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A RATIONALIZATION OF ORIENTATION AND REACTIVITY IN THE NUCLEOPHILIC REPLACEMENT REACTIONS OF AROMATIC POLYHALO-COMPOUNDS

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Abstract—C_6F_5X compounds react with nucleophiles at the position *para* to X in some cases ($X = H, CH_3, NMe_2$, SMe, CF_3), *meta* in others ($X = NH_2, O^-$) and occasionally at both *meta* and *para* in comparable amounts (X = OMe, NHMe); significant amounts of *ortho*-replacement also occur (X = Cl, OMe). These orientations, and those in polychloro-aromatics and polyfluoro-polynuclear aromatics, can be rationalized by considering the relative stabilities of the Wheland-type intermediates involved (I, II, III), provided the halogens are taken as electron-repelling in π-systems. Reactivities can be rationalized if ground state stabilities are considered as well. A number of predictions have been made on the basis of these arguments.

A LARGE number of nucleophilic replacement reactions of C_6F_5X compounds are now known.[1,2] In most cases ($X = H, CH_3$, SMe, CF_3, NMe_2, SO_2Me) the fluorine *para* to X is the main (>90%) one replaced, but in a few ($X = NH_2, O^-$) *meta*-replacement predominates.[3-5] In two cases (X = OMe, NHMe) comparable amounts of *meta*- and *para*-replacement occur. There is, as yet, no completely satisfactory rationalization for these reactions. It has been suggested[1-4,6,7] that the five fluorines direct replacement *para* to X, and that X itself may either enhance this effect or oppose it.

This argument is unsatisfactory in a number of cases, however. For example, chloropentafluorobenzene[8] and pentafluoroanisole[4] give substantially more *ortho*-replacement (about 25% and 15% respectively) than do any of the other substrates (except for certain reactions of pentafluoronitrobenzene—this is discussed later). Again, chloropentafluorobenzene reacts with sodium methoxide much faster than pentafluorobenzene does[9]; this implies that chlorine activates the *para* attack more than hydrogen does. However, pentachlorobenzene reacts with nucleophiles at the position *para* to the hydrogen,[10] which implies the reverse. There is also no real explanation for the preferential attack of nucleophiles on octafluoronaphthalene at the 2-position,[11] or on octafluoroacenaphthalene at the 3,5,6 and 8 positions.[12]

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[1] J. C. Tatlow, *Endeavour* **22**, 89 (1963).

[2] J. G. Allen, J. Burdon and J. C. Tatlow, *J. Chem. Soc.* 1045 (1965) and other parts in this series.

[3] G. M. Brooke, J. Burdon, M. Stacey and J. C. Tatlow, *J. Chem. Soc.* 1768 (1960); J. G. Allen, J. G. Burdon and J. C. Tatlow, submitted to *J. Chem. Soc.*

[4] J. Burdon, W. B. Hollyhead and J. C. Tatlow, submitted to *J. Chem. Soc.*

[5] L. A. Wall, W. J. Pummer, J. E. Fearn and J. M. Antonucci, *J. Res. Natl. Bur. Stand.* **67A**, 481 (1963);

[6] G. M. Brooke, J. Burdon and J. C. Tatlow, *J. Chem. Soc.* 802 (1961).

[7] D. J. Alsop, J. Burdon and J. C. Tatlow, *J. Chem. Soc.* 1801 (1962);

[8] G. M. Brooke, R. D. Chambers, J. Heyes and W. K. R. Musgrave, *Proc. Chem. Soc.* 213 (1963).

[9] J. Burdon, W. B. Hollyhead, K. V. Wilson and C. R. Patrick, submitted to *J. Chem. Soc.*

[10] A. F. Holleman, *Rec. Trav. Chim.* **39**, 736 (1920).

[11] B. Gething, C. R. Patrick and J. C. Tatlow, *J. Chem. Soc.* 186 (1963).

[12] J. Burdon, D. Harrison and R. Stephens, *Tetrahedron* **21**, 927 (1965).

Wall[5] has suggested that the nucleophile plays a dominating role in determining orientation; while this is true in a few cases, it is not in general.

