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An Unexpected γ-Hydrogen Rearrangement in the Mass Spectra of Di-*ortho*-substituted Alkylbenzenes

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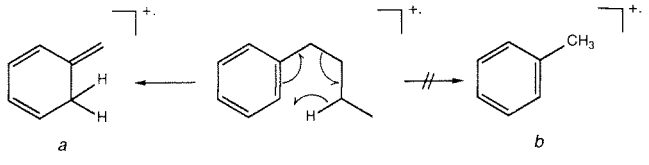
In contradiction of long-accepted mass spectrometric dogma, the site-specific γ-hydrogen rearrangement is observed in alkylbenzenes in which both *ortho* positions are blocked with methyl substituents. Mass spectrometric studies of a series of five trimethyl- and three tetramethylisopentylbenzenes have shown that this rearrangement is only suppressed to a significant degree in those compounds in which all three positions *ortho* and *para* to the isopentyl group are blocked. Deuterium labelling has confirmed the γ-site-specific origin of the migrating H atom while metastable studies have been used to investigate the mechanism of the rearrangement process.

INTRODUCTION

The mass spectra of alkylbenzenes have been extensively investigated and the preferred fragmentation processes are considered to be well understood.[1] For monosubstituted rings, cleavage of the carbon–carbon bond β to the aromatic ring yields the stable tropylium ion at *m/z* 91. When the side chain is of sufficient length to have an available γ-hydrogen, a rearrangement process in which β-fission is accompanied by a specific γ-hydrogen rearrangement becomes a strongly competitive fragmentation route. The spectrum of *n*-butylbenzene, for example, has *m/z* 91 ($[C_7H_7]^+$) as its base peak, but has in addition an ion at *m/z* 92 ($[C_7H_8]^{+\cdot}$) which, at 52% of the base peak, is the second most intense peak in the spectrum.[1a]

The mechanism which generates the $[C_7H_8]^{+\cdot}$ species has been shown to be a six-centred McLafferty rearrangement to yield the stable methene cyclohexadiene ion *a* rather than a four-centred rearrangement which would generate the toluene molecular ion *b* (Scheme 1). Evidence in support of the above comes from the observation of structure-specific ion–molecule reactions in an ion-cyclotron resonance spectrometer,[2] photodissociation studies,[3] collision-induced dissociation (CID) and charge-stripping (CS) studies.[4,5]



Scheme 1

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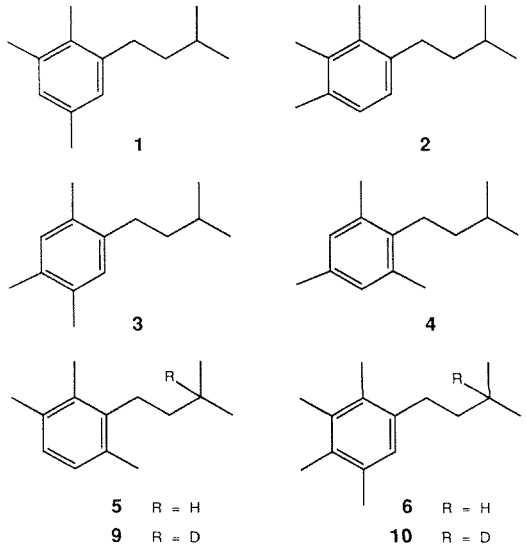
It has long been accepted as a standard rule in organic mass spectrometry that '... this rearrangement process does not occur if both *ortho* positions are substituted so that the six-membered transition state becomes sterically unfavourable.'[6] The example cited is that of 1-octadecyl-2,4,6-trimethylbenzene, for which no rearrangement species is observed.

In a recent geochemical study[7] of carotenoid-derived alkyl benzenes found in crude oils and their source rocks it was discovered that these compounds, which were 2,3,6-trimethyl-substituted with respect to the alkyl side chain, gave mass spectra which showed an appreciable rearrangement peak, in contrast to the general rule described above. This paper describes investigations of this unexpected fragmentation process.

