PTC in PracTiCe

Kjell Sjöberg
Department of Chemical Technology
Royal Institute of Technology
S-10044 Stockholm, Sweden

During the last few years articles and books on phase-transfer catalysis — PTC — have appeared in a steadily increasing stream.[1] The stream is likely to continue increasing and will change conventional chemical syntheses and processes greatly as many areas have been touched upon only briefly.

The transfer of hydrophilic ions into a lipophilic organic medium seems strange at first, but in practice the technique is remarkably simple.

For this article I have abstracted PTC information that has been valuable in our own process development work. Some ideas are taken directly from the literature while others have been developed further through our daily use. Areas focused upon are:

- replacement of sodium or sodium hydride by 50% NaOH in alkylation reactions
- extended uses of inorganic salts in organic reactions
- C- vs. O-alkylations
- transfer of "nonionic" species like H_2O_2 and HCl
- extractive separations.

I will also discuss catalyst cost and advantages of catalyst recovery. A simple quantitative analytical method for quaternary ammonium ions, the most common PTC catalysts, is described.

The reader who has had only brief contact with PTC techniques will find background information in the literature given in reference 1.

Use of 50% NaOH instead of sodium in alkylations

PTC sometimes allows strong bases like sodium hydride or sodium amide to be replaced by 50% aqueous sodium hydroxide[2] or, better still, a mixture of solid sodium hydroxide and sodium carbonate.[3] Zwierzak has shown that benzamides and formamides can be N-alkylated in good yields in such a solid base-organic liquid two-phase system.[4a] He uses about 10 mole % of TBAHSO$_4$, but this figure can probably be lowered under optimized industrial conditions. However, at a conventional PTC catalyst level of 1 mole % the yield is halved. One of Brändström's coworkers, Ulf Junggren, in his thesis of 1972, showed that benzamide could not be alkylated using 50% sodium hydroxide in the "Extractive Alkylation Procedure."[4b] Junggren states that "the limit for the practical application of this procedure is for compounds with a pKa of about 15." For the alkylations of weaker acids he gives sodium hydride as the alternative. Using Zwierzak's modification, however, this limit moves to a pKa of 22-25.

Alkylation of *N*-alkylformamides, general procedure
The mixture of the *N*-alkylformamide (0.1mol), finely powdered sodium hydroxide (14.0g), potassium carbonate (8.0g), tetra-*n*-butylammonium hydrogen sulfate (3.4g, 0.01mol), and benzene (60ml) is stirred vigorously at 35-40°C for 30 min. The resultant slurry of the sodium salt of the amide is heated to 60° and a solution of the alkylating agent (0.2mol of dimethyl sulfate or 0.11mol of alkyl halide) in benzene (40ml) is then added at this temperature over a period of 1h. Stirring is continued at 60-70° for 4h. The mixture is then cooled to room temperature, diluted with benzene (50ml) and filtered. The precipitate is washed with benzene (2 x 30ml) and the washings are combined with the filtrate. The benzene solution is washed with water (2 x 20ml), dried with anhydrous magnesium sulfate and evaporated. The oily residue is kept at 30-40°/0.2 torr for 1h to remove volatile impurities. Crude products are analytically pure.

Uses of "new" inorganic anions

TBA salts of a number of common inorganic ions which have not been found to have extensive organic chemical use earlier are now being reported. The high solubility of inorganic anions as their TBA salts in nonpolar organic solvents never ceases to surprise traditional chemists. Try 40% TBAOH in water with an equal amount of petroleum ether!

