Ipso Substitution in Free-Radical Aromatic Substitution Reactions

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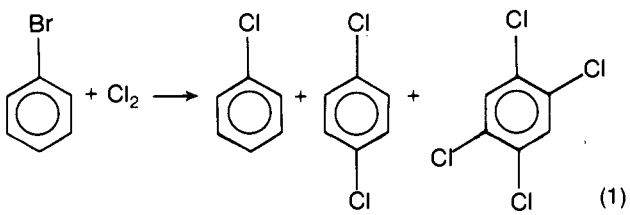
I. Introduction

To most organic chemists, the unembellished phrase, "aromatic substitution reaction", probably implies replacement of hydrogen by some substituent group. Yet replacement of a substituent already present characterizes nucleophilic aromatic substitution reactions.[1] Replacements of substituent groups by electrophilic substitution reactions (for example, protodesulfonation) have been known for many years, but only during the past decade has electrophilic ipso substitution as a mechanism been seriously acknowledged.[2] In spite of recurring examples of ipso substitution in free-radical aromatic substitutions, dating from 1903, advocacy of an ipso intermediate mechanism for free-radical processes has been slower than it was for nucleophilic and electrophilic substitutions. The numerous and varied examples of ipso free-radical substitution which are collected in this article indicate that attack at an already substituted position is likely in free-radical aromatic reactions, just as it is in nucleophilic and electrophilic ones. In considering the possible products from an aromatic substitution reaction, one can no longer confidently discount an already substituted position as a probable site for substitution to occur, whatever the charge type of the reaction.

II. Halogen Exchanges

Halogen exchanges during free-radical halogenations of aromatic substrates have been reported from time to time during the past 89 years. Srpek first reported that chlorination of *p*-bromotoluene at room temperature gave an inseparable mixture of chlorobenzyl and bromobenzyl chlorides and bromides.[3] Other investigators subsequently reported the prosaic chlorination of isomeric bromotoluenes to bromobenzyl chlorides, but Asinger later confirmed the replacement of nuclear bromo by chloro in these reactions.[4] Chlorinations of bromotoluenes with sulfonyl chloride–benzoyl peroxide also led to extensive chlorodebromination; the product mixtures contained bromobenzyl chloride (32–53% yields), chlorotoluene (22–30%), chlorobenzyl chloride (1–2%), and bromobenzyl bromide (9–18%).[5]

Eibner reported the exchange (chlorodebromination) without the accompanying complexity of the methyl side chain; chlorination of bromobenzene, without and (faster) with light, produced chlorobenzene (28% of pure product), *p*-dichlorobenzene (17% maximum), and 1,2,4,5-tetrachlorobenzene (17% maximum) (eq 1).[6] No mention of any bromochlorobenzene was made.



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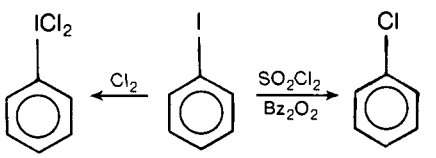
Free-radical chlorodebromination products were produced in high yields from bromobenzene (68%), *p*-bromotoluene (95%), and various bromohalobenzenes (79–80%).[7] These reactions were photoinitiated in refluxing CCl_4 solutions and utilized chlorine gas. In most of them, bromine evolution began immediately. Other investigators have reported a long induction period, however, in CCl_4 at 25 °C.[8]

Miller and Walling established the free-radical (halogen atom) character of the reaction.[9] Confirming the earlier reports of the formation of chlorobenzene from bromobenzene, they showed that the reaction is facilitated by light and inhibited by nitrobenzene, azobenzene, and azoxybenzene. The exchange reaction is about as fast as benzyl H abstraction by chlorine atoms. Yields of chlorobenzene were lower when sulfonyl chloride rather than chlorine was the reagent. Slower bromine exchange was demonstrated by use of ^{82}Br. *p*-Bromonitrobenzene was reported to be unreactive.[9]

Iodobenzene reacts with chlorine to produce iodobenzene dichloride, but chlorodeiodination has been accomplished by use of ICl or sulfonyl chloride–benzyl peroxide as reagent in place of chlorine (eq 2).[10]



(2)

None of the above citations involves the replacement of a halo substituent of lower atomic number by one of higher atomic number. That direction of reaction, which is contrary to expectations based on bond energy data, has been reported for gas-phase bromination of chlorobenzene: low conversions to bromobenzene, dibromobenzenes, and dichlorobenzenes occurred.[11] Rather extensive (5–50%) bromodechlorinations were reported for liquid-phase, photoinitiated brominations of chlorobenzene, *o*- and *p*-dichlorobenzenes, and *p*-fluoro- and *p*-bromochlorobenzenes.[12] Little or no replacements of chloro occurred with *m*-dihalobenzenes when Br_2 was the reagent, but extensive replacement with *m*-, as well as *o*- and *p*-, dihalobenzenes occurred when *N*-bromosuccinimide (NBS) was used as the Br reagent (eq 3). As in the gas-phase brominations,[11] substantial amounts of chlorination products (e.g., dichloro-

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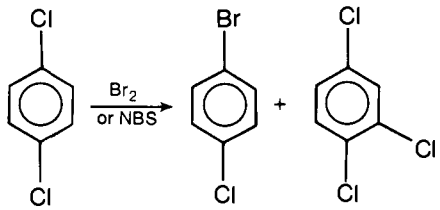
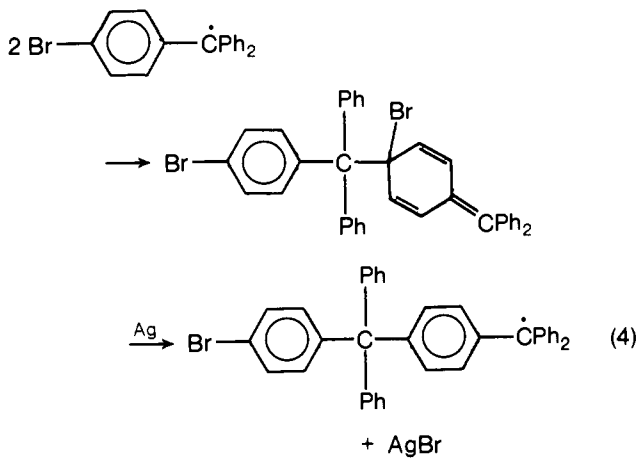


(3)

benzenes from chlorobenzene and trichlorobenzenes from dichlorobenzenes) were also obtained in the NBS photobrominations.[12]

III. Other Replacements of Halo

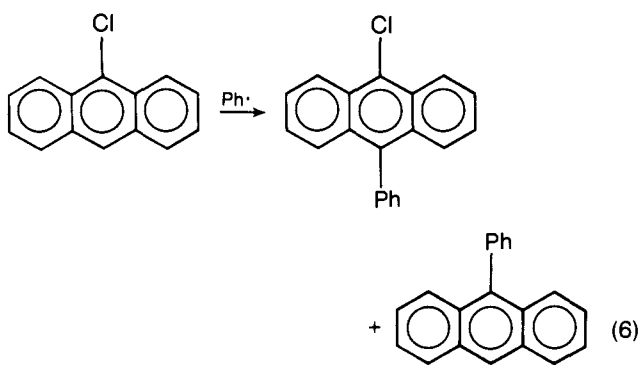
The susceptibility of halo substituents in aromatic reactants to replacement by alkyl and aryl radicals varies, both among the halo substituents and with respect to the attacking free radical. One of the earliest examples of such replacement involves the dimerization of (4-bromophenyl)diphenylmethyl radical; ipso attack was suggested[13] to account for the loss of half of the bromine in the parent compound (eq 4).



