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A review of recent developments in the selective electrochemical fluorination of organic compounds

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Abstract

Recent developments in the area of selective electrochemical fluorination of organic compounds (usually termed as ''Mild fluorination'') are reviewed with specific emphasis towards optimum operating conditions for improved yields. A brief historic outline of the developments in the area is presented. The role of electrode materials (Pt, Ni, C etc.) solvents (CH_3CN, THF, sulfolane etc.) supporting electrolyte and fluoride sources ($Et_3N \cdot 3HF$, $Et_4NF \cdot 3HF$, py · HF etc.) and operating conditions (constant potential, constant current, potential pulse, and divided cell etc.) on the overall yields and efficiency are critically evaluated based on recent research work. The types of reactants employed and the nature of products formed are also emphasised. © 1997 Elsevier Science S.A.

Keywords: Electrochemical fluorination; Fluorinated organic compounds; Selective fluorination

1. Introduction and historic background

A wide range of fluorinating agents from aqueous fluoride solutions through anhydrous HF (AHF) [1] to highly reactive fluorine gas itself [2] are employed in the synthesis of organic fluorine compounds. Electrochemical methods are frequently employed to perform fluorination reactions involving conversion of C–H to C–F bonds. Three general methods of electrochemical fluorination are known [3–7]. Electrochemical fluorination of organic compounds in liquid HF at nickel anodes developed by J.H Simons and his coworkers is a well established commercial process known for more than four decades. In a KF · 2HF melt on carbon anodes, low molecular weight organic compounds can be effectively fluorinated. Both these processes are used to produce perfluorinated organic compounds by converting all the C–H to C–F bonds. Efforts were also made starting from about 1950 to develop electrochemical techniques for selective oxidative fluorination of organic compounds. Some of the landmarks in the evolution of this mild or selective fluorination technique are summarised in Table 1.

Initial attempts were mainly confined to the oxidative addition of fluorine to alkenes [8]. The choice of appropriate medium for fluorination evolved quite slowly. Acetic acid (AcOH) containing KHF_2 was used initially [8]. Selective fluorination was also attempted in liquid HF [9]. AHF dissolved in solvents such as acetonitrile [MeCN], ethanol [EtOH] and acetic acid were also employed [10]. Even silver fluoride in acetonitrile was employed as the fluoride source [11].

The first major breakthrough in selective electrochemical fluorination occurred when triethylamine–HF dissolved in acetonitrile was employed as the electrolyte medium [12]. Nuclear fluorination of aromatic compounds could be achieved in this medium. Acetonitrile became the solvent of choice for further fluorination work. In addition, $Et_3N \cdot nHF$ and $Et_4NF \cdot nHF$ were found to be quite effective in selective fluorination [13]. Even aromatic compounds containing electron withdrawing substituents could be fluorinated when $Et_4NF \cdot nHF$ was employed as the supporting electrolyte [14].

Pyridine–HF is a convenient solvent-supporting electrolyte medium with a reasonably good conductivity. Hence, efforts were also made to use this medium for selective electrochemical fluorination [15]. Selective fluorination leading to the formation of heteroatom fluorine bonds should also be considered as a significant development [16].

Despite all these developments, selective electrochemical fluorination remained as an area of academic interest only for a very long time. This is primarily due to the competitive polymerisation processes at the high anodic potential generally required for the fluorination process. This leads to poor

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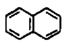
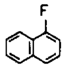
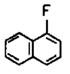
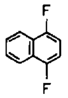
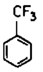
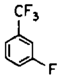
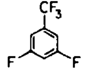
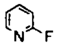
Table 1
Historical development in the selective electrochemical fluorination of organic compounds

Year	Substrate	Solvent Supporting Electrolyte	Product	Yield %	Ref.
1953	$Ph_2C=CH_2$	KHF_2-ACOH	Ph_2CF-CH_2F	70	8
1955	CH_3CH_2COOH	AHF	CH_2FCH_2COOH	–	9
1955	$CCl_2=CCl_2$	HF-MeCN HF-EtOH HF-AcOH	$CFCl_2-CFCl_2$	trace	10
1960	$Ph_2C=CH_2$	AgF/MeCN	Ph_2CF-CH_2F	-	11
1970		$Et_3N.HF$-MeCN		4.5	12
1970		$Et_4NF.3HF$-MeCN		40	13
1971		$Et_4NF.3HF$-MeCN		60	
				12	14
1979		30%Py-70%HF		9	15
1982	$Et_2NP(OEt)_2$	$(Et_3NH)_2SiF_6$ + MeCN	$(EtO)_2POF$	-	16
1984	P-$MeOC_6H_4CH_2CN$	($Et_3N.3HF$-MeCN)	p-$MeOC_6H_4CHFCN$	70	17
			p-$MeOC_6H_4CF_2CN$	50	
1990	$PhSCH_2CF_3$	$Et_3N.3HF$-MeCN	$PhSCHFCF_3$	35	18

overall yield and current efficiencies. Frequent electrode fouling also made long term electrolysis quite difficult.

