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CHARACTERISTIC CHEMICAL PROPERTIES OF ORGANIC COMPOUNDS CONTAINING POSITIVE HALOGEN

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CONTENTS

1. Introduction 671
2. Properties common also to alkyl halides 672
3. Hydrolysis 672
4. Oxidising properties 673
5. Halogenating properties 674
6. Addition to multiple bonds 677

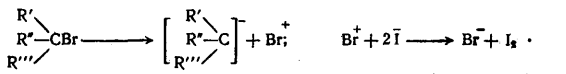
1. INTRODUCTION

Reviews of the chemistry of compounds containing positive halogen are very few[1-3], or are concerned mainly with the use of such compounds for preparative purposes[4]: substantial parts of them are devoted to preparative problems and also to the consideration of inorganic compounds of similar type. Consequently these reviews are usually confined to discussion of only a narrow range of reactions of organic compounds containing positive halogen.

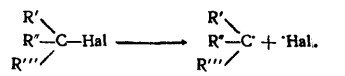
Our aim in compiling the present survey was to examine and compare, from a broader point of view, the characteristic reactions of different classes of organic compounds containing positive halogen, and to describe present views of their chemical behaviour.

We have not attempted to given an exhaustive survey of the literature on these questions, for such a task would be beyond the scope of a journal review, and have chosen mainly aliphatic compounds for consideration. Such a choice, it seems to us, enables all the characteristic features of the chemistry of positive halogen to be followed with quite striking examples.

Compounds containing positive halogen are characterisedi experimentally by the ability to displace iodine from potassium iodide or hydriodic acid. The view is generally held that this reaction involves heterolytic cleavage of the carbon–halogen bond with formation of halogen cations rather than the corresponding anions



However, there also exists a different view of the mechanism of this reaction. Thus Waters[5] considers that rupture of a carbon–halogen bond in compounds containing positive halogen takes place homolytically with formation of free radicals



Ordinary alkyl halides do not oxidise potassium iodide. Even carbon tetrabromide does not displace iodine from this salt, but if a bromine atom is replaced by a nitro-group, the resulting tribromonitromethane is now able to effect such a reaction. An ester group has a similar activating influence, although it is considerably weaker than that of the nitro-group. The presence of only one such group is insufficient to make the bromine labile (tribromoacetic ester does not react with potassium iodide), and only the presence of at least two ester groups (bromomalonic and dibromomalonic esters) makes the halogen sufficiently labile[6]. A bromine atom acquires a well defined positive character also if it is adjacent to an ester and a carbonyl group or to two carbonyl groups. Thus the halogen in cyclic compounds containing a $-COCBr_2CO-$ group (dibromoindanedione, dibromobarbituric acid) is highly active. Positive properties are less well defined in compounds containing one carbonyl group (α-halogeno-ketones). Reactions characteristic of positive halogen can

also be given by compounds in which the halogen is adjacent to a multiple bond, especially those containing the grouping $-C:C\cdot CBr_2\cdot C:C-$.

Apart from the many compounds in which positive halogen is linked to a carbon atom, several compounds are known in which it is combined with a nitrogen atom, among them being *N*-halogenated acid amides, *N*-halogenoamines, and *N*-halogenoarenesulphonamides.

Finally, alkyl hypohalites, compounds of type RCOOHal, and several others provide examples of substances in which a positive halogen atom is combined with oxygen.

Thus compounds containing positive halogen belong to the most varied types, but fundamentally they are united by a common property: the organic radicals which confer a positive character on the halogen are invariably groups which strongly attract electrons. This structural peculiarity definitely diminishes the tendency to cleavage with formation of a halide anion which is normal in a covalent halogen compound.

2. PROPERTIES COMMON ALSO TO ALKYL HALIDES

Before describing the characteristic properties of compounds containing positive halogen, let us consider a few similarities between these compounds and ordinary alkyl halides. Coleman and his coworkers showed that chloroamines of various structures react with a Grignard reagent according to the scheme[7,8]

$$NH_2Cl + RMgX \longrightarrow RNH_2 + MgXCl.$$

The yield of amine is higher in the case of RMgCl and lower on reaction with RMgI, and it increases when R is a secondary or a tertiary hydrocarbon radical. If the chloroamine is replaced by alkylchloroamines of the type $RNCl_2$, R_2NCl, and RNHCl, the corresponding secondary and tertiary amines can be obtained by this reaction[9]. The reaction is interesting, since it is not always a simple task to obtain individual amines by other methods.

Like alkyl halides, several substances containing positive halogen react with formation of a new carbon–carbon bond under the influence of alkaline reagents or the sodium derivatives of some organic compounds. Bischoff and his collaborators studied this reaction with chloro- and bromo-malonic esters, and showed that sodiomalonic ester reacts quite readily with chloromalonic ester to form an ethanetetracarboxylic ester[10]

$$(C_2H_5OOC)_2CHNa + ClHC(COOC_2H_5)_2 \longrightarrow (C_2H_5OOC)_2CHCH(COOC_2H_5)_2 + NaCl.$$

If chloromalonic or bromomalonic ester is treated with an alkaline reagent (sodium ethoxide or methoxide, potassium carbonate), an ethylenetetracarboxylic ester is formed[11–14]

$$2CHBr(COOR)_2 \xrightarrow{K_2CO_3} 2HBr + (ROOC)_2C=C(COOR)_2.$$

Bischoff[15] made a detailed study of the reaction of various bromomalonic esters with the sodium derivative of nitrophenol, and obtained various nitrophenoxymalonic esters

$$NO_2C_6H_4ONa + BrCX(COOR')(COOR'') \longrightarrow NaBr + NO_2C_6H_4OCX(COOR')(COOR'').$$

A similar reaction takes place also with *N*-bromoamines, although the yields are low. Farenhorst and Koogman[16] showed that t-butyl-*N*-bromoamine reacts with silver oxide according to the equation

$$2(CH_3)_3CNHBr + Ag_2O \longrightarrow 2AgBr + H_2O + (CH_3)_3C-N=N-C(CH_3)_3.$$

A peculiar "dimerisation" of bromomalonic ester has been described by Arbuzov and Abramov[17], who established that on reaction with derivatives of phosphorous acid this compound yields an ethanetetracarboxylic ester

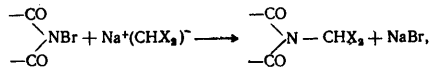
$$2(C_2H_5O)_2PONa + 2BrCH(COOC_2H_5)_2 \longrightarrow 2NaBr + (C_2H_5OOC)_2CHCH(COOC_2H_5)_2 + [(C_2H_5O)_2PO]_2.$$

This reaction does not occur with chloromalonic ester.

