

## CYCLODEXTRINS IN INVERSE PHASE TRANSFER CATALYSIS

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Cyclodextrins act as Inverse Phase Transfer catalyst in the hydrolysis of benzyl halides. The reaction is affected by the choice and by the amount of the selected cyclodextrin. The reaction proceeds under mild reaction conditions and provides almost exclusively the corresponding benzyl alcohol as reaction product. No organic solvent are required.

Циклодекстрины действуют в качестве обратной фазы трансфер-катализатора в процессе гидролиза бензилгалогенов. Реакция зависит от выбора и количества циклодекстрина. Реакция протекает в умеренных условиях и обеспечивает образование почти исключительно только бензил спирта как продукта реакции. Никаких органических растворителей не требуется.

Ցիկլոդեքստինները գործում են որպես տրանսֆեր-կատալիզատորի հակադարձ ֆազա բենզիլհալոգենների հիդրոլիզի պրոցեսում: Ռեակցիայի ազդեցությունը կախված է ցիկլոդեքստրինի ընտրությունից և քանակից: Ռեակցիան ընթանում է չափավոր պայմաններում և ապահովում է համարյա բացառապես միայն բենզիլ սպիրտի առաջացումը որպես ռեկցիայի արդյունք: Ոչ մի օրգանական լուծիչ չի պահանջվում:

### Introduction

Reactions involving reagents soluble in non miscible layers proceed only with low reaction rates or, eventually, they do not occur at all. On the other hand, the reactions between organic compounds and inorganic anions are very common, and to try to overcome this problem is an important goal in organic syntheses.

Phase Transfer Catalysis (PTC) [1] actually represents the better solution to carry out under mild reaction conditions many reaction between molecules soluble in water and different compounds soluble only in a immiscible organic phase. Up to now thousands and thousands of papers and patents have expanded the use of PTC to a wide range of reactions and processes. In any case the PTC catalyst (usually an onium salt or a crown ether) allows to transfer the activated anion in the organic layer according to a mechanism fully proved by Montanari [2].

Recently it was reported that by working under Inverse Phase Transfer Catalysis (IPTC) [3] conditions, the organic molecule is transferred to react in the aqueous phase. In particular it was proved that also cyclodextrins (non reducing, stable and non toxic oligosacchararides) act as IPTC catalyst [4].

By using this synthetic procedure good results were obtained, for instance, in the oxidation of terminal alkenes [5] (Wacker process) and in the carboxylic acid esters hydrolysis reaction [6].

The hydrolysis of the alkyl halides (Figure 1) to form the corresponding alcohol is a well known reaction in organic chemistry, but industrially it is of negligible importance since, generally, alkyl halides are obtained starting from the parent alcohol [7]. The main



exception is represented by the synthesis of benzyl alcohol carried out industrially hydrolysing benzyl chloride being this latter produced by the chlorination of toluene [8].

Because benzyl chloride is insoluble in water, the reaction rate is very low. On the other hand under classical LL-PTC conditions the hydrolysis of benzyl halides is fast, but due to the strong anionic activation, the reaction leads to the formation of the corresponding symmetric ethers [9] following the classical Williamson synthesis for symmetric ethers.

We have found that carrying out the hydrolysis of benzyl chloride or benzyl bromide in the presence of suitable cyclodextrins, the reaction proceeds faster, under milder reaction conditions providing almost exclusively benzyl alcohol as reaction product. No organic solvent was used.

