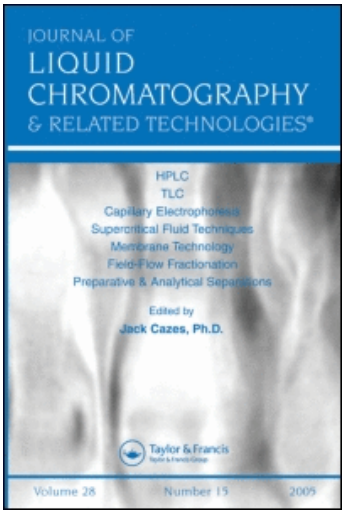

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

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Online publication date: 19 September 2000

To cite this Article Koivusalmi, E. , Haatainen, E. and Nikkilä, K.(2000) 'RP-HPLC ANALYSIS OF THE COMPOUNDS IN THE SYNTHESIS MIXTURES OF 2,2-DIMETHYL-3-HYDROXYPROPIONALDEHYDE BY TWO METHODS COMBINED TO ONE INSTRUMENT BY A COLUMN SWITCHING TECHNIQUE', Journal of Liquid Chromatography & Related Technologies, 23: 16, 2447 — 2458
To link to this Article: DOI: 10.1081/JLC-100100500
URL: http://dx.doi.org/10.1081/JLC-100100500

J. LIQ. CHROM. & REL. TECHNOL., 23(16), 2447–2458 (2000)

RP-HPLC ANALYSIS OF THE COMPOUNDS IN THE SYNTHESIS MIXTURES OF 2,2-DIMETHYL-3-HYDROXYPROPIONALDEHYDE BY TWO METHODS COMBINED TO ONE INSTRUMENT BY A COLUMN SWITCHING TECHNIQUE

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ABSTRACT

Two RP-HPLC methods are described for the determination of the compounds in 2,2-dimethyl-3-propionaldehyde synthesis mixtures. All the other compounds, except aliphatic aldehydes, are determined by a gradient programmed method using UV/DAD and RI detectors in series. Aldehydes are determined as their 2,4-dinitrophenylhydrazone derivatives using a UV/DAD detector. The selection between different columns and detectors is made with a column switching technique. The eluents and column temperature are selected so, that only one HPLC instrument is needed.

INTRODUCTION

2,2-Dimethyl-3-hydroxypropionaldehyde (DHPAL) is used as an intermediate for several industrial products in this study for neopentylglycol (2,2-dimethyl-1,3-propandiol, DMPD). The production, properties, and reactions of DHPAL are described by Arpe.[1] The analysis of the composition of the reaction mixtures is required for process optimization, since in the study of reaction kinetics, a better knowledge of the components present help to indicate which side reactions are important under different reaction conditions. When analyzing such a mixture, one has to take into account the reactivity of the compounds, in order to stop the base catalyzed aldol addition reactions. Furthermore, the equilibrium reactions between the different forms of DHPAL needs special attention in the sample preparation, in order to get reliable quantitative results. The features of the equilibrium reactions are described elsewhere,[2,3] and in the sample preparation, the dimeric form of DHPAL can be shifted to monomeric form by heating or by diluting the sample with acids.[4,5]

In literature, various methods for the determination of aldehydes and hydroxy aldehydes are described. In one study, isobutyraldehyde was determined polarographically as its phenylhydrazone derivative in the presence of DHPAL.[6] In another study, formaldehyde (FA) was determined as its lutidine derivative by UV spectrometer when retroaldolization of DHPAL was studied.[7] The different forms of DHPAL were determined in reaction mixtures by GC as oxime derivatives, and the dimeric form was shifted quantitatively to monomeric DHPAL by oxime/trimethylsilyl-derivatization.[8] The RP-HPLC method for determination of formaldehyde, isobutyraldehyde, and DHPAL as their 2,4-dinitrophenylhydrazone (DNPH) derivatives was described in an earlier study of the authors.[4] More recently, both GC and RP-HPLC techniques were used for quantitative analysis of all the other components but FA in reaction mixtures similar to this study.[5]

In this paper, two RP-HPLC methods are described which were used for quantitative analysis of all the components in the aldol addition reaction of formaldehyde and isobutyraldehyde to produce DHPAL and DMPD. All the other compounds but aliphatic aldehydes are determined by a gradient programmed method using UV/DAD and RI detectors in series. Aldehydes are determined as their 2,4-DNPH derivatives using a UV/DAD detector. The selection between different columns and detectors is made with a column switching technique. The eluents and the column temperature are selected, so that only one HPLC instrument is needed, instead of the three devices used earlier for this kind of analysis. The results obtained by the developed RP-HPLC method are compared to the separate GC and HPLC methods. The detection limits of the methods are evaluated.

