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FORMATION AND FATE OF RADICAL IPSO INTERMEDIATES IN THE REACTIONS OF CARBON RADICALS WITH AROMATICS. RADICAL IPSO SUBSTITUTION

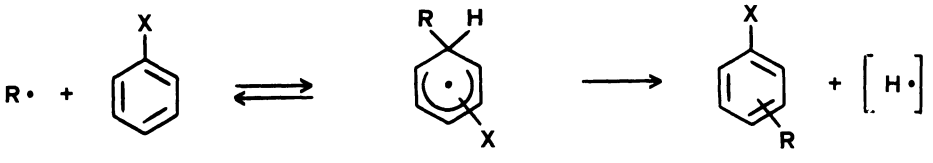
Marcello Tiecco

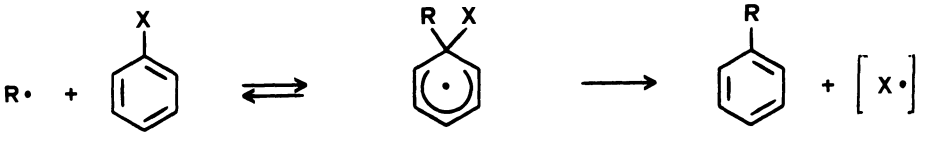
Institute of Organic Chemistry, Faculty of Pharmacy, Perugia, Italy

Abstract - Several examples of ipso attack and ipso substitution by alkyl radicals are reported. Of particular interest, also from the synthetic point of view, are the alkyldenitration and the alkyldeacylation processes. The factors which control the selectivity of the radical addition at the ipso positions and the fate of the resulting ipso-σ-complex intermediates are discussed.

The interaction of a radical R• with an aromatic substrate, as for instance a monosubstituted benzene, generally leads to the formation of the σ-complex intermediates by addition at all the unsubstituted ring positions; elimination of the hydrogen atom then affords a mixture of ortho, meta and para isomers. This is the generally accepted mechanism of Homolytic Aromatic Substitution reactions which have been extensively studied and which also have a great synthetic importance particularly in the field of heteroaromatic compounds.

SCHEME 1





The displacement of the substituent X was very seldom encountered in the past. For instance, in the case of halogeno benzenes it represented a secondary process and in some cases it was proposed to occur with different mechanisms, as for instance the direct attack of the radical R• at the substituent X (Ref.1). Thus, in spite of the fact that ipso attack is the usual process occurring with nucleophiles, and that it is also well documented with electrophiles, the corresponding attack by a radical at a substituted position was considered to

be an unlikely process. Very recently, however, many examples of radical ipso substitutions have been observed and these reactions have therefore been investigated in some detail. Quantitative investigations are still lacking and most of the suggested interpretations of the results obtained are mainly drawn from the identification of the reaction products.

As first examples, let us consider the reactions of some representative alkyl radicals with 2-substituted benzothiazoles. The alkyl radicals were produced, in acetonitrile/water, by the silver catalyzed oxidative decarboxylation of carboxylic acids with ammonium persulphate, according to the procedure introduced by Anderson and Kochi (Ref.2) (Reactions 1 and 2)

$$S_2O_8^{=} + 2\,Ag^{+} \longrightarrow 2\,SO_4^{=} + 2\,Ag^{++} \qquad (1)$$

$$R\text{-}CO_2H + Ag^{++} \longrightarrow R\cdot + CO_2 + H^{+} + Ag^{+} \qquad (2)$$

The bridgehead 1-adamantyl radical reacts with 2-nitrobenzothiazole to give the alkyldenitration product, 2-adamantylbenzothiazole, in almost quantitative yield (Ref.3). The same reaction also occurs with the secondary i-propyl and the primary n-propyl radicals, but with a progressively decreasing efficiency (Scheme 2).

SCHEME 2

R•	Ad•	Me_2CH•	$EtCH_2$•
% Yields	95	45	20

A similar situation was observed in the case of 2-acetylbenzothiazole. The alkyldeacylation product was easily obtained with the adamantyl radical, whereas with the i-propyl and with the methyl radicals the reactions were not so clean and the ipso substitution products were formed in low yields (Scheme 3) (Ref.4&5). The displaced acetyl group was finally recovered, in part, as the corresponding carboxylic acid.

SCHEME 3

R•	Ad•	Me_2CH•	Me•
% Yields	70	30	9

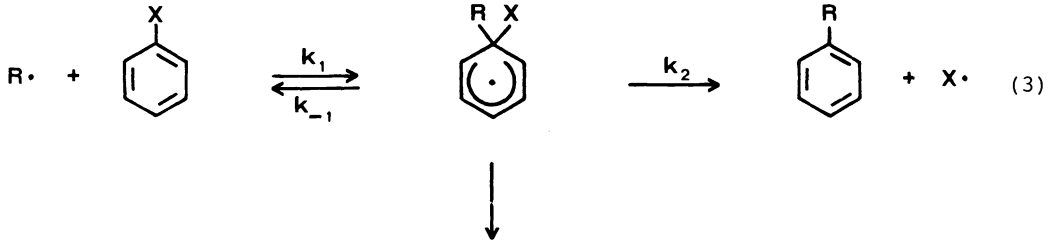
So, the nature of the alkyl radical has a strong influence on the efficiency of this radical displacement process. The best results were obtained with the bridgehead 1-adamantyl radical and we have therefore used this particular radical to investigate which other groups can be displaced. A series of 2-substituted benzothiazoles have been subjected to this analysis (Ref.5) and the results obtained are quite informative (Scheme 4).

SCHEME 4

X	NO_2	$PhSO_2$	PhSO	MeCO	F	Cl	Br	I	SMe	OMe
% Conver.	100	100	100	100	50	40	40	50	50	10
% Yield	95	80	80	70	50	50	60	60	60	40

It can soon be noticed that very good results are obtained whenever the substituent X is a strongly electron-withdrawing group such as nitro, sulfonyl, sulfinyl and acetyl; conversions and yields become considerably lower with other substituents such as halogens, thiomethoxy and methoxy. From these results it can be said that radical ipso substitution is not an unlikely process. On the contrary the alkyldenitration and the alkyldeacylation represent new and interesting reactions which can also have synthetic importance.

In order to understand the importance and the limits of radical ipso attack and ipso substitution, we need to find an answer to a number of questions which arise by simply considering the general addition-elimination mechanism through which these reactions are believed to occur (Reaction 3).



(3)

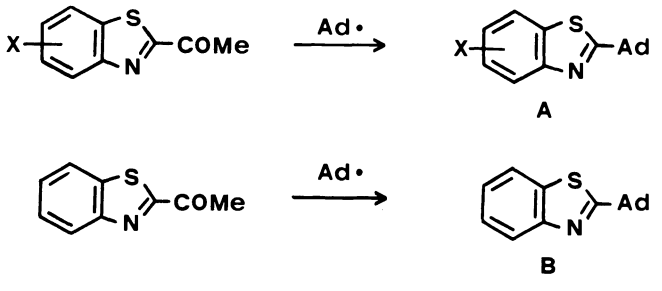
In those substrates in which the possibility exists we must first of all gain information about the factors which control the selectivity of the addition at an ipso or at an unsubstituted position. In particular, it is important to know the requisites that the attacking radical, the substituent X and the aromatic substrate must possess to make ipso attack the preferred process. In this respect we already have some preliminary information. We have seen that the best results were obtained with the adamantyl radical when the substituent X was an electron-withdrawing group. This, however, has been observed in the case of benzothiazole and it is obviously necessary to demonstrate whether these requirements can be considered of general validity or not.

