Highly Efficient Discrimination of Fluorous Tags by β-Cyclodextrin Columns: New Isolation Method for Fluorous Mixture Synthesis

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Abstract: High performance liquid chromatography (HPLC) packed with β-cyclodextrin columns eluted by reversed phase or fluorous phase shows excellent discrimination of fluorous tags. β-Cyclodextrin columns are superior to fluorous silica gel columns in view of efficient separation of compounds bearing short (CF_3) to long (C_9F_{19}) tag.

Key words: β-cyclodextrin, chromatography, separation technique, combinatorial chemistry, fluorine chemistry

In preparation of lanthanide tris(perfluoroalkylsulfonyl)methide- and bis(perfluoroalkylsulfonyl)amide-cyclodextrins (CDs) inclusion complexes, we observed that one β- or γ-CD included four carbon perfluoroalkyl group and two β- or γ-CDs included eight carbon perfluoroalkyl group (Figure 1).[1] Wilson and Verrall also reported similar carbon number-dependent inclusion phenomena by measuring the apparent molar volumes of perfluorocarbon surfactants and β-CD in water and in ternary aqueous solutions.[2] It occured to us that HPLC columns packed with β- or γ-CD might discriminate a variety of fluorous tags defending on the difference in fluorocarbon numbers. Recently, Curran has reported fluorous tagging technique (fluorous mixture synthesis),[3] where a combinatorial library of compounds can be prepared in solution phase rather than in solid phase. Compounds bearing different fluorine content of tags can be separated using HPLC columns with branched fluorocarbon-bonded silica gel[4] (Fluofix® 120E[5] originally produced by Neos Company, Japan). Fluorous silica gel columns are suitable for separation of a mixture of compounds bearing medium to long fluorous tags but not for short to long fluorous tags in short time. In order to construct many combinatorial libraries, a new method has to be developed for separation of a mixture of compounds bearing a wide range of fluorous tags in short time.

We tested the separation ability of β-CD column (SUMICHIRAL® OA-7000 series[6]) for various compounds bearing different fluorous tags. SUMICHIRAL OA-7000 series are of three types, depending on the difference of the spacer between silica gel and β-CD.[7] Esters **1** and sulfonates **2** were selected as test samples, because these functional groups are important as the protecting group of alcohols in organic synthesis.

We first examined discrimination of fluorous tag in reversed phase because β-CD formed the inclusion complexes with perfluoroalkyl compounds efficiently in aqueous solution. The separation conditions for a series of fluorinated esters **1** were as follows; column: SUMICHIRAL OA-7500, mobile phase: acetonitrile/water, flow rate: 0.7 mL/min. In acetonitrile/water = 65/35, five fluorinated esters were eluted in order of fluorine content from CF_3 up to C_9F_{19} (Figure 2). This observation was consistent with the degree of inclusion of perfluoroalkyl compounds for β-CD. The retention time of esters bearing long fluorous tag was long in the β-CD column. This separation became more obvious by changing the ratio of water in mobile phase. In changing the ratio of acetonitrile/water from 65/35 to 60/40 and 55/45, separation ability of the β-CD column was improved; especially the retention time of **1d** and **1e** was longer than that of the other esters (Figure 2).

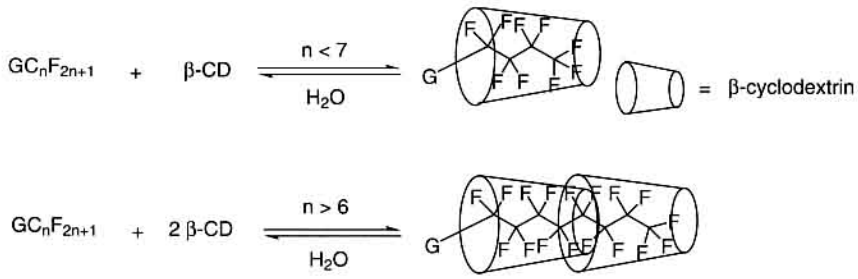

Figure 1 Formation of inclusion complexes with fluorous compounds in aqueous media.