Activity in the area of selective electrochemical fluorination has been revived during the past ten years. This is mainly due to the observation that side chain methylene groups undergo efficient fluorination with fairly high yields without the significant electrode fouling effect mentioned above [17]. This is found to be especially true in the case of side chain compounds containing active methylene groups with a sulfide linkage [18,19].

Developments in the area of selective fluorination have been reviewed along with other methods of fluorination, [2], especially with electrochemical fluorination [3–7]. Recent developments in the selective fluorination of heteroatom containing organic compounds have also been briefly reviewed [19]. However, these reviews generally describe the overall results and the products obtained from different classes of compounds. It was felt that a more critical review covering various specific developments in the choice of electrode materials, electrolyte medium and other operating parameters could be useful. The overall mechanistic pathways and product distribution pattern for different classes of organic compounds also deserve critical evaluation. This is the objective of the present review.

Broadly, two periods may be distinguished in the development of selective electrochemical fluorination methodology. Addition to C=C bonds and aromatic nuclear fluorination dominated the scenario up to the early eighties. The comprehensive reviews cited above [2–7] cover this development extensively. The critical review by Rozhkov [3] deserves special mention from the point of view of mechanistic discussions. Hence, these developments are not covered extensively in this review. The primary objective of this review would be to critically evaluate the role of different operating parameters and identify the best guidelines for further experimental work in this area. No attempt is made to provide an exhaustive list of compounds that have been subjected to electrofluorination.

2. Electrochemical procedure

In general, selective electrochemical fluorination procedure is quite similar to other electroorganic synthetic reactions in non-aqueous solvents. Since more positive oxidative potentials are involved, careful handling of the solvent supporting electrolyte system is needed, avoiding moisture, to ensure polymerisation-free electrolysis. Platinum generally serves as cathode and anode and constant potential electrolysis was the method of choice until recently. Acetonitrile has been the solvent of choice over a long period. $Et_4NF \cdot nHF$ is generally employed as supporting electrolyte medium and as the source for fluoride ion. In recent times, however, modifications of almost all the aspects mentioned above have been attempted. The implication of these modifications is the basis of this present review.

3. Electrode materials

Platinum, compact carbon and nickel exhibit very high corrosion resistance in anhydrous HF [20]. These are the electrodes of choice in selective electrochemical fluorination, fluorine generation and perfluorination in liquid HF. Most of the basic studies on these electrodes in fluoride media are aimed at understanding the mechanism of industrially important electrochemical perfluorination processes and hence have been mainly carried out in liquid HF. However, it is worthwhile to look at some of these studies in the present context in order to understand the role of electrode material in selective electrochemical fluorination as well.

Typical cyclic voltammograms obtained on vitreous carbon, platinum and nickel electrodes in liquid HF containing 1 M NaF obtained by Doughty and his coworkers [21] are presented in Fig. 1. On Pt electrodes electrooxidation due to PtF_2 and PtF_4 film formation starts around 1 V and fluorine evolution occurs around 2.5 V [22]. Fluoride film formation on carbon electrode starts around 1.5 V. However, the film growth and fluorine generation rates are considerably higher on this electrode. (Compare the current density scales of

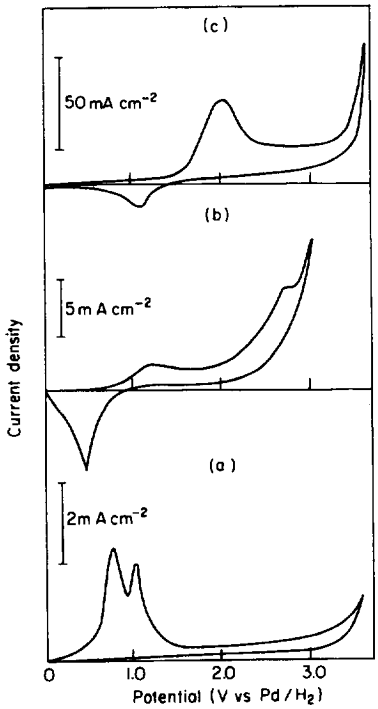


Fig. 1. Cyclic voltammograms of (a) nickel, (b) platinum and (c) vitreous carbon electrodes in liquid HF/1 M NaF. Potential scan rate, 0.1 V s^{-1}.

cyclic voltammograms of platinum and vitreous carbon electrodes.) On Ni, however, the fluoride film formation processes start around 0 V. The passive NiF$_2$ layer is not easily soluble in liquid HF. Organic compounds such as hydroquinone which can undergo redox reactions below 1.2 V generally give well defined diffusion controlled CV curves on platinum and vitreous carbon electrodes [21,22]. A few other aromatic hydrocarbons are also found to give distinct oxidation peaks on platinum [23,24] and carbon [24]. Even compounds such as hydroquinone do not give distinct redox peaks on a nickel electrode, since the passive layer present on these electrodes prevents direct oxidation of organic compounds to give cation radicals in liquid HF. Electrochemical perfluorination reactions are thus assumed to proceed through active fluorine generated in the NiF$_2$ layer at fairly high oxidation potentials [21,25,26].

