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The Haloform Reaction in the Presence of Cyclodextrins

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Abstract. Cyclodextrins act as inverse phase transfer catalysts in the oxidation of methyl ketones by hypochloride (the haloform reaction). The reaction is affected by the choice and the amount of cyclodextrin. The reaction proceeds under mild reaction conditions and it provides only the corresponding carboxylic acid as reaction product. No organic solvent is required.

Key words: cyclodextrins, inverse phase transfer catalysis, haloform reaction

1. Introduction

It is well known that reactions carried out between molecules soluble in water and substances soluble only in an organic non-miscible phase, are slowed down or prevented. Because the reactions between organic compounds and inorganic anions are very common, the problem becomes very important since the latter are preferentially soluble in water.

Phase Transfer Catalysis (PTC) represents a better way to perform, under mild reaction conditions, many reactions between molecules soluble in water and compounds soluble in an immiscible organic phase. To date thousands of papers and patents have expanded the use of PTC [1] to a wide range of reactions and processes.

In any case the PTC catalyst (usually an onium salt or a crown ether) allows transfer of the anion into the organic phase where it is poorly solvated (naked anions) and able to react with a high reaction rate. This synthetic procedure is widely applied and very often leads to positive results. Among the few unsuccessful reactions are, for example, the hydrolysis of carboxylic acid esters having a long alkyl chain and, generally speaking, all the reactions where the PTC catalyst is poisoned by the formation of a stable ion pair between the onium salt and its counterion [2] (i.e., iodide).

Recently Inverse Phase Transfer Catalysis (IPTC) [3] was also reported. By working under IPTC conditions, it is the organic molecule that is transferred to react in the aqueous phase where the reaction occurs effectively.

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Due to their typical truncated cone shape and to their atoms spatial disposition, cyclodextrins (CD) [4], non reducing, stable and non toxic cyclic oligosaccharides, are able to form inclusion compounds stable also in solution with a large number of organic molecules of suitable size and polarity and were used as an IPTC catalyst.

In recent years some papers have already shown the effectiveness of the cyclodextrins as Inverse Phase Transfer Catalysts in several organic reactions such as: oxidation of terminal alkenes (Wacker process) [5], hydrolysis of carboxylic acid esters [6], oxidation of alcohol to the corresponding aldehyde [7].

In the literature, however, are not reported studies to date of the oxidation of methyl ketones by means of hypohalides (the haloform reaction) in the presence of cyclodextrins.

The haloform reaction [8] is a well known reaction in organic chemistry which allows the formation of carboxylic acid from the corresponding methyl ketones and it is used both for analytical and preparative purposes.

Since methyl ketones are often of low solubility in water where the hypohalide is soluble, it is clear that the use of a suitable cylodextrin as IPTC catalyst could be useful to increase the reaction rate.

We have found that carrying out the haloform reaction in the presence of cyclodextrins, the reaction proceeds faster under milder reaction condition, providing exclusively the corresponding carboxylic acid as reaction product. No organic solvent is required.

2. Materials and Methods

β-Cyclodextrin was kindly supplied by Roquette-Italia (Cassano Spinola – Italy) while α and γ-cyclodextrin were gifted by Wacker – Chemie (Germany).

2-Acetonaphthone, sodium bisulfite and concentrated hydrochloric acid were bought from Aldrich (U.S.A.). Ethyl ether (Normapur) and acetophenone were obtained from Merck (Germany). All the reactions were carried out at controlled temperatures by using a Lauda RC6 thermostat. The magnetic stirring rate was controlled by a Cole–Palmer 09199 phototachometer.

The solubility tests of organic compounds in water were carried out following the enhancement in the selected absorbance by using a Perkin–Elmer lambda 15 UV-Vis spectrophotometer.

Melting points were determined with an Electrothermal IA 9100 apparatus.

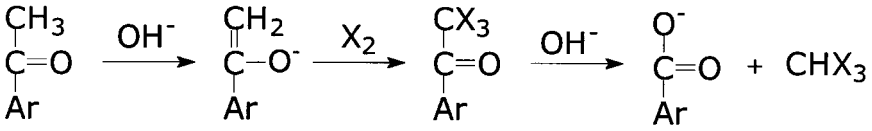
In a typical experiment the required amount of cyclodextrin was added to 20 mL of a solution of sodium hypochloride (14%). The solution obtained was thermostated to the selected temperature and methyl ketone was added and the reaction was allowed to react under constant magnetic stirring.

