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Recent advances in practice and theory of polyfluoroarene hydrodehalogenation

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Dedicated to the memory of Academician I.L. Knunyants on the occasion of his 100th birthday.

Abstract

The development of concise and highly selective ways to prepare partially fluorinated arenes from readily available polyfluoro ones, the former being valuable building blocks in fine synthesis and material production but much less accessible, remains a challenging synthetic problem. Results achieved in this area over the last one and a half decade, particularly those relating to reductive hydrodehalogenation/defluorination of perfluoro- and perfluorochloroarenes by zinc, are reviewed in the present article. Mechanistic aspects of this chemistry as associated with structure and reactivity of intermediate polyfluoroarene radical anions are also considered.

Keywords: Polyfluoroarenes; Hydrodehalogenation; Zinc; Radical anions

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1. Introduction

Since about half a century ago there has been a rush into the polyfluoroarene area, which has become possible owing to the methods of partial and/or complete arene fluorination using one-pot procedures. In doing so, perfluoro- and perfluorochloroarenes, and also some of the functional derivatives became more accessible, than partially fluorinated arenes, which themselves could only be prepared through step by step repeated inconvenient and laborious procedures, each inserting but a single fluorine. Thus, considering the great value of partially fluorinated arenes as versatile synthetic intermediates, one can understand why the development of concise and highly selective ways to procede from perfluoro- and perfluorochloroarenes to less fluorinated arenes by substitution of hydrogen for halogen remains a live and challenging problem.

The work in this direction was done for a long time, and approaches found can be divided into two categories. The first one embraces methods involving insertion into a perfluoro- or a perfluorochloroarene of a functional group (carboxylic, hydrazo, metallic group) which can be subsequently substituted by hydrogen. These "indirect" methods, being earlier reviewed [1], are not considered in the present article. However, despite a diversity of such approaches, multistep routes do not completely solve the problem of restricted accessibility of partially fluorinated arenes.

Evidently, the direct hydrogen substitution for halogen (hydrodehalogenation) in readily available highly fluorinated arenes is a most expeditious achievement of the goal. Rather attractive is reductive hydrodehalogenation but its scope of application, particularly that of hydrodefluorination, was quite limited until recently [2–4]. To replace halogens heavier than fluorine, catalytic hydrogenation and reduction by metals (Zn, Cu(I)) in the presence of proton sources were used [1]. However, polyfluoroarenes with heavy halogens, especially functionalized ones, are, as a whole, less accessible than perfluoroarenes. Already at the initial stage of polyfluoroarene chemistry, hydrodefluorination by metal hydrides was practiced as one of the fluorine nucleophilic substitution reactions which are most typical for these compounds [5,6]. However, this mode of hydrodefluorination is often insufficiently selective and only restrictedly applicable to functionalized polyfluoroarenes.

Thus, the problem of easy transition from highly to less fluorinated arenes, first of all by means of selective hydrodehalogenation, remains relevant. The present article reflects

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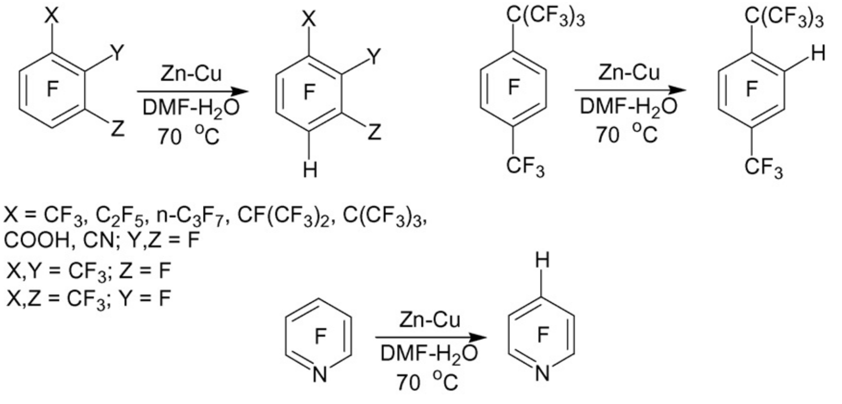


Scheme 1.

the progress achieved in this area in the last one and a half decade.

2. Experimental data and synthetic applications

Recently hydrodefluorination of polyfluoroarenes by the reducing systems based on zinc was intensively studied. Being treated with Zn/Cu couple in aqueous DMF at 70 °C, perfluoroarenes with electron-accepting substituents and pentafluoropyridine undergo single hydrodefluorination at *para*- or *ortho*-position (γ- and α-position in a pyridine framework) to give corresponding products in 30–50% yields [7–9]. The yields can be increased up to 70–80% by using an electrolyte (NH_4Cl, NaCl) additive [10] (Scheme 1).

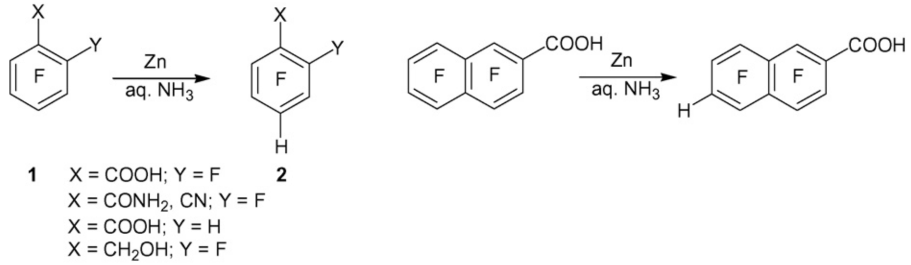
Unlike perfluoroalkylbenzenes depicted, perfluoro-*para*-xylene and -*para*-cymene undergo hydrogenolysis on the α-C–F bond of a perfluoroalkyl substituent. Hexafluorobenzene stays intact under these conditions [8].

para-Hydrodefluorination of pentafluorobenzonitrile to yield 2,3,5,6-tetrafluorobenzonitrile was accomplished by metals, e.g. zinc, in aqueous solution in the presence of salts, e.g. KH_2PO_4, to prevent formation of HF [11].

