

## Short Communication

# Enantiomeric separation of racemic hydroperoxides and related alcohols

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### ABSTRACT

Racemic hydroperoxides and alcohols were chromatographed on a chiral stationary phase consisting of cellulose tris(3,5-dimethylphenyl carbamate) coated on macroporous silica using hexane–2-propanol mobile phases. It was found that the retention ( $k'$ ) and the stereoselectivity ( $\alpha$ ) of secondary and tertiary chiral hydroperoxides and related alcohols are influenced by both the ambient temperature and water saturation of the mobile phase. The results indicate that water saturation of the mobile phase leads to decreased  $k'$  values and increased  $\alpha$ . Increasing the temperature causes a clear decrease in  $k'$  but only a slightly decrease in  $\alpha$ .

### INTRODUCTION

Organic hydroperoxides are useful oxidants for many organic substrates. In some instances non-racemic hydroperoxides have been used for the asymmetric oxidation of sulphides, but up to now with low enantioselectivity. Such optically active hydroperoxides were obtained in solution by singlet oxygenation of thiazolidine derivatives [1], as stable substances by oxidation of 2,3-unsaturated glycosides [2] or by resolution of racemic hydroperoxides by means of liquid chromatography of diastereomeric derivatives [3]. The optical purity of the hydroperoxides obtained was proved by optical rotation data or by derivatization and high-performance liquid or capillary gas chromatography of the diastereomers [3].

A direct enantiomeric separation of chiral hydro-

peroxides has not been described so far, but chiral aromatic alcohols have been separated on cellulose tribenzoate and cinnamate chiral stationary phases (CSP) [4,5]. In this work, we used a CSP consisting of cellulose tris(3,5-dimethylphenyl carbamate) coated on macroporous silica and hexane–2-propanol mobile phases. The method was found suitable for analysing enantiomers of hydroperoxides and related alcohols in the same solution.

### EXPERIMENTAL

#### *Reagents and chemicals*

The racemic alcohol **1** (Fig. 1) was purchased from E. Merck (Darmstadt, Germany); **2** was obtained by reduction of 1,2,3,4-tetrahydro-1-naphthalenone with  $\text{LiAlH}_4$  and **3** was purchased from Aldrich (Milwaukee, WI, USA). Compounds **4** and

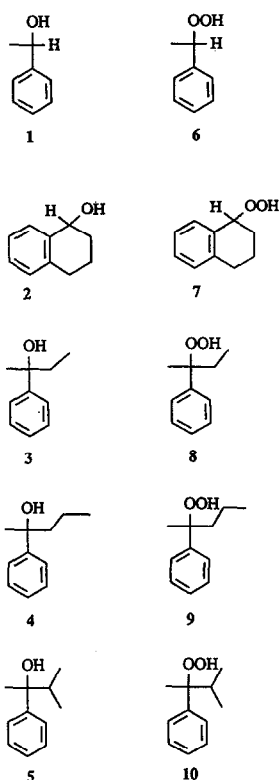


Fig. 1. Structures of racemic alcohols and hydroperoxides used.

5 were synthesized by reaction of the Grignard reagents of 1- and 2-propyl bromide, respectively, with acetophenone. The hydroperoxides 6 and 7 were obtained by autoxidation of the corresponding aralkanes [6,7]. Tertiary hydroperoxides 8–10 were prepared by the known reaction of the appropriate tertiary alcohols with hydrogen peroxide (44%) in the presence of a trace amount of sulphuric acid [8]. The purity of the hydroperoxides was determined by iodometric titration and found to be 70–95%.

The CSP cellulose tris(3,5-dimethylphenyl carbamate)-coated Nucleosil-4000-NH<sub>2</sub> (CDMPC) was prepared according to a procedure described by Okamoto *et al.* [9]. The column (250 × 4.6 mm I.D.) was packed by a slurry method at 300 kg/cm<sup>2</sup> with hexane as the eluent. The plate number [*N* for benzene; hexane–2-propanol (90:10), 0.5 ml/min] and the dead time (*t*<sub>0</sub> of 1,3,5-tri-*tert.*-butylbenzene as a non-retained compound [10]) of the column were estimated to be 3800 and 6.0 min, respectively.

The mobile phase was composed of UV-grade

hexane (PCK, Schwedt, Germany) and analytical reagent grade 2-propanol (Riedel-de Haën, Seelze-Hannover, Germany).

