TWO-PHASE REACTIONS IN THE CHEMISTRY OF CARBANIONS AND HALOCARBENES—A USEFUL TOOL IN ORGANIC SYNTHESIS

M. MĄKOSZA

Institute of Organic Chemistry and Technology,
Technical University (Politechnika), 00-662 Warsaw, Poland

ABSTRACT

Among numerous base–solvent systems usually applied for the generation of carbanions the two-phase system in which a concentrated aqueous sodium hydroxide solution in the presence of quaternary ammonium compounds acts as the proton acceptor seems to be particularly useful. Under these conditions, C—H acids up to 22 pK_a value can be converted into carbanions which exist in the organic phase as ion-pairs with the quaternary ammonium cation. Though the concentration of the carbanions is very low, and does not exceed that of the catalyst, numerous reactions have been successfully performed under these conditions. Thus, alkylation of various C—H acids, such as arylacetonitriles, some esters, ketones, aldehydes, cyclopentadiene hydrocarbons etc. proceeds in this way with higher selectivity and yield as compared to the traditional conditions. The two-phase system is of particular advantage for the generation of trihalomethylanions and dihalocarbenes thereafter, as it allows us to carry out all the reactions typical for these species in the simplest and most effective manner. It is moreover mostly convenient for the reactions of some carbanions with aromatic nitrocompounds (substitution of halogen and nitro group or electron-transfer) which otherwise give rather poor results. And the latest so far recognized application of this system in carbanion chemistry is the reaction of halocarbanions and ylides leading to oxiranes, cyclopropanes and alkenes.

The author's point of view is that the first common step of all these reactions, namely proton abstraction with the formation of a carbanion quaternary ammonium cation ion-pair, occurs on the phase boundary.

The ion-pair thus formed penetrates inside the organic phase where all subsequent steps (reactions of carbanions with various electrophiles, formation and reactions of halocarbenes etc.) take place.

INTRODUCTION

Reactions of carbanions with various electrophilic molecules are widely used as a key step in organic synthesis—the formation of C—C bonds. The same can be said about reactions of halocarbenes with a variety of reactants. Great possibilities offered by these reactions make searching for efficient and simple methods of generation of these species always very attractive. Carbanions are usually formed by proton abstraction from organic molecules.

There are numerous basic agents employed for this purpose, most of them being rather dangerous and expensive. A strictly anhydrous medium and a great excess of organic solvents are usually required making the procedures somewhat troublesome. Almost all of these disadvantages are eliminated when the reactions are carried out in two-phase systems in which concentrated aqueous sodium hydroxide is used in the presence of catalytic amounts of some quaternary ammonium compounds and serves for proton abstraction. These conditions introduced to practice mainly in our laboratory have attracted recently considerable attention. The interest in these two-phase conditions is well illustrated by many recent reviews concerning this and related topics by E. V. Dehmlow[1], J. Dockx[2], J. M. Fendler[3], A. Brändström[4] etc. The aim of this review is to present examples of the successful application of two-phase systems in organic synthesis and to discuss their scope and limitations. The author's suggestions concerning the mechanism of these catalytic processes will also be shown.

HISTORY

Alkali metal hydroxides are the most popular and widely used basic agents. Their application in carbanionic reactions is, however, restricted to relatively strong C—H acids and considerably limited by numerous side reactions (e.g. hydrolysis). Separately prepared quaternary ammonium hydroxides have also been applied as basic catalysts in some carbanionic reactions, e.g. Michael addition.

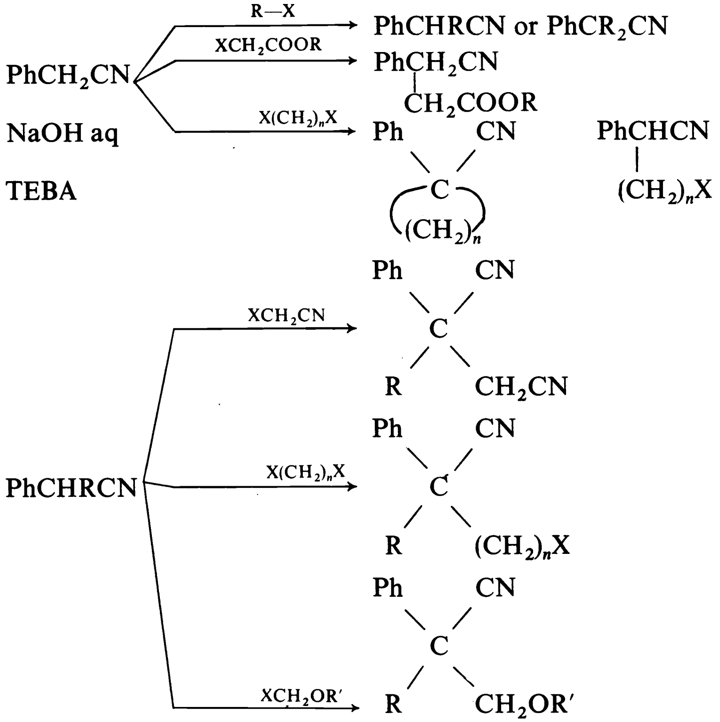
Reports that some quaternary ammonium compounds assist more or less effectively the reactions of carbanions carried out in the presence of aqueous alkali hydroxides in two-phase systems appeared in the early 'fifties. Jarousse[5] described ethylation and benzylation of phenylacetonitrile with corresponding chlorides in the presence of 50 per cent aqueous sodium hydroxide and 20 per cent molar triethylbenzyl ammonium chloride (TEBA). A few years later papers by Babayan[6] concerning the catalytic action of some quaternary ammonium compounds on the alkylation of ethyl acetoacetate and malonate in the presence of aqueous potassium hydroxide appeared.

Starting from this point we have elaborated the 'catalytic method' of generation of the various carbanions and halocarbenes in two-phase aqueous media[7]. Subsequently A. Brändström developed and applied in the chemistry of carbanions the 'ion-pair extraction' procedures[8] and C. M. Starks introduced the concept of 'phase-transfer catalysis'[9]. All of these phenomena seem to have a common driving force—the formation of organic phase soluble ion-pairs including quaternary ammonium cations.

ALKYLATION OF CARBANIONS

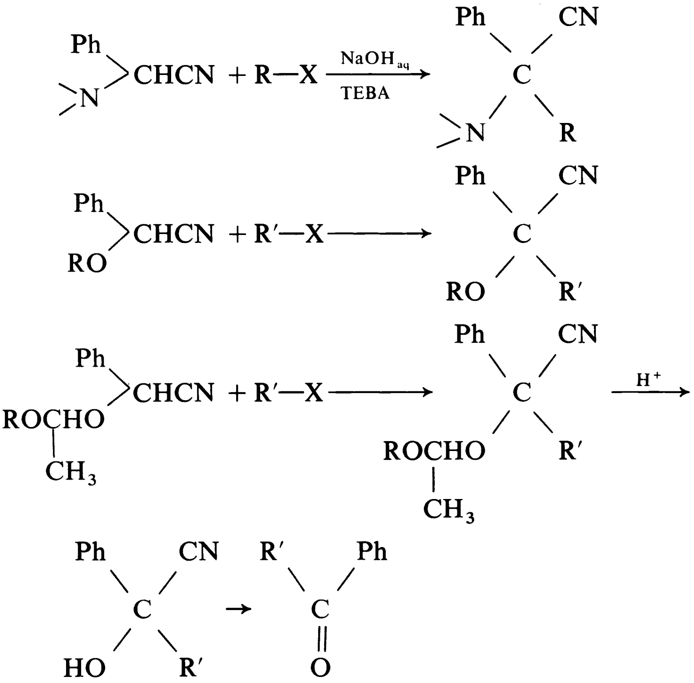
Arylacetonitriles

This reaction is widely used in synthesis since the arylacetic acids moiety is often encountered in drugs, natural products etc. The two-phase catalytic method has been widely applied to start with in the alkylation of phenylacetonitrile and its derivatives[7]. The procedure of alkylation is very simple: the nitrile and alkylating agent are stirred in the presence of aqueous 50 per cent sodium hydroxide and about 1 molar per cent of quaternary ammonium catalyst (we use mainly triethylbenzylammonium chloride, TEBA). The reaction is usually exothermic and gives the required product in high yield. Alkyl halides[10], tert- or sec-alkyl haloacetates[11], halonitriles[12], many other substituted haloalkanes[13] and even α-chloroethers[14] are sufficiently stable to be used as alkylating agents under these conditions. With dihaloalkanes many kinds of products can be obtained: ω-haloalkyl nitriles, isocyclic and heterocyclic nitriles[15, 16] etc.



