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Radical Ipso Attack and Ipso Substitution in Aromatic Compounds

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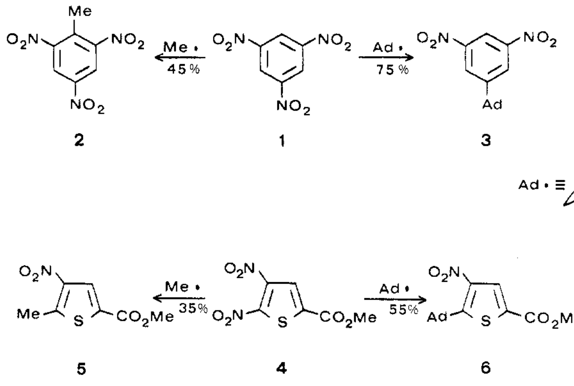
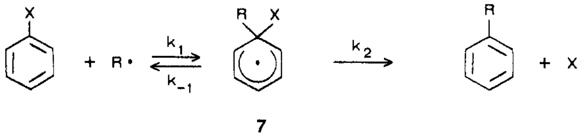
After the introduction by Perrin and Skinner[1] of the prefix "ipso" to denote a substituted position in an aromatic ring, displacements of groups other than hydrogen have been generally referred to as ipso substitutions.[2] Ipso substitution is the usual process occurring in nucleophilic aromatic substitutions, and it is also well documented in electrophilic substitutions.[2,3] In the field of radical reactions, on the contrary, ipso substitution has not received particular attention; until a few years ago, in fact, in the examples reported in the literature,[4] the displacement of the substituent represented a secondary process, the main reaction being the well-established displacement of hydrogen from the unsubstituted ring positions. Very recently, however, many examples of synthetically useful radical ipso substitution have been observed, and these reactions have therefore been investigated in some detail. For example, if 1,3,5-trinitrobenzene (**1**) is allowed to react with methyl radicals (Scheme I) the only product observed is the expected 2,4,6-trinitrotoluene (**2**); however, when the bridgehead 1-adamantyl (Ad·) radical is employed, the product of ipso substitution, 1-(1-adamantyl)-3,5-dinitrobenzene (**3**), is formed in 75% yields.[5] Moreover, 4,5-dinitro-2-carbomethoxythiophene (**4**) reacts with Me· and Ad· to give in both cases the products of ipso substitution, **5** and **6**, respectively.[6]

It is believed that these radical ipso substitutions occur via the addition–elimination mechanism of Scheme II, i.e., by the generally accepted mechanism for homolytic aromatic substitutions.

Scheme I



Scheme II

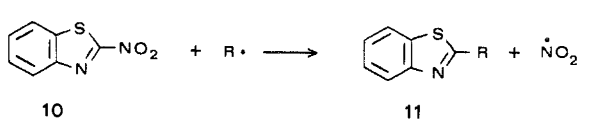


Scheme III

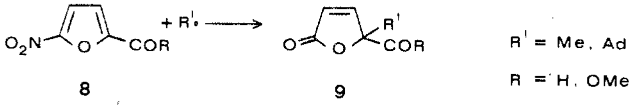
$$S_2O_8^{=} + Ag^+ \longrightarrow SO_4^{=} + SO_4^{\cdot -} + Ag^{++}$$

$$SO_4^{\cdot -} + Ag^+ \longrightarrow SO_4^{=} + Ag^{++}$$

$$RCOOH + Ag^{++} \longrightarrow R\cdot + CO_2 + H^+ + Ag^+$$



Ipso substitution is not always the only consequence of ipso attack. Very recently examples have been observed in which the ipso intermediate **7** gives rise to other processes. Thus, for example, the reaction of methyl and adamantyl radicals with the furan derivatives **8** gives rise, among other products, to the lactones **9** in which both the substituents linked to the ipso carbon are retained.[7]



The examples reported above suggest a number of questions which need to be answered in order to understand the importance and the limits of radical ipso attack and ipso substitution. In the first place it is necessary to gain information about the factors which control the selectivity of the attack at an ipso or at an unsubstituted position; in particular, it is important to know the requisites that the attacking radicals and the aromatic substrates must possess to make ipso attack

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(1) C. L. Perrin and G. A. Skinner, *J. Am. Chem. Soc.*, **93**, 3389 (1971).

(2) R. B. Moodie and K. Schofield, *Acc. Chem. Res.*, **9**, 287 (1976).

(3) S. R. Hartshorn, *Chem. Soc. Rev.*, **3**, 167 (1974).

(4) Most of the reported examples concern the displacement of halogen atoms from aryl halides which can be effected by phenyl [P. Lewis and G. H. Williams, *J. Chem. Soc. B*, 120 (1969)], cyclohexyl [J. R. Shelton and C. W. Uzelmeier, *Recl. Trav. Chem. Pays-Bas*, **87**, 1211 (1968)], 1-adamantyl [A. Mangini, P. Spagnolo, D. Tassi, M. Tiecco, and P. Zanirato, *Tetrahedron*, **28**, 3485 (1972)], pentafluorophenyl [J. M. Birchal, R. H. Haszeldine, and A. R. Parkinson, *J. Chem. Soc. C*, 4966 (1962)], pentafluorobenzoyloxy [P. H. Holdam and G. H. Williams, *ibid.*, 1260 (1970)], and phenylsulfonyl radicals [L. Benati, C. M. Camaggi, and G. Zanardi, *J. Chem. Soc., Perkin Trans. 1*, 2817 (1972)]. Some interesting radical rearrangements involve an ipso intermediate and can therefore be seen as the intramolecular version of radical ipso substitution. See, for example, S. Winstein, R. Meck, S. Lapporte, and R. Baird, *Experientia*, **12**, 138 (1956); D. H. Hey, G. H. Jones, and M. J. Perkins, *Chem. Commun.*, 1438 (1970); H. Sukurai and A. Hosomi, *J. Am. Chem. Soc.*, **92**, 7507 (1970); R. H. Thomson and A. G. Wylie, *J. Chem. Soc. C*, 231 (1966).

