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THE ELECTROPHILIC NATURE OF THE SIDE-CHAIN HALOGENATION OF METHYLBENZENES IN ACETIC ACID[1]

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MOLECULAR halogen is known as a reagent source in both electrophilic and free-radical reactions with alkylbenzenes, depending on experimental conditions. Polar media, catalysis by iodine and metal halides and electron-releasing substituents in the aromatic substrate are typical conditions favouring electrophilic halogenation at the aromatic carbon.[2] Free-radical halogenations occur in non-polar media, are relatively slow reactions unless catalysed by light or peroxides, and are only slightly favoured by alkyl substituents. They typically lead to side-chain substitution and to addition to the aromatic nucleus.[2,3]

Although it has become customary to identify the side-chain halogenation of an alkylbenzene with a free-radical reaction, this assumption is not obvious in some cases where the side-chain and the nuclear substitution coexist under the conditions of electrophilic substitution. For example, side-chain halogenation products usually accompany the nuclear substituted products to a small, but definite extent in the bromination of several polymethylbenzene derivatives in acetic acid and nitromethane[4] and

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[1] Substitution in Polymethylbenzenes. XIV. For the preceding paper in this series see ref. 5.

[2] P.B.D. de la Mare and J.H. Ridd, Aromatic Substitution Chapters 8, 9 and 10. Butterworths, London (1959).

[3] C. Walling, Free Radicals in Solution Chapter 8. John Wiley, New York (1957).

[4] R.M. Keefer, A. Ottenberg and L.J. Andrews, J. Amer. Chem. Soc. **78**, 255 (1956); G. Illuminati and G. Marino, Ibid. **78**, 4975 (1956).

in more substantial amounts in the chlorination reaction.[5] The most striking feature about these findings is that the side-chain reaction accompanies the electrophilic nuclear substitution whatever the aromatic reactivity of the substrate may be, so the two reactions often seem to proceed at roughly the same rate within one order of magnitude or so. The free-radical nature of the side-chain chlorination of pentamethylbenzene appears to be questionable even in carbon tetrachloride solution.[6]

In connexion with our current studies on the aromatic reactivity of methylbenzenes, we have gathered a very consistent body of information showing that the side-chain chlorination in acetic acid is electrophilic in nature with strong kinetic analogies to the nuclear substitution. The importance of the subject prompts us to report on the most significant results obtained with hexasubstituted benzenes.

Using the same technique developed in this Laboratory to follow the chlorination of the most reactive hydrocarbons,[5] we found that hexamethylbenzene chlorinates very rapidly in 2×10^{-4}M acetic acid solution with the exclusion of light and catalysts, the half-life being ca. 1.2 sec at 18°. The reaction product consists of side-chain chlorination derivatives, mainly chloromethylpentamethylbenzene. No evidence was found of either chlorine addition compounds or demethylated derivatives. The reaction can be applied to the preparative scale.

Since by the free-radical mechanism bulk toluene chlorinates slowly in the dark[7] and substituent effects are poor (see below), the very high reactivity of hexamethylbenzene in dil. solution can hardly be accounted for by a chlorine atom attack of the side-chains: it is in fact greater than that corresponding to the electrophilic nuclear chlorination of penta-

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[5] E. Baciocchi and G. Illuminati, Gazz. Chim. Ital. **92**, 89 (1962).

[6] L.J. Andrews and R.M. Keefer, J. Amer. Chem. Soc. **79**, 5169 (1957).

[7] M.S. Kharasch and M.G. Berkman, J. Org. Chem. **6**, 810 (1941).

methylbenzene[5] and approaches that calculated by Condon's method for an hypothetical nuclear substitution of hexamethylbenzene ($k_{obs.}$ ca. 0.4 x 10^4 at 18^o, $k_{calc.}$ 1.2 x 10^4 at 25^o (l x $mole^{-1}$x sec^{-1}); in the computation of $k_{calc.}$ the effect of the methyl group <u>at</u> the position of attack was neglected).

Polar effects of the substituents on reactivity were examined in more detail by measuring the chlorination rates of the series C_6Me_5R (R=Me, Cl, Br, CN). The reaction was found to be very sensitive to the electron-donor properties of the aromatic substrate, which were gradually reduced in the order Me > hal > CN. The relative reactivities k_{Me}/k_R are reported in Table 1 and compared with the corresponding ratios for the radical chlorination of p-substituted toluenes[8] and for the nuclear chlorination of 3-substituted durenes.[9] These data show that while the substituent effects for the radical reaction are small, those for the hexasubstituted benzene reaction are very large involving factors of several orders of magnitude. Again, the latter effects are close to those observed for the nuclear chlorination reaction.

A more complete kinetic picture was obtained with the slower-reacting members of the series C_6Me_5R. Cyanopentamethylbenzene reacts with chlorine in anhydrous acetic acid solution (in the dark) by strictly second-order kinetics. Addition of water strongly accelerates the reaction. Also, I_2 and $ZnCl_2$ were found to act as mild catalysts. All these effects were found to be quantitatively similar to those observed in aromatic chlorination in the same solvent.

The present data consistently point to the following conclusions with regard to the reaction mechanism. Besides a free-radical chlorination,

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[8] C. Walling and B. Miller, J. Amer. Chem. Soc. 79, 4181 (1957).

[9] E. Baciocchi and G. Illuminati, unpublished work.

TABLE 1

Relative Reaction Rates k_{Me}/k_R in Three Chlorination Reactions with Cl_2

Reaction	C_6Me_5R (this work)	p-C_6H_4MeR[a] (radical side-chain substn.)	3-R-durene[b] (aromatic substn.)
k_{Me}/k_{Cl}	ca. 3×10^3[c]	2.2	0.8×10^3[c]
k_{Me}/k_{CN}	ca. 1.4×10^6[c]	4.3	12.8×10^6[c]

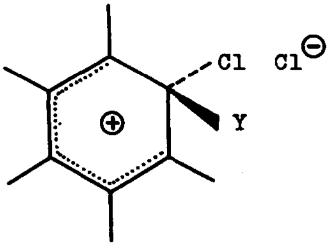
[a] Ref. 8.

[b] Ref. 9.

[c] For experimental convenience these values were all expressed by using the data at 18° for the Me compounds and at 30° for the R compounds.

there exists a side-chain chlorination involving electrophilic chlorine. The conditions for the latter reaction correspond to the general conditions known for aromatic halogenation. This novel reaction becomes evident only when the aromatic substrate is very reactive toward electrophilic reagents and especially when there are no positions available for competition by normal aromatic substitutions.

Hexasubstituted alkylbenzenes are the best examples now at hand of substrates suitable to the reaction. Because of the close, quantitative analogy to normal aromatic substitution we suggest that the rate-determining steps of the two reactions be essentially similar in that they involve the attack of the electrophile on aromatic carbon, as follows



If Y=H, C-H bond-breaking is likely to be the subsequent step leading to nuclear substitution. However, if Y=CH_3, C-CH_3 bond-breaking may require such a high energy as to make other paths leading to side-chain substitution more favoured. Further work is needed in order to ascertain the most probable paths for the subsequent steps of the reaction.

A full account of this work will be reported elsewhere.

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