# CHAPTER - 1

# A REVIEW ON THE APPLICATIONS OF PHASE TRANSFER CATALYSTS IN ORGANIC SYNTHESIS

## INTRODUCTION

Uniquely interesting, complex and useful activities and phenomena occur at the chemical interfaces, although sometimes it is the lack of activity that draws our attention. In many chemical situations where two spcies cannot collide and therefore cannot react because they are separated by an interface, the lack of activity has been overcome by use of the technique of Phase Transfer Catalysis (PT catalysis), which not only allows the reaction to occur, but often to occur in very selective ways.

No new catalytic method in organic synthesis has been so rapidly adopted and applied so extensively as PT catalysis. It has become in recent years a widely used, well established synthetic technique applied with advantage to a multitude of organic transformations. Phase Transfer catalyst (PTC) has recently been used for accelerating aqueous phase/ organic phase reactions in several synthetic transformations. PT catalysis has the advantage of being extremely simple and economical and so met with immediate success in industrial applications. In fact, PTC has become one of the most useful weapons in the arsenal of the organic chemist and more often the method of choice for processes in which one of the reactants is an anionic species, either added as an alkali salt or generated in solution by a base.

Reactions are conducted in a two phase system consisting of mutually insoluble aqueous and organic layers. Ionic reagents (i.e. salts, bases or acids) are dissolved in aqueous phase, the substrate in the organic phase (i.e. liquid-liquid PT catalysis). Alternatively ionic reagents can be used in the solid state as a suspension in the organic medium (i.e. solid-liquid PT catalysis). The transport of anion from aqueous or solid phase to the organic one, in which the reaction occurs, is ensured by catalytic amounts of lipophilic transport agents, usually quaternary onium salts (quaternary ammonium[1-3] or phosphonium salts[1,3,4]) or uncharged catalysts such as crown ethers and cryptands[1,5,6]. However, one practical limitation to this method is that many PTCs promote the formation of stable emulsions which make the experimental workup more difficult. In the absence of the latter, the reactions proceed at a very low rate or not at all. In the simplest case dealing with nucleophilic substitution reactions, PTC can be schematised as follows :

$$R - X_{org.} + Y^{-}_{aq.} \xrightarrow{\text{Transport agent}} R - Y_{org} + X^{-}_{aq.}$$

( Eq. 1.1 )

Although PT catalysis has been most often used for nucleophilic substitutions, it is not confined to those reactions that need an insoluble anion dissolved in organic solvent. Such reactions can be accelerated by use of an appropriate PTC. In fact, the method is not limited to anions, small amount of work has been done in transporting cations[7], radicals and molecules.

## MECHANISM OF PT CATALYSIS

The original PTC mechanism for displacement reactions proposed by Starks[8,9] (Eq.1.2) is shown below. An ionpair, formed by the extraction of anion $Y^-$ into the organic phase by the onium salt cation $Q^+$, undergoes a fast displacement with RX. The new salt $[Q^+X^-]$ then returns to the aqueous phase, where $Q^+$ picks up a new $Y^-$ ion for the next cycle.

$$\begin{array}{cccccccl}
R-X & + & Q^+Y^- & \longrightarrow & R-Y & + & Q^+X^- & \text{Organic phase} \\
 & & \uparrow\downarrow & & & & \uparrow\downarrow & \\
\hline
M^+X^- & + & Q^+Y^- & \rightleftharpoons & M^+Y^- & + & Q^+X^- & \text{Aqueous phase}
\end{array}$$

( Eq. 1.2 )

The mechanism involves various factors which may be summarized as follows :

a) Partition of the quaternary salt (or of another transport agent) between the aqueous and organic phases or alternatively partition of the anions between the two phases (if $Q^+$ is exclusively in organic state).

b) Structure of catalyst (and eventually its aggregation state).

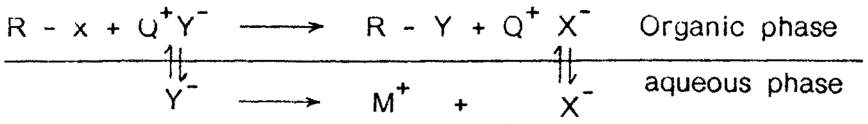
c) Reactivity of ionpairs in low polarity organic medium.

d) Reaction kinetics.

e) Hydration state of the anions in the organic phase.

f) Comparison of the reactivity under PTC conditions with that under different reaction conditions.

The quaternary onium salt transfers the anion from the aqueous phase into the organic one, where the reaction takes place. It then transfers the leaving group into the aqueous phase. This mechanism assumes a partition of the catalyst between the two phases. On the other hand, other conditions being the same, the efficiency of PTC is directly related to its solubility in organic phase[8-13]. The modified scheme may thus be proposed alternatively, in this case the electronegativity of the phase is simply maintained by the transport of the anions.



$$\begin{array}{ccccl} R - x + Q^{+}Y^{-} & \longrightarrow & R - Y + Q^{+} X^{-} & & \text{Organic phase} \\ \hline \upharpoonleft\!\downharpoonright & & & \upharpoonleft\!\downharpoonright & \\ Y^{-} & \longrightarrow & M^{+} \quad + & X^{-} & \text{aqueous phase} \end{array}$$

( Eq. 1.3 )

It is not possioble to make a distinction between the two mechanisms by kinetic determinations[14]. However, the use of liquid membranes[10,12] has shown that anion exchange occurs at the interface without concomitant transfer of the quaternary cation $Q^+$, in the case of a catalyst completely insoluble in the aqueous phase (Eq. 1.3).

## EFFECT OF SOLVENT

PT catalyzed reactions involve conversion between chemical species situated in different phases. Common cases are the reactions between on one hand salts dissolved in water or present in the solid state and on the other substances dissolved in organic media. Without a catalyst such reactions are usually slow and inefficient or do not occur at all. The procedure would involve dissolving the reactants in a homogeneous medium.

If polar protic solvents are used, they readily solvate both anions and cations. Inorganic cations interact with the free electron pairs while anions are solvated by means of hydrogen bonds. In these solvents there is a high degree of dissociation into free solvated ions. However, many anions show a relatively low reactivity (nucleophilicity) because of strong shielding by the solvation shell.

In polar aprotic solvents (e.g. DMSO, DMF etc.) cations are readily solvated. However, anions are poorly solvated since the positive end of the solvent dipole cannot be approached easily and reaction rates are therefore high. Salts are highly dissociated in such solvents.

PT catalyzed reactions are usually carried out in aprotic solvents of low polarity. Although the solubility of typical inorganic salts in these solvents is negligible, organic quaternary ammonium, phosphonium and other onium salts, as well as organically 'masked' alkali metal salts are often quite soluble especially in methylene chloride and chloroform. In these solvents the concentration of free ions is negligible, ion pairs being the dominant species. Since interactions between the ion pairs and solvent molecules are weak, reaction with electrophiles in the organic medium is fast, and some weak nucleophiles (e.g. acetate) appear strong.