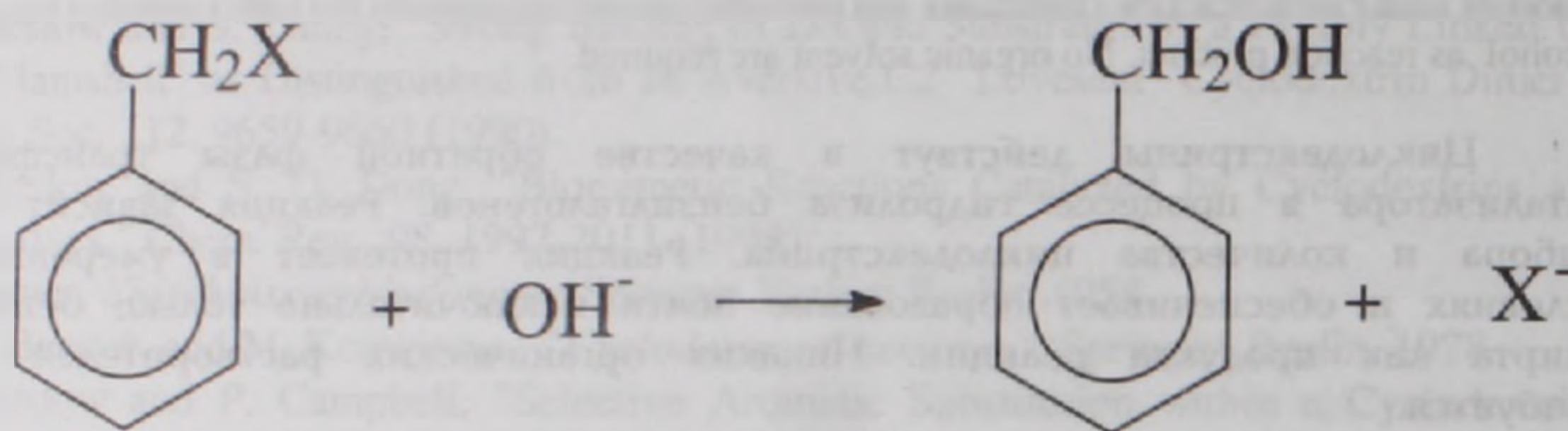


Figure 1. Hydrolysis of alkyl halides.

### Material and Methods

$\beta$ -cyclodextrin was kindly supplied from Roquette-Italia (Cassano Spinola – Italy). Other cyclodextrins were gifted by Wacker-Chemie (Germany). All solvents and reagents employed (ACS grade) were bought from Aldrich (U.S.A.) and used without further purification. GC-MS analysis were performed on a HP 5890 A spectrometer. Magnetic stirring rate was measured with a Cole-Palmer 08199 phototachometer. Reaction environment was thermostated with a Lauda RC6 thermostat.

In a typical experiment to 30 ml of a  $\text{K}_2\text{CO}_3$  solution (20% w/v) the required amount of catalyst was dissolved. Then 0.1 ml of benzyl chloride was added and the mixture allowed to react at  $50^\circ\text{C}$  and 500 rpm. Once the reaction was over, the reaction mixture was extracted twice with diethyl ether and the organic layer analysed to GC-MS. definitive confirmations were obtained by comparison with authentic samples.