Quaternary ammonium dithionite has already been used in reductions of ketones to alcohols.[5] It may become a cheap alternative to established reducing agents.
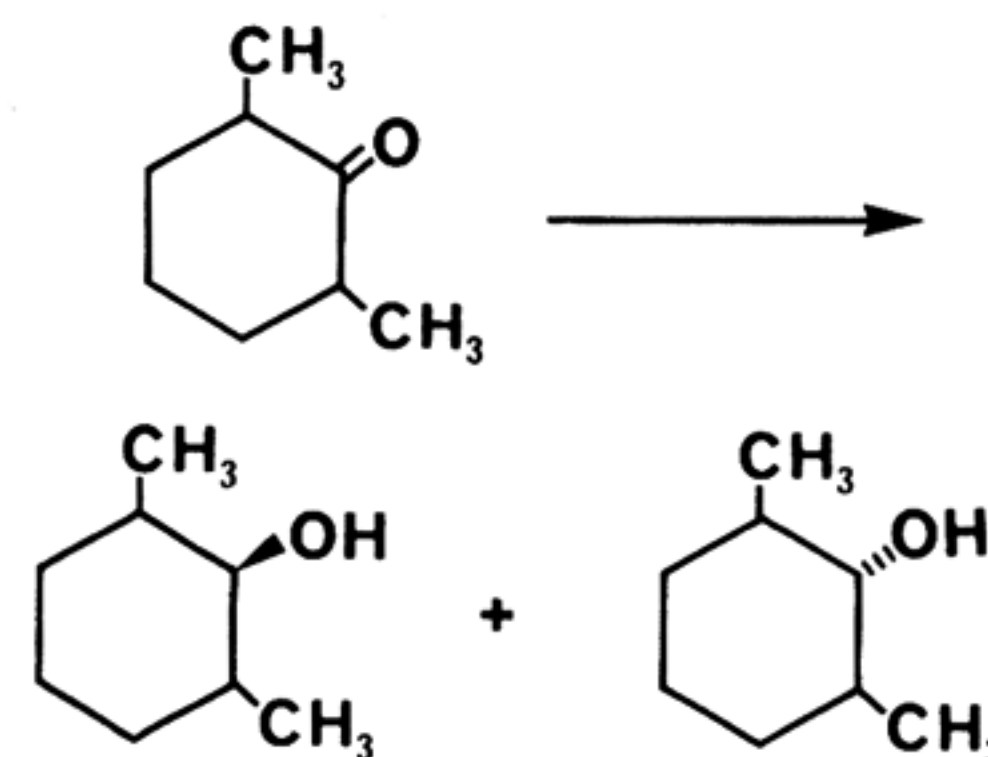
To our knowledge the anion of sodium carbonate peroxyhydrate ("solid H_2O_2") has not yet been tried with the PTC technique. This salt has been put on the market recently by Interox America and might find use as an oxidizing or epoxidizing agent using the PTC technique.[6]

$TBABF_4$ is reported as a useful electrolyte in electrochemical synthesis.[7]

$TBAClO_4$ has interesting solubility properties. It is almost insoluble in water.

$TBAMnO_4$ is frequently used in oxidations.[8] However, it is unstable and thus dangerous to use as an isolated salt.[9]

Although borohydrides are well established in organic synthesis, an extra advantage of using $TBABH_4$ deserves attention. In an earlier survey on "Applications of Phase-Transfer Catalysis in Organic Synthesis," reduction with $TBABH_4$ was reported.[1a] $TBABH_4$ is readily obtained from $TBAHSO_4$. Applications of this lipophilic BH_4^- salt are presently arousing interest.

Not only can solid $TBABH_4$ be isolated, its solution in a non-ethereal solvent can be obtained.[10] The replacement of ether or THF by dichloromethane is a contribution to laboratory and industrial safety. Diborane is easily obtained from a dry solution of $TBABH_4$ in dichloromethane by treatment with an alkyl halide such as methyl iodide or 1,2-dichloroethane. The diborane solution thus obtained can be used for all the common reductions and hydroboration reactions.

C- vs. O-alkylation

Solvents have a well-known effect on C- vs. O-alkylation. Similarly, application of the PTC technique can change the C/O ratio.

