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X-Philic Reactions

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Contents

I. Introduction

The whole set of reactions classed as nucleophilic substitutions can be expressed by the formal eq 1, where

$$Z^- + X\text{–}Y \rightarrow Z\text{–}X + Y^- \quad (1)$$

Z is a nucleophile (written as an anion for convenience) and X–Y is a molecule of a substrate. Every specific representation of this equation must include the symbols of proper elements instead of the symbols of X, Y, and Z. Let us consider the specific case of substrates containing the carbon atom. The insertion of the symbol for carbon can be accomplished by *two* different ways to give eq 2 and 3. (In addition to the usual

$$Z^- + {>}C\text{–}Y \rightarrow Z\text{–}C + Y^- \qquad S_NC,\ A_{ZC}D_{CY} \quad (2)$$

$$Z^- + X\text{–}C{<} \rightarrow Z\text{–}X + {}^-C \qquad S_NX,\ A_{ZX}D_{XC} \quad (3)$$

designation of mechanistic schemes (e.g., S_N2, S_NC, etc.) we shall occasionally use the notation system developed by Guthrie[1] because it takes into account the types of bond broken and formed, and is very convenient for our discussions.)

Hence, such a primitive treatment (for more sophisticated formal logical approaches to chemical problems see references 2 and 3) gives a result that actually has not been widely recognized: *there exists in principle an ambident type of reactivity of C–X bond in reactions with nucleophiles.*

However, in speaking about "nucleophilic substitution" one usually means the case of eq 2, which is the well-known reaction type of substitution on carbon. For many years only this case has been the object of a great deal of theoretical and experimental investigations, and most textbooks on organic chemistry describe in detail only this aspect. We shall designate it as "carbonophilic" reactions (S_NC).

The second case expressed by eq 3 represents nucleophilic substitution at X with the carbon atom playing the role of the leaving group. Hence, one can suppose the existence of a variety of "X-philic" reactions (S_NX), and the particular cases of protophilic (eq 4),

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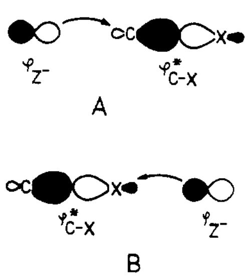


Figure 1. Orbital representation of nucleophilic substitutions: (A) rear-side attack at carbon; (B) X-philic attack.

chlorophilic (eq 5), and cyanophilic (eq 6) reactions serve as examples.

$$Z^- + H\text{-}C\!< \rightarrow Z\text{-}H + {}^-C\!< \qquad S_NH, A_{ZH}D_{HC} \quad (4)$$

$$Z^- + Cl\text{-}C\!< \rightarrow Z\text{-}Cl + {}^-C\!< \qquad S_NCl;\ A_{Z,Cl}D_{Cl,C} \quad (5)$$

$$Z^- + NC\text{-}C\!< \rightarrow Z\text{-}CN + {}^-C\!< \qquad S_NCN,\ A_{Z,CN}D_{CN,C} \quad (6)$$

The abstraction of a proton by a nucleophile (base) in accordance with eq 4 has been considered as one of the important mechanistic steps in the chemistry of carbanions, as, for example, in $E1_{cb}$ elimination and base-catalyzed olefin isomerization. However, the other types of X-philic reactions are much less familiar, and the aim of this review is to summarize some of the chemistry of this rather unusual X-philic type of reactivity of C–X bond with special attention to the areas where these reactions may be of potential application in synthesis.[4]

II. General Regularities of X-philic Reactions

A. Simple PMO Treatment of X-philic Processes

Generalized perturbation theory (PMO) of chemical reactivity considers the "normal" nucleophilic substitution of S_N2 type (eq 2) to proceed via a transfer of electrons from an occupied orbital of the nucleophile to an unoccupied antibonding orbital of C–X bond, σ^*_{C-X}.[5] The frontier orbital approximation can be schematically represented as in Figure 1A. However, the general theory of nucleophilic reactions might provide a rational basis for the qualitative prediction of the competition between S_NC and S_NX processes as a function of the nature of X and Z, of substituents at the carbon atom, etc. Unfortunately, to the best of our knowledge, special theoretical treatment of this problem is lacking and most MO calculations deal with the S_N2-like processes involving the attack at a central carbon atom,[5-18] with the possibility of the alternative attack at group X being completely ignored.

Nevertheless, it can easily be shown that the analogous PMO description can be adapted to X-philic processes; the orbital picture of this substitution is shown in Figure 1B. PMO approach assumes that the antibonding orbital σ^*_{C-X} is essentially φ_C, mixed out of phase with a smaller quantity of φ_X if the electronegativity of X is greater than the electronegativity of C. As a rule, this is the case, and the nucleophilic substitution proceeds via rear-side attack on a small lobe of C (Figure 1A), but not via the attack on a back lobe of X (Figure 1B). To increase the probability of an attack on a small lobe of X by a nucleophile one needs (i) to enhance the contribution of φ_X in σ^*_{C-X} and (ii) to diminish the contribution of φ_C in σ^*_{C-X}. Hence, the decrease of electronegativity of X (e.g., going down the same column in the periodic table) and the increase of electronegativity of the carbon atom (for example, due to the change of hybridization or to bonding with strongly electronegative substituents) should be considered as factors favorable for X-philic pathways of substitution.

It is of interest to compare the general structural requirements for X-philic processes, deduced from above simple PMO arguments, with the general regularities, which could be deduced from the experimental data. This consideration will be the focus of next two sections.

