Side-chain Nitrooxylation of Polyalkylbenzenes through Ionic Process[1]

Kiyomi NAKAMURA

Department of Chemistry, Faculty of Science, Kyoto University, Sakyo-ku, Kyoto

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The reaction of polyalkylated aromatic compounds with fuming nitric acid has been investigated with respect to the effects of substituents and added electrolytes on the ease and extent of the concurrent side-chain nitrooxylation and nuclear nitration. Relative reactivity of substituted pentamethylbenzenes $C_6(CH_3)_5X$ for side-chain substitution decreases from 1 to 2×10^{-2} to 4×10^{-4} to 3×10^{-6} with the change of substituent groups from methyl to hydrogen to bromine to nitro in accordance with the ionic character of the reaction. Added electrolytes have profound influence on the reaction rates, but the ratio of products from side-chain nitrooxylation and nuclear nitration remains almost unchanged, indicating that both processes share a common intermediate. The relative amount of side-chain substitution depends closely on the positional relationship of alkyl groups in the nucleus, and preferential formation of *p*-alkylbenzyl nitrates is always observed. It is concluded from the results, that the side-chain nitrooxylation products are formed by way of the polar intermediate common with the ring nitration products. Some plausible reaction sequences are briefly discussed.

Electrophilic reaction of highly alkylated aromatic compounds often gives products which are rather unexpected from the reaction of less substituted compounds. The acylation,[2] halogenation,[3] hydroxylation,[4] and nitration[5] of these systems have been studied by several workers to determine the pattern of electrophilic substitution. In a previous paper,[6] we showed that the actions of fuming nitric acid upon pentamethylbenzene and pentaethylbenzene give as the major product 2,3,4,5-tetramethylbenzyl nitrate and α-methyl-2,3,4,5-tetraethylbenzyl nitrate, respectively, and that these unusual nitrations are characterized by their high positional selectivity and peculiar orientation. In the present work, the effects of substituents, added electrolytes and structural features of the substrate upon the rate and extent of the concurrent side-chain nitrooxylation (SNO) and ring nitration (RNA) have been investigated with the aim of providing information on how the displacement of a side-chain proton by ONO_2 group occurs in preference to that of a ring proton by NO_2 group under typical ionic conditions. From the results the possible reaction sequences leading to the formation of side-chain substituted products are briefly discussed.

Experimental

Materials. Hexamethylbenzene,[7] hexaethylbenzene,[8] pentamethylbenzene[7] and its bromo[9] and nitro derivatives,[10] two ethyltetramethylbenzenes,[11] three tetramethylbenzenes[7,12] and thier mononitro derivatives,[13] bromodurene,[14] bromonitrodurene, ethylmesitylene,[15] 5-*t*-butylhemimellitene[16] and its mononitro derivative,[17] mesitylene,[18] pseudocumene,[19] and ethylxylenes[15] were prepared as described in literature. 5-Ethylhemimellitene was obtained by the Clemmensen reduction of 3,4,5-trimethylacetophenone.[20] Nitromethane was distilled after drying over anhydrous sodium sulfate. Nitric acid ($d=1.50$) of guaranteed grade was used without purification.

Kinetic Measurement and Product Analysis. All kinetic measurements were made on a Shimadzu QV-50 spectrophotometer. A volumetric flask containing a nitromethane solution of the reaction mixture was immersed in a constant-temperature bath at 25.0°C. Ten milliliters of aliquots was withdrawn periodically and quenched by pouring into aqueous sodium bicarbonate. The organic part was separated by extraction with ether. The aqueous part was analysed for nitrite ion by Shinn's method[21] and nitrate ion was determined spectrometrically[22] to obtain the amount of nitric acid consumed. The residue from the ether extract was diluted with nitromethane to a suitable concentration and the amount of ring nitration was determined by calculation from the optical densities of nitro compounds at appropriate wavelengths. Adherance to Beer's law was excellent. Since nitromethane used as a solvent had deep absorption below 350 mμ, a comparatively weak band ($\varepsilon=2\times10^2-4\times10^2$) at around 380 mμ was used for the determination of nitro compounds. The wavelengths λ_{max} used were

