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# Chapter 4

# SYNTHESIS OF C-F BONDS: THE PIONEERING YEARS, 1835 - 1940

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Of all the single bonds formed by carbon, the strongest is with fluorine [1], which therefore occupies a special place as a substituent in organic chemistry. Despite this, knowledge of organic fluorine compounds accumulated very much more slowly in the early days than that of organohalogen compounds in general. This was due partly to the extreme scarcity of naturally-occurring organofluorides — only a handful of which have been discovered to this day [2].[1] In view of the relative abundance of combined fluorine in the Earth's crust, the synthesis of C—F bonds does not appear to proceed too readily in Nature, nor has it proved to be easy to achieve in the laboratory. The pioneers encountered acute problems when trying to prepare anhydrous hydrogen fluoride and harness it for organic synthesis. Also, when elemental fluorine was finally isolated, its great reactivity towards organic matter delayed considerably its synthetic utilisation.

Some information bearing on the very early history of organofluorine chemistry can be gleaned from the famous *Treatise on Chemistry* by Roscoe and Schorlemmer [5] (1881, 1889) and from the review [6] by Moissan's important pupil Meslans (1894). The best source, however, is Moissan's classic book [7] (1900), which contains a bibliography of all scientific papers dealing with fluorine chemistry from 1558 to 1899, listed in chronological order. The scarcity of information on the fluorides, particularly those of the aliphatic class, contrasted markedly with the situation obtaining for organic derivatives of the other halogens, particularly chlorides [5].

General synthetic routes to the simpler types of aliphatic fluorides were eventually developed in the period after 1890. Then, suddenly, from being chemical curiosities, chlorofluoromethanes were catapulted to the forefront of modern chemical technology in the 1930s through their commercialisation as refrigerants (an endeavour requiring anhydrous hydrogen fluoride).

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[1] The first and best known of these is monofluoroacetic acid ($CH_2FCO_2H$), identified by Marais [3] in 1944 as the toxic principle of 'Gifblaar' (*Dichapetalum cymosum*), one of South Africa's most poisonous plants. Other highly toxic organofluorides have been made synthetically [4].

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Subsequently, during World War II, requirements for the Atomic Bomb Project placed fluorocarbons — compounds composed of carbon and fluorine only — firmly in the vanguard of organohalogen science and technology; in their case, production of elemental fluorine on a commercial scale was a prerequisite to large-scale availability. The chemistry of compounds with fluorine attached directly to an aromatic nucleus developed differently. From about 1870 onwards, fairly steady synthetic progress was made through the adaptation of standard organic techniques, and significant numbers of monofluoroarenes and even some difluoroarenes were prepared.

Organofluorine chemistry as a whole is now in a very healthy state, and more than a quarter of a million compounds containing C—F bonds have been synthesised [8]. There exists [9] a firmly-established and broadly-based (albeit specialised) segment of the chemical industry involved with materials containing carbon and fluorine and in many (but by no means all) cases a variety of other elements as well. Monographs, books and review articles dealing with organofluorine chemicals are numerous, and outnumber those centred on the other halogens.

This chapter is sub-divided into sections concerned with the following branches of the subject: (i) advances in aliphatic fluorine chemistry during the period up to 1886; (ii) aromatic compounds containing fluorine as a nuclear substituent (1870 - 1940); (iii) synthesis of C—F bonds using elemental fluorine (1886 - 1940); and (iv), synthesis, via indirect fluorination procedures, of aliphatic fluorides, including some with fluorine carried on side-chains in aromatic systems (1886 - 1940).

## The first 50 years: advances in aliphatic fluorine chemistry, 1835 - 1886

Unsuccessful attempts to convert alcohols directly into alkyl fluorides date back to the 18th century [5 - 7], when Scheele (1782) treated spirit of wine (ethanol) with vapours evolved from fluorspar and sulphuric acid; Reinsch [10] later reported similar reactions. Many other such failures have been recorded, and, even today, the direct substitution of —F for —OH in alcohols is not always easy to achieve, especially in satisfactory yield.

The credit for the first definitive synthesis of an organic fluoride, demonstrating that a stable bond could be formed between carbon and this proposed new element, goes to the French chemists Dumas and Péligot. As disclosed in an addendum to a paper published in 1835 [11a], and described further the year following [11b], during their seminal studies on wood-spirit (methanol) and its derivatives, they heated ('chauffant doucement') a mixture of dimethyl sulphate and potassium fluoride. The gaseous product was identified as methyl fluoride: $(CH_3O)_2SO_2 + 2KF \rightarrow 2CH_3F + K_2SO_4$. Twenty years later [12], Moissan's mentor Fremy heated a mixture of potassium bifluoride (Fremy's salt $KHF_2$) and potassium sulphovinate ($C_2H_5OSO_3K$) in a platinum apparatus, and by analogy with the work of Dumas and Péligot claimed that the gaseous product was ethyl fluoride.

These two experiments were the first examples of what has since become the most important general process for the synthesis of aliphatic C—F bonds, namely, the displacement of a good nucleofugal group by fluoride. A modern equivalent of the Dumas–Péligot reaction would involve leaving groups such as *p*-toluenesulphonate (tosylate) or trifluoromethanesulphonate (triflate), as exemplified in Chapter 11. Halogen exchange is in the same general category. Moissan claimed [7] that when he repeated the Dumas–Péligot experiment, he experienced problems in purifying the product, because the methyl fluoride was contaminated with dimethyl ether; however, it appears that the used methyl hydrogen sulphate as the starting material, not dimethyl sulphate.[2] He then turned to studies on substrates containing other halogens as leaving groups (see p. 92). He was not the first to do so: the original example of a nucleophilic replacement of a different halogen atom by fluorine (halogen exchange) appears to be Borodine's [13] (1863) successful conversion of benzoyl chloride to benzoyl fluoride using potassium bifluoride. Young — a student in Roscoe's department at Manchester — attempted in 1881 [14] to exchange halogens between isobutyl iodide and silver fluoride (of debatable quality, probably hydrated [7]). The experiment failed, and neither were reactions between crude hydrogen fluoride and isobutyl alcohol, amyl alcohol and amylene brought to satisfactory conclusions by today's standards. Importantly, though, the two new synthetic strategies suggested to Young by Roscoe [14] for the introduction of fluorine into aliphatic structures were developed successfully later ($RX + MF \rightarrow RF + MX$; $>C{=}C< + HF \rightarrow >CH{-}CF<$). Clearly, if Young had succeeded in getting hold of good-quality fluorinating agents and had been able to isolate pure products from the complex mixtures he produced, he could well have become a major figure in the development of organic fluorine chemistry!

In brief, though little progress seems to have been made in aliphatic fluorine chemistry prior to the isolation of the parent element, in fact the

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[2] Disagreement exists (*cf.* refs. 6, 7, 38, 136, 137 and 147) among later authors and reviewers as to whether Dumas and Péligot used dimethyl sulphate, methyl hydrogen sulphate or methyl potassium sulphate as their organic starting material. The original papers [11], and Dumas' textbook (*Traité de Chimie Appliquée aux Arts*, Tome V, Béchet Jeune, Paris, 1835, p. 434 - 447), show that dimethyl sulphate (b.p., 188 °C) was used. This raises doubts as to whether Moissan repeated their experiment *exactly*. Stating [7] that they had used methyl hydrogen sulphate (l'acide méthylsulfurique), he presumably did so himself. The methyl fluoride he isolated contained dimethyl ether, which could be removed through its greater solubility in water. Dumas and Péligot collected their product over water, in which any dimethyl ether would have tended to dissolve, and analysed it eudiometrically (ignition in oxygen) and by determination of its vapour density (presumably by Dumas' method [5]). Moissan [7] collected his products over mercury. Hence, his comments about the formation of a mixture of methyl fluoride and dimethyl ether in Dumas and Péligot's experiment may well have been unjustified, especially since the ether would be more likely to be formed by methyl hydrogen sulphate. Also, use of the latter as starting material would have given hydrogen fluoride, and the original preparation was done in a glass vessel.

syntheses actually achieved (MeF, EtF, also PhCOF), or attempted, were the embryos from which developed some of the most important routes to C—F bonds.

## Nuclear-fluorinated aromatic compounds from 1870 to 1940

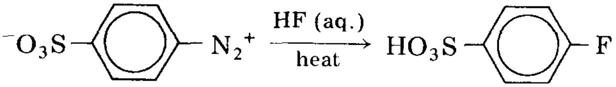
### *The first phase: 1870 - 1925*

Aromatic fluorine chemistry was in far better shape than its aliphatic counterpart by the time Moissan isolated fluorine in mid-1886. The discovery of aromatic diazo compounds by Peter Griess in Marburg towards the end of the 1850s (reported 1858) provided general synthetic approaches to very many aryl derivatives, including, it was found, fluoro compounds:

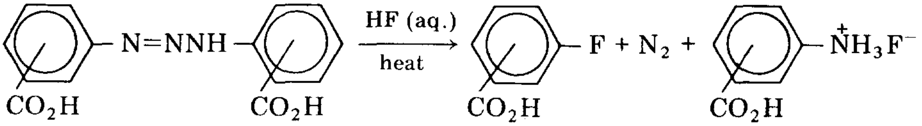
$$\mathrm{ArH} \longrightarrow \mathrm{ArNO_2} \longrightarrow \mathrm{ArNH_2} \longrightarrow \mathrm{ArN_2^+} \longrightarrow \mathrm{ArF}$$

Diazonium-mediated routes to fluorinated aromatics have been of lasting and inestimable value in both academic and commercial circles ever since.[3]

Reports on successful syntheses of aryl C—F bonds date from 1870, when Schmitt and von Gehren [16] described the conversion of a diazoaminobenzoic acid to a fluorobenzoic acid by heating it in strong hydrofluoric acid. Though they apparently believed that they had made the *m*-isomer, the melting point they reported later showed (*cf.* ref. 18) that their product was *p*-fluorobenzoic acid. Subsequently, Lenz [17] in 1877, produced *p*-fluorobenzenesulphonic acid from *p*-diazobenzenesulphonic acid and hydrofluoric acid:



A major advance was then made by Paternò and Oliveri in Italy. They employed Schmitt and von Gehren's process (it has been little used since) to make the three fluorobenzoic acids, and 3-fluoro-4-toluic and -anisic acids [18]:



(ortho, meta and para)

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[3] That diazofluorination via the fluoroborate route is the sole fluorination methodology taught to most students of organic chemistry stems from the excellent coverage provided by textbooks for synthetic intermediates of the status accorded to arenediazonium salts. In the main, however, even modern texts fail to do justice to organofluorine compounds; for an interesting account of such compounds as teaching aids, for those concerned with mechanistic organic chemistry, see ref. 15.

The prime target molecule was obviously fluorobenzene, the phenyl analogue of the first fluoro-alkane, methyl fluoride. Schmitt and von Gehren claimed to have made it by heating calcium fluorobenzoate with lime, but their product (a solid) was now shown by Paternò and Oliveri [19] to have been phenol. Inadvertently and unknowingly, the first example[4] of nucleophilic displacement of so-called aromatic fluorine had been discovered.

The Italian workers then proceeded to make the first genuine sample of fluorobenzene ("a mobile liquid with an odour like that of benzene, which boils at 85 - 86 ° and does not solidify at —20 ° ")[5] by heating potassium *p*-fluorobenzenesulphonate (made by Lenz's method [17]) with concentrated hydrochloric acid in a sealed tube, *i.e.* a standard desulphonation procedure: $p\text{-}FC_6H_4SO_3H + HCl(aq.) \rightarrow C_6H_5F + H_2SO_4$. An analogous sequence of reactions was used [19] to procure the first example of a fluorotoluene.