A solvent useful for PTC work should be immiscible with water because otherwise highly hydrated "shielded" ion pairs of low reactivity are present. In order to avoid the hydrogen bonding to the ion pair anion, the solvent should also be aprotic.

Inspection of the data in table-1,[15] shows the very large range of extraction constants possible. Solvents in the right hand column of the table-1 are generally unsuitable for PTC work. Some of them are partially miscible with water, others are too reactive and would interfere in many processes. However, it can be seen that for the salt of medium lipophilicity, all of these solvents are in the extraction range good to excellent. Structurally related, somewhat polar compounds (e.g. homologs) should have a similar high extracting capability for ion pairs. This leads to an important generalization that if compounds of the general type shown in the third column of table-1 are used as reagents in PTC reactions e.g. alkylations, no additional organic solvent is necessary since the extraction of ion pairs into pure organic phase is very satisfactory.

Table -1 : Apparent Extraction Constants $E_{NBu_4Br} = [NBu_4Br]_{org} / [NBu_4^+]aq.\cdot[Br^-]_{aq}$ (calculated from the distribution of 0.1 M tetra-n-butylammonium bromide between water and the solvents listed).

| Solvent | $E_{NBu_4Br}$ | Solvent | $E_{NBu_4Br}$ | Solvent | $E_{NBu_4Br}$ |
|---|---|---|---|---|---|
| $CH_2Cl_2$ | 35 | $CH_3$-$CHCl$-$CH_2Cl$ | 0.5 | $C_2H_5COCH_3$ | 14 |
| $CHCl_3$ | 47 | $ClCH_2$-$CHCl$-$CH_2Cl$ | 6.1 | $CH_3NO_2$ | 168 |
| $CDCl_3$ | 41 | $C_6H_5Cl$ | < 0.1 | n-$C_3H_7NO_2$ | 9.0 |
| $CCl_4$ | < 0.1 | o-$Cl_2C_6H_4$ | < 0.1 | $ClCH_2COOC_2H_5$ | 1.4 |
| $CH_3CHCl_2$ | 0.5 | $CH_2 = CCl_2$ | < 0.1 | $NCCH_2$ - $COOCH_3$ | 54 |
| $ClCH_2$-$CH_2Cl$ | 6.1 | trans-$ClCH = CHCl$ | < 0.1 | n-$C_4H_9OH$ | 69 |
| $ClCH_2$-$CHCl_2$ | 8.6 | cis-$ClCH = CHCl$ | 33 | $CH_3CHOH$-$C_2H_5$ | 23 |
| $Cl_2CH$-$CHCl_2$ | 145 | $ClCH = CCl_2$ | 0.2 | $ClCH_2CN$ | 17,000 |
| $Cl_2CH$-$CCl_3$ | < 0.1 | $C_2H_5OC_2H_5$ | 0.1 | $CCl_3$-$CN$ | 2.3 |
| n-$C_3H_7Cl$ | < 0.1 | $ClCH_2CH_2$-$O$-$CH_2CH_2Cl$ | 2.8 | $CH_2 = CHCN$ | 130 |
| $Cl$-$(CH_2)_3$-$Cl$ | 2.9 | $CH_3COOC_2H_5$ | 0.2 | $ClCH_2CH_2CN$ | 940 |
| $Cl$-$(CH_2)_4$-$Cl$ | 0.3 | $C_2H_5COC_2H_5$ | 1.1 | n-$C_3H_7CN$ | 13.7 |
| | | n-$C_3H_7COCH_3$ | 1.7 | $CH_2$=$CH$-$CH_2CN$ | 67 |
| | | | | $CH_3O$-$CH_2CN$ | 84 |
| | | | | $CH_3O$-$CH_2$-$CH_2CN$ | 91 |
| | | | | $C_2H_5O$-$CH_2$-$CH_2CN$ | 38 |

In case of compounds listed in the left hand and central columns of table-1, there is a large variation of extraction capability with seemingly small structural changes. Specific interactions between solvent and solute must play a role even in these supposedly "nonsolvating" solvents. Practically the low boiling, chlorinated hydrocarbons appear to be the best solvents. Not only they exhibit the high extraction capability, but they are also cheap and easily removable. One drawback of such solvents is that they could give rise to side reactions, but most PTC reactions are so fast that this is not a big danger.

Diethyl ether and ethyl acetate have a low extraction capability. Chlorobenzene and o-dichlorobenzene also have poor performance. These solvents are often used when there is danger of side reactions with chloroform or methylene chloride. A low extraction constant does not necessarily exclude a solvent as unsuitable, but since this means that at any given time during the reaction, only a small percentage of the theoretically possible amount of ion pairs is in the organic phase, the reaction will be slowed down.

## INFLUENCE OF ONIUM CATION

For PTC purposes quaternary ammonium ions are of special interest because they are less likely to interfere in reactions. The high molecular weight amines can be extracted as ammonium salt ion pairs using various counter ions, from aqueous solution into organic media. It is obvious that an increasing no. of carbon atoms surrounding the central N atom of the ammonium cation will increase their lipophilicity, thus raising the extraction constant $E_{Qx}$.

Gustavii[16] observed a linear relationship between log $E_{Qx}$ and 'n', no. of carbon atoms in ammonium ions. He extracted picrates into methylene chloride using primary amines as well as symmetrical secondary and tertiary amines and symmertical quaternary ammonium salts. He gives the extraction constants for picrates[16,17] in a variety of solvents (Table-2)

Table - 2 : Extraction Constants $E_{NR_4pic} = [NR_{4}pic]_{org}/\{[NR_4]_{aq}\cdot[pic^-]_{aq}\}$ of Quaternary Ammonium Picrates, Extraction from Water into an Organic Solvent.

| Solvent | Cation | | | | |
|---|---|---|---|---|---|
| | $N(CH_3)_4$ | $N(C_2H_5)_4$ | $N(n\text{-}C_3H_7)_4$ | $N(n\text{-}C_4H_9)_4$ | $N(n\text{-}C_5H_{11})_4$ |
| $CH_2Cl_2$ | 1.5 | 220 | $2.9\times10^4$ | $4.8\times10^6$ | $2.45\times10^8$ |
| $CHCl_3$ | 0.22 | 21 | $4.4\times10^3$ | $8.1\times10^5$ | - |
| $C_6H_6$ | - | 0.22 | 35 | $3.9\times10^3$ | $7.9\times10^5$ |
| $CCl_4$ | - | - | - | 87 | $2.9\times10^4$ |

An average increase of log $E_{Qx}$ of about 0.54 units per carbon atom is evident. Again it is observed that methylene chloride and chloroform are the best solvents for extraction.

