# Analysis of Residual Products in Triethylbenzylammonium Chloride by HPLC. Study of the Retention Mechanism

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## Abstract

**The control of industrial products for minimization of their impact on the environment and human health requires the development of specific analysis methods. Information provided by these methods about toxic components, by-products, and other derivatives may also be useful to reduce the possible impact of industrial products. The studied compound in this paper, triethylbenzylammonium chloride (TEBA), is mainly used in industrial synthesis. This quaternary compound and its residual products coming from quaternization reaction (benzyl chloride, benzaldehyde, and benzyl alcohol) are analyzed by HPLC. The separation is based on control of the silanophilic contribution to TEBA retention because of the quaternary nature of this compound. The effect of the three buffers (sodium acetate, ammonium acetate, and sodium formate) and their concentrations in the chromatographic behavior of the quaternary compound is examined. The buffer cation and anion regulate TEBA retention. Also, the concentration of the quaternary compound is another parameter that had influence in some aspects of its chromatographic behavior (e.g., retention and symmetry). The proposed method is applied to TEBA synthesis along, with the formation and removal of impurities with the results compared with those obtained for the quaternary compound benzalkonium chloride.**

## Introduction

Triethylbenzylammonium chloride (TEBA) is a quaternary ammonium compound, considered as a cationic surfactant, which possesses numerous applications in the field of industrial chemistry. One of its principal uses is as a catalyst for reactions in aqueous–organic two-phase solvent systems, that is, as phase transfer catalyst (1) in a wide range of reactions (2–4). In addition, TEBA is also effective for other applications: in electrochemistry (5), in photochemistry (6), as booster accelerator for vulcanization of natural rubber (7) and as agent decontaminant (8).

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In the analytical literature, TEBA was employed as an analytical reagent as well as the object of the analysis. Several techniques for the analysis of TEBA, such as NMR (9), thin-layer chromatography (10), and ion selective electrode in titrimetric determination with sodium tetraphenylborate as titrant, have been applied (11). Concerning the use of TEBA as an analytical reagent, TEBA was employed for spectrophotometric and chromatographic determination of metals (12,13) and as an absorbing counter ion for the determination of alkyl quaternary compound by liquid chromatography with indirect photometric detection (14).

High-performance liquid chromatography (HPLC) (14,15) and capillary electrophoresis (CE) (16–19) have been applied for the separation of TEBA from other quaternary ammonium compounds but not of its possible impurities (benzyl chloride, benzaldehyde, and benzyl alcohol). To our knowledge, this paper is the first to deal with the analysis of its residual products.

The chromatographic behavior of quaternary compounds and other basic drug compounds containing an amine group in the molecule, such as peptides, amines, and dibenzocrown-ethers, show special characteristics: high retention on the column, tailed and asymmetric peaks, poor resolution, and dependence of retention on injected sample size. These undesirable chemical properties create a challenging analytical problem. Bij et al. (20) proposed a dual retention mechanism of hydrophobic and hydrophilic interactions, the latter because of the interactions with the silanol groups at the surface of the silica-based stationary phase.

The adopted solutions in the literature are focused on the improvement of the stationary phase (encapping, base-deactivated column, etc.) and modification of the mobile phase using buffer, amine modifiers, ion-pair reagent (20–29), and divalent metals (30). These modifications block stationary phase silanol groups from silanophilic contribution, reducing or eliminating this undesirable effect. Several amines (triethylamine, diisopropylamine, and ethanolamines) have been employed as modifiers for removing the dependence of TEBA on injected sample load (20).

TEBA is synthesized in water via the quaternization reaction of triethylamine and benzyl chloride to 40% or more. Benzyl chloride is considered as a toxic product (inhalation-human, lowest toxic concentration = 16 ppm/1M, oral-rat lethal dose 50 = 1231 mg/kg, oral-rat lethal concentration 50 = 150 ppm/2 h) (31). Concurrent formation of the quaternary compound and a secondary reaction involving nucleophilic substitution of benzyl chloride to form benzyl alcohol and triethylammonium chloride may produce by-products at percentage levels (Figure 1). In a previous paper (32), a method for the determination of residual products (benzyl chloride, benzyl alcohol, and benzaldehyde) in a long-chain quaternary compound, benzalkonium chloride (BAK), was established with application during synthesis. The objective of the present paper was the determination of residual products in a short-chain quaternary compound, triethylbenzylammonium chloride, with application during synthesis. The control of TEBA chromatographic behavior is indispensable to achieve the separation of nonionic (residual products) and quaternary compounds. Besides, the retention mechanism of TEBA must be discussed because it is responsible for its chromatographic behavior.