(4)

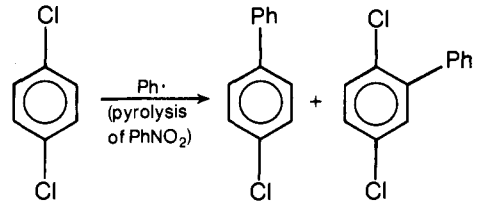
In solution, phenyl radicals (from benzoyl peroxide) react with fluorobenzene to give both fluorobiphenyls (Ph· replacing H) and biphenyl (Ph· replacing F) in a ratio of 95:5 (eq 5)[14] and react with

$$C_6H_5F + Ph\cdot \longrightarrow PhC_6H_4F + PhC_6H_5 \qquad (5)$$



(6)

9-chloroanthracene to produce both 9-phenyl- and 9-chloro-10-phenylanthracene (eq 6),[15] but phenyl radical (from phenylhydrazine + silver oxide) does not displace bromo in bromobenzene.[16] On the other hand, in the gas phase, phenyl radicals generated by pyrolysis of nitrobenzene (600 °C) do displace Cl, Br, and I but not F in reaction with halobenzenes,[17] and those generated by pyrolysis of azobenzene (500 °C) appear to replace Cl in chlorobenzene to a small extent.[18] Relative to the amounts of halobiphenyl produced in the pyrolysis reactions, the amounts of biphenyl produced (by displacement of halo, not by dimerization of Ph·) are approximately statistical with chloro and bromo, larger with iodo.[17] As in the halogen exchange reactions, replacement of chloro is more extensive with dichlorobenzene than with chlorobenzene in these pyrolysis reactions; formation of chlorobiphenyls exceeds formation of dichlorobiphenyls from dichlorobenzene (eq 7).[17]



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The greater susceptibility of fluoro, compared to other halo, to replacement by aryl radicals in solution has been further revealed by investigations with polyfluorobenzenes. Decomposition of benzoyl peroxide in hexafluorobenzene produces 2,3,4,5,6-pentafluorobiphenyl in substantial yield (eq 8);[19,20] a competitive experiment with a mixture of benzene and hexafluorobenzene showed comparable F:H reactivities.[21] Decomposition of benzoyl peroxide in both chloropentafluorobenzene and bromopentafluorobenzene led to replacement only of fluoro by phenyl (eq 9).[20] Similarly, pentafluorophenyl radicals (from

$$C_6F_6 + Bz_2O_2 \xrightarrow{heat} C_6F_5Ph \qquad (8)$$

$$BrC_6F_5 + Bz_2O_2 \xrightarrow{heat} BrC_6F_4Ph \qquad (9)$$

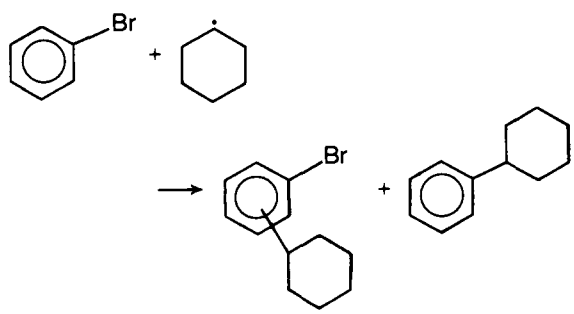
pentafluoroaniline and pentyl nitrite) replaced fluoro in both chloro- and bromopentafluorobenzene, but that strongly electrophilic radical failed to substitute into hexafluorobenzene.[22] Earlier attempts to study reactions of pentafluorophenyl radicals by decomposition of pentafluorobenzoyl peroxide in chloro- and bromobenzene produced, not the expected biphenyls, but phenyl pentafluorobenzoate (eq 10).[23] The initially formed pentafluo-

$$C_6H_5Cl + (C_6F_5CO)_2O_2 \xrightarrow{heat} C_6H_5OCOC_6F_5 \qquad (10)$$

robenzoyloxyl radical, before losing CO_2 as usual, reacted by ipso substitution. By contrast, very little substitution product was obtained from pentafluorobenzoyl peroxide and hexafluorobenzene, although a high-boiling residue indicated that some addition of radicals to the hexafluorobenzene and subsequent reactions did occur.[23]

Phenyl radicals are essentially electroneutral, pentafluorophenyl radicals are strongly electrophilic,[21] and alkyl radicals are nucleophilic. Several examples of halo displacement by alkyl radicals have been reported.

Reaction between bromobenzene and cyclohexyl radicals yields the statistical ratio (1:5) of Br:H replacement (eq 11).[24]



(11)

The bromo(cyclohexyl)benzene isomer distribution reported[16] can be used to calculate that the relative rates of substitution at different positions are: ipso, 17; each ortho, 24; each meta, 13; and para, 8; that is, substitution at the ipso position is second only to that at an ortho position, and the possibility of some rearrangement of Br from ipso to ortho positions (see later discussion of mechanism) increases the probable relative importance of ipso attack in this system.