The effect of cation size on the extraction of other anions has also been determined. The same rise of about 0.54 units per added carbon atom was found again. It can be seen that even for unsymmetrical cations in yet another solvent, log $E_{Qx}$ rises by 0.54 to 0.61 units per carbon atom if one of the substrate chains is elongated. As expected, however, the no. of carbon atoms is not the only factor controlling the extraction constant, e.g. benzyl groups are much less lipophilic than n-heptyl groups and their contribution to the extraction capability lies some where between butyl and propyl. Thus, benzyltriethylammonium chloride (TEBA) is partitioned mainly into the aqueous phase unless a 'salting out effect' as in the case of conc. NaOH is operative.

In summing up, therefore, the logarithems of extraction constants of homologous series of quaternary ammonium salts rise by a more or less constant factor of about 0.54 per added carbon atom, irrespective of the nonpolar aprotic solvent and anion.

Similar general trends are observed with alkyltri-phenyl phosphonium and -arsonium ions.Arsonium ions seem to be slightly more lipophilic. An allyl residue makes a phosphonium ion hydrophilic relative to the n-propyl analogue. The following order of lipophilicities has also been obtained.[18]

$$NHex_4^+ > NPent_4^+ \gg AsPh_4^+ > N(iso\text{-}C_5H_{11})_4^+ > PBu_4^+ > NBu_4^+$$

## INFLUENCE OF THE ANION

Partial or complete anion exchange by equilibrating an organic quaternaryammonium salt solution $[Q^+X^-]$ with an aqueous NaY solution have been performed repeatedly. For such studies, scales of lipophilicities may be constructed. Clifford and Irving[19] arrived at the following order of extractibilities, going from the lipophilic ion $ClO_4^-$ to the most hydrophilic ion $PO_4^{3-}$ for chloroform/water system.

$$ClO_4^- \gg ClO_3^- > NO_3^- > Cl^- \gg HSO_4^- > OH^- > SO_4^{2-} > CO_3^{2-} > PO_4^{3-}$$

Ivanov et al.[20] have reported the results for order of extractibilities for water /toluene or water/dichloromethane system as,

$$ClO_4 > I^-, NO_3 > C_6H_5CO_2^- > Br^- > Cl^- > HSO_4^- > HCO_3^- > CH_3CO_2^- > F^- > OH^-$$

Y. Marcus[21] investigated the order of extractabilities of some other anions with tetraphenylphosphonium cations as,

$$MnO_4^- > ClO_4^- > I^- > HCrO_4^- > NO_3^- > Br^- > BrO_3^- > NO_2^-, Cl^- >$$
$$IO_4^- > IO_3^- > S_2O_3^{2-} > S^{2-} > SO_4^{2-}$$

It is clear that the same order is found in the various nonprotic solvents. This is plausible for dilute solutions, where the difference in solvation energies for the anions $X^-$ and $Y^-$ in the organic solvents and water are the major factors governing extractability. It is possible, however, that for some of the salts used (since different cations were employed) solubility limits in either phase, as well as hydration, dissociation or association behaviour will change the order of extractability.

The order of lipophilicites as shown below has usually been observed with various alkyltriphenyl phosphonium[22], tetraphenyl phosphonium, -arsonium and triphenylsulfonium cations[21].

Picrate >> $MnO_4^-$ > $ClO_4^-$ > $SCN^-$ > $I^-$ > ($ClO_3^-$, toluene sulfonate)
> $NO_3^-$ > $Br^-$ > ($CN^-$, $BrO_3^-$, benzoate) > ($NO_2^-$, $Cl^-$) > $HSO_4^-$
> $HCO_3^-$ > acetate > ($F^-$, $OH^-$) > $SO_4^{2-}$ > $CO_3^{2-}$ > $PO_4^{3-}$

## RATE OF STIRRING

Most laboratory PTC preparations may be performed using magnetic stirring. It must be mentioned, however, that results are sometimes not reproducible, especially in the presence of viscous 50% NaOH, when stirring is too slow. Recommended stirring rates are, > 200 rpm for essentially neutral PTC reactions in water/organic medium[23], 700-800 rpm for solid-liquid reactions and reactions in the presence of NaOH[24,25]. For some solid-liquid reactions high-shear stirring may be necessary.

In a typical ether synthesis from alcohol, alkyl chloride and NaOH/catalyst only 80 rpm stirring rate was required[26], whereas the reactions between alcohols, dimethyl sulfate and NaOH/catalyst needed much more effective intermixing[27]. Dihalocarbene reactions with haloform, 50% aqueous NaOH and TEBA requires the stirring rate of 750-800 rpm for reproducible results[28]. For ethylation of phenylacetonitrile with ethyl bromide in presence of 30% NaOH and $NBu_4Br$ at 55°C, the largest increase in the rate (20 fold) was observed in the area of 110 to 200 rpm, in which two originally separately visible layers become intimately mixed.[29]

## AMOUNT OF CATALYST

In the literature, quantities varying from between a few mole-percent and several moles have been used with various systems. Since reaction rates are dependent on catalyst concentration, a very small amount of catalyst seems desirable only if the conversion is highly exothermic or the catalyst is very expensive. In most cases 1-3 mole-% is normal.

In some cases a molar amount of catalyst is desirable e.g.

a) if iodide ion is set free in the course of the reaction, and tends to tie up the onium salt in the organic phase,

b) if the alkylating agent is very unreactive,

c) if alkylating agent is prone to side reactions (e.g. hydrolysis with water/alkali metal hydroxide present),

d) if a selective reaction in a polyfunctional molecule is desired.

## DIFFERENT TYPES OF CATALYSTS

The catalysts most commonly used are onium salts or complexing agents which can mask and thereby solubilise alkali metal ion. The basic function of the catalyst is to transfer the anions of the reacting salt into organic medium in the form of ion pairs.

The choice of which PTC to use - quaternary ammonium ($Q^+$), phosphonium ($QP^+$), crown ether or a polyethylene glycol (PEG), will depend upon a no. of process factors such as reaction type, solvent, temperature, base strength, ease of catalyst recovery & removal and also on the cost of the catalyst.

Polyethers presumably function similarly as cation complexes. Where the -OH grs. of the PEGs are detrimental (i.e. for oxidations), their mono and dialkylated derivatives are available and can be substituted. Recent work suggests that the PEGs can replace the expensive 18-crown-6. The synthesis of 1-cyanooctane[30], esterification,[31] phenol alkylation,[32] matrix immobilization[33] and alkaline hydrolysis of poly(methyl methacrylate)[34] are the examples where PEGs outperformed or equalled the crown ethers. PEGs have been termed as 'the poor chemist's crown'. A no. of applications are known which increases the importance of PEGs as PT catalysts.

