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PHASE-TRANSFER CATALYSIS AND SOME OF ITS APPLICATIONS TO ORGANIC CHEMISTRY

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R.A.B. Bannard

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ABSTRACT

The origin and development of phase-transfer catalysis as a technique for the efficient conduct of organic ractions in two-phase media is described and the mechanism of the process is discussed. Some examples of its application to substitution, addition and elimination reactions, to oxidations, reductions and carbene chemistry are cited to illustrate the broad scope and general utility of the method.

RÉSUMÉ

Cette étude traite de l'origine et du développement des catalyseurs hétérogènes utilisés pour augmenter le rendement des réactions organiques se produisant entre deux phases (solide - liquide ou liquide-liquide) et comporte une critique du mécanisme de ce procédé. Afin de montrer la grande utilité du procédé, on trouve aussi dans cette étude, quelques exemples de l'application de ce procédé à la chimie des carbènes, aux réactions de substitution, d'addition, d'élimination, d'oxydation, et de réduction.

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INTRODUCTION

The organic chemist has traditionally avoided two-phase systems if at all possible as media in which to conduct synthetic organic reactions, such as nucleophilic substitutions, since reactions between substances which are located partially in two phases are frequently slow and inefficient. Consequently media are sought in which all the reactants are soluble, to increase the frequency of collision between reactive species and thus increase the reaction rate. If hydroxylic solvents are used, however, many reactions still proceed at a relatively leisurely pace because of the extensive solvation of anions. In addition, solvolytic reactions frequently intervene and compete with the intended reactant to decrease the yield of the compound desired. Polar aprotic solvents, such as dimethylsulfoxide (DMSO), dimethylformamide (DMF) and acetonitrile, are frequently more suitable as media for such reactions than are hydroxylic solvents, but are not without their disadvantages since they are often more toxic, more expensive and more difficult to recover or to separate from desired products. Moreover, they sometimes lead to reactions which are difficult to control or which are unpredictably violent which add a significant degree of hazard to the operation.

During the past ten years a new technique has been developed for conducting reactions in two-phase media in the presence of ammonium or phosphonium salts. Some idea of the scope of the method is provided by the following summary of reaction types to which it has been applied.

Substitution Reactions

1. C-Alkylation of active methylene compounds (β-ketoesters, aliphatic dicarboxylates, cyanoacetates etc.)
2. O-Alkylation of alcohols and phenols
3. Halogen exchange reactions
4. Preparation of nitriles and thiocyanates
5. Hydrolysis of esters and acid chlorides
6. Esterification

Elimination Reactions

1. Dehydrohalogenations
2. Dehalogenations
3. Dehydrations

Addition Reactions

1. Additions to ethylene oxide (synthesis of dioxolanes from aldehydes)
2. Condensation reactions (self-addition with or without elimination)
3. Additions to olefins and alkynes

Trihalomethyl Anion and Carbene Formation and Subsequent Reactions

1. Trihalomethyl anion additions to olefins
2. Trihalomethyl anion substitutions
3. Dihalocarbene additions to olefins
4. Dihalocarbene insertion reactions
5. Nitriles from amides
6. Chlorides from alcohols
7. Isocyanides from amines
8. Bisdehydroxylation of glycols
9. Alkylidene carbene formation
10. Tetrachlorospiropentane formation

Miscellaneous

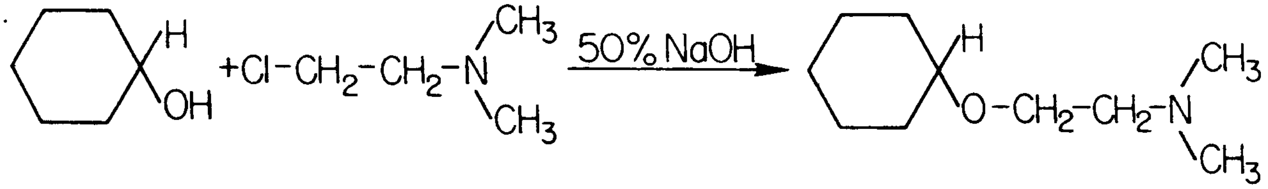
1. Deuterium exchange of active hydrogens
2. Permanganate oxidations of olefins
3. Reductions with boron hydrides
4. Wittig Reaction
5. Sulfur ylide formation

No uniform terminology has been adopted for the method. Brandstrom(1) has proposed the term "extractive alkylation" for the specific case of alkylation in the presence of molar amounts of catalyst, and where smaller than molar amounts of catalyst are used speaks of applications of ion-pair extraction in organic synthesis. Makosza(2) uses the terms "catalytic alkylation" and catalytic development of dihalocarbenes(3). Starks(4) has referred to the process as "phase-transfer catalysis", and his terminology will be used throughout this review.

From the large number of publications which have appeared on the subject during the past five years(5,6) it is clear that phase-transfer catalysis has already shown considerable utility as a synthetic organic technique. Its potential for future application is even greater because of its ability to facilitate reactions in two-phase aqueous-organic systems which traditionally have been conducted under strictly anhydrous conditions, thus making large-scale industrial production a practical possibility.

HISTORICAL

In 1951 Jarousse(7) described the O-alkylation of cyclohexanol with N,N-dimethylaminoethyl chloride in 50% aqueous sodium hydroxide.



Small amounts of N,N,N',N'-tetramethylpiperazinium dichloride were formed during the reaction and were recognized by Jarousse as a potential catalyst. Jarousse also alkylated benzyl cyanide and cyclohexanol with alkyl halides using triethylamine as a proton acceptor, and demonstrated the catalytic effect of benzyltriethylammonium chloride. These significant observations went almost unnoticed for 15 years, until Makosza applied the two-phase alkylation technique to several active methylene compounds, using simple alkyl halides, unsaturated alkyl halides, dialkylaminoalkyl halides, alkylidene dihalides, benzyl halides, p-nitrophenyl halides, α-haloalkyl ethers, bis-2-haloethyl ethers and α-haloesters. In general, the reactions were conducted at or near room temperature, using neat organic reactants in contact with 50% aqueous sodium hydroxide and a small quantity (0.02 mole %) of benzyltriethylammonium chloride as catalyst. Sometimes dropwise addition of the alkylating agent was necessary to moderate the vigor of the reaction and facilitate control of the temperature. Increasing the catalyst above 0.02 mole % did not produce a beneficial effect, nor did the addition of greater than three moles of alkali per mole of active methylene compound. In these reactions, a reversed order of reactivity of alkylating halides is observed, namely R-Cl > RBr > RI. This circumstance owes its origin to the fact that as little as 0.01 mole of iodide ion per mole of quaternary ammonium chloride poisons the catalyst. Bromide ion also exerts an inhibitory effect on the reaction but it is not as severe as that of the iodide ion. Chloride ion does not inhibit the reaction and thus chlorides are the preferred alkylating agents. Some examples typical of Makosza's studies (8-11) are shown in Table I in which phenylacetonitrile (benzyl cyanide) is used as the active methylene substrate.

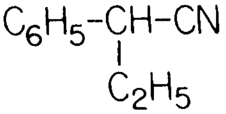
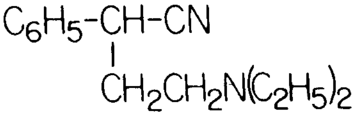
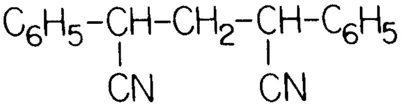
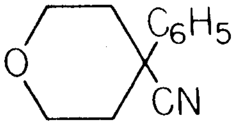
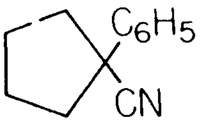
The use of a simple alkylating agent such as ethyl chloride furnishes a high yield of the alkyl-substituted phenylacetonitrile and dialkylation can be readily effected using two moles rather than one mole of alkylating agent per mole of active methylene compound. Even the use of a considerably more complex alkylating agent such as diethylaminoethyl chloride provides a high yield of the desired monoalkylated derivative. Dihalides can behave as dialkylating agents and the adjustment of molar ratios and reaction conditions can be used to control the predominant occurrence of inter- or intramolecular dialkylation during the second alkylation step, as indicated in the last three examples in Table I. Yields of desired reaction products are somewhat lower in these processes because of the formation of undesired by-products.

For "Makosza type" alkylations it is best to work without a solvent. If the substrate and alkylating agent are solids at the reaction temperature, it is desirable to use solvents such as tetrahydrofuran, dimethyl sulfoxide, dioxane or pyridine. Alcohols and nitrobenzene as solvents have an inhibitory effect. Makosza observed a different degree of catalytic activity for different quaternary ammonium halides in the ethylation of phenylacetonitrile. For example, poor yields were obtained where one of the alkyl groups was cyclopropyl, or where two alkyl groups were part of an alicyclic ring. The best catalysts appeared to be those which contained four identical short-chain n-alkyl groups, e.g. ethyl, propyl, butyl, or three such groups and a benzyl or p-methoxybenzyl group.