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3) L. J. Andrews and R. M. Keefer, *J. Amer. Chem. Soc.*, **86**, 4158 (1964); E. Baciocchi, A. Ciana. G. Illuminati, and C. Pasini, *ibid.*, **87**, 3953 (1965); R. M. Keefer, and L. J. Andrews, *J. Org. Chem.*, **31**, 541 (1966).
4) H. Hart and R. M. Lange, *J. Org. Chem.*, **31**, 3776 (1966); H. Hart and R. K. Murray, Jr., *ibid.*, **32**, 2448 (1967).
5) A. Huender, *Rec. Trav. Chim. Pays-Bas*, **34**, 1 (1915); I. J. Rinkes, *ibid.*, **57**, 1405 (1938); **58**, 538 (1939); **63**, 89 (1944); L. I. Smith and C. O. Guss, *J. Amer. Chem. Soc.*, **62**, 2635 (1940).
6) H. Suzuki and K. Nakamura, This Bulletin, **43**, 473 (1970).
7) L. I. Smith, "Organic Syntheses," Coll. Vol. II, 32 (1943).
8) E. Wertyporoch and T. Firla, *Ann. Chem.*, **500**, 293 (1933).
9) A. Kovczynski, *Ber.*, **35**, 868 (1902).
10) R. Willstatter and H. Kubli, *ibid.*, **42**, 4162 (1909).
11) M. S. Newman, J. R. Leblanc, H. A. Karnes, and G. Axelrad, *J. Amer. Chem. Soc.*, **86**, 868 (1964).
12) L. I. Smith and O. W. Cass, *ibid.*, **54**, 1609 (1932).
13) G. Illuminati, *ibid.*, **74**, 4951 (1952); G. Illuminati and G. Marino, *ibid.*, **75**, 4594 (1953).
14) O. Jacobsen, *Ber.*, **20**, 2837 (1887).
15) S. F. Birch, R. A. Dean, F. A. Fidler, and R. A. Lowry, *J. Amer. Chem. Soc.*, **71**, 1362 (1949).
16) M. J. Schlatter, *ibid.*, **76**, 4952 (1954).
17) R. C. Fuson, J. J. Denton, and J. W. Kneisley, *ibid.*, **63**, 2652 (1941).
18) R. Adams and R. W. Hufferd, "Organic Syntheses," Coll. Vol. I., p. 341 (1956).
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20) D. E. Pearson and J. D. Bruton, *J. Org. Chem.*, **19**, 961 (1954).
21) M. B. Shinn, *Ind. Eng. Chem., Anal. Ed.*, **13**, 33 (1941).
22) A. M. Hartley and R. I. Asai, *Anal. Chem.*, **35**, 1214 (1963).

nitropentamethylbenzene (380), nitrodurene (377), nitroisodurene (379), nitroprehnitene (381), nitromesitylene (379), bromonitrodurene (378), and 4-nitro-5-*t*-butylhemimellitene (378), respectively. Both nitrooxylated products and hydrocarbons exhibited no interference in this region. Nitromethane solutions were concentrated after optical density measurements, and the side-chain nitrooxylated compounds were hydrolyzed by refluxing with a mixture of sodium acetate (2 g), acetic acid (7 m*l*) and water (17 m*l*) for several hours. The organic part was removed by ether extraction and the aqueous part was analyzed for the nitrite ion derived from nitrooxylated products. Results of a typical run are summarized in Table 1. Since the amounts of nitrous acid[23] and benzyl nitrate are comparable at the initial stages of the reaction, the former can be used as a measure of side-chain nitrooxylation. Time t_{10} and t_1, which denote the time required for each of the substrates examined to attain 10% and 1% completion in SNO under identical conditions, were determined graphically. All runs were conducted at least twice and the values obtained were corrected by blank experiments.

Nitrations of polyalkylbenzenes for product analyses were carried out as described previously.[6] The structures of major nitration products were determined.

Mesitylene gave nitromesitylene. Pseudocumene[24] 4-ethyl-*o*-xylene, 4-ethyl-*m*-xylene, and 2-ethyl-*p*-xylene all underwent side-chain substitution at 4-alkyl group. Isodurene and its structure analogs were mainly nitrooxylated at 5-alkyl group: the major nitrooxylation product from 5-ethylhemimellitene was identified as α,3,4,5-tetramethyl-2-nitrobenzyl nitrate. No attempt was made to separate components of the product mixture from isodurene and ethylmesitylene because only small amounts of benzyl nitrates were formed. Prehnitene gave nitro compounds along with a small amount of side-chain substituted product, the structure of which has not yet been established. Durene gave a considerable amount of 2,4,5-trimethylbenzyl nitrate. 5-*t*-Butylhemimellitene yielded mono and dinitro derivatives as sole products.