B. Structural Effects of the Substrate

The crucial factor determining the competition of the aforementioned pathways (A vs. B in Figure 1) is usually the structure of the substrate. As can be seen from eq 3, the X-philic reaction occurs with the release of a carbanion. Hence, *the structural features favorable to this incipient carbanion will facilitate the X-philic reactions.*

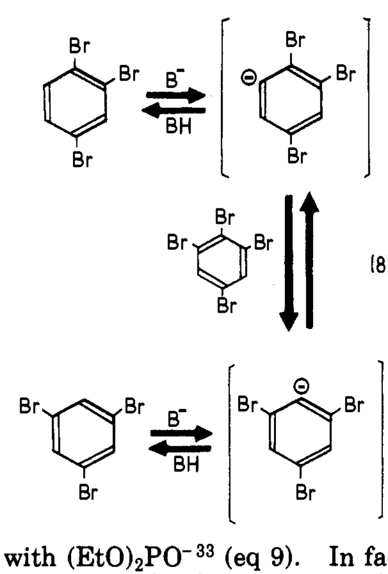
In accordance with this statement a general tendency toward reactions of X-philic type must increase in the series $C_{sp^3} < C_{sp^2} < C_{sp}$ (also a decrease, on the same order, of the nucleophilic reactivity toward carbon).

Indeed, haloacetylenes are the typical model compounds that exhibit halogenophilic, S_N2Hal (eq 5), type of reactivity[19-28] as illustrated by eq 7.[19]

$$R\text{—}C\equiv C\text{—}Hal \xrightarrow{Z^-} [R\text{—}C\equiv C^-] \xrightarrow[(a)]{H_2O} R\text{—}C\equiv CH$$
$$\xrightarrow[(b)]{RC\equiv CHal} RC\equiv CC\equiv CR \quad (7)$$

R = Ar, Het; Z =
OAlk, SR′, NH_2, Ph_3C, $MeSOCH_2$, etc.

Aryl halides are a second class that may be involved in reactions with attack by nucleophile on halogen.[29-35] A classical example is the "halogen dance" in tribromobenzenes[26] (eq 8) and the reaction of o-dihalobenzenes with $(EtO)_2PO^-$ [33] (eq 9). In fact, this is a remarkable aspect of the chemistry of aryl halides because they are unreactive toward nucleophiles under ordinary conditions.



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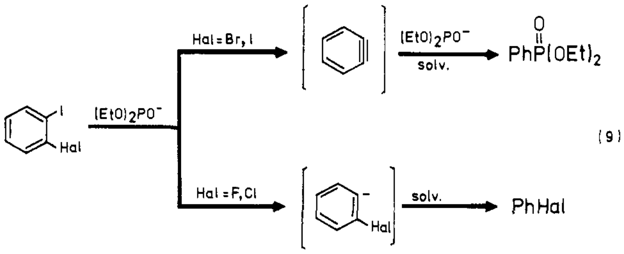
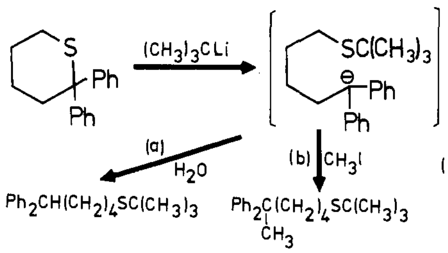


Finally, a displacement at the halogen atom bound to an sp^3 carbon atom can occur if either the normal (S_NC) reaction on carbon is made difficult (e.g., for bridgehead halides)[36–38] or the resulting carbanion is stabilized by substituents. This stabilization can be achieved either by conjugation with unsaturated groups or by the presence of electron-withdrawing substituents. For example, in the reaction of *tert*-butyllithium with 2,2-diphenylthiacyclohexane that produces to *tert*-butyl thioether, the driving force seems to be the stability of carbanion formed (eq 10).[39]



(10)

Another example involves tetrasubstituted methanes. The reactions of tetrahalogenated methanes and other polyhalogenated compounds with nucleophiles are not usually considered in textbooks because these compounds are fairly unreactive toward the *usual* nucleophilic agents. Moreover, they are often used as inert media in oganic synthesis (e.g., CCl_4). In fact, polyhalogenated compounds prove to be especially liable toward the halogenophilic attack. For example, the reagent system CCl_4/PPh_3[40–45] and its variants[46–51] are widely used for synthetic purposes (vide infra).

In addition, such compounds as tetranitromethane[52,53] and tetracyanomethane[54–57] are extremely reactive. The cyano group is often regarded as a "pseudohalogenic" one. However, organic cyano derivatives, namely nitriles, do not generally possess the properties that allows one to consider them as "pseudohalogenic" derivatives. At the same time, though the ability to react by an S_N2X mechanism is considered a characteristic feature of tetrahalogenomethanes, this tendency is characteristic of tetracyanomethane to a much greater degree.[57] Thus, one is able to assert that the accumulation of cyano groups at the carbon atom is accompanied by the appearance of "pseudohalogenic" characteristics. In fact, a qualitative PMO analysis of substituted methanes predicts the relative stabilization of fluoromethanes and destabilization of cyanomethanes with the accumulation of the functional groups.[54,58] The same conclusion can be drawn from thermochemical data (see ref 57–59). If one considers isodesmic reactions (eq 11), the thermal effect, Q, must clearly be zero

$$CX_nH_{4-n} + (n - 1)CH_4 = nCH_3X + Q \qquad (11)$$

on the condition of strict additivity in the bond energies. The magnitude of Q can therefore serve as a measure of the "intramolecular interaction" of the C–X bonds. The Q value of 53.5 kcal/mol for CF_4 (see ref 57) shows that a great expenditure of energy is required for "separation" of the four C–F bonds in CF_4. In contrast, the Q values of −23.1[57,58] and −42.0[57,59] kcal/mol for $C(CN)_4$ and $C(NO_2)_4$, respectively, clearly show that the accumulation of four such groups results in extremely high thermodynamic destabilization of these molecules, which can be regarded as additional driving forces for carbanion formation.

