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Nucleophilic substitution at the halogen atom (halogenophilic reactions)

P K Sazonov, G A Artamkina, I P Beletskaya

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Abstract. The key features of halogenophilic reactions defining their role in organic chemistry are considered. The results of studies of mechanisms involving a nucleophilic attack at the halogen atom (S_N2Hal) are summarized. The main mechanistic evidence comes from the studies of halogen – metal exchange reactions. Primary attention is paid to the role of halogenophilic reaction as a competing process or a concealed mechanism in ordinary nucleophilic substitution reaction at carbon atoms. The bibliography includes 249 references.

I. Introduction

Nucleophilicity and nucleophilic substitution belong to the most important concepts and processes of organic chemistry. The study of nucleophilic aliphatic substitution in the 1930s (C K Ingold) marked the beginning of the 'mechanistic era' in organic chemistry. This was followed by mechanistic studies of nucleophilic substitution reactions in other classes of organic compounds, *i.e.*, aromatic, carbonyl and unsaturated compounds. Traditionally, the term 'nucleophilic substitution' in organic chemistry implies substitution exactly at the carbon atom [reaction (1a)], but there is a rather wide class of reactions in which the nucleophile attacks a halogen atom, while the organic moiety R in RHal acts as a leaving group, forming a carbanion [the S_N2Hal mechanism, reaction (1b)]. Such reactions, named halophilic or halogenophilic,† demonstrate the ambident behaviour of a C–Hal bond as an electrophile, in spite of the $C^{\delta+}-Hal^{\delta-}$ polarization, which seems unsuitable for a halogenophilic attack.

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$$Nu^- + HalR \longrightarrow NuR + Hal^- \quad (S_N2C) \qquad (1a)$$

$$Nu^- + HalR \longrightarrow NuHal + R^- \quad (S_N2Hal) \qquad (1b)$$

Nu^- is nucleophile.

The ability of a σ-bound halogen atom to act as an electrophilic centre finds an unexpected proof in structural chemistry. The existence of 'halogen bonds', which are similar to hydrogen bonds but have C–Hal bond (as a rule, C–I) instead of the O–H bond as the electron pair acceptor, was demonstrated.[1–5] An obvious analogy between the stability of a C–Hal···B 'halogen' bond[5] and the activity of the corresponding C–Hal bond in halogenophilic reactions is observed. The possible role of 'halogen' bond in halogenophilic reactions has been analyzed in recent computational studies.[6,7]

It should be noted that the ambident behaviour of the C–Hal bond is not always revealed. The high-level quantum chemical calculations [G2(+) level of theory] show that in the gas phase for systems MeHal + Hal^- (including Hal = I), the nucleophilic attack at the carbon atom is thermodynamically more favourable than the attack at the halogen atom.[8] The feasibility of halogenophilic reaction is determined by the structure of organic halide (this is rather widely known) but it also equally depends on the nature of the nucleophile. The trapping of the carbanion that is formed in the halogenophilic reaction and competition with common ('carbophilic') reactions may also play a certain role. These and many other factors are considered in Sections II and III of the present review.

In organophosphorus or organofluorine chemistry, halogenophilic reactions have become conventional long ago but still a wide circle of chemists have little acquaintance with such reactions. There are several reviews covering certain groups or aspects of synthetic applications of halogenophilic reactions.[4,9–26] However, only N S Zefirov and D I Makhon'kov's review[27] considers halogenophilic

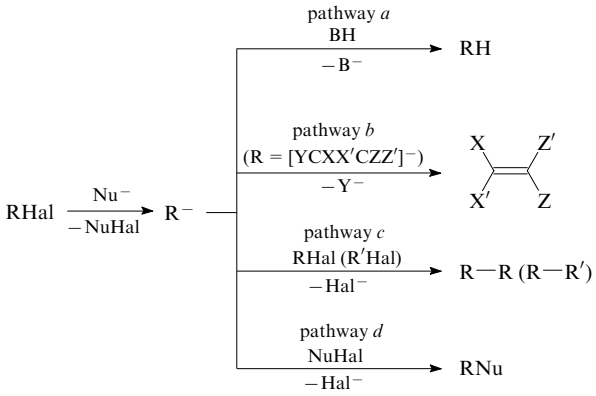
† The term 'halogenophilic' is preferred to avoid confusion with halophilic (meaning 'loving salts') objects (*e.g.*, bacteria).

reactions as a whole, although in the context of a more general concept of X-philic processes. Quite a number of typical examples of halogenophilic reactions published before 1982 can be found in that review; hence, when necessary we will refer to this review instead of original literature.

If the nucleophile is an organometallic compound (*e.g.*, R′Li), then such halogenophilic reaction will result in the replacement of the halogen atom in RHal by a metal. The halogen–metal exchange reactions form the most extensive and practically important class of halogenophilic reactions, but they have never been considered in this context in the existing reviews. Meanwhile, the mechanism involving the nucleophilic attack at the halogen atom (S_N2Hal) was first proposed and studied in detail for the halogen–metal exchange reaction. Whereas the S_N2Hal-hypothesis appeared back in the 1950s,[28,29] the experimental and theoretical substantiation of this mechanism was obtained only in the last decades. The study of halogen–metal exchange reaction against the changing background of different concepts of its mechanism is also an impressive chapter in the history of organometallic chemistry. That is why the consideration of S_N2Hal mechanism in Section IV of the present review includes a small historical sketch revealing the development of the ideas about the mechanism of halogen–metal exchange reactions.

It is worth noting that the halogen–metal exchange is not necessarily the final outcome of a halogenophilic reaction. As a rule, the incipient carbanion (or organometallic compound) is rather reactive and can undergo subsequent transformations. From the synthetic point of view, the interaction of a carbanion with an electrophile (Me_3SiCl, R′Hal, aldehyde, *etc.*) specially added to the system seems most interesting. However the most frequent outcome is its protonation, which leads to hydrodehalogenation of the organic substrate (Scheme 1, pathway *a*). If a good leaving group is present in the carbanion, then the process can result in its elimination (Scheme 1, pathway *b*). The synchronous version of halogenophilic β-elimination (E_2Hal) without the formation of intermediate carbanion is also possible and described in detail.[27,30] Another pathway of transformation of halogenophilic reaction intermediates includes the interaction of carbanion with the starting organic halide, resulting in R–R dimers (Scheme 1, pathway *c*), *i.e.*, in the outcome that is nominally indistinguishable from the radical coupling. The reaction of the carbanion with an electrophilic species arising from the nucleophile NuHal is quite a special case because such an interaction results in the same products as a common nucleophilic substitution reaction (Scheme 1, pathway *d*). In fact, it is a peculiar 'halogenophilic' mechanism of nucleophilic substitution; these reactions are considered in the last part of the present review (Section V).

Scheme 1



II. Key features and typical objects of halogenophilic reactions

In a halogenophilic reaction, the carbon–halogen bond is cleaved and, therefore, the ease of the reaction has to be related to the strength of this bond, which decreases from fluorine to iodine. In the same order, the polarizability increases and the polarization of $C^{\delta+}-Hal^{\delta-}$ bond unfavourable for the reaction with nucleophile at the halogen atom decreases. Note that in many typical substrates of halogenophilic reactions, the halogen atom becomes the positive end of the dipole (*e.g.*, the I atom in perfluoroalkyl iodides). Actually, it seems that the crucial role is played by orbital rather than charge interactions. The consideration of the simple correlation diagram of the interacting molecular orbitals (MOs) reveals an increase of the bonding, stabilizing interaction (ΔE) on going from fluorine to iodine with lowering of the energy of the antibonding σ*-orbital of the C–Hal bond (Fig. 1):

$$\Delta E \sim \frac{[c_{(Hal)}c_{(Nu)}\beta_{(Nu-Hal)}]^2}{E_{(C-Hal)} - E_{(Nu)}},$$

where $c_{(Hal)}$ and $c_{(Nu)}$ are the corresponding orbital coefficients, $\beta_{(Nu-Hal)}$ is the resonance integral, $E_{(C-Hal)}$ and $E_{(Nu)}$ are the energies of the $\sigma^*_{(C-Hal)}$ MO and HOMO of the nucleophile.

Apparently, the carbon–fluorine bond is not subjected to halogenophilic attack at all, although in the litera-

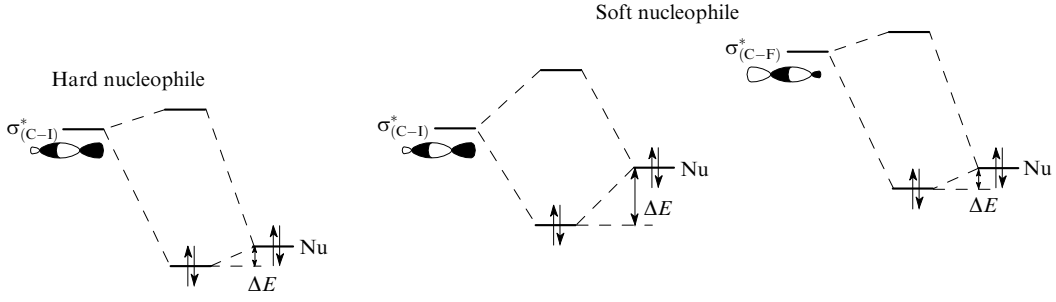
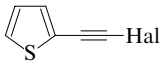


Figure 1. Interaction of the frontier orbitals in a halogenophilic reaction.

ture,[31,32] the occurrence of 'fluorophilic' reactions was postulated.‡ As for the other, 'heavy' halogens, as expected, the reactivity of their derivatives increases from chlorine to iodine. This tendency is qualitatively confirmed by many examples, first of all, by the metallation of organic halides by the halogen–metal exchange reaction.[23,24,33]

The range of chlorophilic reactions is rather narrow. Practically it is limited to the substrates containing electron-withdrawing substituents in α-position relative to halogen,[27,34–37] polyhalogenated derivatives[10,12,13,26,27,37–44] and also chloroacetylenes.[21,45,46] Though bromides are less reactive than iodides, in this respect they represent the most well-studied class of compounds due to their greater availability. The quantitative data concerning the influence of the nature of the halogen on the rates of halogenophilic reactions are rather limited. However, it all demonstrates a sharper increase of the rate of halogenophilic reaction on going from chlorine to bromine and further to iodine as compared with nucleophilic substitution reactions at the sp^3 carbon atom (S_N2C).

Mechanism of the reaction	Example	Rate ratio for different Hal (Cl : Br : I)	Ref.
S_N2Hal	$Me_3Sn^- + ArHal$	$1 : 10^5 : > 10^6$	47
	$EtS^- +$ 	$1 : 3 \times 10^3 : 3 \times 10^7$	14
S_N2C	$Cl^- + MeHal$	$1 : 40 : 3 \times 10^3$	48

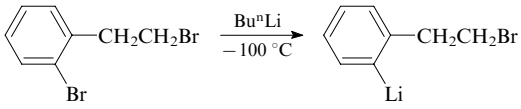
In nucleophilic substitution at the halogen atom, as in the nucleophilic substitution at sp^3 carbon atom, the nature of the leaving group is also essential, but in this case, the leaving group is a carbanion rather than a halide ion. The factors that stabilize the carbanion being formed would facilitate the halogenophilic reaction. The acidity of the corresponding CH-acid (RH) is a good estimation criterion for the feasibility of a reaction. These values for a number of CH-acids are given below (the corresponding hydrogen atoms are italicized).[49]

Compound RH (bond)	pK_a	Compound RH	pK_a
Alkane [$C(sp^3)-H$], CH_4	$\geqslant 45$	CH_3SO_2X	~ 26
Alkene ($C(sp^2)-H$), $CH_2{=}CH_2$	36	$CHCl_3$	15
Arene ($C(sp^2)-H$), Ph*H*	37	CHF_3	26
Alkyne ($C(sp)-H$), $CH{\equiv}CH$	25	$CF_2{=}CFH$	~ 25
Toluene ($C(sp^3)-H$), $PhCH_3$	35	C_6F_5H	24
CH_3COOEt	~ 27	$(CF_3)_3CH$	7
CH_3CN	29	$(NO_2)_3CH$	< -1

In this respect it is noteworthy that for unsubstituted hydrocarbons, the general susceptibility for halogenophilic processes increases in the order $C(sp^3) < C(sp^2) < C(sp)$ in spite of the simultaneous increase of the C–Hal bond strength. Interestingly, the strength of CHal···B halogen bond increases in the same order.[5]

