Analysis of Residual Products in Benzyl Chloride Used for the Industrial Synthesis of Quaternary Compounds by Liquid Chromatography with Diode-Array Detection

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Abstract

In industrial and pharmaceutical processes, the study of residual products becomes essential to guarantee the quality of compounds and to eliminate or minimize toxic residual products. Knowledge about the origin of impurities (raw materials, processes, the contamination of industrial plants, etc.) is necessary in preventive treatment and in the control of a product's lifecycle. Benzyl chloride is used as raw material to synthesize several quaternary ammonium compounds, such as benzalkonium chloride, which may have pharmaceutical applications. Benzaldehyde, benzyl alcohol, toluene, chloro derivatives of toluene, and dibenzyl ether are compounds that may be found as impurities in technical benzyl chloride. We proposed a high-performance liquid chromatography method for the separation of these compounds, testing two stationary phases with different dimensions and particle sizes, with the application of photodiode array-detection. The linearity for four possible impurities (benzaldehyde, toluene, α,α-dichlorotoluene, and 2-chlorotoluene) ranged from 0.1 to 10 µg/mL, limits of detection from 11 to 34 ng/mL, and repeatability from 1% to 2.9% for a 0.3–1.2 µg/mL concentration range. The method was applied to samples of technical benzyl chloride, and α,α-dichlorotoluene and benzaldehyde were identified by spectral analysis and quantitated. The selection of benzyl chloride with lower levels of impurities is important to guarantee the reduction of residual products in further syntheses.
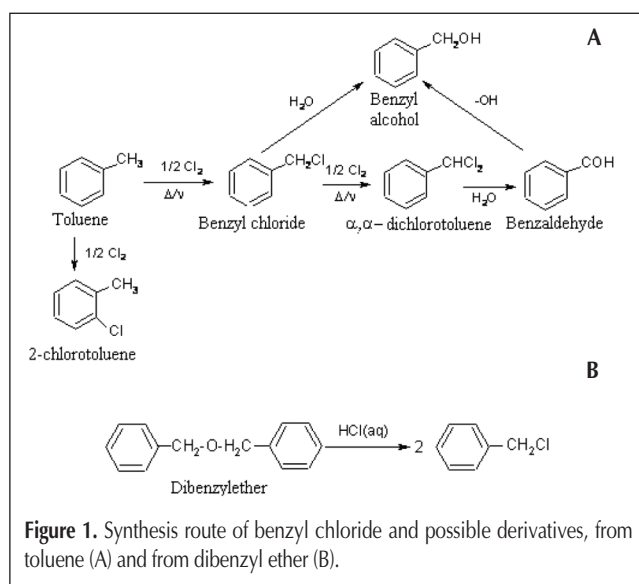
Introduction

Benzyl chloride is a volatile organic compound that is considered toxic for human health and the environment, according to Directive 76/464/CEE (1). It is used as a quaternizant agent in synthesis of cationic surfactants and betaines (2,3). Benzyl chloride is synthesized from chlorination of toluene by means of light, heat, or catalysis (4). In this synthesis route, other compounds may be synthesized from toluene (2-chlorotoluene and α,α-dichlorotoluene) or originated from further reactions (benzaldehyde and benzyl alcohol), as is shown in Figure 1A. Another

alternative synthesis of benzyl chloride is acid hydrolysis of dibenzyl ether (5) (Figure 1B).

The analysis of technical benzyl chloride impurities is described in two papers and by one patent under various separation conditions using gas chromatography (GC) (6–8). Rao and Subbaram have determined α,α-dichlorotoluene as a principal impurity at < 1% levels (6). In addition to α,α-dichlorotoluene, Babina and Kvartalnova have detected toluene and chlorotoluene using a glass column to avoid the corrosion of metallic parts (7). Galazka has proposed two methods, one for benzyl chloride and another for benzyl alcohol using a column packed with two materials. Benzaldehyde, toluene, α,α-dichlorotoluene, and chlorotoluene were separated from technical benzyl chloride and dichlorotoluene, dibenzyl ether, and benzyl benzoate from benzyl alcohol (8).

In addition, benzyl chloride as a residual product may be analyzed in conjunction with α,α-dichlorotoluene in other technical products as benzaldehyde by GC (9) and normal-phase high-performance liquid chromatography (HPLC) (10). These two compounds were detected in 2-chlorobenzaldehyde using GC coupled with mass spectrometry (MS) (11). Also, benzyl chlo-

Figure 1. Synthesis route of benzyl chloride and possible derivatives, from toluene (A) and from dibenzyl ether (B).