(5) L. Testaferri, M. Tiecco, and M. Tingoli, *J. Chem. Soc., Perkin Trans. 2*, 469 (1979).

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the preferred process. Once the addition step has occurred and the ipso intermediate, **7**, has been formed, a further problem concerns the factors which govern the fate of the ipso intermediate and direct the reaction toward the ipso substitution product, the return to starting materials, or other products.

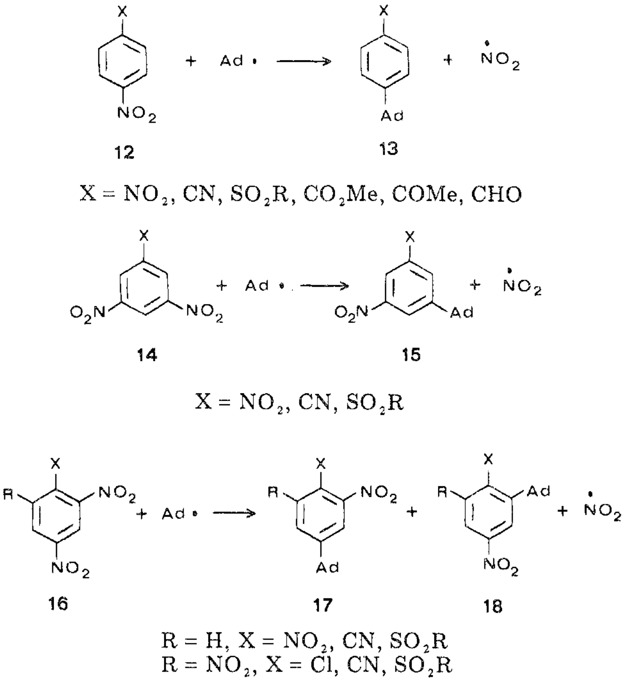
Ipso Substitution

In this section we will examine those examples in which the only observed consequence of ipso attack is the elimination of group X (Scheme II), i.e., the ipso substitution. Most of these reactions involve alkyl radicals. Unless otherwise specified, alkyl radicals were produced by the silver-catalyzed oxidative decarboxylation of the corresponding carboxylic acids[8] (Scheme III), and the reactions were carried out in acetonitrile-water solutions.

One of the most interesting examples of radical ipso substitution is the process of alkyldenitration which has been observed to occur both in homoaromatic and in heteroaromatic compounds. The reaction of 1-adamantyl radicals with 2-nitrobenzothiazole (**10**, Scheme III) affords 2-(1-adamantyl)benzothiazole (**11**, R = Ad) in quantitative yields; other radicals, as Et(Me)CH· or Me_2CHCH_2·, give the same reaction but in lower yields (40%).[9]

Alkyldenitration by 1-adamantyl radicals can be 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, and *o*- and *m*-dinitrobenzenes,[9] very good results were obtained with 4-nitro-1-X-benzenes (**12**, X = NO_2, CN, SO_2R, CO_2Me, COMe, CHO), 3,5-dinitro-1-X-benzenes (**14**, X = NO_2, CN, SO_2R), 2,4-dinitro-1-X-benzenes (**16**, R = H, X = NO_2, CN, SO_2R), and 2,4,6-trinitro-1-X-benzenes (**16**, R = NO_2, X = Cl, CN, SO_2R) whenever X was an electron-withdrawing substituent[5,9] (Scheme IV).

Scheme IV

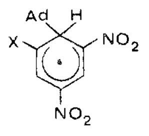


X = NO_2, CN, SO_2R, CO_2Me, COMe, CHO

X = NO_2, CN, SO_2R

R = H, X = NO_2, CN, SO_2R
R = NO_2, X = Cl, CN, SO_2R

As indicated in Scheme IV, the reactions are very selective, the only products obtained being those of adamantyldenitration, **13**, **15**, **17**, and **18**, in yields ranging from 50 to 75%; displacement of group X was never observed, unless X was a nitro group as in 1,4-dinitrobenzene (**12**, X = NO_2) and in 1,2,4-trinitrobenzene (**16**, R = H, X = NO_2). Attack at the unsubstituted nuclear positions was never detected. Once the nitro group has been replaced by the bridgehead alkyl group the reactions do not proceed further; only compound **18** (R = NO_2, X = CN) gives the disubstituted product 2,4-bis(1-adamantyl)-6-nitrobenzonitrile. These results clearly indicate that the presence of electron-withdrawing substituents which subtract negative charge from the ring is one of the requisites that the aromatic compounds must possess in order to give ipso substitution with Ad·. Competition between the displacement of the nitro groups from the 4 and the 2 positions is observed in compounds **16**; in every case ipso substitution at 4 is preferred (2:1) and becomes the only process when X is a sulfonyl group. Substitution of the nitro group from the 4 position is preferred, compared with substitution from the 1 position (2:1), also in the case of the 1,2,4-trinitrobenzene, in spite of the fact that the competitive attack at 1 would give a more stable σ-complex intermediate. The results obtained with nitrobenzenes lead to the general conclusion that the selectivity of these substitution reactions by adamantyl radical is not governed by the stability of the intermediates; in fact, the most stable σ complex from **14** is **19** and those deriving from **16** are **20** and **21**, but the products which should form from these intermediates were not observed.