These significant studies by Makosza, which began to appear in about 1965, also went unnnoticed for almost five years because they were published in a Polish chemical journal. It was not until the phase-transfer process was reported by Makosza in relation to dihalocarbene generation in 1969(3) that chemists began to appreciate the potential of this technique.

TABLE I

Alkylations of Benzyl Cyanide (8-11)

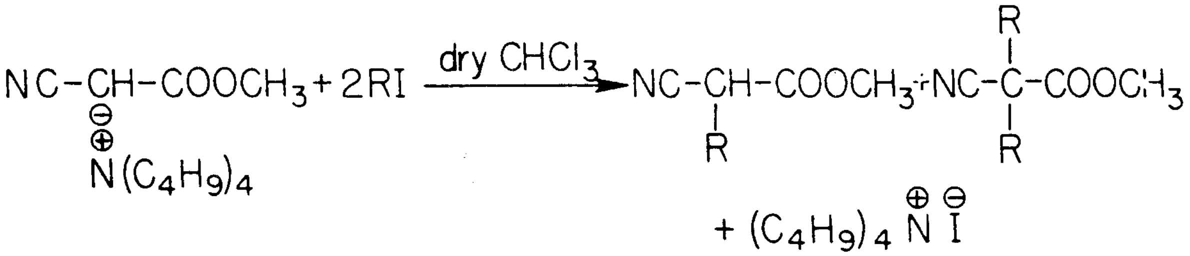
Alkylating Agent	Product	% Yield
C_2H_5Cl	 $C_6H_5{-}\underset{C_2H_5}{\underset{\vert}{CH}}{-}CN$	90
$Cl(CH_2)_2N(C_2H_5)_2$	 $C_6H_5{-}\underset{CH_2CH_2N(C_2H_5)_2}{\underset{\vert}{CH}}{-}CN$	76
H_2CCl_2	 $C_6H_5{-}\underset{CN}{\underset{\vert}{CH}}{-}CH_2{-}\underset{CN}{\underset{\vert}{CH}}{-}C_6H_5$	69
$Cl(CH_2{-}CH_2)_2O$		67
$Cl(CH_2)_4Cl$		60

ION-PAIR EXTRACTION

At about the same time as Makosza was conducting his studies in Poland, Brandstrom and his co-workers(9) in Sweden were examining the utility of ion-pair extraction from aqueous into organic media as a means for the purification of amine salts. It has been well known for many years in analytical and inorganic chemistry that typical ionic compounds are often extracted from aqueous solutions into organic solvents in the form of ion pairs(13,14). Organic chemists also noted that salts of amines are readily extracted from aqueous solutions which contain an excess of the acid component of the salt, if they are shaken with organic solvents such as chloroform or methylene chloride. However, until Brandstrom's studies, organic chemists tended to look upon this phenomenon more as an annoyance rather than as a potentially useful technique for the purification of amine salts. Brandstrom showed that salts of amines with monobasic acids can often be recovered virtually quantitatively in a very pure condition by ion-pair extraction of an aqueous solution of the amine salt which contains an excess of the anion. The extraction is facilitated by the circumstance that ion pairs are often associated in the organic solvent and by the common-ion effect produced by the excess of anion. The degree of extraction increases as the concentration of the amine is increased. Tertiary amines are more readily extracted than secondary and primary amines. Salts of most monobasic acids are extracted as easily as, or better than the hydrochlorides. High molecular weight and the absence of hydrophilic groups in the amine favour the extraction of the salt. The choice of organic solvent used to effect ion-pair extraction is also very important. Those which have proven to be most useful are acetone, ethyl acetate, benzene, petroleum ether, and particularly chloroform and methylene chloride.

Brandstrom and his co-workers(15-17) immediately applied the ion-pair extraction technique for the purification of amines to the alkylation of active methylene compounds. The reason for taking this approach was to circumvent the requirement to use non-aqueous, highly polar, aprotic solvents as media for nucleophilic substitution reactions. These workers(15) achieved the ion-pair extraction of numerous anions such as cyanide, cyanate, azide, nitrite, iodide, bromide, benzoate, phenolate, enolates of β-diketones, and carbanions of active methylene compounds such as β-ketoesters, β-cyanoesters, acylmalonic esters, benzamide etc., from aqueous alkaline solutions by using quaternary ammonium salts such as tetrabutylammonium ion derivatives as the cationic species. Quantitative ion-pair extraction is unsuccessful with still weaker acids such as alcohols, benzyl cyanide, benzyl ketones, aliphatic carbonyl compounds and malonic esters.

In the first alkylations examined, Brandstrom and Junggren(16,17) added two moles of an alkyl iodide dropwise to a solution of the tetrabutylammonium salt of methylcyanoacetate in anhydrous chloroform producing both the mono- and dialkyl-derivatives and leaving some unreacted substrate. The exothermic reaction was quite rapid. Ether was added to precipitate the quaternary ammonium iodide and, following filtration, the alkyl derivatives were recovered by evaporation of the ether-chloroform solution. The identities of the products were established by NMR analysis and their relative amounts were estimated by vapour phase chromatography (VPC).



$$NC-\underset{\substack{\ominus\\ \oplus\\ N(C_4H_9)_4}}{C}H-COOCH_3 + 2RI \xrightarrow{\text{dry } CHCl_3} NC-\underset{R}{C}H-COOCH_3 + NC-\overset{R}{\underset{R}{C}}-COOCH_3 + (C_4H_9)_4\overset{\oplus}{N}\overset{\ominus}{I}$$

R	Reaction Time (min)
CH_3	10
C_2H_5	20
$i-C_3H_7$	120
$n-C_4H_9$	60

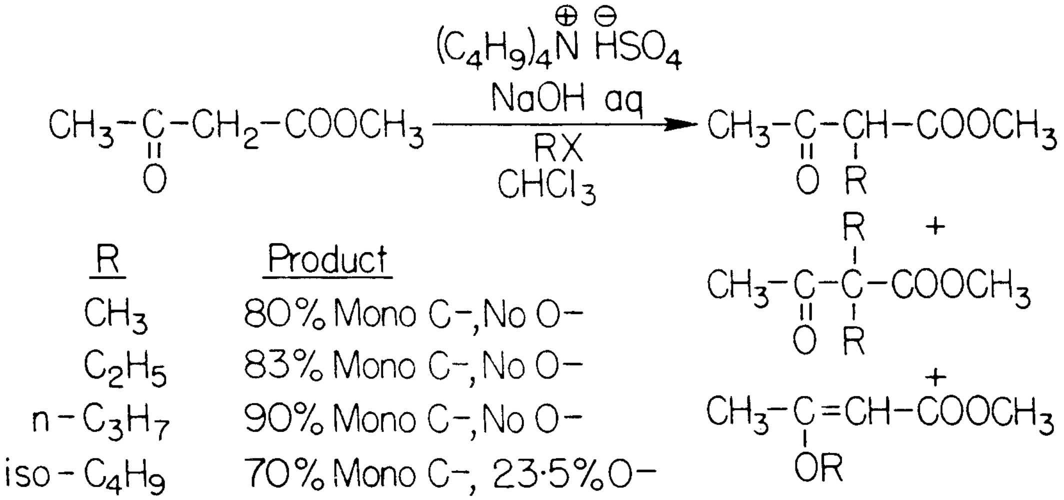
The isolated tetrabutylammonium salts of carbanions are thus valuable synthetic intermediates. They can be alkylated readily within seconds or minutes in anhydrous media and a judicious choice of solvent can promote C-alkylation as opposed to O-alkylation. C-Alkylation proceed best in non-polar solvents and O-alkylation proceed best in polar aprotic media as indicated in Table II (18).

