

REVIEW

THE STABILITIES OF ORGANIC FLUORINE COMPOUNDS

J.C. TATLOW

Joint Editor-in-Chief, Journal of Fluorine Chemistry

A significant part of the justification for the existence of organic fluorine chemistry as a distinct sub-discipline lies in the high stabilities of most fluoro-organic compounds [1,2]. Not only is the typical carbon-fluorine bond strength high for a single bond, but the bond strengths increase, and the bond lengths decrease with multiple fluorine substitution on carbon [1,3]. Further, carbon-carbon bonds in fluoro-compounds are not weakened electronically, and the small size of the fluorine atom means that multiple substitution produces no steric strains in carbon systems that cannot normally be accommodated. It is almost too well known to need stating that saturated fluoro-carbons, and, to a lesser extent, substituent groups derived from them, have few reactions and even these require extreme forcing conditions. Further, very few organic fluoro-compounds (except acyl of sulphonyl fluorides) react primarily by rupture of C-F bonds.

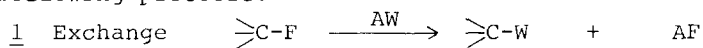
Organic fluorine chemistry is fascinating because of the rich variety of reactions exhibited by the multiplicity of possible functional groups, their reactivities dependent upon, or modified significantly by, the fluorine substituents. Usually implicit in this is the stability of the fluorine atom or of the poly-fluoro cluster present.

There are however many examples of carbon-fluorine bonds which are sufficiently reactive to be broken under non-forcing conditions, and in a few cases they are extremely reactive. It

seems timely to summarize the main features of this aspect of the subject; this little review is aimed at the non-specialist, new to fluorine chemistry, but desirous of incorporating fluorine into particular molecules, and who might be saved some trouble.

Reaction Types

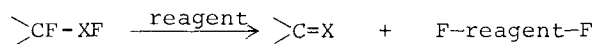
Most losses of fluorine from organic fluorides are by one of the following processes



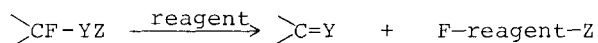
Reactions of this sort are almost entirely nucleophilic in type, and authenticated examples do not exist so far of specific homolytic C-F bond breakage, or of formation of F^+ , under controlled conditions.

2 Elimination

A of fluorine alone



B of a fluoride



Though a reagent is specified here, such processes can sometimes be promoted by heat or by solvation of the eliminated species.

Few of these reactions go readily; there are some that can proceed under the usual organic chemical conditions, but many need forcing conditions. Then, of course, there may well be further repercussions, in that the products are unstable under the conditions of their generation, so that deep-seated breakdown occurs. Hence the lack of useful reactions of perfluoroalkanes.

Fluorine Loss by Reactions of Type 1 : Exchange Processes

1A Saturated Systems

Simple exchanges of fluorine involving nucleophilic reagents proceed normally for alkyl monofluorides though not as readily as for the other alkyl halides [1,2,4]. However, few such reactions

have been reported for saturated polyfluorides, or fluorocarbons, and normally only extensive decomposition is possible under forcing conditions. Such exchanges rarely interfere with the usual run of chemical reactions on compounds containing per-fluoroalkyl groups.

One reagent that does attack many C-F bonds is anhydrous aluminium chloride, giving exchange to C-Cl [4,5]. Even saturated fluorocarbons can be made to react, at high temperatures, though mostly not selectively. Fully fluorinated ethers and tertiary amines are highly stable compounds, but with aluminium chloride at 150-200°C, functions of the type $-CF_2-O-$ [6] and $-CF_2-N<$ [7] are exchanged preferentially, and CCl_2 groups are introduced α to the hetero-atom.

Oddly, though highly-fluorinated ethers and tertiary amines are usually stable in the presence of bases, the α - CF_2 groups can sometimes be converted to carbonyl by hot concentrated mineral acid notably sulphuric [4,7]. If the compound is not highly fluorinated, the hydrolysis of fluorine α to the tertiary amino group can be rapid, and the compound $CHClF \cdot CF_2NMe_2$ is used as a mild fluorinating agent, to convert C-OH to C-F [4]. Instabilities associated with primary and secondary amines are discussed in Section 2 Bb.

