Russian Chemical Reviews, **44** (4), 1975

Translated from *Uspekhi Khimii*, **44**, 685-714 (1975)

U.D.C. 547.471

Advances in the Synthesis and Investigation of Organofluorine Compounds

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Modern data concerning the wide variety of the physical and chemical properties of organofluorine compounds are reviewed. The studies in recent years, carried out using non-empirical quantum-mechanical calculations, photoelectronic spectroscopy, ^{19}F and ^{13}C NMR, as well as other latest research techniques, have introduced a number of refinements into ideas on the effect of fluorine atoms on the properties of both stable molecules and reaction intermediates.
The principal fields of practical application of organofluorine compounds are also examined. New data on the methods of introducing fluorine into organic molecules are presented in the concluding section.
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I. THE SCOPE OF MODERN FLUORINE CHEMISTRY

Classical organic chemistry constituted an elegant system the fundamental components of which were hydrocarbons—not only as the basis for the classification of any compound containing carbon–carbon bonds but also as a class of substances from which all these compounds can be synthesised by an appropriate sequence of experimental procedures.

The problem of the possibility of another non-hydrocarbon system, comparable in its chemical scope to the classical system, evidently arose simultaneously with organic chemistry. In the search for an answer to this problem twentieth century chemists undertook comprehensive studies on compounds in which both or at least one of the fundamental organogenic elements (carbon and hydrogen) is fully substituted by another element.

Saturated fluorocarbons, the study of which began as late as the 1930s, initially attracted attention by their complete chemical inertness. In combination with excellent thermodynamic characteristics, this property made Freons—derivatives of methane or ethane substituted by fluorine and chlorine atoms—ideal cooling agents in refrigeration engineering.

The set of properties of saturated fluorocarbons and fluorinated polymers made them essential materials for the most important branches of industry which arose in the 1940s—atomic and aerospace engineering. Their resistance to the action of the most powerful oxidising agents permitted the employment of fluorocarbons as lubricants for apparatus in contact with uranium hexafluoride or rocket fuel oxidants.

Even a very powerful oxidising agent such as atomic fluorine reacts only slightly with CF_4 (exchange with ^{18}F)[1]; on the other hand, when perfluorocycloalkanes, for example cyclo-C_4F_8, react with ^{18}F, the dissociation of C–C bonds is twice as likely as that of C–F bonds[2]. As a result of the accumulation of C–F bonds in fluoropolymer molecules, they are not only resistant to chemical action (Teflon is not acted upon either by aqua regia or concentrated alkali, which dissolve even platinum) but also have a low coefficient of friction. This property is associated with the very weak intermolecular interactions characteristic of fluorocarbons. Thus the boiling points of the lowest saturated fluorocarbons are close to those of the corresponding hydrocarbons, but, starting with the C_5 compounds, normal fluorocarbons boil at lower temperatures than hydrocarbons. On the other hand, when account is taken of the high molecular weight of fluorocarbons, it is found that the curve relating their boiling points to molecular weight is close to the corresponding curve for the inert gases[3].

In consequence of their high volatility in combination with chemical inertness, fluorocarbons have found extensive applications as components of aerosol compositions; their high vapour density makes them excellent fire-extinguishing agents.

Owing to the lack of polar interactions of the long fluorocarbon chains with the surrounding medium, fluorocarbon derivatives containing ionogenic groups (carboxylic and sulphonic acids, quaternary ammonium salts[4]) proved to be most valuable surface-active substances. Thus the addition of 0.35% of perfluorocaprylic acid lowers the surface tension of water to 15.3 dyn cm^{-1} (cf. the usual carboxylic acids for which the decrease is at most to 24 dyn cm^{-1}). Fluorocarbon residues interact weakly also with hydrocarbon chains. Thus successive substitution of hydrogen atoms in benzene derivatives by fluorine leads to a decrease of the solubility of alkanes in the latter (determined by gas–liquid chromatography[5]).

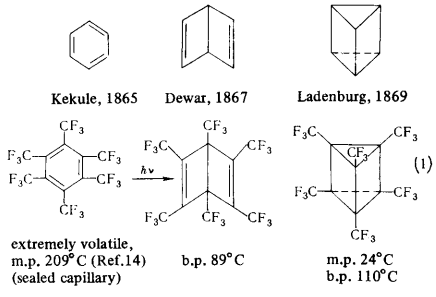
For this reason, impregnation of textiles with fluorocarbon derivatives imparts to them not only hydrophobic but also oil-repellent properties.

Their high breakdown voltage and thermal conductivity have led to the use of fluorocarbons and some of their derivatives as cooling dielectrics.

The industrial applications of fluorocarbons enumerated above (reviewed in detail elsewhere[6-11]) have led to interest in the development of convenient methods for their synthesis and in the 1940s and 1950s there was an explosive growth of the stream of empirical data on organofluorine chemistry. New facts did not always fit within the framework of ideas current at the time, which led to a tendency towards some autonomy in fluorine chemistry. However, progress in theoretical organic chemistry, which was particularly enriched by the method of investigation of electronic effects of substituents by measurements of the chemical shift of the fluorine label (see the review of Emsley and Phillips[12]) and also the adoption by many chemists working in synthetic chemistry of the

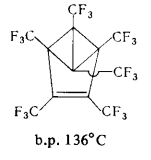
experimental achievements in fluorine chemistry made it a kind of branch of organic chemistry, a distinctive feature of which is the extreme richness of its synthetic possibilities. One may say that fluorocarbons constitute the non-hydrocarbon system which was sought by the chemists of the past, the wide variety of whose reactions surpasses the classical hydrocarbon system in certain respects.

The introduction of fluorine atoms makes it possible to isolate in a pure form structures which were regarded in classical organic chemistry as short-lived or as hypothetical reaction intermediates. Thus the introduction of six trifluoromethyl groups into the benzene ring makes it possible to isolate valence isomers corresponding to the different benzene formulae proposed in the XIXth century[13]:



(1)

The derivative corresponding to benzvalene, the existence of which had not been postulated in the XIXth century, was also isolated:



In this case the valence isomers are thermodynamically much more stable than the non-fluorinated analogues: their free energies of aromatisation are almost twice as small as for the isomers of hexamethylbenzene. The activation energy for this transformation also exceeds the value characteristic of hexamethylbenzene[15]. For comparison, we may point out that prismane C_6H_6, which was recently obtained by an elegant synthesis from benzvalene, has explosive properties[16].

Functional groups with highly oxidising properties can be introduced into fluorocarbons, i.e. it is possible to synthesise compounds whose hydrocarbon analogues are difficult to imagine: organic hypofluorites (CF_3OF)[17], superoxides (CF_3OOOCF_3)[18], derivatives of quinquevalent iodine (CF_3IF_4)[19] or halogenoperoxides (CF_3OOCl)[20].

The stabilising effect of fluorine atoms is also very marked when they are introduced into organometallic compounds. Thus the best method for the purification of fluoroalkyl derivatives of mercury[21] is distillation from concentrated sulphuric acid.

The physical properties of fluoroalkyl derivatives of metals are also sharply different from those of their hydrogen analogues. Whereas dimethylmercury is a mobile liquid with all features of a typical covalent compound, bis(trifluoromethyl)mercury is a solid (albeit volatile), which melts at 163°C in a sealed capillary; it dissolves readily in water forming conducting solutions[22].

Owing to the stabilising effect of fluorine atoms, it is possible to isolate in a pure crystalline form compounds containing a σ bond between the fluoroalkyl residue and the transition metal atom. Hydrogen-containing analogues of such compounds are frequently either unstable at room temperature or their existence as intermediates is merely postulated. Thus dehalogenation by iron pentacarbonyl[23] may involve a stage in which unstable σ derivatives of iron are formed.