### Results and Discussion

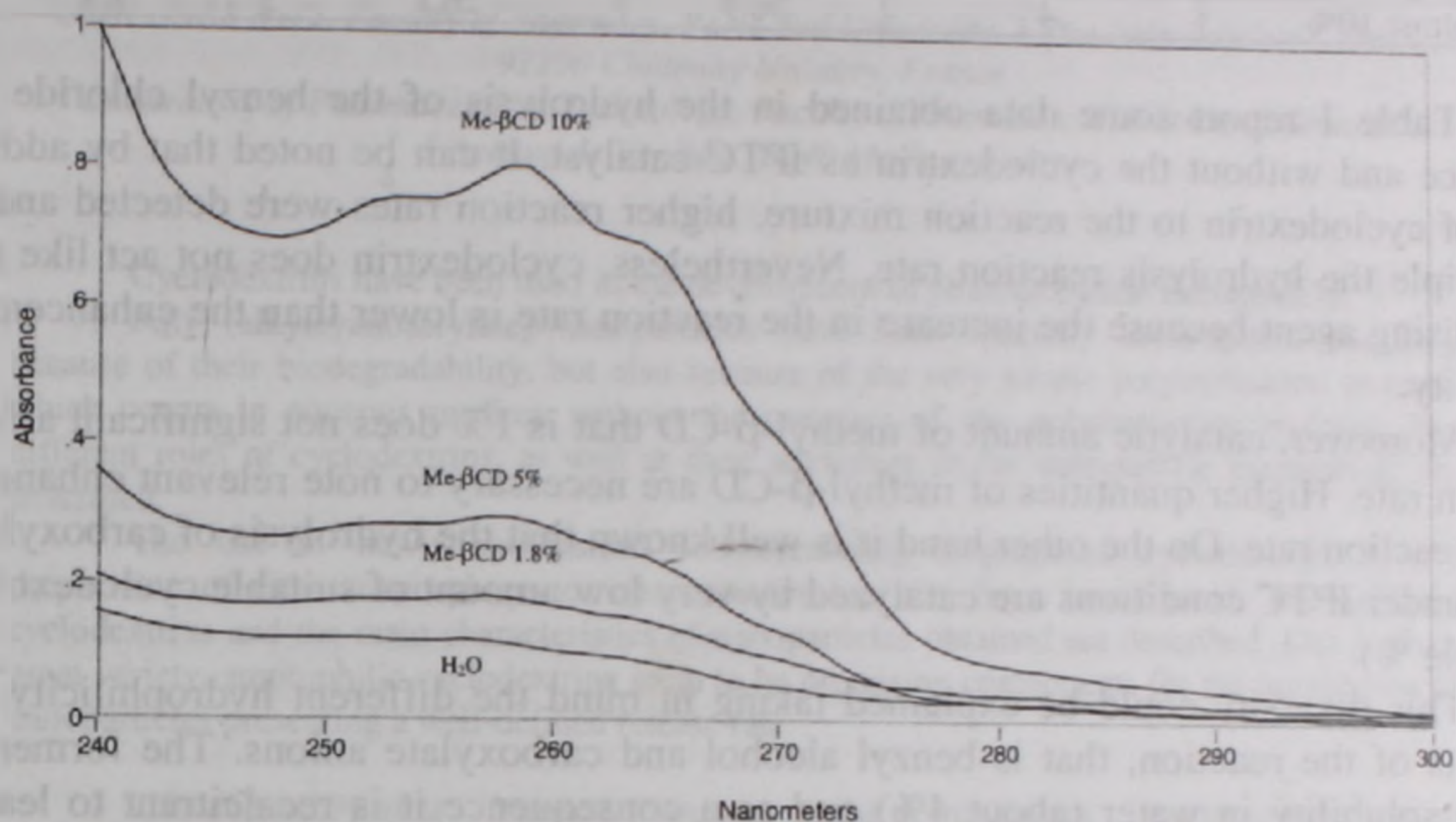
Since alkyl halides are insoluble in water, their hydrolysis is a reaction extremely low even under drastic stirring of the biphasic system. The use of PTC catalysts increases the reaction rate, but leads to the formation of the corresponding ethers. That is, alcohols could not be obtained by simple hydrolysis of the parent alkyl halide by working under classical PTC conditions.

On the other hand, cyclodextrins greatly affect the solubility in water of the benzyl halides. For example Figure 2 reports the solubilizing effect of different amount of methyl- $\beta$ -cyclodextrin on benzyl chloride in aqueous solution at room temperature. It is clear that the enhancement in the absorbance at 258 nm of the solution of benzyl chloride in pure water and in presence of progressive higher amount of methyl- $\beta$ -cyclodextrin no doubt proves the solubilizing effect of the selected cyclodextrin on benzyl chloride. In particular 10 wt%



