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Reactions of Carbanions and Halogenocarbenes in Two-phase Systems

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The review surveys studies on a new two-phase catalytic method whereby reactions between carbanions and halogenocarbenes can be carried out. Numerous examples of the successful application of this method to various (mainly alkylation) reactions of carbanions and halogenocarbenes are given and the advantages, disadvantages, and limitations of the method compared with the traditional single-phase or pseudo-single-phase methods are discussed. Also considered are possible mechanisms of catalysis by ammonium salts in these systems.
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I. INTRODUCTION

The reactions of carbanions and halogenocarbenes with various compounds are widely used to form new C–C bonds, which constitutes one of the most important problems in organic synthesis. In this connection, the development of new highly effective methods for the generation of carbanions and halogenocarbenes is of considerable interest.

The principal method for the generation of carbanions involves the abstraction of a proton from a carbon atom in an organic molecule; this process is also the first stage in the formation of halogenocarbenes in the so called α-elimination reaction. Many different bases, the majority of which are very sensitive to moisture and air, require the use of considerable amounts of thoroughly dehydrated organic solvents, are explosive, and expensive, have been used for this purpose. It is therefore desirable to carry out the process in a homophase system, which is by no means always possible. Even when the system is apparently single-phase, it is frequently in essence a pseudo-homogeneous system in which the solution of a base or carbanion is colloidal, the molecular weights of the species amounting to thousands of units.

Many of the difficulties and disadvantages enumerated above are eliminated when the synthesis is carried out in a two-phase catalytic system where a concentrated solution of sodium hydroxide in the presence of catalytic amounts of quaternary ammonium compounds plays the role of the base which abstracts protons from the C–H acid in the organic phase. This method, which was introduced into laboratory practice mainly by the present author[1], proved to be extremely effective for many types of reactions of carbanions and particularly halogenocarbenes. The large-scale application of two-phase systems in the chemistry of carbanions and halogenocarbenes began as late as 1970, but since then more than two hundred original publications and several reviews have appeared[2-7]. This provides a good illustration of the increasing interest in these procedures and their extensive possibilities.

The first example of the known use of a two-phase system in the chemistry of anions is provided by Jarousse's[8] brief communication about the possibility of the benzylation and ethylation of phenylacetonitrile by the corresponding chlorides in the presence of 50% aqueous sodium hydroxide and 20 mole % of benzyltriethylammonium chloride. The catalytic action of certain tetra-alkylammonium salts on the alkylation of acetoacetic and malonic esters in the presence of aqueous potassium hydroxide was subsequently described by Babayan[9,10]. Using these data, the present author developed a catalytic method for the alkylation of phenylacetonitrile and its derivatives[1] and the catalytic system was subsequently applied to other reactions of carbanions and also for the generation of halogenocarbenes.

Brändström and Junggren[11] subsequently demonstrated the considerable possibilities in organic chemistry of the method involving the extraction of ion pairs and applied it to the reaction of enolate anions (mainly alkylation reactions). A distinctive feature of the ion pair extraction method, for example "extractive alkylation", is the use of an equimolar amount of a tetra-alkylammonium compound, which in many cases makes it possible to isolate the tetra-alkylammonium–carbanion pair. In 1971 Starks[12] used the concept of "phase-transfer catalysis", based on the transfer of the regulating species by tetra-alkyl-ammonium or phosphonium cations from one phase to another (usually from the aqueous to the organic phase) in reactions involving inorganic atoms. The above methods are based on the formation of ion pairs comprising the tetra-alkylammonium cation and an organic or inorganic anion, which are soluble in organic non-polar solvents. It has been recently discovered that, apart from tetra-alkylammonium or phosphonium salts, crown ethers, which form very stable endocyclic complexes with potassium or sodium ions, can also play the role of catalysts in the two-phase system considered[13]. Potassium and sodium ions are capable of forming ion pairs, soluble in non-polar solvents, with organic and even inorganic anions[14].

The subject of the present review is reactions of carbanions and halogenocarbenes in liquid two-phase systems. The influence of tetra-alkylammonium salts or crown ethers on the reactions of anions in homophase systems as well as on the reactions of inorganic anions in two-phase systems will not be considered.

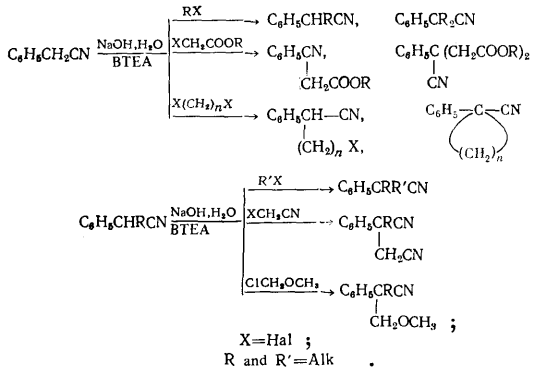
II. REACTIONS OF CARBANIONS

1. Alkylation of Arylacetonitriles

The two-phase catalytic method was first widely used to alkylate phenylacetonitrile and its derivatives. This process is important from the practical point of view, since the structural elements of phenylacetic acid are frequently encountered in drugs, natural products, etc. Compared with previously available procedures, the method is extremely simple[15]: the nitrile, the alkylating agent, and an excess of 50% aqueous sodium hydroxide solutions are stirred vigorously, usually at room temperature, in the presence of ~1 mole % of a quaternary ammonium compound. Benzyltriethylammonium chloride (BTEA) is usually employed, being most readily available and convenient, although it does suffer from a number of disadvantages. In particular, the stability of BTEA is limited in a highly basic medium and it can act as an alkylating agent itself. Alkylation proceeds with a moderate exothermicity, giving high yields of the expected compounds. Despite the fact that the process proceeds in an aqueous solution of alkali, appreciable hydrolysis of phenylacetonitrile begins under these conditions only at temperatures above 90°C; the majority of alkylating agents are also fairly stable under these conditions.

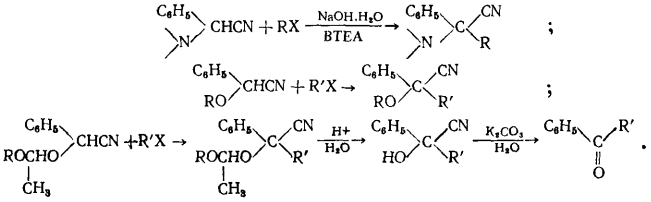
Thus, catalytic alkylation of phenylacetonitrile can be achieved using alkyl and alkenyl halides[16-18], halogenoacetates derived from secondary and tertiary alcohols[19], halogenonitriles[20-21], and certain other substituted halogenoalkanes[17,22]. Even α-chloroalkyl ethers are fairly stable under these conditions and can be used as effective alkylating agents[23]. Alkylation by dihalogenoalkanes makes it possible to obtain ω-halogenoalkyl derivatives, iso- and hetero-cyclic nitriles, dinitriles, etc.[24-26]

Analogous alkylation reactions proceed successfully in the case of diphenylacetonitrile[23,27-31] and phenylalkylacetonitriles[18,23,28,30,32]. In almost all the instances enumerated above, the results of alkylation (the yield and purity of the products) are much superior to those obtained by traditional methods.



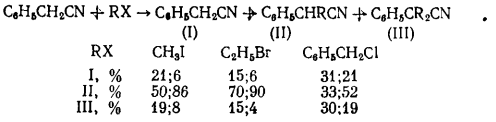
The two-phase method also gave excellent results in the alkylation of phenylacetonitrile derivatives substituted in the aromatic ring[33-35] and of naphthylacetonitrile[36]. Alkylation of phenylacetonitrile by *p*-nitrobenzyl chloride in the presence of dilute alkali (2 *N* NaOH) and a tetraalkylammonium catalyst is believed[37] to proceed via an electron transfer stage as a free-radical process. In the present author's view, typical conditions (50% NaOH) are more suitable for the alkylation of arylacetonitriles by *o*-, *m*-, and *p*-nitrobenzyl chlorides, the electron transfer stage being non-obligatory[38]. Brändström's "extraction of ion pairs"[39] gives very satisfactory results in the alkylation of phenylacetonitrile, but the use of an equimolar amount of expensive tetrabutylammonium hydrogen sulphate makes this method less convenient in practice than the catalytic procedure.