Reductive cleavage of C-F bonds during hydrogenations or reduction-type reactions does not usually occur [8]. However, where functional groups are present, so that neighbouring group participation is possible, such cleavage can occur [9].

1B Aromatic and Heterocyclic Systems

1Ba Nuclear fluorine. The nucleophilic replacement of aryl fluorine by many reagents under normal laboratory conditions for such processes is well known [1,4,5,10]. Suffice it to say that here, multiple substitution does not confer lower reactivity, and hexafluorobenzene loses fluorine far more readily than does monofluorobenzene.

1Bb Benzylic fluorine. Fluorine in a benzylic position is considerably activated, a single fluorine particularly so, being replaced readily. Even the CF_3 group, which is normally very stable, can be hydrolysed when in a benzylic position. Benzotrifluoride ($\text{C}_6\text{H}_5\cdot\text{CF}_3$) though quite stable towards bases, is converted to $\text{C}_6\text{H}_5\cdot\text{COOH}$ by hot concentrated sulphuric acid, a general reaction which goes preferentially to sulphonation [2]. Also noteworthy is conversion of $\text{Ar}\cdot\text{CF}_3$ to $\text{Ar}\cdot\text{CCl}_3$ by aluminium chloride [1,4,5], (in both reactions, aryl fluorine is much more stable). Further, if electron-withdrawing substituents are present in the ortho- or para- positions of the benzene ring, the CF_3 group is also quite reactive towards bases. Presumably, the benzylic fluorine of all perfluoroalkyl groups will show some analogous activation.

It is clear that many aryl and likewise hetero-aryl C-F bonds are sufficiently reactive to undergo normal replacement processes under quite mild conditions.

1C Unsaturated Aliphatic Systems

Both allylic and vinylic fluorine can be exchanged readily for other groups, and much of organic fluorine chemistry has been concerned with reactions of this type. All fluoro-olefins react with nucleophiles, and though the end products have lost a vinylic or an allylic fluorine, with the incorporation of a group from the attacking nucleophile, the reactions are not replacements but addition-elimination sequences, going through intermediate carbanions [1,4,5,11]. As such they will be mentioned again in section 2Bd.

There are also some, apparently direct, replacements of allylic fluorine carried out under acidic conditions. For example, octafluorocyclohexa-1,4-diene afforded tetrafluoro-p-benzoquinone with oleum at 100°C [12]. 1,2-Diethoxytetrafluorocyclobutene gave with sulphuric acid the remarkable 'squaric acid'. Even moist air converted octafluorocyclohepta-1,3,5-triene into hexafluorotropone [14]. However, even such reactions as these may still be addition-elimination sequences.

Hence, allylic C-F bonds can be quite reactive, and since a high degree of fluorination near a double bond enhances its reactivity towards nucleophiles, multiple substitution does not necessarily confer lower reactivity.

Fluorine loss by Reactions of Type 2 : Elimination Process

2A Eliminations of Fluorine Alone

Examples of this type of reaction are limited. Polyfluorinated 6-membered rings, such as in highly fluorinated cyclohexanes, are defluorinated by passage over finely divided metals at 500°C or so, to give arenes with the same carbon skeletons and polyfluoro-benzenes and -polycyclic aryl compounds have been synthesised this way [11]. Even more rarely, isolated double bonds can sometimes be created [11]. Such eliminations are possible in principle from compounds containing hetero-atoms, but often the hetero-atom fluoride is eliminated (cf. Section 2Bc).

