EQUILIBRATION AND VAPOUR-PHASE HALOGENATION OF BENZENE DERIVATIVES

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INTRODUCTION

The study of isomer distributions in benzene derivatives is one of several major investigations stimulated by August Kekulé's famous paper " Sur la constitution des substances aromatiques " which was published nearly a century ago[1]. Thus, Kekulé's bold theory required the existence of three disubstituted isomers as well as several other regularities which the organic chemist takes for granted today. In the ten years following this publication, various successful attempts were made to find definite evidence for these symmetry properties by means of substitution reactions. In several instances, however, some difficulties were encountered, the number of direct substitution products obtained being less than that expected on the grounds of symmetry requirements. Consequently, these discrepancies began to receive detailed attention. The subject of *isomer patterns* in benzene derivatives has since been actively studied, first from the experimental standpoint and later theoretically.

Holleman was probably one of the first to recognize the importance of obtaining detailed quantitative information on *isomer patterns*. His work on electrophilic substitutions, a survey of which appeared in the first volume of *Chemical Reviews*[2], led him to distinguish two main types of substituents: those such as CH_3, OCH_3 and Cl, which are " *ortho/para*-directing ", and those like NO_2, CN and $COOH$, which are " *meta*-directing ". Whereas Holleman preferred the phenomenological approach, Ingold, using many of Holleman's data as a starting point, embarked on the problem along theoretical lines. From his work emerged our present concepts of electrophilic aromatic substitution, important features of which are the sigma-complex intermediate and the dependence of substituent effects on the reagent[3].

Meanwhile, quite different isomer patterns had been found when carrying out aromatic substitutions with other types of reagents, or under different experimental conditions, compared with those in electrophilic processes. Thus, using the phenyl radical as the reagent, Hey and his co-workers established that comparable proportions of all three isomers are formed in the arylation of monosubstituted benzenes; in nearly all cases there was a certain small preference for *ortho*- and *para*-substitution[4]. Until recently, it appeared to be impossible to achieve high yields of arylation products. Here, the interpretation of the isomer patterns is based on the theory of localization, *i.e.* in terms of relative heats of reaction[5].

In Amsterdam, Holleman's successor Wibaut discovered that gas-phase halogenation may lead to isomer distributions distinctly different from those observed in either electrophilic halogenation or in arylation. Bromination of bromobenzene at 425°, for example, produces appreciable proportions of *meta*-isomer; at lower temperatures, electrophilic substitution—presumably taking place at the wall of the reactor—predominated and *para-* and *ortho*-dibromobenzene were the main products. Yields were, however, moderate; so far, a satisfactory interpretation of the mechanisms involved in these high-temperature halogenations has not been offered[6].

The foregoing brief outline of possible isomer patterns of benzene derivatives will have to suffice as a starting point for my present discussion. This will deal with the isomer distribution in *equilibria among benzene derivatives*—in particular among bromobenzenes—and in *gas-phase halogenations of substituted benzenes*. An attempt will be made to demonstrate that the classical problem of isomer distribution is still revealing novel features, even when only simple structural or experimental variations are applied. Whereas the emphasis will be on the isomer distributions proper, some attention will also be given to possible theoretical interpretations for the particular isomer patterns observed.

EQUILIBRIA AMONG BROMOBENZENES AND OTHER BENZENE DERIVATIVES

Whereas much effort has been devoted to various types of aromatic substitution reactions, especially with regard to substituent effects, the equilibration of substituted benzenes has received relatively little attention. This would seem to be somewhat surprising in view of the fact that equili-brated isomer patterns could supply interesting information on substituent effects in the ground state. No assumptions would be needed as regards the transition states of the reactions.

So far, however, most of the scattered data apply to alkylated benzenes—presumably because of their industrial significance. Admittedly, positional isomerization of benzene derivatives generally meets with difficulties, side reactions taking place which obscure the equilibrium pattern.

