The Chemistry of Positive Halogen Organic Compounds
Reactions with Trivalent Phosphorus Derivatives*

By P. A. Chopard

Cyanamid European Research Institute, Cologny-Geneva (Switzerland)

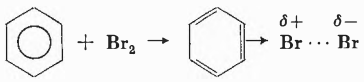
1. Introduction

Typical aspects of the chemistry of organic halogeno compounds are generally related to the atomic electroaffinities of the halogens (relative to carbon) and to their molecular electronegativities in closely related series of molecules. Thus the "negative" character of halogen substituents in organic molecules is illustrated by such well known examples as the strong acidities of α-halo carboxylic acids and the reactivities of saturated halogeno compounds with a very wide range of nucleophiles. Electron release by halogen atoms in organic molecules appears to be relatively unimportant and the contribution of polar forms (of type **1b**) to the ground state of, for example, halogeno aromatic compounds,

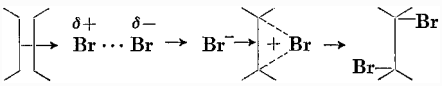
$$\underset{\textbf{1a}}{A_r{-}X} \longleftrightarrow \underset{\textbf{1b}}{A_r^-{=}X^+}$$

is generally considered weak, although it is widely used to explain directive effect in substitution reactions.

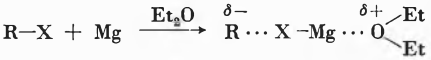
Many reactions exist however in which the halogen atom appears to act as an electron acceptor in the univalent state and, in this respect, it can be compared to other elements of groups Vb and VIb which are commonly found in organic molecules. Typical cases of such a behaviour can be found in many fields of organic chemistry; the formation of halogen-aromatic complexes, for example,



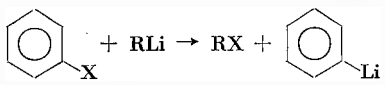
or the simple halogenation of an olefin,



The formation of Grignard reagents may also proceed similarly, i.e.



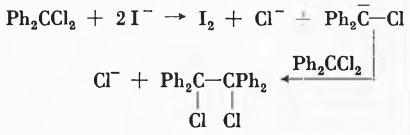
as well as the metallation of aromatic halides,



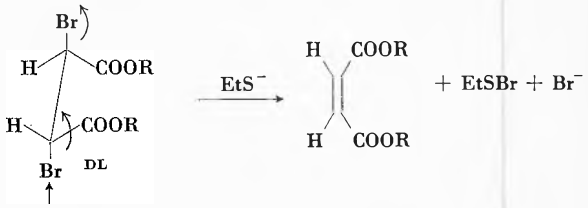
Chlorinated methane derivatives have been shown to react with iodide to form elementary iodine and carbanions[1]; for example with carbon tetrachloride,

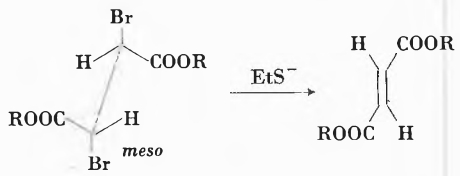
$$Cl_4C + 2\,I^- \rightarrow I_2 + Cl^- + [Cl_3\bar{C}]$$

or with dichlorodiphenylmethane, where the formation of the carbanion was indicated by the following subsequent dimerization reaction,



Some vicinal dihalides form olefins when treated with nucleophiles. This has been observed by Winstein[2] for 2,3-dibromobutanes with iodide ion and more recently by Weygand with sulfide ions on a series of substituted dibromides.[3] The reaction mechanism in these cases, is identical to that of a normal β-elimination where the carbanion is produced by removal of a proton. Thus, for example, the ester of DL-dibromo succinic acid gave the ester of maleic acid when treated with ethyl sulfide salts, while the *meso*-compound gave the ester of fumaric acid in the same conditions,





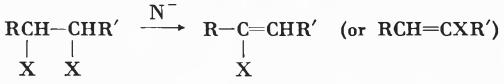
* Presented at the Summer Meeting of the Swiss Chemical Society, October 1, 1966, in Solothurn.

[1] A. Perret and R. Perrot, *Bull. Soc. Chim. 1* (1934) 1531.