The two-phase method has been found superior for the alkylation of some aromatic ring substituted phenylacetonitrile derivatives[17] as well as for 1-naphthylacetonitrile and its derivatives[18].

The alkylation of phenylacetonitrile with *p*-nitrobenzylchloride in the presence of relatively dilute aqueous sodium hydroxide (2N) and tetraalkylammonium catalyst has been described and claimed as a free radical process[19]. It seems, however, that the typical procedure employing concentrated alkali is more convenient for alkylation with this and isomeric *o*- and *m*-nitrobenzylchlorides[20]. The alkylation of phenylacetonitrile is also superbly performed through Brändström's procedure of 'ion-pair extraction'[21]; however, the use of an equimolar amount of tetrabutylammonium hydrogen sulphate makes this procedure less practical as compared with the catalytic one. Phenylacetonitrile derivatives substituted with heteroatoms in the α-position like α-dialkylamino or α-alkoxyphenylacetonitriles can be considered as 'masked' benzaldehyde cyanohydrine. They are easily alkylated in the presence of aqueous sodium hydroxide and TEBA[22]. The most interesting seems to be mixed acetal of benzaldehyde cyanohydrine which after alkylation and mild hydrolysis gives pure cyanohydrines of arylketones and then ketones[23].



Also the Reissert compound which can be considered as an α-acylamino derivative of phenylacetonitrile is readily alkylated in the presence of aqueous sodium hydroxide and TEBA[24]. The alkylation of arylacetonitriles under these two-phase catalytic conditions almost always gives higher yields than under other conditions. Another significant advantage is higher selectivity in the alkylation of phenylacetonitrile, which allows us to avoid considerable difficulties in the synthesis of practically important monoalkyl derivatives of phenylacetonitrile. The corresponding data are given below:

$$PhCH_2CN + RX \rightarrow \underset{\text{I}}{n\,PhCH_2CN} + \underset{\text{II}}{(1-n)PhCHRCN} + \underset{\text{III}}{n\,PhCR_2CN}$$

R—X	CH_3X		C_2H_5Br		$C_6H_5CH_2Cl$	
I%	21	6	15	6	31	21
II%	50	86	70	90	33	52
III%	19	8	15	4	30	19

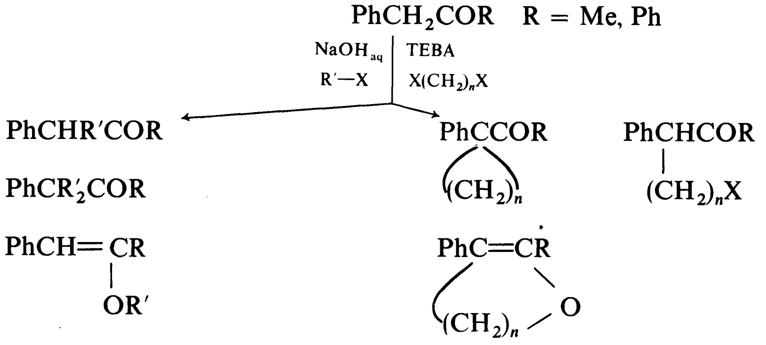
The first numbers: alkylation has been carried out using $NaNH_2/NH_3$, the second NaOH aq, TEBA.

The main reason for this high selectivity under catalytic conditions seems to be a low concentration of carbanions in the mixture (not exceeding the concentration of the catalyst)[25].

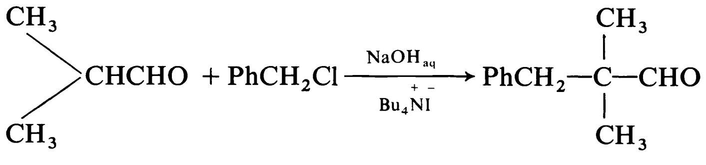
Pure aliphatic nitriles are rather weak C—H acids and cannot be anionized and then alkylated under these conditions. *S*-Phenylthioglycolonitrile, due to additional stabilization of the carbanion with divalent sulphur atom, is readily alkylated in the presence of aqueous sodium hydroxide and TEBA[26]. In a similar manner intramolecular alkylation of aliphatic nitriles leading to three-member rings can be performed[27].

Esters and other carbonyl compounds

The alkylation of malonic, cyanoacetic and acetylacetic esters in the presence of aqueous sodium hydroxide has interfered with the hydrolysis of the ester function. This limitation has been successfully overcome by using the 'ion-pair extraction' or 'extractive alkylation' technique in which relatively dilute sodium hydroxide solution and an equimolar amount of tetrabutylammonium hydrogen sulphate have been applied[8, 21, 28]. The catalytic procedure requires, however, an excess of concentrated sodium hydroxide solution so methyl or ethyl esters are mainly hydrolysed; *t*-butyl malonate, phenyl and diphenylacetate are considerably more stable towards alkali and are readily alkylated under these conditions[29]. The two-phase system with TEBA catalyst seems to be the most convenient for alkylation of benzylic ketones like desoxybenzoine or phenylacetone[30]. The ion-pair extraction procedure has also been found very convenient for the alkylation of these ketones[21]. In the case of acenaphthenone or β-tetralone dialkylated products are mainly formed[31]. Of particular value is alkylation of these ketones with dihaloalkanes leading to iso- and heterocyclic products (C, C or C, O alkylation) and ω-haloalkylketones.



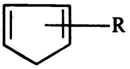
Even aliphatic aldehydes containing one 'active hydrogen' are readily alkylated with active alkylating agents in the presence of concentrated aqueous alkali and tetrabutylammonium iodide catalyst[32], for example:

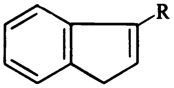


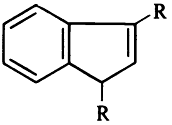
β-Diketones being relatively strong acids are readily extracted from aqueous alkali to chloroform or methylene chloride to form an ion-pair with tetrabutylammonium cation and then alkylated in high yield[33]. Similar procedures have been found most convenient for the alkylation of β-ketosulphones[34], benzoylmalonic ester[35] and methyl acetylpyruvate[36]. The problem of O versus C alkylation has been thoroughly studied in these reactions. Some heterocyclic compounds like 2-hydroxyfuran, 2-hydroxythiophene[37] and 1-benzothiophen-2(3H)-one[38] are also able to be alkylated by Brändström's extractive procedure. Alkylation of 1-substituted oxindoles has been described as proceeding in high yield under catalytic conditions[39].