As reported in a recent paper, the bromobenzenes are exceptional in undergoing isomerization quite readily at room temperature under the influence of small proportions of aluminium bromide[7]. Presumably the process involves reversible protonation at the carbon atom carrying the bromine atom; the protonated sigma-complex loses a proton more readily than a bromine " cation ". Isomerization thus takes place through re-bromination of the debrominated product in a different position:

$$H^+ + ArBr \rightleftharpoons (HArBr)^+ \qquad (1)$$
$$(HArBr)^+ \rightleftharpoons ArH + Br^+ \qquad (2)$$

Figure 1. Proto-debromination

The intermolecular nature of these reactions was established by the occurrence of *transbromination* when adding an excess of suitable acceptors.

Thus, reaction of bromobenzene and chlorobenzene leads to a mixture of benzene and *ortho*- and *para*-bromochlorobenzene; in a later stage of the reaction, the *meta*-isomer appears and the whole system becomes equilibrated.

Starting from these findings, a number of liquid-phase isomer equilibria as well as transbromination equilibria among different bromobenzenes were determined; moreover, relative rates of debromination were measured, but their discussion is beyond the scope of this lecture. In special cases, isomerization may proceed (partly) through 1,2-shifts. It was demonstrated, however, that the transbromination of chlorobenzene with bromobenzene under the influence of bromine-labelled aluminium bromide is appreciably faster than the exchange between organic and inorganic bromine, indicating that the brominating species is not in a rapid equilibrium with the catalyst[7a].

Table 1 represents some of our results obtained on equilibrating monosubstituted bromobenzenes.

Table 1. Isomer equilibria among monosubstituted bromobenzenes

Substituent	Equilibrium†			
	% ortho	% meta	% para	o/m
Br	6 (4·5)	60 (62)	34 (33·5)	0·10
Cl	5 (5)	63 (62)	32 (33)	0·08
F	5 (5)	58 (63)	37 (32)	0·09
CH_3	39 (38)	42 (45)	19 (18)	0·93
C_2H_5	24–5	53–4	22	0·46

† Figures in brackets are those reported by Olah *et al.*[7]

Isomer distribution appears to be markedly different from that observed in direct substitutions; whereas the patterns of dihalobenzenes are characterized by low proportions of *ortho*-isomers, the alkylbromobenzenes contain an appreciable percentage of the *ortho*-isomer. It would seem plausible to attribute this difference to dipole–dipole interactions having opposite signs in the two cases.

Table 2 gives data on disubstituted bromobenzenes at equilibrium.

With the exception of the results for bromo-orthoxylene, isomer distributions are in good agreement with values computed from the previous data on the basis of additivity of substituent effects. As has been pointed out by various authors, the steric requirements of two adjacent methyl groups are greater than those of a single group, presumably as a result of the " interlocking " of carbon–hydrogen bonds in the two groups[8].

Table 3 gives some information as regards exchange equilibria, indicating a preference for the bromine atom to be in the same benzene ring with a given substituent in the order CH_3 H Br Cl F.

Combination of the latter data with those shown earlier leads to " partial equilibrium constants " relating to the exchange of a bromine atom and a hydrogen atom in a given position of a substituted benzene relative to benzene. These data are represented in *Table 4* which also gives the free energy effects involved in these exchange processes.

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Table 2. Isomer equilibria among disubstituted bromobenzenes

Substituents	Equilibrium	
	Found	Calculated from Table 1 on the basis of additivity
1,2-Dimethyl	26% 3-Bromo 74% 4-Bromo	51% 3-Bromo 49% 4-Bromo
1,3-Dimethyl	23% 2-Bromo 43% 4-Bromo 33% 5-Bromo	24% 2-Bromo 48% 4-Bromo 28% 5-Bromo
1-Chloro-4-methyl	7% 2-Bromo 93% 3-Bromo	8% 2-Bromo 92% 3-Bromo
1-Fluoro-4-methyl	7% 2-Bromo 93% 3-Bromo	8% 2-Bromo 92% 3-Bromo
1,2-Dichloro	6% 3-Bromo 94% 4-Bromo	7% 3-Bromo 93% 4-Bromo

Table 3. Equilibrium constants for various combinations containing bromobenzene as the donor molecule

$$\left(K_z = \frac{BrC_6H_4Z \times PhH}{PhBr \times PhZ} \right)$$

Bromine acceptor PhZ	K_z
$PhCH_3$	1.4_5
PhH	1
PhCl	0.10
PhF	0.07_5
PhBr	0.05_5

Table 4. Partial equilibrium factors and free energy effects for the exchange reaction
$$PhBr + PhZ \rightleftarrows x\text{-}BrC_6H_4Z + PhH + \Delta F$$