Once the addition step has occurred, other problems concern the factors which

control the fate of the ipso σ-complex. In principle, several possibilities can be anticipated. The ipso intermediate can revert to the starting materials by elimination of the group R, or it can evolve towards the ipso substitution product by elimination of the group X and this process can occur spontaneously or with the assistance of another radical or molecule. Finally, cases can be found in which neither of the two groups, R and X, can be easily eliminated and the intermediate is forced to decay by other routes.

We shall now examine the results of some selected experiments which have been carried out in the hope of finding the answers to the questions posed above. Initially we have studied the effect of substituents on the adamantyldeacylation reactions. For this purpose competitive experiments between 5- and 6-substituted-2-acetylbenzothiazoles and 2-acetylbenzothiazole were carried out (Ref.6). As it is generally done in this kind of experiment, the ratios of the displacement products A and B, formed from the two substrates in competition, are assumed to give directly the values of the relative rates, $^{X}_{H}K$. The values obtained are collected in Scheme 5. A satisfying Hammett correlation (with a ρ value of 1.4) was obtained using σ_p values for the substituents in the 6 position and σ_m values for those in the 5-position (Ref.7).

SCHEME 5



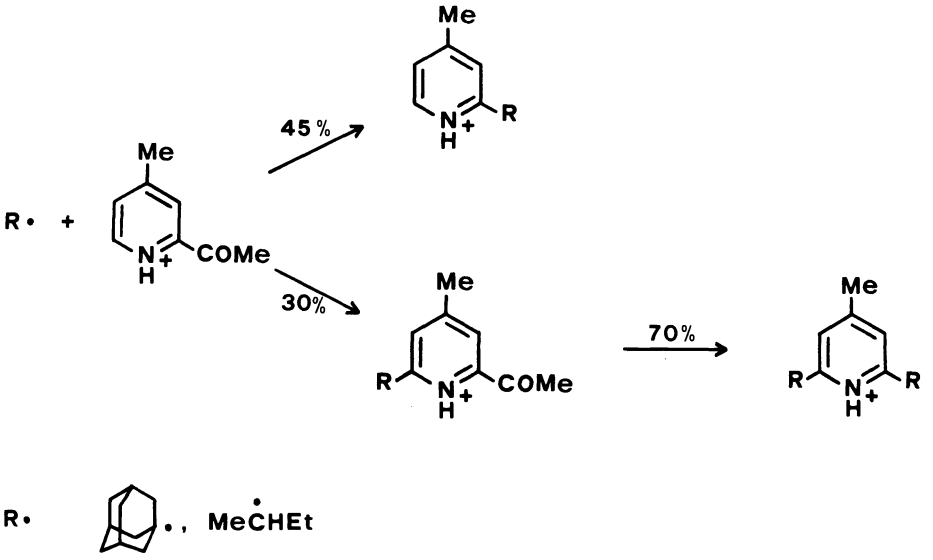
Relative Rates, $^{X}_{H}K = [A]/[B]$

X	6-CN	6-Cl	5-Cl	5-OMe	H	5-Me	6-Me	6-OMe
$^{X}_{H}K$	10.9	2.3	2.2	1.25	1	0.86	0.6	0.46

These results indicate that the electron density at the ring position suffering attack by the adamantyl radical is important in determining the reactivity of these substrates and, in particular, that the reaction is facilitated by electron-withdrawing substituents and retarded by electron-releasing groups.

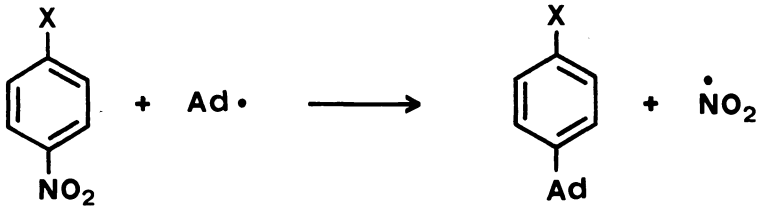
Let now examine other cases in which other ring positions are available for the attack of the alkyl radicals so that we can have some idea about the competition of the addition at an ipso or at an unsubstituted position. The reactions of adamantyl and s-butyl radicals with the protonated 4-methyl-2-acetylpyridine (Ref.4) afforded a mixture of two products deriving from the displacement of the acetyl group and from the addition at the unsubstituted 6-position; this latter product can further react with alkyl radicals to give the ipso substitution product in good yields. In no case could products deriving from the attack at the β-positions be identified (Scheme 6). These results once again indicate that the addition of the alkyl radicals occurs selectively at the most positive sites of the molecule. In the present case attack at the ipso carbon atom (which is made more positive by the presence of the acetyl group) occurs more easily than the addition at the unsubstituted position.

SCHEME 6



The most informative results come, however, from the reactions of some representative radicals (adamantyl, methyl, phenyl) with nitro aromatic compounds. Alkyldenitration by the adamantyl radicals can be easily effected in nitrobenzenes, provided the aromatic ring is made sufficiently electron-deficient by the presence of other electron-withdrawing substituents. Thus, while products of ipso substitution were not observed with nitrobenzene, p-nitrotoluene, p-nitroanisole, ortho- and m-dinitrobenzene, very good results were obtained with 1-X,4-nitrobenzenes with X=NO_2, SO_2R, CO_2Me, COMe, CHO, CN (50-70% yields) (Scheme 7) (Ref.3).

SCHEME 7

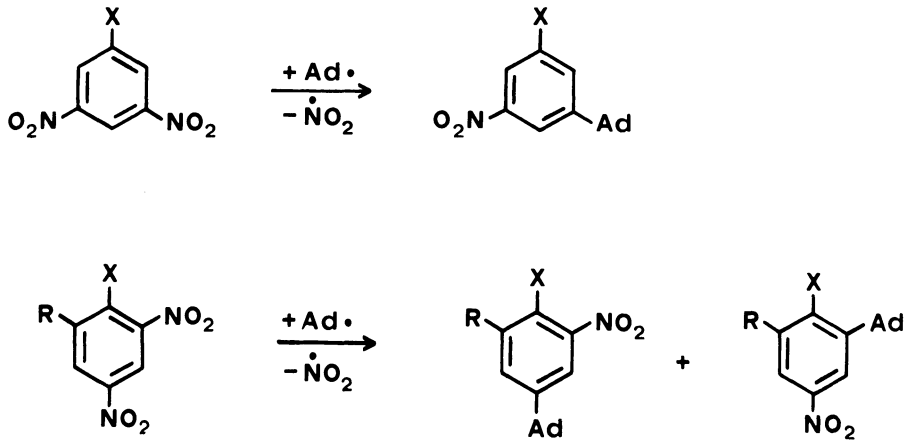


X = NO_2, SO_2R, CO_2Me, COMe, CHO, CN

Yields = 50 - 70 %

Good results were similarly obtained with 1-X,3,5-dinitrobenzenes, 1-X-2,4-dinitrobenzenes and 1-X,2,4,6-trinitrobenzenes with X=NO_2, SO_2R, CN (Scheme 8) (Ref.8).