On the other hand, when 1,2-dibromotetrafluoro-ethane is introduced into the reaction with $Fe(CO)_5$, the main product is an organometallic compound. Tetrafluoroethylene is isolated only on heating[24]:

$$BrCF_2CF_2Br + Fe(CO)_5 \rightarrow BrCF_2CF_2{-}Fe(CO)_4Br + CO \xrightarrow{\Delta} CF_2{=}CF_2\ (+CF_2{=}CFBr). \quad (2)$$

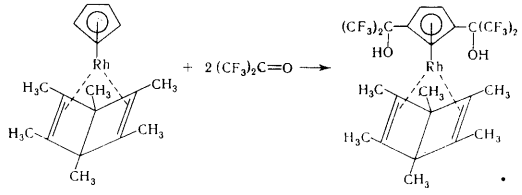
Yet another reaction in which the intermediate formation of σ compounds of transition metals was merely postulated is the synthesis of biphenyls by allowing cobalt salts to react with arylmagnesium halides. When pentafluorophenylmagnesium bromide is introduced into the reaction, the product is a blue solid—bis(pentafluorophenyl)cobalt—stable on long storage in solution. Decafluorobiphenyl is obtained only on heating this compound or on oxidising it with air[25]:

$$C_6F_5MgBr + CoBr_2 \rightarrow (C_6F_5)_2Co \xrightarrow{O_2} C_6F_5{-}C_6F_5. \quad (3)$$

Many organofluorine compounds are extremely reactive. Thus the carbonyl group in fully fluorinated ketones is so electrophilic that hexafluoroacetone is "inserted" in the C–H bond of isobutene at room temperature[26]:

$$(CF_3)_2C{=}O + \begin{matrix} H_3C \\ H_3C \end{matrix}\!\!>\!C{=}CH_2 \rightarrow (CF_3)_2C(OH){-}CH_2{-}C(CH_3){=}CH_2 \quad (4)$$

or into the bond of cyclopentadiene coordinated to a rhodium atom[27]:

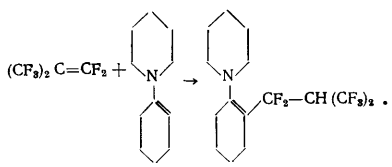


(5)

The immediate proximity of the fluorine atoms results in an extremely marked increase of the electrophilicity of carbon–carbon double bonds too. Thus octafluoroisobutene reacts at room temperature with comparatively weak nucleophilic agents such as alcohols[28]:

$$(CF_3)_2C{=}CF_2 + ROH \rightarrow (CF_3)_2CH{-}CF_2OR + (CF_3)_2C{=}CFOR \quad (6)$$

or enamines[29]



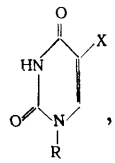
(7)

Evidently the high toxicity of octafluoroisobutene is due precisely to the ease of its reaction with nucleophilic centres and its nature is therefore analogous to that of the toxicity of many alkylating agents[30].

The physiological activity of organofluorine compounds is by no means always manifested by their toxicity. Certain fluorine-containing derivatives of ethane ("fluorotan" $CF_3CHClBr$, "inhalan" $CCl_2HCF_2OCH_3$ and its numerous analogues[31]) are valuable anaesthetics, which are almost free from side effects; fluorotan is used in paediatric surgery.

It is remarkable that the anaesthetic property of these compounds is associated with their low polarity. This property is more pronounced the greater the solubility of the substance in the non-polar lipids forming part of the membrane of the nerve cell[32].

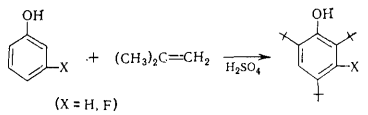
The introduction of fluorine atoms into the molecules of medicinal preparations frequently makes it possible to achieve striking results. Thus the substitution of hydrogen in the 5-position of the uracil molecule by fluorine[33] or the CF_3 group[34] leads to the formation of very effective antitumour preparations:



where X = F and R = H, , or riboside or X = CF_3

and R = riboside. Despite the fact that both preparations are antimetabolites, the mechanisms of their actions are completely different.

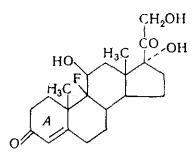
The action of 5-fluorouracil is based on the fact that the small fluorine atom leads to only a slight alteration in the geometry of the molecule, which thus retains its ability to combine the enzymes controlling its metabolic transformations. However, the latter become impossible owing to the presence of the firmly bound substituent in the 5-position. As an illustration of the low degree of steric hindrance associated with the replacement of the hydrogen atom by fluorine, one may quote an instance from the syntheses of hindered phenols: on alkylation with isobutene, three t-butyl groups can be introduced when only hydrogen or fluorine are present in the *m*-position[35]:



(X = H, F) (8)

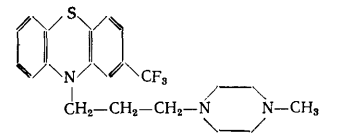
5-Trifluoromethyluridine suppresses the action of enzymes in a different way: the fluorine atoms in its molecules possess some mobility as a result of which it can alkylate the active centres of enzymes[36].

However, in the case of steroids, the slight change in molecular geometry caused by the introduction of a fluorine atom is sufficient to influence their physiological activity very significantly. Thus 9-α-fluorocortisol, whose antitumour activity exceeds that of cortisol by a factor of 7–10, differs from the latter only by the position of the *A* ring in space, which makes its molecular geometry similar to that of 6-methylprednisolone. On the other hand, the electronic defects associated with the introduction of fluorine do not play a significant role, contrary to expectation[37]:



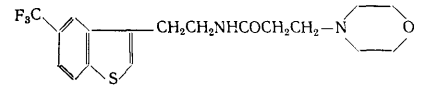
Fluorine-containing derivatives of phenothiazine and benzodiazepine are used as cyclotropic preparations.

According to polarographic data, *N*-substituted phenothiazines, including triphthazine which is used in clinical practice, form complexes with molecular oxygen.

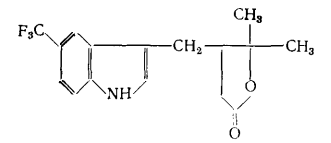


It may be that the mechanism of the action of derivatives of phenothiazine preparations consists in the formation of such complexes, which leads to a change in the energetics of cell respiration[38]. The especially high efficiency of the fluoroalkyl derivative can probably be related to the high solubility of oxygen in fluorocarbons. As a result of this property, solutions of oxygen in inert organofluorine compounds (fully fluorinated ethers, tertiary amines, and others) can find applications as substitutes for blood which, are hardly inferior to the latter in their oxygen capacity[39].

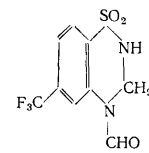
According to patent literature, fluorine-containing heterocycles can exhibit a depressive activity[40]:



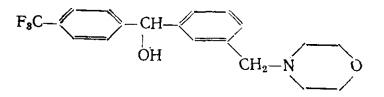
can stimulate the contraction of cardiac muscle[41]:



can reduce blood pressure[42]:



and can exhibit anti-inflammatory and antidiabetic activity[43]:



as well as diuretic[44], antimalarial,[45] and antifungal[46] activity. In addition they can have anticonvulsant properties[47], can reduce appetite[48], and can be used as sugar substitutes for diabetics[49].

The examples enumerated above, chosen from a number of patents published as late as 1972, clearly illustrate the continuous expansion of the applications of organofluorine compounds. As a result of this process, studies in the field of organofluorine chemistry have begun to develop at an ever increasing rate, the rate of growth of the number of publications in this field exceeding the average (which is also very high) for chemical literature as a whole. Thus the number of publications in 1970 on fluorine chemistry was three times greater than in 1960 and the number of new compounds described in these papers was five times greater[50]. On the other hand, the total number of chemical publications (and the compounds synthesised) doubles only every 8.3 years[51].

The available information about organofluorine compounds has been distributed in recent years among a large number of publications, many of which are difficult to obtain. Thus in 1969–1970 90% of the entire information on this field was distributed among 100 publications. Bearing in mind the fact that the role of patent literature has been continuously increasing (24% of the entire information in 1960 and 33% in 1970), the need for a working survey of this field of information becomes evident.

In the present review attention is concentrated on the publications of the 1970s (the earlier data have been largely covered in the monograph of Sheppard and Sharts [52] and also in Paleta's review [53], which include the literature for 1968 and 1969 respectively)—studies of fundamental importance or with an extensive bibliography.

The separate concluding section describes data on methods for the specific introduction of fluorine atoms into organic molecules, which is of specially great importance for investigators interested in applied chemistry.

One should note that the "Fluorine" information-research system, developed at the All-Union Institute of Scientific and Technical Information, significantly aided the authors in the selection of material for the review. A particularly valuable feature of this system is that it makes it possible to retrieve instantly detailed information about patent publications.

Certain references to the patent literature in the present review are based on data obtained from the above system.

II. THE FLUORINE ATOM AS A SUBSTITUENT

This section constitutes an attempt to survey the results of studies on organofluorine compounds by certain physical methods from the standpoint of their value for synthetic chemistry.

