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REACTIVITY AND REACTION PATTERNS OF ALKYL ALKOXYBENZENE RADICAL CATIONS. MECHANISTIC PATHWAYS OF THE REACTIONS BETWEEN 2,5-DI-*TERT*-BUTYL-1,4-DIMETHOXYBENZENE AND PERFLUORODIACYL PEROXIDES

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In the reactions of 2,5-di-*tert*-butyl-1,4-dimethoxybenzene (1) with different oxidants, the radical cation $1^{+\cdot}$ is always detectable by EPR. However, the observed reactivity of $1^{+\cdot}$ depends greatly on the oxidation systems employed. In $S_2O_8^{2-}$–Cu^{2+}–HOAc and Ce^{4+}–HOAc systems (HOAc = acetic acid), $1^{+\cdot}$ appears to have long lifetimes and does not undergo fragmentation spontaneously. In contrast, in $(R_FCO_2)_2$–$CF_2ClCFCl_2$ (F113) systems, the readily formed $1^{+\cdot}$ is short-lived, and large amounts of de-*tert*-butylation products have been isolated. Experimental results imply that the C—C bond cleavage involved in de-*tert*-butylation could be a consequence of an attack by perfluoroacyloxy radical on $1^{+\cdot}$ in their original solvent cage. The fact that addition of methanol to the reaction mixture leads to the formation of a large amount of *t*-$BuOCH_3$ (46%) and other evidence suggest that the *tert*-butyl group leaves as a carbocation. On the basis of these results, we conclude that the reactions of 1 with $(R_FCO_2)_2$ are initiated by electron transfer and followed by a fast coupling of various radical species, namely, $1^{+\cdot}$ with $R_FCO_2^{\cdot}$ or with $R_F^{\cdot}$ in the solvent cage, to form σ-complexes which collapse or react with nucleophiles to yield the final products.

INTRODUCTION

The chemistry of ion radicals has become an interesting and important subject of study, and an increasing number of reports on both mechanistic investigations[1–5] and synthetic applications[6,7] have been published in recent years. The structure, properties and reactions of radical cations have been widely investigated by means of EPR,[8] anodic oxidations,[9] radiolysis[10] and fast spectroscopy,[11] etc. The important reaction pathways of radical cations include deprotonation, oxidation, addition, substitution, dimerization and fragmentation. Some of these, e.g. deprotonation processes,[12] have been subjected to extensive studies.[4,13] However, a few problems, especially mechanistic details, still remain unsolved for this elementary step. Also, there are other questions of basic significance. For instance, what is the reactivity pattern of arene radical cations in their reactions with nucleophiles? Can arene radical cations fragment, and how?

Radical reactions of alkyl alkoxybenzene with diacyl peroxides, e.g. substituted benzoyl peroxides[14] and perfluorodiacyl peroxides,[15,16] have been found to be good models for studying some of the aforesaid problems. A general mechanism involving several reaction channels of the arene radical cations has been proposed by Walling and Zhao[14] (Scheme 1). As shown in Scheme 1, unsubstituted dimethoxybenzenes and $(ArCO_2)_2$ gave products (3) mainly derived from ring substitution. In contrast, reaction of 2,5-dialkyl-1,4-dimethoxybenzenes only yielded small amounts of ring-substituted products. In fact, from 2,5-dimethyl-1,4-dimethoxybenzene (2) a 90% yield of substituted benzyl ester 4 was obtained, and from 2,5-di-*tert*-butyl-1,4-dimethoxybenzene (1) an appreciable amount of the de-*tert*-butylation–benzoyloxylation product 5 was isolated. Conceivably, the benzyl ester 4 could be formed via deprotonation of the radical cation $2^{+\cdot}$. However, it was not clear whether the C—C bond cleavage involved in debutylation gave a butyl radical or a butyl cation. In fact, the problem of knowing and understanding all the possible pathways of the radical cation $1^{+\cdot}$ remained intriguing and unsolved.

