

ate), the necessary internal return results in insignificant oxygen scrambling.⁷⁴ If ion pairs formed under solvolytic conditions undergo rearrangement, attack by an added nucleophile, although rate limiting, must *always* suppress rearrangement^{20,38k,39} since no example of skeletal rearrangement accompanying second-order substitution has ever been reported, even for the potentially favorable neopentyl case.⁷⁵

These ion pairs must be "more intimate than intimate",⁷⁶ and must thus behave like polarized RX molecules. This is what we believe they are, but we see no reason to call them ion pairs, for in such terms a methyl iodide molecule could be regarded as an ion pair by virtue of the C-I bond polarity.⁴³ This would be fine in the present context since mechanistic distinction would be lost, but chemical problems cannot be solved by such semantic extensions, although we agree with the view that genuine ion pairs may possess a degree of covalent character. In fact, the postulation of ion-pair intermediates (and their formation with solvent assistance) in simple primary and secondary substrate solvolysis in reasonably nucleophilic solvents may be incorrect, and SN2 solvent attack may be the favored mode. We know of no evidence that demands *intermediates* in such simple solvolyses, and specifically intermediates formed without solvent or neighboring group assistance. If so,

(74) A. F. Diaz, I. Lazdins, and S. Winstein, *J. Am. Chem. Soc.*, **90**, 1904 (1968). If such scrambling were detected it would still be difficult to prove that it did not occur in a mechanistic blind alley (see also ref 5).

(75) Reference 1, p 742. See also G. M. Fraser and H. M. R. Hoffmann, *Chem. Commun.*, 561 (1967).

(76) Reference 7, p 366.

there is no reason why they should intervene in non-solvolytic substitutions with stronger nucleophiles.

In summary, the "extra-intimate ion pair" is in our opinion a polarized RX molecule. The polarization arises from approach of N⁻, and the energy buildup needed to cross the SN2 potential barrier arises largely from solvent reorganization⁷⁷ attendant on the merging of the original N⁻ and RX solvation shells. We deliberately choose these words to mimic Bordwell's description of an ion-sandwich intermediate,²⁶ noting that Bordwell himself has not been definite in postulating actual intermediacy. His results could equally well be rationalized in terms of a loose SN2 transition state (4) for his tertiary substrate and a tighter transition state (3) for the model primary system.

In conclusion, the verdict which must be passed on Snee's proposed universal unification of SN1 and SN2 mechanisms is one which is unique to the Scottish legal system, and so I turn to the words of my forbears in stating "not proven". A more positive conclusion is not presently available, but we note that strides in this direction are being made through heavy atom isotope effect studies.⁴⁵

I warmly thank Professors P. B. D. de la Mare, J. M. Harris, P. v. R. Schleyer, J. Seyden-Penne, R. A. Snee, and J. Warkentin for exchanges of information and (often provocative but invariably helpful) views. I appreciate the continuing attention of Peter Martin to experimental problems.

(77) E. D. German and R. R. Dogonadze, *Int. J. Chem. Kinetics*, **6**, 467 (1974).

Ips0 Attack in Aromatic Nitration

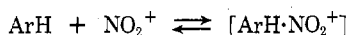
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Received February 6, 1976

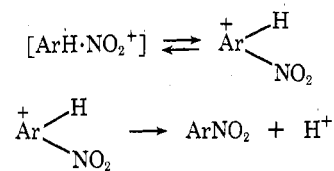
The mechanism of aromatic nitration was admirably discussed¹ by J. H. Ridd in 1971, and it might be doubted that in 4 years the subject could develop enough to justify another Account. There is, however, a protean quality about this reaction, and we hope to show that there is indeed more to be said.

Ridd showed¹ that the major mechanism of nitration in solutions of nitric acid in sulfuric or perchloric acid and in inert organic solvents is as follows.



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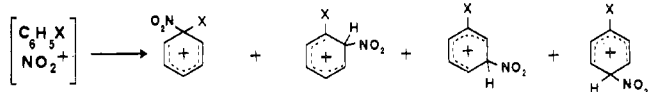


The nitronium ion and the aromatic diffuse together to give an "encounter pair", represented by [ArH·NO₂⁺] but of undefined structure. The encounter pair produces Wheland intermediates (W's) which, by loss of proton, generate nitro compounds. Depending on the conditions and the aromatic any of the steps (or the one which produces the nitronium ion) may be rate determining. Recently studies of positional selectivity in the nitration of 1,2,4-trimethylbenzene, taking into account the possible fates of W's (see below), support the view

(1) J. H. Ridd, *Acc. Chem. Res.*, **4**, 248 (1971).

that an intermediate does occur as represented in the first step of the mechanism.²

Discussion of this mechanism, of the nature of the encounter pair, and of the information which nitration provides about substituent effects and positional reactivities has been complicated by recognition of the importance in nitration of ipso attack. If nitronium reacts with a benzene derivative C_6H_5X , the resulting encounter pair can produce four W_i 's, by ipso, ortho, meta, and para attachment of nitronium to the ring. The



prefix "ipso" was introduced by Perrin and Skinner³ to denote attack by a reagent at a substituted nuclear position. Recognition of the variety of fates awaiting the W_i has complicated the study of nitration. (We denote an ipso-Wheland intermediate by W_i and one formed at a nuclear position carrying a substituent X by W_i^X .)