EXPERIMENTAL

Apparatus

In both methods a Hewlett-Packard model 1090 HPLC with a diode array detector (10 mm flow cell, 8 μm slit) and a column switching valve was used. The column in direct RP-HPLC determination was Merck LiChrosorb RP-18 (250-4 mm, 5 μm particle size) at 36°C. The UV detection wavelength was 210 nm and reference wavelength 550 nm. The Waters 410 RI detector at 40°C with sensitivity 4, was in series with the UV detector. The column in the DNPH method was Waters Nova-Pak C18 (150-4 mm, 60 Å pore size, 4 μm particle size) at 36°C. The detection wavelength was 360 nm and reference wavelength 550 nm. Peak spectra were scanned from 190 to 400 nm for compound identification in both cases. The operation of the column switches between the columns and between the detectors was programmed in the HPLC methods by Chemstation program. The RI detector was switched off the system during gradient steps and during DNPH determinations by a Waters switching valve P/N 60057.

The schematic diagram of the HPLC apparatus is shown in Figure 1. In both methods, the injection volume was 5 μL. The eluents were (A): a pre-prepared mixture of 8% acetonitrile in ultra pure water, the pH of which was adjusted to 2.3 with concentrated phosphoric acid, and (B): acetonitrile. The flowrate of the eluent was 1 mL/min and the gradient program as follows:

Direct RP-HPLC:

time/min	0	14	15	20	21	26	28	43
% B	0	0	34	34	98	98	0	0.

DNPH RP-HPLC:

time/min	0	2	10	15	16	26
% B	32	32	90	90	32	32.

Reagents and Materials

The water used in HPLC and sample preparation was deionized and further purified via a Milli-Q Water System (Millipore). Acetonitrile (ACN) was HPLC grade from Rathburn (Walkerburn, Scotland), H_3PO_4 was 85% p.a. from