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ride and amines are determined as toxic impurities of pharmaceutical process by solid-phase microextraction–GC (12). On the order hand, mixtures of toluene, benzyl chloride, α,α-dichlorotoluene, and benzitrichloride were separated without any reference to real samples by GC (13).

In environmental analysis, benzyl chloride is separated from other pollutants in atmospheric matrices by GC–MS, GC, and HPLC. Benzyl chloride is analyzed in the air by capillary GC (14) and, together with other compounds of interest to this study, toluene (15) and chlorotoluene (16), by means of GC–MS. These compounds have been quantitated in aqueous matrices (tap water and river water) by reversed-phase HPLC (17), and in natural waters, benzyl chloride is determined with monochlorotoluenes by GC (18). Martínez et al. (1) have analyzed 40 volatile organic compounds from different chemical groups (such as benzyl chloride and monochlorotoluenes) in surface rivers, effluents, and coastal waters by GC–MS. In industrial emissions and chemical waste disposal sites, benzyl chloride is determined with dichlorotoluene and chlorotoluene (19) by GC–MS and with chlorobenzene, naphthalene, and biphenyl in waste gas by HPLC (20). In wastewater from factories for benzyl chloride production, α,α-dichlorotoluene, benzyl chloride, and benzitrichloride were quantitated by means of capillary GC–MS after the extraction with activated carbon fiber in solid-phase microextraction (21).

HPLC studies for retention prediction and structure–retention relationships have separated analyte series, such as benzyl chloride, benzyl alcohol, toluene, chlorotoluene, and benzaldehyde with different stationary phases, and with methanol–water and acetonitrile–water as mobile phases (22–23). Also, Nesterenko et al. (24) separated benzaldehyde, benzyl alcohol, and benzyl chloride (among others) in normal-phase to evaluate a novel phase stationary and to compare it with conventional phases (silica and alumina).

Ocular and respiratory irritation has been used to assess for chlorinated compounds as benzyl chloride, mono-, and dichlorotoluene (25–28). The irritability potential increases when hydrogen atoms are substituted by halogen atoms in toluene structures with halogen atoms (16). Also, the toxicity of toluene and monochlorotoluene in water (29–30), as well as the carcino-

genicity and mutagenicity of benzyl chloride and α,α-dichlorotoluene, has been studied (31–32).

United Nations Environment Programme (33) includes a Cleaner Production Programme that recommends environmental prevention of processes, products, and services. In previous papers, we proposed various methods for the analysis of residual products formed during the synthesis of quaternary compounds and the removal of benzyl chloride (2,3). Nevertheless, another important aspect remains the analysis of residual products from quaternizing agents.

We have opted for the HPLC method for the analysis of benzyl chloride that is used to synthesize quaternary compounds because we needed a set of methods for the routine analysis of their production cycle, from raw materials to final products. The composition of alkyl chains of quaternary compounds may be analyzed by GC but with a previous treatment (Hoffman degradation or other treatments with debenzylation) (34). HPLC methods in reversed-phase with photodiode-array detection allow analysis of the alkyl chain and its impurities without pretreatment. The technique chosen for the analysis of benzyl chloride is the same as that used for quaternary compounds because the use of a single technique (HPLC) within the whole process, instead of using different ones (GC, HPLC), represents great advantages, such as saving both time and chemicals and requiring less personnel training. Besides, HPLC is more readily available in industrial control laboratories.
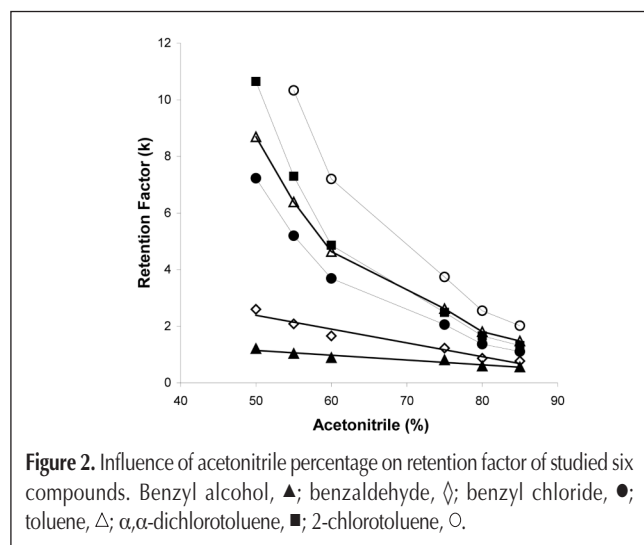
As mentioned earlier in the literature review, benzyl chloride and potential impurities have been separated in normal- and reversed-phase using several types of stationary phases and mobile phases. Also, HPLC was a suitable technique for the determination of these analytes in technical products (benzaldehyde) and in environmental matrices (benzyl chloride and chlorotoluene). The purpose of this work is to develop a routine and direct HPLC method for the determination of impurities in technical benzyl chloride, offering low detection limits, short analysis time, and compatibility with HPLC methods of quaternary compounds. The use of photodiode array detection allows the verification of the identity of impurities by comparison with standards.