In order to answer these questions, we have redesigned our experiments by studying the reactions of the

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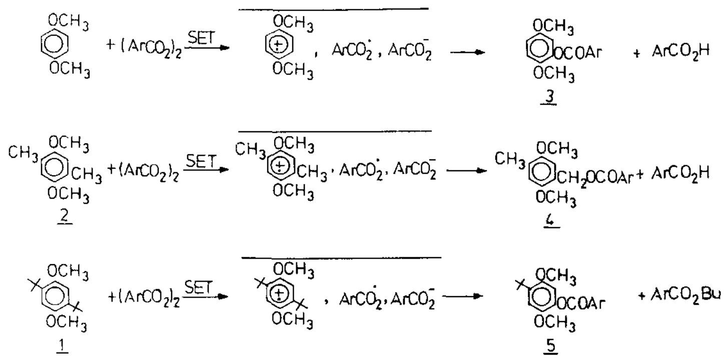
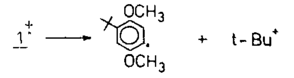


Scheme 1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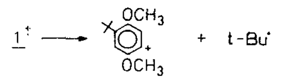
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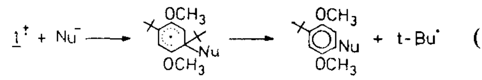
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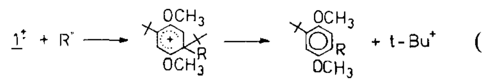
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same substrate **1** in different oxidation systems. In this work, our attention was focused on whether the radical cation $\mathbf{1}^{+\cdot}$ fragments spontaneously, as shown in equations (1)–(2), or whether it fragments only after a nucleophile [equation (3)] or a radical [equation (4)] has attacked. A highly interesting situation exists here, viz. within the same solvent cage the radical cation $\mathbf{1}^{+\cdot}$ can either pick a nucleophile ($ArCO_2^-$) or a structurally 'identical' radical ($ArCO_2^\cdot$) as its reaction partner. Identification of *t*-Bu$^\cdot$ as the sole fragmentation product would confirm the former course [equation (3)] and of *t*-Bu$^+$ the latter [equation (4)]. Incidentally, the topic of radical cation reactivity with nucleophiles has recently aroused much concern among chemists.[1-3]

RESULTS AND DISCUSSION

EPR study

When substrate **1** was added to each of the four different oxidation systems, namely $Ce(SO_4)_2$–HOAc (HOAc = acetic acid), $S_2O_8^{2-}$–Cu^{2+}–HOAc, $(C_6F_5CO_2)_2$–$CF_2ClCFCl_2$ (F113) and $(n\text{-}C_3F_7CO_2)_2$–F113, in each instance a well resolved and identical EPR spectrum was readily obtained. The EPR spectrum of the radical species, a heptet–triplet ($g = 2{\cdot}0025$) as shown in Figure 1, clearly shows that the observed radical species has six equivalent methoxy protons with a hyperfine splitting constant (hfsc) of 3·24 G and two equivalent aromatic protons with hfsc of 1·00 G. Thus the characterization of radical cation $\mathbf{1}^{+\cdot}$ is unequivocally established.

The observed stability of the radical cation $\mathbf{1}^{+\cdot}$ varied greatly with the oxidation systems used. In the $Ce(SO_4)_2$–HOAc system, the EPR signal of $\mathbf{1}^{+\cdot}$ was fairly strong and well resolved. No significant decay was noticed for several hours, hence this system was useful for making arene radical cations of this kind in solution. In contrast, the strong EPR signal of the same radical recorded immediately after mixing **1** with the $(R_FCO_2)_2$–F113 solution disappeared within a few minutes at room temperature. The simultaneous observation of the colour change of the reaction mixture, i.e. from green–yellowish to slightly yellow, could also be taken as an indication of the easy formation and the fast decay of the radical cation $\mathbf{1}^{+\cdot}$.

We believe that such large differences in the stability and reactivity of the radical cation $\mathbf{1}^{+\cdot}$ generated in different oxidation systems might lead to the formation of different products. Product studies of these interesting reactions are presented here.