Ipso substitution, in which X is displaced by nitro, has long been known, occurring in some cases where X = alkyl, acyl, $-SiR_3$, $-SO_3H$, and $-N_2Ar$.⁴ It, and other reactions, have been classified as "anomalous nitrations".⁵ Ipso substitution in reactions other than nitration is also well known and has been described as "nonconventional".⁶

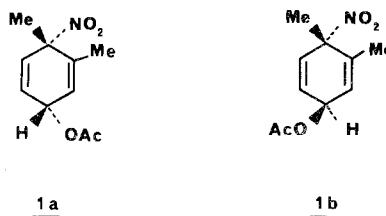
Possible fates of W_i^X are: (i) capture by a nucleophile; (ii) rearrangement by 1,2 migration of nitro, with loss of a proton; (iii) similar migration of X; (iv) loss of X, i.e., ipso substitution; (v) loss of proton or related group from a substituent remote from the ipso position; (vi) return to encounter pair or starting materials.

Consequences of Ipso Attack

Capture by a Nucleophile. Striking examples arise from nitrations with solutions prepared from nitric acid and acetic anhydride, reagents for which there is still doubt about the identity of the electrophile.⁷ All involve intermediates of the type W_i^R , where R is methyl or some related hydrocarbon side chain.⁸⁻²⁴ Examples are

- (2) J. W. Barnett, R. B. Moodie, K. Schofield, and J. B. Weston, *J. Chem. Soc., Perkin Trans. 2*, 648 (1975).
- (3) C. L. Perrin and G. A. Skinner, *J. Am. Chem. Soc.*, **93**, 3389 (1971).
- (4) R. Taylor in "Chemical Kinetics", Vol. 13, C. H. Bamford and C. F. H. Tipper, Eds., Elsevier, London, 1972; N. J. Bunce, *J. Chem. Soc., Perkin Trans. 2*, 942 (1974).
- (5) D. V. Nightingale, *Chem. Rev.*, **40**, 117 (1947).
- (6) S. R. Hartshorn, *Chem. Soc. Rev.*, **3**, 167 (1974).
- (7) N. C. Marziano, J. H. Rees, and J. H. Ridd, *J. Chem. Soc., Perkin Trans. 2*, 600 (1974).
- (8) D. J. Blackstock, A. Fischer, K. E. Richards, and G. J. Wright, *Chem. Commun.*, 641 (1970).
- (9) D. J. Blackstock, J. R. Cretney, A. Fischer, M. R. Hartshorn, K. E. Richards, J. Vaughan, and G. J. Wright, *Tetrahedron Lett.*, **32**, 2793 (1970).
- (10) D. J. Blackstock, M. P. Hartshorn, A. J. Lewis, K. E. Richards, J. Vaughan, and G. J. Wright, *J. Chem. Soc. B*, 1212 (1971).
- (11) A. Fischer, C. C. Greig, A. L. Wilkinson, and D. R. A. Leonard, *Can. J. Chem.*, **50**, 2211 (1972).
- (12) A. Fischer and D. R. A. Leonard, *Can. J. Chem.*, **50**, 3367 (1972).
- (13) A. Fischer and A. L. Wilkinson, *Can. J. Chem.*, **50**, 3988 (1972).
- (14) A. Fischer and J. N. Ramsay, *J. Chem. Soc., Perkin Trans. 2*, 237 (1973).
- (15) A. Fischer and D. R. A. Leonard, *J. Chem. Soc., Chem. Commun.*, 300 (1973).
- (16) A. Fischer and C. C. Greig, *J. Chem. Soc., Chem. Commun.*, 369 (1973).
- (17) A. Fischer and C. C. Greig, *J. Chem. Soc., Chem. Commun.*, 50 (1974).
- (18) A. Fischer and J. N. Ramsay, *J. Am. Chem. Soc.*, **96**, 1614 (1974).
- (19) A. Fischer and C. C. Greig, *Can. J. Chem.*, **52**, 1231 (1974).
- (20) A. Fischer and J. N. Ramsay, *Can. J. Chem.*, **52**, 3960 (1974).
- (21) A. Fischer, C. C. Greig, and R. Röderer, *Can. J. Chem.*, **53**, 1570 (1975).
- (22) A. Fischer and R. Röderer, *J. Chem. Soc., Chem. Commun.*, 798 (1975).