Experimental

Apparatus and reagents

The HPLC system, a Waters (Milford, MA) chromatograph, consisted of a 600 quaternary gradient system, 996 photodiode array detector, Rheodyne injector, and Millenium 32 software. The tested analytical C_{18} columns were Symmetry 3.5 µm particle size, (150 × 4.6 mm i.d.) with a precolumn 5 µm (20 mm × 3.9 mm i.d.) (Waters) and LiChrospher, 5 µm particle size (250 × 4.0 mm i.d.) (Merck, Darmstadt, Germany).

The following solvents and reagents were used as mobile phase: water obtained from Direct-Q 3 (Millipore, Milford, MA) and acetonitrile (grade gradient) and triethylamine from Merck, sodium acetate from BDH (Poole, England), and phosphoric acid (85%) and acetic acid from Panreac (Barcelona, Spain). An aqueous eluent containing 0.15% of triethylamine was adjusted

Figure 2. Influence of acetonitrile percentage on retention factor of studied six compounds. Benzyl alcohol, ▲; benzaldehyde, ◊; benzyl chloride, ●; toluene, △; α,α-dichlorotoluene, ■; 2-chlorotoluene, ○.

at pH = 7 with phosphoric acid and filtered through 0.2 μm filters (MSI Separations, Westborough, MA).

The reagents: benzyl alcohol (99.8%), benzaldehyde (99.5%), α,α-dichlorotoluene (98%), and 2-chlorobenzyl chloride (> 99%) were supplied by Aldrich (St. Louis, MO); 2-chlorotoluene from Merck; dibenzyl ether (99%) from Avocado (Lancashire, England), and toluene from Panreac. Technical benzyl chloride was obtained from different commercial sources.

Preparation of standards and technical benzyl chloride

Stock solutions of benzyl alcohol, benzyl chloride, benzaldehyde, toluene, α,α-dichlorotoluene, and 2-chlorotoluene were prepared at a concentration of 3 mg/mL in acetonitrile. A mixture of these compounds was made up by suitable dilution using mobile phase or acetonitrile according to tested conditions. Technical benzyl chloride was diluted into the mobile phase to a concentration of 3 mg/mL.

Chromatographic conditions

Chromatographic conditions were performed on a Symmetry C_{18} column with precolumn using as mobile phase 55% of acetonitrile and 45% of aqueous eluent at flow-rate of 1.0 mL/min. The injection volume was 20 μL and detection was carried out at maximum of absorption of each compound in interval 190–202 nm.

Results and Discussion

Chromatographic separation

The separation of six structurally similar compounds: toluene, chloro derivatives of toluene (benzyl chloride, α,α-dichlorotoluene, 2-chlorotoluene) benzaldehyde, and benzyl alcohol, was tried on a C_{18} column with acetonitrile–water (0.15% triethylamine neutralized to pH = 7 with phosphoric acid) systems.

Initially, a column (Lichrospher C_{18}) with standard dimensions (5 μm particle size, 250 × 4 mm i.d.) and different percentages of acetonitrile were tested. The results are presented in Figure 2, and they show an increase of retention according to the increase of mobile phase polarity, obtaining a negative lineal relation to benzyl alcohol and benzaldehyde. The retention of mono- and dichlorotoluenes and toluene is hardly affected by the decrease in organic solvent, producing a remarkable increase in retention from 60% acetonitrile. A critical separation of α,α-dichlorotoluene and toluene is observed. Two isocratic conditions with different elution order for the six compounds separation are achieved (at 85% acetonitrile in 5 min and 55% acetonitrile in 18 min). The latter conditions were more suitable for the application of benzyl chloride samples because the selectivity between benzyl chloride and benzaldehyde and benzyl chloride and toluene or α,α-dichlorotoluene is greater.