RESULTS AND DISCUSSION



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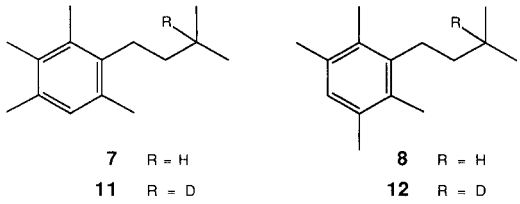


Tetrasubstituted benzenes

The 70-eV electron impact mass spectra of five unambiguously synthesized isomeric isopentyltrimethylbenzenes[7a] (**1–5**) are given in Fig. 1. β-Carbon–carbon bond cleavage in the isopentyl side chain leads to the formation of the peak at *m/z* 133 ($[C_{10}H_{13}]^+$), which is the base peak in all but spectrum **1a**. In spectra **1a–c**, where the compounds **1**, **2** and **3** have one *ortho* position unsubstituted, the expected rearrangement peak at *m/z* 134 ($[C_{10}H_{14}]^{+\cdot}$) is observed. In spectrum **1d**, for

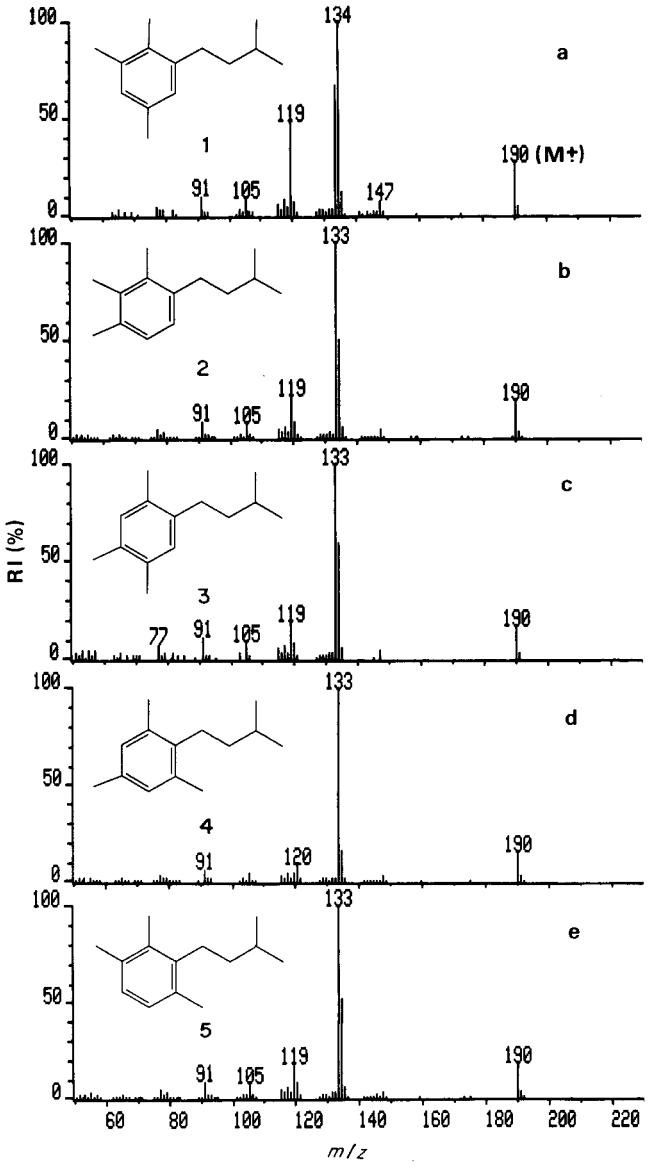


Figure 1. 70 eV EI mass spectra of (a) 1-isopentyl-2,3,5-trimethylbenzene, **1**; (b) 1-isopentyl-2,3,4-trimethylbenzene, **2**; (c) 1-isopentyl-2,4,5-trimethylbenzene, **3**; (d) 1-isopentyl-2,4,6-trimethylbenzene, **4**; (e) 1-isopentyl-2,3,6-trimethylbenzene, **5**.

