CHAPTER-1

A REVIEW ON THE APPLICATIONS OF PHASE TRANSFER CATALYSTS AND CROWN ETHERS IN ORGANIC SYNTHESIS.

INTRODUCTION

Uniquely interesting, complex and useful activities and phenomena occur at the chemical interfaces, although some times it is the lack of activity that draws our attention. In many chemical situations where two species 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 :

(Eq.1.1)

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

(Eq.1.1)

Although PT catalysis has been most often used for nucleophilic substitution, 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.

$$\begin{tikzcd}
R - X + & Q^+Y^- \arrow[r] \arrow[d, shift left] & R - Y + & Q^+X^- \arrow[d, shift left] & \text{Organic phase} \\
M^+X^- + & Q^+Y^- \arrow[r, shift left] \arrow[u, shift left] & M^+Y^- + \arrow[l, shift left] & Q^+X^- \arrow[u, shift left] & \text{Aqueous phase}
\end{tikzcd}$$

(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.

$$\begin{tikzcd}
R - X + Q^+Y^- \arrow[r] \arrow[d, leftrightarrow] & R - Y + Q^+ X^- \arrow[d, leftrightarrow] & \text{Organic phase} \\
Y^- \arrow[r] & M^+ \quad + \quad X^- & \text{aqueous phase}
\end{tikzcd}$$

(Eq. 1.3)

It is not possible 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 reactions 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 solvent is negligible, organic quaternary ammonium, phosphonium and 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.

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[15] observed a linear relationship between log E_{QX} and 'n', number of carbon atoms in ammonium ions[15,16]. An average increase of log E_{QX} of about 0.54 units per carbon atom is evident. It is observed that methylene chloride and chloroform are the best solvents for extraction.

The effect of cation size on the extraction of other anion has been also 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 number 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.[17]

$N^+Hex_4 > N^+Pent_4 > As^+Ph_4 > N^+(iso\text{-}C_5H_{11})_4 > P^+Bu_4 > N^+Bu_4$

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[18] 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

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

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[20] 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 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[21], tetraphenyl phosphonium, arsonium and triphenylsulfonium cations[20].

Picrate >> MnO_4^- > ClO_4 > SCN^- > I^- > (ClO_3^-, toluene sulfonate) > NO_3^- > Br^- > (CN^-, BrO_3^-, benzonate) >(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[22], 700-800 rpm for solid-liquid reactions and reactions in the presence of NaOH[23,24]. For some solid-liquid reactions high-shear stirring may be necessary.

AMOUNT OF CATALYST

In the literature, quantities varying from between a few molepercent 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.

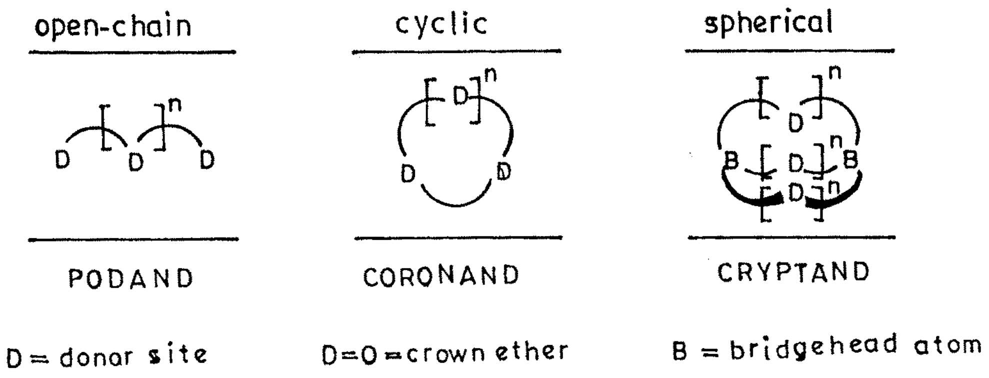
The choice of which PTC to use - quaternary ammonium (QN^+), phosphonium (QP^+), crown ether or a polyethylene glycol (PEG), will depend upon number of process factors such as reaction type, solvent, temperature, base strength ease of catalyst recovery & removal and also on the cost of the catalyst.