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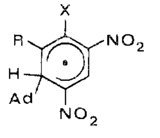

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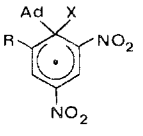

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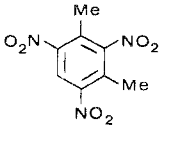
A completely different behavior was shown by the methyl and the phenyl radicals. In their reactions with polynitrobenzenes these two radicals, in fact, gave rise exclusively to the products deriving from the attack at the unsubstituted ring positions. Thus a mixture of 2,4,6-trinitrotoluene (**2**) and 2,4,6-trinitro-*m*-xylene (**22**) was obtained from 1,3,5-trinitrotoluene (**1**) and methyl radicals;[5,10] similarly, phenyl radicals reacted with **1** and **16** (R = H, X = NO_2) to give the trinitrobiphenyls **23** and **24**, respectively.[5] In no case could products deriving



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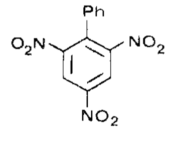

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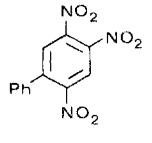

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(6) P. Cogolli, F. Maiolo, L. Testaferri, M. Tiecco, and M. Tingoli, unpublished results.

(7) P. Cogolli, L. Testaferri, M. Tiecco, and M. Tingoli, *J. Chem. Soc., Chem. Commun.*, 800 (1979).

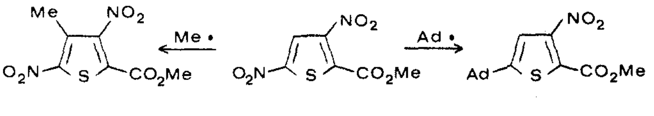
(8) J. H. Anderson and J. K. Kochi, *J. Am. Chem. Soc.*, **92**, 1961 (1970).

(9) L. Testaferri, M. Tiecco, M. Tingoli, M. Fiorentino, and L. Troisi, *J. Chem. Soc., Chem. Commun.*, 93 (1978).

(10) U. Rudqvist and K. Torssell, *Acta Chem. Scand.*, **25**, 2183 (1971); K. Torssell, *Angew. Chem. Int. Ed. Engl.*, **11**, 241 (1972).

from displacement of the nitro group be observed.

The reactions of Ad· and Me· radicals with the two isomers 3,5-dinitro-2-carbomethoxythiophene (**25**) and 4,5-dinitro-2-carbomethoxythiophene (**4**) gave further interesting results;[6] with **25**, once again, methyl radicals attack the unsubstituted ring position to give **26**, while the adamantyl radicals give the ipso substitution product, **27**, by displacing the nitro group from the 5 position. With compound **4**, on the other hand, both the Me· and Ad· radicals give the alkyldenitration products **5** and **6**, respectively (see above), from the attack at the ipso carbon atom in position 5.

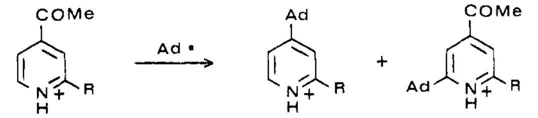


26 **25** **27**

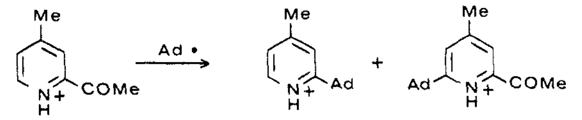
The formation of 4-nitro-5-methyl-2-carbomethoxythiophene (**5**) represents the first example of an ipso substitution effected by methyl radicals and, as we shall see below, has a relevant mechanistic importance.

Radical denitration products were also detected in the chlorination of *p*-chloro- and *p*-bromonitrobenzenes[11] and in the reactions of pentafluoronitrobenzene with C_6F_5· and $C_6F_5CO_2$·.[12] Displacement of the nitro group by hydroxy radicals, produced in several ways, has also been reported.[13]

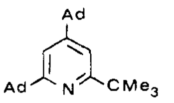
A second class of ipso substitution reactions which has been investigated in detail is alkyldeacylation; this process occurs in the field of the heteroaromatic compounds. When an acyl group is present in the 2 or 4 positions of pyridine or quinoline, attack by an alkyl radical at the ipso carbon competes with attack at the unsubstituted 2 or 4 positions; in no case could products deriving from the addition at the β positions be identified. The reaction of 4-acetylpyridine (**28**, R = H) or 2-*tert*-butyl-4-acetylpyridine (**28**, R = CMe_3) with adamantyl radicals[14,15] afforded the products of ipso substitution, **29**, but attack at the 6 position to give **30** was largely preferred (the ratio of **29** to **30** was 1:3). Similar results were obtained with the *sec*-butyl radical.[15] With 2-acetyl-4-methylpyridine (**31**) again competition between the two reactions was observed, but in this case ipso substitution was preferred (the ratio of **32** to **33** was 3:2). These reactions were carried out as indicated in Scheme III, and the reactive species are very likely the protonated pyridines.