Paternò and Oliveri clearly were pleased to find that the boiling point of fluorobenzene seemed to confirm the analogy between fluorine and the other halogens (note the comment on p. 16), although they had not expected the value to be quite so close to that of benzene (modern values: $C_6H_6$, 80.1 °C; $C_6H_5F$, $C_6H_5Cl$, $C_6H_5Br$ and $C_6H_5I$: 85.1, 132, 156 and 183.3 °C, respectively; they quoted 132 °, 155 ° and 185 ° for chloro-, bromo- and iodo-benzene). Schmitt and von Gehren analysed quantitatively their supposed fluorobenzene for only carbon and hydrogen; since replacement of F (19 mass units) by OH (17) scarcely affects molecular weight, the values found were close to those expected for $C_6H_5F$. This seems to be the primaeval demonstration that organofluorine chemists needed to have at their disposal reliable means for the quantitative determination of fluorine via mineralisation of C—F bonds and estimation of fluoride ion so produced.[6]

Griess himself briefly entered the field of fluorine chemistry in 1885 [20], reporting the synthesis of a number of fluoro-acids — benzoic, cinnamic, and hippuric — via the action of hydrofluoric acid on diazonium

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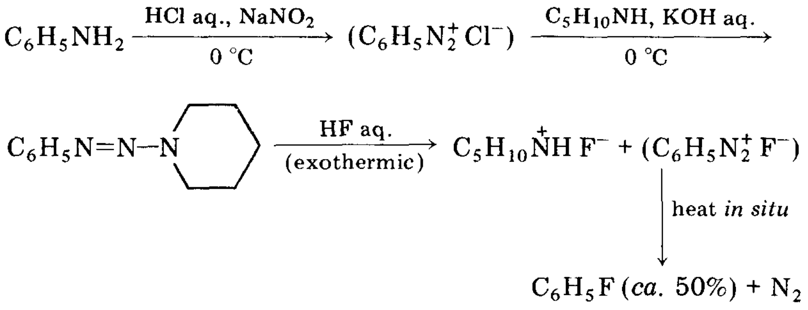
[4] Presumably the fluorine was lost before the decarboxylation occurred: it would be more activated towards nucleophilic replacement in the fluorobenzoate anion than in fluorobenzene. The (less likely) alternative would be a benzyne-type mechanism.

[5] We are indebted to Dr J. M. Birchall (UMIST) for translating the paper [19] into English.

[6] The history of the determination of fluorine in organic compounds has not been covered here, important though the subject is. Pre-war (World War II) methods for the decomposition of organic compounds were classified by Elving and Ligett [80] in thir well-known paper of 45 years ago dealing with the determination of fluorine and other halogens via fusion of samples with sodium or potassium, followed by measurement of alkali-metal halides produced: *Oxidation Methods* (combustion in oxygen; fusion with sodium peroxide; alkaline oxidation); *Reduction Methods* (combustion in hydrogen; treatment with sodium in liquid ammonia; alkali-metal fusion; treatment with alkali metal in organic solvent); *Methods Involving Alkaline Fusion* (fusion with calcium oxide; fusion with sodium carbonate); *Methods Involving Reactions with Silicon Dioxide* (corrosive action on glass; combustion over silicon dioxide using oxygen and hydrogen); *Hydrolytic Methods*. Reviews of methods devised for the detection and determination of fluoride ion prior to 1950 can be found in two appropriate editions of Mellor's book [81]. See also Chapter 11, Appendix 3, on this point.

sulphates. A curious off-beat paper in the same year [21] claimed that arenes reacted with 'chromium hexafluoride' to replace —H by —F, but apparently was never followed up.

Strong (presumably *ca.* 50%) commercial hydrofluoric acid,[7] *i.e. aqueous* hydrogen fluoride, was used in the pioneering work under discussion here. Yields of fluoroaromatics suffered markedly because the water present solvated the fluoride ion, thus reducing its nucleophilicity to the level where the water itself competed effectively for the diazonium cations, giving phenols and tar. To counter this, a method was developed which remained that of choice until the Balz–Schiemann reaction appeared in the late 1920s, namely the *in situ* thermal decomposition of arenediazonium fluorides generated by adding strong hydrofluoric acid to diazopiperidides, e.g.



This method was introduced by the great Prussian terpene chemist Otto Wallach. His first report included the successful one-pot conversion of aniline to fluorobenzene. Submitted for publication just one month after Moissan isolated fluorine in 1886, the paper [22] provided brief details of how cold aqueous benzenediazonium fluoride, prepared from aniline, hydrofluoric acid and aqueous sodium nitrite was mixed with fuming hydrofluoric acid and heated to give fluorobenzene in 20% yield. Wallach then went on, later with Heusler [22], to develop the superior diazopiperidide route; they prepared more than a dozen fluoroaromatic compounds, including 1,4-difluorobenzene and 4,4′-difluorobiphenyl. They also carried out the first systematic synthetic sequences on aryl fluorides, including diazotisations of *p*-fluoroaniline, and subsequent conversions to *p*-fluorophenol and the *p*-fluorohalogenobenzenes. The first electrophilic substitution (nitration) on a fluoroaromatic compound (fluorobenzene) was reported. They worked out a method for the determination of fluorine in their products via treatment with sodium (in benzene at 100 °C) and subsequent estimation of the fluoride ion released (as calcium fluoride). Altogether, a most significant contribution was made.

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[7] See footnote 30, on p. 18.

Shortly afterwards, syntheses and reactions were reported for fluoronaphthalenes [23] (1889) and polyalkylfluorobenzenes [24] (1892). Technological interest was shown by the synthesis of a fluorosaccharin [25] (1891), and by the filing of patents [26] (1896) on the diazo process to make aryl fluorides.

From the start of the present century, aromatic fluorine chemistry developed slowly but steadily; the range of known compounds was expanded and knowledge of the area became systematised. Important work [27] was done by Holleman and his co-workers in Holland in the period up to 1915. Interconnected series of fluoro-nitrobenzenes, -anilines, -toluenes and -benzoic acids were made. Electrophilic nitration of fluorobenzene gave mainly the *para* with some *ortho* product, and the isomer ratio was studied. Further, it was shown that the fluorine substituent in fluorobenzene was little affected by nucleophilic reagents, but that in fluoronitrobenzenes could be replaced, and with particular ease when in the *ortho* and *para* positions. Thus it became established that aromatic fluorine could be *activated* towards nucleophilic displacement. Hollemans's group were the first to make 2,4-dinitrofluorobenzene, later to become known as Sanger's reagent.

Alongside his outstanding work on aliphatic fluorides, Swarts did some careful studies [28] on interconnected families of aryl fluorides carrying $-NO_2$, $-NH_2$, $-OH$, —alkoxy and $-Cl$ groups. Rinkes [29] synthesised the first fluoro compounds with $-NHNH_2$, $-NHOH$, $-NO$ and $-N{=}N-$ groups. Van Hove [30] studied fluorobiphenyls, whilst Reid [31] made fluoroanthraquinones via benzophenones.

Thus, by the mid-1920s, synthetic sequences starting from arenes containing fluorine substituents could be undertaken with some confidence, general rules concerning the stabilities of aryl C—F bonds were known, and the directive influence of a fluorine substituent during electrophilic substitution reactions had been established.

### *The Balz–Schiemann reaction*

Though the reaction of hydrofluoric acid with diazopiperidides [22] may have had theoretical advantages as a route to aryl fluorides, obviously it was not without its practical problems (*cf.* ref. 51a), since in much of the work outlined above the starting materials were made from hydrofluoric acid and diazonium salts: Holleman [27] and Swarts [28], for example, used the latter route. A new synthetic impetus was needed, and its discovery was duly reported in 1927.

As early as 1913, a patent claim by Bart [32] had shown that arenediazonium cations formed stable solid salts with the tetrafluoroborate anion. Further investigation [33] was followed rapidly by the announcement [34] that if certain of these salts were isolated, dried and heated (many decompose at 100 - 130 °C) then they afforded good yields of the corresponding aryl fluorides (fluorobenzene, *p*-fluorotoluene, 4-fluoro-1,3-dimethylbenzene, $\alpha$-fluoronaphthalene and 4,4′-difluorobiphenyl):

$$ArNH_2 \rightarrow ArN_2^+X^- \rightarrow ArN_2^+BF_4^- \rightarrow ArF + N_2 + BF_3$$

This particular paper [34], by Balz and Schiemann, is one of the most important ever published in organofluorine chemistry. It opened up the field of aryl fluorides to general study, since synthesis of a range of compounds could be tackled by anyone skilled in normal practical chemistry. Diazotisation of an aryl amine in the usual way was followed by addition of the readily available fluoroboric acid or its salts, and standard apparatus could be used. The method was applicable to a wide variety of compounds, though obviously some examples worked less well than others (the presence of $-NO_2$ or $-OH$ groups usually caused difficulties).

Good reviews of the Balz–Schiemann reaction are available; the first to appear were by Schiemann himself [35], and later ones by Roe [36] and by Suschitzky [37] are much quoted. Books by Bockemüller [38] (1936) and by Schiemann and Cornils [39] (1969) also contain information on the 'fluoroborate route' as part of admirable state-of-the-art accounts of aromatic fluorine chemistry at the respective publication dates.

Organic fluorine chemistry certainly took a very significant step forward through the introduction of this new synthesis. By the 1930s, aryl fluorides were no longer chemical curiosities, studied only by a few devotees.[8] This is indicated clearly by the publication rate for the area: 1870 - 1928, *ca.* 60 papers; 1929 - 34, *ca.* 85; 1935 - 40, *ca.* 45. The vast majority of those published after 1930 used the Balz–Schiemann reaction for the synthesis of aryl C—F bonds. Obviously, only the highlights of this considerable body of later work can be summarised in this short review.

Schiemann himself with various co-workers rapidly extended the scope of his reaction. Starting from readily available aryl fluorides, further nitrations, reductions and fluorinations were carried out, and many functional derivatives were made on the way. Difluorobenzenes [40], various fluorobiphenyl derivatives [41] (though at first some of the orientations were incorrect) and the three fluorotolyl series [42] were studied. Alkylfluorobenzenes were made from fluorophenyl bromides [43], and fluoronaphthalenes, including the 1,4- and 1,5-difluoro compounds, were synthesised [44]. Extensive sequences which gave fluoro-tyrosine, -phenylalanines and -thyronine were also worked out [45]. *p*-Fluoroaniline was converted [46] into dialkylamino derivatives and also into *p*-fluorophenylhydrazine, and thence to fluoro-indoles and -phenylpyrazolones, whilst nitrations of fluoroanisoles and -phenetoles indicated [47] the relative strengths of the *ortho*- and *para*-directing influences of —F and —OR. Diphenyl ethers [48], *o*-fluorobenzoic acid derivatives [49], and 2,4-difluoro-aniline and -phenol

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[8] It is an interesting commentary on the appeal of fluorine chemistry (and also on the significance of the Balz–Schiemann reaction) that between World Wars I and II so many of the leading organic chemists with aromatic interests published something involving fluorine compounds; this is in contrast to the aliphatic area, which remained highly specialised.

were other compounds studied [50]. Experimental details for making fluorobenzene and 4,4′-difluorobiphenyl appeared in *Organic Syntheses* [51]. Clearly, the activities of Schiemann's group gave rise to a great all-round advance in fluoroaromatic chemistry.

Others quickly adopted the Balz–Schiemann fluorination process. For example, its use was reported as early as 1929 to make fluorophthalic acid and a fluorobenzanthrenone [52], and other work [53] on fluoronaphthalenes was only a little behind Schiemann's own; many other examples followed. Its success prompted the investigation of diazonium salts of other complex fluoro acids, e.g. hexafluorophosphates [54], but, though they did decompose to aryl fluorides, no obvious advantages resulted in most cases [37].