1. The Fluorine Atom at a Saturated Carbon Atom

The majority of applications of fluorocarbons and their derivatives enumerated in section I are associated with the extremely low polarity of these compounds and the consequent weakness of their intermolecular interactions. The quantities which determine the non-specific intermolecular interactions are molecular dipole moments and polarisabilities. The dipole moments of fully fluorinated alkanes with both normal and iso-structures are zero [54]. The introduction of only one hydrogen atom in the 1-position of the hexadecafluoroheptane molecule leads to the appearance of a significant dipole moment (1.60 D) and alkanes having the general formula $H(CF_2)_nH$, where $n = 4–10$, have dipole moments in the range 2–2.2 D. [55] On the other hand, 1,2-difluoroethane, a substance containing only two C–F bonds, is a liquid miscible with water. Its dielectric constant is 34.4 at 32 °C. [56] Evidently intermolecular H...F hydrogen bonds play a significant role in the solvation of 1,2-difluoroethane by water. The ability of fluorine atoms to form intramolecular hydrogen bonds is indicated by the infrared spectra of fluorine-containing alcohols and phenols [57] and also by the study of the structure of β-fluoroethanol by electron diffraction (90% of the *gauche*-conformation). [58]

The substitution of hydrogen atoms in alkane molecules by fluorine does not increase significantly their polarisability [59]. The weak solvation of fully fluorinated alkanes by various solvents is also consistent with these findings. It has been shown by ^{19}F NMR that dispersion interactions play a decisive role in this [60]: the dependence of the chemical shifts of CF_4, cyclo-C_4F_8, and cyclo-C_6F_{12} on the SV constant, characterising the properties of the solvent, is the same for both polar and non-polar media. The situation changes when chlorine or bromine molecules are introduced into the fluoroalkane molecule. The variation of the chemical shift in polar solvents becomes more pronounced owing to dipole–dipole interaction. It is significant that the chemical shifts of compounds usually employed as standards also change appreciably on passing from non-polar to polar solvents (the range of variation is 1.79 p.p.m. for CCl_3F, 1.88 p.p.m. for $C_6H_5CF_3$, and even as much as 4.88 p.p.m. for C_6F_6). [60] This fact is extremely important for investigators studying correlations in various solvents. The C_6F_6 chemical shift depends appreciably also on temperature: its change by 10 deg shifts the signal by 0.115 ± 0.021 p.p.m. [61]

Intermolecular interaction plays a significant role also in the chemical properties of organofluorine compounds. Thus the acidity of trihalogenoacetic acids in the gas phase varies in the sequence Br > Cl > F, i.e. in the order opposite to that widely known to hold for an aqueous medium. Evidently this finding is related to the greater polarisability of the bromine and chlorine atoms. On the other hand, in an aqueous medium the tendency of fluorine towards the formation of hydrogen bonds, leading to a more effective solvation of the trifluoroacetate ion, plays a decisive role [62].

Table 1. The binding energies of 1*s* electrons of the carbon atom in substituted methanes (in eV relative to CH_4). [63]

Formula	X = F	X = Cl	X = Br
CH_3X	2.8	1.6	1.0
CH_2X_2	—	3.1	—
CHX_3	8.3	4.3	—
CX_4	11.0	5.5	—

Photoelectronic spectroscopic data for halogenomethanes have shown that, as halogens accumulate, the binding energies of the electrons in the 1*s* level of carbon increase significantly, i.e. the formal atomic charge increases. This is particularly marked on accumulation of fluorine atoms [63] (the perfluoro-effect), which withdraw particularly strongly the valence electrons of carbon (Table 1). Photoelectronic spectroscopy can be used to analyse fluorine-containing polymers. The resolving power of existing instruments is sufficient to obtain resolved signals corresponding to the carbon atoms in the CF_3-, $-CF_2-$, $\gtrless CF$, and $-CH_2-$ groups. For this reason, it is possible to distinguish polymers with regular and irregular structures and by integrating the spectra one can also estimate the quantitative composition of the copolymers (for example $CF_2{=}CFCl$ can be distinguished from $CH_2{=}CF_2$). [64]

Quantum-mechanical calculations by non-empirical methods confirmed the increase of the charge of the carbon atoms in substituted methanes as fluorine atoms

accumulate (Table 2). Despite the appreciable difference between the charges obtained by different workers (the differences arise, in particular, from the choice of the *ab initio* set of wave functions, as shown by a methodological study[68]), the above tendency has been shown quite clearly in all investigations.

Table 2. The results of quantum-mechanical calculations on methane and its fluoro-derivatives.

Formula	Charge of C atom	Charge of H atom	Charge of F atom	References
CH_4	−0.114	+0.028		65
	−0.739	+0.185		65
	−1.104	+0.276	—	67*
	−0.751	+0.188		68*
	−0.076	+0.019		68*
CH_3F	+0.054	+0.029	−0.138	65
	−0.140	+0.174	−0.383	66
	−0.544	+0.296	−0.344	67*
	−0.129	+0.171	−0.385	68*
	+0.168	−0.004	−0.155	68*
CH_2F_2	+0.242	+0.022	−0.142	65
	+0.327	+0.175	−0.338	66
	+0.016	+0.317	−0.325	67*
CHF_3	+0.665	+0.184	−0.283	66
	+0.577	+0.344	−0.307	67*
CF_4	+0.936	—	−0.234	67*
	+0.68	—	−0.17	69

*Population data are quoted.

Fully fluorinated cycloalkanes behave as electron acceptors albeit to a slight extent. Thus the formation of charge-transfer complexes by these compounds with tetrakis(dimethylamino)ethylene has been demonstrated[70]. The reason for the enhanced (compared with linear analogues) electron-accepting properties of cyclic fluoroalkanes is probably that in their molecules the majority of the fluorine atoms are in the "eclipsed" conformation at short distances from one another. Under these conditions, the role of the interaction of the orbitals of these atoms, which may lower the thermodynamic stability of the molecule, becomes more marked. Nevertheless, owing to the pronounced screening of the positive charge of the carbon skeleton of the molecule by fluorine atoms, its chemical inertness can increase at the same time[71].

As will be shown below, the interaction between fluorine atoms plays an appreciable role also in the properties of fluoro-olefins.

The ability of fluoroalkanes containing bromine or iodine atoms to accept electrons is much more marked. The interaction of these compounds with mercury or amalgams[72], Grignard reagents[73], and the carbonyls of transition metals or their other derivatives in the lowest valence state[74] makes it possible to synthesise the corresponding σ-fluoroalkyl organometallic compounds. Nevertheless, the reaction between tertiary amines and fluoroalkyl iodides is not accompanied by irreversible electron transfer (leading ultimately to the formation of quaternary ammonium salts in the case of the usual halides—see Bubnov et al[75]) but consists merely in the formation of comparatively unstable complexes[76], which have been investigated by infrared[77] and NMR[78] spectroscopy.

Polarographic data have shown that fluoroalkylmercury derivatives are reduced at appreciably lower half-wave potentials than their hydrocarbon analogues (an electrochemical acidity scale has been constructed for hydrocarbons on the basis of these measurements[79,80]). The tendency of fluoroalkyl derivatives of mercury towards the formation of complexes with nucleophilic species is just as pronounced as their oxidising properties[81].

Thus the fluoroalkyl group, which exhibits a high electronegativity, reduces markedly the electron density at the metal atom to which it is linked. The resulting polarisation of the carbon–metal bond is evidently the main cause of the high, compared with non-fluorinated analogues, stability of fluoroalkyl σ derivatives of transition metals. Comparison of the photoelectronic spectra of $CF_3Mn(CO)_5$ and $CH_3Mn(CO)_5$[82] as well as the parameters of the NMR spectra of methyl and trifluoromethyl complexes of platinum[83] led to the conclusion that "back bonding", i.e. supply of the metal *d* electrons to the antibonding orbitals of the C–F bonds, does not play a significant role in the stabilisation of fluoroalkyl complexes.

The study of the relation between the parameters of ^{19}F NMR spectra of fluoroalkyl derivatives of mercury and the nature of the solvent revealed an anomalous behaviour of the *gem* constant for the $^{19}F-^{199}Hg$ spin-spin interaction, which decreases with increase of the solvating capacity of the medium (in contrast to the $^{19}F-^{199}Hg$ vicinal constant and the $^{1}H-^{199}He$ *gem* constant). This behaviour is evidence in support of the coordination of the mercury atom to the unshared electron pairs of the fluorine atom. This coordination, which lowers the capacity of mercury to combine with external nucleophiles, can play a significant role in the chemical behaviour of fluoroalkyl derivatives in metals[84].

The influence of the fluoroalkyl groups on the properties of the hydrocarbon groups bound to them is to a large extent determined by their strong negative inductive effect, which lowers the electron density at the adjacent carbon atoms. Conjugation effects play a certain role in aromatic systems. However, the absolute value of σ_I for fluoroalkyl groups exceeds significantly σ_R, which is of the same sign, the difference increasing with decrease of the number of fluorine atoms in the α-position, i.e. on passing from the CF_3 group to $C(CF_3)_3$, for which $\sigma_R = 0$ (see the review of Yagupol'skii et al.[85]). These data indicate the occurrence of a specific interaction between the π system and the orbitals of the fluorine atoms located in the benzyl position.

