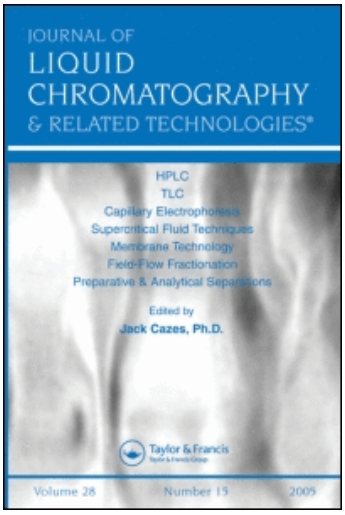

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ENANTIOMERIC SEPARATION OF UNDERIVATIZED ALIPHATIC AND AROMATIC β-AMINOALCOHOLS BY REVERSED-PHASE LIQUID CHROMATOGRAPHY WITH A CHIRAL MOBILE PHASE

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ABSTRACT

Underivatized aliphatic and aromatic β-aminoalcohols with a primary or secondary alcohol moiety could be separated into enatiomers by revered-phase liquid chromatography with a chiral mobile phase containing copper(II), L-proline and barbital(or its analogues).

INTRODUCTION

Since the compounds containing chiral β-aminoalcohol moiety are important in pharmaceutical science[1-3] and organic chemistry[4,5], a number of enantiomeric separation

methods by high-performance liquid chromatography have been developed[6]. Indirect methods using chiral[7] or achiral[8] precolumn derivatizing reagents could be applicable in separating both aliphatic and aromatic β-aminoalcohols as into enantiomers. Direct methods using no precolumn derivatization have applicability that is limited to only aromatic β-aminoalcohols, such as ephedrine-like and propranolol-like compounds[9], and not to any aliphatic β-aminoalcohols.

Previous studies[10] in our laboratory showed that underivatized aromatic β-aminoalcohols could be separated into enantiomers by ligand exchange chromatography (LEC) using a copper(II) solution as a mobile phase and octadecylsilanized silica gel (ODS) coated with N-n-dodecyl-L-hydroxyproline(C12-Hyp) as a stationary phase.

On the other hand, for underivatized aliphatic β-aminoalcohols, our attempts using this methodology were unsuccessful, resulting in no retention or a low separation factor.

Gil-Av and coworkers reported enantiomeric separation of underivatized amino acids by LEC using an ODS column and a chiral mobile phase which was an aqueous solution of copper(II) and L-proline[11]. Their method was also

inapplicable to underivatized aliphatic and aromatic β-aminoalcohols. We discovered that addition of barbital to their mobile phase improved the separations of various β-aminoalcohols on ODS column.

EXPERIMENTAL

Samples

The β-aminoalcohols studied are listed in Table 1. Compound 1, 2, 3, (S)-1, (S)-2, (R)-4, and (S)-4 were purchased from commercial sources. Compound (R)-3 was prepared by amination of[12] of (R)-styrene oxide (commercially available).

Chromatography

Chromatography used in this work is described in the caption of Figure 1.

RESULTS AND DISCUSSION

Examples of the direct separation of aminopropanols using a mobile phase containing phenobarbital are shown in Figure 1. The β-aminoalcohols shown in Table 1 were all well separated. Compound 1 and 3 contain an amino group attached to a primary carbon atom and a secondary alcohol

TABLE 1 Enantiomeric Separation of β-Aminoalcohol[a]

$H_2NCHR_2CH(OH)R_1$

compound	R_1	R_2	k'_1[b]	EF[c]	α[d]	mobile phase
1	H	CH_3	2.77	R	1.34	a
2	CH_3	H	1.04	R	1.66	a
3	H	C_6H_5	3.96	R	1.26	b
4	C_6H_5	H	4.43	R	1.59	b

[a]Conditions are shown in Figure 2. [b]Taurine was used as a marker for t_0, $k'=(t_R-t_0)/t_0$, $\alpha=k'_1/k'_2$, where t_0 is the retention time of nonretarded solute, k'_1, the capacity factor of the first eluted enantiomer, [c]EF, the configuration of the first eluted enantiomer and [d]α, the separation factor. Mobile phase: a), 10 mM MOPS buffer solution (pH 7.5) containing 4 mM copper(II) acetate, 8 mM L-proline, 10 mM barbital and 20 mM triethylamine ; b), mixture of one volume of acetonitrile and 9 volumes of mobile phase a (pH 7.0). Other conditions are as in Figure 1.

group, conversely, compound 2 and 4 contain an amino group attached to a secondary carbon atom and a primary alcohol group. To shorten the retention time of the aromatic β-aminoalcohols, the mobile phase with minor modification was used. It should be notice that the elution order of all the enantiomers is R before S.

Figure 2 shows the effect of the barbital concentration in the mobile phase on the separation of aiphatic β-aminoalcohols. Though barbital is achiral, the barbital concentration in the mobile phase was critical for the