Brändström and Junggren have studied factors influencing C- vs. O-alkylation of ambient anions such as those of methyl acetoacetate and dimethyl benzoylmalonate. The expected importance of the alkylating agent is verified.[11,12,13]

These three papers introduce the concept of "extractive alkylation." The authors have isolated the crystalline TBA salts of dimethyl benzoylmalonate and acetylacetone.
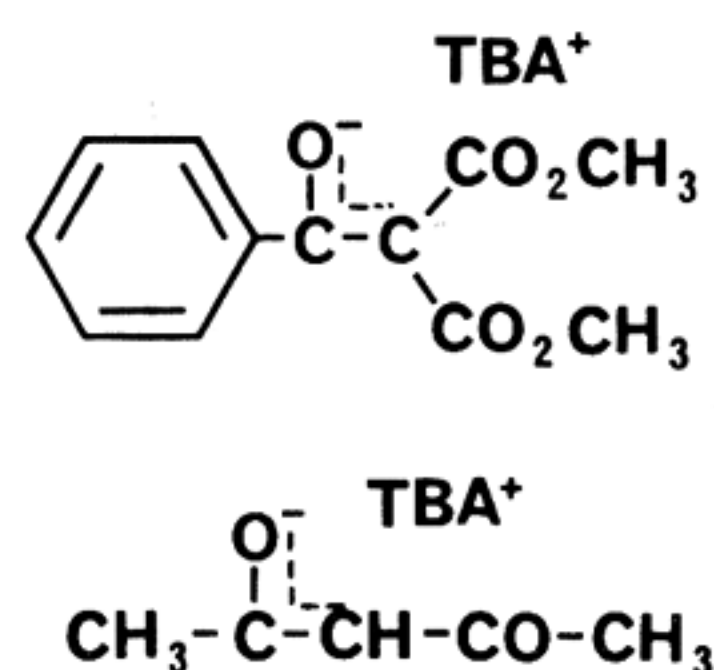
C- vs. O-alkylation of aldehydes

We have studied the alkylation of isobutyraldehyde in our laboratories.[14] In the manufacture of 1-butanol by the OXO-process between 10 and 25% of isobutyraldehyde is formed as a by-product. This compound is available worldwide in quantities of 500 million lbs/year and premium outlets are sought. After treating isobutyraldehyde with benzyl chloride, we have isolated, not only the C-alkylated product, but also the O-alkylated one which has not been previously reported.
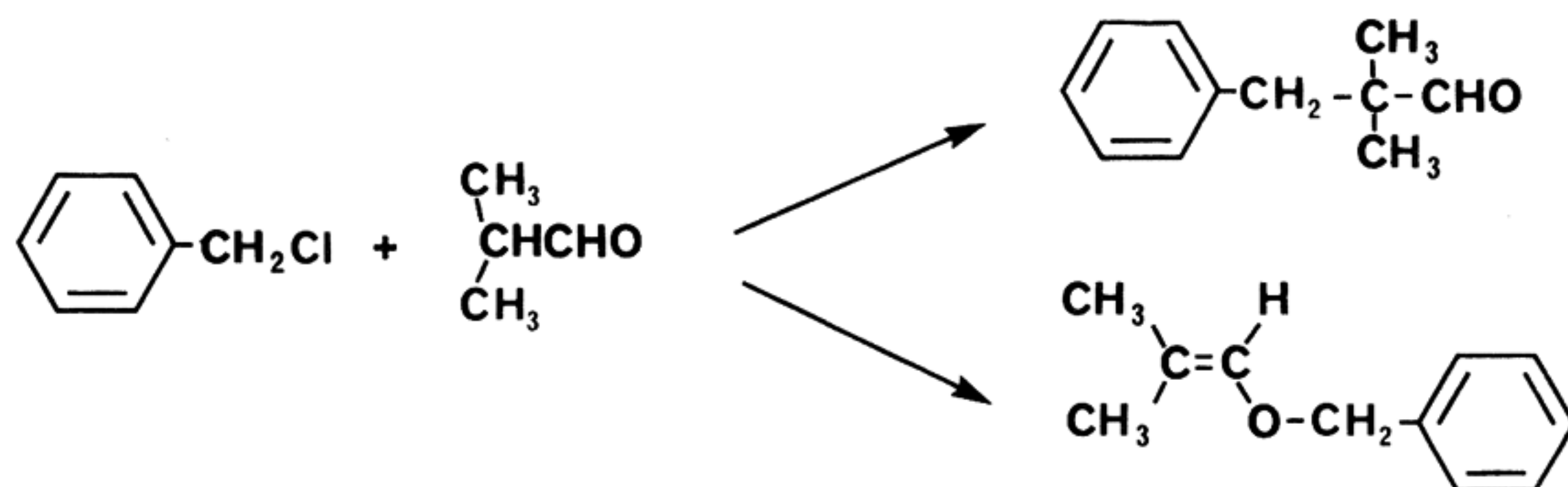
The highest C/O ratio (10.9) is obtained using tetrapropylammonium iodide. The bigger tetrabutylammonium ion gives a smaller C/O ratio. TBA counterions less lipophilic than iodide, viz., bromide, chloride and sulfate all give smaller C/O ratios (see Table 1).