It is the purpose of this paper to show that all these orientations can be rationalized by considering a simple picture of the relative stabilities of the transition states concerned, and that the reactivities of the fluoro-aromatics can also be rationalized by considering the relative ground state stabilities as well. The reactivities of the polychloro-aromatics will not be considered as there is the possibility of steric interactions between *ortho*-chlorines in both ground and transition states.

Ground state stabilities

Thermodynamic evidence[13] suggests that an increase in fluorine substitution decreases the stability of an aromatic compound. (Stability is used here in an absolute sense; one compound is more stable than another if more free energy is required to decompose it into its constituent atoms in their standard states. In the present case this ought to be modified to take solvation effects into account; to a first approximation these can be assumed to be equal for all the substrates.) If this is due mainly to electron-deficiency caused by the electronegativity of fluorine, then C_6F_5X compounds can be placed in an approximate order of stability. Figure 1 gives some examples (this diagram is only a guide to relative stabilities and is not drawn to any scale). To the degree of accuracy required in this paper, all the pentafluorohalobenzenes ($X = F$, Cl, Br, I) will have the same stability; they will be less stable than pentafluorobenzene, which has one less halogen. The actual difference between hexa- and pentafluorobenzene is most probably in the range 1–5 K cals/mole,[13] which is of the magnitude required for the rationalizations discussed in this paper. It is suggested that pentafluoroaniline and -anisole will be more stable than pentafluorobenzene because some of the electron-deficiency caused by the five fluorines can be compensated by mesomeric electron donation by the nitrogen and the oxygen. Pentafluoro-NN-dimethylaniline, however, will be little different from pentafluorobenzene, because steric interactions between the N-methyls and the *ortho*-fluorines bend or twist the NMe_2-group out of the ring plane and hence reduce the mesomeric electron donation[3]; the same effect will occur to a lesser extent with pentafluoro-N-methylaniline[3] and -anisole. Pentafluoronitrobenzene and octafluorotoluene, which have strongly electron-attracting X-substituents, should be of equal or lesser stability than the pentafluorohalobenzenes.

Transition state stabilities

The transition states for the reactions of aromatic polyfluoro- (and polyhalo-) compounds with nucleophiles will be discussed in terms of Wheland-type intermediates (I), as these usually provide good guides to transition states.

The resonance hybrid (II) will be assumed to be the main contributor to this intermediate, with the hybrid (III) of only secondary importance. This assumption receives considerable justification from the results of advanced molecular orbital calculations,[14a] which give the charge density distribution shown in I. Other authors[14b] have also argued that *p*-quinonoid structures (II) are more important than *o*-quinonoid (III) in nucleophilic aromatic substitutions.

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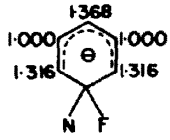
[13] C. R. Patrick, unpublished calculations.

[14a] H. E. Zimmerman, *Tetrahedron* **16**, 169 (1961);

[b] N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.* 1563 (1956).

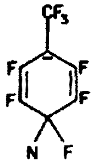
N = Nucleophile



I

II

III



IV

The effect of substituents on the stability of contributors of type II, and to a lesser extent III, will now be considered; this largely resolves into a discussion of the influence of the substituent attached to the carbon bearing the negative charge on the stability of the charge. If a substituent, X, stabilizes the negative charge, then nucleophilic attack will take place at the carbon *para* to it, and to a lesser extent *ortho*; whereas if it destabilizes the charge more than fluorine, then in C_6F_5X compounds *meta* attack will occur. Of course, this approach is an over simplification since many substituents can interact with the π-electrons to form an extended π-system. Nevertheless, a simple qualitative rationalization for these nucleophilic aromatic substitutions is possible if substituents are considered to have only a stabilizing or destabilising influence on intermediates of types II and III. A similar approach has successfully been made by Carrington[15] to the qualitative interpretation of the ESR spectra of aromatic radicals.