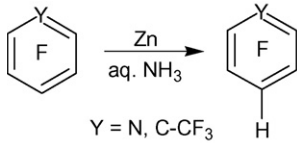
Electrochemical hydrodefluorination of pentafluorobenzoic acid (**1**) is known to occur at the *para*-position to provide 2,3,5,6-tetrafluorobenzoic acid (**2**) [12]. Unlike this, *ortho*-fluorine is predominantly removed upon reduction of acid **1** by Yb(II) compounds followed by hydrolysis to give 2,3,4,5-tetrafluorobenzoic acid (**3**) [13].

Reduction of acid **1** (actually pentafluorobenzoate under the experiment conditions) with sodium in liquid ammonia [14] is non-selective and occurs as multiple hydrodefluorination even at small conversion. Regardless of the order of reactants mixing the reaction gives a complex product mixture consisting of small and comparable (1–9%) quantities of acid **2**, 3,5-difluoro-, 3-fluorobenzoic and benzoic acid (alongside with significant amounts of unidentified products, obviously, cyclohexadiene derivatives). The reason of such non-selectivity is believed to be much faster electronic diffusion as compared with molecular diffusion [15]. Owing to this electrons occupy much more quickly the limited zone tightly contiguous with a reagent species carried into the reaction medium (a particle of acid **1** added to a liquid ammonia solution of sodium or a sodium bit added to a solution of **1**). As a consequence, a primary hydrodefluorination product undergoes further reduction in this unequilibrium zone before molecules of starting compound come there. So far as one can judge from the product distribution, the positional hydrodefluorination rate increases in the order *meta* < *ortho* < *para*.

The situation changes dramatically with replacement of sodium by zinc. In the last case electrons do not get off from the metal into the solution, and the reduction occurs much more slowly and, apparently, at the immediate contact of a substrate molecule with the metal surface. In so doing the effective zinc reduction potential appears to suffice for reducing acid **1**, but not products of its hydrodefluorination. As a result, acid **2** is formed in a more than 90% yield. Some later *para*-hydrodefluorinations of acid **1**, as well as its amide, pentafluorobenzylic alcohol and *ortho*-hydrodefluorination of acid **2** were shown to smoothly occur in aqueous ammonia at room temperature (70–95% yields). The primary *para*-hydrodefluorination of pentafluorobenzonitrile also proceeds, but the reaction is complicated by formation of significant amounts of by-products. In these



Scheme 2.



Scheme 3.

conditions also the hydrodefluorination of heptafluoro-2-naphthoic acid proceeds easily, but in the ring containing no carboxylic group [16,17] (Scheme 2).

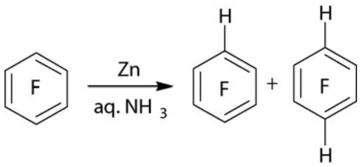
This ultimately simple reducing system turned out effective also in selective hydrodefluorination of non-functionalized polyfluoroarenes [8,18]. Perfluorotoluene and -pyridine exchange fluorine by hydrogen precisely at the *para*- and γ-position, accordingly (70–90% yields) (Scheme 3).

Perfluoroarenes containing no electron-accepting groups also undergo hydrodefluorination by zinc in aqueous ammonia, but, unlike above examples, their primary transformation products also undergo defluorination. From hexafluorobenzene a 1:3 mixture of starting compound and pentafluorobenzene with a minor amount of 2,3,5,6-tetrafluorobenzene was obtained. In so doing appreciable acceleration of the reaction by presence of ammonium chloride has been noted (Scheme 4).

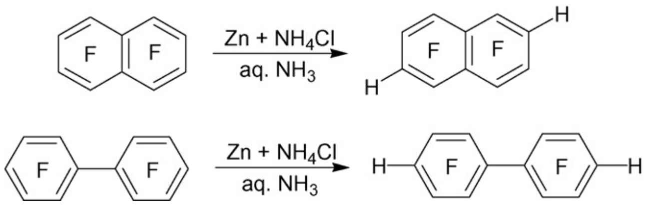
However, upon reduction of both octafluoronaphthalene and decafluorobiphenyl the monohydrodefluorination products either can be recorded only at very small conversion, or cannot be at all, the corresponding double defluorinated products with two hydrogen atoms in different rings being obtained. In these cases necessitated is the presence of NH_4Cl and, for hydrodefluorination of decafluorobiphenyl, THF as a cosolvent [17] (Scheme 5).

With hexafluorobenzene and octafluoronaphthalene the same results were obtained by using the system $(C_5H_5)_2$–$ZrCl_2$–Mg–$HgCl_2$ [19]. Hexa- and pentafluorobenzene, octafluoronaphthalene and pentafluoropyridine react easily with zinc dust in the presence of a complex formed by $NiCl_2$ with 2,2′-bipyridyl (Bipy) or 1,10-phenanthroline (Phen) to give less fluorinated derivatives of the corresponding aromatic systems [20].

