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Review

Footsteps of a fluorine chemist

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Free radicals

Dedicated to the memories and magnificent achievements of the late Professors Neil Bartlett, Colin Tatlow, and Lev Yagupolskii.

ABSTRACT

A review of how and why work in organofluorine chemistry developed in the group over the career of Professor Chambers is presented, based on a Plenary Lecture presented in the Moissan session at the 19th International Symposium on Fluorine Chemistry, August, 2009.

Contents

1. Introduction

This is a very broad review, based on a Plenary Lecture presented at the 19th International Symposium on Fluorine Chemistry, held at Jackson Lake Lodge, Wyoming, USA, August, 2009. It is hoped that the reader will be interested in some of the factors that have influenced the direction of our work in Durham and the intention is to highlight some of the outcomes that we consider to be of general interest. No predictions for the future will be made, beyond stating that the subject of Organofluorine Chemistry is in excellent young hands.

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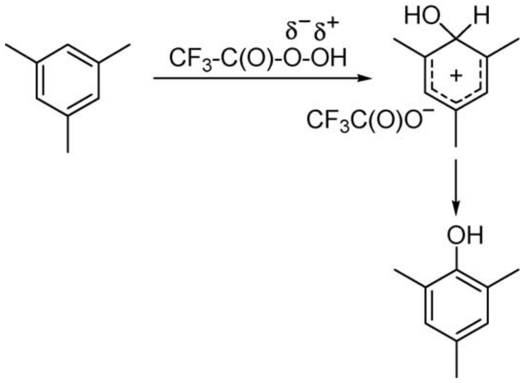

Fig. 1. Electrophilic hydroxylation [1].

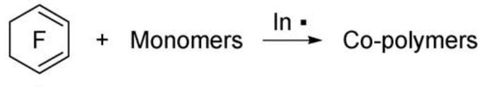

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Fig. 2. Polymers [2].

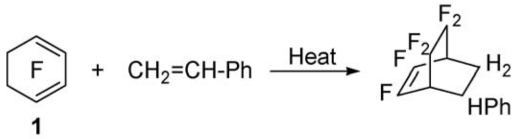

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Fig. 3. A Diels–Alder reaction of a perfluorinated diene [3].

Some of the influences and stimuli that have led us in our research interests and activities include the following:

- People and places (even competitors have had major effects) with, of course, outstanding co-workers having the greatest influence.
- Much of our work in synthesis has been mechanism led because, it was an exciting period at the beginning of RDC's career, when 'lasso chemistry' was ending and mechanistic understanding was unfolding, to provide models on which modern organic chemistry is now based. Consequently, integration of the chemistry of organofluorine compounds into mechanistic models was a major task for workers in the field.
- Inevitably, reactive intermediates featured highly in many people's interests during this period, including our own.
- There have been various concepts that we have pursued, such as 'mirror–image chemistry', or 'the use of the C–H bond as a functional group', but curiosity and serendipity are important in fluorine chemistry in particular, because it is usually difficult to anticipate much of the chemistry of such novel systems.
- If questions and problems are not continuously posed, then the solutions are not recognized when they come along. Regarding luck, the comment of a celebrated golfer is relevant "The more that I practice, the luckier I get".
- Last, but by no means least, have been our contacts with industry, which have been wholly stimulating and we do not see any divide between chemistry in Industry and in Academia, except that Industry usually poses the more difficult problems.

2. The early years

Starting in 1956, RDC worked for his Ph.D. with Dr. Ken Musgrave as his supervisor and then two problems were set: the first being to establish that peroxytrifluoroacetic acid acts as an electrophilic hydroxylating agent in reactions with aromatic systems (Fig. 1) [1]. The project may seem obvious at this time but it was the first such case to be established.

The second project was to make polymers for the Ministry of Defence, starting from perfluorocyclohexa-1,3-diene (**1**) (Fig. 2) a diene that had been made at the University of Birmingham, with whom we were collaborating. We established that the diene itself did not homopolymerise, using free-radical initiators, but it formed co-polymers with a wide variety of monomers. However, at that time we lacked interrogation techniques for polymers and, essentially, we were unable do little more than admire the samples.

Perhaps the most important development that emerged was the first Diels–Alder reaction of a perfluorinated diene (Fig. 3) [3]. This is an excellent example of a reverse-polarity system, with the diene having the electron-withdrawing substituents.

These studies sparked our interest in free-radical chemistry (see later) where there seemed to be enormous potential in the use of the C–H bond as a functional group, for reactions with fluorinated alkenes especially. From an experimental point of view the project encouraged the development of vacuum techniques, acquired from Professor Geoffrey Coates, our eccentric but enthusiastic Head of Department. At the time, it was unusual for organic chemists to use vacuum systems but we have found these techniques hugely effective for our needs. Also, we developed our use of autoclaves, albeit using equipment that would be, correctly, considered unsafe by the standards of today. In addition, we developed the use of preparative scale g.l.c. for the isolation and purification of compounds, from mixtures, but the displacement of packed columns by capillary g.l.c. columns appears to have led to the demise of this technique.

In 1959, Dr. Howard Clark, an organometallic chemist (who later became President of the of Dalhousie University) working at U.B.C. in Vancouver, offered RDC a Post-Doctoral position, funded by the US Navy, to work on fluorocarbon derivatives of tin, as potential anti-fouling agents. The offer was eagerly accepted. Also, RDC and his wife Anne gladly accepted the offer of temporary accommodation in the home of Neil and Chris Bartlett (we all hailed from the North East of England), while an apartment was sought, and we all became lasting friends. RDC shared a laboratory with Neil, Dr. Chris Willis (who later moved to London Ontario), and Dr. Ron Cavell (a graduate student at the time, who moved to a faculty position at Edmonton). Memories of Neil Bartlett, a superb experimentalist, burning platinum in fluorine to give PtF_6 are still vivid, as well as the alarming realization that a large cylinder of fluorine was situated in the path between the only door of the laboratory, and the bench of RDC.

RDC's free-radical experience turned out to be useful as, with Chris Willis (an outstanding experimentalist), we developed a free-radical route to trimethyltrifluoromethyltin (**2**), from hexamethyldi-tin (Fig. 4) [4]. The reaction was efficiently initiated by U.V. light, and was an early example of the use of organo-tin radicals in synthesis. One of the curious reactions of (**2**) is the cleavage of trifluoromethyl by boron trifluoride; the trifluoromethyl group acts as a pseudo-halogen but initial attack by the electrophile must surely occur on the electron pairs of fluorine, followed by migration to boron, rather than direct electrophilic attack on the highly electrophilic carbon of trifluoromethyl.

3. A return to Durham

In 1960, RDC accepted an offer of a Lectureship back in Durham, even though it meant leaving Vancouver, many friends, and the

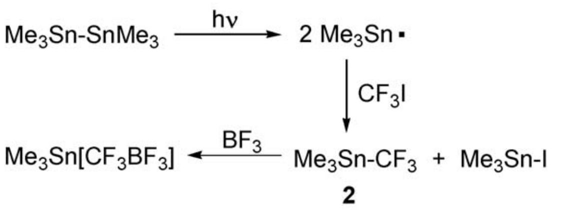


Fig. 4. Organometallic chemistry in Vancouver [4].