C. Structural Effects of Attacked Groups and Nucleophiles

Let us consider the variation of the X group. The first candidates are the halogen and "halogenophilic" reactions (eq 5), which have been intensively studied and, in part, reviewed.[4,19,30,60]

To our knowledge, there are no examples of this reaction for X = F.[60,61] This fact may be associated with the strength of the C–F bond and with the high negative charge that exists on the F atom in most molecules, and hence the attacking nucleophile and this atom undergo a long-range repulsion that is greater than that for Cl, Br, and I. Actually, the direction of polarization of the C–Hal bond ($C^{\delta+} \rightarrow Hal^{\delta-}$) is unfavorable for halogenophilic process, which must be controlled by orbital interactions rather than by charge distribution. Hence, the decrease of the energy gap between the interacting orbitals (Figure 1B) will facilitate this reaction. Experimental data show that the order of reactivity for halogenophilic processes is usually I > Br >> Cl,[4,19–26,30,62] which is in agreement with the order of decreasing of antibonding levels of C–X orbitals.[63]

However, the order of halogen reactivity is not universally retained for all cases, and, moreover, it depends on the nature of the nucleophile used.

For example, in the reaction of α-halo sulfones with a wide range of nucleophiles (eq 12), the general order

$$\underset{\textbf{1a}}{RCHXSO_2Ph} \xrightarrow[2. H_2O\text{–}DMF]{1.\ Z^-} RCH_2SO_2Ph \qquad (12)$$

$R = Ar, C_5H_5N, C_5H_5N \rightarrow O, C_5H_5N^+Alk(Cl^-)$
$X = Cl, Br, I$
$Z = Ar_3,P, Alk\ PPh_2,$
$(ArO)_3P, (AlkO)_3P, PhS, ArSO_2^-,$
DBH (1,5-diazabicyclo[4.3.0]non-5-ene)

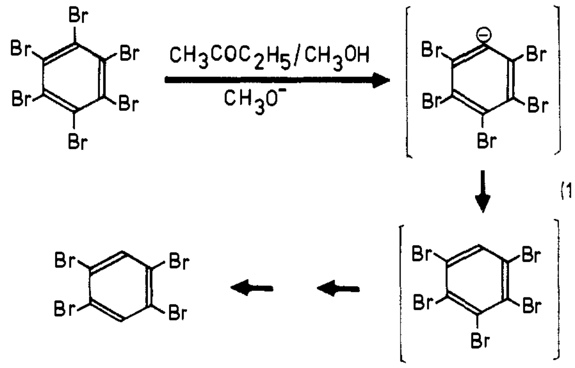
of reactivity is Br > I >> Cl.[64–70] This can be explained in terms of the relative bond strengths of the C–Hal and Hal–Z bonds being made and broken in the transition state.

At the same time, iodo sulfone **1a** (R = *m*-NCC_6H_4) reacts considerably faster than the corresponding bromo sulfone with DBH and sodium *p*-chlorobenzenesulfonate, though in the reaction with sodium benzenesulfonate iodo sulfone **1a** reacts slower than the bromo analogue.[64,67]

In addition, the general order of nucleophilicity for tertiary phosphorus(III) compounds is $R_3P > Ar_3P > (RO)_3P > (ArO)_3P$; however, in reaction 12 the triarylphosphites, reacts more readily than trialkyl phosphites, contrary to expectation.

These data clearly indicate that these reactions are sensitive to variations in nucleophile structure and the whole problem is worthy of special theoretical investigation (cf. the problem of nucleophilic orders in "normal" substitution; see, for example, ref 71).

The HSAB principle and PMO criteria permit the conclusion that soft nucleophiles, for example, mercaptide vs. alkoxide or iodide vs. chloride ions, will be more reactive toward halogens, and experimental data support these conclusions. For instance, phenylhaloacetylenes are triphilic toward methoxide ion in methanol. Methoxide attacks 0.2% on chlorine but 5% on bromine.[20] At the same time, SH^- ion attacks exclusively halogen in haloacetylenylthiophenes.[26] The carbanions stabilized by carbonyl, sulfonyl, and sulfinyl groups have been shown to be especially reactive nucleophiles in the reactions that proceed by the attack on halogen atoms. For example, hexabromobenzene was found to be unaffected upon treatment with methanolic sodium methoxide; however, the addition of methyl ethyl ketone, which is capable of forming an enolate anion, led to the formation of tetrabromobenzene (eq 13).[29]



(13)

It is important to emphasize that noncharged compounds can successfully play the role of nucleophiles in X-philic reactions (eq 14). In this case the reaction

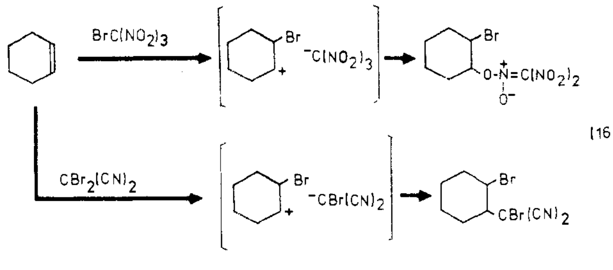
$$Z + X\text{-}C< \rightarrow [Z\text{-}X]^+[C<]^- \quad (14)$$

occurs with charge separation and ion-pair formation (cf. eq 3 and 14). Again soft nucleophiles are more reactive (R_3P vs. R_3N, etc.). This situation is clearly visualized in the reaction of $R_2P\text{-}NHR$ with CCl_4 (eq 15), which proceeds with transfer of chlorine to the

$$R_2P\text{—}NHR' + CCl_4 \rightarrow$$
$$[CCl_3^- + R_2P^+(Cl)\text{—}NHR'] \rightarrow R_2P(Cl){=}NR' \quad (15)$$

phosphorus but not to the nitrogen atom.[72]