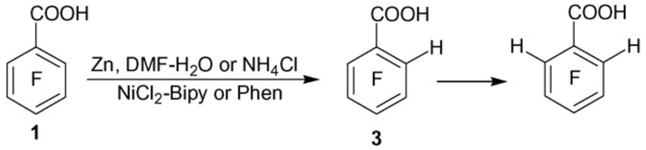
Acid **1** does not react with zinc dust or the Zn–$NiCl_2$ (5 mol%) system in aqueous DMF at 70 °C. However, in the presence of *in situ* generated complexes of $NiCl_2$ with Bipy or Phen (1 mol%) in DMF-H_2O or DMF-NH_4Cl (the hydride complex $HNiXL_n$ was suggested to operate as an active reagent of a nucleophile type [21]) acid **3** was obtained. Both *ortho*-fluorines were removed with using an increased quantity of catalyst (up to 5 mol%) and a longer reaction duration to provide 3,4,5-trifluorobenzoic acid, practically quantitative yields being reached in both cases (Scheme 6).



Scheme 4.



Scheme 5.



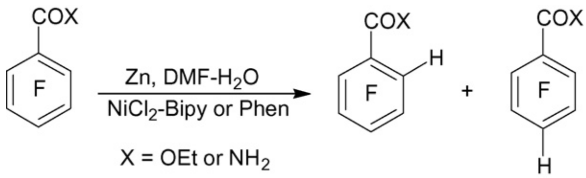
Scheme 6.

Unlike acid **1**, both ethylpentafluorobenzoate and pentafluorobenzamide react with zinc in the presence of $NiCl_2$–Bipy or $NiCl_2$–Phen less selectively to yield comparable quantities of 2,3,4,5- and 2,3,5,6-C_6F_4HCOX (X = OC_2H_5, NH_2) (Scheme 7) [21].

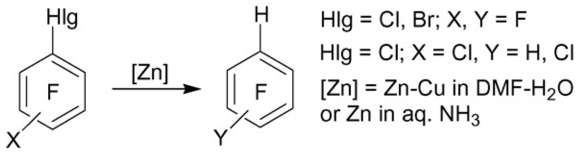
Essentially easier than hydrodefluorination of perfluoroarenes and strictly selectively proceeds hydrodechlorination of chloropolyfluoroarenes, which are readily available as transient products on the way from perchloroarenes to corresponding perfluoroarenes. Pentafluorobenzene is quantitatively formed from chloro- or bromopentafluorobenzene. A mixture of dichlorotetrafluorobenzenes is readily converted into a potentially separated mixture of corresponding tetrafluorobenzenes (Scheme 8) [8,17].

In a similar way, reasonably accessible 1,3,5-trichloro-2,4,6-trifluorobenzene can be utilized as a precursor for Cl_n-1,3,5-trifluorobenzenes (n = 0, 1, or 2) (Scheme 9) [8,17].

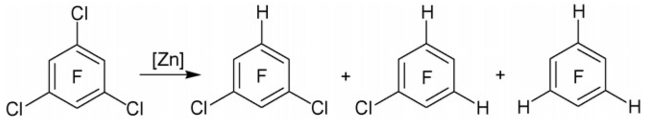
By this example it was shown, that at use of the system Zn–NH_3–H_2O a degree of hydrodechlorination can be varied with ammonia concentration and temperature. In 20% ammonia the reaction as a whole proceeds slowly, but a



Scheme 7.



Scheme 8.



Scheme 9.

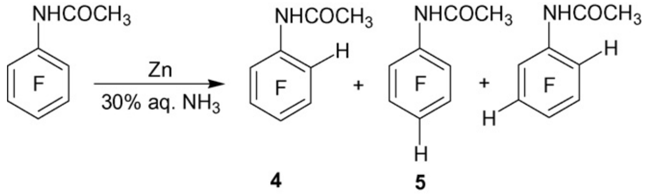
double dechlorination product—1-chloro-2,4,6-trifluorobenzene is formed mainly with a minimal impurity of products of the removal of one and three chlorines. In 30% ammonia and with an acetone additive or at higher temperature (60 °C), the yield raises of the full hydrodechlorination product—1,3,5-trifluorobenzene [17].

Reduction of 2-chloroheptafluoronaphthalene (a 3:1 mixture with the 1-isomer) with zinc in 20% aqueous ammonia is limited to selective removal a chlorine atom only at small conversion because 2-*H*-heptafluoronaphthalene thus derived undergo easy hydrodefluorination under the same conditions (see Scheme 5). So, upon nearly full consumption of the starting compound a product of the reaction is 2,6-di-*H*-hexafluoronaphthalene [17].

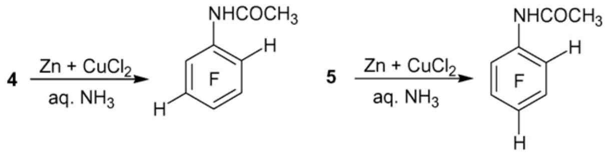
Interaction of 4-chlorotetrafluorobenzoic acid with zinc in 20% aqueous ammonia results in the selective removal of chlorine to produce acid **2** [17]. The regioselectivity observed is the same as in electrochemical reduction of the same starting compound [12].