An improvement of separation concerning parameters of retention time, resolution, and peak symmetry was attempted

using a second column (Symmetry C_{18}) of shorter length (150 mm) and smaller particle size (3.5 μm). It is expected that by decreasing column length and maintaining a constant flow rate, a reduction of time analysis may be reached. Another consequence, the diminution of the resolution could be compensated by decreasing particle size, which would cause an increase of the resolution. Using 55% acetonitrile, the analysis time decreases 4 min, due to a decrease in retention factor for all compounds. The resolution and symmetry, as it is shown in Figure 3, did not suffer a substantial change in studied compounds. The standard solution was prepared in acetonitrile because of its low solubility in water. But the solution in mobile phase from stock solutions was possible and the change of sample solvent (acetonitrile by 55% acetonitrile–45% aqueous eluent) in injected samples was the decisive variable in the improvement of these two parameters. Acetonitrile is a stronger solvent with lower viscosity than mobile phase. These characteristics can affect peak shape (35). Stronger solvent than mobile phase can interfere with the adsorption of the sample at column head, causing broadening of
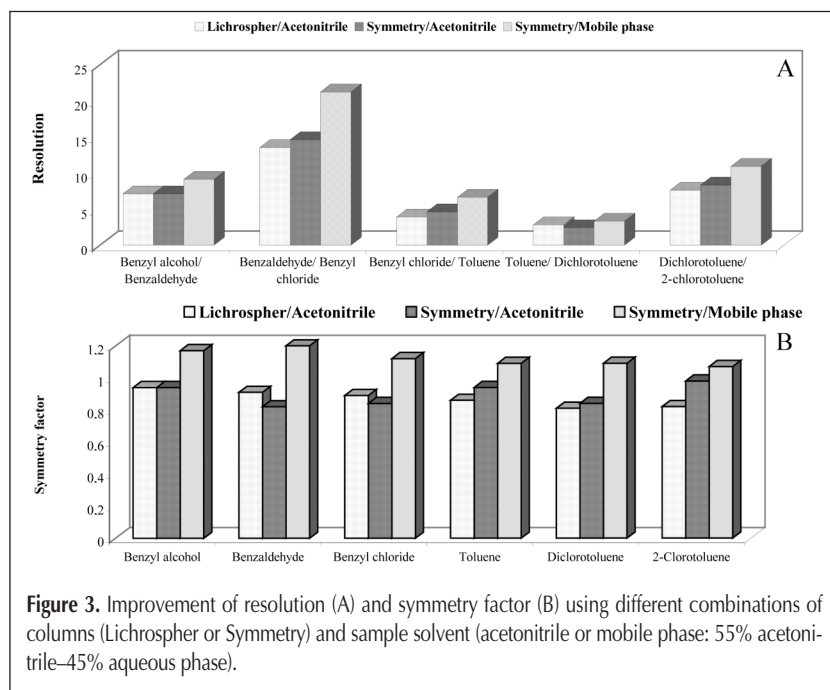
Figure 3. Improvement of resolution (A) and symmetry factor (B) using different combinations of columns (Lichrospher or Symmetry) and sample solvent (acetonitrile or mobile phase: 55% acetonitrile–45% aqueous phase).
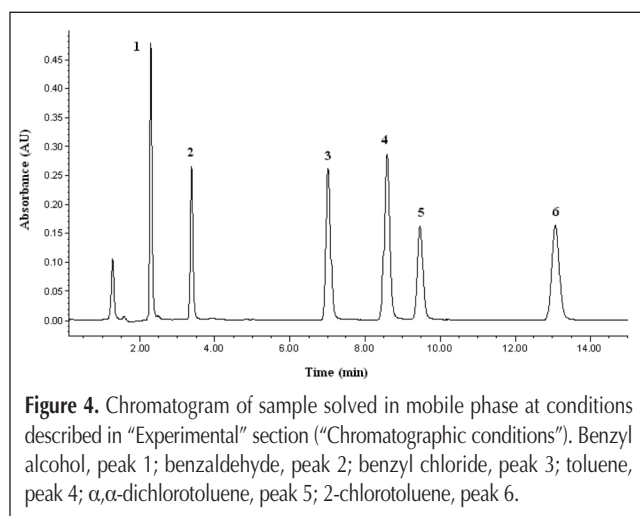
Figure 4. Chromatogram of sample solved in mobile phase at conditions described in "Experimental" section ("Chromatographic conditions"). Benzyl alcohol, peak 1; benzaldehyde, peak 2; benzyl chloride, peak 3; toluene, peak 4; α,α-dichlorotoluene, peak 5; 2-chlorotoluene, peak 6.

the peak and consequently a decrease of resolution. Different viscosities between mobile phase and sample solvent can produce peak distortions (fronting or tailing), which can be measured by a symmetry factor. In this case, acetonitrile is less viscous than mobile phase and the distortion was observed in front of peak; as a result the symmetry factor less than 1. Figure 4 shows the separation of six compounds in less than 15 min with a symmetry factor approximately 1 and resolution 5, except for toluene and α,α-dichlorotoluene.