The solvent supporting electrolyte media usually employed for selective electrochemical fluorination is CH$_3$CN containing R$_3$N·nHF or R$_4$NF·nHF. Platinum and vitreous carbon behave as inert electrodes over a wide potential range (say between 0 and 3 V). Under these conditions, no significant fluoride film formation has been noticed so far on platinum and vitreous carbon electrodes. Hence, these electrodes serve as a conducting inert surface for organic oxidative processes. Many organic compounds are directly oxidised on these surfaces leading to the formation of carbocations. This is followed by proton-elimination, further one electron oxidation and nucleophilic attack by fluoride ions. This is frequently referred to as EC$_B$EC$_N$ mechanism. There is considerable evidence for this mechanistic pathway under selective fluorination conditions on platinum electrode [3].

Quite similar processes also seem to occur on carbon electrodes. The performance of platinum and carbon electrodes under otherwise identical experimental conditions are quite similar, for example in Py-HF media [27]. Pt, dimensionally stable anode (DSA) and carbon sheet give similar conversion efficiencies during monofluorination of phenylsulfenylacetate [28]. Carbon electrodes are also interchangeably used in place of platinum electrodes in some of the recent synthetic works [29–31]. Cyclic voltammetric behaviour of methylphenylthioacetate in the absence and in the presence of flu-

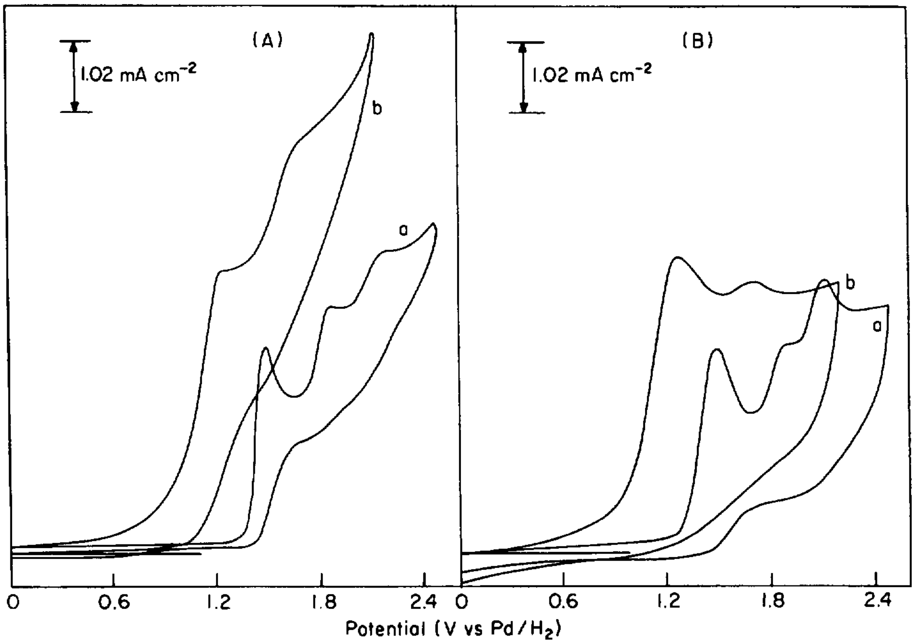


Fig. 2. Cyclic voltammograms of 4 mM methyl phenylthioacetate in MeCN containing (a) 0.1 M TBAP and (b) 0.1 M Et$_3$N·3HF at 80 mV s^{-1} on (A) Pt and (B) GCE.

oride ions, for example, are found to be quite similar on platinum and glassy carbon electrodes (Fig. 2). This further confirms the electrochemical pathway on platinum and glassy carbon electrodes.

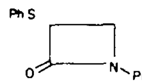
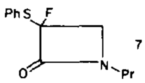
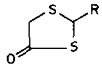
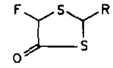
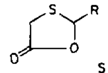
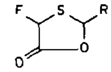
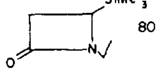
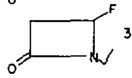
Under selective electrofluorination conditions in contrast to platinum and carbon electrodes, nickel electrodes still form a compact passive layer. The passive nature of nickel electrodes in CH_3CN–Et_3N–HF media, for example, has been studied in detail in this laboratory [32,33]. Distinct oxidative or reductive behaviour could not be observed on these electrodes even for compounds that show facile electrochemical reaction on other electrodes. Quite naturally, nickel cannot be employed for selective electrochemical fluorination. There is only one report known indicating selective fluorination on nickel electrodes in sulfolane media [34]. However, preliminary studies in this laboratory also suggest the formation of a passive layer on nickel in sulfolane. Hence, the validity of above report [34] requires further confirmation.