The United Nations Environment Program (UNEP) (33) includes the Cleaner Production Program, which recommends environmental prevention of process, products, and services. The control of raw material and by-products in an industrial product such as TEBA is one of the approaches to reduce its impact on the environment, health, and security.

## Experimental

### Apparatus and reagents

The HPLC system, a Hitachi-Merck (Tokyo, Japan), consisted of a gradient control L-500, pump 655A-12, variable wavelength detector 655A, and chromato-integrator D-2000 (Merck, Darmstadt, Germany). The analytical column was LiChrosorb CN (250- × 4.0-mm i.d., 5-µm particle size) (Merck). The solvents and reagents used were acetonitrile, water, benzyl chloride, benzaldehyde, and benzyltriethylammonium chloride and were supplied by Merck. Sodium acetate trihydrate, sodium formate, and ammonium acetate were from Scharlau (Barcelona, Spain), and benzyl alcohol was from Panreac (Barcelona, Spain). An eluent was prepared with 0.035M $CH_3COONa$; glacial acetic acid was used to adjust the pH to 7 and was filtered through 0.2-µm filters (MSI Separations, Westboro, MA). The reagents used for synthesis were purchased from commercial sources.

### Preparation of standards and TEBA samples

Stock solutions of benzyl chloride, benzaldehyde, and benzyl alcohol (2 to 3 mg/mL) were prepared in acetonitrile. Working solutions of these were appropriately diluted using mobile phase. The TEBA solution was diluted in mobile phase to a concentration of 10 and 2 mg/mL on the anhydrous basis for quantitation of residual products and benzyl alcohol, respectively, and 100 mg/L for TEBA.

### Preparation of TEBA

A mixture of triethylamine (110 g or 1.09 mol), benzyl chloride (138 g or 1.09 mol), and 254 mL of water was warmed up to 50°C. When this temperature was reached, heating was stopped and the temperature rose up to 80°C because of exothermic reaction. In the first step, the mixture was not homogeneous; when the homogeneity was achieved, several samplings were done until the benzyl chloride was consumed. It was verified (different injections in several days) that the reaction stopped when the samples were diluted to concentration for analysis.

### Chromatographic conditions

Analyses were performed on the cyano column using a mobile phase consisting of 55% sodium acetate 0.035–0.025M at pH 7 and 45% acetonitrile. The flow rate was maintained at 1.5 mL/min. The injection volume was 20 µL. Benzyl chloride and benzaldehyde were detected at 220 nm and TEBA and benzyl alcohol at 210 nm. Retention factor values were evaluated from the buffer blank.

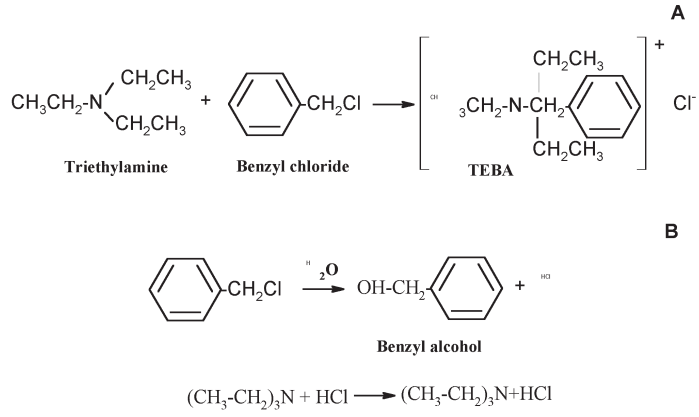


**Figure 1.** Reaction of TEBA formation (A) and secondary reaction of benzyl chloride to form benzyl alcohol (B)

## Results and Discussion

### Chromatographic separation: Influence of acetonitrile, mobile phase pH, and nature and concentration of the buffer

In a previous study, the separation of benzyl chloride, benzyl alcohol, and benzaldehyde in BAK with isocratic and gradient elution was achieved (32). The method could be applied in TEBA samples because two quaternary compounds have common residual products. But this method did not permit the separation of benzyl chloride and TEBA. The following mobile phase parameters were examined: proportion of acetonitrile, aqueous-phase pH, nature and concentration of buffer, and concentration of quaternary.