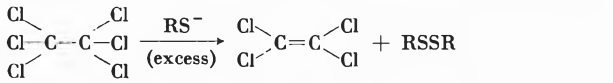
[2] S. Winstein, D. Pressman and W. G. Young, *J. Amer. Chem. Soc. 61* (1939) 1645.

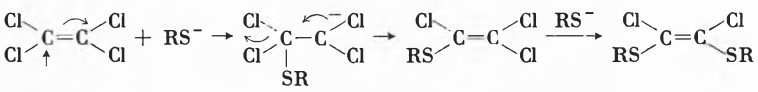
[3] F. Weygand and H. G. Peine, *Rev. Chim.* (Rumania) *7* (1962) 1379.

The above reactions are particularly interesting in the sense that one might expect also normal β-elimination to vinyl halides to occur and this is indeed the case when other nucleophiles such as RO^-, OH^- or amines are used,

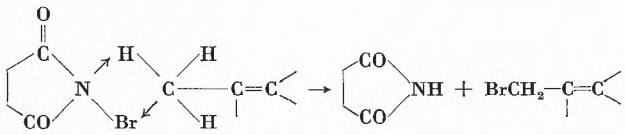


Comparable reactions have been reported to occur with hexachloroethane;[4] these are, however, more complex and may involve also attack at a halogenated vinyl center. The mechanism is probably similar to the displacement of a halogen ion from an acyl halide,

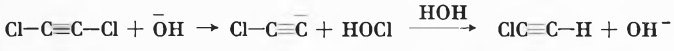




Also halogeno amines and amides are considered as sources of positive halogen and allylic bromination by N-Bromo succinimide can formally be interpreted as attack on positive bromine,[5]



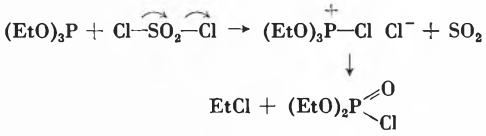
Recently ARENS[6] has shown that dichloroacetylene is reduced to the monohalo compound in aqueous alkali; the simultaneous formation of HOCl illustrates the strong "positivity" of the halogen in this reaction,



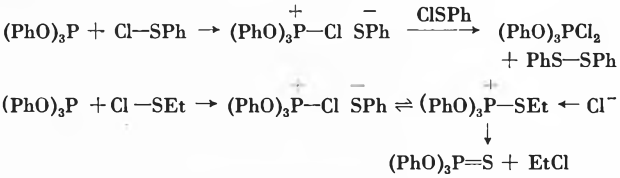
From the above examples (except the last one) it appears that reactions at positive halogen will depend not only on the structure of the halogenated substrate but also on the nature of the attacking species. To a first approximation one might put forward two crude criterions to characterize such a nucleophile: a) It should preferably be derived from a second row or heavier element; b) It should be relatively deficient in non bonding valence electrons. Without developing this concept any further at the moment, one may still predict that derivatives of trivalent phosphorus (either neutral or negatively charged) should be good nucleophiles toward positive halogen compounds.[7] It is the purpose of the present work, to discuss a few of such characteristic reactions where good evidence of attack at positive halogen has been obtained, then, to give a tentative interpretation of the results in relation to the nature of the reactants.

2. The reactions of trivalent phosphorus derivatives with "positive halogen" compounds

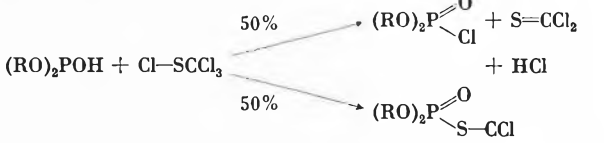
Some of the most striking examples of such reactions are perhaps those of tertiary phosphites with sulfur-halogen derivatives. Thus, triethylphosphite, with Sulfuryl chloride gives diethylphosphochloridate, SO_2 and ethyl chloride. Complicated mechanisms[8] have been proposed for this reaction, involving attack at the oxygen atom; however, reaction at the halogen is far more simple; it will be noticed



that the initially formed quaternary phosphorus compound is subsequently deethylated to the chloridate. This facile dealkylation by the counter ion is extremely frequent in organo phosphorus chemistry and is one of the main features of the celebrated Arbusov Reaction of phosphites to phosphonates.[9] This is not surprising in view of the energy of the P=O bond in tetracoordinated phosphorus compounds (130 to 150 kcal/mole). Also the reaction of triphenylphosphite with phenyl sulfenyl chloride gives the expected chlorophosphonium salt since no further dealkylation is possible, while with ethyl sulfenyl chloride the corresponding thiophosphate is formed,[10]