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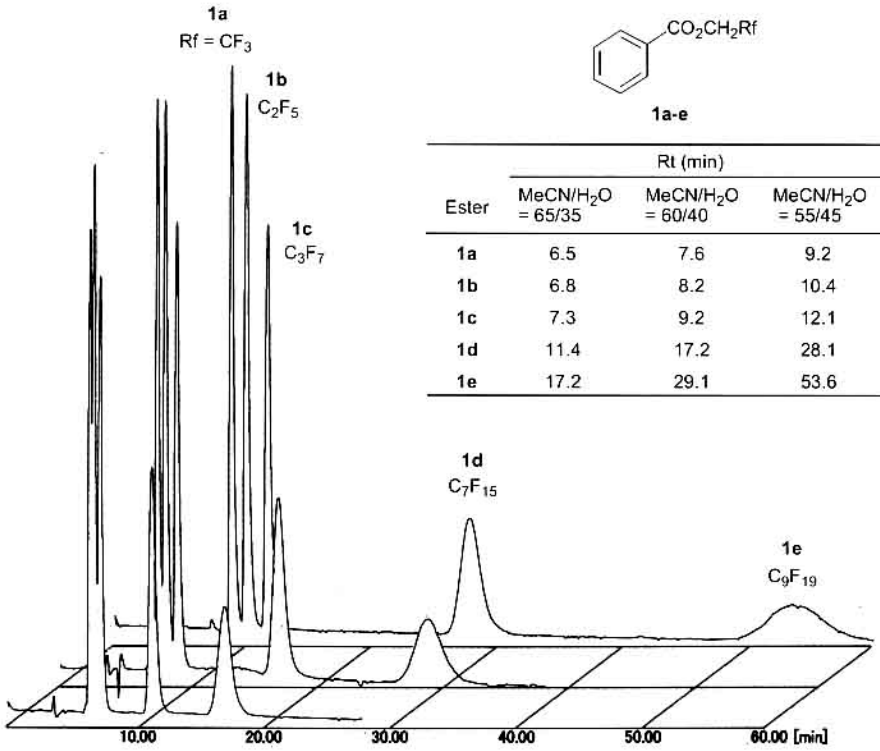


1a-e

Ester	Rt (min) MeCN/H_2O = 65/35	MeCN/H_2O = 60/40	MeCN/H_2O = 55/45
1a	6.5	7.6	9.2
1b	6.8	8.2	10.4
1c	7.3	9.2	12.1
1d	11.4	17.2	28.1
1e	17.2	29.1	53.6

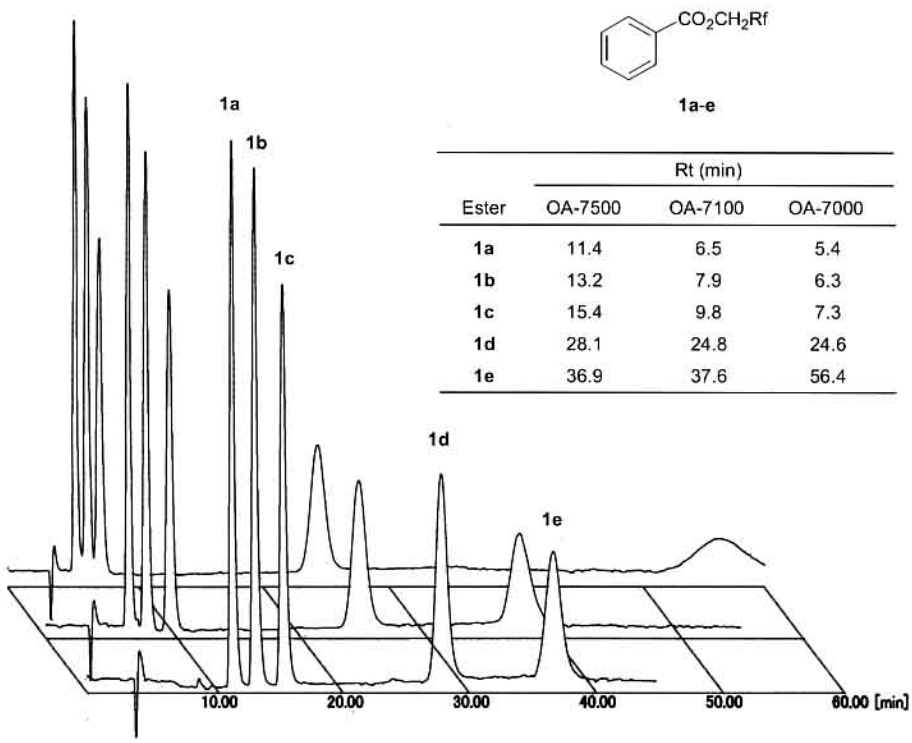
Figure 2 Separation of fluorinated esters **1a–e** with OA-7500. Bottom: CH_3CN/H_2O = 65/35. Middle: CH_3CN/H_2O = 60/40. Top: CH_3CN/H_2O = 55/45. Flow rate: 0.7 mL/min.