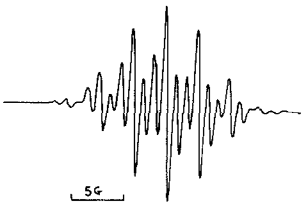


Figure 1. EPR spectrum of the radical cation $\mathbf{1}^{+\cdot}$

Oxidation of 1 by $Ce(SO_4)_2$ in HOAc

The substrate **1** was readily oxidized by cerium(IV) sulphate in glacial acetic acid at room temperature to the radical cation $\mathbf{1}^{+\cdot}$, as indicated by colour changes and proved by EPR identification. After stirring for 48 h, the green–yellowish mixture was treated with water and the crude mixture was analysed by ^1H NMR spectroscopy and gas chromatography (GC). Surprisingly, no product formation was detectable; rather, complete recovery of the substrate **1** was obtained. These observations indicate that the one-electron oxidation of **1** by Ce(IV) in HOAc is a reversible reaction and that the radical cation $\mathbf{1}^{+\cdot}$ thus generated, possibly in a highly solvated state, does not undergo fragmentation by itself and is relatively unreactive toward attacks by nucleophiles, e.g. AcO^- or HOAc molecules. If the latter statement were true, then equation (4) would represent a much faster reaction than equation (3), i.e. the radical cation $\mathbf{1}^{+\cdot}$ might prefer to react with a radical rather than with an anion.

Oxidation of 1 by $(C_6F_5CO_2)_2$ in F113

This reaction is similar to that with non-fluorinated benzoyl peroxides,[14] and the debutylated product **6** was isolated as the predominant product [see equation (5)]. Therefore, this system can be used as one of the model systems for studying the fragmentation patterns of $\mathbf{1}^{+\cdot}$ and other related radical cations.

In addition to the major product **6** and *tert*-butyl pentafluorobenzoate (**7**), pentafluorobenzoic acid was also detected by titration, and the considerable amount of isobutene (yield 23% based on reacted **1**) evolved was identified by GC and quantitatively converted into its dibromide. Further, small amounts of 2,5-di-*tert*-butyl-*p*-benzoquinone (**8**) and methyl pentafluorobenzoate together with a trace of 2,5-di-*tert*-butyl-3,6-dimethoxyphenyl pentafluorobenzoate (**9**) were detected by GC and mass spectrometry (MS), but no carbon dioxide could be detected by careful GC.

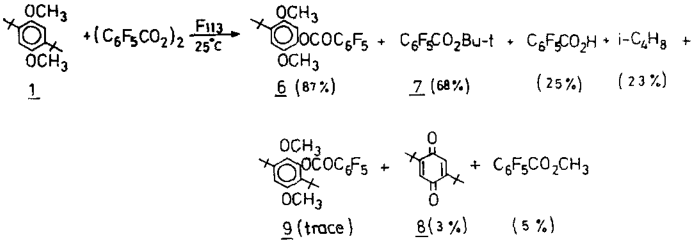
The careful product studies described above have already given us an initial and tentative answer to the question posed in the Introduction, namely that after $\mathbf{1}^{+\cdot}$ has been attacked by a radical species, e.g. $C_6F_5CO_2^{\cdot}$, it will eject a t-Bu^+ ion because isobutene is a product. In order to demonstrate this preliminary conclusion more rigorously, we further carried out product studies on the same reaction in solvent systems with F113 mixed with different co-solvents. The results are summarized in Table 1. Clearly, all the following facts vindicate our preliminary conclusion: (1) in the $BrCCl_3$–F113 mixture, t-BuBr, an expected product from t-$Bu^{\cdot}$, is not formed, whereas isobutene (20%) rather than isobutane is one of the products; (2) the yields of **7** decrease along the series $BrCCl_3$, MeOH, HOAc, H_2O, which is roughly also a series with ascending polarity and proton donicity (two H atoms in H_2O); (3) all the predicted products derived from t-Bu^+, i.e. t-BuOMe, t-BuOAc and t-BuOH, are isolated in moderate yields from each of the solvent mixtures with MeOH, HOAc and H_2O, respectively. Apparently, these products are formed at the expense of the *tert*-butyl ester **7**. If this is true, then the ester product **7** is probably only partly (perhaps no more than 22%) formed in the solvent cage.

Table 1. Yields of produces (%) of the reactions of **1** with $(C_6F_5CO_2)_2$ in solvent mixtures of F113 with a co-solvent at 20 °C[a]

Co-solvent	6	7	*t*-BuOH	*t*-BuOMe	*t*-BuOAc
$BrCCl_3$	86	68	None	None	None
CH_3OH	82	38	5	46	None
AcOH	80	26	None	None	49
H_2O	70	22	22	None	None

[a] **1** (25 mg, 0·1 mmol), $(C_6F_5CO_2)_2$ (42·2 mg, 0·1 mmol), F113 (0·2 ml), Co-solvent (0·2 ml). Yields are calculated on the basis of Scheme 2.