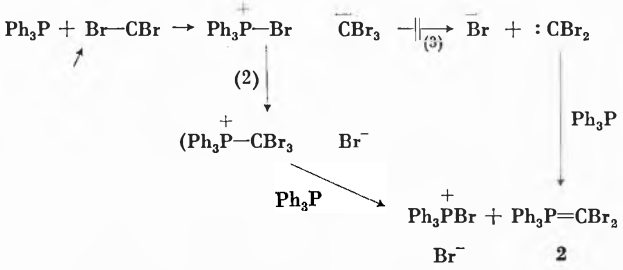


It is obvious that this last reaction may be also interpreted as a displacement on the sulfur atom and this may indeed be the case since the related reaction of dialkyl phosphites on trichloromethylsulfenyl chloride has been shown to proceed simultaneously by both mechanisms,[11]



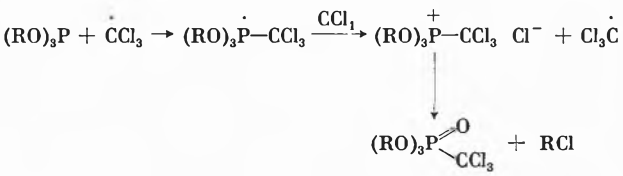
[4] H. BAGANZ and K. E. KRÜGER, *Chem. Ber. 91* (1958) 809.
[5] L. HORNER and E. H. WINKELMANN, *Angew. Chem. 71* (1959) 349.
[6] J. F. ARENS, *Rec. Trav. Chim. Pays-Bas 82* (1963) 183.
[7] B. MILLER, *Topics in Phosphorus Chemistry*, Vol. 2, Interscience Publishers, New York 1965.
[8] A. C. POSHKUS and J. E. HERWEH, *J. Amer. Chem. Soc. 79* (1957) 6127.
[9] J. ARBUZOV, *J. Russ. Physic. Chem. Soc. 38* (1906) 687; see G. M. KOSOLAPOFF, *Organophosphorus Compounds*, John Wiley & Sons, New York 1958.
[10] K. A. PETROW, G. A. SOKOLSKII and B. M. POLEES, *Zh. Obshch. Khim. 26* (1956) 3381; A. C. POSHKUS and J. E. HERWEH, *J. Amer. Chem. Soc. 79* (1957) 4245.
[11] V. ETTEL and M. ZBIROWSKI, *Chem. Listy 50* (1956) 1265.

Related to the above reactions are those with polyhalogenated methane. For example, triphenylphosphine reacts with carbon tetrabromide[12] (or CCl_4)[13] to give the phosphine dibromide and dibromomethylene phosphorane **2**, a halogeno derivative of the famous Wittig reagent which converts aldehydes and ketones to olefins,

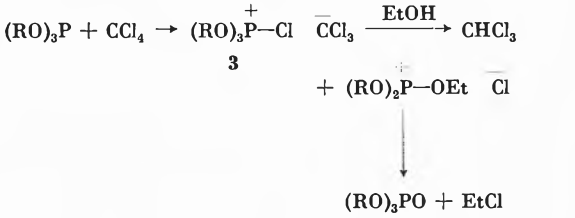


$(Ph_3P{=}CBr_3 + R_1R_2C{=}O \rightarrow Ph_3PO + R_1R_2C{=}CBr_2)$

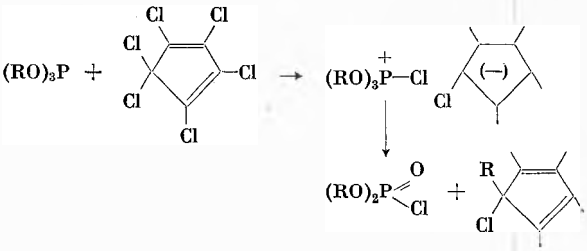
The course of the reaction, which normally proceeds in the dark, is not influenced by light or free radical initiators and a carbene mechanism (3) is improbable since no dihalocarbene could be detected by usual trapping procedures. Hence the sequence of two successive reactions at positive halogen [mechanism (2)] is favoured. In contrast, the corresponding reactions with phosphites,[14] although they also proceeded in the dark,[15] were catalyzed by light and peroxides,[16] and inhibited by hydroquinone.[17] This is good evidence for a radical mecanism superimposed on that of attack at the halogen and has been formulated as follows,[16]