2B Eliminations of a Compound of Fluorine

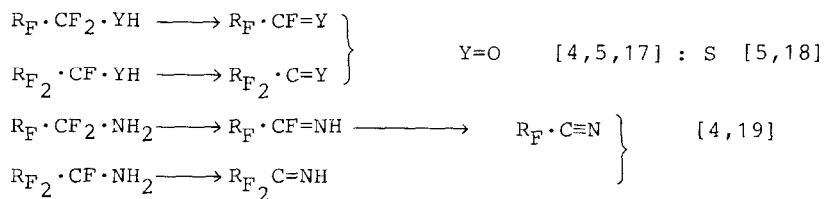
2Ba Hydrogen fluoride from fluorohydrocarbons. Though olefin formation by dehydrofluorinations involving the other halogens (if present) proceed preferentially, dehydrofluorination can often be carried out : $R_{F_2}CF-CHR_{F_2} \longrightarrow R_{F_2}C=CR_{F_2}$. Such reactions are usually fairly sluggish, by normal standards, and strong bases are required. Reaction conditions must be chosen carefully, since the olefin formed is usually itself susceptible to nucleophilic attack, especially if a co-solvent is used, for example, alcoholic alkali. Heterogeneous systems are usually preferable, potassium hydroxide in water or a hydrocarbon. Compounds with the groupings $-CF_2-CF_2H$ and $-CF_2CH_2-$ will usually not eliminate successfully, but most other polyfluorides will give olefins, the detailed products arising by a subtle interplay of factors [4,11,15]. The order of stability of groups in highly fluorinated systems is : $-CF_3 > >CF_2 > \Rightarrow CF$. Surprisingly, acyclic polyfluorides are more stable than cyclic ones [11]. In the cases of fluorocyclohexanes, stereochemical factors are important [15]. It

seems likely that synchronous eliminations are involved in many of these reactions of cyclic systems, but carbanion intermediates may well be involved in other cases. Since a hydrogen atom in a highly fluorinated compound is somewhat acidic, it is even possible that, in a highly basic medium, an organometallic intermediate is formed (see Section 2Bc).

The presence of functional groups in the molecules does not usually prevent these olefin-forming dehydrofluorinations from proceeding, and may in fact assist, e.g. by giving a conjugated structure in an intermediate or product (e.g. 2,2-difluorosuccinic acid [16]). One factor which will inhibit such eliminations is when the resultant double bonds would be highly strained [11].

Fluorohydrocarbons will usually also eliminate HF under the influence of heat, (300-500°C), the process being assisted by passage over a packing of fluoride salt. Clearly, no hydrogen-containing structures will show the extremes of stability of fluorocarbons.

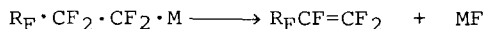
2Bb Hydrogen fluoride from hetero-atom systems. The following systems eliminate hydrogen fluoride quite readily



These eliminations are all much more ready than those discussed in Section 2Ba above, and the compounds concerned are often difficult to isolate (the order of stability is usually : S compound > N > O). Often the mere presence of a polar solvent will cause loss of HF. Presumably, where a stable double or triple bond can be formed, other hetero-atom systems would behave similarly. Since the fluorines α to the hetero-atom are lost, the presence of one non-fluorinated group, e.g. CH_2 , between the hetero-atom and the fluorocarbon chain will give a stable compound.

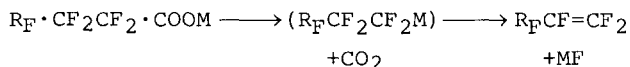
2Bc Eliminations from Organometallic Fluorocarbon Systems.

These are well-known in organic fluorine chemistry [1,2,4,5]. Many fluorocarbon-metal compounds lose fluorine very readily from a β -position, the general reaction being :



Grignard reagents and lithium derivatives of this type are often difficult to use and they must be handled at low temperatures ($\ll 0^\circ C$) or they decompose before they can react synthetically.

The well known olefin synthesis from the heating of carboxylic acid salts is presumably a reaction of a similar type :



Excluding possibly those with hydrogen on the hetero-atom, derivatives of elements such as boron and silicon decompose similarly, with evolution of species having strong $F-B \lt$ or $F-Si \leq$ bonds. However, with some of the less electropositive metals (e.g. Hg, Cu, Ag) the metal-carbon bond may be induced to break before a C-F bond, and their compounds are very useful synthetically.

Since, when fluorine is eliminated from this class of compound, it comes from a β -carbon, a single carbon unit (such as CH_2) between the hetero-atom and the fluorocarbon group will not confer stability; two are needed.