The nature and concentration of the buffer (pH 5, Na $CH_3COO$) and pH were held constant, according to the reference method (32), whereas the proportion of acetonitrile was modified. The plot of retention factor logarithm of each compound versus acetonitrile content is shown in Figure 2. Benzyl chloride, benzaldehyde, and benzyl alcohol present a negative linear relationship (log *K* vs. % acetonitrile) because of decreasing polarity of the mobile phase.

Unlike long-chained quaternary compounds, the increased acetonitrile content has minimal effect on TEBA retention. Interaction between the alkyl chain and the stationary phase cyano-propyl group was minimized using a short-chain quaternary compound.

TEBA retention was greater under neutral than acidic conditions (Figure 2). Under the first conditions, the quaternary compound had a greater interaction with the stationary phase. Possibly because under neutral conditions, a smaller competition between the mobile phase and the quaternary compound for the stationary phase takes place than under acid conditions.

Changes of pH have no effect on the retention of benzyl alcohol, benzyl chloride, and benzaldehyde. The best conditions for separation of residual products were obtained at 45% acetonitrile. But with this acetonitrile percentage and at pH 7, TEBA was not separated from benzyl chloride and was also not separated at pH 5 from benzaldehyde.

The influence of buffer nature and concentration on the separation was tested with sodium acetate and two other buffers (ammonium acetate and sodium formate), which have (in common with the former) the sodium cation in the case of sodium formate and the acetate anion in the case of ammonium acetate. This strategy allows independent study of the cation and anion effects on the separation of the quaternary compound.

The effect of three tested buffers on the TEBA capacity factor for a quaternary concentration of 10 mg/mL and pH 7 is shown in Figure 3. A concentration increase in any one of the tested buffers causes a decrease in TEBA retention, which may be justified by a silanophilic and hydrophobic mechanism. TEBA retention could be because of the two types of interactions with the stationary phase, those produced with the siloxane groups by hydrophobic mechanism and those produced with the silanol groups by silanophilic mechanism. The addition of buffer in the mobile phase that competes with the quaternary compound for the silanol groups could reduce the silanophilic interactions of TEBA with the stationary phase. Thus, a higher concentration of buffer makes the retention fall up to the limit of hydrophobic interactions (20,34).

The role that the buffer anion plays in TEBA retention was examined with two salts, which possess a common cation (see sodium acetate vs. sodium formate in Figure 3). In the buffer concentration range study, the quaternary compound was more retained with the acetate ion in the mobile phase than with formate. This fact could be explained as a result of the greater interaction of the quaternary compound with the formate counter ion than acetate. Thus, the silanophilic interactions of TEBA with the stationary phase were smaller when the mobile phase contained the formate ion than the acetate ion.

Also under the described conditions in Figure 3, the influence of buffer cation on TEBA retention was assessed with sodium acetate and ammonium acetate, which have a common anion. The obtained values indicate that the quaternary compound was more highly retained with the sodium ion in the mobile phase than with the ammonium ion. Possibly, it was because of the smaller competition of sodium with the quaternary compound for the silanol groups of the stationary phase than the ammonium ion. This latter was a better blocking agent of silanol groups, and thus the TEBA silanophilic interactions were reduced. The results shown in Figure 3 also suggest that the cation had greater influence than the anion on the retention of the quaternary compound for the studied salts because a greater retention was observed with sodium formate than with ammonium acetate