The reaction was stopped by adding sodium bisulfite and afterwards was slowly acidified by adding concentrated HCl. The solution was extracted three times with ethyl ether and the organic fractions were combined and extracted three times with 5% NaOH solution.

The corresponding carboxylic acid was precipitated by acidification with HCl, recovered by filtration under vacuum, dried and weighed. Carboxylic acid was confirmed by determining its melting point and by TLC analysis by comparison with authentic samples.

3. Results and Discussion

The haloform reaction is concerned with the oxidation of methyl ketone (as well as methyl alcohol) to the corresponding carboxylic acid by using hypohalide (i.e., halogen in a basic environment) through the accepted mechanism (reaction 1):



The reaction proceeds through a preliminary halogenation on the carbon in the α position followed by hydrolysis under basic conditions of the trihalogenated derivative obtained. The reaction is quite exothermic.

In the literature it is reported that hypohalide anion could be transferred to react in organic solutions by using onium salts to oxidize alcohols, amines [9] and even polynuclear aromatic rings [10] through a typical PTC mechanism. However by working under PTC conditions no data were found on the haloform reaction. Since acetophenone is of low water solubility, its reaction rate could be increased by using Inverse Phase Transfer catalysts.

Figure 1 reports the solubilizing effect of some cyclodextrins on acetophenone in aqueous solution. The enhancement in the absorbance at 245 nm of the solutions of acetophenone in pure water and in the presence of a small amount of α or β cyclodextrin no doubt proves the higher water solubility of the acetophenone in the presence of the β-cyclodextrin. This fact is of particular importance when considering that the β-cyclodextrin was used in a 1.8% (w : v) solution (i.e., a saturated solution at room temperature) while α and γ cyclodextrin were 5% (w : v) solutions. Curiously the γ-cyclodextrin solution gives a decrease in acetophenone water solubility in comparison to pure water. The solubilizing effects of the cyclodextrins, although significant are not, however, very high and thus little effect on the reaction rate is predicted. In fact, by working with a catalytic amount (less than 1%) of the IPTC catalyst, no catalytic effect on the haloform reaction was observed.

Moreover, it is well known that the formation of the inclusion compound can have two opposite effects on the reaction rate. First the CD cavity could protect the organic molecule from the attack of the inorganic reagent thus lowering the reaction rate. On the other hand the formation of a suitable inclusion compound could place the substrate in a favourable position leading to great enhancement in the reaction rate because of the greater number of effective collisions between the

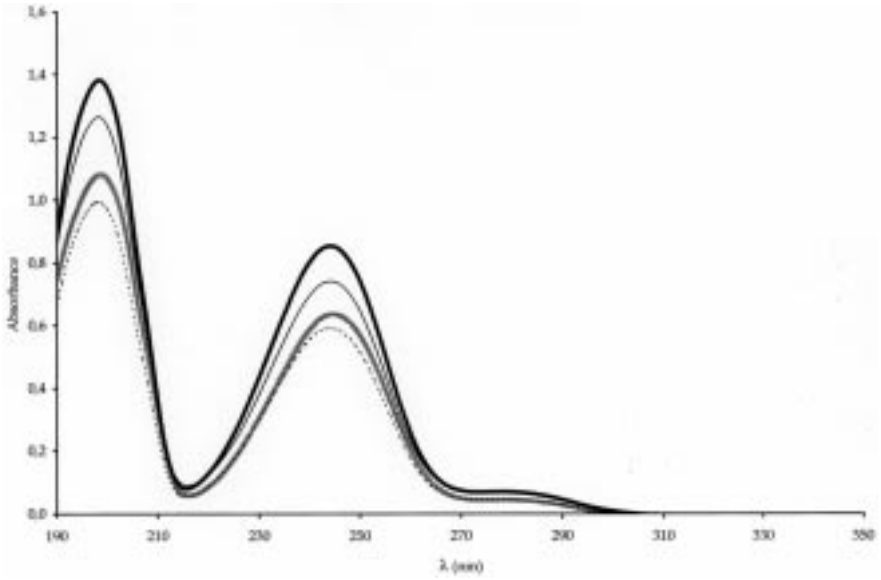


Figure 1. UV spectra of 2-acetophenone in water and CD solutions. T = 25 °C. (▬▬▬), 1.8% β-CD; (————), 5% α-CD; (▬ ▬ ▬), without CD; (- - - - - - - -), 5% γ-CD.

reagents. The predominance of one of these factors leads to an inhibition rather than a catalysis.