Even greater selectivity for a substituted position over an unsubstituted position characterizes the reaction of the nucleophilic cyclohexyl radical with some dihalobenzenes.[25] Among different halo substituents, the ease of replacement in these reactions of dihalobenzenes is F > I ≳ Br > Cl.[25] Substitutions by cyclohexyl into *o*- and *p*-dihalobenzenes are faster (6–35 times) than into benzene, and positions ortho to a halo substituent are substituted about 3–4 times as often as positions meta to one.[25]

In the gas phase, methyl radicals (from pyrolysis of nitromethane at 550 °C) react with benzene to produce mainly biphenyl (dimerization of Ph·) (eq 12) and little toluene (CH_3· replacing H), but they react under the same conditions with hexafluorobenzene to produce little perfluorobiphenyl and mainly 2,3,4,5,6-pentafluorotoluene (CH_3· replacing F) (eq 13).[17] This

$$C_6H_6 + CH_3NO_2\ (CH_3\cdot + \cdot ONO) \xrightarrow{550\ °C} C_6H_5C_6H_5 \quad (12)$$

$$C_6F_6 + CH_3NO_2\ (CH_3\cdot + \cdot ONO) \xrightarrow{550\ °C} C_6F_5CH_3 + C_6F_5OH \quad (13)$$

difference in behavior has been attributed to the greater susceptibility of C_6F_6 to attack (addition) of the nucleophilic methyl radical.[17] A substantial amount of pentafluorophenol is also formed from C_6F_6 (little from C_6H_6), indicating attack by ONO· to form a C–O bond and subsequent reaction(s) of the intermediate.[17] The competition between CH_3· and ONO· in attacks on the aromatic substrate depends on the electrophilicity of the substrate; fewer fluoro substituents reduce the relative reactivity of CH_3·. Fluorophenol is the major product formed by pyrolysis (550 °C) of a mixture of nitromethane and *p*-difluorobenzene; attack at a F-substituted position by ONO· is 66 times that at an unsubstituted one and very little displacement of either F or H by CH_3· occurs.[17]

Elemental sulfur, at about 240 °C, reacted with substituted bromobenzenes to replace bromo and produce polysulfides, which were subsequently reduced with lithium aluminum hydride to thiophenols (about 30% yields); reaction with chlorobenzene was sluggish, and very small amounts of thiophenol and chlorothiophenol were formed (Cl and H replaced competitively).[29] At the temperatures used, sulfur is present as a mixture of allotropes, which probably behave as diradical species.

Benzenesulfenyl (C_6H_5S·) and benzenesulfonyl radicals ($C_6H_5SO_2$·) react but little (if at all) with benzene; instead of substitution products, dimerization/disproportionation products are obtained.[27] With chloro-, bromo-, and iodobenzene, however, in addition to the dimerization/disproportionation products, ipso-substitution products (diphenyl sulfide or diphenyl sulfone, respectively) are obtained (eq 14).[27] Replacement of H in the

$$C_6H_5X + \dot{S}C_6H_5\ (\text{or } O_2\dot{S}C_6H_5) \rightarrow C_6H_5SC_6H_5\ (\text{or } C_6H_5SO_2C_6H_5) \quad (14)$$
$$X = Cl, Br, I$$

halobenzenes does not compete with ipso substitution. When *p*-toluenesulfenyl and *p*-toluenesulfonyl radicals react with the halobenzenes, only the mixed sulfide or sulfone, respectively, is formed; that is, the sulfide and sulfone products are definitely formed from reaction between the radical and the halobenzene rather than from some extrusion reaction of a disulfide or disulfone.[27] These ipso substitutions have substantial activation energies; appreciable amounts of sulfides and sulfones are obtained only at temperatures above 150 °C, at which the favored radical dimerization products (disulfide, disulfone) are unstable and regenerate the free radicals.[27]

Ultraviolet irradiation of a mixture of trimethylsilane and hexafluorobenzene produces pentafluoro(trimethylsilyl)benzene, presumably by attack of trimethylsilyl radicals on the aromatic substrate.[21]

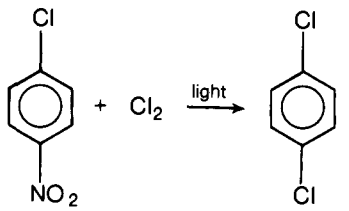
A substantial amount of HBr was produced by reaction of *p*-bromotoluene with hydrogen atoms (from ultraviolet photolysis of thiols), and some evidence for replacement of a thio and/or a methyl substituent by tritium atoms has been reported.[28] These reactions are essentially the reverse of free-radical attack at an unsubstituted position in the benzene ring.

IV. Replacements of Other Substituents

Reports of attack at a halo-substituted position outnumber all others pertaining to ipso substitution in free-radical aromatic substitution reactions, but other substituents have been replaced by free-radical reactants, sometimes in competition with halo replacements. Photoinitiated chlorinations of benzenesulfonyl chloride, *p*-bromobenzenesulfonyl chloride, and diphenyl sulfone produce, in nearly quantitative yields, chlorobenzene, *p*-dichlorobenzene, and chlorobenzene, respectively (eq 15).[9,29]

$$PhSO_2G + Cl_2 \xrightarrow{light} PhCl \quad (15)$$
$$G = Cl, Ph$$

Nitro substituents have been replaced by several free-radical reagents. Although *p*-bromonitrobenzene was reported to be unreactive in photoinitiated chlorination during 90 min (carbon tetrachloride solution),[9] both it and *p*-chloronitrobenzene were later found, after several hours reaction time, to be converted mainly to *p*-dichlorobenzene (eq 16).[30] The product mixture from

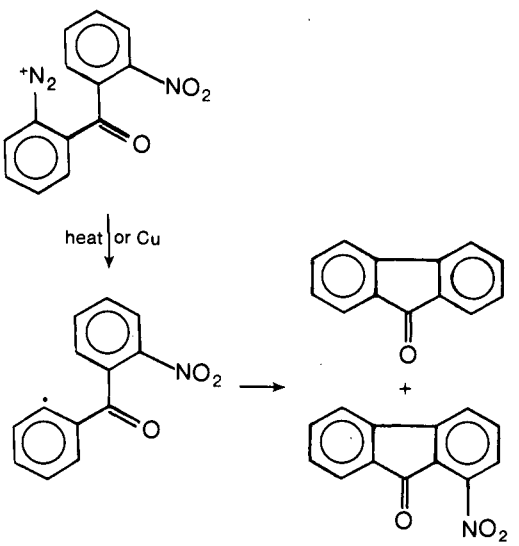


(16)

p-bromonitrobenzene also included *p*-chloronitrobenzene and *p*-bromochlorobenzene, showing that nitro and bromo were replaced competitively.[30] Under similar conditions, nitrobenzene is slowly converted to chlorobenzene.[10]

In the gas phase, nitro is also replaced by chloro; chlorobenzene was the principal product obtained from nitrobenzene and chlorine at 375 °C (46-s contact time), exceeding the "expected" chloronitrobenzenes 45:2.[11,31]

Some aryl radicals displace nitro. The diazonium salts derived from 2-benzoylaniline and *N*-methyl-*N*-phenyl-1,2-benzenediamine decompose in aqueous solution by heat or copper powder to produce intermediate aryl radicals which cyclize to



(17)

produce fluorenone and carbazole, respectively.[32] When a 2′-nitro substituent is present in the parent compound, it, in competition with the 6′-hydrogen, is lost extensively in the cyclization step (eq 17).[32] Arylations of nitrobenzene with pentafluorophenyl radicals[23] and, to a lesser extent, of pentafluoronitrobenzene with phenyl radicals[22] give pentafluorobiphenyl (loss of NO_2); in both cases polyfluoronitrobiphenyls (loss of H or F, respectively) are also formed.[22,23]