Simple aliphatic halides containing $C(sp^3)-Hal$ bond are not prone to the nucleophilic attack at the halogen atom at all. The only, although notable exception is the halogen–metal exchange under the action of organolithium compounds and some element-centred anions.[50–52] Nevertheless, the reactions of organolithium compounds with alkyl halides proceed more slowly and, above all, they are much less selective than the reactions with aryl halides.[16,53–56]

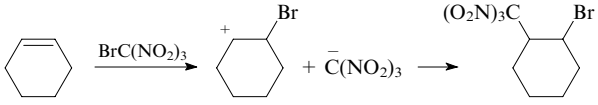
The halogen–metal exchange reactions and halogenophilic processes in general are much more typical and widespread in the series of aromatic and vinyl halides [$C(sp^2)-Hal$]. A higher rate of the bromine atom exchange in aromatic nucleus compared with that in the aliphatic side chain has been demonstrated for bromophenethyl bromide.[15] It has also been shown that the bromine atom in the aromatic nucleus exchanges at nearly the same rate as the iodine atom in an aliphatic chain.[57]



Finally, halogenophilic processes are becoming quite common for halogenated acetylenes [$C(sp)-Hal$]. Even the 'halogenophilicity' of thiolate ions is enough to promote the halogenophilic reaction in alkynyl bromides and iodides. No wonder that the halogenophilic mechanism was identified in the chemistry of acetylenes much earlier than in other classes of organic compounds.[14,21,45,46,58]

The carbanion forming in the halogenophilic reaction may also be stabilized by electron-withdrawing substituents in the molecule of organic halide. α-Halogen-substituted ketones,[26,27,59–66] sulfones,[20,27,36,67,68] nitriles,[61,62,73,74] esters,[18,27,62,65,66,69–72] and nitro [74,75] and nitroso compounds [76] are typical substrates of halogenophilic reactions with the participation of carbanions, thiolates or P^{III}-nucleophiles. It has been shown that introduction of electron-withdrawing groups into the α-position relative to the halogen atom increases the rate of halogenophilic reaction of polyhalogenated alkanes with carbanions.[41] If a strong electron-withdrawing substituent is present in the aromatic ring, even benzyl bromides [18,35,77] and (bromomethyl)furans [78,79] can react with dialkyl phosphite anions by the halogenophilic mechanism.

The introduction of more than one electron-withdrawing group further increases the electrophilicity of the halogen atom. For example, bromotrinitromethane [$pK_{a\,(NO_2)_3CH} < -1$] is a very strong 'positive' halogen donor even towards weak nucleophiles such as alkenes.[27]



Cyclic bromonium ions are no less active donors of cationoid bromine in the reactions with alkenes.[80,81]

Electron-withdrawing substituents in aryl halides exert a similar activating effect, and in this case, it can be characterized quantitatively. The rate constants of halogenophilic reactions correlate with the Hammett σ-constants,

‡ The formation of products such as $(RO)_2P(O)F$ in reactions of bromofluoromethanes or perfluoarenes with P-nucleophiles may be explained by decomposition of quasiphosphonium intermediates with intramolecular nucleophilic migration of the fluoride ion from the carbon atom to phosphorus. In other words, the formation of $(RO)_2P(O)F$ is a 'fluorophilic' process, but not a 'fluorophilic' one.

the obtained dependences being characterized by positive coefficients ρ.

ρ	Ref.	ρ	Ref.
4.0	82	4.2	85
4.1	83	2.7	86
2	84	4.3	87

All of these values (except for the last one) have been obtained for halogen–metal exchange reactions of *para*-substituted aryl bromides under the action of organomagnesium and organolithium compounds. The ρ values for nucleophilic aromatic substitution reactions are also positive, but, as a rule, they are considerably greater in magnitude,§ for example, the reactions of *para*-substituted chlorobenzenes with sodium methoxide have $\rho = 6.6$.[88] In the halogen–magnesium exchange reactions of bromobenzenes on treatment with $Pr^iMgCl \cdot LiCl$, the influence of electron-withdrawing substituents increases in the order *para* < *meta* < *ortho* and, therefore, it is generally caused by the inductive effect. Meanwhile, the $\log k_{rel}$ value of the exchange reaction obeys a negative linear correlation with the basicity of the corresponding aryllithium derivatives (expressed by pK_a value) with a slope close to unity (0.8).[86]

2-Bromothiophene and 2-bromothiazole should be mentioned among hetaryl bromides.[89] They are 10^5 and 10^7 times, respectively, more reactive in the halogen–magnesium exchange than bromobenzene.[90]

An especially high reactivity in halogenophilic reactions is exhibited by polyhalogenated organic compounds including polyfluoroalkyl halides (R_fHal) (*cf.* pK_a values of the corresponding hydrocarbons given above). Polyhalogenated derivatives are also most practically important donors of the cationoid halogen. It was for polyfluoroalkyl halides that the possibility of attack at the halogen atom of nucleophiles of various classes was demonstrated (however, see the beginning of Section III).[4, 10, 38, 41, 91–102] It should be noted that in the gas phase, the halogenophilic attack is also the main pathway of reactions of tetrachloro-,[103] trifluorochloro- and trifluorobromo-methanes with carbanions and other nucleophiles including HO^-, while no S_N2C processes occur at all.[104] The preference of the halogenophilic attack over the usual attack at the carbon atom (S_N2C) in tetrahalomethanes is supported by the results of quantum chemical calculations.[6, 105, 106]

Polyhalogenated alkanes, first of all tetrahalomethanes, are used as specific halogenating agents for the preparation of poorly accessible halogenated derivatives from the corresponding carbanions.[4, 13, 27] The compounds of $HalCR_2CR_2Lg$ type where Lg is the leaving group find a similar application.[107] This is due to the ease of E2Hal-reactions (see the end of Section II). The interaction of perfluorohalomethanes [108, 109] (and also bromoperfluoroalkenes [110] and bromoperfluoroarenes [111]) with $(Et_2N)_3P$ can be used to generate the corresponding fluorocarbanions under mild conditions. The reaction is carried out in the presence of an electrophilic reagent (as a rule, R_3ECl, E = Si, Ge, Sn), which immediately traps the carbanion being formed.

A widely used method of preparation of chlorinated derivatives from alcohols is based on the halogenophilic reaction of CCl_4 with PPh_3.[4, 12, 27]

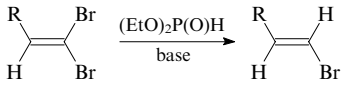
$$Ph_3P + CCl_4 \longrightarrow [Ph_3\overset{+}{P}Cl\cdots\overset{-}{C}Cl_3] \xrightarrow[-CHCl_3]{ROH} \longrightarrow [Ph_3POR]^+Cl^- \longrightarrow RCl + Ph_3PO$$

The equally important Todd–Atherton reaction also includes, as the first step, the halogenophilic reaction of CCl_4 (or another source of Hal^+) with a nucleophilic derivative of trivalent phosphorus.[42, 112]

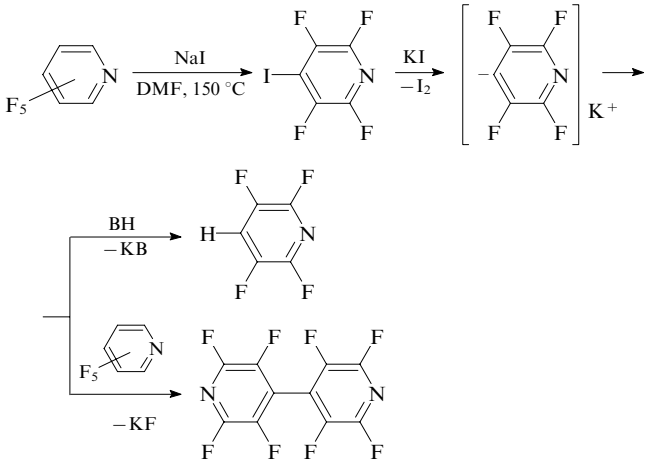
$$R_2\bar{P}(O) + CCl_4 \longrightarrow [R_2P(O)Cl + \bar{C}Cl_3] \xrightarrow[-CHCl_3,\ -Cl^-]{NuH} R_2P(O)Nu,$$

Nu = R′OH, R'_2NH, R′SH.

In the case of the most active halogenophiles such as dialkyl phosphite anions or carbanions, the presence of even two halogen atoms (Hal = Br, I) at the same carbon atom is enough for the halogenophilic reaction to take place.[41, 42, 61] The dehalogenation of *gem*-dibromoalkenes under the action of diethyl phosphite anion should be particularly noted. This gives *trans*-bromoalkenes in high yields and with high stereoselectivity:[113, 114]



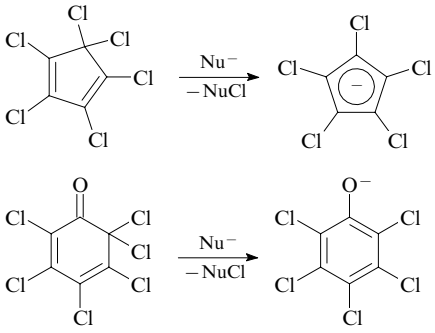
Polyfluoroaryl bromides and iodides are also good substrates of halogenophilic reactions.[32, 110, 111, 115, 116] Experimental evidence was obtained for the halogenophilic mechanism in the dehalogenation of iodo- and bromopentafluorobenzenes under the action of enolate ions (see Scheme 5 in Section III),[87] sodium hydroxymethanesulfinate (rongalite) and related sulfur(II) and sulfur(III) anions [117] and also in the dehalogenation of 4-iodotetrafluoropyridine under the action of iodide ion In the latter case, the intermediate aryl carbanion may be trapped by pentafluoropyridine to give perfluoro-4,4′-bipyridine.[118]



A special case is stabilization of the carbanion centre formed in the halogenophilic reaction upon its inclusion in

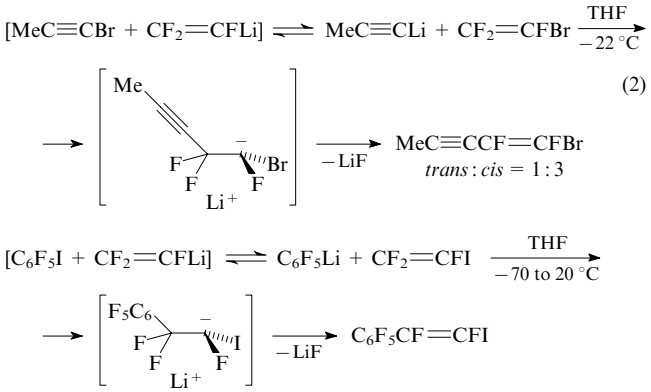
§ The weaker (mainly inductive) effect of electron-withdrawing substituents in S_N2Hal reactions compared with S_N2Ar is generally reasonable. The direct conjugation between the developing carbanion and the substituent in the aromatic ring is absent in S_N2Hal reactions but is present in the anionic σ-complex in S_N2Ar reactions.

the aromatic π-system. For example, the cationoid elimination of chlorine converts hexachlorocyclopentadiene to the pentachlorocyclopentadienyl anion [26,27] and converts hexachlorocyclohexa-2,4-dienone [37] to the pentachlorophenoxide ion. The above-mentioned and related compounds show high reactivity in halogenophilic reactions and, like polyhalogenated alkanes, they find wide application as electrophilic halogenating agents.



In many cases, the crucial factor determining the halogenophilic route for a particular reaction is not only the ease of the route itself but also hindrances to other routes of the process. The high susceptibility of perhaloalkanes to halogenophilic reactions is to a large extent connected with the fact that in such compounds both the usual S_N2 and S_N1 nucleophilic substitution at the carbon atom is hampered. Yet another example is the reaction of the $(RO)_2PO^-$ anions with substituted benzyl chlorides, the mechanism of which switches from 'carbophilic' (S_N2) with the primary chloride 4-$O_2NC_6H_4CH_2Cl$ to halogenophilic with the secondary chloride 4-$O_2NC_6H_4CHMeCl$.[35] A similar feature has been found for the reactions of α-chlorocarboxylic esters with carbonylmetallate anions.[66]

Quite the opposite situation is also possible. A compound may be a potentially active substrate of halogenophilic reaction but react with the nucleophile *via* another more advantageous route. For example, trifluorovinyl halides should be no less active in halogenophilic processes than the corresponding polyfluoroalkyl halides (for $CF_2{=}CFH$ p$K_a \approx 25$). At the same time, the double bond in such compounds is activated towards a nucleophilic attack, so the nucleophilic replacement of the fluoride ion following the addition–elimination (Ad_NE) mechanism is also possible. Unlike halogenophilic reaction, the latter is irreversible.[17] In the reactions with such good 'halogenophiles' as organolithium compounds, bromotrifluoroethylene [119] and even iodotrifluoroethylene [120] form the products of nucleophilic substitution of the fluoride ion.