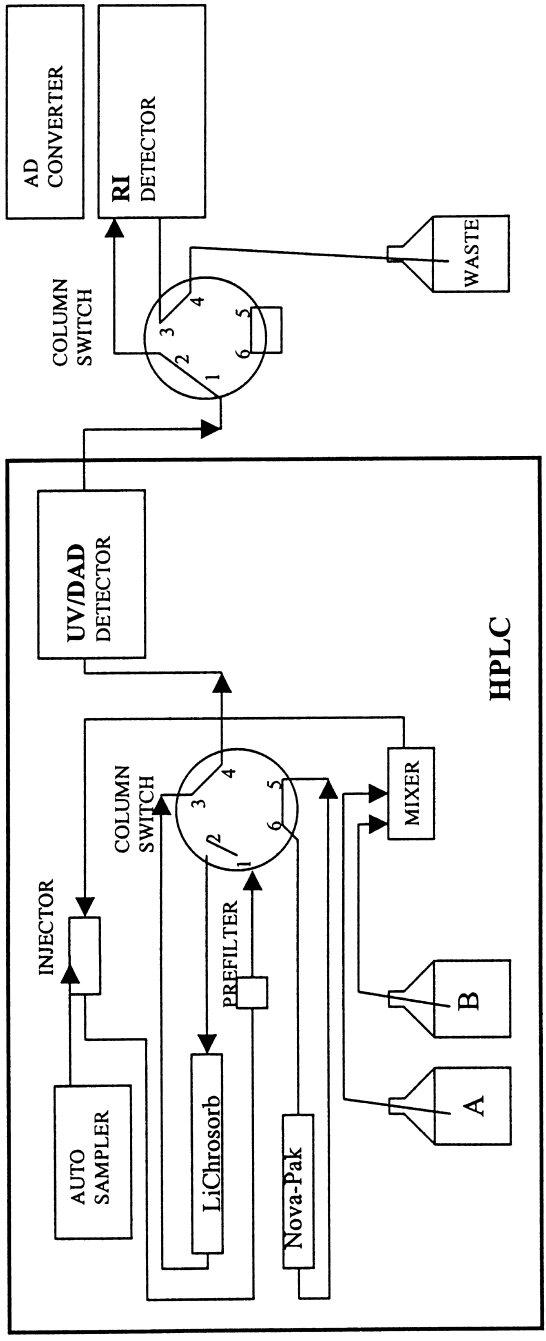

Figure 1. Schematic diagram of the HPLC apparatus used in studies.

J. T. Baker (Deventer, Holland), H_2SO_4 was 0.5 M solution from FF Chemicals (Yli-Ii, Finland), methanol (MeOH) was HPLC grade from Merck (Darmstadt, Germany), isobutyraldehyde (IBAL) was 98% from Aldrich, formic acid (HCOOH) was 98 - 100% from Riedel De-Haen (Seelze, Germany), isobutyric acid (IBuCOOH) was 99% from Aldrich, DHPAL was a 99.6% in-house synthesis product, methacrylic acid (MAA) was 98% from Fluka (Buchs, Switzerland), 3-hydroxy-2,2-dimethylpropionic acid (DHPA) was from Tokyo Kasei Japan, 2,2-dimethylmalonic acid (DMMA) was 98% from Fluka, 2,2-dimethyl-1,3-propandiol (DMPD) was 99% from Aldrich, neopentyl glycol mono(hydroxypivalate) (DPDP) was from Tokyo Kasei Japan, DMPD-monoisobutyrate (DMPD-mIBA) was a 99% in-house synthesis product, and isobutanol (IBUOH) was 99% from Fluka. 2,4-DNPH ($H_2O \cong 50$ %) was p.a. grade from Fluka. FA-DNPH, IBAL-DNPH and DHPAL-DNPH derivatives were in-house synthesis products for analytical purposes prepared in a method described elsewhere.[4]

Preparation of the Standards and Samples

Standards for direct RP-HPLC were prepared in 0.01 M sulphuric acid. Lots of MeOH were added until DMPD, IBAL, and IBUOH dissolved. Bottles of all the standard solutions were kept in an ultrasonic bath to help the dissolution. Samples from synthesis (80 - 300 mg) were collected directly into sample bottles in which 2 mL of ACN and 5 or 8 mL of 0.01 M sulphuric acid were weighed beforehand. The samples were diluted further, 10, 5, or 2 fold for DHPAL analysis, depending on the DHPAL concentration in the sample.

The standard solutions for DNPH RP-HPLC analysis were prepared by weighing 25 mg of each standard derivative into a 100 mL volumetric flask and filled to the mark with ACN. The stock solutions were diluted further, just prior to use, to four different concentrations, so that water/ACN content is about 50/50. Out of the sample solution obtained for direct RP-HPLC method above, a 100 mg portion was weighed into a 50 mL volumetric flask with 20 mL of DNPH solution and 1 mL of conc. phosphoric acid. After a derivatization reaction of 1 h, the flask was filled to the mark with 50/50 water/ACN-mixture. The sample solution was diluted further with 50/50 water/ACN-mixture for the peaks of high intensity to be in a linear part of the calibration lines. All samples and standards were filtered through a 0.45 μm Millex HV filter for analysis.