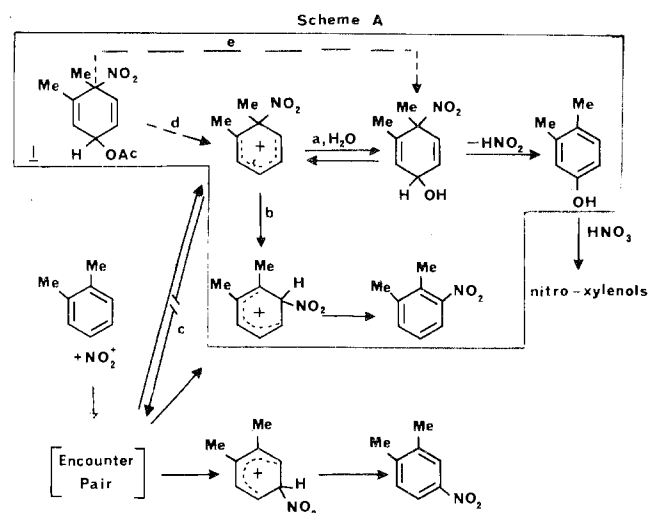
the stereoisomers **1a** and **1b** from *o*-xylene.^{8,9} The position which captures acetate can also be substituted, as in the adducts from *p*-xylene^{9,20} and 3,4-dimethylanisole.¹⁵



Other nucleophiles such as the nitrate ion can capture W_i 's.¹³ Acidolysis of nitroacetates of the kind mentioned regenerates the W_i which can attack reactive aromatics; loss of nitrous acid then gives biaryls.^{17,21}

An important capture process involves water as the nucleophile (see below).

Rearrangement by 1,2 Migration of Nitro, Followed by Loss of a Proton. Nitration of *o*-xylene in sulfuric acid gives 3- and 4-nitro-*o*-xylene in yields dependent upon acidity.²⁵ Myhre suggested²⁶ that W_i^{Me} is captured by nucleophilic attack of water at low acidities (Scheme A, step a), but that with increasing



acidity 1,2 migration (Scheme A, step b) becomes increasingly preferred. Acidolysis of ester **1** also gives 3-nitro-*o*-xylene in yields which increase with acidity.²⁶ This supports the mechanism whether hydrolysis of **1** (boxed region of Scheme A) occurs by the A_{Al1} (step d) or the A_{Ac2} (step e) route,²⁷ or by a mixture of these processes.

Since hydrolysis of **1** does not give 4-nitro-*o*-xylene,^{2,26} return of W_i^{Me} to the encounter pair (Scheme A, step c) does not compete in this case with steps a and b. In other cases return to encounter pair does occur (see below).

Many examples of 1,2 migration of nitro in W_i^R 's generated by acidolysis of esters similar to **1** have been reported.^{17-21,23,24} Similarly, evidence from the variation with acidity of isomer yields is not restricted to the nitration of *o*-xylene. In the nitration of 1,2,4-trimethyl-

- (23) R. C. Hahn and M. B. Groen, *J. Am. Chem. Soc.*, **95**, 6128 (1973).
- (24) R. C. Hahn and D. L. Strack, *J. Am. Chem. Soc.*, **96**, 4335 (1974).
- (25) R. G. Coombes and L. W. Russell, *J. Chem. Soc. B*, 2443 (1971).
- (26) P. C. Myhre, *J. Am. Chem. Soc.*, **94**, 7921 (1972).
- (27) K. Yates, *Acc. Chem. Res.*, **4**, 136 (1971).

Table I
Yields of Nitro Isomers from Nitrations in Acetic Anhydride, Compared with Those from Nitrations in 54 (±1)% H₂SO₄

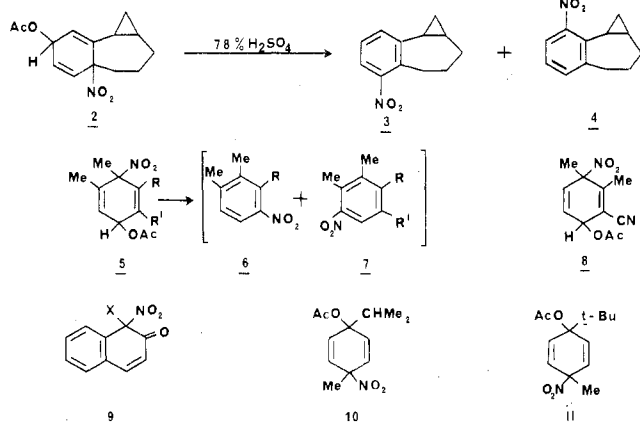
Medium	Nitrotoluenes			Nitro- <i>o</i> -xyl- enes		Nitro- <i>m</i> -xylenes			Nitro-1,2,4- trimethylbenzenes			Nitro-1,2,3- trimethyl- benzenes	
	<i>o</i>	<i>m</i>	<i>p</i>	3	4	2	4	5	3	5	6	4	5
Ac ₂ O	60 ^a	3 ^a	34 ^a	13 ^b	24 ^b				7 ^b	38 ^b	4 ^b		
	58 ^c	3 ^c	36 ^c	14 ^c	28 ^c	15 ^c	85 ^c	0 ^c	10 ^d	35 ^d	4 ^d	46 ^c	8 ^c
54 (±1)% H ₂ SO ₄	61 ^b	4 ^b	31 ^b	12 ^b	23 ^b	17 ^b	74 ^b	2 ^b	9 ^b	34 ^b	3 ^b	41 ^b	9 ^b

^a Reference 33a. ^b Reference 2. ^c Reference 33b. ^d Reference 33c.

benzene in sulfuric acid the increase with acidity of the yields of 1,2,4-trimethyl-5- and 1,2,4-trimethyl-6-nitrobenzene (Figure 1) is attributable to migration of nitro from C-4 to C-5 and from C-1 to C-6, respectively.² The increase in yield of 1,2,4-trimethyl-5-nitrobenzene occurs at lower acidity than that of 1,2,4-trimethyl-6-nitrobenzene (Figure 1). This may reflect a difference in the ease of the two capture processes, but a more significant factor is probably the fact that the migration C-4 → C-5 is more "downhill" than C-1 → C-6 from the point of view of the migrating electrophile.