The result of optimum separation conditions of fluorinated esters **1** in OA-7500 is shown in Figure 3. When the mobile phase was a gradient starting with 50% acetonitrile/water and increasing the ratio to 65% acetonitrile/water over 30 minutes, five fluorinated esters could be separated efficiently and eluted within 40 minutes The comparison of separability of OA-7000 series was performed in these separation conditions (Figure 3). When OA-7100, which had the spacer similar to OA-7500 and unmodified β-CD, was used, the separability of OA-7100 was poor than that of OA-7500 and retention time of **1a**, **1b** and **1c** was short. When OA-7000, which had unmodified β-CD and saccharide spacer, was used, the retention time of esters was shorter than that of esters with OA-7100. Interestingly, retention time of ester **1e** bearing C_9F_{19} tag was only long with OA-7000.

Figure 4 shows the HPLC chromatogram of fluorinated sulfonates **2** with OA-7000 series. By testing OA-7000 series, OA-7000 and OA-7100 gave the best separation of these samples (mobile phase: methanol/water). Separation of fluorinated esters **1** and sulfonates **2** with OA-7000 series indicates that the polarity of samples determines the suitable OA-7000 series; OA-7500 is suitable for less polar samples such as an ester, OA-7000 and OA-7100 are suitable for highly polar samples such as a sulfonate.[8] The difference of this separability is explained by polarity of the β-CD columns. OA-7000 and OA-7100 are of high polarity of unmodified β-CDs bonded to silica gel, whereas OA-7500 is of less polarity of methylated β-CDs. When fluorinated sulfonates **2** were separated with OA-7000, the retention time of sulfonate **2e** bearing C_9F_{19} tag was only long in similar to separate ester **1** with OA-7000.

The separability of β-CD column (OA-7500) was then compared with that of fluorous silica gel column (Fluofix 120E) using fluorinated esters **1** as a sample. In order to compare easily with Fluofix 120E, the mobile phase giving a good separation of fluorinated esters with OA-7500 was employed. Although Fluofix 120E was able to separate esters **1a**, **1b** and **1c** within 40 minutes, the others **1d** and **1e** were not eluted within 60 minutes.[9] So we next examined the mobile phase which gave the good separation of esters **1** within 40 minutes by Fluofix 120E. The optimal mobile phase for Fluofix 120E was a gradient starting with 85% acetonitrile/water and increasing to 100% acetonitrile over 30 minutes (Figure 5). Under the best gradient conditions for OA-7500, it may be concluded that Fluofix 120E is suitable for the separation of esters bearing long fluorous tag but not for the separation of esters bearing short fluorous tag (CF_3, C_2F_5, C_3F_7). If Fluofix 120E gave good separation of esters bearing short fluorous tag, elution time of esters bearing long fluorous tag would be too long. Contrary to Fluofix 120E, the β-CD column could efficiently separate all fluorinated compounds within reasonable retention time.

