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Selective Aliphatic Hydrogen Exchange in 2,4,6-Triisopropyltoluene

ÅKE NILSSON and KÅRE OLSSON

Department of Organic Chemistry, University of Göteborg and Chalmers University of Technology, Fack, S-402 20 Göteborg 5, Sweden

2,4,6-Triisopropyltoluene has been treated with deuteriated trifluoroacetic acid in carbon tetrachloride. In addition to the exchange of the aromatic hydrogens, the hydrogen atoms of the methyl groups in the isopropyl group at position 4 were exchanged. The isopropyl groups at positions 2 and 6 were unaffected, as were the methine hydrogens of all the isopropyl groups. A mechanism for the observed aliphatic hydrogen exchange is proposed. Several other compounds were treated with the same reagent, but no aliphatic hydrogen exchange was observed.

In order to exchange the aromatic hydrogens of 2,4,6-triisopropyltoluene for deuterium, this compound was treated with deuteriated trifluoroacetic acid. The desired exchange occurred, but in addition an exchange of some of the aliphatic hydrogens was also observed. The present paper deals with the last-mentioned exchange reaction for which a mechanism is proposed. The behaviour of several other compounds under the actual experimental conditions is also reported.

EXPERIMENTAL

Mass spectrometric determinations were performed on an AEI MS 902 instrument (at the Department of Medical Biochemistry, University of Göteborg) under the following conditions: electron energy 70 eV, accelerating voltage 8 kV and emission 100 μA. For the mass spectrometric analyses of 2,4,6-tri-*tert*-butyltoluene, *p*-cymene, 2-bromo-1,3,5-triisopropylbenzene, and 2,4-dibromo-1,3,5-triisopropylbenzene an LKB 9000 instrument (at the Department of Medical Chemistry, University of Göteborg) fitted with a gas chromatograph was used. The electron energy was 70 eV. The intensities of the peaks of the mass spectrograms are reported in parentheses as percentages of the base peak, and only the most abundant peaks are reported together with the parent peaks and the isotope peaks corresponding to them. For the NMR analyses Varian A 60 and XL 100 instruments (the latter at the Chemical Centre, University of Lund) were used. The chemical shifts are reported in ppm downfield from tetramethylsilane as internal standard. Gas chromatographic analyses were performed on a Perkin Elmer 900 instrument using columns packed with SE-30 silicon gum rubber.

Deuteriated trifluoroacetic acid with an isotopic purity of 99.5 % ($d_0 = 1.535$) obtained from CIBA was used. The deuteriated sulfuric acid used was CIBA 95 – 98 %, density 1.86×10^3 kg m^{-3}, > 99 % deuterium. Deuterium oxide with an isotopic purity of 99.75 % obtained from CIBA was used.

The following compounds were analytical grade commercial products and were used without further purification: carbon tetrachloride, *p*-cymene, and 1,3,5-triisopropylbenzene (P). Other commercial products were all of reagent grade purity.

2,4,6-Triethyltoluene (MeE) and *1,3,5-triethyl-2,4-dimethylbenzene* (Me_2E) were prepared according to a reported method.[1] *1,3,5-Tri*-tert-*butylbenzene* (B) was prepared according to Baas *et al.*[2] and *2,4,6-tri*-tert-*butyltoluene* (MeB) was prepared according to Myhre *et al.*[3]

2,4,6-Triisopropyltoluene (MeP) was prepared by lithium tetrahydridoaluminate reduction of 2-chloromethyl-1,3,5-triisopropylbenzene, which had been obtained by chloromethylation of 1,3,5-triisopropylbenzene with chloromethyl methyl ether. A similar preparative method has previously been reported.[1] The product was pure according to gas chromatography.

Physical properties of 2-chloromethyl-1,3,5-triisopropylbenzene. Mp. 26 – 28 °C, b.p. 119 °C at 2 – 3 Torr. NMR: δ 6.91 (singlet, 2 H, aromatic), 4.65 (singlet, 2 H, CH_2Cl), 3.28 (heptet, $J = 7.2$ Hz, 2 H, CH), 2.84 (heptet, $J = 7.2$ Hz, 1 H, CH), 1.28 (doublet, $J = 7.2$ Hz, 12 H, CH_3), 1.24 (doublet, J 7.2 Hz, 6 H, CH_3).

Physical properties of MeP. MS: 41 (24), 43 (47), 55 (19), 57 (28), 69 (18), 71 (18), 81 (10),

83 (13), 85 (10), 97 (15), 105 (10), 119 (10), 175 (19), 203 (100), 204 (19), 218 (44.1). 219 (9.1). NMR: δ 6.82 (singlet, 2 H, aromatic), 3.15 (heptet, J 7.2 Hz, 2 H, CH), 2.78 (heptet, J7.2 Hz, 1 H, CH), 2.20 (singlet, 3 H, CH_3), 1.20 (doublet, J 7.2 Hz, 18 H, CH_3).