CROWN ETHERS

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[25]. The open chain compounds are called 'podands', the simple cyclic compounds are called 'coronands' while the oligocyclic spherical representatives are called 'cryptands'. For

For those coronands which only contain ether oxygens the name 'crown ether' is retained.



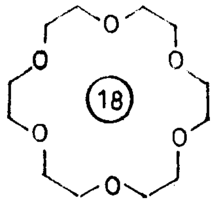
A common feature of all crowns and related substances is a central hole or cavity. By chelation within this hole complexes of varying stability can be formed with other species depending on the appropriate radii and electronic configurations. Cations, anions, neutral zerovalent metals and neutral molecules such as nitriles are capable of such behaviour[26]. Chart-1 shows some examples of crown ethers of different width with ring members ranging from 12 to 30 and 4 to 10 donar atoms, where [12]-crown-4 (1.4) is the smallest crown ether, ring known upto now, but dibenzo-[30]-crown-10 (1.6) does not represent the upper limit.

PROPERTIES OF CROWN COMPOUNDS

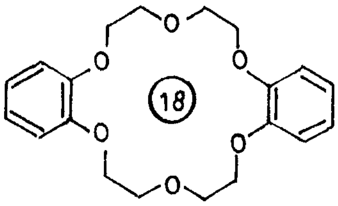
Polarity and Solubility:

Crown compounds represent a rather well balanced species as bond symmetry and polarity are concerned. A

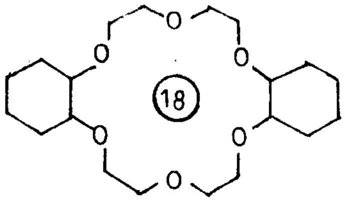
CHART–1



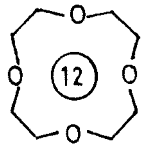
[18] Crown-6
18 C6
(1)



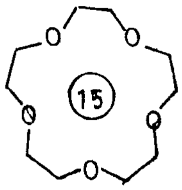
dibenzo [18] Crown-6
DB 18 C6
(2)



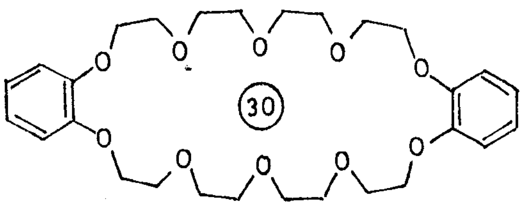
dicyclohexano[18]-Crown-6
DCH 18 C6
(3)



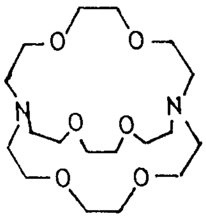
[12] Crown 4
12 C4
(4)



[15] Crown 5
15 C5
(5)

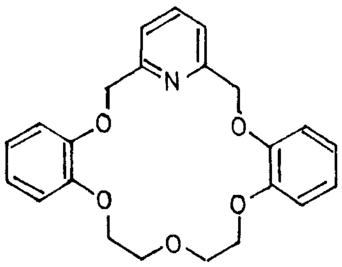


dibenzo[30] Crown 10
DB 30 C10
(6)



Kryptofix-222

(7)



dibenzo pyridino
[18] Crown-6
(8)

lipophilic ethylene group corresponds to each highly hydrophilic oxygen. In the Hansch's range of lipophilia[27] the value 'zero' is assigned to crown compounds, a fact which indicates that hydrophilia and lipophilia are ideally balanced. This is the reason for the universal stability properties of crown compounds. Many crown ethers, e.g. 18C6 are easily soluble in hydrophilic media such as water and alcohols as well as in lipophilic media, e.g. benzene or chloroform. However, the nature of the surrounding solvent exerts a drastic influence on the manifestation of the crown ether ring (Figure 1).