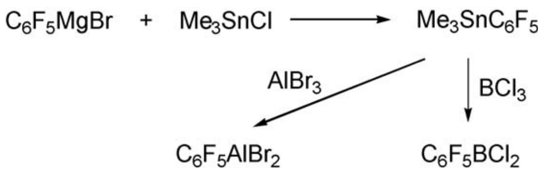


Fig. 5. Pentafluorophenyl organometallic compounds [6,7].

project; he re-joined the now Professor Ken Musgrave (in an exciting new building) for what transpired to be, many satisfying years of fluorine chemistry.

In Vancouver, RDC had developed an interest in fluorocarbon boron compounds, trifluoromethyl-boron compounds being unstable due to migration of fluorine from carbon to boron, and it was anticipated that perfluoroaryl-boron systems would be more stable. This proved to be the case and it was the beginning of a new field of activity (Fig. 5) [5,6]. Pentafluorophenyl-organometallics had not been explored beyond the report by other workers of pentafluorophenyl-silicon and -phosphorus derivatives via the Grignard reagent [7]. Subsequently, we made pentafluorophenyl-tin and -mercury derivatives and cleavage of these systems with boron- and aluminium-halides gave the first stable fluorocarbon derivatives of these elements. We reported that pentafluorophenylaluminium halides were found to be polymerisation catalysts [8] but this attracted no interest at the time, although subsequent patent applications were made, many years later. The field of pentafluorophenyl derivatives of the elements rapidly grew [7] and the group eventually concentrated on other areas.

The group had an interest in fluorocarbon iodides but these were unavailable commercially, in the U.K. at that time. Consequently, we developed a route to some of these compounds by adding the elements of IF to fluorinated alkenes, using a stoichiometric mixture of iodine and iodine pentafluoride, Fig. 6, [9]. For example, the new compound 2-iododoperfluoropropane, was obtained from hexafluoropropene. This methodology turned out to be more important than we realized at the time because iodopentafluoroethane, which has been manufactured for many years using this process, is used as a telogen in reactions with tetrafluoroethene as a step in the manufacture of highly efficient straight-chain surfactants. ICI were offered the opportunity to patent our work on preparation of iodides but declined the offer! Fortunately, we later developed a close working relationship with the company in other areas, thus making such oversights much less likely.

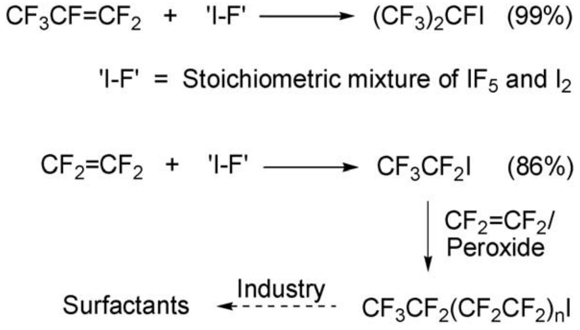


Fig. 6. A simple route to fluorocarbon iodides [9].

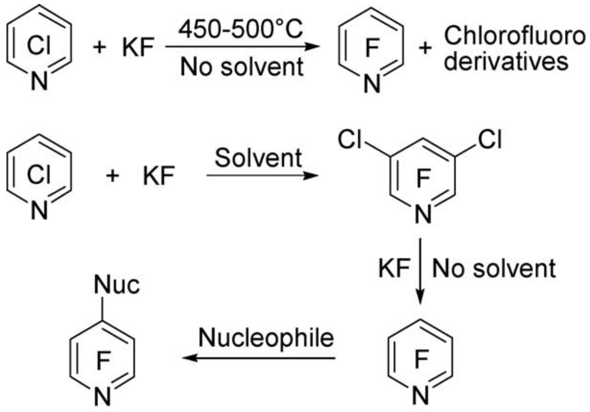


Fig. 7. Early developments in the synthesis of fluorinated heterocycles [11].

In the early years, we began our work on highly fluorinated heterocycles; pentafluoropyridine was known but via a low yield process involving electrochemical fluorination, followed by defluorination of the intermediate piperidine derivative [10].

We adopted a more traditional approach (Fig. 7) [11], using the reaction of potassium fluoride with pentachloropyridine which, itself, was extremely difficult for us to prepare, although fortunately, it soon became commercially available. Using conditions that Vorozhtsov and co-workers had used successfully for the analogous synthesis of hexachlorobenzene [12] we were able to make pentafluoropyridine from the pentachloro derivative, using an autoclave at high temperature and without a solvent. Using a solvent, reaction stopped at the dichlorotrifluoro derivative (Fig. 7) and this compound was used as the starting material for Dow's route to their herbicide, Starane. Pentafluoropyridine undergoes attack by a wide range of nucleophiles and, with minor exceptions, leads to exclusive attack at the 4-position which, as we will see, arises because this maximizes the number of activating fluorine substituents in the ring.

Using the two-step process of first, making the perchloro compound and then reacting the perchloro derivatives with potassium fluoride, either in solution, or without a solvent but at higher temperatures, then a range of new heterocyclic systems have been made in this way (Fig. 8) [13]. Indeed, the most difficult part of the process was preparation of the perchloro derivatives which in most cases were unreported. It is interesting to note that the chemistry of these perchloro systems is little explored and this stems from the difficulty in establishing the structures of products formed. Carbon-^{13}NMR spectroscopy is of limited application but perhaps the advent of relatively routine single crystal X-ray crystallography may now open up the subject. All of the perfluorinated heterocycles are susceptible to nucleophilic attack and the chemistry of these systems is under active investigation to this day.

There is a mirror–image relationship (Fig. 9) between the chemistry of unsaturated fluorocarbons and that of the corresponding hydrocarbons, a simple concept but one that has taken us in many directions over the years [13]. Thus, the fluorocarbons are reactive towards nucleophiles, in contrast to the familiar reactions of arenes and alkenes. While reactivity and orientation rules for

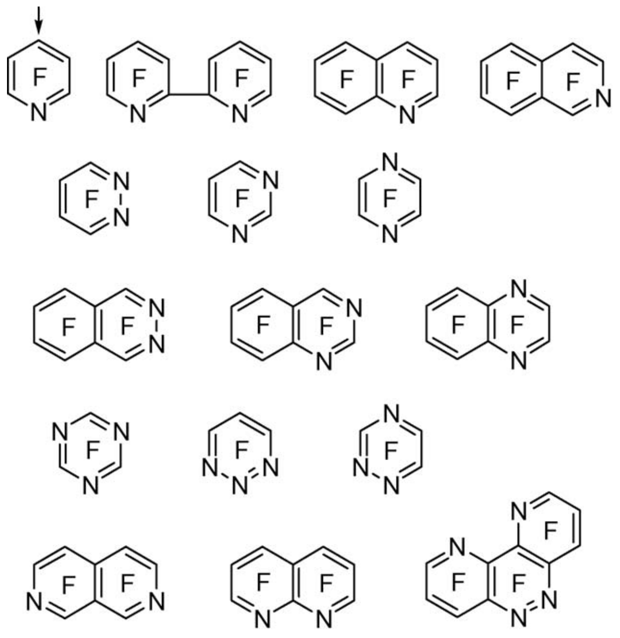


Fig. 8. Some syntheses, using KF [13].