Triplet methanesulfonylnitrene, generated thermally from methanesulfonyl azide in nitrobenzene solution, reacts with the solvent to produce both *N*-(nitrophenyl)methanesulfonamides and *N*-phenylmethanesulfonamide (eq 18).[33] Nitro is replaced more extensively than H, but in reactions with methyl benzoate and (trifluoromethyl)benzene, the nitrene substitutes only at unsubstituted positions (eq 19).[33]

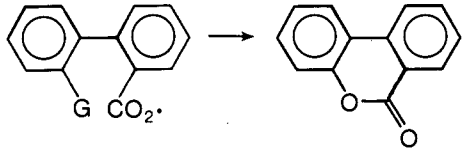
$$C_6H_5NO_2 + CH_3SO_2\ddot{N}: \rightarrow CH_3SO_2NHC_6H_5 + CH_3SO_2NHC_6H_4NO_2 \quad (18)$$

$$C_6H_5G + CH_3SO_2\ddot{N}: \rightarrow CH_3SO_2NHC_6H_4G \text{ only} \quad (19)$$

$$G = CF_3 \text{ or } CO_2CH_3$$

Hydroxyl radicals, usually generated by radiolysis of aqueous solutions, react with substituted benzenes to produce phenols, with varying extents of ipso substitution.[34-42] Fluoro and methoxy appear to be most susceptible to replacement by the electrophilic hydroxyl radical, even competitive with hydrogen;[35-37,39a,40] less extensive but still substantial replacement of carboxy and chloro occurred;[34,38,40] amino and nitro were replaced but little;[34,39b] and replacement of cyano was not detected.[35] Nitro (and to some extent, bromo) rather than carboxy is replaced by hydroxyl radical reacting with 5-nitro- (or 5-bromo-) 2-furancarboxylate.[42] Some evidence for replacement of nitro and sulfo groups by hydroxyl during electrolytic oxidation of acidic aqueous solutions of substituted benzenes was reported, but the presumed products were not isolated.[43]

Several 2′-substituents are lost by attack of 2-carbonyloxyl radicals generated by lead tetraacetate oxidations of 2′-substituted 2-biphenylcarboxylic acids in benzene solution (eq 20).[44]



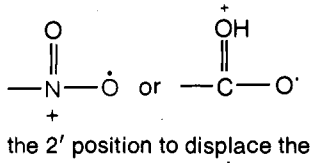
(20)

G = NO_2, OMe, Cl, COOMe, H

The lactone, 10-oxo-10*H*-9-oxaphenanthrene, is the principal product; it was formed in 18% yield with 2′-NO_2, in 99% yield with 2′-OCH_3, and in intermediate yields with 2′-Cl and 2′-COOMe.

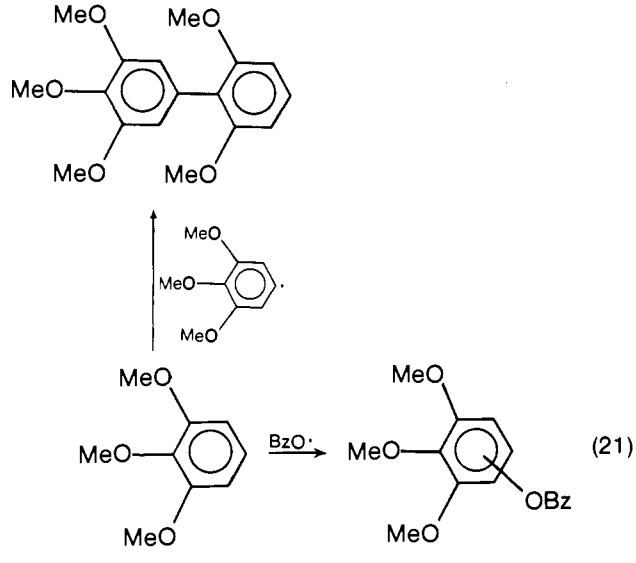
The more electronegative the 2′-substitutent, the less extensively is lactone formed by attack of the electrophilic carbonyloxyl radical. Except for a small amount with 2′-NO_2, no lactone with the 2′-substituent retained was obtained, even though an 89% yield of lactone was obtained from (unsubstituted) 2-biphenylcarboxylic acid. No more than a trace of lactone was formed with 2′-Me and none with 2′-phenyl.

Related reactions have been reported for the mass spectrometry of 2′-nitro-2-nitrobiphenyl[45] and some 2′-substituted (NO_2, COOH, COOR) 2-biphenylcarboxylic acids[45,46] and esters.[46] Major peaks are associated with loss of the 2′-substituent, but interpretation differs on whether an oxyl radical at the 2



position attacks the 2′ position to displace the substituent[45] or the parent cation–radical loses the 2′-substituent without assistance from the 2-substituent.[46]

In addition to the reactions of hydroxyl radicals cited above,[35,36,39a,40] occasional replacement of methoxy by other free radicals has been reported. In a lactone-forming reaction related to those abovei methoxy was lost in the peroxysulfate oxidation of 2′-methoxy-2-biphenylcarboxylic acid to 10-oxo-10*H*-9-oxaphenanthrene.[47] Similarly, peroxysulfate oxidation of *o*-methoxycinnamic acid gives 2-oxo-2*H*-1-oxanaphthalene as the only lactone.[47] These oxidations presumably involve intramolecular attack on the aromatic nucleus by carbonyloxyl radicals.[47] Intermolecular attack by 3,4,5-trimethoxyphenyl radicals [from thermolysis of 3,3-dimethyl-1-(3,4,5-trimethoxyphenyl)triazene] on 1,2,3-trimethoxybenzene produces only 2,3′,4′,5′,6-pentamethoxybiphenyl (eq 21).[48] The most crowded



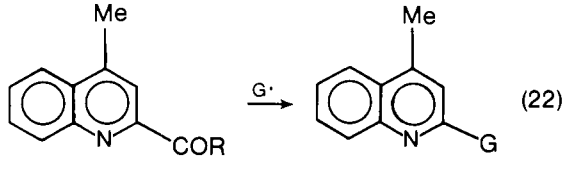
(21)

methoxy is the one replaced. Attempts to react the trimethoxybenzene with phenyl radicals were unsuccessful; benzoyloxyl radicals (from benzoyl peroxide) replaced hydrogen rather than methoxy (eq 21),[48] indicating that the susceptibility of a substituent to ipso substitution depends on the nature of the attacking radical.

In the gas phase, methyl is apparently replaced to some extent by ipso attack of phenyl radicals (from pyrolysis of nitrobenzene) on toluene (biphenyl product), but the major components of the reaction mixture (methylbiphenyl and diphenylmethane) retained the methyl carbon.[17]

In nearly all of the above examples of ipso replacement, the substituted position has been in a benzenoid ring. Several replacements of substitutents in nitrogen-containing heterocyclic ring systems have been reported.