All the above hydrodehalogenations by zinc were performed either with perhaloarenes or with their derivatives containing electron-accepting functional groups. However, of much interest are partially fluorinated arenes with electron-donating substituents. In particular, polyfluorinated arylamines with the non-substituted or appropriately functionalized position *ortho* to an amino group are versatile scaffolds adapted to build an azaheterocycle on a polyfluorinated aromatic ring. The earlier described syntheses of such amines are multistage and labour-consuming. Hence the development of new essentially more simple methods, such as hydrodefluorination of accessible polyfluoroarylamines, would open an unprecedented short way from aromatic raw material into the earlier very poorly studied area of polyfluorobenzo azaheterocycles. Compounds of this type are obvious candidates as starting materials to design biologically active compounds.

In this connection, the selective hydrodehalogenation of amines which can be easily prepared by the direct ammonolysis of base polyfluoroarenes, such as hexa- and pentafluorobenzene, perfluorotoluene, chloropentafluoro- and 1,3,5-trifluorotrichlorobenzene, pentafluoropyridine, is a topical task. However, the introduction into a perfluoroarene of the electron-donating substituent—ethoxy [8] or amino group [22] has been established to make impossible hydrodefluorination by the Zn/Cu couple or merely Zn, respectively, under the above specified conditions of perfluoroarene hydrodefluorination. At the same time, an attempt to suppress the electronic effect of the amino group by *N*-acetylation turned out successful. Thus, the pentafluoroacetanilide reduction by Zn in 30% aqueous ammonia at room temperature gave mainly the *ortho*-defluorinated product—2,3,4,5-tetrafluoroacetanilide (**4**) with small impurities of the *para*-defluorinated product—2,3,5,6-tetrafluoroacetanilide (**5**) and the doubly defluorinated one—2,4,5-trifluoroacetanilide (Scheme 10) [22].



Scheme 10.



Scheme 11.

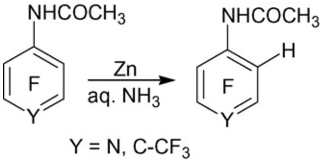
The hydrodefluorination regioselectivity was revealed to change with the process duration. In the initial stage, corresponding to no more than 10% consumption of the starting material, the *para*-hydrodefluorination occurs to give mainly anilide **5**. However, after the ∼30% transformation, the *ortho*-defluorinated anilide **4** becomes predominant. It was reasonable to account for such a change of the orientation by accumulation of zinc ions in the reaction mixture. In support of this, the primary addition of $ZnCl_2$ into the reaction system led to a prevalence of *ortho*-defluorination already from the very start of the reaction [23].

As potential products of further hydrodefluorination also are of the great synthetic value, when seeking additional possibilities to intensify the process the reaction was found to be pronouncedly accelerated by the additive of a copper salt ($CuCl_2$ or $CuSO_4$). In so doing the conversion degree of anilide **4** increased essentially, and anilide **5** underwent defluorination, the latter having been intact without the additive [23] (Scheme 11).

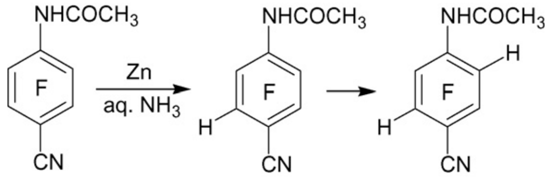
Reductions of 4-acetamido-2,3,5,6-tetrafluorobenzotrifluoride and 4-acetamido-2,3,5,6-tetrafluoropyridine gave exclusively corresponding products of *ortho*-defluorination to an acetamido group (Scheme 12) [22,23].

4-Acetamido-2,3,5,6-tetrafluorobenzonitrile was revealed to be very easily hydrodefluorinated but at the position *ortho* to the cyano group, and only the second reaction occured as hydrodefluorination *ortho* to the acetamido group (Scheme 13) [22].

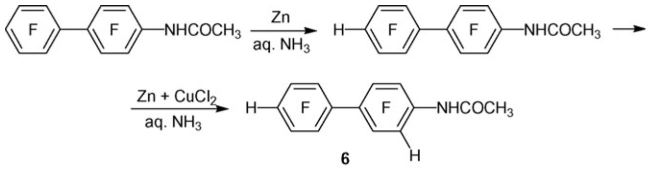
The reduction of 4-acetamidononafluorobiphenyl, irrespective of whether a zinc salt was or was not added, gave a product of *para*-hydrodefluorination of the pentafluorophenyl fragment—4-acetamido-2,2′,3,3′,5,5′,6,6′-octafluorobiphenyl.



Scheme 12.



Scheme 13.



Scheme 14.

When additives of a copper salt and ethanol as a cosolvent were used, the 53% isolated yield was achieved and a twice defluorinated product—the acetamide **6** also appeared. So, the secondary hydrodefluorination takes place at the position *ortho* to the acetamido group (Scheme 14) [22,23].

Unlike perfluoroarylamines, their chlorine-containing analogues upon the action of zinc in aqueous ammonia undergo hydrodehalogenation very easily but with removal of chlorine (Scheme 15) [24].

Thus, an amino group, blocking a defluorination, does not hinder dechlorination.

3. Mechanism

The conventional mechanism of reductive hydrodefluorination is a reaction cascade triggered by the single electron reduction of a polyfluoroarene substrate with an odd electron invading its π*–MO to form a corresponding radical anion (RA). This initiating event is followed by the RA fragmentation along a C–F bond. An aryl radical thus formed is quickly reduced to an aryl anion, the final protonation of which yields a hydrodefluorination product (Scheme 16) [25,26].