SUMICHIRAL OA-7000 series do not deteriorate with normal mobile phase. Therefore fluorous tag discrimination of β-CD was also examined in normal phase (Figure 6). When fluorinated esters **1** were separated with



Ester	Rt (min) OA-7500	OA-7100	OA-7000
1a	11.4	6.5	5.4
1b	13.2	7.9	6.3
1c	15.4	9.8	7.3
1d	28.1	24.8	24.6
1e	36.9	37.6	56.4

Figure 3 Separation of fluorinated esters **1a–e** with SUMICHIRAL OA-7000 series. Bottom: OA-7500, Middle: OA-7100, Top: OA-7000. Mobile phase: 0 to 30 min, 50% CH_3CN/H_2O up to 65% CH_3CN/H_2O; 30 to 60 min, 65% CH_3CN/H_2O. Flow rate: 0.7 mL/min.

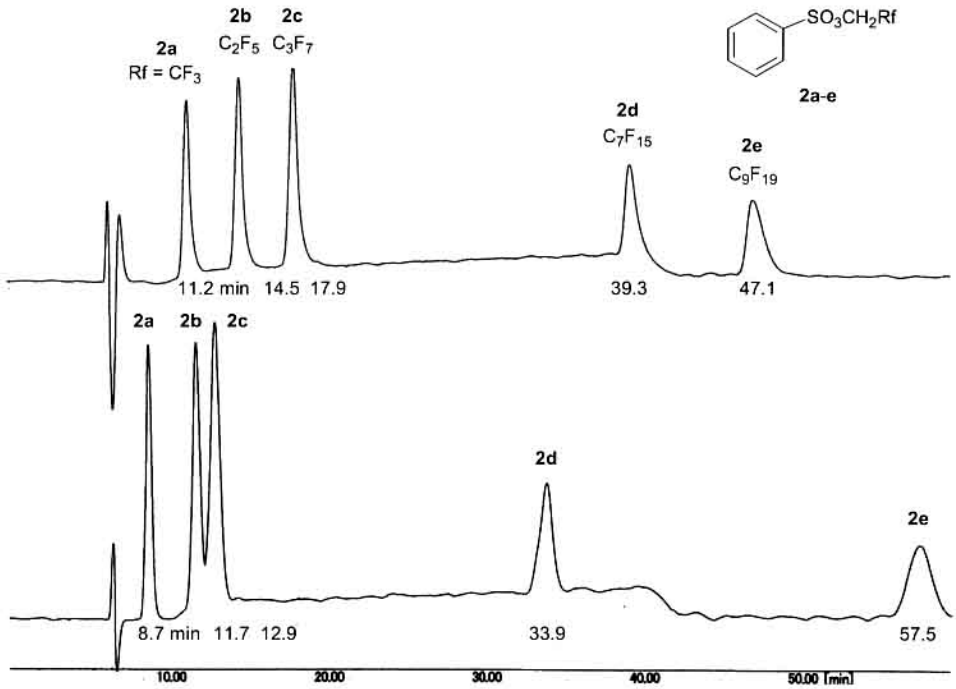


Figure 4 Separation of fluorinated sulfonates **2a–e** with OA-7000 and OA-7100. Bottom: OA-7000, Top: OA-7100. Mobile phase: 0 to 30 min, 70% CH_3OH/H_2O up to 85% CH_3OH/H_2O; 30 to 60 min, 85% CH_3OH/H_2O. Flow rate: 0.5 mL/min.