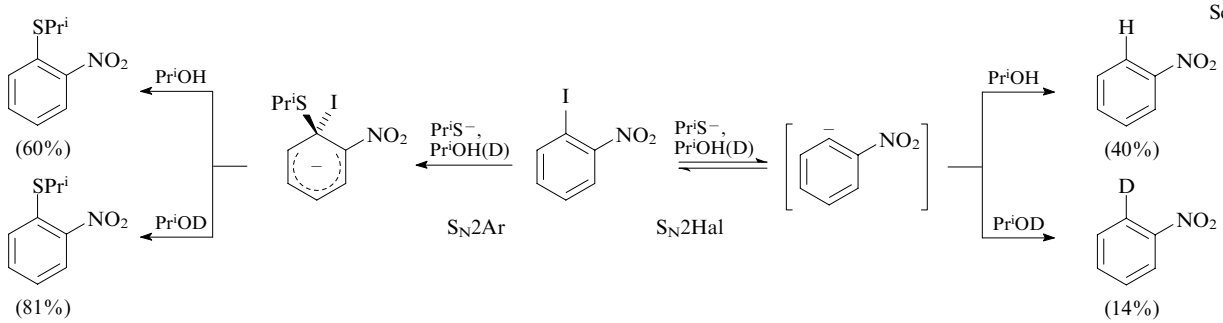


As another example, mention should be made of the reaction of bromotrifluoroethylene with P-nucleophiles. In the absence of electrophile that traps the vinyl carbanion, the reaction of $CF_2{=}CFBr$ with $(R_2N)_2P(O)R$ results in $(R_2N)_2P(O)CF{=}CFBr$, the products of fluorine replacement.[121] Note that this reaction proceeds under much more drastic conditions than the halogenophilic reaction of $CF_2{=}CFBr$ with $(R_2N)_3P$ in the presence of Me_3SiCl.[110]

In many reactions of activated aryl and vinyl halides (Hal = Br, I and sometimes Cl) with soft nucleophiles (see, *e.g.*, Refs 20, 87, 115, 122–128) and also Scheme 5 in Section III), the halogenophilic reaction route is realized as a side process competing with the nucleophilic aromatic (S_NAr) or vinyl (Ad_NE) substitution. Often in case of polybrominated benzenes, the halogenophilic reduction becomes the main reaction route, for example, in the reactions with carbanions.[9,122,123] A similar competition of halogenophilic (S_N2Hal) and conventional S_N2C-processes is observed in the reactions of activated alkyl halides with good halogenophiles, first of all with P-nucleophiles.[18,35,36,61,64,72,77]

There are particularly many examples of competition of S_N2Hal and S_N2Ar (or in the case of vinyl halides, Ad_NE) processes in the reactions of sulfur nucleophiles.[17,125–127] One such reaction, namely, the reaction of *o*-halonitrobenzenes with thiolate ions, has been studied in detail by Scorrano and co-workers.[124] Based on the kinetic data and the experimental results obtained in partially deuterated isopropyl alcohol (Scheme 2), it has been shown that dehalogenation of *o*-iodonitrobenzene actually includes the attack of the thiolate ion at the iodine atom. It is notable that in the reaction with thiolates, both *o*-bromonitrobenzene and *p*-iodonitrobenzene [129] form only the products of S_N2Ar nucleophilic aromatic substitution. Similar dichotomic behaviour of *o*- and *p*-iodonitobenzenes is observed in reactions with MeONa in a DMSO–MeOH mixture (9 : 1)

Scheme 2

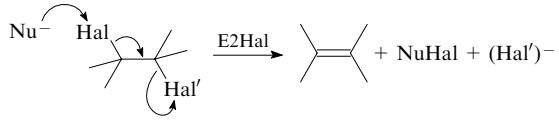


where the dimsyl anion [MeS(O)$\bar{C}$H$_2$] acts as the 'halogenophile'.[116]

Nevertheless, in some cases, even pronounced activation of aryl halide towards nucleophilic aromatic substitution does not prevent the halogenophilic reaction. Thus, 2,4,6-trinitroiodobenzene is easily (at 20 °C) dehalogenated under the action of the iodide ion.[130] It seems that the reaction of picryl iodide with the R_3Sn^- anion also follows a halogenophilic mechanism.[131]

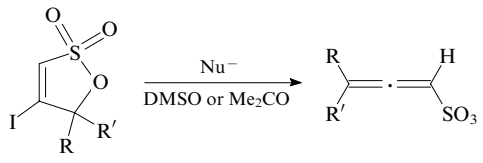
Finally, the pathway of the reaction of a nucleophile with organic halide (S_N2C or S_N2Hal) may be determined by the nature of the solvent. In protic solvents, the C-nucleophilicity of anions is dramatically decreased and, what is more important, carbanions that are formed in halogenophilic reaction can be protonated. If the reaction is reversible, this shifts the equilibrium towards the products, *i.e.*, RH and NuHal. This is a typical situation for reactions of alkynyl halides (though it is also observed for alkenyl halides[125]) where nucleophilic substitution at the carbon atom follows the Ad_NE mechanism in dipolar aprotic solvent, whereas in protic solvents, halogenophilic hydrodehalogenation takes place under the action of the same nucleophile.[14]

Concerted β-dehalogenation (E2Hal) represents a separate and a fairly abundant class of halogenophilic processes.[27, 30, 59, 107, 128, 132–136]



However, it should be mentioned that the assignment of many such reactions to the halogenophilic type is arbitrary and rather reflects the final outcome than the true mechanism of the process.

The nucleophilic attack at the halogen atom in this case is considerably facilitated by concerted elimination of the leaving group from the β-position. Unsurprisingly, β-dehalogenation can be induced by all kinds of nucleophiles including RO^-, Cl^-, R_3N for which 'pure' S_N2Hal-processes are not typical or even impossible. Halogenophilic ring-opening in β-iodo-α,β-unsaturated sultones may serve as a striking example demonstrating the ease of E2Hal reactions. The reaction proceeds under the action of various nucleophiles, even bromide and cyanide ions, in spite of the good double bond activation towards nucleophilic substitution of the iodine atom by the Ad_NE-mechanism.[128]



$Nu^- = SCN^-, I^-, CN^-, AcS^-, Br^-$.

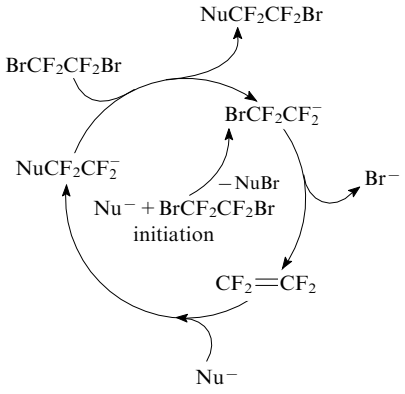
The *anti*-stereospecificity of E2Hal-elimination, quite expected for a concerted process, has been repeatedly demonstrated.[27, 132, 134, 137–139] In the case of incomplete stereospecificity of dehalogenation, the halogenophilic version of the E1cB mechanism (cB is conjugated base) is considered.[134, 137] Note that the reductive dehalogenation under the action of single-electron donors, *e.g.* aromatic radical anions, follows a different mechanism, namely, the outer-sphere single electron transfer (SET). Unlike E2Hal reactions, the SET dehalogenation is non-stereospecific.[30]

III. The influence of the nucleophile in halogenophilic reactions. Anionic chain processes

The influence of the nature of the nucleophile is still the least studied aspect of halogenophilic reactions. A general trend is higher reactivity of soft, easily polarizable nucleophiles. This follows from the principle of hard and soft acids and bases (HSAB) and simple MO approach (see Fig. 1) and is generally confirmed in practice. However, the amount of available quantitative data still does not suffice for constructing a nucleophilicity scale relative to the halogen atom.

The range of nucleophiles that are assumed to attack the halogen atom is rather wide (especially if concerted E2Hal processes are also included) and comprises virtually all of the main types of nucleophilic reagents. However, it is necessary to note that the reports concerning halogenophilic reactions for hard nucleophiles such as phenoxides and amines and polyhalogenated alkanes[10, 92–95, 99, 140] refer only to the presumptive step of initiation of the anionic chain mechanism of nucleophilic substitution, while the halogenophilic agent in the propagation step is a carbanion (Scheme 3). Moreover, owing to the presence of a good leaving group in the β-position, the halogenophilic chain initiation is probably an E2Hal rather than an S_N2Hal process. The latter assumption is also confirmed by calculation results (SCIPCM-B3LYP method), which show that $[ClCF_2CFCl]^-$ type anions are actually complexes of the chloride ion with $CF_2{=}CFCl$.[141] It should be noted that Bunnett was the first to resort to the carbanion chain mechanism in order to explain the formation of *o*-iodophenylphosphonate in the reaction of *o*-diiodobenzenes with the diethyl phosphite anion.[142]

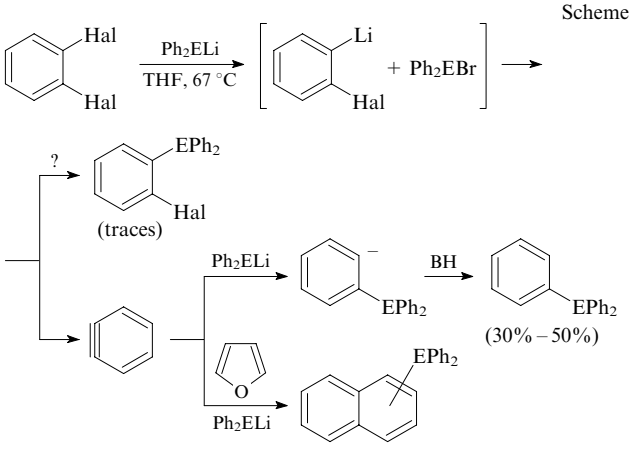
Scheme 3



$Nu^- = RO^-, R_2N^-$ (R_2NH).

A non-chain version of this mechanism is also known. This is exemplified by the reaction of 1,2-dihalobenzenes with Ph_2ELi (E = P, As)[135, 143] (Scheme 4) and $(EtO)_2PO^-$ (see Refs 27 and 142).

Scheme 4

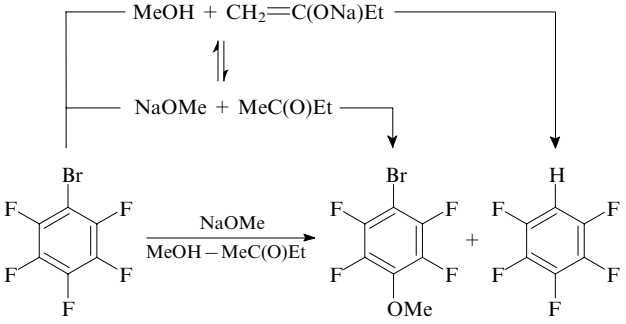


Hal = Br, I; E = P, As.

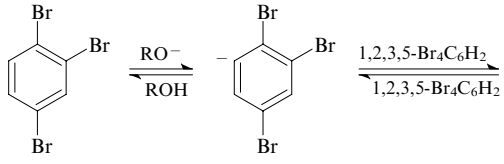
A similar mechanism but involving carbenoid intermediates has been accepted for the reactions of RLi with *gem*-dihalides,[144] and has also been suggested for the reaction of polyhalogenated methanes with phosphines[91] and thiolates,[10] although in the latter case, the $S_{RN}1$ mechanism is also possible.[140]

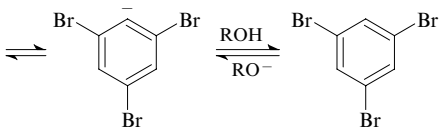
In most cases, dehalogenation of organic compounds under the action of alkoxides (or other strong bases that are also hard nucleophiles) is related to the formation of carbanions under these conditions.[62, 126] A source of carbanions may be represented by the solvent,[10, 126] by the starting substrate, *e.g.*, pentabromotoluene ($pK_a \approx 16$),[123] or some undefined impurities. It is the carbanions that act as true reagents of halogenophilic reactions. For example, hydrodebromination of bromopolyfluorobenzenes in the NaOMe – MeOH – MeC(O)Et system occurs under the action of the enolate ion forming in the system (Scheme 5).[87] Often, dimethyl sulfoxide serves as the 'dehalogenating solvent' (see papers[9, 116, 122] and references cited therein).

