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FLUORINATIONS WITH HIGH VALENCY METAL FLUORIDES AND BY THE ELECTROCHEMICAL METHOD

ARE THEY OXIDATION PROCESSES?

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Abstract—It is suggested that fluorination with high valency metal fluorides (e.g. AgF_2, CoF_3, MnF_3, CeF_4) involves the initial oxidation of the substrate by the metal ion either to a radical-cation or, less commonly, by the abstraction of a hydrogen atom. This is essentially the same as many aqueous oxidations, the difference coming in the next step where the first-formed intermediate is quenched by fluorine (as an ion or atom) instead of some hydroxylic species. It is possible to rationalize many features of the fluorinations of benzene and some of its derivatives, thiophen and tetrahydrofuran in this way. The fluorinations of olefins, hydrocarbons and hetero-atom compounds are also discussed as oxidation processes. The fluorinating powers of the reagents vary with the oxidation potentials of the metal ions in accord with the oxidation hypothesis, i.e., $AgF_2 > CoF_3 > MnF_3$. More tentatively, it is also suggested that electrochemical fluorination is an anodic oxidation process. Fluorination with xenon difluoride is also discussed in terms of radical-cation intermediates.

THERE are three main methods of exhaustive fluorination of organic compounds, that is, methods which are capable of replacing hydrogen by fluorine, saturating double bonds with fluorine and destroying many functional groups. They are: (a) fluorination with elemental fluorine;[1] (b) fluorination with high valency metal fluorides such as CoF_3, MnF_3, AgF_2, etc;[2] and (c) electrochemical fluorination,[3] which involves the electrolysis of an organic substrate dissolved in anhydrous hydrogen fluoride. It is generally agreed[1] that method (a) involves a radical chain mechanism. Whether the same is true of processes using halogen fluorides (ClF, ClF_3, BrF_3 etc) is uncertain. Reactions with these are more complex and the second halogen is usually introduced with the fluorine; these will not be discussed further here.

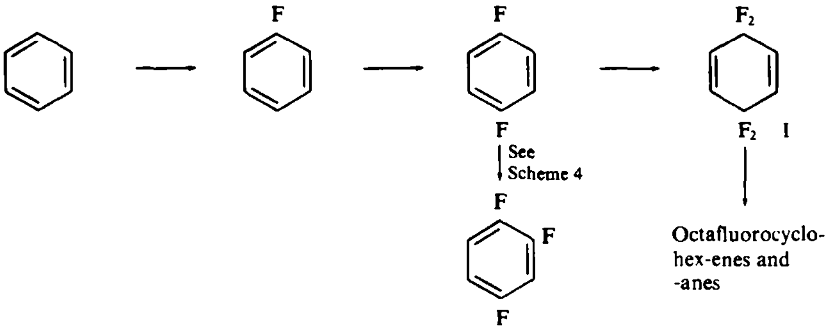
No mechanisms, apart from tentative suggestions,[2–11] have been advanced for processes (b) and (c), and in this paper it is argued that both are oxidation reactions, analogous to better known oxidations in aqueous and other media.

In what follows we stress the importance of oxidative processes in fluorinations with metal fluorides. We accept that various factors such as, *inter alia*, the surface properties of the reagents, correspondence of interatomic distances in inorganic and organic reagents, eliminations of hydrogen fluoride (both thermal and fluoride ion catalyzed), fluoride ion catalyzed rearrangements, and Lewis acid behaviour of the inorganic species will probably all have some part to play. The present paper seeks, however, to make the case for a general, overall, oxidative mechanism and concentrates on this aspect.

In the past we have suggested,[2, 4–10] with varying degrees of certainty, the pathways, but not the mechanisms, taken by a number of fluorinations with high valency metal fluorides. One difficulty in elucidating these pathways is the great complexity usually found in the product mixtures: for example, cobalt trifluoride gives[2] 25–30 products from benzene.

The main sequence suggested[2] for the early stages in the fluorination of benzene is shown in Scheme 1. This sequence was proposed[2] for cobalt trifluoride, but it is probably followed by other fluorinating agents ($KCoF_4$,[10] MnF_3,[11a] etc).