RESULTS AND DISCUSSION

Optimization of the Methods

DHPAL is produced in a base catalyzed aldol reaction from formaldehyde and isobutyraldehyde. DMPD is produced either by a Cannizzaro reaction or

by catalytic hydrogenation of DHPAL. The reactants (FA, IBAL), and the intermediate DHPAL may be oxidised to corresponding acids, which can form an ester with the alcohols obtained in hydrogenation. In addition, DHPAL can form a Tishchenko ester (DPDP) in a base catalyzed reaction. Thus, a mixture of several compounds is obtained. In addition to the reactions presented above, there is also an equilibrium reaction between the different forms of DHPAL: monomeric, acyclic dimer, and cyclic dimer.[2,3]

In the analysis one has to take into account this reaction in sample preparation, in order to get reliable quantitative results. The samples and DHPAL standards must be dilute and acidic enough for the equilibrium to set down to the monomer, as described previously.[5] At room temperature the time needed is 1.5 hours. Acidic conditions are also needed to change acidic compounds from ions to acids or hydroxy acids at a pH below the pKa value of the compounds. The eluent pH was kept clearly higher than 2 in order to prevent the hydrolysis of the silica based columns, even though DHPAL elutes more sharply at lower pH values. The amount of organic solvent in the eluent was also optimized.

The best separation for IBuCOOH and MAA was achieved by isocratic conditions of 8% ACN at column temperature 36°C. In the method, a stepwise gradient profile was used to elute the other compounds more rapidly. The RI detector was switched off when eluent composition was changed. Typical chromatograms are shown in Figure 2.

In a DNPH-HPLC method, the amount of water in sample and standard dilutions must be about 50% to avoid peak broadening and to enhance the linearity of the calibration lines. The derivatization reaction of an aldehyde and DNPH is an addition reaction, followed by dehydration, and needs an acid catalyst. The reaction rate increases with decreasing pH, and a large excess of the DNPH-reagent is needed to shift the equilibrium of the reaction to the side of the derivative.[9]

Addition of water either in dilution of the stock standard solution or in the sample preparation, causes the derivative to decompose relatively quickly, because the higher water content shifts the equilibrium of the derivatization reaction to the side of the reactants. The time needed for the derivatization reaction varies from 30 min to 1 h depending on the pH and the aldehyde.[9, 10] In this study, a reaction time of 60 min was used, since the presence of a hydroxy group may sterically hinder the reaction of 2,4-DNPH with the aldehyde carbonyl of DHPAL.

The gradient method using 68/32 eluent A/ACN to 10/90 eluent A/ACN in 10 minutes, gave the best resolution for early eluting hydroxy aldehydes and for late eluting aliphatic aldehydes, as shown in Figure 3. The sequence of samples