3-Bromo-2,4,6-triisopropyltoluene (BrMeP) was prepared by bromination of 2,4,6-triisopropyltoluene with molecular bromine in dimethylformamide according to a method previously described.[4] MS: 43 (72), 128 (15), 129 (17), 131 (18), 143 (12), 159 (14), 281 (100), 282 (18), 283 (99), 284 (21), 296 (79.5), 297 (15.3), 298 (78.5), 299 (5.1). NMR: δ 6.92 (singlet, 1 H, aromatic), 4.00 (heptet, J 7.2 Hz, 1 H, CH), 3.48 (heptet, J 7.2 Hz, 1 H, CH), 3.13 (heptet, J 7.2 Hz, 1 H, CH), 2.33 (singlet, 3 H, CH_3),1.38 (doublet, J 7.2 Hz, 6 H, CH_3), 1.21 (doublet, J 7.2 Hz, 12 H, CH_3).

2-Bromo-1,3,5-triisopropylbenzene (BrP) and *2,4-dibromo-1,3,5-triisoprobylbenzene* (Br_2P) were prepared from 1,3,5-triisopropylbenzene according to a method previously described.[4] Mass spectrum for BrP: 43 (62), 115 (17), 117 (15), 128 (18), 129 (17), 145 (13), 239 (15), 241 (15), 267 (100), 268 (19), 269 (98), 270 (16), 282 (43.0), 283 (9.4), 284 (42.8), 285 (7.7). Mass spectrum for Br_2P: 43 (58), 105 (18), 128 (23), 129 (20), 141 (14), 143 (12), 305 (12), 345 (44), 347 (100), 349 (43), 360 (23.8), 361 (6.1), 362 (47.6), 363 (8.5), 364 (22.7).

1,3,5-Triisopropyl-2,4-dimethylbenzene (Me_2P) was prepared from 3-bromo-2,4,6-triisopropyltoluene by treatment first with butyllithium and then with iodomethane. The method has been described by Myhre.[3] Mass spectrum for Me_2P: 41 (25), 43 (37), 119 (12), 133 (14), 147 (16), 217 (100), 218 (18), 232 (32.2), 233 (5.5).

Hydrogen exchange reactions

A. To a solution of 2,4,6-triisopropyltoluene (50 mg, 0.23 mmol) in 1 ml of carbon tetrachloride, 2 ml (26.6 mmol) of deuteriated trifluoroacetic acid was added. The reaction flask was closed in order to avoid contamination with moisture and kept at 40 °C for 60 h. The solvent and the trifluoroacetic acid were then distilled off at reduced pressure. The procedure was repeated three times. The residue, which was found to be pure according to gas chromatography, was then analyzed by means of NMR and mass spectrometry. The product was identified as 3,5-dideuterio-2,6-diisopropyl-4-(1,1,1,3,3,3-hexadeuterio-2-propyl)-toluene (MeP-d_8). Mass spectrum of the product: 41 (10), 43 (21), 49 (12), 177 (60), 183 (26), 207 (62), 208 (75), 211 (100), 226 (69.0), 227 (11.9). NMR: δ 3.15 (heptet, J 7.2 Hz, 2 H, CH), 2.76 (broad singlet, 1 H, CH), 2.21 (singlet, 3 H, CH_3), 1.21 (doublet, J 7.2 Hz, 12 H, CH_3).

B. MeP-d_8 was also obtained when MeP (15 mg, 0.07 mmol) was treated with an excess of deuteriated trifluoroacetic acid (4 ml, 53.2 (mmol) in 1 ml of carbon tetrachloride for 48 h. After 12 h an aliquot was withdrawn, and according to mass spectrometry only two types of molecules had been formed. One of them was 3,5-dideuterio-2,4,6-triisopropyltoluene (MeP-d_2) and the other was MeP-d_8. These compounds had been formed in about equal amounts. It might be noted that no random deuterium distribution occurred among the hydrogen atoms capable of undergoing exchange.

C. Exchange experiments were carried out using the concentrations described under A, once under a nitrogen atmosphere and with solutions freed from oxygen and once under an oxygen atmosphere and with solutions treated with oxygen. The reaction times were in all cases 12 h. By means of mass spectrometry the products were identified as mixtures of MeP, MeP-d_2 and MeP-d_8 The compositions of the mixtures were the same in both cases.