Results and Discussion

Substituent Effects for Side-chain Nitrooxylation. In previous papers[25] of this series, the mode in which a substituent group determines the orientation of side-chain nitrooxylation (SNO) was briefly described. Strongly electron-withdrawing substituents such as nitro, carboxyl and carbomethoxy groups brought about almost exclusive ortho substitution to give 6-substituted tetramethylbenzyl nitrate, while halogen atoms were found to lead to comparable amounts of 5- and 6-halotetramethylbenzyl nitrates. Pentamethylphenol and its methyl ether gave mainly cyclohexadienones, with a concomitant formation of 3-substituted tetramethylbenzyl nitrate in a small amount.

In order to get further insight into the mechanism of SNO, the substituent effect on the reactivity has been examined for a series of pentamethylbenzene derivatives. The overall process of SNO may be expressed in the stoichiometric equation

$$C_6X_5CH_3+2HNO_3 = C_6X_5CH_2ONO_2+HNO_2+H_2O \quad (1)$$

Preliminary experiments carried out for dilute nitromethane solutions of hexamethylbenzene and fuming nitric acid at 10°C and 25°C have shown that the rate of SNO can be followed successfully by measuring the increase in the amount of nitrous acid (Table 1).

Table 1. Nitration of hexamethylbenzene in nitromethane at 10°C

$[C_6(CH_3)_6]=2\times10^{-2}$ mol l^{-1}; $[HNO_3]=10\times10^{-2}$ mol l^{-1}

Time (sec)	$[HNO_2$[23]$]$ (mol l^{-1})	[benzyl nitrate] (mol l^{-1})	$[HNO_3$ consumed] (mol l^{-1})
135	0.27×10^{-2}	0.24×10^{-2}	0.60×10^{-2}
210	0.41	0.46	1.06
230	0.47	0.45	1.12
300	0.67	0.63	1.46
324	0.74	0.62	1.66

With the lapse of time, the amount of nitrous acid gradually outweighs that of benzyl nitrate, indicating that nitrous acid can be no longer used as the measure of SNO. This would probably be due to the secondary reactions involving the oxidation or the condensation of the initially formed benzyl nitrate.[26] SNO of polyalkylbenzenes is quite sensitive to the reaction conditions, and the benzyl nitrates produced are usually highly reactive so that they can act as a benzylating agent in the presence of acid catalyst, or undergo further transformation with excess of nitric acid. Thus direct kinetic treatment of the nitration of polyalkylated aromatics for the purpose of determining their relative rates is very difficult. To avoid these complexities, relative rates of hydrocarbons were determined by comparing the time t_{10}, which denotes the time required for each of the substrates examined for 10% completion in SNO under identical conditions. Such a method has been successfully used by several groups of workers in some electrophilic aromatic substitutions.[27] Ob-

Table 2. Substituent effect on the rate of side-chain nitrooxylation of $C_6(CH_3)_5X$ in nitromethane at 25°C

$[C_6(CH_3)_5X]=2\times10^{-2}$ mol l^{-1}; $[HNO_3]=10\times10^{-2}$ mol l^{-1}

	X	Relative basicity (*p*-xylene=1)	t_{10}[a] (sec)
Hexamethylbenzene	CH_3	44500	15
Pentamethylbenzene	H	4350	660
Bromopentamethylbenzene	Br		4×10^4
Nitropentamethylbenzene	NO_2		5×10^6
Hexaethylbenzene		13500	800

a) t_{10} denotes the time required for 10% completion in SNO for each of the substrates examined.

23) The term "nitrous acid" used hereafter refers to all the products in the reaction mixture, which after dilution with water could be estimated as nitrous acid by ordinary procedures.

24) M. Dolinsky, J. H. Jones, C. D. Ritchie, R. L. Yates, and M. A. Hall, *J. Ass. Offic. Agri. Chem.*, **42**, 709 (1959).

25) H. Suzuki, This Bulletin, **43**, 481 (1970); K. Nakamura and H. Suzuki, *ibid.*, 227 (1971).

26) H. Suzuki, *ibid.*, **43**, 879 (1970).

27) H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.*, **79**, 1421 (1957); P. W. Robertson, P. B. D. de la Mare, and W. T. G. Johnston, *J. Chem. Soc.*, **1943**, 276; G. Illuminati and G. Marino, *J. Amer. Chem. Soc.*, **78**, 4975 (1956); E. Berliner and F. Berliner, *ibid.*, **71**, 1195 (1949).