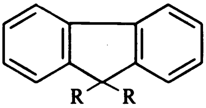
Hydrocarbons

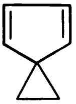
The acidity of cyclopentadiene, indene and fluorene enables us to convert them into carbanions under catalytic conditions. The carbanions formed are efficiently alkylated with mono- and dihaloalkanes. Particularly valuable results have been obtained in the case of indene[40]; the alkylation of fluorene is more difficult[41] due to its lower acidity. Some compounds thus obtained are:

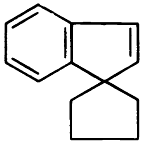


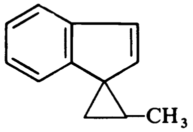


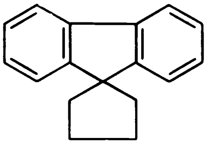








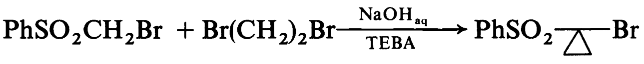




α-Halosulphones

We have found that halomethyl and dihalomethylphenylsulphones are sufficiently strong C—H acids to form carbanions under the action of aqueous sodium hydroxide in the presence of TEBA. These carbanions are stable enough to be effectively alkylated with a variety of alkylating agents[42].

$$PhSO_2CHBr_2 + R\text{—}X \xrightarrow[\text{TEBA}]{\text{NaOH}_{aq}} PhSO_2CBr_2R$$



$$PhSO_2CH_2Br + Br(CH_2)_2Br \xrightarrow[\text{TEBA}]{\text{NaOH}_{aq}} PhSO_2\text{—}\triangle\text{—}Br$$

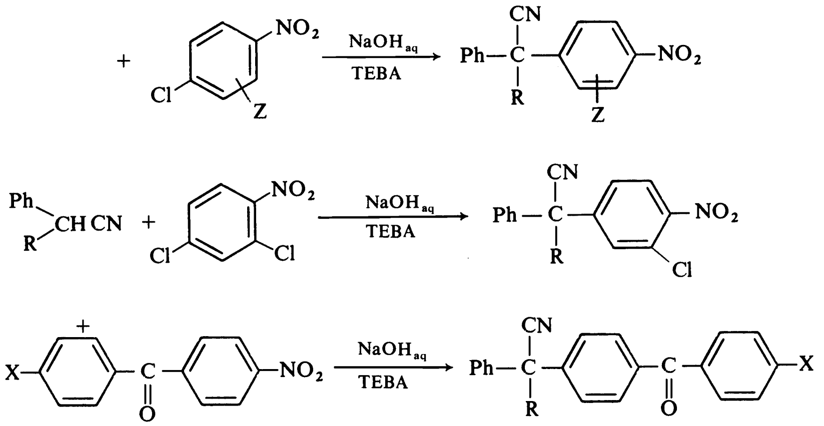
The scope and practical application of these reactions are not yet recognized, but the products are rather versatile materials for synthesis.

COMPOUNDS FORMING HETEROANIONS

Although the subject of this review is the reactions of carbanions in two-phase systems, it seems reasonable to present some examples of the alkylation of heteroanions. Alcohols usually do not react satisfactorily with alkylating agents in the presence of aqueous sodium hydroxide. In the presence of a quaternary ammonium catalyst this reaction gives rise to the formation of the corresponding ethers in high yields[43]. The alkylation of compounds containing N—H acidic groups is a process of great practical value. It can be efficiently achieved under catalytic two-phase conditions. Thus this method seems to be the most convenient for *N*-alkylation of phenothiazine, indole, diphenylamine, carbazole etc.[44] The ambident indole anion gives both *C*- and *N*-alkylated products. The intramolecular *N*-alkylation of *N*-carboethoxy β-iodoamine gave the aziridine derivative[45].

REACTIONS OF ARYLACETONITRILES WITH AROMATIC NITROCOMPOUNDS

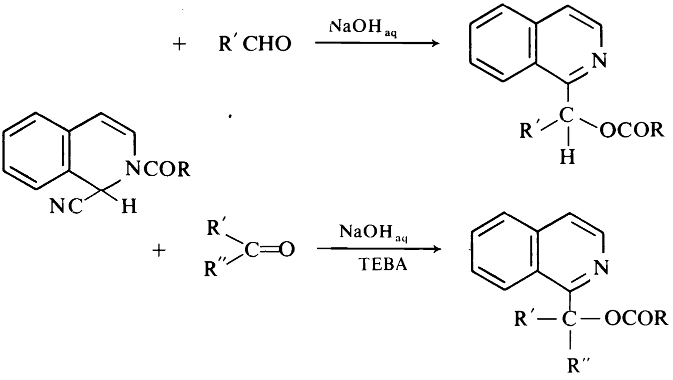
Catalytic two-phase conditions are the most convenient ones for the nitroarylation of phenylalkyl and diphenylacetonitriles with *o*- and *p*-halonitrobenzenes and their derivatives. Substitution of halogen by these carbanions results in the introduction of *o*- or *p*-nitroaryl substituents to the nitrile molecule. The reaction gives high yields of these products and is not accompanied by the formation of tars. The latter process usually takes place under other conditions. The nitroarylation proceeds satisfactorily with *o*- and *p*-halonitrobenzenes containing a variety of substituents if they are stable under the reaction conditions (halogen, CN, COR, CH_3, NO_2, COOR (tert), etc.)[21, 46, 47]. In 2,4-dichloronitrobenzene the 4-chloroatom is mainly substituted by phenylalkanenitrile carbanions[48]. These carbanions are also able to replace the aromatic nitrogroup when it is located ortho or para to strong electrophilic substituents. Thus reaction between phenylalkanenitriles and 4-halo-4′-nitrobenzophenones carried out in the presence of concentrated aqueous sodium hydroxide and TEBA results exclusively in substitution of the nitrogroup[46b, 49]. The substitution of the nitrogroup with these carbanions has also been observed in 3,4-dinitrochlorobenzene[46b].



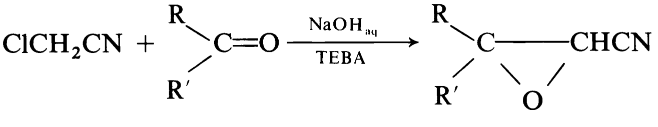
The reaction of diphenylacetonitrile with many aromatic nitrocompounds often proceeds under these conditions as electron-transfer leading to tetraphenylsuccinonitrile[46b].

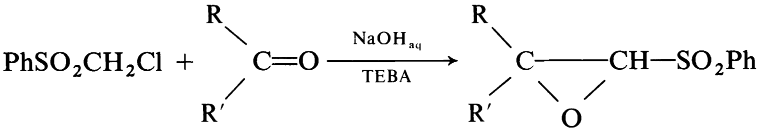
REACTIONS OF CARBANIONS WITH CARBONYL COMPOUNDS

The well-known condensation of Reissert compounds with aldehydes leading to the formation of esters-isoquinolenyl carbinol is usually carried out with butyllithium or sodium hydride as basic agents. This reaction proceeds considerably better in the presence of aqueous sodium hydroxide under two-phase conditions even without the quaternary ammonium catalyst. In the presence of the catalyst, Reissert compounds react also with ketones giving esters of tert-carbinols[50].

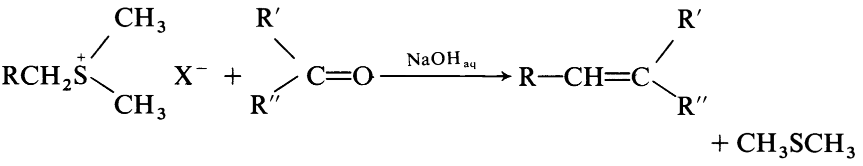


Two-phase catalytic conditions are very convenient for Darzens condensation of α-chloronitriles (chloroacetonitrile, 2-chloropropionitrile etc.) with aldehydes and ketones leading to glycidonitriles[51]. The condensation of α-halocarbonyl compounds (*t*-butylchloroacetate, phenacylchloride etc.) with aldehydes and ketones proceeds somewhat less satisfactorily. However, excellent yields of sulphonyl-substituted oxiranes have been obtained when α-halosulphones have been condensed with carbonyl compounds under these conditions[42].



