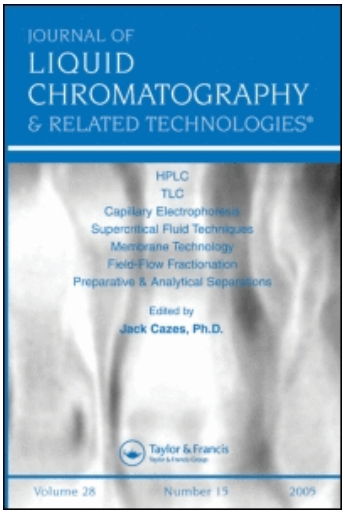

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DETERMINATION OF HIGHLY POLAR COMPOUNDS IN REACTION MIXTURES OF 2,2-BIS(HYDROXYMETHYL)PROPIONIC ACID AND 3-HYDROXY-2,2-BIS(HYDROXYMETHYL)PROPIONIC ACID BY HPLC

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ABSTRACT

A liquid chromatographic method is described for the quantitative determination of the compounds present in the reaction mixtures producing highly polar hydroxy carboxylic acids bis(hydroxymethyl)propionic acid and 2,2-bis(hydroxymethyl)-1-ol propionic acid. Two columns with different separation mechanisms are connected in series; thus, an efficient separation of polyol, hydroxy aldehyde, and hydroxy acid is achieved. The separated compounds are detected by UV/DAD and RI detectors.

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Key Words: Liquid chromatography; Hydroxy acid; Hydroxy aldehyde; Polyol; UV detector; RI detector

INTRODUCTION

2-Methyl-2-hydroxymethylpropan-1,3-diol (MHPD), and 2,2-bis(hydroxymethyl)-1,3-propanediol (pentaerythritol, PET) are polyols used in the chemical industry, either as polyolic monomers or as intermediates, which are oxidized to corresponding hydroxy acids. Polyols are widely used for producing plasticisers and lubricants. In the coating industry, the main applications are in the production of solvent-free water-soluble polyester resins and pulverized paints.

There are no β-hydrogens relative to the hydroxyl groups in these molecules, and due to this neo-structure, the esters derived from these kind of polyols have excellent hydrolytic-, thermal-, and UV-stability, as well as good chemical and wash resistivity. The polyol component affects the leveling, drying, and weatherability of the resin. When used in paints, the surface of the paint has high gloss and durability. Hydroxy acids are utilised in lubricating esters, engineering plastics, and powder coatings in applications where high hydrolytic stability is needed.

The polyols are produced from hydroxy aldehydes in an aldol reaction, which is the reaction of one carbonyl compound with another. The reaction is subjected to either acid or base catalysis. Base-catalyzed self-addition of aldehydes to form β-hydroxy aldehydes is successful under mild conditions, but only with relatively low molecular weight aldehydes up to six carbons (1). Typically used conditions are sodium hydroxide in aqueous solvents, alkalimetal alkoxides in the corresponding alcoholic solvents, or protic acids. When the reaction is carried out under these enol- or enolate-equilibrating conditions, there are several side reactions: 1) Because of the modest intrinsic driving force for the reaction, self addition processes often proceed in low yield. 2) Mixed aldol reactions often give complex mixtures of products, especially when the two reactants have α-hydrogens of comparable acidity and if the two carbonyl groups are of comparable electrophilicity. 3) Dehydration of the initially formed aldol presents a further complication (1).

In the reactions described in this study, the aldehyde group of the initial β-hydroxy aldehyde is reduced by formaldehyde in crossed Cannizzaro reaction leading to triol and tetraol. The polyol compound is then catalytically oxidized to corresponding hydroxy carboxylic acid. The structures of the compounds under analysis, and the reaction schemes of the syntheses are shown in Figure 1. If polyols are produced by hydrogenation of the aldol, instead of the crossed Cannizzaro reaction, the reactant aldehydes are also hydrogenated to corresponding alcohols. In oxidation, these are converted to carboxylic acids, thus, a mixture of several compounds is obtained.