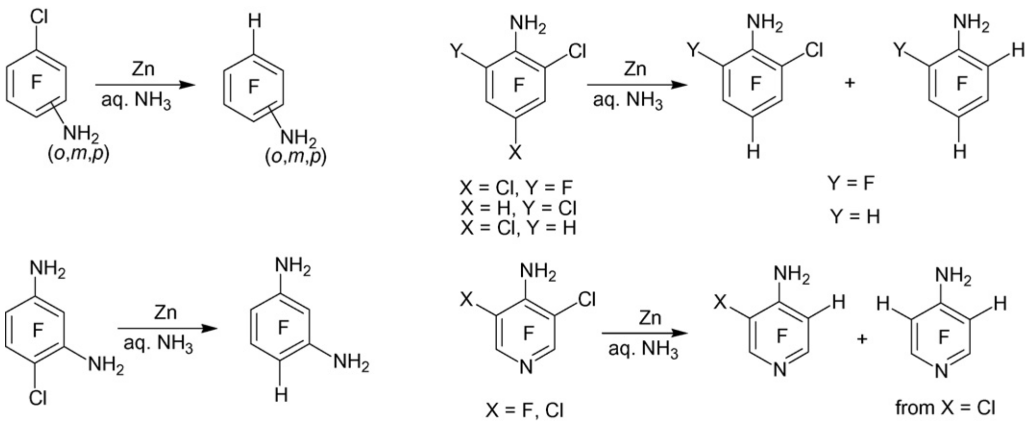
Validity of this concept with reference to the reduction by zinc is supported by the formation of RA from non-halogenated arenes in the system Zn/OH$^-$/DMSO [27] and from hypercin in the systems Zn/DMF and Zn/DMF/H_2O [28], as well as by the formation of organozinc compounds from perfluoroarenes under the action of zinc in anhydrous DMF in the presence of some salts [29]. At the same time, the way via protonation of RA as the second stage and the subsequent transformation of an arising cyclohexadienyl radical seems improbable, as the formation of such radical was not recorded spectrophotometrically in the pentafluorophenolate hydrodefluorination effected by hydrated electrons [26].

Table 1
Fragmentation rate constants (k_c) of fluorinated benzoate RAs

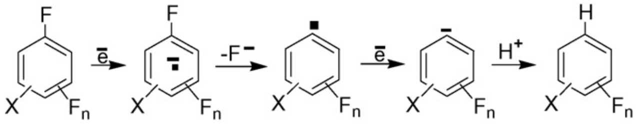
Compound	k_c (s^{-1})
$2\text{-}FC_6H_4CO_2^-$	1.5×10^4
$3\text{-}FC_6H_4CO_2^-$	$\leq 3 \times 10^3$
$4\text{-}FC_6H_4CO_2^-$	5×10^5
$2,3\text{-}F_2C_6H_3CO_2^-$	1.6×10^7
$2,4\text{-}F_2C_6H_3CO_2^-$	1.5×10^7
$2,5\text{-}F_2C_6H_3CO_2^-$	1.4×10^5
$2,6\text{-}F_2C_6H_3CO_2^-$	1.9×10^6
$3,4\text{-}F_2C_6H_3CO_2^-$	7×10^7
$3,5\text{-}F_2C_6H_3CO_2^-$	1×10^4
$2,3,5\text{-}F_3C_6H_2CO_2^-$	6.5×10^5
$2,3,6\text{-}F_3C_6H_2CO_2^-$	1.1×10^8
$2,4,5\text{-}F_3C_6H_2CO_2^-$	1.1×10^8
$2,4,6\text{-}F_3C_6H_2CO_2^-$	6.5×10^7
$3,4,5\text{-}F_3C_6H_2CO_2^-$	2×10^8
$2,3,4,5\text{-}F_4C_6HCO_2^-$	1.7×10^8
$2,3,4,6\text{-}F_4C_6HCO_2^-$	1.2×10^9
$2,3,5,6\text{-}F_4C_6HCO_2^-$	2.1×10^7
$C_6F_5CO_2^-$	1.2×10^9

Reasonably, the propensity of a polyfluoroarene to undergo reductive hydrodefluorination should be connected with the influence of its structure on a rate of any of two or both key stages depicted first in Scheme 16. In so doing the principal structural factors influencing the ease of their realization are the fluorination degree and the nature of non-fluorine substituents.

The electron affinity (EA) in the fluoroarene series is known to increase with fluorine accumulation [25,30,31], thereby promoting the first stage. However, one could expect [32,33] the stability of a RA toward fragmentation also to increase with growing EA of its neutral precursor. This should also be due to the increase in the C–F bond strength with progressive arene fluorination [25,34,35]. However, the available experimental data [30,36] testify to the opposite tendency. So, the decay rate of a fluorinated benzonitrile RA was shown to increase in the series (k, s^{-1}) $4\text{-}FC_6H_4CN$ (11) < $2,4\text{-}F_2C_6H_3CN$ (~50) < $2,4,6\text{-}F_3C_6H_2CN$ (~8×10^2) < C_6F_5CN (>10^3) [30]. The same tendency was established for the full series of fluorinated benzoates, the presence of fluorine *ortho* to a fragmentation site being additionally favorable (see Table 1) [36]. Thus, the fragmentation kinetics of polyfluoroarene RAs



Scheme 15.



Scheme 16.

does not follow its thermodynamics, that is, the intrinsic energy barrier of the reaction is not connected with its driving force. As for to a dependence of the reaction rate on the fluorine location relatively a functional group (CN or COO^-), it increases in the sequence *meta* < *ortho* < *para* [25,30,36].