SCHEME 8



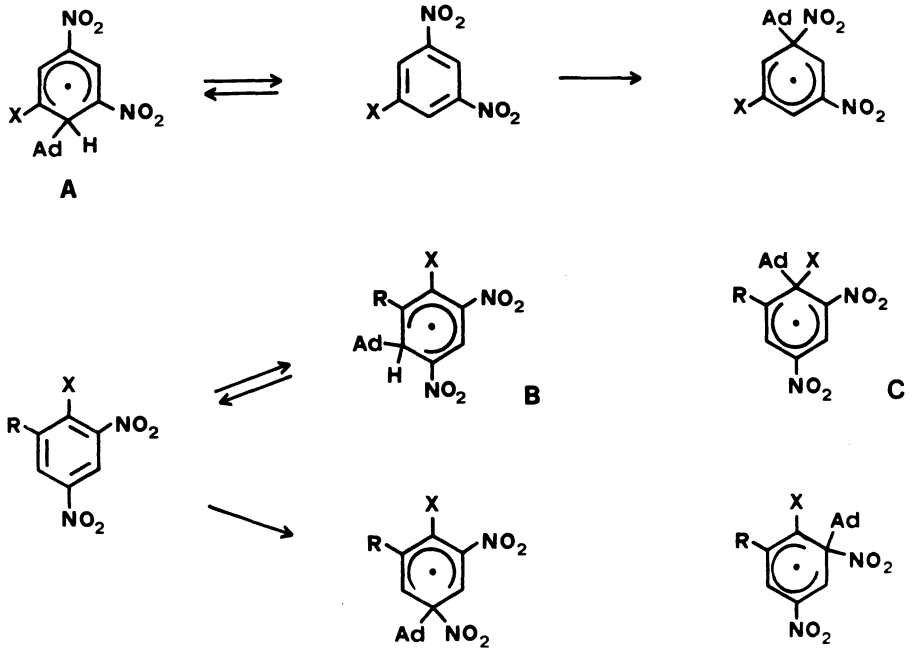
R = H, NO_2

X = NO_2, SO_2R, CN

These reactions proceed selectively to give the nitro displacement products in 50 to 75% yields. Substitution of the X group was never observed, unless X was a nitro group as in the 1,3,5- and 1,2,4-trinitrobenzenes. Products deriving from the attack at the unsubstituted positions could neither be observed. In the last two series of reactions competition between the ipso substitution at the 4- and at the 2- positions was observed, but in every case the 4 position was largely preferred. Once one of the nitro groups has been displaced the reaction does not proceed further, thus confirming that the presence of groups which substract negative charge from the ring is one of the requisites that the aromatic substrates must possess in order to suffer attack by the alkyl radicals.

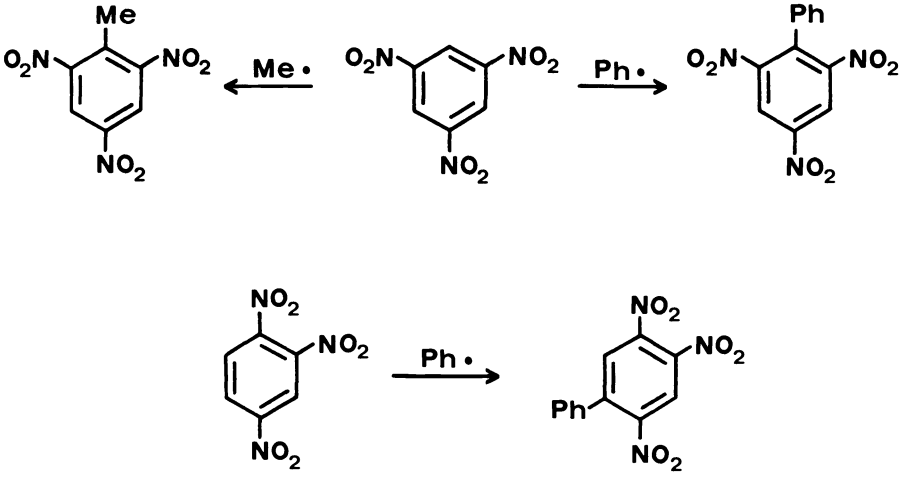
The important point which arises from these experiments is that the selectivity of the substitution process is not governed by the stability of the σ-complex intermediates. In fact, attack at the unsubstituted positions, or at the 1- position, should give rise to the radicals A, B and C (Scheme 9) which could be strongly stabilized by delocalization of the odd electrons into the substituents; nevertheless the products which should form from these intermediates were never observed. Thus radicals A, B, and C either are not formed at all or, less likely, they are formed but they revert to the starting products. The only observed reaction compounds are those deriving from the addition at the carbon atoms holding the nitro groups. These results are therefore in agreement with those observed with the benzothiazoles (Scheme 4) and with the acetylpyridines (Scheme 6); in every case the addition of the adamantyl radical occurs at the most positive carbon atoms of the aromatic ring, which generally are the ipso carbon atoms bearing the electron-withdrawing groups.

SCHEME 9



Completely different behavior was shown by the methyl and the phenyl radicals (Ref.8). In their reactions with polynitrobenzenes these two radicals, in fact, gave rise exclusively to the products deriving from attack at the unsubstituted positions (Scheme 10).

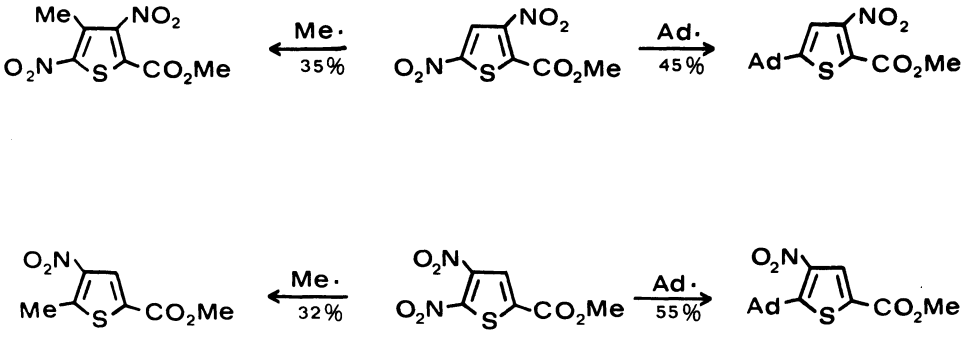
SCHEME 10



Thus with 1,3,5-trinitrobenzene methyl radicals gave the 2,4,6-trinitrotoluene, and phenyl radicals gave the 2,4,6-trinitrobiphenyl; similarly, from the reaction of phenyl radicals with 1,2,4-trinitrobenzene the only product obtained was the 2,4,5-trinitrobiphenyl. In no case could products deriving from displacement of the nitro group be observed. In these cases, the addition of the methyl and phenyl radicals occurs at the ring positions from which the most stable σ-complexes can be formed.