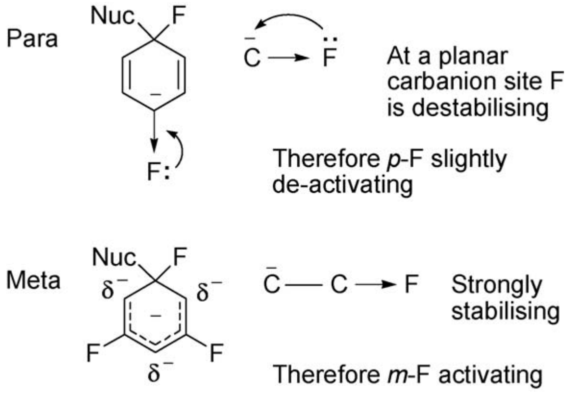


Fig. 10. Substituent effects of *meta*-F and *para*-F [13,14].

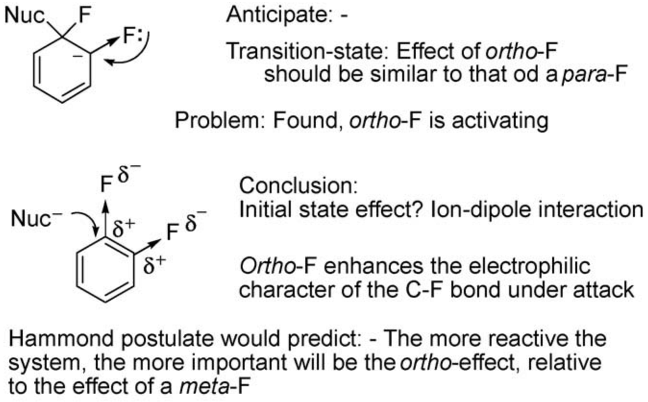


Fig. 11. Effect of *ortho*-F [14,15].

electrophilic substitution are taught to us in our chemical infancy, we did not have an understanding of the factors that effect orientation and reactivity in unsaturated fluorocarbons. For example, pentafluorobenzene derivatives react with a variety of nucleophiles to give predominantly 4-attack (Fig. 9) and this is the case with both electron donating (deactivating) and electron-withdrawing groups (activating) present [13].

In order to provide more understanding, we set out (with our colleague, the late Professor Lyn Williams) to establish the separate effects of fluorine as a substituent in the ring, at positions that are *ortho*-, *meta*-, and *para*- to the site of attack by a nucleophile (Figs. 10–12) [14,15]. This was achieved by comparison of rate constants for systems that differed only in having H or F at the appropriate positions in the ring. Using this approach, we were able to establish the following: that a fluorine atom which is situated *para*- to the position of nucleophilic attack is slightly deactivating with respect to having H at the same position; a fluorine atom that is *meta*- is strongly activating; and, surprisingly, one that is *ortho*- is *activating*. The effects of *para*- and *meta*-F substituents are relatively easy to understand on the basis of the knowledge that we have about the influence of F on the stabilities of carbanions. *Para*-F is attached to what is, in effect, a planar developing carbanion and we know that in such systems, e-pair repulsion effectively negates the inductive stabilization by F. In contrast, a *meta*-F is adjacent to a developing carbanion and is therefore strongly stabilizing because e-pair repulsions fall off rapidly with distance.

However, the observed activating effect of *ortho*-F (Fig. 11) is more problematic because, intuitively, we would anticipate an effect similar to that of a *para*-F and this would undoubtedly be the case if we only needed to consider the relative stabilities of corresponding Meisenheimer complexes as models for the transition states but, clearly, there must be another factor involved. In order to account for this experimentally observed activating effect of *ortho*-F, we have found it necessary to incorporate a significant polar effect; that is, where the effect of an *ortho*-F enhances the already electrophilic character of the carbon under attack and this dipole encourages the approach of the nucleophile. It is necessary to emphasise this point because some workers are still ignoring this experimentally observed activating effect of

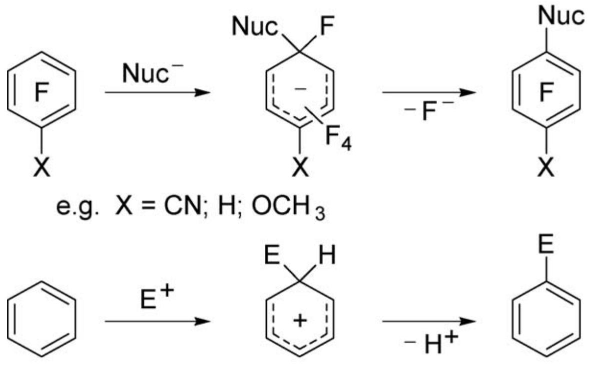
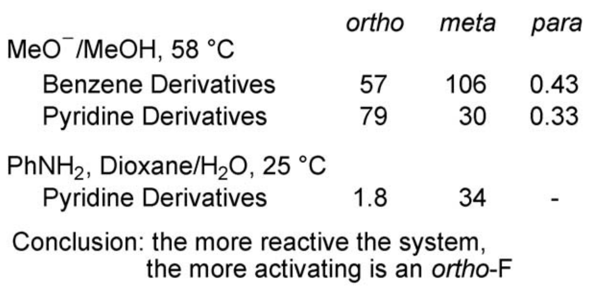


Fig. 9. A mirror–image relationship.



	ortho	*meta*	*para*
MeO^-/MeOH, 58 °C			
Benzene Derivatives	57	106	0.43
Pyridine Derivatives	79	30	0.33
$PhNH_2$, Dioxane/H_2O, 25 °C			
Pyridine Derivatives	1.8	34	-

Conclusion: the more reactive the system, the more activating is an *ortho*-F

Fig. 12. Comparisons of k_F/k_H values [16].