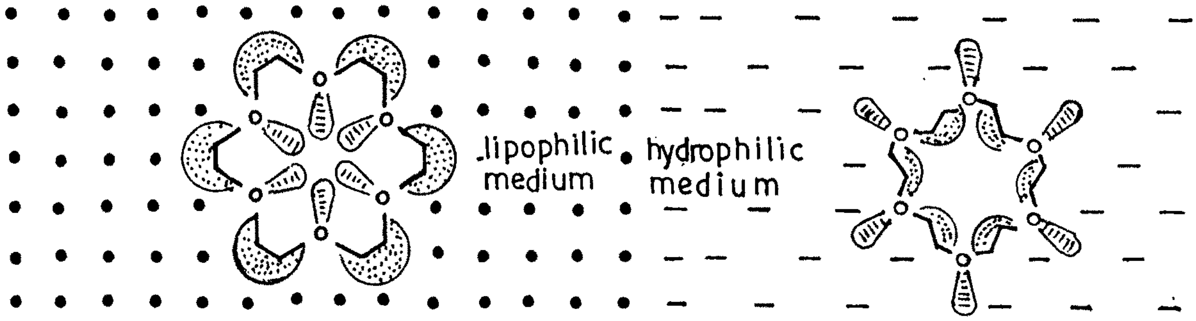


Fig.1. Solvent dependence and hydrophilia/lipophilia balance of [18] crown-6 .

In hydrophilic media the polar oxygens are directed outwards and so create a lipophilic hydrocarbon nucleus. Under these circumstances the crown ether molecule can be compared to an oil droplet in water. On the other hand in lipophilic media the polarity of the molecule is reversed. The oxygen atoms are pressed to the interior and fat-compatible CH_2-groups are directed outwards. In this case a hydrophilic and electronegative molecular cavity is formed which is suited for inclusion, e.g. complexation of cations.

Complex Formation with Metal Cations :
Influence of Solvent, Ring Size and Donar Sites -

Comparable complexes show a much higher stability in less polar media than in more polar ones. DCH 18C6 (1.3) binds K^+ in water with a complex formation constant (Ks) of $\sim 10^2$, on the other hand in methanol the complex formation constant is near 10^6.[28,29,30]. The crown ethers (1.1, 1.2, 1.3) binds Na^+ ions by one to two orders of magnitude weaker than K^+ under comparable conditions. This introduces a further parameter meaning first and foremost the spatial coordination of ion and ligand cavity. Obviously the effective cavity volume of the 18-membered crown ether ring is better suited to the ion diameter of K^+ (2.66A°) than to the one of Na^+ (1.90 A°); consequently K^+ ions find more favourable conditions in (1.1, 1.2, 1.3) than Na^+ ions and are bound more strongly.

18C6 (1.1) of which the cavity diameter is known better (2.6 - 3.2 A° depending on conformation) behave accordingly[29]. For the smaller and larger alkali metal ions also crown ethers with suitably dimensional inner cavities do exist.

Table-1: Cation ionic and crown ether cavity diameters[30,31,32].

cation	diameter (A°)	diameter (A°)	crown
Li^+	1.36	1.2 - 1.5	12C4
Na^+	1.90	1.7 - 2.2	15C5
K^+	2.66	2.6 - 3.2	18C6
Cs^+	3.38	3.4 - 4.3	21C7

APPLICATIONS OF CROWN COMPOUNDS

The applications of crown ethers in organic synthesis is based on their ability to form stable lipophilic complexes with metal cations and some organic molecules[33].

Crown ethers are able to complex cations. Thus cations become compatible to a fatty medium and soluble in organic solvents. In order to keep the electroneutrality of the solution, the corresponding anion has to be solved, too. Not being complexed and only weakly solvated in the organic medium, it is in a very active state and is able to initiate unusual reactions. In extreme cases Weber et. al. has observed even 'naked anions'[34 - 37].

Many reactions which in former times were impossible or only possible with low yields can be carried out in the presence of crown compounds without any difficulty.

In principle any chemical reaction where ions or ionic intermediates are involved in any form can be modified or improved through crown compounds. Among others nucleophilic substitutions (e.g. halogen - and pseudohalogen substitutions, O-, N-, S-alkylations), reactions with carbanions, C-C bond formation (e.g. Darzen's Knoevenagel condensation, etc.), additions, eliminations, carben generation, gas extrusions (N_2, CO_2) oxidations, reductions (dissolving metal, metal hydrides), rearrangements (Favorskii, Cope), isomerizations and polymerizations are concerned. Further application fields of crown compounds are in the range of macrolide synthesis, of organo metal and protecting group reactions as well as problems of phosphorus and silicon chemistry.