TABLE II

Isopropylation of Tetrabutylammonium Pentanedionate (18)

Solvent	C/O-Alkylation
Dimethyl Sulfoxide	0·72
Acetone	0·72
Acetonitrile	0·92
Chloroform	1·04
Dioxane	1·91
Toluene	13·8

In the next step in the evolution of the process, Brandstrom and Junggren(17) described their extractive alkylation technique, in which the prior preparation, isolation and purification of the tetrabutylammonium salt of methyl acetoacetate was rendered unnecessary. The reaction was conducted by adding a solution of tetrabutylammonium hydrogen sulphate (0.1 mole) in aqueous sodium hydroxide (0.2 mole) to a stirred solution of methylacetoacetate (0.1 mole) and alkyl halide (0.2 mole) in chloroform. The reaction was exothermic and was completed in a few minutes. After separation of the layers, the chloroform was removed by evaporation, ether was added to the residue to precipitate the by-product tetrabutylammonium salt, and the alkylated products were recovered by filtration. The structures of the products were established by NMR analysis and product ratios were determined by VPC. Where n-alkyl halides were used C-alkylation occurred exclusively and monoalkylation predominated. With branched-chain alkyl halides a small amount of O-alkylation was also observed.



$$CH_3-\underset{\underset{O}{\parallel}}{C}-CH_2-COOCH_3 \xrightarrow[\substack{RX \\ CHCl_3}]{\substack{(C_4H_9)_4\overset{\oplus}{N}\,\overset{\ominus}{HSO_4} \\ NaOH\ aq}} CH_3-\underset{\underset{O}{\parallel}}{C}-\underset{\underset{R}{|}}{CH}-COOCH_3 + CH_3-\underset{\underset{O}{\parallel}}{C}-\overset{\overset{R}{|}}{\underset{\underset{R}{|}}{C}}-COOCH_3 + CH_3-\underset{\underset{OR}{|}}{C}=CH-COOCH_3$$

R	Product
CH_3	80% Mono C-, No O-
C_2H_5	83% Mono C-, No O-
n-C_3H_7	90% Mono C-, No O-
iso-C_4H_9	70% Mono C-, 23·5% O-

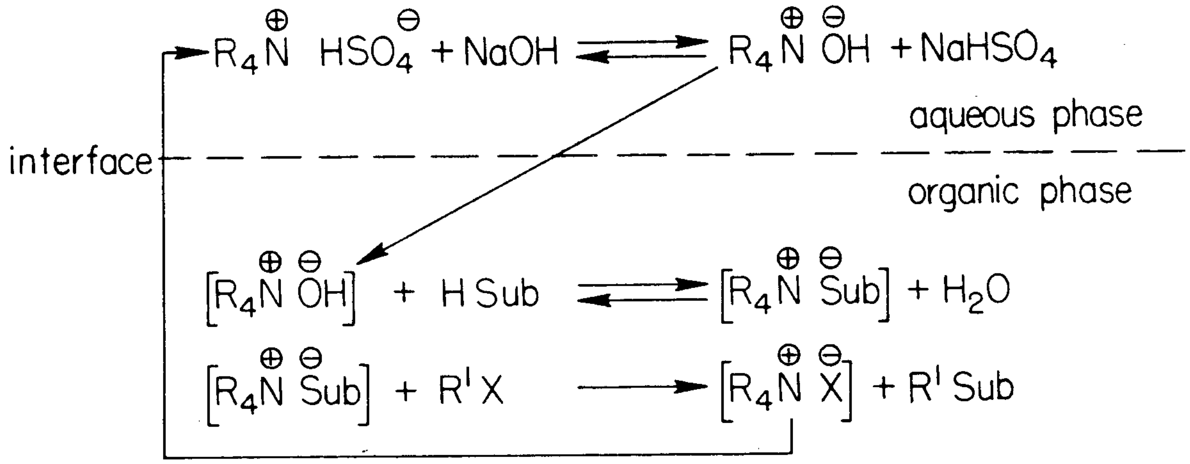
To gain an idea of the real value of the extractive alkylation method it should be contrasted with standard C-alkylation procedures which require the use of anhydrous conditions. With sodium ethoxide in ethanol, the reaction is rather slow and requires at least a day to perform. Using a base, such as sodium hydride or potassium carbonate in an aprotic solvent, such as dimethyl formamide (DMF), the reaction is faster than in alcohol, but the product is contaminated with substantial quantities of O-alkylated products.

The phase-transfer catalytic process as now conducted evolved basically from the work of Makosza et al and of Brandstrom et al. In 1971 Starks(4) reported the use of quaternary phosphonium compounds as catalysts for a wide variety of chemical processes in which the reactions were conducted by dissolving an organic substrate in a hydrocarbon solvent, to which was added an aqueous phase containing the appropriate reactant, together with a catalytic amount of a quaternary ammonium or phosphonium salt. The reaction mixture was heated with stirring and only in the presence of the catalyst did the desired reaction proceed at a useful rate for preparative purposes. Since 1971, other workers have used a variety of solvents, most frequently chloroform and methylene chloride. The process is essentially the same as described earlier by Makosza except for the addition of the solvent. Makosza used an excess of the organic substrate.

MECHANISM OF PHASE TRANSFER CATALYSIS

The mechanism of the catalytic process can be described as a combination of ion-exchange and phase-transfer equilbria. If the case of an alkylation reaction conducted under Brandstrom's extractive alkylation conditions is considered it will facilitate an understanding of the catalytic process. Under these circumstances, reaction is conducted without the isolation of the quaternary ammonium salt and tetrabutylammonium hydrogen sulphate is dissolved in two molar equivalents of aqueous sodium hydroxide and is added dropwise to a molar equivalent of the alkyl halide and the compound to be alkylated in a solvent, e.g. chloroform. The reaction is often exothermic and the mixture becomes neutral within a few minutes. The reactions which occur are shown in Scheme 1.

SCHEME 1



[ ] = ion-pair
Sub = organic substrate

In this process the tetrabutylammonium ion carries the hydroxide ion across the phase boundary as an ion pair to react with the organic substrate to produce a carbanion, which immediately forms an ion pair with the tetrabutylammonium ion. The ion pair is alkylated, yielding the desired product and a tetrabutylammonium halide as an ion pair. The first step, which occurs in the aqueous phase, is an ion exchange. The second step is the transfer of the quaternary ammonium hydroxide ion pair across the phase boundary. The efficiency of this part of the process is governed by the phase-transfer equilibrium, which depends on the partition coefficient of the quaternary ammonium hydroxide between the aqueous and the organic phases.

The third step is an ion exchange and the fourth is the nucleophilic displacement. The entire process works best when the ion-exchange equilibrium in the aqueous phase is well displaced toward the quaternary ammonium hydroxide and the latter is readily extractable from the aqueous phase by the solvent chosen for the organic phase. In this process a stoichiometric amount of quaternary ammonium salt was used.

In the next step, the procedure is extended to compounds whose low acidity precludes their quantitative extraction as ion pairs, e.g., benzyl cyanide. The organic phase will then likely contain both ion pairs and unchanged organic substrate. Although the local concentration of the ion pairs [R_4N^+ Sub^-] is low because the equilibrium in this ion-exchange process favours the quaternary hydroxide, the reactivity of the anion in the alkylation step is so high in the organic medium because of lack of solvation, that it is always rapidly removed from the equilibrium. Because of the slower generation of the desired ion pair, however, the alkylation is slower, requiring ca thirty minutes. Sometimes it is exothermic and sometimes it requires heating.

Provided that the partition equilibrium favours the transfer of the quarternary ammonium halide back to the aqueous phase and the ion-exchange processes work efficiently, a cyclical process involving this quaternary ammonium ion can be set up between the aqueous and the organic phases, using only a catalytic amount of quaternary salt. It carries hydroxide ion from the aqueous to the organic phase, as an ion pair, which is converted to an ion pair with the substrate. The latter is then alkylated, liberating a quaternary ammonium ion pair which migrates back to the aqueous phase.

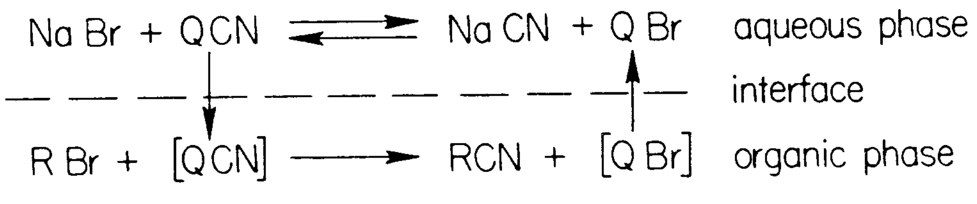
The mechanism just outlined is essentially that proposed by Starks(4) in 1971 in which he introduced the terminology "phase-transfer catalysis" to describe a large number of nucleophilic displacements, oxidations and reductions which can be readily conducted in two-phase aqueous-organic systems in the presence of quaternary ammonium or phosphonium ions as catalysts. His paper was very important for two reasons. First, he recognized the very general utility of the processes. Second, he recognized that Makosza's and Brandstrom's studies on alkylation and dichlorocarbene formation in analogous reactions were special cases of the more general process and drew attention to them.

Although Starks' mechanism for the catalytic process is a very reasonable one, alternative explanations have been proposed. The catalysts used are all more or less typical detergents, and Makosza et al.(3,19) suggested that the reactions were occurring at the phase interface. On the other hand, Tabushi et al.(20) suggested that the presence of a micellar phase is responsible for the catalytic effect of the quaternary salt. Catalysis by micelles is a well established phenomenon and much interest has currently been focused on its application to organic reactions(21,22).