The analysis of the composition of the reaction mixture is used for the optimization of synthesis conditions. An accurate determination of the composition of

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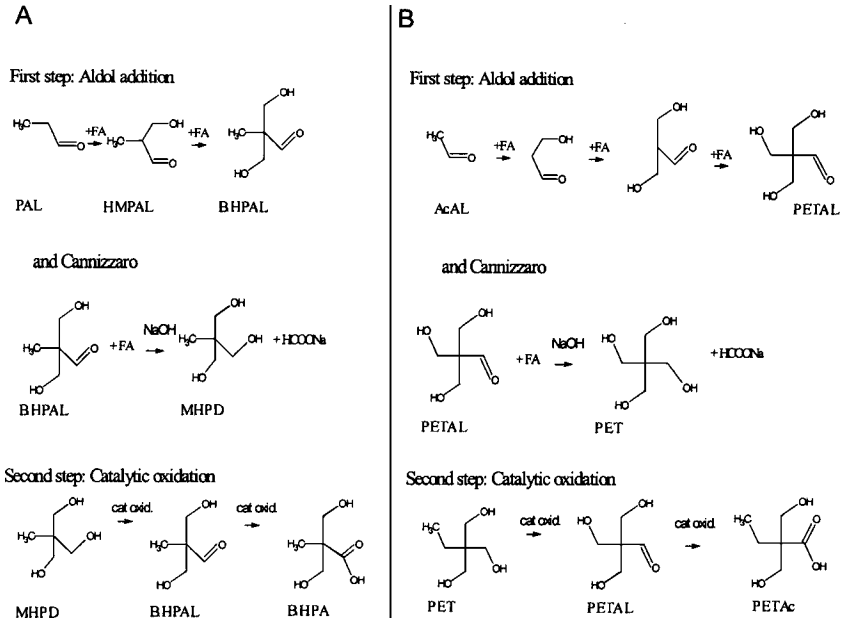

Figure 1. Structures of the main compounds and reaction schemes possible in (A) MHPD and (B) PET synthesis.

the reaction mixture is needed for the study of reaction kinetics. A better knowledge of the components present help to indicate which type of side reactions are important under different reaction conditions, and how these conditions should be chosen in order to improve the quality and yield of the process. Direct analysis of the reaction mixture is not that simple because of the differing chemical nature and reactivity of the compounds present. In addition, various parameters affect the equilibrium reaction between the monomeric and dimeric form of hydroxy aldehydes, which must be taken into account in the analysis.

Under normal storage conditions, aldehydes tend to form cyclic or polymeric acetals (dimers, trimers, or oligomers), which are difficult to analyze separately. In Figure 2, acetal formation reactions of the BHPAL or PETAL are shown. In solution, the equilibrium position depends on the solvent and temperature. At room temperature the equilibrium is reached slowly, and in water solutions it takes about two days (2). For analysis of hydroxy aldehydes, the equilibrium can be quenched by acetylating and silylating, or shifted to monomeric form by derivatization of the carbonyl group. In recent studies, the equilibrium has been shifted to the monomeric hydroxy aldehyde by preparing the standards and samples in acidic and quite dilute solutions (3,4).

Various methods have been published for the analysis of each of the compound types separately, but only a few papers have been published on the

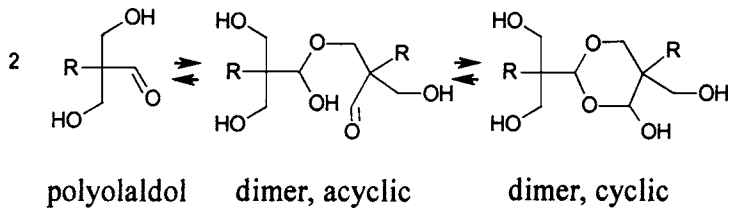

Figure 2. Acetal formation reactions of the hydroxy aldehydes. R=CH_3 for BHPAL and R=CH_2OH for PETAL.

analysis of synthesis matrices similar to this paper. Conventionally, derivatization is used in the analysis of alcohols and aldehydes. The mixture of mono-, di-, and tripentaerytritol have been determined by GC as acetate esters after direct treatment with acetic anhydride (5). The dimeric forms of hydroxypivalaldehyde were shifted to the monomeric aldehydes by formation of the oxime derivatives, and hydroxypivalaldehyde was determined as the TMS-derivative of the corresponding oxime (6). A GC method without derivatization was used for the synthesis mixture of TMP (7).