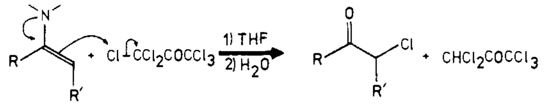
Some cases of electrophilic addition to the double bond may also be regarded as X-philic reactions, and eq 16 could serve as an example.[73,74]



(16)

In many cases the solvent plays an important role in the reactions of the S_N2X type.[37,73,74,79] Thus, in the solution of bromotrinitromethane in dimethyl sulfoxide considerable C–Br separation takes place; this enables the trinitromethyl group to acquire the most planar configuration.[73]

Another representative example of the double bond playing the role of a nucleophile is in the reaction of enamines with hexachloroacetone (eq 17).[75]



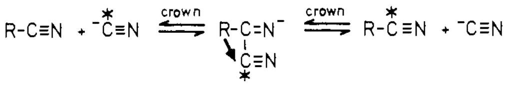
(17)

The next candidates for the appropriate attacked group are cyano (eq 6)[51-54,76-78] and nitro (eq 18)[52,79,80]

$$Z^- + O_2N\text{-}C< \rightarrow$$
$$Z\text{-}NO_2 + {}^-C< \qquad S_NNO_2,\ A_{Z,NO_2}D_{NO_2,C} \quad (18)$$

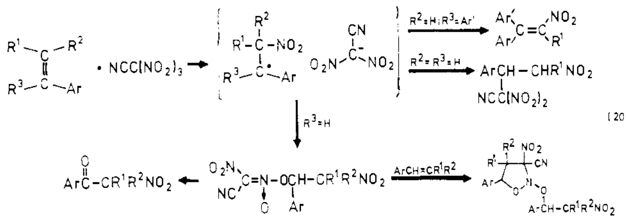
groups. In these cases the atom attacked (carbon of CN and nitrogen of NO_2) carried a partial positive charge and reaction can be favored by this factor.

In this connection it should be noted that the use of acetonitrile as a solvent in the reactions of labeled potassium cyanide is strongly limited by the fact that under such conditions exchange occurs with nitrile function of the solvent, resulting in labeled acetonitrile (eq 19).[77]



$$R\text{-}C{\equiv}N + {}^-\overset{*}{C}{\equiv}N \xrightleftharpoons{\text{crown}} R\text{-}C(=N^-)\text{-}\overset{*}{C}{\equiv}N \xrightleftharpoons{\text{crown}} R\text{-}\overset{*}{C}{\equiv}N + {}^-C{\equiv}N \quad (19)$$

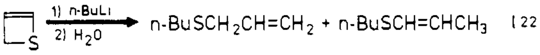
The synthetic use of compounds such as cyanotrinitromethane can be illustrated by eq 20.[80]



(20)

Nucleophilic substitution at sulfur is a common reaction of organosulfur compounds and has been extensively studied for dicoordinate, tricoordinate, and tetracoordinate sulfur.[39,81-92] A few examples are given by eq 9 and 21–23.[81-92]

$$(PhS)_4C + BuLi \rightarrow BuSPh + (PhS)_3CLi \quad (21)$$



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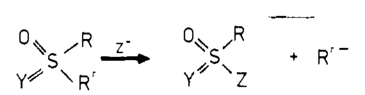


(23)

R = Alk, Ar, $ArCH_2$; Y = O, NR ; Z = OH^-, H_2O, $R'O^-$, NO_2^-, Cl^-, Br^-, R'_2N^-

$R' = C(NO_2)_3$, $R^2C(NO_2)_2$, OAr

D. Mechanistic Alternatives to X-philic Reactions

Concluding this section, we have to emphasize that the assignment of X-philic mechanism is often based only on the structures of the initial and final compounds without careful examination of the mechanistic pathway. For example, the X-philic pathway has been supported by the isolation of the product due to the transfer of a "positive" halogen moiety, as, for example, BrCN in eq 24.[93]

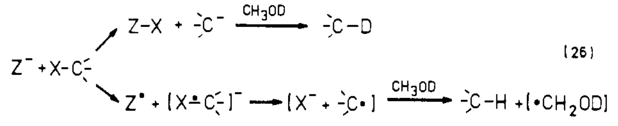
$$(C_6F_5)_2CHBr + CN^- \rightarrow BrCN +$$
$$(C_6F_5)_2CH^- \xrightarrow{(C_6F_5)_2CHBr} (C_6F_5)_2CHCH(C_6F_5)_2 \quad (24)$$

In fact, in most cases the real mechanism is not well understood, and it is useful to discuss briefly the mechanistic alternative to the X-philic pathway, namely, the possibility of the single electron transfer (SET) mechanism shown in eq 25.

$$>C - X + Z^- \rightarrow Z\cdot + [X\overset{\cdot}{-}C<]^- \rightarrow >C\cdot + X^- \tag{25}$$

The SET mechanism has been enthusiastically advanced for the great number of typical "heterolytical" processes in the literature[94-96] (for criticism, see ref 97 and 98). Moreover, recent investigations reveal the general phenomenon that certain substitution reactions occur as the chain anion-radical processes of the $S_{RN}1$ type.[99-111]

In any case, the SET mechanism is often postulated[112-118] on the basis of the structure of the reaction products, but special studies are necessary to distinguish this mechanistic pathway. For example, a clue to the mechanism may be provided by the use of isotopically labeled compounds, as shown in eq 26.[30]



Another example, the use of deuterated tributylamine, has resulted in the elucidation of the radical mechanism of its dark reaction with CCl_4.[119] However, thus far the detailed mechanism has been elucidated only in rare cases, and most of the emphasis in this field has a synthetic bent.