Several further cases can be mentioned in which compounds containing positive halogen react in a similar manner to alkyl halides. Thus sodium azide reacts with bromomethylmalonic ester to form the ester of azidomethylmalonic acid[18]. The reaction of potassium xanthate and alkali-metal salts of brominated malonic acids was studied by Bülmann and Madsen[19], who showed that the reaction is represented by

$$C_2H_5OCSSK + RBrC(COOH)_2 \longrightarrow C_2H_5OCSSCR(COOH)_2 + KBr.$$

Scheiber and Haun[20] found that *N*-bromosuccinimide and *N*-bromophthalimide are able to exchange their halogen for an organic radical when treated with compounds containing an active hydrogen atom:



where X = $COOC_2H_5$, $COCH_3$, COC_6H_5, CN.

From these examples it is evident that compounds containing positive halogen can in several cases react like ordinary alkyl halides. However, the behaviour of positive halogen is in general markedly different from that of halogen in alkyl halides being characterised by a series of special reactions, as will be shown subsequently in this review.

3. HYDROLYSIS

Compounds containing positive halogen behave differently from alkyl halides on hydrolysis: the reaction involves replacement of the halogen by hydrogen or other positive group. Birckenbach and his coworkers[21] have done some interesting work on the hydrolysis of such compounds. They consider that the radicals of strong acids, such as $(CN)_3C-$ and $(CH_3CO)_3C-$, are similar to a free halogen, and belong to the group of pseudohalogens. The chemical properties of the corresponding halogenated derivatives show them to be typical compounds containing positive halogen. When potassium cyanide reacts with a halogenated triacetylmethane, for example, the halogen is replaced by the positive potassium ion. Hydrolysis of a triacetylhalogenomethane results in formation of the hypohalous acid and of triacetylmethane itself.

Haszeldine and coworkers[22] made a detailed investigation of the nature of the carbon–iodine bond in trifluoroiodomethane. This work merits thorough examination as one of the few rigorous studies which show clearly that, depending on the conditions, the same halogenated derivative can yield either free radicals or the halogen cation.

The carbon–iodine bond in trifluoroiodomethane is known to undergo homolytic fission with the formation of a free trifluoromethyl radical, which yields an organometallic derivative and also initiates the polymerisation of alkenes. In solvents of high dielectric constant, however,

trifluoroiodomethane behaves as a compound containing positive halogen, and on treatment with caustic potash gives fluoroform and the hypoiodite:

$$CF_3I + KOH \longrightarrow CHF_3 + KOI.$$

The reaction velocity increases with increase in the dielectric constant of the solvent. In ether, for example, reaction is slow, while in alcohol and acetone it is rapid and complete. It is assumed that the reaction involves attack on the trifluoroiodomethane by the hydroxyl ion with subsequent reaction of the trifluoromethyl anion with the solvent, or by decomposition of CF_3K, formed as an intermediate product, by water:

$$OH^- + ICF_3 \longrightarrow CF_3^- + HOI \xrightarrow{KOH} KOI + H_2O.$$

The positive character of iodine in trifluoroiodomethane is supported also by the fact that it did not prove possible to obtain the usual nucleophilic substitution products with such reagents as moist silver oxide, potassium phthalimide, and metal cyanides and nitrates, which are known to react readily with methyl iodide. The iodine atom in pentafluoroiodoethane, which on hydrolysis yields pentafluoroethane[23], is similar in character.

It was concluded from a radiochemical investigation of the mechanism of the hydrolysis of trifluoroiodomethane in a solvent of high dielectric constant that the fluorinated iodides (trifluoroiodomethane and pentafluoroiodoethane) do not ionise appreciably; they do not liberate iodine from potassium iodide. But ions are formed in a solvent of high dielectric constant and at elevated temperatures, as is confirmed by exchange between trifluoroiodomethane and sodium iodide containing radioactive iodine:

$$CF_3I + Na^{131}I \longrightarrow CF_3{}^{131}I + NaI.$$

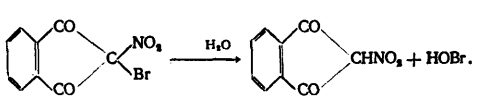
The reaction takes place by the unimolecular ionic mechanism (1) with electron transfer (2) and recombination (3)

$$CF_3I \rightleftarrows CF_3^- + I^+, \quad (1)$$

$$I^+ + (^{131}I)^- \rightleftarrows I_2 \rightleftarrows I^- + (^{131}I)^+, \quad (2)$$

$$CF_3^- + (^{131}I)^+ \rightleftarrows CF_3{}^{131}I. \quad (3)$$

Bromoindane-1,3-dione is hydrolysed, on being boiled with water, to indane-1,3-dione and hypobromous acid. Bromonitroindane-1,3-dione is hydrolysed still more readily, at room temperature, yielding nitroindanedione and hypobromous acid[24,25]:



Halogen is readily eliminated from nitro-compounds containing a halogen atom and more than one nitro-group, or a nitro-group and more than one halogen atom, attached to the same carbon atom. In neutral or acid medium the positive halogen in such compounds is replaced by hydrogen, and in alkaline medium by a metal[26-29]; the iodine derivatives are hydrolysed more readily than the corresponding bromine derivatives, and still more readily than the chlorine derivatives[26,30].

Conrad studied the reactions of halogenomalonic acids and esters on treatment with alkaline reagents and showed that the presence of only two carboxyl groups is insufficient to make the halogen labile. Thus chlorine is not eliminated when chloromalonic acid is treated with potassium hydroxide. Dichloromalonic ester on treatment with alcoholic ammonia yields dichloromalonamide. Hence the chlorine remains untouched by the ammonia. In the case of bromochloromalonic ester, however, the bromine atom reacts as well as the ester groups[31,32], and bromonitromalonic ester reacts still more readily with alkaline reagents: with ammonia, potassium hydroxide, or dimethylamine, it undergoes a reaction typical of positive halogen, the latter being replaced by the cation of the alkaline reagent[33]. Bromonitroacetic ester is incapable of such a change[34].

With α-bromoketones[35,36] and halogenated β-keto-esters[37] cases are known in which positive bromine is replaced by a hydrogen atom or an amino-group.

N-Halogenated compounds hydrolyse still more readily than do *C*-halogenated derivatives. The labile halogen in such compounds is replaced by hydrogen by the action of water, hydrobromic or hydrocyanic acid, or hydrogen peroxide[38-42].

$$CH_3CONHBr + H_2O \longrightarrow CH_3CONH_2 + BrOH,$$

$$CH_3CONHBr + HCN \longrightarrow CH_3CONH_2 + BrCN.$$

It is quite evident from the above work that hydrolysis is a very characteristic reaction of compounds containing positive halogen: when such compounds are hydrolysed, the halogen is replaced by hydrogen, in contrast to ordinary halogenated compounds, in which it is replaced by hydroxyl†.