#### Apparatus and chromatographic conditions

The high-performance liquid chromatographic equipment consisted of a Type 7095 injection valve (20- $\mu$ l loop), a Type 364.00 pump, a Type 287.00 variable-wavelength spectrophotometer, a Model A1000 chiral detector (all from Knauer, Berlin, Germany) and a Model K201 recorder (Carl Zeiss, Jena, Germany).

The detection wavelength and the flow-rate were set at 254 nm and 1 ml/min, respectively. The column temperature was maintained either using a column oven (25 and 52°C) or by cooling the column in a Dewar container with ice–water (0°C). The solutes were dissolved in hexane–2-propanol (90:10) at a concentration of 0.1 and 1 mg/ml, respectively, when the UV and chiral detector were used in series.

#### RESULTS AND DISCUSSION

The chiral alcohols and hydroperoxides used as solutes are shown in Fig. 1. The chromatographic results obtained with dried and water-saturated mobile phase on the one hand and changing the column temperature on the other are given in Tables I and II, respectively. Fig. 2 shows the chromatogram

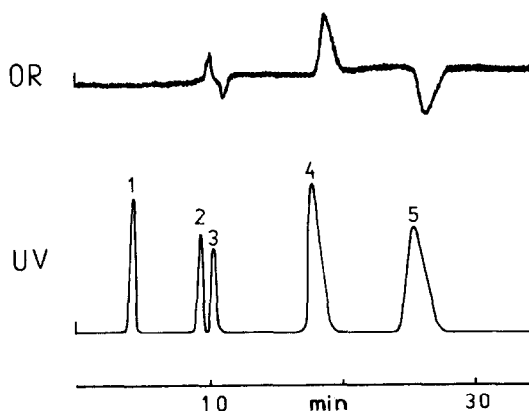


Fig. 2. Optical resolution of partly decomposed 1-methyl-1-phenylpropyl hydroperoxide (8). Eluent: water-saturated hexane–2-propanol (98:2, v/v). Top, optical rotation; bottom, UV detection. Peaks: (1) unknown; (2) (+)-enantiomer and (3) (–)-enantiomer of the related alcohol; (4) (+)-enantiomer and (5) (–)-enantiomer of the hydroperoxide.

TABLE I

EFFECT OF WATER SATURATION OF THE MOBILE PHASE ON THE RETENTION AND STEREOCHEMICAL RESOLUTION OF RACEMIC ALCOHOLS AND HYDROPEROXIDES (1-10)

Mobile phase: hexane-2-propanol (98:2, v/v). Column temperature: 25°C.

Compounds	Solute <sup>a</sup>	A <sup>b</sup>			B <sup>b</sup>			Enantiomeric elution order
		$k_1^c$	$\alpha$	$R_s$	$k_1^c$	$\alpha$	$R_s$	
Alcohols	<b>1</b>	4.34	1.28	2.69	3.78	1.44	3.34	+/-
	<b>2</b>	4.18	1.11	1.03	3.51	1.21	1.97	+/-
	<b>3</b>	2.09	1.00	0.00	1.88	1.24	1.83	+/-
	<b>4</b>	2.63	1.04	0.52	2.27	1.22	1.85	+/-
	<b>5</b>	1.91	1.21	1.94	1.50	1.34	2.71	+/-
Hydroperoxides	<b>6</b>	8.15	1.33	3.70	6.82	1.35	4.09	+/-
	<b>7</b>	10.76	1.17	1.86	8.65	1.20	2.24	+/-
	<b>8</b>	5.84	1.49	4.16	4.86	1.53	4.62	+/-
	<b>9</b>	7.06	1.49	4.42	5.49	1.56	4.95	+/-
	<b>10</b>	5.82	1.96	6.25	4.41	2.22	7.17	+/-

<sup>a</sup> See Fig. 1 for structures.<sup>b</sup> A, mobile phase dried with molecular sieve; B, mobile phase water saturated.<sup>c</sup> Capacity factor of the first-eluted enantiomer.

of the partly decomposed hydroperoxide **8**. In all instances the optical rotation of the first-eluting enantiomer of the alcohols and of the hydroperoxides was positive. Generally, a better optical resolution and longer retention times were obtained for

appropriate hydroperoxides.

#### *Effect of water on retention and stereoselectivity*

As can be seen from Table I, the amount of water in the mobile phase influences the retention ( $k'$ ), the

TABLE II

EFFECT OF COLUMN TEMPERATURE ON THE RETENTION AND STEREOCHEMICAL RESOLUTION OF RACEMIC ALCOHOLS AND HYDROPEROXIDES (1-10)

Mobile phase: hexane-2-propanol (98:2, v/v) dried with molecular sieve.