Crown compounds are a tool of great importance in modern chemistry both in synthesis and analysis. They led to an enormous advance in chemistry due to organic neutral ligands.

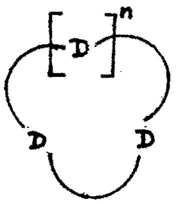
'Crowns' are defined as macroheterocycles usually containing the basic unit $(-Y-CH_2-CH_2)_n$, where Y is O, S or N. From topological points of view, these are subdivided into three large groups.[35] The open chain compounds are called 'podands', the simple cyclic compounds are called 'coronands' while the oligocyclic spherical representatives are called 'cryptands'. For those coronands which only contain ether oxygens the name 'crown ether' is retained.

open chain

PODAND

D = donar site

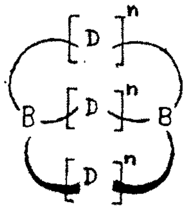
cyclic



CORONAND

D = O = crownether

spherical



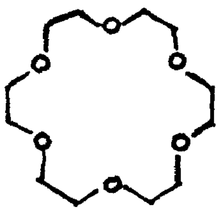
CRYPTAND

B = bridgehead atom

A common feature of all crowns and related substances is a central hole or cavity. By chelation within this hole complexes of varying stability can be formed with other species depending on the appropriate radii and electronic configurations. Cations, anions, neutral zerovalent metals and neutral molecules such as nitriles are capable of such behaviour.[36] Chart-1 shows some examples of crown ethers.

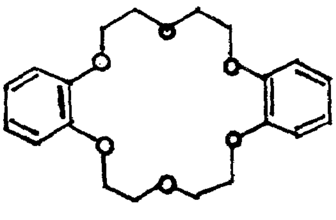
The cation complexes formed with potassium and sodium metal cations are of general interest for PTC. The most stable potassium complexes contain the 18 membered rings of compounds 1.1, 1.2, 1.3 or 1.5 while sodium is chelated preferentially by 1.4 and other similar 15-membered crowns. Among the other complexing cations are hydronium ion[37] ($H_3O^+$), ammonium ions[38] and diazonium ions[39,40]. Cram and co-workers have shown that when this 'host-guest complexation' is extended to chiral crown ethers

# CHART - 1



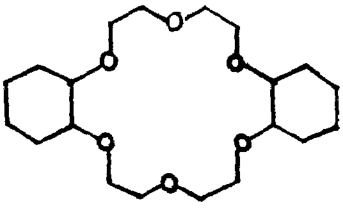
1

[18]crown-6.



2

dibenzo [18] crown-6.



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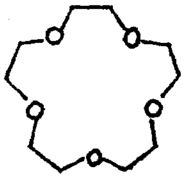
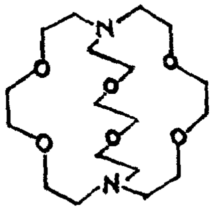
dicyclohexano [18] crown-6.



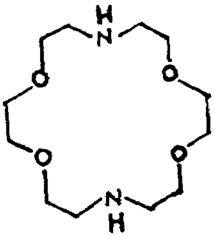
4

[15] crown-5.



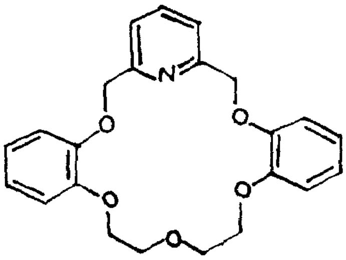
5

Kryptofix 222.



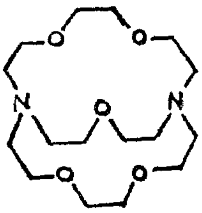
6

Kryptofix 22.



7

dibenzo pyridino [18] crown-6.



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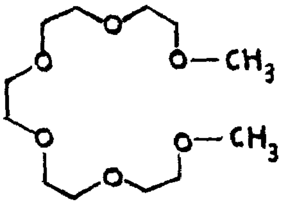
Kryptofix 221.



9

Pentaglyme (Glyme-6).

and substituted racemic primary ammonium salts, it can be utilized for optical resolution.[38]

'Organic masking' of the alkali metal provides on 'onium ion' like entity that can be extracted or solubilized with the accompanying anion, just like onium salts themselves, into nonpolar organic solvents. Although their stabilities are lower in most cases, open chain polyethers and polyamines form similar complexes and can be used to extract salts too.[41] Crown ether complexes can also be used as models for the transport and differentiation of ions through liquid membranes and even an 'active ion transport' can be achieved if photosensitive crowns are employed.[42]

The quaternary ammonium and phosphonium salt is often abbreviated as "$Q^+X^-$". The cation $Q^+$ of this catalyst extracts the anion necessary for the transfer from aqueous or solid phase into the nonpolar organic phase in the form of an ion pair. Said anion is not solvated strongly, and therefore behaves as a powerful nucleophile.

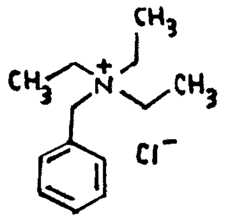
The simple notation $R_4N^+X^-$ etc. for quaternary salts conceals the wide range of structures and properties possible in this kind of PTC. Chart-2 shows some examples of quaternary ammonium and phosphonium salts which may be used as PTCs.

The structural features which influence the catalytic activity of quaternary salts to a significant degree may be summarized as follows.

a) Various Combinations of R Groups :

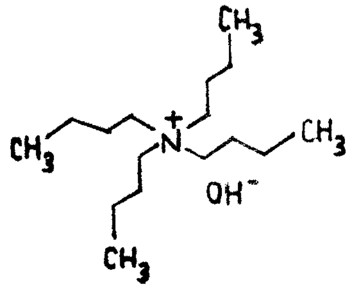
The primary requirement of the substituent R is that they collectively have sufficient organic structure to transfer the desired anion into the organic phase. The required amount of organic structure will depend

# CHART – 2



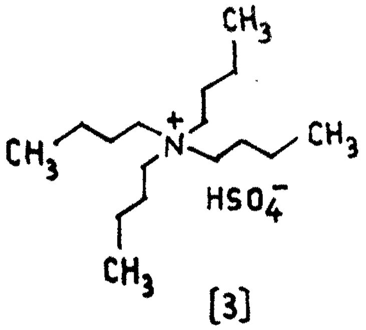
[1]

Benzyl triethyl ammonium chloride.



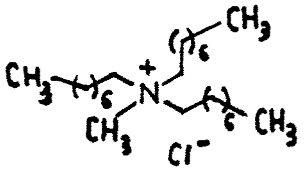
[2]

Tetrabutyl ammonium Hydroxide.