Table 3. Comparison of substituent effects on the relative rates of side-chain nitrooxylation, ring nitration and dilute nitric acid oxidation

	X	Side-chain nitrooxylation of $C_6(CH_3)_5X$[a]	Ring nitration of C_6H_5X[b]	Oxidation by HNO_3 of $X\cdot C_6H_4CH_2OR$[c]
I	CH_3	1	1	1
II	H	2×10^{-2}	10^{-1}—10^{-2}	1—10^{-1}
III	Br	4×10^{-4}	10^{-3}	10^{-1}—10^{-2} [d]
IV	NO_2	3×10^{-6}	10^{-5}—10^{-8}	10^{-2}

a) II/I, III/I, and IV/I are reactivities of II, III, and IV relative to I calculated from the ratios of the reciprocals of t_{10} for each of them.
b) Ref. 29—31)
c) Ref. 28)
d) This value is the reactivity of chloro-substituted compound relative to methyl-substituted.

served t_{10} and reactivity relative to hexamethylbenzene are collected in Table 2. Comparisons are made with the substituent effects on the ring nitration of C_6H_5X, and on the oxidation of benzyl alcohols and their methyl ethers by dilute nitric acid (Table 3).

As is apparent from Table 2, the reactivity for SNO follows the order $C_6(CH_3)_6>C_6(CH_3)_5H>C_6(CH_3)_5Br>C_6(CH_3)_5NO_2$ and electron-withdrawing bromo and nitro groups remarkably retard the reaction. Similar orders are followed in ordinary nuclear nitrations, and in the oxidation of benzyl alcohols and their methyl ethers by dilute nitric acid to the corresponding benzaldehydes (Table 3). However, the magnitude of difference in relative rate for SNO differs remarkably from that of the latter process in which the hydrogen abstraction by radical is rate-determining.[28] Relative reactivities for SNO are $II/I=2\times10^{-2}$, $III/I=4\times10^{-4}$ and $IV/I=3\times10^{-6}$, and the overall reactivity range is covered by a factor of as large as 10^5. Marked dependence in the relative rates of SNO on the electronic effect of the substituent groups parallels that found in the nitration of C_6H_5X, $II/I=10^{-1}$—10^{-2},[29] $III/I=10^{-3}$,[30] and $IV/I=10^{-5}$—10^{-8},[31] where the attack of an electrophile to the nucleus to form benzenonium ion is rate-determining. In contrast, the relative rates of the hydrogen atom abstraction from side-chain vary very little with the change of substituents; $II/I=1$—10^{-1}, $III/I=10^{-1}$—10^{-2} and $IV/I=10^{-2}$.[28] A similar response of SNO and RNA to the change of substituents suggests that the processes of SNO and RNA are mechanistically alike and argues against any participation of free-radical pathway in the reaction. SNO proceeds with fuming nitric acid at low temperatures, while the nitric acid oxidation of alkylbenzenes can be effected with dilute aqueous nitric acid only at elevated temperatures. Additional support for the ionic process is put forward by the observation that SNO takes place with primary alkyl groups such as methyl and ethyl, but not with isopropyl or *t*-butyl group.[6] Excellent positional selectivity of SNO leads to the reaction products of simple composition and high purity,[6,25] which are opposed to the free-radical mechanism in which reactive benzyl nitrates would have been oxidized to a complicated mixture of benzaldehydes, benzoic acids and others.

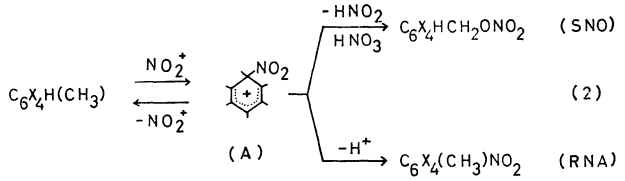
Effects of Added Electrolytes on the Ease and Extent of Side-chain Nitrooxylation. Table 4 shows the effects of added electrolytes on SNO and RNA of pentamethylbenzene, which were carried out with nitric acid ($d=1.50$) in nitromethane at 5°C. The time required for 10% completion in the overall reaction—the sum of SNO and RNA — is indicated by t'_{10}. The relative percentage of the products from SNO and RNA at t'_{10} is also included. As is apparent from the Table, the ratios of both reaction products are almost independent of the concentration of nitric acid or the presence of the added electrolytes such as nitrite, nitrate or hydrogen sulfate. This might indicate that the reaction leading to RNA and SNO shares a common intermediate, presumably benzenonium ion (A) as described in the equation below:

Table 4. Effects of added electrolytes on the ease and extent of side-chain nitrooxylation of pentamethylbenzene with nitric acid in nitromethane at 5°C