Substituent	Partial equilibrium factor	Free energy change (kcal)	Substituent	Partial equilibrium factor	Free energy change (kcal)
o-CH_3	1.7	+0.30	o-Cl	0.015	−2.45
m-CH_3	1.8	+0.34	m-Cl	0.19	−0.97
p-CH_3	1.6	+0.27	p-Cl	0.19	−0.97
o-Br	0.018	−2.35	o-F	0.011	−2.64
m-Br	0.20	−0.94	m-F	0.13	−1.20
p-Br	0.22	−0.89	p-F	0.17	−1.02

In view of the huge amount of information on aromatic substitution reactions, it is surprising to note that a theory on substituent effects on isomer equilibria and on ground state stabilities does not exist.

This is probably mainly due to the fact that only few experimental data have, so far, been available. It seems appropriate, therefore, to make an

attempt at an interpretation. As a first approximation we will assume that nuclear substituents have no effect on the strengths of nuclear carbon–hydrogen bonds, and that the substituent effects observed are *solely due to differences in carbon–bromine bond strengths*, thereby neglecting solvation effects, differences in heats of vaporization, *etc., etc.*

Starting from the fractional charges present at the substituents and the nuclear carbon atoms to which they are attached, and which can be evaluated from dipole measurements, one may compute the substituent interactions on a purely electrostatic basis. Using a mean value for the dielectric constant of 2, one finds the correct order of magnitude for the free energy effects, even for the *ortho*-positions; moreover, the order of increasing looseness of carbon–bromine bonds is the same as that found experimentally.

A second type of effect probably arises from the fact that many substituent groups, such as halogen atoms or methyl groups, are conjugated with the ring; in that case, polar resonance forms will contribute to the stability of the molecule. In a disubstituted compound, a given polar substituent should therefore affect the energy level of the polar resonance form arising from the other substituent. This should in turn affect *meta/para* equilibrium ratios, depending upon the polarity of the substituents. In the case of the xylenes, the stability of the *para*-isomer should then be lowered relative to that of the *meta*-isomer; with the toluene sulphonic acids or the chloro-benzene sulphonic acids the *para*-isomer should be favoured. The concept is illustrated in *Figure 2*. This expectation appears to be in agreement with
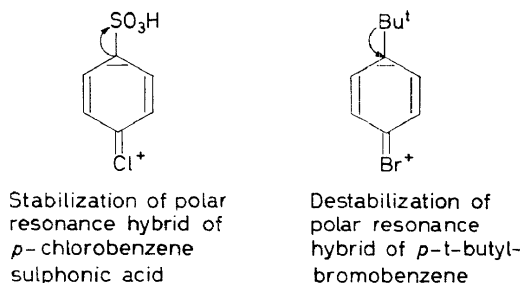

Stabilization of polar
resonance hybrid of
p-chlorobenzene
sulphonic acid

Destabilization of
polar resonance
hybrid of *p*-t-butyl-
bromobenzene

Figure 2

the experimental equilibrium *meta/para* ratios, which are greater than the statistical ratio of 2 for the xylenes (*viz.* about[9] 2·5) and only about 1·5 for the other two compounds[10]. The fact that we found[7] the *meta/para* ratio for the t-butyl-chloro- and bromobenzenes to be 3·0, whereas it is about 2·5 for the bromo-ethylbenzenes and slightly smaller for the bromotoluenes may be probably explained along the same lines; conjugation between the alkyl group and the aromatic ring decreases in the direction t-butyl, ethyl, methyl and, accordingly, the *meta/para* ratios should decrease in the same direction. Recent results obtained with other t-butylbenzene derivatives are also in agreement with these concepts.

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It may be noted that this type of group interaction should lead to deviations from additivity of substituent effects in those cases where the substituents are in *ortho* or *para* positions with respect to one another.

Before concluding this first part of my lecture, I should add that, very recently, the above problems have also been taken up by the groups of Dr Olah in Canada and of Professor Hine in the United States. Time has not permitted me to incorporate these interesting contributions into the above survey; the somewhat overlapping experimental data would appear to be in satisfactory agreement with our results.