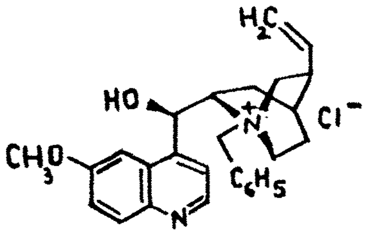
[3]

Tetrabutyl ammonium Hydrogen sulfate.



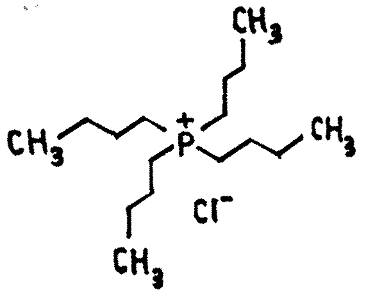
[4]

Methyl trioctyl ammonium chloride.



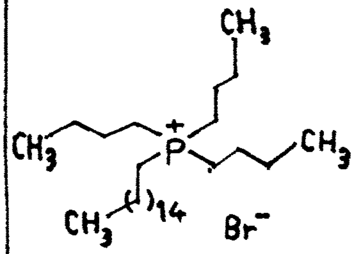
[5]

(–)-N-Benzyl quininium chloride.



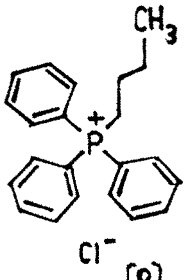
[6]

Tetrabutyl phosphonium chloride.



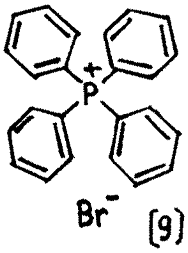
[7]

Tributyl hexadecyl phosphonium bromide.



[8]

Butyltriphenyl phosphonium chloride.



[9]

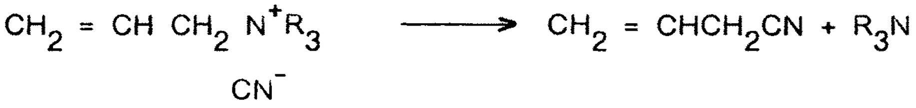
Tetraphenyl phosphonium bromide.

on the anion transferred, the polarity of the organic phase, the concentration of inorganic reagent in the aqueous phase and sometimes the presence of solvating organic compounds.

It has generally been found that tetramethyl- and tetraethyl ammonium salts do not have sufficient oleophilicity to function well as anion transfer catalysts. Tetrabutylammonium salts are usually stable enough and sufficiently well partitioned into the organic phase (particularly if the organic phase is moderately polar) to be good catalysts for many reactions. These are frequently used because these cations are commercially available in association with different anions and its salts are easily removed from the final products. Still higher alkyl groups extends the ability of quaternary salt to transfer almost all simple monovalent anions into the organic phase and thus be useful PTCs.

Quaternary salts of the type $R\text{-}N^{+}(R')_3X$ are frequently used because of their ease of preparation or commercial availability. The salts where $R' = CH_3$ are avoided because they form stable emulsions. There is exception to this generalisation in reactions where the cationic center is highly hydrated (e.g. in the transfer of $OH^{-}$) or in reactions where water is a reagent (e.g. in H/D exchange of active hydrogens). Catalysts with R'=butyl or larger groups appear to activate anions most strongly because they provide for near maximum cation-anion interionic distances. These catalysts (e.g. tricaprylylmethylammonium chloride, Aliquat-336, hexadecyltributyl phosphonium bromide, trioctyl methyl ammonium chloride) are particularly useful when the organic phase reaction is relatively slow, as in simple displacement reactions. These are also useful in most other types of PT catalyzed reactions. Benzyltriethyl ammonium chloride has been widely used for a variety of reactions, particularly alkylation and dichlorocarbene reactions, but it is usually a poor catalyst for simple displacement reactions.

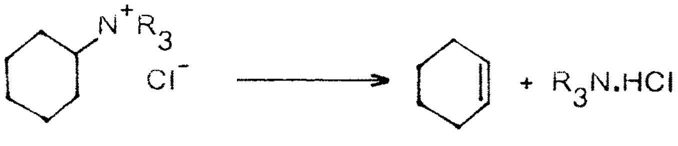
Highly reactive alkyl groups, such as benzyl & allyl and to a lesser extent methyl undergo intramolecular displacements[43-49] much more readily than n-alkyl groups and quaternary salts containing these may decompose during their use as a catalyst. e.g.



$$CH_2 = CH\ CH_2\ \underset{CN^-}{N^+R_3} \longrightarrow CH_2 = CHCH_2CN + R_3N$$

This is particularly true with highly nucleophilic anions such as cyanide & chloride and may not allow the reaction to go to completion unless excess catalyst is used. For this reason, as well as for higher reactivity, quaternary salts where all four groups are n-alkyl (preferably n-butyl or higher) are usually better catalysts with simple displacement reactions. However, for anions such as $OH^-$ which are not highly nucleophilic, benzyl-, alkyl-, methyl- substituted quaternary salts function well as PTCs.

Quaternary ammonium salts containing secondary alkyl groups tend to undergo rapid intramolecular elimination reactions[43-49], e.g.



This kind of reaction is not rapid with n-alkyl substituted ammonium salts.

Aryl substituted quaternary ammonium and phosphonium salts have almost been found to be poor PTCs.

b) Different Central Onium Atoms :

Quaternary ammonium, phosphonium and arsonium salts have all been successfully used as PTCs. Ammonium salts are widely commercially available and are much less expensive. Quaternary phosphonium and arsonium salts tend to be more active catalysts and may easily be prepared if trialkyl phosphine or arsine is available.

Phosphonium salts are thermally more stable than the corresponding arsonium salts. Being reasonably stable catalysts upto temperature of 150-170°C, phosphonium salts are less prone to intramolecular displacement when associated with chloride, bromide or cyanide ions, whereas ammonium salts lose their activity rather rapidly at temperatures greater than 110-120°C.

Phosphonium cations are exceedingly sensitive to hydroxide ion, therefore they undergo a reaction of the type,[50-53]

$$R_4P^+OH^- \longrightarrow R_3PO + RH$$

Under these conditions, $R_3PO$ is not reconvertible to $R_4P^+X^-$ and hence the catalytic activity is irreversibly lost. This reaction is usually more rapid than Hoffman elimination from the corresponding ammonium analogs, so with strongly basic solutions $R_4N^+$ catalysts are generally preferred over $R_4P^+$ catalysts. The exceptions to this generalization are,

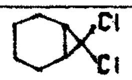
( i) when alcohols are present and most of the cation will be in the $R_4P^{+-}OR$ form, which is much more stable[54,55] than $R_4P^+OH^-$ and

(ii) when $R_3PO$ has enough organic structure for it to function on its own as a PT or micelle catalyst[56].