$C_6(CH_3)_5H$ (mol l^{-1})	HNO_3 (mol l^{-1})	Added electrolytes (mol l^{-1})	t'_{10}[a] (min)	SNO (%)	RNA (%)	t_{10}[b] (min)
0.1	0.5	None	9.5	86	14	10.5
0.1	0.5	None	9	88	12	10
0.1	0.5	Et_4NHSO_4: 0.022	9	86	14	10
0.1	0.5	Et_4NNO_3: 0.022	15.5	90	10	16.5
0.1	0.5	$NaNO_2$: 0.0043	4	84	16	4.5
0.1	0.1	None	80	85	15	96
0.2	0.5	None	9.5	90	10	10
0.05	0.5	None	6.5	86	14	8
0.1	0.5	H_2SO_4: 0.01	7	76	24	8

a) The time required for 10% completion in the overall reaction—the sum of SNO and RNA—is indicated by t'_{10}.
b) The time required for 10% completion in SNO is indicated by t_{10}.

28) Y. Ogata, Y. Sawaki, F. Matsunaga, and H. Tezuka, *Tetrahedron*, **22**, 2655 (1966); Y. Ogata and Y. Sawaki, *J. Amer. Chem. Soc.*, **88**, 5832 (1966).
29) L. M. Stock, *J. Org. Chem.*, **26**, 4120 (1961).
30) J. D. Roberts, J. K. Sanford, F. L. J. Sixma, H. Cerfontain, and R. Zagt, *J. Amer. Chem. Soc.*, **76**, 4525 (1954).
31) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution, Nitration and Halogenation," Butterworth Scientific Publications, London (1959), p. 83.



The reaction rates are subject to the influence of the added electrolytes. The reaction is accelerated by the addition of a small amount of sulfuric acid, the role of which is no doubt to form the nitric acidium ion $H_2NO_3^+$, the precursor of the reactive nitronium ion NO_2^+, HSO_4^- acting as a base. A negative effect has been shown by nitrate ion, which retards the reaction by decreasing the concentration of nitric acidium ion according to the equation

$$HNO_3 + HNO_3 \rightleftharpoons H_2NO_3^+ + NO_3^- \qquad (3)$$

Addition of a small amount of nitrite ion into the system brings about a remarkable enhancement of the reaction rate, but the relative ratio of SNO and RNA remains unchanged. Nitrooxylation of hexamethylbenzene and pentamethylbenzene according to Eq. (1) inevitably produces a large amount of nitrous acid with progress of the reaction, and the nitrous acid thus formed restricts the supply of the nitronium ion by lowering the concentration of the nitric acidium ion in the system following the equation[32]

$$H_2NO_3^+ + NO_2^- = N_2O_4 + H_2O \qquad (4)$$

Since the reaction of pentamethylbenzene is apparently autocatalysed, the nitrosonium ion may play some role in the substitution as has been suggested by Shofield and coworkers in the nitration of some activated aromatic systems.[33,34] The reaction rate of SNO is also more enhanced in nitromethane than in acetic acid. This trend has already been well substantiated for ordinary nuclear nitration.[32] Thus it is concluded that the effective species for SNO is the nitronium ion or its precursors ($H_2NO_3^+$ and N_2O_5) depending on the reagent and conditions employed, and the electrophilic attack of these ionic species on the aromatic substrate constitutes the initial stage of the reaction; the proton transfer from the nucleus leads to RNA and the proton removal from the side-chain results in SNO, as in Eq. (2).

Relative Reactivities of Polyalkylbenzenes towards Side-chain Nitrooxylation. Comparison of relative reactivities towards SNO has been made with 18 alkylbenzenes listed in Table 5. With durene and pentaalkylbenzenes, SNO predominates over RNA, but with the decreasing number of alkyl substituents, the situation is gradually reversed so that t_{10} should be replaced by t_1 to provide a sound basis of comparison for the diminished tendency of substrate towards side-chain substitution. In Table 5, a similar comparison of overall reactivities of seven polyalkylated aromatic systems has been made on the basis of t'_{10}, relative basicity and the percentage ratios of SNO and RNA at t'_{10}.

Tetralin and diphenylmethane, which have reactive hydrogen atoms and are readily oxidized by dilute nitric acid, remain mostly unchanged in support of the ionic process for SNO. The basicity of hydrocarbon decreases in the order: isodurene>mesitylene>prehnitene>durene>pseudocumene, whereas a partial reversal of the order was observed in the relative rates of these hydrocarbons for SNO: xylenes<mesitylene<pseudocumene<prehnitene<isodurene<durene. This is rather surprising since it means that mesitylene, which is highly reactive in ordinary electrophilic reactions, reacts more slowly for SNO than durene or pseudocumene, which are much less basic than the former and not so highly reactive in the ordinary sense. The reactivity for SNO is, therefore, closely related to the positional relationship of the substituents in the alkylated aromatic systems. The significance of this aspect of the reaction will be discussed in due course.