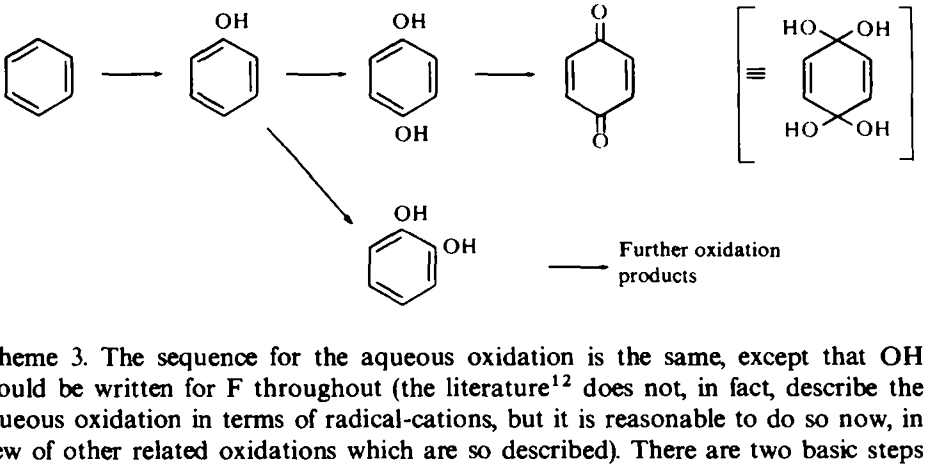
SCHEME 1



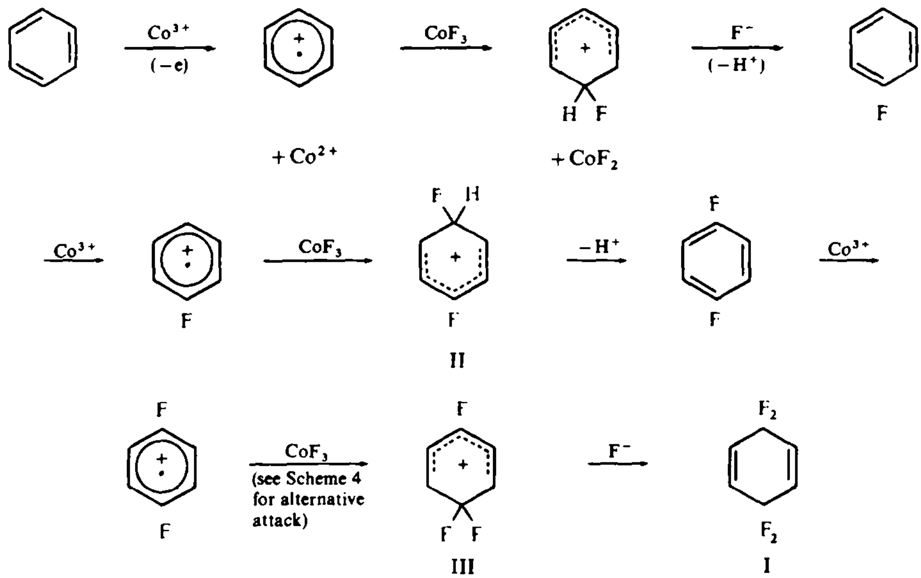
The octafluorocyclohexanes, together with more highly fluorinated species, are major products from CoF_3. The intermediates in Scheme 1 have been isolated as minor products[2,10,11b] and fluoro- and p-difluorobenzene have been shown[2,10] to give product mixtures similar to those from benzene.

In our search for a rationalization of fluorinations, we were struck by the similarity of the sequence in Scheme 1 to that given in the literature[12] for the aqueous oxidation of benzene by Co^{3+} (Scheme 2). We suggest, then, that the mechanisms of aqueous oxidation and fluorination are basically the same: that for fluorination is shown in Scheme 3. The sequence for the aqueous oxidation is the same, except that OH should be written for F throughout (the literature[12] does not, in fact, describe the aqueous oxidation in terms of radical-cations, but it is reasonable to do so now, in view of other related oxidations which are so described). There are two basic steps in these oxidations: (i) removal of an electron from the aromatic by the metal ion (shown as Co^{3+}, but it could be Ag^{2+}, Ce^{4+}, Mn^{3+}, Pb^{4+}, etc) to give a radical-cation: and (ii) the quenching of the radical cation by a fluorine atom derived from cobalt trifluoride or by an OH radical from some $Co(OH)^{2+}$ species. Step (i) has ample[13,14]