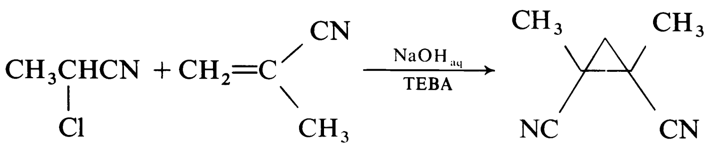


Two-phase systems with aqueous sodium hydroxide have been found very convenient for the generation of ylides from sulphonium and phosphonium compounds. Since these compounds contain an 'onium' cationic centre the reaction usually does not require a catalyst. M. J. Hatch has found that dimethylalkylsulphonium chlorides react with benzaldehyde in the presence of concentrated aqueous sodium hydroxide giving oxiranes[52]. Similar reactions have also been reported with ketones[53, 54].



The formation of ylides from trimethylsulphonium or sulphoxonium salts requires, however, the presence of a tetraalkylammonium catalyst, probably because these 'onium' cations are not sufficiently organophilic[54]. Despite the relative instability of phosphonium ylides in an aqueous medium, the Wittig reaction with aldehydes can be carried out successfully in the presence of concentrated aqueous sodium hydroxide[55a].

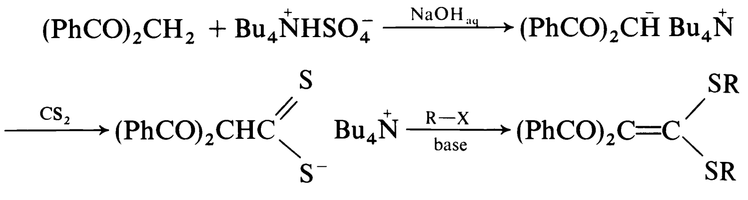
The carbanions of α-halonitriles[55b] and some sulphonium ylides[55a] generated under catalytic two-phase conditions are able to react with electrophilic double bonds giving corresponding cyclopropane derivatives. Particularly good yields have been obtained with 2-chloropropionitrile.



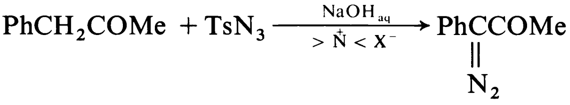
The reaction of 1-chloronitroethane and propane with acrylonitrile simply gives nitrocyclopropane derivatives[27].

REACTIONS OF CARBANIONS WITH VARIOUS ELECTROPHILIC MOLECULES

β-Diketones and malonic acid derivatives under ion-pair extraction conditions react with carbon disulphide giving salts of the corresponding dithiocarboxylic acids which in the presence of an excess of base form dianions. The latter have been alkylated to give ketene mercaptals[56].

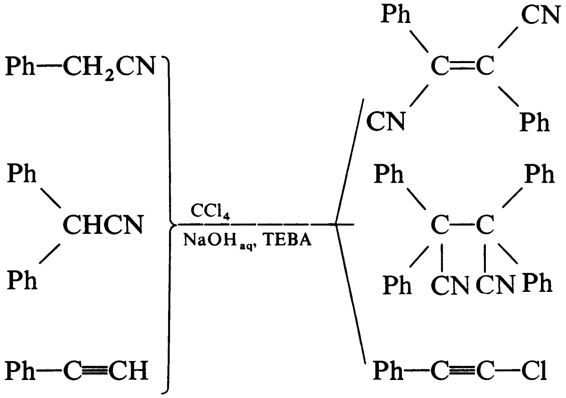


The application of the two-phase system seems to be very convenient in the synthesis of some aliphatic diazo compounds by diazogroup transfer to the carbanions of *t*-butyl malonate, ethyl acetoacetate, phenylacetone etc.[57].

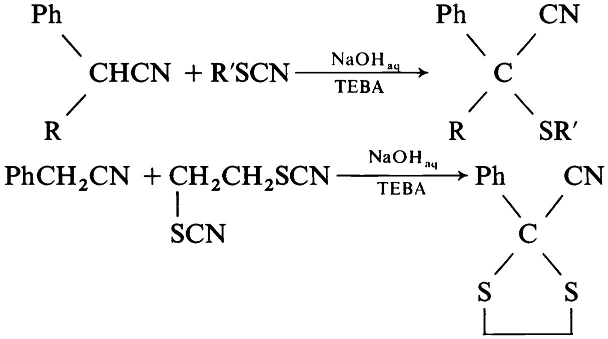


$$PhCH_2COMe + TsN_3 \xrightarrow[>\overset{+}{N}<X^-]{NaOH_{aq}} \underset{\underset{N_2}{\|}}{PhCCOMe}$$

Phenylacetonitrile reacts smoothly in the presence of concentrated aqueous sodium hydroxide with carbon tetrachloride giving dicyanostilbene; while diphenylacetonitrile gives in this reaction tetraphenylsuccinonitrile[58]. Even phenylacetylene is able to react under these conditions with carbon tetrachloride to give phenylchloroacetylene[59]. This is a unique example of the reaction of acetylenic carbanions under two-phase conditions.



Considerable attention has been turned recently to the direct thioalkylation of carbanions mainly with disulphides. We have found recently that arylacetonitriles and even some acetylenes are extremely easily thioalkylated under these conditions with organic thiocyanates[60].



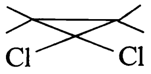
REACTIONS OF HALOCARBENES AND POLYHALOCARBANIONS

The application of two-phase catalytic systems in the chemistry of polyhalomethylcarbanions and halocarbenes is particularly important and attracts significant attention. In 1969 we reported that in the presence of concentrated aqueous sodium hydroxide and triethylbenzylammonium chloride (TEBA) catalyst chloroform is readily converted into trichloromethyl anion and then dichlorocarbene which in turn can be effectively trapped with alkenes giving corresponding dichlorocyclopropane derivatives in high yield[61].

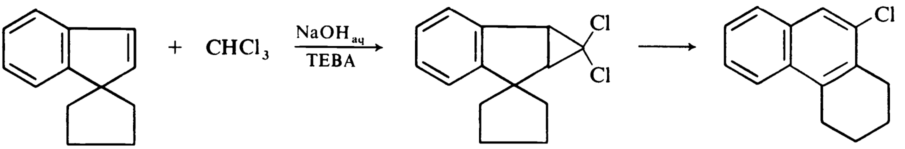
$$CHCl_3 + NaOH\,aq + {>}\overset{+}{N}{<}\overline{Cl} \rightleftharpoons CCl_3^- {>}\overset{+}{N}{<} + NaCl + H_2O$$

$$CCl_3^- {>}\overset{+}{N}{<} \rightleftharpoons CCl_2 + {>}\overset{+}{N}{<}Cl^-$$

$$CCl_2 + {>}C{=}C{<} \longrightarrow$$

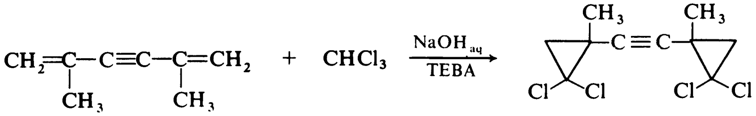


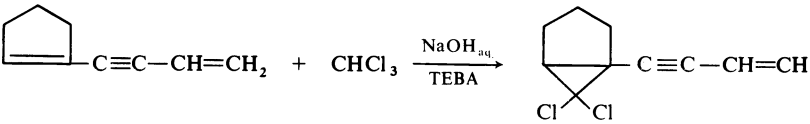
Despite the fact that the reaction occurs generally speaking in 'an aqueous medium' only a small fraction of the dichlorocarbene formed is hydrolysed (e.g. equimolar amounts of styrene and chloroform give about 90 per cent of dichlorocyclopropane with only seven per cent of hydrolysis). Considering the high sensitivity of dichlorocarbene towards OH^- anions and water it is obvious that the carbene is formed and reacts within the organic phase (Doering attempting to produce dichlorocarbene adducts in the presence of aqueous potassium hydroxide has observed almost exclusively hydrolysis and only 0.5 per cent adduct formation)[62]. This dramatic difference is due to the presence of quaternary ammonium cations which form organic phase soluble ion-pairs with trichloromethyl anions thus enabling them to pass from the phase boundary to the body of the organic phase. The method has been widely applied in many reactions of dichlorocarbene and for the generation of various other dihalocarbenes and is now considered the most convenient one. Dehmlow and Schönefeld have shown that dichlorocarbene produced in this way exhibits slightly increased activity—adds effectively to *trans*-stilbene and some acetylenic bonds[63]. Due to the high activity of dichlorocarbene di- and polyenes can be completely cyclopropanated under these conditions. Application of this method in the preparation of dichlorocyclopropane derivatives from monoalkenes has been described in many papers[61, 63–69]. As usually dichlorocarbene 'adducts' to cyclopentene or oxacyclopentene double bonds rearrange easily to six-membered ring derivatives[66, 67]. Reactions with the indene derivatives studied in our laboratory can also illustrate this point[70].