The reactions of the adamantyl and methyl radicals with the two isomers 3,5-dinitro- and 4,5-dinitro-2-carbomethoxythiophenes gave some further important information (Scheme 11) (Ref.9). In the first case, we once again observe that the adamantyl gives the ipso substitution product by displacing the nitro group from the 5 position, whereas the methyl radical attacks the unsubstituted 4 position. In the second example, both radicals effect the alkyldenitration process by adding at the ipso carbon atom in position 5. The behavior of the methyl radical in this last case is particularly significant; this is the first substrate in which the two radicals present a similar reactivity.

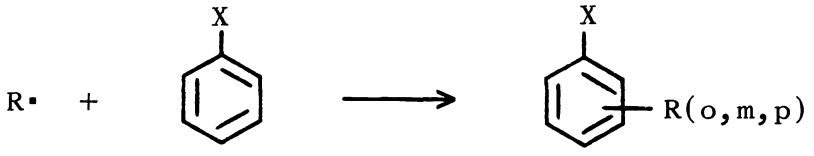
SCHEME 11



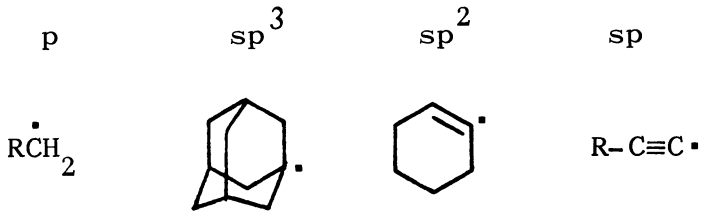
Let us now try to rationalize all these experimental results and attempt to draw some general conclusions in order to explain the observed selectivities of radical attack at the ipso or at the unsubstituted positions.

It is necessary to recall briefly some general concepts concerning the polarity of carbon radicals and the importance of polar effects in the homolytic aromatic substitution reactions. Carbon radicals present a more or less pronounced polar character, in the sense that they behave as slightly electrophilic or nucleophilic species. One way of investigating the polar characteristics of these radicals consists of measurement of the relative rates and of the distribution of isomers obtained from their reactions with benzene derivatives containing substituents with different electronic effects. From this kind of investigations the conclusion was reached that one of the most important factors, which determines the polar character of a carbon radical, is the nature of the orbital occupied by the unpaired electron (Scheme 12). Thus,

SCHEME 12



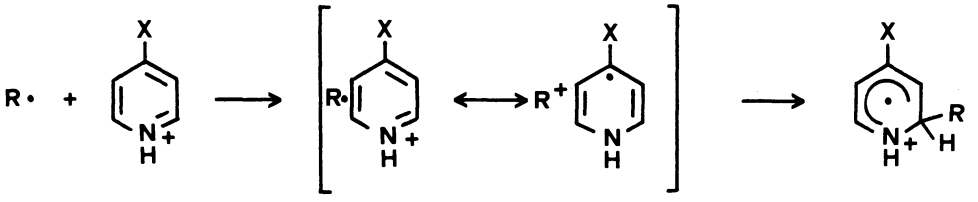
Nucleophilicity Sequence of Carbon Radicals



while phenyl and vinyl radicals possess a substantially neutral character, being rather insensitive to substituent effects, alkyl and bridgehead alkyl radicals are nucleophilic, and acetylenic radicals are slightly electrophilic (Ref.1&10).

A more sensitive model to study the structure/nucleophilicity relationship of carbon radicals has been developed by Minisci and coworkers (Ref.11). Alkyl radicals react with protonated heteroaromatic bases to give selectively the substitution products at the ring positions which are α and γ to the protonated nitrogen atom. The selectivity of these reactions has been attributed to polar effects which operate during the addition step. It has been suggested

SCHEME 13



that, with nucleophilic radicals and with strongly electron-deficient substrates (such as the protonated heteroaromatic bases), the transition state of the addition is similar to a charge transfer complex with important contribution of polar structures of the type indicated in Scheme 13. In this case the positional selectivity is dominated by the local charge density at the various ring positions and this would explain the preference of the nucleophilic radicals for attack at the α and γ positions which are conjugated with the positive nitrogen. The degree of charge development in the transition state (and hence the importance of polar effects) will obviously depend on the acceptor character of the aromatic compound and on the donor character of the radical.

Protonated 4-substituted pyridines, which are selectively substituted at the 2 position, can thus be employed as a very useful system to determine the nucleophilic character of carbon radicals as a function of their structure. The results of these works are collected in the Table 1. As expected, the 4-cyano-

TABLE 1. Relative Rates in the Homolytic Alkylation of Protonated 4-X-Pyridines

X	Me[a]	n-Bu[a]	s-Bu[a]	t-Bu[a]	Ad[b]	Ph[c]
CN	12.5	20.3	259.0	1890.0	260.0	1.9
COMe	3.6	5.6	95.6	144.0	95.0	---
Cl	2.4	---	---	11.1	9.0	1.6
H	1.0	1.0	1.0	1.0	1.0	1.0
Me	0.5	0.3	0.3	0.15	0.1	0.6
OMe	0.3	0.1	0.02	0.005	0.05	0.3

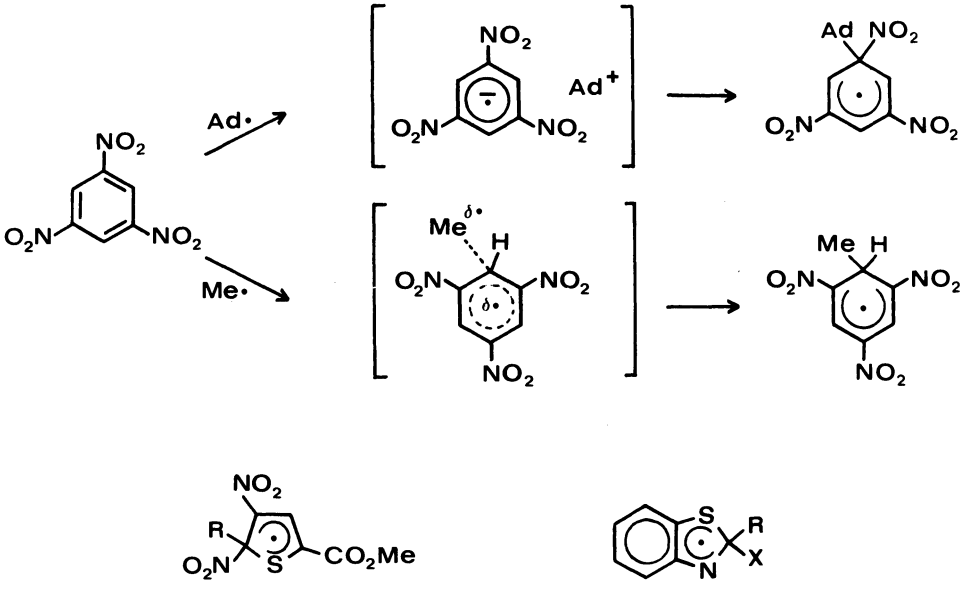
a) Ref.11. b) Ref.12. c) Ref.13.-

pyridine was the most reactive and the 4-methoxypyridine the least reactive with all the radicals employed. It can also be observed that the sensitivity to substituent effects gradually increases on passing from primary to secondary and tertiary radicals, indicating a progressively increasing nucleophilic character.