Repeated 1,2 Shifts of a Nitro Group. Reactions are known which, though formally 1,3 shifts, are best regarded as repeated 1,2 shifts. Their important characteristic is that a nitro group moves from an ipso position through an adjacent substituted position to one from which it displaces a proton. Thus, acidolysis of **2** gave the isomers **3** and **4**.²³ Similarly **5** (R = Me; R' = H) gave **6** (R = Me), but not 1,2,3-trimethyl-5-nitrobenzene,²⁸ while **5** (R = Cl; R' = H) gave **6** (R = Cl) and **7** (R = Cl; R' = H)¹⁷ and **5** (R = H; R' = CN, COMe, or COPh) gave **7** (R = H; R' = CN, COMe, or COPh).^{19,21} The transfers are thought to be intramolecular because addition of mesitylene gives no nitromesitylene.

In three cases migration of nitro across an unsubstituted position appears to occur: decomposition of **8** under various conditions gave some 2,3-dimethyl-5-nitrobenzonitrile;^{16,19} in acidic conditions **9** (X = Cl) gave some 1-chloro-6-nitro-2-naphthol;²⁹ in the acidolysis of **2** some of the two nitro compounds isomeric with **3** and **4** were formed.²³ For each of the first two instances not wholly conclusive evidence for the intramolecular nature of the change was obtained, but the mechanisms operating have not been fully elucidated. As regards the reactions of **8**, it is not clear in which entity (**8** or some structure derived from it) migration



(28) P. C. Myhre, quoted in ref 21.

(29) C. L. Perrin, *J. Org. Chem.*, **36**, 420 (1971).

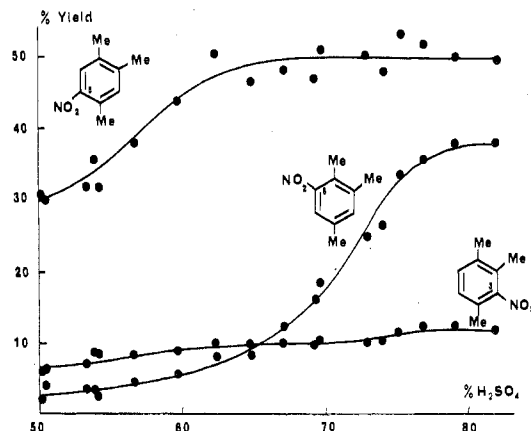


Figure 1. Nitration of pseudocumene.

is occurring. In the third case the additional nitro compounds probably arise from reversion of W_i to encounter pair followed by renitration.²³

1-X-Pentamethylbenzenes (X = Me, F, Cl) with nitronium tetrafluoroborate in fluorosulfonic acid-sulfur dioxide at -70 °C give the W_i^{Me} 's with nitro para to "X". When X = Br all three isomeric W_i^{Me} 's are formed. Except when X = F the NMR spectra of the W_i 's are temperature dependent, revealing equilibration through repeated 1,2 shifts of the nitro group.³⁰

Positional Reactivities. The demonstration of 1,2 migration of nitro in W_i^R makes uncertain the extent to which ortho-substituted products arise by direct ortho attack.

One approach to this problem is to use the independent route to W_i^{Me} 's provided by acidolysis of esters such as **1**.^{2,26} If the mechanism of the acidolysis were purely A_{A1} (Scheme A, step d), the fractional yield of, in this case, 3-nitro-*o*-xylene would be the ratio [migration/(migration + capture)] for W_i^{Me} . However, current investigations show that **1** reacts by a mechanism which changes with acidity. At low acidities elimination of nitrous acid from **1** occurs rapidly,³¹ and is followed by A_{Ac2} hydrolysis of 3,4-dimethylphenyl acetate to the phenol. However, above 55% H₂SO₄ the A_{A1} mechanism is dominant, and the results are relevant to the nitration process.³²

(30) G. A. Olah, H. C. Lin, and Y. K. Mo, *J. Am. Chem. Soc.*, **94**, 3367 (1972); G. A. Olah, H. C. Lin, and D. A. Forsyth, *ibid.*, **96**, 6908 (1974); A. N. Datsina and V. J. Mamatyuk, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **10**, 2337 (1973); A. N. Detsina and V. A. Koptug, *Zh. Org. Khim.*, **8**, 2215 (1972); A. N. Detsina, V. I. Mamatyuk, and V. A. Koptug, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **10**, 2163 (1973).