A preparatively even more useful example is the application of 'naked hydroxyl' in the hydrolysis of sterically hindered esters[38,39]. Pederson already discovered that esters of the bulky mesitylenecarboxylic acid with potassium hydroxide solution in toluene in presence of DCH18C6 are easily saponified[38]. But under normal conditions, the esters of this acid are absolutely inert. The effect is due to the highly basic naked hydroxyl. Under normal condition, e.g. in alcoholic solution, the hydroxyl ion is highly solvated and is not able just because of its size to reach the centre of reaction. Being naked this seems to be easily managed. Therefore anion activation mostly means a sterical allevation, too.

The cation complexes formed with potassium and sodium metal cations are of general interest for PTC. Among the other complexing cations are hydronium ion[40] (H_3O^+), ammonium ions[41] and diazonium ions[42,43]. Cram and co-workers have shown that when this 'host-guest complexation' is extended to chiral crown ethers and substituted racemic primary ammonium salts, it can be used for optical resolution.[41].

'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.[44]. 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.[45]

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.

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.

A new drift type crown ether phase transfer catalyst - 4' carboxybenzo [15] - crown - 5 absorbed on poly (styrene/divinylbenzene) - NR_2 resin was found to be more effective[46].

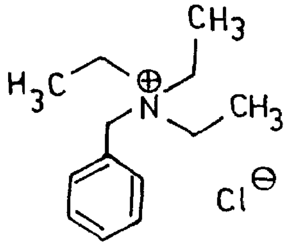
QUATERNARY AMMONIUM AND PHOSPHONIUM SALTS

The quaternary ammonium and phosphonium salt are 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.

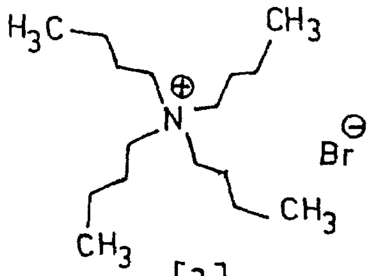
The structural features which influence the catalytic activity of quaternary salts to a significant

CHART-2



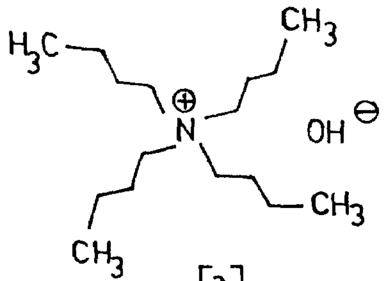
[1]

Benzyl triethyl ammonium chloride



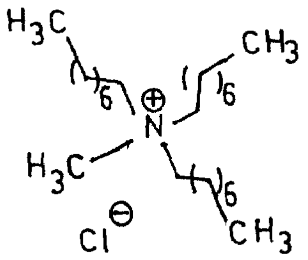
[2]

Tetrabutyl ammonium bromide



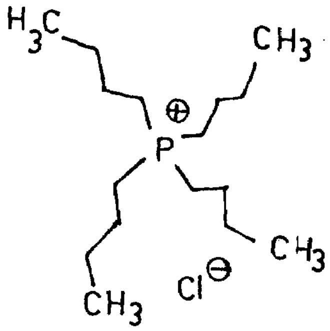
[3]

Tetrabutyl ammonium hydroxide



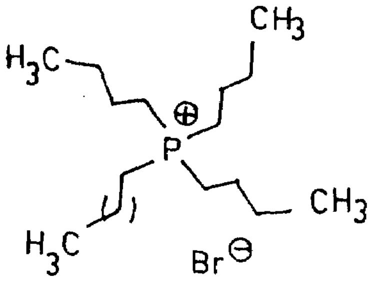
[4]