4. Solvent and supporting electrolyte

From the early stages CH_3CN has been employed as the solvent of choice for mild fluorination [3,6]. However, different supporting electrolytes have been used as the fluoride sources. $Et_3N \cdot n$HF and $Et_4NF \cdot n$HF are the most commonly employed fluoride sources. Some studies have also used pyridine–HF as the fluoride source. Use of excess HF in the above system is quite common. In the case of tri- and tetraalkyl ammonium salts, it is generally found that 3–5 mol of HF per mole of amine or ammonium salt gives better fluorination yields. However, presence of excess is not a necessary precondition. Even tetraethylammonium fluoroborate (Et_4NBF_4) has been successfully used as supporting electrolyte and fluoride source [35]. In one study, Et_3N and Py–HF were employed together as supporting electrolyte in CH_3CN [27].

There are, however, few experimental investigations in which the efficiency of different supporting electrolytes in CH_3CN towards selective fluorination are compared. A few studies in this direction are summarised in Table 2 [28,31,36–39]. In CH_3CN media, $Et_3N \cdot 3HF$ as well as $Et_4NF \cdot 3HF$ appear to perform quite efficiently for most compounds. Some exceptions to this general guidelines seem to exist [39]. For some compounds, yield in $Et_3N \cdot 3HF$ is found to be higher [38] while in other cases yield in $Et_4NF \cdot 3HF$ is higher [39]. In general, py–HF appears to be a poorer supporting electrolyte medium. However, one report indicates fairly good yields in this medium as well [31]. More detailed comparative evaluation of different supporting electrolytes for selective electrochemical fluorination in CH_3CN are necessary before any specific conclusion regarding their relative efficiencies are predicted. It is also likely that different supporting electrolytes are efficient for different starting materials. (Table 2).

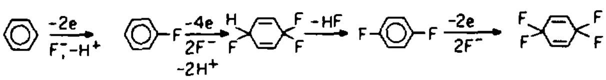
Table 2
Effect of supporting electrolytes in CH_3CN on anodic fluorination of organic compounds

		Product Yield in %				
No.	Substrate	$Et_3N.3HF$	$Et_4NF.3HF$	Py.nHF	Main Pdt.	Ref.
1.	$PhSCH_2CF_3^{(a)}$	62	-	0	$PhSCHFCF_3$	36
2.	$PhSCH_2COOEt$	61	61	-	$PhSCHFCOOEt$	28
3.		77	64	trace		7
4.	$PhSCH_2COOR^{bc}$	54	37	-	$PhSCHFCOOR$	38
5.		26	72	-		39
6.		0	73	-		39
7.		80	-	66		31

[a] $Et_3N \cdot 2HF$: 33%.
[b] R = 8-phenylmenthyl.
[c] $Et_4NF \cdot 2HF$: 55%.
[d] Carbon anode.

As mentioned above, CH_3CN has been the solvent of choice for selective electrofluorination. This solvent, however, is not exclusive. Other solvents such as sulfolane [40] and methylene chloride [41,42] have also been used. Once again, there are few reports relating to the effect of different solvents on the selective electrofluorination process. (Table 3) [36,38,43]. Acetonitrile (MeCN), dimethoxy ethane (DME) and tetrahydrofuran (THF) appear to be good solvents for these processes. Dimethyl formamide (DMF) and dioxane appear to be rather poor solvents. The efficiency of fluorination in methylene chloride appears to depend on the nature of the compound involved (Table 3). Further investigations are indeed necessary to understand the dependence on the solvent employed.

The supporting electrolytes mentioned above, namely $Et_3N \cdot 3HF$, $Et_4NF \cdot n$HF and py $\cdot\, n$HF, are themselves quite stable at room temperature. They can dissolve organic compounds and they are also reasonably good ionic conductors. Hence, they can be employed as the electrolyte medium. Since no other solvent is employed here, one may essentially achieve fluorination reaction, which are quite difficult or impossible in presence of other solvents. Momato and his coworkers, for example have shown that one can obtain only fluorobenzene and a small fraction of difluorobenzene in CH_3CN–$Et_4NF \cdot n$HF media [44]. In the absence of solvents even a tetrafluorobenzene derivative could be obtained [45].

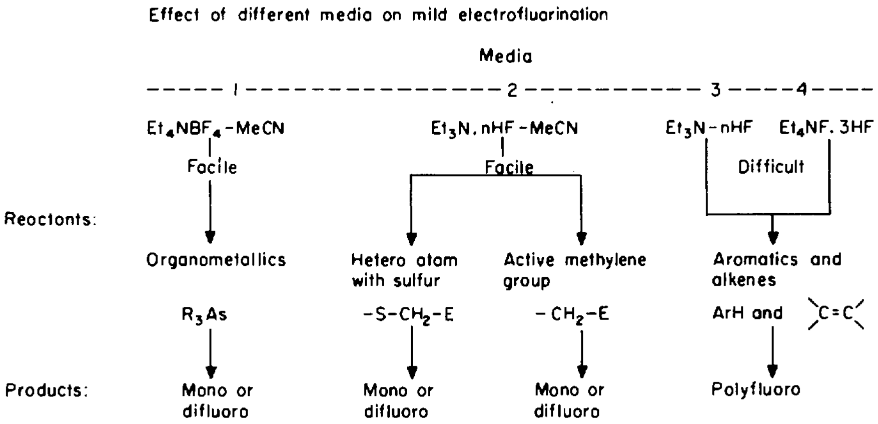


Polyfluoro derivatives could also be obtained from di and trifluorobenzene [46], trifluoromethylbenzene [47] and chlorobenzene [48]. Similar polyfluorinated products could