These decomposition processes could be of the essentially covalent (if polarised) organometallic molecules, or could involve carbanions. If the latter they could be related mechanistically to decompositions of hydrofluorocarbons (Section 2Ba). As with the latter type, if the derived unsaturated product has a multiple bond unfavourable energetically, loss of fluorine occurs much more sluggishly. However, decompositions of fluorocarbon compounds containing metallic atoms can usually be induced, and such species do not show the extremes of stability associated with some fluorocarbon types.

It will be noted that a new double bond is generated in this reaction (even if protonation occurs the product could lose HF). Accordingly, with excess of a strong base under forcing conditions, this process is capable of extensive breakdown (or even complete destruction) of fluorocarbon materials if they possess, or can generate, a double bond.

2Be Perfluoroalkoxides. Though primary and secondary perfluoro-alcohols are unstable (Section 2Bb), their alkoxides are readily available from the reactions of fluoride salts with, respectively, acid fluorides and ketones under aprotic conditions. Though obviously not very stable to heat, these alkoxides can be used quite generally in syntheses [21]. Derivatives of other elements can be made analogously.

Polyfluoroepoxides are readily generated from fluoro-alkenes and are also synthetically very valuable [22]. Nucleophiles effect ring-opening to give alkoxides of a different type as reaction intermediates, which usually lose fluoride ion in their reaction pathways, giving useful products.

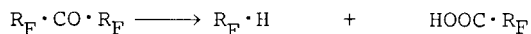
In reactions of class 2, the trifluoromethyl group often occupies a special position. In line with the higher stabilities associated with multiple fluorine substitution, loss of fluorine from longer-chain perfluoroalkyl groups usually occurs preferentially to that from trifluoromethyl, where both are present and equally adjacent to the same reaction centre. Decomposition of a derivative of type CF_3-M again is often less ready than that of compounds of the type R_FCF_2-M . It is of course one of the ways of generating difluoro-carbene [23].

3 Carbon-Carbon Bonds

Though this review is concerned primarily with reactivities of C-F bonds, there are some cases known of enhanced reactivities of C-C bonds, under the influence of perfluorination, and two examples will be considered.

In the saturated fluorocarbons themselves, C-C bonds are usually very stable, except where, for example, very highly strained rings are involved. However C-C bonds between quaternary and tertiary carbon atoms are significantly weaker, *i.e.* break more readily at high temperatures than bonds in a chain of >CF_2 groups [24]. A quaternary-tertiary fluorocarbon bond breaks at ca. 300°C and there is clearly a progressive lowering of stability with increasing carbon substitution on a C-C bond in a fluorocarbon. Presumably, the effect is largely steric, and the radicals formed by homolytic C-C bond breaking are stabilized. A high degree of chain branching can cause surprisingly low thermal stabilities. For highest stabilities the fewer chain branches the better.

A reaction quite general in fluorocarbon chemistry [2] is haloform cleavage of aldehydes and ketones



It occurs quite readily in warm bases, and since these compounds have carbonyl groups very susceptible to nucleophiles, probably the reaction is actually with an alkoxy-form of the gem-diol or related species.

Another interesting and related effect occurs with carboxylic acids. As in general organic chemistry, β -keto acids are readily decarboxylated. Though acids of the type $\text{R}_F\text{CF}_2 \cdot \text{CO}_2\text{H}$ have normal stabilities, those with branched chains, e.g. $\text{R}_F\text{CF}_2\text{CF} \cdot \text{COOH}$ [25], and particularly $\text{R}_F\text{C}(\text{CF}_3) \cdot \text{COOH}$ [26], are readily decarboxylated. Some tertiary acids lose their carboxyl groups, as CO_2 , in hydroxylic solvents well below 100°C.

CONCLUSIONS

There are many examples of reactive C-F and even C-C bonds in fluorocarbon chemistry, and clearly fluorocarbon derivatives do not behave as completely unreactive moieties attached to reactive functional groups. Reactivity, as ever, is associated

with the molecule as a whole. However, these effects should not be over-emphasised. In most cases, fluorocarbon groups can be left unchanged during standard chemical processes to effect transformations elsewhere in the compounds. Though there are weaker C-F bonds near to functional groups, serious difficulties can usually be avoided during normal synthetic sequences.