Figure 2 reports the yield of benzoic acid obtained in the oxidation of acetophenone in the presence of different amounts of β-cyclodextrin at 50 °C and 500 rpm stirring rate. It is evident that a β-cyclodextrin concentration of less than 20 mole% (compared to acetophenone) leads to minor enhancement in the reaction rate, higher results could be obtained by working with concentrations of β-cyclodextrin as high as 50 mole%: in this case an almost threefold enhancement in reaction rate was observed. The necessity of working with a large amount of IPTC catalyst, could mean that the cyclodextrin cavity remains occupied for a long time in a step of the catalysis mechanism.

As predictable from the solubility data, β-cyclodextrin was proved to be the best IPTC catalyst in the oxidation of acetophenone by hypochloride. Table I (entries 1–3) reports, in fact, the yields in benzoic acid obtained after 15 minutes by working with the three different native cyclodextrins. β-Cyclodextrin triples the reaction rate and it is more effective than α or γ-cyclodextrin. The latter, however, shows a relevant catalytic effect and apparently disagrees with the observed solubility behaviour.

The formation of the inclusion compound between the cyclodextrin and the methyl ketone seems to be a prerequisite for the catalysis. In fact, by using linear (Table I entries 4, 5) oligisaccharides such as maltose or dextrin 10, no catalytic effects were observed; on the contrary they act even like inhibitors in the haloform reaction.

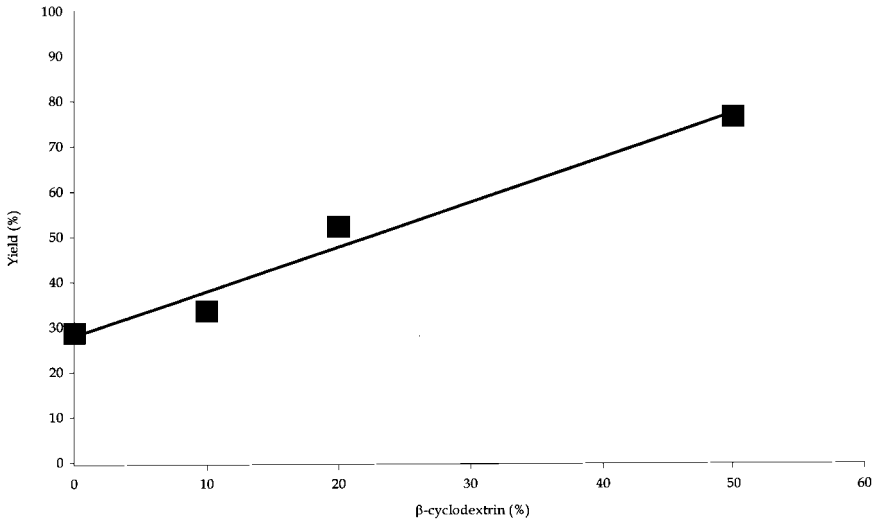


Figure 2. Yield of benzoic acid from acetophenone and NaClO 14% in the presence of different amounts of β-CD. T = 30 °C, 15 minutes, 500 rpm.

Table I. Influence of CDs on the haloform reaction under constant stirring.