Table 3
Effect of solvents in $Et_3N \cdot 3HF$ on anodic fluorination of organic compounds

No.	Substrate	Product yield (%)				Main product	Ref.
		MeCN	DME	CH_2Cl_2	DMF		
1	$PhSCH_3^{a,b}$	21	57	22	5	$PhSCH_2F$	[36]
2	$(Ph)_2C{=}NNH_2$	–	62	95	31	Ph_2CHF	[43]
3	$PhSCH_2COOR$ [c]	54	–	43	12	PhSCHFCOOR	[38]

[a] THF yield 52%.
[b] Dioxane yield 42%.
[c] R = 8-phenylmenthyl.



Scheme 1.

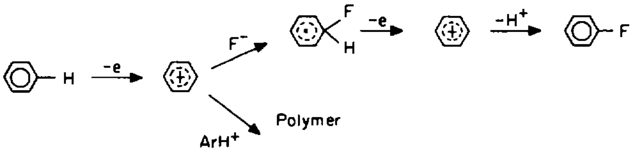
also be obtained from $Et_3N \cdot nHF$ [49,50] and Py–HF [51,52].

A general overall view of the effect of medium on electrochemical fluorination is presented in Scheme 1. The choice of medium generally depends on the nature of reactants chosen and the level of fluorination desired. Organometallic compounds and active methylene groups attached to heteroatoms are examples that undergo facile mono fluorination. In such cases solvents containing any fluoride ion source may be employed. Nuclear fluorination of benzene with or without electron withdrawing substituents are rather difficult to achieve. Syntheses of difluoro-, trifluoro- and tetrafluoro derivatives are also difficult to achieve. It may necessary to use a medium without solvent. Even here one may preferably choose $Et_4NF \cdot nHF$ rather than $Et_3N \cdot nHF$ or Py–HF. Within this broad perspective one can see very wide scope for further synthetic work and basic understanding.

5. Operating parameters

Apart from electrode material and solvent supporting a particular electrolyte, we may still consider a number of other operating parameters to achieve improvements in selective electrochemical fluorination.

Polymer formation during constant potential electrolysis has been a serious problem in selective electrochemical fluorination. This is probably one of the main factors hindering scale up and technology development. Polymerisation occurs on the electrode surface especially when the rate of generation of cation radical is much higher than the rate of further reaction leading to fluorination.



A variety of current interruption techniques such as pulse electrolysis [37,53,54] with different pulse intervals, polarity reversal [55] or the combination of these two may be attempted to overcome this problem. The overall current time programme may also be controlled through sophisticated control instrumentation [51]. These methods and their relative significance require further investigations. The problem associated with polymerisation on the electrode surface seems to occur predominantly when $Et_3N \cdot nHF$ systems or Py–HF systems are employed as supporting electrolytes in the presence of a solvent such as CH_3CN. In the presence of $R_4NF \cdot nHF$ the polymerisation problem occurs less frequently especially when n is greater than or equal to 3 [44]. The existence of free base such as pyridine or triethylamine and fairly low concentration of fluoride ion source probably lead to more polymerisation on electrode surfaces.

$$R_3N + 2HF \rightarrow R_3NH^+ + HF_2^- \qquad (1)$$

Often, platinum is employed as the cathode. Since hydrogen evolution is the predominant cathodic reaction, the organic intermediates generated at the cathode do not undergo reduction at the cathode surface. Hence, in most cases one can employ undivided cells. But, in compounds such as $PhSeCH_2CONH_2$ direct reduction of the compound itself is possible at the cathode. In these cases, one should employ divided cells. Ion exchange membranes appear to be the best separators in these cases [56].

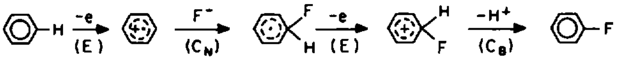
Organic adsorption on the electrode surface (reactants, intermediates or products) can also inhibit the fluorination reaction. This can become a serious problem especially when high molecular weight reactants are employed. Fuchigami and his co-workers have established the possibility of using *p*-methoxyiodobenzene as mediators in such cases [57]. Electrochemically generated *p*-methoxydifluoro iodo benzene acts as a chemical fluorination agent for high molecular weight compounds in the same solvent supporting electrolyte medium. There is considerable scope for achieving efficient selective fluorination using such a redox mediator approach.

When the starting material contains an optically active group, it can also induce the formation of stereoisomers during selective electrofluorination. This has also been established by Fuchigami et al. [38].

