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[a031]

# Utilization of piperazine for interphase catalytic systems

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## *Abstract*

Phase transfer catalysis (PTC) is an important modern synthetic method where reagents are located in different phases. Generally, it is transfer of inorganic reagent (base or nucleophile) from aqueous medium or solid phase to organic phase. Current catalysts for „classic" PTC are –onium salts (N, P, S), macrocyclic polyesters (crown-ethers), aza--macrobicyclic ethers (cryptands), polyethylenglycols (PEGs) and their dimethylethers. Both in laboratory and industry, the most widely used catalysts are ammonium salts for their good price and availability.

The other trend which is implementing within the frame of „Chemistry for sustainable development" are supported catalysts. Generally catalyst is bound on inorganic or organic polymer support and the system is insoluble in water and organic solvents as well. Supported catalyst can be easily separated from the reaction mixture and it can be reused again.

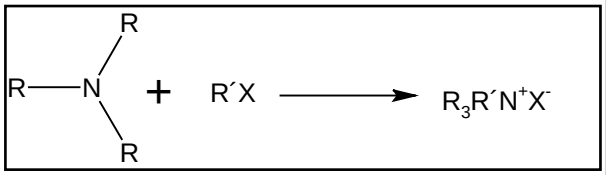
Piperazine **(A)** as secondary cyclic 1,4-diamine offers two functional centers on its nitrogen atoms – one for preparation of quaternary catalytical place and second for immobilization on solid support, organic polymer.

## *Introduction*

Generally used quaternary ammonium salts for PTC are:

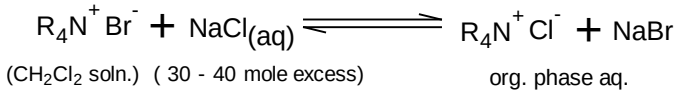
1) **TEBA:** (benzyl triethylammonium chloride or bromide) - $N^+(C_2H_5)_3CH_2C_6H_5X^-$ (X = Cl or Br)
2) **TBA:** (tetrabutylammonium bromide) - $N^+(C_4H_9)_4Br^-$
3) **Cetrimide:** (cetyl trimethylammonium chloride or bromide) - $N^+(CH_3)_3(CH_2)_{15}CH_3X^-$ (X = Cl or Br)
4) **Aliquat:** (methyl trioctylammonium chloride) - $N^+CH_3(C_8H_{17})_3\ Cl^-$

The most widely used method for their preparation is simple alkylation of tertiary amines[1,2] **(Eq. 1)** or exchange anions in the quaternary salts **(Eq. 2)** for maximum activity of the PTC catalyst.




**Eq. 1**

**Conditions of reaction:**
**molar rate:** 1:1
**temperature:** 50 – 100 °C
**time of reaction**: 2 – 3 days
**solvent:** methanol, acetonitrile
**recrystallisation:** ethanol – ether mixture, ethyl acetate (lower salts), benzene, ethanol, isopropyl alcohol (for medium salts), hexane, benzene – hexane (higher salts)