Soon after the general adoption of the Balz–Schiemann process, however, it was revealed in a patent [55] that good yields of aryl fluorides could be obtained in many cases, if the older direct diazotisation process was carried out in anhydrous hydrogen fluoride, and the diazonium fluoride so formed decomposed thermally *in situ*. This process has been slow to gain recognition (*cf.* ref. 37), but it is probably the better for many commercial purposes. However, the Balz–Schiemann reaction is still preferred in laboratory work because it avoids the need to handle anhydrous hydrogen fluoride.

Studies of reaction kinetics in the fluoroaromatic field began in the early 1920s with measurements of the rates of nucleophilic exchange of —OMe for —F in *p*-fluorobenzoic acid [56]. Ingold [57] worked on electrophilic nitrations of compounds where the directive influences of —F *versus* —OMe and —Cl were in competition, and on measurements of reaction rates for nitrations. Later, Bennett and Brynmor Jones made comparisons [58] of the electronic effects of fluorine compared with those of the other halogens, as measured by reactions such as replacement of chlorine in a series of benzyl chlorides, and also rates of halogenations of various types of compound.

An extensive study of the three fluorophenols and very many nitro, amino, halogeno, formyl and carboxy derivatives, as well as methyl ethers and related quinones, was reported by Hodgson [59], whilst Dyson [60] made mustard oils, benzothiazoles and other sulphur compounds as possible perfumery agents. There was strong contemporary interest in *ortho*-substituted biphenyl derivatives: if the groups placed *ortho* were sufficiently large, interaction between them restricted free rotation about the C—C bond joining the rings, giving rise to atropisomerism. Various examples of such compounds with *ortho*-fluorines were made by Adams [61]. The steric requirements of fluorine as a substituent were defined, and it was obviously not a very bulky group; four *ortho*-fluorines in a biphenyl did not interact sufficiently to give rise to a resolvable compound. Bigger groups such as —$NO_2$ or —$CO_2H$ had to be present in *ortho* positions with say two fluorines, to give optical activity. Fluorobiphenyls were also studied by Turner [62] from a synthetic standpoint, and, by showing that the nitration of 4,4′-difluorobiphenyl gave the 2-nitro derivative, some of Schiemann's orientations [41] were corrected. Bergmann [63] investigated fluorobenzophenones and 1,1-diphenylethylenes and made fluorofluorene derivatives via diazonium fluoroborates.

Continuing technological interest was shown by the filing of patents for anthraquinone [64] and triphenylmethane [65] dyestuffs containing nuclear fluorine, and for bactericidal fluorophenols [66]. Early recognition that fluorine substitution might have interesting effects on biological activities[9] was shown by papers [67] on fluorosalicylic acid derivatives and sulphonamides.

A fair number of miscellaneous studies also appeared, some synthetic, others describing electronic effects and stabilities of C—F bonds. 2,4-Dinitrofluorobenzene was made [68] by halogen exchange using KF, a notable first in the arene field. Under orthodox conditions, fluorobenzene reacted extremely sluggishly with magnesium to form a Grignard reagent; this stability led to an early example [69] of metallation (lithiation) of an aryl C—H bond in a fluoroarene. Hydrolysis of bis(aryl)-magnesium and -mercury derivatives with differing substituents in each ring gave measurements [70] of the relative electronic effects of fluorine, hydrogen and chlorine. Contemporary interest in triphenylmethane derivatives no doubt led to the synthesis of fluoro analogues, and to the observation [71] that nuclear fluorine substituents in triphenylmethane compounds were more readily displaced by free radicals than was the tertiary side-chain fluorine in triphenylmethyl fluoride.

Though most of the compounds touched on in this section were benzene derivatives, certain polycyclic fluorides were also known. Many of these have been mentioned already, particularly various biphenyls [22, 30, 34, 41, 61, 62], and naphthalenes [23, 44, 48, 53], mostly made by direct conversions of diazotised amines. 4,4'-Difluoro-biphenyl and -stilbene had also been made [72] by pyrolysis of fluoro-benzene and -toluene, respectively, and the former from *p*-fluorobenzoyl peroxide also [73]. A few compounds containing fluorene [63], phenanthrene and acenaphthene skeletons [74] were described; fluoro-anthraquinones were made by ring-closure techniques [31, 64], though the earliest, 2-fluoroquinizarin [75], had arisen from addition of HF to a diquinone.

Very few fluorinated heterocyclic compounds were reported in this period. Several fused-ring systems with fluorine in the benzene residue were made in general synthetic work, namely benzothiazoles [60, 76], oxazolones in amino acid synthesis [45] and acridones [77]. However, the first true nuclear-fluorinated heterocyclic compounds were in fact synthesised at quite an early stage. In 1915, the Russians Chichibabin and Rjazancev reported [78] the preparation of 2-fluoropyridine via the diazotisation of 2-aminopyridine in concentrated hydrofluoric acid. Räth made 3-fluoropyridine by

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[9] The earliest paper on biological effects of fluorine substitution appears to be Coppola's significant report that when the three fluorobenzoic acids were fed to dogs, the corresponding fluorohippuric acids were excreted [82].

a Gatterman-type reaction in 1931 [79]. Nothing else was published on such compounds until after World War II, and not until much later still did systematic knowledge on fluoroheterocycles begin to accumulate.

Finally, it must be emphasised that the great majority of the compounds mentioned so far possessed only one fluorine substituent in an aryl ring. Biphenyls and naphthalenes with one in each ring were known, but only a few derivatives with two fluorines in one aryl residue. It has been found that the diazotisation approach becomes laborious and progressively more difficult when the insertion of three or four nuclear fluorines is required. Compounds with highly-fluorinated aryl rings did not become commonplace until exhaustive fluorination methods had been developed, well after 1940 (see Chapter 11).

## Enter elemental fluorine

Not unexpectedly, Moissan was the first experimentalist[10] to observe the effects — now widely known — of simply allowing neat fluorine to encounter hydrocarbon-based materials at room temperature: in general, reactions commence immediately and proceed vigorously in an uncontrollable manner, combustion and even detonation occurring, leading ultimately to destruction of the organic molecules and the formation of carbon, hydrogen fluoride and mixtures of low-molecular-weight gaseous fluoroalkanes. In Moissan's own words [7]:

"L'action directe du fluor sur les composés organiques est le plus souvent très violente. Dès que la décomposition du corps organique a commencé, la chaleur dégagée est assez grande pour que la destruction devienne totale et que l'on n'obtienne finalement que de l'acide fluorhydrique et des fluorures de carbone. Cette décomposition est surtout rapide pour les composés riches en hydrogène. Nous allons en trouver un exemple bien net dans l'action du fluor sur les carbures d'hydrogène."[10]

Moissan also studied the action of fluorine on carbon itself [83], reporting in 1890 that he had separated carbon tetrafluoride from products obtained via ignition of the finely-divided element in his new halogen. The boiling point of Moissan's material (−15 °C) is so grossly incorrect, however, that credit for the isolation of carbon tetrafluoride ($CF_4$, b.p., −129 °C, the simplest *fluorocarbon*, *i.e.* a compound comprised of only *carbon* and *fluorine*) belongs to his countrymen Lebeau and Damiens [84], who reinvestigated the direct fluorination of carbon in the 1920s. Moissan's last unsuccessful attempts to effect direct fluorination of an organic compound seem to have involved the use of liquid fluorine [85], and culminated in a

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[10] Moissan's review [7] of his work contains descriptions of the action of fluorine on 41 well-known organic substances, including methane, ethylene, chloroform, iodoform, benzene, anthracene, ethyl alcohol, chloral, glucose, citric acid, benzoic acid, aniline, pyridine, nicotine and strychnine.

reaction carried out with the aid of Chavanne, whereby solid methane (m.p., —182.5 °C) was treated with the halogen at liquid-air temperatures; the resulting explosion pulverised the glass apparatus. As late as 1931, Japanese workers [86] were finding that organic liquids burned when treated with fluorine.

Owing to the difficulty and expense[11] of producing fluorine by Moissan's method, and the general fear — certainly not unwarranted (see Chapter 1) — of handling anhydrous hydrogen fluoride, the chemistry of elemental fluorine was seriously neglected for quite a long time post-Moissan.[12] Thus, no further studies on the direct fluorination route to organofluorine compounds seem to have been undertaken until more than a decade after the maestro's death in 1907, and significant progress was not made until the 1930s.

As revealed by Roscoe's and Schorlemmer's treatise [5], this situation contrasts markedly with that for the other halogens, particularly chlorine, which resembles fluorine most in terms of reactivity and physical properties. By comparison with fluorine, of course, chlorine is so easy to obtain, to manipulate and to convert into organic derivatives; the same distinction holds true between their hydrogen derivatives (HF and HCl). Thus, for example, by the time Moissan had isolated fluorine, stepwise direct chlorination of acetic acid was textbook stuff ($CH_3CO_2H \rightarrow CH_2ClCO_2H \rightarrow CHCl_2CO_2H \rightarrow CCl_3CO_2H$), and vast quantities of chloral hydrate [$CCl_3CH(OH)_2$] were being manufactured[13] for medicinal purposes via treatment of ethyl alcohol with gaseous chlorine [5]. Using similar reaction conditions, Moissan found that fluorine reacts fiercely with these substrates, causing fires and explosions; his report concerning acetic acid reads [7]:

"L'action du fluor sur l'acide acétique est très énergique. La décomposition de la vapeur par le fluor se produit avec flamme, et, lorsque le gaz fluor traverse bulle à bulle l'acide liquide, chaque bulle détermine la production d'une lueur très vive et la réaction a lieu le plus souvent avec détonation."

### *The root of the problem*

Blunt comparisons between fluorine and chlorine of the type just presented circulated widely long after Moissan's time and certainly did

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[11] The platinum or platinium–iridium anodes in a low-temperature Moissan U-type cell corroded rapidly (the latter type lasted longer). Ruff indicated a platinum loss rate of 5 g/g fluorine produced [87]. Clearly, fluorine could never have been produced commercially in this way [88].

[12] According [87] to H. R. Leech (1906 - 83), one of I.C.I.'s pioneering experts on fluorine chemistry, only some six papers dealing with elementary fluorine were published between 1886, when Moissan isolated it, and 1919, when the important paper of Mathers *et al.* [88] disclosed how to produce fluorine in quantity via electrolysis of molten $KHF_2$ in a cylindrical copper diaphragm cell fitted with a graphite anode. During the next 20 years (1919 - 39), at least 25 papers (and nine patents) appeared, as well as numerous publications dealing with the chemistry of the element.

[13] During 1873, only four years after Liebreich discovered that chloral hydrate induces sleep and acts as an anaesthetic agent, one factory in Berlin produced 13 000 kg of it [5].

nothing to encourage research in the area. As pointed out by Tedder in his review [89] of the fluorination of organic compounds with elemental fluorine, one of the obstacles to progress in fluorine chemistry as a whole has been the excessive attention paid to differences between fluorine and the other halogens at the expense of similarities. "Direct fluorination", he continued, "is a case in point; so much emphasis has been placed on the fact that organic compounds ignite when they are brought into contact with fluorine that it is usually overlooked that exactly the same phenomenon can occur with chlorine if the temperature is at all elevated" [89].

Thermochemical considerations provide an obvious explanation for the fluorine-ignition phenomenon, as first indicated in 1933 by Wilhelm Bockmüller of the University of Würzburg [90]. Using the best bond-energy data then available, including, of course, an 'old' value (66.8 kcal $\text{mol}^{-1}$) for the dissociation energy of molecular fluorine,[14] he computed that the heats of reaction for the exothermic changes $C—H + X_2 \rightarrow C—X + H—X$ and $C{=}C + X_2 \rightarrow CX—CX$ are far greater when X = F (−102.5 kcal $\text{mol}^{-1}$ and −107.2 kcal $\text{mol}^{-1}$, respectively) than when the other halogens are involved [e.g. for substitution of hydrogen: −22.9 (X = Cl), −6.2 (X = Br), +13.7 (endothermic; X = I) kcal $\text{mol}^{-1}$]. Arguing that the heat liberated via substitution or addition in the case of fluorine was ample to disrupt an adjacent C—C linkage (average energy 71 kcal $\text{mol}^{-1}$),[14] Bockemüller decided that the way to achieve successful direct fluorination of an organic substrate was to arrange for adequate dissipation of the heat generated.