The retroaldolisation of several polyols has been studied by analyzing free formaldehyde (FA) as its lutidine derivative by UV-vis spectroscopy (8). Aldehydes and hydroxy aldehydes have been determined as their 2,4-dinitrophenylhydratzine (DNPH) derivatives by reversed phase HPLC analysis (9). The acids, hydroxy acids, hydroxy aldehydes, and polyols can be analyzed by HPLC without derivatization. In one study, the intermediate products of the 2-ethyl-2-hydroxymethyl-propan-1,3-diol (EHPD) synthesis were studied by thin layer chromatography and reversed phase HPLC, using an RI detector (10). In another study, RP-HPLC with 0.35 *M* borate buffer at pH 7 was used to analyze reaction solutions of EHPD with an RI detector (11). Both GC and HPLC techniques were used to analyze the compounds in the 2,2-dimethyl-1,3-propandiol (DMPD) synthesis matrix (12).

Quite recently, a DNPH derivatisation and an underivatisated method were connected to one HPLC instrument with two columns and UV and RI detectors for analysing compounds in synthesis mixtures of DMPD (4). Ion exchange columns are widely used for analysing organic adids, aliphatic aldehydes, ketones, alcohols, and carbohydrates. Polystyrene-divinylbenzene cation-exchange resins in H^+ form with an acidic eluent was employed for organic acid and polyol analysis (13). A radially compressed silica column modified with tetraethylenepentamine was used to analyze polyols with an RI detector (14).

This paper deals with the direct quantitative analysis of the compounds in synthesis mixtures where hydroxy acids BHPA and PETA are prepared. Special attention is paid to the separation of PET and PETA, which we have not been able to determine in a same sample before now. Another aim of this study was to further develope the HPLC method of MHPD, HMPAL, and BHPA for better

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resolution between these compounds. BHBA samples are not included in this study because the separation and quantitative analysis in BHBA synthesis is achieved satisfactorily by the method developed earlier (3). Due to low solubility of PET and PETA in organic solvents, normal phase chromatography couldn't be used. The columns were selected so that lots of water can be used in sample preparation and in HPLC runs. Both UV-vis and RI detectors were used because of the different responses of the compounds present in synthesis mixtures.

EXPERIMENTAL

Apparatus

In HPLC methods, a Hewlett-Packard model 1090 liquid chromatograph with two columns connected in series with a column switching valve was used. The reversed phase column was Luna C18 (150–4.6 mm, 3 μm particle size), and the ion exchange column was InterActive ARH-601 (100–6 mm).

The column oven temperature was 60°C. The diode array detector (10 mm flow cell, 8 μm slit) with detection wavelength of 210 nm and reference wavelength 550 nm was used for quantitation, and peak spectra were scanned from 190 to 400 nm for compound identification. The refractive index detector Waters 410 with sensitivity 32 and time constant 1 at 40°C was in series with the UV detector. The RI detector was switched off the system during the C18 column washing gradients by a Waters switching valve P/N 60057.

The injection volume was 10 μL. The eluents were (A) 0.005 *M* H_2SO_4 pH 2.1, and (B) acetonitrile. The flowrate of the eluent was 0.65 mL/min. The connections of the apparatus used in the studies are presented in Figure 3.

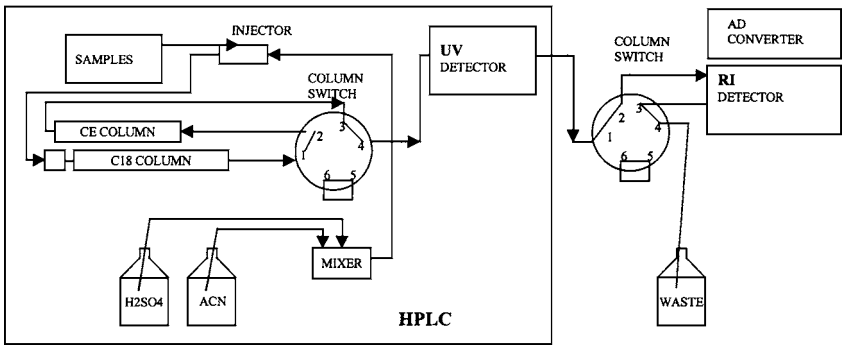

Figure 3. Construction of the HPLC apparatus used in the studies.