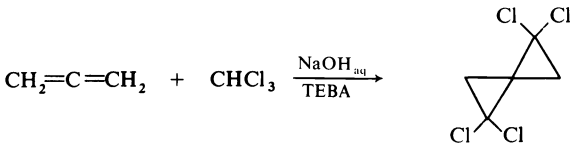
The above-mentioned high activity makes dichlorocarbene produced in the two-phase system an ideal reagent for the synthesis of polydichlorocyclopropanes from polyenes. Thus one-step synthesis of bis-adducts has been carried out from divinylbenzenes[71], conjugate dienes[63, 72] and polyenes—it was even possible to obtain the bis-adduct to cyclopentadiene[72] and the tetraadduct to cyclooctatetraene[73].

With conjugated enynes dichlorocarbene adds exclusively to double bonds[74].

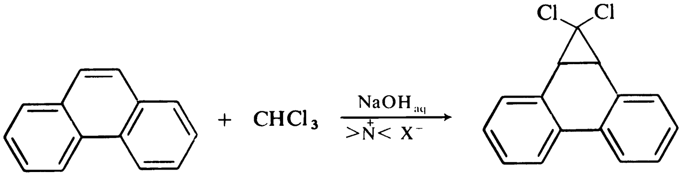




Polyadducts of dichlorocarbene have been obtained also from allenes and higher cumulenes[63, 75]



Dichlorocarbene generated in the two-phase system reacts efficiently with many aromatic compounds—phenanthrene[64, 76], alkyl derivatives of benzene and naphthalene[77], and 1,4,5,8-tetramethoxynaphthalene[78] giving a variety of products.



The insertion into C—H bonds is a typical reaction of carbenes. However, only thermally generated dichlorocarbene gives acceptable yields of the insertion products. Dichlorocarbene generated in the catalytic two-phase system inserts effectively into bridgehead C—H bonds in adamantane[79], and other polycyclic hydrocarbons[80] giving corresponding dichloromethyl derivatives in high yield. In the cases of simple substrates yields of the insertion products are moderate[81, 82]; nevertheless the reaction is of practical value since starting materials can usually be completely regenerated.

Dichlorocarbene generated in the two-phase system reacts in an unusual manner with higher alcohols giving corresponding chlorides in high yields[83]. Low aliphatic alcohols give a variety of products—mainly orthoformates, formates, alkenes, alkyl chlorides etc.[84]. Also α-glycols have been reported to react under these conditions in many directions[85]

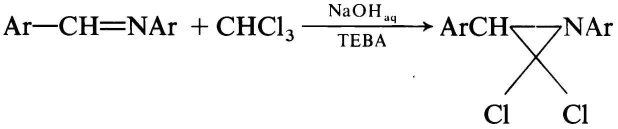
$$\geq C—OH + CHCl_3 \xrightarrow[\text{TEBA}]{\text{NaOH}_{\text{aq}}} \geq C—Cl$$

$$C_2H_5OH + CHCl_3 \xrightarrow[\text{TEBA}]{\text{NaOH}_{\text{aq}}} CH(OC_2H_5)_3 + (COOC_2H_5)_2 + CO(OC_2H_5)_2 \text{ etc.}$$

REACTIONS WITH NITROGEN COMPOUNDS

Primary amines are known to react with chloroform in the presence of alkali to form isonitriles; the yields obtained are, however, moderate. Considerably better yields of isonitriles have been obtained with dichlorocarbene generated in the two-phase system making this procedure useful in practice[86].

Similarly dichlorocarbene reacts with secondary amines giving corresponding formamides in high yield[87]. This simple formylation procedure can also be of interest for synthesis. Again, tertiary amines react with dichlorocarbene under these conditions. Initially formed nitrogen ylides rearrange in at least three modes to give a variety of products: formyl derivatives of secondary amines, dialkylamides of carboxylic acids, alkyl chlorides etc.[87]. Polycyclic tert.-α-diamine is cleaved by dichlorocarbene giving a bis-*N*-formyl derivative[88]. Another representative of tertiary amines, 1-methyl-1,2-dihydroisoquinoline, reacts with dichlorocarbene to give both insertion and addition products[82]. Both enamines and Schiff bases are rather sensitive towards aqueous alkali; nevertheless they react under catalytic conditions with dichlorocarbene giving the addition products: dichloroaziridine derivatives or dialkylaminodichlorocyclopropanes or products of their further transformations[89].



Relatively stable dichlorocyclopropane derivatives have been obtained from enamines of bicyclic ketones[90]. Dichlorocarbene generated in the two-phase system can be used as an efficient dehydrating agent to convert amides and oximes into nitriles, often in high yield[91].

$$\begin{array}{l} R\text{—}CONH_2 \\ \\ R\text{—}CH\text{=}NOH \end{array} + CHCl_3 \xrightarrow[\text{TEBA}]{\text{NaOH}_{aq}} R\text{—}CN$$

Dichlorocarbene adds in a simple manner to vinylsulphides giving corresponding dichlorocyclopropane derivatives[92]. It was observed that some allylic sulphides rearrange upon action of dichlorocarbene with C—S bond rupture to give esters of monothiocarbonic acids[93].

The high activity of dichlorocarbene generated in the two-phase system needs an explanation. Trichloromethyl anions which lose chlorine anions to form dichlorocarbene exist under these conditions in the form of ion-pairs with quaternary ammonium cations dissolved in the organic phase. There are no alkali metal cations within the organic phase, thus no possibilities for any carbenoid-like states. Despite the fact that the system as a whole is heterogeneous, dichlorocarbene is produced and reacts under homogeneous conditions—within the organic phase. This is not so when dichlorocarbene is generated by the action of potassium *t*-butoxide on chloroform (or by other typical methods) since the solubility of potassium trichloromethylide in the system is doubtful. Under catalytic conditions simultaneously with dichlorocarbene equivalent amounts of quaternary ammonium chloride are formed. The latter is soluble in the organic phase, thus the fast reversible reaction

$$CCl_3^- > \overset{+}{N} < \rightleftharpoons CCl_2 + > \overset{+}{N} < Cl^-$$

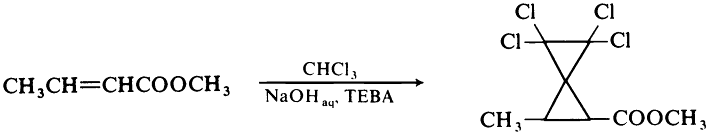
keeps dichlorocarbene 'ready for use' for quite a long time and allows it to react with reactants of low activity. This explanation is supported by the fact that the total rate of chloroform consumption is small in the absence of alkene in the organic phase and also depends on its nucleophilicity.