Methyl trioctyl ammonium chloride



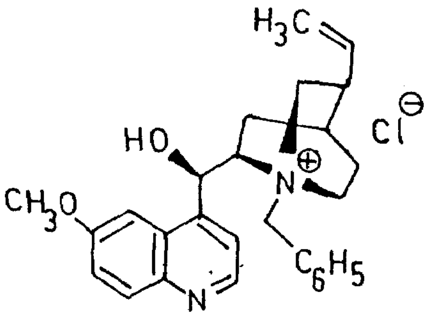
[5]

Tetrabutyl Phosphonium chloride



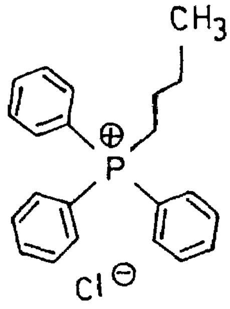
[6]

Tributyl hexadecyl Phosphonium bromide



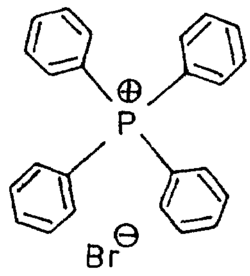
[7]

(−)−N−Benzyl quinium chloride



[8]

Butyltriphenyl Phosphonium chloride



[9]

Tetraphenyl Phosphonium bromide

degree may be summarized as follows :

STRUCTURAL FEATURES OF QUATERNARY SALTS

Various Combinations of R Groups :

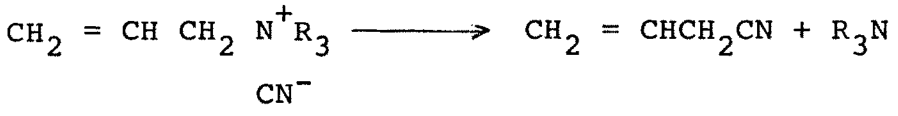
The primary requirement of the substituent R is that they collectively have sufficient organic structure to transfer the desired anion into the organic phase. The required amount of organic structure will depend on the anion transferred, the polarity of the organic phase, the concentration of inorganic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

Zhao et. al.[47] have shown that the length of alkyl chain of the quaternary ammonium salts affects only the hydrophobicity rather than lipophilicity. Thus it has a larger effect on the liq-liq. phase transfer equillibrium but little on the solid-liq. phase transfer equillibrium.

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 genralisation 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, alkylation and dichlorocarbene reactions, but it is usually a poor catalyst for simple displacement reactions.

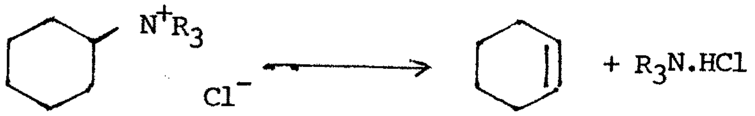
Highly reactive alkyl groups, such as benzyl & allyl and to a lesser extent methyl undergo intramolecular displacements[48-54] much more readily than n-alkyl groups and quaternary salts containing these may decompose during their use as a catalyst. e.g.



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

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[48-54], 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.

The reactions of carboxylic acids with halides which could not take place by conventional heating are promoted by microwave irradiation in the presence of quaternary ammonium salts as a catalyst without base[55].

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,[56-59]

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

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 $R_4P^+\bar{O}R$ form, which is much more stable[60,61] than $R_4P^+\bar{O}H$ and

ii) when R_3PO has enough organic structure for it to function on its own as a PT or micelle catalyst[62].

Arsonium salts may also be used as PTCs. Trialkyl sulfonium salts, $R_3S^+X^-$, have been generally found to be poor PTCs.[63] Other related salts such as tetraalkyl stibonium, diphenyliodonium, diazonium and oxonium have apparently not been reported as PTCs.

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.

$$R_4N^+\bar{O}H_{\text{org.}} + I^-_{\text{aq.}} \longrightarrow R_4N^+I^-_{\text{org.}} + \bar{O}H_{\text{aq.}}$$

Thus, if $\bar{O}H$ 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 $R_4N^+\bar{O}H$ 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 $R_4N^+\bar{O}H$ form in the organic phase.

Likewise, catalysts in the iodide form perform less actively than those in the chloride or bromide form in cyanide displacement reactions[64].

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%)[65].

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

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^-.

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

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.

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[66-68].