Quantitative and spectral analysis

Linearity and precision for four studied compounds (benzaldehyde, α,α-dichlorotoluene, toluene, and 2-chlorotoluene)
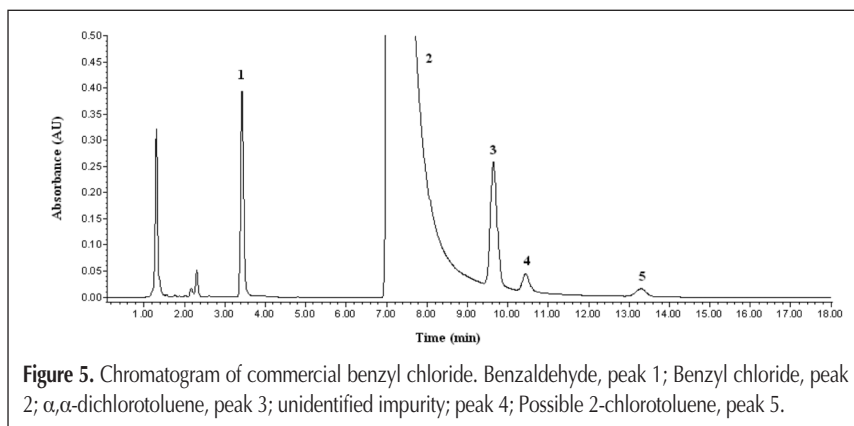

Figure 5. Chromatogram of commercial benzyl chloride. Benzaldehyde, peak 1; Benzyl chloride, peak 2; α,α-dichlorotoluene, peak 3; unidentified impurity; peak 4; Possible 2-chlorotoluene, peak 5.

at concentrations that are present in the samples were studied. Detection and quantitation limits based on Miller and Miller (36) was also obtained (Table I). The detection limits are lower than those obtained for others HPLC methods without preconcentration reported in literature. Lehotay and Hromuláková (17) obtained a detection limit of 2.5 ppm for chlorotoluene in isocratic elution and 285 ppb in gradient elution with a methanol–water as mobile phase, and detection at 220 nm.

The precision evaluated at one concentration of benzaldehyde, α,α-dichlorotoluene, and 2-chlorotoluene, for 10 repetitions, was 2.9% at 0.3 µg/mL and 1.4% at 1.2 µg/mL, and 1.0% at 0.6 µg/mL, respectively.

Initially, the chromatogram is gathered in wavelength interval 190–400 nm for the identification of the compounds. The first step is identification by retention time; then, by applying a spectral contrast technique (37) (incorporated in the Millenium 32 software), peak purity, or peak spectral homogeneity is assessed to look for the presence of the other spectrally different components into chromatographic peak. Finally, again by means of the spectral contrast technique, the sample peak is compared against library created from standard spectra at similar concentration level of samples for spectral identification. If peak purity is obtained and the identification against standard is positive. Two maxima were found for all the compounds, the former in the range 190–202 nm and the later in the range 205–250 nm. A relative absorption maximum for each analyte was in the narrow range of (190–202 nm) and therefore this was chosen for the quantitation.

Application to samples of technical benzyl chloride

Five samples of technical benzyl chloride of different commercial sources were analyzed. In these samples, toluene was not detected, and benzaldehyde and α,α-dichlorotoluene were identify as impurities by retention time and spectral identification with peak purity. Also, 2-chlorotoluene is found by using retention time criterion in four samples. Even so, in three samples the peak has not passed the criteria of purity and, in one sample, this peak has not passed the criteria for spectra library identification. Consequently, quantitation of this peak in these samples was not possible. Possibly, they could contain a mixture of isomers (2-,3- and 4-chlorotoluene) (Table II).