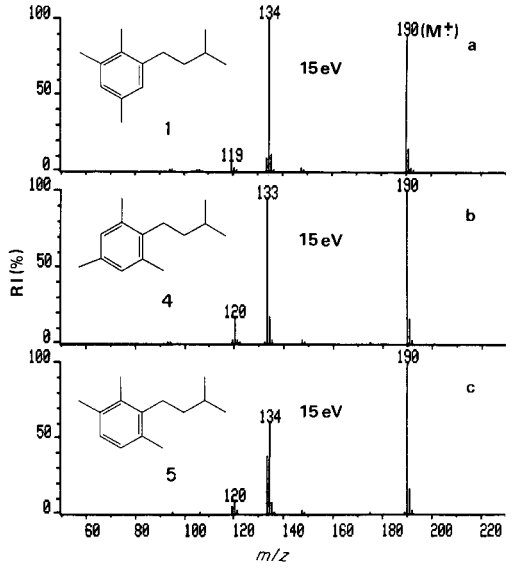


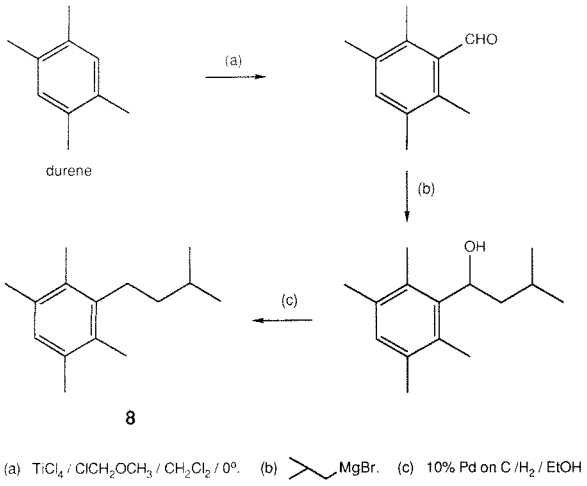
Figure 2. 15 eV EI mass spectra of (a) 1-isopentyl-2,3,5-trimethylbenzene, **1**; (b) 1-isopentyl-2,4,6-trimethylbenzene, **4**; (c) 1-isopentyl-2,3,6-trimethylbenzene, **5**.

the isomer **4** with di-*ortho*- and *para*-methyl substitution, this rearrangement is virtually absent (<2% relative intensity after ^{13}C correction). The spectrum of 1-isopentyl-2,3,6-trimethylbenzene (**5**) (Fig. 1(e)), however, shows an entirely unexpected rearrangement peak at *m/z* 134 which is 42% of the base peak at *m/z* 133 (after ^{13}C correction). This compound has both *ortho* positions substituted with methyl groups and therefore this result is in complete contradiction to the accepted rule.

Examination of the low-energy (15-eV) mass spectra of three of these isomers (Fig. 2(a)–(c)) confirms these findings. Figure 2(c) shows that the rearrangement peak at *m/z* 134 increases considerably, relative to the benzylic cleavage peak at *m/z* 133, for the 2,3,6-trimethyl-substituted isomer **5**. By contrast the isomer **4** with both *ortho* and *para* positions substituted shows a low-electron-volt spectrum (Fig. 2(b)) in which the cleavage peak remains by far the dominant fragmentation pathway.

Pentasubstituted benzenes

The results obtained for the tetrasubstituted benzenes **1–5** suggested the synthesis of the three tetramethyl isomers **6**, **7** and **8**, which each have only one position unsubstituted, *ortho*, *meta* or *para* to the isopentyl substituent. This was achieved as outlined in Scheme 2 for the synthesis of **8**, starting from the readily available isomeric tetramethylbenzenes. Their ^1H NMR spectra (Table 1) confirmed the structural identity of the products. Figure 3(a)–(f) gives the 70-eV and 15-eV spectra of these three isomers. It can be seen that the rearrangement ion, this time at *m/z* 148, is significant only in the two isomers which have either the *ortho* position (**6**) or the *para* position (**8**) unsubstituted. The isomer **7**, which has only the *meta* position unsubstituted, shows the cleavage peak at *m/z* 147 to be predominant, although the rearrangement ion at *m/z* 148 is somewhat larger than in the corresponding tetrasubstituted benzene (**4**).