REACTIONS OF TRICHLOROMETHYL ANIONS

Despite the fact that trichloromethyl anions are rather short-lived species, they can be trapped with suitable electrophilic reagents. The catalytic conditions are particularly convenient for these reactions since both the reactants, trichloromethyl anion and an electrophilic reagent, are dissolved in the organic phase. Thus catalytic two-phase conditions are the most convenient for Michael addition of chloroform to electrophilic alkenes[94, 95] (acrylonitrile, acrylic acid esters, vinylsulphones, vinyl acetate, etc.).

$$CH_2{=}CHY + CHCl_3 \xrightarrow[\text{TEBA}]{\text{NaOH}_{aq}} CCl_3CH_2CH_2Y$$
$$Y = CN, COOR, SO_2R$$

The yields of the corresponding trichloromethyl derivatives are usually high, far exceeding those described under other conditions. In the case of weaker electrophilic alkenes, the addition of both trichloromethyl anion and dichlorocarbene occurs competitively being in fine balance depending on the alkene structure[94]. Dehmlow studying this reaction in detail has observed a variety of further transformations of the first-formed dichlorocarbene adducts[94a] e.g.



The addition of dichlorocarbene in place of trichloromethyl anion to electrophilic alkenes can be promoted by a high dilution technique. Polymethylated vinylketones add exclusively dichlorocarbene but not trichloromethyl anion[96].

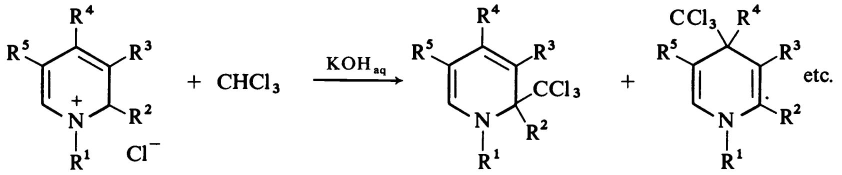
Very effective reagents for trapping trichloromethyl anions are organic thiocyanates; the reaction proceeds as CN group substitution with the formation of trichloromethyl sulphides in high yield[60]

$$CHCl_3 + RSCN \xrightarrow[\text{TEBA}]{\text{NaOH}_{aq}} RSCCl_3$$

On the other hand 'standard' two-phase conditions have been found to be insufficient for the synthesis of important phenyltrichloromethyl mercury (the source of dichlorocarbene under neutral conditions). These difficulties have been overcome using an aqueous sodium hydroxide–potassium fluoride solution instead of concentrated alkali. These changes being made, the two-phase catalytic method can be successfully applied in the preparation of phenyltrihalomethyl mercury[97].

$$PhHgCl + CHCl_3 \xrightarrow[\text{TEBA}]{\text{NaOH + KF}_{aq}} PhHgCCl_3$$

Kröhnke *et al.* have reported that some *N*-benzylpyridinium chlorides, when treated in chloroform solution with concentrated aqueous potassium hydroxide, add trichloromethyl anions giving rise to the formation of 2- and 4-trichloromethyl dihydropyridine derivatives[98].



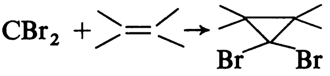
Our study of this reaction revealed that the addition occurs directly on the phase boundary[99].

FORMATION AND REACTIONS OF OTHER HALOCARBENES

Two-phase catalytic conditions have been found very convenient for proton abstraction followed by the formation of carbenes from all other trihalomethanes (excluding fluoroform and difluorochloromethane which are very weak C—H acids). Under typical catalytic conditions the yield of dibromocyclopropane derivatives obtained from bromoform and alkenes have not been high[63, 100, 101]. The method has nevertheless been applied even for the addition of dibromocarbene to dienes and polyenes[73, 74a, 102]. Skattebøl *et al.* have claimed an improved procedure which consists of using an excess of bromoform and prolonging the reaction for many hours[103]. A more advanced procedure employs the addition to the standard reaction mixture of 1–2 molar per cent of low alcohol which results in 10–30 per cent increase in the yield of dibromocyclopropane derivatives[104].

$$CHBr_3 + {>}\overset{+}{N}{<}Cl^- + NaOH \rightleftharpoons CBr_3^- \, {>}\overset{+}{N}{<} + NaCl + H_2O$$

$$CBr_3^- \, {>}\overset{+}{N}{<} \rightarrow CBr_2 + {>}\overset{+}{N}{<}Br^-$$

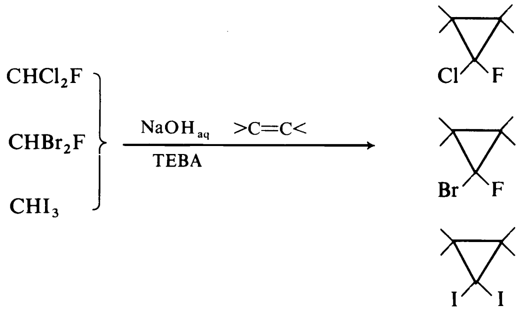


The reaction with dibromocarbene generated in the two-phase system has been used for substitution of the OH group by bromine in hydroxyadamantane derivatives[105]

Two-phase conditions can be applied to some reactions of tribromomethyl anions—addition to electrophilic alkenes[63, 95], and after corresponding modification (NaOH + KF solution instead of concentrated NaOH) to the synthesis of phenyltribromomethyl mercury[97]. Tribromomethyl anions stabilized with a small amount of alcohol can even be alkylated with active alkylating agents though in low yield[106].

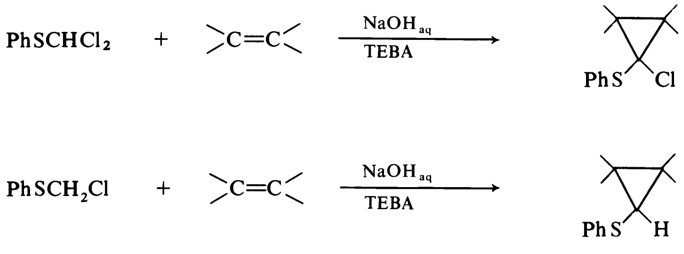
$$CHBr_3 + PhCH_2Cl \xrightarrow[\text{TEBA}]{NaOH_{aq}} PhCH_2CBr_3$$

Two-phase catalytic conditions have been successfully applied for the generation of a variety of other dihalocarbenes mainly by P. Weyerstahl and co-workers. They have reported the synthesis of chlorofluoro-[107]; bromofluoro-[107] and fluoroiodo-[108] cyclopropane derivatives in reactions of dichlorofluoromethane, dibromofluoromethane and fluorodiiodomethane and alkene with aqueous sodium hydroxide in the presence of TEBA. A similar reaction with chlorofluorocarbene occurs satisfactorily even with unsaturated alcohols[109] and enamines[90].

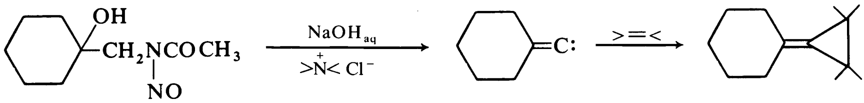


The effectiveness of the two-phase catalytic system is well illustrated in the synthesis of diiodocyclopropane derivatives by the addition of diiodocarbene (from iodoform) to alkenes[110].

