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Efficient enantiomeric resolution via introduction of a fluorous tag as a resolving reagent with β-cyclodextrin columns: model study on fluorinated *O*-acetylmandelate and ibuprofen amide

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Abstract—Efficient enantiomeric resolution of racemates is performed by introduction of fluorous tags using β-cyclodextrin columns. Selection of appropriate length of tag and mobile phase leads to an efficient resolution of racemates (fluorinated *O*-acetylmandelate and ibuprofen amide) by those columns.

β and γ-Cyclodextrin (CD) form two types of inclusion complexes with fluorous compounds depending on the length of perfluoroalkyl group in aqueous solution.[1,2] Recently, we have reported that this feature can be applied to separate a mixture of compounds bearing different lengths of fluorous tags by β-CD columns (SUMICHIRAL® OA-7000 series).[3] SUMICHIRAL OA-7000 series can separate several racemic compounds depending on the chirality of glucose in reverse phase.[4] It occurred to us that enantiomeric resolution of fluorous-tagged compounds with β-CD columns could be more efficient than that with ordinary chiral columns, in combination of the fluorous tag discrimination and the asymmetric discrimination of β-CD. Herein, we report the enantiomeric resolution of racemic compounds bearing fluorous tags with β-CD columns.

First, the effect of the length of fluorous tags in enantiomeric resolution was examined using *O*-acetylmandelate (Scheme 1). SUMICHIRAL OA-7100 and OA-7500 were used as β-CD columns. These columns have alkyl spacer linking β-CD and silica gel. OA-7100 is packed with unmodified β-CD, while OA-7500 is packed with β-CD in which the hydroxyl groups are protected by methyl groups. Therefore, OA-7500 is effective for the resolution of less polar *O*-acetylmandelate (mobile phase: methanol/water = 80/20). The longer the length of fluorous tag was, the larger R_s values[5] could be obtained, and R_s value of ester bearing C7 fluorous tag was very large (Scheme 1, (c)). However, R_s value of ester bearing C9 fluorous tag was lower than that of ester bearing C3 fluorous tag (Scheme 1, (d)). The reason might be the low solubility of ester bearing C9 fluorous tag in the reverse phase (F content of C_9F_{19} *O*-acetylmandelate: 53.4%).

The comparison of fluorous and hydrocarbon tags in view of efficiency for enantiomeric resolution was envisioned using *O*-acetylmandelate (Scheme 2). The following separation conditions were used; column: OA-7500, mobile phase: methanol/water = 75/25. The racemic ester bearing C7 fluorous tag was separated completely, while the racemic ester bearing C7 hydrocarbon tag was not separated at all. This clearly shows the efficiency of fluorous tag over the corresponding hydrocarbon tags in enantiomeric resolution with β-CD columns.

The effect of water in enantiomeric resolution was further examined using *O*-acetylmandelate bearing C7 fluorous tag (Scheme 3). R_s value increased with increase in the ratio of water in the mobile phase. Therefore, hydrophobic effect of β-CD column is probably important for the discriminating racemates bearing fluorous tags.

Keywords: β-cyclodextrin; liquid chromatography; optical resolution; fluorine chemistry.

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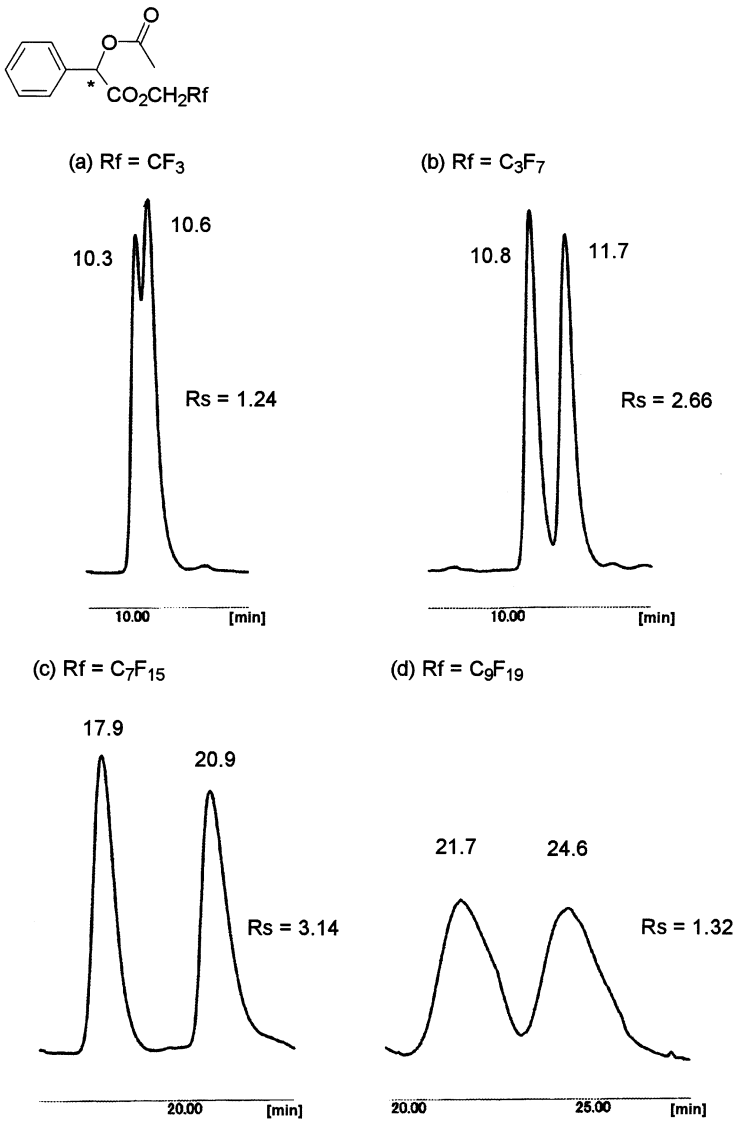