Scheme 5

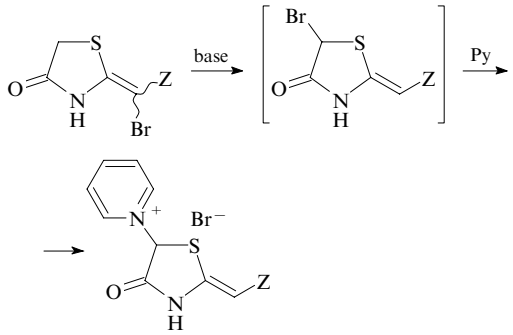


A classical example of a halogenophilic reaction is the so-called halogen dance, which is the rearrangement of 1,2,4-tribromobenzene under the action of strong bases. Its mechanism is represented by a chain sequence of halogenophilic reactions of aryl carbanions with participation of tetrabromobenzene as a chain transfer agent.[9, 145]





Similar rearrangements are observed for many haloaromatic and heterocyclic compounds including tetra- and pentachlorobenzenes[40] and polybromothiophenes,[146, 147] and they are used in organic synthesis.[11] Disproportionation of halomethyl sulfones (to methyl- and dihalomethyl sulfones)[68] and diethyl dibromomalonate[71] and the halogen exchange in perhaloalkanes[98] under the action of bases occur by a similar mechanism. The reaction of 2-(bromoalkylidene)thiazolidinones with pyridine (Py) in which the corresponding 5-substituted pyridinium salts are formed may be classified as the same type of rearrangement.[62, 148]

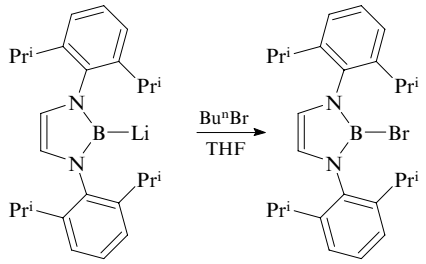


Z = CN, C(O)NHR, CO_2Et, Bz.

In the majority of cases, halogenophilic reactions are induced by only three large groups of nucleophiles, namely, thiolates (RS^-), derivatives of trivalent phosphorus and carbanions including organolithium and organomagnesium compounds. The most active among them are simple AlkLi, especially Bu^{t}Li, which enter into halogenophilic reactions with non-activated aryl, vinyl and alkyl halides. The halogenophilic pathway of the reaction of RLi with alkyl halides demonstrates a high relative halogenophilicity of RLi, *i.e.*, the ability to attack the halogen atom relative to the ability to attack carbon [$k(S_N2Hal)/k(S_N2C)$]. A very high relative halogenophilicity is also inherent in Te-nucleophiles.[60, 149] Indeed, dialkyl tellurides react at the halogen atom with phenacyl bromides and even with phenacyl chlorides.[65]

Certain element- and metal-centred anions are also highly halogenophilic. The most active of them such as R_3Si^-, R_3Sn^-, R_2As^- and $[CpFe(CO)_2]^-$ (Cp = η^5-C_5H_5) approach RLi as regards their reactivity and they undergo halogenophilic reactions with non-activated aryl and vinyl halides.[47, 50, 83, 145, 150–153] Moreover, R_3SiLi reacts by the halogenophilic mechanism even with benzyl bromide [see reaction (6) in Section V], although the reaction with benzyl chloride follows the usual S_N2C mechanism.[52] The preference of the S_N2Hal mechanism over the S_N2C mechanism for the reactions of silyl anions with alkyl bromides is also confirmed by the calculation data.[50] Evidently, the record-high relative halogenophilicity is inherent in the recently obtained boryl anions that can be regarded as boron analogues of heterocyclic carbenes. Thus, boryllithium attacks at the halogen atom not only benzyl bromide but also n-butyl bromide. Only in the case of n-butyl chloride, is the attack directed at the carbon atom.[51, 154] A higher halogenophilicity of boryllithium in comparison with meth-

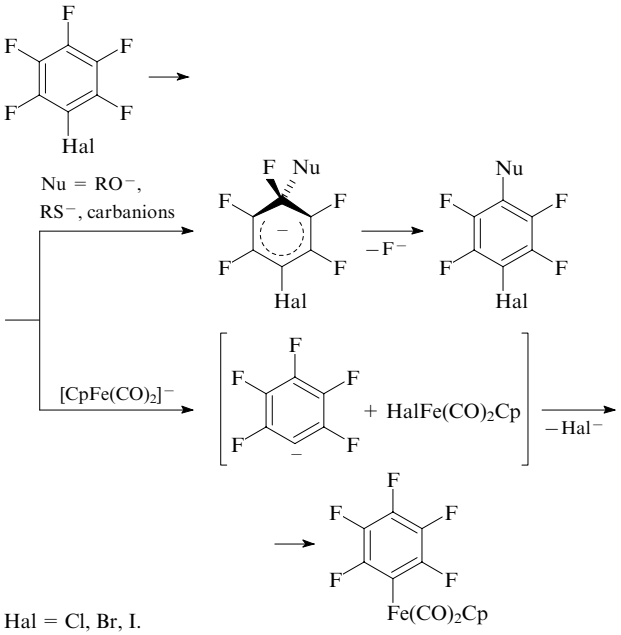
yllithium is also confirmed by quantum chemical calculations.[154]



Owing to high halogenophilicity, Se-, Te-, P- and Sn-nucleophiles and also transition metal carbonyl anions (carbonylmetallates) are used in organic synthesis as selective dehalogenating agents.[60, 65, 113, 114, 136, 149, 155–157]

Carbonylmetallates surpass both thiolates and stabilized carbanions and probably many of P-nucleophiles as regards their relative halogenophilicity. For example, bromotrifluoroethylene reacts with carbonyl metallates solely by halogenophilic mechanism,[158] whereas its reactions with carbanions [see reaction (2)] and phosphinodiamidites[121] proceed by the 'carbophilic' Ad_NE mechanism. Quite the same relation is typical of reactions with pentafluorochlorobenzene (Scheme 6),[159–161] and also with (α-halobenzylidene)malonates and -malononitriles $PhCHal{=}CZ_2$ (Hal = Br, I; Z = CN, CO_2Et).[162, 163] It should be noted that in the case of bromotrifluoroethylene and pentafluorochlorobenzene, the change of the mechanism (from Ad_NE to halogenophilic) leads to the change of reaction regioselectivity, *i.e.*, instead of the fluorine atom, a heavier halogen atom is replaced.[158–160, 164]

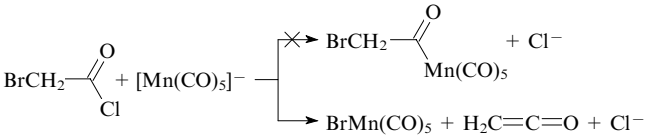
Scheme 6



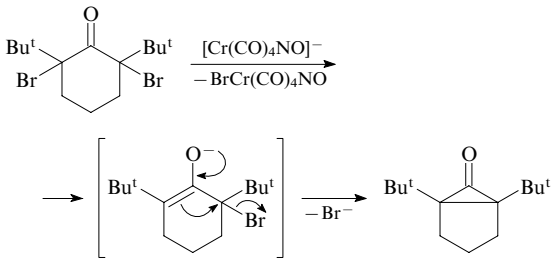
Hal = Cl, Br, I.

The higher halogenophilicity of carbonyl metallates compared with carbanions is also manifested in the pathway of their reaction with 2-[bromo(cyano)methylidene]thiazolidin-4-one. The $[Re(CO)_5]^-$ anion [for $HRe(CO)_5$, $pK_a = 21.1$ (Ref. 165)] reacts at the bromine atom [reaction (10) in Section V], despite the fairly high acidity of the lactam group ($pK_a \sim 17–18$). For comparison, the 9-methylfluorene carbanion having a similar basicity ($pK_a = 22.3$)[49] reacts with the same substrate exclusively by protophilic pathway, by deprotonating the NH group.[166]

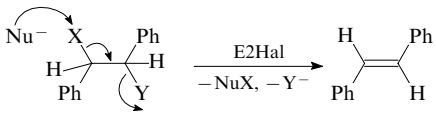
In reactions of carbonylmetallates with the activated alkyl bromides RCHBrZ, the halogenophilic attack competes with common nucleophilic S_N2C substitution;[66, 72] this makes them similar to the most halogenophilic derivatives of tellurium[65] and phosphorus.[61] For example, in the reaction with 2-bromoacetyl chloride, the $[Mn(CO)_5]^-$ ion attacks only at the bromine atom, despite the presence of highly electrophilic C(O)Cl group in the molecule.[167]



Debromination of α,α-dibromo ketones under the action of carbonylmetallates occurs almost instantaneously even at −100 °C and is used for the *in situ* generation of unstable cyclopropanones, which are difficult to obtain by other methods.[156, 157]



Until now, there are little kinetic data characterizing the relative reactivities of various nucleophiles and their halogenophilicity that could become the basis for constructing the nucleophilicity scale relative to the halogen atom.



X = Y = Br

Nu	I^-	Ph_3P	Br^-
k_{rel} (DMF)	70	23	1

X = I, Y = Cl

Nu	I^-	Br^-	Cl^-
k_{rel} (DMF)	7	1.2	1

X = I, Y = Cl

Nu	Ph_3P	$SeCN^-$	I^-	CN^-	pip	SCN^-	Br^-	Cl^-
k_{rel} (MeOH)	4000	400	170	100	17	14	6	1

pip is piperidine.

Such investigations have been carried out only for E2Hal but not for S_N2Hal processes, furthermore, for the dehalogenation reactions (E2Hal) of rather active vicinal dihalides.[133, 138, 139] This predetermined the range of the nucleophiles being studied, which covers low-activity anions and neutral compounds that normally do not participate in S_N2Hal reactions but neglects the strong halogenophiles such as thiolates or carbanions.

The obtained halogenophilicity series differs from the known Swain–Scott series (for S_N2C reaction),[48, 168] first of all, by higher reactivity of 'heavy' nucleophiles, *i.e.*, com-

pounds of elements of the third and subsequent periods of the periodic table. It is significant that even in a polar aprotic solvent, the halogenophilicity of halide ions decreases in the order I > Br > Cl.[133]

Recently, it was shown that the nucleophilicity of enamines in halogenophilic reaction with hexachlorocyclohexa-2,4-dienone and other similar chlorinating agents obeys the Mayr equation, $\log k = s_N(N+E)$, where k is second order rate constant, N and E are the nucleophilicity and electrophilicity parameters, s_N is the sensitivity factor of nucleophile,[169] *i.e.*, it may be described by the same parameters N and s_N as the nucleophilicity in carbophilic reactions with various π-acceptors.[37] It is noteworthy that the halogenophilicity of carbonylmetallates in reactions with activated vinyl halides changes approximately in the same proportion as their nucleophilicity in Ad_NE reactions, despite the fundamentally different reaction centres participating in these reactions (the carbon atom and the halogen atom).[162, 170] For both processes (Ad_NE and S_N2Hal), the nucleophilicity of carbonylmetallates varies in a much wider range, $[Mn(CO)_5]^-$ $[(1-3)\times 10^2)]$ > $[CpW(CO)_3]^-$ [5–10] > $[CpMo(CO)_3]^-$ (1), than in the aliphatic S_N2 substitution reactions.

IV. Evolving concepts of the halogen–metal exchange reaction mechanism

The halogen–metal exchange reaction is the most numerous and practically important class of halogenophilic reactions. After having been discovered independently by G Wittig[171] and H Gilman[172] in 1938, this reaction has rapidly found its well-deserved place in a wealth of synthetic methods of organometallic chemistry as the second most important one used to prepare RLi compounds, right after the direct interaction of RHal with metal.[15, 23, 24, 33, 43, 44] This method is still being actively developed. Quite recently, in the 21st century, a halogen–metal exchange procedure with participation of organomagnesium compounds was developed.[19, 34, 173–176] Using zincates, it is possible to carry out the exchange reaction at room temperature without affecting many functional groups.[177–179] Performing the reaction in flow type (micro)reactors[178, 180] and asymmetric version of the reaction[181–183] are being investigated.