Of particular interest is the different behavior shown by the methyl and the adamantyl radicals. While the first can be considered as electroneutral, being rather insensitive to substituent effects, the adamantyl behaves as a strongly nucleophilic species. The phenyl radical is even less polar than the methyl (Ref.13). Polar effects will therefore be expected to intervene during the addition of the adamantyl radical to an electron-deficient aromatic substrate, provided it is made sufficiently electron-deficient by the presence of electron withdrawing substituents, and to be negligible with the methyl and phenyl radicals, in every case.

In the examples of ipso substitution discussed so far, the best results were always obtained with the strongly nucleophilic adamantyl radical and with strongly electron-deficient substrates.

SCHEME 14



Under these circumstances polar effects can operate in stabilizing the transition state of the addition step and the positional selectivity will be governed by the local charge density at the ring positions. This can explain the preference for the attack by the adamantyl radical at the ipso positions holding the nitro group in the 1,3,5-trinitrobenzene and in other nitrobenzene derivatives. In a similar way one can explain the competition in the attack at the ipso and at the 6 position of the 4-methyl-2-acetylpyridine by the adamantyl and s-butyl radicals.

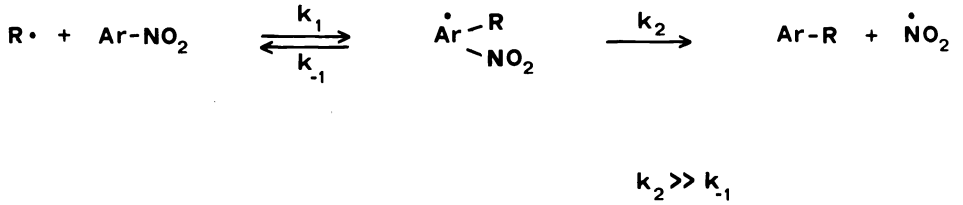
On the other hand, it is difficult to imagine that polar effects can operate in the case of the scarcely polar methyl radicals and phenyl radicals. With these species, the transition state of the addition step can rather be suggested to be close to the σ-complex intermediate; it follows that the positional selectivity will be governed by the stability of the σ-complex and addition will therefore occur at the unsubstituted positions so that the unpaired elec-

tron can be delocalized into the substituents. This argument suggests that ipso attack and ipso substitution by electroneutral radicals will occur selectively only in those particular cases in which attack at the ipso carbon atom affords the most stable σ-complex. Indeed, the reaction of methyl radicals with the 4,5-dinitro-2-carbomethoxythiophene gives the displacement product; the addition at the 5 position gives in fact the most stable intermediate (Scheme 14) which can be formed from this molecule. Other examples which confirm this idea will be presented below. Finally, in the case of the 2-X-benzothiazoles, the 2-position will always be favoured in respect to the benzo positions (Scheme 14); however the efficiency of the ipso attack and hence of the ipso substitution will be greater whenever the nature of the attacking radical and of the substituent X will allow polar effects to operate.

In all the examples discussed so far the only observed way through which the σ-complex intermediates evolve is the elimination of the group X to give the ipso substitution products. Two important questions arise at this point. In which cases the addition step can be reversible? And, how the group X is eliminated? Is this a spontaneous or an assisted process? Within the wide range of ipso σ-complex encountered it can be expected that both direct loss of the substituent and abstraction of it by some reactant probably occur with different intermediates.

In the case of nitroderivatives (Scheme 15) it can reasonably be suggested that the stability of the $\dot{N}O_2$ radical will greatly assist the elimination step, making $k_2 >> k_{-1}$, and thus leading to a practically irreversible process. The $\dot{N}O_2$ is a stable species and it is probably the best radicofugal group. All the results we have accumulated indicate that any kind of ipso intermediate in which X is equal to NO_2 will easily and spontaneously evolve towards the ipso substitution products, whatever the nature of the attacking radical and of the aromatic substrate may be. As a matter of fact, we have seen that alkyldenitration occurs with adamantyl, methyl, n-propyl and i-propyl radicals in nitrobenzenes, nitrobenzothiazole and nitrothiophenes. We shall see later on that displacement of the nitro group can easily be effected also with nitrofuran derivatives.

SCHEME 15



R• = Ad•, Me•, $EtCH_2$•, Me_2CH•

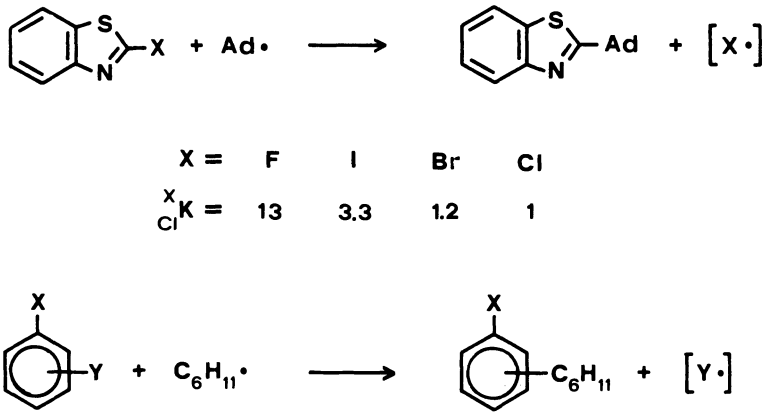
Ar = Benzene, Benzothiazole, Thiophene, Furan

Other groups X, however, can be eliminated less easily than NO_2, and some of them very likely require the assistance of another species. In some of these cases, therefore, the addition step might be reversible.

An example of the consequence of the reversibility of the addition step can be found in some alkyldehalogenation reactions (Scheme 16). The relative rates of halogen displacement in 2-halogenobenzothiazoles by the adamantyl radicals have the values, F 13, I 3.3, Br 1.2, Cl 1 (Ref.14); the same reactivity se-

quence F>I>Br>Cl was also observed by Shelton and Uzelmeier in the reaction of cyclohexyl radicals with benzene dihalides (Ref.15). The preference for

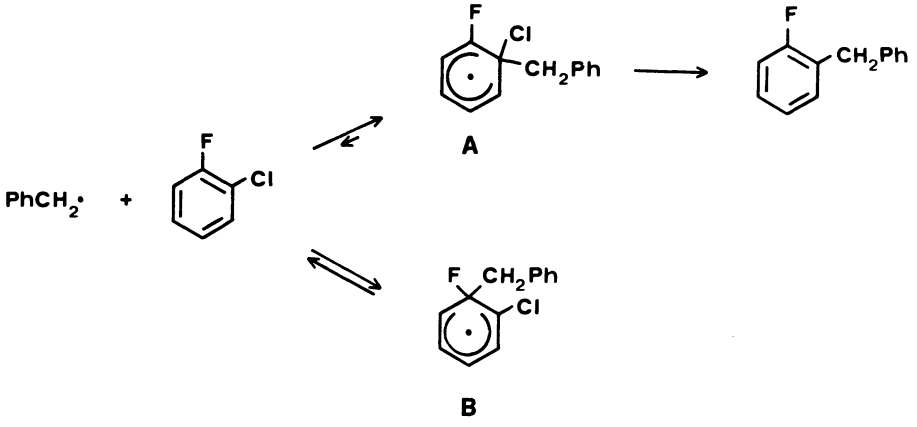
SCHEME 16



fluorine displacement may be explained by considering that fluorine has a stronger electron-withdrawing power than the other halogens, and that the attacking radicals are nucleophilic.