A good selectivity of TEBA with residual products was

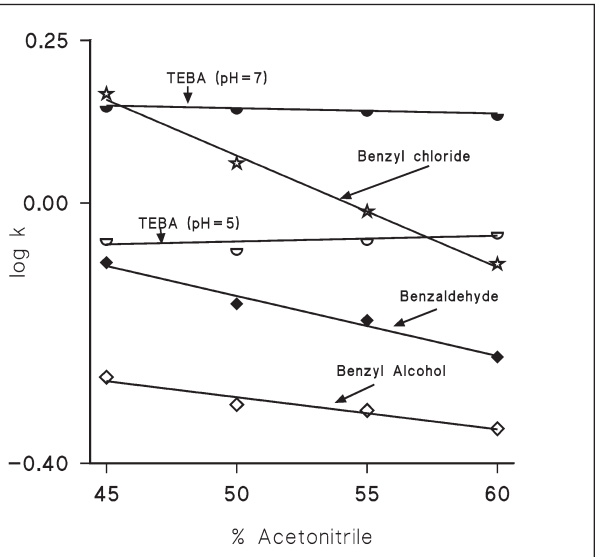


**Figure 2.** Influence of acetonitrile and mobile phase pH on the retention of studied compounds.

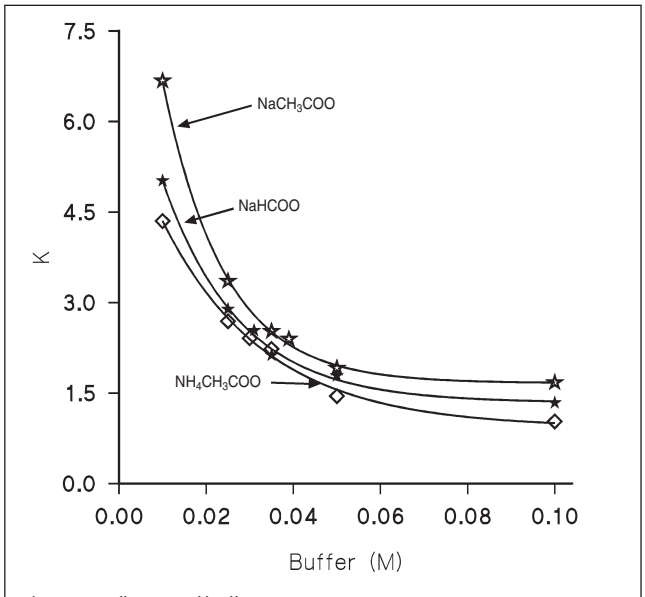


**Figure 3.** Influence of buffer concentration on TEBA retention.

achieved for values of approximately 2.6 of the TEBA capacity factor at a concentration of 0.025M $NH4CH_3COO$, 0.030M NaHCOO, and 0.035M $NaCH_3COO$. The buffer concentration had no effect on retention of residual products, but when buffer concentration increases, resolution improved so much for the quaternary compound as for residual products. Finally, the adopted separation conditions were 55% of 0.035M sodium acetate, pH = 7, and 45% of acetonitrile.

Because of the relevance of silanophilic interactions in the separation and because the silanol groups were the residual components of the stationary phase, two columns of different batches and different lifetime were tested. In order to obtain a 2.6 TEBA capacity factor, the buffer concentration was 0.035M for the column used in the study of separation parameters. A buffer concentration of 0.025M was enough for a second column at the beginning of its lifetime.

**Sample load effect and retention mechanism of TEBA**

In addition to the separation factors studied, the influence of TEBA concentration on its capacity factor was observed. In Figure 4, an increase in the TEBA concentration from 0.44mM (close to quaternary quantitation concentration) to 44mM (TEBA concentration for quantitation of residuals products) produces a decrease of its capacity factor for the optimized three conditions containing salts.

In the concentration range studied, variation of capacity factor had presented some differences, depending on the buffer employed. The variation was practically equal with sodium acetate and formate in the mobile phase except for the lower levels of concentration. If the mobile phase contained ammonium acetate, the capacity factor variation was lower than for the other buffers. Hence, it can be conclude that the cation plays a determining role in this effect. The ammonium buffer cation exhibited smaller retention variation between two TEBA concentrations (0.44mM and 44mM) but did not eliminate it.