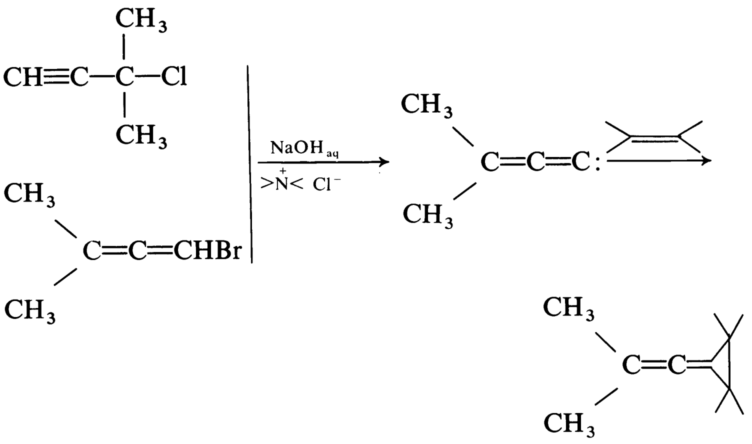
Dichloromethyl sulphides are relatively close analogues of haloforms since the 3*d* orbital effect of divalent sulphur stabilizes carbanions to a similar extent as that of chlorine or bromine. Thus dichloromethylphenyl sulphide treated with concentrated aqueous sodium hydroxide in the presence of TEBA forms chloro(phenyl)thiocarbene (via the corresponding carbanion), which is effectively trapped by alkenes with the formation of chloro(phenyl)-thiocyclopropane derivatives[111]. A similar reaction takes place with dichloromethylmethyl sulphide[112]. It should be pointed out that even chloromethylphenyl sulphide is able to form carbanion and then corresponding phenylthiocarbene which in turn is trapped with alkenes giving phenylthiocyclopropane derivatives[113]. This result indicates that the phenylthio-substituent stabilizes carbanions more effectively than chlorine does since methylene chloride does not form the carbanion and chlorocarbene under catalytic conditions[1]. Unfortunately there are no reports of attempts to trap the corresponding sulphur- and chlorine-stabilized carbanions.



The two-phase catalytic method has been successfully applied in the generation of unsaturated carbenes. Newman and his colleagues have reported that base-induced decomposition of *N*-(β-hydroxyalkyl)-*N*-nitrosoacetamides leading to alkylidene carbenes proceeds most conveniently in the presence of concentrated aqueous alkali and quaternary ammonium catalyst under two-phase conditions. The carbenes react with alkenes to give alkylidenecyclopropanes[114] or they can be trapped by some inorganic anions[115]. Their reactions with carbonyl compounds should also be mentioned[115].



2-Chloro-2-methylbutin-3 treated with potassium *t*-butoxide forms dimethylvinylidenecarbene which adds to alkenes with the formation of dimethylvinylidenecyclopropanes. In the presence of concentrated aqueous sodium hydroxide and TEBA the reaction proceeds better giving the addition products in higher yield[116]. Dimethylvinylidene carbene has also been formed under these conditions from 3,3-dimethyl-1-bromoallene[117].



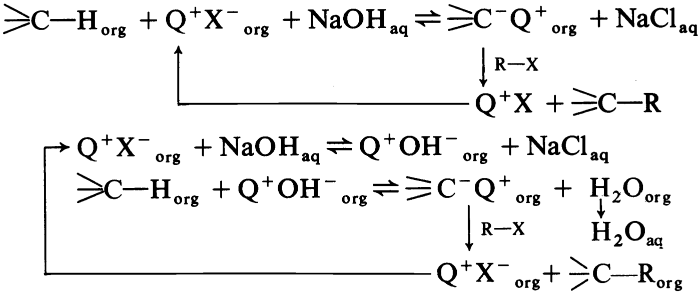
LIMITATIONS

The numerous examples of the successful application of two-phase catalytic and ion-pair extractive methods in the reactions of carbanions and halocarbenes illustrate the great versatility and value of these methods in organic synthesis. There are of course severe limitations in these methods. The most important one results from the fact that only relatively strong C—H acids can be anionized in the presence of aqueous sodium hydroxide. So far it seems that the upper pK_a limit is around 22, since the alkylation of fluorene still occurs whereas that of acetonitrile does not under these conditions. The second limitation is due to the instability of some C—H acids in the presence of aqueous alkali (e.g. hydrolysis of ester or other functional groups). This limitation can often be overcome by the use of more stable *t*-butyl esters, less concentrated sodium hydroxide solutions, larger amounts (up to equimolar) of quaternary ammonium compounds etc. The compounds reacting with carbanions or halocarbenes should also be stable in the presence of aqueous alkali. This limitation is, however, often overestimated since many alkali-sensitive compounds have been successfully used in these reactions. Another significant limitation of the catalytic procedure is that the products must not be stronger C—H acids than the starting compounds, otherwise the former produce relatively unreactive ion-pairs with the quaternary ammonium cations and the reaction is arrested. In these cases and in the cases of relatively strong C—H acids, the application of ion-pair extraction procedures is usually advantageous as compared to the catalytic or traditional homogeneous ones. The requirement that poorly solvated inorganic anions (e.g. I^-) should not be formed in the catalytic process has not been confirmed in some cases. Of course it does not limit the 'ion-pair' extractive procedure.

MECHANISM

All the reactions discussed above consist of at least two steps. The first step is the formation of carbanion by the abstraction of proton from C—H acid, the second the further transformation of the carbanion (the reaction with electrophilic reagent, the conversion into carbene etc.). The main question is where these two steps occur: in the aqueous phase, in the organic phase or at the interface (on the phase boundary). It is evident that carbanions exist in the organic phase in the form of ion-pairs with quaternary ammonium cations. This fact has been observed many times and does not require any additional evidence. Thus the reactions of carbanions proceed obviously within the organic phase. Specific features of these reactions connected with the existence of the ion-pairs in non-polar media have been discussed in detail by Brändström[4]. More difficult is the solution of the question where the abstraction of a proton and the ion-pair formation takes place. The catalytic reactions of carbanions in two-phase systems are generally considered as 'phase-transfer catalysed'[1]. This term introduced in 1971 by C. M. Starks[9, 118] came from a consideration such as that two reagents located in two immiscible liquid phases cannot react one with another since they cannot come together. A third compound able to bring the reagent from one phase to another, thus enabling the reaction to proceed, acts as a catalyst (phase-transfer agent). This approach can be illustrated by the cyanation of alkyl halide dissolved in hydrocarbon solvent with an aqueous solution of sodium cyanide. This reaction proceeds only in the presence of catalytic amounts of quaternary ammonium or phosphonium compounds which transfer CN^- anions to the organic phase where the reaction with alkyl halide takes place. Returning to the reactions of carbanions and halocarbenes one should understand the term 'phase-transfer catalysis' in such a way that OH^- anions are transferred from concentrated aqueous sodium hydroxide solution to the organic phase in the form of quaternary ammonium or phosphonium hydroxides. Thus according to the phase-transfer catalysis scheme abstraction of a proton from C—H acids and the formation of the ion-pairs carbanion–quaternary ammonium cation should occur also within the organic phase. In 1969 we proposed the formation of the organic phase soluble quaternary ammonium hydroxide as a step in the generation of trichloromethyl anion and dichlorocarbene in the presence of aqueous sodium hydroxide and TEBA[61].

Many observations are, however, better explained by the supposition that the first step of the carbanionic reactions—the abstraction of proton and the formation of ion-pair in the two-phase system—occurs on the phase boundary. The ion-pair migrates subsequently into the organic phase where all further reactions with the liberation of the catalyst take place. These two alternative mechanisms are visualized as follows:



$$>C{-}H_{org} + Q^+X^-_{org} + NaOH_{aq} \rightleftharpoons >C^-Q^+_{org} + NaCl_{aq} \xrightarrow{R-X} Q^+X + >C{-}R$$