Alkylation of phenylacetonitrile derivatives substituted in the α-position by dialkylamino- or alkoxy-groups, whose properties are similar to those of cyanohydrins, is important for organic synthesis. The alkylation of these compounds in the presence of an aqueous solution of NaOH and BTEA proceeds without difficulty[40,41]. The example of the mixed acetal of benzaldehyde cyanohydrin, which gives rise to aryl ketone cyanohydrins (which are in essence unobtainable by other methods) after alkylation and mild hydrolysis, is particularly interesting[42]. Attempts at the alkylation of aliphatic aldehyde cyanohydrins in a two-phase system led to only moderate yields of cyanohydrin esters: *C*-alkylation was not observed[43]:



Reissert compounds, which are structurally related to α-acylamino-derivatives of phenylacetonitrile, are also readily alkylated in the presence of an aqueous solution of concentrated alkali and BTEA.[44]

Thus the advantages of the two-phase system do not consist solely in the simplicity of the reactions, the use of a cheap base, and the elimination of experimental difficulties associated with the consumption of amides, hydrides, organometallic compounds, etc. A factor which is no less important is the improvement of yields and the high selectivity of the reactions, as a result of which it is possible to avoid difficulties in the synthesis of monoalkylated phenylacetonitrile derivatives which are important in practice. This is clearly illustrated by the following scheme:

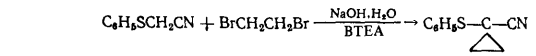


RX	CH_3I	C_2H_5Br	$C_6H_5CH_2Cl$
I, %	21;6	15;6	31;21
II, %	50;86	70;90	33;52
III, %	19;8	15;4	30;19

In each column, the first set of numbers characterises the composition of the alkylation products obtained in the presence of $NaNH_2$ in liquid ammonia[45,46] and the second set characterises the product compositions in a two-phase catalytic system[46]. The main cause of the high selectivity of alkylation under catalytic conditions is apparently the low concentration of the carbanions present simultaneously in the system, which does not exceed the concentration of the catalyst[46].

Unsubstituted aliphatic nitriles, which are very weak C–H acids, do not form carbanions under these conditions and are naturally incapable of being alkylated. The presence of carbanion-stabilising substituents, such as the arylthio-group in *S*-phenylthioglycolonitrile, permits

the alkylation of these nitriles in the presence of an aqueous solution of NaOH and BTEA [47]:

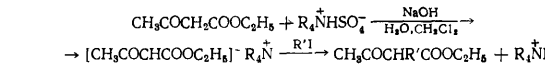


Under analogous conditions, the nitriles of aliphatic 3-chloro-3-nitroacids cyclise to form a three-membered ring [48].

2. Alkylation of Carbonyl Compounds

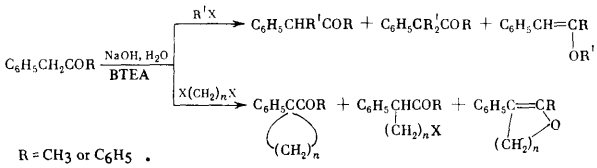
The ester group is usually readily hydrolysed by an aqueous solution of alkali, which hinders the alkylation of malonic, acetoacetic, and cyanoacetic esters. Nevertheless, Babayan succeeded in alkylating these esters in the presence of an aqueous KOH solution [9,10].

The method based on the extraction of ion pairs (the so called extractive alkylation), requiring the use of fairly dilute alkali and equimolar amounts of tetrabutylammonium hydrogen sulphate, gives excellent results in such instances [11,39,49,50]:



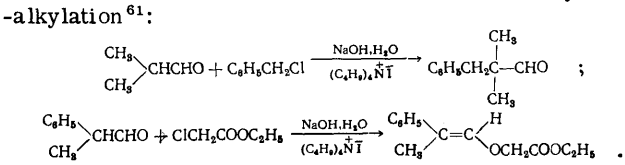
A typical catalytic process requires the use of concentrated alkali, which causes the hydrolysis of methyl or ethyl esters. t-Butyl esters are much more resistant to base hydrolysis and t-butyl malonates, phenylacetates, and diphenylacetates can be alkylated with high yields under these conditions [51].

The two-phase catalytic system is very convenient for the alkylation of α-phenylketones, such as desoxybenzoin or phenylacetone [52-54]. A high yield was also obtained when a crown ether was used as the catalyst [55]. The method of the extraction of ion pairs also gives satisfactory yields in such cases [39]. Cyclic α-arylketones, acenaphthenone [56], and β-tetralone [57] usually form dialkylation products under these conditions. The results of the alkylation of ketones by dihalogenalkanes, which leads to the formation of iso- and hetero-cyclic structures, ω-halogenoketones, etc., are particularly interesting [53,54]:

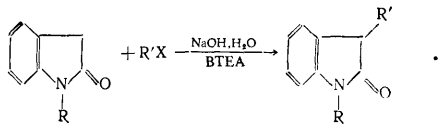


Alkylation by α-chloroesters yields mainly *O*-derivatives [58].

Even simple ketones may be successfully alkylated by allyl chlorides in a two-phase catalytic system [59]. Direct alkylation of α-substituted aliphatic aldehydes in the presence of concentrated alkali and a tetrabutylammonium salt gives unexpectedly satisfactory results [60]. The use of chloroacetate esters in such cases leads exclusively to *O*-alkylation [61]:



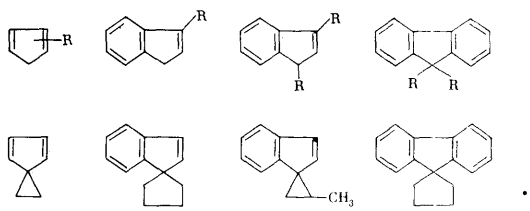
β-Diketones, which exhibit a high acidity, can be readily converted into tetrabutylammonium derivatives by extraction from aqueous solutions into chloroform or methylene chloride with subsequent alkylation to give a very high yield of the product [62,63]. The same ion pair extraction procedure is the most suitable for the alkylation of α-ketosulphones [64,65], benzoylmalonic ester [66], and acetopyruvic acid [67]. The problem of *CO*-alkylation was also thoroughly investigated in the above studies. Certain C–H acid heterocycles, for example 2-hydroxyfuran, 2-hydroxythiophen [68], and derivatives of 2-hydroxybenzothiophen [69], are capable of being alkylated by Brändström's extractive method. Many oxindoles substituted in the 1-position can be alkylated catalytically with excellent yields [70]:



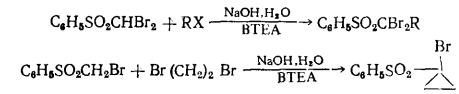
An interesting example of liquid–solid two-phase systems has been described in a study [71] where sodioacetoacetic ester, which is insoluble in the solvents employed, was alkylated in the presence of a tetra-alkylammonium salt. A detailed study has been made of the alkylation of acetoacetic ester by ammonium salts in a two-phase system [72].

3. Alkylation of Hydrocarbons and Other Compounds

Hydrocarbons of the cyclopentadienyl series (cyclopentadiene, indene, and fluorene) are sufficiently acid to be converted into carbanions under our conditions. These carbanions may be successfully alkylated by mono-, and di-halogenoalkanes. The alkylation of indene proceeds particularly satisfactorily [73]. Fluorene is alkylated with somewhat more difficulty because of its lower acidity [74]:



The present author found that the C–H acidity of aryl halogenomethyl and aryl dihalogenomethyl sulphones is sufficient for the formation of carbanions when they react with an aqueous solution of sodium hydroxide in the presence of BTEA. These carbanions are fairly stable, so that their alkylation usually takes place with satisfactory yields [75]:



Although the possibilities of these reactions are far from having been elucidated, presumably the alkylation products will serve as useful starting materials in many syntheses.

4. Compounds Forming Heteroanions

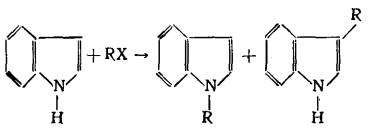
Despite the fact that the subject of the present review is the reactions of carbanions in two-phase systems, it is useful to quote certain examples of the alkylation of heteroanions. In the first place, mention should be made of Babayan's study of the influence of tetra-alkylammonium

salts giving rise to the exclusive *O*-alkylation of phenoxide anions in an aqueous two-phase system[76]. Systematic studies of the alkylation of phenoxide anions in a catalytic two-phase system have been described[78] and the problem of *CO*-alkylation has been discussed[72].