Acyl and cyano substituents in pyridine[49-51] and quinoline[52,53] derivatives appear to be particularly susceptible to replacement by free radical reagents. Acyl substituents at the 2 and 4 positions of substituted pyridines[51] and in 2-acyl-4-methylquinoline[53] are replaced by alkyl radicals (eq 22), and acyl exchange in 2-



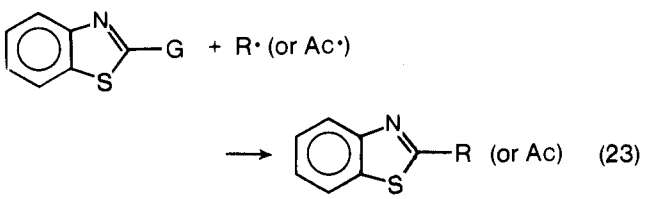
(22)

G = alkyl or acyl

acyl-4-methylquinoline illustrates the reversibility of homolytic aromatic acylation.[53] But no ipso-substitution products were obtained from 4-cyano-, 4-methoxycarbonyl-, 4-chloro-, 4-methyl-, or 4-methoxypyridines, nor from 2-acetyl-4-cyanopyridine, reacting with alkyl radicals.[51]

Cyano substituents in protonated pyridines[49,50] and in 2-cyanoquinoline[52] are replaced, however, by 1-hydroxyalkyl[49,50,52] and 1-ethoxyethyl[52] radicals photoproduced in alcohol or ethyl ether solutions, respectively. Yet 4-cyanoquinoline reacts with the free radicals derived from 1-propanol to give hydroxyalkyl substitution only at the 2 position.[52b] 4-Methoxypyridinium ion did not react with hydroxy(diphenyl)methyl radical (which does give ipso substitution in 4-cyanopyridinium ion), and 4-cyanopyridinium ion did not react with hydroxy(phenyl)-(2,3,5,6-tetramethylphenyl)methyl radical, presumably because of steric hindrance.[49] Alkyl radicals generated by photodecarboxylation of carboxylic acids in benzene solution also replace the cyano group in 2-cyanoquinoline; substitution at the 4 position occurs to about the same extent (yields of each product below 20%).[52]

Several substituents in the 2 position of 1-thia-3-azaindenes (benzothiazoles) have been replaced by alkyl (particularly 1-adamantyl) and acetyl radicals (eq 23).[54] With $-SO_2Ph$, -SOPh,

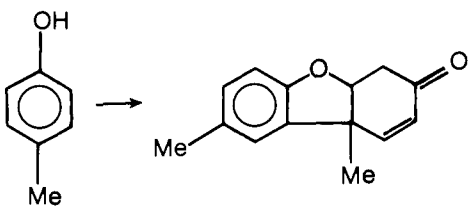


(23)

G = SO_2Ph, SOPh, COPh, SR, OR, halogen, Ac

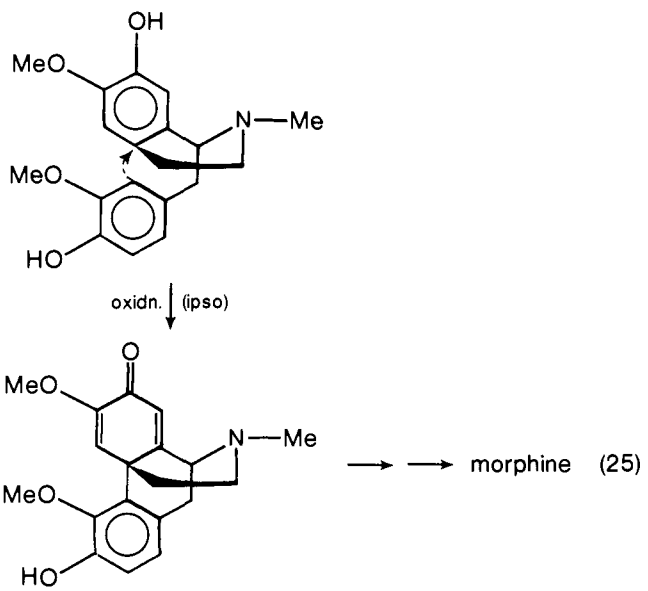
-COPh and -COR as the 2-substituent, the reactant was completely or almost completely consumed, and high yields of ipso substitution product were obtained. With -SR, -OR, and halo as the 2-substituent, low yields of substitution product were obtained, and substantial amounts of reactant were recovered.[54] No other substituted 1-thia-3-azaindene was obtained.

Some oxidations of phenols, through phenoxyl radicals, give products suggestive of ipso attack, although loss of the original substituent does not usually occur.[55] For example, oxidation of 4-methylphenol (eq 24) produces, among other, non-ipso



(24)

products, a gem-disubstituted ketone in about 22% yield (higher yield at lower temperature). Some natural product syntheses,



morphine (25)

including one of morphine (eq 25),[55b] have depended on similar reactions.

V. Substituent Effects

The effects of other substituents on ipso substitution in substituted aromatic substrates depend on the identity and position of the other substituent and on the identity (nature) of the attacking radical. These effects have usually been assessed by use of competitive kinetic studies, although relative yields of products are sometimes useful.

For chlorodebrominations, electron-withdrawing substituents in ortho, meta, and para positions generally reduce the rate of ipso substitution; however, reports about the effect of *p*-Cl conflict.[8,9] The rate is increased by *o*- and *p*-OMe. The temperature dependence of some substituent effects has been measured; higher reaction temperatures decrease the substituent effects.[56] Although chlorodebromination was first reported not to occur with *p*-bromonitrobenzene,[9] the exchange did occur in later experiments, with longer reaction times, with that reactant[30] and with its isomer, *m*-bromonitrobenzene.[8]

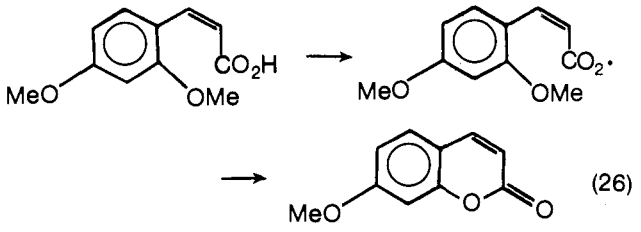
In the reverse exchange, bromodechlorination (eq 3), *o*-Cl, *p*-Cl, and *p*-Br increased the extent of exchange, but *o*-F, *m*-F, *m*-Cl, and *o*-Br did not.[12] In all these cases, brominations at unsubstituted positions were competing reactions.