Scheme 2 Synthesis of compound **8**.

From these spectra, it can be deduced that the rearrangement ion is significant not only when an *ortho* position on the ring is unsubstituted, but also when the *para* position is unsubstituted. The behaviour of 1-isopentyl-2,3,5-trimethylbenzene (**1**), which has both an *ortho* position and the *para* position unsubstituted, can be seen as supporting this proposal. Figures 1(a) and 2(a) show that this compound undergoes the most favourable formation of $[C_{10}H_{14}]^{+\cdot}$ ions (*m/z* 134) of all of the trimethyl isomers examined (the 1-isopentyl-3,4,5-trimethyl isomer was not included).

Metastable studies

Molecular ions of the 2,3,5- and 2,3,6-trisubstituted compounds **1** and **5** show virtually only one unimolecular fragmentation in the first field-free region (1st FFR), namely, the formation of ions with *m/z* 134.

An attempt was made to investigate the structure of the *m/z* 134 daughter ions formed in the ion source, by the use of CID. The three isomeric tetramethylbenzenes—prehnitol, durene and isodurene—were examined to provide reference spectra. The CID spectra of their molecular ions, generated with electron energies of 70 eV or 15 eV, were identical. This is in accord with recent findings on the xylene molecular ions,[8] where differences in the CID spectra were small and could only be observed with a nominal 10 eV as electron ionizing energy.

Table 1. ^{1}H NMR assignments[a] (200 MHz) for compounds 6, 7 and 8

Proton(s)	6	7	8
ArH	6.82s	6.84s	6.82s
$ArCH_2$	2.56m	2.60m	2.64m
$ArCH_3$	2.25s(3H)	2.26s(3H)	2.22s(6H)
	2.20bs(6H)	2.23s(6H)	2.18s(6H)
	2.17s(3H)	2.16a(3H)	
Me_2CH	1.63m[b]	1.68m[b]	1.68m[b]
$CH-CH_2$	1.40m	1.31m	1.31m
$(CH_3)_2CH$	0.96d *J*6.6 Hz[c]	0.98d *J*6.6 Hz[c]	0.98d *J*6.6 Hz[c]

[a] *δ*, ppm from internal Me_4Si, in $CDCl_3$.
[b] Not present in spectra of deuterated analogues **10–12**.
[c] Present as a singlet in spectra of deuterated analogues.

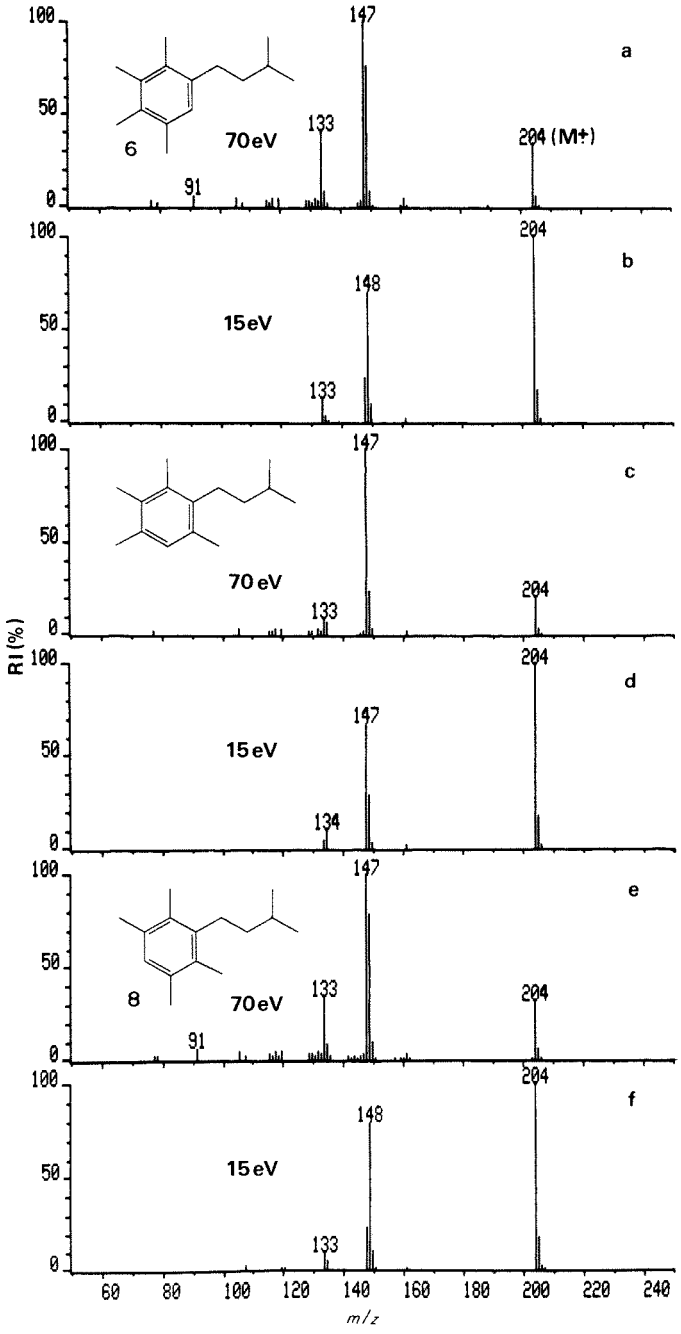
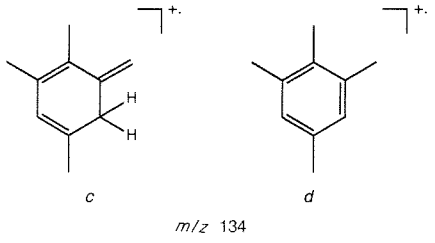