The influence of TEBA concentration versus peak symmetry was also observed. The peak of TEBA shows asymmetry at high concentrations (ca. 44mM). If TEBA concentration decreases, the asymmetry also decreases, and for a concentration of 0.44mM, the peak was symmetric (Figure 5).

In the analytical literature, sample load effect was already described for TEBA and other quaternary ammonium salts using different additives in the mobile phase (20,35–38). Bij et al. (20) explained the retention dependence of sample load by an interaction of the quaternary compounds with the silanol groups of the stationary phase. Concerning peak symmetry, several authors (36–39) had examined the effect of steric factors, $pK_a$, and sample load of basic solutes on silanophilic interactions by symmetry of peak measuring. Ebble et al. (40) concluded that the peak asymmetry observed with a sample size increase was because of the overloading conditions for silanol groups in the stationary phase. Considering the results obtained along with conclusions presented in the previously mentioned reference, asymmetry dependence on sample load in TEBA may be explained as follows. A TEBA concentration of 100 µg/mL or sample load of 2 µg onto the column was the maximum sample that interacts with silanol groups and produces a symmetrical peak. When the sample load increases, only an amount (2 µg) interacts with the silanol group, and the remainder (without silanophilic interaction) elutes with less retention. The result was non-Gaussian distribution of the chromatographic peak (Figure 5).

**Linearity and precision**

Peak heights were linear with relation to benzyl chloride, benzyl alcohol, and benzaldehyde concentrations over the 0.4–100, 0.4–90, and 0.7–13 µg/mL range (20 µL injection volume), respectively. For TEBA, a linear dependence of peak area on a concentration over the 1–150 µg/mL range was tested. The correlation coefficients > 0.9990 were obtained. The

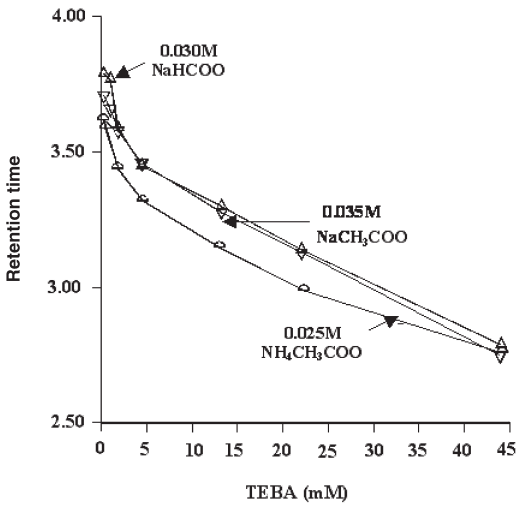


**Figure 4.** Influence of TEBA concentration on TEBA retention.

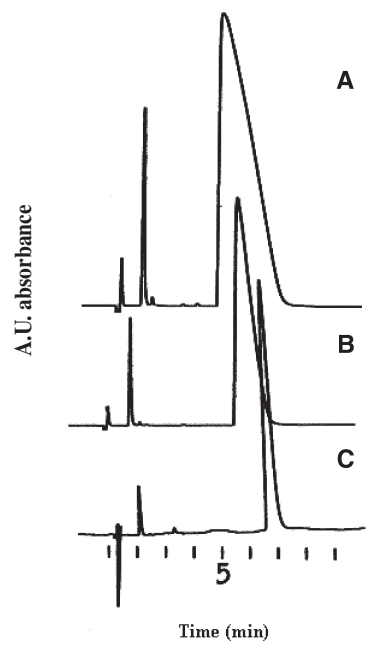


**Figure 5.** Dependence of TEBA peak symmetry on its concentration. Chromatogram of TEBA at different concentrations of injected sample: 9500 µg/mL (A), 1900 µg/mL (B), and 91 µg/mL (C).

relative standard deviation (RSD) of TEBA and benzyl alcohol, for 10 repetitions, was 0.8% at 81 µg/mL and 0.3% at 68 µg/mL. The RSD of TEBA retention time was 0.7% at 81 µg/mL.

The quantitation of residual products (benzyl chloride and benzaldehyde) was performed at 220 nm wavelength and sample concentration of 10 mg/mL on anhydrous basis. Benzyl alcohol and TEBA were determined at 210 nm and sample concentration of 2 mg/mL and 200 µg/mL on anhydrous basis.