Because unidentified impurities were found in technical benzyl chloride (Figure 5) the capacity of the method for the separation and other related compounds was tested. An isomer of α,α-dichlorotoluene, 2-chlorobenzyl chloride, may be separated between α,α-

Table I. Linear Equation, Correlation Coefficient, Detection Limits, and Quantitation Limit of Impurities of Benzyl Chloride ($n = 15$)

Compound	$y = a + bx$	R^2	Concentration range (µg/mL)	Detection limit (ng/mL)	Quantitation limit (ng/mL)
Benzaldehyde	$a \pm S_a = 3245 \pm 1528$ $b \pm S_b = 39563 \pm 276$	0.9994	0.1–8.7	34	110
Toluene	$a \pm S_a = 7861 \pm 2935$ $b \pm S_b = 48865 \pm 487$	0.9987	0.5–9.4	11	36
α,α-Dichloro-toluene	$a \pm S_a = 1318 \pm 736$ $b \pm S_b = 24898 \pm 130$	0.9996	0.1–8.9	28	94
2-Chloro-toluene	$a \pm S_a = 661 \pm 859$ $b \pm S_b = 30297 \pm 149$	0.9998	0.5–9.0	18	61

Table II. Concentration of Impurities (µg/mL) and Variation Coefficients (%) in Samples of Technical Benzyl Chloride ($n = 3$)

Sample No.	Benzaldehyde	Toluene	α,α-Dichlorotoluene	Chlorotoluene
A-2017	54.1 (12.1%)	n.d.*	68.2 (2.1%)	u.l.[†]
B-2097	50.1 (7.8%)	n.d.	64.8 (11.7%)	n.p.[‡]
C-2164	919 (0.65%)	n.d.	658 (0.72%)	n.p.
D-0098	3477 (0.45%)	n.d.	3163 (0.37%)	u.l.
E-1475	110 (3.7%)	n.d.	401 (0.6%)	n.p.

* n.d. = not detected.
[†] u.l. = unidentified in spectra library.
[‡] n.p. = has not passed criteria of peak purity.

dichlorotoluene and 2-chlorotoluene with retention time of 10.3 min. In addition, if benzyl chloride is synthesized by route B (Figure 1), dibenzylether as a possible impurity could be separated by this method at an elution time ~ 16 min. However, these compounds were not encountered in the quantitated samples.

Commercial specifications of technical benzyl chloride using GC vary according to the manufacturers, possibly due to their production process, process efficiency, and/or selected quality parameters. Some commercial sources, for instance, have a specifications of less than 1,000, and 25,000 µg/mL for α,α-dichlorotoluene. Also, the quantitated values of benzaldehyde and α,α-dichlorotoluene by the HPLC method in five samples (50 to 35000 µg/mL for benzaldehyde and 65 to 31000 µg/mL for α,α-dichlorotoluene) were obtained in a wide range of concentrations (Table II).

An additional possible impurity as benzyl alcohol could not be determined because an increase of the benzyl alcohol peak as a function of time passed because the sample preparation was observed. This fact had not been detected for standard solutions but perhaps sample solutions of benzyl chloride at a working concentration (3 mg/mL) may be hydrolyzed. A sample of technical benzyl chloride at 3 mg/mL concentration and dissolved in mobile phase was successively injected into the chromatographic system during a period of 5 h. Only the evolution of the benzyl alcohol peak was observed. Although the hydrolysis of α,α-dichlorotoluene to benzaldehyde could be possible (Figure 1), we did not observe a progress of the peak area for these compounds.

If α,α-dichlorotoluene and benzaldehyde are present in technical benzyl chloride, their presence in quaternary compounds such as benzalkonium chloride (BAK) synthesized from benzyl chloride, may be expected. BAK in commercial formulation is presented in solution of water or alcohols as isopropyl alcohol (IPA) at 50% or more. In a previous paper (2), impurities of BAK synthesized in laboratory using water and IPA were determined but some were not identified. A review of these unidentified impurities, applying spectral contrast technique, allowed the detection of α,α-dichlorotoluene in BAK samples in IPA. Spectra treatment of standards and samples using Savitsky-Golay filter (mathematical process) (32) intended to reduce the noise and reveal the spectral shape were performed in order to identify the α,α-dichlorotoluene. Possibly, α,α-dichlorotoluene from benzyl chloride yields benzaldehyde in aqueous medium, but this reaction would not occur in IPA.