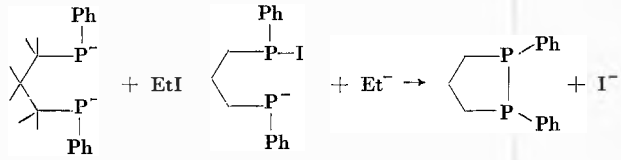
However the presence of the ion pair **3** resulting from initial attack at positive halogen was strongly supported by the results of the above reaction carried in alcohol,[18] that is, formation of chloroform and trialkylphosphate,



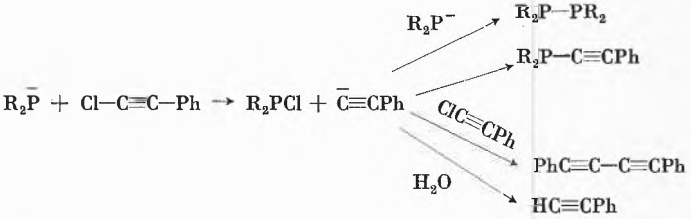
Somewhat similar to the above are the reactions of trialkylphosphites and hexahalogeno-cyclopentadiene;[19] in this case, the attack at halogen is favoured by the strong π stabilization of the cyclopentadienyl anion,



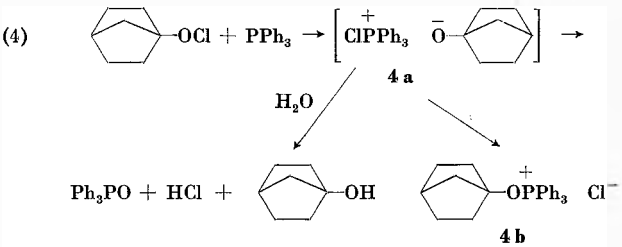
The action of phosphides on positive halogen is illustrated by the following formation of a cyclodiphosphine,[20]

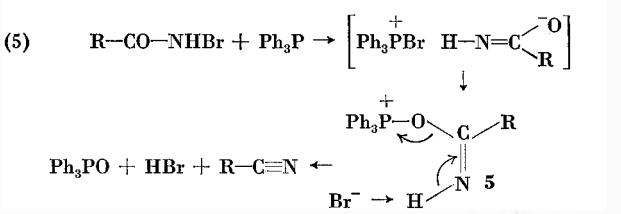


and the reaction with halogeno acetylenes,[21] in which the many products isolated can all be formed at the expense of the initial acetylide and phosphide.

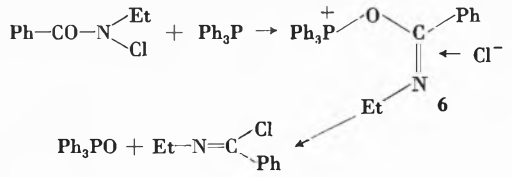


With hypochlorites[22] and N-halogeno amides,[23] there are numerous examples of reactions at positive halogen of phosphorus compounds,





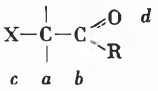
[12] F. Ramirez, N. B. Desai and N. McKelvie, *J. Amer. Chem. Soc. 84* (1962) 1745.
[13] R. Rabinowitz and R. Marcus, *J. Amer. Chem. Soc. 84* (1962) 1312.
[14] G. Kamai and L. P. Egorova, *Zh. Obshch. Khim. 16* (1946) 1521.
[15] J. I. G. Cadogan and W. R. Foster, *J. Chem. Soc. 1961*, 3071.
[16] G. Kamai and F. M. Kharrasova, *Zh. Obshch. Khim. 27* (1957) 953.
[17] C. E. Griffin, *Chem. & Ind. 1958*, 415.
[18] A. J. Burn and J. I. G. Cadogan, *J. Chem. Soc. 1963*, 5788.
[19] V. Mark, *Tetrahedron Letters 1961*, 295.
[20] K. Issleib and F. Krech, *Chem. Ber. 94* (1961) 2656.
[21] K. Issleib and G. Harzfeld, *Chem. Ber. 95* (1962) 268.
[22] D. B. Denney and R. Dileone, *J. Amer. Chem. Soc. 84* (1962) 4737.
[23] S. Trippett and D. M. Walker, *J. Chem. Soc. 1960*, 2976; A. J. Speziale and L. R. Smith, *J. Amer. Chem. Soc. 84* (1962) 1868.