In the presence of a tetra-alkylammonium catalyst, an aqueous solution of sodium hydroxide is a very convenient condensing agent in the synthesis of ethers by Williamson's method[79].

Ammonium catalysts and crown ethers catalyse very effectively the formation of acetates by the alkylation of potassium acetate in benzene or acetonitrile[80,81]. The use of tributylhexadecylphosphonium proved very convenient for the preparation of dialkyl and alkyl aryl sulphides[82].

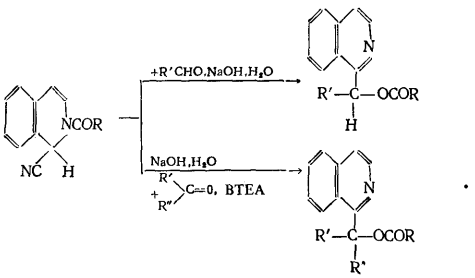
The alkylation of compounds containing N–H acid groups is of considerable practical importance. *N*-Alkylation of phenothiazine, diphenylamine, carbazole, indole, etc. proceeds satisfactorily under two-phase catalytic conditions[83]:



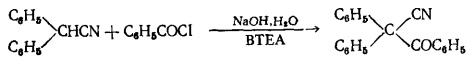
The ambident indole anion forms small amounts of *C*-alkylation products in this reaction. The formation of the aziridine ring by the intramolecular alkylation of *N*-ethoxycarbonyl-β-iodoethylamine has also been described[84].

5. The Reactions of Carbanions and Ylids with Polar Double Bonds.

The condensation of Reissert compounds with aldehydes, which results in the formation of isoquinolinyl methyl esters, is carried out mainly in the presence of bases such as butyl-lithium or sodium hydride[85]. This reaction proceeds much more satisfactorily in the presence of concentrated aqueous alkali in a two-phase system even without a quaternary ammonium catalyst, which, however, is necessary for the reaction of a Reissert compound with a ketone[86]:

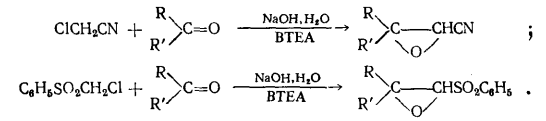


The reaction of the carbanion takes place in the organic phase, as shown by the finding that diphenylacetonitrile is acylated by benzoyl chloride with a high yield[29]:

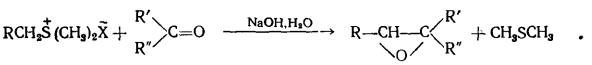


Two-phase catalytic conditions are very convenient for the reaction of α-chloronitriles with aldehydes and ketones (the Darzens reaction). The corresponding nitriles of glycidic acids are usually formed in high yields[87]. The condensation of α-chlorocarbonyl compounds (t-butyl chloroacetate, phenacyl chloride, etc.) proceeds less effectively under these conditions.

Excellent yields of epoxides substituted by an arenesulphonyl group have been obtained by the condensation of α-halogenosulphones with carbonyl compounds[75].

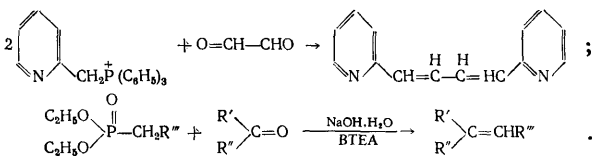


Two-phase systems in which an aqueous solution of sodium hydroxide plays the role of the base are very convenient and effective for the generation of ylids from sulphonium and phosphonium compounds. Since these compounds contain an onium cationic centre, the reactions of ylids in a two-system usually do not require catalysts. Thus Hatch[88] found that dimethylalkylsulphonium chlorides react with benzaldehyde in the presence of concentrated aqueous alkali to form epoxy-compounds. Analogous reactions have been described for many other aldehydes and ketones[89–91]:

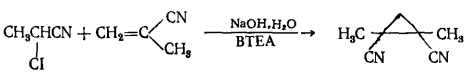


Nevertheless the conversion of trimethylsulphonium or trimethylsulphoxonium salts into ylids requires the use of tetra-alkylammonium salts[92].

Although according to generally accepted views phosphonium ylids are very sensitive to moisture, the benzene–aqueous sodium hydroxide solution system is extremely convenient for carrying out the Wittig reaction with aldehydes[93,94]. The methylene chloride–concentrated aqueous NaOH solution system is particularly suitable for the synthesis of dienes in the reactions of ylids with glyoxal[95] and for the reaction of a stabilised allyl ylid with aldehydes[96]. The use of this system for the Wittig–Horner reaction has also been described[97]:



The α-halogenonitrile carbanions generated in a two-phase system[98] and sulphonium ylids[92] also react with activated double bonds, forming the corresponding cyclopropane derivatives. Particularly satisfactory results were obtained for α-chloropropionitrile:

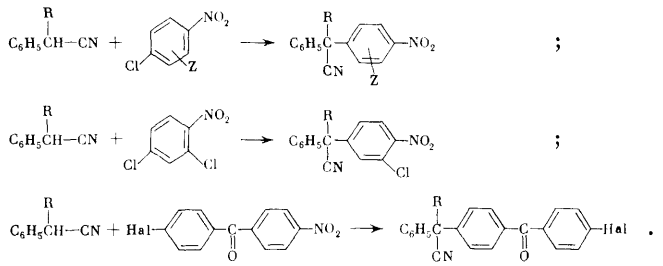


The cyanoethylation of 1-chloronitroethane in a two-phase system can lead directly to a substituted nitrocyclopropane[48].

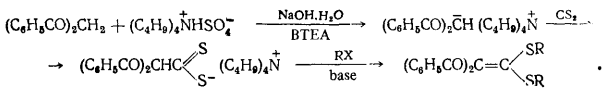
6. Reactions of Carbanions with Various Electrophiles

Two-phase catalytic conditions are the most convenient for the nitroarylation of alkylphenyl- and diphenylacetonitriles by *o*- and *p*-halogenonitrobenzenes and their derivatives. The substitution of the halogen atom by the carbanions derived from these nitriles results in the formation of compounds containing *o*- or *p*-nitroaryl

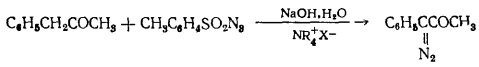
groups, as a rule with high yields. Under other conditions, the yields are small and considerable amounts of tar are formed. The presence of many substituents (halogen, >CO, CH_3, NO_2, COOR-t, etc.) in *o*- or *p*-halogenonitro-compounds does not interfere with the nitroarylation reaction [13,44,99-102]. Alkylphenylacetonitrile carbanions substitute mainly the chlorine atom in the *p*-position relative to the nitro-group in 2,4-dichloronitrobenzene [102]. Alkylphenylacetonitrile carbanions are capable of substituting not only the halogen atom, but also aromatic nitro-groups in the *o*- or *p*-positions relative to strong electrophilic substituents. For example, their reaction with 4-halogeno-4′-nitrobenzophenones involves exclusively the substitution of the nitro-group [101,103]:



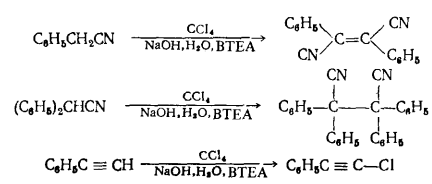
In the reaction of 3,4-dinitrochlorobenzene, the 3-nitro-group is substituted [101]. Sometimes substitution of the halogen or the nitro-group is accompanied by electron transfer, being particularly characteristic of the reaction of the diphenylacetonitrile carbanion, which forms tetraphenylsuccinonitrile [101,103]. Many β-dicarbonyl compounds react with carbon disulphide under the ion pair extraction conditions with formation of salts of the corresponding dithiocarboxylic acids. In the presence of an excess of the base, these salts are converted into dianions whose alkylation leads to the formation of keten mercaptals [104,105]:



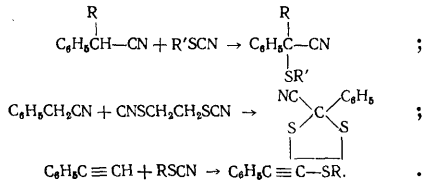
Similar reactions can also be carried out with acetophenone [107]. The use of a two-phase system for the synthesis of aliphatic diazo-compounds is very promising [108]:



Phenylacetonitrile also reacts with carbon tetrachloride, forming *trans*-dicyanostilbene. Under analogous conditions, diphenylacetonitrile is converted into tetraphenylsuccinonitrile [109] and phenylacetylene is converted into phenylchloroactylene [110]:



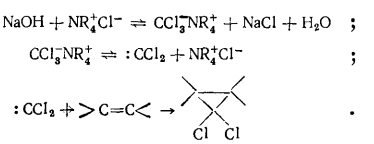
The direct introduction of an alkylthio-group into an organic molecule, usually as a result of the reaction between carbanions and disulphides, has aroused considerable interest in recent years. The present author found that excellent agents for the introduction of alkylthio-groups are the much more readily available thiocyanates, which effectively introduce alkylthio-groups into many C–H acids under two-phase catalytic conditions [110,111]:



III. REACTIONS OF HALOGENOCARBENES AND POLYHALOGENOCARBANIONS

The use of two-phase catalytic systems in the chemistry of polyhalogenomethyl carbanions and halogenocarbenes gave particularly satisfactory results and has aroused much attention. In 1969 the present author developed a method for the synthesis of dichlorocylopropanes by the addition to alkenes of dichlorocarbene generated by treating chloroform with concentrated alkali in the presence of benzyltriethylammonium chloride [112].

Despite the fact that this reaction proceeds in an aqueous medium, only an insignificant proportion of the resulting dichlorocarbene is hydrolysed. For example, equimolar amounts of styrene and chloroform give approximately 90% of a substituted dichlorocyclopropane and only 7% of the chloroform is hydrolysed. Dichlorocarbene is formed in the organic phase as a result of the decomposition of the tetra-alkylammonium derivative of the trichloromethyl carbanion as a consequence of the high rate of reaction of dichlorocarbene with hydroxide ions and water. Doering and Hoffman [113], who attempted to obtain the products of the addition of dichlorocarbene to alkenes in the presence of a concentrated aqueous KOH solution, observed mainly hydrolysis. The yield of the desired product did not exceed 0.5%. These fundamental differences are a consequence of the presence of the quaternary ammonium cation, which transports the trichloromethyl anion into the bulk of the organic phase in the form of an ion pair soluble in a non-polar medium. The subsequent formation of dichlorocarbene takes place in the organic medium, as a result of which it is capable of reacting effectively with the alkene:



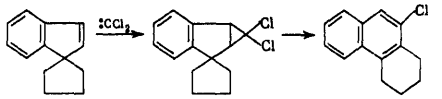
The method immediately found extensive applications in many reactions of halogenocarbenes and is now believed to be one of the most convenient.

1. Generation and Reactions of Dichlorocarbene

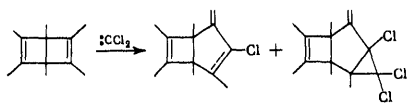
Examples of reactions of dichlorocarbenes in a two-phase system are particularly numerous. In most cases the authors note that the yields of the products of its addition to monoalkenes are usually higher than in cases where other methods were used [12,13,112,114-124]. In some studies it is emphasised that dichlorocarbene, generated by the two-phase catalytic method, is also much more

reactive and gives high yields of adducts, even with alkenes having weakened nucleophilic properties, such as *trans*-stilbene, and with certain acetylenes [114]. These data conflict somewhat with the results of the determination of the relative rates of addition of dichlorocarbene, generated in a catalytic system, to various alkenes, which, according to Starks' study [12], do not differ from the relative rates measured for dichlorocarbene obtained by other methods. These apparent contradictions will be discussed below.

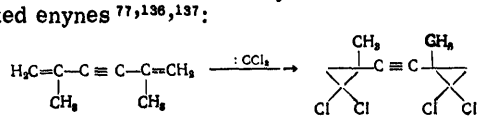
At the end of 1974, Isagawa et al. reported that the addition of dichlorocarbene to alkenes in a two-phase system is very effectively catalysed by trialkylamines [125]. This unexpected catalytic effect is apparently due to the formation of an ammonium ylid at the interface [126]. The addition of dichlorocarbene to cyclopentenes is usually accompanied by a rearrangement with formation of six-membered rings. The addition reaction carried out in a two-phase catalytic system proceeds in the same way [119-121,127-129]. Interesting transformations have been observed in the reactions of dichlorocarbene with indene derivatives [130]:



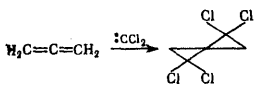
The increased reactivity of dichlorocarbene generated in a two-phase system, noted above, makes it an ideal reagent for the conversion of polyenes into polydichlorocyclopropanes. Bisadducts with divinylbenzene [131], conjugated dienes [114,132], and polyenes [115] have been obtained by single-stage syntheses using this procedure. It also proved possible to obtain a bisadduct with cyclopentadiene [132] and a tetra-adduct with cyclo-octatetrane [133]. By regulating appropriately the reactant ratio and the reaction time, it is possible to obtain mono-, di-, and tri-addition products [133,134]. Hexamethyl Dewar benzene forms under these conditions bisadducts, which undergo further transformations during the reaction [132,135]:



Dichlorocarbene adds exclusively to the double bond of conjugated enynes [77,136,137]:

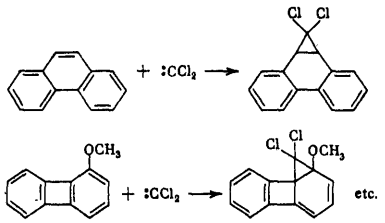


Polyadducts of dichlorocarbene have been obtained in a single stage also as a result of reactions with allenes and other higher cumulenes [114,138-140]:

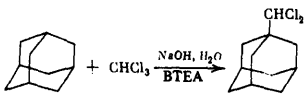


The addition of dichlorocarbenes in a two-phase system to vinyl ethers [141-143] and enol ethers and esters [121,129,144] gives very satisfactory results, although some workers believe that these compounds are insufficiently stable in an aqueous medium [145]. The limitations associated with instability in the presence of aqueous alkali have apparently been overestimated, since, according to Miller, even trimethylsilyl derivatives of alkenes combine with dichlorocarbene in a two-phase system to give excellent yields of products [146].

Dichlorocarbene generated in a two-phase system reacts effectively with many aromatic compounds—phenanthrene [115,147-149], alkyl derivatives of benzene and naphthalene [150,151], 1,4,5,8-tetramethoxynaphthalene [152], 1-methoxybiphenylene [153], etc. This results in the formation of both primary dichlorocarbene addition products as well as the products of their subsequent transformations:



One of the characteristic reactions of dichlorocarbene is insertion in C–H bonds. Usually only thermally generated dichlorocarbene gives acceptable yields of insertion products. In a two-phase system the reactivity of dichlorocarbene is also considerable, as a result of which it is successfully inserted in the C–H bonds in the bridgeheads of adamantane [154,155] and other polycyclic hydrocarbons [156], giving satisfactory yields of the corresponding dichloromethyl derivatives. In the reactions with simpler hydrocarbons (isopropylbenzene, decalin, etc) the yields of dichloromethyl derivatives are moderate, but the reaction may nevertheless be of practical importance, since the unreacted initial compounds are almost completely recovered [157,158]:



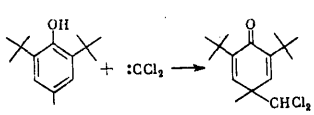
Dichlorocarbene generated in a two-phase system undergoes an unusual reaction with higher alcohols, substituting the hydroxy-group by chlorine with high yields [159]:

$$R_3OH \xrightarrow{+\,:CCl_2} R_3C{-}Cl$$

Lower aliphatic alcohols give rise to a multiplicity of products. The reaction with ethyl alcohol, where the main product is ethyl orthoformate, is of practical importance [160]:

$$C_2H_5OH + :CCl_2 \rightarrow CH(OC_2H_5)_3 + (COOC_2H_5)_2 \text{ etc.}$$

Various types of transformations have been observed also in the reaction with α-diols [161]. Nevertheless many allyl alcohols react with dichlorocarbene under these conditions to form products of addition to the double bond without involving the hydroxy-group [162]. There are as yet no data concerning the influence of tetra-alkylammonium catalysts on the interaction of phenoxide anions with dichlorocarbene (the Reimer–Tiemann reaction). Nozaki and coworkers [163] found that polyalkylphenols form dichloromethyl derivatives of cyclohexadienones:



The reaction of dichlorocarbene with benzaldehyde results in a high yield of mandelic acid [164].