Recent reviews [89, 92] of the fluorine-ignition problem, and its control, couple Bockemüller's heat-of-reaction argument with the important question of initiation of the free-radical chain processes involved. In particular, they address the question of why fluorine reacts at a significant rate with hydrocarbons even in the dark at temperatures lower than −78 °C. All will be revealed later (Ch. 11), but note here that molecular fluorine's low bond-dissociation energy (37 kcal $\text{mol}^{-1}$) is involved. That the value of $D_0(F_2)$ is considerably different from that which Bockemüller had to use (66.8 kcal $\text{mol}^{-1}$) became accepted in the 1950s following the publication of values based on thermochemical and spectroscopic data for chlorine monofluoride {Schmitz and Schumacher (30 - 33 kcal $\text{mol}^{-1}$) [93]; Evans, Warhurst and Whittle (37 ± 8 kcal $\text{mol}^{-1}$) [91]}.

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[14] The dissociation energy of molecular fluorine, *i.e.* the energy absorbed when the gaseous molecule is converted into two atoms in the ground state, $D_0(F_2 \rightarrow 2F\cdot)$, has been the subject of much controversy [91]. Older values were usually based on extrapolation of those for $Cl_2$, $Br_2$ and $I_2$, and fell in the range 60 - 70 kcal $\text{mol}^{-1}$ (to convert kcal $\text{mol}^{-1}$ to kJ $\text{mol}^{-1}$, multiply by 4.184). The bond dissociation energy values utilised by Bockemüller [38, 90] were as follows (with a set [1] of modern values in parentheses): F—F, 66.8 (37); Cl—Cl, 56.8 (57.9); Br—Br, 45.2 (46.1); I—I, 35.6 (35.5); H—F, 148 (135); H—Cl, 101 (103.1); H—Br, 85 (87.4); H—I, 70 (71.4); C—H, 93 (98.8); C—C, 71 (82.6); C=C, 125 (145.8); C—F, 114 (116); C—Cl, 72(81); C—Br, 59 (68); C—I, 45 (51) kcal $\text{mol}^{-1}$.

### *Progress at last*

#### *Liquid-phase work*

In the early 1930s, Bockemüller [38, 90] moderated reactions between organic substrates and fluorine by adopting so-called *liquid-phase fluorination* techniques, which involve passing fluorine — normally diluted with an inert gas (often nitrogen) — into dilute suspensions or, preferably, solutions (usually cooled) of organic compounds in inert (or relatively inert) solvents contained in vessels designed to effect rapid and efficient dispersion of the gaseous reactant. Using fluorine diluted with carbon dioxide, and carbon tetrachloride or dichlorodifluoromethane as the solvent, he studied the fluorination of numerous organic compounds — aliphatic and aromatic. Notable achievements were the conversion of cyclohexane (in $CF_2Cl_2$ at $-80$ °C) to monofluorocyclohexane (*ca.* 33% yield), of n-butyric acid (in $CCl_4$ at 0 °C) to mainly a mixture of $\beta$- and $\gamma$-fluorobutyric acids ($CH_3CHFCH_2CO_2H$ and $CH_2FCH_2CH_2CO_2H$; total yield *ca.* 30%) and of tetrachloroethylene (in $CF_2Cl_2$ at $-80$ °C) to a mixture of the chlorofluorocarbons $CFCl_2CFCl_2$, $CFCl_2CCl_3$ and $CFCl_2CCl_2CCl_2CFCl_2$, and the provision of evidence that elemental fluorine tends to saturate an aromatic nucleus. Full details of this highly important work, which laid the foundations for numerous recent syntheses achieved via direct liquid-phase fluorination, can be found in an excellent review [94] by the American chemist L. A. Bigelow, which covers all knowledge of the action of fluorine on organic compounds disclosed prior to entry of the U.S. into World War II.

Bigelow's own first two papers [95, 96] dealt with liquid-phase fluorination of various aromatic compounds either dissolved or suspended in cold (0 °C) carbon tetrachloride. From a synthesis viewpoint, no worthwhile results were achieved. However, Bockemüller's postulate that addition rather than substitution occurs with aromatic substrates was confirmed, and release of chlorine from the solvent was proved to be a complicating factor — as, no doubt, was the oxygen content of the fluorine used, since it was derived from a Mathers-type generator.[15]

Shortly before hostilities began, one of Bigelow's ex-students, William (Bill) T. Miller, who was to become — like his mentor — an outstanding fluorine chemist, confirmed and extended Bockemüller's work on the liquid-phase fluorination of tetrachloroethylene [97]. Using a U-shaped brass vessel which enabled *undiluted* fluorine to be fed in above a counter-

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[15] Bigelow's review [94] includes a critical discussion of the fluorine generators developed by Moissan, Mathers *et al.*, Fredenhagen and Krefft, Cady, and Miller/Bigelow. Of the Mathers type, Bigelow commented:
"The advantages of this unit were clearly obvious even to the more casual observer. It was rugged in construction and relatively inexpensive, the anode was cheap and but little attacked, the procedure did not require the services of very skilled operators, and the apparatus could be easily adapted to larger-scale production. Unfortunately, however, this type of generator has a number of serious limitations, some of which, at least, were probably not fully realised by the original investigators who were engaged in an effort to produce toxic gases under the pressure of wartime conditions."

current flow of liquid substrate (not always diluted or cooled), Miller established that controlled reactions between polychlorinated alkanes ($CHCl_3$, $CHCl_2CCl_3$, $CHCl_2CHCl_2$) or alkenes ($CCl_2{=}CCl_2$, $CHCl{=}CCl_2$) and fluorine could easily be effected but gave rise to complex products. The types of reaction observed were substitution of hydrogen attached to saturated ($sp^3$) or unsaturated carbon ($sp^2$), addition to olefinic links, dimerisation of alkanes or alkenes, and secondary reactions caused by displacement of chlorine atoms, e.g. $CCl_3CHCl_2 \xrightarrow{\text{at } ca. \text{ } 90\ ^\circ\text{C}} CCl_3CFCl_2$, $CFCl_2CFCl_2$, $CCl_2{=}CCl_2$, $C_2Cl_6$, $CCl_3CCl_2CCl_2CCl_3$. The hypothesis was advanced that radical mechanisms prevailed, but none were actually written in the paper. Miller — by then working independently at Cornell University — used fluorine generated in such a manner that its oxygen content was at a minimum. This stemmed from his experience as a graduate student in Bigelow's research group at Duke University, where a cell capable of providing fluorine with a purity[16] of at least 94% was developed; the best sample, prepared from an electrolyte ($KHF_2$ at 257 °C) dried finally with fluorine itself, gave an anode gas comprising 99% $F_2$, 0.4% $O_2$, 0.2% $CO_2 + COF_2$ and 0.4% 'inerts' presumed to be gaseous fluorocarbons [99].

Recalling his early days in fluorine chemistry recently, Bill Miller wrote [99]:

"My first contact with fluorine chemistry was at Duke University where I worked as a graduate student with Professor L. A. Bigelow. Professor Bigelow was interested in fluorinating aromatic compounds with elemental fluorine. However, at the time I began work unsatisfactory results were being obtained. I undertook the analysis of the fluorine being used and was able to show that considerable and variable amounts of oxygen and oxygen fluoride were present. The trouble was that the fused electrolyte which was open to the atmosphere at the cathode was hygroscopic. We constructed a closed cell which gave fluorine of high purity and obtained much improved results, in my case, first with hexachlorobenzene in the vapor phase [98, 100]. I found that it was possible to show from the literature that much of the early work with fluorine was carried out with fluorine containing considerable amounts of oxygen[17] and presumably oxygen fluoride [102], a very different reagent from pure fluorine."

Finally, note that although Bockemüller was the first to achieve the synthesis of identifiable C—F compounds via direct liquid-phase fluorination, valuable pioneering studies had been carried out previously by Humiston

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[16] When Bigelow wrote his mammoth fluorination review [94] in 1945, he commented that the only strictly quantitative method for the analysis of anode gas from fluorine generators readily available was that which he and Miller used to obtain the data quoted above. Their procedure used Moissan's observation that mercury, when agitated, absorbs fluorine quantitatively at room temperature, but when undisturbed becomes coated with a protective layer of mercuric fluoride. A Pyrex gas burette was used.

[17] Probably the first quantitative analyses of the gas from a fluorine cell were by Cuthbertson and Prideaux [101].

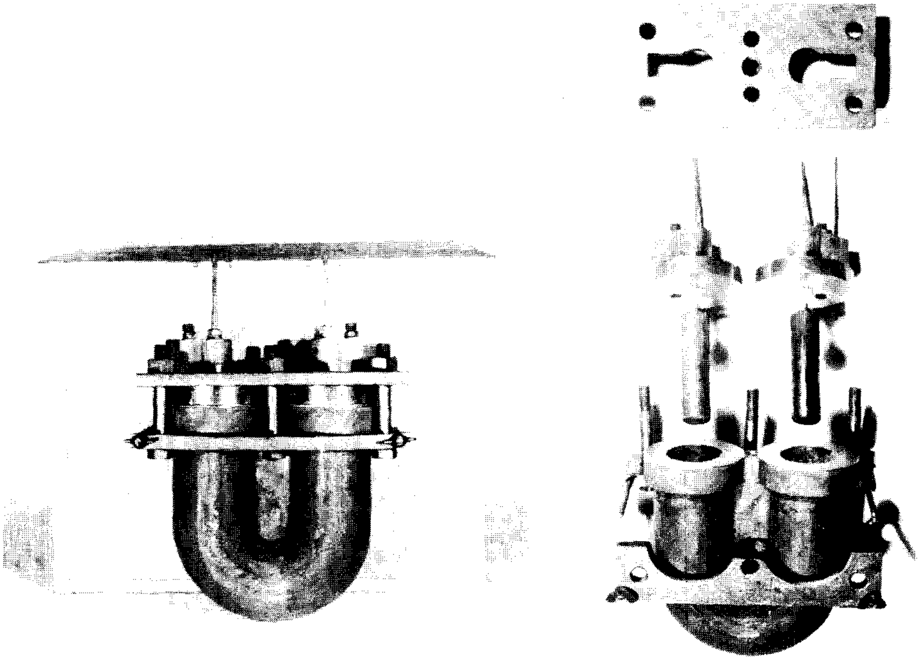

Fig. 4.1. (Left) High-temperature ($KHF_2$, 250 - 260 °C) U-type (cast nickel, 18 cm × 7 cm o.d.) closed-cell laboratory fluorine generator designed and used by Miller and Bigelow [98]. Under normal operating conditions (250 °C; 5 A at 18 - 20 V) it delivered approximately 2 l $h^{-1}$ of $F_2$. (Right) Dismantled cell, showing the graphite electrodes (anode on the right), which were threaded directly on to 6 mm nickel rods. These rods were insulated from the nickel caps by means of a cement prepared from powdered fluorspar and sodium silicate and made tight at the cell end with the visible nickel nuts and fluorite washers. The nickel parts exposed to fluorine became coated with a protective layer of nickel fluoride. (Photographs by courtesy of Emeritus Professor W. T. Miller [100].)

[103] and Whearty [104] under the general direction of Col. W. D. Bancroft for the Research Division of the American Chemical Warfare Service. The Mathers high-temperature fluorine generator* had been developed during World War I with the aid of Humiston [88], who introduced the technique of diluting fluorine with nitrogen and showed that neat fluorine liberated chlorine when passed into ice-cold stirred carbon tetrachloride containing tetrachloroethylene, the latter becoming converted to hexachloroethane [103]. Interestingly, Mathers *et al.* utilised the ability of traces of fluorine to instantly ignite the unlit gas mixture from a Bunsen burner as a test for the halogen. "This test is delicate, but less so than the odor", they wrote, following the amazing statement (*cf.* p. 4) that "Apparently fluorine possesses but little toxic action, although long exposure to rather large quantities produces headache" [88].