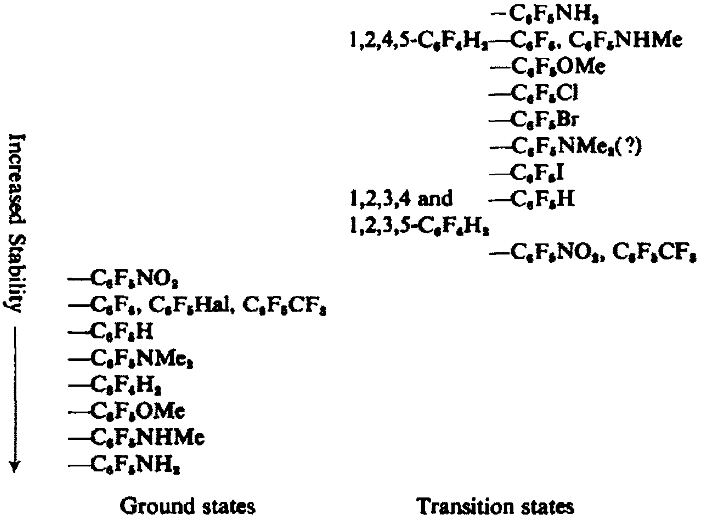


FIG. 1. Relative stabilities of ground states of some C_6F_5X compounds and also of their transition states for reactions (*para* to X) with nucleophiles (not to scale).

The relative stabilities of some transition states for the reactions of C_6F_5X compounds are shown in Fig. 1; in every case the transition state referred to is the one in which the carbon *para* to X is being attacked. The nitro and trifluoromethyl groups will clearly stabilize negative charges on the carbons to which they are attached by inductive effects (cf. IV), and in the former case by delocalization as well. The

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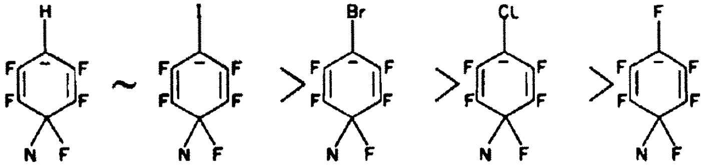
[15] A. Carrington, *Quart. Revs.* 17, 67 (1963).

halogens destabilize a negative charge on the carbon atom to which they are attached, in the order F > Cl > Br > I ~ H. Although this is contrary to the normal electron-attracting behaviour of the halogens, it arises because the negative charge in question is in a π-electron system. Such electron-repulsion (I_π repulsion)[16] by halogens in π-systems, in the order F > Cl > Br > I, has been postulated before[16,17] in the interpretation of the UV spectra of the halobenzenes. It has been suggested that this effect is due either to Coulombic repulsion between the p-electrons on the halogen and the ring π-electrons on the neighbouring carbon,[16] or to unfavourable penetration of filled orbitals containing the same electrons.[17] Hence, the order of stability of hybrids of type II is:



N = nucleophile

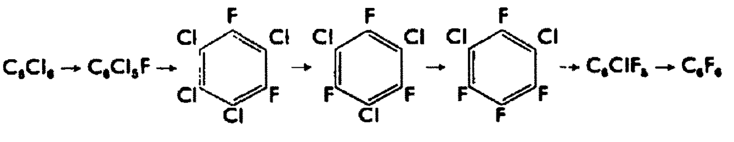
as indicated in Fig. 1. d-Orbital overlap by chlorine, bromine and iodine must therefore be insignificant; there is some justification[18] for neglecting it.

The magnitudes of the I_π repulsive effects of oxygen and nitrogen are not derivable from spectroscopic measurements[17]; they will be taken as decreasing in the order N > O > F. A similar complication arises here as in the ground state argument; steric interactions will reduce the I_π repulsive effect of a nitrogen considerably in pentafluoro-NN-dimethylaniline and to a lesser extent in pentafluoro-N-methylaniline.[3] The same applies to pentafluoroanisole.

Orientation and reactivity

A rationalization for the pentafluorobenzene–pentachlorobenzene–chloropentafluorobenzene anomaly mentioned in the introduction is immediately obvious from Fig. 1. The first two compounds react *para* to the hydrogen and the last *para* to the chlorine because the relative stabilities of negative charges on carbons bearing hydrogen, chlorine and fluorine are in the order H > Cl > F. Chloropentafluorobenzene reacts faster[9] than pentafluorobenzene with nucleophiles because the lesser transition state stability of the former compound is more than compensated by its lesser ground state stability.

A further consequence of the I_π repulsion of chlorine being less than that of fluorine is a rationalization of the path taken by the hexachlorobenzene–alkali fluoride reaction.[19]



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[16] D. T. Clark, J. N. Murrell and J. M. Tedder, *J. Chem. Soc.* 1250 (1963).