Reactions with nitrogen compounds. On reacting with chloroform in the presence of alkali, primary amines form isonitriles. This reaction, which

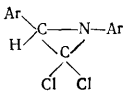
has been known for approximately one hundred years, has not found practical synthetic applications. The use of a catalytic two-phase system greatly improved yields and made it useful in practice [165-168]:

$$RNH_2 + :CCl_2 \rightarrow RNC \quad .$$

Simple formylation of secondary amines by dichlorocarbene in a two-phase system may also find practical applications [169].

Tertiary amines also react with dichlorocarbene under these conditions. The ammonium ylids formed initially rearranges in at least three ways, giving rise to formyl derivatives of secondary amines, carboxylic acid dialkylamides, alkyl chlorides, etc, [170] Polycyclic tertiary α-diamines are cleaved by dichlorocarbene to bis-*N*-formyl derivatives [171]. 1-Methyl-1,2-dihydroisoquinoline reacts with dichlorocarbene to form addition and insertion products, but is not cleaved [172]. Despite the fact that enamines and Schiff bases are fairly unstable in the presence of aqueous alkali, their reactions with dichlorocarbene take place successfully under conditions of two-phase catalysis. Depending on the structure of the initial substance, it is possible to isolate the primary addition products—dialkylamino-derivatives of dichlorocyclopropane [173] and dichloroaziridines [174]—or the products of their further transformations:

$$Ar{-}CH{=}N{-}Ar + :CCl_2 \rightarrow$$



.

The enamines derived from certain bicyclic ketones form relatively stable adducts with dichlorocarbene [175].

Dichlorocarbene generated in a two-phase catalytic system may serve as a vigorous dehydrating agent, which converts amides, oximes, and thioamides into nitriles [176,177]:

$$RCONH_2 + :CCl_2 \rightarrow RCN \quad ;$$

$$RCH{=}NOH + :CCl_2 \rightarrow RCN \quad .$$

Webber and coworkers recently used successfully a two-phase system with BTEA or a crown ether in order to obtain diazomethane by treating hydrazine with dichlorocarbene [178]. This method will undoubtedly prove to be of practical importance:

$$N_2H_4 + :CCl_2 \rightarrow CH_2N_2 \quad .$$

The addition of dichlorocarbene to vinyl sulphides proceeds in the usual way with formation of the corresponding dichlorocyclopropane derivatives [179], but certain allyl sulphides rearrange under these conditions with cleavage of the C–S bond, giving rise to monothiocarboxylate esters [180].

The high reactivity of dichlorocarbene generated in a two-phase catalytic system undoubtedly requires explanation. Dichlorocarbene is formed in the organic phase, where its precursor (the trichloromethyl anion) exists in the form of a soluble ion pair with the tetra-alkylammonium cation. Since alkali metal cations are absent from the organic phase, the formation of the corresponding carbenoids is impossible. Despite the fact that the system as a whole is heterogeneous, dichlorocarbene is formed and reacts in a homogeneous medium—the organic phase. An equivalent amount of a tetra-alkylammonium chloride, which is also soluble in the organic phase, is formed simultaneously with dichlorocarbene. As a result of this, the rapid reversible reaction

$$CCl_3^-NR_4^+ \rightleftharpoons NR_4^+Cl^- + :CCl_2$$

ensures the existence of sufficient amounts of dichlorocarbene over a relatively long period, to enable it to react with relatively unreactive compounds. This cannot occur when, for example, dichlorocarbene is generated by treating chloroform with potassium t-butoxide, since the solubility of the potassium derivative of the trichloromethyl anion (and even more so that of potassium chloride) is apparently insignificant in a non-polar medium. This explanation is confirmed by the finding that the overall rate of disappearance of chloroform in a two-phase system is low in the absence of an alkene and depends on its nucleophilic properties.

2. Reactions of Trichloromethyl Anions

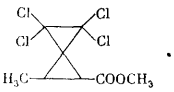
Trichloromethyl anions are fairly short-lived, but they can be trapped successfully by suitable electrophiles. Catalytic conditions are particularly convenient for these reactions, since both reacting species—the trichloromethyl anion and the organic electrophile—are dissolved in the organic phase. Thus it has been found that two-phase catalytic conditions are the most suitable for the Michael reaction between chloroform and electrophilic alkenes (acrylonitrile, acrylate, esters, vinyl sulphones, vinyl acetate, etc.)[181-183]:

$$CH_2{=}CH{-}Y + CHCl_3 \xrightarrow[\text{BTEA}]{NaOH,H_2O} CCl_3CH_2CH_2Y \quad ;$$

$$Y{=}CN,\ COOR,\ or\ SO_2R \quad .$$

The yields of the corresponding trichloromethyl derivatives are usually high, greatly exceeding the yields of the same compounds obtained by other methods. When the acceptors Y are moderately electrophilic, the simultaneous addition of trichloromethyl anions or dichlorocarbenes is observed. The mode of these competing reactions depends mainly on the structure of the acceptor and to some extent also on the way in which the reaction is performed. Thus, on diluting the organic phase with an inert solvent (for example, methylene chloride), the reaction may be driven towards the addition of dichlorocarbene. In a detailed study of this reaction, Dehmlow and Höfle observed further interesting transformations of the compounds formed initially [184]:

$$CH_3CH{=}CH{-}COOCH_3 \xrightarrow[NaOH,\ H_2O]{CHCl_3,\ BTEA}$$



.

Polymethylated vinyl ketones combine exclusively with dichlorocarbene and not with the trichloromethyl anion [185].

Organic thiocyanates are very effective electrophiles, trapping trichloromethyl anions. Their CN group is substituted and trichloromethyl sulphides are formed in satisfactory yields [111]:

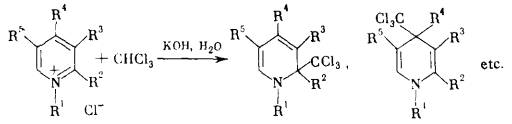
$$CHCl_3 + RSCN \xrightarrow[\text{BTEA}]{NaOH,H_2O} RSCCl_3 \quad .$$

However, standard two-phase conditions proved to be unsuitable for the synthesis of trichloromethylphenylmercury—an important source of dichlorocarbene under neutral conditions. The difficulties in the application of the two-phase method in this synthesis were overcome by replacing the concentrated solution of alkali by a mixed

solution of sodium hydroxide and potassium fluoride in water [186]:

$$C_6H_5HgCl + CHCl_3 \xrightarrow[BTEA]{NaOH,KF,H_2O} C_6H_5HgCCl_3 \quad .$$

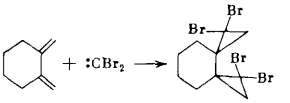
Krőhnke and coworkers [187] found recently that certain *N*-benzylpyridinium chlorides combine with the trichloromethyl anion, forming 2- and 4-trichloromethyldihydropyridine derivatives:



A more detailed study of this reaction showed that it proceeds at the interface [188].

3. The Formation and Reactions of Other Carbenes

Two-phase catalytic conditions proved to be very convenient for the conversion into carbanions and then into carbenes of all the remaining trihalogenomethyl derivatives of methane with the exception of fluoroform, which is too weak a C–H acid. The yields of dibromocyclopropane derivatives, obtained from bromoform and alkenes under standard two-phase catalytic conditions, are usually moderate [114,189,190]. Nevertheless, this method has been frequently used for the addition of dibromocarbene to dienes and polyenes [133,136,191]:



The yields increase in the presence of a considerable excess of bromoform [192,193] or when 1–2 mole % of lower alcohols is added to the reaction mixture [194–196].