Table 1

Alkylation of isobutyraldehyde with benzyl chloride in 50% sodium hydroxide/toluene at 70° C for 4 hours

No.	Catalyst (1.25 mole %)	C/O ratio	Benzyl chloride reacted (%)
1	TBA iodide	7.6	82.7
2	TBA hydrogen sulfate	4.3	71.0
3	TBA bromide	3.7	74.0
4	Tetrapropylammonium iodide	10.9	79.3
5	Methyltrioctylammonium chloride	5.8	68.5
6	TBA chloride	4.3	69.2

Most surprising is the higher yield obtained when iodide is the counterion. The known poisoning effect of iodide in PTC reactions seems not to apply to this reaction. A yield of 80% is obtained although only 1 mole % of catalyst is used. Furthermore, the reaction is faster when iodide is the counterion.

Transfer of neutral molecules

Transfer of hydrogen peroxide **anions** from an alkaline aqueous phase is not practically possible.[15] Hydrogen peroxide anions remain mainly in the aqueous phase. However, in neutral or acidic media hydrogen peroxide **molecules** are indeed

transferred, probably solvated, by TBA bromide. Dehmlow has demonstrated that the more lipophilic the ion pair, the better it transfers H_2O_2.[15] $TBAHSO_4$ transfers only 10% of the equivalent amount of H_2O_2, whereas TBABr transfers 68%. The still more lipophilic tetrahexylammonium bromide transfers H_2O_2 equivalently. Similarly, hydrogen chloride can be transferred into benzene.

Recovery of TBA ions

Catalysts are expensive and are normally used over and over again. In industrial processes, recovery and regeneration of ineffective catalysts are standard procedures.[3] The cost of these operations plus make-up catalyst is included as catalyst cost in the process cost calculation. The price/lb of the catalyst itself is seldom representative of catalyst cost in a process.

Let us examine the figure used as catalyst cost in the PTC field. A PTC catalyst is recovered by an extractive procedure. Regeneration (i.e., requaternization of a tertiary amine) is probably not of interest.

We have made a catalyst-cost calculation on the propylation of phenylacetonitrile by 1-chloropropane.[16] We use $TBAHSO_4$ as a catalyst at $8/lb and 50% NaOH as a base. At the laboratory scale it was possible to recover 87% of the catalyst as TBACl after the reaction. This puts the figure for catalyst cost, including recovery cost, at about $2 per pound of $TBAHSO_4$ charged in an industrial scale.

Recovery at such a high percentage is only possible for quaternary ammonium ions with a balanced hydrophilicity/lipophilicity. The TBA ion outstandingly combines the lipophilicity necessary for an efficient PTC catalyst with the hydrophilicity necessary for efficient recovery.

How is this recovery achieved?