(31) P. C. Myhre, *ACS Symp. Ser.*, **No. 22** (1975).

(32) H. W. Gibbs, R. B. Moodie, and K. Schofield, in press.

(33) (a) S. R. Hartshorn, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 1256 (1971); (b) A. Fischer, J. Vaughan, and G. J. Wright, *ibid.*, 368 (1967); (c) D. J. Blackstock, A. Fischer, K. E. Richards, and G. J. Wright, *Aust. J. Chem.*, **26**, 775 (1973).

Table II
Products of Nitrating *p*-Cymene^{22,24,39}

Reagent	Products			10
	2-Nitro- <i>p</i> -cymene	3-Nitro- <i>p</i> -cymene	<i>p</i> -Nitro-toluene	
NO ₂ ⁺ BF ₄ ⁻ -sulfolan, 25 °C	85	5	10	
HNO ₃ -H ₂ SO ₄ 25 °C	82	7	11	
AcONO ₂ -Ac ₂ O, 0 °C	41	8	10	41

An alternative approach is to find media for nitration which give complete capture of W_i^{Me}'s. There is no certain way of recognizing such media. However, the yields of mononitro products obtained from toluene and the polymethylbenzenes upon nitration in acetic anhydride (undoubtedly a good medium for capture) are similar to those from the most aqueous sulfuric acid solutions studied (Table I), making it likely that in both cases capture is substantially complete.² If so, these isomer proportions are those for direct nitration, and the departure from quantitative in the yield of these isomers measures the extent of ipso attack.

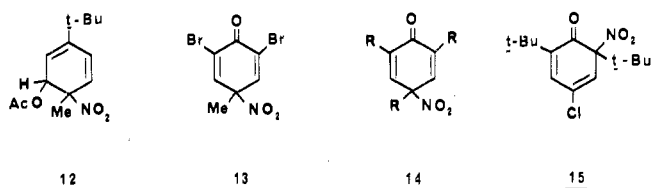
Migration of the Ipso Substituent. Isotopic labeling revealed no alkyl migration in the acidolysis of 2.²³ In the nitration of methylbenzenes there is no methyl migration,² and in the case of halogenobenzenes (see below) no intramolecular halogen migration.³⁴

Thus, 1,2 migration of X in W_i^X occurs very rarely, if at all.³⁵

Ipso Substitution. As already mentioned, this is the longest recognized consequence of ipso attack. Nevertheless, mechanistic studies are only now beginning. Many ipso substitutions occur in aromatics which are strongly activated toward electrophilic attack, and this, combined with the conditions used, may have led to nitration via nitrosation; that is the initial substitution process might be nitrosation, the nitro compound arising by oxidation of the nitroso compound.^{36,37} We shall mention here nitrodealkylation and nitrodehalogenation.

Demethylation occurs with polymethylbenzenes and is accompanied by side-chain substitution.^{5,38} Secondary and tertiary alkyl groups are more easily displaced, and numerous examples of deisopropylation and *tert*-butylation are known.³⁹

The nitration of *p*-cymene^{24,39} gives the products shown in Table II. The yields of 3-nitro-*p*-cymene and



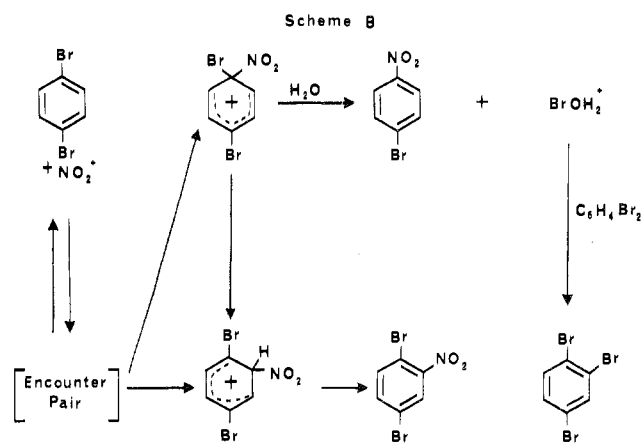
- (34) R. B. Moodie, K. Schofield, and J. B. Weston, in press.
 (35) H. Suzuki, M. Sawaki, and R. Sakimoto, *Bull. Chem. Soc. Jpn.*, **45**, 1515, 1834 (1972); H. Suzuki and K. Nakamura, *ibid.*, **45**, 2534 (1972).
 (36) "Nitration and Aromatic Reactivity", J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, Cambridge University Press, Cambridge, England, 1971.
 (37) C. Eaborn, Z. S. Salih, and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 2*, 172 (1972).
 (38) (a) H. Suzuki, *Bull. Chem. Soc. Jpn.*, **43**, 473, 879 (1970); (b) E. Hunziker, J. R. Penton, and H. Zollinger, *Helv. Chem. Acta*, **54**, 2043 (1971); (c) H. Suzuki, *Bull. Inst. Chem. Res. Kyoto Univ.*, **50**, 407 (1972).
 (39) G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **86**, 1067 (1964); P. C. Myhre and M. Beug, *ibid.*, **88**, 1568 (1966).