Different results were obtained with another nucleophilic radical. Nonhebel and coworkers have recently reported that benzyl radicals react with o-chlorofluorobenzene to give exclusively o-fluorodiphenylmethane with no traces of the product deriving from the displacement of fluorine (Ref.16). These results were explained assuming that the addition of the benzyl radical to the ipso positions is a reversible process (Scheme 17). Thus, because the carbon-fluorine bond is stronger than the carbon-chlorine bond, the ipso intermediate A is more likely to proceed to the products, whereas B would preferentially revert to the starting materials.

SCHEME 17



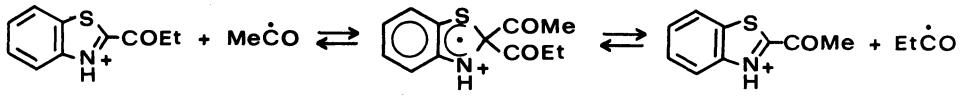
A clear-cut example of reversible radical ipso attack was found in the acyldeacylation reactions which occur in benzothiazole. Acyl radicals are nucleophilic and can easily be produced from the corresponding aldehydes by hydrogen abstraction; the electrophilic abstracting species generally is the t-butoxy

radical, easily produced in the redox reaction of t-butylhydroperoxide and ferrous salts (Scheme 18). Thus, acetyl radicals react with 2-propanoylbenzo-

SCHEME 18

$$ButOOH + Fe^{++} \longrightarrow Fe^{+++} + ButO\cdot + OH^-$$

$$ButO\cdot + MeCHO \longrightarrow ButOH + Me\dot{C}O$$



In CH_3COOH/H_2SO_4 · Yields 75%

thiazole to give the ipso substitution product, 2-acetylbenzothiazole. High yields can be obtained only by working with a large excess of acetyl radicals (Ref.17). The reverse reaction between propanoyl radicals and 2-acetylbenzothiazole can also be effected under similar conditions and with similar results. In this case the loss of one of the two acyl groups may be unassisted. Acetyl radicals are also capable of displacing a series of other groups from the 2 position of benzothiazole (Scheme 19) (Ref.17).

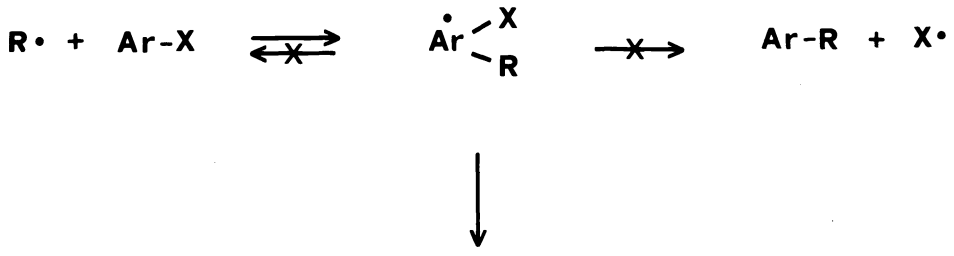
SCHEME 19

X	SO_2Ph	SOPh	COEt	SPh	F	Cl
%Conv.	90	90	90	76	70	60
%Yields	75	75	73	36	26	5

Also, in this case, the best results are obtained when polar effects can operate, i.e. when the substituent is strongly electron-withdrawing. Information about the reversibility of the addition step cannot be obtained with substituents different from the propanoyl.

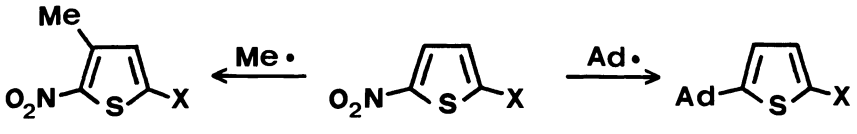
As a final aspect of the consequences of the radical ipso attack, it remains now to consider the possibility that the ipso intermediate can evolve in a different way. When the radical addition occurs at the ipso positions of an aromatic substrate which does not possess a great resonance energy, and the two substituents R and X form strong bonds with the ipso carbon atom, it can be imagined that neither of the two can be easily eliminated, and that the ipso intermediate is forced to decay by other processes different from the reversion to the starting products or the ipso substitution. Products having different structures should be formed (Scheme 20).

SCHEME 20



This is what has been observed to occur in some thiophene and furan derivatives. It is known from previous works (Ref.18) of our group that in these heteroaromatic compounds radical addition occurs almost exclusively at the α positions; it is therefore expected that the reactions of alkyl radicals with 2,5-disubstituted thiophenes and furans should preferentially give the products derived from attack at the ipso positions, particularly when polar effects can also operate. As a matter of fact, the reactions of adamantyl radicals with several 2-X,5-nitrothiophenes (with X=CO_2Me, CHO, SO_2Ph) (Scheme 21) gave rise to the

SCHEME 21

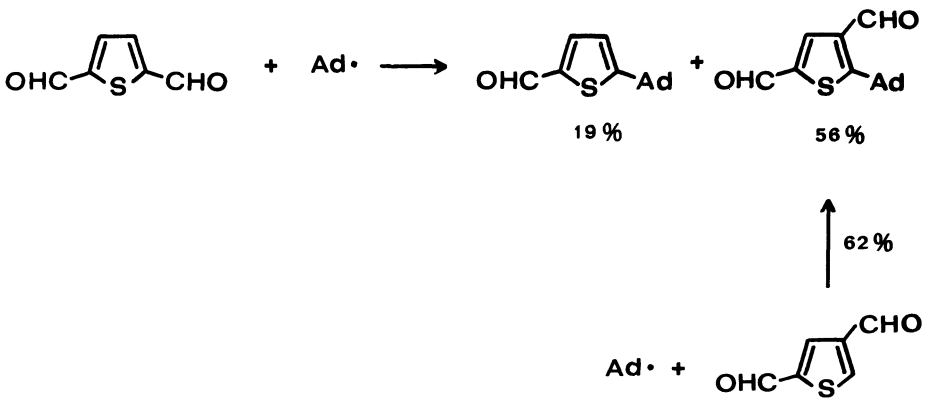


X = CO_2Me, CHO, SO_2Ph

adamantyldenitration products, whereas methyl radicals effected the substitution at the 4 position, i.e. at the ortho-like position to the strongly radical stabilizing nitro group (Ref.9). This is, therefore, a further example of the already explained different behavior of the two radicals.