There are three different ways to recover a quaternary ammonium ion.
1) Salt it out from an aqueous phase with sodium hydroxide.[17]
2) Transfer it selectively into the desired phase using a suitable counterion.[18]
3) Transfer it selectively into the aqueous phase by cooling.[19]

Recovery according to method 1 is accomplished as follows. The solubility of tetrabutylammonium bromide in sodium hydroxide solutions varies markedly with the concentration. A solution of 1% NaOH can dissolve 27% TBABr, whereas a 15% NaOH solution only dissolves 0.07% of TBABr. This spectacular difference in solubility can be utilized in synthetic work as well as in process design. The factor to keep in mind is that hydroxide ions often are consumed during the course of the reaction. If NaOH is not in excess during the latter part of the reaction, the availability of the PTC catalyst will drop, thus changing the reaction conditions.

An example of method 2 is the addition of a lipophilic sulfonate, such as sodium naphthalenesulfonate, or a lipophilic carbonic acid to an aqueous solution containing a quaternary ammonium compound.[18] By this procedure TBA[+] is transferred into an organic phase. If TBA[+] is to be moved into an aqueous phase, the system should be acidified with sulfuric acid. The naphthalenesulfonic acid will remain in the organic layer and TBA[+] as the hydrogen sulfate will move into the water. Unfortunately, this simple procedure does not work for all quaternary ions. The more lipophilic they are, the less easy it is to transfer them into water.

Walters has demonstrated the third method of recovery by showing that the distribution of TBA salts between an aqueous and an organic phase is strongly temperature-dependent.[19] In the hydrodimerization of acrylonitrile to adiponitrile TBA salts are used as electrolytes. When the adiponitrile is purified there is the problem of removing TBA salts dissolved in the product. This has been done effectively by cooling the product emulsion from 25°C to 0°C.

$$K = \frac{\text{wt \% of TBA in the organic phase}}{\text{wt \% of TBA in the aqueous phase}}$$

$$K_{25°C} = 1.4; \quad K_{0°C} = 0.01$$

The distribution of the organic products is not affected by the change in temperature.

In the recovery of quaternary ammonium ions the best results are obtained with TBA ions. Generally, methyltrioctyl ions are too lipophilic to reenter an aqueous phase to a practical degree.

Extractive separations

Quaternary ammonium salts may also be used in purifications. Harmful ions like cyanides or phenolates can be transferred from an aqueous waste stream into an organic phase. Valuable compounds like penicillins can be separated as TBA salts and thus recovered.

Aldehydes are purified as bisulfite complexes. $TBAHSO_3$ is easily transferred into the organic phase and the formation of bisulfite complexes of lipophilic aldehydes is rapid. Mizutani and co-workers report the purification of 3-phenoxybenzaldehyde in this manner. The impure aldehyde itself serves as the organic phase and the crystalline bisulfite adduct is easily separated from the impurities. Again TBA salts give the best results and purities of more than 99% are obtained. The purity of the aldehyde is important in the manufacture of chrysanthemic esters, well-known insecticides.[20]
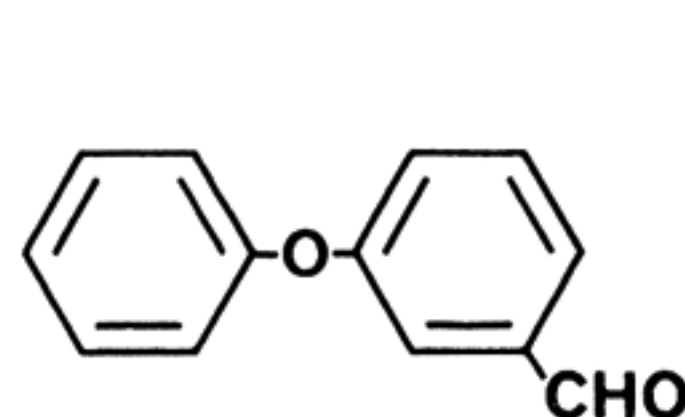
In the subsequent esterification of chrysanthemic acid with 3-phenoxybenzyl chloride, PTC is also favorably used.