Entry	Ketone	Catalyst	Time (min)	Temp. (°C)	Yield		Cat./ Uncat.
					Uncatalyzed	Catalyzed	
1	Acetophenone	α-CD[a]	15	50	28.7	45.9	1.6
2	Acetophenone	β-CD[a]	15	50	28.7	76.5	2.7
3	Acetophenone	γ-CD[a]	15	50	28.7	63.1	2.2
4	Acetophenone	Maltose[a]	15	50	28.7	21.5	0.7
5	Acetophenone	Dextrin 10[a]	15	50	28.7	15.3	0.5
6	2-Acetonaphthone	α-CD[b]	30	55	3.0	3.0	1.0
7	2-Acetonaphthone	β-CD[b]	30	55	3.0	54.5	18.2
8	2-Acetonaphthone	γ-CD[b]	30	55	3.0	27.0	9.0

[a] Catalyst 50 mole% compared to ketone.
[b] Catalyst 150 mole% compared to ketone.

Figure 3 shows the yield of benzoic acid observed at different reaction times with and without IPTC catalyst. In the presence of cyclodextrin a higher reaction rate was observed already after 5 minutes and the reaction was almost complete after 30 minutes. On the other hand without catalyst the reaction is much slower and only minor differences in the reaction rate were observed after prolonged time.

It can be asserted in a reasonable manner that cyclodextrins are able to improve the reaction rate in the acetophenone oxidation, but a significant amount of cyclodextrin (at least 20 mole% in comparison with the substrate) is required. Taking into consideration other IPTC reactions such as the hydrolysis of carboxylic acid esters, where less than 1 mole% of cyclodextrin was highly effective in promot-

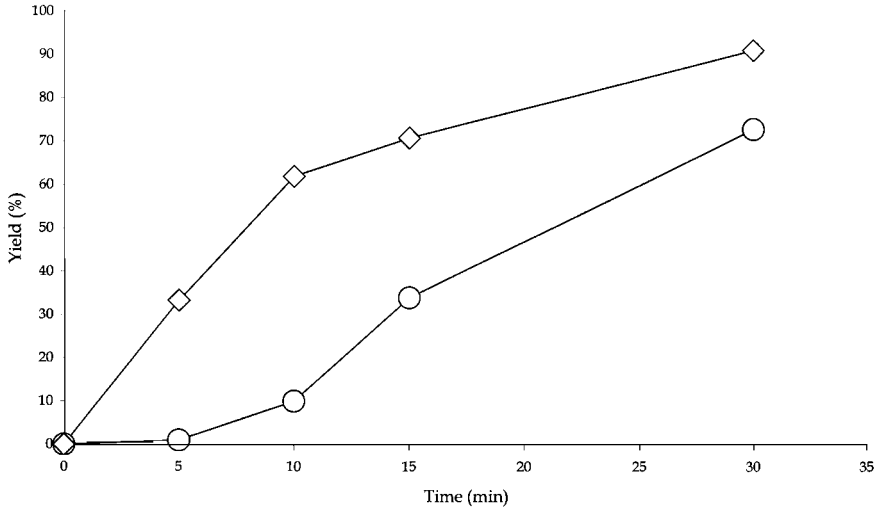


Figure 3. Yield of benzoic acid from acetophenone and NaClO 14% for various reaction times. β-CD = 150 mole%, T = 50 °C, 500 rpm.

ing the hydrolysis, this different behaviour in the haloform reaction requires an explanation.

The accepted mechanism of the haloform reaction (reaction 1) assumes that the first step is the substitution of all the hydrogen atoms of the methyl group with halogen atoms. This leads to a halogenated compound that is less hydrophilic than the parent methyl ketone and, as consequence, a less water soluble compound is obtained. The lypophilic guest probably remains for a prolonged time in the cyclodextrin host cavity until its hydrolysis to benzoate anion occurred. The latter, more hydrophilic and water soluble, immediately leaves the cyclodextrin cavity allowing the start of another catalytic cycle.

Obviously, the prolonged stay of the reaction intermediate in the CD cavity slows down the transfer of molecules from the organic phase to the aqueous phase and a low reaction rate results. Probably the reaction intermediate acts like a "poison" for the IPTC catalyst similar to that in classical PTC when a stable onium salt ion pair is formed. Under PTC conditions this problem was overcome by working with a sligthly molar excess of the catalyst leading to a more expansive process.

Under IPTC conditions, the inclusion compound shows only a weak hydrophobic interaction and it is readily dissociated. This means that at any given time we can always find free cyclodextrin molecules able to act like a IPTC catalyst by working at a concentration lower than equimolar.