The above specificity of the process is associated with the influence of fluorine accumulation on electronic and spatial structures of arene RAs [25,37,38]. The correlation of RA resistance to the fragmentation along a C–Hlg bond with EA of a RA precursor is characteristic for RAs which are stabilized by the structural fragments capable to a conjugative dispersion of the extra electron density. Thereby it is diminished in a ring in which a C–Hlg bond is located thus approaching this ring character to that of a neutral arene. Unlike this, fluorine is a π-donating substituent, and its electron-accepting effect operates in a σ-framework. In so doing the energy of a π*-MO, which is occupied by an electron in course of the RA formation, goes down, but even in an greater degree is simultaneously stabilized a σ*-MO and the energy gap separating these MOs narrows. This favors occurrence of the pseudo-Jahn–Teller effect (PJTE) resulting in spatial deformation of a molecule, basically realizing through C–F bonds bending out of a ring plane (see also [31]). A single electron MO (SOMO) becomes a combination of π- and σ*-MO. As a whole the RA electronic state can be represented as resulting from the interaction of its planar ground Π- and out-of-plane distorted Σ*-state. This ΠΣ*-interaction is governed by the selection rules connected with the interacting states symmetry. All these trends strengthen with the fluorination degree of an aromatic ring. The above basic distinction in the electronic effects of π-accepting substituents, on the one hand, and fluorine, on the other, exhibits itself by the fact that in the first case the ΠΣ* energy gap ($\Delta E_{\Pi\Sigma*}$) depends practically only on the energy of the ground Π state, whereas in the polyfluoroarene RA series the $\Delta E_{\Pi\Sigma*}$ variation with the number of fluorines is governed mainly by the Σ* state energy [37,38].

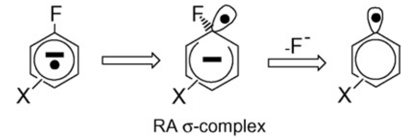
This is of crucial significance for RA fragmentation. For a planar π-RA the fragmentation along a C–Hlg bond is forbidden because the starting π-SOMO and the σ-SOMO in an emerging aryl radical are mutually orthogonal. To overcome this orbital symmetry restriction, an out-of-plane bending of cleaving C–Hlg bond is required in a transition state (TS) [33,39,40], and essentially greater than the one occurring, if any, in the starting RA. In going from a RA to its fragmentation TS, the ΠΣ* energy gap is even more narrowing with stretching a C–Hlg bond. This strengthens PJTE, and its increase with fluorine accumulation is greater for the TS stabilization as compared to the RA itself. This circumstance, together with full absence of similar effects in fragmentation products, causes obviously the intrinsic energy barrier to defy following a reaction free energy and a parallelism of kinetics and thermodynamics to get broken [36]. Nevertheless, a certain correlation exists between these effects in a RA and in its fragmentation TS in the polyfluoroarene series [35,36,38]. This allows estimating in a first approximation the relative RA propensity to fragmentation and predicting its regioselectivity on a $\Delta E_{\Pi\Sigma*}$ value and a magnitude of the out-of-plane bending of various C–F bonds in a starting RA, the sites of maximal coincidence of π- and σ*-electron densities being most favorable [35–37]. So, $\Delta E_{\Pi\Sigma*}$ values correctly predict an acceleration of RA fragmentation rates with fluorine accumulation in the series of fluorinated benzoates and a preferability of the *para* fluorine removal (Table 1). However, the calculated order *ortho* < *meta* mismatches the correlations of the RA cleavage rates (k_c) and hydrodefluorination regioselectivities experimentally observed in this series. The most probable reason of it is concluded in neglecting solvation effects. Meanwhile, local specific (hydrogen bonding) and non-specific interactions of the carboxylate group of a RA with solvent molecules or a counterion can be essential. Really, according to the results of quantum chemical calculations, the SOMO density in the ground states of the benzoic acid RA, considered as a simplest model of the specifically solvated benzoate RA in proton solvents, and of the ammonium benzoate RA is shifted from the *meta* to *ortho* position as compared to the benzoate RA. The calculated energetics of non-specific solvation of the benzoate RA gives the same result, which is believed to be due to neutralization of the carboxylate negative charge. Besides, the $\Delta E_{\Pi\Sigma*}$ values for the RAs of fluorinated benzoic acids perfectly correlate with those for the corresponding ammonium salt RAs, and the increase of $\Delta E_{\Pi\Sigma*}$ values in the order *para* < *ortho* < *meta* agrees with the experimentally observed regioselectivity of the reductive hydrodefluorination of fluorinated benzoic acids. As a whole, the change of a minimal for each RA $\Delta E_{\Pi\Sigma*}$ value reflects the k_c variation presented in Table 1.

The correlation of the $\Delta E_{\Pi\Sigma*}$ values of the isomeric perfluoroxylene RAs is, probably, one of the reasons for the *ortho* and *meta* isomers to lose fluoride anion from the ring, whereas the *para* isomer loses it from the trifluoromethyl group (see above) [8,9].