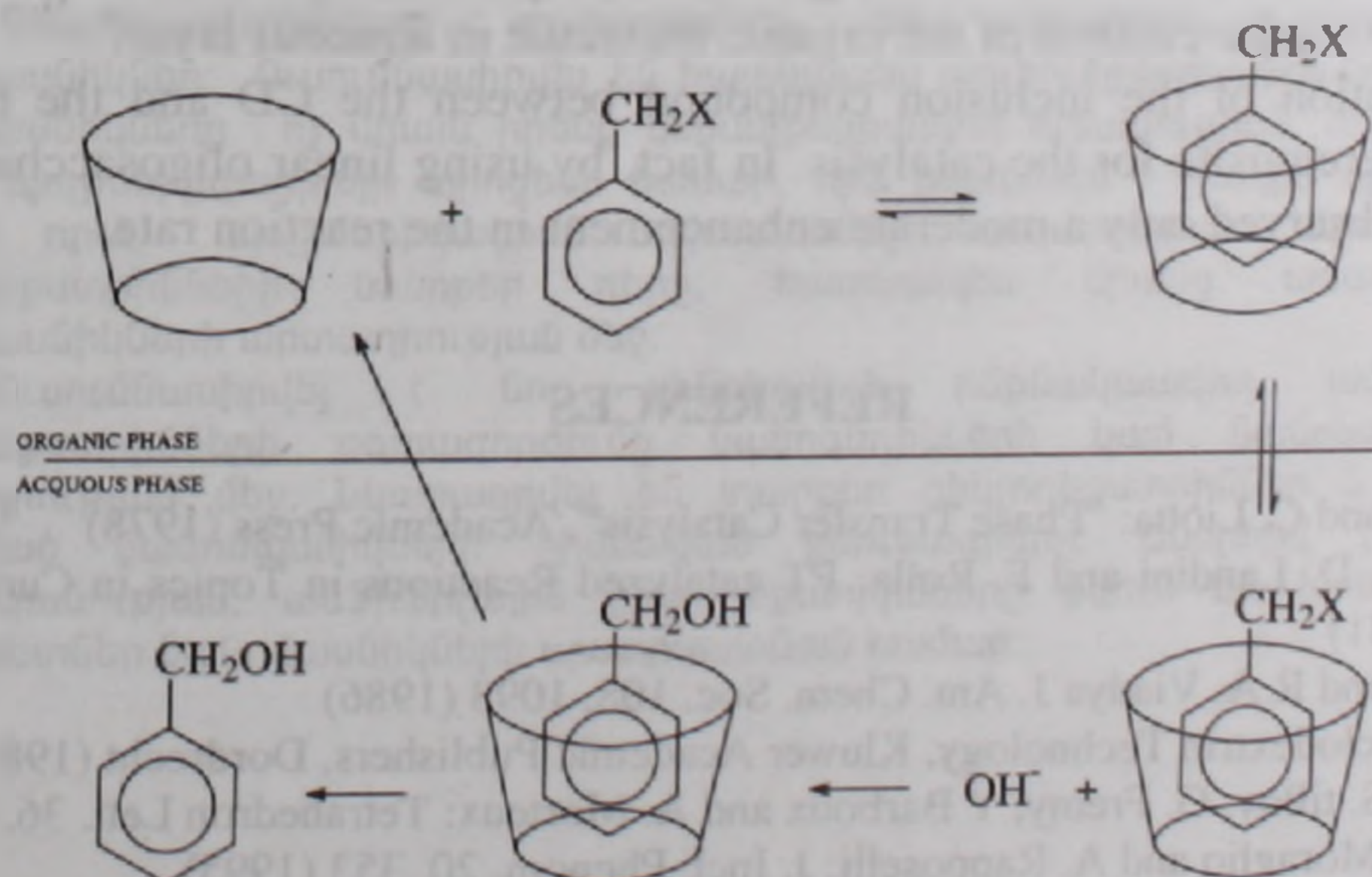
solution of methyl- $\beta$ -cyclodextrin leads to an increase in the solubility in water more than seven times.

Benzyl halides reaction could be profitably carried out in the presence of cyclodextrins as IPTC catalysts.



**Figure 2.** The solubilizing effect of different amount of methyl- $\beta$ -cyclodextrin on benzyl chloride in aqueous solution at room temperature.