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*See footnote 15 on page 84.

*Vapour-phase work*

The second method devised for moderating direct fluorinations was to mix gaseous fluorine with organic vapours within the meshes of copper gauze. This technique was first used [105] by the German chemists Fredenhagen and Cadenbach in the early 1930s, and later patented by Krefft [106], but many of their reactions must have involved liquid films of the organic substrates.

It was Bigelow and his student collaborators who applied the idea to fluorinations entirely in the vapour phase. An outstanding contribution was the first demonstration that a hydrocarbon containing several carbon atoms can be converted into a fluorocarbon with elemental fluorine — work which provided a basis for the production of fluorocarbons via direct fluorination during World War II, as part of the Manhattan Project (see Chapter 5).

Following the lead given [105] by Fredenhagen and Cadenbach, and using [98] a closed $F_2$-generator (Fig. 4.1), Bigelow, with Miller and Calfee [107], showed that the chlorofluorocarbon $CFCl_2CFCl_2$ could be synthesised in at least 20% yield by allowing the vapour of the chlorocarbon $CCl_3CCl_3$ or the corresponding olefin $CCl_2{=}CCl_2$ to mingle with fluorine–nitrogen mixtures within the meshes of heated (range 125 - 160 °C) rolls of copper gauze sited in a Pyrex tube. Hexachlorobenzene, when treated similarly [108] gave a complex mixture of unidentified non-aromatic chlorofluorocarbons. Note that in the absence of hydrogen fluoride (as in the above experiments), fluorine can be handled readily in glass, harder glasses being the more resistant and silica excellent; borosilicate glasses, like Pyrex, are said to be little affected by exposure for a few hours to fluorine at temperatures up to 200 °C and silica up to 250 °C [87, 109].

Turning to the much more important and demanding challenge of retaining skeletal integrity during direct *poly*fluorination of *hydrocarbons*, Bigelow's group proceeded to achieve the smooth conversion of ethane in externally-unheated gauze-packed brass pipes to mixtures of the fluoroethanes $C_2F_6$, $CF_3CHF_2$, $CHF_2CHF_2$ and $CHF_2CH_2F$ contaminated with products of C—C fission ($CF_4$, $CHF_3$, possibly $CH_2F_2$), the actual compositions depending upon the reaction conditions [110]. Similar fluorination of ethyl chloride gave a complex mixture containing, *inter alia*, $CF_4$, $CF_3Cl$ and $C_2F_5Cl$ [111]. Using a more sophisticated apparatus, benzene was converted at 90 °C to a complex mixture, including 'tar', from which the fluorocarbons $CF_4$, $C_2F_6$, $C_3F_8$, $C_4F_{10}$, $C_5F_{10}$, $C_6F_{12}$ (perfluorocyclohexane) and $C_{12}F_{22}$, and a hydrofluorocarbon $C_6F_{11}H$, were isolated but no aromatic fluoro compounds [112].

The research on benzene was published in 1941, some months after a paper [113] dealing with the vapour-phase fluorination of acetone, also carried out in collaboration with Fukuhara. Initiated within the interstices of copper gauze at 60 °C (subsequently the temperature rose "considerably"), the fluorine–acetone reaction provided a complex mixture comprised principally of hexafluoroacetone ($CF_3COCF_3$), monofluoroacetone ($CH_2FCOCH_3$), trifluoroacetyl fluoride ($CF_3COF$), oxalyl fluoride [$(COF)_2$],

## L. A. Bigelow (1892 - 1973) — an appreciation by W. T. Miller


L. A. Bigelow

Lucius Aurelius Bigelow was born in Boston, Massachusetts on January 31, 1892, less than six years after Moissan isolated fluorine. He resolved early in life to do the things he wanted to do. Science and teaching seemed an ideal combination for him, while maintaining moral values consistent with his Unitarian background. He graduated from the Boston English High School, where Henry Gilman was one of his classmates. In spite of poor eyesight that was to be a lifelong handicap and restricted his financial circumstances, the young Bigelow received his S.B. degree from the Massachusetts Institute of Technology in 1915, studied at Harvard, and took his Ph.D. degree in organic chemistry from Yale in 1919. He began his teaching career at St. Lawrence University but quickly moved to Brown University, where he remained for nine years. In 1929 he joined the faculty of Duke University where he spent the rest of his life, retiring in 1961 at the age of 69. He died of leukemia on December 11, 1973, surviving his wife, Mary Cummings Bigelow, by one year. As his eyesight failed, Mrs. Bigelow played an increasingly important rôle in his professional life.

At Duke, Professor Bigelow's interest in the chemistry of elemental fluorine was aroused by the availability of a Mathers-type fluorine cell. He was encouraged to attempt the direct fluorination of organic compounds by Dr. Paul M. Gross. However, his first experiment resulted in a violent explosion. Instead of being discouraged, he resolved to obtain controlled reactions. The story of the research with his students that followed is best told by his scientific papers, the contents of which are summarised in Chapters 4 and 11 of this book. A fundamental result was the demonstration for the first time that a fluorocarbon containing an appreciable number of carbon atoms could be produced by reaction of a hydrocarbon with elemental fluorine. The Duke work provided the basis for the preparation of fluorocarbons by direct fluorination carried out during World War II as part of the Manhattan Project (see Chapter 5).

Lucius Bigelow maintained his keen interest in fluorine research and was a familiar figure at meetings of the Fluorine Division of the American Chemical Society into his retirement. However, he was even more strongly committed to teaching and his greatest concern was always for his students. This feeling was reciprocated.

The following remarks were made by J. Herbert Pearson when Professor Bigelow was awarded the Herty medal, as an outstanding southern chemist, by the Georgia Section of the American Chemical Society in 1958. Dr. Pearson was one of Bigelow's undergraduate students at Brown University, and the first fluorine research student (Ph.D.) at Duke.

"It is my opinion that one of the nicest things you can say about a person is that he has been an honor to his chosen profession. This criterion of a person's contribution to his fellow man is particularly adaptable to the profession of teaching others. Never have I known a person who put in so much effort to teach others, even, I dare say, at some sacrifice to other aspects of his career. It was fortunate for so many that he was blessed with the gift to convey knowledge to others. In this day of hectic research effort, both academic and industrial, too many of those charged with the responsibility of teaching often lose sight of this objective in the face of other demands. Dr. Bigelow never lost the sense of his primary responsibility of teaching, no matter how heavy or demanding the research load."*

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**Duke Alumni Register*, Sept. 1958, p. 10.

carbonyl fluoride ($COF_2$) and carbon tetrafluoride. The first and fourth of these were new compounds at the time, and, despite the low yield (not quantifiable), production of the former — the first ketone of the fluorocarbon class — was a benchmark achievement: the first successful one-step fluorine-mediated conversion of an organic feedstock containing a carbon-based functional group to its fluorocarbon counterpart. By this time, Bigelow was openly rationalising his group's results on the basis of free-radical mechanisms analogous to those already associated with thermal or photochemical chlorination of hydrocarbons [114]. The first clear-cut example appeared [115] in a paper published with Hadley in 1940, and was written exactly as follows to explain the production of all the possible fluoromethanes, hexafluoroethane, and octafluoropropane when methane was directly fluorinated over copper gauze:

$$\begin{aligned} F_2 &\longrightarrow 2F\cdot \\ CH_4 + F\cdot &\longrightarrow CH_3\cdot + HF \\ CH_3\cdot + F_2 &\longrightarrow CH_3F + F\cdot \end{aligned}$$

and so on until $CF_4$ is formed finally.

$$\begin{aligned} CHF_3 + F\cdot &\longrightarrow CF_3\cdot + HF \\ 2CF_3\cdot &\longrightarrow C_2F_6 \end{aligned}$$

$$\begin{aligned} CH_2F_2 + F\cdot &\longrightarrow CHF_2\cdot + HF \\ CHF_2\cdot + CF_3\cdot &\longrightarrow CF_3CHF_2 \\ CF_3CHF_2 + F\cdot &\longrightarrow CF_3CF_2\cdot + HF \\ CF_3CF_2\cdot + CF_3\cdot &\longrightarrow C_3F_8 \end{aligned}$$

Hydrogen fluoride liberated during fluorinations of hydrocarbons was removed by passing exit gases from the Cu-packed brass reactors over sodium fluoride ($NaF + HF \rightarrow NaHF_2$) in brass tubes prior to condensation of organic material in glass cold traps. Separation and identification of the complex volatile mixture always produced required great skill and patience on the parts of Bigelow's collaborators. Fortunately they had at their disposal excellent distillation equipment, including a Podbielniak-based Booth–Bozarth low-temperature rectification unit equipped with a gas density balance [110].

*Solid-phase fluorination*

It was by using this approach that the reactions of elementary fluorine with organic matter were harnessed for the first time to give chemical species which could be isolated in a pure state. This was a major advance.

Fluorine — neat or diluted with nitrogen — was passed over or through a bed of a solid substrate mixed with an inert diluent (e.g. fluorite, nickel shot) or a catalyst, where appropriate, and maintained at a temperature compatible with avoidance of 'catastrophic' reactions. Bigelow's review [94] should be consulted in the first place by those wishing to obtain details of the results published in this area before 1945. The most significant work involved the fluorination of carbon itself. It will be recalled that Moissan had fluorinated various forms of carbon and claimed to have isolated carbon tetrafluoride from the volatile products — the first report concerning a fluorocarbon. As noted previously (p. 91), however, the boiling point (−15 °C) Moissan gave for his material is far too high, and the definitive original isolation of $CF_4$ was achieved by his compatriots Lebeau and Damiens [84]. Initially (1926), they separated it from fluorine liberated at a carbon anode during the electrolysis of fused beryllium fluoride (this seems to have been the first electrochemical fluorination to give a defined fluoro-organic product)[18] and placed its boiling point near to −150 °C; later, in 1930, they described the isolation of a sample boiling at −126 °C (−129 °C is the accepted value nowadays) from the products obtained by direct fluorination of carbon [84]. Also in 1930, the German chemists Ruff and Keim reported [118] how they had isolated pure carbon tetrafluoride by careful distillation of products arising from the fluorination of wood charcoal in a glass tube; the carbon ignited spontaneously when fluorine was passed over it.

Products with boiling points higher than that of carbon tetrafluoride were obtained by Lebeau and Damiens [84] and Ruff and Keim [118] from the fluorination of carbon. Both sets of workers believed that these contained higher homologues of $CF_4$, but were unable to isolate sufficient material for proper investigation owing to frequent and often violent explosions encountered when fluorine was brought into contact with carbon. Investigations reported by Ruff, Bretschneider and Ebert in 1934 [119] threw some light on the cause of these explosions: Norite or graphite at 280 °C was found to absorb fluorine at low pressure (25 mmHg) to yield a grey

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[18] Much earlier (1905), the Americans Lyons and Broadwell patented [116] a process for the manufacture of 'carbon tetrafluorid gas' (sic), by electrolysis of molten metal fluorides in a cell fitted with a hard carbon or graphite anode surrounded by charcoal or lampblack floating on the electrolyte; no genuine experiments were described, however, and no information whatsoever concerning carbon tetrafluoride was provided. Bigelow did not even mention the claim in his review [94].