PTC techniques originated in the work of Makosza and co-workers in 1965[69]. 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 PTC alkylation 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[70].

There are two well tested PTC alkylation procedures in the series 'Organic Synthesis', namely the alkylation of phenyl acetonitrile[71] and preparation of cyclopropane-1, 1-dicarboxylic acid from malonic ester and 1, 2-dibromoethane[72]. Here, as in most cases of carbon alkylation the catalyst is benzyltriethylammonium chloride and reaction temperatures are 20 - 25°C.

O-Alkylation :

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[73] should be used. No such problems occur with methyl halides or dimethyl sulfates[74]. The PTC method also has been employed advantageously for the benzylation of partially protected carbohydrates.[75]

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[76]. 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.[77] PTC can be used in O-methylation of salicylic acid esters[78].

Benzyl acetate was prepared by reaction of potassium acetate with benzyl chloride using benzyltriethylammonium chloride or triethylamine as PTC and acetone or acetonitrile as solvent[79].

Diacyl disulfides were prepared from sodium disulfide with acyl halides at 65 °C under PTC[80].

Ethers and esters of 2, 3 bis (hydroxymethyl) quinoxaline 1,4 dioxide were prepared by reaction of 2, 3 bis (bromomethyl) quinoxaline 1,4 dioxide with phenols and carboxylic acid in phase transfer system[81].

REFERENCES

1. Merrifield R.B., J.Am. Chem.Soc., 85, 2149 (1963).
2. Letsinger R.L. and Kornet M.J., J.Am. Chem.Soc., 85, 3045 (1963).
3. Merrifield R.B., Science, 150, 178 (1965).
4. Merrifield R.B., Advan. Enzymol., 32, 221 (1969).
5. Pittman C.U., Evans C.D., Chem. Technol. 650 (1973).
6. Leznoff C.C., Chem. Soc. Rev., 3, 65 (1974).
7. Overberger C.G., Int. Ed. Engl., 13, 99 (1974).
8. Neckers D.C., J.Chem. Educ.52, 695 (1975).
9. Patchornik A., Kraus M.A., Pure Appl. Chem., 43, 503 (1975), 46, 183 (1976).
10. Crowley J.I., Rapport H., Acc.Chem. Res.9, 135 (1976)
11. Hermann R., Chem. Unserrer. Zeit., 11, 54 (1977).
12. Mckillop A., Young D.W., Synthesis, 402, 481 (1979).
13. Parker A.J., Chem. Rev. 69, 1 (1969).
14. Pederson C.J., J.Am. Chem. Soc., 89, 2495, 7017 (1967).
15. Gustavii K., Acta Pharm. Suec., 4, 233 (1967).
16. Gustavii K., Schill G., Acta. Pharm. Succ., 3, 241 (1966).
17. Antoine J.P., Aguirre I.de., Janssens F. and Thyrion F., Bull. Soc. Chim. Fr., 207 (1980).
18. Clifford W.E., Irving H., Anal. Chim. Acta, 31, 1 (1964).
19. Ivanov I.M., Gindin L.M., Chichagova G.N., Chem.

Abstr., 69, 13377 (1968) and Chem. Abstr., 78, 8481 (1973).

20. Marcus Y., Kerts A.S., "Ion Exchange and Solvent Extraction of Metal Complexes", Wiley-Interscience, New York, P. 796 (1969), Beilstein G.M. and Bock R., Z. Anal. Chem., 192, 44 (1963)., Bock R. and Jainz J. Z. Anal. Chem., 198, 315 (1963).

21. Gibson N.A. and Weatherburn D.C., Anal. Chim. Acta., 58, 159 (1972).

22. Herriot A.W. and Picker D.J.Am. Chem.Soc., 97, 2345 (1975).

23. Dehmlow and Remmler T., J.Chem. Res., (S) 72, (M), 766 (1977).

24. Dehmlow E.V. and Lissel M., Tetrahedron Lett., 1783 (1976).

25. Weber E., Vogtle F., Inorg. Chim. Acta, 45 L65 (1980)., Weber E., Posel H.P., J. Incl. Phenom. 1, 79 (1983).

26. Bosyony A. el, Klimes J., Knochel A. and Rudolph G., Z.Naturforsch., Teil B, 31, 1192 (1976).

27. Review: Leo A., Hansch C., Elkins D., 'Partition Coefficients and their uses,' Chem. Rev., 71, 525 (1971).

28. Vogtle F., Weber E., 'Crown Ethers - Complexes and selectivity', in The Chemistry of the Ether Linkage Supplement E, part 1, S. Patai (Ed.), Wiley, London, P 59 (1981).