28 **29** **30**



31 **32** **33**



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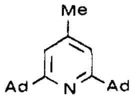

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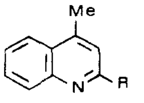

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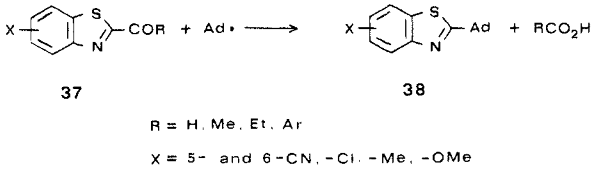
Compounds **30** (R = CMe_3) and **33** further react with Ad· to afford exclusively the ipso substitution products **34** and **35** in 70% yields.[15] In a similar way 2-(2-methylpropanoyl)-4-methylquinoline reacts with $CH_3(CH_2)_2CH_2$· and $CH_3CH_2\dot{C}HCH_3$ radicals to give quantitatively the alkyldeacylation compounds **36**.[16,17]

Scheme V



Displacement of acyl groups from the 2 position of benzothiazoles (**37**) can be easily effected by the adamantyl radical to give the 2-(1-adamantyl)benzothiazoles (**38**) in 50–60% yields[18,19] (Scheme V). Competitive experiments between 2-acetylbenzothiazole and 5- and 6-substituted 2-acetylbenzothiazoles were performed in order to determine the effect of substituents in these adamantyldeacylation reactions. The following values of relative rates were obtained: 6-CN, 10.92; 6-Cl, 2.3; 5-Cl, 2.18; 5-OMe, 1.26; 5,6-H, 1.00; 5-Me, 0.86; 6-Me, 0.60; 6-OMe, 0.46; a satisfying Hammett correlation ($\rho = 1.4$) was obtained using σ_p values for the substituents in the 6 position and σ_m values for those in the 5 position.[20] These results indicate that the electron density at the ring position suffering attack by the alkyl radical is important in determining the reactivity of these substrates and, in particular, that the reaction is facilitated by electron-withdrawing substituents. A similar conclusion was reached from the results of the alkyldenitration reactions described above.

Finally, displacement of the acetyl group from **37** (R = Me, X = H) can also be effected by other radicals, but with considerably lower efficiency; thus, Et(Me)CH·, Me_2CH·, and Me· radicals give the ipso substitution products in 30%, 32%, and 9% yields, respectively.[19]

We have now sufficient experimental data to attempt to draw some general conclusions and to suggest an

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(11) C. R. Everly and J. G. Traynham, *J. Am. Chem. Soc.*, **100**, 4316 (1978); *J. Org. Chem.*, **44**, 1784 (1979).

(12) P. H. Oldham and G. H. Williams, *J. Chem. Soc. C*, 1260 (1970).

(13) Fr. Fichter and G. Bonhote, *Helv. Chim. Acta*, **3**, 395 (1920); H. Loebl, G. Stein, and J. Weiss, *J. Chem. Soc.*, 2704 (1950); K. Eiben, D. Schulte-Frohlinde, C. Suarez, and H. Zorn, *Int. J. Radiation Phys. Chem.*, **3**, 409 (1971).

(14) M. Fiorentino, L. Testaferri, M. Tiecco, and L. Troisi, *J. Chem. Soc., Perkin Trans. 2*, 87 (1977).

(15) M. Fiorentino, L. Testaferri, M. Tiecco, and L. Troisi, *J. Chem. Soc., Chem. Commun.*, 329 (1976).

(16) T. Caronna, A. Citterio, and M. Bellatti, *J. Chem. Soc., Chem. Commun.*, 987 (1976).

(17) A. Arnoldi, M. Bellatti, T. Caronna, A. Citterio, F. Minisci, O. Porta, and G. Sesana, *Gazz. Chim. Ital.*, **107**, 491 (1977). The alkyl radicals were produced by the cuprous acetate catalyzed decomposition of the corresponding acyl peroxides.

(18) M. Fiorentino, L. Testaferri, M. Tiecco, and L. Troisi, *J. Chem. Soc., Chem. Commun.*, 316 (1977).

(19) M. Fiorentino, L. Testaferri, M. Tiecco, and L. Troisi, *J. Chem. Soc., Perkin Trans. 2*, 1679 (1977).

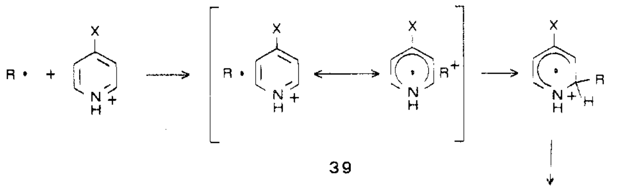
(20) This is justified by the fact that the effect of substituents in benzothiazole is mainly transmitted through the nitrogen atom with little intervention by the sulfur atom: P. E. Todesco and P. Vivarelli, *Gazz. Chim. Ital.*, **92**, 1221 (1962).