The quantum chemical description of a hydrodefluorination process is rather sophisticated and is a subject of the specialized theoretical research. Therefore, the qualitative regularities, reflecting the influence of a polyfluoroarene structure on the rate and regioselectivity of the reaction, are necessary for planning synthesis on its basis. The above facts elucidate the ease of hydrodefuorination to qualitatively correlate with a polyfluoroarene EA. Indicatively in this respect, with Zn/Cu couple in aqueous DMF hexafluorobenzene displays a distinctly smaller reactivity than its perfluorinated homologs and pentafluoropyridine, and pentafluoroaniline is inert to Zn in aqueous ammonia (*vide supra*). In the latter case, the substituent blocking effect ensues from its electron-donating influence, reducing a substrate EA and, accordingly, a rate of the first stage in Scheme 16, rather than from retarding the second stage. This is borne out by a lack of the experimental EA value for pentafluoroaniline and by B3LYP/6-31+G* results [23], which predict for this compound the EA_{ad} value of 0.13 eV. This value is much less than the calculated (0.60 eV) and experimental (0.5–0.9 eV [25]) ones for hexafluorobenzene. At the same time, the calculation results predict the pentafluoroaniline RA to be structurally flexible and to alter easily its electronic state. This alteration is concomitant with redistribution of the electronic density between all C–F fragments, thereby allowing easy fragmentations along all C–F bonds. The calculated energies of isomeric aminotetrafluorophenyl radicals predict the *para*-fragmentation of pentafluoroaniline RA to be more thermodynamically preferable, and also in comparison with that of hexafluorobenzene RA. However, the predictive significance of these computational data should be perceived cautiously, taking into account what was mentioned above about an inherent disparity of kinetics and thermodynamics peculiar to the mechanism of the reaction.

The analysis of possible reasons of suppressing the blocking effect of the amino group by its acetylation also supports the above rationalization [23]. The fact that the *N*-acetylation suppresses an electron-donating effect of the substituent, is illustrated by comparison of the electrochemical reduction potentials (CVA, Pt electrode, DMF, Et_4NClO_4 as supporting electrolyte) of hexafluorobenzene (−2.10 V) and pentafluoroacetanilide (−1.60 V). From this follows, that the acetamido group is a weaker π-electron-donor than fluorine, that is in line with the RB3LYP/6-31+G* calculated value EA_{ad} of 0.71 eV for pentafluoroacetanilide as compared with the above value for hexafluorobenzene. Based on experimental and calculated data, one should consider that this is caused both by an electronic effect of the acetyl group and by its spatial interaction with *ortho* fluorines, which forces the acetamido group to turn from a plane of the benzene ring.

The aforesaid about the detailed hydrodefluorination mechanism means that the strict theoretical rationalization of its regioselectivity necessitates calculating a potential energy surface of the reacting system. However, for estimating possibility to qualitatively predict the hydrodefluorination regioselectivity, indicative is the fact that in the most cases it coincides with the orientation, which is typical for the fluorine nucleophilic substitution reactions of polyfluoroarenes [5,41]. This is most obvious in the case of C_6F_5X compounds, which undergo fluorine nucleophilic substitution as a rule at the *para* position. Such regiochemistry is due to the collective inductive influence on the stability of an anionic cyclohexadienyl system of fluorines, located *ortho* and *meta* to a site of nucleophile addition, combined with avoiding fluorine as a π-electron-donating substituent in the position *para*. The conformity of hydrodefluorination and fluorine nucleophilic substitution regioselectivities does not seem to be casual and was accounted for by some similarity of the TS of the polyfluoroarene RA cleavage along a C–F bond to the σ-complex with an anionic cyclohexadienyl moiety. Indeed, in as much as in the actual RA fragmentation the C–F bond out-of-plane bending occurs synchronously with the bond stretching, the fragmentation mechanism resembles the one-step S_NAr-like mechanism. The respective TS can be modelled by a RA σ-complex with an unpaired electron located on the carbon atom of the out-of-plane deviated C–F bond, thus mimicking an added nucleophile [23] (cf. [42]) (the RA σ-complex depicted in Scheme 17).



Scheme 17.

Taking into account this similarity, the b_1-type of SOMO in the pentafluoroacetanilide RA is believed to favor crucially its transformation into the TS of the *para*-C–F-bond cleavage, since it is the bond that is most out-of-plane bent, and the HOMOs of the RA and the corresponding RA σ-complex ideally fit each other by symmetry (see Fig. 1). Implying that an acetamido group, besides neighbored by two fluorines, does not exert a significant π-donating effect, one may anticipate pentafluoroacetanilide, by analogy with S_NAr reactions of C_6F_5X compounds, to undergo *para*-hydrodefluorination. Exactly this is observed at the initial phase of pentafluoroacetanilide reduction by zinc in aqueous ammonia [23], as well as in the reductive hydrodefluorinations of other C_6F_5X compounds [16,17].

Thus, the rationale presented allows one to foresee an expected hydrodefluorination regioselectivity, a deviation from this prediction being considered as an evidence for a possible operation of some specific effects. So, the above *ortho*-hydrodefluorinations of polyfluorinated benzoic acids by ytterbium compounds [13] and by zinc in the presence of nickel complexes [21] were explained by bonding the carboxylate oxygen with a metal cation followed by intramolecular electron transfer and *ortho*-fluorine abstraction in a cyclic six membered TS. The hydrodefluorination of pentafluoroacetanilide by zinc in aqueous ammonia only at the short initial stage proceeds at the *para*-position, thus corresponding to an orientation expected on the basis of the