Note that $CF_4$ and $C_2F_6$ are released [117] during the all-important electrowinning of aluminium via the 100 year old Hall–Heroult process, *i.e.* electrolytic reduction of $Al_2O_3$ dissolved in molten cryolite ($Na_3AlF_6$) in a carbon-lined steel cell (cathode) equipped with carbon anodes (see Ch. 10).

solid[19] of composition approaching CF, which decomposed violently when heated rapidly, giving clouds of soot, carbon tetrafluoride and small quantities of higher-boiling fluorocarbon material. Carbon tetrafluoride having been isolated, Ruff and Bretschneider [120] passed it through an arc between carbon electrodes, to give hexafluoroethane and tetrafluoroethylene. The latter was purified by bromination, isolation of the $CF_2BrCF_2Br$ formed and then debromination by zinc. This was the first authentic example of a perfluoroalkene.

Subsequently, in 1937, [121] the Americans Simons[20] and Block reported that the reaction of fluorine with carbon provided $C_3$ - $C_6$ fluorocarbons, in addition to $CF_4$ and $C_2F_6$; a full paper followed in 1939. Passage of fluorine over Norite or sugar charcoal impregnated with catalytic amounts of mercurous or mercuric chloride at temperatures just below dull red heat provided — "steadily and without explosions" — a complex, wide-boiling mixture of fluorocarbons [b.p., −128 °C ($CF_4$) to 160 °C]. From this were isolated the new compound $C_3F_8$ (b.p., −38 °C) and fractions corresponding to $C_4F_{10}$ (at least two isomers, b.p., −4.7 °C and 3 °C), $C_5F_{10}$ (b.p., 23 °C), $C_6F_{12}$ (b.p., 51 °C) and $C_7F_{14}$ (b.p., 80 °C), the last three being thought to possess cyclic structures. These fluorocarbons were found to be chemically and thermally very stable, and their surprisingly low boiling points were attributed to weak intermolecular forces. The important fact which emerged was that open and closed chains of $CF_2$ groups are stable, and this led to the realisation that all structures associated with saturated hydrocarbons should be capable of duplication in terms of carbon and fluorine. Note that serendipity played a rôle in the vital work of Simons and Block: that mercuric fluoride (formed *in situ* from mercury chlorides + $F_2$) promotes the smooth production of a range of fluorocarbons from carbon and fluorine was discovered when an amalgamated copper tube was inadvertently used as the reactor [121, 122].

Various other studies on reactions between elemental fluorine and organic substrates during the period under consideration deserve a mention. It was used [123] as an oxidising agent for aqueous potassium acetate in chemical Kolbé-type reactions. Halogen exchange with carbon tetrachloride was employed to make chlorofluoromethanes (Ruff [124], Simons [125]; iodine pentafluoride was also used successfully in broadly similar processes). Work of commercial interest involved fluorinations using chlorofluorocarbons, fluorosulphonic acid and AHF as inert solvents, and calcium fluoride as an inert filler [126]. There was rare work by Henne on elementary fluorine [127], and also the direct fluorination of rubbers [128].

Finally, some work by Ruff's group was a portent of things to come in terms of structural types to become available later in organofluorine chem-

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[19] This is the so-called *carbon monofluoride,* $(CF)_n$, now a well-known commercial product (see Ch. 11).

[20] J. H. Simons (1897 - 1983) became a very famous fluorine chemist, particularly through his invention of an electrochemical fluorination technique (see Ch. 11). For biographical details, see ref. 122.

istry. Three papers [129] stemmed from the passage of fluorine through a mixed bed of silver cyanide and calcium fluoride (added as a moderator) cooled to 0 °C. The products included $CF_4$, $C_2F_6$, $CF_3NF_2$ and a substance $C_2F_6N_2$, formulated as $CF_3N{=}NCF_3$. The fascinating blue gas $CF_3NO$ was also claimed as a product (the silver cyanide used contained silver nitrate). More recently, trifluoronitrosomethane has been studied extensively by Haszeldine's group and by many others. Ruff did not exploit his organic discoveries much further; his contributions to the inorganic branch of fluorine chemistry are discussed in Chapter 3.

Despite the promise of great things to come, following the achievements of Bigelow, Ruff, Simons and their collaborators, it must have appeared unlikely at the time that large-scale syntheses of a range of fluorocarbon structures, especially of a functionalised variety, would be realised in the near future. However, events soon occurred in the U.S.A. and Great Britain which completely changed the picture and gave fluorocarbon chemistry an impetus that has remained to the present day. Before these events are described (Chapter 5), important developments in synthetic routes to organofluorine compounds not involving elemental fluorine need to be considered.

## Aliphatic fluorine chemistry from 1886 to 1940

### *The preliminaries: 1886 - 96*

Moissan and Meslans must have been very disappointed to find that they could not harness elementary fluorine to organic synthesis. In fact, though fluorine's isolation obviously stimulated general interest, and finally settled the question of its elemental nature, it had virtually no direct influence on organic fluorine chemistry for almost 50 years. Progress in the synthesis of aliphatic fluorides came from exchange processes using metal fluorides as fluorinating agents and could presumably have been achieved even if the element itself had remained unisolated.

Moissan and Meslans had supplemented their work on direct fluorination by trying to develop further the indirect methods introduced by the very early workers and already outlined. Reactions of alcohols with hydrogen fluoride and with phosphorus fluorides were studied thoroughly and still found to be unsatisfactory for the preparation of alkyl fluorides [6, 7, 130]. Attention was then turned to the action of metal fluorides on alkyl halides [6, 7, 131]. By a series of reactions involving silver monofluoride and the corresponding alkyl iodides, the lower alkyl fluorides (Me, Et, $Pr^n$, $Pr^i$, $Bu^i$, allyl) were made and characterised. All were pretty resistant towards alkaline hydrolysis. Additions by Meslans [6, 132] of chlorine and bromine across the C=C bond of allyl fluoride must have been the first reactions of this type. A series of papers by Moissan, Meslans and Chabrié then followed, in which preparations of fluoroform [6, 133] and ethylene difluoride [134] were claimed by the reactions of silver fluoride with iodoform and ethylene dibromide, respectively. Other papers, cited by Moissan [7, 83], reported related reactions to make polyfluorides, including $CF_4$, but judging by the properties quoted, the products must have been very impure. Meslans used AgF, $AsF_3$, $ZnF_2$ and $SbF_3$ to make acetyl fluoride and other acid fluorides [6, 135].

The work of Collie deserves special mention [136]. He made methyl fluoride by heating tetramethylammonium fluoride, and carried out the first substitution reaction on a fluorohydrocarbon, chlorination in sunlight affording $CH_2ClF$. This new product was hardly flammable but was hydrolysed more easily than was $CH_3F$. Attempts to make $CF_4$ by passing a mixture of $CO_2$ and $SiF_4$ through a red-hot platinum tube were unsuccessful. The spark spectrum of $CH_3F$ was measured.

None of these workers made any more recorded contributions to organic fluorine chemistry, and the scene was set for one of its greatest contributors to take up the challenge of the synthesis of polyfluoro compounds.

### *The subject becomes established — the seminal work of Frédéric Swarts*

Almost single-handedly during the period 1890 - 1930, this Belgian chemist so built upon the very modest body of existing knowledge that he created a new sub-discipline of aliphatic fluorine chemistry. Whatever Moissan's achievements in other areas, it is Swarts who ranks as the Founding Father of this part of the subject. The earlier work had largely involved alkyl and acyl monofluorides, novel in type, but not so different in reactivity from their chloro counterparts. It was Swarts who systematically prepared polyhalogeno compounds, at first with chlorine or bromine accompanying the fluorine, and later containing the polyfluoro groups $-CHF_2$ and $-CF_3$. These were not only novel compounds in terms of structure, but possessed unique chemical and physical properties, and often conspicuously lacked expected reactivity. Swarts' work at the University of Ghent was published in Belgian journals, and to many was available only in abstract form. Though highly regarded by fellow fluorine chemists, it did not always receive full international recognition among non-specialists. His work and career have been summarised [137], and a short biography is included below.

Swarts used antimony trifluoride for most of his C—F bond syntheses. This reagent had been introduced by Meslans [135] to make acetyl fluoride, from the chloride — an easy halogen exchange to achieve. Swarts discovered that the fluorinating activity was much enhanced if the antimony was made pentavalent by addition of bromine; thus the compound $SbF_3Br_2$ was easily prepared and shown to act as a fluorinating (not a brominating) agent with organic polyhalides. Starting in 1892, his first papers covered the action of $SbF_3Br_2$ with carbon tetrachloride to give $CFCl_3$, with chloroform to give $CHFCl_2$, and with $CHBr_2Cl$ to give CHFBrCl [138]. A steady stream of papers covering synthetic work followed, the first batch [139] involving fluorinations of dibromochloroacetic acid derivatives by $SbF_3Br_2$ and by

## Frédéric Swarts, 1866 - 1940

F Swarts

Frédéric Swarts was born on 2 September, 1866 at Ixelles, a suburb of Brussels, shortly after his father, Théodore Swarts, had been appointed Professor of Chemistry at the Ecole Militaire. Théodore was a collaborator with Kekulé at the University of Ghent (Gand), and he succeeded him there as Professor in 1867. Frédéric entered the University of Ghent as a student in 1883, pursuing studies in chemistry and medicine. He was awarded the degree of Doctor in Natural Sciences in 1889 (and that of Doctor in Medicine in 1899).

He became assistant to his father in 1889, and published his first research paper in that year. On his father's retirement in 1912, he assumed charge of chemistry teaching to beginners and to advanced students. He continued with this, and of course, with his researches on fluorine chemistry, until his retirement in 1936, his whole professional career being practised in the University of Ghent. He continued to work in his personal laboratory until a few months before his death, which occurred on 6 September, 1940, and was due to a lung infection, exacerbated by the onset of World War II.

From 1890 onwards, he pursued his unique and fine researches into the synthesis and reactions of organofluorine compounds and their detailed physico-chemical properties with remarkable dedication and continuity. The discovery of a whole new section of organic chemistry may truly be said to be due entirely to his own personal work. His ability as a teacher was also very high, and he was venerated by his students.

The Académie Royale de Belgique awarded him its Médaille d'Or in 1900, and the Classe des Sciences of that Institution made him a corresponding member in 1904, and Titular Member in 1911. He was awarded the Decennial Prize for Chemistry and Physics in Belgium for the period 1909 - 18, and was Chairman of the Belgian National Committee for Chemistry. The Belgian and French Governments honoured him, as did a number of foreign Societies and Universities.

Frédéric Swarts was apparently a shy and retiring person, and though a stern critic of others, he applied such rigorous standards firstly to his own efforts. He was a chemist of truly great stature.

L. H. Baekeland, the inventor of Velox photographic paper and of Bakelite synthetic resin was born in Ghent and was a little senior to F. Swarts as a student at the University there; he married into the Swarts family.

AgF, to give bromochlorofluoroacetic acid derivatives. The acid was resolved into enantiomers, but the product of its decarboxylation (CHFBrCl) did not show optical activity, the reaction causing racemisation. Fluorination of methyl iodoacetate by antimony fluorides or zinc fluoride failed, but use of AgF or of mercurous fluoride (its first application) gave methyl fluoroacetate. Dichlorofluoroacetic acid derivatives were also made using $SbF_3Br_2$.

A further series of papers followed [140] on the fluorination by $SbF_3Br_2$ of tetra- and tri-bromoethanes, affording various poly(bromofluoro)ethanes. Proceeding from these products, two reactions fundamental to the progress of the subject were developed, and have been used ever since. In the first, with metallic zinc, it was found that vicinal bromines were removed preferentially in an efficient olefin-forming elimination process:

$$\begin{tikzcd}
CFBr{=}CHF & CFBr_2CHFBr \arrow[l, "Zn"'] \arrow[r, "NaOEt"] \arrow[d, "SbF_3Br_2"] & CFBr{=}CFBr \\
CF_2{=}CHF & CF_2BrCHFBr \arrow[l, "Zn"'] \arrow[r, "NaOEt"] & CF_2{=}CFBr
\end{tikzcd}$$

The other reaction was with ethoxides or alkalis, hydrogen bromide being removed preferentially, though, in this case, side-reactions could interfere sometimes. Simultaneous loss of HF occurred occasionally, and nucleophilic addition of ethoxide to the olefinic products was possible (as became clear later). Among the products derived ultimately from tribromoethane by use of these sequences were vinyl and vinylidene fluoride.