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Reagents and Materials

The water used in HPLC and sample preparation was deionized and further purified via a Milli-Q Water System (Millipore), methanol (MeOH) was HPLC grade from Merck (Darmstadt, Germany), H_2SO_4 was 0.5 *M* p.a. from FF-Chemicals (Yli-Ii, Finland). Formic acid (HCOOH) was 98–100% from Riedel-de Haen (Seelze, Germany).

Propionic acid (PrCOOH) 99.5%, butyric acid (BuCOOH) 99.5%, and methacrylic acid (MAA) 98% practical grade were from Fluka (Buchs, Switzerland).

Propionaldehyde (PAL) 97% was from Aldrich (Steinheim, Germany). 2-Methyl-2-hydroxymethylpropan-1,3-diol (MHPD) 98% and 2,2-bis(hydroxymethyl)propionic acid (BHPA) 97% were from Fluka.

2,2-Bis(hydroxymethyl)-1,3-propandiol (PET) was 98% from Aldrich and 2,2-bis(hydroxymethyl)-1-ol propionic acid (PETA) was a synthesis product from University of Helsinki, Finland.

Propanol (PrOH) was 99% from Merck. 2,2-Bis(hydroxy-methyl)propanal (BHPAL) was prepared in-house. The purity of the aldehydes and hydroxy aldehydes prepared in-house were determined by a DNPH method (9).

Preparation of Standards and Samples

Standards for HPLC were prepared by weighing an adequate amount of each standard into a volumetric flask. The preferred concentrations are shown below:

	RCOOH	Hydroxy Acid	Polyol	Hydroxy Aldehyde Unsaturated Compound
Stock solution	80 mg/20 mL = 4.0 g/L	120 mg/20 mL = 6.0 g/L	70 mg/10 mL = 7.0 g/L	40 mg/100 mL = 0.4 g/L

The acid standards were filled to the mark with 0.005 *M* sulphuric acid. The PAL standard was prepared with 0.005 *M* sulphuric acid and ACN was added until standard dissolved. The stock solutions were diluted further with 0.005 *M* sulphuric acid for method calibration. Samples were prepared by accurately weighing about 50–100 mg of the reaction mixture into a 5.0-mL volumetric flask and filled to the mark with 0.005 *M* sulfuric acid. The sample was diluted further, 10-fold, for analysis of hydroxy aldehydes, hydroxy acids, and unsaturated aldehydes.

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RESULTS AND DISCUSSION

Optimisation of HPLC Method

In the RP-HPLC method developed earlier for the quantitative analysis of BHPA synthesis mixtures, the small or polar compounds elute from the column very rapidly: MeOH, HCOOH, MHPD, BHPA, and BHPAL all elute in the retention range 2.6–3.3 min. It was not possible to obtain a baseline separation for these compounds with several C18 columns tested (3). Several reversed phase columns were tested for separation of PET and PETA from each other. No separation was achieved by Merck LiChrosorb, Luna, or Vydac C18 columns. The resolution of MHPD and BHPA was not enhanced either. Because of the high polarity of the compounds, more polar CN and NH_2 columns were also tested in reversed phase mode.

Since poor results were obtained in reversed phase mode, a NH_2 column was used as normal phase column with heptane as eluent. However, the water used in standard and sample preparation caused problems because of the insolubility of heptane and water. Acetonitrile, which is suitable to use together with water, was tested as an organic eluent, but still no separation was obtained for PET and PETA. It was not possible to use the more polar normal phase silica or alumina columns, because PET and PETA did not dissolve in any common organic solvents typically used as eluents in NP-HPLC applications.