Arsonium salts may also be used as PTCs. Trialkyl sulfonium salts, $R_3S^+X^-$, have been generally found to be poor PTCs.[57] Other related salts such as tetraalkyl stibonium, diphenyliodonium, diazonium and oxonium have apparently not been reported as PTCs.

Table 3 shows the comparison between catalysts with different central onium atoms.

Table 3 - Comparison of Quaternary Cations with Different Central Onium Atoms.

| Catalyst | Rate constant for 1-$C_8H_{17}Br$ with $C_6H_5S$ (x $10^3$) (liters/mole sec.) | Yield of  under standard conditions (%) |
|---|---|---|
| $(C_4H_9)_4N^+Cl^-$ | - | 38.8 |
| $(C_4H_9)_4N^+Br^-$ | 5.2 | - |
| $(C_4H_9)_4N^+I^-$ | 7.4 | - |
| $(C_4H_9)_4P^+Cl^-$ | 37 | 38.3 |
| $C_{16}H_{33}N^+(C_4H_9)_3Br^-$ | - | 35.5 |
| $C_{16}H_{33}P^+(C_4H_9)_3Br^-$ | - | 39.5 |
| $(C_6H_5)_4P^+Br^-$ | 2.5 | - |
| $(C_6H_5)_4P^+Cl^-$ | 2.7 | < 1 |
| $(C_6H_5)_4As^+Cl^-$ | 1.4 | 62.0 |

c) Different Anions with the Catalyst Cation :

The activity of a quaternary salt selected for use as PTC may depend markedly on the anion originally present. For example, many quaternary salts are commercially available or prepared easily in the iodide form and would be convinient to use as PTCs. However, iodide ion associates much more strongly with quaternary cations in organic media than many other anions.

e.g. An iodide-hydroxide exchange.

$$R_4N^+OH^-_{org.} + I^-_{aq.} \longrightarrow R_4N^+I^-_{org.} + OH^-_{aq.}$$

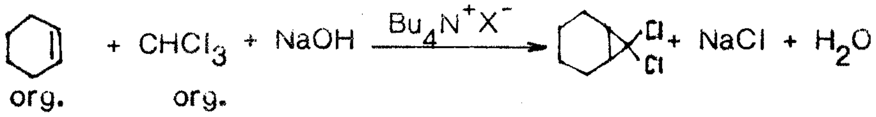
Thus, if $OH^-$ transfer from aqueous to organic phase is desired and 100 moles of NaOH is present for each mole of $R_4N^+I^-$ catalyst present, then only about 0.002% of the catalyst will be in the active $R_4N^+OH^-$ form in the organic phase. However, if $R_4N^+Cl^-$ is used rather than the iodide form, about 50% of the catalyst would be in the active $R_4N^+OH^-$ form in the organic phase.

The effect of using different anions $X^-$ with catalyst $Bu_4N^+X^-$ for the PT catalyzed preparation of dichloronorcarane from cyclohexene is shown in table-4.

Table - 4 Effect of Anion $X^-$ in catalyst $Bu_4N^+X^-$ on Yield of Dichloronorcarane under Standard Conditions.

| Anion $X^-$ | Yield of  (%) |
|---|---|
| Bisulfate | 45.7 |
| Chloride | 38.8 |
| Picrate | 36.6 |
| Bromide | 29.0 |
| Benzoate | 24.5 |
| Iodide | 22.6 |
| p-Nitrobenzoate | 16.3 |
| Perchlorate | 13.6 |
| β-Napthalene sulfonate | 8.6 |

Standard conditions : 0.1 mole cyclohexene, 0.4 mole $CHCl_3$, 0.2 mole 50% NaOH, 1 mmole catalyst; 4 hr. at 23°C, magnetically stirred.



In above reaction, decreasing catalyst activity is clearly associated with increasing tendency of $X^-$ to associate with the quaternary cation. The apparent exception, high activity when $X^-$ = picrate, may be due to relatively rapid destruction of the picrate anion by dichlorocarbene formed during reaction.

Likewise, catalysts in the iodide form perform less actively than those in the chloride or bromide form in cyanide displacement reactions.[58]

However, this situation with iodides is not universally true, since in the reaction of 1-chlorobutane with sodium benzoate, the yield of butyl benzoate under standard conditions is significantly higher (∿ 90%) when $X = I^-$ than when $X = Br^-$ (∿ 70%)[59].

$$1-C_4H_9Cl_{org.} + C_6H_5COONa_{aq.} \xrightarrow{Q^+X^-} C_6H_5COOC_4H_9 + NaCl$$

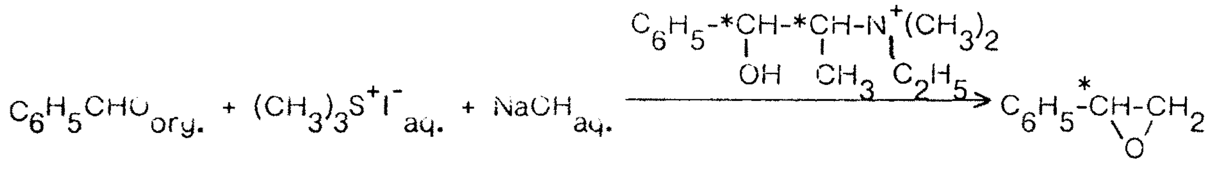
In this situation $Q^+I^-$ most likely reacts rapidly with 1-chlorobutane to yield 1-iodobutane and this then reacts with benzoate, such that the overall rate of this sequence is 2 or 3 times faster than when $X = Cl^-$ or $Br^-$.

$$1-C_4H_9Cl + Q^+I^- \longrightarrow 1-C_4H_9I \xrightarrow{Q^+C_6H_5COO^-} C_6H_5COOC_4H_9$$

At this stage we must conclude that although the anion initially associated with the catalyst may have a significant influence on the performance of the catalyst, it is not always possible to predict the direction of the influence.