Scheme 1. The effect of length of fluorous tag in enantiomeric resolution. Column: OA-7500; mobile phase, methanol–water (80/20, v/v); flow rate, 0.5 mL/min; detecter, absorption at 254 nm; column temperature, 20°C.

Enantiomeric resolution of ibuprofen, a very common drug, was also examined (Scheme 4). Ibuprofen has only a carboxyl group as a functional group and hence the effect of fluorous tags in optical resolution can be precisely estimated. Ibuprofen ester bearing C7 fluorous tag was not well separated irrespective of the ratio of water in mobile phase and column temperature. However, transformation of ibuprofen ester to higher polar ibuprofen amide led to a complete resolution of the enantiomers by OA-7100. Unmodified β-CD-based OA-7100 is more effective for the resolution of higher polar racemic compounds than the methyl-protected β-CD-based OA-7500.

We have thus established efficient optical resolution of racemic compounds by introduction of fluorous tags using β-CD columns. Fluorous tags, after removal from the enantiopure compounds after optical resolution, can be easily recovered by liquid-liquid or liquid-solid extraction[6] and recycled in the next resolution.

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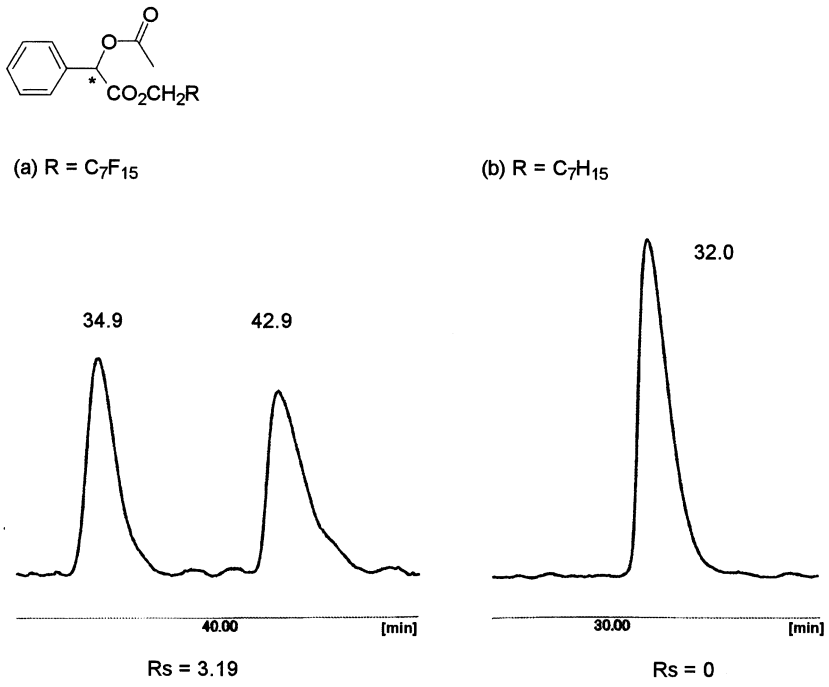
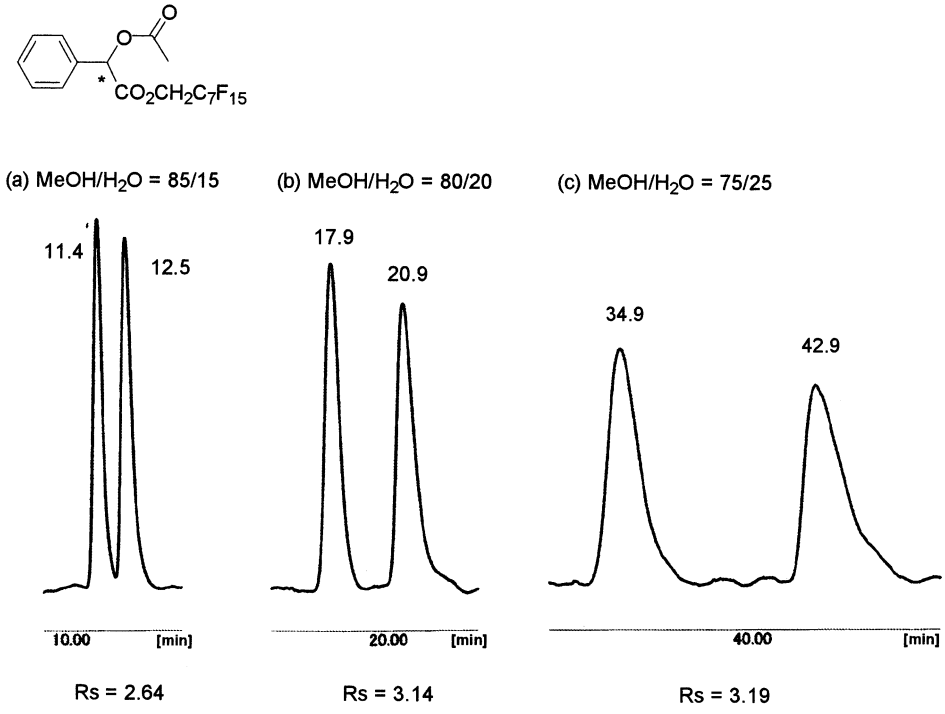
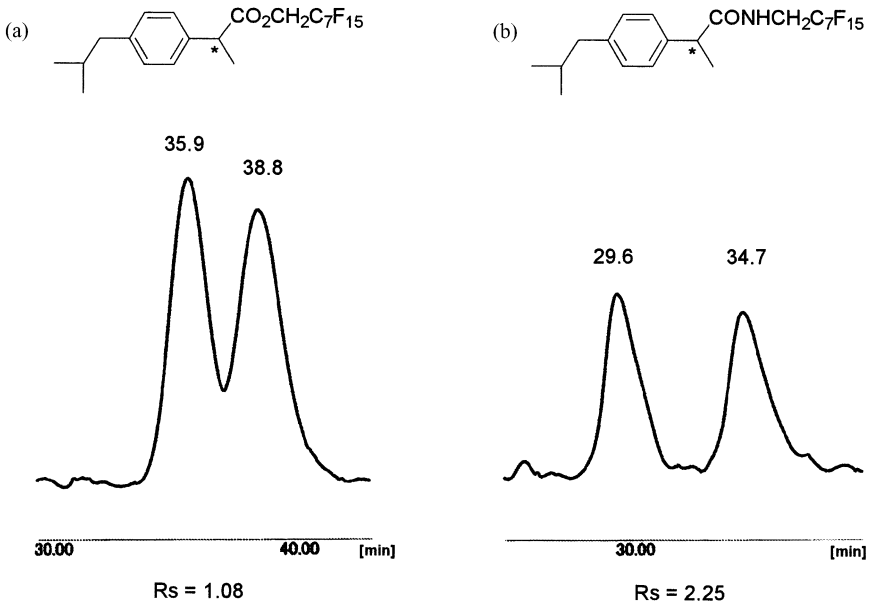


