Resolution of Alcohols as Esters by HPLC on (+)-Poly(triphenylmethyl methacrylate)[1]

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Synopsis. Various secondary alcohols were resolved as benzoates or 3,5-dichlorobenzoates by high-performance liquid chromatography on optically active (+)-poly(triphenylmethyl methacrylate). Almost completely resolved alcohols include 2-butanol, 2-pentanol, 2-octanol, 3-octanol, 1-phenylethanol, *cis*-2-methylcyclohexanol, *trans*- and *cis*-3-methyl-cyclohexanol, and tetrahydrofurfuryl alcohol.

A unique optically active polymer bearing a stable helical conformation, poly(triphenylmethyl methacrylate) (PTrMA),[2] has been widely used as a chiral stationary phase for high-performance liquid chromatography (HPLC) to resolve various racemic compounds.[3] The PTrMA usually resolves nonpolar compounds rather than polar ones under reversed-phase chromatographic conditions with a polar eluent like methanol. Thus, a direct resolution of alcohols was not effected but it was attained as esters and even 2-butanol was completely resolved in a form of 3,5-dichlorobenzoate. Usually, the resolution of simple aliphatic alcohols is not easy and is a time-consuming process.

Experimental

All esters used in this work were synthesized from racemic alcohols and acid chlorides. The preparations of (+)-PTrMA[4] and the packing material[3c,5] for HPLC were reported previously. The material was packed in a stainless steel column (25×0.46 (id) cm) by a slurry method. The resolution was accomplished with a JASCO TRIROTOR II chromatograph equipped with a JASCO UVIDEC-100-III UV detector at 15 °C, methanol being used as the eluent.

Results and Discussion

Figure 1 demonstrates the chromatograms of the resolution of *s*-butyl 3,5-dichlorobenzoate and 1-ethylhexyl benzoate on a (+)-PTrMA column. Both compounds were completely resolved. The resolution results are summarized in Table 1. In the resolution of 2-butanol and 2-pentanol, 3,5-dichlorobenzoates were better resolved than benzoates (Entries **1—4**). Separation factor (α) increased in the order of 2-octanol>2-pentanol>2-butanol (Entries **6**, **3**, and **1**). However, 3-methyl-2-butanol was not resolved even as 3,5-dichlorobenzoate (Entry **5**). 3-Octanol was resolved more efficiently than 2-octanol (Entries **6** and **7**). Simple primary alcohols were difficult to resolve (Entries **9** and **10**), although Yoshii and coworkers have reported that a racemic primary alcohol having a more bulky group is completely resolved as benzoate on a (+)-PTrMA column.[3h]

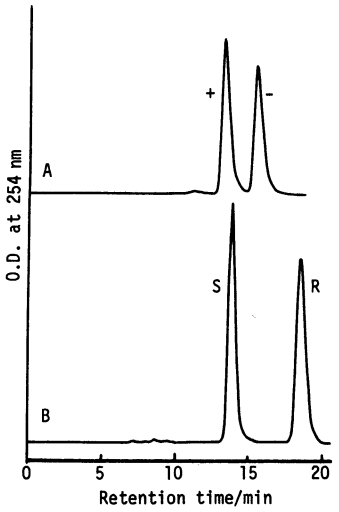

Fig. 1. Chromatograms of the resolution of *s*-butyl 3,5-dichlorobenzoate (A) and 1-ethylhexyl benzoate (B) on a (+)-PTrMA column. (Column: 25 cm×0.46 (id) cm, eluent: methanol (0.5 ml/min), 15 °C).

In the resolution of 1-phenylethanol, the benzoate was the most suitable ester (Entry **11**). Other esters showed rather broad peaks, which resulted in low resolution factors (R_s) as seen in Entries **12—15**. Several cyclic aliphatic alcohols were well resolved as benzoates (Entries **16—21**). *cis*- and *trans*-3-Methylcyclohexyl benzoates showed rather different capacity factors (k_1'), indicating that the separation of cis- and trans-isomers is possible as well as their resolution.