Table I
Relative Rates in the Radical Alkylation of Protonated 4-Substituted Pyridines

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

[a] Reference 25. [b] Reference 24. [c] Reference 14.

explanation for the observed selectivity of radical attack at the ipso or at the unsubstituted ring positions. In order to discuss this aspect it is worthwhile to briefly recall some general concepts concerning the polarity of carbon radicals and the importance of polar effects in free-radical reactions and in aromatic substitutions in particular.[21] It is now well documented that organic free radicals possess 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 carbon radicals consists of the 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 investigation the conclusion was reached that while aryl 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.[22,23] A more sensitive model to study the structure/nucleophilicity relationship of carbon radicals has been developed by Minisci and co-workers.[21,24,25] Alkyl radicals react with protonated heteroaromatic bases (pyridine, quinoline, benzothiazole, etc.) to give excellent yields of the substitution products; radical attack occurs selectively at the ring positions which are α or 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 that with nucleophilic radicals and with strongly electron-deficient aromatic compounds (such as protonated pyridines) the transition state is similar to a charge transfer complex, **39**, and that the positional selectivity is governed by the local charge density at the various positions of the aromatic ring; this would explain the preference of the nucleophilic radical for attack at the α and γ positions which are conjugated with the positive nitrogen. The degree of charge development in the transition state will 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 in 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 Table I. As expected, the 4-cyanopyridine 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.



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Of particular interest is the different behavior shown by the methyl and phenyl radicals on one hand and the 1-adamantyl on the other. While the first two can be considered as electroneutral, being rather insensitive to substituent effects, the Ad• behaves as a strongly nucleophilic radical;[14,26] polar effects will therefore be expected to intervene during the addition of Ad• to aromatic compounds (provided they are made sufficiently electron deficient by the presence of electron-withdrawing substituents) and to be negligible with the Me• and Ph• in every case.

For the reactions of alkyldeacylation which have been observed with protonated pyridines and quinolines it is reasonable to assume that the transition state of the addition is similar to **39**. The activation of the α and γ positions would thus explain the competition of the attack at the ipso and at the unsubstituted positions observed with the acetylpyridines **28** and **31**; in compounds **30** (R = CMe_3), **33**, and **36**, on the contrary, the attack at the ipso positions possessing the acyl groups is the only possible process because the other α and γ positions are occupied by the alkyl groups. With the acylbenzothiazoles **37** very good results are obtained with the adamantyl radical; with other less nucleophilic radicals polar effects cannot be so important as with the Ad•, and the ipso substitution reaction becomes less efficient. Of particular relevance are the reactions of alkyl radicals with nitrobenzenes. The displacement of the nitro group is observed only with the nucleophilic adamantyl radical and with the strongly electron-deficient compounds **12**, **14**, **16**, **25**, and **4** (for the reaction of **4** with Me•, see below); under these circumstances the transition state of the addition step can be suggested to have the character of a charge-transfer complex. As in the case of protonated pyridines, the positional selectivity will be governed by the charge density at the various ring positions, and this would explain the preference of the Ad• for addition at the carbon atoms holding the nitro groups, even if this does not lead to the formation of the most stable σ-complex intermediates.

On the other hand, it is difficult to imagine that polar effects can operate in the case of the scarcely polar methyl and phenyl radicals. With these species the transition state of the addition step can rather be sug-

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(21) A number of excellent reviews are available for a more detailed discussion of this subject: F. Minisci, *Top. Curr. Chem.*, **62**, 1 (1976); F. Minisci and O. Porta, *Adv. Heterocycl. Chem.*, **16**, 123 (1974); A. Citterio, F. Minisci, O. Porta, and G. Sesana, *J. Am. Chem. Soc.*, **99**, 7960 (1977); F. Minisci and A. Citterio, *Adv. Free Radicals*, **6**, in press.

(22) M. J. Perkins, "Free Radicals", J. K. Kochi, Ed., Vol. 2, Wiley, New York, 1973, p 123.

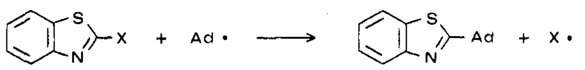
(23) M. Tiecco, *MTP Int. Rev. Sci., Org. Chem. Ser. Two*, **10**, 25 (1975).

(24) F. Minisci, R. Mondelli, G. P. Gardini, and O. Porta, *Tetrahedron*, **28**, 2403 (1972).

(25) A. Clerici, F. Minisci, and O. Porta, *Gazz. Chim. Ital.*, **103**, 171 (1973).

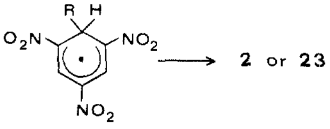
(26) L. Testaferri, M. Tiecco, P. Spagnolo, P. Zanirato, and G. Martelli, *J. Chem. Soc., Perkin Trans. 2*, 662 (1976).

Scheme VI

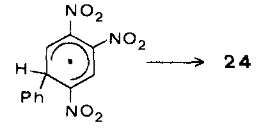


X	NO_2	SO_2Ph	SOPh	COMe	F	Cl	Br	I	SMe	OMe
% convn	100	100	100	100	50	40	40	50	50	10
% yields	95	80	80	70	50	50	60	60	60	40

gested 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 ring positions from which the most stable intermediates can be formed. Thus the reaction of Me· and Ph· with 1,3,5-trinitrobenzene (**1**) and 1,2,4-trinitrobenzene (**16**, R = H, X = NO_2) will proceed through the intermediates **40** (R = Me or Ph)



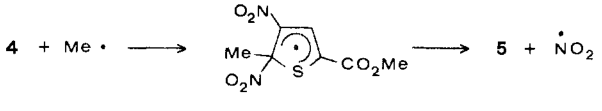
40



41

and **41** so that the unpaired electron can be delocalized by the nitro groups.