Meanwhile, the views on the mechanism of the halogen–metal exchange remained indistinct and contradictory till the 1990s. There are several objective challenges in the investigation of the mechanism of halogen–metal exchange (they are mentioned below) but it seems that the human factor has also played a certain role. The rapid progress in the demonstration of the synthetic potential of the reaction is mainly related to the studies of Gilman's group, which played the crucial role in the initial stage of investigation of this reaction (before the 1960s). However, Gilman was a chemist of classical empirical mentality, so he did not set himself the task of investigating the reaction mechanism, at least, not in the modern interpretation of this term.[184] Studies of the reaction mechanism started only in the 1960s with investigation of the reaction equilibrium and then kinetics.

The in-principle reversibility of halogen–metal exchange was disclosed by Gilman soon after its discovery.[23, 53] The position of the equilibrium

$$RLi + R'Hal \rightleftharpoons RHal + R'Li$$

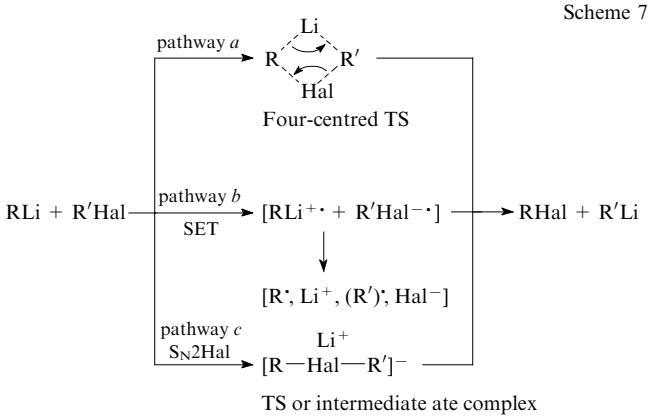
is determined by the relative stabilities of the corresponding R^- and $(R')^-$ carbanions.[185, 186] This was used by Cram for the development of the first universal scale of CH-acidity of hydrocarbons (MSAD scale).[49] At the same time, if the difference between the electronegativities of R and R′ is rather large, *e.g.*, as in the reaction of AlkLi with ArHal, the exchange becomes almost irreversible.

The kinetics of halogen–lithium exchange was studied by the example of reactions of ArLi + Ar′Br in diethyl ether[82, 85] and Bu^nLi + ArBr in hexane,[84] which are slow even at room temperature. The reactions followed first-order kinetics with respect to each reactant; they slowed down in the presence of lithium salts and accelerated in the presence of lithium-solvating agents. The relatively large negative activation entropy ($\Delta S^{\neq}$ from −23 to −26 e.u.) and accelerating influence of electron-withdrawing substituents in ArBr well-correlated with the Hammett constants attested to an associative mechanism of the reaction with negative charge accumulation on the reaction centre in the transition state (TS). Nevertheless, the results of these first kinetic studies did not allow definite conclusions about the mechanism of this process or the structure of transition state of the halogen–metal exchange.

The interpretation of kinetic data is also complicated by the uncertain physical state of RLi and its possible change during the reaction. Organolithium compounds are known to be associated in solutions, the association degree depending on the nature of the R moiety in RLi, the temperature, the solution concentration and the basicity of the solvent.

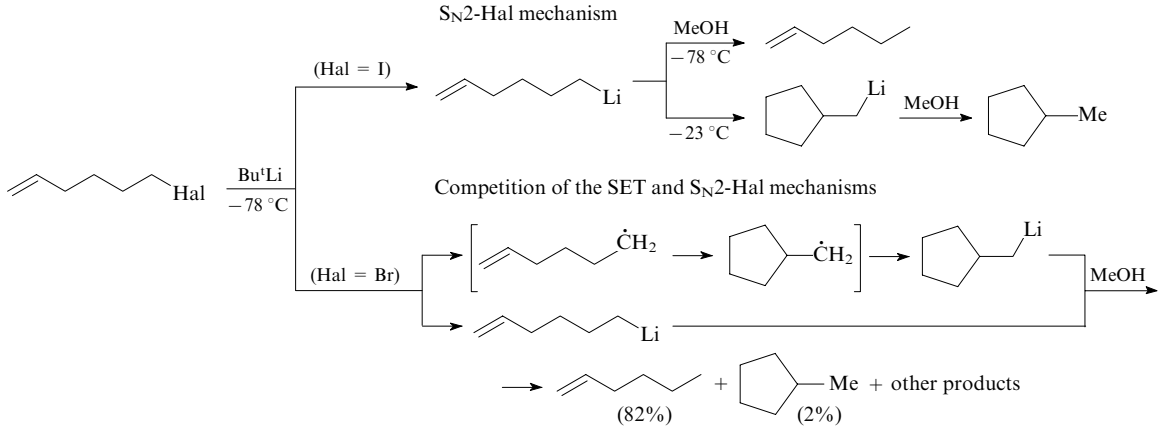
Originally (in the 1950s–1970s), a concerted mechanism involving a four-centred transition state was the most popular hypothesis about the mechanism of halogen–metal exchange (Scheme 7, pathway *a*).[33, 85, 186] This consideration has explained the simultaneous bond cleavage and formation of two new bonds (C—Hal and C—Li), and it placed the halogen–metal exchange reaction in the general series of organometallic electrophilic exchange reactions (S_E2),¶ which were actively studied during that period. Note that the mechanism with the four-centred transition state has always been regarded as some kind of idealized scheme that could give only a general idea about the reaction, it has never been thought to be a strictly proven mechanism.

Scheme 7



¶ When halogen–metal exchange is considered as electrophilic substitution at the carbon atom, metal acts as elecrophile and halogen acts as electrofuge.

Scheme 8



The halogen–metal exchange reaction, especially with alkyl halides, is often accompanied by side coupling (the Würtz reaction) and R$^{\bullet}$ and (R′)$^{\bullet}$ radical disproportionation processes, which is another factor that complicates investigation of the reaction mechanism. In the 1970s, on the tide of general revision of mechanisms of heterolytic reactions within the bounds of single electron transfer concept, an attempt was made to interpret all the processes taking place in the system RLi + R′Hal within a common mechanism initiated by the SET step.[16, 25, 187–189] Both a simple SET mechanism with radical redistribution within the solvent cage (Scheme 7, pathway *b*) and a chain process with participation of free radicals have been proposed.[190]

Initiation:

$$RLi + R'Hal \xrightarrow{SET} [RLi^{+\bullet} + R'Hal^{-\bullet}] \longrightarrow [R^{\bullet}, Li^{+}, (R')^{\bullet}, Hal^{-}].$$

Chain propagation:

$$R^{\bullet} + R'Hal \longrightarrow (R')^{\bullet} + RHal,$$

$$(R')^{\bullet} + RLi \longrightarrow R^{\bullet} + R'Li.$$

Chain termination:

$$(R')^{\bullet} + R^{\bullet} \longrightarrow \text{alkanes, alkenes.}$$

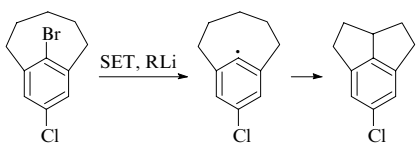
It should be noted that there were some reasons for such revision. Thus, the detection of EPR signals[190] and chemically induced dynamic nuclear polarization (CIDNP) effects[55, 188, 191, 192] in the reactions of AlkHal with AlkLi served as evidence for the SET mechanism, as it unambiguously indicated the formation of radical species in these systems. However, the CIDNP effects have never been observed in the starting or formed AlkLi. Also, no CIDNP was found in the 'pure' exchange reaction between Bu^{t}Li and Bu^{n}I carried out at −70 °C.[187, 188] In the latter system, CIDNP was observed only at elevated temperatures with simultaneous appearance of side products of radical disproportionation and recombination. Finally, even detection of significant CINDP effects in the products does not imply that the whole reaction follows a radical mechanism.

Subsequently (in the 1970s–1990s), in order to finally elucidate the role of SET in the reactions of AlkHal with AlkLi (Bu^{t}Li), several research groups (including Ashby's and Bailey's groups) used the so-called radical clock method based on the use of specially constructed alkyl halides, *e.g.*, 6-bromohexene, whose alkyl radicals can undergo a very fast intramolecular rearrangement (Scheme 8).[16, 54, 189] However, the interpretation of the results of such experiments is faced with a wide range of difficulties and contradictions.[16, 193, 194] A fundamental condition is the specificity of this rearrangement for exactly a radical but not an anion. Unfortunately, the last condition is not always satisfied and often the corresponding organolithium compound may undergo a similar rearrangement, though it is slower.[195–197] This prejudices some results obtained by this method. There are also other difficulties in proving the SET mechanism, *e.g.*, the influence of impurities or (in case of R_3SnLi) the 'age' of reactant solutions on the reaction outcome.

Eventually, the researchers succeeded in demonstrating that some part of the products of halogen–metal exchange in reactions of Bu^{t}Li with AlkBr and *sec*-AlkI could be formed *via* free radical intermediates (see Scheme 8),[56] *i.e.*, the SET mechanism has been proven to some extent.[54, 56] However, in fast exchange reactions between primary AlkI and Bu^{t} Li at low temperature, no reliable evidence for the SET were found.[54, 198] The same is true for the halogen–metal exchange reactions with participation of ArHal for which the SET mechanism has never been regarded as a serious alternative and the results of various tests on the participation of free radicals have always led to negative† results.[57, 84, 196, 200] It should also be noted that the stereochemical outcome of halogen–metal exchange for alkyl and alkenyl halides is most often retention of the configuration at the carbon atom.[16, 25, 144, 187, 201–203]

The assumption that halogen–metal exchange occurs upon nucleophilic attack of the carbanion (from RLi) at the halogen atom ('halogenophilic' attack, Scheme 7 pathway *c*) appeared almost immediately[29] after the discovery of the reaction itself and later it was repeatedly expressed in the literature, but it took many years to obtain the experimental proof and acceptance of this hypothesis. In 1958, Wittig and Schöllkopf[28] suggested that due to the expansion of the halogen electron shell up to a decet (10 e), the nucleophilic attack at the halogen atom may lead to the formation of an intermediate. Wittig has proposed the name 'ate-complex' for such intermediate by analogy with borates and metallates.

† An exception is provided by reactions of bromo[5]metacyclophanes in which nucleophilic attack at the bromine atom is sterically hindered.[199]



The first experimental proof of the formation of ate-complexes in reaction of ArLi with Ar′I was obtained by Reich only in 1985;[204] obviously, ate-complexes were observed earlier by a number of researchers though they were not identified then. As early as 1969, Johncock[205] suggested the formation of some kind of associate of perfluoroalkyllithium with perfluoroalkyl iodide in order to explain a lower reactivity of the $Bu^nLi - R_fI$ system at temperatures below -90 °C. Subsequently, the formation of ate-complexes $[R_fIR_f]Li$ was confirmed by other researchers.[206, 207] Original communication of Reich *et al.*[204] was based on similar observations but they were already supported by quantitative data. Thus, a decrease in the rate of the reaction of PhLi with Bu^nI and other electrophiles in the presence of iodobenzene was observed. The effect is most visible in the presence of hexamethylphosphoric triamide (HMPA) when the addition of one equivalent of PhI reduced the rate of the reaction of PhLi with Bu^nI by a factor of ten. The dependence of the reaction rate on the concentration of iodobenzene was used to determine the stoichiometry (1 : 1) of the PhLi – PhI complex.[204] In later studies, the formation of the $[PhIPh]^-$ ate-complex was directly proven by low-temperature NMR spectroscopy.[208, 209] Simultaneously, Farnham and Calabrese[206] demonstrated the formation of perfluoroalkyl and perfluoroaryl iodine ate-complexes and isolated for the first time the ate-complex $[C_6F_5IC_6F_5]^-[Li \cdot TMEDA]^+$ (TMEDA is tetramethylethylenediamine) in the crystalline state. According to X-ray diffractions data, the ate-complex $[C_6F_5IC_6F_5]^-$ has an almost linear structure (the C–I–C angle is 174°).