SCHEME 2



SCHEME 3



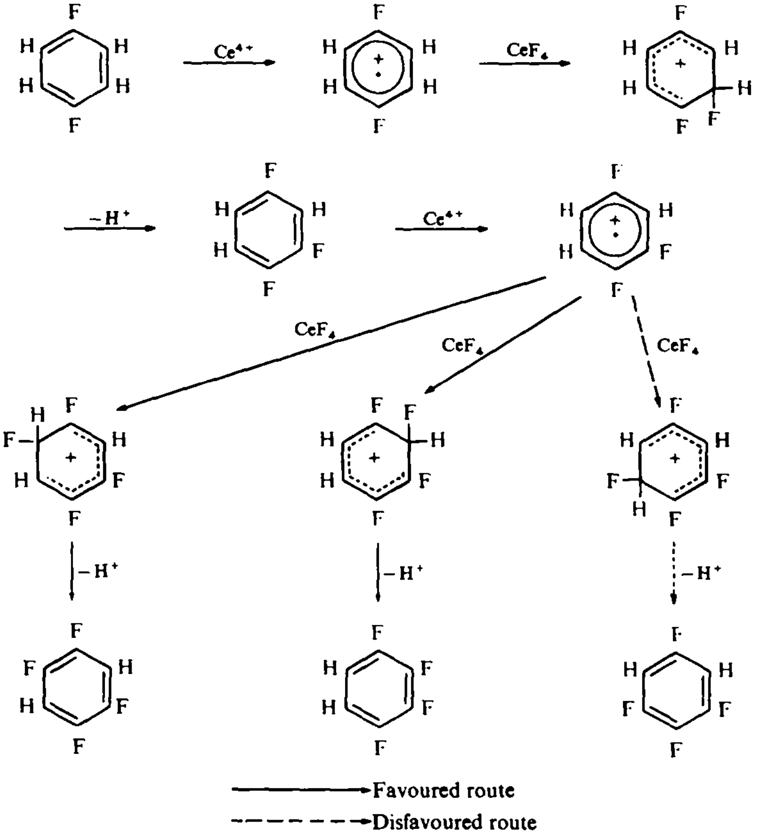
All unmarked bonds are to hydrogen

precedent for a variety of oxidants, and step (ii) has some.[14] It is the central thesis of this paper that fluorinations by high valency metal fluorides differ from more familiar oxidations only in step (ii): quenching is by fluorine and not by some oxygen-containing species.

The intermediates (e.g. II, III] formed by quenching of these radical-cations with F atoms (obviously not with free F atoms, but with some species acting as sources of them) are, of course, very closely related to the familiar cationic Wheland intermediates. This immediately suggests that isomer distributions should be similar to those found in electrophilic aromatic substitution, and, although the analogy must be employed with caution (see later), it is at least possible that the usual electrophilic aromatic substitution arguments may be applicable here.

The following fluorinations may be quoted in support of this idea; benzene itself, phenol (which apparently gives 2,4,6-trifluorophenol as a major intermediate),[15] the heterocycles tetrahydrofuran[5] and thiophen[6] (both of which seem to fluorinate by exclusive 2-attack—see later), and benzotrifluoride. The latter's fluorination products from CoF_3,[16] and CeF_4[17] may be plausibly derived from an initial substitution mainly or entirely of the hydrogen *meta* to the trifluoromethyl group by fluorine [the product distribution makes complete replacement of *para* hydrogen impossible]. There are also the cases of the three tetrafluorobenzenes, which fluorinate[18] as though initial attack was by F^+. The isolation[2] of 1,2,4-trifluorobenzene, but none of its isomers, from a cobalt trifluoride fluorination of benzene (Schemes 3 and 4) is possibly a further example, but fluoride ion catalyzed rearrangement is an alternative explanation here.[2] The isolation of 1,2,3,4- and 1,2,4,5-tetrafluorobenzenes, but not the 1,2,3,5-isomer, from the fluorination[19] of benzene over cerium tetrafluoride may also be cited (Scheme 4) (See Scheme 3 for the route to *p*-difluorobenzene)

SCHEME 4

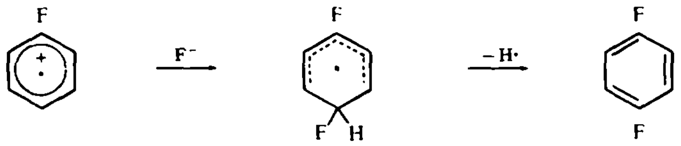


(Addition reactions omitted for clarity)

The intermediates leading to the 1,2,4,5- and 1,2,3,4-isomers are favoured because they have a predominance of fluorines *ortho* and *para* to the point of apparent F^+ attack; the intermediate leading to the 1,2,3,5-isomer is disfavoured because it has a predominance of *meta*-fluorines [note that fluorobenzene is attacked by electrophiles *o* and *p*; for example, nitration gives[20] $o{:}m{:}p = 12{:}0{:}87$].