(6) 

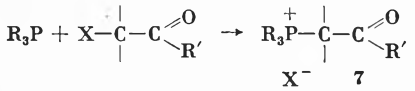
The three examples shown above all have in common the formation of oxygen-phosphorus bonded quaternary salts so it may well be asked whether the reaction does not simply proceed by attack on the oxygen atom. Answer to this question is furnished by the fact that compound **4b** is stable to water although when reaction (4) is performed in moist solvents, only the phosphine and bicycloheptanol are formed. Obviously the chlorophosphonium cation of **4a** should be most unstable to water or alcohols. It must be said, however, that phosphorus-oxygen bonded salts of type **5** and **6** (quasi-phosphonium salts) are usually very unstable to protolytic solvents and decompose to the phosphine oxide and hydrocarbons. Concerning the rearrangement of intermediates **5** and **6** it is of interest to note that in the absence of a labile proton to be removed (**5**), the anion attacks the vinyl center to form an imidoyl halide. Again in this case, the driving force must be the strong tendency of P=O bond formation.

In view of the above reactions it may be predicted that compounds having several electrophilic centers, such as α-halo carbonyl compounds, will behave in a great variety of ways with a range of different nucleophiles. This is typified by the reactions of phosphorus nucleophiles which form themselves a complex field which is presently thoroughly examined by several groups of investigators. Only the most significant features of these reactions will now be discussed.

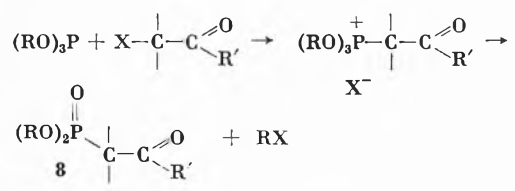
Important electrophilic centers in α-halogeno carbonyl compounds can be listed as follows,



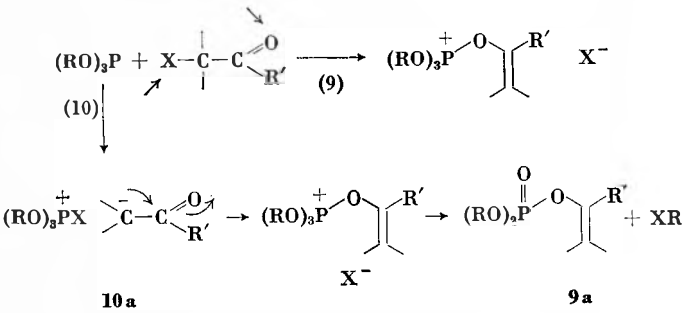
a, the α-carbon, *b*, the carbonyl carbon, *c*, the halogen and *d*, the carbonyl oxygen. Most early reactions of trivalent phosphorus compounds appeared to involve only displacement of the halogens, that is, reaction at center *a;* with tertiary phosphines, keto phosphonium salts are formed,

(7) 

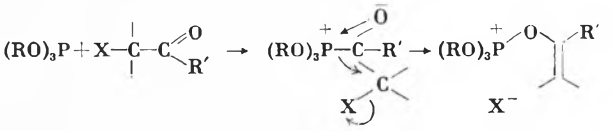
and, phosphonates **8** are formed with tertiary phosphites.[9]

(8) 