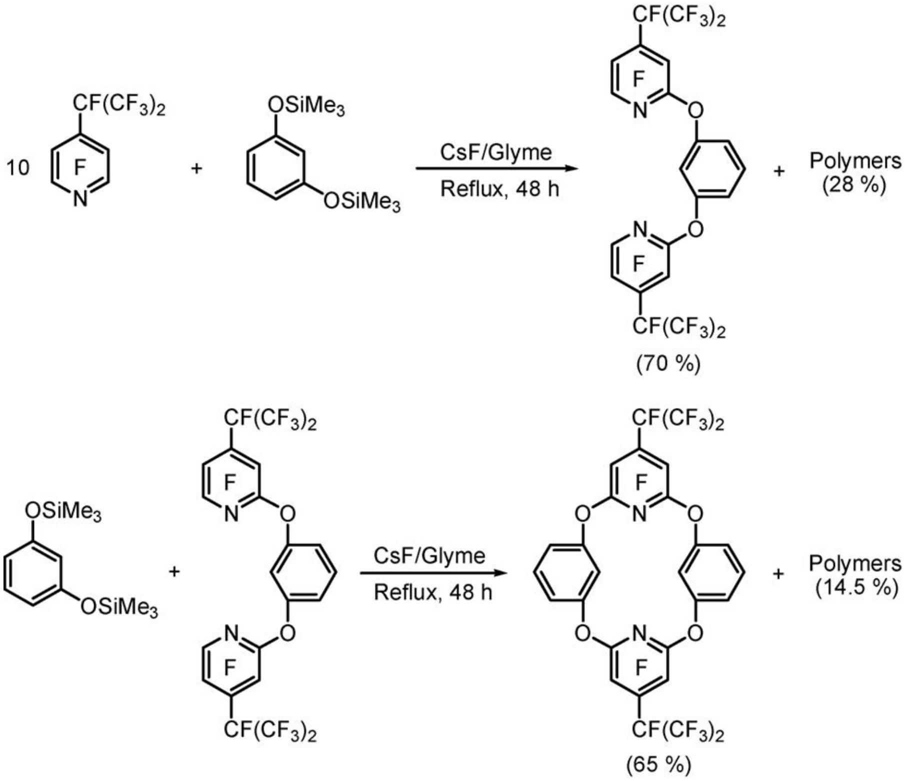


Fig. 13. Formation of macrocycles [17].

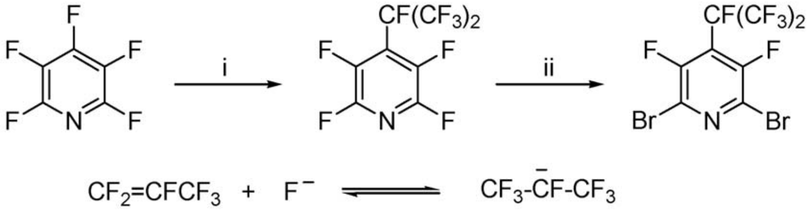
ortho-F by simply calculating relative stabilities of intermediate Meisenheimer complexes, to account for orientation of substitution and this is clearly invalid.

If this polar effect is the real source of *ortho*- activation, then the Hammond Postulate would predict that the polar effect (Fig. 11) would be more important for the more reactive systems, that is, where the transition state is early and resembles the initial state: thus the more reactive the system, the more important should be the *ortho*-effect, relative to the effect of a *meta*-F and this is what we observe Fig. 12, [16]. For reactions of methoxide in methanol, going from benzenoid systems to more reactive pyridine derivatives, then we observe that *ortho*-F becomes more activating than a *meta*-F, whereas for the much less reactive aniline, activation by an *ortho*-F virtually disappears, thus consistent with our model. Therefore it is clear that at least the gross factors affecting the orientation of nucleophilic attack in these systems is understood, i.e. attack occurs in a way that maximizes the activating effects of fluorine substituents in the ring.

If, however, we block attack at the most reactive 4-position in a polyfluoropyridine, in this case by a perfluoroisopropyl group, which we will return to, then there is the opportunity to form macrocycles- by nucleophilic attack at the 2,6-positions and indeed, macrocycles are formed in surprisingly good yields. In the case shown in Fig. 13 [17], the di-anion derived from resorcinol reacts to give an intermediate which may be isolated; further reaction of this intermediate with the di-anion then gives a 16-membered ring system. Complexes of the macrocycle with metals are formed and, curiously, also with fluoride ion.

The introduction of a perfluoroisopropyl group was referred to above and this is achieved by trapping the anion that is derived from hexafluoropropene by additions of fluoride ion, giving the starting material that is indicated in Fig. 14 [19]. We had earlier demonstrated that this is a general process, that works with other perfluorinated-alkenes and -heterocycles (see later), introducing different fluoroalkyl groups, etc., and we like to think of the process as the negative equivalent of Friedel–Crafts reactions [18,20].

Consequently, different fluoroalkyl groups may be introduced and we can also easily replace F by bromine, using the superacid mixture of hydrogen bromide and aluminium tribromide. This



$$CF_2{=}CFCF_3 + F^- \rightleftharpoons CF_3\text{-}\bar{C}F\text{-}CF_3$$

Reagents and Conditions: i, $CF_2{=}CF\text{-}CF_3$, tetrakis(dimethylamino)ethylene, 60°C;
ii, $AlBr_3$ (2.2. eq.), HBr (2.2 eq.), 160°C, 48 h.

Fig. 14. Multisubstituted pyridine derivatives [17,18].

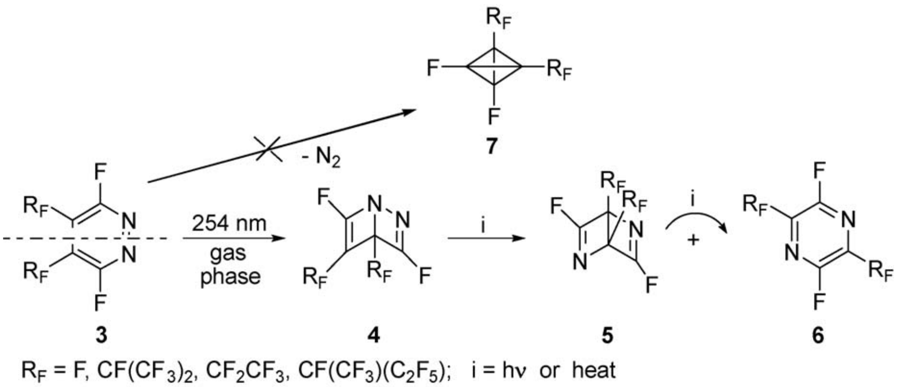


Fig. 15. Fluorocarbons for photochemistry [21].

availability of bromo derivatives enables us to explore platinum chemistry of these systems, but this is discussed elsewhere [19].