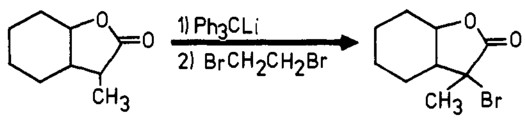
III. Synthetic Applications of X-philic Reactions

As mentioned above, the net result of an X-philic reaction is the transfer of a "positive" X moiety from a carbon atom of the substrate to the nucleophile with the formation of a carbanion. Both results can be synthetically useful. Hence, the preparative applications of X-philic processes can be connected with the use of these reactions as the method for (i) "X-ation" (e.g., halogenation, cyanation) of the nucleophilic moiety and (ii) the generation of a carbanion and its utilization for synthetic purposes. Both aspects are covered in this chapter.

A. Applications of X Transfer: "X-ation" Reactions

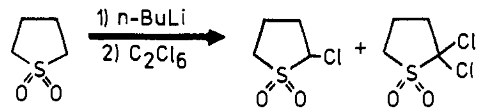
In accord with eq 3 and 14, it is possible to accomplish a transfer of X to both the charged and noncharged nucleophiles. In the first case the reaction results in the formation of a Z–X bond in a neutral compound; in the second case the result is the formation of onium (quasi-onium) ion.

The most investigated processes of both types are for X = Hal. α-Halogenation of olefins,[120] ketones,[116] esters,[121,122] sulfones,[123,124] nitriles,[125,126] phosphates,[127] diarylmethanes,[128] and N-substituted amides[129] and imides[129] can be easily achieved via a halogenophilic pathway by the treatment of the corresponding α-metalated derivatives (or carbanions) by appropriate halides (eq 27–29).



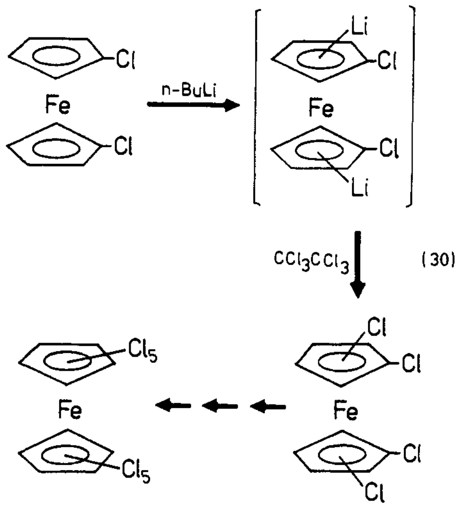
(27)

$$R_2CHCOOR' \xrightarrow[2)\,CCl_4]{1)\ i\text{-}Pr_2NLi} R_2CClCOOR' \tag{28}$$



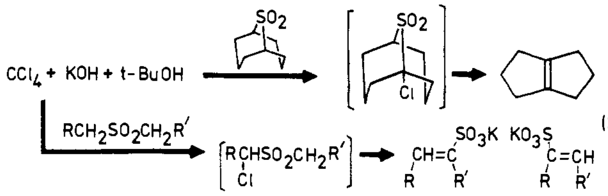
(29)

As a source of halogen atom such compounds as CCl_4,[116-118,121-129] CBr_4,[116-118,122,125] 1,2-dibromoethane-,[120,121,128] hexachloroethane,[124,128,130] 2,3-dibromo-2,3-dimethylbutane,[128] and hexachloroacetone[47,75] have been preferentially used. The synthesis of perchloroferrocene (eq 30) from 1,1-dichloroferrocene by a sequence of repetitive metalation and halogenation steps[130] can serve as a good example of the synthetic utility of this method.



(30)

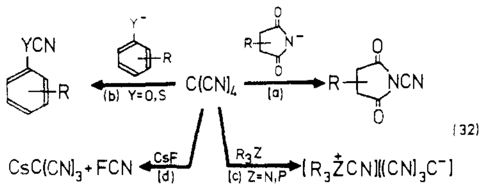
The useful modifications involve use of some specific ways of generation of transient carbanion. For example, the simple method of chlorination of sulfones includes their treatment with CCl_4-KOH-*t*-BuOH.[116,123] Some applications of this method are illustrated by eq 31.



Another method of carbanion generation is the use of a two-phase system.[126] Some additional examples of halogen transfer have been reviewed.[131]

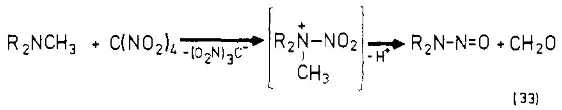
X transfer to a neutral nucleophile, e.g., R_3P, leads to the formation of normally very reactive onium ion, and such reactions may be used for the specific transformations of some classes of organic compounds. It is worth reminding readers of the wide application of $CCl_4 + R_3P$ and related systems for the chlorination (and deoxygenation) reactions.[40,51] The first step of these reactions is the formation of the intermediate reagent of type $CCl_3^-ClP^+R_3$ (cf. with PCl_5, which is $PCl_4^+PCl_6^-$) via a halogenophilic pathway.