The analogy between fluorination and electrophilic aromatic substitution affords a suggestive working hypothesis for predicting favoured positions of attack in the fluorination of aromatic molecules. However, it may not be a true analogy. An alternative to quenching the radical-cations with fluorine atoms (or OH radicals) is quenching by anions[13, 14] (Scheme 5; again OH may be written for F).

SCHEME 5



IV

This appears at first sight less attractive than quenching by radicals, since the intermediate thus formed (e.g. IV) resembles one arising from attack of a F atom on fluorobenzene, and such a process might therefore be expected to give the more random isomer distributions typical of homolytic aromatic substitution: as stated above, this is contrary to the experimental evidence we have at present.

However, for fluoride ion quenching, the energy difference between the ground state (the radical-cation) and the transition state will be similar to the energy difference between the transition state and the intermediate (IV). There will be much greater disparity between the corresponding energy differences in normal homolytic aromatic substitution, where the ground state is an aromatic molecule instead of its radical cation. Consequently, IV may not necessarily be taken[21] as a good model for the product-determining transition state between the radical-cation and IV.

Since this is clearly so, there is a strong possibility that the isomer distribution in such a fluorination would be controlled to a significant extent, or even principally, by charge-density distributions in the radical-cation. Electrochemical cyanations,* which very probably[22] proceed *via* the radical-cation of the aromatic substrate, give typically electrophilic isomer distributions; since there are very few cyanide radicals present in these electrolyses and a great number of cyanide ions, quenching must be mainly by the latter and may therefore follow charge density distributions in the radical-cations. There are other electrochemical examples of this phenomenon.[13a]

If the general argument concerning quenching of the radical-cation by fluoride ion is accepted, it is of course equally true that the F-atom quenching process could be controlled by unpaired electron-spin density distribution in the radical-cation. This is an alternative to control by relative stabilities of cationic Wheland intermediates.

We are currently investigating the three likely possibilities using CNDO/2 and INDO calculations of spin- and charge-densities in the radical-cations.

There are other possible fates[23] for radical-cations which involve equilibrations between cations, radical-cations, radicals, and di-cations; such processes may well be involved in fluorinations, but we refrain from discussing them now.

In spite of all these difficulties with the quenching of radical-cations, it seems most fruitful at present to pursue the analogy between fluorination and electrophilic aromatic substitution: that is, to assume as a working hypothesis that radical-cations are quenched effectively by fluorine atoms with directional effects arising from the relative stabilities of familiar Wheland intermediates.

Further examples of directional effects arise in the fluorinations of tetrahydrofuran and of thiophen over potassium tetrafluorocobaltate (III). Compounds of structure VII (Scheme 6) are major products. These fluorinations have been rationalized[5,6] as passing through the 2-fluoro- and 2,5-difluoro-derivatives of furan and thiophen respectively, though none were actually isolated. These could be formed as shown in Scheme 6: intermediates V and VI reflect the well-known preference of electrophiles for attack on furan and thiophen in the 2-position. It seems likely[5] that fluorinations of tetrahydrofuran proceed *via* dehydrogenation in the early stages, a conclusion supported[24] by later work on Me-substituted tetrahydrofurans. As mentioned above, quenching of the radical-cations by fluoride ions is also possible, to give, in these cases, intermediates of type VIII; here, however, radical attack on furan and