This argument suggests that selective ipso attack and ipso substitution by electroneutral radicals will occur only in those particular cases in which attack at the ipso carbon atom affords the most stable σ complex. Indeed, the reaction of Me· with 4,5-dinitro-2-carbomethoxythiophene (**4**) does give the displacement product **5**; the intermediate **42** is in fact the most stable radical which can be formed from **4**.

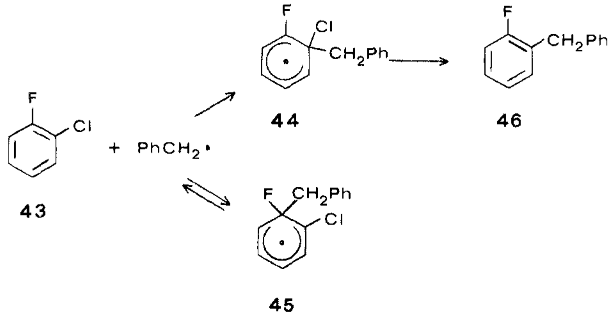


42

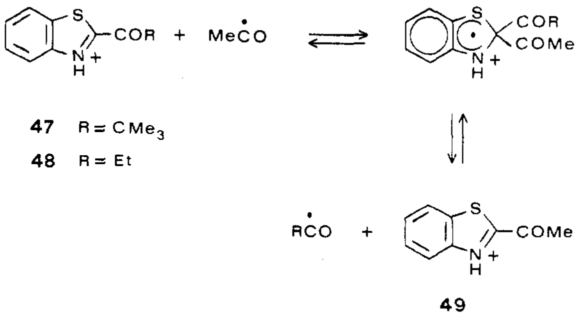
With aromatic compounds in which the σ complexes deriving from addition at the ipso or at the unsubstituted positions have comparable stability the two processes will be in competition, and mixtures of products deriving from the displacement of the substituent and of the hydrogen atoms will be obtained. This is indeed what occurs in the previously reported examples of ipso substitution (see ref 4) which have been observed in substituted benzenes.

Besides alkyldenitration and alkyldeacylation, several other radical ipso substitutions have been recently described. As is indicated in Scheme VI, many groups can be displaced from the 2 position of benzothiazole by the adamantyl radical.[18]

Scheme VII



Scheme VIII



It can soon be noticed that very good results are obtained whenever the substituent X is a strongly electron-withdrawing substituent; conversion and yields become considerably lower with other groups such as halogens, thiomethoxy, and methoxy. Competitive experiments were carried out with the 2-halogenobenzothiazoles in order to measure the relative rates of the halogen displacements by the 1-adamantyl radical.[27] The following values were obtained: F, 13; I, 3.3; Br, 1.2; Cl, 1.0. The same reactivity sequence, F > I > Br > Cl, was also observed in the reaction of cyclohexyl radicals with aryl dihalides in which ipso substitution was in competition with substitution of hydrogen.[28] The preference for fluorine displacement may be explained by considering that the attacking radicals are nucleophilic and that fluorine has a stronger electron-withdrawing power than the other halogens. On the contrary, benzyl radicals, produced by the thermal decomposition of dibenzylmercury, react with *o*-chloro- (**43**) and *o*-bromofluorobenzene to give exclusively *o*-fluorodiphenylmethane (**46**); products deriving from the displacement of fluorine or hydrogen were not observed.[29] This was explained by assuming that, owing to the nucleophilic character of the benzyl radical,[30] the substitution occurs by a route involving significant electron transfer, and indeed the more electron-deficient tri- and tetrachlorobenzenes gave better yields of the substitution products.[29] The preference for chlorine displacement is very likely due to the fact that the addition of the benzyl radicals is a reversible process; thus, because the C–F bond is stronger than the C–Cl bond, the ipso intermediate **44** is more likely to proceed to the product **46**, whereas **45** would preferentially revert to the starting materials (Scheme VII). As a matter of fact, the reversibility of the addition of benzyl radicals in the benzylation of benzene has been suggested on the basis of thermochemical data,[31] and it has

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(27) M. Fiorentino, L. Testaferri, M. Tiecco, and L. Troisi, unpublished results.

(28) J. R. Shelton and C. W. Uzelmeier, *Recl. Trav. Chem. Pays-Bas*, 87, 1211 (1968).

(29) R. Henriquez, W. N. Mackenzie, N. McPhail, and D. C. Nonhebel, "Radicaux Libres Organiques", CNRS, Paris, 1978, p 309; abstract of paper presented at the 2nd International Symposium on Organic Free Radicals, Aix-en-Provence, July 1977.

(30) A. Clerici, F. Minisci, and O. Porta, *Tetrahedron*, **29**, 2775 (1973).

been demonstrated recently in the benzylation of protonated quinoline.[32]