Starks(4) was aware of the alternative explanations for the phenomena which he had observed but concluded that the mechanism which he had proposed seemed more reasonable on the following grounds. Poor surfactants such as tetrabutylammonium and tetradodecylammonium salts, which are poor micellar catalysts, are excellent phase-transfer catalysts and small quaternary ions (e.g. tetramethylammonium) which are effective micellar catalysts and good surfactants are not good phase-transfer catalysts - they tend to form stable emulsions. He found tricaprylmethylammonium chloride and hexadecyltributyl phosphonium bromide to be the most suitable phase-transfer catalysts. Also, phase-transfer-catalyzed reactions show a first-order dependence of reaction rate on the concentration of quaternary salt, whereas in micellar-catalyzed processes, the reaction rate remains relatively constant once the critical micelle concentration has been reached. The reaction between 1-chlorooctane and aqueous sodium cyanide is, for example, catalyzed by the anionic surfactant sodium dodecylbenzenesulfonate but the rate is lower by a factor of 100 - 1000 than when the reaction is quaternary-salt-catalyzed. It is well known that the micellar catalytic effect is relatively small, e.g. in the 10-100 fold range(23). It is possible to adjust the rates of phase-transfer-catalyzed reactions by changing the catalyst concentration. The known ability of quaternary ammonium salts to participate in displacement reactions at high rates, even in non-polar media, as reported by Ugelstad et al(24) has also been cited in support of the phase-transfer mechanism.

In subsequent studies Starks and Owens(25) showed that in the tetrabutylphosphonium bromide-catalyzed cyanide displacement on 1-bromooctane the rate of reaction is directly proportional to the organic-phase solubility of the catalyst. The obvious conclusion is that the displacement reaction must occur in the organic phase, as indicated in Starks' phase-transfer catalytic interpretation shown in Scheme 2 which demands that the phase-transfer agent must serve as a vehicle to bring one reactant into the same phase as the second, and the transferred species must be in a suitable environment for reaction. In the reaction between 1-bromooctane and aqueous sodium cyanide, several agents were examined which were not capable of both functions. For example, certain metal chelates were found which were capable of transporting cyanide to the organic phase, but in these the cyanide was so tightly bound to the cation that a displacement reaction could not occur.

SCHEME 2



There are actually two phase-transfer processes shown by the vertical arrows in Scheme 2, one carrying cyanide ion from the aqueous to the organic phase and the other carrying bromide ion from the organic to the aqueous phase to complete the cyclic catalytic process. The efficiency of the phase-transfer process depends upon the partition between anions associated with quaternary cations in an organic phase and in an aqueous phase, which is in turn related to the anion equilibrium occurring in the aqueous phase. Quaternary cations in a nonpolar phase preferentially associate with large and minimally hydrated (solvated) anions and also with anions which have considerable organic structure. This selectivity is important to the reaction step since in anion-transfer reactions it dictates which anion will predominate in the organic phase. The CN^-/Br^- partitioning is so balanced that sufficient quaternary cyanide is present in the 1-bromooctane phase to allow the displacement reaction to proceed readily to completion. Ugelstad et al(24) have suggested that, in non-polar media, the ion-pair form of the quaternary salt is the reactive entity and that the abnormal reactivity is explained by a reduced cation-anion interaction energy in the ion-pair. However, an alternative explanation proposed by Starks is the formation of a weak complex in which the alkyl halide penetrates deeply into the web of alkyl groups around the quaternary nitrogen or phosphorus atom. Such complex formation is favoured not only by Coulombic ion-dipole attractions but also by van der Waals attraction between the alkyl groups of the quaternary cation and that of the alkyl halide. From such a complex a "push-pull" transition state analogous to that described by Swain et al(26,27) can be readily formed, although in this case it is not necessary that the displacing anion be separated from the cation (ionized). Starks and Owens(25) also confirmed that the partitioning of anions was occurring between the aqueous and organic phases by measuring the anion transfer equilbrium, the position of which depends on the relative concentrations of the anions, the amount of water present and the polarity of the organic medium. The rates of phase-transfer-catalyzed reactions were shown to be independent of the stirring rate above a limiting rate of ca 250 r.p.m. This behaviour is not characteristic of reactions which occur at an aqueous-organic phase boundary, where the reaction rate is directly proportional to the stirring rate(28).

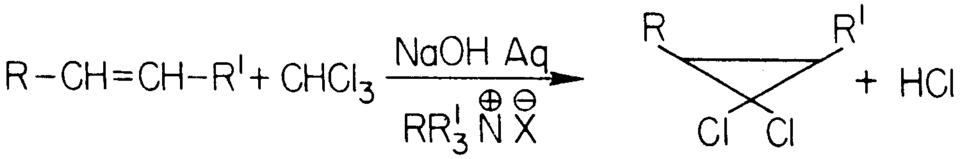
Quite recently, Herriott and Picker(29) studied the catalytic effect of quaternary ammonium and phosphonium ions on the reaction of thiophenoxide ion with 1-bromooctane in benzene/2N NaOH, and confirmed the essential details of Starks' phase-transfer mechanism, in that the reaction rate followed good second order kinetics, was not affected by stirring rates exceeding 200 r.p.m., but was linearly dependent on catalyst concentration over the range 1.34 to 14×10^{-4} molar. Relative reaction rates increased as the size of quaternary ion increased and as the length of the longest chain increased. More symmetrical ions, e.g. $(C_4H_9)_4\overset{\oplus}{N}$ or $(C_8H_{17})_3\overset{\oplus}{N}CH_3$ are better catalysts than those with only one long chain, e.g. $C_6H_{13}\overset{\oplus}{N}(C_2H_5)_3$. Phosphonium ions are somewhat more effective than ammonium ions bearing the same substituents, and alkyl groups are more effective in promoting catalytic efficiency than are aryl groups. An increase in the ionic strength of the aqueous phase by the addition of a salt or a change to a more polar solvent also increases the reaction rate; e.g. rates are slower in heptane than in benzene, but faster in o-dichlorobenzene. These increases in rates are believed to be due to increased partitioning into the organic layer. The rate increase in changing the solvent from benzene to o-dichlorobenzene is most pronounced for the weaker catalysts, e.g. tetrapropylammonium bromide (factor of 80), and much less for the better catalysts, e.g. tetrabutylphosphonium chloride (factor of 5). Contrary to the results reported earlier by Makosza et al(8-11) no appreciable counterion effect was observed. Although maximum rates were observed with the large phosphonium ions, these are more prone to decomposition. Trioctylmethylammonium chloride is nearly as effective and is much more stable. The rates tend to converge in more polar solvents and the choice of catalyst is much less critical. Reaction rates can be increased by increasing the catalyst concentration.

Further evidence in favor of the phase-transfer mechanism was obtained by showing that there is a correlation between the distribution coefficients of the ions in the organic layer and the reaction rate(29). Additional support for this explanation came from the observation that dicyclohexyl-18-crown-6 serves as an effective phase-transfer catalyst in the benzene/water system, transferring the thiophenoxide ion efficiently into the benzene layer where reaction with the 1-bromooctane occurs. The rate constant is almost identical to that of the fastest quaternary ion catalyst(29).

SOME APPLICATIONS OF PHASE TRANSFER CATALYSIS TO ORGANIC CHEMISTRY

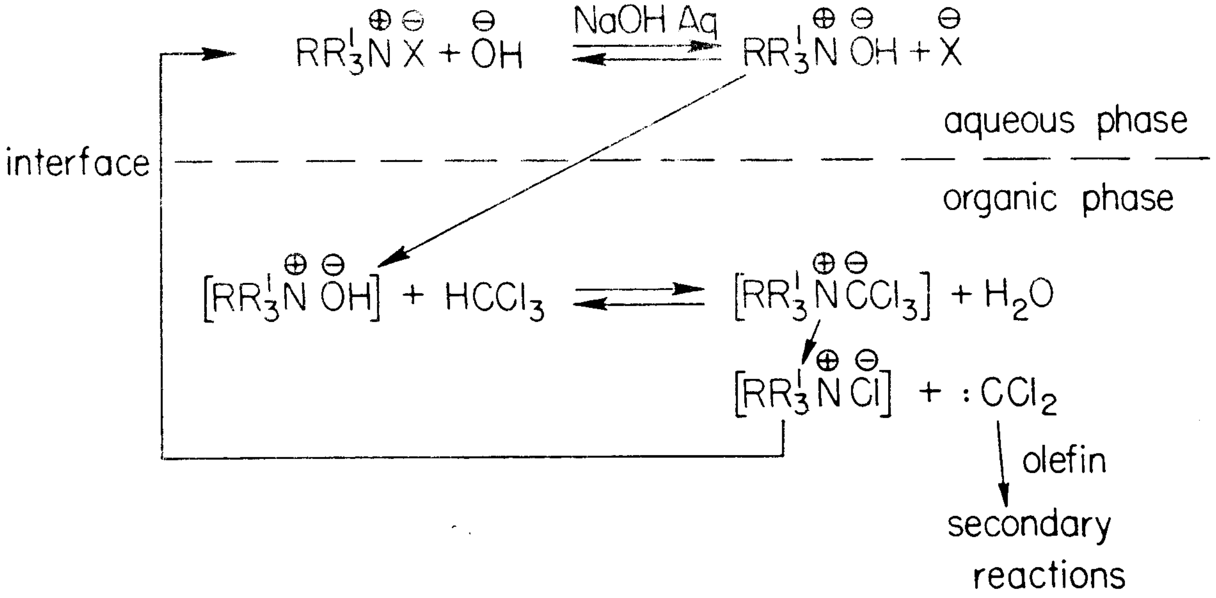
Dichlorocarbene Additions (Makosza Reaction)