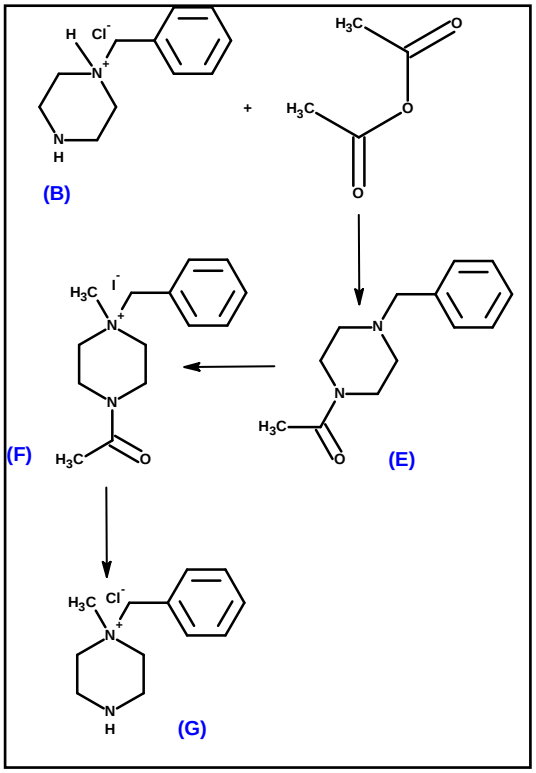

**Eq. 2** – Conversion of a bromide to chloride

***Results and discussion***

The purpose of our work was to prepare analogues of comercially accessible quaternary ammonium salts (TEBA, TBA, Cetrimide, Aliquat). ***N*-Benzylpiperazine.HCl (B)**, **1-(2-methoxycarbonylethyl)piperazine.HCl (C)** and ***N*-methoxycarbonylpiperazine.HCl (D)** were used as starting compounds for quaternary ammonium salts preparation.

1) ***N*-Benzyl-*N*-methylpiperazinium chloride (G)** (analogue to TEBA):

The first step of compound **G** preparation is based on the reaction between substance **B** and acetic anhydride in toluene yielding ***N*-benzyl-*N´*-acetylpiperazine (E)** as the main product. Quaternization of **E** by methyl iodide gave a solid compound ***N*-benzyl-*N*-methyl--*N´*-acetylpiperazinium iodide (F)**. In the last step protecting acetylate group was removed from nitrogen atom to form ***N*-benzyl-*N*-methylpiperazinium chloride (G) (Eq. 3)**.




**Eq. 3 –** Preparation of TEBA analogue

**Reaction conditions:**

| ***Product/Method*** | ***Mol. rate (eq.)*** | ***Temperature (°C)*** | ***Time (h)*** | ***Solvent*** | ***Yield (%)*** |
|---|---|---|---|---|---|
| **(E)** | 1:1,3 | room | 0,17 | toluene | 52 |
| **(F)** | 1:3 | room | 31 | methanol | 31 |
| | 1:3 | reflux | 20 | methanol | 74 |
| | 1:3 | room | 31 | nitromethane | 69 |
| **(G)** | 1:1 | reflux | 4 | MeOH/HCl | 61 |

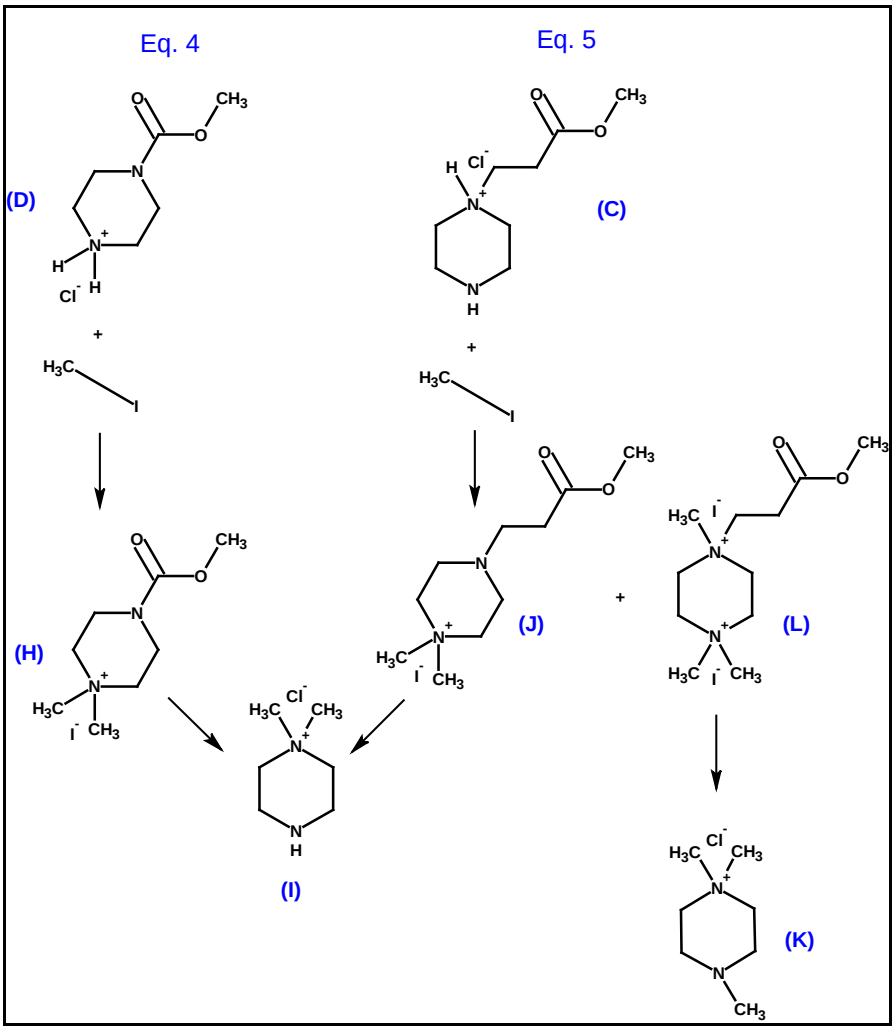
2) ***N,N*-Dimethylpiperazinium chloride (I) (**analogue to TBA):