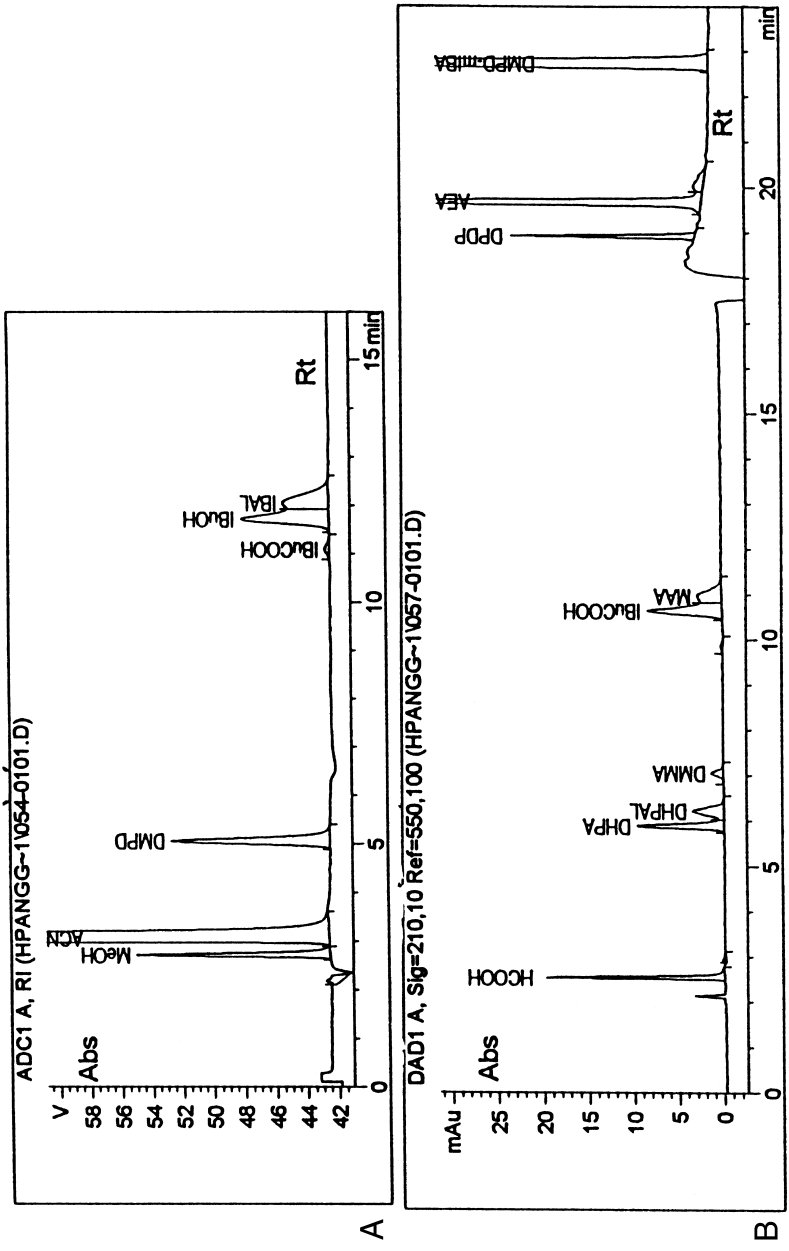

Figure 2. Chromatograms of the standard mixtures in direct RP-HPLC. Concentrations of the compounds in mg/L: (A) RI detector: MeOH 285, DMPD 198, IBuOH 213, IBAL 210. (B) UV/vis detector: HCOOH 262, DHPA 377, DHPAL 194, DMMA 32, IBuCOOH 381, MAA 0.002, DPDP 529, AEA unknown conc., DMPD-mIBA 2700.

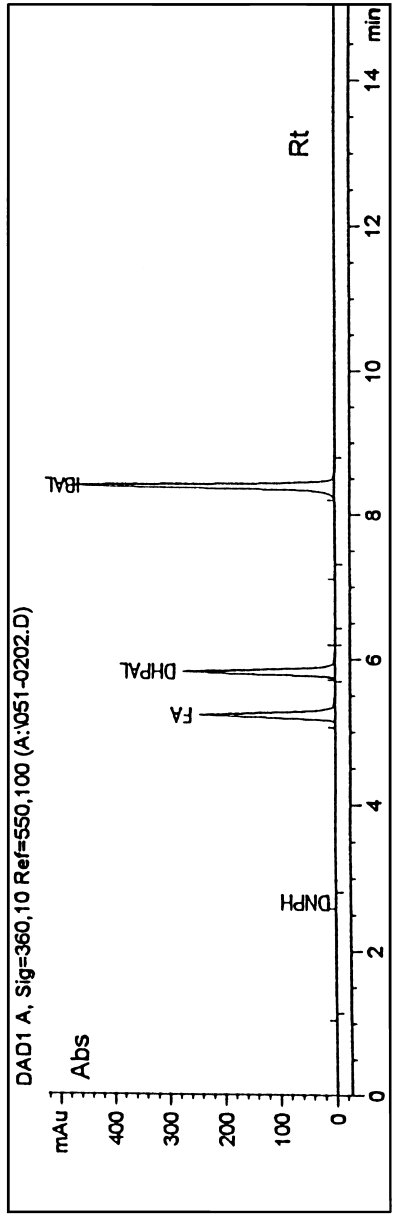

Figure 3. Chromatogram of the standard mixture of DNPH method. Concentrations of the compounds in mg/L: FA 6.3, DHPAL 25.2, IBAL 19.6.

were run daily, so, that the DNPH-derivatives in water/ACN were run first in order to prevent the derivative to decompose. After that, the longer column was switched on and the more stable samples in dilute acid were run. In that case, the longer waiting time before analysis is desirable, because then the equilibrium reaction for monomers is achieved quantitatively.

Comparison of the Results

The results obtained by a GC,[5] by a RP-HPLC,[5] and by the RP-HPLC with combined UV/RI and DNPH methods described in this paper are collected in Table 1. The first sample is from aldol addition reaction to produce DHPAL, and it is used as a feed for DMPD production (second sample).