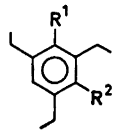
D. The influence of peroxides and of radical inhibitors on the rate of the aliphatic hydrogen exchange was determined. The experimental conditions described under A were used, and after 12 h the reaction products were analyzed by means of mass spectrometry and the relative amounts of MeP, MeP-d_2, and MeP-d_8 were determined. It was found that addition of dibenzoyl peroxide had a marked accelerating influence on the rate of exchange of the aliphatic protons, and it was also found that if the MeP was freed from peroxides (chromatographed on alumina with hexane as eluent) prior to the experiment, the exchange was slowed down. Radical inhibitors like pyrocathecol and iodine had no influence on the rate of exchange, whereas hydroquinone had a marked decelerating influence.

E. Treatments with deuteriated trifluoroacetic acid under the same conditions as used in A were carried out with 1,3,5-triisopropyl-2,4-dimethylbenzene, 2-bromo-1,3,5-triisopropylbenzene, 2,4-dibromo-1,3,5-triisopropylbenzene, 3-bromo-2,4,6-triisopropyltoluene, 1,3,5-triisopropylbenzene, 2,4,6-triethyltoluene, 1,3,5-triethyl-2,4-dimethylbenzene, and *p*-cymene. For none of these compounds could an exchange of aliphatic protons be detected by mass spectrometry. The aromatic protons were exchanged in all compounds except 2-bromo-1,3,5-triisopropylbenzene, 2,4-dibromo-1,3,5-triisopropylbenzene, and *p*-cymene.

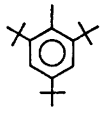
When the same experiment was performed with 2,4,6-tri-*tert*-butyltoluene, the compound underwent a partial decomposition as found by Myhre.[3] The product mixture was analyzed by means of combined gas chromatography and mass spectrometry. In the remaining 2,4,6-tri-*tert*-butyltoluene (amounting to *ca.* 10 %) only the aromatic protons were exchanged.

F. 2,4,6-Triisopropyltoluene (100 mg, 0.46 mmol) was added to a mixture of deuteriated sulfuric acid (9.0 ml, 170 mmol) and deuterium oxide (2 ml, 100 mmol). The reaction mixture was stirred at room temperature for 60 h and was then worked up as previously

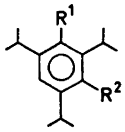
described.[1] According to NMR and mass spectrometry the product consisted of a mixture of 2,4,6-triisopropyltoluene, 3,5-dideuterio-2,4,6-triisopropyltoluene (MeP-d_2), 3,5-dideuterio-2,6-diisopropyl-4-(1,1,1,3,3,3-hexadeuterio-2-propyl)-toluene (MeP-d_8), 3,5-dideuterio-2-isopropyl-4,6-bis(1,1,1,3,3,3-hexadeuterio-2-propyl)-toluene (MeP-d_{14}) and 3,5-dideuterio-2,4,6-tris (1,1,1,3,3,3-hexadeuterio-2-propyl)-toluene (MeP-d_{20}). The two *ortho* isopropyl groups reacted more slowly than the *para* isopropyl group as is evident from the fact that the only species with eight deuterons was the isomer MeP-d_8, identified in section A. As observed in the previous experiments, no partial deuteriation of the methyl groups in an isopropyl group had occurred. The experiment was repeated with 1,3,5-triisopropylbenzene, but, in this case, exchange was found only in the aromatic positions.



$R^1 = CH_3$, $R^2 = H$	MeE
$R^1 = R^2 = CH_3$	Me_2E



Me B



$R^1 = R^2 = H$	P
$R^1 = CH_3$, $R^2 = H$	MeP
$R^1 = R^2 = CH_3$	Me_2P
$R^1 = Br$, $R^2 = H$	BrP
$R^1 = R^2 = Br$	Br_2P
$R^1 = Br$, $R^2 = CH_3$	BrMeP

DISCUSSION

When MeP is treated with deuteriated trifluoroacetic acid in carbon tetrachloride the aromatic protons are exchanged for deuterons as expected. In addition, the protons of the two methyl groups of the isopropyl group in the 4-position are also exchanged. The methine proton of that isopropyl group is not exchanged, however, and the product is MeP-d_8.

When BrP, Br_2P, and *p*-cymene undergo the treatment in question no protons at all are exchanged. When MeE, Me_2E, P, Me_2P and BrMeP are treated as described above, they undergo exchange of the aromatic protons, but all the aliphatic protons are retained.

The compound MeB undergoes decomposition under the actual conditions, but if the reaction is stopped before all the starting material is consumed, only the aromatic protons are exchanged in the remaining MeB.