***N,N*-Dimethyl-*N´*-methoxycarbonylpiperazinium iodide (H)** was prepared by the quaternization of **D** using methyl iodide and the subsequent removal of methoxycarbonylic group from **H** resulted in ***N,N*-dimethylpiperazinium chloride (I)** formation **(Eq. 4)**.

Compound **I** can be also prepared by quaternization of **C**. Nitrogen atom of incurred salt ***N,N*-dimethyl-*N´*-2-methoxycarbonylethylpiperazinium iodide (J)** was then deprotected as well. ***N,N,N´*-Trimethylpiperazinium iodide (K) (Eq. 5)** arises as by-product of this reaction.

**Reaction conditions:**

| ***Product*** | ***Mol. rate (eq.)*** | ***Temperature (°C)*** | ***Time (h)*** | ***Solvent*** | ***Yield (%)*** |
|---|---|---|---|---|---|
| **(H)** | 1:4 | room | 32 | methanol | 53 |
| | 1:4 | reflux | 24 | methanol | 69 |
| **(I) reaction IV** | 1:1 | reflux | 4 | MeOH/HCl | 59 |
| **(I) reaction V** | 1:1 | reflux | 4 | MeOH/HCl | 56 |
| **(J)** | 1:4 | room → 50 | 6 | nitromethane | 26 |
| **(L)** | 1:4 | room → 50 | 6 | nitromethane | 26 |
| **(K)** | 1:1 | reflux | 4 | MeOH/HCl | 71 |



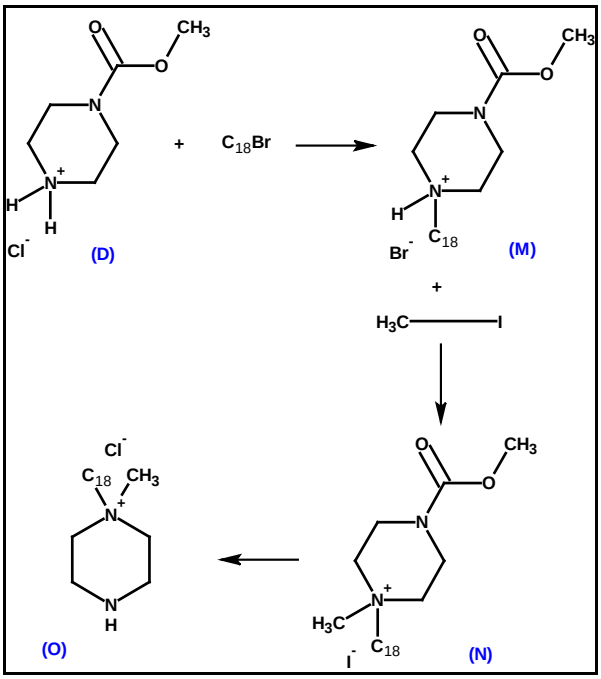

**Eq. 4, Eq. 5** - Preparation of TBA analogue

3) ***N*-Methyl-*N*-octadecylpiperazinium chloride (O)** (analogue to Cetrimide):

Reaction between **D** and octadecyl bromide gave ***N*-octadecyl-*N´*--methoxycarbonylpiperazinium bromide (M)**. **M** was subsequently quaternizated by methyl iodide to yield ***N*-octadecyl-*N*-methyl-*N´*-methoxycarbonylpiperazinium iodide (N)**. ***N*-Methyl-*N*-octadecylpiperazinium chloride (O)** was then obtained by the deprotection of nitrogen atom **(Eq. 6)**.