2. The Fluorine Atom at an Unsaturated Carbon Atom

The fluorine atom linked directly to an unsaturated carbon atom can both "strip" the multiple bond via the inductive effect and can supply to it electrons from its lone pairs. The acceptance of these electrons by the antibonding π* orbital should reduce the order of the C=C bond in fluoro-olefins, i.e. should lengthen it. However, owing to the inductive effect transmitted via the σ component, the length of the bond should diminish. As a result of the simultaneous action of these effects, the C=C bond in tetrafluoroethylene is nevertheless somewhat shorter than in ethylene[86]. According to photoelectronic spectroscopic data, the first ionisation potential (removal of a π electron) is virtually the same for ethylene and tetrafluoroethylene. Nevertheless the second potential (the removal of a σ electron from the C=C bond) of tetrafluoroethylene is higher by about 3 eV. On this basis, it has been concluded[87] that the filled orbitals of the fluorine atoms are mixed with the bonding π orbitals to an extremely slight extent and that the "perfluoro-effect" influences mainly the σ component of the C=C bond.

Furthermore, the overlapping of the p_X orbitals of the fluorine atoms, for example in the terminal CF_2 group, plays some role in the unusual properties of fluoro-olefins. This leads to the mutual approach of the fluorine atoms and the decrease of the angle between the C–F bonds to a value close to that of the tetrahedral angle[88] (previously this made it possible to attribute sp^3 hybridisation to the CF_2 group regardless of its environment[89]). The greater stability of *cis*-1,2-difluoroethylene compared with the *trans*-isomer has been explained similarly[88].

A chemical consequence of the dual effect of the fluorine atoms on the properties of the multiple bonds is electronic amphoteric properties of fluoro-olefins, i.e. their ability to react with both electrophilic and nucleophilic agents. As electronegative substituents accumulate at the multiple bond, the tendency to undergo nucleophilic reactions increases. A striking example of this is a reversal of the mechanism of the addition of nitrosyl fluoride on passing from tetrafluoroethylene (electrophilic process catalysed by BF_3) to hexafluoropropene (nucleophilic process catalysed by KF)[90]:

$$CF_2=CF_2+FNO \xrightarrow[BF_3,40^\circ]{} [\overset{\oplus}{C}F_2CF_2NO] \rightarrow CF_3CF_2NO\ , \qquad (9)$$

$$CF_3-CF=CF_2+FNO \xrightarrow[KF,80^\circ]{} \left[\begin{matrix}CF_3\\CF_3\end{matrix}\!\!>\!\!CF^{\ominus}\right] \rightarrow \begin{matrix}CF_3\\CF_3\end{matrix}\!\!>\!\!CFNO\ . \qquad (10)$$

In view of the reversal of the mechanism, it is possible to achieve the same reaction with the opposite mode of addition, depending on the nature of the catalyst. Thus, using the fact that perfluoromethyl vinyl ether is attacked by both electrophilic and nucleophilic agents at the CF_2 group, Lur'e et al.[91] succeeded in directing the mercury atom to the α- and β-positions in its molecule:

$$CF_3OCF=CF_2+HgCl_2 \xrightarrow[KF,20^\circ]{} [\overset{\ominus}{C}F_3OCFCF_3] \longrightarrow \underset{\displaystyle HgCl}{CF_3OCFCF_3}\ , \qquad (11)$$

$$CF_3\overset{\curvearrowright}{O}-CF=CF_2+HgF_2 \xrightarrow[HF,150^\circ]{} [\overset{\oplus}{C}F_3OCFCF_2HgF] \longrightarrow (CF_3OCF_2CF_2)_2Hg\ . \qquad (12)$$

Table 3. The full charges of the carbon atoms in fluoroethylenes.

Olefin	Group			References
	CH_2	CHF	CF_2	
$CH_2=CH_2$	−0.064			92
$CH_2=CHF$	−0.112	+0.218		92
	−0.046	+0.078		93
$CH_2=CF_2$	−0.138		+0.478	92
	−0.030		+0.219	93
$CHF=CF_2$		+0.121	+0.446	92
		+0.109	+0.235	93
$CF_2=CF_2$			+0.400	92

Quantum-mechanical calculations have shown that the charge at the olefinic carbon atom increases as fluorine atoms are attached to it, as happens in the series of saturated compounds (Table 3).

The results of the calculations of Borisova et al.[92] have not been confirmed by the familiar series of comparative reactivities of fluoro-olefins in reactions with nucleophilic and electrophilic agents:

ease of electrophilic reactions

$$\longleftarrow CH_2=CH_2 \quad CH_2=CHF \quad CH_2=CF_2 \quad CHF=CF_2 \quad CF_2=CF_2 \longrightarrow$$

ease of nucleophilic reactions

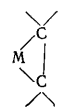
(on the other hand, according to these calculations vinylidene fluoride was the most reactive in any reaction).

Nevertheless the results obtained agree well with the measurements of the ^{13}C chemical shifts of fluoroethylenes, according to which the carbon atom of the CF_2 group of vinylidene fluoride is least shielded, while the carbon atom of the CH_2 group in the same compound is most strongly shielded[94] (Table 4).

Table 4. ^{13}C chemical shifts of fluoroethylenes (in p.p.m., quoted relative to ethylene).

Olefin	Group		
	CH_2	CHF	CF_2
$CH_2=CH_2$	0		
$CH_2=CHF$	+24.0	−24.94	
$CH_2=CF_2$	+58.22		−38.22
$CHF=CF_2$		+2.20	−25.24
$CF_2=CF_2$			−21.20

The calculated data quoted by Jolly and Perry[93] are remarkable in that the calculation of the binding energies of the 1*s* electrons of the carbon atom carried out on their basis makes it possible to estimate (in relation to experimental photoelectronic spectroscopic data) in which direction the calculated charge deviates. The distribution of the charges corresponds in this case to the series of comparative reactivities of fluoro-olefins in ionic reactions. The fairly stable π complexes formed by fluoro-olefins and transition metals are extremely promising from the standpoint of synthesis. The dative interaction, i.e. the supply of the *d* electrons of the metal to the antibonding π orbital of the olefin, makes the main contribution to the formation of the metal–olefin bond in this instance. However, the chemical behaviour of these complexes, frequently resembling that of small rings, and the relevant NMR data are described satisfactorily by formulae with two carbon–metal σ bonds (see Stone's review[95]):



The study of the properties of fluorine-containing dienes has shown that the conjugation of the multiple bonds in fully fluorinated 1,3-dienes is weakened. Thus comparison of the photoelectronic and ultraviolet spectra of 1,1,4,4-tetrafluorobutadiene and hexafluorobutadiene led to the conclusion[96] that there is a significant difference between their properties. Whereas the first compound has a *trans*-planar structure like normal butadiene, the second is not planar according to ultraviolet[96] and NMR[97] spectroscopic data. This conclusion has been confirmed by electron diffraction, which shows that the dihedral angle between the two $CF_3=CF$ groups in hexafluorobutadiene

is 47.4° ± 2.4°.[98] Evidently the breakdown of conjugation is associated with the interactions of the fluorine atoms in the CF groups.

The introduction of fluorine atoms into the aromatic ring also leads to the appearance of a significant positive charge at the carbon atom linked to it. Thus the ^{13}C NMR signal of hexafluorobenzene is displaced downfield by 38.34 p.p.m., compared with the signal of the 1-C atom of pentafluorobenzene[99]. Analysis of the photoelectronic spectra (the 1*s* levels of fluorine) has shown that the charge on this atom, linked to the ring, amounts to −0.15–0.20.[100] This is consistent with quantum-mechanical calculations (the charges in C_6F_6 are +0.132 for carbon and −0.132 for fluorine[93]). The changes in the charges of the carbon atoms which are not linked directly to fluorine are much smaller, amounting to zero for the *p*-position in fluorobenzene[100] and to −0.016 for the 9- and 10-positions in octafluoronaphthalene[101]. The ionisation potentials of the levels of aromatic fluoro-compounds (photoelectronic spectroscopy) differ from the corresponding values for the non-fluorinated analogues fairly slightly[102], i.e. the introduction of fluorine atoms does not prevent the aromatic system from retaining its capacity to behave as an electron donor. Indeed hexafluorobenzene forms charge-transfer complexes both with alkylbenzenes[103], behaving as an electron acceptor, and with the strong Lewis acid MoF_6,[104] behaving as an electron donor. Thus aromatic fluoro-compounds exhibit electronic amphoteric properties like fluoro-olefins.

The properties of the C_6F_5 group as a substituent are determined by the combination of the strong negative inductive effect (which is greater than for the C_6H_5 group but smaller than for CF_3) and the electron-donating properties associated with the presence of the lone electron pairs in the fluorine atoms. The electron-donating properties are manifested particularly clearly in the interaction of the C_6F_5 group with a cationoid reaction centre. The review of Vlasov and Yakobson[105] is devoted to a detailed consideration of these problems.