The second part of the present paper will be dealing with another class of isomer patterns, namely those arising through

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Some years ago, it was found that these reactions may be carried out in such a fashion as to produce high yields of halogenation products without any by-products except at low halogen/benzene intake ratios. Nitrogen has to be used as a diluent in order to avoid carbonization; this probably constitutes the main experimental improvement over the earlier procedures, used by Wibaut and his co-workers[11]. The reactions appear to be little affected by the presence of small amounts of oxygen, iodine or nitric oxide, both as regards rates and isomer distribution.

In the absence of contact substances, no change of isomer patterns occurred with rise in temperature; at the lowest reaction temperature studied—namely 300° in the chlorinations, and 375° in the brominations—conversions were practically zero. Isomer distributions underwent little change when the reaction temperature was increased by about 100°. A number of these is given in *Table 5*.

Table 5. Gas phase halogenation of some benzene derivatives PhZ
(Chlorinations at 375, brominations at 425°)

Halogen	Substituent Z	Isomer distribution		Behaviour of PhZ in electrophilic substitution
		$\frac{1}{2}$ m/p ratio	o/p ratio	
Cl_2	—OPh	2–2·5	0	$2p \gg o \gg m$
Cl_2, Br_2	—F	1·4	0·3	$2p > o \gg m$
Cl_2	—Cl	1·3	0·4	$2p \sim o \gg m$
Br_2	—Br	1·4	0·9	$2p \sim o \gg m$
Cl_2, Br_2	—CN	0·8	0·7	$2p < o < m$

Table 5 also gives a comparison of the gas-phase halogenation patterns with those observed in electrophilic substitution reactions, thereby illustrating the appreciable differences between the two processes. It may be noted that the " gas-phase pattern " is not affected by isomerization reactions; thus, the pure isomers of dichlorobenzene did not undergo any isomerization when passed through the reactor at 375° in the presence of chlorine and hydrogen chloride[12].

Isomer distribution appears to be peculiar also in that, apparently, substitution occurs preferentially at those positions which have the lowest reactivity in electrophilic halogenation or nitration. Phenoxybenzene which has a high selectivity for *para*-substitution in the latter processes, produces the highest amount of *meta*-isomer, namely about 80 per cent, in the series of gas-phase reactions studied. Benzonitrile is at the other end of the scale; whereas its nitration gives about 80 per cent *meta*-isomer and one or two per cent *para*-derivative, gas-phase halogenation occurs preferentially in the *para*-position, namely 30 per cent, whereas the two *meta* positions are each contributing 25 per cent. In other words, one is dealing here with a pattern which seems to be the reverse of that mentioned by Holleman!

The behaviour of naphthalene forms a very interesting case; gas-phase halogenation leads to about equal proportions of both monohalides[13], whereas both electrophilic[14] and homolytic[15] substitution produce mainly the 1-isomer. The equilibrium[16] appears to be at about 65 per cent of the 2-halide at room temperature.

The similarity of isomer patterns observed in the chlorination and bromination of fluorobenzene and in the chlorination and bromination of benzonitrile† led us to investigate possible isotope effects. Starting from 1,3,5-trideuterobenzene, chlorinations as well as brominations were performed at 410°. From the mass spectra of the monohalides obtained it was concluded that hydrogen atoms are replaced about 1·4 times more readily than were deuterium atoms in both halogenations[17]. The latter similarities of chlorination and bromination results tend to suggest that an intermediate is formed which is more-or-less independent of the nature of the halogen.

Before making an attempt at giving an interpretation of the mechanisms of gas-phase halogenation *Table 6* summarizes the above and other pertinent data to be accounted for.

Table 6. Data on gas-phase halogenation of benzenes pertinent to mechanism

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(1) Substitution preferentially at positions of lowest reactivity in electrophilic substitution
(2) Little effect of O_2, NO or I_2, on rates or patterns; slight retarding effect of HCl
(3) Same pattern in chlorination and bromination (PhCN, PhF) and same H/D isotope effect
(4) Decreasing over-all chlorination rates in the order PhO, H, (F, Cl), CN, dichlorobenzene.