The percentage ratio of SNO tends to decrease in the following order: pentamethylbenzene>durene>isodurene>prehnitene>5-*t*-butylhemimellitene>mesitylene. From the results in Table 5 it appears that the more a hydrocarbon possesses a pair of alkyl groups located at ortho and/or para position, the more readily it undergoes SNO. This is clearly understood from the reactions of hexamethylbenzene, pentamethylbenzene, durene, pseudocumene and *p*-xylene. On the other hand, mesitylene and *m*-xylene which have no comparable alkyl group yield only RNA products. It follows, therefore, that a fine balance exists between SNO and RNA, and that the positional features of the substrate are likely to be an important factor for deciding the way the reaction will take place, SNO or RNA.

High positional selectivity for SNO is very likely connected with the slow step of the proton removal from the alkyl side-chain of the benzenonium ion intermediate. Although the nitration of benzene proceeds without any primary isotope effect,[35] sterically hindered compounds usually exhibit some effect since the slow proton transfer now becomes rate-determining.[36] The diminished facility of proton transfer from the nucleus necessarily increases the chance of hyperconjugative release of a proton from the alkyl side-chain. Thus, SNO and RNA are able to compete effectively in a crowded system such as durene, penta-alkylbenzenes and hexamethylbenzene. Taking the nitration of durene as an example, the process can be outlined as follows:

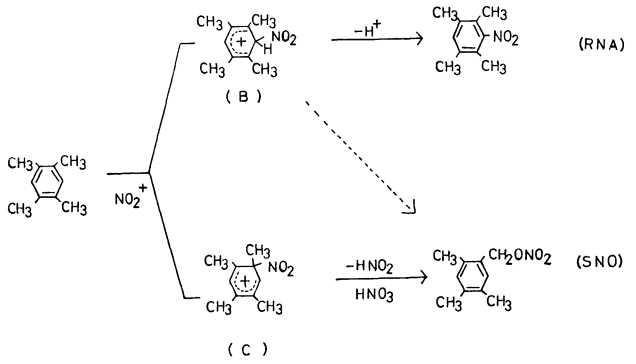
32) E. D. Hughes, C. K. Ingold, and R. I. Reed, *J. Chem. Soc.*, **1950**, 2400.

33) R. G. Coombes, R. B. Moodie, and K. Schofield, *ibid.*, *B*, **1968**, 800; J. G. Hoggett, R. B. Moodie, and K. Schofield, *ibid.*, *B*, **1969**, 1.

34) C. A. Bunton, E. D. Hughes, C. K. Ingold, D. I. H. Jacobs, M. H. Jones, G. J. Minkoff, and R. I. Reed, *J. Chem. Soc.*, **1950**, 2628.

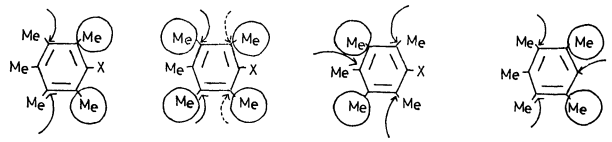
35) H. Zollinger, "Advances in Physical Organic Chemistry," in V. Gold Ed., Academic Press, London, (1964), p. 163; H. Cerfontain, H. J. Hofman, and A. Telder, *Rec. Trav. Chim Pays-Bas*, **83**, 493 (1964).

36) H. Cerfontain and A. Telder, *ibid.*, **86**, 371 (1967); P. C. Myhre, M. Beug, and L. L. James, *J. Amer. Chem. Soc.*, **90**, 2105 (1968).



The attack of the nitronium ion upon durene will give two benzenonium intermediates (B) and (C), the latter outweighing the former in amount not only for statistical reasons, but also for more effective stabilization by one methyl group in an ortho position and one in para position than two methyl groups in ortho as (B). Steric factor also favors the formation of (C), in which the position of attack is flanked by one methyl group, over (B) where both sides are flanked. Ordinary proton removal from (B) will lead to RNA, and unusual proton removal from alkyl side-chain will result in the formation of SNO product. The predominance of the latter process in the reaction of durene may be rationalized by the greater contribution of the intermediate (C) over (B), and by the slower removal of the ring proton from (B). Further, the formation of nitrooxylated compound only as a minor product in the nitration of pentamethylphenol may be accounted for by easier proton transfer from the hydroxy group, leading to conversion into cyclohexadienone derivatives.