p-nitrotoluene remain roughly constant, while that of 2-nitro-*p*-cymene varies from 82 to 85% in sulfuric acid and sulfolan to 41% in acetic anhydride. Thus, in the first two conditions about half of the 2-nitro compound comes from formation of W_i^{Me} followed by 1,2 migration. In acetic anhydride W_i^{Me} is captured, giving 10. No W_i^{*i*-Pr} is captured, but isopropyl is lost to give *p*-nitrotoluene. The C-Me position is thus the most reactive in *p*-cymene (41% of the reaction occurring there), and the true ratio of reactivities of C-2 and C-3 is 5:1.²⁴ The argument assumes that W_i^{*i*-Pr} always undergoes deisopropylation, so that the yield of *p*-nitrotoluene indicates the extent of attack at C-*i*-Pr; the evidence does not, however, exclude the possibilities of some regression from or 1,2 migration in W_i^{*i*-Pr}.

Ipso attack at and migration from C-Me occur similarly in *p*-*tert*-butyltoluene.^{22,39} A new feature is the production of both ortho and para adducts (11 and 12).²² It is surprising that some *de-tert*-butylation was not observed since 20% of this occurred with *p*-*di-tert*-butylbenzene.³⁹

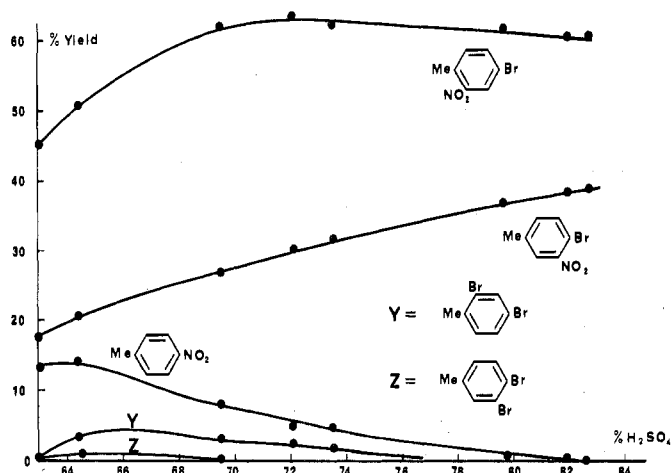
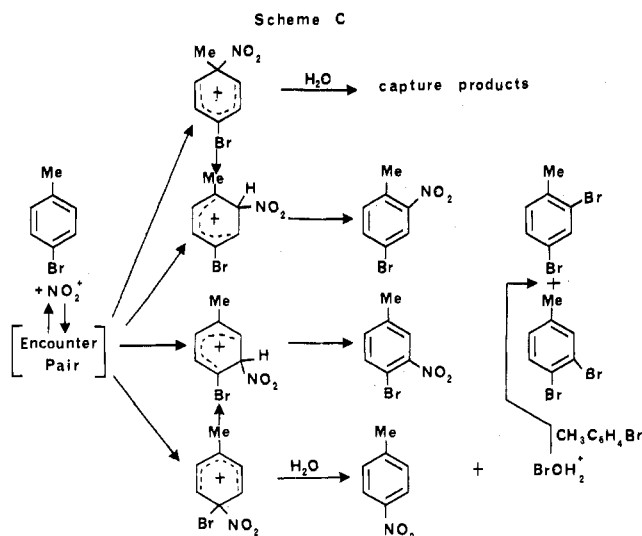
Nitrodechlorination has rarely been observed. Some apparent nitrodebrominations may be nitrosodebrominations.⁴⁰ *p*-Bromoanisole, nitrated in acetic anhydride containing urea, gave 31% of *p*-nitroanisole. Similarly, "in the absence of nitrous acid" 4-bromo-2,6-dimethylanisole underwent some nitrodebromination.⁴¹

With less reactive substrates nitrosation is not a problem. *p*-Dibromobenzene shows normal kinetic behavior when nitrated in sulfuric acid, but the products change with acidity: in the range 69–90% H₂SO₄ the yield of 2,5-dibromonitrobenzene rises from 60 to 100%, while that of *p*-bromonitrobenzene falls from 34 to 0%. 1,2,4-Tribromobenzene is also formed. These results are interpreted³⁴ as shown in Scheme B, the involvement



of water being consonant with the proposed mechanism of "positive" bromination.⁴² The 1,2 migration of nitro represented in Scheme B cannot be distinguished from the possible regression of W_i^{Br} to starting materials and renitration. The migration is made probable by the behavior of *p*-bromotoluene (Figure 2),³⁴ represented in Scheme C. This indicates that W_i^{Me} can be captured or rearranged intramolecularly, while W_i^{Br} can rearrange or lose "Br⁺". The results could not be accounted

- (40) H. Barbier, *Helv. Chim. Acta*, **11**, 157 (1928); T. Heap, T. G. H. Jones, and R. Robinson, *J. Chem. Soc.*, 2021 (1927).
 (41) A. R. Butler and A. P. Sanderson, *J. Chem. Soc., Perkin Trans. 2*, 1671, 1784 (1974).
 (42) H. M. Gilow and J. H. Ridd, *J. Chem. Soc., Perkin Trans. 2*, 1321 (1973).