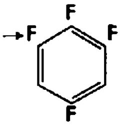
[17] D. P. Craig and G. Doggett, *Mol. Phys.* 8, 485 (1964).

[18] W. Klemperer, *J. Amer. Chem. Soc.* 83, 3910 (1961).

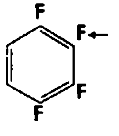
[19] N. N. Vorozhtsov, V. E. Platanov and G. G. Yakobson, *Isv. Akad. Nauk SSR. ser. Khim.* 8, 1524 (1963).

As penta- and hexa-fluorobenzene react at approximately the same rate,[9] the difference in their grounds state stabilities is about the same as the difference in their transition state stabilities.

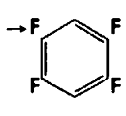
The tetrahalobenzenes reinforce the I_π repulsion argument mentioned in the previous section. The tetrafluorobenzenes react at the arrowed positions[20]; the tetrachloro-compounds behave analogously.[21]



V



VI



VII

In cases V and VI the positions attacked are those which lead to intermediates of type II in which the negative charge is localized on a hydrogen-bearing carbon. With tetrafluorobenzene (VII), there is, of course, no orientation problem, but the compound reacts about 10^3 times more slowly with sodium methoxide than the other two tetrafluorobenzenes do.[22] In this case the intermediate of type II requires that a negative charge be localized on a fluorine-bearing carbon. As the three tetrafluorobenzenes will have comparable ground state energies (Fig. 1), it can be concluded that fluorine does destabilize a negative charge in a nearby π-system, and also that contributors to the transition state of type III are of only secondary importance; if they were equivalent to type II, then the tetrafluorobenzenes should react at comparable rates. The tetrachlorobenzenes behave similarly, although here the relative rates are not accurately known[10,21]; in any case the reactivities of the tetrachlorobenzenes may not exactly parallel those of the tetrafluorobenzenes because of steric interactions between the *ortho*-chlorines. 1,2,3,5-Tetranitrobenzene reacts with nucleophiles with replacement of the 2-nitro-group[23]; this shows that there is nothing peculiar to the 1,2,3,5-arrangement of substituents which might otherwise explain the reactions of the tetrahalobenzenes, and also that the nitro-group is superior to hydrogen in stabilizing a negative charge in a π-system.

The effect of substituents at positions other than those at which negative charges can be regarded as localized has not been discussed. In general, electronegative substituents should stabilize a charge in such circumstances and electropositive ones destabilize it. This should only be a secondary effect, but it necessitates that the transition states for the tetrahalobenzenes be less stable, and hence the compounds less reactive, than the previous discussion implies.

ortho-Replacement in the pentafluorohalobenzenes will now be considered. Isomer distribution in a substitution reaction of any compound depends only on the stabilities of the transition states leading to the various isomers, and not at all on the ground state stability of the substrate. If a substituent X in a C_6F_5X compound had exactly the same effect as a fluorine on the stability of a negative charge on the carbon to which it was attached, then the *ortho*:*meta*:*para* replacement ratio would be the statistical 2:2:1. If, however, the substituent were considerably more effective than

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[20] J. Burdon and W. B. Hollyhead, submitted to *J. Chem. Soc.*

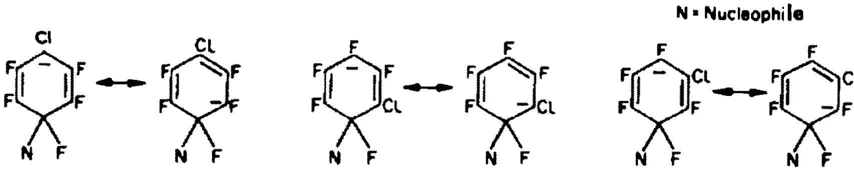
[21] T. de Crauw, *Rec. Trav. Chim.* **50**, 753 (1931).

[22] J. Burdon, W. B. Hollyhead and C. R. Patrick, unpublished.

[23] A. F. Holleman, *Rec. Trav. Chim.* **49**, 112 (1930).

fluorine in stabilizing the charge, then the replacement order would be *para* > *ortho* > *meta*; if the substituent were much less effective the order would be *meta* > *ortho* > *para*. The more nearly equivalent the substituent to fluorine the more nearly these orders would approach the statistical one. In other words, the nearer a C_6F_5X compound is to hexafluorobenzene in the transition state part of Fig. 1, the nearer the isomer distribution will be to statistical; if a compound is below hexafluorobenzene, *para* replacement will exceed such expectations, and if it is above it, *meta* will.