4. Photochemistry

The strength of the carbon fluorine bond enables fluorocarbon systems to be used to great advantage in photochemistry, because fewer side-reactions occur than in studies with corresponding hydrocarbon derivatives. This is especially the case in studies of skeletal rearrangements. We entered the area via pyridazine derivatives (**3**) (Fig. 15) that contain perfluoroalkyl groups; for example at the 4,5-positions [21]. Our aim was to eliminate nitrogen from these systems and produce either cyclobutadiene derivatives or perhaps a tetrahedrane (**7**). Maier and Pfriem [22] had made tetra-*tert*-buyltetrahedrane and we were hoping that the fluorocarbon groups might exercise the so-called 'corset effect' that Maier proposed to account for the stabilizing effect of *tert*-butyl groups on the tetrahedrane system [22]. On irradiation, however, instead of loss of nitrogen, we observed a quite dramatic rearrangement; the product was a pyrazine derivative, that is, where the nitrogen atoms and the perfluoroalkyl groups had changed relative positions from being *ortho*- in the starting material, to *para*- in the product. Remarkably, this amounts to a rearrangement where one half of the molecule is formally rotated through 180° with respect to the other half. In summary of this work: we isolated a valence isomer (**4**), corresponding to the substitution pattern of the starting material, i.e. where only the π-system had changed. Then, we found that this isomer rearranged on passing through a gas chromatography column to give another valence isomer (**5**), which was also isolated and characterized. The driving force for this rearrangement is to remove the weak nitrogen–nitrogen bond. Finally, the valence isomer (**5**) was converted to the corresponding pyrazine product (**6**). The significance of all of our studies in this area lies in the fact that there had been much interest in photochemically induced aromatic rearrangements. The intermediacy of valence isomers in these processes had been postulated but not isolated and characterized. So, it was possible to establish each stage of this interesting process (Fig. 15) where, for the first time, the clear relationship between the formation of intermediate valence isomers and skeletal rearrangements was established.

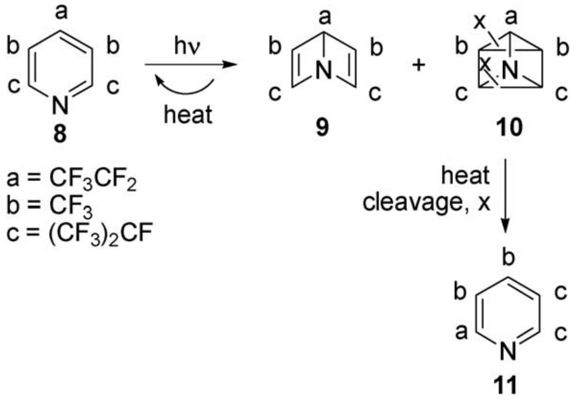


Fig. 16. Rearrangements via azaprismanes [24].

The group of Haszeldine and co-workers [23] had shown that azaprismanes may be obtained from perfluoroalkylpyridine derivatives and we set out to detect and identify rearrangements corresponding to those observed for the pyridazine system. We constructed a system with extensive substituent labeling by starting with perfluoro-3,5-bistrifluormethylpyridine then, by employing the Negative Friedel–Crafts chemistry that was mentioned above, we introduced a pentafluoroethyl group at the 4-position and then perfluoroisopropyl at the sterically less demanding 2,6-positions (Fig. 16) [24]. Photolysis led to a *para*-bonded isomer of the starting material, as well as azaprismanes. As an example, heating one of the azaprismanes (**10**) gave the final product (**11**) with a changed substitution pattern from that of the starting compound, which is accounted for by cleavage of the azaprismane (**10**) in the manner shown. So, again, rearrangements were established and the intermediate valence isomers were isolated on the way.

We did eventually succeed in eliminating nitrogen and generating an azete, but this was achieved by starting with the 1,2,3-triazine (**12**) shown in Fig. 17 [25]. Photolysis occurred by elimination of nitrogen and we were able to make a direct observation of the resulting azete by matrix isolation techniques (Dr. C. Ludman); the azete then dimerised on warming, eventually giving azacyclo-octatetraene derivatives, which we were able to isolate, but further photolysis led to a pyridine derivative. It was also possible to trap the azete by furan to give an isolable adduct.

5. Chemistry of perfluorinated alkenes

Our research group has had a long-standing interest in the chemistry of F-alkenes because they are the most readily accessible fluorinated building blocks and, therefore, procedures that convert these systems to synthetically more sophisticated systems are clearly significant. Several people, especially the late Professor Miller, have drawn analogies between the role of fluoride ion in fluorocarbon systems and that of the proton in reactions with hydrocarbon systems. Fielding at ICI [26] and Graham [27] at

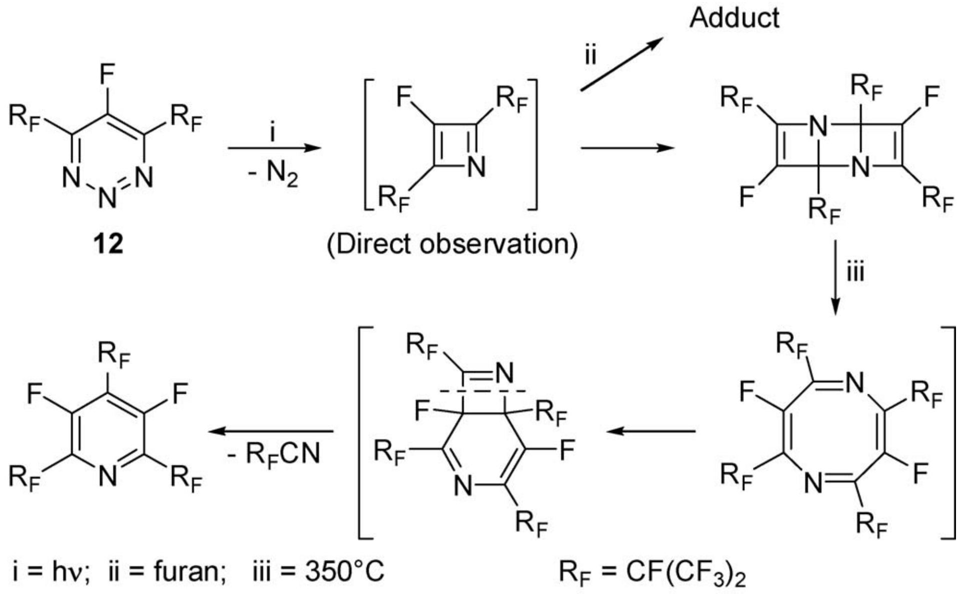


Fig. 17. Formation of azetes [25].

duPont showed that tetrafluoroethene (TFE) can be converted into oligomers, using fluoride ion; carbanions are generated which successively produce dimers, trimers, etc. We were engaged on work with the tetramer (**14**), which we had made by analogous dimerisation of perfluro-2-butene, and this compound interested us because the system is susceptible to nucleophilic attack but can only eliminate fluoride via S_N2' processes. The tetramer became even more interesting when ICI gave us generous samples! Perfluorocyclobutene also gives a dimer (**15**), with fluoride ion, and a comparison of the reactivity of these two systems was especially significant (Fig. 18).

It will be noted that, electronically, these two systems are essentially the same but the cyclic system suffers from severe angle strain. Consequently, we compared the two systems, (**14**) and (**15**), in Diels–Alder additions (Fig. 19) [28] and you see that (**14**) gave no Diels–Alder products whereas (**15**) gave smooth addition in reactions with dienes, under mild conditions, and also an ene-reaction with propene. This is a striking illustration of the effect of angle-strain on reactivity.