PET/PETA and MHPD/BHPA/BHPAL analyses were tested with an Inter-Action cation-exchange (CE) polymeric column, which is designed specifically for separating organic acids, alcohols, sugars, and aldehydes, using aqueous eluent. Organic eluents cannot be used with this column, because shrinking and swelling phenomena break down the resin based column support. The primary mechanism for separation in CE is ion exclusion, and secondary mechanisms is steric exclusion and partitioning. Separation on C18 column is based on solvation of the analytes in the eluents used. The CE column, based on sulphonic acid functionality, seemed to work rather well for PET and PETA, so the HPLC method was optimized with both Luna C18 and Interaction ARH-601 in series.

Neither of the columns separates PETA from HCOOH, FA from HCOOH, or MHPD from BHPAL if used alone. But, a combination of the both columns in series allow one to analyse all the compounds present in samples by simple sample preparation, one HPLC instrument, and quite cheap eluents. A C18 column was installed before the cation-exchange column in order to retain the possible impurities present in the sample solutions. After the most polar and badly resolved compounds were eluted from C18 column to the cation-exchange column, they were separated further. C18 column was activated and washed frequently with 98% ACN/2% 0.005 *M* H_2SO_4. In washing periods, both the RI and the CE column were switched off the system.

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The separation was optimized by testing different eluents, pH's, eluent flow rates, and column temperatures. When strong acids are used as eluents in the cation-exchange column, the column is self-regenerating and special regeneration steps are not required. Stronger acids increase retention times for most weak acid analytes. Phosphoric acid at pH 2.3 and sulphuric acid at pH 2.1 or 1.7 were tested. The H_3PO_4 added in standards and samples interfered with the analysis. Methanol, which was added to help dissolution of some compounds, did not interfere in BHPA or PETA cases. The H_2SO_4 used in sample preparation could not be detected in the chromatograms, and was selected as an eluent in the HPLC run and as a solvent for sample preparation.

The more acidic eluent is preferable in determination of hydroxy aldehydes, since narrower peaks are obtained. Conventionally, the pH range of silica based columns is 2–7, but the Luna column, was claimed to stand pH range 1.5–10. However, after some days runs at pH 1.7, the back pressure of the column raised vastly, probably due to destruction of the silica based column packing. Thus, in the method, 0.005 *M* H_2SO_4 at pH 2.1 was used as eluent.

A relatively high column temperature of 60°C was selected because reduced retention time, higher separation efficiency, and lower column pressure were obtained. Cation-exchange columns are used even at higher temperatures of 90°C, but 60°C is already critical for the C18 column. The flow rate of 0.65 mL/min was optimal for separation of PETA from HCOOH. High flow rates accelerate analysis at the expense of resolution; lower flow rates result in improved resolution but slightly longer analysis time. At the lowest flow rates, maximum column separation efficiencies are achieved. As an example, a typical chromatogram of PETA standard mixture obtained by the HPLC method developed in this study is shown in Figure 4.

Standard and Sample Preparation

Standard solutions, and samples from synthesis, were made acidic with eluent (A). The acidic conditions in the sample preparation were needed for four reasons: 1) in order to change all of the acidic compounds from ions to free acids, 2) in the studies of reaction kinetics, one can stop the base catalyzed aldol addition reaction by adjusting the pH to the acidic side, 3) the equilibrium reactions of the hemiacetals of hydroxy aldehydes are shifted totally to the side of the monomers (Fig. 2), because acetals can be cleaved to free aldehydes in dilute acidic conditions, 4) the polyolaldol formates, which can be formed as a side reaction products are hydrolyzed to the corresponding acids and polyols.

The equilibrium position of the acetal formation reaction of hydroxy aldehydes is reached slowly. According to our experience, the highly diluted solutions must stand at room temperature overnight for the equilibrium of the acetals to quantitatively react to the monomers. If the samples or standards were analysed