3. The Fluorine Atom in the Intermediate Species

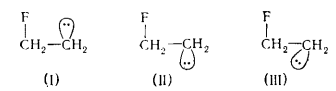
The mode and rate of a chemical reaction depend both on the structure of the reactant molecules and on the stability of the intermediate species formed. These two factors frequently act in different directions: the charge distribution in the attacked molecule can be unfavourable for the orientation leading to the formation of the more stable intermediate species. This effect is shown particularly clearly in reactions of organofluorine compounds: it has been shown that the charge separation between the atoms entering into the composition of their molecules is very pronounced.

For this reason, it is interesting to compare the stabilities of reaction intermediates with the observed mode of the processes, which has in fact been done below—mainly for fluoro-olefins. It is assumed that the findings obtained in the study of kinetically independent ions and radicals are valid also in these extremely common instances, where such species are not formed independently and there exists merely a transition state of the system which is of a type similar to them.

Among organofluorine compounds, reactions involving the intermediate formation of carbanions are most common. Despite their high electronegativity, fluorine atoms do not always stabilise these species, which is due to the presence of lone electron pairs in fluorine.

Thus, being bound directly to a negatively charged carbon atom, they can reduce significantly the stability of the carbanion as a result of the formation of the "back bond" between the electrons of the *p* orbital and the anionic centres. This phenomenon, sometimes referred to as the "Hine effect",[106] is evidently the cause of the decrease of the ionisation constant on passing from $CF_3CH_2NO_2$ to CF_3CHFNO_2[107] and also of the much lower kinetic acidity of $(CF_3)_2CHF$ compared with its analogues $(CF_3)_2CHX$ (X = Cl, Br, or I).[108]

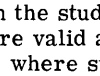
The stabilisation of carbanions by the fluorine atoms in the β-position relative to the charged atom is difficult to account for exhaustively within the framework of the inductive effect. Calculation on the β-fluoroethyl anion, carried out in several versions using various semi-empirical approximations[109], has shown that the preferred conformations of the species are *"syn"* or *"anti"* (I, II), but not the "perpendicular" conformation (III), in which there is evidently a strong repulsion of the lone electron pairs of fluorine and the negatively charged carbon atom.



(I) (II) (III)

Analysis of the charge distribution among orbitals of the C–F bonds indicates a significant contribution of the π component, i.e. confirms the occurrence of "hyperconjugation" (an effect the nature of which requires further investigation). A non-empirical calculation on the FCH_2CH_2 cation, anion, and the radical led to analogous results. The preferred conformations are *syn*- or *anti*- for the anion and the perpendicular conformation for the cation[110]. As a result of the combination of these effects, tertiary monohydroperfluoroalkanes have an extremely "acid" hydrogen atom: according to deuterium exchange data, $pK_a = 11$ for $(CF_3)_3CH$,[108] and the value obtained in terms of the polarographic scale is as low as 7.[80]

It is believed[111] that the comparative reactivity series for the substituted benzenes $C_6F_5R_f$ in the reaction with ammonia [$R_f = (CF_3)_3C > CF_3CF_2 > (CF_3)_2CF > CF_3 \gg F$] indicates the absence of hyperconjugation in the intermediate species. However, since the σ_I for fluoroalkyl groups increase in the same direction[85], it may be that the higher reactivity of benzenes containing secondary and tertiary fluoroalkyl groups as substituents is associated merely with the greater positive charge in the *p*-positions in their molecules, which facilitates nucleophilic attack.

In contrast to carbanions, carbonium ions containing fluorine atoms at a charged carbon atom are stabilised. The lone electron pairs of the fluorine atoms are involved in "back bonding", as a result of which the fluoromethyl cations have a planar structure. The effect decreases somewhat (per fluorine atom) on passing from the CH_2F cation to CF_3. At the same time, the inductive effect of fluorine acting via the σ bond leads to an increase of the charge of the carbon atom from +0.659 in CH_2F^+ to +1.095 in CF_3^+ (calculation via the INDO method†)[112]. The ethyl cation with a fluorine atom in the β-position is less stable than the 1-fluoroethyl cation (the difference between the stabilisation energies is 29.23 kcal mole^{-1}). Its destabilisation compared with $C_2H_5^+$ can be partly compensated by the formation of the "non-classical" onium cation,  which is more favourable on energy grounds than

† INDO = Incomplete neglect of differential overlapping.

the classical cation by 3.58 kcal mole^{-1}. However, in solution the more favourable species may be the more effectively solvated classical β-fluoroethyl cation (non-empirical calculations).[113]

Stabilisation as a result of the formation of a halogenonium cation is much more marked in the case of chlorine—the energy gain then amounts to 15.81 kcal mole^{-1}. This has been confirmed experimentally by the finding that the NMR spectrum of the β-chloroethyl cation at −80°C shows a singlet[114] (the applications of the NMR method in the study of fluorine-containing carbonium ions in highly acid media have been reviewed[115]).

The accumulation of fluorine atoms in the β-position relative to the positively charged carbon atom leads to the destabilisation of the cation compared with CF_3^+: whereas the ionisation potential of the $\dot{C}F_3$ radical does not exceed 9.5 V, it amounts to 9.98 V for $\dot{C}_2F_5$, 10.06 V for n-$\dot{C}_3F_7$, and 10.5 V for $(CF_3)_2\dot{C}F$ (mass spectroscopy).[116]

Quantum-mechanical calculations by the INDO method of the distribution of spin density in the series of radicals $\dot{C}H_3$, $\dot{C}H_2F$, $\dot{C}HF_2$, and $\dot{C}F_3$ showed that the unpaired electron density at the 2*s* orbitals of carbon and fluorine increases following the accumulation of fluorine atoms. This is consistent with the increase of the hyperfine interaction constants with the ^{13}C and ^{19}F nuclei in the ESR spectra of these radicals and also the change in their geometry, which gradually deviates from the planar structure of $\dot{C}H_3$.[117] On the other hand, owing to the high electronegativity of the fluorine atoms, the formal charge of the carbon atom in $\dot{C}F_3$ is +0.402 ($\sigma + \pi$, calculated from population data), while the charge in $\dot{C}H_3$ is 0.574.[118] Thus fluoroalkyl radicals should exhibit strong electrophilic properties. The enhanced stability of $\dot{C}F_3$ leads to a decrease of the energy of the C–C bond in hexafluoroethane to 60–70 kcal mole^{-1} compared with 79–81 established for alkanes. As a result, hexafluoroethane dissociates into radicals when acted upon by a glow discharge. Incidentally $(CF_3)_4Sn$ was synthesised by this unusual procedure (following addition to $C_2F_6SnI_4$), the yield exceeding 90%.[119] (Previously the C–C bond energy in C_2F_6 was assumed to be 94 kcal mole^{-1}; see Errede[120]. Possibly the C–H bond energy in CF_3H requires revision: the activation energy for the reaction of $\dot{C}F_3$ with alkanes, calculated on the basis of the value 106 kcal mole^{-1} adopted at the present time agrees poorly with the experimental results[121].)

In free-radical addition to fluoro-olefins an inconsistency is observed between the charge distribution in the initial molecule on the one hand, and the relative stabilities of the intermediate radicals on the other.

Thus, the addition of fluoroalkyl iodides to vinylidene fluoride or trifluoroethylene proceeds with a high degree of selectivity:

$$R_fI + CH_2{=}CF_2 \rightarrow R_fCH_2CF_2I\,, \qquad (13)$$

$$R_fI + CHF{=}CF_2 \rightarrow R_fCHFCF_2I\,. \qquad (14)$$

The selectivity increases on passing from $\dot{C}F_3$ to $\dot{C}_2F_5$ and $\dot{C}F(CF_3)_2$,[122] reaching in the latter case 97% for reaction (13) and 96% for reaction (14),[123] i.e. the process proceeds as if its mode were determined by the formation of the more stable radical $R_f\dot{C}H_2CF_2$. However, the opposite orientation is observed in the reaction of trifluoroethylene with the $\dot{C}H_3$ radical: the attack is directed to the CF_3 group to the extent of 88%.[124]

In the light of this finding, it becomes evident that the direction of attack on the olefin is not determined so much by the stability of the intermediate species as by polar effects. In the case of electrophilic fluoroalkyl radicals both factors act in concert, but the nucleophilic radical $\dot{C}H_3$ attacks trifluoroethylene via the carbon atom, which carries a more positive charge. In this connection the extremely high affinity of tetrafluoroethylene for $\dot{C}H_3$, which is ten times greater than in the case of ethylene[125] (the affinity of fluorobenzene exceeds that of benzene by a factor of 1.5)[126], is understandable.

Nevertheless in the reaction with an electrophilic species, such as the fluorine atom, the order of the reactivities of olefins is reversed: $CH_2{=}CHF > CH_2{=}CF_2 > CF_2{=}CF_2$ (kinetic data[127]).