The release of the reaction intermediate from the cyclodextrin cavity seems to be the slow step of the catalysis. On the other hand, the data collected on the haloform reaction agree well with others obtained in different IPTC reactions and, particularly, with the data obtained in the hydrolysis of benzyl halides [11].

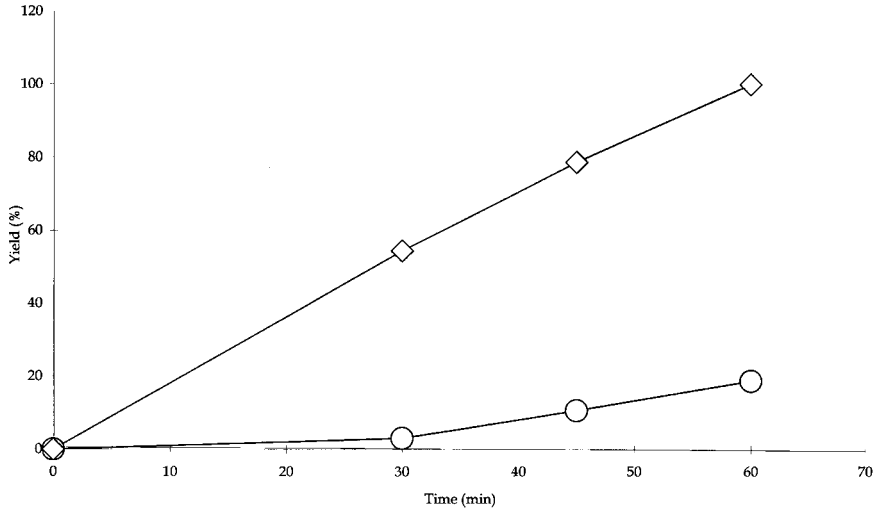


Figure 4. Yields of naphthoic acid from 2-acetophenone and NaClO 14% for various reaction times. β-CD 150 mole%, T = 55 °C, 500 rpm.

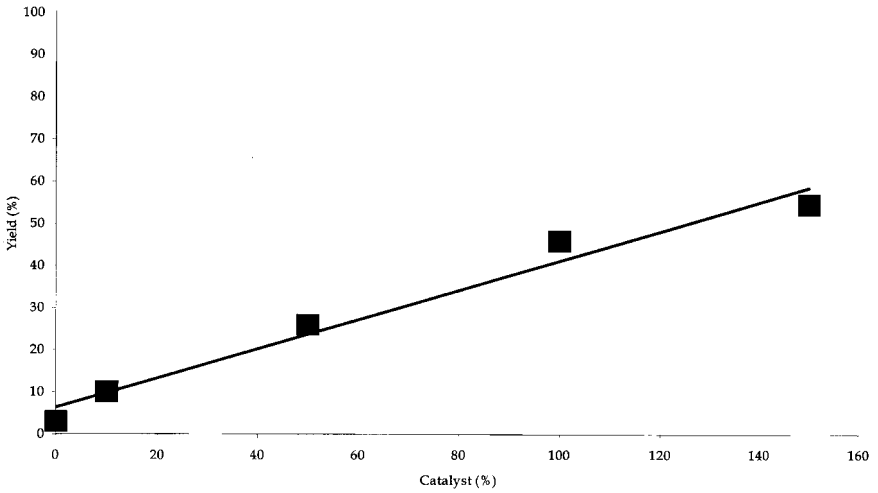


Figure 5. Effect on the yields of the amount of β-CD employed in the oxidation of 2-acetonaphthone. T = 55 °C, 30 minutes, 500 rpm.

Also in this latter case a considerable amount (5–10 mole%) of CD was required to obtain a similar enhancement in the hydrolysis reaction rate as well as those observed in the hydrolysis of the carboxylic acid esters with a small amount of IPTC catalyst (<1 mole%).