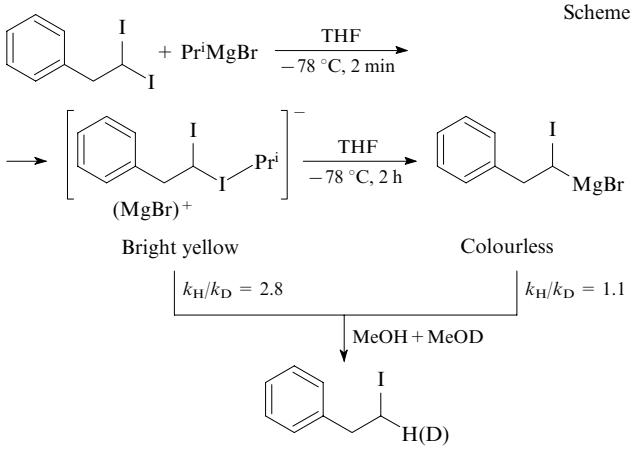
Later, the formation of iodine ate-complexes was established for 2-iodo-5-methylthiophene[210] and for a number of *gem*-diiodoalkanes.[173, 175, 211, 212] The detection of asymmetric ate-complexes in reactions of $R'CHI_2$ with RLi and RMgHal is of special interest, because their transformation into the exchange products, *i.e.*, R′CHIMgHal (Scheme 9) and R′CHILi, was simultaneously demonstrated for the first time.[173, 174, 212] Thus, it was shown that ate-complex may occur as an intermediate of halogen – metal exchange reaction.

Apparently, the interaction with a metal cation (or another Lewis acid) destabilizes ate-complexes,[213] which can be observed at lower temperatures‡ and in the presence of additives that solvate metal cation (HMPA, TMEDA).[204, 206, 208] Ate-complexes may act as donors of carbanions in the reactions with electrophiles, thus mimicking the behaviour of the corresponding RLi compounds; however, they are much less reactive.[173, 204, 206] It is possible that in some cases, it is the ate-complexes but not free RLi that are true nucleophilic agents in the systems obtained by halogen – metal exchange at low temperatures. It was proposed to use deuterium isotope effect as a test for distinguishing the ate-complex from the exchange product. This effect is observed upon protonation of ate-complexes ($k_H/k_D = 0.6 - 2.8$) and is almost absent in the protonation of RLi or RMgHal (see Scheme 9).[173 – 175, 212]

Iodine ate-complexes are often coloured yellow or red.[173, 211, 212] The intermediate appearance of this colour in the reactions of RLi with RHal was first noted as early as 1927.[214] Considering the modern data, it may indicate the formation of ate-complexes as intermediates under such conditions.

‡ The solvation capacity of the solvent increases with a decrease in temperature.

Scheme 9



The structure and stability of ate-complexes of iodine and other halogens and their role in halogen – metal exchange processes were studied in detail with the help of quantum chemical calculation methods. The results obtained by different methods (B3LYP,[215 – 218] MP2[217, 219] and MP2//CCSD[220]) are in good agreement with each other and with experimental data. Free anions of ate complexes have linear structure.[215, 218, 219] The insertion of lithium cation into the system slightly decreases the C–Hal–C angle (to 160 – 172°), resulting in T-shaped adducts (Fig. 2).[215, 216, 218, 219] The structure of lithium salts of ate-complexes is more similar to a linear model of ate-complex than to the formerly popular model of four-centred transition state of halogen – metal exchange reaction. The stability of ate-complexes decreases on going from iodine to chlorine and especially to fluorine. Iodine and bromine ate-complexes are usually minima on the potential energy surface, and the formation of ate-complexes from R^- and RHal is an exothermic process.[215, 219] The addition of lithium cation to the ate-complex anion leads to destabilization of the system (relative to starting RLi and RHal). In most cases, lithium salts of bromine and iodine ate-complexes are rather transition states but not intermediates.[215 – 219] An exception is represented by fluorinated complexes $[C_6F_5]_2HalLi$ with $[CH_{3-n}F_n]_2HalLi$ ($n = 1 - 3$; Hal = Br, I), which match a shallow minimum on the potential energy surface, obviously, due to the coordination of lithium cation to fluorine atoms.[215, 218] It has been shown that the simplest account of lithium cation solvation (by one or two molecules of water) leads to stabilization of the TS

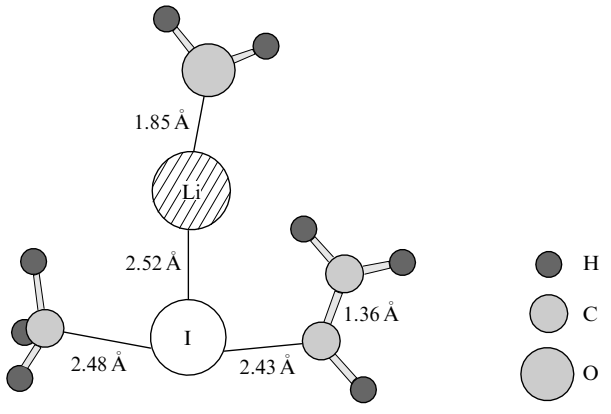


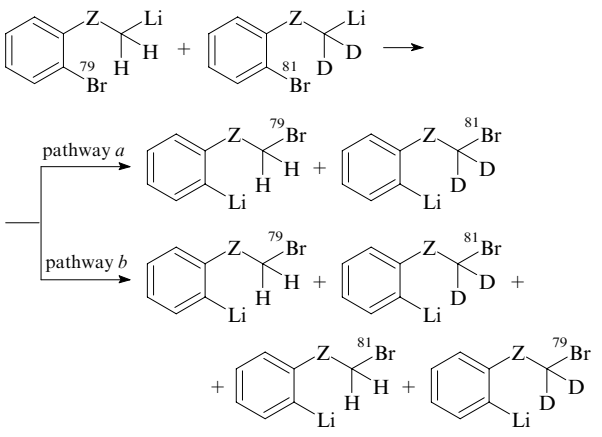
Figure 2. Structure of the halogen – metal exchange transition state based on the results of B3LYP calculations.

corresponding to the ate-complex, and, on the contrary, to destabilization of the starting compound RLi, which significantly lowers the activation barrier of halogen–metal exchange reaction (from 16–20 to 12 kcal mol^{-1}).[215,216] Similar trends were obtained by quantum chemical investigations of halogen–lithium exchange in 1,1-dihaloalkenes. The solvation of the lithium cation lowers the activation barrier of exchange reaction of MeLi from 13–14 to ~6 kcal mol^{-1} (Ref. 217). It is interesting that the ate-complex of MeLi dimer is more stable and is not a transition state, but an intermediate of the reaction. The mechanism of halogen–zinc exchange with the participation of lithium zincates has been studied in detail by the DFT method. The activation barrier of the exchange reaction with RI was found to decrease in the order ethyl > vinyl > allyl > α-chloroethyl > ethynyl.[221]

In recent years, experimental[213] and theoretical[215] data indicating relative ease of homolytical transformations of alkyl ate-complexes were obtained. Hence, it was assumed that radical intermediates that are undoubtedly present in some of halogen–metal exchange reactions may be related to the secondary oxidation and decomposition reactions of the intermediate ate-complexes rather than to the primary single electron transfer from RLi to R′I.

An independent proof of the linear geometry of the transition state of halogen–metal exchange (or the intermediate ate-complex) and, hence, of the S_N2Hal mechanism (see Scheme 7, pathway *c*) was obtained in a study of the exchange in ω-(2-bromophenyl)-n-alkyllithium derivatives with varying length of the alkyl substituent (Scheme 10).[57] In these systems, the exchange reaction may proceed both by intra- and intermolecular pathways (pathways *a* and *b*, respectively). With the help of isotopic labelling, it was demonstrated that the intramolecular pathway is realized only for sufficiently long alkyl moieties when the formation of endocyclic transition state with C–Br–C angle close to 180° becomes possible. This attests to the existence of rather strict geometrical constraints for the geometry of the transition state of halogen–metal exchange and provides grounds for rejecting both the four-centred transition state mechanism (see Scheme 7, pathway *a*; angle C–Hal–C ≈100–120°) and the SET mechanism.

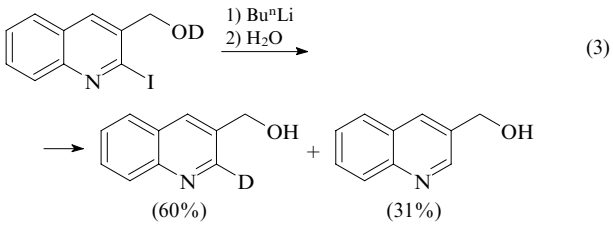
Scheme 10



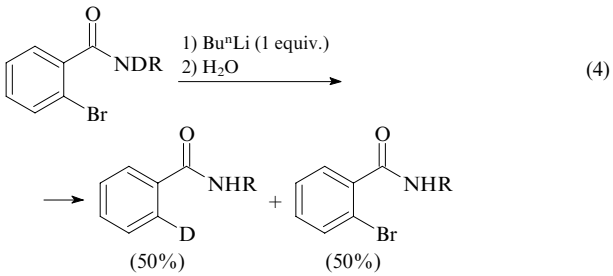
Z = $(CH_2)_3O(CH_2)_{10}$ (pathway *a*); $(CH_2)_2$, $(CH_2)_4$ (pathway *b*).

A similar conclusion about the linear geometry of the transition state of halogenophilic reactions was also drawn in a study of the halogenation of arenes by *N*-chloroamines.[222]

The halogen–metal exchange, like halogenophilic reactions involving other active halogenophiles, is among the fastest heterolytic processes. The halogen–metal exchange reaction in ether solvents rapidly proceeds at −100 °C and even at −131 °C. At the latter temperature, the reaction of Bu^{t}Li with primary AlkI is completed in several minutes.[44,223] Aryl iodides are evidently even more reactive. Carrying out the reaction at temperatures below −100 °C makes it possible to preserve most of the functional groups that commonly react with RLi. At this temperature, it is possible to carry out selective exchange of Br with Li in aryl bromides containing CN, CO_2R, CO_2Li, *o*-NO_2, CH_2Cl and CH_2CH_2Br groups.[15,43,44,224] In 3,3,3-trichloroepoxypropane and chloral, the halogen–metal exchange goes faster than the epoxide opening and addition to the aldehyde group, respectively.[39] Owing to high rate, the halogen–metal exchange can be carried out *in situ*, by adding AlkLi to a mixture of ArBr (RHal) and an electrophilic reagent, *e.g.*, aldehyde or ketone, at low temperature.[22,34,225] Moreover, there are data indicating the possibility to perform the halogen–metal exchange without affecting the acidic C(O)NHR, CO_2H and OH groups present in ArHal molecules, and in some cases, even in the presence of excess of alcohol in the reaction mixture.[173,174,198,203,212] These observations and specially planned experiments [reaction (3)][224] were interpreted by some authors as being indicative of the fact that the halogen–metal exchange is faster than the transfer of the acidic proton to RLi,[224,226] which was a subject of debate in the literature. A more cautious opinion that has an experimental substantiation [reaction (4)][§] is that halogen–metal exchange does not, after all, proceed faster than deprotonation but still faster than the complete mixing of the reactants.[227–230] This gives local domains of excess RLi concentration in which dilithium derivatives (at the oxygen and carbon atoms) may be formed even at an equimolar ratio of ArBr and RLi.