An accepted possible reaction mechanism is sketched in Figure 3. The cyclodextrins are able to form stable inclusion compounds with the benzyl halide. This latter could be transferred in aqueous phase where the reaction takes place. Actually the cyclodextrin acts as a co-catalyst being the hydroxyl anions the true catalysts in the hydrolysis reaction.



**Figure 3.** Inverse Phase Transfer Catalysis.



**Table 1.** Hydrolysis of benzyl halide under IPTC conditions. 50°C 500 rpm.  
Conversion, %

Catalyst	Time(h)	Catalyzed (a)	Uncatalyzed (b)	A/b ratio
Methyl- $\beta$ -CD 1%	4	38.3	26.1	1.5
Methyl- $\beta$ -CD 10%	4	85.9	26.1	3.3
$\beta$ -CD 10%	4	42.4	26.1	1.6
Maltose 10%	4	36.9	26.1	1.4

Table 1 report some data obtained in the hydrolysis of the benzyl chloride in the presence and without the cyclodextrin as IPTC catalyst. It can be noted that by adding 10 wt% of cyclodextrin to the reaction mixture, higher reaction rates were detected and more than triple the hydrolysis reaction rate. Nevertheless, cyclodextrin does not act like simple solubilising agent because the increase in the reaction rate is lower than the enhancement of solubility.

Moreover, catalytic amount of methyl- $\beta$ -CD that is 1% does not significant affect the reaction rate. Higher quantities of methyl- $\beta$ -CD are necessary to note relevant enhancement in the reaction rate. On the other hand it is well known that the hydrolysis of carboxylic acid esters under IPTC conditions are catalyzed by very low amount of suitable cyclodextrin (i.e. < 1 mole %).

This diversity could be explained taking in mind the different hydrophilicity of the products of the reaction, that is benzyl alcohol and carboxylate anions. The former has a limited solubility in water (about 4%) and as a consequence it is recalcitrant to leave the apolar cavity of the cyclodextrin thus partially blocking the catalysis. As far as carboxylic acid ester hydrolysis is concerned, highly hydrophylic carboxylate anions are obtained that immediately pass in to water solution breaking the inclusion compound and restoring free cyclodextrin cavity to start another catalytic cycle.

Because the hydrolysis of benzyl halide leads to quite lypophilic benzyl alcohol which have a low water solubility, greater amount of the IPTC catalyst, in comparison with other IPTC reactions, is required to show significant enhancement in the reaction rate.

In particular the methyl- $\beta$ -cyclodextrin acts as better catalyst in comparison with the parent  $\beta$ -cyclodextrin.

This fact could be ascribed to its higher solubility in both phases. As a consequence it is a better phase transfer catalyst of the organic molecule in aqueous layer.

The formation of the inclusion compound between the CD and the benzyl halide seems to be a prerequisite for the catalysis. In fact, by using linear oligosaccharides such as maltose, it was observed only a moderate enhancement in the reaction rate.

## REFERENCES

1. C. M. Starks and C. Liotta: "Phase Transfer Catalysis", Academic Press (1978)
2. F. Montanari, D. Landini and F. Rolla: PT catalyzed Reactions in Topics in Current Chemistry 101, 147 (1981)
3. L.J. Mathias and R.A. Viadya J. Am. Chem. Soc. 108, 1093 (1986)
4. J. Szejtli: Cyclodextrin Technology, Kluwer Academic Publishers, Dordrecht (1988)
5. E. Monflier, S. tilloy, G. Fremy, Y Barboux and A. Morteux: Tetrahedron Lett. 36, 387 (1995)
6. F. Trotta, G. Moraglio and A. Rapposelli: J. Incl. Phenom. 20, 353 (1995)
7. Kirk-Othmer "Concise Encyclopedia of Chemical Technology" p.275 Wiley (1985)
8. Kirk-Othmer "Concise Encyclopedia of Chemical Technology" p. 163 Wiley (1985)
9. E.V. Demhlow and S.S. Dehmlow: Phase Transfer catalysis, p. 182 Verlag Chemie (1983)