Figure 3. EI mass spectra of 1-isopentyl-2,3,4,5-tetramethylbenzene (**6**) at (a) 70 eV and (b) 15 eV: 1-isopentyl-2,3,4,6-tetramethylbenzene (**7**) at (c) 70 eV and (d) 15 eV; 1-isopentyl-2,3,5,6-tetramethylbenzene (**8**) at (e) 70 eV and (f) 15 eV.

The CID spectra of the *m/z* 134 ions, generated at 70 eV from the 2,3,5- and 2,3,6-trisubstituted compounds **1** and **5**, appeared to be identical but, for the 2,3,6- compound in particular, the spectrum contained significant interferences from the ^{13}C of the *m/z* 133 base peak (Fig. 1(e)). Lowering the electron energy to 15 eV (Fig. 2(c)) reduced this problem to some extent and a further comparison of the CID spectra with the CID spectrum of *m/z* 133 from the 2,4,6-tetrasubstituted compound **4** (Figs 1(d) and 2(b)) accounted for these interfering peaks. The final conclusion was that the CID spectra of

the 2,3,5- and 2,3,6- compounds were indeed identical and further, they showed no differences from the CID spectra of the three reference isomeric molecular ions of the tetramethylbenzenes.

It had been previously observed,[4,5] for the case of *n*-butylbenzene and toluene, that the two $[C_7H_8]^{+\cdot}$ species *a* and *b* could be differentiated using CID. The $[C_7H_8]^{+\cdot}$ ion in the *n*-butylbenzene spectrum has the methene cyclohexadiene structure *a*, which shows a considerably enhanced loss of 14 u in its CID spectrum.[5] In the present work, this enhanced loss of 14 u was not observed in the CID spectrum of those ions which might be expected initially to have the trimethyl-substituted methene cyclohexadiene structure *c*, i.e. the *m/z* 134 ions formed in the ion source from 1-isopentyl-2,3,5-trimethylbenzene (**1**). This region of the CID spectrum was identical to that of the molecular ions of isodurene *d*.



It would appear, therefore, that the threshold for isomerization of these $C_{10}H_{14}$ ionic species to a common fragmenting structure is lower than the threshold for fragmentation in the CID experiment and therefore they cannot be distinguished by this method.