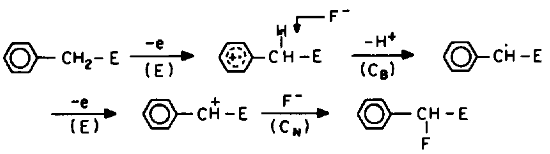
Most of the preparative work on this electrochemical fluorination process has been carried out under constant potential electrolysis conditions. This is indeed a serious limitation for scaling up and process development. One recent study suggests the possibility of carrying out selective fluorination under constant current condition employing a flow cell and an N_2 atmosphere [28].

6. Mechanism

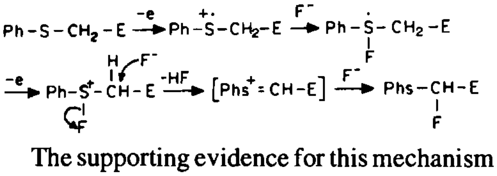
A wide variety of experimental evidence clearly points to the oxidation of the organic reactant leading to the formation of cation radicals as the first step in the selective electrochemical fluorination reaction. Nuclear fluorination for example, proceeds more efficiently when the reactant is easily oxidisable. Side chain fluorination proceeds more efficiently when the reactant contains an active methylene group facilitating proton release after the electrochemical oxidation step. Hence, it is generally agreed that selective electrochemical fluorination proceeds via a EC_BEC_N mechanism. In the case of nuclear substitution the first chemical step is of fluoride attack and the second chemical step is proton release [3].



In the case of side chain fluorination, proton release appears to be possibly the first chemical step [53].



Fuchigami et al. have proposed a novel mechanism called a "Pummerer mechanism" in the case of active methylene group attached to sulfur [58].

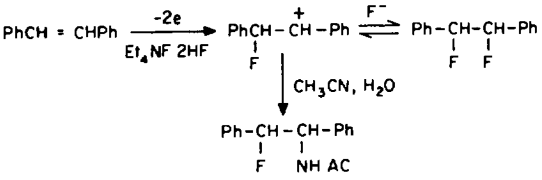


The supporting evidence for this mechanism comes mainly from a comparison of anodic methoxylation and fluorination reaction in the presence and in the absence of $Et_3N \cdot 3HF$. However, the product distribution pattern observed may be explained simply using the EC_BEC_N mechanism itself if one assumes that MeO^- is a better nucleophile than F^-. In general therefore, it appears that the simple EC_BEC_N mechanism pathway can explain all the available experimental results on selective fluorination.

7. Types of reactants and products

7.1. *Fluorination of unsaturated compounds*

Alkenes are generally expected to give addition products namely 1,2-difluorides. Styrene, for example, was found to give fairly good yields (60%) of difluoro derivatives [3]. However, on further substitution with bulky alkyl or aryl groups fluoroacetamidation was found to be the predominant process in CH_3CN. This was found to be the case of for example, stilbene [3,59] 2-phenyl propene [59] and other compounds [59]. The stability of the cation radicals of the monofluorinated intermediate leads to substitution by solvent molecules (CH_3CN) and hydrolysis results in fluoroacetamidation.



One approach to avoid the formation of fluoroacetamide derivatives would be to select a solvent of lower nucleophilicity. Methylene chloride (CH_2Cl_2) has been employed as one such solvent. Even in this case, chlorofluoro derivatives are formed at least in some cases due to the chloride ion (Cl^-) generated in situ by the exchange reaction between CH_2Cl_2 and $Et_3N \cdot HF$ [41].

Selective fluorination is also possible with enol acetates. Monofluoroketones are obtained as products [60,61]. Cycloalkenes also undergo selective fluorination. Fluoroacetamidation once again is the predominant process in CH_3CN [62–64]. The stereochemistry and the crystalline structure of the fluoro derivatives obtained has also been investigated in detail [63,64]. In CH_2Cl_2, the difluoro derivative is once again predominant [41].

Quite similar behaviour is also exhibited by indenes and substituted indenes [42,65–67]. The crystal structure of the fluorinated product has been evaluated [65]. In the case of indene molecules, containing bulky substituents, fluoroacetamidation once again predominates and stereoselectivity decreases. In general, electrochemical fluorination leads to substitution from the side of the double bond as the stereoselective product. This has been attributed to adsorption on the electrode with a specific orientation. Electrochemical fluorination in presence of *N*-bromosuccinamide (NBS), on the other hand, leads to a bromonium intermediate and hence, once again, the stereoselectivity decreases. This study lends further support to the orientation effect of the electrode during electrofluorination [67].

Interesting transformations have also been noticed during the selective fluorination of some special classes of alkenes. In the case of alkenes containing α-methyl substituents, the methyl group shifts from the α to the β position leading to gem difluoro compound formation [49]. Fluorination is also possible with other double bonded compounds. Diphenyl hydrazone undergoes fluorination leading to mono as well as difluorodiphenylmethane [43].