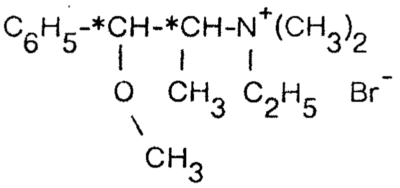
d) Introduction of Optical Activity in the Catalyst :

In some reactions, the use of optically active catalysts have induced optical activity in the products[60-62]. For example,



$$C_6H_5CHO_{org.} + (CH_3)_3S^+I^-_{aq.} + NaOH_{aq.} \xrightarrow{\underset{OH\qquad CH_3\quad C_2H_5}{C_6H_5\text{-}{*}CH\text{-}{*}CH\text{-}N^+(CH_3)_2}} C_6H_5\text{-}\overset{*}{C}H\text{-}CH_2 \atop \quad\diagdown O \diagup$$

In the reaction of benzaldehyde with trimethylsulfonium iodide in the presence of aqueous sodium hydroxide[60], use of optically active catalyst based on ephidrine gives optically active 52% enantiomeric excess(ee), phenyloxirane in 81% chemical yield. The hydroxyl group of the catalyst plays an important role in producing an optically active product, since when this group is capped by methyl ( I ), 72% chemical yield of the

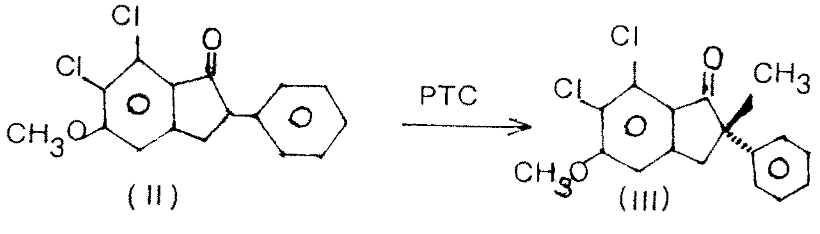


$$C_6H_5\text{-}{*}\underset{OCH_3}{CH}\text{-}{*}\underset{CH_3}{CH}\text{-}\underset{C_2H_5}{N^+}(CH_3)_2\ Br^-$$

( I )

oxirane was realized, but with no trace of optical activity. This suggests that strongly orienting factors in the catalysts are necessary to induce optical activity in the product, particularly in rapid reactions.

Dolling and co-workers[63] have successfully demonstrated the first efficient chiral PTC alkylation, the conversion of (II) to (III) in 95% yield and 92% ee using as catalyst 8-R, 9-S,N-(p-trifluoromethylbenzyl) cinchonium bromide.



( II ) ( III )

An interesting example of kinetic resolution by PTC[64] has recently appeared. Using resolved $Et_3N^+CH_2CH(Me)EtBr^-$ as catalyst, $\alpha$-methyl benzyl alcohol was methylated in 50% NaOH/pentane to yield 84% of the R(+) methyl ether with 48% ee, while the recovered alcohol has 40% ee.

e) Binding of PTCs to Insoluble Resins :

Binding of PTCs to insoluble resins as catalysts for two-phase reactions is an attractive concept, on both a laboratory and an industrial scale, since in principle it allows repeated use of catalyst and provides a simple method for its removal.

By far the broadest investigation of this type was reported by Cinouni, Colonna, Molinari, Montanari and Tundo[65], who prepared and studied the catalytic activities of resin bound PT agents. From the study they arrived at the following conclusions.

i) Reactions with polymer-supported catalysts are relatively slower than those carried out in the presence of similar non-immobilized PTC catalysts. However, the dependence of catalytic activity on the structure of the catalyst is very similar in both cases, and the presence of an alkyl chain capable of imparting a sufficient oleophilicity to the system seems to be a determinant factor. For example, the polymer $[Resin]-N^+(CH_3)_3X^-$ shows very poor catalytic activity for two-phase iodide and cyanide displacement on 1-bromooctane, whereas $[Resin]-N^+(C_4H_9)_3X^-$ or $[Resin]-P^+(C_4H_9)_3X^-$ shows high reactivity.

ii) Polymer anchored phosphonium salts, crown ethers, and cryptands are better catalysts than the corresponding ammonium salts, not only in terms of their higher reactivity, but also in terms of their higher thermal stability, at least some ammonium salts become unstable above 80-90°C.

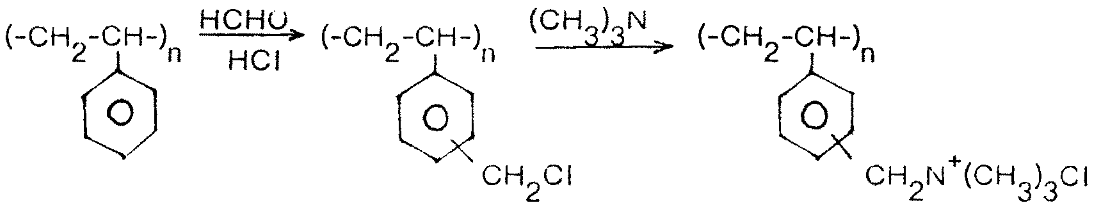
iii) The reaction rates are only slightly sensitive to the frequency of active sites on the polymeric skeleton.

iv) In contrast to the previously observed behaviour of nonsupported PTC catalysts, no direct relationship was found between conversion times and concentration of the anchored catalysts when the concentration increases from 1 to 10% with respect to the substrate. The fact that for high catalyst concentrations, large amounts of the solvent are absorbed by the resin could be one cause of this behaviour.

v) When the amount of cross-linking is 4% instead of 2%, the activity of the phosphonium salt is practically zero, the influence of crosslinking is small in the case of crown ether.

vi) The catalyst can be removed at the end of the reaction by simple filtration and reused (the catalytic activity was shown to be practically unaltered after 5 times).

It is possible to prepare a wide variety of resins containing quaternary ammonium groups, although in practice the resins used most frequently have been based on chloromethylated polystyrene (cross-linked with varying amounts of divinylbenzene) followed by quaternization with trimethylamine.



These kinds of resins, which are widely available commercially, appear to work reasonably well as catalysts for reactions when the anion transferred is hydroxide and high aquation around the quaternary center is desirable, such as ester hydrolysis[66] and other reactions which appear to be transfer step limited rather than organic phase reaction limited.

In simple displacement reactions, catalyst of the type [resin]-$\overset{+}{N}(CH_3)_3X^-$ do not function well, not only because of unfavourably short interionic distances, but also because these resins tend to be strongly swollen with water, inhibiting entrance of alkyl halide into the resin. Regen[67,68] solved the swelling problem by reducing the frequency of quaternary centers from that normally found in commercial anion exchange resins (60-70% of the aromatic ring substituted) to 8-10%. Here the resin itself behaves as more of an organic solvent, more easily invaded by the alkylhalide and functioning as a reservoir for the alkylhalide.

## ADVANTAGES OF PTC OVER CONVENTIONAL PROCEDURES

Not only does PTC promote the reaction between reagents which are mutually immiscible, but it has considerable advantages over conventional procedures. These may be listed as follows :

i) expensive anhydrous or aprotic solvents no longer required
ii) improved reaction rates and/or
iii) lower reaction temperatures
iv) in many cases easier workup
v) aqueous alkali metal hydroxides can be employed instead of alkoxides, sodamide, sodium hydride or metallic sodium.

Further some special advantages are also found, e.g.

a) occurrence of reactions that do not otherwise proceed.
b) modification of the selectivity.

c) modification of the product ratio (e.g. O v/s C alkylation)

d) increased yields through the suppression of the side reactions.