The observations made may be interpreted in the following way. BrP, Br_2P, and *p*-cymene are not activated enough so as to undergo an electrophilic aromatic hydrogen exchange under the actual conditions. BrP and MeP have different electronic properties but should sterically be quite similar. Their different behaviour indicates that there is a correlation between the ability to undergo aliphatic hydrogen exchange and the reactivity towards electrophiles. The same conclusion can be drawn from a comparison of MeP and *p*-cymene.

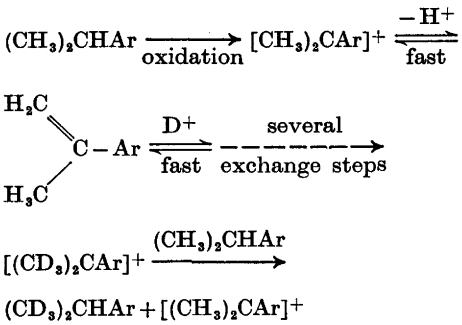
From a comparison between MeE, MeP, and MeB, it can be concluded that it is only in an isopropyl group that the methyl hydrogens can exchange under the experimental conditions used. Ethyl and *tert*-butyl groups are left unaffected, as are the methyl groups directly attached to the benzene rings.

When the behaviour of P, MeP, and Me_2P is compared it is found that not only the electronic properties, but also the steric ones are of importance for the aliphatic hydrogen exchange. P does not exchange any aliphatic hydrogens but MeP does. MeP ought to be more reactive towards electrophiles than P and their difference concerning aliphatic hydrogen exchange is thus consistent with the above-mentioned correlation. Me_2P, on the other hand, does not exchange aliphatic hydrogens. This may be due to steric hindrance since all the isopropyl groups of Me_2P have at least one methyl group in an *ortho* position. In the case of MeP it is only the isopropyl group without an *ortho* substituent that undergoes exchange.

The aliphatic hydrogens of BrMeP are unaffected, but the aromatic hydrogens do ex-

change. This behaviour may be due either to steric hindrance or to the electronic properties of the substrate.

Since it was found that dibenzoyl peroxide had a catalytic effect on the exchange of the aliphatic protons in MeP, the mechanism in Scheme 1 seems to be the most likely one for that reaction.



Scheme 1. Ar denotes a 3,5-diisopropyl-4-methylphenyl group.

A similar mechanism has been suggested by Setkina *et al.*[5] for hydrogen exchange occurring when benzene derivatives containing condensed polymethylene rings were treated with deuteriated sulfuric acid in nitrobenzene. The same result was also obtained when these compounds were treated with deuteriated trifluoroacetic acid[6] and when hexaethylbenzene was treated with a mixture of deuteriated sulfuric acid and deuteriated trifluoroacetic acid.[7]

In the proposed mechanism the substrate is oxidized and a tertiary carbocation is formed. For maximum stabilization of this ion the two methyl groups directly attached to the positive carbon of the side-chain should lie in the plane of the benzene ring. This explains the selectivity of the aliphatic hydrogen exchange (the isopropyl groups without *ortho* substituents are much more reactive than the others). For steric reasons, the isopropyl groups which are next neighbours to other substituents cannot become coplanar with the benzene ring and lose the methine proton as easily as those without such substituents. The carbocation undergoes a rapid hydrogen exchange which occurs *via* an olefin. This step must be faster than the step leading to the deuteriated MeP since only hexadeuteriated or completely nondeuteriated isopropyl groups were observed. Molecules with no methyl deuterons and those with six (or even twelve or eighteen) methyl deuterons were thus found together if the reaction time was short enough. See cases B and F in the Experimental section. The step leading from the carbocation to the product is thought to be a hydride-ion transfer from a methine position of another molecule, and thus the reaction is expected to be of the chain type.

The proposed mechanism explains why there is a correlation with the ability to undergo aliphatic hydrogen exchange and the reactivity towards electrophiles. The intermediate carbocation that is formed in the aliphatic hydrogen exchange has the positive charge delocalized in a way that resembles the delocalization of the positive charge in the intermediate cyclohexadienyl cation formed during electrophilic aromatic substitution. For a discussion of similar cases, see Ref. 8.

Since it is well-known that the methine protons of isopropyl groups attached to aromatic rings can be easily oxidized (one example is the oxidation of cumene [9,10]), the first step in the proposed mechanism seems quite probable.

When strong sulfuric acid was used as the medium, it was indeed possible to exchange the methyl hydrogens of the isopropyl groups *ortho* to the methyl group attached to the ring in MeP. This observation may be explained as a consequence of the more severe conditions in this case, as compared with the case of trifluoroacetic acid. The two *ortho* isopropyl groups underwent exchange more slowly than the *para* group.

Hydrogen exchange in the α-positions of polyalkylated aromatic hydrocarbons has been reported on treatment with trifluoroacetic acid.[11] No such exchange could be detected in the present investigation.

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