Conclusion

Six compounds (benzyl chloride, benzyl alcohol, benzaldehyde, toluene, α,α-dichlorotoluene, and 2-chlorotoluene) which possess similar synthesis routes were separated with isocratic elution using octadecylsilica column. Application of the technique to samples of benzyl chloride for the determination of the mentioned compounds and also 2-chlorobenzyl chloride and dibenzylether was achieved. However, the quantitation of benzyl alcohol is not possible in this matrix. Detection by means of a photodiode array detector and treatment with spectral contrast technique provided greater reliability in the identification of impurities.

α,α-Dichlorotoluene and benzaldehyde, two possible impurities, were determined in technical benzyl chloride at wide range concentration (from part per million to per cent) depending on commercial sources. These compounds could be residual products in quaternary compounds synthesized from benzyl chloride.

Acknowledgments

References

1. E. Martínez, S. Lacorte, I. Llobet, P. Viana, and D. Barceló. Multicomponent analysis of volatile organic compounds in water by automated purge and trap coupled to gas chromatography-mass spectrometry. *J. Chromatogr. A* **959:** 181–90 (2002).
2. M.C. Prieto-Blanco, P. Lopez-Mahía, and D. Prada-Rodríguez. Analysis of residual products in benzalkonium chloride by high-performance liquid chromatography. *J. Chromatogr. Sci.* **37:** 295–99 (1999).
3. M.C. Prieto-Blanco, P. Lopez-Mahía, and D. Prada-Rodríguez. Analysis of residual products in triethylbenzylammonium chloride by high-performance liquid chromatography. Study of the retention mechanism. *J. Chromatogr. Sci.* **44:** 187–92 (2006).
4. X. Tang, G. Shi, and P. Liu. New catalytic synthesis of benzyl chloride. *Xiandaj Huagong* **17:** 23–25 (1997).
5. H.J. Buysch, E.G. Hoffmann, U. Jansen, P. Ooms, and B.U. Schenke. German Patent 19703906 (1998).
6. G.K. Rao and M.R. Subbaram. Quantitative determination of trace amounts of benzylidene chloride in benzyl chloride by gas-liquid chromatography. *Indian J. Technol.* **10:** 203–204 (1972).
7. Y.K. Babina and A.N. Kvartalnova. Gas-chromatographic analysis of benzyl chloride. *Zavod Lab* **44:** 412–414 (1978).
8. S. Galazka. Polish Patent 117665 (1983).
9. Y.K. Babina and A.N. Kvartalnova. Gas-chromatographic determination of impurities in benzaldehyde. *Khim Prom-st Ser Metody Anal Kontrolya Kach Prod Khim Prom-sti* **3:** 1–6 (1979).
10. J. Block and H. Levine. Rapid and sensitive high-pressure liquid chromatography technique for detecting impurities in benzaldehyde USP. *J. Chromatogr.* **166:** 313–15 (1978).
11. S. Fan, D. Qiou, and T. Zheng. Determination of industrial 2-chlorobenzaldehyde by GC/MS. *Ranliao Gongye* **38:** 42–43 (2001).
12. R.P. Frost, M.S. Hussain, and A.R. Raghani. Determination of pharmaceutical process impurities by solid-phase microextraction gas chromatography. *J. Sep. Sci.* **26:** 1097–1103 (2003).
13. R. Ramakrishnan and N. Subramanian. Quantitative analysis of mixtures of toluene and its side-chain-chlorinated derivatives by gas chromatography. *J. Chromatogr.* **114:** 247–49 (1975).
14. T. Maeda, K. Funaki, Y. Yanaguchi, K. Ichioka, K. Suzuki, N. Yamamoto, and M. Morita. On-site monitoring system for hazardous air pollutants using an adsorption-thermal desorption-capillary GC system equipped with a photoionization detector and an electrolytic conductivity detector. *J. High Resol. Chromatogr.* **21:** 471–74 (1998).
15. W.A. McClenny, J.D. Pleil, M.E. Holdren, and R.N. Smith. Automated cryogenic preconcentration and gas chromatographic determination of volatile organic compounds in air. *Anal. Chem.* **56:** 2947–51 (1984).

16. D.W.M. Sin, Y.C. Wong, W.C.D. Sham, and D. Wang. Development of an analytical technique and stability evaluation of 143 C3-C12 volatile organic compounds in Summa canisters by gas chromatography-mass spectrometry. *Analyst* **126:** 310–21 (2001).

17. J. Lehotay and H. Hromulákova. HPLC determination of trace levels of benzylchoride, chlorobenzene, naphthalene and biphenyl in environmental samples. *J. Liq. Chromatogr. Relat. Technol.* **20:** 3193–3202 (1997).