The methyl groups preferentially nitrooxylated and the most probable positions to be attacked initially by the nitronium ion are illustrated below for some polyalkylated aromatic systems.

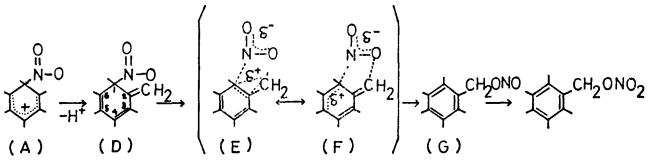


X=NO_2, COOH, $COOCH_3$ X=Cl, Br X=OH, OCH_3, NHAc

A circle indicates the methyl group preferentially nitrooxylated, and an arrow shows the preferred position for electrophilic attack by nitronium ion. Solid line —— the most preferred; dotted line ------ the next preferred.

As can be seen from the figures, the presence of methyl groups in positions ortho and/or para one another seems critical for the facile formation of benzyl nitrates. This might indicate that the hyperconjugative electron release from the methyl group will play some role for side-chain nitrooxylation. In fact, most benzyl nitrates obtained in high yields from the nitration products possess *p*-methyl group, and those having an electron-withdrawing substituent in para position are rarely formed.

On the basis of this study and related previous works,[6,25] we can tentatively construct some plausible sequences for side-chain substitution under heterolytic conditions. The cyclic process involving the migration of nitro group from nucleus to side-chain has been suggested for SNO of pentaalkylbenzenes.[6] This proceeds through a sort of allylic migration of nitro group from the attacking site to α-carbon of the alkyl group, from which the preferential proton removal took place. The benzyl nitrite thus formed will be transformed with nitric acid into the benzyl nitrate and nitrous acid.



(5)

Many findings obtained from SNO are consistent with this mechanism, which has a formal resemblance to those proposed for some Claisen-type rearrangements[37] such as allyl amine oxides, nitramine and alkylpyridine *N*-oxide rearrangement. Transformation from the benzenonium intermediate (A) to the benzyl nitrite (G) can take place in two different ways; a direct conversion, and the intervention of an intermediate methylene cyclohexadiene, (D) and (H). The former process

Table 5. Reactivities of polyalkylbenzenes towards the side-chain nitrooxylation in nitromethane at 5°C

[Polyalkylbenzenes] = 0.1 mol l^{-1}; [HNO_3] = 0.5 mol l^{-1}

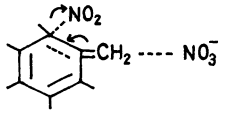
Polyalkylbenzenes	Basicity	t_{10}[a] (min)	t'_{10}[b] (min)	SNO (%)	RNA (%)
Pentamethylbenzene	4350	10.5	9.5	86	14
Ethyldurene		11			
Ethylprehnitene		15			
Pentaethylbenzene		15			
Durene	60	18	13.5	70	30
Tetralin		*ca.* 20 hr			
		t_1[c]			
Prehnitene	85	105	230	25	75
Isodurene	2800	45	200	43	57
5-*t*-Butylhemimellitene		600	690	12	88
Bromodurene		150[d]	450	38	62
Mesitylene	1400	very large			100
Ethylmesitylene		120			
5-Ethylhemimellitene		50			
Pseudocumene	18	570			
4-Ethyl-*o*-xylene		540			
4-Ethyl-*m*-xylene		660			
2-Ethyl-*p*-xylene		680			
Diphenylmethane		*ca.* 50 hr			

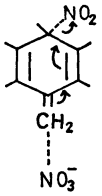
a) The time required for 10% completion in SNO is expressed by t_{10}.
b) The time required for 10% completion in the overall reaction the sum of SNO and RNA is indicated by t'_{10}.
c) The time required for 1% completion in SNO is indicated by t_1.
d) at 22.5°C

37) B. S. Thyagarajan, "Mechanisms of Molecular Migrations," Vol. II, Interscience Publishers, London, (1969); H. J. Shine, "Aromatic Rearrangements," Elsevier Publishing Company, London, (1967).