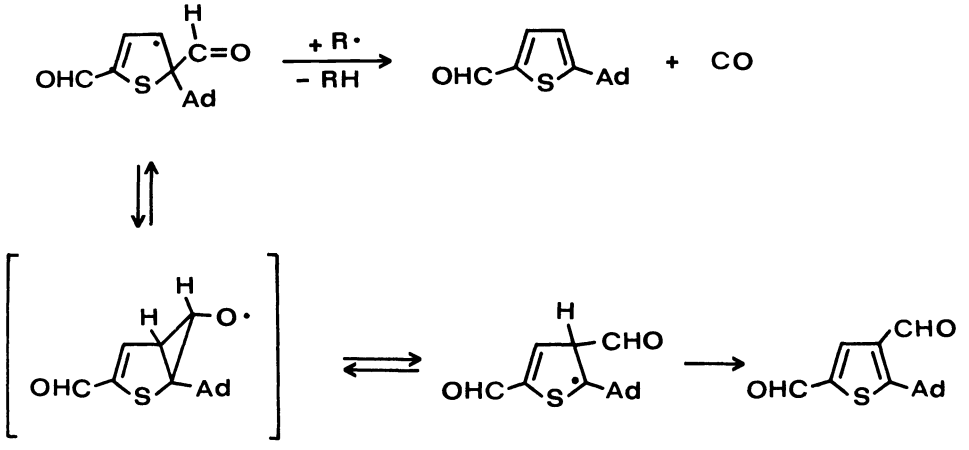
A new interesting case is observed if the adamantyl radical is allowed to react with 2,5-thiophenedicarbaldehyde (Scheme 22). The two major reaction products were the 2-adamantyl-5-thiophenecarbaldehyde and the rather unexpected rearrangement compound, 2-adamantyl-3,5-thiophenedicarbaldehyde. The structure of this latter compound was also confirmed by independent synthesis; it was obtained as the sole reaction product, from the radical adamantylation of the 2,4-thiophenedicarbaldehyde (Ref.19).

SCHEME 22



The formation of these two compounds can be explained assuming that they derive from the same ipso intermediate generated by addition at the 2 position (Scheme 23). The first compound is the product of the adamantyldeformylation. The loss of the formyl group, however, very likely requires the assistance of another species which abstracts the aldehydic hydrogen. The ipso intermediate, therefore, preferentially gives rise to another reaction and we suggest that the rearrangement product originates from that. Intramolecular addition of the carbon radical in the 3 position to the aldehydic carbonyl affords a cyclopropoxy radical which then can fragment from both sides; cleavage at carbon 2 affords a new σ-complex intermediate, which is no longer ipso, and which can easily rearomatize to give the rearrangement compound.

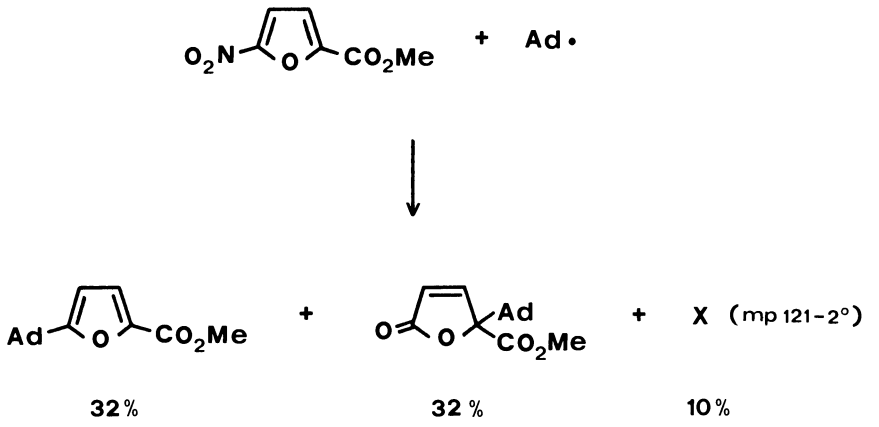
SCHEME 23



The formation of this latter compound represents a remarkable example of one of the possible ways through which the ipso intermediates can evolve, namely the 1,2-shift of the ipso substituent.

Other possible fates of radical ipso intermediates were observed in the case of furan derivatives (Ref.20). The reaction of adamantyl radicals with the 5-nitro-2-carbomethoxyfuran afforded a mixture of three products (Scheme 24). The first one was simply the product of adamantyldenitration and the second one could easily be identified as an α,β-unsaturated γ-lactone. Identification

SCHEME 24



of the third compound, on the contrary, was not straightforward; its spectral properties, in fact, presented some ambiguities (Scheme 25). The proton nmr

SCHEME 25

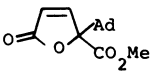
COMPOUND "X"

a) H nmr : δ 6.9 (d,1H), 6.3 (d,1H,J=6Hz), 3.8 (3H), 2.0 (3H), 1.7 (12H)

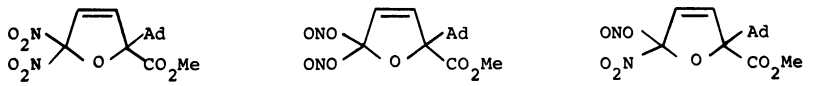
b) ^{13}C nmr : the absorption due to carbon 5 was not observed

c) Ir : the absorption band in the 1300-1370 cm^{-1} region was extremely weak

d) C.I.Mass Sp.: M = 352 : $C_{16}H_{20}N_2O_7$

e) X decomposes on heating to give nitrous vapours and 

Possible Structures

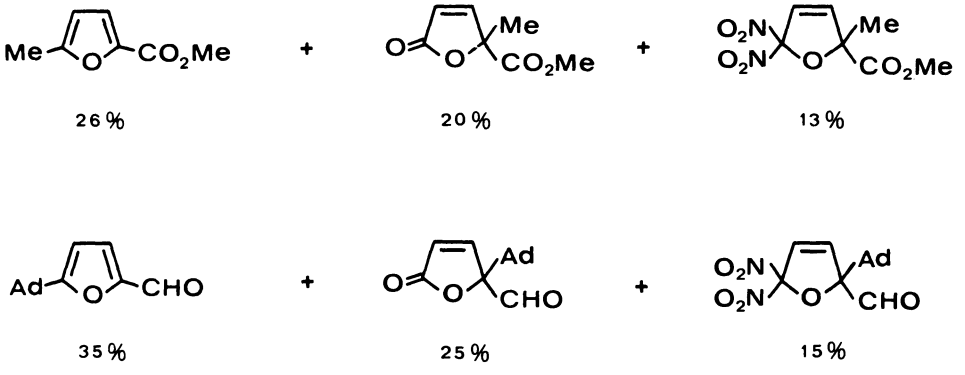


spectrum clearly indicated the presence of two olefinic protons, the carbomethoxy and the adamantyl groups. However in the ^{13}C nmr spectrum the absorption due to the carbon atom in the 5 position was not observed; this could be due to the fact that this is a quaternary carbon atom with an unusually long relaxation time. The absorption due to the symmetric stretching of the NO_2 group in the 1300-1370 cm^{-1} region of the infrared spectrum was extremely weak. In the electron impact mass spectrum the molecular ion could not be observed. However, from the chemical ionization mass spectrum (run with ammonia) a molecular weight of 352 could be obtained, which corresponds to the empirical formula $C_{16}H_{20}N_2O_7$. This indicates that one or two groups, accounting for two nitrogen and four oxygen atoms, must be linked at the carbon 5. Moreover, from the chemical point of view, compound X decomposes on heating to yield quantitatively the lactone and liberating nitrous vapours. All this information leads

one to write three possible structures; a geminal dinitro,or dinitrite derivative, and a nitro-nitrite compound. This problem was finally solved by X-ray analysis,which unambiguously demonstrated that compound X has the structure of a geminal dinitro derivative, namely the 5,5-dinitro-2-adamantyl-2-carbomethoxy-2,5-dihydrofuran.