There are some other types of "X-ation" reactions, but they have not yet received appreciable application. Tetracyanomethane is a powerful cyanating agent,[54-56,132-134] as illustrated in eq 32. The cyanophilic reaction of eq 32d has even been suggested as a preparative synthesis of pure cyanogen fluoride.[132] Unfortunately, $C(CN)_4$ is not readily available[54] while the related compounds, e.g., $ClC(CN)_3$, exhibit chloro-donating rather than cyano-donating behavior.[54-57] There exist also some examples of displacement of CN from saturated carbon via the SET mechanism.[104,135]



(32)

Transfer of the nitro group from readily available $C(NO_2)_4$ is a much more useful process. For example, the nitrophilic step (eq 18) is involved in the reactions of $C(NO_2)_4$ with some inorganic anions (OH^-, CN^-, SCN^-, NO_2^-, N_3^-),[53] potassium ethoxide, and chloramine B.[52] Probably the analogous mechanism operates for the nitrozation of tertiary amines (eq 33).[52] Ion-pair formation (see eq 14) is believed to be the first step of the reaction of $C(NO_2)_4$ with olefins, the type of final products being drastically dependent on the conditions of the reaction and the substituents in the olefin moiety.[52]



$$R_2NCH_3 + C(NO_2)_4 \xrightarrow[-(O_2N)_3C^-]{} \left[R_2\overset{+}{N}(CH_3)-NO_2 \right] \xrightarrow[-H^+]{} R_2N-N{=}O + CH_2O \quad (33)$$

B. Principal Pathways of Carbanionic Transformation

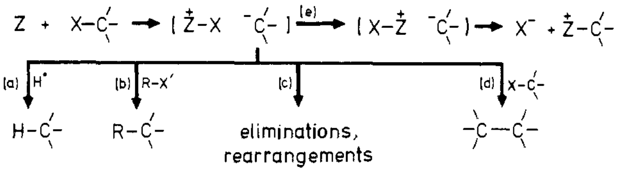
The subsequent fate of the carbanion depends on its structure and reactivity as well as on the presence of additional reagents in the reaction media. The variety of types of carbanion transformations and the principal types of products are shown in Chart I.

If the formed carbanion is sufficiently stable and weakly nucleophilic, the natural result of the reaction will be the isolation of the salt of this carbanion with its counterion. For example, this pathway was often realized for the reactions of $C(CN)_4$ (eq 32) due to the stability of salts of the $C(CN)_3^-$ ion, which can be isolated. However, for the most cases this net result is rather unattainable due to the high reactivity of the carbanionic species.

More usually the incipient carbanion is trapped by a proton, which can be abstracted from any proton-donating species. The net result of this pathway is the reduction of the C–X bond of the substrate (Chart I, path a). Addition of electrophilic alkylating agents can lead to the products of alkylation of the carbanion (Chart I, path b). X-philic attack with carbanion formation can be followed by α or β elimination of halide ion or some other appropriate leaving group (Chart I, path c) or by a carbanionic rearrangement.

The remarkable pathway involving dimerization with displacement (Chart I, path d) has also been observed. In this case the formed carbanion attacks the second molecule of initial substrate to produce the "dimeric" product (e.g., eq 7). This process can be regarded as a viable synthetic alternative to some radical coupling pathways.

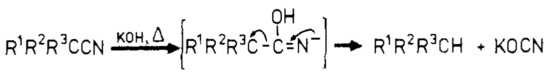
Chart I



Finally, the reorientation of charged species within the initially formed ion-pair intermediate can lead to the subsequent nucleophilic substitution at Z–X species by the carbanion (Chart I, path e) to give the product, which is identical with the one of "normal" nucleophilic substitution. In some sense it is a "concealed" case of an X-philic reaction. If the carbanion is ambident in nature, this pathway can lead to a product in which the nucleophilic moiety is linked with another reaction center of this carbanion. Thus, the modes of reactivity in X-philic processes are quite variable, giving chemists a useful tool for the synthesis of organic molecules of different types.

1. Reduction of the C–X Bond

Pathway a of Chart I can be used as a synthetic method for reduction of the C–X bond in polyhalides. Such carbanionic reduction in aryl halides in exemplified in eq 8 and 13. The analogous S_N2X mechanism has been suggested for the reduction of nitriles[78] (eq 34),



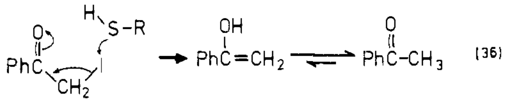
$$R^1R^2R^3CCN \xrightarrow{KOH,\,\Delta} \left[R^1R^2R^3C-\overset{OH}{C}{=}N^- \right] \rightarrow R^1R^2R^3CH + KOCN \quad (34)$$

benzyl halides[136] (eq 35), α-halogeno derivatives of esters

$$ArCH_2X + RY^-Et_3NH^+ \rightarrow ArCH_3 + ArCH_2YR \quad (35)$$

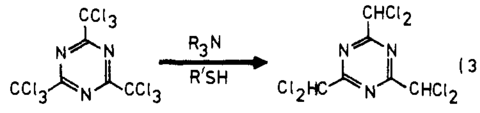
$$X = Cl, Br, I;\ Y = S, Se$$

and ketones with RS^-[137,138] (eq 36), ketones with Ph_3P



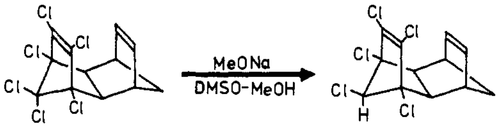
(36)

and Ph_2PH[139] and with I^-,[140] sulfones with R_3P (eq 12),[64-70] haloacetylenes with a number of nucleophiles (eq 7),[19] and CCl_3 groups into $CHCl_2$ in *s*-triazine (eq 37).[141]



(37)

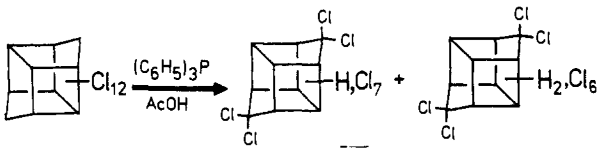
The application of this type of reduction for perchlorinated cage compounds is of special interest.[142-144] For example, the treatment of isodrine with MeO^- in $MeOH + Me_2SO$ leads to mild selective dechlorination (eq 38).[143]



(38)

Dodecachlorodihomocubane (mirex) has been found extremely resistant toward nucleophiles. However, its reaction with $R_3P + AcOH$ leads to a mixture of partial reduction products (eq 39).[144]

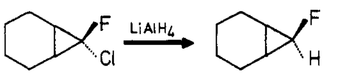
In section IIIA the application of $R_3P + CCl_4$ systems for the transformation of the compounds of type ROH



(39)

into the corresponding chlorides has been mentioned.[40-43] The example given in eq 39 shows that this reaction may be used in a *reverse synthetic sense*: the system R_3P + ROH (e.g., Ph_3P + AcOH) may be used for the (partial) reduction of polyhalogenated compounds.