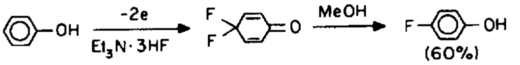
7.2. *Fluorination of aromatic compounds*

Right from the early stages, nuclear fluorination of aromatic compounds has occupied the centre stage of electrochemical methodology. Rozhkov and his coworkers, have investigated the electrochemical fluorination of benzenes, substituted benzenes containing both electron donating and electron withdrawing substituents and other polynuclear aromatic systems in Et_4NF–2HF–CH_3CN. Rozhkov has comprehensively reviewed this and other work [3]. The results are also available in tabular forms (two tables and 160 references).

A few further studies have also appeared subsequently on nuclear fluorination in CH_3CN–$Et_4NF\cdot n$HF media. O'Malley and his coworkers, for example, have investigated the oxidative fluorination of anthracene [68] and benz[a]anthrazene [69]. Molecular orbital theory (MoT) has been used to correlate molecular structure and yield of selective fluorination products [70]. Electrofluorination of pyridine leads to 2-fluoropyridine, the yield, however, was only around 22% [71]. Patents covering electrofluorination of pyrazole [72] and pyridazinones [73] have also been filed.

A more interesting recent development in this area is the electrofluorination of aromatic compounds in $Et_3N\cdot n$HF or $Et_4NF\cdot n$HF media itself. In the absence of any other solvents, the results obtained in these studies with regard to benzene and substituted benzene have been discussed in detail in the earlier section on medium effects (Section 3). In addition to mono and difluoro compounds, some tri- and tetrafluoro derivatives could also be synthesised by this method.

Even phenols could be oxidised in $Et_3N\cdot n$HF media. The fluorinated dienone derivative can be converted into the corresponding fluoro phenol by subsequent chemical reaction [74].

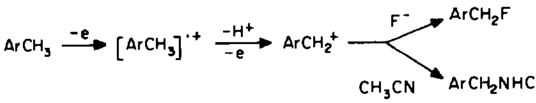


(2)

For these compounds, however, chemical oxidation using PbO_2 in Py–HF appears to be an easier pathway yielding slightly better results [74]. Quite similar fluorination was also achieved in the case of benzofuran and phenanthroline [49]. Momota and his coworkers have achieved similar polyfluorination of bromobenzene using $Et_4NF\cdot n$HF systems [75].

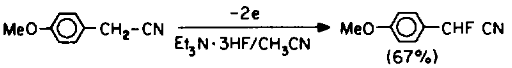
7.3. *Fluorination of side chain compounds without sulfur*

Fluorination studies of alkyl aromatic compounds have also been extensively covered by the Rozhkov review [3]. The main problem, once again, is the formation of acetamides along with the monofluoro alkyl derivatives. Formation of acetamide is in fact predominant when the methyl group remains unsubstituted leading to the formation of highly reactive cation radicals in the first electrochemical oxidation step [59]. Similar trends were noticed in CH_3CN containing Py.HF or $Et_4NF\cdot 3$HF [76]. In CH_2Cl_2 media, acetamidation is totally eliminated. However, small amount of chloroalkyl derivatives are obtained as side products.



$$ArCH_3 \xrightarrow{-e} [ArCH_3]^{\cdot+} \underset{-e}{\xrightarrow{-H^+}} ArCH_2^+ \begin{cases} \xrightarrow{F^-} ArCH_2F \\ \xrightarrow{CH_3CN} ArCH_2NHCOCH_3 \end{cases}$$

The cation radical formation becomes easier and the stability of the cation radical increases when the side chain alkyl group is attached to an electron withdrawing substituent. The stability improves further when the phenyl ring contains electron donating groups such as *p*-methoxy, *p*-methyl and *p*-chloro groups. Compounds such as *p*-methoxyphenyl acetone undergo facile fluorination at the methylene group [17,53,77–79]. Increased cation radical stability in this case leads to more selective fluoride attack.



(3)

Similar results are also obtained in the case of compounds containing a *p*-methyl substituent [79]. Sulfolane was also tried as a alternative solvent to CH_3CN. In this case also, acetamidation can be totally eliminated. However, side chain fluorination seems to occur simultaneously with nuclear fluorination in this medium [40].

In the fluorination of active methylene groups, $Et_3N\cdot n$HF appears to activate the overall process by assisting the abstraction of a proton from the active methylene group. The yield of fluorinated product, for example, is found to increase with increasing concentration of $Et_3N\cdot n$HF [40].

The electron withdrawing group attached to the active methylene group plays a significant role in the orientation of the fluorine substitution, if the electron withdrawing group, for example, is optically active, stereoselectivity is found to be induced in the $-CH_2-$ centre undergoing fluorination [80,81].