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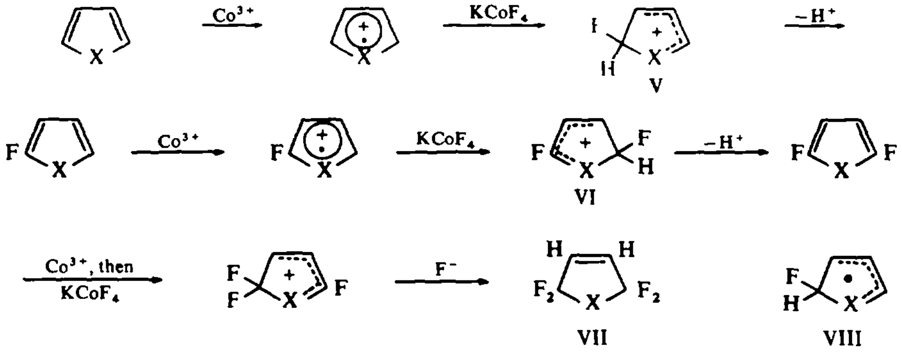
* The substitution of aromatic hydrogen by CN proceeds[22a] when an aromatic compound is electrolyzed in acetonitrile solution containing cyanide ions.

thiophen is also known[25] to show a strong preference for attack at 2, unlike C_6H_5R compounds where radical attack is usually much less selective than electrophilic.

SCHEME 6

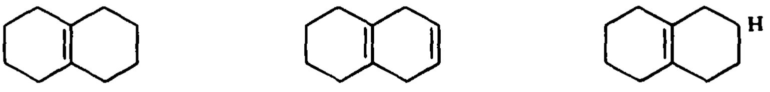


X = O or S

If fluorination by metal fluorides is indeed an oxidation by a metal ion followed by quenching of the ensuing radical-cation with fluorine, then the fluorinating power of a particular reagent should follow the oxidizing power of the metal ion. This is so; oxidation potentials fall in the order $Ag^{2+} > Co^{3+} > Mn^{3+} > Ce^{4+} > Fe^{3+}$ (this applies to aqueous media, that is, OH^- and H_2O ligands: the same *order* should be followed with fluorine ligands). As far as is known,[26] the fluorinating power of the corresponding fluorides falls in the same order.

Again, if fluorination is an oxidation process, then it is reasonable to expect that compounds which differ in their ease of oxidation (ionization potentials can be used as guides here) will be fluorinated to differing extents. There is some evidence for this: cobalt trifluoride saturates benzene almost completely[2] to give polyfluorocyclohexanes, but the weaker manganic trifluoride gives mainly[27] polyfluorocyclohexenes, and the still weaker[19] cerium tetrafluoride affords polyfluorocyclohexenes, -cyclohexadienes and -aromatics. The expected ease of oxidation of these species accords with this; polyfluoro-aromatics and -1,3-dienes > polyfluoromono-enes > saturated polyfluoro-compounds.* It is of interest here that αβ-unsaturated ethers (probable intermediates in the fluorination of dioxan[7] and oxathian[7]), which are more easily oxidized than ordinary mono-enes, are completely saturated (by fluorine) even by potassium tetrafluorocobaltate (III), which is a marginally weaker fluorinating agent[6, 10] than manganese trifluoride.

A concincing example of this type arises in the recently studied fluorinations[28] of naphthalene and tetralin over potassium tetrafluorocobaltate (III) at 250°. Almost



(All unmarked bonds are to fluorine)

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* Ionisation potentials for these compounds are not given in the literature: it is obvious from tabulated values of the ionisation potentials of related compounds (e.g. Handbook of Chemistry and Physics, 50th Ed., The Chemical Rubber Co., Cleveland, Ohio, p. E80) that the order given is correct.

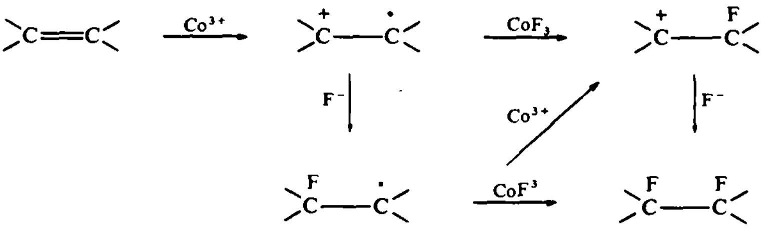
identical product mixtures were formed, with only three major components as follows:

The structures of the products are as would be expected if the α-position were attacked first, and the extent of the fluorination is much greater than from benzene at 280°, where[10] the major products all have three or four hydrogen atoms remaining (the ionisation potential of naphthalene is significantly less than that from benzene).

Olefins could also be fluorinated *via* radical-cations (Scheme 7); a similar mechanism has been suggested[29] for the aqueous oxidation of olefins by Co^{3+}. The problem discussed above, concerning the quenching of radical-cations with fluorine atoms or fluoride ions, arises here also.