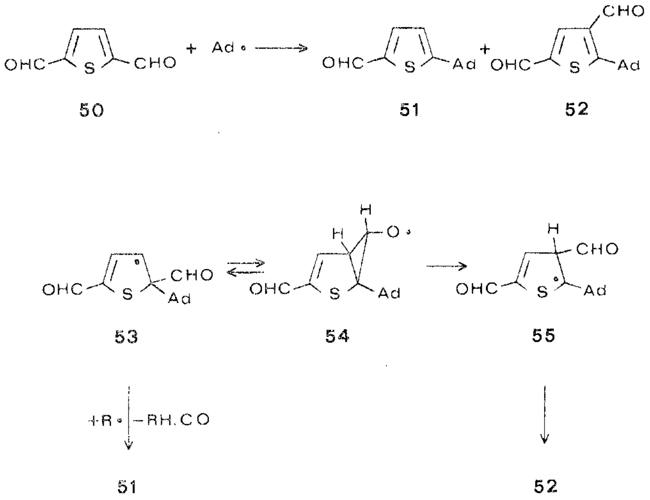
A final interesting example of radical ipso substitution is the reaction of acyldeacylation which occurs in benzothiazoles. The reaction of acetyl radicals, produced by hydrogen abstraction from acetaldehyde, with 2-pivaloylbenzothiazole (**47**)[16,17] or 2-propanoylbenzothiazole (**48**)[33] in $CH_3COOH-H_2SO_4$ afforded almost quantitative yields of the displacement product, 2-acetylbenzothiazole (**49**, Scheme VIII). In this case ipso attack is obviously reversible, but the equilibrium is shifted to the right by the irreversible decarbonylation of the displaced pivaloyl radical in the first case and by the use of a large excess of the precursor of the acetyl radicals in the second example. Like the alkyl radicals employed for other ipso substitutions, acyl radicals are nucleophilic,[34] and the reaction proceeds easily because the substrates are made strongly electron deficient by protonation of the heterocyclic nitrogen. Acetyl radicals also effect the displacement of other groups from the 2 position of benzothiazole.[33] Good results were obtained when the groups to be displaced were strongly electron withdrawing, such as $PhSO_2$ and PhSO (**49** was obtained in 75% yields); lower yields (36, 26, and 9%, respectively) were obtained from the substitution of PhS, F, and Cl. These results emphasize once again the important role played by polar effects in these reactions.

In the examples reported so far the only way through which the ipso intermediate **7** evolves is the loss of one of the two ipso substituents, X or R, to give the ipso substitution products or to revert to the starting compounds. In the case of the nitro derivatives the stability of the leaving $NO_2\cdot$ radical will greatly assist the elimination step, making $k_2 \gg k_{-1}$, and thus will lead to a practically irreversible process. $NO_2\cdot$ is a stable species, and it can be suggested that any kind of ipso intermediate in which $X = NO_2$ will easily evolve toward the ipso substitution products whatever the nature of the radical R and the aromatic substrate may be. Other groups X, however, can probably be eliminated less easily than the $NO_2\cdot$, and some of them very likely require the assistance of another species. In most of the examples reported above the addition step might therefore be reversible.

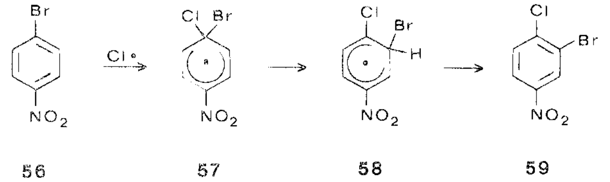
Other Consequences of the Ipso Attack

When the radical addition occurs at the ipso positions of an aromatic compound which does not possess a great resonance energy and when 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 reversion or ipso substitution, to give products of different nature. This is what has been observed to occur in some thiophene and furan derivatives. It is well-known from previous works that in these heteroaromatic compounds radical addition occurs almost exclusively at the α positions;[35,36] it is therefore expected that the reaction of alkyl radicals with 2,5-disubstituted thiophenes and furans should preferentially give the products deriving from the attack at the ipso positions, particularly when polar effects can also operate.

Scheme IX



Scheme X



The first example concerns the reaction of Ad· with 2,5-thiophenedicarbaldehyde (**50**); the two major reaction products were the 2-(1-adamantyl)-5-thiophenecarbaldehyde **51** (19%) and the rather unexpected rearrangement compound, 2-(1-adamantyl)-3,5-thiophenedicarbaldehyde (**52** (56%), Scheme IX).[37] The formation of these two products can be explained by assuming that they derive from the same radical ipso intermediate, **53**. Compound **51** is the product of ipso substitution; other alkyl radicals are also capable of effecting the alkyldeformylation reaction.[37] The loss of the formyl group, however, very likely requires the assistance of another radical which effects the abstraction of the aldehydic hydrogen; hence, the preferred reaction given by **53** is the rearrangement to **55**, which can be suggested to occur through the intermediate radical cyclopropane derivative **54**. The σ-complex **55** will then easily rearomatize to give **52**.

The formation of the rearrangement product **52** represents a remarkable example of one of the possible ways through which the ipso intermediates can evolve, i.e., by the 1,2-shift of the ipso substituent. The only previous convincing example of the occurrence of this process can be found in the photoinitiated chlorination of the *p*-bromonitrobenzene (**56**). This reaction afforded 3-bromo-4-chloronitrobenzene (**59**) together with a mixture of other products deriving from the dis-

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(31) R. A. Jackson, *J. Chem. Soc., Chem. Commun.*, 573 (1974).

(32) O. Porta and G. Sesana, *Tetrahedron Lett.*, 3571 (1978).

(33) M. Fiorentino, L. Testaferri, M. Tiecco, and L. Troisi, *J. Chem. Soc., Chem. Commun.*, 317 (1977).