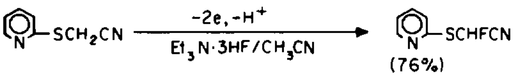
7.4. *Fluorination of sulfur containing side chain and heterocyclic compounds*

Aromatic sulfides undergo very facile oxidation leading to the formation of sulfonium salts and sulfoxides. However, when the sulfur atom is linked to an active methylene group, the same sulfide linkage assists selective fluorination significantly [82]. This observation led to a series of investigations in this class of compounds. The effect of different substituents and the fluoro compound yield have been reported in detail [82,83]. When the sulfur atom is linked to two methylene groups [$-CH_2SCH_2-$], the substituents on either side significantly influence the fluorination site [36].

$$PhCH_2SCH_2R \xrightarrow[Et_3N\cdot 3HF]{-2e\ -H^+} PhCH_2SCHFR + PhCHFSCH_2R \qquad (4)$$

The electrofluorination is once again found to be stereoselective [38]. The recent review by Fuchigami is a comprehensive survey of recent developments in this area [19].

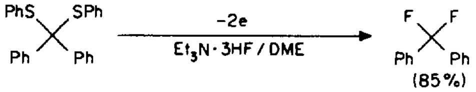
Apart from the active methylene groups connected to the phenyl thio function [$Ph-S-CH_2-E$], other types of cyclic derivatives of sulfides have also received attention. Selective fluorination of 2-pyridyl and 4-pyrimidinyl sulfide derivatives, for example has led to very good yields of fluoro derivatives [54].



(5)

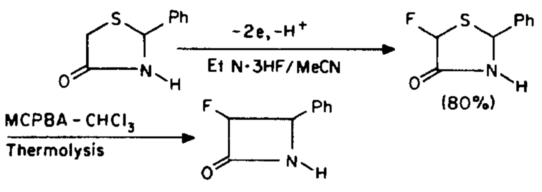
In the case of cyclohexyl sulfide derivatives the α-position of the cyclohexyl group is found to be the active centre for the selective fluorination [84]. The active methylene group attached to aromatic selenides also undergo facile electrofluorination [56].

If a compound containing a single carbon attached to two sulfur atom is subjected to selective electrofluorination, C–S bond cleavage leading to formation of two C–F bonds is often observed. This appears to be a convenient method for the synthesis of gem difluorides [85,86].



(6)

Fluorine containing heterocyclic compounds are being investigated for potential drug development. Fuchigami and his co-workers have reported selective fluorination of 4-thiazolidinones and subsequent conversion of fluorothiazolidinones to fluoro-β-lactams which are of pharmaceutical importance. [55,87].



(7)

Electrofluorination of β-lactams [37], 4-thianone derivatives [88] and other heterocyclic compounds [89] have also been reported. This class of compounds probably would be the first to achieve commercial success through a selective electrofluorination route.

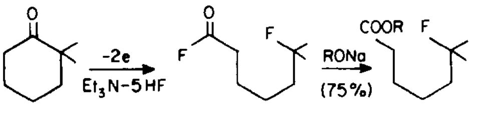
7.5. *Miscellaneous*

As noted above, active methylene groups attached to sulfur and selenium atom undergo facile selective fluorination. However, this type of fluorination was not obtained with tellurides. The $-Te-CH_2-$ group was instead converted to $-TeF_2-CH_2-$ during selective fluorination [90].

Nikitin et al. have reported fluorination of the heteroatom in a variety of organometallic compounds during the early 1980s [16,91–94]. No further development in this area is noted in recent times.

$$R_3As \rightarrow R_3AsF_2 \qquad (8)$$

Selective fluorination is found to be assisted by some facile leaving groups such as $-SnBu_3$ [30] and $-SiMe_3$ [31]. Some interesting cyclisations coupled with fluorination [30] and regioselective fluorination [31] were achieved through the route. Cyclic ketones with two substituents in the α-position are found to undergo electrofluorination followed by cleavage.



(9)

Another interesting fluorination conversion occurs in the case of aliphatic aldehydes. Under selective electrofluorination conditions, RCHO is found to be converted to RCOF [52].

8. Conclusions

Despite eluding commercial success, selective electrochemical fluorination continues to attract active research interest. The focus seems to have shifted from aromatic nuclear fluorination to the fluorination of side chains containing active methylene groups and heterocyclic compounds. Platinum is still the electrode of choice, but other anode materials such as graphite do yield good results. CH_3CN still remains the solvent of choice, but there is scope for investigation of other solvents such as THF and sulfolane. $Et_3N\cdot n HF$ and $Et_4NF\cdot n HF$ are the most widely employed supporting electrolyte and fluoride sources. The possibility of synthesising polyfluorinated hydrocarbons using $Et_4NF\cdot n HF$ without any solvent appears to be a promising area of research for the future.

Pulse techniques show promise in the case of reactants which form very active cation radicals whose high concentration may lead to polymerisation instead of fluorination. Constant current electrolysis is certainly possible at least for many of the selective electrochemical fluorination reactions.

Many recent successes in this area come from selective fluorination of active methylene groups connected to sulfur. The commercial utility of these compounds, however, are not clear. Selective fluorination in the future would be oriented towards the synthesis of compounds of commercial importance.

Acknowledgements

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