Deuterium labelling studies

To confirm that the migrating hydrogen atom originates from the γ-(3′)-position of the sidechain, the deuterium-labelled analogues **9** to **12** of the three penta- and one tetra-alkylated benzenes **5** to **8** were synthesized. In the 70- and 15-eV mass spectra of all four compounds, the rearrangement ion shifted up almost quantitatively by 1 u to *m/z* 135 (**9**) or *m/z* 149 (**10**, **11**, **12**) (Fig. 4(a)). This observation was supported by *B/E* scans of the $M^{+\cdot}$ of **9**, **10** and **12** which showed only the deuterium-containing rearrangement species as a daughter ion (Fig. 4(b)).

A *B/E* scan of the rearrangement ion at *m/z* 135 in **9** and 149 in **10** and **12** (Fig. 4(c)) showed that the major unimolecular 1st FFR metastable fragmentation in all three cases was the loss of a CH_3 radical accompanied by only a weak loss of CH_2D.

Mechanism of the rearrangement process

On the basis of the above results, it is possible to draw some conclusions concerning the mechanism of the rearrangement process in the di-*ortho*-substituted compounds under study.

(i) The rearrangement involves the specific transfer of the hydrogen in the γ-(3′)-position of the isopentyl side chain.

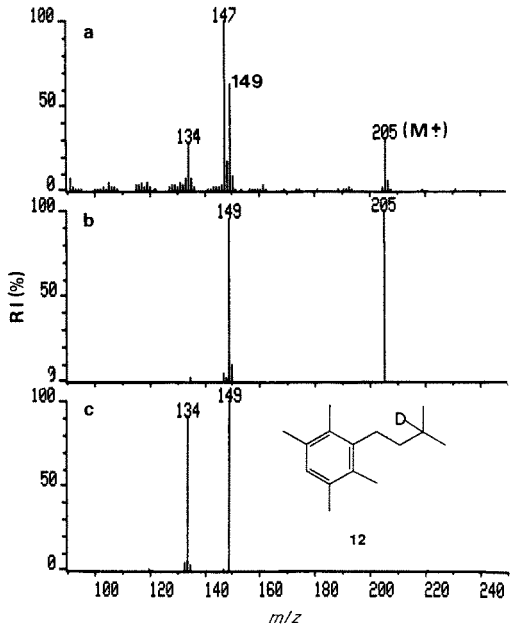
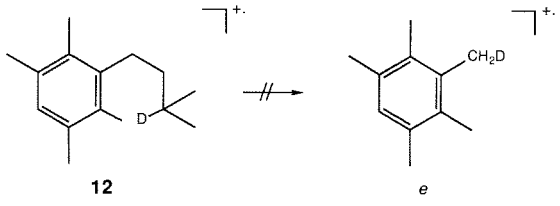


Figure 4. (a) 70-eV EI mass spectrum of deuterated compound **12**. (b) and (c) *B/E* linked scans of $M^{+\cdot}$ (*m/z* 205) and rearrangement ion (*m/z* 149) in the mass spectrum of **12**.

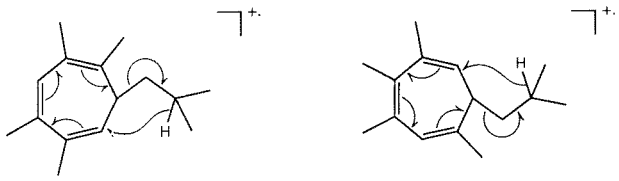
(ii) When both *ortho* positions are blocked, the γ-hydrogen does not undergo a 1,4-transfer to the benzylic position, i.e. **12** ↛ *e*. If this were the case, one would expect that the unimolecular metastable losses of CH_3 and CH_2D from ion *e* would show a statistical value of 4:1, whereas the observed value is approximately 20:1 (Fig. 4(c)).



(iii) Except in the unlikely event of homolytic cleavage of the benzylic C—C bond occurring prior to hydrogen transfer, giving rise to a loose association of the resulting alkyl radical and the benzylic cation, it is sterically impossible for the γ-hydrogen atom to migrate to a vacant *meta* or *para* position.