4. OXIDISING PROPERTIES

As noted above, the ability to oxidise potassium iodide or hydriodic acid serves as a criterion of the positive character of halogen in a given compound[5,45,46]. This reaction, which goes rapidly in the cold, can serve for the quantitative determination of compounds containing positive halogen. This method is used to estimate, for example, α-halogenonitro-compounds (chlorides, bromides, and iodides) containing two, three, or more nitro-groups in the molecule[47-49].

The oxidation of hydrazine by substances containing positive halogen (which is characteristic of compounds of this class) was studied in detail by Macbeth and his collaborators[45,50,51]. Compounds in which the halogen is electronegative in character, for example acid halides, sulphonyl chlorides, picryl chloride, yield hydrazides on reaction with hydrazine. Those containing positive halogen, however, readily oxidise the hydrazine with the evolution of nitrogen. This reaction not only demonstrates the lability of positive halogen but also provides a method for determining it quantitatively.

With *NN*-dichlorosulphonamides, *N*-chloroacetanilide, *N*-bromoacetamide, and series of bromomalonic esters and α-halogenonitro-compounds, this reaction is represented by the following equations:

$$RSO_2NCl_2 + NH_2NH_2 \longrightarrow RSO_2NH_2 + N_2 + 2HCl,$$

$$2C_6H_5NClCOCH_3 + NH_2NH_2 \longrightarrow 2C_6H_5NHCOCH_3 + N_2 + 2HCl,$$

$$2CH_3CONHBr + NH_2NH_2 \longrightarrow 2CH_3CONH_2 + N_2 + 2HBr,$$

$$2CRBr(COOC_2H_5)_2 + NH_2NH_2 \longrightarrow 2CRH(COOC_2H_5)_2 + N_2 + 2HBr,$$

$$2(NO_2)_2CBr_2 + NH_2NH_2 + 4KOH \longrightarrow 2(NO)_2C{=}NO_2K + 2KBr + N_2 + 4H_2O.$$

Hirst and Macbeth[45] note that hydrazine reacts more readily with *N*- than with *C*-halogenated compounds, and hence conclude that halogen linked with nitrogen is the more labile.

† Only a few cases are described in the literature of the replacement of positive halogen by a hydroxy-group (for example the alkaline hydrolysis of bromo- and chloro-malonic esters[43,44]).

Compounds containing positive halogen are able to oxidise also (in solution) potassium cyanide, sodium sulphide, hydrogen bromide and especially hydrogen iodide, and also several other inorganic compounds. Thus the oxidation of hydrogen bromide with the separation of free bromine is a general property of α-bromoketones [35,36,52], the ease with which this reaction occurs depending on the mobility of the positive bromine in the ketone. The simplest α-bromoketones (for example bromoacetophenone) react only in the presence of an acceptor for the bromine. Compounds in which the positive bromine is activated by two carbonyl groups (for example bromo-derivatives of methone‡, dibenzoylbromomethane, etc.) react considerably more readily, as do also di- and tri-bromoketones (dibromoacetophenone, etc.). Bromoacetoacetic ester [52,53] and brominated malonic acids [54] are active oxidants of hydrogen bromide and iodide [54].

Compounds containing positive bromine or iodine react in a characteristic manner with hydrogen chloride, the bromine or iodine atom being replaced by chlorine. In this way *N*-chloroacetamide is formed from *N*-bromoacetamide [55], chlorobarbituric acid from bromobarbituric acid [56], and chlorotrinitromethane from iodotrinitromethane [6].

Organic compounds are more difficult than inorganic compounds to oxidise with positive halogen.

The oxidising properties of *N*-halogenated compounds towards organic substances were noted by Selivanov as long ago as 1892. [39] He showed that chlorosuccinimide in the presence of water oxidises primary and secondary, but not tertiary, alcohols.

Chattaway and Orton [40] observed, together with other characteristic properties of *N*-bromoacylamides, their oxidising ability. Thus acetaldehyde was detected among the reaction products with ethanol. These workers suggested that the acetaldehyde is formed according to the equations:

$$RCON(R')Br + C_2H_5OH \longrightarrow RCONHR' + CH_3CH_2OBr,$$

$$CH_3CH_2OBr \longrightarrow CH_3CHO + HBr.$$

Somewhat later Tscherniac [42] showed convincingly that the oxidising action of *N*-halogenated imides is a property of these compounds themselves, and not of the hypohalous acid formed by their interaction with water. The opposite, incorrect, view of the mechanism of this reaction was held by Selivanov [39].

A thorough study of the oxidising properties of *N*-bromosuccinimide was made by Blair *et al.* [57] with some substituted aromatic alcohols as examples. The fact that ultra-violet irradiation of the reaction mixture increases the yields of the final products suggests that the oxidation takes place by a free-radical mechanism.

The dehydrogenation of primary and secondary alcohols by *N*-chlorosuccinimide was later studied by Grob and Schmidt [58], who obtained good yields of the corresponding aldehydes and ketones in this way; the lower aliphatic alcohols are the most easily oxidised, the reaction taking place rapidly and under mild conditions. Similar work was carried out simultaneously by Hebbelynck and Martin [59], who in particular confirmed the observations of other workers on the comparative oxidising power of chloro- and bromo-derivatives§: the oxidising action of positive chlorine is more strongly marked than that of positive bromine. Hebbelynck and Martin showed that primary and secondary aromatic alcohols are oxidised on being heated with *N*-chlorosuccinimide, the reaction usually being carried out in anhydrous medium. It is interesting that the reactions take place even in the dark, in contrast to Blair's experiments, in which oxidation with *N*-bromosuccinimide was effected under ultra-violet irradiation [57].

Lecomte and Dufour [60] used *N*-bromoacetamide to oxidise aromatic alcohols, and found that primary and secondary alcohols in which the hydroxy-group is attached to a carbon atom directly linked to the aromatic nucleus are oxidised quantitatively to the corresponding aldehydes and ketones. When the hydroxyl group is more remote from the aromatic ring, the yield of aldehydes and ketones drops sharply.

Many other investigators have studied the oxidising action on organic compounds of substances containing positive halogen. Thus Dale [61], by dehydrogenating squalene with *N*-bromosuccinimide, obtained a mixture of carotenoid pigments. Schönberg *et al.* [62] showed that the action of *N*-bromosuccinimide on α-amino-acids yields aldehydes containing one carbon atom fewer than in the original acid.