However, (**14**) reacted smoothly with diazomethane, giving a dihydropyrazole derivative but we realized that we did not understand the factors affecting addition of 1,3-dipoles to fluorinated alkenes. Subsequently, we established that the reactivity order is that shown in Fig. 20, and that the system with the largest number of perfluoroalkyl groups attached to the double bond is the most reactive, i.e. (**14**) is the most reactive fluorinated alkene of the series. Photoelectron spectroscopy showed a long time ago that F attached to a double bond, or an aromatic system, has little effect on orbital energies, relative to H, whereas a perfluoroalkyl group significantly reduces orbital energies [30]. Therefore, the most reactive member of the series is (**14**), with four perfluoroalkyl groups attached to the double bond, and therefore with the lowest LUMO energy. Note also, that chlorine attached to a double bond is more activating than F.

6. Carbanions and carbocations

The mirror–image analogy that was outlined above would not have been complete without attempting the direct observation of fluorinated carbanions, to mirror the now classical work of Nobel Laureate Professor George Olah. The first system that we had

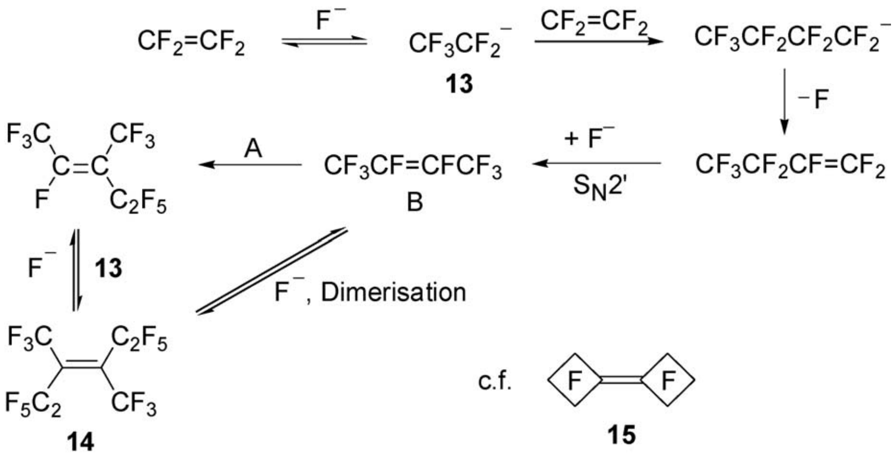


Fig. 18. Formation of oligomers of perfluorinated alkenes [26,27].

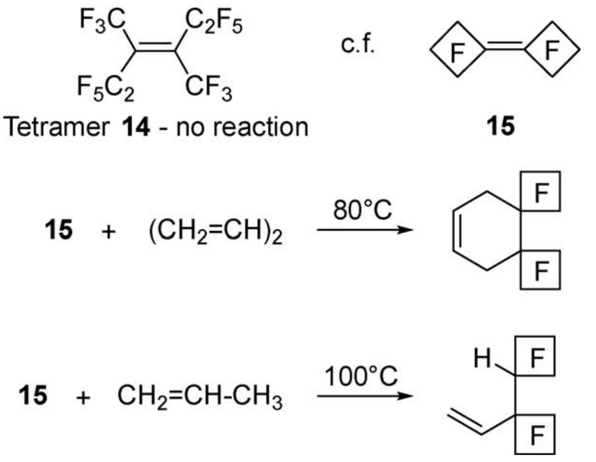


Fig. 19. Effect of angle-strain on Diels–Alder additions [28].

success with was the strained bicyclobutadiene derivative (**15**) (Fig. 21).

Neither of the starting materials, separately, is soluble in DMF but stirring together gave a solution which clearly showed the anion, by ^{19}F and ^{13}C NMR spectroscopy. Quenching with bromine gave the bromide. We went on to observe the F-*tert*-buyl anion and this salt could be precipitated and re-dissolved as the anion. (*Note that this work was undertaken with the utmost care, using breathing apparatus, employing this extremely toxic system.*) We made caesium salts and also compared them with the TAS fluoride derivatives made later by workers at the duPont company [32]. Caesium fluoride was unable to form a salt with compound (**13**), but Farnham and co-workers [32] were able to make the corresponding anion as the TAS salt. This result suggested that the TAS salts would be the more stable but, to our surprise, the caesium salts were shown to be the more stable, as evidenced by variation of line-widths with temperature, in the ^{19}F NMR spectra [31].

It will be noted that all of the long-lived carbanions that have been described, up to this point, have only perfluoroalkyl groups directly attached to the carbanion centre, and the only carbanion system that has been observed, so far, with a fluorine atom directly attached to the charged centre, is that derived from a diene (**16**) (Fig. 22) [33]. Curiously, in this case, trapping with bromine gave a product that arises from a net addition of fluorine and, we presume, this occurs via an S_N2' displacement of bromide which, of course, is not possible for the saturated systems described above.

It has been emphasized that oligomers of fluoroalkenes are potentially important building blocks and the prospect of dienes

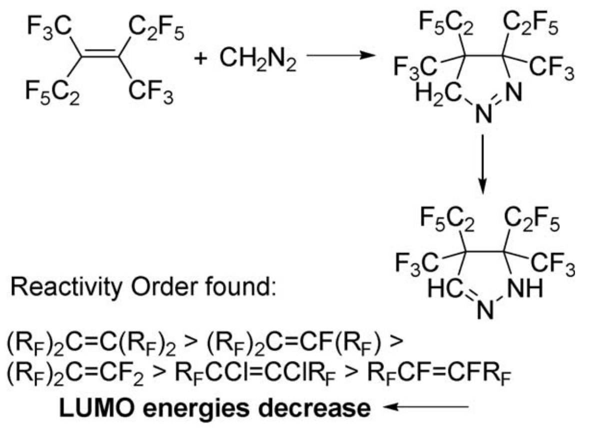


Fig. 20. Factors affecting additions of 1,3-dipoles [29].

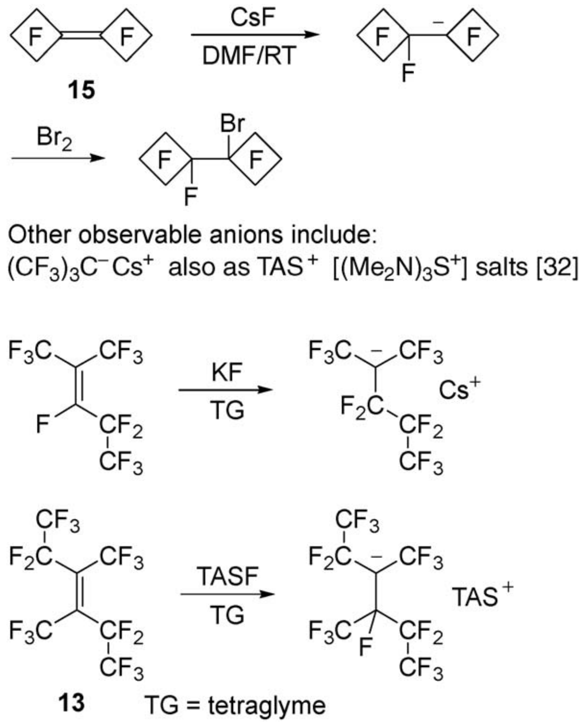


Fig. 21. Direct observation of perfluorinated anions [30–32].