One of the earliest applications of phase-transfer catalysis is due to Makosza and Wawrzyniewicz(3) who observed that it was possible to prepare dichlorocyclopropane derivatives from olefins by treating them with chloroform and aqueous sodium hydroxide in the presence of catalytic amounts of triethylbenzylammonium chloride (TEBA).



It had been known for fifteen years, following Doering's discovery(30), that dichlorocyclopropanes could be readily prepared by the action of dichlorocarbene on olefins. However, prior to Makosza's work it had always been necessary to generate the dichlorocarbene under strictly anhydrous conditions because of its rapid hydrolytic destruction. Typical procedures for generating dichlorocarbene involved the use of very reactive and dangerous systems, e.g. chloroform and potassium t-butoxide, bromotrichloromethane and n-butyl lithium, methyl trichloroacetate and sodium methoxide etc. Makosza's procedure made the preparation of dichlorocyclopropanes a very simple matter. The reactions which occur in this catalytic phase-transfer system are shown in Scheme 3.

SCHEME 3

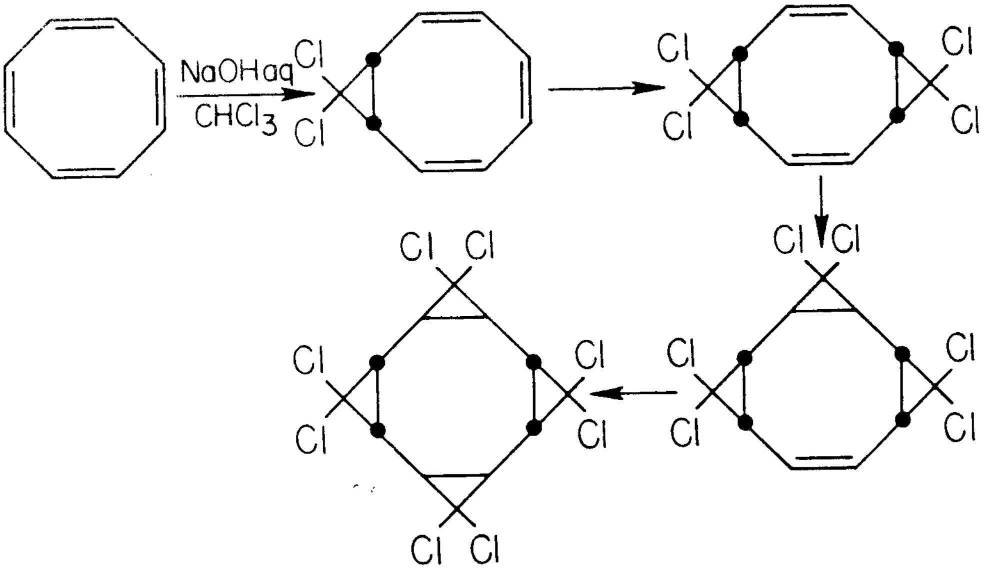


Makosza considered that the triethylbenzylammonium chloride was converted to the corresponding hydroxide in the aqueous phase. Since the quaternary ammonium hydroxide is insoluble in the aqueous phase, it migrates across the phase boundary into the organic layer as an ion-pair, where it reacts with the chloroform to produce the quaternary ammonium salt of the trichloromethyl anion also as an ion-pair. The latter is transformed into dichlorocarbene and triethylbenzylammonium chloride ion-pair. The dichlorocarbene reacts rapidly with the olefin present in the organic layer, and the quaternary ammonium chloride passes to the phase boundary to reenter the transformation cycle. Dichlorocarbene is believed to be formed in an anhydrous medium, and consequently it is hydrolyzed to only a slight extent. The high degree of dichlorocarbene utilization is due to the fact that the quantity of dichlorocarbene which can be formed at any time is small and does not exceed the amount of the catalyst. Consequently, dichlorocarbene is always confronted with a large excess of olefin.

Dichlorocarbene generated by the phase-transfer reaction is exceptionally reactive toward substrates which react slightly, if at all, with conventionally generated dichlorocarbene. This is believed to be because the carbene is formed close to its site of further reaction. The preferred catalyst for generation of dichlorocarbenes from haloform with 50% sodium hydroxide is triethylammonium chloride.

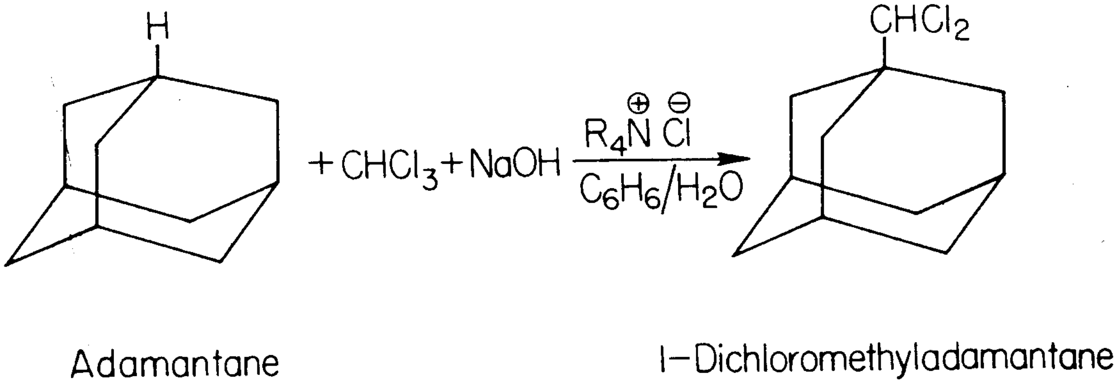
The Makosza reaction can be used to dichlorocyclopropanate normal alkenes, enol ethers(3), sterically-hindered olefins (e.g. triphenylethylene), electron-deficient olefins (e.g. methacrylonitrile) and acetylenes(31,32). Addition does not occur to tetraphenylethylene and to the di-, tri-, and tetrachloroethylenes. Conventional dichlorocarbene reagents usually add only once to conjugated olefins - electron withdrawal by the chlorine atoms deactivates the molecule toward a second attack. However, both single and multiple additions can be readily accomplished with "phase transfer dichlorocarbene" depending on reaction conditions (31,33). A typical example is shown in Scheme 4.

SCHEME 4



Dichlorocarbene Insertions

The insertion of dichlorocarbene into C-H bonds occurs more readily with dichlorocarbene generated by phase-transfer catalysis than with dichlorocarbene generated by more conventional "anhydrous" procedures. However, yields of preparative utility only occur on insertion into bridgehead positions or α to activating groups, as exemplified by the conversion of adamantane to 1-dichloromethyladamantane(34).



Insertions into C-X (X = Cl and Br but not F), C-O, C-N and N-H bonds are also well substantiated(35).

Nitriles from Amides

Saraie et al(36) and Hofle(37) found that aromatic and aliphatic amides, thioamides, aldoximes and ureas are converted into nitriles by dichlorocarbene generated from a phase-transfer reaction. Yields generally lie in the 10-20% range for lower aliphatic amides and up to 95% for long-chain or branched compounds.

Preparation of Isonitriles

The well known carbylamine reaction in which amines give poor yields of isonitriles on treatment with aqueous caustic alkali and chloroform can be greatly improved by the addition of a phase-transfer catalyst(38,39).