(3)



(4)

The halogenophilic reactions of stabilized benzyl carbanions [PhC$^-$XCF$_2$Y] with bromo- and chloropolyfluoro-

§ For example, it was demonstrated that the yield of deuterated product does not exceed 50% and dramatically decreases when the reactants are mixed in the opposite order and when stirring of the reaction mixture is more vigorous.[227,228]

alkanes may successfully compete with proton transfer from MeOH (Ref. 100) and β-elimination of the fluoride ion from the same carbanion.[101] These reactions, like the hydrodeiodination of polychloroiodobenzenes under the action of dimsyl anion,[116] are so fast that they should be mainly diffusion-controlled. The considerably higher rate of bromophilic reaction in comparison with deprotonation of acidic NH group is also observed in the above-mentioned reaction of carbonyl metallate $[Re(CO)_5]Na$ with 2-[bromo(cyano)methylidene]thiazolidin-4-one.[166]

Study of the kinetics of transfer of the bromine atom in $RCBr(CN)_2$ and $RCHBrNO_2$ (R = H, Ph) to the corresponding carbanions $[RC(CN)_2]^-$ and $[RCHNO_2]^-$ allowed researchers[74] to make the conclusion that the intrinsic activation barrier to the transfer of X^+ ($RX + R^- \rightarrow R^- + RX$) increases in the order Br < H ≪ Me. This means that other things being equal, the bromophilic reaction with the participation of a carbanion occurs more easily than the proton transfer and considerably more easily than the CH_3 group transfer (S_N2C). Calculation data also indicate that halogen transfer from CCl_4 to $[CH_2NO_2]^-$ in the gas phase should be almost a barrier-free process.[106]

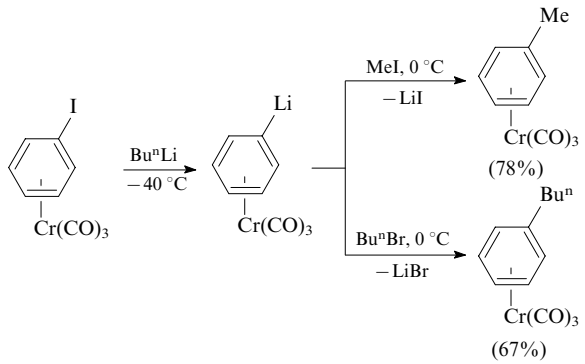
V. Halogenophilic mechanism in the nucleophilic substitution reactions

A nucleophilic attack at the halogen atom and halogen–metal exchange as its specific case lead to the formation of a new pair of electrophilic (NuX) and nucleophilic (R^-) reagents, which may, in principle, react with each other giving the coupling product RNu [reaction (5)].

$$RHal + Nu^- \longrightarrow [R^- + NuHal] \longrightarrow RNu + Hal^- \qquad (5)$$

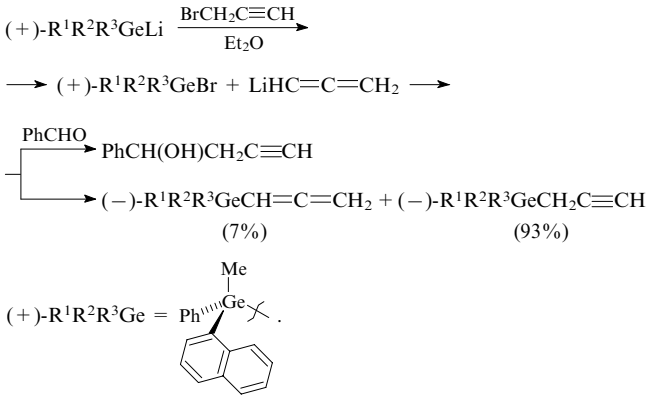
In this case, the halogen–metal exchange serves as the initial step of the halogen replacement by a nucleophile. This 'halogenophilic' mechanism of nucleophilic substitution is, indeed, found in systems susceptible to halogenophilic attack, especially in those cases where direct nucleophilic substitution reaction is hampered and, on the contrary, the reverse $NuX + R^-$ reaction easily occurs, resulting in the substitution product in high yield. Unfortunately, this mechanism sometimes remains unrecognized. Papers that present convincing evidence for this pathway of substitution are not numerous.

There is almost no doubt that halogen–metal exchange is the first step in the formation of cross-coupling products ArAlk in reactions of AlkLi with ArHal (Hal = Br, I).[27, 43, 44, 178, 231–236] High yields of products are obtained only with primary AlkLi, when the reverse nucleophilic substitution reaction proceeds smoothly.[233, 236] The first step (halogen–metal exchange) in such systems is much faster than the second one, and if RLi and R′Hal are sequentially added to ArHal, then it is possible to trap the ArLi intermediate.[234]

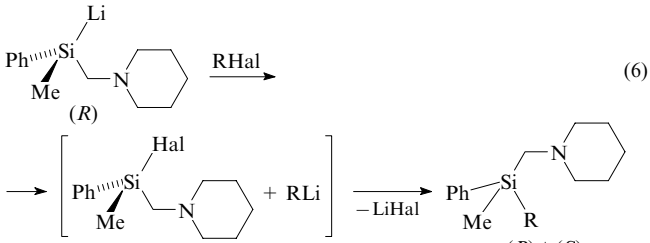


The vinylation of AlkLi by vinyl bromides and iodides, obviously, proceeds by the same mechanism.[236]

Nucleophilic substitution in propargyl bromides under the action of Me(1-Naph)PhGeLi proceeds *via* a halogen–metal exchange step.[237] The reaction mechanism is confirmed by trapping of the intermediate (allenyllithium) if the reaction is carried out in the presence of benzaldehyde. This explains the inversion of the configuration at the germanium atom observed in the reaction.

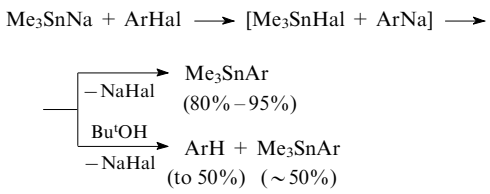


The inversion of the configuration at the silicon atom was used as the key evidence for the halogenophilic mechanism of nucleophilic substitution under the action of (*R*)-PhMe(PipCH$_2$)SiLi (Pip = cyclo-$C_5H_{10}N$) in benzyl bromide and Me_3SiCH_2Br.[50, 52] The configuration inversion shows that the pathway to the products involves the step of substitution at the silicon atom, which is possible only if the a halosilane and a carbanion are formed as intermediates. In the reaction with benzyl bromide, almost complete configuration inversion is observed. On the contrary, the reaction with benzyl chloride results in retention of the configuration at the silicon atom by a common S_N2C mechanism. The predominant inversion of the configuration in the reaction of chloro- and bromobenzenes with (*S*)-Me(Me_3Si)(PipCH$_2$)SiLi is similarly regarded as evidence for the halogenophilic mechanism. The predominant racemization in the reactions with alkyl iodides is explained by a contribution of a radical mechanism.



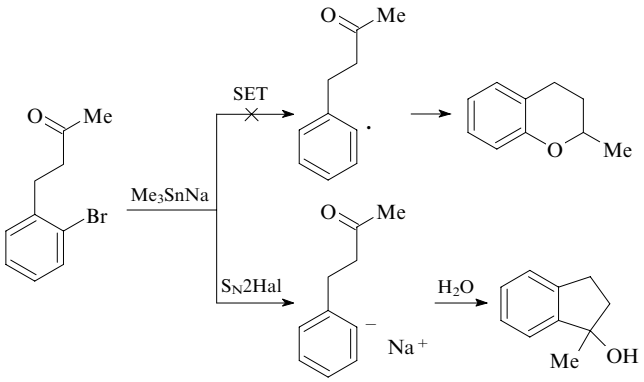
RHal	$PhCH_2Br$	Me_3SiCH_2Br
S : *R*	5 : 95	22 : 78

The halogenophilic mechanism of nucleophilic aromatic substitution in the reaction of non-activated aryl halides with trialkylstannylide anions has been studied in detail.[47, 83] The decrease of the yield of R_3SnAr (and formation of ArH) in the presence of proton donor prove the intermediate formation of aryl carbanions in the process of substitution.



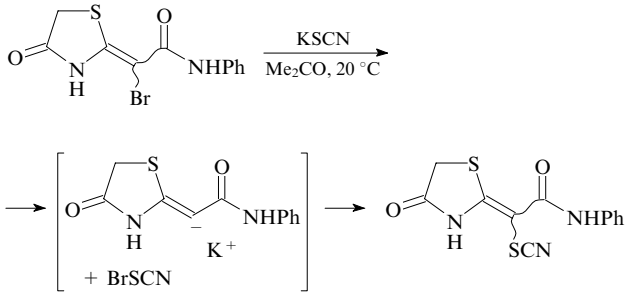
Hal = I, Br, Cl.

However, the intermolecular protonation does not allow for complete trapping of the $[Ar]^-$ intermediate, the degree of protonation (the decrease in the yield of R_3SnAr) depending not only on the proton donor concentration (Bu^tOH) but also on the viscosity of the medium. Then the second step of the reaction in this system is faster than the primary halogen–metal exchange and the interaction of Ar^- and R_3SnHal partially occurs in the solvent cage before the intermediates migrate to the solution bulk. Additional experiments also made it possible to rule out the SET mechanism and the aryne mechanism (the absence of dehydrobenzene derived products when the reaction is performed in the presence of furan).[47] It should be noted that halogenophilic reactions involving the $[R_3Sn]^-$ anions have a preparative value (see, *e.g.*, Refs 150, 151 and 153) and even in the case of tri- and tetrabromobenzenes, they provide high yields of the substitution products.[238]

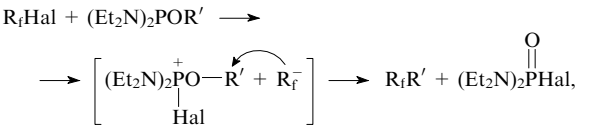


Presumably, the nucleophilic vinylic substitution under the action of Me_3SnLi in 1,1-dibromoalkenes proceeds by a similar mechanism.[150] In highly intricate (as regards both the products and the range of competing mechanisms) reactions of $[R_3Sn]^-$ with alkyl halides, some of the substitution products ($AlkSnR_3$) are also formed *via* the halogenophilic pathway.[137, 194, 239–241]

Halogenophilic mechanism has been proposed to account for the formation of substitution products in the reactions of bromo- and chloroketosulfones with thiolates[36] and in the reaction of 2-[bromo(phenylcarbamoyl)-methylidene]thiazolidinone with thiocyanate.[62]



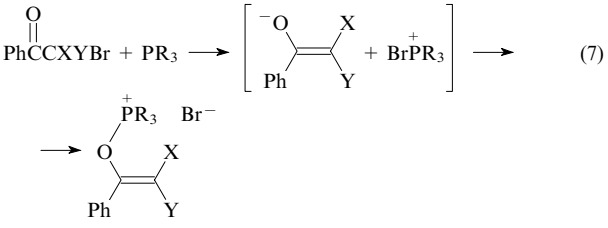
Quite a few examples of halogenophilic mechanism of nucleophilic substitution can be found in the chemistry of polyhalogenated alkanes. This is the route [see reaction (5)] to the nucleophilic substitution products in the reactions of Me_3SnNa with CCl_4 and $CHCl_3$,[38] PhSNa with CF_3CCl_3 (Ref. 10) and halopolyfluoromethanes with tertiary phosphines.[4, 91, 97] The halogenophilic mechanism of substitution is rather widespread in the chemistry of trivalent phosphorus,[26] though in many cases it remains 'concealed' and unrecognized.[27] A halogenophilic version of the Arbuzov reaction is also known,[26] for example, the reaction involving perfluoroalkyl(aryl) halides R_fHal (Hal = Cl, Br) and $(Et_2N)_2POR'$.[102]



Hal = Cl, Br.

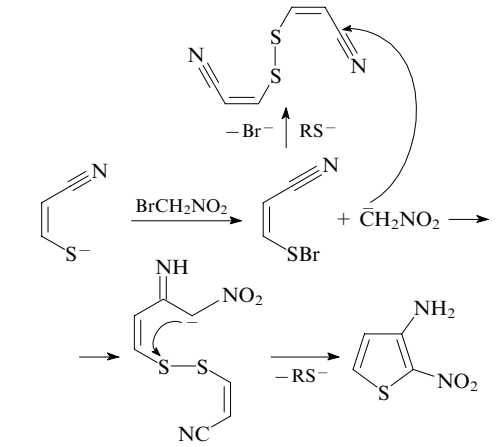
The synthesis of diaryl tellurides by the reaction of aryl halides with sodium telluride is a probable example of concealed halogenophilic mechanism of nucleophilic aromatic substitution. Non-activated aryl iodides enter into this reaction;[242] the introduction of two fluorine atoms in the *ortho*-position activates also the reaction with aryl bromides.[243] In bromopentafluorobenzene, only the bromine atom is replaced,[243] which as a typical attribute of a halogenophilic reaction. The reactions proceed in the dark, and, as it is known, tellurides are very strong halogenophiles,[60, 65, 149] but unfortunately the substitution mechanism is not discussed in the papers mentioned.

Coupling of carbanionic and electrophilic (NuHal) intermediates of halogenophilic reaction may lead to the products differing from the direct substitution products. This is observed in those cases where the carbanion or NuHal show an ambident reactivity. The formation of enol phosphonium salts in the reaction of phosphines with α-bromo ketones [*via* the ambident enolate ion, reaction (7)][64] and the products of nucleophilic attack at the CO ligand of $M(CO)_nHal$ (ambident electrophile) in the halogenophilic reactions of some carbonylmetallates [see below, reactions (8)–(10)][160] may serve as examples.



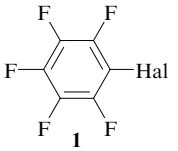
X = Br: Y = H, Me, Ph; X = Y = Ph; PR_3 = PPh_3, $PMePr^nPh$.