Difluoroacetic acid was made [141] by prolonged high-temperature hydrolysis of a bromodifluoroethane catalysed by mercuric oxide, to remove bromine preferentially, followed by oxidation of the resultant alcohol:

$$CHF_2CH_2Br \longrightarrow CHF_2CH_2OH \longrightarrow CHF_2CO_2H$$

Other acids were prepared [142] by oxygenation/rearrangement (not oxidative cleavage of the double bonds) of some of the available fluorobromoethylenes, to afford acyl halides, followed by hydrolysis; e.g.

$$CHF{=}CBr_2 \longrightarrow CHFBrCOBr \longrightarrow CHFBrCO_2H$$

$$CFBr{=}CFBr \longrightarrow CFBr_2COF \longrightarrow CFBr_2CO_2H$$

Chlorodifluoroacetic acid came from chlorination of difluoroacetic acid [143].

In the early 1900s, the first paper [144] appeared on the fluorination of a chloroethane ($CHCl_2CHCl_2$), and also described the use of a mixture of $SbF_3$ and $SbCl_5$ as the fluorinating agent; later on, this became the standard process. Previously [145], the first disclosure of the fluorination of a $-CCl_3$ group linked to an aromatic nucleus was reported, benzotrichloride having been found to react rapidly with $SbF_3$ alone:

$$PhCCl_3 \longrightarrow PhCFCl_2 \longrightarrow PhCF_2Cl \longrightarrow PhCF_3$$

In fact, benzotrifluoride was by far the easiest of these products to make. It was shown [145] that although fluorine itself was an *ortho-* and *para-*directing nuclear substituent, the $CF_3$ group in benzotrifluoride directed electrophilic attack by $NO_2^+$ into the *meta* position of the arene ring. The corresponding *m*-amino compound was then made by reduction.

Subsequently [146], further typically detailed studies centred on the fluorinations of bromoform and of tri- and tetra-bromoethane were undertaken, and the polybromofluoro-ethanes and -ethenes encountered were carefully characterised. Throughout all of the work, it was found that the poly(halogenofluoro) systems examined were generally stable, and that the C—F bonds were broken less readily than the other C—halogen bonds.

This short summary shows that during a 20-year period prior to World War I, Swarts transformed the entire subject of aliphatic fluorine chemistry into a well-ordered body of knowledge encompassing synthesis and reactivity. He also studied the physical properties of many of the compounds he made. His work was never published with co-authors, and virtually no other papers on aliphatic fluoro compounds appeared at that time. He formulated rules to codify the ease of replacement of various types of halogen atoms by fluorine using his reagents. Perhaps less important now than then, these rules are included in reviews by Henne [147]. These provide accounts of the status of aliphatic fluorine chemistry at the start of World War II, and are centred on the American work of the 1930s, but also summarise much of Swarts' contributions.

After World War I, Swarts turned back to aromatic chemistry (see p. 77) to look again at side-chain fluorinated derivatives. Up to that time, his fluorination systems had not made available any simple aliphatic compounds having $CF_3$ groups or $CF_2$ within a carbon chain [137, 147]. However, the synthesis of an aryl derivative with a fully fluorinated side-chain ($C_6H_5$-$CF_3$) had been easy. He examined benzotrifluoride further [148] (showing that the $-CF_3$ group could be hydrolysed to $-CO_2H$ by hydrogen bromide) and then re-made *m*-aminobenzotrifluoride. He also prepared (trifluoromethyl)cyclohexane by catalytic hydrogenation of benzotrifluoride [149] and converted it to bromo and hydroxy derivatives and thence into (trifluoromethyl)cyclohexene. Whilst engaged in this, he nitrated (trifluoromethyl)cyclohexane, and then oxidatively degraded the ring, to obtain the first sample of a perfluorocarboxylic acid, trifluoroacetic acid. This important compound was made most efficiently by oxidation of *m*-aminobenzotrifluoride using chromium trioxide [150].

Trifluoroacetic acid was the strongest organic acid then known. However, the carboxyl group gave rise to the usual derivatives. The ethyl ester underwent a classical Claisen condensation with ethyl acetate in the presence of sodium ethoxide to give [151] ethyl trifluoroacetoacetate ($CF_3$-$COCH_2CO_2Et$), which was an unusually stable $\beta$-keto ester, and contained a high proportion of the enol form. Its acidic decomposition afforded trifluoroacetone ($CF_3COCH_3$). Classical reactions led to alcohols containing the $CF_3$ group [152]: $CF_3CH_2OH$ by reduction of trifluoroacetic anhydride; $CF_3CH(OH)Me$ by reduction of trifluoroacetone; $CF_3C(OH)Me_2$ via reaction of a trifluoroacetate ester with a Grignard reagent. The tertiary alcohol was very stable; thus, in contrast to t-butanol, forcing conditions were needed to dehydrate it to a butene.

Electrolysis [153] of trifluoroacetic acid or of its salts provided an unusually efficient example of the Kolbé reaction, affording hexafluoroethane. Swarts must have found satisfaction in achieving the first synthesis of this fluorocarbon — it might have been made before by use of elementary fluorine but not isolated and characterised.

In addition to the synthetic work, Swarts was greatly interested in the physicochemical properties of his organo-fluorides, particularly their thermochemistry, intermolecular forces (as manifested by volatilities and viscosities) and refractivities (very low) [summarised in refs. 137, 147 and 166].

No more eulogies are necessary. Swarts' total contribution speaks for itself, and will surely never be surpassed.

*Organic fluorides go commercial*

Up to this time, most chemists must have viewed organic fluorides as laboratory curiosities. Some patents had been filed here and there in case any useful properties turned up, e.g. fluorinated dyestuffs amongst the arenes. In 1928, however, Thomas Midgley of the Frigidaire Corporation (part of General Motors) in the U.S.A. decided to try to find a new working fluid for refrigerators, because the existing ones were very unsatisfactory. The story of what followed has been told in full [154, 155]. He and his colleagues, Henne and McNary, based their search on the Periodic Table, and concluded that for a desired boiling range of 0 °C to −40 °C, aliphatic fluorides might provide the answer, despite the general belief that they were toxic. Feeling that carbon tetrafluoride would be difficult to make, and that its then recorded boiling point of −15 °C was wrong (see pp. 81, 90), they decided to prepare a sample of dichlorodifluoromethane,[21] one of the compounds characterised by Swarts [156], and mentioned also by Ruff [157]. Midgley recorded what happened next in an address he gave [154] when awarded the Perkin Medal of the Society of Chemical Industry, for introducing tetraethyl-lead as a petrol antiknock agent and organofluorides as refrigerants. Apparently, they bought up the entire American stock of antimony trifluoride (5 × 1 oz bottles) and carried out a Swarts-type reaction[22] using the contents of one of the bottles: $CCl_4 + SbF_3 + SbCl_5$ (small amount) $\rightarrow CF_2Cl_2$. The product was non-toxic and seemed to be just what they were seeking. However, samples made subsequently contained phosgene and were highly toxic, because the antimony trifluoride in the other bottles was contaminated with a double salt containing water of crystallisation. Fortuitously, they had chosen first the one bottle containing good-quality $SbF_3$! As Midgley said [154] "you must be lucky as

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[21] In two places in Midgley's written account [154b] of his Perkin Medal address, he refers to the compound first selected for preparation as dichloromonofluoromethane. However, since his previous discussion [154a, b] centred on the boiling point of dichlorodifluoromethane, and all his later papers refer only to the latter, it seems that an unfortunate printing error crept into this account.

[22] Swarts himself did not apparently report this specific synthesis. His original paper [138] recorded the conversion of $CCl_4$ to $CFCl_3$, using $SbF_3Br_2$. Subsequently, the chlorination of difluoroethanol to give principally derivatives of chlorodifluoroacetic acid was reported [143]; $CF_2Cl_2$ was characterised as a minor product arising by chlorinolysis.

well as have good associates and assistants to succeed in this world of applied chemistry".

Midgley demonstrated the discovery in a highly spectacular manner at the National Meeting of the American Chemical Society in April 1930. Inhaling a lungful of $CF_2Cl_2$, he then exhaled it — to extinguish a burning candle. In view of the recent controversy about possible harmful effects of accumulations of chlorofluorocarbons in the upper atmosphere, it is important to emphasise just how great an advance the introduction of $CF_2Cl_2$ as a refrigerant represented in the 1930s, by providing an alternative to toxic or flammable materials such as ammonia, sulphur dioxide and methyl chloride.

### *Freons®*

The 1930s saw rapid progress in the commercialisation of chlorofluoroalkanes. Frigidaire (General Motors) and Du Pont founded a joint company (Kinetic Chemicals) which began manufacture of the new materials under the trade name Freons®. Following the originators' patents [158], and using large-scale processes worked out by Daudt and Youker, Freons 11 ($CFCl_3$), 12 ($CF_2Cl_2$), 113 ($CF_2ClCFCl_2$) and 114 ($CF_2ClCF_2Cl$) were introduced early in the decade followed later by Freon 22 ($CHF_2Cl$) as a result of process improvements by Benning [155b]. These compounds are still the most important ones commercially. Other companies, both in the U.S.A. and in many other countries, later began to produce them, under new trade names (*cf.* ref. 155b), and quickly filed their own patents on the process. A vast commercial literature arose, which is still being extended.

For large-scale manufacture of chlorofluoroalkanes, the native ore calcium fluoride would be an attractive fluorine source, but it is not sufficiently reactive and practicable processes based on it have not yet been found. That left anhydrous hydrogen fluoride as the next best, and in the original systems it was employed under slight pressure in a closed vessel in the presence of antimony pentachloride as a catalyst at temperatures below 200 °C. This type of procedure is still used. Vapour-phase processes have also been developed, involving passing mixtures of hydrogen fluoride, chlorocarbons and recycled material (incompletely converted) over solid catalysts (many types have been suggested) at high temperatures (up to 500 °C).

There followed a tremendous upsurge in investigations of all types of aliphatic chlorofluoro compounds and the products derivable therefrom. General accounts of this work, from both academic and commercial establishments, are recorded in reviews [38, 147, 155], including a very comprehensive one [159] covering the period up to about 1960.

### *Later work by Henne*

Later in the 1930s, A. L. Henne, who was born in Belgium (see p. 100), went to Ohio State University, to become Director of Research at the Midgley Foundation there. He co-authored many high-quality papers on several aspects of organofluorine chemistry, and continued as an academic leader at the forefront of the subject for many years. Highlights only of his work can be mentioned here. Fluorinations of hexa- [160], penta- and tetrachloroethane [161] with $SbF_3Cl_2$ gave ranges of chlorofluoroethanes, which were dechlorinated by zinc to provide various chlorofluoroethylenes; 1,2-dichlorotetrafluoroethane, for example, afforded tetrafluoroethylene. The use of mercuric fluoride was introduced [162] as an alternative to antimony fluorides and with differing reactivity. Mercurous fluoride was used for the synthesis of monofluorides by Henne (and also by Swarts in late papers) [163]. Henne went on to study fluorinations of chloropropanes [164], and an extensive interconnected series of chlorofluoro derivatives was built up. At the end of the period under review, the facile fluorination of C—Cl bonds located next to olefinic groups was discovered [165], paralleling the easy fluorination of benzotrichloride.

$$CCl_3CCl{=}CCl_2 \longrightarrow CF_3CCl{=}CCl_2$$

$$CF_2ClCCl{=}CF_2 \longrightarrow CF_3CCl{=}CF_2$$

However, several years elapsed before it was fully appreciated that very high degrees of fluorination could be achieved by replacing activated (usually allylic) $CCl_3$ groups by $CF_3$ using reagents such as $SbF_3Cl_2$, taken in proper sequence with chlorine addition and with dechlorination by zinc.