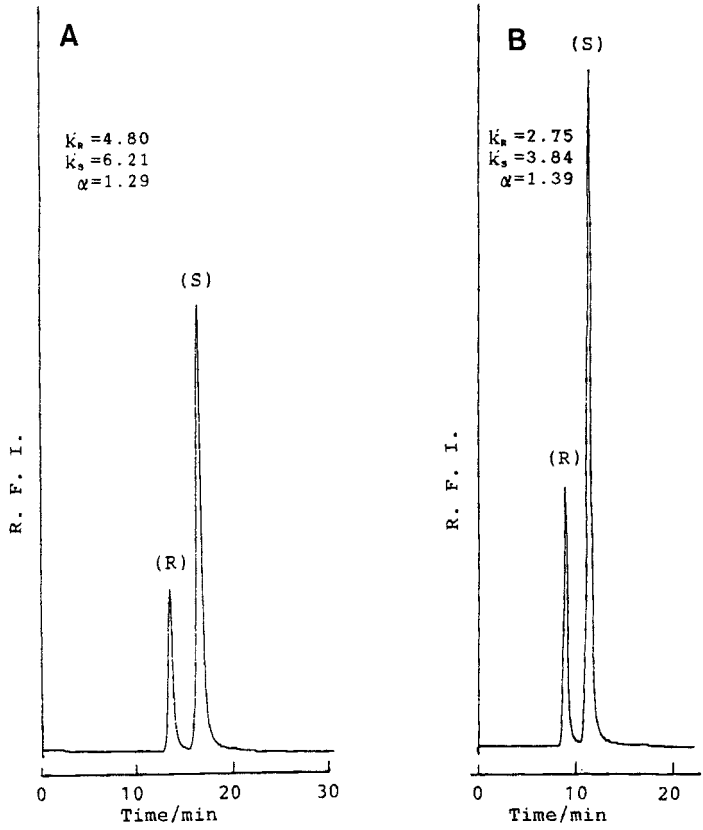

FIGURE 1. Chromatograms of (A) 1-amino-2-propanol and (B) 2-amino-1-propanol. Column: 150 × 4 (i.d.) mm self packed with Develosil ODS-5 (Nomura Chemicals, Gifu, Japan). Mobile phase: 4-morpholinepropanesulfonic acid(MOPS) buffer containing 4 mM copper(II) acetate, 8 mM L-proline, 2 mM phenobarbital and 20 mM triethylamine. The pH was adjusted with NaOH or acetic acid to 7.5. Flow rate, 0.5 ml/min; sample size, 20 μl containing 2μg of aminopropanol (R/S=1/3); detection, postcolumn reaction using o-phthaldehyde (See Reference 11). R. F. I. ▫ relative fluorescence intensity.

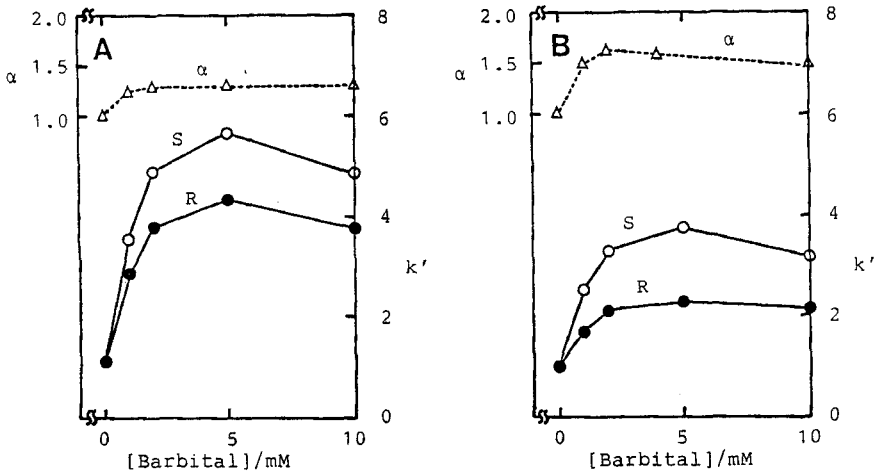

FIGURE 2. Effect of the barbital concentration in the mobile phase on the separation of (A) 1-amino-2-propanol and(B) 2-amino-1-propanol enantiomers. Mobile phase: MOPS buffer containing 4 mM copper(II) acetate, 8 mM L-proline, barbital of varying concentration(pH 7.5). Other conditions as in Figure 1.

separation. Separation did not occur in the absence of the barbital. Also, aromatic β-aminoalcohols could not be separated with a mobile phase containing no barbital.

To secure the buffer action of the mobile phase containing no barbital, MOPS, which is one of Good's buffer reagent was used. Similar compound such as barbituric acid, ε-caprolactum, glycine anhydride and 3,3'-dimethylglutarimide were used as the barbital subsitutes. The capacity factors of aminopropanols under

the conditions described in Figure 1 using a mobile phase containing the subsitute(2 mM) were ≦0.6. Substantially, these compounds had no effect on the separations. Barbital can be replacedby other barbital analogues such as amobatbital and phenobarbital (Fig. 1). However, the mechanism of the barbital synergistic effect cannot be inferred from the present results.

The separation was also strongly dependent on the pH of the mobile phase. The influences on the separation of aminopropanol enantiomers were studied over the pH range of 5-8. Increasing the pH of the mobile phase results in greater retention and better separation of the enantiomers. To avoid the deterioration of the ODS, pH values above 8.0 were not studied. Because of smaller capacity factors and/or separation factors, the unsatisfactory separations were obtained at pH value below 6.0. The pH 7-7.5 was sufficient for the separation on the ODS column.

To decrease the tailing of the aminopropanol peak on a silica-base column trietylamine was added to the mobile phase. The triethylamine addition influenced the capacity factors for decreasing and did not the separation factors when triethylamine was used in the concentration

range 0-30 mM. Use of a 20 mM concentration of treiethylamine results in increased the separation.

This study has shown that the enantiomeric separation of underivatized aliphatic or aromatic β-aminoalcohols with a primary or secondary alcohol moiety on ODS column could be improved by barbital(or its analogues) addition to the mobile phase containing copper(II) and L-proline.

After this work, also we found that enanantiomeric separation of aiphatic aminoalcohols by LEC using C12-Hyp coated ODS as a stationary phase could be improved by barbital addtion to the mobile phase containing copper(II). The details will be published elsewhere.

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