The charge distribution in the ground state of the fluoro-olefin molecule is frequently of decisive importance also in ionic reactions. Thus in electrophilic addition reactions $\alpha\beta\beta$-trifluorostyrene gives rise to a mixture of products instead of the expected unambiguous result determined by the dominant stability of the benzyl cation[128]:

$$C_6H_5{-}CF{=}CF_2 + HBr \rightarrow C_6H_5CHF{-}CF_2Br + C_6H_5CFBr{-}CF_2H\,. \qquad (15)$$

Evidently the appreciable positive charge of the carbon atom in the CF_2 group, which hinders its protonation, has a significant influence in this case.

The stability of the recently synthesised enolic forms of the polyfluorinated ketones $CF_2{=}\underset{\displaystyle OH}{\underset{|}{C}}{-}CF_2X$, where X = F or Cl,[129] is apparently to some extent related to the difficulty of protonating the CF_2 group.

The stabilising effect which fluorine has on anion onoid species is also pronounced in the case of radical-anions:

$$R_2\dot{C}{-}OH \xrightarrow{-H^{\oplus}} [R_2C{=}O]^{\cdot-}\,. \qquad (16)$$

Owing to the formation of the more stable ketyl, the acidity of the hexafluoro-2-hydroxyisopropyl radical (R = CF_3) exceeds that of hexafluoroisopropyl alcohol by 8.1 pK units, while the corresponding difference for R = CH_3 amounts to only 5.7 units[130].

The stabilising effect of fluorine leads to an increase of the hyperfine interaction constants for the ESR spectra of the radical-anions of fluorine-containing ketones[131] or nitro-compounds[132]. This constant is appreciably higher than for protons. Evidently the hyperconjugation effect plays a significant role in this[133]. ESR data for fluorocarbon radicals have been reviewed[134]. More recent data, obtained in liquid media, have been surveyed by Lloyd and Rogers[135].

The radical-cations derived from polyfluorinated benzenes are also stable. According to quantum-mechanical calculation (the INDO method), the charge on the carbon atom in $C_6F_6^{+\cdot}$ is +0.24 (cf + 0.132 in C_6F_6) and the unpaired electron density at the carbon atom is 0.12.[136]

The study of voltage–current curves in fluorosulphonic acid has shown that the radical-cations derived from pentafluorobenzene and 1,2,3,5-tetrafluorobenzene have lifetimes of the order of several minutes, while the radical-cations from hexafluorobenzene and octafluoronaphthalene exist in a highly acid medium for a very long time[137]. The formation of such radical-cations, which proceeds readily under the influence of antimony pentafluoride[138], apparently plays an important role in electrophilic reactions of aromatic fluoro-compounds (see, the review of Shteingarts and Yakobson[139]).

The influence of fluorine atoms on the properties of radicals is extremely important, because the radicals or the transition states resembling them are more common in the reactions of real organofluorine compounds than might have been supposed on the basis of traditional ideas

concerning the mechanisms of ionic processes. The transfer of single electrons, leading to the formation of radical species, frequently constitutes a decisive reaction stage. Biradical species (carbenes) and also triplet states of unsaturated systems, whose properties resemble those of biradicals, also play an extremely important role in reactions of organofluorine compounds.

Fluorine-containing carbenes are involved in many reactions of preparative value, particularly in pyrolytic industrial syntheses of fluoro-olefins. According to quantum-mechanical data (the Roothaan method), the positive charge on the carbon atom in carbenes, as in all other species, increases following the accumulation of fluorine atoms ($CF_2 > CHF > CH_2$). However, the presence of an unfilled π orbital in carbenes introduces its own specific features: its population also increases as a result of the interaction with the p electrons of the fluorine atoms. Since the interaction of the carbenes with unsaturated systems (the commonest type of reaction undergone by carbenes) probably begins with charge transfer to this orbital, the CH_2 group, in which the orbital is completely vacant, is more electrophilic than CHF. The electrophilicity of CF_2 is lower still and this carbene is one of the most selective[140].

On the other hand, the stability of the triplet states of aromatic fluoro-compounds is lower than for the analogues without fluorine. The study of laser flash photolysis of fluorobenzene has shown that the emission spectrum can be observed in the course of 250 ns (weaker approximately by a factor of two than the benzene spectrum), while the triplet state of pentafluorobenzene exists only in the course of 140 ± 5 ns.[141]

III. THE INTRODUCTION OF FLUORINE INTO ORGANIC MOLECULES

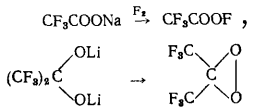
For a long time the introduction of fluorine atoms into organic molecules with the aid of an apparently natural reagent for this purpose such as free fluorine was regarded as virtually impossible in view of its extremely pronounced corrosive properties. Nevertheless, as early as 1933, the possibility of substituting by fluorine one hydrogen atom, for example in cyclohexane and carboxylic acids, or of the "fluorodimerisation" of tetrachloromethylene was demonstrated in a pioneer study by Bockemüller[142]:

$$2\,CCl_2{=}CCl_2 + F_2 \rightarrow FCCl_2CCl_2CCl_2CCl_2F\,, \qquad (17)$$

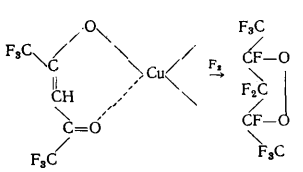
(subsequently this reaction was developed in detail for fluoro-olefins[143]); fluorination by free fluorine has not found extensive applications.

Only in recent years a number of reports have been published indicating the possibility of successful fluorination without degradation even of systems containing heteroatoms. Thus interesting peroxide compounds can be synthesised with the aid of fluorine[144,145]:

$$CF_3COONa \xrightarrow{F_2} CF_3COOF\,, \qquad (18)$$



(19)



(20)

Fluorine atoms have been introduced successfully into the α-position with respect to the nitro-group by treating salts of nitro-compounds with fluorine (see Nagase's review[146]).

Direct fluorination shows promise of wide scale applications also in the synthesis of fully fluorinated fluoroalkanes and their derivatives used in practical applications. The reactor with a highly efficient heat elimination system, which has been developed for this process, makes possible exhaustive fluorination of complex compounds such as $(CH_3)_3C{-}C(CH_3)_3$,[147] $CH_3OCH_2CH_2OCH_3$,[148] or m-carborane[149]. The reaction is not accompanied by degradation and the yield of desired products is extremely high in the second and third instants.

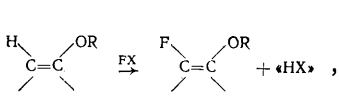
Fluorination by elemental fluorine is evidently a free-radical process. Its extremely high exothermic heat is associated with certain characteristics of the fluorine molecule, in particular with its low dissociation energy (37 kcal mole^{-1} compared with 58 kcal mole^{-1} for Cl_2).[150] In reactions with aromatic systems fluorine behaves as an electrophilic agent: despite the radical mechanism of the process, *ortho–para* orientation is observed predominantly for benzene containing substituents of the first kind[151-154] and *meta*-orientation for substituents of the second kind[151,152]. The selectivity of substitution characteristic of fluorine made it possible to achieve the preparative synthesis of the valuable antimetabolite 5-fluorouracil (see Section I) by direct fluorination of uracil[155].

Apart from direct fluorination, methods for the introduction of fluorine with the aid of a wide variety of fluorinating agents are widely used; in terms of their action on organic molecules, these can be divided into oxidative and non-oxidative.

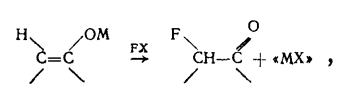
1. Oxidative Methods for the Introduction of Fluorine

The development of methods for the specific introduction of fluorine atoms is clearly important for the synthesis of fluorine-containing physiologically active substances which have been finding increasing application in recent years. The possibility of modifying finished (for example natural) structures by treatment with a fairly mild fluorinating agent is particularly valuable. A number of agents, whose activity varies over a fairly wide range, have been developed for this purpose. Thus perchloryl fluoride ($FClO_3$) has been used successfully to fluorinate steroids[156] or penicillin derivatives[157] in the presence of bases. Comparison of $FClO_3$ with CF_3OF shows that the latter acts more vigorously[156]. Nevertheless fluorine atoms have been introduced successfully with its aid into griseofulvin[158] or an anhydro-sugar[159] (see Lustig and Shreeve[160] for a review of the chemistry of hypofluorites).

The mode of substitution when such agents are employed is usually determined by the presence of an electron-donating substituent at the multiple bond:



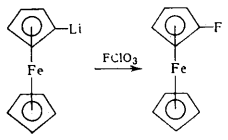
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(22)

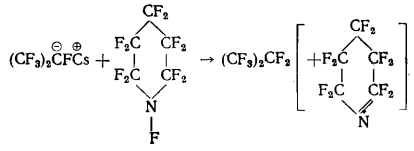
where M = Li or Na and X = OCF_3 or ClO_3.