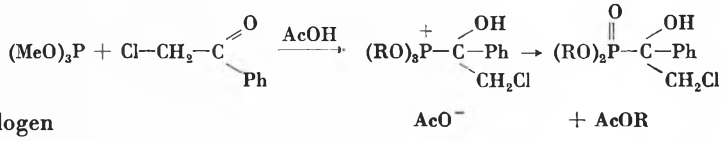
However, the discovery that vinyl esters **9a** were often obtained in place of the phosphonate **8** showed that other mechanisms were involved[24] and that **9a** might be formed consecutively to halogen attack followed by rearrangement of the ion pair in a manner similar to that postulated for N-halogeno amides, or by direct attack on oxygen,[25]



Although mechanism (10) is considered more likely than (9) and is probably valid in many instances, cases are known where the formation of the vinyl ester is not prevented by the presence of alcohol[26] (which should normally destroy rapidly the initial halogeno phosphonium salt). A third mechanism has therefore been postulated which involves attack at the carbonyl carbon followed by rearrangement,[25]



A mechanism of that sort is supported by the isolation of an intermediate corresponding to the initial stage, when the reaction is carried in presence of a suitable proton donor,

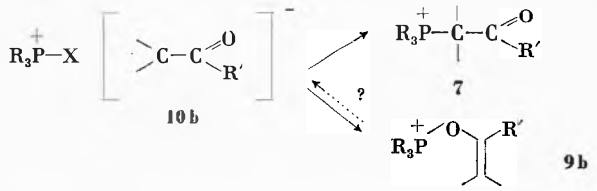


However, it should be kept in mind that these processes which may involve several simultaneous reversible initial steps with different centers of comparable electrophilicity are necessarily very sensitive to conditions and that distinguishing between, for example, attack at carbonyl oxygen or carbon may be an extremely difficult task.

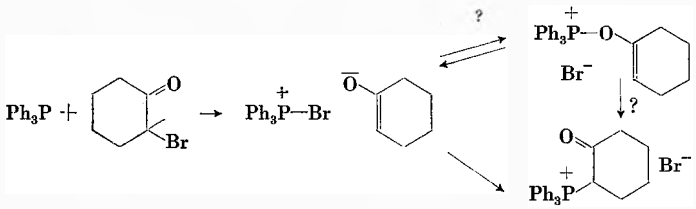
With trisubstituted phosphines, no evidence has been detected of a reaction at the carbonyl carbon and attack

[24] F. W. Lichtenthaler, *Chem. Rev. 61* (1961) 607.
[25] For a detailed discussion of these mechanisms, see P. A. Chopard, V. M. Clark, R. F. Hudson and A. J. Kirby, *Tetrahedron 21* (1965) 1961.
[26] R. F. Hudson, P. A. Chopard and G. Salvadori, *Helv. Chim. Acta 47* (1964) 635.

at oxygen is doubtful. The two main processes to be considered are therefore, displacement of the halogen (7) or attack at the halogen atom (10). It is very important to mention now that in many cases ample evidence has been found that where reaction (10) takes place, the initial ion pair may rearrange[27] to either the phosphonium salt **7** or to the quasi-phosphonium salt **9b.**

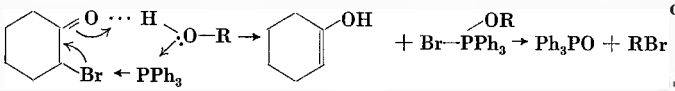


The factors which promote one or the other rearrangement have not been clearly determined and are related to the charge distribution in the anion of **10** as well as to the nature of the phosphonium center. Also very little is known about the reversibility of the reactions leading to **7** and **9,** so that it is possible that kinetic versus thermodynamic control factors are important in the rearrangement process. Thus, in the case of the reaction of triphenylphosphine with α-bromocyclohexanone, predictions based on calculations[28] and spectral evidence[29] support the formation of the quasi-phosphonium salt (which was too unstable to be isolated). After processing the reaction mixture, however, an appreciable yield of the keto-phosphonium salt was obtained which suggests the simultaneous existence of both rearrangements, since a direct displacement is

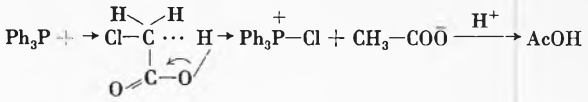


practically prohibited on steric grounds.