Figure 2. Nitration of *p*-bromotoluene.

for by regression of W_1^{Br} to starting materials followed by renitration, for then yields of both bromonitrotoluenes would increase with acidity. In fact the yield of 4-bromo-2-nitrotoluene changes very little above 70% H_2SO_4 , while the increase in 4-bromo-3-nitrotoluene reflects the decrease in *p*-nitrotoluene. The conclusions from these and other examples are that W_1^{Me} 's can rearrange or be captured (see above), that W_1^{Br} 's can rearrange or lose "Br⁺", and that W_1^{Cl} 's are probably formed (nitrodechlorination is not observed), but that it is not possible to say whether they regress or rearrange.

Such studies permit positional reactivities to be assigned as in the following cases (Table III). The uncertainties arise because maximum debromination may not have been observed, because full capture of W_1^{Me} 's may not have been achieved, and because nitrodechlorination did not occur.

Apparent nitrodeiodinations have often been reported.⁵ One of the best known, in which 4-iodoanisole gives 2-iodo-4-nitroanisole (the Reverdin rearrangement), proceeds by nitrosodeiodination, giving initially *p*-nitroanisole (after oxidation) and 2,4-diiodoanisole (by iodination of starting material). The latter is then slowly nitrosodeiodinated, and the former more slowly iodinated, giving 2-iodo-4-nitroanisole.⁴³ True nitrodeiodination is claimed to occur in the reaction of 2-

(43) A. R. Butler and A. P. Sanderson, *J. Chem. Soc., Perkin Trans. 2*, 989 (1972); see also A. R. Butler and A. P. Sanderson, *ibid.*, 1784 (1974).

Table III
Nitration of 1-X-4-Y-Benzenes

Substituents	% attack at position					
	1	2	3	4	5	6
X = Br, Y = H	?	≤30	~0.4	~38		
X = Me, Y = Br ^a	≥15.4	≤22.4	≤8.9	≥17.0		
X = Me, Y = Cl	≥27.2	≤17		~30 ^b		
X = Y = Br	≥16.8	≤15.1				
X = Br, Y = Cl	≥28.3	≤15.0		~33 ^b		

^a See Figure 2. % attack at C-1 given by difference between maximum and minimum yields and % attack at C-2 by half the minimum yield of 4-bromo-2-nitrotoluene. Similarly for the other positions. ^b Total for the 3, 4, and 5 positions, assuming 1,2 migration to occur.

iodo-1,3,5-trineopentylbenzene with fuming nitric acid.⁴⁴

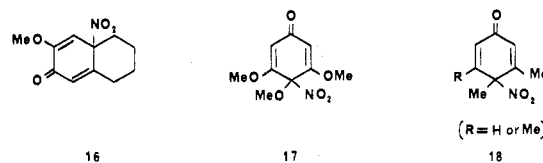
Relative Leaving Abilities. The results suggest that leaving ability is in the order $\text{Cl} < \text{NO}_2 < \text{Br} < \text{I}$. Perrin has discussed relative leaving abilities in a wider range of substituents, and related the problem to the presence or absence of kinetic isotope effects in substitutions.²⁹ There can be no absolute sequence of leaving abilities, for the departure of one group from a W_1 may have requirements different from the departure of another. Thus loss of bromine requires a nucleophile such as water, whereas loss of some groups may not. Their relative leaving abilities will therefore change with conditions.

Loss of Proton or Related Group from Remote Positions. Three cases occur frequently: deprotonation of hydroxyl, demethylation of methoxyl, and deprotonation of methyl.

1-Bromo- and 1-chloro-2-naphthols give the ketones **9** (X = Br or Cl) when nitrated.^{29,45} Phenols only give stable cyclohexadienones when the positions on each side of the ipso position or the hydroxyl group carry bulky groups. Examples are the formation of **13** from 2,6-dibromo-4-methylphenol⁴⁶ and of **14** from 2,4,6-trialkylphenols. 2,6-Di-*t*-butyl-4-chlorophenol gives **15**.⁴⁷

6,7-Dimethoxy-1,2,3,4-tetrahydronaphthalene gives **16** with nitric acid in acetic acid (**16** apparently provided the first case of nitro group migration, giving in water or ethanol a compound believed to be 6-hydroxy-7-methoxy-8-nitro-1,2,3,4-tetrahydronaphthalene.⁴⁸ **17** and **18** are other nitrodienones formed by demethylation of methoxyl (and by deacetylation of the related aryl acetates).^{16,49}