N-Bromosuccinimide is used for the dehydrogenation of more complicated cyclic systems to give aromatic compounds as reaction products [63-66]. The selective oxidising action of this compound is utilised in steroid chemistry [67-71].

It is interesting that the chain oxidation of tetralin is catalysed by compounds containing positive halogen, both *N*- and *C*-derivatives, which act as sources of free radicals [5].

These results show that oxidising properties are very characteristic of compounds containing positive halogen, and can be exploited for preparative purposes.

5. HALOGENATING PROPERTIES

The halogenating action of compounds containing positive halogen has been studied most fully. The most important application of this reaction is the halogenation of alkenes in the allyl position¶. Substances containing positive halogen are also used for the addition of halogens to a double bond, in the halogenation of aromatic and heterocyclic compounds (in the ring), and also for the halogenation of amines (on the nitrogen). We shall examine the literature in this field in the same sequence.

The halogenating properties of positive halogen were first studied early in this century by Wohl [75,76], who used *N*-bromoacetamide. However, the bromination of unsaturated compounds with this agent gave low yields and was accompanied by side reactions.

It is not so long ago that Ziegler *et al.* [77] succeeded in working out a preparative method for the halogenation of unsaturated compounds in the allyl position. They found that *N*-bromosuccinimide possessed the best brominating properties: hydrogen in a methyl and especially in a

‡ 5,5-Dimethyl-1,3-cyclohexanedione (Ed. of Translation).

§ For a brief review of work on this question see Hebbelynck [1].

¶ A great deal of factual information on this question can be found in the reviews of Djerassi [72] and of Machinskaya and Barkhash [73] (see also Waters [74]).

methylene group can be replaced by bromine; a tertiary carbon atom is not brominated, and it is impossible to brominate a methyl or a methylene group directly linked to a system of conjugated double bonds. On the other hand, dienes containing two isolated double bonds are readily brominated in the allyl position. Apart from *N*-bromosuccinimide, Ziegler studied the halogenating properties of *N*-bromophthalimide and various *N*-halogenated sulphonamides and imides, and showed that, in contrast to *N*-bromosuccinimide, these compounds do not possess a selective halogenating action; in these cases more than one reaction takes place at the same time. The ability of alkenes to be halogenated in the allyl position is linked with the fact that the hydrogen atoms in the β and β' positions in a $-CH_2-CH=CH-CH_2-$ chain are more reactive than those in the α and α' positions. If a β-methylene group is linked to an alkyl substituent, the substitution becomes easier with increasing chain length of the substituent, which is consistent with the inductive effect of alkyl groups [78].

It can now be regarded as proved that the halogenation of unsaturated compounds in the allyl position by means of compounds containing positive halogen has a radical mechanism.

Thus Waters [79] remarks that compounds containing positive halogen are preferentially decomposed with the formation of free radicals. This has been confirmed by several later investigations.

Schmid and Karrer [80], investigating the effect of catalysts on bromination in the allyl position, found that bromination with *N*-bromosuccinimide is greatly accelerated by the addition of 5–10% of freshly prepared benzoyl peroxide to the reaction mixture. Use of a catalyst not only speeds up the process but also enables several substances to be brominated which, according to Ziegler [77], do not react under normal conditions with *N*-bromosuccinimide. For example, the former workers [80] succeeded in substituting bromine for hydrogen attached to a tertiary carbon atom and in a methyl group adjacent to two conjugated bonds.

The use of peroxides enables halogenation to be carried out smoothly in several other cases as well. Thus the bromination of hexa-1,5-diene with *N*-bromosuccinimide is greatly accelerated in the presence of benzoyl peroxide, with the formation of mono- and di-bromo-derivatives [81]

$$CH_2=CHCH_2CH_2CH=CH_2 \xrightarrow{NBS} CH_2=CHCHBrCH_2CH=CH_2 \xrightarrow{NBS}$$

$$\longrightarrow CH_2=CHCHBrCHBrCH=CH_2.$$

Methylenecyclobutane is also brominated in the allyl position by *N*-bromosuccinimide in the presence of benzoyl peroxide [82]. Bromination of cyclohexa-1,4-diene yields either 3-bromo- or 3,6-dibromo-cyclohexadiene depending on the reaction conditions [83].

The fact that ultra-violet irradiation accelerates bromination in the allyl position is further evidence of the radical character of this reaction [84].

Tertiary aliphatic azo-compounds, which are typical initiators of radical reactions, also catalyse bromination with *N*-bromosuccinimide. In the presence of these catalysts a 75% yield of 3-bromocyclohexene can be obtained from cyclohexene (no reaction takes place in the absence of catalyst) [85].

The mechanism of substitution with halogen was studied by Bloomfield [86], who also held the view that allyl bromination takes place by a radical mechanism represented by the following scheme:

$$(C_4H_4O_2)NBr \longrightarrow (C_4H_4O_2)N^{\cdot} + Br^{\cdot},$$

$$-CH_2CH=CH- + (C_4H_4O_2)N^{\cdot} \longrightarrow -\dot{C}H-CH=CH- + (C_4H_4O_2)NH,$$

$$-\dot{C}HCH=CH- + Br^{\cdot} \longrightarrow -CHBrCH=CH- \text{ chain termination},$$

$$-\dot{C}HCH=CH- + (C_4H_4O_2)NBr \longrightarrow -CHBrCH=CH- + (C_4H_4O_2)N^{\cdot}.$$

This mechanism is to some extent confirmed by results obtained by Ford and Waters [85] showing that the succinimido-radical $\begin{matrix}CH_2-CO\\ \\ CH_2-CO\end{matrix}\!\!>\!N^{\cdot}$ is strongly dehydrogenating, and readily removes an active hydrogen atom from the α-methyl-end-group of an unsaturated compound.

Several of the *N*-chloro-derivatives, for example *N*–*p*-dichloroacetanilide and *N*-chloro-*p*-nitroacetanilide, are able to chlorinate unsaturated compounds in the allyl position [77]. *NN*-Dichlorosulphonamides such as Chloramines B and T, which are well known disinfectants and decontaminants, are unsuitable for allyl chlorination.