29. Izatt R.M., Bradshaw J.S., Nielsen S.A., Lamb J.D., Christensen J.J., Sen D., 'Thermodynamic and Kinetic Data for Cation-Macrocycle Interaction', Chem. Rev., 85, 271 (1985).

30. Alkali Metal Complexes with Organic Ligands, Struct. Bonding, 16, Spriner-Verlag, Berlin, Heidelberg, New York, (1973).

31. Vogtle F. Neumann, 'Stereochemie im Innern Cyclischer Verbindungen: Kronenather, Katapinate and Kryptate', Chemiker-Ztg., 97, 600 (1973).

32. Review: Weber E., Vogtle F., 'Crown-Type compounds- An Introductory Overview', in ref. 11, p. 1; ref.14, P.1.

33. Lukyanenko W (A.V. Bogatskii Phys. Chem. Inst., 270080 Odessa, USSR) Janssen Chim Acta (Spec Ecl.), 5 (1992).

34. Vogtle F., Weber E., 'Neutrale Organische Komplexliganden und ihre Alkalikomplexe II - Kronenather, Cryptanden und Pondanden als Reagenzien und Katalysatoren (Teil A)', Kontakte (Merck), 2, 16 (1977).

35. Weber E., Vogtle F., 'Neutrale Organische Komplexliganden und ihre Alkalikomplexe II-Kronenather, Cryptanden als Reagenzein und Katalysatoren (Teil B)', Kontakte (Merck) 3, 36 (1977).

36. Weber E., 'Progress in Crown Ether Chemistry (Part IV C)', Kontakte (Merck), 1, 24 (1982).

37. Weber E., 'Progress in Crown Ether Chemistry (Part IV D): New Types of Neutral Ligand-assisted Chemical Reactions', Kontakte (Merck), 1, 38 (1983).

38. Pedersen C.J., Us-Pat. 3686225 (1972)., Brit Pat. 1149229 (1969) (C.A. 71, 606585 M (1969)).

39. Dietrich B., J.M. Lehn, Tetrahedron Lett., 1225 (1973).

40. Gokel G.W. and Garcia B.J. Tetrahedron Lett., 317 (1977).

41. Helgeson R.C., Koga K., Timko J.M. and Cram D.J., J.Am. Chem.Soc., 95, 3021 (1973); Peacock S.C. and Cram D.J., J.Chem. Soc. Chem. Commun., 282 (1976)., Gokel G.W., Timko J.M. and Cram D.J., J.Chem. Soc. Chem. Commun; 394, 444 (1975)., Curtis W.D., King R.M., Stoddart J.F. and Jones G.H., J.Chem. Soc. Chem. Commun., 284 (1976).

42. Gokel G.W. and Cram D.J., J. Chem.Soc., 96, 7203 (1974). J.Am. Chem. Soc., 98, 6753 (1976).

43. Bartsch R.A., Chen H., Haddock N.F., and Juri P.N., J.Am. Chem. Soc., 98, 6753 (1976).

44. Vogtle F. and Weber E., Angew. Chem. 86, 896 (1974); Angew Chem. Int. Ed. Engl., 13, 814 (1974)., Vogtle F. and Sieger H., Angew. Chem. 89, 410 (1977)., Angew. Chem. Int. Ed. Engl., 16, 396 (1977)., Tummler B., Maass G., Weber E., Wehner W., and Vogtle F., J.Am. Chem. Soc., 99, 4683 (1977).,

Vogtle F., Muller W.M. and Buhleier E., Angew. Chem. 89, 564 (1977); Angew Chem. Int. Ed. Engl., 16 548 (1977).