Environmental aspects

In earlier days the LD_{50} value of a compound gave sufficient information about its toxicity. Today additional information, such as fish toxicity (LC_{50}), plays an important environmental role. A comparison of the LD_{50} and LC_{50} values of the two TBA salts seems to show a practical PTC example. The LD_{50} values on $TBAHSO_4$ and TBABr are both between 500 and 600mg per kilo of body weight. In the case where the salt is administered into the test animal, the impact of the counterion is low.
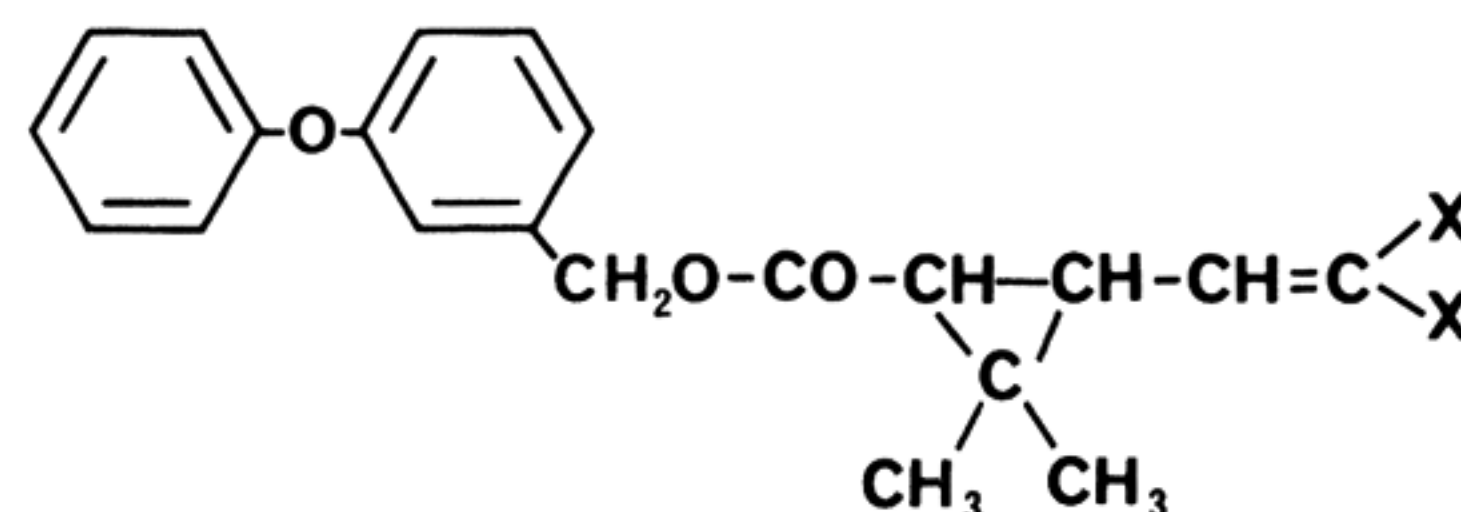
A look at the LC_{50} values gives a very different picture of the two salts. A zebrafish, generally accepted as a representative test fish, tolerates a 2.5 times higher concentration of $TBAHSO_4$. This can be attributed to the more lipophilic nature of TBABr. The values are:

$TBAHSO_4$	3370mg/l,	96 hours
TBABr	1380mg/l,	96 hours

Titration of TBA ions

An important method of titration of lipophilic cations like TBA ions is well-hidden in Brändström's "Preparative Ion-Pair Extraction".[18] The method is important because it is a simple quantitative analytical technique for quaternary ammonium ions. Other methods used to determine quaternary ammonium ions, e.g., ion-exchange to the quaternary ammonium iodide, then transfer of the iodide to an organic phase followed by treatment with mercuric acetate and titration of acetate ions with perchloric acid, gives the amount of the counterion from which the figure for TBA ions can be calculated indirectly only.