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The first information on the addition of halogen to a double bond by means of compounds containing positive halogen was obtained by Wohl [75,76], who isolated dibromides as well as allyl bromination products from the reaction of unsaturated compounds with *N*-bromoacetamide. Later Buckles [87] made a detailed investigation of halogenation at a double bond with this reagent, and found that in all cases the reaction is accelerated by heating or by ultra-violet irradiation. From this he concluded that the halogenation of unsaturated compounds with *N*-bromoacetamide takes place by a radical mechanism:

$$AcNHBr + h\nu \longrightarrow AcNH^{\cdot} + Br^{\cdot},$$

$$>C=C< + Br^{\cdot} \longrightarrow >CBr-\dot{C}<,$$

$$>CBr-\dot{C}< + AcNHBr \longrightarrow >CBr-\underset{|}{C}Br + AcNH^{\cdot},$$

$$Br^{\cdot} + AcNHBr \longrightarrow Br_2 + AcNH^{\cdot},$$

$$Br_2 + h\nu \longrightarrow 2Br^{\cdot},$$

$$Br_2 + >CBr-\dot{C}< \longrightarrow >CBr-\underset{|}{C}Br + Br^{\cdot}.$$

The action of *N*-bromosuccinimide on $\alpha\beta$-unsaturated β-phenyl-ketones in the presence of a peroxide also results in the formation predominantly of dibromides [88]. In the bromination of the triple bond in ethyl tetrolate† under Ziegler's reaction conditions, the sole product isolated in a pure form was the 2,3-dibromocrotonic ester, formed by addition of bromine at the triple bond [89].

It is interesting that, if the halogenation of alkenes by *N*-bromoacetamide is carried out in the presence of hydrobromic acid or molecular bromine, the reaction takes place by an ionic mechanism [87]

$$AcNHBr + HBr \rightleftarrows AcNH_2Br^+ + Br^-,$$

$$AcNH_2Br^+ + Br^- \longrightarrow AcNH_2 + Br_2.$$

Thus under these conditions the double bond is brominated in effect by free bromine.

Braude and Waight [90] found that, in the presence of tetraethylammonium bromide or other similar salts which catalyse ionic reactions, *N*-bromosuccinimide reacts with cyclohexene to form 1,2-dibromocyclohexane. Reaction

† Ethyl 2-butynoate (Ed. of Translation).

takes place in a similar way with allylbenzene; it is not accelerated by benzoyl peroxide. These workers conclude that the mechanism of the addition consists in heterolytic cleavage of the N–Br bond, which is the primary and rate-determining stage. Under different conditions (in the absence of catalysts for ionic reactions), *N*-bromosuccinimide brominates cyclohexene mainly in the allyl position[82,91]. These examples again show that *N*-bromosuccinimide can react by different mechanisms depending on the conditions (see also Djerassi[72] and Ford[92] on this question).

Bromination with *N*-bromosuccinimide requires a source of hydrogen for recombination with the succinimido-group. In the case of bromination at the allyl position, the compound undergoing bromination itself acts as such a source, but in the case of bromination at the double bond an additional hydrogen-donor is required, and the solvent can fill this role.

Buckles *et al.*[93] have recently concluded from a comparative study that *N*-bromoacetamide brominates predominantly at the double bond, whereas *N*-bromosuccinimide brominates in the allyl position. In an attempt to explain the difference in behaviour of these brominating agents, these workers also suggest, on the basis of the radical reaction scheme proposed by Bloomfield[86], that hydrogen-donors must take part in the addition.

The direction of bromination, at the allyl position or at the double bond, depends not only on the nature of the brominating agent but also on the structure of the unsaturated compound.

Corey[94] showed that, in the reaction between *N*-bromosuccinimide and four unsaturated compounds — methyl crotonate, crotononitrile, methyl vinylacetate, and vinylacetonitrile — the first two, which contain a system of conjugated bonds, are brominated in the allyl position, while the last two compounds, containing a system of isolated bonds, add on bromine mainly at the double bond.

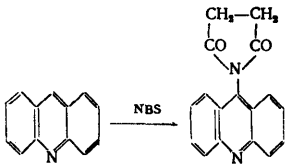
The bromination of vinylacetonitrile with *N*-bromosuccinimide has been investigated also by Baily and Bello[95]. In the presence of a peroxide, both 4-bromocrotononitrile and 3,4-dibromobutyronitrile are formed at the same time. If the peroxide is replaced by *p*-t-butylcatechol, an inhibitor of radical reactions, the yield of the bromine addition product is increased. Hence it can be concluded that *N*-bromosuccinimide can react both by an ionic and by a free-radical mechanism.

The halogenation of aromatic and of heterocyclic compounds with *N*-chloro- and *N*-bromo-acetamides was first studied by Wohl[75,76] and by Steinkopf[96], who showed that mono- and poly-halogenated derivatives can be obtained in this way.

However, the use of these two compounds as halogenating agents did not expand to any considerable extent, since it gave no advantage over other well-known methods for halogenating aromatic and heterocyclic systems.

In 1944 Buu-Hoi[97] demonstrated that *N*-bromosuccinimide is an excellent reagent for the halogenation of such systems. He showed that increase in the mobility of hydrogen in an aromatic compound facilitates its bromination. For example, benzene is brominated neither by *N*-bromoacetamide nor by *N*-bromosuccinimide; naphthalene is brominated by the latter reagent, yielding 1-bromonaphthalene; phenanthrene reacts still more readily; and anthracene reacts vigorously with *N*-bromosuccinimide to form 9-bromoanthracene.

The bromination of heterocyclic compounds also gives high yields of monobromo-derivatives: thiophen gives 2-bromothiophen, 1-benzoylindole yields 1-benzoyl-3-bromoindole, and indene forms 1-bromoindene; although anthracene is brominated vigorously by *N*-bromosuccinimide, acridine is not brominated, but forms a substitution product[98]:



Parke *et al.*[99] studied the mechanism of the bromination of toluene with *N*-bromoacetamide and some of its derivatives containing different numbers of halogen atoms attached to the α-carbon atom: $CH_3CONHBr$, $CCl_3CONHBr$, $CHCl_2CONHBr$, $CH_2ClCONHBr$, and $CF_3CONHBr$. They found that these compounds are able to brominate toluene both in the ring and in the side-chain, the reaction taking place by an ionic mechanism in the former case, and by a free-radical mechanism in the latter.

The experimental data in the accompanying Table show that *N*-bromo-derivatives containing electronegative substituents attached to the α-carbon atom tend to effect bromination predominantly by an ionic mechanism. In other words, the bromine in these compounds is obviously more readily split off as a cation. The differences in brominating power of the compounds in the Table no doubt depend on the strength of the positive character of the bromine which they contain.

Other similar results have been obtained, and are summarised in the review by Pierce and McBee[100]. The use of perfluorinated *N*-bromoimides strengthens the positive character of the bromine and its brominating power. Toluene can be readily brominated in the nucleus by means of perfluorinated *N*-bromosuccinimide[101].