**Reaction conditions:**

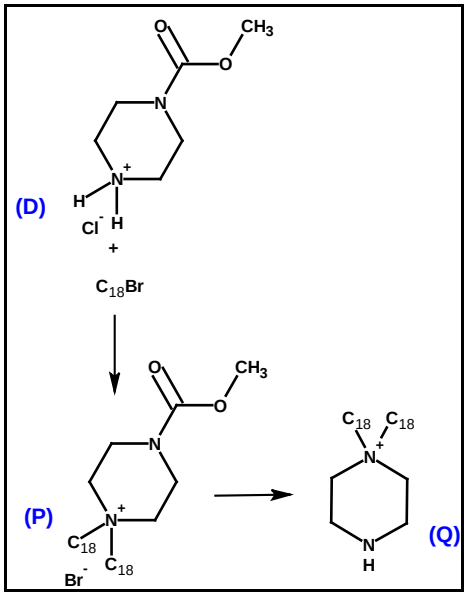
| *Product* | *Mol. rate (eq.)* | *Temperature (°C)* | *Time (h)* | *Solvent* | *Yield (%)* |
|---|---|---|---|---|---|
| **(M)** | 1:1,2 | room → 80 | 79 | nitromethane | 40 |
| **(N)** | 1:4 | room → 50 | 24 | nitromethane | 50 |
| **(O)** | 1:1 | reflux | 4 | MeOH/HCl | 65 |




**Eq. 6** - Preparation of Cetrimide analogue

4) ***N,N*-Dioctadecylpiperazinium chloride (Q) (**analogue to Aliquat):

Compound **D** reacts with octadecyl bromide to form ***N,N*-dioctadecyl-*N´*--methoxycarbonylpiperazinium bromide (P).** In a similar way ***N,N*-dioctadecyl--piperazinium chloride (Q) (Eq. 7)** was obtained when protecting group bound to nitrogen atom of **P** was removed.




**Eq. 7** - Preparation of Aliquat analogue

**Reaction conditions:**

| ***Product*** | ***Mol. rate*** ***(eq.)*** | ***Temperature*** ***(°C)*** | ***Time*** ***(h)*** | ***Solvent*** | ***Yield*** ***(%)*** |
|---|---|---|---|---|---|
| **(P)** | 1:2,5 | room → 80 | 18 | nitromethane | 58 |
| **(Q)** | 1:1 | reflux | 4 | MeOH/HCl | 77 |

***General experimental procedure***

Reaction conditions are given in tables, reactants were put together with solvent used and stirred at room or higher temperature for desired time. Reaction mixtures were then filtered (charcoal or silicagel were used when needed to remove soluble impurities). Solvents were removed to dryness in vacuo to yield solid products (crude products were recrystalized if necessary). Compounds **G**, **I**, **K**, **O** and **Q** were characterized by TLC (Silica gel 60 $F_{254}$, solvent – methanol or acetic acid), $^{1}H$ and $^{13}C$ NMR (Bruker Avance 300, using TMS as standard) and melting point determination (Böetius type).

***Conclusion***

Substances **G**, **I**, **K**, **O** and **Q** were prepared as building blocks for quaternary ammonium salts supported on polymers such as polystyrene-divinylbenzene copolymer.

***References***


1) M. J. Earle; K. R. Seddon; *Pure Appl. Chem.*; 2000; 72 (7), 1391 – 1398.
2) R. Sheldom; *Chem. Commun.*; 2001, 2399 – 2407.