It is known that some saturated ring compounds, such as cyclohexane[2] and tetrahydrothiophen,[6] are dehydrogenated to the corresponding aromatics (by metal fluoride fluorinating agents), at least to some extent and possibly completely, before the further reactions of fluorination take place. Furthermore, naphthalene and tetralin give[28] identical products as mentioned earlier. This aromatisation could occur in two ways (Scheme 8). The first possibility is oxidation (loss of an electron) of the hydrocarbon to a radical-cation, followed by loss of a proton. The second alternative is direct abstraction of an H atom. In either case a series of plausible steps follow. Hydrogen abstractions are well-known[31] with other oxidizing agents. It is possible[7] that all hydrocarbons, and not just those which are convertible into aromatics, are dehydrogenated before being fluorinated. Saturated compounds containing oxygen and other hetero-atoms might also commence fluorination with either of these two oxidation steps (Scheme 8), although loss of an electron from the hetero-atom should be easier than from a saturated hydrocarbon. Again, loss of hydrogen to give an olefin, followed by further dehydrogenation or saturation, could take place.

Scheme 7

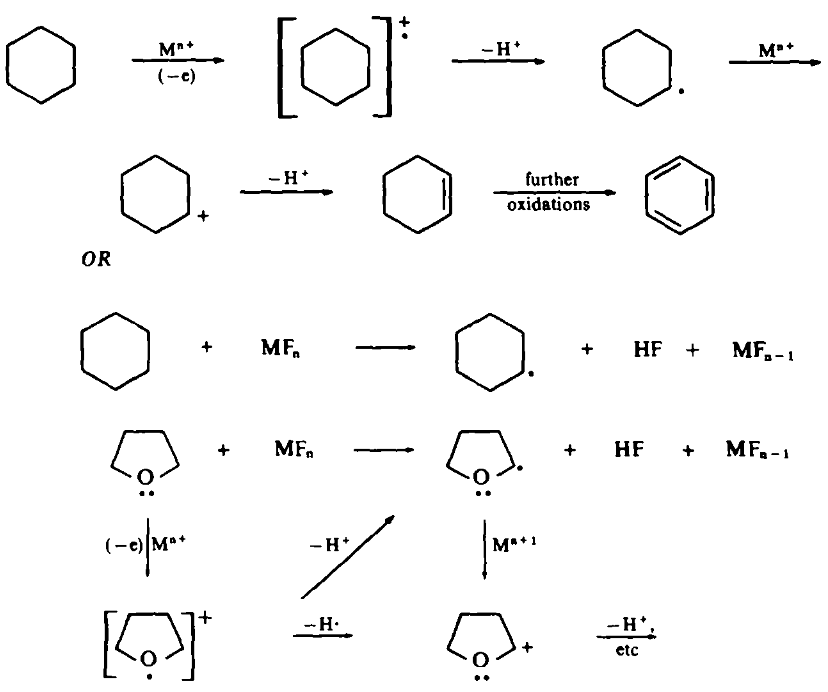


Carbonium ions have been mentioned frequently and there is experimental evidence for their formation in some metal fluoride fluorinations of hydrocarbons; for example, neopentane gives only polyfluoroisopentane products,[32] and bicyclo-2,2,2-octane gives polyfluorobicyclo-3,2,1-, -3,3,0- and -2,2,2-octanes.[33]

Radical-cations, radicals, and cations could also react with substrates to give dimers, trimers, etc. The usual experimental procedure[2] for metal fluoride fluorinations precludes the isolation of high polymers, but polyfluoro-dimeric products have been obtained in small amounts in rare cases.[2]

In summary then, our belief is that fluorinations with high valency metal fluorides involve the same opening step as for more orthodox oxidations: that is, removal of an electron or hydrogen atom. It is only the subsequent step that differs in that the

SCHEME 8



$M^{n+} = Co^{3+}, Mn^{3+}$, etc.

quenching of the intermediate thus formed is by fluorine and not by some oxygen-containing species. We have, as mentioned earlier, overstated the case here by erring on the side of simplicity.

On a more tentative note, it is possible that the mechanism of electrochemical fluorination,[3] long a mystery, also requires an initial oxidation. This was first postulated some years ago by two of us,[3a] but not developed further. For example, the fluorination of methanesulphonyl fluoride might proceed as shown in Scheme 9. The process (a multiple ECE sequence in the usual jargon)[34] is one of anodic oxidation.