No clear summary about substituent effects on ipso substitutions in bromobenzenes by sulfur-containing radicals emerges from the available data. The yields of product from reaction of substituted bromobenzenes with elemental sulfur at 240 °C are little changed by *p*-Cl, *p*-F, and *p*-Ph substituents, but *p*-PhO does appear to speed up the reaction (same yield in shorter reaction time).[26] The relative rates of reaction of bromobenzenes with benzenesulfonyl radicals (eq 14) are in the order *p*-OMe > *p*-Me > *m*-Me > H > *m*-OMe > *p*-COOMe > *m*-COOMe, and those with benzenesulfenyl radicals are in the order *p*-OMe ≫ *p*-NO_2 > *p*-Me > *m*-Me > H > *m*-OMe > *m*-NO_2.[27]

A Hammett correlation ($\rho = +1.1$) of homolytic aromatic cyclohexylation (eq 11) rates indicates that the cyclohexyl radical is nucleophilic in these reactions.[24] Partial rate factors for substitutions in *o*- and *p*-dihalobenzenes have been determined.[57] All of the dichloro- and dibromobenzenes reacted with cyclohexyl radicals appreciably faster than did benzene (12–35 times in excess cyclohexane). The partial rate factor at an ipso position is larger (factor of 2 for dichloro, factor of 5 for dibromo) with the ortho isomer than with the para one. Similarly, a second chloro substituent increases the proportion of ipso substitution (over twice the statistical factor) by phenyl radicals at 600 °C.[17] The selectivity of cyclohexyl radicals between dihalobenzene and benzene and among positions in the dihalobenzene is reduced by use of excess aromatic compound rather than cyclohexane as solvent.[57] This result was attributed to the stabilization by the more polar aromatic solvent of change-transfer contributions to the transition state of the radical reaction.[57]

In reactions of aryl radicals with hexafluorobenzene, however, electron-withdrawing substituents (3-Cl, 3-Br, 4-NO_2) in the aryl radical reduce the yield of substitution product considerably,[20] although chloro and bromo substituents affect the rate of phenyldefluorination of polyfluorobenzenes by phenyl radicals (eq 9) but little.[21]

Ipso substitution in intramolecular cyclization reactions of electrophilic radicals appears to be facilitated by electron-donating substituents[47] and retarded by electron-withdrawing ones,[45] although few data are available. In conversion of 2-methoxycinnamic acids to the 2-oxo-2*H*-1-oxanaphthalenes through the intermediate carbonyloxyl radical (eq 26), the 4-OMe substituted reactant gave about twice the yield of lactone as did the unsubstituted one.[47] In mass spectrometry of some 2,2′-dinitrobiphenyls, which appear to lose NO_2 by attack of -NO-O· radicals (M − NO_2 peak), 4-nitro and 4,4′-dinitro substituents reduce the relative intensity of the M − NO_2 peak.[45]



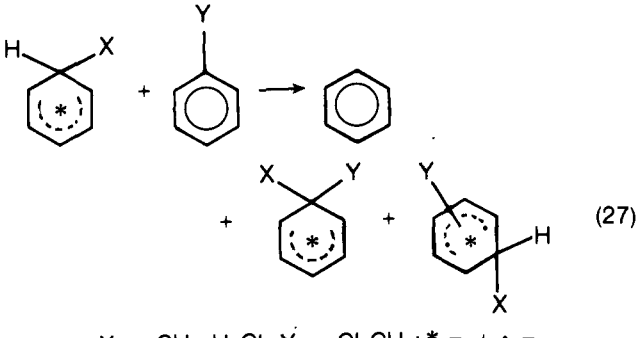
(26)

The relative rates of substitution at the 2 position of 5- and 6-substituted 2-acetyl-1-thia-3-azaindenes by the nucleophilic 1-adamantyl radical (see eq 23) are well correlated by a Hammett treatment ($\rho = +1.4$; $r = 0.98$) as are the relative rates for the corresponding series without the 2-acetyl substituent ($\rho = 0.9$; $r = 0.98$).[54b] Electron-withdrawing substituents (CN, Cl, 5-OMe) increase and electron-releasing ones (Me, 6-OMe) decrease the rate of replacement of a 2-Ac or a 2-H by 1-adamantyl radical; the 2-Ac series (ipso substitution) is more sensitive to the substituent effects.[54b] σ_p values were used for substituents at the 6 position (para to N), and σ_m for ones at the 5 position (meta to N). The excellent correlations imply that the substituent effects are transmitted mainly through the N rather than the S to the 2 position,[54b] in accord with data for nucleophilic substitutions in 2-halo-1-thia-3-azaindenes.[58]

VI. Mechanism

Only during the past several years have speculations about the mechanism of free-radical ipso substitutions focused on a geminally substituted intermediate.[62] Earlier investigations considered attack at a substituted position to be unlikely, and various schemes to avoid a simple ipso intermediate, like the σ intermediate written for free-radical substitution at other positions except for the geminally substituted carbon, were proposed. The accumulating evidence for the ipso intermediate is persuasive, however, and some investigators who first advocated an alternative mechanism now describe their reactions in terms of the ipso intermediate.

How reasonable is an ipso intermediate? The relative energies of isomeric intermediates (disubstituted: ipso, ortho, meta, para) which could be formed in aromatic substitution reactions have been assessed by MINDO/3 calculations based on the isodesmic reactions represented by eq 27.[59] The calculations indicate that,



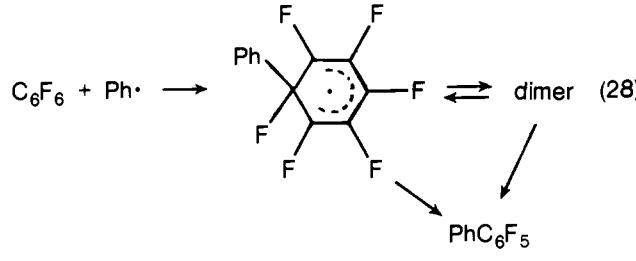
(27)

$X = CH_3, H, Cl$; $Y = Cl, CH_3$; * = +, ·, −

in free-radical reactions with X = CH_3 or H and Y = Cl, the ipso intermediate is the one of lowest energy, but with X = Y = Cl or CH_3, it is the one of highest energy. (According to CNDO/2 calculations for cyclohexadienyl radical intermediates formed by attack of hydroxyl radicals on chlorobenzene, the ipso intermediate is substantially more stable than the ortho, meta, and para ones[35]). In the MINDO/3 calculations for isodesmic reactions differing only in charge type, whatever the combination of X and Y, the ipso intermediate is relatively more favorable in the free-radical substitution than in the cationic one.[59] Since ipso intermediates have been identified and shown to be significant in electrophilic aromatic nitrations,[2] these calculations strongly support the formulation of ipso intermediates for free-radical aromatic substitutions.