Table 1

Results of Analysis Performed with a GC Method, HPLC Method and the Developed RP-HPLC Method.

	DHPAL Feed				DMPD Product			
			HPLC				HPLC	
Compound	**GC**	**HPLC**	**DNPH +**	**UV + RI**	**GC**	**HPLC**	**DNPH +**	**UV + RI**
FA			0.46				0.01	
MeOH	49.99			48.26	49.84			48.98
HCOOH		0.06		0.00		0.04		0.00
IBAL	4.05		4.70	3.20	0.01		0.03	
IBuOH	0.00			0.00	4.59			4.50
IBuCOOH		0.00		0.03		0.00		0.00
DHPAL	**36.03**	**31.70**	**32.90**	**33.63**	**0.14**	**0.13**	**0.16**	**0.10**
DMPD	**0.22**			**0.15**	**35.87**			**34.56**
DHPA		0.04		0.12		0.01		0.01
DPDP	0.28	0.20		0.20	0.49	0.25		0.26
DMPD-mIBA	0.10			0.16	0.11			0.21
TOT %	*90.67*	*32.00*	*38.06*	*85.75*	*91.05*	*0.43*	*0.02*	*88.62*
AEA				Present				Not Present

Table 2

Limits of Detection (mg/L) for Different Compounds

Functionality	Detector	Compound	Limits of Detection
Acid	DAD, 210 nm	HCOOH	2.8
		IBuCOOH	12.5
		MAA	0.1
		DMMA	4.7
Hydroxy Acid	DAD, 210 nm	DHPA	9.4
Hydroxy aldehyde	DAD, 210 nm	DHPAL	12.4
Ester	DAD, 210 nm	DPDP	5.8
		DMPD-mIBA	16.5
Aliphatic-aldehyde	DAD, 360 nm	FA-DNPH	0.002
		DHPAL-DNPH	0.004
		IBAL-DNPH	0.003
	RI, sens 4	IBAL	195.8
Alcohol	RI, sens 4	MeOH	70.8
		DMPD	48.2
		IBuOH	94.5

Previously, the alcohols, IBAL, and esters were determined by GC; acids, hydroxy acids, and hydroxy aldehydes by HPLC; and FA as a DNPH derivative. With the developed method, all the main compounds can be determined by one HPLC instrument - only the sample preparation is divided in two parts since derivatization is needed for aliphatic aldehydes. There are slight, but not significant, differences between the results obtained for DHPAL and DMPD by the GC and HPLC methods. If one compares the GC results of the feed and the product with each other, and the HPLC results with each other, one can note that all the aldehydes present in feed are converted to corresponding alcohols.

In addition to the compounds determined previously by HPLC, one can also determine alcohols, polyols, and aldehydes. The results show that all the compounds analyzed previously by three different instruments and methods can

now be analyzed by one HPLC instrument and by two methods. In addition to the main compounds, a side product α-ethyl acrolein (AEA) also can be seen in aldolization samples. This arises from aldol addition reaction of the impurity n-butyraldehyde followed by a dehydration of the produced aldol.

Detection Limit and Linearity

The detection limit was calculated from a system noise of 0.07 V (RI), 0.12 mAU (DAD 210 nm), and 0.03 mAU (DAD 360 nm) against the peak height of the smallest standards multiplied by two. The limits of detection are presented in Table 2. The method is most sensitive to DNPH derivatives and unsaturated compounds (AMA, MAA), and not so sensitive to aliphatic aldehydes and alcohols analyzed by RI detector. The accuracy of 0.01% is enough, though, for synthesis optimization. Peak intensities of the RI detector can be enhanced by using more sensitive settings, for example 16 or 32. The linearity of the calibration lines in UV/RI and DNPH methods are good for all the other compounds, except DHPAL and later eluting IBAL, and alcohols where peak broadening is observed. Thus, calibration was carried out using a quadratic function passing through the origin.

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Received January 31, 2000
Accepted March 22, 2000

Author's Revisions May 20, 2000
Manuscript 5252