SCHEME 9

$$CH_3SO_2F \xrightarrow{-e} [CH_3SO_2F]^{+\cdot} \xrightarrow{-H^+} {}^{\cdot}CH_2SO_2F$$

$$\xrightarrow{-e} {}^{+}CH_2SO_2F \xrightarrow{F^-} CH_2FSO_2F \xrightarrow{\text{repeat}} CF_3SO_2F$$

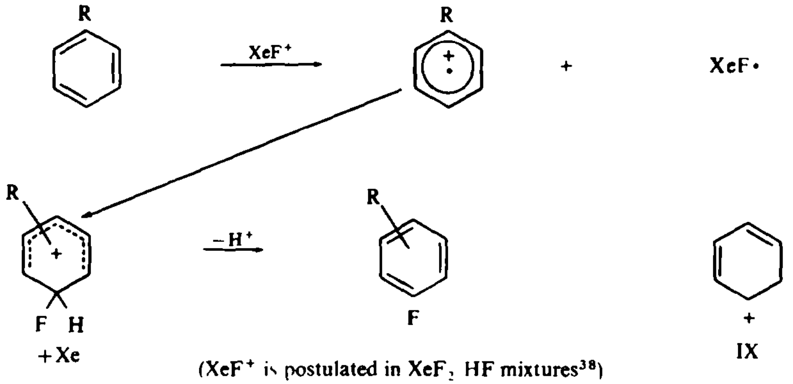
It is possible to speculate further along these lines and to explain many of the rearrangements, fragmentations and cyclizations that commonly occur[3] in this process. Indeed, if electrochemical fluorination is, in essence, oxidation, then much of our previous discussion concerning fluorinations with high valency metal fluorides could apply; it is dangerous to extrapolate too far at this stage because electrode processes take place at one type of surface and the metal fluoride fluorinations at another. Furthermore, cathodic reductions are possible in the electrochemical process.

Russian workers[35] have very recently reported the partial fluorination of naphthalene by electrolysis in acetonitrile in the presence of fluoride ion. They obtained 1-fluoro- and 1,4-difluoronaphthalene and 1,1,4,4-tetrafluoro-1,4-dihydronaphthalene as major products. This reaction is clearly related to electrochemical fluorination and the products are in accord with the oxidation mechanism discussed here; the Russian workers also subscribed to a mechanism which involved radical-cations, followed by quenching with fluoride ion at the positions of greatest charge density.

There are a number of examples in the literature[13a] of electrochemical processes which involve the replacement of hydrogen by some other moiety. Such processes are generally rationalized as anodic oxidations, with mechanisms formally similar to the one given in Scheme 9. The major difference is that much lower potentials are usually used compared to electrochemical fluorinations; hence only relatively more easily oxidizable substrates have been employed. This is because relatively high potentials can be applied without discharging fluoride ions, whereas in the other electrochemical processes referred to this is not so. For example, hydroxide ion would be discharged from aqueous media at a potential lower than that at which many organic compounds would be oxidized; in electrochemical fluorination, however, almost all organic compounds would be oxidized before fluoride ion were discharged.

There is yet another fluorination process which might involve oxidation-fluorination with xenon difluoride. Indeed, a mechanism involving radical-cations has been invoked for the fluorination of benzene,[36] although the authors write such species as though they are localized [Scheme 10, (IX)]. Further fluorinations with xenon difluoride on C_6H_5R compounds have also been described,[37] but no mechanism was given.

SCHEME 10



(XeF^+ is postulated in XeF_2 HF mixtures[38])

It is reasonable to suppose that the FC_6H_4R products are derived in a manner very similar to that described for fluorinations with high-valency metal fluorides—oxidation to a radical-cation, followed by quenching with a fluorine atom from XeF (Scheme 10). In support of this, the isomer ratios in the FC_6H_4R products[37] are consistent with attack of an electrophile on C_6H_5R; the earlier discussion concerning the danger of expecting typical electrophilic isomer ratios for the quenching products from aromatic radical-cations should, however, be borne in mind here. Some further caution is necessary since much polymerization occurs[37] in the xenon difluoride fluorinations, and it may conceivably occur selectively on certain isomers; the polymerization itself could, as mentioned earlier, take place *via* radical-cations, etc.

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