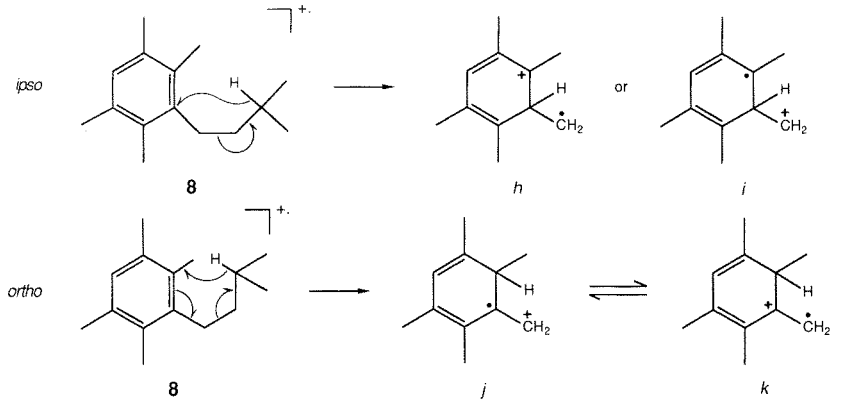
(iv) Methyl group migration around the aromatic ring prior to rearrangement to create a free position *ortho* to the isopentyl substituent can be ruled out. If this were to take place, all three isomers **6**, **7** and **8** would be expected to show the rearrangement to a similar extent. While the rearrangement ion at *m/z* 148 in **6** and **8** has about the same relative intensity (~65%, Fig. 3(a) and (e)) it is significantly reduced in **7** (~12%, Fig. 3(c)).

(v) Ring expansion of the $M^{+\cdot}$ of **8** to the cycloheptatriene radical ion *f* could provide an explanation for the facile rearrangement of the γ-hydrogen atom. One would also, however, expect the $M^{+\cdot}$ of **7** to undergo a similar ring expansion to give ion *g*, which in turn should show γ-hydrogen transfer to a comparable degree. That it is not a significant process in **7** would again tend to exclude this mechanism.



f *g*

(vi) Two remaining rationalizations for the process are that the γ-hydrogen can migrate either to the *ipso* position to give *h* or *i* or to the blocked *ortho* positions to give *j*/*k*, as shown in Scheme 3 for compound **8**.



Scheme 3

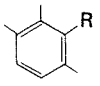
While our studies to date do not permit us to distinguish between the above two processes, the distonic ions *h* and *i* would be expected to be of higher energy than ions *j*/*k*, in which the charge radical can be delocalized over six carbon atoms. There should be little difference in the steric requirements for both processes. Like the two previously proposed mechanisms, however, it is difficult to explain the difference in the observed extent of the rearrangement in **7** and **8** based on either the *ipso* or the *ortho* rearrangement pathways. One relevant observation documented by McLafferty[9] is the difference between the relative intensities of the $[C_8H_{10}]^{+\cdot}$ rearrangement ion in the mass spectra of 1-methyl-3-*n*-propyl- and 1-methyl-4-*n*-propylbenzene (5.5 and 0.9%, respectively). This has been rationalized 'in terms of the relative charge stabilization in their initiating canonical forms'. Thus, even with both *ortho* positions free, substitution at the *para* position exerts a marked retarding effect on the McLafferty rearrangement process.

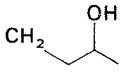
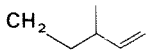
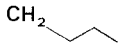
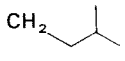
One interesting additional observation is the presence of a prominent odd-electron ion at *m*/*z* 120 in the 70- and 15-eV mass spectra of 1-isopentyl-2,4,6-trimethylbenzene (**4**) (Figs 1(d) and 2(b)), which is of minor significance in the spectra of the other isomers. A *B*/*E* scan established that this ion was derived from the $M^{+\cdot}$ and formally corresponds to loss of the complete isopentyl side chain with a hydrogen transfer to the benzene ring. In the spectrum of 1-isopentyl-2,3,4,6-tetramethylbenzene (**7**) (Fig. 3(c)), the corresponding ion is present at *m*/*z* 134 and becomes more significant at lower electron voltages (Fig. 3(d)). The 15-eV mass spectrum of **11**, the deuterated analogue of **7**, showed that the *m*/*z* 134 ion had shifted to *m*/*z* 135, confirming that it is the γ-hydrogen that migrates to the ring during this side chain cleavage process.