Furthermore, in the presence of moisture or alcohols the rate of the above reaction was considerably increased, showing evidence for proton catalysis,[29] as follows,

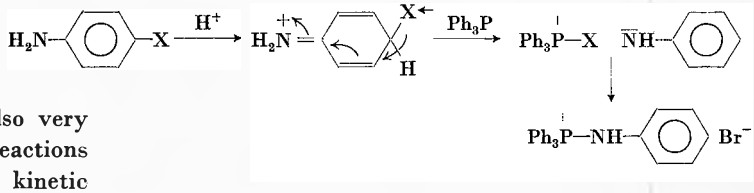


Evidence of proton "auto-catalysis" for the reaction at positive halogen was also obtained for the corresponding reaction with chloracetic acid,[30] which gave acetic acid in good yield,



This was not expected since direct displacement occurs simultaneously and attack on chlorine by tertiary phosphines has not been observed for other α-chloroacetyl compounds such as chloracetone, phenacyl chloride, chloracetic anhydride or ethyl chloracetate.

Other cases of acid catalysis in reactions with positive halogen have however been reported, for example,[31]



3. Discussion

It is now convenient to summarize the information derived from the many results reported in the literature on α-halo keto compounds, in the form of a few statements which can be accepted with a reasonable degree of confidence.

1. *Phosphines are better nucleophiles*[32] *than phosphites with regard to displacement reactions* [at saturated carbon (a) or halogen (b)]. For example, (a), triphenyl phosphine reacts faster than triethyl phosphite with ethyl bromoacetate[33] to give the corresponding $Ph_3\overset{+}{P}–CH_2–COOEt$ and $(EtO)_3\overset{+}{P}–CH_2–COOEt$ salts; (b) In inert solvents, triphenylphosphine reacts easily (exothermic reaction) on the halogen atom of bromoacetone, while phosphites require high temperature and, in these conditions, react simultaneously at the saturated carbon and on the carbonyl groups.[34]

2. *For reactions at saturated carbon or halogen the order of reactivity of trivalent P compounds follows the order of normal halogen displacement* $I > Br > Cl$; but with a much greater selectivity* in the second case. For example (a), to react with triphenylphosphine, ethyl bromo- and chloroacetate require comparable reaction conditions[33]

* Selectivity refers to the value of $\ln \frac{k_1}{k_2}$ where k_1 and k_2 are the rate constants of two comparable reactions. For example the reactions of a nucleophile on two related electrophiles.

[27] I. J. Borowitz and R. Virkhaus, *J. Amer. Chem. Soc. 85* (1963) 2183.

[28] P. A. Chopard, R. F. Hudson and G. Klopman, *J. Chem. Soc. 1965*, 1379.

[29] P. A. Chopard and R. F. Hudson, *J. Chem. Soc.* (in press).

[30] P. A. Chopard, submitted to *J. Amer. Chem. Soc.*

[31] H. Hoffmann and D. Michael, *Chem. Ber. 95* (1962) 528.

[32] For a kinetic study of the reactivity of phosphines and phosphites toward alkyl halides, see G. Aksnes and D. Aksnes, *Acta Chem. Scand. 18* (1964) 38.

[33] P. A. Chopard, unpublished results.

[34] A. N. Pudovik, *Zh. Obshch. Khim. 25* (1955) 2173; A. N. Pudovik and V. P. Averyanova, *Zh. Obshch. Khim. 26* (1956) 1426.

although Cl < Br. (b) Bromocyclohexanone reacts much faster than chlorocyclohexanone with Ph_3P[28] (difference estimated 10^5 to 10^6).

3. *Phosphites react preferentially to phosphines at the carbonyl center.* For example the yield ratio, vinyl phosphate to phosphonate, with halogeno acetones is in the order Cl > Br > I[34] (this is the order of electrophilicity of the C=O groups), while in anhydrous conditions, phosphines give only the phosphonium salts with the same reagents. Also trimethylphosphite reacts rapidly with chlorocyclohexanone in conditions where Ph_3P is inert.[25]