No other fluorinating agents introduced before or during the 1930s had as profound an influence on organofluorine chemistry as did the antimony halides.

### *Other types of fluorination*

Aqueous hydrofluoric acid was never very useful as an organic fluorinating agent, and the harnessing of anhydrous hydrogen fluoride (AHF) for organic synthesis took a long time to achieve. It was only in the late 1930s that it was employed in direct additions to multiple bonds in alkenes and alkynes (see ref. 147). The industrial use of AHF in conjunction with antimony halides to effect halogen exchange was mentioned above, but (as indicated earlier for the synthesis of aromatic nuclear fluorides) most research workers disliked handling it and used antimony fluorochlorides instead. Following Swarts' work however, it was realised in the 1930s that the sequence $ArCH_3 \rightarrow ArCCl_3 \rightarrow ArCF_3$ could be accomplished easily and efficiently with anhydrous hydrogen fluoride alone. Thus, much research was done, both in academia and industry (see refs. 147 and 159), on arenes containing $CF_3$ side-chains. The group was introduced into various ring systems by sequences of the type given above, and standard synthetic procedures were then used to give a wide range of derivatives. Analogues of many dyestuffs were investigated as part of this work. In the distinctive German national flag of the period, the red dye used was reputed to have a $CF_3$-naphthyl skeleton (see refs. 147 and 167).

At the end of the 1930s, it was found that AHF was capable of promoting reactions between isoparaffins and olefins, to give branched-chain hydro-

## A. L. Henne, 1901 - 67

A. L. Henne

Albert Leon Henne, born in Brussels, Belgium, received his Ph.D. (cum laude) from the University of Brussels in 1925. He spent the following year at the Massachusetts Institute of Technology as a fellow of the Belgian–American Education Foundation, but his career as a fluorine chemist started at the Ohio State University where he joined Thomas Midgley, Jr. Together they discovered the modern refrigerants (Freons), chlorofluoro derivatives of methane and ethane. This historical invention (1930) marked a cornerstone which changed fluorine chemistry from a laboratory curiosity to a large-scale industrial subject. Fluorohalocarbons still dominate the fluorine industry as refrigerants, propellants, intermediates for fluorinated polymers (Teflon), inhalation anesthetics (Halothane) and many other products.

The practical applications of fluorine chemistry triggered interest in basic research whose objective was preparation and knowledge of more fluorinated compounds. Henne's merit lies in the development of methodology for the synthesis of fluororganic compounds at the time when only a few fluorinating agents were known. He and his coworkers prepared countless chlorofluoro and fluoro compounds and thoroughly investigated their physical, and physicochemical properties and their chemical behavior. His basic research culminated with the preparation of perfluorinated Grignard reagents which proved to be indispensable for the syntheses of more complex poly- and per-fluoro compounds. His work in fluorine chemistry spans more than a quarter of a century and comprises over 80 concise and matter-of-fact papers and patents of fundamental value.

Being an authority in fluorine chemistry, Henne was very active as a consultant for chemical industry in the years 1941 - 6. He spent several summers teaching at the University of Brussels where he helped establish chemistry courses for the degree in chemical engineering. For that he was decorated by the Belgian Government as Chevalier de Premier Ordre du Roi Leopold II. In 1933 - 7 he cooperated with the University of Cincinnati as a Research Associate. He spent some time as a visiting professor at the University of Colorado (1948), California Institute of Technology (1950), Cambridge University in England (Guggenheim Fellow, 1952) and at the American University in Beirut (1954 - 5). He was married in 1926 to Jeanette Leyder who died in 1951. He later (1961) married Mary Tashtjian.

(Written by M. Hudlicky and based on Henne's obituary written by M. L. Wolfrom and published in *Chemistry Department News*, Ohio State University, Columbus, Ohio, in April, 1968.)

carbons. Thus, the so-called 'HF-alkylation process' was developed, and used during World War II to make large quantities of high-octane aviation gasoline — of inestimable benefit to the war effort of the Allies. This is a good example of the increasing importance of fluorine compounds in the general chemical scene; they may have the ability to catalyse or promote reactions in general chemistry, often very efficiently, or to function as reactive intermediates. In this type of application, the desired product is one that does not have organically-bound fluorine, and in the alkylation process the formation of organofluorides clearly had to be minimised. Further examples of this general type will be mentioned in Chapters 11 and 14.

A brief but useful account [167] of the impact of compounds of fluorine on the organic chemical industry at the time of World War II has been provided by Finger[23]. It describes the alkylation process, and also considers the commercial status of organofluorides at that time, particularly the Freons® and aromatic derivatives, including dyestuffs.

*Serendipity strikes again: the discovery of poly(tetrafluoroethylene)*

Towards the end of the period under review here, a young chemist at Du Pont, R. J. Plunkett, accidentally discovered poly(tetrafluoroethylene) — a fabulous fluorocarbon resin which nowadays touches on peoples' lives in countless ways (see Chapter 11), and, not long after its discovery, proved to be of inestimable value to the Manhattan Project (see Chapter 5). Plunkett was using tetrafluoroethylene (TFE, b.p. −76 °C), obtainable by zinc dechlorination [160] of Freon® 114 ($CF_2ClCF_2Cl$), as a chemical intermediate in a search for new fluorine-containing refrigerants. On 6 April, 1938, whilst cleaning up a supposedly empty storage cylinder which initially had held approximately 1 kg of TFE, and had been stored in Dry Ice, he found it to contain about 11 g of a white solid — the first poly(tetrafluoroethylene) (PTFE). TFE had been stored in several dozen cylinders, and 'spontaneous' polymerisation occurred in many of them.[24] A second cylinder was emptied of TFE on 8 April, and, of the original monomer (850 g), 60 g was recovered as PTFE by removing the valve from the vessel (see Fig. 4.2). A storage cylinder was also sawn in half to recover the PTFE it contained (Fig. 4.3). Subsequent research and development on monomer synthesis, on methods of controlling the polymerisation, and on polymer fabrication techniques (see Chapter 5) led to commercialisation of PTFE by Du Pont in 1948 under the trade name Teflon® [168]. This provided the plastics industry with a material possessing outstanding chemical, solvent and flame resistance, heat stability, lubricity, electrical insulation, weatherability and impermeability to moisture. Spanning, as it does, a working temperature range of near absolute zero to +260 °C, PTFE is truly an amazing substance [169].

## Concluding remarks

By the time World War II began both the aliphatic and aromatic branches of organofluorine chemistry were well-developed sub-disciplines. A

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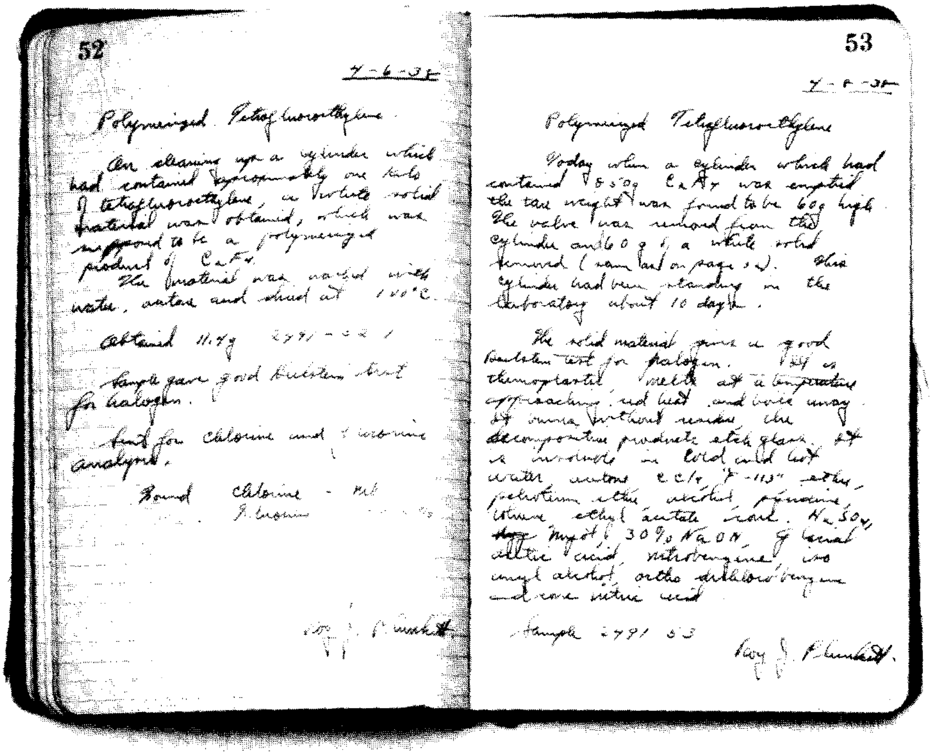
[23] G. C. Finger was a senior scientist at the Illinois State Geological Survey. Most of the fluorspar produced in the U.S.A. originates in Illinois, and the State Geological Survey has long been interested in chemical research based on the State's minerals. Finger and his colleagues worked for many years on aromatic and heterocyclic fluoro compounds [170].

[24] R. J. Plunkett, personal communication.



52

7-6-38

Polymerized Tetrafluoroethylene

On cleaning up a cylinder which had contained approximately one kilo of tetrafluoroethylene, a white solid material was obtained, which was supposed to be a polymerized product of $C_2F_4$.

The material was washed with water, acetone and dried at 100°C.

Obtained 11.4g 2491-52-1

Sample gave good Beilstein test for halogen.

Sent for chlorine and fluorine analysis.

Found Chlorine - nil
Fluorine - [illegible]

Roy J. Plunkett

53

7-8-38

Polymerized Tetrafluoroethylene

Today when a cylinder which had contained 850g $C_2F_4$ was emptied the tare weight was found to be 60g high. The valve was removed from the cylinder and 60g of a white solid removed (same as on page 52). This cylinder had been standing in the laboratory about 10 days.

The solid material gave a good Beilstein test for halogen. It is thermoplastic, melts at a temperature approaching red heat and boils away. It burns without residue, the decomposition products etch glass. It is insoluble in cold and hot water, acetone, $CCl_4$, "F-113" ether, petroleum ether, alcohol, pyridine, toluene, ethyl acetate, conc. $H_2SO_4$, ~~[illegible]~~ Nujol, 30% NaOH, glacial acetic acid, nitrobenzene, iso amyl alcohol, ortho dichlorobenzene and conc. nitric acid.

Sample 2491-53

Roy J. Plunkett.

Fig. 4.2. The two pages from Roy J. Plunkett's laboratory notebook which record the first sightings of poly(tetrafluoroethylene). (Photograph by courtesy of the Du Pont Company.)

Fig. 4.3. Dr. R. J. Plunkett (right) and his technician Jack Rebok (left) recovering PTFE from a cylinder used to store $CF_2{=}CF_2$. Robert McHarness (centre) looks on. (Photograph by courtesy of the Du Pont Company.)

flourishing industrial base had been established, particularly in the aliphatic area, and active research groups were rapidly extending the frontiers of knowledge over the whole field. Only in the control of C—F bond formation duing reactions involving elemental fluorine was the position still uncertain, and this was to be rectified dramatically within the next few years.

## Acknowledgements

We gratefully acknowledge assistance from Professor H. G. Viehe of the University of Louvain for providing some information about F. and T. Swarts, from Dr. E. A. Tyczkowski of the Armageddon Chemical Co., for information about L. A. Bigelow, from Dr. J. M. Hamilton formerly of the Du Pont Co. for details about the early work on Freons® and from Helen R. Kirch of Du Pont's Public Affairs Dept. for supplying information and photographs relating to the discovery of Teflon®.

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