The reaction with dibromocarbene has been used to substitute the hydroxy-group by bromine in hydroxyadamantanes [197]. Two-phase conditions have been used successfully to achieve the addition of tribromomethyl anions to electrophilic alkenes and, after some modification of the conditions (aqueous NaOH solution with addition of potassium fluoride instead of concentrated alkali), for the synthesis of tribromomethylphenylmercury [186]. A certain degree of stabilisation of tribromomethyl anions by small amounts of alcohols, mentioned above, makes it possible to achieve their alkylation by reactive alkylating agents, but the yields are low [198]:

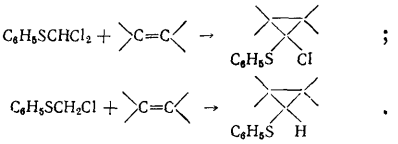
$$CHBr_3 + C_6H_5CH_2Cl \xrightarrow[BTEA]{NaOH,H_2O} C_6H_5CH_2CBr_3 \quad .$$

The formation of derivatives of chlorofluoro-, bromofluoro-, [199] and fluoroiodo-cyclopropanes [200] as a result of the reaction of the corresponding trihalogenomethanes and alkenes in the presence of aqueous sodium hydroxide and BTEA has also been described. Chlorofluorocarbene has been used successfully to synthesise chlorofluorocyclopropyl alcohols [201] and enamines [175] from the corresponding unsaturated compounds:

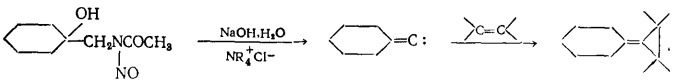
$$H_2C{=}CHCH_2OH + CHCl_2F \xrightarrow[BTEA]{NaOH,H_2O} H_2C(Cl,F)CHCH_2OH \quad .$$

Even di-iodocarbene can be obtained by treating iodoform with an aqueous solution of alkali and BTEA in the presence of alkenes [202].

Dichloromethyl sulphides are relatively close analogues of haloforms, since the 3*d* orbital effect of bivalent sulphur presumably stabilises the carbanions similarly to the influence of chlorine or bromine. Thus, on treatment with a concentrated aqueous solution of alkali in the presence of BTEA, dichloromethyl phenyl sulphide forms the corresponding carbanion and then phenylthiochlorocarbene, which reacts with alkenes to form phenylthiochlorocyclopropane derivatives [203]. The same has also been found for dichloromethyl methyl sulphide [204]. It must be emphasised tha even chloromethyl phenyl sulphide is capable of abstracting a proton under these conditions and of converting alkenes into phenylthiocyclopropane derivatives [205]:

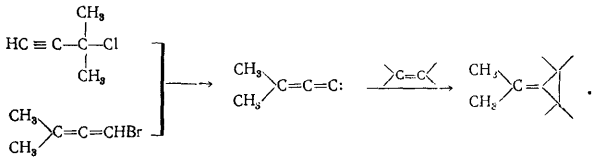


This result is to some extent unexpected, because it indicates a greater ability of the phenylthio-group to stabilise carbanions than that of chlorine, since methylene chloride is incapable of forming a carbanion and monochlorocarbene under these conditions [2]. Unfortunately, the problem of trapping the corresponding carbanions—precursors of alkyl(aryl)thiocarbenes—was not considered by the authors. The two-phase catalytic method gave very satisfactory results in the generation of unsaturated carbenes. Newman and coworkers used this method to convert *N*-(β-hydroxyalkyl)-*N*-nitrosoacetamides into alkylidenecarbenes and found that under these conditions the yields of the products of addition to alkenes or inorganic anions are considerably higher than those of any other products [206,207]:



The alkylidenecarbenes generated in this way also react with carbonyl compounds [208].

The successful addition of vinylidenecarbenes under these conditions to dienes (cyclopentadiene, norbornadiene) [209] and enol ethers [210] has been described. Dimethylvinylidenecarbene has been obtained by the same procedure from methylallenes [211] and butynes [212,213]:



IV. CONCLUSION

1. Applications of the Method

Numerous examples of the use of two-phase catalytic systems and of the ion pair extraction method in many reactions of carbanions and halogenocarbenes constitute a good illustration of the scope and importance of these methods for organic synthesis. However, the two-phase method has many serious limitations. The most important one is that only relatively strong C–H acids may be converted into anions by treatment with aqueous sodium

hydroxide. Naturally, owing to the presence of two phases and catalysts, the acid–base equilibrium is displaced towards the formation of organic anions, but the methods are nevertheless inapplicable to C–H acids whose pK_a is greater than 22. For example, fluorene can be alkylated, while acetonitrile cannot.

The second limitation is a consequence of the instability of certain C–H acids or electrophiles in the presence of an aqueous solution of alkali (for example, the hydrolysis of esters or other functional groups). This limitation can be frequently eliminated by employing more stable t-butyl esters and a less concentrated solution of sodium hydroxide or by increasing the amount of the tetra-alkylammonium salt up to an equimolar proportion. Compounds reacting with carbanions or halogenocarbenes should also be stable in the presence of aqueous alkali. On the other hand, one must not overestimate these limitations, since many readily hydrolysable compounds have been used successfully in the reaction under these conditions.

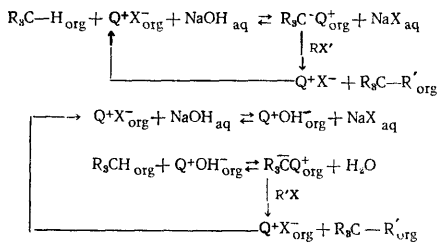
An important limitation of the use of the two-phase catalytic method is that the reaction product cannot be more acid than the initial compound. Otherwise it is converted into the anion more readily than the initial compound and forms a relatively unreactive ion pair with the ammonium cation, whereupon the catalytic reaction stops. Under these conditions and even in the presence of relatively strong C–H acids, the use of equimolar amounts of quaternary ammonium salts, recommended in the ion pair extraction method, appears to be more convenient. Catalytic reactions are frequently inhibited by inorganic anions with a low charge density and poorly solvated by water (I^-, ClO_4^-, etc.), which restricts the application of iodides as alkylating agents. This is a consequence of the high solubility of the corresponding tetra-alkylammonium salts in organic solvents. Nevertheless, this inhibiting effect is not always observed. It is unimportant when the extraction of ion pairs is employed.

2. The Possible Mechanisms of Catalysis in Two-Phase Systems

All the reactions discussed above consist of at least two stages. The first stage involves the formation of a carbanion by the abstraction of a proton from the C–H acid, and the second involves subsequent transformations of the carbanion (reaction with electrophiles, conversion into a carbene, etc.). One of the most important problems is that of the site where the processes occur: in the aqueous phase, in the organic phase, or at the interface. There is no doubt that the second and subsequent stages take place in the organic phase, where the carbanions exist as ion pairs with tetra-alkylammonium cations. This is frequently observed and in fact constitutes the essential feature of catalytic and extractive two-phase methods. The behaviour of these ion pairs in non-polar solvents has been discussed in detail by Brändström[6].

It is much more difficult to determine where the proton is abstracted from the C–H acid and the ion pair is formed. The majority of workers do not consider this problem and refer to all catalytic reactions of carbanions in two-phase systems as "phase-transfer catalysis"[2], a term which was introduced by Starks[12,215]. It arises from the following considerations: two reactants present in two immiscible liquid phases and insoluble in the other phase are unable to react with one another, since they cannot come into direct contact. A third component, capable of transferring one of the reactants from one phase to the other, and thereby enabling the reaction to occur, acts as the catalyst (the "phase-transfer agent"). This approach is well illustrated by the cyanation of alkyl halides in hydrocarbons by an aqueous solution of sodium cyanide. Vigorous stirring of this two-phase system does not lead to the exchange reaction even at an elevated temperature. On the other hand, the addition of catalytic amounts of a quaternary ammonium or phosphonium compound, capable of transporting CN^- ions in the form of the ion pairs $NR_4^+CN^-$ into the organic phase, gives rise to a vigorous reaction. In the reactions of halogenocarbenes or carbanions (derivatives of relatively weak C–H acids) in the presence of a concentrated aqueous sodium hydroxide solution the role of phase transfer catalysis reduces to the transfer of hydroxide anions in the form of tetra-alkylammonium or phosphonium hydroxides from the aqueous to the organic phase.