In the reactions of chloropentafluorobenzene with nucleophiles, the intermediate with hybrids (VIII and IX) will be most stable, followed by the X–XI pair, and finally XII and XIII. This arises because of the greater I_π repulsive effect of fluorine compared with chlorine. In order to explain the isomer distribution actually found[8] (ca, 25% *ortho*, 5% *meta* and 75% *para*), chloropentafluorobenzene would have to be placed about 1–2 K cals/mole below hexafluorobenzene in the transition state part of Fig. 1. As the transition state for bromopentafluorobenzene is more stable than that for chloropentafluorobenzene, then there will be even more difference in stability between the bromo-analogues of VIII–IX and X–XI than in the chloro-case. This should lead to even less *ortho* replacement with bromo- than with chloro-pentafluorobenzene; in fact, about 12% is observed.[5,24] As pentafluoroiodobenzene and pentafluorobenzene come lower still in the transition state diagram, they should give even less *ortho*-replacement; in both cases[24,25] less than 5% is formed, although steric influences could affect the iodo-case.



VIII IX X XI XII XIII

By an extension of this argument, pentachlorobenzene should give more *ortho*-replacement, as in fact it does,[10,26] than pentafluorobenzene.

Pentafluoroaniline has a very stable ground state and relatively unstable transition states for either *meta* or *para* attack; it therefore reacts very slowly with nucleophiles, and as the I_π repulsion of nitrogen is greater than that of fluorine, mainly at the position *meta* to the NH_2 group.[3] Pentachloroaniline reacts with ammonia to give tetrachloro-*m*-phenylenediamine.[27] This illustrates the greater I_π repulsion of nitrogen over chlorine; this is directly deducible from the transition state side of Fig. 1 as pentafluoroaniline is higher up than chloropentafluorobenzene. Pentafluoro-NN-dimethylaniline reacts at a similar rate to pentafluorobenzene,[9] and at the position *para* to the NMe_2 group, for the steric reasons discussed earlier.

Since pentafluoro-N-methylaniline and pentafluoroanisole are plausibly placed near to hexafluorobenzene in the transition state part of Fig. 1 (the observed *meta*:*para* replacement ratios determined the exact placings), comparable amounts of *ortho*,

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[24] J. Burdon, P. L. Coe and C. R. Marsh, unpublished.

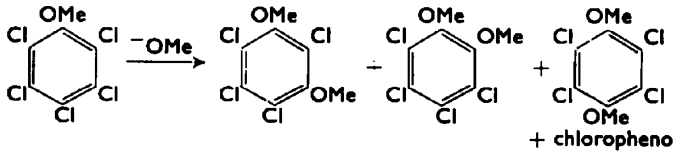
[25] G. M. Brooke, J. Burdon and J. C. Tatlow, *J. Chem. Soc.* 3253 (1962).

[26] L. S. Kobrina, G. G. Yakobson and N. N. Vorozhtsov, *Zh. Obshch. Khim.* **35**, 137 and 142 (1965).

[27] G. G. Yakobson, L. S. Kobrina, T. D. Rubina and N. N. Vorozhtsov, *Zh. Obshch. Khim.* **33**, 1273 (1963).

meta and *para*-replacement should occur, according to the argument advanced above. Pentafluoro-N-methylaniline gives approximately equal quantities of *meta*- and *para*-replacement products with nucleophiles,[3] with the amount of *ortho*-replacement undetermined for experimental reasons, but possibly about 10% of the total product. Pentafluoroanisole gives 50% *para*-replacement, 35% *meta* and 15% *ortho*.[4] In both cases the amount of *ortho*-replacement is lower than expected and a primary steric effect between the incoming nucleophiles and the OMe or NHMe groups is postulated; primary steric effects are well-known[28] in aromatic nucleophilic substitution and the 0·5–1·0 K cal/mole required to bring the *ortho*-percentages up to the *meta* and *para* in the present cases are well in line with the energies actually observed in the other examples.[28] Transition state stabilities alone would imply that pentafluoroanisole and pentafluoro-N-methylaniline had about the same reactivity as hexafluorobenzene, whereas in fact they are both much less reactive; this is due to their much greater ground state stabilities (Fig. 1).