CONCLUSIONS

The observation of this unexpected rearrangement prompted a search of the literature to see whether mass spectral data on structurally similar compounds could be found. As has been shown in this work, for the rearrangement to proceed when both *ortho* positions are blocked, one requirement is that the *para* position must be unsubstituted. Some relevant examples of other 2,3,6-trimethylalkylbenzenes are given in Table 2.

Table 2. Mass spectral data (70 eV) for rearrangement ion versus benzylic cleavage ion (taken as 100) in selected 2,3,6-trimethylalkylbenzenes



R	*m*/*z* 133	*m*/*z* 134[a]	Ref.
	100[b]	87	10
	100[b]	35	11
n-$C_{19}H_{39}$	100[c]	39	12
	100[b]	6	13
	100[b]	42	This work

[a] Corrected for ^{13}C of *m*/*z* 133.
[b] Base peak in spectrum.
[c] Base peak is *m*/*z* 386.

For all compounds listed except that possessing an *n*-butyl side chain, the rearrangement ion is very significant. It is interesting to note that no comment was made in any of the papers (Refs 10–13) regarding the origin of the *m*/*z* 134 ion. The extent of the rearrangement appears to be related both to the stability of the neutral fragment lost as well as to the γ-C—H bond energy, assuming γ-specificity of H transfer in all cases. Similar energy considerations pertain to the McLafferty rearrangement in simple alkylbenzenes. For example,

the *m/z* 92 rearrangement ion *a* has a relative intensity (corrected for ^{13}C) of 2%, 45%, 50%, 100%, 100% in the mass spectra of *n*-propyl-, *n*-butyl, 2′-methylpropyl-, 2′-methyl-1-butyl-, and 3′-methyl-1′-butylbenzenes and is also the base peak in *n*-alkylbenzenes where the chain is longer than 8 carbon atoms.[1a] In all the above cases, the *m/z* 91 ion *b* is either the base peak or the next most abundant peak in the spectrum.

Although the precise nature of the γ-hydrogen rearrangement process in di-*ortho*-substituted alkylbenzenes is as yet unresolved, the evidence favours a six-membered McLafferty rearrangement to the blocked *ortho* position to give a methene cyclohexadiene radical ion species.

EXPERIMENTAL

Mass spectrometry

Mass spectra were run on VG7070F or VG70E mass spectrometers using either an AGHIS, septum inlet or a gas chromatograph as the sample introduction system. Unimolecular and collision-induced (helium gas) decompositions occurring in the 1st FFR were recorded using *B/E* scans. The electron energy was set at a nominal value of 70 or 15 eV.

Synthesis

The synthesis and characterization of the five isomeric isopentyltrimethylbenzenes **1–5** has been reported.[7a]

The preparation of the three isomeric isopentyltetramethylbenzenes **6**, **7** and **8** was carried out using as starting materials the commercially available tetramethylbenzenes, durene (1,2,4,5-tetramethylbenzene), isodurene (1,2,3,5-tetramethylbenzene) and prehnitol (1,2,3,4-tetramethylbenzene). These were converted to their corresponding tetramethylbenzaldehyde[14] which, on treatment with 2-methylpropylmagnesium bromide followed by hydrogenolysis to remove the benzylic alcohol functionality, furnished the required isopentyltetramethylbenzene (Scheme 2). The 3′-[$^2H_1$]-analogues were prepared in high isotopic purity (>95%) by the same procedure, using 2-[$^2H_1$]-2-methyl-1-bromopropane for the Grignard reaction. 2-[$^2H_1$]-2-Methyl-1-bromopropane was prepared from diethyl-2,2-dimethylmalonate following the procedure reported by Duffield *et al.*[15] for the synthesis of 2,2-[$^2H_2$]-bromopropane from diethyl 2-methylmalonate.

All intermediates in and products of the syntheses were fully characterized by ^1H NMR and mass spectra. The isopentyltetramethylbenzenes **6–8** were purified by MPLC on silica gel using *n*-pentane as eluent. The purity of these compounds was checked by gas chromatography and gas chromatography/mass spectrometry on a 2% OV-17 column.

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