By analogy with aliphatic chlorinations, a scheme might be postulated which consists of abstraction of a hydrogen atom from the aromatic ring by a chlorine atom to form a phenyl radical; this in turn should rapidly react with a chlorine molecule. In view of the well-known substituent effects on hydrogen removal by atomic chlorine in the aliphatic series[18], such a scheme should lead to predominantly *ortho*- and *para*-substitution with compounds such as the halobenzenes. Moreover, it does not explain most of the other features of the reactions just summarized.

† *Note added in proof*
Chlorination and bromination of benzonitrile also led to the same isomer distribution, *viz.* about 12 per cent *ortho*, 53·55 per cent *meta* and 33–35 per cent *para*[21].

As a tentative interpretation it is proposed that the essential intermediate operative in gas-phase halogenations is an ion-pair (ArH^+X^-), which loses a molecule of hydrogen halide to form a phenyl radical; the latter fragment is known to react readily with a halogen molecule, thereby forming the substitution product. A possible alternative might be to assume the formation of an ion pair $ArH^+Cl_2^-$ decomposing to $Ar\cdot$, HX and $X\cdot$ Thus, the reactions shown in *Figure 3* should take place.

$$(ArH)^+(X)^- \xrightarrow[\text{Fast}]{\text{Isomer ratio determining step}} Ar\cdot + HX$$

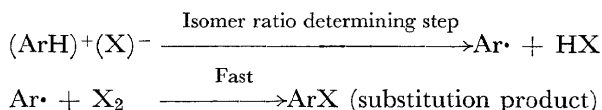$$Ar\cdot + X_2 \xrightarrow{} ArX \text{ (substitution product)}$$

Figure 3. Formation of substitution products through ion pair $(ArH)^+(X)^-$

Substituent effects on the proton-losing step should be responsible for the isomer distribution pattern, every phenyl radical forming a molecule of the substitution product; the effects should apply to the relative acidities of the various nuclear hydrogens, that is, they should be roughly opposite to those observed in electrophilic substitution. According to this picture, directive effects should depend on the substituents rather than on the nature of the halogen. Retardation by hydrogen halide should arise from the phenyl radical reacting with HX rather than with a molecule of the halogen. Over-all rates should depend on the rate of formation of the ion-pair as well as on that of the proton-losing step; substituent effects on these two processes should operate in opposite directions. It would not seem to be obvious which of the two—*i.e.* the effect on ionization or that on acidity—should predominate; the experimental order of over-all rates would be in agreement with the former effect being the more important. Finally, it may be added that, as in ester pyrolysis[19], formation of an ion-pair cannot be readily dismissed on energetic grounds, Coulombic attraction compensating for the energy expenditure involved in ionizing the aromatic compound. It is believed, therefore, that the ion-pair concept might provide a plausible interpretation of the experimental data so far available.

Kinetic data recently obtained by means of a stationary state stirred-flow reactor[20] indicate that the chlorination of chlorobenzene occurs by a process which is somewhat less than first order with respect to both reactants. In combination with the low sensitivity of the reactions towards added oxygen, nitric oxide and even iodine, this might mean that the ion-pair intermediate proposed is formed in a simple bimolecular reaction between the reactants.

Using the same reactor, it was found[21] that hexadeuterobenzene reacted 1·5 times more slowly than benzene at 375°, a value close to that observed for the *internal* H/D isotope effect. This supports our contention that hydrogen loss constitutes one of the rate-determining steps.

Table 7 may serve as a summary of the various isomer patterns involved in the different processes discussed.

Since my main object has been to call your attention to certain novel features regarding isomer distribution in benzene derivatives, some justification would now seem appropriate for the speculations I have made. For this, I may refer once again to one of Kekule's papers[22], using a quotation which is even more applicable now than in the year 1866: " . . . at the

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present stage of development of our science, attempts at a mechanistic approach could be—and should be—made."

Table 7. Substituent effects on various processes involving nuclear hydrogen

Reaction	Intermediate	Isomer pattern dependent on	Over-all rate dependent on
Electrophilic substitution	ArHX+	Relative electron availability	Electron availability
Arylation	ArHPh·	Relative localization energy (or relative free valence)	Localization energy (or free valence)
Gas-phase halogenation	(ArH)+(X)−	Relative acidity of nuclear hydrogen	Ionization energy; " acidity "
Equilibration	—	Electrostatic and mesomeric interaction of substituents	—

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