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REACTION SELECTIVITY, HYDROGEN ISOTOPE EFFECT AND STERIC HINDRANCE IN THE AROMATIC HALOGENATION OF POLYALKYLBENZENES[1]

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The observation that aromatic halogenation with molecular halogen is a less selective reaction with polymethylbenzenes than with monosubstituted benzenes, as based on the reaction constants of the reactions in each individual series[2,3], suggests that the two methyl groups ortho to the attacked position in the former molecules may effectively lower the sensitivity of the reagent to the changes of the electron density of the aromatic substrate by hindering the approach of the attacking entity. Presumably a steric effect of this kind may alter the detailed timing of the process and be accompanied by a shift of the reaction coordinate for the rate-determining transition state toward increasing extents of C-H bond breaking, in the potential energy curve of the reaction. If bond breaking made enough progress, a hydrogen isotope effect would result in the aromatic halogenation of hindered polymethylbenzenes.

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[1] Substitution in Polymethylbenzenes. XII.

[2] H.C.Brown and Y.Okamoto, J.Am.Chem.Soc.**80**, 4979 (1958).

[3] (a) G.Illuminati, J.Am.Chem.Soc. **80**, 4941 (1958); (b) E.Baciocchi and G.Illuminati, Ric.Sci. **28**, 1159 (1958).

The possible connection of the specific steric environment characteristic of these systems to the selectivity of the reaction and to hydrogen isotope effects is being tested in this Laboratory by extension of our studies to more hindered polyalkylbenzenes. The results concerning isotope effects in the case of one of the polyalkylbenzene structures involving two <u>ortho</u> methyl groups flanking the attacked position (bromodurene) have been obtained recently in this Laboratory and the very recent report of a hydrogen isotope effect in the bromination of T-labeled 1,3,5-tri-<u>t</u>-butylbenzene[4] prompts us to communicate our present halogenation data with 3-bromo-6-deuterodurene and 3-bromodurene.

Consistent syntheses of the two compounds were effected starting from the same stock of 3,6-dibromodurene and letting it to react with <u>n</u>-butyl lithium in ether solution 0.06 M in each reactant and under standard conditions for the synthesis of deuterated compounds[5]. 3-Bromoduryl lithium, which was formed quantitatively by halogen-metal interconversion within twelve minutes at room temperature, was then hydrolyzed with 96% heavy water or water to give 3-bromo-6-deuterodurene and 3-bromodurene, respectively. The consistency in the synthesis of the two compounds insured the validity of the comparison of the subsequent rate measurements. The latter were carried out according to the procedure described previously for the study of bromination with Br_2

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[4] P.C.Myhre, <u>Acta Chem.Scand.</u> <u>14</u>, 219 (1960).

[5] See, for example, L.H.P.Weldon and C.L.Wilson, <u>J.Chem.Soc.</u>235 (1946).

in nitromethane[6] and chlorination with Cl_2 in glacial acetic acid[3b]. The results are collected in Table 1.

TABLE 1

Halogenation Data at 30°C for the Hydrogen Isotope Effect in Bromodurene

Aromatic compound	Bromination in $MeNO_2$		Chlorination in AcOH	
	t_{10}(mins.)(a)	k_H/k_D	$k, l \times mole^{-1} \times sec^{-1}$	k_H/k_D
3-Bromodurene	22.9±1.2	1.4	0.098	~1
3-Bromo-6-deuterodurene	32.7±1.8		0.107	

(a) Times for 10% reaction with solutions 0.01 M in each reactant. Data obtained with a single stock of nitromethane, for which relative rates of bromination were ascertained to be identical to those reported previously[3a,6].

The k_H/k_D ratios were calculated by neglecting any nuclear hydrogen content in the deuterium compound and infrared analysis in fact indicated such a content to be low. Thus, Table 1 shows that there

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[6] G.Illuminati and G.Marino, J.Am.Chem.Soc. 78, 4975 (1956).

is a definite, even though small, isotope effect in the bromination of bromodurene and that, presumably, the corresponding k_H/k_D value, 1.4, is a lower experimental limit. In contrast to this, chlorination of the same system shows no isotope effect.

Since the demonstration that isotope effects are absent in the bromination of such simple aromatic hydrocarbons as benzene[7,8], a number of recent papers reports varying extents of such effects in the halogenation of more perturbed or more complex aromatic molecules. Thus, small to fairly large effects have been found in the halogenation of anisole[9], aniline[10] and dimethylaniline[10,11], i.e., of systems containing strong electron-releasing substituents and a large effect in the bromination of the highly hindered 1,3,5-tri-_t_-butylbenzene[4]. Clearly, from the published data isotope effects depend not only on the isotope used (T > D) but also on the type of the halogenation reaction (iodination > bromination > chlorination) and on the structure of the aromatic substrate. In the case of the bromination of monosubstituted benzenes with molecular bromine, an isotope effect has been clearly established with the dimethylamino group[11] but not with the less strongly electron-releasing methoxy group[9]. Our present

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[7] L.Melander, Arkiv f.Kemi 2, 211 (1950).

[8] P.B.D.De La Mare, T.M.Dunn and J.T.Harvey, J.Chem.Soc. 923 (1957).

[9] E.Berliner, Chem.& Ind. 177 (1960)

[10] E.Shilov and F.Weinstein, Nature 182, 1300 (1958)

[11] P.G.Farrell and S.F.Mason, Nature 183 , 250 (1959)

results with bromodurene now offer another case of a hydrogen isotope effect for the bromination reaction with molecular bromine. Bromodurene does not contain any strong electron-releasing group, but the seat of the reaction is hindered by two <u>ortho</u> methyl groups : it is then probable that the small effect found belongs to the same class of that shown by 1,3,5-tri-<u>t</u>-butylbenzene. The over-all activation does not seem to be alone a determining factor[10] and, in any case, on the base of the additivity of the electronic effects in polysubstituted aromatic compounds, the only available nuclear position of bromodurene is less activated than the <u>para</u>-position of anisole, for which no more than an effect within experimental uncertainty was found[9]. The influence of steric hindrance on hydrogen isotope effects was well established by Zollinger for the diazo-coupling of naphthalene systems; however, the announced isotope effect in the bromination of 2-naphthol-6,8-disulphonic acid[12] might result from a combination of steric and electronic effects because of the presence of the OH substituent.

From the above, it should be clear that further experimentation is needed to neatly distinguish among all possible correlations of isotope effects with the nature of the reagent and the structure of the substrate in aromatic halogenation. Extension of the present work to other molecules in the polyalkylbenzene area will be reported in due course.

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[12] Hch.Zollinger, <u>Experientia</u> **12**, 165 (1956).