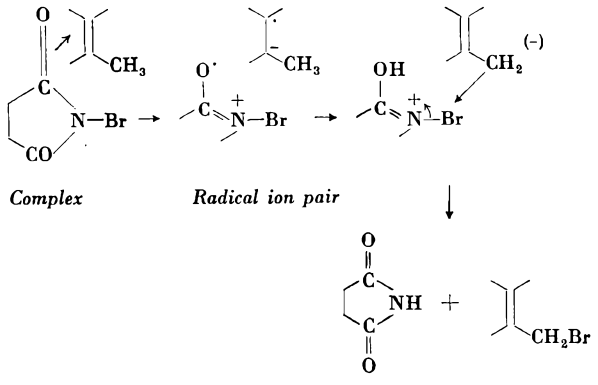
4. *The selectivity with respect to the leaving group is much greater for the reaction on halogen than at saturated carbon,* i.e. small changes in stabilization of the carbanion produce great changes in the rates. For example Ph_3P reacts at the bromine atom of bromoacetone but not of ethylbromoacetate.

In view of the above, the following generalizations can be made. Phosphines and phosphites appear to be quite different kinds of nucleophiles toward different electrophilic centers. The high affinity of phosphites compared to that of phosphines for carbonyl centers, which involves a large extent of bond formation, indicates a high degree of negativity which can be related to the density of non bonded electrons, as mentioned earlier. An additional factor is the possibility of ionic forms, such as $RO\overset{+}{=}\underset{|}{P}\overset{-}{}$, to contribute to the charge density on the P atom. Conversely, tertiary phosphines which should allow more distortion of the charge in the nucleophile (greater polarization energy) favor centers where the extent of bond formation and bond break in the transition state is of a quite different order of magnitude. According to the nucleophilic treatment of HUDSON,[35] the reactions (at carbon or halogen) observed for phosphines may both belong to the class of S_N2 displacement where nucleophilic selectivity increases with bond formation in the transition state. The apparent greater selectivity observed for reactions at halogen would imply greater bond formation and consequently greater charge transfer to the substrate. This is not unreasonable for systems involving essentially neutral nucleophiles and carbanions (or other soft bases) as leaving groups, where affinity and solvation energy factors should be relatively low and bonding energy factors relatively high.

One fact, however, appears to remain incompatible with the above interpretation: This is the very great difference between the rates of attack at Bromine and Chlorine in spite of the similarity in their properties (polarisability, Pauling electronegativity). It is unlikely that a relation can be found with the ionization potentials of simple halogenated molecules (for example, $\Delta I_p = 0.7$ ev for MeCl and MeBr) because a) according to the above definition, the charge transfer in the transition state should be large, therefore, the positive charge built on the electrophilic center should remain small. b) Ionization potentials of methyl halides must refer only to the non bonding electrons.

An explanation may be proposed by assuming a similarity between the X–C (or X–S or X–N) bond of organic halogenated molecules and the X–X bond which as mentioned earlier, may form charge-transfer complexes with donors of low ionization potential. In these cases one electron from the highest occupied orbital of the donor is transferred to the lowest unoccupied orbital of the acceptor. This might effectively describe a transition state structure in a nucleophilic displacement, provided that a leaving group exists; otherwise the excited complex will only dissociate to reactants or to radical ions. Although it might be very difficult to detect the existence of transient charge transfer formation in reactions at positive halogen compounds, some information may be derived from the charge transfer absorptions which exist in the solutions of tertiary amines and CCl_4 or $Br–CCl_3$.[36] A difference of ~ 0.3 ev has been observed for these two compounds, which is equivalent to ~ 7 kcal/mole and means a difference of $\sim 10^5$ in the electrophilic reactivities of Br and Cl. Although this interpretation is highly speculative, it can be paralleled with the observation, mentioned earlier, that some reactions of phosphites with carbon tetrahalides are light catalized, while phosphines, being better nucleophiles toward halogen than phosphites, may not require such an activation.

Furthermore, it is known that light and orientation factors are important with regard to the allylic bromination with N-bromosuccinimide; it is therefore tempting to propose, for this reaction, a mechanism involving the initial formation of a charge transfer complex where the carbonyl would act as a donor toward the allyl compound and the bromine as an indirect acceptor. This is illustrated in the following scheme,



Although more experimental work is required to provide a firmer basis to the above concepts, their development may prove useful to gain more information on the various processes involving positive halogen compounds.

[35] R.F.HUDSON, *Chimia 16* (1962) 173.

[36] E.M.KOSOWER, *Progr. Physic. Org. Chem. 3* (1965) 81.