The halogenophilic mechanism underlies the cyclization of β-carbonyl- or β-cyano-substituted thiolates into the corresponding thiophenes upon the reaction with bromonitromethane. Though it seems that in this case the electrophilic partner of the carbanionic intermediate is represented by disulfide formed from sulfenyl bromide but not by the proper sulfenyl bromide. If the reaction is carried out in the presence of the phenyl sulfinate anion, it is possible to partially trap the RSBr intermediate.[75]



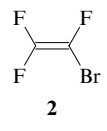
$RS^- = {}^-S\!\!\diagup\!\!\!=\!\!\diagdown CN$.

It should be mentioned that nucleophilic substitution by the halogenophilic mechanism [see reaction (5)] is quite typical of transition metal carbonyl anions in the reactions with aromatic, vinyl and acetylene halogenated derivatives. The halogenophilic mechanism is confirmed for the reactions of carbonyl metallates $[CpFe(CO)_2]K$ and $[Re(CO)_5]Na$ with a number of activated aryl and alkenyl bromides, iodides and chlorides (compounds **1**–**9**), primarily, by using the method of anion traps. In the presence of proton donors (most often, Bu^{t}OH) the nucleophilic substitution is completely suppressed, and the hydrodehalogenation product [89, 158–160, 162, 170, 244, 245] is simultaneously formed.

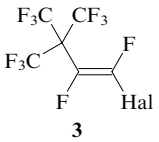


1

Hal = Cl, Br, I.

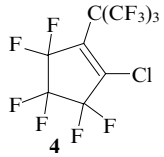


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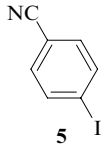


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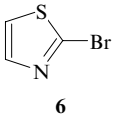
Hal = Cl, Br.



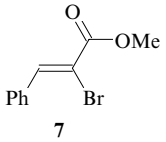
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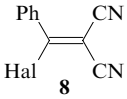
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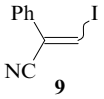
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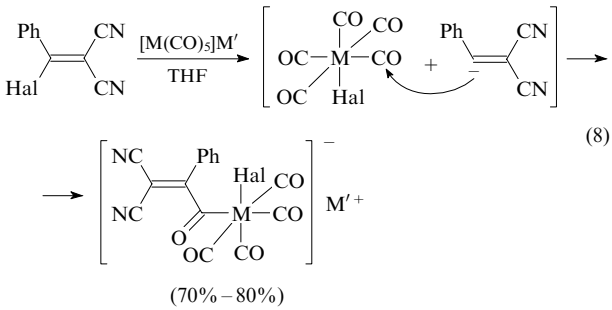


9

Hal = Br, I.

The halogenophilic reaction of $[CpFe(CO)_2]K$ with pentafluorochlorobenzene (see Scheme 6) has already been mentioned above, but this mechanism is not restricted to perfluorinated compounds.[158–160] It is also possible in the reactions with non-fluorinated vinyl bromides and iodides [89] and even with such substrates as $PhHalC{=}C(CN)_2$ [reaction (8)],[162] despite the fact that the latter are strongly activated towards the substitution by the classical addition–elimination mechanism (Ad_NE). At the same time, most of vinyl chlorides (except for perfluorinated compounds **3**, **4**), primary alkenyl bromides and even $BzCH{=}CHI$ react with carbonyl metallates by the Ad_NE mechanism.[162, 170, 244] The choice between the halogenophilic mechanism and Ad_NE is first of all determined by the structure of vinyl halide, that is, by the stability of carbanion intermediates of the Ad_NE or halogenophilic reaction and by the presence of steric hindrance to the attack of the carbonylmetallate anion at the double bond.[162]

A typical feature of the halogenophilic reactions of anionic rhenium and, in some cases, manganese carbonyl complexes is the formation of anionic halo(acyl)metallates [reaction (8)] instead of neutral complexes $RM(CO)_5$, which are expected of a usual nucleophilic substitution reaction.



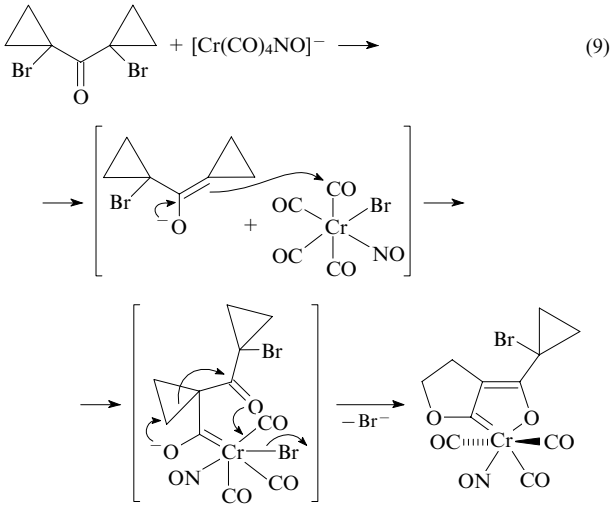
(8)

(70%–80%)

Hal = Br, I; M = Re, M′ = Na (at −50 °C);
Hal = I, M = Mn, M′ = K (at 22 °C).

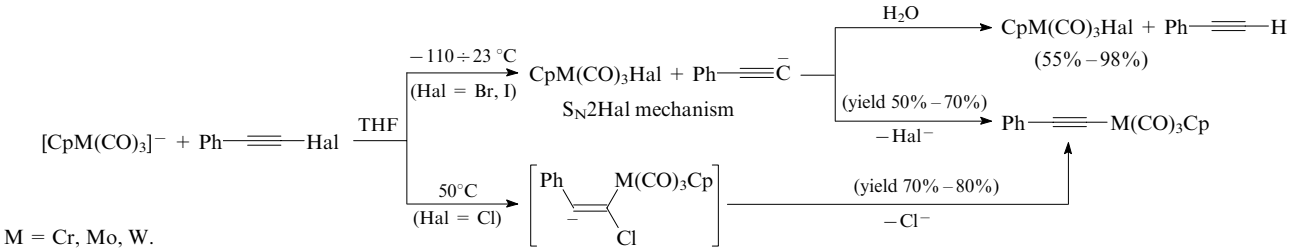
The formation of halo(acyl)metallates includes the nucleophilic attack of the carbanion at the CO carbon atom of $HalM(CO)_5$ and may serve as an independent diagnostic criterion of the halogenophilic mechanism.[89, 158, 160, 162, 244, 245] Halo(acyl)metallates are formed in high yields (up to 90%–95% with perfluorinated substrates [158, 160]), but halo(acyl)manganates are rather unstable and can transform into the corresponding σ-perfluorophenyl complexes.[160]

The halogenophilic reaction with transition metal carbonyl anions may also lead to more unexpected products. Thus, halo(acyl)metallate that forms from the enolate ion and $[Cr(CO)_4(NO)Br]$ may undergo subsequent transformations with opening of the three-membered ring, elimination of the bromide ion and the formation of metallacycle [reaction (9)]. The reaction mechanism is confirmed by trapping of the carbanionic intermediate by trimethylchlorosilane, enol silyl ether being formed instead of the organometallic product.[246]

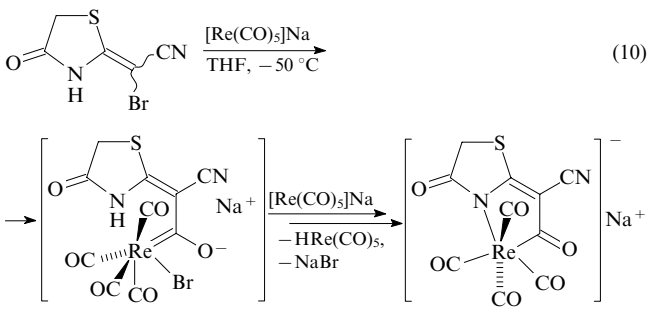


(9)

Scheme 11



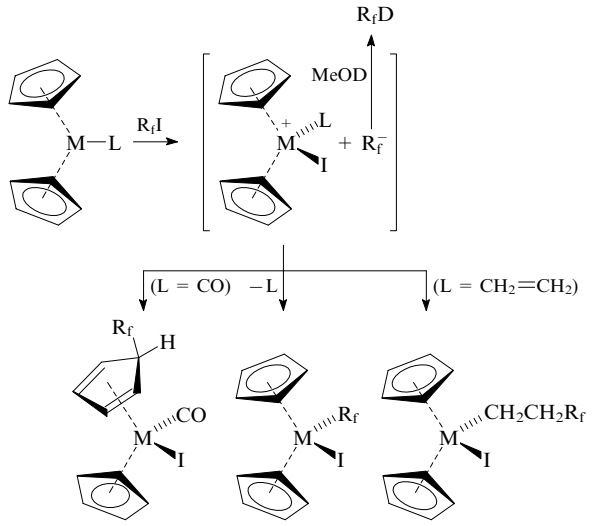
The reaction of $[Re(CO)_5]Na$ with 2-[bromo(cyano)methylidene]thiazolidin-4-one does not stop after the formation of halo(acyl)rhenate and finally gives a metallacycle [reaction (10)].[166]



It is of interest that the halogenophilic mechanism [see reaction (5)] has been considered earlier as the main pathway of nucleophilic substitution in haloacetylenes, for which it was formulated for the first time by Arens.[21] Later, for most of cases, it was revised in favour of the addition–elimination mechanism.[14] However, the reactions of bromoacetylenes with tributylphosphine and sodium diethyl phosphite remain classical examples of nucleophilic substitution by halogenophilic mechanism.[14, 45, 46, 58] The significant influence of the nature of halogen ($k_{Br} \gg k_{Cl}$) typical of halogenophilic processes is observed in these reactions, the formation of substitution products being completely suppressed in the presence of alcohols that protonate the alkynyl carbanion. In reactions with $(EtO)_2PONa$, it is possible to trap another intermediate of the halogenophilic reaction, *i.e.*, $(EtO)_2P(O)Br$.[58, 70]

Halogenophilic mechanism has also been proven for nucleophilic substitution in bromo- and iodophenylacetylenes under the action of the $[CpM(CO)_3]^-$ and $[Cp^*M(CO)_3]^-$ anions (M = Cr, Mo, W; $Cp^* = \eta^5\text{-}C_5Me_5$) (Scheme 11).[247] If the reaction is terminated at low temperature by adding water, the halide $CpM(CO)_3Hal$ (Hal = Br, I) and phenylacetylene are formed instead of the substitution product. It should be noted that phenylchloroacetylene reacts with $[CpM(CO)_3]^-$ not by halogenophilic but by the usual Ad_NE mechanism.

A peculiar halogenophilic reaction that may also be referred to as nucleophilic substitution takes place when perfluoroalkyl iodides are made to react with the complexes Cp_2ML (M = Mo, W; L = CO, $CH_2{=}CH_2$).[248] The carbanion R_f^-, which is formed as a result of halogenophilic attack, may react with the cationic complex $[Cp_2MLI]^+$ at three different reaction centres, *i.e.*, the metal atom, the ligand L and Cp, depending on the nature of the metal and on the carbanion R_f^-. A similar reaction has been described for rhodium complexes $CpRhL_2$ (L = CO, PMe_3).[249]



VI. Conclusion

The discovery of halogenophilic reactions and the subsequent proof of the mechanism with nucleophilic attack at the halogen atom (S_N2Hal) was an important advance in the development of organic chemistry that significantly broadened our ideas about the nucleophilicity and nucleophilic substitution.

Halogenophilic reactions are possible for any organic halides, except for fluorides, in the presence of sufficiently active halogenophilic reagent, as can be seen by the example of halogen–metal exchange reactions with the participation of organolithium compounds. These reactions are still more typical of activated organic halides and such nucleophiles as thiolates, stabilized carbanions and trivalent phosphorus derivatives. However, especially high halogenophilicity is inherent in AlkLi and various element- and metal-centred anions. In reactions with such nucleophiles, especially with metal-centred anions, the halogenophilic mechanism is often responsible for the formation of common (and sometimes unusual) nucleophilic substitution products [see reaction (5)] in aryl, vinyl, alkynyl and sometimes alkyl halides. The halogenophilic reactions are characterized by a very low activation barrier and under the favourable thermodynamics, they are among the fastest heterolytic processes.

The issue concerning the relative and absolute halogenophilicity of various nucleophiles and the role of the nature of element in the nucleophilic centre is rather interesting. Although the general tendencies are obvious, *i.e.*, the halogenophilicity of nucleophiles that are formed by heavier and more electropositive elements of the Periodic Table is higher, for the development of a halogenophilicity scale, it is still necessary to obtain quantitative data, both experimental and computational.

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