Demethylation of methoxyl occurs in the nitration



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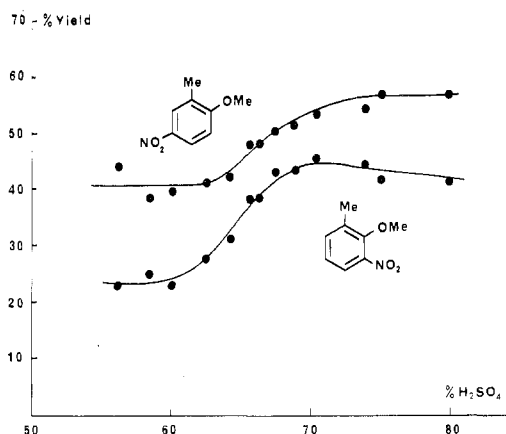
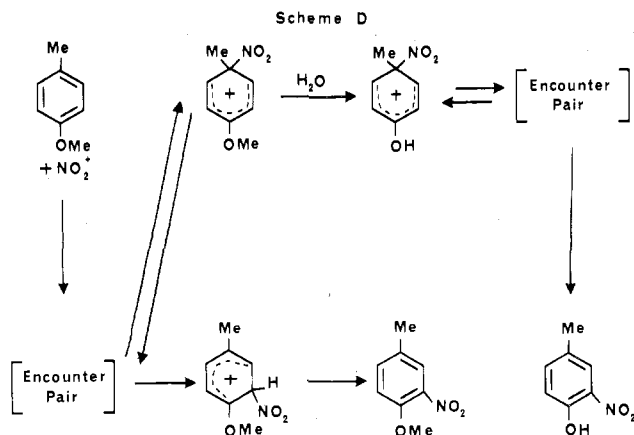


Figure 3. Nitration of *o*-methoxytoluene.

of *p*-methoxytoluene in aqueous sulfuric acid.⁵⁰ The sole products, 4-methyl-2-nitroanisole and 4-methyl-2-nitrophenol, are formed in constant ratio (about 1.6:1) in 48–78% H_2SO_4 , but from 78 to 83% H_2SO_4 the relative yield of the phenol decreases. Scheme D suggests a



mechanism. Demethylation probably involves capture by attack of water, followed by loss of methanol from the hemiacetal (ring-protonated methyl phenyl ethers are hydrolyzed in this way).⁵¹ It is the dominant fate of W_i^{Me} up to ~78% H_2SO_4 , but gives way to the competing process of return to encounter pair at higher acidities. 1,2 Migration, which would be “uphill”, does not occur. The extent of demethylation at low acidities shows the extent of ipso attack at C-Me.

The latter point was appreciated by Bunnett and Cook in relation to the nitration of *p*-chloroanisole.⁵² In acetic anhydride this gives only 4-chloro-2-nitroanisole, whereas in increasingly aqueous acetic acid more and more 4-chloro-2-nitrophenol, to a maximum of 37%, is formed. Thus, in general, demethylation is a consequence of ipso attack at carbon bearing a substituent which is not readily lost.³

Deprotonation of methyl, consequent upon ipso at-

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tack at the para position, has not been substantiated by isolation of the methine intermediate. Nevertheless many authors have postulated the existence of such intermediates in the side-chain nitration of polymethylbenzenes.^{38b,c,53} The nitration of 1,4-dimethylnaphthalene to give 1-methyl-4-nitromethylnaphthalene has been represented in this way.⁵⁴ This mechanism has been supported,^{38c,55} but is not certain.^{13,56} NMR spectrometry did not detect the methine.¹³

Return to Encounter Pair or to Starting Materials. These unproductive pathways are not detectable unless a change of conditions alters the degree of return by encouraging a competing process which gives a new product. *p*-Methoxytoluene provides one example (see above). *o*-Methoxytoluene gives, in aqueous sulfuric acid, 1-methoxy-2-methyl-4-nitro- and 1-methoxy-2-methyl-6-nitrobenzene, in yields which vary with acidity (Figure 3).⁵⁰ Since *both* yields increase as the overall yield becomes quantitative, return to encounter pair rather than repeated 1,2 migration via C-OMe is the process competing with nucleophilic capture. We note the indication that methoxyl is not strongly ipso directing, even though attack at such a position can occur when it is activated strongly by other substituents.⁴⁹

o- and *p*-methoxytoluenes are nitrated at the encounter rate in aqueous sulfuric acid. Significant further return to starting materials from the encounter pair does not therefore occur, but is probably the process which competes with demethylation in the destruction of the W_i^{Cl} formed in the nitration of *p*-chloroanisole, which does not react at the encounter rate.

The Future

Ipso attack at aromatic ring carbons bearing various substituents is known to occur because it is followed by ipso substitution. With alkyl, methoxyl, and halo substitution other important consequences have been demonstrated, and with other substituents evidence for similar occurrences will probably be forthcoming.

Various processes are known to compete for W_i^{X} , but the rules of the competition are not well understood. Advances in this regard are likely, and the use of diene adducts such as 1 to generate these intermediates will be helpful. Diene adducts, however, can undergo reactions other than formation of W_i^{X} , and the relevance of their acidolysis to nitration studies must be demonstrated.

The modes of rearrangement open to W_i^{R} 's may prove to be more various than is at present apparent.⁵⁷

Nitration studies are following a path similar to that taken by halogenation studies,⁵⁸ and are revealing a situation more complicated than has been generally appreciated.

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