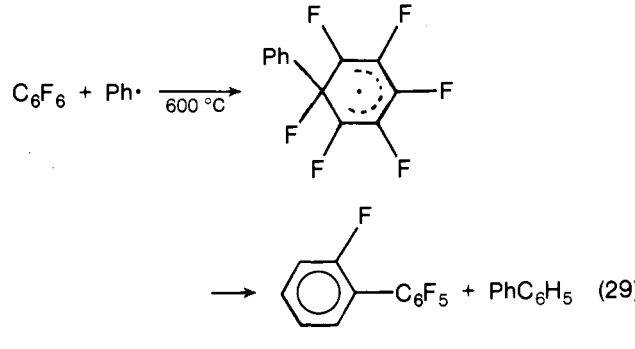
Free-radical attack on aromatic nuclei at unsubstituted positions leads to the formation of σ complexes as intermediates.[60] Experimental evidence now virtually requires similar complexes for ipso substitution. No evidence for direct abstraction of the replaced substituent (to generate aryl radicals) has been reported, and, for some systems, such a mechanism has been rejected on the basis of experimental data. In the reaction of arenesulfenyl and -sulfonyl radicals with chlorobenzene (eq 14), no products expected from phenyl radicals were detected; therefore, chloro is not abstracted directly from chlorobenzene by the sulfur radicals, although it is replaced by them.[27] The adduct (σ complex) has been detected by UV spectral methods in hydroxylation reactions.[37]

The yield of pentafluorobiphenyl formed by phenylation of hexafluorobenzene (eq 8) was substantially increased by reduced pressure distillation of the reaction mixture over that detected by analysis before distillation.[20,22] This fact indicates that a moderately stable intermediate, such as a dimer of an initial σ complex (ipso intermediate), is formed and subsequently decomposed (to pentafluorobiphenyl) during distillation (eq 28).[20,22]



(28)

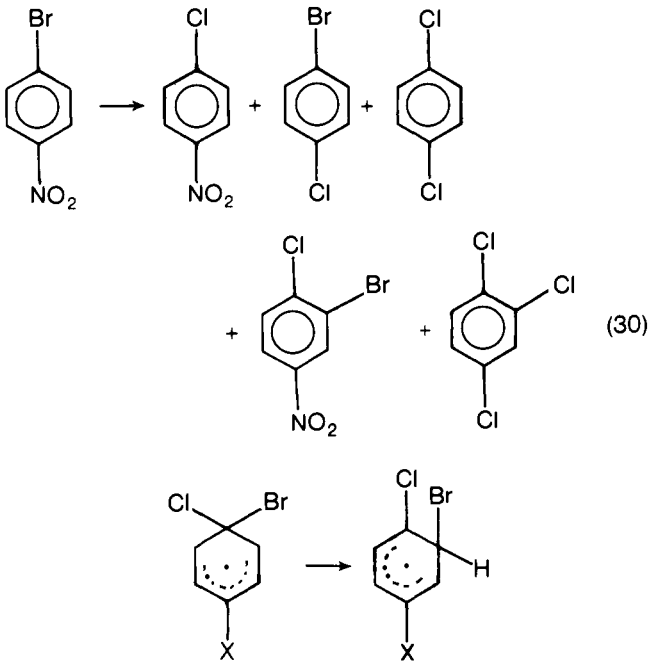
The probability that an ipso intermediate is formed increased with the detection of substantial amounts of 2,2′,3,4,5,6-hexafluorobiphenyl (as well as 2,3,4,5,6-pentafluorobiphenyl) from the high-temperature (600 °C) phenylation of hexafluorobenzene (eq 29).[17] Apparently some 1,3-shift of F in the ipso intermediate occurs.[17] (Similarly, pyrolytic phenylation of C_6D_6 gave some hexadeuteriobiphenyl.[17])



(29)

1,2-Rearrangement of bromo occurs to an appreciable extent when *p*-bromonitrobenzene is photochlorinated; 2-bromo-1-chloro-4-nitrobenzene and ipso-chlorination products derived from it were found among the products of the reaction (eq 30).[30] An ipso intermediate is virtually necessary to account for the rearrangement product and thereby becomes credible for the replacement reactions as well.[30] This identification of rearrangement of a geminal substituent to an ortho position implies that, in some cases, such rearrangement of an initially formed ipso intermediate may account for the high proportion of ortho substitution that is characteristic of many free-radical aromatic substitution reactions.

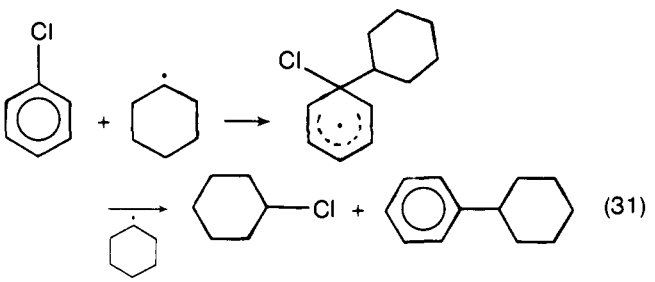
How is the ipso intermediate converted to aromatic product? Direct loss of one of the geminal substituents has been presumed by some investigators but opposed by others who consider the strengths of particular C–X bonds to be unfavorable for such unassisted loss. Within the wide range of radicals and reaction conditions for which ipso substitutions have been reported, both



(30)

direct loss of the substituent and abstraction of it by some reactant probably occur with different intermediates.

In some cases, experimental evidence strongly favors abstraction of the leaving substituent by a free radical. For example, cyclohexyl radicals react with halobenzenes to produce cyclohexylbenzene and halocyclohexane (eq 11), but no hydrogen halide.[57] Cyclohexyl radical abstracts halogen from the ipso



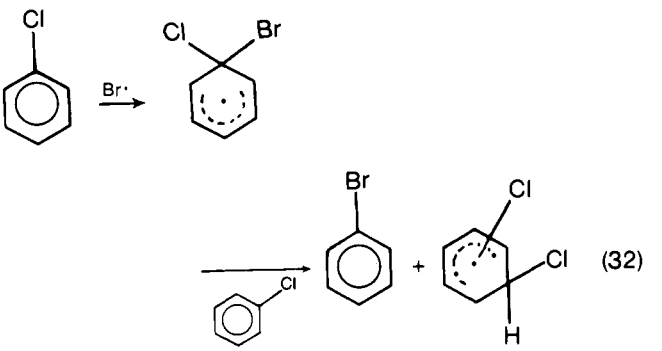
(31)

intermediate to form the two products (eq 31); expulsion of halogen atom would be expected to lead to the formation of hydrogen halide.[57] Likewise, phenyl radicals react with hexafluorobenzene to produce pentafluorobiphenyl and fluorobenzene.[22] The low yield of phenylation product (pentafluorobiphenyl) was attributed, at least in part, to the consumption of phenyl radicals in the defluorination of the intermediate σ complex.[22]