We have already reported that the resolution of dibenzoates of 2,4-pentanediol, *trans*-1,2- and *trans*-1,3-cyclohexanediol is also possible on (+)-PTrMA.[3b,c] These data indicate that the (+)-PTrMA column is useful for the resolution of various alcohols in the form of benzoate derivatives. Oi and Kitahara[6] reported the resolution of various alcohols as 3,5-dinitrophenylurethane derivatives on chiral columns consisting of chiral 1-(1-naphthyl)ethylamine and 2-(4-chlorophenyl)isovaleric acid; a hexane-1,2-dichloroethane mixture containing a small amount of ethanol was used as the eluent. A similar resolution has also been reported by Pirkle and Hyun.[7] The chiral recognition mechanism of our system seems different from such work in which a polar interaction plays an important role in chiral recognition. In our system, a nonpolar interaction or a π-π interaction is likely to be more important than the polar interaction.

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Table 1. Resolution of esters (R_1R_2CH-$OCOR_3$) on a (+)-PTrMA column[a]

Entry	Ester			k_1'[c]	α[d]	R_s[e]
	R_1	R_2	R_3[b]			
1	C_2H_5	CH_3	Ph	0.86(R)	~1	0
2	C_2H_5	CH_3	3,5-$Cl_2C_6H_3$	1.17(+)	1.36	1.47
3	*n*-C_3H_7	CH_3	Ph	0.94(R)	1.18	1.32
4	*n*-C_3H_7	CH_3	3,5-$Cl_2C_6H_3$	1.12(+)	1.40	1.56
5	i-C_3H_7	CH_3	3,5-$Cl_2C_6H_3$	1.35	1	0
6	*n*-C_6H_{13}	CH_3	Ph	0.89(S)	1.23	1.56
7	*n*-C_5H_{11}	C_2H_5	Ph	1.32(S)	1.60	4.44
8	CH_2=CH	CH_3	3,5-$Cl_2C_6H_3$	1.13	1.03	>0
9	$C_2H_5(CH_3)CH$	H	3,5-$Cl_2C_6H_3$	1.40	1	0
10	*n*-$C_3H_7(CH_3)CH$	H	3,5-$Cl_2C_6H_3$	1.49	1	0
11	Ph	CH_3	Ph	2.16(R)	2.42	6.19
12	Ph	CH_3	4-$NO_2C_6H_4$	1.04	1.22	0.81
13	Ph	CH_3	3,5-$(NO_2)_2C_6H_3$	0.67	1.18	0.65
14	Ph	CH_3	3,5-$Cl_2C_6H_3$	1.74	1.42	>0
15	Ph	CH_3	2-Naphthyl	2.39	1.55	1.28
16	Methyl		Ph	2.50	1.15	0.91
17	*cis*-2-Methylcyclohexyl		Ph	1.34	1.34	1.90
18	*cis*-3-Methylcyclohexyl		Ph	1.43	1.26	1.27
19	*trans*-3-Methylcyclohexyl		Ph	2.70	1.19	0.91
20	*trans*-2-Cyclohexylcyclohexyl		Ph	8.02	1.22	1.16
21	Tetrahydrofurfuryl		Ph	1.37	1.11	1.04

a) Chromatographic conditions are given in Fig. 1. b) 3,5-$Cl_2C_6H_3$=3,5-dichlorophenyl, 3,5-$(NO_2)_2C_6H_3$=3,5-dinitrophenyl. c) k_1' (capacity factor to the first-eluted enantiomer)=(retention time of the first-eluted enantiomer-dead time)/dead time. The sign in parenthesis is that of optical rotation at 365 nm or absoluted configuration. d) α(separation factor)=(capacity factor of the second-eluted enantiomer)/k_1'. e) Resolution factor=2×(difference of retention time of the second-and first-eluted enantiomers)/(sum of the band widths of the two enantiomer peaks).

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