OA-7500 in hexane as a mobile phase, five esters were eluted in order of fluorine content from C_9F_{19} up to CF_3 without inclusion in β-CD and esters **1a**, **1b** and **1c** were separated. In addition, when fluorinated sulfonates **2**, which were higher polarity than fluorinated esters **1**, were separated with OA-7100 in hexane as a mobile phase, sulfonates **2a**, **2b** and **2c** were completely separated.[10] Separation of the compounds bearing short fluorous tag in

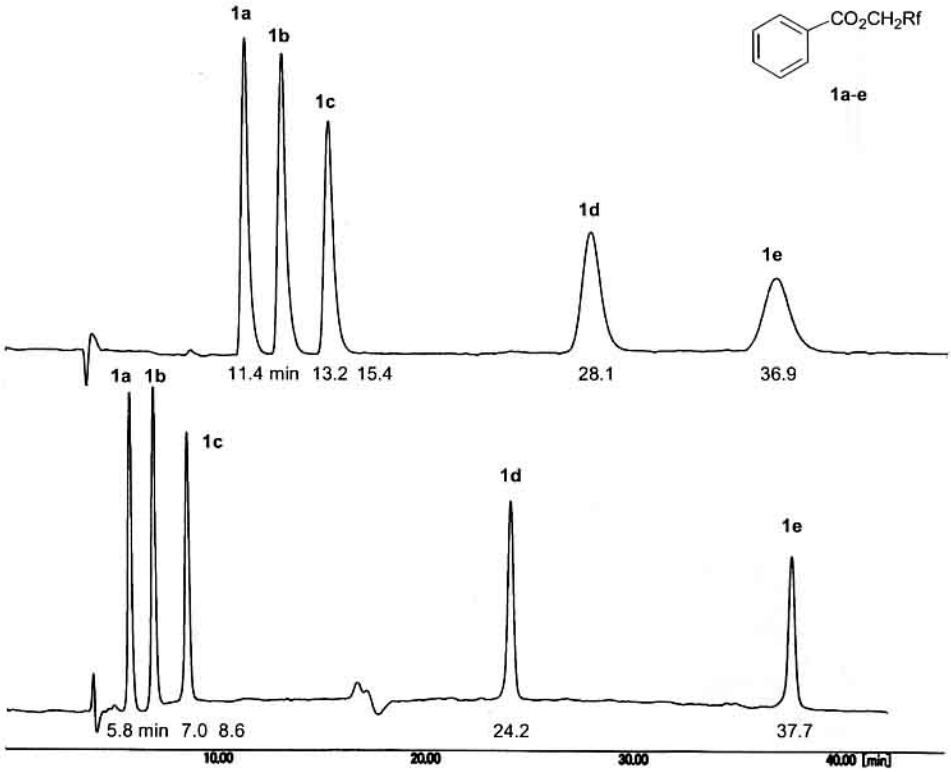


Figure 5 The comparison of OA-7500 and Fluofix 120E using fluorinated esters **1a–e**. Bottom: Fluofix 120E, Top: OA-7500. Flow rate: 0.7 mL/min.