It was assumed that the reaction of *gem*-chlorofluorocyclopropanes with $LiAlH_4$ proceeds via a chlorophilic step and formation of carbanion, and the net result is reduction with retention of configuration (eq 40).[145]



(40)

2. Alkylation Reactions

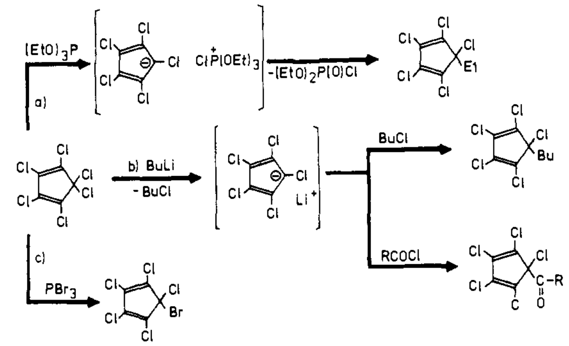
Trapping of incipient carbanions with alkylation agents (Chart I, path b) has been illustrated by eq 9. The methylation of halonitroforms and tetranitromethane by MeI and dipolar aprotic solvents also may be regarded in this connection (eq 41) because the in-

$$(NO_2)_3CX + S \rightleftarrows (NO_2)_3C^- (X\text{–}S)^+ \xrightarrow{CH_3I} (NO_2)_3CCH_3 \quad (41)$$

$$X = \text{Hal, } NO_2\text{; } S = Me_2SO\text{, DMF, HMPTA}$$

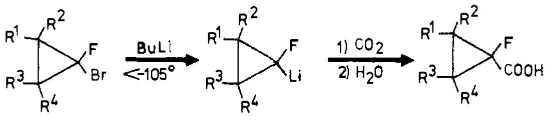
termediate complexes are almost completely ionized in these media[79,146] (see also ref 73, 147, and 148).

A number of alkylation reactions was described for the trichloromethylphosphonates.[127,149] Hexachlorocyclopentadiene is usually resistant to the substitution of chlorine atoms by alkyl groups. However, its treatment with phosphites and thiophosphites nicely gives the substitution product in accord with eq 42.[150-153] A halogenophilic mechanism for reactions of this type is strongly suggested by the ^{31}P NMR evidence.[154]



(42)

Many examples of the reactions of the carbanions prepared by X-philic processes may be found in the chemistry of Li organic reagents (e.g., eq 10, 21, 22, 27, 29, 30, 42b, 43).[39,81,82,120,128,155,156] The alkyl halides formed in halogenophilic reactions can act as alkylating agents in these reactions, giving the products of "normal" nucleophilic substitution (e.g., eq 42b).[156]



(43)

3. Eliminations and Rearrangements

In the presence of the proper substituent capable of being expelled as an anion, further transformation of the intermediate carbanion may involve various types of elimination (Chart I, path c). α elimination results in an incipient carbene, and we shall not discuss this type of reactivity because it has been extensively studied and reviewed, especially the processes involving protophilic attack and subsequent elimination of halogen anion.

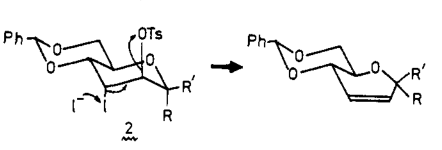
To the best of our knowledge, the first example of β-halogenophilic elimination, namely, iodide-induced debromination of coumarin dibromide, was observed as early as 1871 by Perkin.[157] Since that time a vast body of data concerning the scope and limitation of vicinal dehalogenation (eq 44) has been reported in literature.[158-189]

$$Z^- + X\text{—}C\text{—}C\text{—}X \rightarrow Z\text{—}X + C\text{=}C + X^- \quad (44)$$

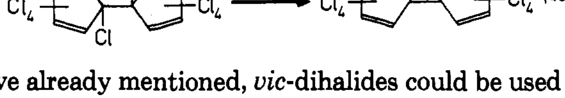
It is necessary to note that this type of dehalogenation does not involve the formation of a carbanion (see eq 3) in many cases. The interpretation of these reactions is often conducted from the viewpoint of a concerted pathway or a stepwise process involving bridged species. Nevertheless, these reactions are typical halogenophilic processes, and we briefly summarize them in this section.

A wide range of nucleophiles has been used, including halide ions,[159-172] RO^-,[173,174] PhS^-,[175-177] Me_3Sn^-,[178] CN^-, SCN^-, $SeCN^-$, dimsyl anion, thiourea,[172] R_3N,[172,173,179,180] R_3P,[173,181-184] $(RO)_3P$.[184-186] This type of reaction is convenient for the study of comparative halogenophilicity of nucleophiles because it permits a wide variation of the structures of substrate and nucleophile.[60-62] It is especially noteworthy that *o*-dihaloarenes also are capable of halogenophilic β elimination[33,187] with formation of benzyne (eq 9).

We should like to emphasize some useful features of these eliminations. First of all, β eliminations of this type proceed preferentially via anti stereochemistry,[172,178] which has been occasionally used in synthesis. For example, dehalotosylation of glucoside 2 by iodide ion leads to the unsaturated product 3, as shown in eq 45.[189] In contrast, β elimination via an SET mechanism may proceed in a nonstereospecific manner.[112] Second, the use of halogenophilic dehalogenation often permits formation of elimination products not available by other methods. For example, perchlorofulvalene was obtained via a β-dechlorination reaction (eq 46).[185] Third, as we have already mentioned, *vic*-dihalides could be used for the halogen transfer reactions (see section IIIa).