The anhydrous chlorides of aluminium, iron, and zinc have been investigated[102] as catalysts for the bromination of benzene with *N*-bromosuccinimide. In the presence of these catalysts, 40–70% yields of bromobenzene and bromotoluene can be obtained from benzene and toluene respectively; benzene cannot be brominated with *N*-bromosuccinimide in the absence of a catalyst. In the presence of these catalysts bromination probably takes place by an ionic mechanism. These results can be appropriately compared with those of Derbyshire and Waters[103] on the bromination of aromatic compounds with elementary bromine in the presence of the same catalysts. These

TABLE.

Brominating agent	Proportion of reaction products, %	
	$Br—C_6H_4—CH_3$	$C_6H_5CH_2Br$
$CH_3CONHBr$	0	100
$CCl_3CONHBr$	17	83
$CHCl_2CONHBr$	62	38
$CClH_2CONHBr$	82	18
$CF_3CONHBr$	88	12

workers consider that the active brominating agent is the bromine cation, which is formed as follows:

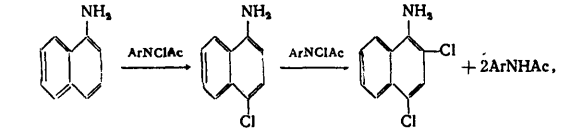
$$Br_2 + FeBr_3 \longrightarrow (Br^+)(FeBr_4^-).$$

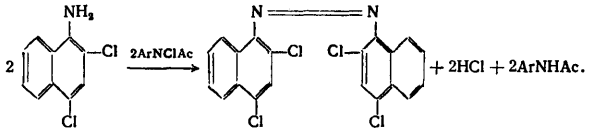
There is undoubtedly a close connection between the (nuclear) bromination of aromatic systems with the elementary halogen and with compounds containing the positive halogen: in both cases the halogen cation is the brominating agent.

Orazi and his coworkers [104-112] have made a detailed investigation of the halogenating properties of 3-mono- and 1,3-di-halogenated derivatives of 5,5-dimethylhydantoin, which contain positive halogen. With these compounds he obtained high yields of halogenated aromatic compounds which already contained various substituents. Halogenation with halogenated 5,5-dimethylhydantoins is carried out under roughly the same conditions as with *N*-bromosuccinimide. In both cases halogenation is accelerated by addition of peroxide compounds and by illumination.

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Insufficient work has been done on the halogenation of amines with positive halogen, existing data indicating that this reaction cannot yet serve as a reliable method for introducing halogen into the amino-group. Datta [113] studied the chlorination of benzylamine with dichlorourea, and obtained a mixture of the mono- and di-chloroamines. He found that chlorination takes place slowly, with considerable resin formation and gas evolution. Likhosherstov [114] attempted to introduce chlorine into the amino-group of aniline and other aromatic amines by means of dichlorourea, but obtained only resinous products. Danilov and Koz'mina [115] studied the possibility of using *N*-chloroacylanilines to chlorinate the amino-group in aromatic, aliphatic, and mixed amines. It was found that interaction of the reactants in anhydrous medium resulted first in chlorination of the benzene ring containing the amino-group, and with excess of the chlorinating agent the nuclear-chlorinated amine is oxidised to an azo-compound:





With primary and secondary aliphatic amines the chloroacylamines undergo double decomposition with the formation of *N*-chloroamines:

$$ArNClAc + RNH_2 \longrightarrow RNHCl + ArNHAc,$$

$$2ArNClAc + RNH_2 \longrightarrow RNCl_2 + 2ArNHAc,$$

$$2ArNClAc + R_2NH \longrightarrow R_2NCl + ArNHAc.$$

Reaction of chloroacylamines with tertiary aliphatic and mixed aliphatic–aromatic amines involves the elimination of one alkyl group, its oxidation to an aldehyde, and chlorination of the resulting dialkylamine.

Waters and coworkers [46] studied the chlorinating action of *N*-chloro-2,4,6-trichlorobenzanilide on aliphatic amines of the type $NR(CH_2CH_2Cl)_2$, and found that halogenation of the radical R takes place first of all, for example:

$$NCH_3(CH_2CH_2Cl)_2 \longrightarrow NCH_2Cl(CH_2CH_2Cl)_2.$$

Treatment of this base with water entails dealkylation:

$$NCH_2Cl(CH_2CH_2Cl)_2 + H_2O \longrightarrow HCl + CH_2O + NH(CH_2CH_2Cl)_2.$$

Dealkylation of amines in this way might have provided a new method for the controlled cleavage of cyclic amines such as nicotine and other alkaloids. However, later work showed [116] that this process is exceptional in character, and cannot be of practical value. Thus when cyclic amines (*N*-methylpiperidine, 1,2,3,4-tetrahydro-1,6,8-trimethylquinoline, nicotine, and ergotoxine) are treated with *N*-chloro-2,4,6-trichlorobenzanilide, the ring is chlorinated in all possible positions.

Summarising the literature on the halogenation of organic compounds with compounds containing positive halogen, we conclude that *N*-halogenated agents have become widely used in the practice of synthetic organic chemistry, and have made it possible to obtain several halogeno-derivatives which cannot be readily prepared in other ways.

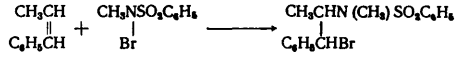
In contrast, compounds having positive halogen linked to carbon find no great application as halogenating agents, although halogenation by means of them is in principle possible (for example, see Henderson and Macbeth [117], also Gabriel [118]).

The mechanism of the characteristic reactions of compounds containing positive halogen has been studied in the greatest detail in work on halogenation with *N*-halogenated amides and it can be concluded that compounds containing positive halogen can react either by an ionic or by a free-radical mechanism depending on the reaction conditions. This emphasises yet again the very labile and peculiar character of the halogen in these compounds.

6. ADDITION TO MULTIPLE BONDS

The addition of compounds containing positive halogen to multiple bonds has been investigated mainly in connection with halogenation by *N*-halogenated compounds. Apart from general cognitive purposes, work on these lines has been pursued with the aim of developing a method for synthesising halogenated multifunctional compounds.

Földi showed [119] that *N*-bromo-*N*-methylbenzenesulphonamide readily adds to the double bond of 1-phenylpropene giving a 90% yield of addition product:



He was unable to extend this reaction to purely aliphatic unsaturated compounds, since under his conditions the corresponding bromination products were mainly formed.