It is well known that benzyl alcohol is the reaction product of the hydrolysis of benzyl halides, but also benzyl alcohol has a limited solubility in water (about 4 mole%) and as a consequence it is recalcitrant to leave the apolar cavity of the

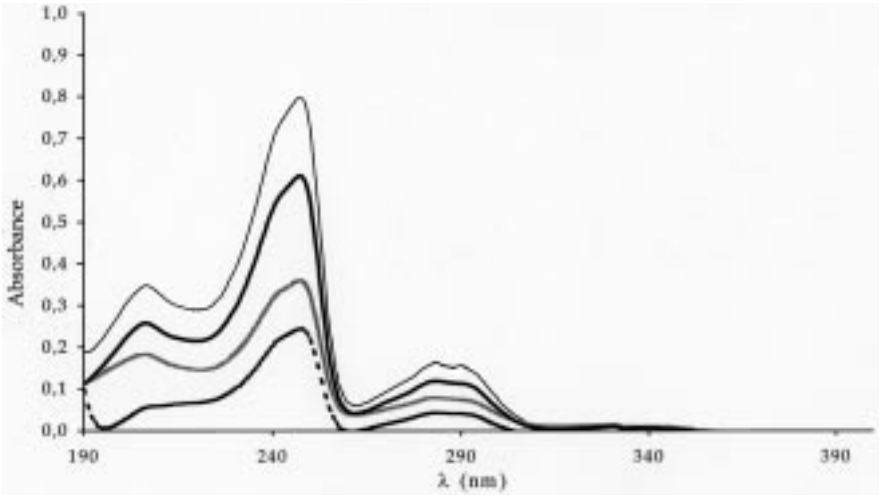


Figure 6. UV spectra of 2-acetonaphthone in water and CD solutions. (▬▬▬), β-CD; (——————), α-CD; (▬▬▬), without CD; (- - - - - -), γ-CD.

cyclodextrin thus blocking the catalysis. As far as carboxylic acid ester hydrolysis is concerned, however, hydrophilic and highly water soluble carboxylate anions are obtained, here quick dissociation of the inclusion compound was observed and the free CD cavity could restart a new catalytic cycle. The oxidation of methyl ketones also leads to water soluble carboxylate anions and a similar behaviour to esters hydrolysis could be predicted. However, it is important to point out that the haloform reaction proceeds through two steps, the first of these leads to the trihalogenated intermediate surely more lipophilic than the native ketone blocking the CD cavity for a prolonged time and slowing down the catalysis.

Other methyl ketones behave similarly. For instance many experiments were carried out on the oxidation of 2-acetonaphthone by sodium hypochloride. Acetonaphthone has a greater molecular dimension and a lower solubility in water thus the catalytic effect could be magnified.

In fact, in the absence of the IPTC catalyst the haloform reaction for naphthyl methyl ketone is very slow in comparison with the acetophenone reaction. Figure 4 shows that after 30 minutes the yields of naphthoic acid in the absence of CD is less than 5%. Under the same reaction conditions, but in the presence of a large excess of β-cyclodextrin, a 54% yield was observed after 30 minutes and the reaction was quantitative in 60 minutes while in the absence of the catalyst the yield was only less than 20%. In the case of the less soluble naphthyl methyl ketone the catalytic effect of β-cyclodextrin is magnified.

Figure 5 shows that, as observed for acetophenone, the reaction rate increases by enhancing the amount of catalyst following a linear relationship. In this case the analogy with the PTC ion pair extraction is evident and we can speak of molecular extraction under IPTC conditions.