A similar mixture of three products having analogous structures (Scheme 26) was also obtained from the reactions of the same substrate with methyl radicals and of the 5-nitro-2-furancarbaldehyde with adamantyl radicals (Ref.20).

SCHEME 26

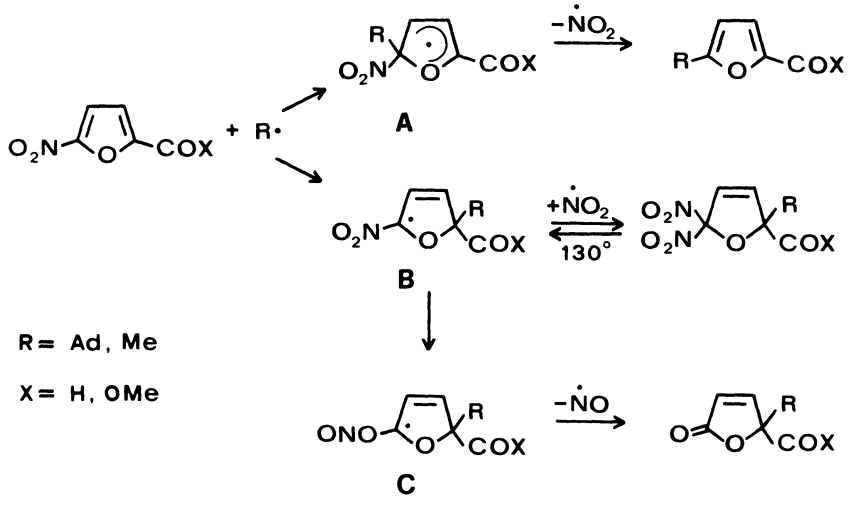


It is important to note that in the case of this furan derivative the methyl radical adds easily to the ipso positions, because the intermediates which form from these positions are more stable than those which should form from the addition at the unsubstituted 3 or 4 positions. The two latter compounds formed in the second example indicate once again that elimination of the formyl group from the ipso position is not an easy process: products of adamantyldeformylation in fact were not formed.

The proposed mechanism to explain the formation of these three compounds is reported in Scheme 27. Addition of the alkyl radicals clearly occurs at both the ipso positions to give the two ipso intermediates A and B; the fates of these two σ-complexes are completely different, however. The radical A easily eliminates the ipso NO_2 substituent, to give the alkyldenitration product. In contrast, ipso substitution is not observed from the radical B, formed by addition at the 2 position. In this case both the alkyl and acyl groups form strong bonds with the ipso carbon atom and, moreover, the energy gain in rearomatization to furan is rather low; as a consequence neither of the two substituents can be easily eliminated and the intermediate B will survive enough to give other types of reactions.

Coupling with the other stable radical present in solution, i.e. the $\dot{N}O_2$ produced in the alkyldenitration reactions, can reasonably explain the formation of the geminal dinitro compound. The formation of the lactone is not so straightforward, however. Although direct evidence is difficult to obtain, we suggest that the nitro group in B isomerizes to a nitrite giving the new σ-complex C, which then fragments into the $\dot{N}O$ radical and the lactone. This reaction shows a close resemblance to the photochemical rearrangement of nitro aromatic compounds into aryloxy radicals; these rearrangements in fact are often postulated to proceed via the nitrite (Ref.21). The quantitative transformation of the dinitro compound into the lactone, which occurs on heating, very likely follows the same route. This reaction is suggested to proceed through the homolytic fission of the carbon-nitrogen bond to regenerate B which then rearranges and fragments as indicated above.

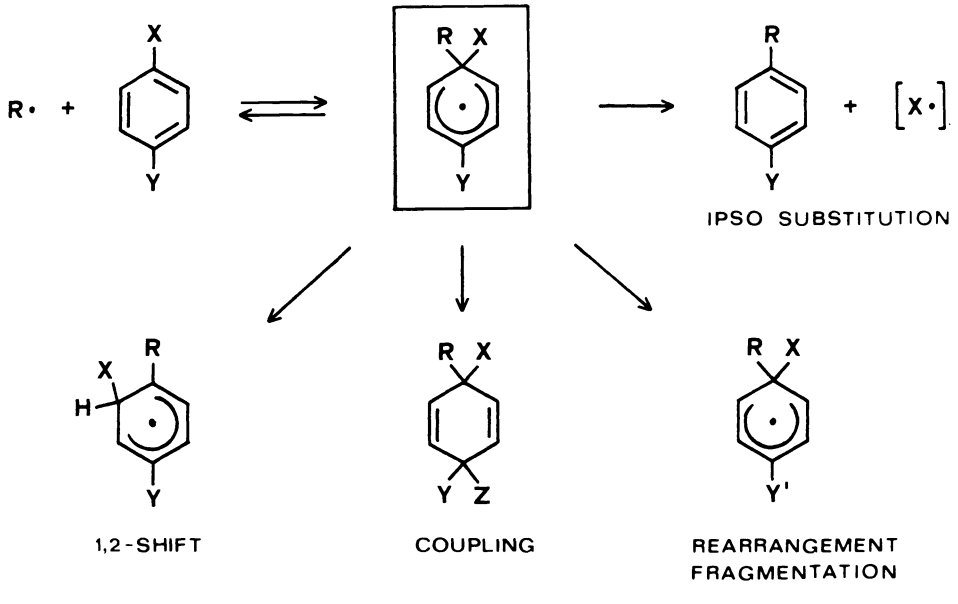
SCHEME 27



From these reactions we can thus find several other examples of the possible behavior of radical ipso intermediates, namely the coupling with other radicals, the rearrangement and the fragmentation of a substituent remote from the ipso position.

In conclusion we can say that it is now quite clear that, as with electrophiles and nucleophiles, the addition of a radical at an ipso position can be as important or even more important than the addition at the unsubstituted positions of aromatic compounds. We have seen that radical ipso attack is much more likely to occur when polar effects can intervene and stabilize the transition state of the addition. In the examples we have discussed nucleophilic

SCHEME 28



radicals easily add at the ipso position of aromatic compounds containing electron-withdrawing substituents. It can be suggested that polar effects can equally well facilitate the addition of electrophilic radicals at the ipso positions of aromatic compounds holding electron-releasing substituents, and this could represent a promising area of future investigations.
Depending on the nature of the attacking radical, of the ipso substituent and of the aromatic substrate, radical ipso intermediates can evolve in several ways. The processes which have been observed so far, and which are sketched in Scheme 28, are ipso substitution, return to the starting products, 1,2-shift of the ipso substituent, coupling with other radicals and rearrangement and fragmentation of a group remote from the ipso substituent.

The most important and most frequently encountered consequence of ipso attack is the ipso substitution. Several displacement reactions have been described which occur with great selectivity and in high yields. Thus radical ipso substitutions also have a considerable synthetic importance, particularly as far as the alkyldenitrations and alkyldeacylations are concerned.

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