Thus, according to the mechanism involving transfer from one phase to the other, the abstraction of a proton from C–H acids, and the formation of the carbanion–tetra-alkylammonium cation ion pair should occur in the organic phase. This hypothesis concerning the generation of trichloromethyl anions and dichlorocarbene in a two-phase catalytic system via the formation of a quaternary ammonium base, which then reacts in the organic phase, was put forward by the present author in 1969[112]. However, many observations and the results of careful analysis agree better with the hypothesis that the first stage of the carbanionic reaction—the abstraction of a proton and the formation of ion pairs in the two-phase systems under consideration—takes place at the interface. The ion pairs then diffuse into the bulk of the organic phase, where all further transformations, involving the simultaneous liberation of the ammonium cation, take place. These two alternative mechanisms are represented schematically as follows:

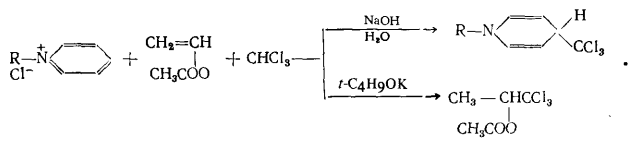


Evidently in the case of relatively strong C–H acids, which are capable of forming anions to a significant extent in the presence of a dilute aqueous NaOH solution, the quaternary ammonium compound acts mainly as a phase-transfer agent, transferring organic anions from the aqueous to the organic phase. However, the most important application of two-phase catalytic systems involves the reaction of weak C–H acids, which do not form water-soluble sodium derivatives. In such cases we are dealing with a distinct immiscibility of the two phases. For example, in the phenylacetonitrile–50% aqueous NaOH solution system the concentration of the first component in the aqueous phase is less than 2 p.p.m., while that of sodium hydroxide in terms of Na^+ ions is less than 5 p.p.m. in the organic phase. These values rule out the extraction of carbanions from the aqueous phase, of the kind that can occur in the case of more acid compounds and a dilute NaOH solution.

Thus two possibilities remain: the abstraction of a proton in the organic phase, into which $NR_4^+OH^-$ is transferred as the base, or at the interface. Numerous experiments on the extraction of ion pairs with inorganic anions have shown that in an organic solvent (for example, benzene or acetonitrile)–50% aqueous NaOH solution two-phase system more than 99% of benzyltriethylammonium chloride remains in the organic phase as the chloride and that each anion in the series SO_4^{2-}, F^-, OH^-, Cl^-, Br^-, and I^- is almost quantitatively displaced from the organic phase by its right-hand neighbour. In view of the small amounts of catalysts used in preparative experiments and the formation of considerable amounts of the Cl^- and Br^- anions in the reaction, the concentration of OH^- anions (i.e. $NR_4^+OH^-$) in the organic phase is presumably negligible. Nevertheless, the rate of attainment of the acid–base equilibrium is usually high compared with other reactions, so that one cannot fully rule out the possibility of the formation of carbanions by the extraction of $NR_4^+OH^-$, although it is unlikely. On the other hand, the possibility of the attainment of the acid–base equilibrium and the formation of carbanions at the interface has been satisfactorily demonstrated by the present author's experiments, in which many reactions of carbanions in a two-phase system without catalysts were observed.

Numerous weak C–H acid exchange hydrogen for deuterium as a result of stirring with a concentrated solution of sodium hydroxide in D_2O. Owing to the almost complete immiscibility of the phases, the formation of the carbanion and its reaction with D_2O presumably take place at the interface. The present author found that certain synthetically impotrant reactions of carbanions occur in a two-phase system without catalysts. Bearing in mind the above miscibility data, one may conclude that the reactions occur at the interface. They include mainly those actions of Reissert's compounds with aldehydes [86], Darzens-type condensations of aldehydes with α-halogenosulphones [75] and α-halogenonitriles, and the addition of CCl_3^- anions to *N*-alkylpyridinium salts [187,188]. The latter reaction is particularly interesting, since pyridinium salts resemble to a considerable degree the catalysts used in the reactions of carbanions.

The formation of adducts of the trichloromethyl anion is not accompanied by the formation of tar. This is evidence against the extraction of OH^- anions into the organic phase, since the products of their addition to pyridinium salts are very unstable. However, the main evidence that the adducts of the trichloromethyl anion are formed at the interface was obtained in competition experiments, where vinyl acetate competed with pyridinium salts for addition to trichloromethyl anions. In a two-phase system, trichloromethyl anions add exclusively to the pyridine ring, while in a homogeneous or pseudohomogeneous system in the presence of potassium t-butoxide, trichloromethylethyl acetate is formed exclusively (when there is competition with styrene, a substituted dichlorocyclopropane is formed) [188]:



Thus it may be regarded as proved that the addition of the CCl_3^- anion to pyridinium salts takes place at the interface, by-passing the ion pair formation stage. Presumably the recently described reactions of dichlorocarbene catalysed by tertiary amines are to some extent associated with the formation of this anion at the interface, where the reaction with the tertiary amine results in the formation of an ammonium ylid. The latter is capable of diffusing into the organic phase, where further transformations occur.

The above observations and considerations permit the conclusion that in a two-phase system comprising a relatively weak C–H acid (in an organic solvent or without it) and a concentrated sodium hydroxide solution, a proton is abstracted with formation of a carbanion even in the absence of a catalyst. However, these carbanions are incapable of leaving the interface, since the sodium cations accompanying them are highly solvated in the aqueous phase and only very slightly in the organic phase; they are therefore incapable of passing to the latter. In this to some extent adsorbed state, carbanions are very unreactive, and react only with strong or positively charged electrophiles. Quaternary ammonium cations react with these carbanions, forming ion pairs soluble in the organic phase. After their migration into the bulk of the organic phase, the ion pairs undergo further transformations. This mechanism is naturally highly simplified. Tetra-alkylammonium cations are in all probability directly involved in the stage where carbanions are formed, lowering the energy of the transition state in the proton abstraction reaction, as a result of the influence of the positive charge from the opposite side of the reaction centre. Not only tetra-alkylammonium and phosphonium compounds but also alkali metal cations, which are highly solvated by certain organic solvents [dimethylformamide (DMF), hexamethylphosphoramide (HMP), etc.], can serve as catalysts in two-phase systems. These solvents in fact catalyse the formation of carbanions in two-phase systems:

$$(C_6H_5)_2CHCN_{org} + NaOH_{aq} \rightleftarrows [(C_6H_5)_2\bar{C}CNNa^+_{solv.}]_{org} + H_2O_{aq}$$

Solvent	C_6H_6	CH_3CN	DME	THF	Pyridine	DMF	HMP
Concn. of carbanion, %	0	1	3	3	12.5	88	94

Crown ethers proved to be very powerful neutral ligands, binding alkali metal cations [14,215]. The stable crown . Na^+ complex behaves as an organic cation, forming with many anions ion pairs which are soluble in non-polar organic solvents. This remarkable property of crown ethers has found an interesting application in many reactions involving inorganic anions in non-polar solvents (reactions of "naked" anions) [80,216–218]. In most cases crown ethers were partly converted into a solid sodium or potassium salt in a benzene or acetonitrile solution. The present author showed that crown ethers are very effective catalysts of the reactions of carbanions in a two-phase system. They are no less active than quaternary ammonium salts, but are more stable than the latter [13,55]. The use of diazapolyoxamacrobicyclic compounds as catalysts in liquid–liquid or liquid–solid two-phase systems is also very promising, because their activity in binding cations into complexes with formation of the so called cryptates is much higher than that of crown ethers [219,220].

Summarising the foregoing, it is possible to distinguish three different types of catalytic action of quaternary ammonium salts in two-phase systems, each of which is based on the formation of ion pairs soluble in the organic phase.

1. Extraction of inorganic anions from the aqueous phase into the organic phase—true-phase transfer catalysis, which is observed mainly in reactions of inorganic anions (CN^-, SCN^-, MnO_4^-, etc.) with organic compounds (alkyl and alkenyl halides, etc.).

