were obtained:

OI: ¹H NMR (270 MHz, CDCl₃): δ 1.25 (12H, d,

$J = 7.12$ Hz), 3.25 (2H, h, $J = 7.12$ Hz), 3.85 (6H, s), 6.88 (2H, d, $J = 8.38$ Hz), 7.31 (2H, $^3J = 8.35$ Hz, $^4J = 2.37$ Hz), 7.37 (2H, d, $J = 2.37$ Hz); MS [IP 70 eV; m/e (% rel. int.)]: 299 (15.5), 298 (100), 283 (32.3), 268 (9.3), 241 (11.8), 226 (11.8), 134 (36.0), 127 (13.6), 119 (10.5).

OII: ^1H NMR (270 MHz, CDCl_3): δ 1.20 (6H, d, $J = 7.0$ Hz), 1.23 (6H, d, $J = 7.0$ Hz), 3.26 (1H, h, $J = 7.0$ Hz), 3.36 (1H, h, $J = 7.0$ Hz), 3.84 (3H, s), 3.87 (3H, s), 5.16 (1H, s), 6.53 (1H, s), 6.94 (1H, d, $J = 7.6$ Hz), 7.01 (1H, s), 7.20 (1H, $^3J = 7.6$ Hz, $^4J = 2.0$ Hz), 7.24 (1H, d, $J = 2.0$ Hz); MS [IP 70 eV; m/e (% rel. int.)]: 314 (68.5), 300 (15.4), 299 (100), 257 (67.9), 142 (38.8), 128 (10.0).

OIII: ^1H NMR (270 MHz, CDCl_3): δ 1.40 (12H, d, $J = 8.0$ Hz), 1.41 (6H, d, $J = 8.0$ Hz), 3.40–3.60 (3H, m), 4.09 (3H, s), 4.10 (6H, s), 7.80 (1H, s), 7.81 (1H, s), 7.88 (1H, s), 8.35 (1H, s), 8.37 (1H, s); MS [IP 70 eV; m/e (% rel. int.)]: 445 (10), 444 (100), 443 (10), 429 (15), 207 (10), 144 (10), 118 (26).

Preparative electrolysis of 4-ethylanisole produced mainly polymeric material and minor amounts of dimeric products, as could be observed from NMR and GLC-MS analyses. Careful analyses of the GLC-MS spectra did not reveal the presence of structures of molecular weight 268, corresponding either to an indane derivative or a dimer of a styrene derivative.

In hydrogen exchange experiments, solutions of the three anisole derivatives were prepared in the same way as for the preparative electrolyses. One-half of each solution was electrolyzed to the extent of 5% of the amount of charge required for one electron and the other half was kept as a reference solution. All solutions were maintained at $40 \pm 0.1^\circ\text{C}$. After electrolysis the substrates were recovered as in the preparative experiments and analyzed by GLC-MS and NMR spectrometry. For 4-isopropylanisole the degree of aliphatic hydrogen exchange amounted to 45% under the influence of electrolysis, whereas for the substrate in the reference solution less than 1% of the aliphatic methyl hydrogens in the isopropyl group were exchanged. An aliphatic hydrogen exchange in 4-isopropylanisole amounting to 45% for the material in the reference solution

was obtained after 45 hours. 4-Ethylanisole and 2-isopropylanisole did not exchange aliphatic hydrogens under any conditions (cf. Refs. 2 and 3). As observed in previous investigations,¹⁻³ no benzylic hydrogen exchange could be observed under the influence of electrolysis, and in the reacted material all six methyl hydrogens were exchanged.

No aliphatic hydrogen exchange could be observed for 4-isopropylanisole on electrolysis when the experiment was carried out in acetic acid-*d*.

Discussion and results

A pronounced effect on the aliphatic hydrogen exchange was observed in electrolysis of 4-isopropylanisole, whereas 2-isopropylanisole and 4-ethylanisole were unaffected. It seems possible that this strong effect in electrolysis of 4-isopropylanisole would be the result if an intermediate benzylic carbocation is formed via anodic oxidation. Strong evidence for such an ion is provided by the formation of the indane derivative **PIII**, which may be formed as shown in Scheme 2 (cf. Ref. 5).

Formation of a benzylic carbocation via electrolysis would have a catalytic effect on the exchange rate if the reaction scheme shown in Scheme 1, as suggested earlier, still holds. The catalytic effect of electrolysis then seems to be consistent with the results of previous experiments,³ where it was noted that addition of a small amount of the suggested styrene derivative **c** in Scheme 2 had a strong influence on the exchange rate which was believed to be due to formation of a benzylic carbocation, a result that supported the reaction mechanism outlined in Scheme 1.

Since the anodic oxidation is carried out at the potential for formation of the radical cation, an alternative mechanism for the exchange reaction would be an $\text{S}_{\text{OE}} 1$ mechanism.¹⁰⁻¹² However, no exchange can be observed for 4-ethylanisole under electrolysis conditions; thus, at the present stage it seems that the mechanism outlined in Scheme 1 should be the most likely.

The resistance of 2-isopropylanisole and 4-ethylanisole to aliphatic hydrogen exchange under the influence of electrolysis might, as claimed previously,² be due to the corresponding benzylic carbocations not being stable enough to be

formed in sufficient amounts. For these two compounds no products related to a benzylic cation could be observed.

The two identified biphenyl derivatives formed by electrolysis of 4-isopropylanisole are products of the kind which could be expected from electrolysis,⁷⁻⁹ as is the structureless polymeric material.

The dimeric product **OII** from oxidation of 2-isopropylanisole was expected. The trimeric product **OIII** may be formed via a reaction between the starting material and a radical cation formed from the dimer **OI** and a subsequent ring-closure after further oxidation. Product **OIII** formed a green coloured solution in TFA, an observation that will be further investigated. The phenolic dimer **OII** probably resulted from hydrolysis, during the isolation procedure, of a nuclear trifluoroacetate formed from **OI** in the electrolysis. No trace of side chain trifluoroacetoxylation could be detected starting from any of the alkylanisoles.

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