45. Sinkai S., Nakaji T. and Manabe O., J.Am. Chem.Soc., 103, 111 (1981).

46. Chou, Ming-Seng Shin Jeng-Shong; Can.J.Chem. 72 (7), 1614 (1994).

47. Zhao, Yingying., Zheng, Luo; Shen, Yusheng., Chem. Res. Chin. Univ. 8(1) 5 (1992).

48. Ross S.D., Finkelstein M. and Petersen R.C., J. Am. Chem. Soc., 83, 4853 (1961).

49. Prelog V. and Piantanidu M., Hoppe-Seyler's Z., Physiol. Chem. 244, 56 (1936).

50. Archer D. and Booth, J. Chem. Soc., 322 (1963).

51. Helman H., Angew. Chem., 65, 473 (1953).

52. Burns J.T. and Leffek K.T., Can. J.Chem. 47, 3725 (1969).

53. Kametani T., Kigasawa K., Hiiragi M., Mineharu W. and Wakisaka K., Tetrahedron Lett., 635 (1969).

54. Davies W.C., and Cox R.G. J.Chem. Soc. 614. (1937).

55. Yuan, Yuncheng., Jiang., Yulin., Gao, Dabin., Syn. Commun., 22 (21) 3109 (1992).

56. Pagilagan R.U. and McEwen W.E., Chem. Commun., 652 (1966).

57. Zanger M., Vander Werf C.A., and McEwen W.E., J. Am. Chem.Soc., 81, 3805 (1959).

58. McEwen W.E., Kumli K.F., Blade-Font A., Zanger M., and Vander Werf C.A., J.Am. Chem.Soc., 86, 2378 (1964).

59. McEwen W.E., Axelrad A., Zanger M. and Vander Werf C.A., J.Am. Chem. Soc., 87, 3948 (1965).

60. Hamid A., and Trippett S., J.Chem. Soc., C 2625 (1967).

61. Eyles C.T. and Trippett S.J. Chem.Soc., 67 (1966).

62. Campbell J.B., U.S. Patent 3, 876, 716 (1975).

63. Freedmann H.H., unpublished observations.

64. Starks C.M., unpublished results.

65. Hennis H.E., Thompson L.R., and Long J.P., Ind. Eng. Chem. Prod. Res. Dev. 7, 96 (1968).

66. Jarrousse J., C.R. Acad. Sci. Paris, 232, 1424 (1921).

67. Babayan A.T., Gambryan N. and Gambryan N.P., Chem. Abstr. 49, 10879 (1955).

68. Maerker G., Carmichael J.F. and Port W., J.Org. Chem. 26, 2681 (1961).

69. Makosza M. and Serafinowa B., Rocz. Chem. 39, 1223 (1965) and subsequent papers.

70. Halpren M., Feldman D., Sasson Y., Robinovitz M., Angew. Chem. 96, 97 (1984)., Angew. Chem. Int. Ed. Engl., 23, 54 (1984); Feldman D., Robinovitz M., J. Org. Chem. 50, 1746 (1985).

71. Makosza M., Jonczyk A., Org. Synth. 55, 91 (1976).

72. Singh R.K., Danishefsky S., Org. Synth. 60, 66 (1981).

73. Freedmann H.H., Dubois R.A., Tetrahedron Lett., 3251 (1975).

74. Merz A., Angew. Chem., 85, 868 (1973)., Angew Chem. Ing. Ed. Engl., 11, 846 (1973).

75. Garegg P.J., Iversen T., Oscarson S., Carbohydr. Res., 50, C12 (1976).

76. Nougier R.M., Mchich M., J. Org. Chem., 50 3296 (1985).

77. Lissel M., Weiffen J., Synth. Commun., 11, 545 (1981).

78. Matei, Simion, Lenta, Lucia. Rev. Chim (Bucharest) 45 (10), 923 (1994).

79. Tong, Xinglong; Xiandai Huagong, 13 (6), 24, 35 (1993).

80. Jin-Xian Wang., Wenfeng Cui, Yulai Hu and Kai Zhao., Commun., 25 (6) 889 (1995).

81. Fridman I.A., Nikonova I.V., Koldobski G.L., Khim. Geterotsikl Soedin 6, 816 (1994).