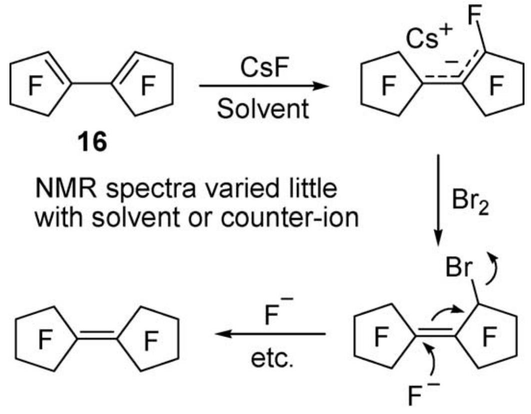


Fig. 22. Addition to a diene [33].

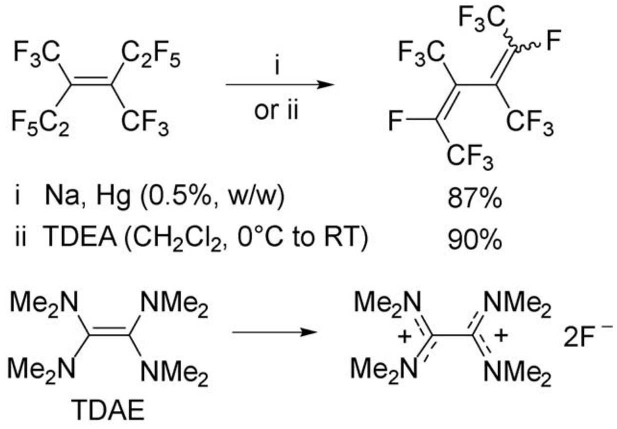


Fig. 23. Formation of dienes by defluorination [34].

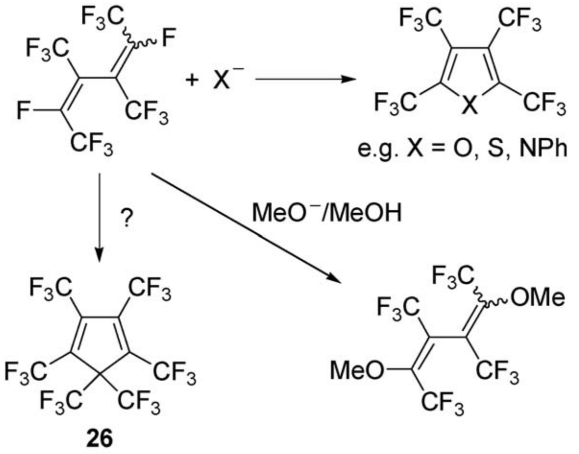


Fig. 24. Reactions with di-functional nucleophiles [34–36].

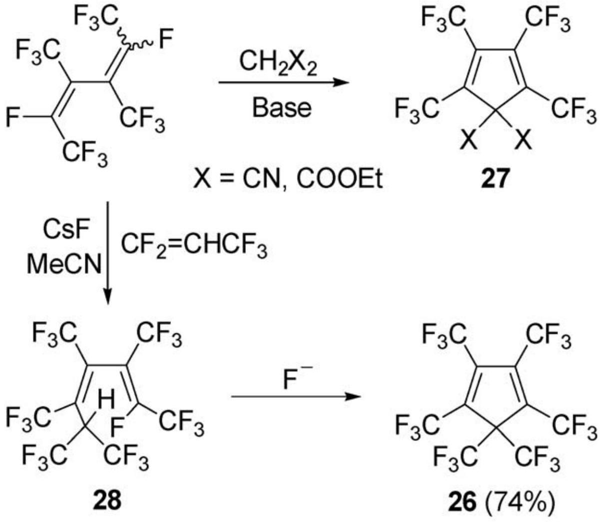


Fig. 25. Cyclopentadiene derivatives [36].

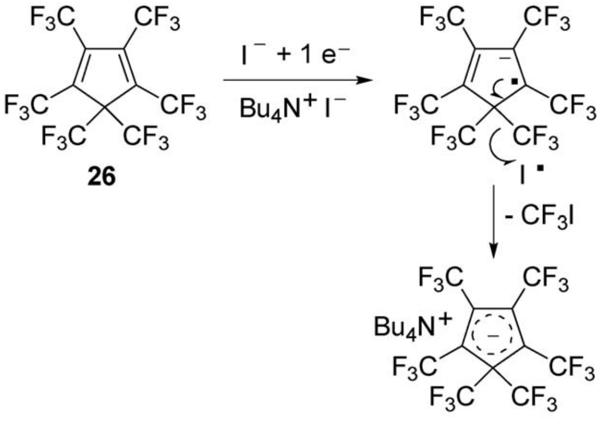


Fig. 26. Cyclopentadienyl derivatives [36].

derived from these oligomers was even more attractive, to provide new di-functional electrophiles. Therefore, we explored convenient methodology for defluorination, to give dienes (Fig. 23) [34]. At first we used sodium amalgam, with very slow addition and continuous cooling; under these conditions defluorination worked well but it was not a safe proposition to scale up this procedure.

Next, we turned to tetrakis(dimethylamino)ethane (TDEA), which has been variously described to have the reducing power of potassium or zinc. Indeed, we found that dropping TDEA into a solution of the tetramer in dichloromethane, worked extremely well and gave a high yield of the corresponding diene, with the fluoride salt being precipitated.

Reaction of the diene with methoxide in methanol gave a product of di-substitution quite easily (Fig. 24) and then water, thiourea, and aniline, which are potentially difunctional nucleophiles, gave the corresponding heterocycles in good yields. So, we then posed the question of how we might synthesise the cyclopentadiene derivative (**26**).

We began with acidic systems like malononitrile and malonic ester, in the presence of a base, and formed the corresponding dienes (**27**) (Fig. 25) [36] relatively easily, and then we utilized fluoride ion chemistry again, to generate the hexafluoropropyl anion, which was trapped by the diene to give an intermediate (**28**), which was not isolated. Instead, this intermediate is very acidic and loses a proton to fluoride ion and the resulting carbanion displaced fluoride on the diene, to give our target molecule (**26**) in surprisingly good yield.

Compound (**26**) is a fascinating diene which has a very low reduction potential because iodide ion transfers an electron and we produce quantitative amounts of iodotrifluoromethane and the pentakis-trifluoromethyl cyclopentadienyl salt, through the loss of a trifluoromethyl radical (Fig. 26) [35]. Indeed, a range of metals reacted with (**26**) to give cyclopentadienyl salts, rather than pi-bonded derivatives, which would have been interesting.