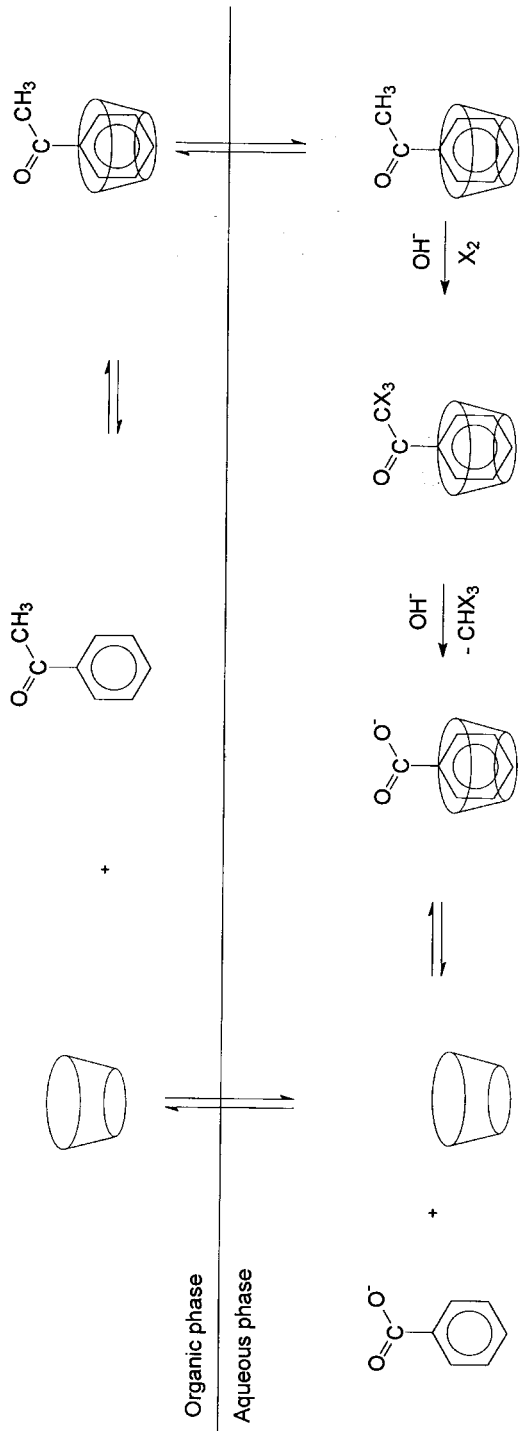


Figure 7. Scheme of a possible reaction mechanism for the haloform reaction under IPTC conditions.

Moreover, the effect of different CDs is greater on the oxidation of acetonaphthone. As shown in Table I (entries 6–8), again we note that the most effective catalyst is β-cyclodextrin which is able to give 55% yield in 30 minutes. Less effective is γ-CD that leads to 27% yield and α-CD is not effective at all.

We note that these experimental data do not fit well with the water solubility of 2-acetonaphthone in the presence of different CDs. In fact, Figure 6 reports the UV spectra of the latter ketone in a saturated aqueous solution of β-cyclodextrin and in solutions of 5% (w : v) of α or γ cyclodextrin. Of course, the β-CD solution has a concentration of only 1.8% (w : v). Again we note the superior solubilizing effect of the β-CD on the aromatic ketone and we also record the non effectiveness of γ-CD. Because the observed catalytic behaviour do not follow completely the increase in solubility we speculate that CDs have proper catalytic behaviour and they are not simple molecule transfer agents.

On the basis of the reported experiments and literature data, we hypothesise that the haloform reaction catalysed by CDs could follow the reaction mechanism sketched in Figure 7 for the acetophenone molecule. The formation of the inclusion compound between the ketone and the CD allows the former to increase its solubility in water where the halogenation reaction occurs. The latter compound remains in the apolar CD cavity and then, being rather soluble in water where it is hydrolyzed to the corresponding carboxylate anion that readily leaves the CD cavity allowing the restart of a new catalytic cycle.

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References

1. E. V. Demhlow and S. S. Dehmlow: *Phase Transfer Catalysis*, Verlag Chemie (1983).
2. C. M. Starks and C. Liotta: *Phase Transfer Catalysis*, Academic Press (1978), p. 67.
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. Barbaux, and A. Morteux: *Tetrahedron. Lett*. **36**, 387 (1995).
6. F. Trotta, G. Moraglio, and A. Rapposelli: *J. Incl. Phenom.* **20**, 353 (1995).
7. Y. Hu, A. Harada, and S. Takahashi: *J. Mol. Catalysis* **60**, L13 (1990).
8. J. March: *Advanced Organic Chemistry*, 4th edn, Wiley (1992), p. 632.
9. C. A. Lee and H. H. Freedman: *Tetrahedron. Lett.* **20**, 1641 (1976).
10. S. Krishnar, D. G. Kuhn, and G. A. Hamilton: *J. Am. Chem. Soc.* **99**, 8121 (1977).
11. F. Trotta and D. Cantamessa: *9th International Symposium on Cyclodextrins*, Santiago de Compostela, Spain, May 31–June 3 1998. Book of Abstracts p. 4P2.