2. Extraction (into the organic phase) of the carbanions of relatively strong C–H acids formed on treatment with dilute aqueous solutions of sodium hydroxide or water-soluble sodium derivatives of these acids. There is no doubt that such extraction displaces the acid–base equilibrium in the direction of the formation of the carbanion. This corresponds either to phase-transfer catalysis or to the extraction of ion pairs as a function of the amount of quaternary ammonium salt consumed (catalytic or equimolar).

3. The formation of ion pairs soluble in the organic phase and incorporating carbanions located at the interface, with a more or less active involvement of the proton abstraction stage. This pathway is the main one in the carbanionic reactions of relatively weak C–H acids, regardless of whether catalytic or equimolar amounts of tetra-alkylammonium salts are used.

It is impossible to separate clearly these three versions; each plays the main role in individual instances. Some workers include the two-phase reaction considered here with those occurring in cationic micelles ("cages")[4]. Despite the apparent similarity of the systems considered to micellar systems, the essential feature of the catalytic action of onium compounds is different from that of micellar catalysis and their catalytic activity does not vary in parallel with surface activity. Nevertheless one cannot completely reject the possibility of the involvement of phenomena similar to those in micellar catalysis, particularly in reactions occurring at the interface.

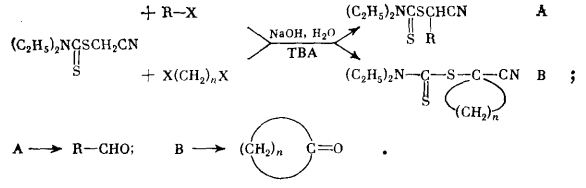
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Two-phase catalytic systems have been used in reactions of carbanions and halogenocarbenes for only about ten years, and they have become more common only in the last five years. The present author's views concerning the potential possibilities of the applications of these methods are therefore by no means exhaustive. In almost all the examples described, both two-phase catalytic methods and methods based on the extraction of ion pairs proved to be better than all other known procedures as regards simplicity, selectivity, yields, etc. Presumably they will be widely used in the immediate future as methods of organic synthesis.

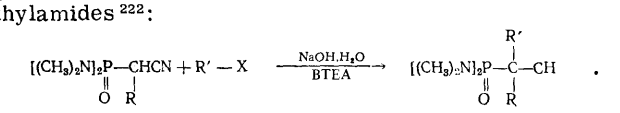
ADDENDUM

Numerous studies have been published recently, in which the two-phase method of generating carbanions and halogenocarbenes was developed further. The most important results are presented below.

2.1. *S*-Cyanomethyl *NN*-diethyldithiocarbamate can be alkylated with excellent yields in the presence of aqueous alkali and an ammonium catalyst. Since both functional groups are readily split off on hydrolysis, the reaction can be used to synthesise aldehydes and ketones[221]:

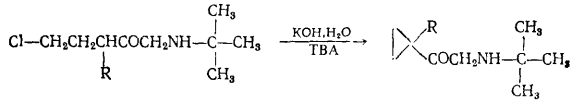


A two-phase catalytic system has been used successfully in the alkylation of cyanoalkylphosphonic tetramethylamides[222]:

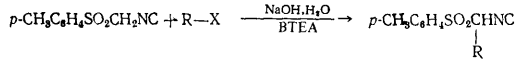


Reeves and Hilbrich reported that the alkylation of phenylacetonitrile and phenylacetone in a two-phase system is catalysed by tertiary amines, which are capable of forming quaternary salts under the reaction conditions[223].

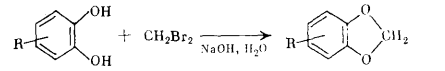
2.2. Using an equimolar amount of BTEA, Singh and Danishefsky[224] alkylated diethyl malonate with ethylene bromide in the presence of concentrated aqueous alkali and obtained directly cyclopropane-1,1-dicarboxylic acid. The application of a two-phase catalytic system in the synthesis of cyclopropyl ketones has been described[225]:



2.3. A two-phase catalytic system proved to be very effective in the alkylation of compounds containing the isonitrile group[226], for example toluene-*p*-sulphonylmethyl isocyanide[227]:

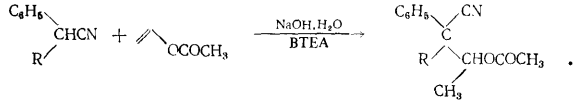


This method gave excellent results in the reaction of methylene bromide with phenols[228,229]:

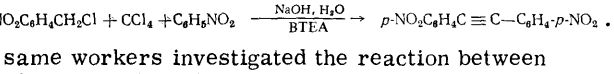


A detailed study of the synthesis of ethers under two-phase conditions has been described[230]. This method has been used in the synthesis of the ethers and acetals of certain sugars[231]. Studies dealing with two-phase *N*-alkylation of indole[232,233], amides[234], phenylhydrazones[235], and aziridine[236] have been published.

2.4. Using aqueous alkali, it was possible to carry out the Wittig reaction with formaldehyde[237]. Among many examples of the Wittig–Horner reaction[238], carried out under two-phase conditions, processes apparently occurring at the interface without catalysts have been discussed[240]. A two-phase catalytic system is very effective in the synthesis of unsaturated compounds by the condensation of aryl methyl sulphones[241], 2-methylbenzothiazoles[242], and similar carbon acids with aromatic aldehydes. Certain carbanions add to vinyl acetate under these conditions[243]:



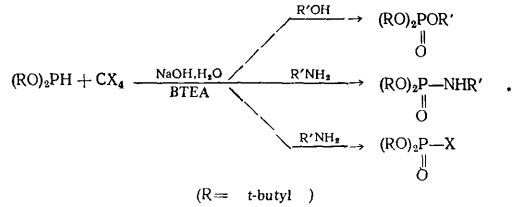
2.5. Using a two-phase system, a direct synthesis of di-(*p*-nitrophenyl)acetylene was achieved[244]:



The same workers investigated the reaction between phenylacetonitrile and nitrobenzene in the presence of aqueous NaOH and BTEA.[245]

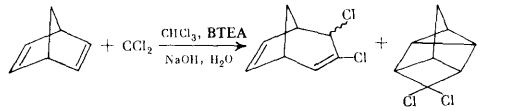
Excellent results were obtained when the Atherton–Todd reaction was carried out under catalytic two-phase conditions. Alcohols, phenols[246], and amines[247] are

phosphorylated with a yield of about 90% and the products do not require additional purification. When t-butyl phosphite is used, it is also possible to obtain the corresponding acid halide[248]:



(R= t-butyl)

3. Dichlorocarbene generated under two-phase catalytic conditions gives rise to products of 1,4-homoaddition to polycyclic hydrocarbons[249,250]:



The high reactivity of dichlorocarbene in a two-phase system can be modified by employing as the catalyst an ammonium salt containing a hydroxy-group[251], which makes the reaction with polyalkenes more selective. Dichloroethane generated under two-phase catalytic conditions is capable of eliminating oxygen from epoxy alkanes[252] and the resulting alkene then combines with dichlorocarbene.

Apart from the studies indicated above, many others have been published in which a two-phase system was used for the synthesis of dihalogenocyclopropanes[253,254].

4. The fact that methyl phenyl sulphone and even dimethyl sulphone[255] react with benzaldehyde in the presence of aqueous NaOH and BTEA demonstrates the considerable ability of this system to abstract a proton. On the other hand, these compounds react only with aromatic aldehydes, so that the existence of carbanions in the organic phase is doubtful. The reactions apparently take place at the interface. New evidence has been obtained for the formation of carbanions at the interface. It has been shown that alkyl iodides are capable of alkylating phenylacetonitrile without a catalyst and that the process takes place at the interface.

The possibility of inducing optical activity by means of an optically active ammonium catalyst has aroused interest. Nazaki's report of a high degree of induced activity in the synthesis of phenyloxiran (styrene oxide) from benzaldehyde and sulphoxonium imide[257] proved to be erroneous. The induction of optical activity in the reaction of dichlorocarbene with styrene is also doubtful[258]. A moderate stereospecificity has been observed in the alkylation of 2-ethoxycarbonylcyclohexanone[259]. Quaternary ephedrinium salts were used as the chiral catalysts in all cases.

Finally, the use as catalysts of quaternary ammonium salts[260] as well as crown ethers[261] attached to solid polymers has been reported. The term three-phase catalysis has actually been proposed[260].

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