To this point a great deal of chemistry has been discussed that involves carbanions and RDC was much influenced by a sabbatical year in Professor Olah's laboratory, at that time in Cleveland, Ohio. In that laboratory, RDC generated the dimethyl fluoro cation (**29**) (Fig. 27) [36]. There is a huge chemical shift from the neutral

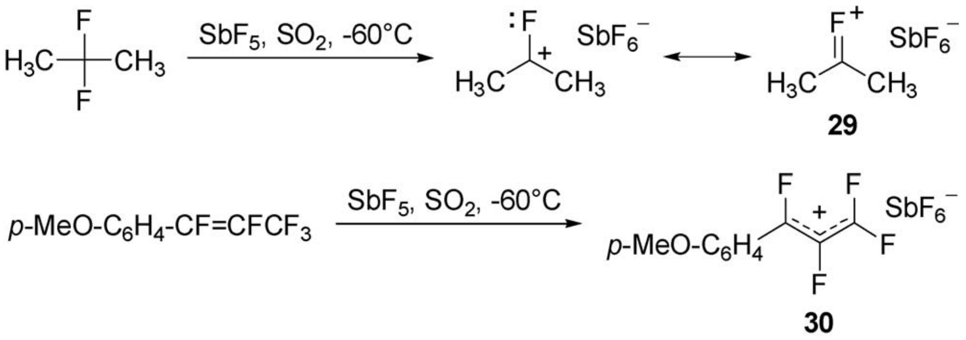


Fig. 27. Positive thinking [37,38]!.

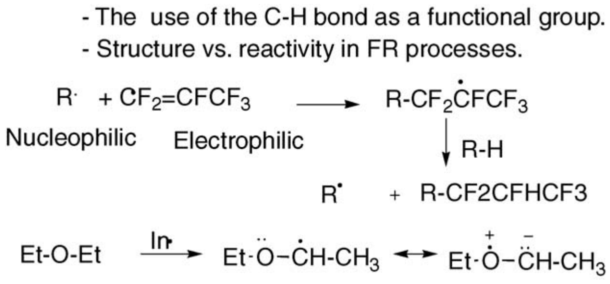


Fig. 28. Nucleophilic radicals [13].

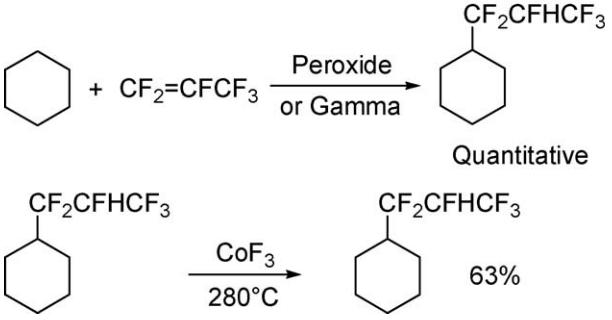


Fig. 29. Hydrocarbons [40].

starting material demonstrating that, perversely, fluorine can have a *stabilizing* influence on carbocation stability, providing that fluorine is actually attached to a centre of high positive charge density, where involvement of lone pairs on fluorine may become operative. This thought led us on to study a variety of multi-fluorinated conjugated systems [38,39] which are very stable and where the first, most simple of the series, is an allyl cation (**30**) (Fig. 27).

7. Free-radical chemistry

It would be remiss not to mention free-radical chemistry (Fig. 28) which has been a continuing interest. Many people have worked on the problem of functionalising hydrocarbons but one of the most efficient processes lies in free-radical reactions with fluorinated alkenes. A hydrocarbon radical is nucleophilic (or high SOMO energy, as is preferred) and, of course, a perfluorinated alkene is very electrophilic (i.e. low LUMO energy), so the reactions are highly efficient. Indeed, the importance of polar effects in reactions of free radicals was recognized early in the work with fluorinated alkenes. In radicals derived from ethers and alcohols this polar effect is enhanced, by the involvement of electron pairs on oxygen, offering direct synthesis of a host of derivatives (Figs. 28 and 29).

Therefore, reaction of a hydrocarbon with a perfluorinated alkene is quantitative, resulting from insertion into a C–H bond (Fig. 29) [40]. These partly fluorinated products can have advantages for making inert fluids because the system is stabilized for further fluorination (Figs. 28 and 29) which occurs at high temperatures, and for which we have employed microreactors.

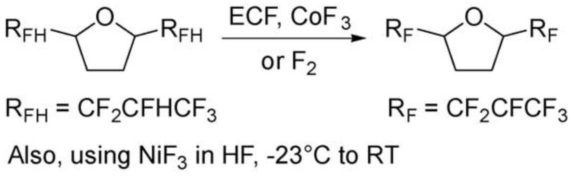


Fig. 30. Ethers [41–43].

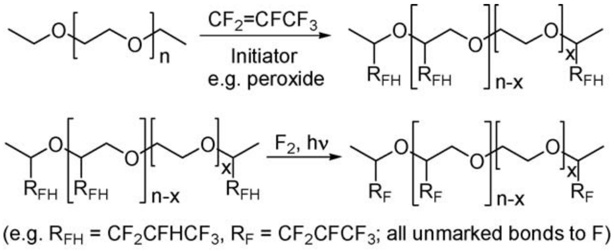


Fig. 31. Polyethers [44].

Ethers form di- and poly-adducts quite readily [41] and some of these adducts are ideal for further fluorination using ECF, cobalt trifluoride, or direct fluorination (Fig. 30) [42].

Professor Neil Bartlett during extended visits to Durham, used some adducts to demonstrate the remarkable reactivity of his nickel trifluoride, which converted various partly fluorinated compounds to perfluorinated systems at astonishingly low temperatures. These results have encouraged us to think of the nickel fluoride as weakly bound fluorine atoms on nickel and we have drawn the analogy with ECF processes [43].

Finally, we applied this approach to polyethers (Fig. 31) [44], giving multi-substituted derivatives, which then were used for further fluorination to give some perfluoropolyethers. Also, some of the adducts were used by ICI as insulators in foam insulation for refrigerators, before they left the business.

8. Elemental fluorine and microreactors

Important areas of activity by the group have not been mentioned in this review because they were covered in previous lectures at the International meetings. We have engaged in close collaboration with the F2 Company, to develop the use of selective direct fluorination in industry and, in the course of this work we developed an interest in micro-reactors for synthesis, especially for the control of fluorine. We have summarized our efforts in both of these areas [45–47].

There can be no more appropriate end to this review than the words of the great Henri Moissan himself [48] at the end of a lecture presented in London. These words express the author's sentiments exactly.

> "— it is curious to see how many continuous efforts, how many different points of view, are involved in the solution of [one of these] scientific questions; or rather, I should say, to advance one of them, for in reality no subject is ever closed. It remains always open to our successors; we can only add a link to an infinite chain."

Acknowledgement

My sincere thanks to my many talented and industrious co-workers, especially those whose work is described here.

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