The reaction with participation of hypofluorites frequently involves an addition–elimination stage[161]. However, direct fluorination of the anionoid centre is also possible[162]



(23)

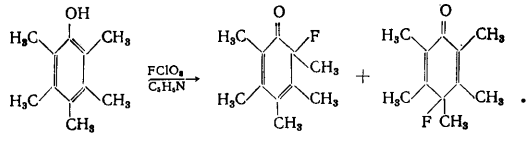
Perfluoropiperidine, a relatively weakly active agent, can act similarly (under severe conditions[163]):



(24)

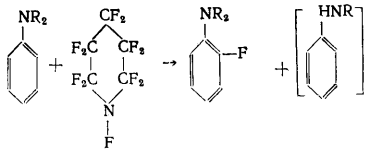
On the other hand, the activity of the bishypofluorite $CF_2(OF)_2$ apparently approaches that of free fluorine: it substitutes by fluorine the hydrogen atoms in acetonitrile or nitrobenzene[164].

Reagents of this type are used successfully also for the introduction of fluorine atoms into aromatic compounds. Thus CF_3OF substitutes one hydrogen atom in benzene or toluene. The reaction yield increases up to preparative values under the influence of intense ultraviolet irradiation. It is remarkable that the substitution in the toluene ring takes place almost exclusively in the *ortho*-position[165]. Xenon difluoride also reacts readily with benzene derivatives C_6H_5X with the preferential formation of *ortho*- and *para*-isomers for X = F, Cl, CH_3, or OCH_3 and *meta*-isomers for X = CF_3 or NO_2.[166] The formation of biphenyls is a side process. IF_4OCH_3 also shows a capacity for the fluorination of benzene rings[167]. In the fluorination by $FClO_3$ of phenols containing substituents in the *ortho*- or *para*-position, fluorodienones are formed[168]:



(25)

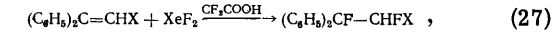
Perfluoropiperidine fluorinates *NN*-dialkylanilines exclusively in the *ortho*-position. Dealkylation and the formation of products of the type of Crystal Violet are side reactions[169]:



(26)

where R = CH_3 or C_2H_5.

In order to account for the orientation of the reactions enumerated above, a mechanism has been put forward involving substitution of the S_N2 type at the fluorine atom in the fluorinating agent[161,163]. However, the observation by ESR of the formation of radical-cations of aromatic compounds in the course of their fluorination by xenon difluoride[166] or perfluoropiperidine[169] and also the preferential or exclusive *ortho*-orientation of the substitution reaction established in a number of instances require a more detailed examination of this mechanism. Like many nucleophilic substitution reactions (see the review of Bilevich and Okhlobystin[170]), oxidative fluorination probably involves a stage in which a single electron is transferred. Nevertheless the radical-cations which can be detected are involved in the formation of side products only[171]. The fluorination of asymmetric diphenylethylenes by XeF_2 is not accompanied by a rearrangement (of the type usual in the generation of carbonium ions from these compounds) when the reaction is catalysed by CF_3COOH:

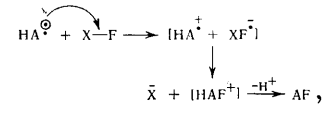


(27)

where X = H, F, or CH_3.

In catalysis by a stronger acid (HF) there is a partial rearrangement, which is probably not related to the fluorination process ($C_6H_5COCHXC_6H_5$ is formed)[172].

Thus fluorination can probably be regarded as a cage process, which involves the abstraction of a fluorine atom from the radical-anion formed by the molecule of the fluorinating agent. The process can be represented in the general form as follows (its outcome is indeed "substitution at the fluorine atom"):

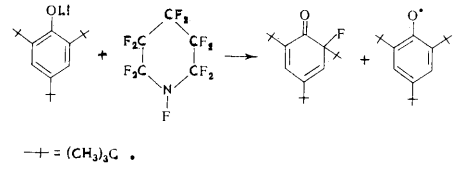


(28)

where HA is the fluorinated substrate with a lone electron pair and HF is the fluorinating agent.

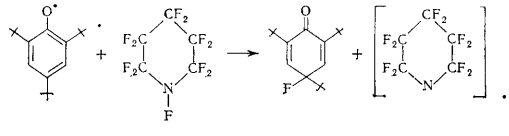
The following facts support this mechanism: if the potassium salt of nitroform is fluorinated by $FClO_3$ in the cavity of the ESR spectrometer in the presence of a radical "trap" (t-butylphenyl nitrone), radicals are formed as a result of the addition of both $(O_2N)_3C^{\cdot}$ and $F^{\cdot}$ to the nitrone. Consequently, the radical-anion $FClO_3^{\cdot-}$, capable of losing the fluorine atom, is formed after electron transfer[173].

Lithium 2,4,6-tris-t-butylphenoxide is rapidly fluorinated by perfluoropiperidine in the *ortho*-position:



(29)

A stable phenoxy-radical is formed as a side product; it cannot be an intermediate in the *ortho*-fluorination process, since it reacts very slowly with perfluoropiperidine (in the *para*-position):



(30)

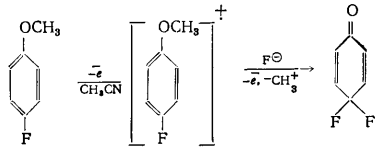
Thus *ortho*-fluorination is probably a process occurring within a cage and *para*-fluorination is a free-radical reaction[174]. The mechanism described is probably common for processes involving "anomalous" electrophilic substitution in aromatic compounds, leading to the preferential formation of *ortho*-isomers (see Pearson's review[175]).

The formation of radical-cations is probably a stage also in the fluorination by traditional agents such as the fluorides of metals in the highest valence state. Quantum-mechanical calculation has shown that the one-electron pathway in the fluorination of C_6F_6 under the influence of CoF_3 is more favourable on energy grounds than direct abstraction of a fluorine atom to an extent of the order of

50 kcal mole^{-1}.[136] Fluorination by lead tetra-acetate in HF is accompanied (as in the case of XeF_2 + HF) by a rearrangement of 1,1-diphenylethylene[176]:

$$(C_6H_5)_2C{=}CH_2 \xrightarrow[HF]{Pb(OCOCH_3)_4} C_6H_5CF_2CH_2C_6H_5 . \qquad (31)$$

The electrochemical generation of radical-cations of aromatic compounds in the presence of the fluoride ion also leads to the introduction of fluorine into the ring. Under these conditions, trifluoromethylbenzene is then substituted in the *meta*-position[177] and fluorobenzene is substituted in the *para*-position[178]. 4,4-Difluorocyclohexadienone is formed from *p*-fluoroanisole[179]:



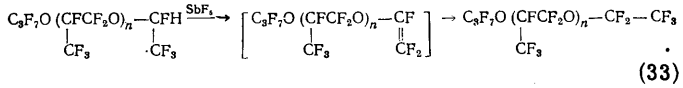
(32)

A similar mechanism may obtain also in the electrochemical fluorination of organic compounds in hydrogen fluoride[180], which is one of the most important industrial methods for the preparation of fully fluorinated organic compounds.

The widely used method for the introduction of fluorine into aromatic systems, involving the decomposition of solid diazonium salts containing the HF_4^-, PF_6^-, and SbF_6^- anions (Schiemann reaction, see Sushitskii's review[181]) probably also involves a one-electron transfer stage like the majority of typical reactions of diazo-compounds[182]. One of the most recent preparative versions of the Schiemann reaction, the photochemical decomposition of diazonium salts, frequently ensures a higher yield of aromatic fluoro-compounds than thermal decomposition[183].

The elimination of CO from benzoyl fluorides catalysed by rhodium complexes[184], the thermal elimination of SO_2F_2 from $C_6H_5OSOF_3$,[185] and also the elimination of groups such as SO_2 from $ArSO_2F$, CO_2 from ArOCOF, or COS from ArSCOF also leads to the introduction of fluorine into the aromatic ring. Examples of reactions of the latter type and also of the action of the fluoride ion on the diaryliodonium cation have been given in a patent[186] devoted to various methods for the synthesis of 4-(4′-fluorophenyl)-salicylic acid. This patent constitutes a kind of compilation of the modern methods for the introduction of fluorine into the benzene ring.