On the basis of all the above-mentioned observations, we propose the steps shown in Scheme 2 as the main possible mechanistic pathways for the reaction. A notable feature of Scheme 2 is that two possible pathways (A–C and B) are postulated for the formation of the σ-complex **10**. In path A–C, the evanescent radical anion of the caged-pair CP-I fragments spontaneously into $C_6F_5CO_2^-$ and $C_6F_5CO_2^{\cdot}$, which quickly attacks the radical cation. In path B, the



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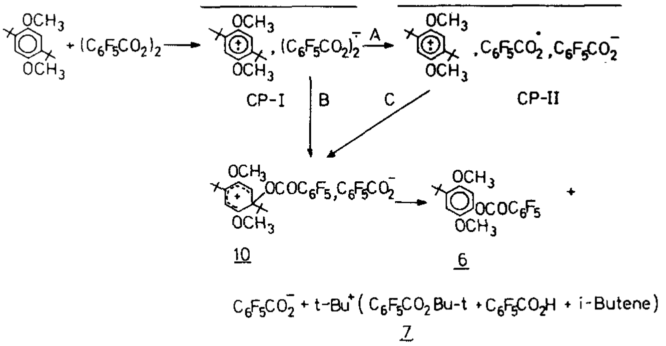


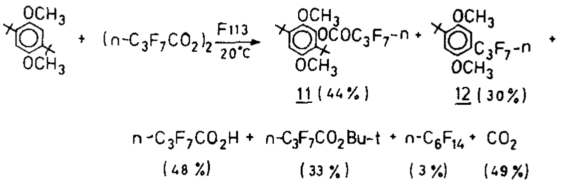
Scheme 2

paired radical ions collapse into products (**10** and $C_6F_5CO_2^-$) before the radical anion can fragment.

At this point we should mention another key observation, namely that no trace of CO_2 has ever been detected in this reaction with $(C_6F_5CO_2)_2$ as the acceptor. This fact can conform with either or both of the following two possibilities: (1) path B overwhelmingly predominates; (2) path A–C operates, and the extremely fast fragmentation of $(C_6F_5CO_2)_2^{-\cdot}$ is followed by the colligation of $\mathbf{1}^{+\cdot}$ with $C_6F_5CO_2^{\cdot}$ with a rate faster than the decarboxylation of $C_6F_5CO_2^{\cdot}$ (estimated $k_{\mathrm{dec}} = 10^7–10^8\,s^{-1}$)[17] and its rate of diffusion from the cage.

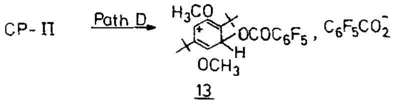
In order to gain more insight into the arguments posed above, we studied the product distribution by GC and ^1H NMR of the reaction with $(n\text{-}C_3F_7CO_2)_2$ as the acceptor, because $n\text{-}C_3F_7CO_2^{\cdot}$ is expected to decarboxylate much faster than $C_6F_5CO_2^{\cdot}$, perhaps with a rate comparable to that of $C_2H_5CO_2^{\cdot}$ ($3 \cdot 3 \times 10^{10}\,s^{-1}$).[17] Indeed, both undecarboxylated and decarboxylated colligation products **11** (44%) and **12** (30%) were formed, together with a large amount of CO_2 (49%) and some colligation product of $n\text{-}C_3F_7^{\cdot}$, i.e. $n\text{-}C_6F_{14}$(3%). Therefore, path A–C appears to be not only viable, but also a more important (or more likely) path than path B. The data also indicate that the rates of combination of the radical cation $\mathbf{1}^{+\cdot}$ with radicals are comparable to the rates of decarboxylation of $RCO_2^{\cdot}$ and diffusion from the cage. The fact that the 2-position is only attacked by the $n\text{-}C_3F_7^{\cdot}$ radical (yielding **12**), whereas the 3-position can be substituted by $n\text{-}C_3F_7CO_2^{\cdot}$ (yielding **11**), might be a consequence brought about by subtle steric factors. For instance, conceivably many more collisions are required for an effective radical attack at the sterically more demanding 2-position than an effective attack at the 3-position, and this situation might lead to very fast decarboxylation of $n\text{-}C_3F_7CO_2^{\cdot}$ radicals that give rise to the more reactive and smaller $n\text{-}C_3F_7^{\cdot}$ radicals, i.e. radicals more capable of making effective attacks at the 2-position.