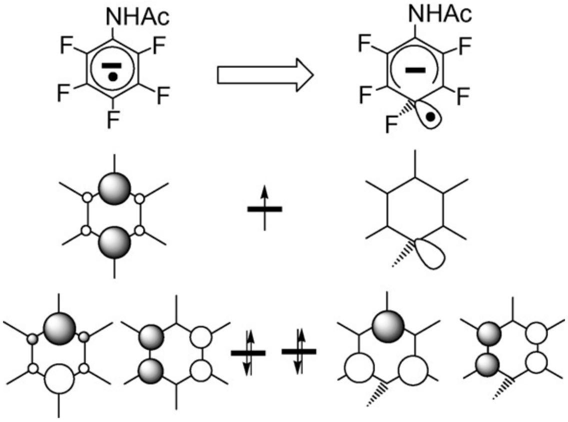
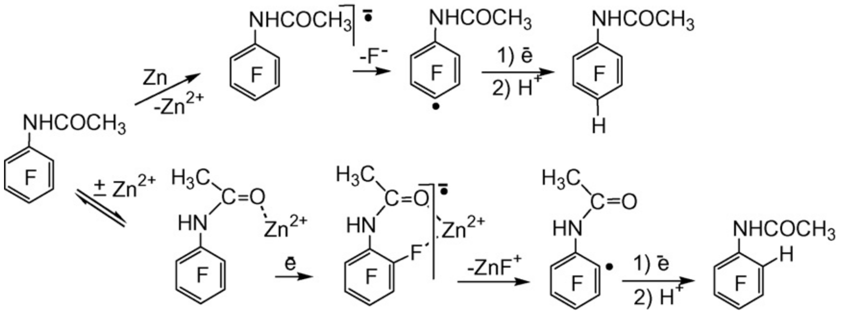


Fig. 1. HOMO's of the pentafluoroacetanilide RA and the corresponding RA σ-complex (the MO images are simplified by omitting the minor lobes associated with the fluorine atoms and the acetamido group). [24]

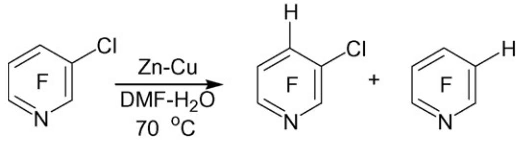


Scheme 18.

S_NAr model. However, as zinc cations accumulate in the reaction medium, prevailing becomes *ortho*-hydrodefluorination, having been explained on the basis of the assumption of formation of a chelate complex of a zinc cation with a substrate. This complex is believed to be reduced much more readily than the free substrate. Moreover, in a product of its one-electron reduction a zinc cation is coordinated with the *ortho*-fluorine, the latter thus being predominantly removed (Scheme 18) [23].

All the aforesaid relates to the hydrodefluorination mechanism. The fragmentation along a bond formed by a carbon with a heavier halogen can occur both through the same route and via an electron attack directly on the σ*-MO of a C–Hlg bond concomitant with its synchronous cleavage. Attention should be paid to the fact that, regardless of number and location of chlorines, the hydrodehalogenation of chloropolyfluoroarenes proceeds as a rule selectively as the chlorine removal. The reason is suggested to lie in the different electronic nature of chloropolyfluoroarene RAs as compared to perfluoroarene RAs. Judging from ESR [43], electrochemical and quantum chemical [44] data, and INDO/UHF results [38], the RAs of chloropolyfluorobenzenes are likely σ-radicals with a SOMO located on a C–Cl bond. Especially indicative in this connection is the easy hydrodechlorination of polyfluorochloroarylamines. This allows believing that in going from arylamines, containing only fluorine, to their chloropolyfluoro analogues, the nature is changed of the MO accepting an electron. In case of a Cl-containing substrate an electron comes, obviously, directly on a σ*-MO of the C–Cl bond to be synchronously cleaved, rather than on a π*-MO, which is strongly influenced by the amino group π-donating effect blocking hydrodehalogenation [24]. However, in case the energies of the MOs involved into hydrodefluorination and hydrodechlorination are obviously close, these two types of hydrodehalogenation can compete (Scheme 19) [7,8].

The authors [45] suppose the RA mechanism for the hydrochlorination. However, the experimental data do not contradict the notion of the mechanism including the direct electron income in the σ*-MO of a C–Cl bond. Indicatively, the hydrodefluorination regioselectivity is as expected for fluorine nucleophilic substitution whereas the hydrodechlorination occurs in the position, which is least favorable for it, thus suggesting the above difference in mechanisms of the competing reactions.



Scheme 19.

4. Conclusion

Last years, mainly in the N.N. Vorozhtsov, Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Russian Academy of Science, have been developed the various versions of hydrodehalogenation of readily available polyfluoroarenes by reductive systems, based on zinc and enabling to obtain earlier inaccessible partially fluorinated arenes rather expeditiously and conveniently for routine experimental work. Simultaneously, the theoretical rationalization of mechanism and regiochemistry of these transformations is developed, allowing an experimentalist to qualitatively predict and plan a synthetic result. These achievements facilitate essentially entering into the chemistry of structurally complicated functional and heterocyclic compounds containing a benzene moiety with three to four fluorines and potentially possessing properties useful for practical applications. Remarkably at the same time, the hydrodehalogenation area is spacious enough for extending search of new effective tools, allowing one to intensify these transformations and to regulate their regioselectivity. The most obvious and attractive is the seeking of new reducing systems and additives (coreductants) intensifying the chemistry, of functional groups, capable to specific interactions and furnishing means to vary the reaction regioselectivity, and of new efficient reaction media. As a whole, the situation looks rather promising for obtaining new essentially important results propelling fine organic synthesis in the fluoroarene area.

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