Later Kharasch and Priestley [120] effected the addition of *N*-bromosulphonamides to propene, isobutene, vinyl chloride, and styrene. They were also able to add on *NN*-dibrominated aromatic sulphonamides to styrene, anethole, and isosafrole. The nature of the radicals, R, R′, and R″ (see equation below) was found to be of secondary importance. Thus phenyl-, *p*-tolyl-, and benzyl-sulphonyl derivatives of methyl-, benzyl-, and phenethyl-amine and other compounds of this type could be used in this reaction equally successfully. Determination of the positions of the nitrogen and bromine atoms in the addition

products is of undoubted theoretical interest, since it can serve as an indirect proof of the ionic or radical mechanism of the process. It was found that *N*-bromosulphonamides add to alkenes with the formation of products in which the bromine atom occupies the same position as in the "normal" addition of hydrogen bromide to these alkenes:

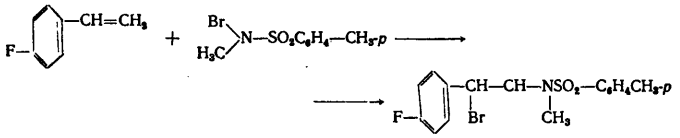
$$RCH=CH_2 + BrNR''SO_2R' \longrightarrow RCHBrCH_2NR''SO_2R'.$$

NN-Dibromosulphonamides add to alkenes to yield products in which the bromine occupies the same position as in the "anomalous" addition of hydrogen bromide (the brominated alkene is formed at the same time):

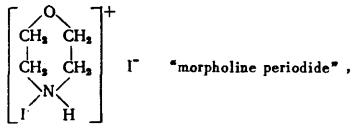
$$2RCH=CH_2 + Br_2NSO_2R' \longrightarrow RCH(NHSO_2R')CH_2Br.$$

There are indications that *N*-chlorinated aromatic sulphonamides, for example, *N*-chlorobenzenesulphonamide [121] and *N*-chlorosaccharin [77], are also able to add to unsaturated compounds.

Fosdick *et al.* [122], in the search for methods of synthesising hypotensive amines containing fluorine and chlorine in the aromatic ring, used the addition of *N*-bromo-*N*-methyl-*p*-toluenesulphonamide to halogenated styrenes and hydroxystyrenes, and obtained the desired products in good yields:



Investigation of the mechanism of the bromination of unsaturated compounds with *N*-bromosuccinimide led Southwick and coworkers to study the reaction of iodamines with $\alpha\beta$-unsaturated ketones [123]. They showed that complexes of iodine with amines, for example, the so-called morpholine periodide:



"morpholine periodide",

react rapidly with *trans*-1,2-dibenzoylethylene, *trans*-3-benzoylacrylic acid, cinnamaldehyde, and β-nitrostyrene at room temperature. In the case of nitrostyrene, a good yield of the addition product of *N*-iodomorpholine was isolated [123-125]:

$$C_6H_5CH=CH-NO_2 \xrightarrow{OC_4H_8NH\cdot I_2} C_6H_5CH(NC_4H_8O)CHINO_2.$$

It is interesting that in this case the orientation of addition is opposite to that observed by Fosdick [122]: the halogen adds at the β-position with respect to the benzene ring.

These workers were also able to add *N*-bromomorpholine to *trans*-benzylideneacetophenone [125]:

$$C_6H_5CH=CHCOC_6H_5 + BrN\langle(CH_2CH_2)_2\rangle O \longrightarrow C_6H_5CH(NC_4H_8O)CHBrCOC_6H_5.$$

Addition to multiple bonds of substances containing positive halogen was observed in the work of Parke *et al.* [99] quoted previously. They noted that *N*-bromotrifluoroacetamide and *N*-bromotrichloroacetamide give up to 40% of addition products with cyclohexene.

Baily and Bello [95] observed the addition of *N*-bromosuccinimide as a secondary process in the bromination of vinylacetonitrile. Since the reaction occurs in the presence of benzoyl peroxide, they assume that addition of *N*-bromosuccinimide to a double bond occurs by a free-radical mechanism.

When *NN*-dibromo-amides react with organic acids and unsaturated compounds, only small amounts of addition products of the bromoamides and the alkenes are formed [126].

Probst investigated the reaction of *N*-bromoacetamide with styrene, cinnamic acid and its methyl and ethyl esters, *trans*-stilbene, and benzylideneacetophenone, and showed that the corresponding dibromide is the only product in every case [127]. The reaction of styrene with several other *N*-brominated compounds, such as *N*-bromobenzamide, *N*-bromophthalimide, *N*-bromosuccinimide, etc., was studied, but none was found to give an addition product with styrene.

Comparison of the reactivities of various compounds containing positive halogen shows that addition is characteristic mainly of *N*-halogenated derivatives, especially *N*-halogenated sulphonamides.

Judging from the available literature, addition to unsaturated compounds is not characteristic of the *C*-halogenated derivatives. Thus Baskakov and Mel'nikov [128] found not long ago that, of the many α-halogenonitroalkanes which they investigated, only bromopicrin reacts at an appreciable rate with unsaturated compounds. The reaction is carried out in the presence of benzoyl peroxide or under ultra-violet irradiation.

The addition of substances containing positive halogen to multiple bonds was investigated in some details also in the reaction of alkyl hypohalites with several unsaturated compounds. Thus Conant and Jackson [129] effected the reaction of bromine with cinnamic acid and benzylidineacetophenone in aqueous methanol and obtained the corresponding bromomethoxy-derivatives. In a later series of papers [130-132] Jackson showed that the reaction involves the intermediate formation of the alkyl hypohalite. For example, the reaction of chlorine with unsaturated compounds in the presence of ethanol occurs as follows:

$$CH_3CH_2OH + Cl_2 \longrightarrow CH_3CH_2OCl + HCl,$$

$$C_6H_5CH=CHCOOH + CH_3CH_2OCl \longrightarrow C_6H_5CH(OC_2H_5)CHClCOOH.$$

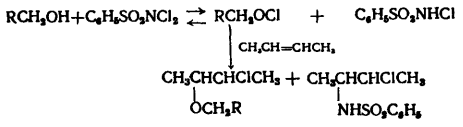
The reaction is carried out at room temperature or by boiling in alcohol. With the bromo-derivatives, dibromides are formed as side-products, but with chlorine only addition products of the alkyl hypochlorite are formed [130].

Methyl hypochlorite adds readily to the triple bond in phenylacetylene [132]

$$C_6H_5C\equiv CH + 2CH_3OH + Cl_2 \longrightarrow C_6H_5C(OCH_3)_2CHCl_2.$$

The possibility of synthesising β-chloroethers by the addition of alkyl hypochlorites to unsaturated compounds has been studied also by Likhosherstov and his coworkers [121,126,133-137]. The source of the hypochlorites was the corresponding alcohol, interacting with free chlorine in the course of the reaction. Diols and also phenols can be used as well as aliphatic alcohols in this reaction. Addition of the elements of an alkyl hypohalite to multiple bonds by interaction with unsaturated compounds in alcoholic media is characteristic of a great variety of compounds containing positive halogen.