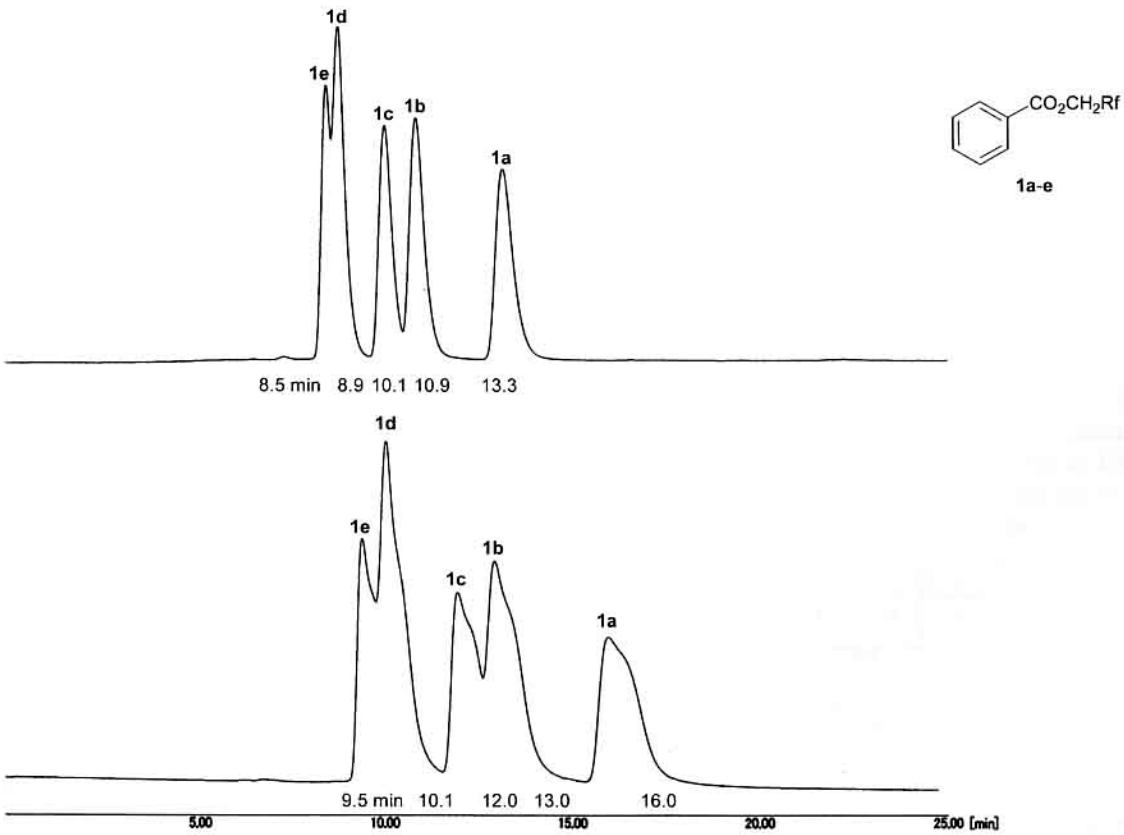


Figure 6 Separation of fluorinated esters **1a–e** with OA-7500 and OD-H in *n*-hexane. Bottom: OD-H, Top: OA-7500. Flow rate: 0.5 mL/min.

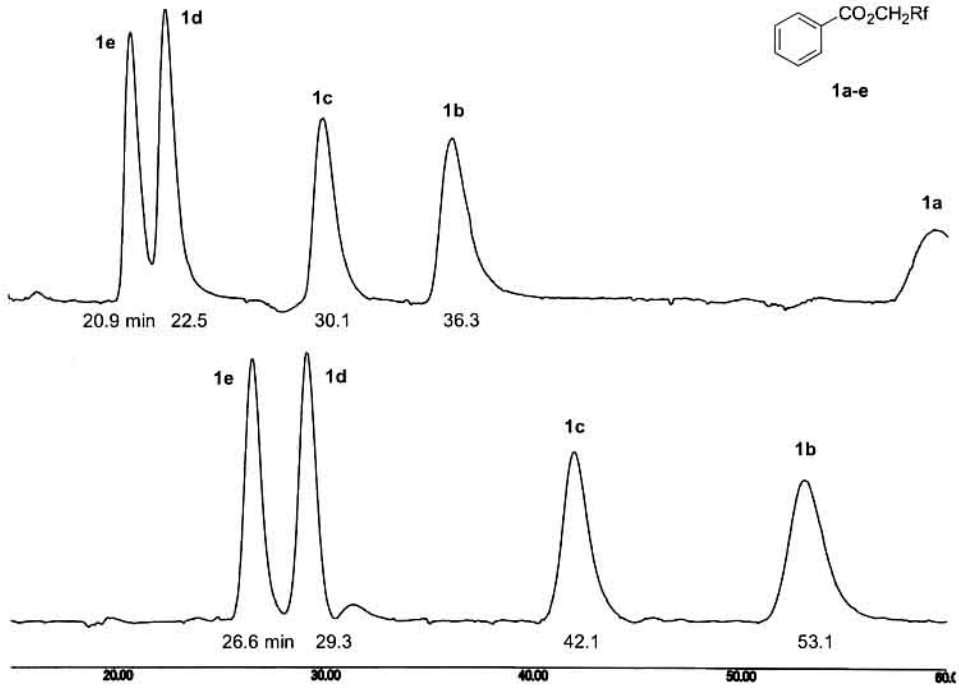


Figure 7 Separation of fluorinated esters **1a–e** with OA-7000 and OA-7100 in fluorous solvent. Bottom: OA-7100, Top: OA-7000. Mobile phase: FC-72/ZEOROLA H = 90/10. Flow rate: 0.5 mL/min.