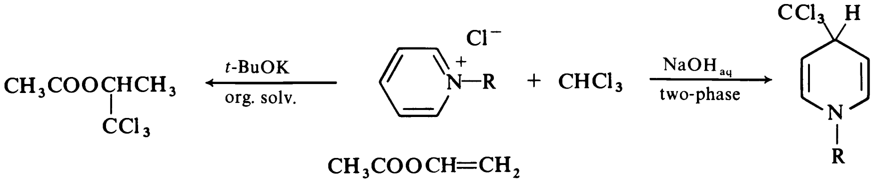
$$Q^+X^-_{org} + NaOH_{aq} \rightleftharpoons Q^+OH^-_{org} + NaCl_{aq}$$

$$>C{-}H_{org} + Q^+OH^-_{org} \rightleftharpoons >C^-Q^+_{org} + H_2O_{org} \rightarrow H_2O_{aq}$$

$$>C^-Q^+_{org} \xrightarrow{R-X} Q^+X^-_{org} + >C{-}R_{org}$$

Of course in the case of strong C—H acids which are anionized to a great extent in the presence of dilute aqueous sodium hydroxide, quaternary ammonium compounds act only as the agent to extract (transfer) the organic anions from the aqueous phase to the organic one. However, the most important application of the two-phase systems deals with those C—H acids which are difficult to anionize and which do not form sodium derivatives in the presence of aqueous sodium hydroxide solutions. In these cases there are no organic anions (carbanions) in the aqueous phase and there is complete immiscibility of both phases (it has been found that in the system $PhCH_2CN/NaOH$ 50 %, concentration of the nitrile in the aqueous phase is below 2 p.p.m., and the base in the organic phase is below 2 p.p.m.). Thus there remain two possibilities for the site of proton abstraction and ion-pair formation—the organic phase (following the scheme of 'phase-transfer catalysis' with OH^- anions to be transferred) and the phase boundary. Extraction experiments have shown that in the two-phase system organic solvent (e.g. acetonitrile)/NaOH, 50 %, more than 99 per cent of triethylbenzylammonium chloride remains in the form of chloride and that in the sequence SO_4^{2-}, F^-, OH^-, Cl^-, Br^-, I^- each anion in the organic phase is replaced by its neighbour on the right. Considering the small amounts of catalyst used in preparative experiments and the fact that during the alkylation or dihalocarbene formation large amounts of halogen anions are produced one can expect only a very low concentration of OH^- anions in the organic phase. However, an acid–base equilibrium reaction is fast as compared to the other reactions so this way of formation of carbanions (though of low probability) cannot be excluded.

Abstraction of a proton on the phase boundary has been well documented since there are some carbanionic reactions proceeding in the two-phase system in the absence of the catalyst. Commonly accepted proof of the formation of carbanions is isotope exchange. Many compounds being weak C—H acids exchange H for D when stirred with concentrated $NaOH/D_2O$ solution in the absence of the catalyst. Because of the complete immiscibility of these two phases this reaction is believed to proceed on the phase boundary. There are also synthetically useful carbanionic reactions occurring in this way, e.g. as discussed earlier, the condensation of Reissert compounds with aldehydes[50] and addition of CCl_3^- anions to *N*-alkylpyridinium salts[98, 99]. The latter reaction is of particular interest since quaternary pyridinium salts resemble catalysts used for carbanionic reactions. The formation of CCl_3^- adducts in 'pure' reactions which is not accompanied by the formation of tars testifies against extraction of OH^- anions, since they add to pyridinium salts giving very unstable products. Moreover there is evidence that new C—C bonds are formed directly on the phase boundary without extraction of Py^+–R CCl_3^- ion-pairs to the body of the organic phase. This evidence came from competitive experiments with vinylacetate competing for the CCl_3^- anions. In the two-phase system only dihydropyridine derivatives are formed whereas in homogeneous conditions (in the presence of *t*-BuOK) exclusively trichloromethyl ethyl acetate was obtained[99].



These and some other observations allow one to come to the conclusion that in the two-phase system comprising relatively weak C—H acid (with or without an organic solvent) and concentrated aqueous sodium hydroxide, abstraction of a proton with the formation of carbanion does occur even in the absence of the catalyst. These carbanions cannot, however, leave the phase boundary to go into the organic phase since their counterions (Na^+) are strongly solvated in the aqueous phase and poorly in the organic one. In this 'adsorbed' state the carbanions are very unreactive being able to react only with strong electrophiles or electrophiles positively charged. Quaternary ammonium compounds serve as a source of organic cations able to form the organic phase soluble ion-pairs with carbanions, thus enabling them to pass into the organic phase and undergo further transformation there. This scheme may be oversimplified; quaternary ammonium compounds seem to play an important role in proton abstraction steps decreasing the energy of the transition state by influence of the positive charge from the opposite side of the reaction centre.

Summarizing this discussion we can formulate three different ways for the action of quaternary ammonium catalysts in two-phase systems, all of them based on the formation of the organic phase soluble quaternary ammonium derivatives.

1. Extraction of inorganic anions to the organic phase—phase transfer catalysis, operative mainly in the reactions of such anions as CN^-, SCN^-, MnO_4^- etc. with alkyl halides, alkenes etc. Formation of carbanions through reaction with extracted OH^- anions is also possible, but seems to take place to a less extent.

2. Extraction to the organic phase of carbanions of relatively strong C—H acids which are formed upon the action of dilute aqueous sodium hydroxide and are soluble in this solution. This corresponds to phase-transfer catalysis

or the ion-pair extraction technique depending upon whether catalytic or equimolar amounts of quaternary ammonium compounds are used.

3. Formation of organic phase soluble ion-pairs with carbanions 'adsorbed' on the phase boundary with more or less active participation of quaternary ammonium cations in the proton abstraction stage. This seems to be the main pathway in carbanionic reactions of relatively weak C—H acids no matter whether catalytic or extractive techniques have been used.

It is obviously impossible to delineate borderlines between these three routes, one of them being dominant in each particular case.

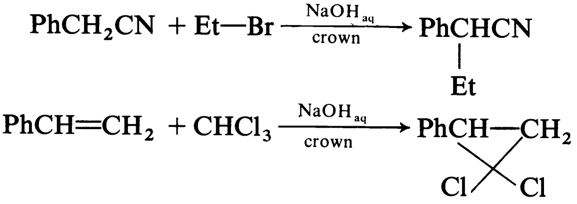
Some authors have classified these reactions as occurring in cationic micelles[3, 83]. Though there are some apparent similarities between the systens discussed and micellar ones, the mode of catalytic action of the onium compounds is different from that in micellar catalysis and their catalytic activity is not parallel with surface activity.

Quaternary ammonium or phosphonium compounds are not the only ones which are able to act as catalysts in two-phase systems. One can imagine that any other non-electrophilic and organophilic cations can behave similarly. These phenomena have been observed in the case of alkali metal cations strongly solvated with some organic solvents (DMF, HMPT etc.). Thus the latter can 'catalyse' the formation of carbanions in two-phase systems, e.g.

$$\mathrm{Ph_2CHCN_{org} + NaOH_{aq} \rightleftharpoons (Ph_2\bar{C}CN\ Na^+_{solv})_{org} + H_2O_{aq}}$$

solvent	C_6H_6	CH_3CN	OME	THF	Py	DMF	HMPT
% of $\geqslant C^-$	0	1	3	3	12.5	88	94

Recently prepared crown ethers have been recognized as very powerful neutral agent complexing alkaline metal cations[119]. One can expect that the complex cation $Na^+ \cdot$ crown will behave entirely as an organic cation and be able to form organic solvent soluble ion-pairs with various anions and thus act as 'phase-transfer' agent for inorganic anions or catalyst in reactions which require the formation of carbanions. These expectations have been completely proved in reactions with inorganic anions (i.e. MnO_4^-)[120] as well as in reactions with carbanions and halocarbenes. In the latter reactions carried out in the presence of 50 per cent aqueous sodium hydroxide dibenzo-crown-6 has shown a catalytic activity equal to TEBA which is then quantitatively regenerated[121].



$$\mathrm{PhCH_2CN + Et{-}Br \xrightarrow[crown]{NaOH_{aq}} \underset{\displaystyle Et}{\underset{|}{PhCHCN}}}$$

Two-phase catalytic systems have been used in the reactions of carbanions and halocarbenes for less than ten years but they became widely accepted only about four years ago. Thus our knowledge of the potential possibilities of such methods is far from sufficient.

In all reported examples the catalytic and ion-pair extractive two-phase methods have been far superior to other methods especially in relation to simplicity, selectivity, yields etc. One can expect that in the near future these methods will be used as a typical tool in organic synthesis.

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