It is tempting to speculate that the stronger O—O bond in $(C_6F_5CO_2)_2$ (30 kcal mol^{-1}) will be reflected in a longer lifetime of $(C_6F_5CO_2)_2^{-\cdot}$ in comparison with that of the $(n\text{-}C_3F_7CO_2)_2^{-\cdot}$ radical anion because of the weaker O—O bond in $(n\text{-}C_3F_7CO_2)_2$ (23 kcal mol^{-1}).[18] Thus if both paths A–C and B were viable, their relative importance might be different for the two different peroxide acceptors.



(6)

We now turn our attention to some other observations. (1) Although from the acceptor $(C_6F_5CO_2)_2$ the debutylated product **6** is the main product (87%) and the undebutylated product **9** is formed only in trace amounts [equation (5)], this state of affairs is completely reversed when $(n\text{-}C_3F_7CO_2)_2$ is the acceptor, i.e. the undebutylated product **11** (44%) rather than the debutylated product **12** (30%) becomes the more abundant [equation (6)]. (2) The demethylated quinone product is also formed [equation (5)], albeit only in small amounts, in F113. These observations might be rationalized by alternative reaction pathways for CP-II in Scheme 2, i.e. by paths D and E depicted in equations (7) and (8). Clearly, deprotonation of the hydrogen on the sp^3-hybridized ring-carbon of **13** by $C_6F_5CO_2^-$ will lead to the formation of the undebutylated product **9**. Certainly, **11** can be formed in a similar manner. On the other hand, two consecutive S_N2-like attacks by $R_FCO_2^-$ or another nucleophile on the methyl groups of **10** or **13** or **14** will give the quinone **8**, as illustrated by equation (9).



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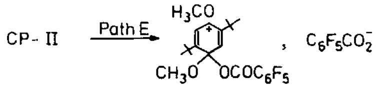

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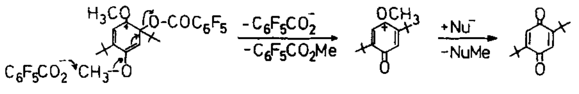

10

8

(9)

It is not known whether the complexes **10**, **13** and **14** can interconvert via very fast 1,2-shifts of the acyl group.

With the objective of further testing the viability of the above-mentioned mechanistic proposition, we made a solvent effect study of the reaction with $(C_6F_5CO_2)_2$ as the acceptor at 5 °C, as summarized in Table 2. Conceivably, the nature of the solvents will affect the lifetimes or even the reaction pattern[11] of CP-I and CP-II and also all the reactive intermediates, and it will also affect the relative importance of paths A–C, B, D and E and the S_N2-like demethylation reactions exemplified by equation (9). Two interesting features can be seen in Table 2: the yield of **6** increases and that of **8** decreases along the solvent series C_6H_6, n-C_6H_{14}, F113 and CH_3CN, as shown by the **6**/**8** ratio, and the yield of $C_6F_5CO_2Bu$-*t* roughly parallels that of **6** and the yield of $C_6F_5CO_2Me$ that of **8**. It is also noteworthy that the data differ much less between the two non-polar solvents, benzene and n-hexane. Evidently, if we presume that the ion pairs are held more tightly or closely in the hydrocarbon-type media and thus the $C_6F_5CO_2^-$ nucleophile can operate much more effectively in the S_N2-like demethylation reactions involving **10**, **13** or **14**, the yield order of **8** can be reasonably understood. If we take the risk of further presuming that the closeness of $C_6F_5CO_2^-$ somehow interferes with the attack of $C_6F_5CO_2^{\bullet}$ on $1^{+\bullet}$, then the trends in the yields of **6** and $C_6F_5CO_2Bu$-*t* are also understandable. If the debutylation step (formation of **6**) is unimolecular and the S_N2-like demethylation steps (formation of **8**) are bimolecular, then higher temperatures might be expected to increase the yield of **6** and lower temperatures that of **8**. Indeed, in F113, the **6**/**8** ratios were found to be 29, 2·4 and 1·5 at 25, 5 and − 10 °C respectively. Finally, the parallel trends in the yields of **8** and $C_6F_5CO_2Me$ also support our mechanistic propositions.