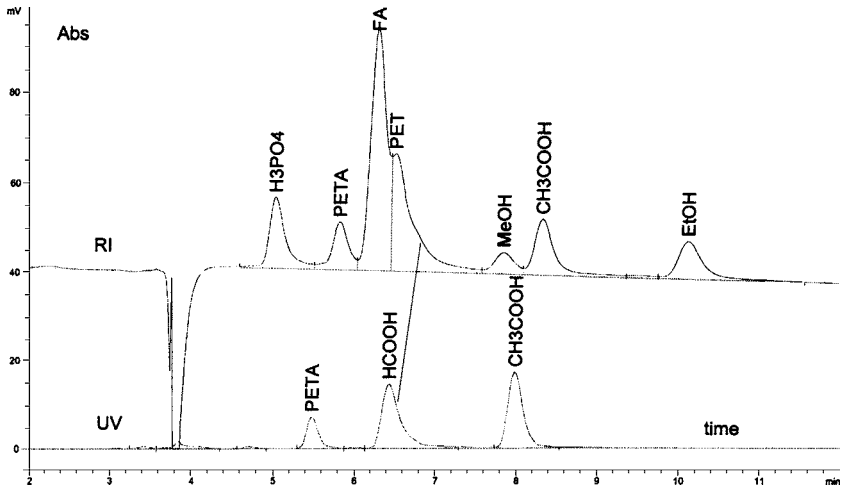

Figure 4. Chromatograms of the standard mixture in PETA analysis. Upper RI detector, lower UV detector.

too fast after dilution, the peak of the analysed hydroxy aldehyde was remarkably smaller than that of a same sample, which was allowed to stabilise overnight before quantitative analysis. As an example, the influence of too fast analysis may be about 10% on the result of the analysis. Similar results were obtained for quantitative analysis of hydroxy acids and unsaturated aldehydes.

Quantitative Analysis and Identification of the Compounds

Polyols, alcohols, and aliphatic aldehydes were analysed quantitatively using an RI detector. Carboxylic acids, hydroxy acids, unsaturated aldehydes, and hydroxy aldehydes were analyzed using a UV detector. Concentrated samples were used for detecting low concentrations of acids by a UV detector and the compounds that could be seen only by an RI detector. Diluted samples were needed for hydroxy aldehydes, hydroxy carboxylic acids, and unsaturated aldehydes to shift the equilibrium position to the side of the monomers, or to set the peak intensities to the linear part of the calibration.

The detection wavelength in the UV detector was selected at 210 nm, near the absorbance maximum of all the compounds. The selected wavelength is not optimum for the unsaturated acids and unsaturated aldehydes, but their response is very high compared to the saturated compounds, so that no other detection wavelengths are needed. The sensitivity of the RI detector was optimised to detect those compounds that have no response in the UV detector.

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The UV spectra of the reference compounds were scanned from 200 to 400 nm and saved to the library for compound identification. The compounds were identified using the retention times and UV-spectra of the above prepared external standards. There are typical spectra for carboxylic acid, hydroxy acid, unsaturated carboxylic acid, hydroxy aldehyde, and unsaturated aldehyde. Hydroxy aldehyde (DHPAL) gives a strong absorption maximum at 190 nm and a low maximum at 290 nm. Hydroxy acid (DHPA) gives absorption maximums with high intensity at 190 and 215 nm and an absorption minimum at 205 nm. Unsaturated acid (MAA) and carboxylic acid (PrCOOH) both give an absorption maximum at 210 nm, but the UV spectrum of the unsaturated acid is clearly narrower. The absorption maximum of unsaturated aldehyde (AMA) is at 220 nm, and the position of the absorption maximum of higher molar mass unsaturated aldehyde (2-et-hexenal) is shifted to a higher wavelength of 240 nm.

When the columns with the two separation mechanisms were connected, the elution order of the polar compounds containing a hydroxy group was hydroxy acid, polyol, and hydroxy aldehyde. And, the less polar compounds without a hydroxy group, eluted in the order: carboxylic acid, aldehyde and alcohol; except the compounds with one carbon atom, FA, HCOOH and MeOH. In Figure 4, the acetonitrile needed for PAL standard preparation overlaps in the chromatogram of the standard mixture of the BHPAL peak at the RI detector. In real, more dilute samples ACN is not needed and the resolution of BHPA/MHPD/BHPAL is better.

Reliability, Linearity, and Limit of Quantification

The reliability of the method was evaluated also by analysing one BHPA sample by other methods. Aldehydes were analysed as their 2,4-dinitrophenylhydrazone derivatives by RP-HPLC (9), and MHPD by a GC method. The results of different methods are compared in Table 1. It was not possible to evaluate the PET/PETAc results because there is no other method to compare the results to. It can be noted that it is possible to determine all the main compounds present in BHPA sample by the developed method, and that the results are quite similar to those obtained by the two other techniques. So, only one instrument is needed instead of two HPLC and one GC used till now.