## SURVEY OF THE WORK ON PT CATALYSIS

PT catalysis is relatively a new field of chemistry that originated in the research work of three independent groups. The foundations were laid in the mid to late 1960s by M.Makosza, C.M.Starks and A.Brandstrom. Reactions involving PT phenomenon were however performed even earlier and a considerable no. of such reactions have been reported[69-71].

PTC techniques originated in the work of Makosza and co-workers in 1965[72]. They began a systematic exploration of alkylations and subsequently of other reactions in two phase systems containing mainly conc. aqueous alkali metal hydroxides. The terms used by them were, 'Catalytic Two Phase Reactions', 'Catalytic Alkylation of Anions', 'Catalytic Generation of Carbenes'etc. The term 'Phase Transfer Catalysis' was coined by Starks and first used in 1968 and is now the most widely accepted name.

PT catalysis has come of age and is used as preparative standard tool now-a-days, since the advantages of the technique seem no obvious. Still there are numerous reactions which may be improved by PTC.

The present investigation deals with the studies on the use of PT catalysis in organic synthesis more specifically to C - and O-alkylation reactions.

### C-Alkylations :

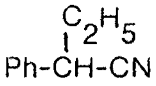
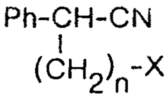
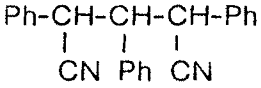
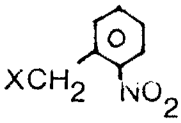
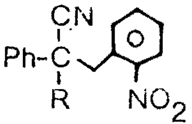
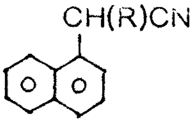
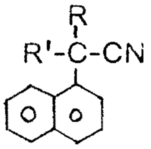
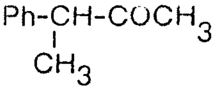
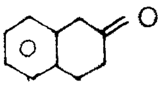
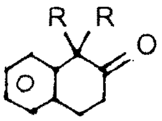
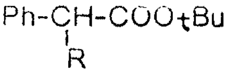
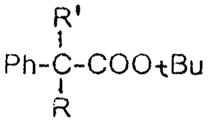
These reactions are conducted mostly in the presence of conc.(50%) sodium hydroxide, and this base permits PTCalkylation upto an approximate listed pKa value of 22 to 23. It can be shown that with above said pKa values only equillibrium deprotonations - as indicated by H/D exchange - are possible and in this case the pKa range may be extended well beyond 30.[73]

Because of its great synthetic interest the alkylation of carbanion is among the most extensively studied PTC reactions. There are two well-tested PTC alkylation procedures, namely the alkylation of phenyl acetonitrile[74] and preparation of cyclopropane-1,1-dicarboxylic acid from malonic ester and 1,2-dibromoethane.[75] In 1951 Jarrousse[69] reported the alkylation of phenylacetonitrile. This reaction was developed and optimized by Makosza, who also established its generality. A no. of reactions have been reported for the alkylation of substituted phenyl acetonitriles.[76-85] The alkylation of p-nitrobenzyl chloride with different alkylating agents and different PTCs have also been reported.

Earlier reports show that in 1954 Babayan[70] alkylated ethyl malonate in presence of quaternary ammonium compounds. Brandstrom applied his extractive alkylation procedure to the alkylation of malonic esters[86,87] and also to the alkylation of phenyl acetone[86,88]. The reports on alkylation of acetone, cyclohexanone, 2-methyl cyclohexanone are also evident.[89-93] The alkylation of acetyl acetone[94,95] and ethyl aceto-acetate[70,96] have also been reported.

A no. of C-alkylation reactions under PT catalyzed conditions have been reported, some of which are collectively given in the table-5.

Table - 5 : Examples of Catalytic C-Alkylations.

| Substrate | Alkylating Agent | Product | Yield(%) | Reference |
|---|---|---|---|---|
| $PhCH_2CN$ | $C_2H_5Br$ |  $Ph\text{-}\overset{\overset{C_2H_5}{\mid}}{C}H\text{-}CN$ | 78-84 | (76) |
| ArCH(R)-CN<br>(R=H,alkyl) | R'X<br>(R'=alkyl,allyl, benzyl,subst. benzyl) | Ar-CRR'-CN | * | (77,78,80, 83,84, 97-99) |
| $PhCH_2CN$ | $X\text{-}(CH_2)_n\text{-}X$ |  $Ph\text{-}\underset{\underset{(CH_2)_n\text{-}X}{\mid}}{C}H\text{-}CN$ | * | (100) |
| $Ph\text{-}CH_2CN$ | $PhCHCl_2$ |  $Ph\text{-}\underset{\underset{CN}{\mid}}{C}H\text{-}\underset{\underset{Ph}{\mid}}{C}H\text{-}\underset{\underset{CN}{\mid}}{C}H\text{-}Ph$ | 93 | (100) |
| Ph-CH(R)-CN |  |  | 56-98 | (101) |
|  | R'X |  | * | (82) |
| $Ph\text{-}CH_2\text{-}COCH_3$ | $CH_3I$ |  $Ph\text{-}\underset{\underset{CH_3}{\mid}}{C}H\text{-}COCH_3$ | 92 | (86) |
|  | RX |  | 30 (R=alkyl)<br>80-90<br>(R=benzyl,allyl) | (102,103) |
|  $Ph\text{-}\underset{\underset{R}{\mid}}{C}H\text{-}COOtBu$ | R'X |  $Ph\text{-}\overset{\overset{R'}{\mid}}{\underset{\underset{R}{\mid}}{C}}\text{-}COOtBu$ | 45-70 | (87) |

* Yields depend on conditions.

O-Alkylations :

Preparations of both alkyl and phenol ethers have been performed in numerous instances. In most cases conc. aqueous sodium hydroxide is present as a base, and this may cause problems, if the alkylating agent is reactive and leads to a symmetrical ether as byproduct. Therefore, an excess of RCl[104] should be used. No such problems occur with methyl halides or dimethyl sulfates.[105] The PTC method also has been employed advantageously for the benzylation of partially protected carbohydrates.[106]

The efficiency of PTC even in solid/liquid processes involving very lipophobic compounds is demonstrated by the ease of alkylation of solid pentaerythrit in the presence of 50% sodium hydroxide and tetrabutyl ammonium bromide, where only tri-and tetra-alkyl products are formed.[107] Trimethylsilyl ethers can be obtained in another solid/liquid PTC process when chlorotrimethylsilane is heated with the alkanol and solid potassium carbonate and a small amount of TEBA in petroleum ether at 60°C.

S-and N-alkylations, nucleophilic substitution reactions, oxidations, reductions, $\alpha$-and $\beta$-eliminations, Michael additions, wittig reactions, organometallic reactions and miscellaneous reactions are the other fields of extensive PTC work and maturation of PTC has led an increase in applications in such diverse areas.

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