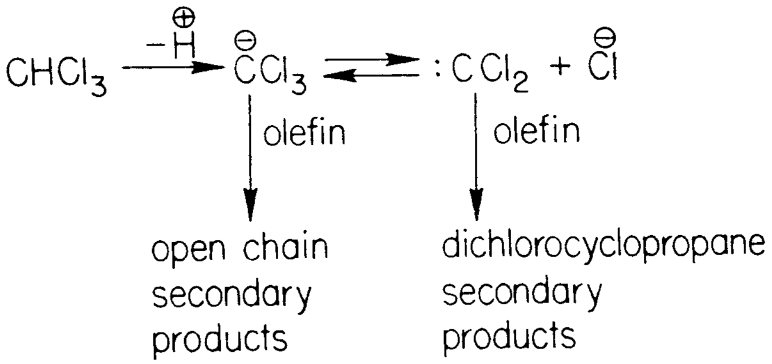
Conversion of Alcohols into Chlorides

Tabushi et al(40) discovered that the phase-transfer-catalyzed generation of dichlorocarbenes in the presence of alcohols produces alkyl chlorides in high yields.

Reaction of Trihalomethyl Anions

The primary product of the phase-transfer reaction between sodium hydroxide and chloroform is the trichloromethyl anion in the form of its ion-pair. It is in equilibrium with dichlorocarbene and chloride ion as shown in Scheme 5.

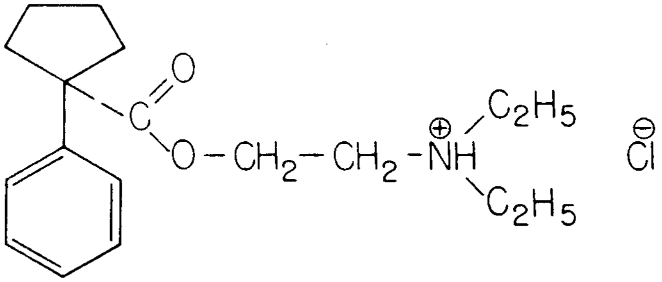
SCHEME 5



Depending on whether electron-rich or electron-poor olefins are present, either the electrophilic dichlorocarbene or the nucleophilic trichloromethyl-anion is scavenged from the equilibrium. The direction taken by the reaction is affected by small changes in electron distribution(34).

Alkylation of Carbanions

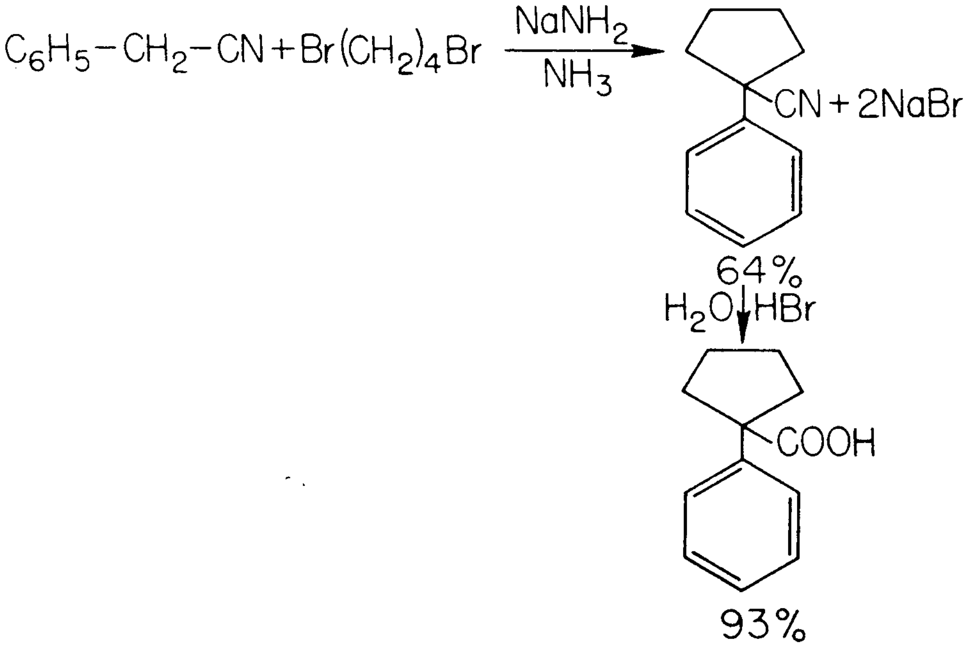
This topic has already been mentioned in connection with the origin of the phase-transfer method, and numerous examples of its synthetic utility could be cited, but only two illustrative examples will be mentioned. During the period 1959-68 at DREO the potential of cholinolytic drugs for the therapeutic treatment of nerve gas poisoning in conjunction with atropine and reactivators, was being examined. One of the more interesting series of compounds studied in this connection was the dialkylaminoalkyl esters of 1-phenylcyclopentanecarboxylic acid, the so-called Parpanit series(41-43), the first number of which is shown below.



Parpanit

The main intermediate for the synthesis of these compounds, 1-phenylcyclopentanecarboxylate, was prepared by the reactions shown in Scheme 6.

SCHEME 6



The first step, which is an internal two-step alkylation of the carbanion of phenylacetonitrile, can be an extremely hazardous operation since sodamide/liquid ammonia systems are prone to violent decomposition. The reaction must be conducted under bone-dry conditions at -50°C for 2.5 hours and finally heated under reflux for 2 hours to furnish a 64% yield of nitrile. The same product can be obtained very readily and safely in 60% yield by the application of a phase-transfer catalytic procedure by the dropwise addition of tetramethylene dichloride to a stirred mixture of phenylacetonitrile and aqueous sodium hydroxide containing 0.02 mole % of a quaternary ammonium chloride at room temperature.

In 1974 Durst and Liebeskind(44) described an interesting application of "solid-liquid" phase-transfer catalysis using methyl acetoacetate as the source of the carbanion for C-alkylation. The catalyst used was a long-chain quaternary ammonium salt, "Alaquat 336" which consists of mixed trialkylmethylammonium chlorides (average mol. wt. 503). It is insoluble in water and soluble in all common organic solvents. The basic process involves the generation of a solid reactive anion which is normally insoluble in organic solvents and to use the phase-transfer catalyst to transport it into the organic phase for reaction with an alkylating agent.

Carbon alkylation is normally favored in protic solvents (e.g. ethanol) in the usual acetoacetic ester condensations, but O-alkylation is favored in polar aprotic solvents (especially in hexamethylphosphoramide). However, the alkylation of methylacetoacetate with benzyl chloride in benzene by phase transfer catalysis gave greater than 99% C-alkylation with no detectable O-alkylation. Thus, the process offers a reversal of the usually observed results in aprotic solvents, thereby giving an alternative to the usual procedure of using protic solvents to favor C-alkylation. The process has another advantage in that no solvolysis products arising from alkylating agent-solvent interactions are possible, thus eliminating a source of major side products from reactions conducted in protic solvents. Optimum yields (85%) were obtained using a 10:1 alkylating agent/catalyst molar ratio and an 8-hour reflux period. The solvent used had a marked effect on the yield. For example, benzene and toluene produced much better yields than did chlorinated hydrocarbons such as chloroform or carbon tetrachloride. Saturated hydrocarbon solvents were the least satisfactory of those examined Table III.

TABLE III

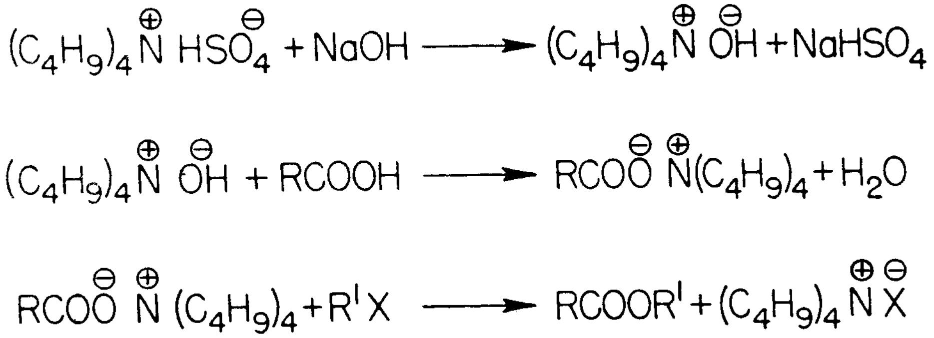
Effect of Solvent on Alkylation Yields(44)

Solvent	% Yield
Benzene	85
Toluene	82
Chloroform	56
Carbon Tetrachloride	42
Hexane	40

Esterification

Esterification can be conducted in neutral solution by treating one equivalent of a carboxylic acid and one equivalent of tetrabutylammonium hydrogen sulphate with two moles of aqueous sodium hydroxide and boiling the resultant mixture with the alkylating agent for 15-30 min(45). Almost quantitative yields are obtained even with sterically hindered acids such as 2,4,6-trimethylbenzoic acid. Dicarboxylic acids can also be esterified in this mannner. The esterification proceeds, apparently via the agency of formation of an intermediate quaternary ammonium salt of the acid as indicated in Scheme 7.