The limit of quantification (LOQ) was calculated from a system noise of 0.11 mAU (DAD) and 0.02 mV (RI) against the peak height of the smallest standards multiplied by four. The limits of quantification are presented in Table 2. The method is most sensitive to unsaturated acids and unsaturated aldehydes, and less sensitive for aliphatic aldehydes. If higher sensitivity is needed, more sample can be injected or sensitivity of the RI detector enhanced. It can be observed that the sensitivity of the RI detector is several times higher than the sensitivity of the UV detector.

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Table 1. Comparison of the Results Obtained from a BHPA Sample by Different Analysis Techniques (Results in w%)

Compound	C18-CE Method	DNPH-HPLC	GC
HCOOH	0.001	–	–
MeOH	8.05	–	–
FA	1.68	1.78	–
BHPA	0.60	–	–
MHPD	1.70	–	2.0
BHPAL	28.39	28.37	–
PrCOOH	0.57	–	–
PrOH	0.00	–	–
PAL	1.08	1.08	–
AMA	0.70	0.73	–
MAA	0.02	–	–

Table 2. Limits of Quantification (mg L^{-1}) of Different Compounds

Detector	Functionality	Compound	Quantification Limit
DAD	Acid	HCOOH	0.013
		PrCOOH	17.92
		EtCOOH	13.89
		MAA	0.18
RI	Acid	HCOOH	0.007
		PrCOOH	3.62
		EtCOOH	3.61
DAD	Hydroxy acid	PETA	11.89
		BHPA	15.18
RI	Hydroxy acid	PETA	1.41
		BHPA	2.12
DAD	Hydroxy aldehyde	PETAL	No reference std
		BHPAL	5.38
RI		BHPAL	1.78
RI	Aliphatic aldehyde	FA	2.01
		PAL	5.69
RI	Polyol	PET	1.58
		MHPD	2.29
	Alcohol	MeOH	13.39
		PrOH	4.65
		EtOH	5.31

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Compared to the RP-HPLC method described earlier (3), the separation of rapidly eluting compounds is better in the method developed here. The sensitivity of RI signal is quite similar to that of DAD signal in the previous RP-HPLC method. The loss of sensitivity of DAD signal might be due to connecting the CE column after the C18, which causes peak broadening. Also the dilute sulphuric acid used as eluent has higher background absorption at 210 nm compared to the phosphoric acid/ACN eluent in the previous study. However, the sensitivity of RI is higher because the difference between refractive indexes of aqueous elution solvent and organic analytes is higher than that in the method where a mixture of organic eluent is used. In the developed method, FA can also be determined directly from the undiluted samples.

The linearity of the calibration lines are good only for formic and propionic acids. The calibration of other compounds are more or less curved, since the polarity of the compounds cause peak broadening when standards of higher concentration are analyzed. In the quantitative analysis on the samples, the calibration was limited to low concentration levels expressed in the Experimental Section. The calibration was carried out using a quadratic function passing through the origin.

CONCLUSIONS

An RP-HPLC method was developed for the quantitative analysis of all the compounds in the synthesis mixtures of hydroxy acids BHPA and PETA. A UV detector was used for carboxylic acids, hydroxy carboxylic acids, unsaturated aldehydes, and hydroxy aldehydes. Polyols, alcohols, and aliphatic aldehydes were detected by an RI detector. Two columns with different separation chemistries were used in series. In the method, the nonpolar hydrocarbons were retained and separated in a C18 column while fast eluting polar compounds were separated in a cation-exchange column. No gradient elution was used during sample runs. The C18 column was washed separately between runs with acetonitrile while the CA column and the RI detector were swiched off the eluent flow. In this way, a very stable RI signal was obtained. Because almost all of the compounds present in the samples are reactive, the sample preparation was developed so that the intermediate hydroxy aldehydes and the side reaction products were cleavaged to the corresponding aldehydes, acids, and alcohols. In dilute and acidic solutions, these could be analyzed quantitatively. In the developed method, it was possible to analyse even FA without derivatisation.

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