Solute <sup>a</sup>	52°C			25°C			0°C		
	$k_1^b$	$\alpha$	$R_s$	$k_1^b$	$\alpha$	$R_s$	$k_1^b$	$\alpha$	$R_s$
<b>1</b>	3.69	1.22	2.24	4.34	1.28	2.69	4.90	1.38	2.81
<b>3</b>	3.54	1.11	1.37	4.18	1.11	1.03	4.59	1.12	0.94
<b>3</b>	1.95	1.00	0.00	2.09	1.00	0.00	2.82	1.08	0.69
<b>4</b>	ND <sup>c</sup>	ND	ND	2.63	1.04	0.52	3.13	1.13	1.15
<b>5</b>	1.58	1.11	1.02	1.91	1.21	1.94	2.78	1.00	0.00
<b>6</b>	6.70	1.28	3.14	8.15	1.33	3.70	10.34	1.41	3.94
<b>7</b>	9.11	1.12	1.64	10.76	1.17	1.86	12.74	1.20	1.68
<b>8</b>	4.69	1.42	3.89	5.84	1.49	4.16	7.77	1.60	4.95
<b>9</b>	ND	ND	ND	7.06	1.49	4.42	8.77	1.68	5.02
<b>10</b>	ND	ND	ND	5.82	1.96	6.25	7.59	3.01	7.97

<sup>a</sup> See Fig. 1 for structures.<sup>b</sup> Capacity factor of the first-eluted enantiomer.<sup>c</sup> ND: not determined.

separation factor ( $\alpha$ ) and the resolution ( $R_s$ ) considerably. Generally, retention times decreased and  $\alpha$  increased when water-saturated eluents were used. Without water **3** could not be separated and only a poor optical resolution of **4** could be achieved. Hydrogen bonding of the OH groups of alcohols and of hydroperoxides with the CSP is one factor affecting the separation of enantiomers. There are not only interactions possible with the cellulose carbamate but also those with the residual OH groups of the silica, which also contribute to retention too. If water interacts with silanol groups, the indifferent interaction of the solutes should become smaller and the retention time could decrease. The chiral interaction with the cellulose carbamate becomes predominant and  $\alpha$  increases.

The most bulky alcohol **5**, was separated with a relatively high  $\alpha$  at a relatively short retention time also without water. This can be caused on the one hand by a better steric fit in the chiral phase and on the other hand by the difficulty of reaching the OH groups of the silica.

We also performed a normal-phase separation (Si-60 column) of a mixture of 1-methyl-1-phenylpropanol (**3**) and the related hydroperoxide **8** in order to obtain more information about the influence of water or indifferent interactions with silanol groups, respectively. Using dried eluent [hexane-2-propanol (99.5:0.5)], the capacity factors of **8** and **3** were 3.31 and 4.02, respectively, whereas with water saturation the  $k'$  values were 4.54 and 4.10, respectively. Hence traces of water in the eluent in a normal-phase separation led to increasing retention times and a reversed elution order, *i.e.*, the retention mechanism changes. Moreover, in a normal-phase separation a much stronger effect of water addition on the hydroperoxide solute compared with the corresponding alcohol was found, the opposite of what happened with the chiral column. However, the effect of water on the retention and stereoselectivity seems to be caused by a more complex retention mechanism and further investigations are necessary.

#### *Effect of temperature*

As can be seen from Table II, there is also an influence of the ambient temperature on the reten-

tion ( $k'$ ), separation factor ( $\alpha$ ) and stereochemical resolution ( $R_s$ ) of solutes **1–10**. Increasing the temperature leads in all instance to decreased  $k'$  values, which means that the mobility of the solutes increases with increasing temperature and the interactions with the CSP decrease.

In most instances, except for **5**,  $\alpha$  decreases slightly with increasing temperature. These findings correspond to a longer retention time at lower temperature, *i.e.*, a longer interaction with the CSP occurs. Most striking is the resolution behaviour of **5**. No separation at all occurs at 0°C, whereas for the corresponding hydroperoxide **10** the highest separation factor of all ( $\alpha = 3.01$ ) was obtained. No explanation can be given.

#### CONCLUSIONS

The CDMPC CSP is suitable for the separation of chiral hydroperoxides and alcohols. Water-saturated eluents effect increasing separation factors of the solutes investigated.

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