**Application of the method in TEBA synthesis**

Under different conditions, TEBA synthesis was monitored using the proposed method intended for control of residual products in order to achieve its removal or reduction (Figure 6).

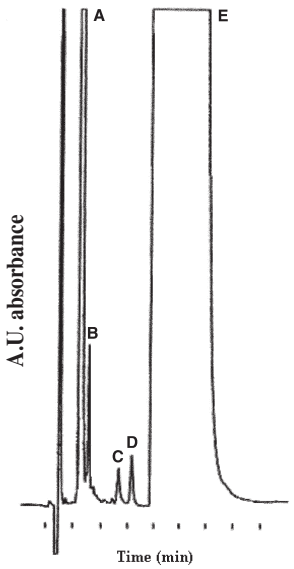


**Figure 6.** Chromatogram of TEBA during synthesis of: benzyl alcohol (A), benzaldehyde (B), benzyl chloride (C), impurity not identified (D), and TEBA (E).

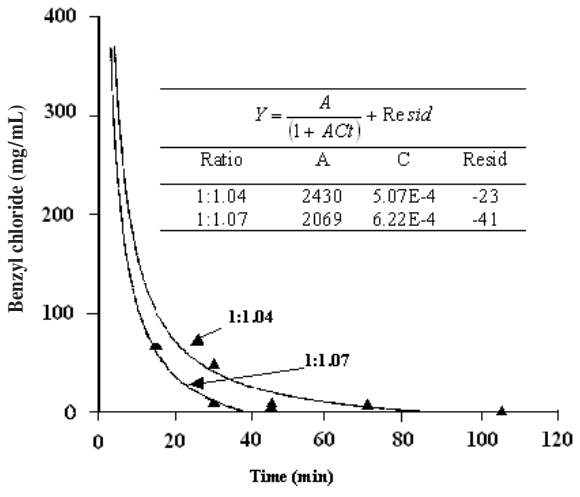


**Figure 7.** Influence of triethylamine excess on the removal of benzyl chloride during the synthesis of TEBA in 50% in water.

Some of the studied parameters in the patents referring to TEBA synthesis were benzyl chloride–triethylamine molar ratio and the reaction solvent. Organic solvents (2,41,42) or water (43) and equimolar molar ratio (42) or an excess of triethylamine (2,41) have been used. In this work, TEBA synthesis to 50% in water at two different molar ratios of benzyl chloride to triethylamine (1:1.04 and 1:1.07) was carried out (Figure 7). The residual products (benzyl chloride, benzyl alcohol, and benzaldehyde) in TEBA were followed during the last step of the synthesis when the reaction mixture was homogeneous. The removal of benzyl chloride was faster with an increase in excess amine, an effect already observed in the BAK synthesis (32). Benzyl chloride was not detected at a molar ratio of 1:1.07 after 45 min, and measured values for two syntheses may be adjusted to a second-order kinetic equation.

Concerning benzyl alcohol and benzaldehyde, practically constant values were encountered at percent levels (1.4% molar ratio for 1:1.04 and 1.2% for 1:1.07) and part-per-million levels (300 mg/L), respectively, during the following kinetic reaction of benzyl chloride. In addition, TEBA was quantitated, obtaining values of 47.4% for 1:1.07 molar relation. Therefore, benzyl alcohol was formatted simultaneously with the quaternary compound in the first step of the reaction, and this secondary reaction had a greater relevance than BAK synthesis (32).

## Conclusion

The proposed method allowed the determination of TEBA, benzyl chloride, benzyl alcohol, and benzaldehyde in a formulation of TEBA to 50% in water.

The cation and anion of tested buffer, which is contained in mobile phase, had an influence on the retention of the quaternary compound. Under tested conditions, the cation had greater influence than the anion. In addition, injected amounts of TEBA had an influence on its retention and peak symmetry. Therefore, control of the silanophilic mechanism was decisive for the separation.

Application of the method in TEBA synthesis permitted residual benzyl chloride removal, and an excess of triethylamine decreased removal time. Benzyl alcohol, formed as a by-product in water, was quantitated at percentage levels.

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