Scheme 2. The tag effect in enantiomeric resolution. Column: OA-7500; mobile phase, methanol–water (75/25, v/v); flow rate, 0.5 mL/min; detecter, absorption at 254 nm; column temperature, 20°C.



Scheme 3. The effect of water in enantiomeric resolution. Column: OA-7500; flow rate, 0.5 mL/min; detecter, absorption at 254 nm; column temperature, 20°C.



Scheme 4. Enantiomeric resolution of ibuprofen derivatives: (a) Column: OA-7500; mobile phase, methanol–water (82/18, v/v); flow rate, 0.5 mL/min; detecter, adsorption at 254 nm; column temperature, 12°C. (b) Column: OA-7100; mobile phase, methanol–water (85/15, v/v); flow rate, 0.5 mL/min; detecter, absorption at 254 nm; column temperature, 20°C.

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5. In this study, normalized value of resolution (R_s) is employed to evaluate the efficiency of resolution. This is the value to be calculated by sharpness, retention time and selectivity of the peak and given by Eq. (1).

$$R_s = 1/4(N)^{1/2}((\alpha-1)/\alpha)(k'/(k'+1)) \quad (1)$$

In Eq. (1), N is theoretical plate number, α is separation factor and k' is capacity factor. In $R_s \geq 1.25$, it is defined that two peaks are completely separated. For detailed account, see: Kirkland, J. J. *Modern Practice of Liquid Chromatography*; Wiley-Interscience: New York, 1971.
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