Sometimes the product presumed to be formed by abstraction from the σ complex does not survive the reaction conditions, and the choice between spontaneous loss and abstraction of a geminal substituent is not clearly supported by experimental data. Pentafluorobenzoyloxyl radical or the corresponding peroxide probably abstracts halo from the ipso intermediate formed by addition of another benzoyloxyl radical to halobenzene (see eq 10), but the expected benzoyl hypohalite would decompose to the (isolated) benzoic acid.[23] Also, chloro may be abstracted from the ipso intermediate by benzenesulfenyl or -sulfonyl radicals in the reaction of those radicals with chlorobenzene (eq 14), but the expected benzenesulfenyl or -sulfonyl chlorides are unstable at the reaction temperature (190 °C) and decompose to the sulfur radical and chlorine atom.[27]

The relative rates of σ-complex formation and decomposition appear to depend on the identities of both the attacking radical and the leaving substituent. That is, with some reactants, the slow step of the ipso substitution has been identified with (reversible) formation of the σ complex, while with others, with the loss of one of the geminal substituents.[23,24,27,37,61] This shift has been associated even with such closely related reactants as fluorobenzene on the one hand (loss of F slow) and other halobenzenes on the other (loss of halo fast).[27] Faster loss of a geminal substituent from an ipso intermediate than of hydrogen from an isomeric intermediate may, in fact, account for ipso substitution when the ipso intermediate is not expected to be especially favorable relative to the isomeric intermediates.[27,61] *o*-Dihalobenzenes are particularly susceptible to ipso substitution.[8,12,25,30] This reactivity has been attributed to relief of steric and electrostatic repulsion between the ortho substituents on forming the σ complex and to resonance stabilization of the σ complex by an *o*-halo substituent.[25] The latter factor is apparently the more important one for halogen exchanges, however, because the *o*-dihalobenzenes do not react more rapidly than do their para isomers.[8]

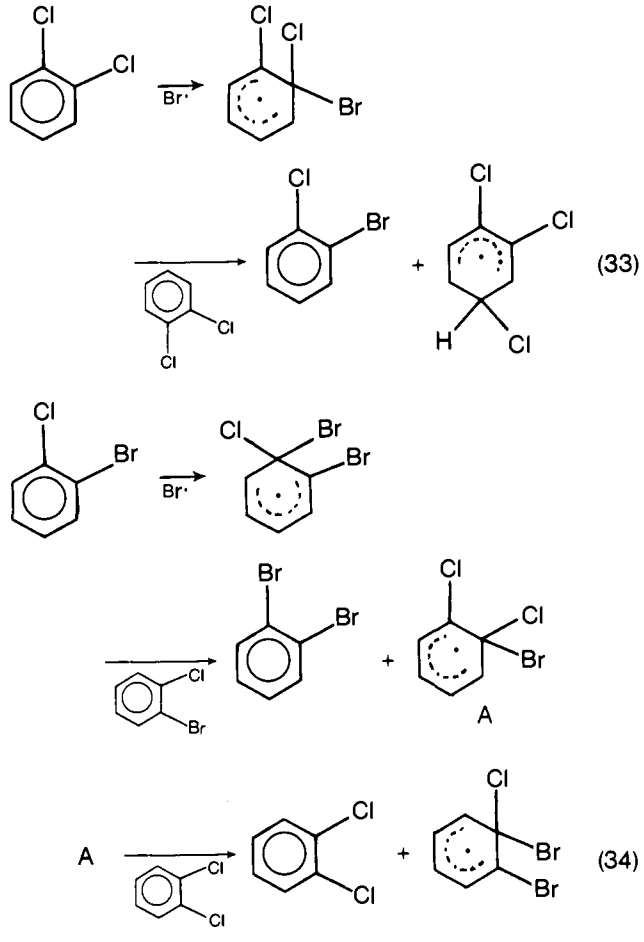
The substituent-abstracting step may play an unexpected role in product formation; that is, it may account for some products in these free-radical aromatic substitution reactions that are a bit troublesome to rationalize. For example, photobromination of chlorobenzene and chlorohalobenzenes (eq 3) leads not only to bromo-substitution products but also to chloro-substitution ones in comparable yields, particularly when *N*-bromosuccinimide (NBS) is used as the brominating agent.[12] This apparent efficacy of chlorine in competition with a much larger amount of brominating agent (reactions restricted to less than 25% conversion[12]) is surprising, since "equilibrium favors bromine atoms over chlorine atoms by a factor of 10^4 or more".[8] The chlorination products may arise, in part, by a reaction that mimics the isodesmic reactions (eq 27) used in the MINDO/3 calculations[59] discussed above. Here, the aromatic substrate (chlorobenzene, for example) may function as the reagent to abstract one of the geminal halo substituents in the ipso intermediate (eq 32). If Br is abstracted, an expected bromodehydrogenation



(32)

product is subsequently formed; if Cl is abstracted, however, the exchange product plus a chlorinated product are formed in equal amounts. With NBS as reagent, the aromatic substrate may be about as good as any other potential abstractor in the reaction mixture. This scheme is particularly attractive in accounting for the formation of trichlorobenzene from 1,2-dichlorobenzene but 1,2-dichlorobenzene from 1-bromo-i-chlorobenzene (eq 33 and 34). When a substantial amount of bromine is present, Br_2 or Br· could abstract Cl, and little or no chlorination would occur. Even though the bond being formed in this case is weaker than the one being formed with aromatic substrate as abstractor, the resulting aromatization unbalanced by dearomatization favors abstraction by bromine.

Acyl addition at the 2 position in protonated 2-acyl-1-thia-3-azaindenes (eq 23) is apparently reversible.[53] For this ipso substitution, loss of one of the geminal diacyl substituents may well be unassisted. Reversible formation of the σ complex was also inferred to account for the relative rates of replacement of different halo substituents by arenesulfenyl and -sulfonyl radicals (eq 14).[27]



(33)

(34)

In several cases, the experimental data have been taken to imply or require the formation of a π complex preceding the σ complex.[8,9,21,24,56] Some of the π complexes appear to be stabilized by charge-transfer contributions. Solvent effects on the ipso substitution of halo by cyclohexyl radicals are concordant with this view,[24] and the formation of phenyl benzoate rather than biphenyl in the reaction of chloro- and bromobenzenes with benzoyloxyl radicals was attributed to charge-transfer stabilization of the benzoyloxyl moiety in the σ complex.[21]

Although all details and implications are not yet clear, free-radical ipso substitution appears to follow the same general mechanism as free-radical substitution at unsubstituted aromatic positions. Substituent effects and the nature of the attacking free radical can shift the preferred reaction site between the ipso and isomeric positions in the aromatic substrate. Overall, ipso substitution is a rather common process, and it often exceeds replacement of hydrogen in an aromatic free-radical substitution reaction.

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