Thus several *N*-halogenated amines and amides can be used to provide the chlorine, and they, as well as the alkyl hypohalite, add to the double bond [121,136]:



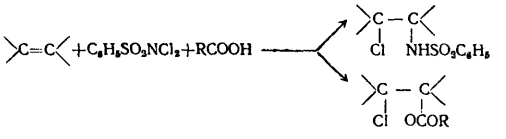
The course of the reaction depends on the properties of alcohol and halogenated amine or amide; a large excess of alcohol results in almost exclusive formation of a β-halogenoether.

In assessing the value of such reactions for preparative purposes, the results of Buckles *et al.*[138] must be borne in mind. Although they showed in several cases the possibility of the addition of bromine plus a radical from a hydroxylated solvent, this reaction is in their opinion of no value as a method of preparation, since it is extremely difficult to purify the desired products from dibromides.

If the halogen is positive in character, *C*-halogenated derivatives can be used, as well as the *N*-halogenated derivatives, to add the elements of an alkyl hypobromite. Methyl and allyl hypobromites, for example, undergo additions to the most varied unsaturated compounds by reaction of the latter with bromonitromalonic ester, bromopicrin [NO_2CBr_3 (Ed. of Translation)] and other α-halogenonitro--compounds in methanol or allyl alcohol respectively[6,139].

If acids are used instead of alcohols as solvents, acyl hypohalites can be added to unsaturated compounds.

Thus Likhosherstov and his coworkers studied the reaction of halogenated sulphonamides with acids in the presence of alkenes and showed that two reactions take place, forming β--chloroethers (and free amides) or β-chlorosulphonamides[137]:



A similar addition of acyl hypochlorites and hypobromites to a double bond was described by Böckemüller and Hoffmann[140].

C-Halogenated compounds can also be successfully used as sources of positive halogen in the addition of acyl hypohalites[141].

It is impossible to discuss the addition of substances containing positive halogen to multiple bonds without mentioning the Meerwein reaction[142], which consists in the halogenoarylation of unsaturated compounds by means of arenediazonium chlorides, these behaving in some reactions like *N*-chloroamines, capable of free-radical reactions[143]. There is no need to consider the Meerwein reaction in any great detail here, since separate reviews have been devoted to it, in particular that published not long ago by Dombrovskii[144]. We may merely note that, even in the case of such an apparently well studied reaction, no uniform view is held concerning the mechanism of addition: up to the present, three mechanisms have been suggested for this reaction — the ionic[142], radical[143,145], and finally the ionic–radical[144] mechanism.

Summarising the literature on the chemistry of compounds containing positive halogen, we readily see that, although these compounds have attracted attention only comparatively recently, convincing evidence has been given of their very specific properties, and the possibility of utilising these properties to solve synthetic problems is already apparent. Nevertheless, although quite wide synthetic possibilities have been demonstrated for compounds containing positive halogen, the problem of controlling these reactions and studying their mechanism cannot be regarded as completely solved.

This problem has proved extremely complicated primarily because compounds containing positive halogen include *N*-, *C*-, and *O*-halogenated derivatives, which differ greatly in reactivity, and can, of course, interact with different organic compounds by different mechanisms and under different conditions.

These specific chemical properties of compounds containing positive halogen are caused by the peculiar state of the N–Hal or C–Hal bond in these compounds. Under the influence of electron-acceptor substituents, which are invariably present in molecules of such compounds, these bonds are polarised so that the halogen atom carries no appreciable negative charge, in contrast to ordinary organic halogen compounds, for example. In limiting cases, when the effect of electron-acceptor substituents is sufficiently great, the halogen atom carries a positive charge. Such a situation occurs, for example, in *N*-iodosuccinimide[146], bromo- and iodo-trinitromethane[147], and iodoacetylene[148].

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A NEW FIELD IN THE STEREOCHEMISTRY OF SUGARS: THE STUDY OF THEIR CONFORMATIONS

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CONTENTS

I. Introduction 681
II. The conformations of monosaccharides 682
A. The conformations of six-membered monosaccharide rings 682
B. The conformation of five-membered monosaccharide rings 685
C. The conformation of acyclic forms of monosaccharides 685
III. The conformations of oligosaccharides 686
IV. The conformations of polysaccharides 686
V. Some particular aspects of the study of the conformations of carbohydrates 687
VI. The concept of conformations as applied to biochemistry 688

I. INTRODUCTION

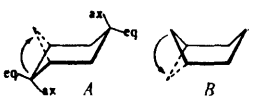
The last decade has been noteworthy for the introduction and vigorous development of a new field in the chemistry of carbohydrates — the study of their conformations[1-4]. It is no exaggeration to say that the new era in carbohydrate chemistry, this new development in the stereochemistry of sugars, is as significant as the period which followed the discovery of the cyclic forms of carbohydrates and the tautomerism between their open-chain and cyclic forms.

Despite this, data on the conformations of carbohydrates, which are relevant to chemists and biochemists, are little used in the USSR. The present knowledge of the conformations of carbohydrates is too broad to be encompassed within a single article, and therefore the object of this review is simply to set out the main theories and consider various examples which illustrate the practical value of this new field.

Conformations are the equilibrium forms of molecules which are taken up by aliphatic compounds because of the free rotation of groups around simple single bonds, or, in the case of cyclic compounds, because of rotation and change of the mutual positions of the individual parts of the molecule; in either case no bonds are broken in the mutual transitions between conformations, which distinguishes this from isomerisation.

In the case of cyclohexane, which may be considered as a model for a pyranose (the most common form of sugars), in addition to unstable transitional forms, the amount of which is usually negligible, two stable forms can exist: the chair form and the boat (or tub) form (Scheme 1). Of these the chair form is the more stable, since it contains the smaller number of mutually "screening" hydrogen atoms; it has 5.6 kcal less energy than the boat form, and under normal conditions it is the conformation taken up almost exclusively (99%) by cyclohexane.

The transition of one of these forms into the other can be considered as a rotation of part of the molecule, as shown by the arrows in Scheme 1, and is associated with a loss or gain of energy. Using the terms introduced into the conformational chemistry of sugars from the chemistry of



Scheme 1. The most stable conformations: *A* chair form, *B* boat form; ax = axial atoms or groups; eq = equatorial atoms or groups.