18. V.S. Kozlova. Determination of monochlorotoluenes in water. *Gig. Sanit.* **2:** 53–54 (1986).

19. E.D. Pellizzari. Analysis of organic vapor emissions near industrial and chemical waste disposal sites. *Environ. Sci. Technol.* **16:** 781–85 (1982).

20. H. Hromulákova and J. Lehotay. Determination of benzyl chloride, chlorobenzene, naphthalene and byphenyl in waste gas by HPLC. *Chem. Listy.* **90:** 933–37 (1996).

21. T.H. Sun, L.K. Cao, and J.P. Jia. Novel activated carbon fiber solid-phase microextraction for determination of benzyl chloride and related compounds in water by gas chromatography-mass spectrometry. *Chromatographia* **61:** 173–79 (2005).

22. J.R. Torres-Lapasio, M.C. Garcia-Alvarez-Coque, M. Roses, E. Bosch, A.M. Zissimos, and M.H. Abraham. Analysis of a solute polarity parameter in reversed-phase liquid chromatography on a linear solvation relationship basis. *Anal. Chim. Acta* **515:** 209–27 (2004).

23. M.A. Al-Haj, R. Kaliszan, and B. Buszewski. Quantitative structure-retention relationships with model analytes as a means of an objective evaluation of chromatographic columns. *J. Chromatogr. Sci.* **39:** 29–38 (2001).

24. P.N. Nesterenko, O.N. Fedyanina, and Y.V. Volgin. Microdispersed sintered nanodiamond as a new phase stationary for high-performance liquid chromatography. *Analyst* **132:** 403–305 (2007).

25. J.C. Stadler and G.L. Kennedy. Evaluation of the sensory irritation potential of volatile organic chemicals from carpets-alone and in combination. *Food Chem. Toxicol.* **34:** 1125–30 (1997).

26. B.R. Dudek, R.D. Short, M.A. Brown, and M.V. Roloff. Structure-activity relationship of a series of sensory irritants. *J. Toxicol. Environ. Health* **37:** 511–18 (1992).

27. European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC). Eye irritation. Reference chemicals data bank (second edition). *Tech Rep* **48:** 1–236 (1998).

28. D.M. Bagley, J.R. Gardner, G. Holland, R.W. Lewis, H. Vrijhof, and A.P. Walter. Eye irritation: updated reference chemicals data bank. *Toxicol. In Vitro* **13:** 505–10 (1999).

29. G.T. Pisko, G.V. Tolstopyatova, T.V. Belyanina, E.V. Borisova, O.V. Gudz, A.M. Zabara, S.M. Zelman, and S.Y. Kozachuk. Substantitation of maximun permissible concentrations of o- and p-chlorotoluenes in reservoir water. *Gig. Sanit.* **2:** 67–68 (1981).

30. G.V. Tolstopyatova and Z.I. Zholdahova. Comparative hygienic characteristics of chloro derivatives of toluene as possible water pollutants. *Gig. Sanit.* **12:** 64–66 (1980).

31. K. Fukuda, H. Matsushita, H. Sakabe, and K. Takemoto. Carcinogenicity of benzyl chloride, benzal chloride, benzotrichloride and benzoyl chloride in mice by skin aplication. *Gann* **72:** 655–64 (1981).

32. K. Yasuo, S. Fuyimoto, M. Katoh, Y. Kikuchi, and T. Kada. Mutagenicity of benzotriazole and related compounds. *Toxicol. Environ. Sci.* **58:** 143–50 (1978).

33. http://www.uneptie.org/pc/cp/declaration. Date accessed: 9/7/2007.

34. S. Suzuki, Y. Nakamura, M. Kaneko, K. Mori, and Y. Watanabe. Analysis of benzalkonium chlorides by gas chromatography. *J. Chromatogr.* **463:** 188–91 (1989).

35. S. Keunchkarian, M. Reta, L. Romero, and C. Castells. Effect of sample solvent on the chromatographic peak shape of analytes eluted under reversed-phase conditions. *J. Chromatogr.* **1119:** 20–28 (2006)

36. J.C. Miller and J.N. Miller. *Statistics for Analytical Chemistry.* Ellis Horwood Limited, Chichester, England, 1988, p. 115–7.

37. A.A. Savitsky and M.J.E. Golay. Smoothing and differentiation of data by least-squares procedures. *Anal. Chem.* **36:** 16–27 (1964).