Brändström titrates in a two-phase system, water and methylene chloride. Thus, the titration itself is a practical application of PTC (what else!). The titrant is a sulfonate, potassium 3,5-di-tert-butyl-2-hydroxybenzenesulfonate, that is very lipophilic. At the beginning of the titration the amount of TBA ions in the sample is distributed between the aqueous and the organic phase. During the titration all TBA ions present in the aqueous phase move as ion pairs with the sulfonate into the organic phase. The TBA ions already present in the organic phase at the beginning of the titration, owing to the distribution, pull an equivalent amount of sulfonate ions into the organic phase. When all TBA ions are present in the organic phase, an indication that the titration end point is reached is necessary. The sulfonate with an o-hydroxy function also acts as a chelating agent for ferric ions. The chelate is greenish blue. The addition of ferric chloride to the aqueous phase gives the indication.

Experimental part

1) Titration of crystalline TBA salts

Dissolve an accurately weighed sample of about 320mg TBABr or 340mg $TBAHSO_4$ in 20ml of dichloromethane. Add 20ml of indicator solution B (see below).

Titrate under stirring with solution A (see below) until the lower dichloromethane layer gets a faint blue color. The upper aqueous layer, at this stage, will have changed from yellow to blue-green.

Calculations:

$$\text{TBABr \%} = \frac{A(322.4)(M)}{100(\text{mg TBABr})}$$

$$\text{TBAHSO}_4 \text{ \%} = \frac{A(339.5)(M)}{100(\text{mg TBAHSO}_4)}$$

A = ml of solution A
M = molarity of solution A

2. Titration of TBA salts in solution

A solution containing about 0.3g of TBABr or TBAHSO₄ is made alkaline and extracted twice with ether if contaminated with organic compounds other than the TBA ion (such as amines) and then acidified. To the sample is then added 20ml of dichloromethane and 10ml of solution B. The mixture is then titrated as in procedure 1.

Solution A: A $0.1M$ solution of potassium 3,5-di-*tert*-butyl-2-hydroxybenzenesulfonate (**I**) is prepared by dissolving 32.4g of **I** in water containing 10% acetone to a total volume of 1 liter.

I   M.W. 324.5
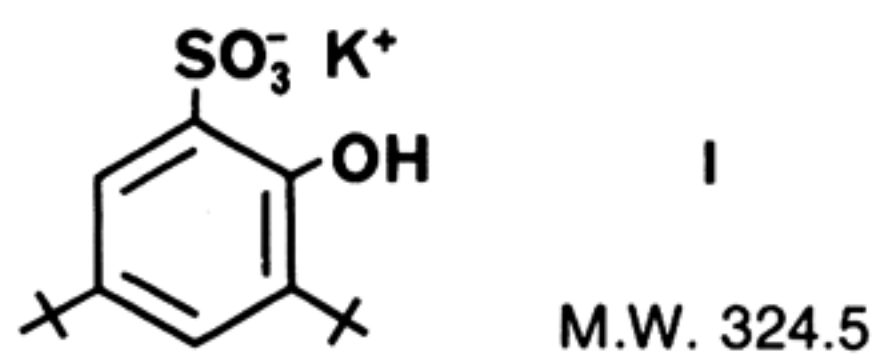
Solution B (indicator): A $0.1M$ solution of FeCl₃·6H₂O in $0.1M$ HCl is prepared by dissolving 27g of FeCl₃·6H₂O (M.W. = 270.3) in 1 liter of $0.1M$ HCl.

Procedures:

Solution A is standardized prior to use with a reference sample of TBABr or TBAHSO₄. See titration procedure 1.

Calculations:

$$\text{Molarity Solution A} = \frac{\text{mg TBABr}}{(322.4)(A)} = \frac{\text{mg TBAHSO}_4}{339.5\,(A)}$$

Accuracy of the method:

Titration of 20ml of a $0.01M$ solution of a TBA salt will give a breakpoint within 0.03ml of the sulfonate solution.

At lower concentrations of TBA ($0.001M$) there is no color in the organic phase, but the aqueous phase will change from light green to light blue. The change interval is now larger.

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