Recent Russian work[26] on polychloroaromatics fits in very well with the rationalizations discussed in this paper. Pentachloroanisole reacts with methoxide with replacement of the *meta*, *ortho* and *para* chlorines in the ratios 70:25:3, respectively.



This is what would be expected from Fig. 1: pentafluoroanisole is higher up on the transition state side than chloropentafluorobenzene. That is, a negative charge on a carbon bearing a chlorine is more stable than on one bearing a methoxyl. In addition, application of the argument advanced in the discussion of *ortho*-replacement in the pentafluorohalobenzenes predicts the correct replacement order: *meta* > *ortho* > *para*. Pentachloroanisole differs from pentafluoroanisole because the I_π repulsions of methoxy, chlorine and fluorine decrease in the order F > OMe > Cl (cf. Fig. 1).

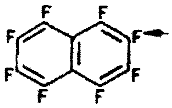
The Russian workers[26] also give a clear example of a steric effect in the polychloroaromatic field; pentachlorobenzene reacted mainly at the position *para* to the hydrogen with ammonia, but mainly at the position *ortho* with the larger dimethylamine. As a difference between these two nucleophiles is not noticeable with pentafluorobenzene (>90% *para* in both cases), steric effects are, as suggested earlier, of considerably more significance in the chloro-field than in the fluoro.

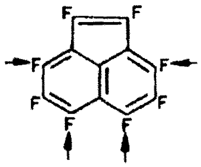
Clearly, none of the arguments in this paper apply to reactions where there is a specific interaction between the nucleophile and the substituent group on the substrate. For example, the high reactivity of amines towards halogen *ortho* to a nitro-group has been attributed[2,29] to hydrogen-bonding between the amine and the nitro-group.

Octafluoro-naphthalene[11] and -acenaphthalene[12] react with nucleophiles at the arrowed positions. It is only by attack at the 2-position of the naphthalene that localization of a negative charge on a *para* carbon bearing a fluorine can be avoided. In the acenaphthalene the 3, 4, and 5 positions are equivalent as regards *para* carbons.

[28] N. B. Chapman and B. Capon, *J. Chem. Soc.* 600 (1957); J. Cortier, P. J. Fierens, M. Gilon and A. Halleux, *Bull. Soc. Chim. Belges* **64**, 709 (1955); C. W. L. Bevan, T. O. Fayiga and J. Hirst, *J. Chem. Soc.* 4284 (1956).

[29] S. D. Ross, *Progress in Physical Organic Chemistry* **1**, 31 (1963).

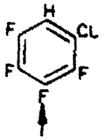




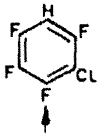
The 3 and 5 positions, however, have only one *ortho* fluorine-bearing carbon, whereas the 4 has two; the 1 postion is difficult to compare with the others on the same basis.

A number of preditions can be made from the theory advanced in this paper. Pentabromobenzene should react at the position *para* to the hydrogen and it should give more *ortho*-replacement than pentachlorobenzene.

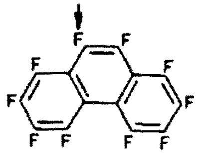
The chlorotetrafluorobenzenes (XIV and XV) should react mainly at the arrowed positions with possibly a small amount of replacement of the fluorine *para* to the chlorine. The bromo-analogues should react similarly, but with slightly more attack at the position *para* to the bromine; the iodo-analogues should give significant amounts of products derived from attack *para* to the iodine and *para* to the hydrogen, although steric hindrance may affect the result with the analogue of XV.

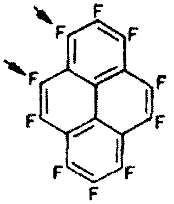


XIV



XV





More tentatively, all the linear polyfluoroacenes (anthracene etc.) should react at the 2-position and perfluoro-phenanthrene and -pyrene[30] at the arrowed positions. The polychloropolynuclear aromatics should react in the same positions as the polyfluoro-ones.

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[30] D. Harrison, M. Stacey, R. Stephens and J. C. Tatlow, *Tetrahedron* **19**, 1893 (1963).