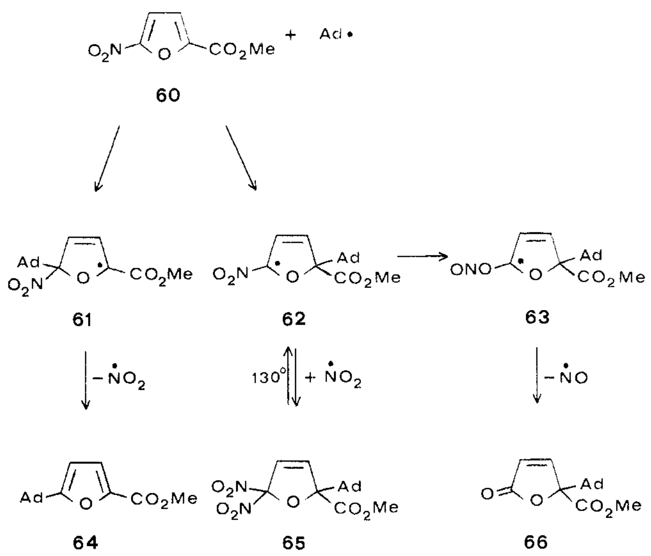
(34) T. Caronna, G. Fronza, F. Minisci, and O. Porta, *J. Chem. Soc., Perkin Trans. 2*, 2035 (1972).

(35) C. M. Camaggi, R. Leardini, M. Tiecco, and A. Tundo, *J. Chem. Soc. B*, 1251 (1969); L. Benati, N. La Barba, M. Tiecco, and A. Tundo, *ibid.*, 1253 (1969).

(36) The nitro group is very efficient in delocalizing the odd electron and exhibits strong ortho-directing properties; thus the reactions of methyl and phenyl radicals with 2-nitrothiophene occur preferentially at the 3 position; see ref 10 and C. M. Camaggi, G. De Luca, and A. Tundo, *J. Chem. Soc., Perkin Trans. 2*, 412 (1972).

(37) P. Cogolli, L. Testaferri, M. Tiecco, and M. Tingoli, unpublished results. A 10% yield of the 3-(1-adamantyl)-2,5-thiophenedicarbaldehyde was also obtained.

Scheme XI



placement of bromine (*p*-chloronitrobenzene) and/or of the nitro group (*p*-bromochlorobenzene, *p*-dichlorobenzene, 1,2,4-trichlorobenzene).[11] The formation of **59** was explained (Scheme X) by assuming the formation of the ipso intermediate **57** from which bromine migrates to the ortho position to give **58**.[11]

Other possible fates of radical ipso intermediates were observed in the case of furan derivatives. The reaction of adamantyl radicals with 5-nitro-2-carbomethoxyfuran (**60**) afforded a mixture of three products,[7] 5-(1-adamantyl)-2-carbomethoxyfuran (**64**, 32%), 5,5-dinitro-2-(1-adamantyl)-2-carbomethoxy-2*H*,5*H*-furan (**65**, 10%), and 2-(1-adamantyl)-2-carbomethoxyfuran-5(2*H*)-one (**66**, 32%) (Scheme XI). A similar mixture of three products having analogous structures was also obtained from the reactions of **60** with methyl radicals[7,10] and of 5-nitro-2-furancarbaldehyde with adamantyl radicals.[7] Addition of the alkyl radical thus occurs at both ipso positions. Attack at the carbon holding the nitro group affords a first ipso intermediate, **61**, which easily eliminates the $NO_2\cdot$ to give the adamantyldenitration product, **64**. Ipso substitution was not observed from the radical **62** formed by addition at the 2 position. In this case both the alkyl and the acyl groups form strong bonds with the carbon atom, and 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 **62** is forced to give other types of reactions. Combination with the $NO_2\cdot$ produced in the alkyldenitration reaction explains the formation of the dinitro compound **65**. The formation of the lactone **66** is not so straightforward. As a reasonable explanation we suggest that the nitro group in **62** isomerizes to a nitrite, giving **63**, which then fragments into NO· and **66**. This interpretation is based on the observation that compound **65** when heated above its melting point (130 °C) is quantitatively transformed into **66** with simultaneous evolution of nitrous vapors;[7] this reaction very likely proceeds through the homolytic fission of the carbon–nitrogen bond to regenerate $NO_2\cdot$ and **62** which then rearranges and fragments as indicated in Scheme XI. If this interpretation is correct, then the reactions **62** → **63** and **63** → **64** represent two further examples of the possible behavior of radical ipso intermediates, namely rearrangement and the fragmentation of a substituent remote from the ipso position.

Concluding Remarks

The results discussed in this Account complete the picture of homolytic aromatic substitution reactions. 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. It has been shown that with electroneutral radicals ipso attack can occur selectively only in those cases in which addition at the ipso position affords a σ-complex intermediate of considerably greater stability than those deriving from the addition at the unsubstituted positions. Ipso attack occurs much more frequently when polar effects can intervene and stabilize the transition state of the addition. In the examples reported in this paper nucleophilic radicals easily add to the ipso positions 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 an interesting area of future investigations.[38]

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 are ipso substitution, return to the starting products, coupling with other radicals, the 1,2-shift of the ipso substituent, and the rearrangement and fragmentation of a group remote from the ipso position. The most important and most frequently encountered consequence of ipso attack is 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.

I thank all collaborators whose names appear in the references for their stimulating enthusiasm and involvement. Acknowledgment is made to the Consiglio Nazionale delle Ricerche, Roma, for current support of this research.

(38) As a matter of fact an example is already available in the literature. The electrophilic benzoyloxy radical (produced from benzoyl peroxide) effects the displacement of the alkoxy groups from aryl ethers to give good yields of arylbenzoates: N. Nowada, H. Sakuragi, K. Tokumaru, and M. Yashida, *Chem. Lett.*, 1243 (1976).