SCHEME 7



$$(C_4H_9)_4\overset{\oplus}{N}\;H\overset{\ominus}{SO_4} + NaOH \longrightarrow (C_4H_9)_4\overset{\oplus}{N}\;\overset{\ominus}{OH} + NaHSO_4$$

$$(C_4H_9)_4\overset{\oplus}{N}\;\overset{\ominus}{OH} + RCOOH \longrightarrow RCO\overset{\ominus}{O}\;\overset{\oplus}{N}(C_4H_9)_4 + H_2O$$

$$RCO\overset{\ominus}{O}\;\overset{\oplus}{N}(C_4H_9)_4 + R^{\prime}X \longrightarrow RCOOR^{\prime} + (C_4H_9)_4\overset{\oplus}{N}\,\overset{\ominus}{X}$$

Esterifications are also catalyzed by quaternary phosphonium and arsonium salts. The most extensive investigation of this reaction was conducted by Merker and Scott(46) who obtained excellent yields of many esters of aliphatic and aromatic carboxylic acids by actually preparing the tertiary amine salts of the acids and treating them with alkyl halides in solvents such as acetone or xylene, or with excess alkyl halide in the absence of a solvent.

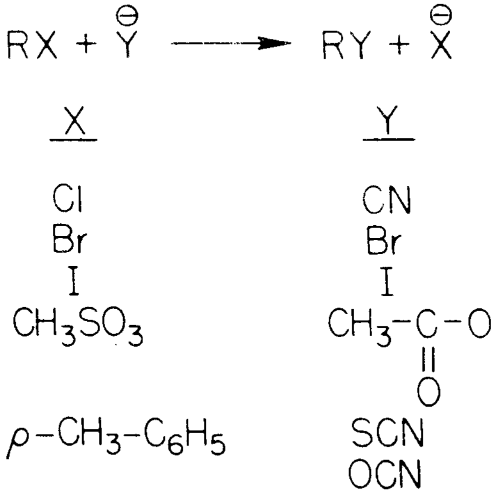
Alkylation of Phenols

This reaction can be effected by the action of an alkyl halide on a phenol in the presence of an excess of a tertiary amine as a hydrogen acceptor(24). The mechanism of the reaction is analogous to that just mentioned for the esterification of carboxylic acids.

Ether Formation

Herriott and Picker(47) obtained high yields of symmetrical ethers by a phase-transfer-catalyzed version of the Williamson ether synthesis using an alkyl halide, an alcohol, caustic soda and a quaternary ammonium catalyst. However, a mixture of symmetrical and unsymmetrical ethers resulted when the alcohol and alkyl halide possessed different alkyl groups.

Freedman and Dubois(48) recently reported a very useful method for the synthesis of a variety of unsymmetrically substituted ethers by phase-transfer catalysis using inexpensive alkyl chlorides as alkylating agents. In this process, a five-fold excess of aqueous sodium hydroxide over alcohol was used, together with an excess of the alkyl chloride which served as solvent. Three to 5 mole % of tetrabutylammonium bisulphate (TBAB) was used as a catalyst. Primary alcohols are alkylated in 3-4 hours at 27-70°C in 72-92% yields, while secondary alcohols require longer times or greater amounts of catalyst. With secondary alkyl halides the yields are no longer preparatively useful.



Nucleophilic Displacements

Starks(4) has shown that the general nucleophilic displacement reaction shown above can be greatly accelerated by phase-transfer catalysis. The systems studied contained chloride, bromide, iodide, methanesulfonate and p-toluenesulfonate as leaving groups, and cyanide, bromide, acetate, iodide, thiocyanate and cyanate as nucleophiles. Halogen exchange reactions, e.g. bromide for chloride can be effected using tricaprylmethylammonium chloride by heating for 5 hours at 100°C. Nitriles and thiocyanates can be readily prepared in high yields using benzylmethylammonium chloride and hexadecyltributylphosphonium bromide as catalysts. If X is iodide or p-toluenesulphonate, the reaction stops on reaching the phase partitioning equilibrium of the anions, and the aqueous phase must be renewed several times to ensure complete reaction. In other cases (e.g. X = Br, Y = Cl) the progress of the reaction is halted by the chemical equilibrium. Here too, the aqueous phase must be replaced to achieve complete reaction.

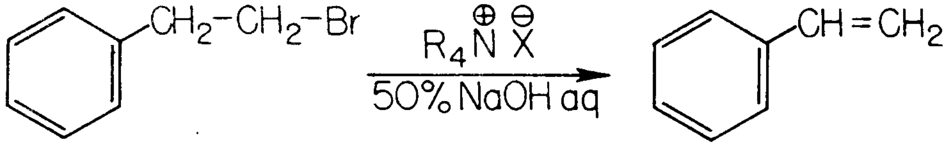
Cyanide displacement was the most thoroughly studied, and in general it was found to behave as expected for SN2 displacement. Reaction is much faster with primary than with secondary alkyl halides, and cyclohexyl and tertiary alkyl halides give predominantly elimination products.

Primary C_4 to C_{16} alcohols have been converted to chlorides by boiling them with concentrated hydrochloric acid in the presence of hexadecyltributylphosphonium bromide(49). Average yields were approximately 60% after 8 hours.

Starks(4) also observed that the hydrolysis of esters and alkanesulfonyl chlorides is accelerated by the addition of a quaternary ammonium salt. The reactions are frequently exothermic and require no external heating. Hydrolysis is complete in 0.5 hour with the esters and is instantaneous with the alkanesulfonyl chlorides.

Elimination Reactions

Elimination is frequently the most common side-reaction accompanying nucleophilic displacement reactions under anhydrous conditions, but it may also become an important side-reaction in aqueous media. Verstraelen et al(50) observed that elimination reactions are catalyzed by quaternary ammonium compounds. For example, the elimination of hydrogen bromide from phenylethyl bromide is catalyzed by n-butyltriethylammonium chloride in a two-phase system.



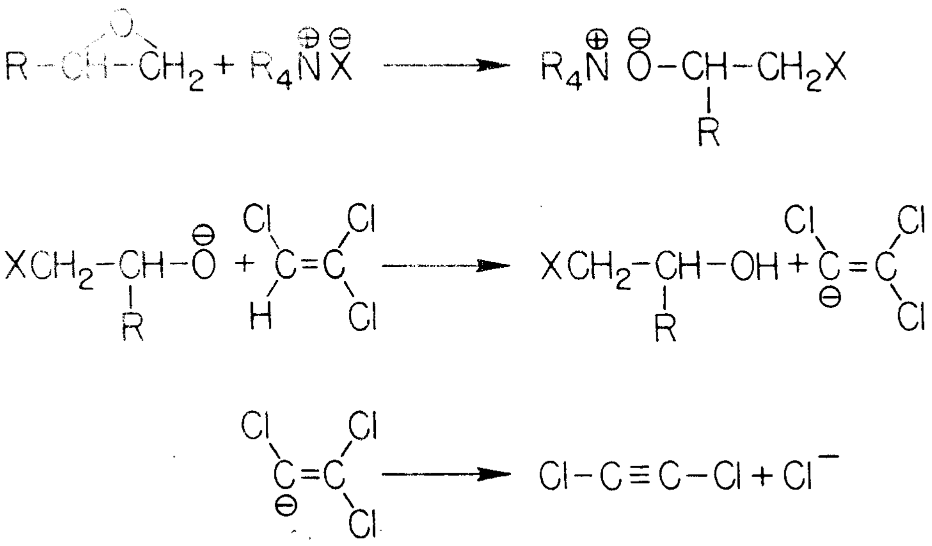
At 90°C the reaction is complete in 2 hours, but in the absence of catalyst only 1% of styrene is formed. The extent of catalysis varies with the structure of the quaternary ammonium salt. It is beneficial to have at least one C_5 n-alkyl group to enhance the solubility of the catalyst in the organic phase.

A particularly elegant example of elimination catalyzed by a quaternary ammonium compound was provided by Dobinson and Green(51) in which trichloroethylene was converted to dichloroacetylene by ethylene oxide, with explosive violence, presumably through the agency of the strongly basic intermediate quaternary ammonium ion-pair of the haloethoxylate anion shown in Scheme 8.