normal phase is attributed to glucose consisted of β-CD, because DAICEL CHIRALCEL® OD-H[11] can also separate the compounds bearing short fluorous tag (Figure 6). When fluorinated esters **1** were separated using OD-H (mobile phase: hexane), OD-H eluted from esters bearing long fluorous tag and separated esters **1a**, **1b** and **1c** in similar manner to β-CD column.

Finally, fluorous solvent was employed as a mobile phase. It is expected that fluorous solvent affect fluorous tag discrimination of β-CD to have different nature from organic solvent. The separation of fluorinated esters **1** with OA-7000 series in fluorous solvent is shown in Figure 7. A part of fluorinated esters **1** was not soluble in FC-72, so mobile phase was 90% FC-72/ZEORORA®-H.[12] As a result, OA-7000 and OA-7100 could completely separate five fluorinated esters. This result is contrary to the observation that OA-7500 gives good separation of fluorinated esters **1** not only in reversed phase but also in organic phase.

We have reported fluorous tag discrimination of β-CD using SUMICHIRAL OA-7000 series as β-CD columns. When reversed phase and organic solvent are employed as a mobile phase, OA-7000 and OA-7100 give good separation of fluorinated sulfonates **2** and OA-7500 gives good separation of fluorinated esters **1**. When fluorous solvent is employed as a mobile phase, OA-7000 and OA-7100 afford good separation of fluorinated esters **1**. In comparison with Fluofix 120E packed fluorous silica gel, the β-CD column is superior to the fluorous silica gel column; the β-CD column can efficiently separate all compounds bearing a CF_3 tag to a C_9F_{19} tag. β-CD is a natural product and hence very cheap. Therefore, it is concluded that the β-CD column is highly suitable method for fluorous mixture synthesis. Further application to chiral compounds bearing fluorous tag is now in progress.

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(6) SUMICHIRAL OA-7000 series are sold by Sumika Chemical Analysis Service. Catalog about SUMICHIRAL OA-7000 series: Welcome to SUMICHIRAL OA third edition. URL: http://www.scas.co.jp/.

(7) SUMICHIRAL OA-7000 is the column with unmodified β-CD bonded to the silica gel via saccharide (glucuroyl gluconoyl group) spacer; SUMICHIRAL OA-7100 is the column with unmodified β-CD bonded to the silica gel via alkyl group spacer; SUMICHIRAL OA-7500 is the column with β-CD, in which hydroxyl group is protected by methyl group, bonded to the silica gel via alkyl group spacer.

(8) Fluorinated sulfonamides ($PhSO_2NHCH_2C_nF_{n+1}$, n = 1, 3, 7) were also separated with OA-7000 or OA-7100 (mobile phase: gradient of $MeOH/H_2O$).

(9) Retention time of esters **1a–c** was as follows; **1a**: 19.1 min, **1b**: 28.6 min, **1c**: 39.2 min.

(10) Retention time of sulfonates **2a–e** with OA-7100 was as follows; **2a**: 23.1 min, **2b**: 16.9 min, **2c**: 14.3 min, **2d**: 10.8 min, **2e**: 10.2 min.

(11) OD-H is packed with the cellulose 3,5-dimethylphenylcarbamate and helical structure is proposed for cellulose tris(phenylcarbamate). Review: (a) Nakano, T.; Okamoto, Y. *Chem. Rev.* **2001**, *101*, 4013. (b) Yashima, E.; Yamamoto, C.; Okamoto, Y. *Synlett* **1998**, 344. (c) Yashima, E.; Okamoto, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3289.

(12) ZEORORA-H is 1,1,2,2,3,3,4-heptafluorocyclopentane and sold by ZEON CORPORATION. URL of ZEON CORPORATION: http://www.zeon.co.jp/.