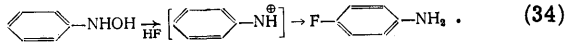
Antimony pentafluoride can behave as an oxidative fluorination agent, which is unusual for this compound: when it is allowed to react with fluoroethylenes, the double bond is readily fluorinated[187]. The reaction, which has been patented as a method for the substitution of the "residual" hydrogen by fluorine in hexafluoroepoxypropane oligomers, may also involve a stage in which the intermediate olefin is fluorinated[188]:



(33)

2. Non-Oxidative Methods for the Introduction of Fluorine

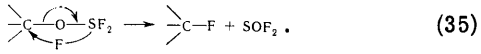
The introduction of fluorine may be a result of the formation of a cationoid species in a medium capable of supplying fluoride ions. Thus treatment of *N*-phenylhydroxylamine with HF leads to the formation of *p*-fluoroaniline[189]:



(34)

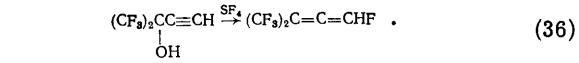
The reaction in which fluorine is introduced by means of sulphur tetrafluoride (a common reagent) and also its analogues (SeF_4,[190] $C_6F_5SF_3$,[191] R_2NSF_3,[192] and MoF_6[193]) also belongs to nucleophilic substitution processes.

These agents make it possible to convert smoothly the C–OH group into C–F, C=O into CF_2, and COOH into CF_3 or COF depending on the reaction conditions. It is suggested that the formation of the C–F bond is the result of an intramolecular nucleophilic substitution in the intermediate ester:



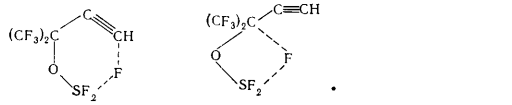
(35)

The side processes accompanying the fluorination by SF_4 are not inconsistent with this hypothesis. Thus, when unsaturated residues are present in the alcohol molecule, the following rearrangement is possible[194]:

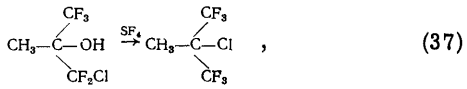


(36)

Evidently the driving force is the preferential formation on steric grounds of a six-membered transition state rather than a four-membered state leading to the normal product:

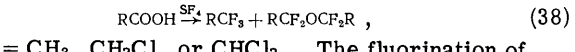


On treatment with SF_4, not only fluorination but also dehydration or rearrangement with transfer of the halogen can occur[195]:



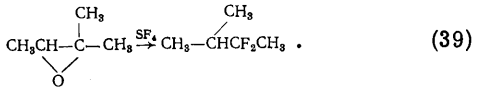
(37)

as well as the formation of ethers together with fluoroalkanes[196]:



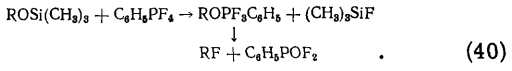
(38)

where R = CH_3, CH_2Cl, or $CHCl_2$. The fluorination of oxirans by SF_4 is also accompanied by rearrangements[197]:



(39)

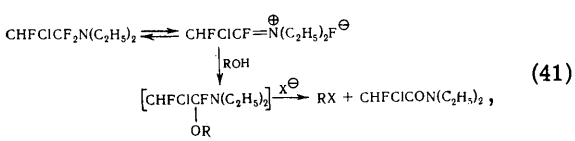
The new fluorinating agent $C_6H_5PF_4$, which smoothly replaces the $-OSi(CH_3)_3$ group by fluorine, probably acts similarly. The formation of intermediates in this case is facilitated owing to the high energy of the Si–F bond[198]:



(40)

The replacement of the hydroxy-group by fluorine with the aid of a mild agent such as the Yarovenko reagent $CHFClCF_2N(C_2H_5)_2$[199] (see Liska's review[200]) evidently also involves attack by the fluoride ion, which, however, is not intramolecular: in the presence of other nucleophilic species in the reaction medium, for example Cl^- or Br^-,

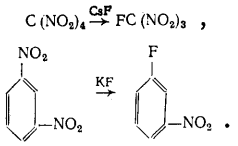
chlorine or bromine are introduced into the organic molecule instead of fluorine. The overall reaction mechanism involves the following stages[201]:



(41)

where X = F, Cl, or Br.

When the organic molecule contains a stable group which is eliminated, the latter can be replaced by fluorine also by means of the usual nucleophilic substitution. Fluorine has been introduced successfully in this way into carbohydrate molecules by the replacement of *p*-toluenesulphonyl[202] or methanesulphonyl[203] residues (see Podesva and Pacak[204] for a review of fluorocarbohydrates). The nitro-group can also be substituted[205,206]:



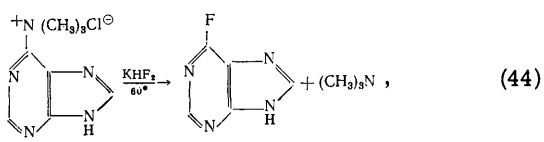
(42)

(43)

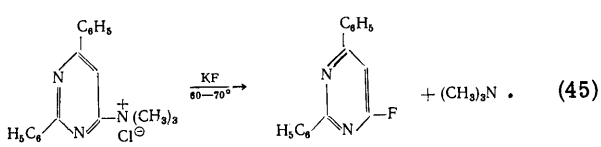
The substitution by fluorine of a nitro-group in purine and 1,2,4-triazole on heating with hydrogen fluoride[207] may involve the activation of the molecule by the protonation of the nitrogen atoms. A similar activation occurs in the *N*-methylation of 4-chloropyridine, which is then involved in halogen exchange with KF at 55°C.[208]

In the absence of activation, this reaction with polychlorinated aromatic (including heterocyclic) compounds requires very severe conditions (200–500°C). It constitutes the main method for the synthesis of polyfluorinated aromatic compounds (see Vorozhtsov's review[209]).

Heating of quaternary ammonium salts with alkali metal fluorides constitutes a promising method for the introduction of fluorine into heterocyclic compounds[210,211]:

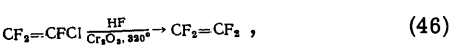


(44)

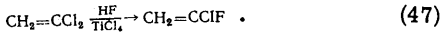


(45)

In many cases substitution of chlorine or bromine by fluorine requires the electrophilic cooperation of a "soft" Lewis acid, which binds the "soft" halogens. Such acids include SbF_3, SbF_5, HgF_2, AgF, and other agents used in this classical method for the introduction of fluorine, which is called the Swarts reaction (see the review of Fialkov and Yagupol'skii[212]). Chromium[213] and titanium[214] can also exhibit an electrophilic cooperation in the exchange of an olefinic halogen:

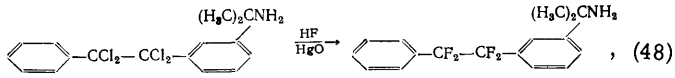


(46)



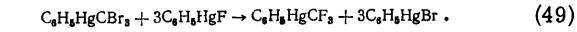
(47)

In the electrophilic cooperative action of mercury the halogen atoms in benzyl position are readily exchanged for fluorine[215]:



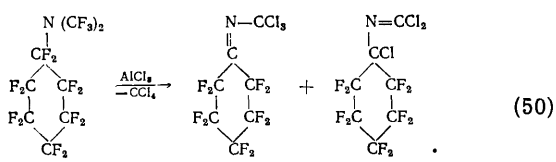
(48)

as well as those in the CBr_3 group linked to the mercury atom[216]:



(49)

However, since phenylmercury fluoride cannot undergo exchange with bromine in any other compound, reaction (49) may include a diahalogenocarbene transfer stage. "Hard" Lewis acids, i.e. derivatives of boron or aluminium, which form high-energy bonds with the "hard" fluorine atom, catalyse the reverse process—the exchange of fluorine for other halogens. Even certain fully fluorinated tertiary amines, which completely lack basic properties, enter into the reaction with $AlCl_3$, all the fluorine atoms in the α-position relative to the nitrogen atom being exchanged with elimination of CCl_4:[217]



(50)

Fluorine atoms in substituted trifluoromethylbenzenes are smoothly exchanged for chlorine with the aid of BCl_3 at 100°C,[218] while in the reaction with $AlCl_3$ the fluorine atoms in both vinyl and allyl positions in octafluorocyclobutene[219] and hexafluoropropene[220] derivatives are replaced.

During the preparation of this review for publication, a number of studies supplementing the data described here were published. The positive and negative ions derived from pentafluoroacetone and its stable enol have been investigated mass-spectrometrically[221]. In combination with ion cyclotron resonance, mass-spectrometry has been used to study the unusual decomposition of the pentafluoroallyl cation[222]. The stereochemical transformations of the corresponding radical have been studied by ESR[223]. New data on the inductive effect of fluorine atoms have been obtained with the aid of photoelectronic spectroscopy of a number of t-butyl alcohols[224]. Quantum-mechanical calculation[225] led to the conclusion that the fluorobenzenium ion is more stable when the fluorine atom is not attached to the sp^3-hybridised carbon atom. Experimental data indicating a greater stability of cycloalkyl carbonium ions containing a fluorine atom at the cationic centre in relation to analogues containing a chlorine atom have been obtained[226]. The one-electron mechanism of the interactions between arylethylenes and lead dioxide in SF_4 or HF has been confirmed by ESR[227].

Examination of new data for the reactions of organofluorine compounds will be the subject of a separate review.

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