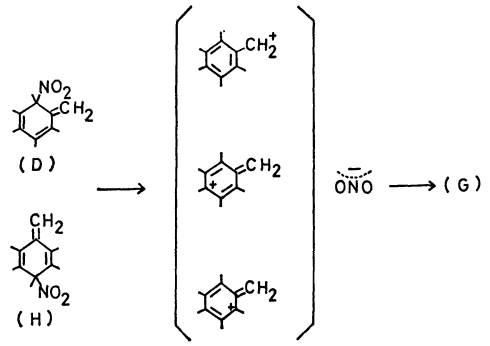
involves a simultaneous proton abstraction and nitro group migration in (A). Each pathway requires a transition state in which the scission of the C–N bond occurs in such a way that the departing nitrogen atom is accommodated with the unshared electron pair, leaving C-1 atom to be electron-deficient. This sort of π-σ electron interaction could occur through the overlap between C-1 carbon atom and the α or C-5 carbon atom.[38] The transition state for such a process may be depicted as (E) or (F). The C-5 methyl group at a position meta to C-1 and para to C-2 methylene can partly supplement this deficiency through the hyperconjugative electron release, thus facilitating the nucleophilic migration of the nitro group to the side-chain. Electron-withdrawing group at C-5, on the other hand, increases the electron deficiency at the carbon atom to which the nitro group is attached, making the departure of nitro group as a nucleophile more difficult. This is probably why the benzyl nitrate with the methyl group at para position is preferentially formed over the other isomeric products.

Two other possibilities are also conceivable, although they lack formal analogies in literature as far as the author is aware. One is a process in which a proton is removed hyperconjugatively from the side-chain to form a sort of methylene cyclohexadiene intermediate (D) and (H). Attachment of the nitrate anion to the terminal methylene carbon, departure of the nitro group as an anion, and rearomatization of the system, if occurring continuously, will lead to the formation of the benzyl nitrate.



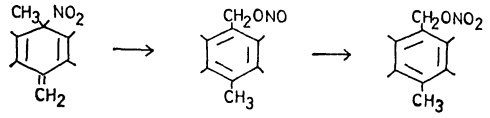


This intermolecular process is apparently difficult for justifying the fact that nitration carried out in dilute acetic acid solution affords a considerable amount of benzyl nitrate along with benzyl acetate at a very early stage of the reaction, and that the ratio of SNO and RNA is nearly independent of the concentration of nitric acid as well as added electrolytes. A speculative alternative may involve the ion-pair intramolecular path proposed for rearrangements of nitramine,[39] and 2- and 4-picoline oxides.[38,40] Formation of ion-pair requires a tight (solvent caged) association of these species, and their combination is required before separation to accommodate this intramolecular process, although the intramolecular nucleophilic cyclization leading to the formation of phthalide, or anthranil analog could not be observed during the nitration of pentamethylbenzoic acid, or pentamethylnitrobenzene.



In view of a preferred attack on the 2-alkyl group in the reaction of 2,4-lutidine *N*-oxide[41] or 2,4-dimethylquinoline *N*-oxide with acetic anhydride, rearrangement to the neighboring ortho position could occur more readily than that to the remote para position. The former would probably proceed intramolecularly, while the latter possibly intermolecularly.[42]

Another possibility is a process similar to the Quinobenzylic rearrangement, where the attacking species migrates intramolecularly to the geminal methyl group to form the benzylic compound.



The principal disadvantage of this mechanism is that the nitropentamethylbenzene and pentamethylbenzoic acid undergo almost exclusive ortho nitrooxylation, because the most favored position for the attack of the nitronium ion in these compounds is not the ortho, but the meta position to the strongly electron-withdrawing nitro or carboxyl groups. Quinobenzylic rearrangement itself has recently been reported to proceed through a radical mechanism.[43]

The author wishes to thank Dr. H. Suzuki, Professor K. Maruyama and Professor J. Osugi for their discussions.

38) T. Koenig, *J. Amer. Chem. Soc.*, **88**, 4045 (1966).
39) W. N. White and J. T. Golden, *Chem. Ind.* (London) **1962**, 138.
40) T. Cohen and G. L. Deets, *J. Amer. Chem. Soc.*, **89**, 3939 (1967); T. Cohen and J. H. Fager, *ibid.*, **87**, 5701 (1965); R. Bodalski and A. R. Katritzky, *Tetrahedron Lett.*, **1968**, 257.
41) S. Furukawa, *Chem. Pharm. Bull* (Tokyo), **3**, 413 (1955).
42) S. Oae and S. Kozuka, *Tetrahedron*, **20**, 2694 (1964).
43) V.D. Pokhodenko and N.N. Kalibabchuk, *Zh. Org. Khim.*, **2**, 1397 (1966); N.N. Kalibabchuk, *ibid.*, **4**, 329 (1968).