In general however, care should always be taken in experiments when highly fluorinated material is exposed to strong bases or to heated metals, or where it involves organo-metallic species, particularly in the solid state. Cases are known of explosive decompositions of materials of this type [27].

REFERENCES

- 1 W.A. Sheppard and C.M. Sharts, *Organic Fluorine Chemistry*, Benjamin, 1969.
- 2 M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, 2nd Edn, Horwood, 1976.
- 3 C.R. Patrick, *Adv. Fluorine Chem.*, Butterworths, 2 (1961) 1.
- 4 R.D. Chambers, *Fluorine in Organic Chemistry*, Wiley-Interscience, 1973.
- 5 R.E. Banks, *Fluorocarbons and Their Derivatives*, Macdonald, 1970.
- 6 G.V.D. Tiers, *J.Am.Ch.Soc.*, 77 (1955) 4837, 6703; T. Abe and S. Nagase, *J.Fluorine Chem.* 12 (1978) 359.
- 7 P.L. Coe, A.G. Holton, J.H. Sleight, P. Smith and J.C. Tatlow, *J. Fluorine Chem.*, 22 (1983) 287.
- 8 F.J. Mettillie and D.J. Burton, *Fluorine Chem. Rev.*, 1 (1967) 315.
- 9 S. Brandsenge, O. Dahlman, and J. Celund, *Acta. Chem. Scand.*, B37 (1983) 141.
- 10 L.S. Kobrina, *Fluorine Chem. Rev.*, 7 (1974) 1 : G.G. Yakobson, T.D. Petrova and I.S. Kobrina, *ibid*, p.115.
- 11 J.C. Tatlow, in *Organofluorine Compounds and their Industrial Applications*, Horwood, 1979, p. 19.
- 12 E. Nield and J.C. Tatlow, *Tetrahedron* 8 (1960) 38.

- 13 J.I. Park, S. Cohen and J.R. Lacher, *J. Am. Chem. Soc.*, 84 (1962) 2919.
- 14 D.J. Dodsworth, C.M. Jenkins, R. Stephens and J.C. Tatlow, *J. Fluorine Chem.*, 24 (1984) 41.
- 15 S.F. Campbell, F. Lancashire, R. Stephens and J.C. Tatlow, *Tetrahedron*, 23 (1967) 4435.
- 16 M. Hudlicky and J.A. Hall, *J. Fluorine Chem.*, 22 (1983) 73.
- 17 K. Seppelt, *Angew. Chem.*, 89 (1977) 325.
- 18 R.N. Haszeldine and J.M. Kidd, *J. Chem. Soc.*, (1953) 3219; (1955) 3871.
- 19 W.J. Middleton and C.J. Krespan, *J. Org. Chem.*, 30 (1965) 1398.
- 20 W.T. Miller, J.H. Fried and H. Goldwhite, *J. Am. Chem. Soc.*, 82 (1960) 3091.
- 21 J.A. Young, *Fluorine Chem. Rev.*, 1 (1967) 359.
- 22 P. Tarrant, C.G. Allison, K.P. Barthold and E.C. Stump, *Fluorine Chem. Rev.*, 5 (1971) 77.
- 23 D.J. Burton and J.L. Hahnfeld, *Fluorine Chem. Rev.*, 8 (1977) 119.
- 24 P.L. Coe, S.F. Sellers, J.C. Tatlow, H.C. Fielding and G. Whittaker, *J. Fluorine Chem.*, 18 (1981) 417.
- 25 T.J. Brice and J.H. Simons, *J. Am. Chem. Soc.*, 73 (1951) 4016; 4017.
- 26 S.F. Campbell, J.M. Leach, R. Stephens and J.C. Tatlow, *J. Fluorine Chem.*, 1 (1971-2) 85.
- 27 K. Von Werner, *J. Fluorine Chem.*, 20 (1982) 215.