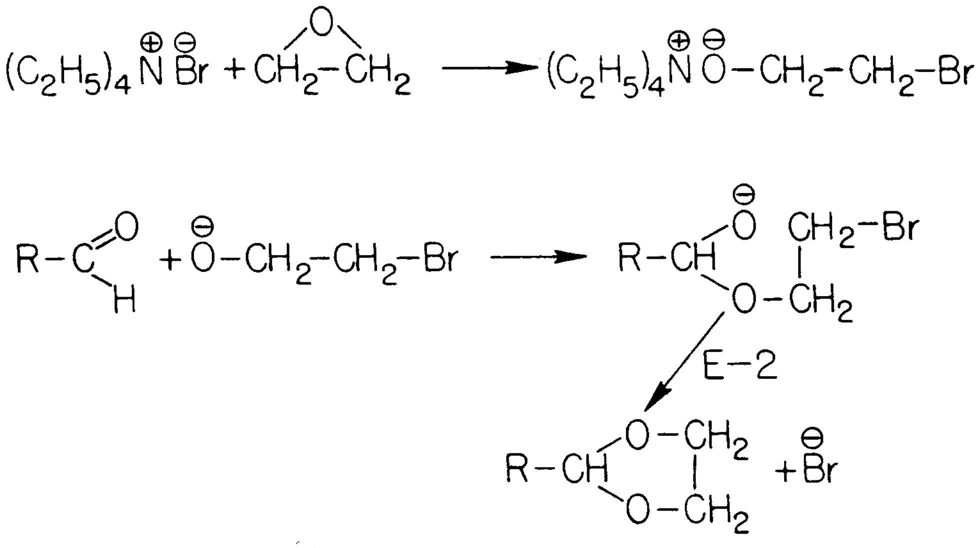
Addition Reactions

Nerdel et al(52) developed useful syntheses for dioxolanes in high yields by the tetraethylammonium bromide-catalyzed addition of ethylene oxide to aldehydes as indicated in Scheme 9.

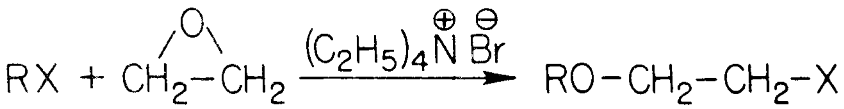
SCHEME 8



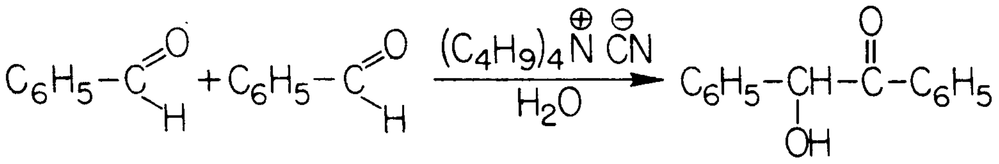
SCHEME 9



One molar equivalent of quaternary ammonium salt must be used, the reactions are conducted at 110 - 220° in homogeneous solution for prolonged periods (1-24 hr), and the reaction is thought to proceed via the formation of tetraethylammonium haloethoxylate, the haloethoxylate anion acting as a nucleophile. The same intermediate is considered to intervene in the reaction between alkyl halides and ethylene oxide in the presence of the same quaternary ammonium salt in which 2-bromoethyl ethers are formed.



Solodar(53) observed that the self-condensation of benzaldehyde to form benzoin, which is catalyzed by cyanide ion (sodium cyanide) at 90° in 50:50 aqueous methanol solution, does not proceed readily in aqueous solution. If tetrabutylammonium cyanide is added to the aqueous solution, the reaction is complete in 1 hour at room temperature.



Oxidation by Potassium Permanganate

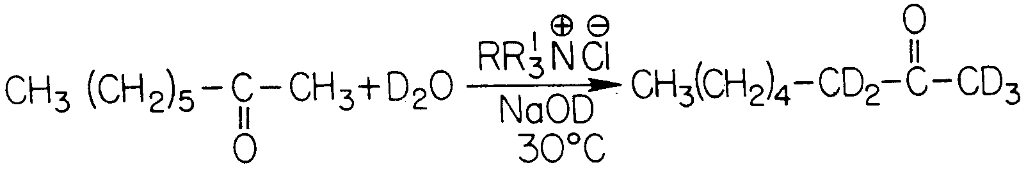
In 1971, Starks(4) observed that in the presence of trihexylmethylammonium chloride, neutral aqueous permanganate oxidizes terminal olefins in two-phase benzene-water systems to carboxylic acids having one less carbon atom. The reaction is exothermic and the temperature is kept at 30-35° by external cooling.

In 1972 Weber and Shepherd(54) reported the oxidation of internal olefins to cis-1,2-glycols in 50% yield with basic permanganate in a well-stirred two-phase methylene chloride/aqueous sodium hydroxide system using benzyltriethylammonium chloride as a phase-transfer catalyst. These workers pointed out that this reaction, as usually conducted in an aqueous medium, furnishes notoriously poor yields. They also observed that phase-transfer catalysis and crown ether catalysis are analogous methods for enhancing the reactivity of inorganic nucleophilic species in organic media by increasing their solubilities.

In 1974 Herriott and Picker(55) found that although permanganate ion normally remains in the aqueous phase of an aqueous potassium permanganate/benzene system, the addition of tetrabutylammonium bromide or tetrabutylphosphonium chloride caused it to migrate into the benzene layer forming so-called "purple benzene". They found this procedure for the preparation of "purple benzene" to be much more convenient and less expensive than the crown ether-catalyzed procedure developed by Sam and Simmons(56). Extraction studies from aqueous potassium permanganate into benzene by tetrabutylammonium bromide revealed mole for mole stoichiometry between permanganate ion and the quaternary ammonium salt. Not all quaternary salts were equally effective. For example, tetramethylammonium chloride and sodium dodecylsulfate (a cationic detergent) were completely ineffective in promoting the phase-transfer. Tetrabutylammonium bromide, tetrabutylphosphonium chloride and trioctylmethylammoniumchlorides were equally effective phase-transfer agents and were significantly more efficient than triethylbenzylammonium chloride (TEBACl) and cetyltrimethylammonium bromide (CTABr). The "purple benzene" produced in this manner can be separated and used for oxidations under anhydrous conditions. These solutions are reasonably stable. The permanganate titre decreased only 17% after 45 hours. More conveniently, the two-phase system can be used directly, requiring only a catalytic amount of quaternary ion to maintain a concentration of permanganate in the organic phase. The oxidation of nitriles, olefins and alcohols is readily effected with these solutions, and unlike the crown ether-catalyzed procedure, there is no requirement to use a ball-mill.

Deuterium Exchange

Starks also noted that deuterium exchange in ketones can be facilitated by phase-transfer catalysis. For example, admixture of 5% sodium deuteroxide in D_2O with 5% tricaprylmethylammonium chloride in 2-octanone at 30°C resulted in complete exchange of the five active hydrogens within 30 min.



$$CH_3(CH_2)_5-\underset{\underset{O}{\|}}{C}-CH_3+D_2O \xrightarrow[NaOD\ \ 30^\circ C]{RR'_3\overset{\oplus}{N}\overset{\ominus}{Cl}} CH_3(CH_2)_4-CD_2-\overset{\overset{O}{\|}}{C}-CD_3$$

Sodium Borohydride Reduction

Starks(4) observed that a 50% solution of octanone in benzene can be reduced to the corresponding alcohol with a solution of sodium borohydride in 2N aqueous sodium hydroxide. The reaction rate is increased 20-fold in the presence of a quaternary ammonium catalyst. However, the reaction is slow and does not offer any advantage over routine reductions.

Brandstrom et al(57) found that tetraalkylammonium tetrahydridoborate can be extracted quantitatively into methylene chloride from the caustic soda/tetraalkylammonium salt/$NaBH_4$ system when the alkyl groups contain more than 12 carbon atoms. After drying, this solution on addition to methyl iodide reduces the latter to methane with the liberation of diborane and iodide ion.

$$2\overset{\ominus}{B}H_4+2CH_3I \longrightarrow B_2H_6+2CH_4+2\overset{\ominus}{I}$$

Tetrabutylammonium cyanotetrahydridoborate can be prepared in an analogous manner(58) and is useful for the reduction of iodides and bromides at room temperature in hexamethylphosphoramide. Under these conditions, carbonyl groups, amides, cyanides, and aromatic nitro groups are not affected. In the presence of 0.1 N acid, however, aldehydes are reduced while ketones are not attacked at room temperature.

CONCLUSION

During the past five years phase-transfer catalysis has become firmly established as a useful and versatile method for the conduct of a wide variety of organic reactions (substitution, addition, elimination, oxidation, reduction, carbene formation etc.) under relatively mild conditions in two-phase aqueous organic systems without requiring the use of expensive reagents. Consequently, it would appear to have somewhat greater potential in certain applications than the crown ether catalysis of similar reactions which usually requires the use of the expensive crown ethers under anhydrous conditions.

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The origin and development of phase-transfer catalysis as a technique for the efficient conduct of organic reactions in two-phase media is described and the mechanism of the process is discussed. Some examples of its application to substitution, addition and elimination reactions, to oxidations, reductions and carbene chemistry are cited to illustrate the broad scope and general utility of the method.

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