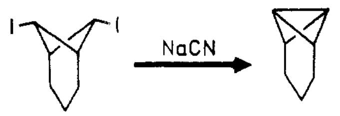


(45)



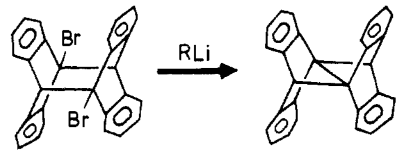
(46)

The cases of γ elimination[190,191] are especially worthwhile; an example is given by eq 47.[191] For this reaction, the authors presented arguments against the



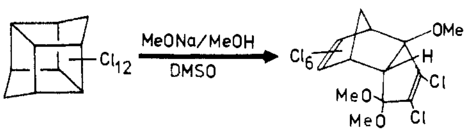
(47)

SET mechanism and accepted the one involving nucleophilic attack on the iodine atom by CN^- with subsequent loss of remaining halogene as I^-. Finally, eq 48 presents an even more fascinating case of ϵ elimination.[192]



(48)

The last example of an elimination that includes the rearrangement of the intermediate carbanion is shown in eq 49.[193] These examples offer clear evidence of the synthetic potency of the halogenophilic elimination, a reaction that has not yet been used to its full potential.



(49)

4. "Dimerizational" Displacement

The intermediate carbanion can interact with a second molecule of a substrate to give a substitution product, i.e., a "dimeric" one, in accord with route d in Chart I. An example of this pathway has been illustrated by eq 24.[93] Another interesting example may be the coupling of acetylene moieties (eq 7b).[21]

For synthetic purposes this method has been modified by the use of metallic (Li, Na, or K) derivatives of the carbanion and generation in situ of the second partner, namely a halogeno compound, via the halogenophilic pathway, as shown in eq 50.[126]

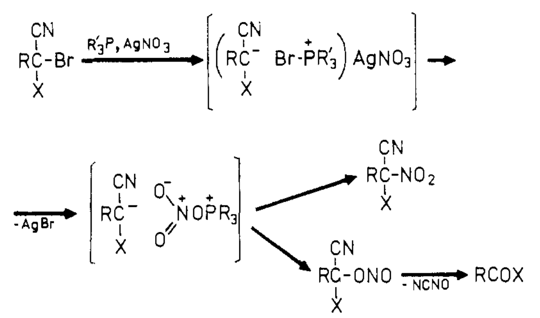
$$C_6H_5CH_2CN \xrightarrow{NaNH_2} [C_6H_5\bar{C}HCN] \xrightarrow{BrC(CH_3)_2C(CH_3)_2Br} C_6H_5CHBrCN \xrightarrow{C_6H_5\bar{C}HCN} C_6H_5CH(CN)\text{—}(CN)CHC_6H_5 \quad (50)$$

The anions of acetonitrile, benzhydryl, and benzyl derivatives have been used to obtain the corresponding substituted ethanes, and CCl_4, 1,2-dihalides (e.g., 2,3-dibromo-2,3-dimethylbutane), and polyhalides (e.g., hexachloroethane) may play the role of halogen-containing component for these couplings.[126,194-199] Such dimerizational processes seem to be potentially useful synthetically, especially in view of the modern development of the chemistry of carbanions.

5. "Concealed" Cases of X-philic Reactions

Equation 12 and Chart I are the schematic representation of the X-philic process for a noncharged nucleophile. Its primary result is the formation of an ion pair (Chart I), which may undergo reorientation of charged components (Chart I, path e) to give a new ion pair followed by the formation of a substitution product that is identical with the one formed via "normal" nucleophilic substitution. Such reactions are widespread in the chemistry of trivalent phosphorus: the transient quasiphosphonium salts containing halogen as a fourth ligand often give phosphonium salts that are identical with the expected ones for the usual S_N2 process. These reactions have been extensively studied from a mechanistic point of view.[19,27]

Halogen exchange in hexachlorocyclopentadiene is an example of a synthetic application of these reactions (eq 42c).[199] An interesting case of "concealed" halogenophilic reaction is the synthesis of α-nitro nitriles in the reaction of the silver nitrate–triarylphosphine complex with α-bromo nitriles (eq 51).[200]



(51)

The reactions for an ambident carbanion may lead to a rearranged product. For example, trialkyl phosphites react with substituted bromomalononitriles to give the corresponding N-phosphorylated ketenimines (eq 52). These compounds, depending upon the nature of the substituents, can be converted into phosphoramides and a number of heterocycles.[201-204] Another example is the reaction of chloronitrosoalkanes with $P(OR)_3$ (eq 53).[205]

$$R'C(CN)_2Br + P(OR)_3 \rightarrow [R'C(CN)_2]^-[BrP(OR)_3]^+ \rightarrow R'(CN)C{=}C{=}N\text{—}P^+(OR)_3Br^- \quad (52)$$

$$(RO)_3P + Cl_2FCNO \rightarrow [(RO)_3P^+Cl][ClFCNO]^- \rightarrow (RO)_3P(ON{=}CFCl)Cl \quad (53)$$

IV. Concluding Remarks

The goal of this paper is to present the current status of X-philic processes with a focus on their synthetic applications. The idea behind this was to attract the attention of organic chemists to this area, which is sufficiently rich in remarkable transformations and interesting reagents to be worthy of further exploration. In fact, carbon atom occupies a privileged position in organic chemistry where usually the discussion is centered on the various ways reagents attack the carbon center. Thus, the methodological aim of this paper is to remind the reader that "there are numerous other reactions of organic compounds which can be interpreted as being nucleophilic substitution at atom other than carbon...".[28]

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