CONCLUSIONS

The radical cation $1^{+\bullet}$ is relatively stable and long-lived and it does not fragment spontaneously. It is relatively inert toward nucleophiles such as the carboxylates, but it colligates very quickly with radicals such as $R_FCO_2^{\bullet}$ and $R_F^{\bullet}$, possibly at all the ring positions. The debutylation reaction of **1** involves the ejection of the *tert*-butyl cation from a cationic σ-complex derived from $1^{+\bullet}$. S_N2-like demethylation reactions between various σ-complexes (**10**, **13**, **14**) and $C_6F_5CO_2^-$ can become important pathways in non-polar solvents at lower temperatures.

EXPERIMENTAL

Materials. The acyl peroxides were prepared from the corresponding acid chlorides in an H_2O_2–NaOH–F113 oxidation system (RCOCl:NaOH:H_2O_2 = 1:1:0·5).[18] Perfluorobutyryl peroxide was prepared, stored and used as an F113 solution. Its purity was determined by iodimetry. Pentafluorobenzoyl peroxide was recrystallized from chloroform–methanol. Commercial cerium(IV) sulphate and ammonium peroxydisulphate were used. The substrate, 2,5-di-*tert*-butyl-1,4-dimethoxybenzene was prepared by butylation of *p*-dimethoxybenzene with *tert*-butyl alcohol in 90% sulphuric acid;[19] m.p. 102–104 °C, yield 85%.

EPR. EPR studies were conducted on a Varian-E112 EPR spectrometer for the reactions of the substrate **1** with four oxidation systems at different temperatures.

Product analysis. A 0·5 mmol amount of peroxide and 0·5 mmol of substrate **1** in 5 ml of Freon-113 were

Table 2. Yields of products (%) of the reactions of **1** with $(C_6F_5CO_2)_2$ in different solvents at 5 °C

Solvent	**6**	**8**	$C_6F_5CO_2Bu$-*t*	$C_6F_5CO_2Me$	Recovered **1**	**6**/**8** ratio
C_6H_6	28	44	23	42	10	0·64
n-C_6H_{14}[a]	40	50	38	47	28	0·80
F113	63	26	58	25	11	2·42
CH_3CN	72	16	62	—	10	4·50

[a] Reaction performed at 40°C because of solubility problems.

allowed to react completely at 20 °C. Of the products, perfluorocarboxylic acid was determined by titration, and others were separated by rotary thin-layer chromatography. The *tert*-butyl esters ($C_6F_5CO_2Bu$-*t*, n-$C_3F_7CO_2Bu$-*t*) were further purified by GC. Quantitative product analyses were conducted on a Model 102 gas chromatograph (Shanghai Analytical Instrument Works). All the major products were characterized by ^1H NMR spectroscopy (Varian XL-200) and mass spectrometry (Finnigan 4021).

5-*tert*-Butyl-1,4-dimethoxyphenyl pentafluorobenzoate (**6**): m.p. 67 °C; *m/z* 404 (M^+), 195 (base peak), 389 ($M - CH_3$) and 374 ($M - 2CH_3$), etc.; ^1H NMR, δ 6·88 (1H, s), 6·58 (1H, s), 3·78 (3H, s), 3·76 (3H, s), 1·34 (9H, s); IR (cm^{-1}), 1762(s); calculated for $C_{19}H_{17}O_4F_5$, C 56·44, H 4·25; found, C 56·01, H 4·25%.

tert-Butyl pentafluorobenzoate (**7**): ^1H NMR, δ 1·65 (9H, s); *m/z* 268 (M^+), 167 (M − bu-*t*), base peak.

2,5-Di-*tert*-butyl-3-(perfluorobutyryl)oxy-1,4-dimethoxybenzene (**11**): ^1H NMR, δ 6·98 (1H, s), 3·83 (3H, s), 3·30 (3H, s) 1·38 (9H, s), 1·33 (9H, s); *m/z* 462 (M^+), base peak, 235 ($M - R_FCO_2 - CH_3 + H$), also 391, 250 and 193.

2,5-Di-*tert*-butyl-*p*-benzoquinone (**8**): m.p. 133 °C; ^1H NMR, δ 6·40 (2H, s), 1·30 (18H, s); IR (cm^{-1}), 1647, 1595; *m/z* 220 (M^+), base peak.

2-*tert*-Butyl-5-perfluoropropyl-1,4-dimethoxybenzene (**12**): ^1H NMR, δ 6·86 (1H, s), 6·80 (1H, s), 3·72 (6H, s), 1·36 (9H, s); *m/z* 362 (M^+), base peak; also 347, 193, etc.

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