Chromatographic Optical Resolution on 3,5-Disubstituted Phenylcarbamates of Cellulose and Amylose

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Synopsis. 3,5-Difluorophenylcarbamates and 3,5-bis(trifluoromethyl)phenylcarbamates of cellulose and amylose were prepared and used as chiral stationary phases for high-performance liquid chromatography to resolve optical isomers. Their optical resolving abilities were compared with those of 3,5-dimethylphenylcarbamates and 3,5-dichlorophenylcarbamates of the polysaccharides. 3,5-Difluorophenylcarbamates afforded practically useful columns.

Phenylcarbamates of polysaccharides, such as cellulose and amylose, have been used as chiral stationary phases for high-performance liquid chromatography (HPLC).[1] Their chiral recognition abilities are altered by the introduction of substituents on the phenyl group of the derivatives.[2,3] Although the introduction of substituents at ortho-position reduces chiral recognition abilities, the introduction at meta- or para-position often improves the chiral recognition ability, and 3,5-disubstituted derivatives, such as 3,5-dimethyl- and 3,5-dichlorophenylcarbamates, show particularly interesting optical resolving abilities for many compounds. In this study we synthesized new 3,5-disubstituted derivatives, 3,5-bis(trifluoromethyl)-phenylcarbamates (**1**) and 3,5-difluorophenylcarbamates (**2**, **5**); their chiral recognition abilities as stationary phases for HPLC were then compared with those of the previous disubstituted derivatives (**3**, **4**, **6**, **7**).

Experimental

The phenylcarbamates of polysaccharides were synthesized by the reaction of cellulose (Merck, Avicel) or amylose (Nacalai Tesque, M_w ≈16000) with an excess of 3,5-bis(trifluoromethyl)phenyl isocyanate or 3,5-difluorophenyl isocyanate in pyridine at 100 °C. The isocyanates were synthesized from the corresponding aniline derivatives. The polysaccharide derivatives were precipitated in a methanol–water mixture. Macroporous silica gel (Macherey-Nagel, NUCLEOSIL 4000-7) was treated with (3-aminopropyl)triethoxysilane. Packing materials were prepared by adsorbing the polysaccharide derivatives (25 wt%) on silanized silica gel, and were packed in a stainless-steel tube (25×0.46 (i.d.)cm) by a slurry method. Optical resolution was carried out with a JASCO TRIROTAR-II chromatograph equipped with a JASCO UVIDEC-100-III UV and DIP-181C polarimetric detectors. Chromatographic analyses were performed at a flow rate of 0.5 ml min^{-1} using a hexane-2-propanol mixture as an eluent. An elution time of 1,3,5-tri-*t*-butylbenzene was used as the dead time (t_0) of the chromatography.[4]

Results and Discussion

Figure 1 shows the optical resolution of Tröger base (**8**) on cellulose tris(3,5-difluorophenylcarbamate) (**2**). (+)-Isomer eluted at 11.7 min (=t_1) and (−)-isomer at 14.4 min (=t_2). The capacity factor of the first eluted enantiomer, $k_1'=(t_1-t_0)/t_0$, and separation factor, $\alpha=(t_2-t_0)/(t_1-t_0)$, have been determined as 0.88 and 1.73, respectively.

In Table 1 are summarized the results of the optical resolution of racemic compounds **8**—**17** on 3,5-disubstituted phenylcarbamates of cellulose (**1**—**4**).

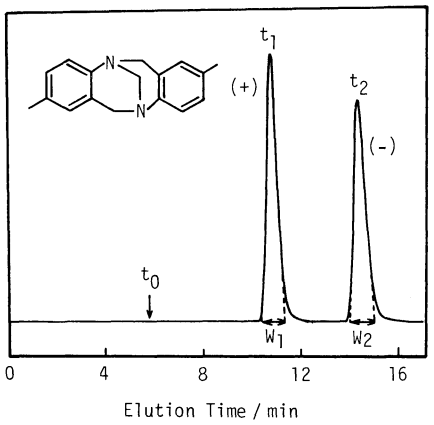
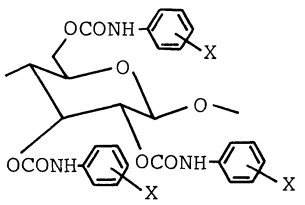
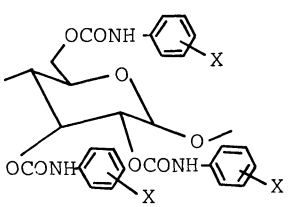


Fig. 1. Optical resolution of Tröger base (**8**) on cellulose tris(3,5-difluorophenylcarbamate) (**2**). (Eluent: hexane–2-propanol (90:10), 0.5 ml min^{-1}).



X =

1: 3,5-$(CF_3)_2$ **3**: 3,5-Cl_2
2: 3,5-F_2 **4**: 3,5-$(CH_3)_2$



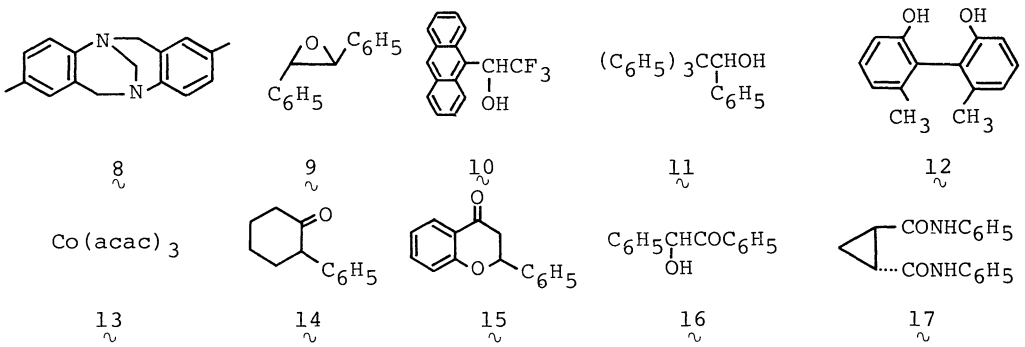
X =

5: 3,5-F_2 **7**: 3,5-$(CH_3)_2$
6: 3,5-Cl_2

Table 1. Optical Resolution and Retention Time of Acetone on Cellulose Tris(3,5-disubstituted phenylcarbamate) Derivatives[a]

Racemate	1(3,5-$(CF_3)_2$)			2(3,5-F_2)			3(3,5-Cl_2)[b]		4(3,5-Me_2)[b]	
	k_1'[c]	α	R_s	k_1'[c]	α	R_s	k_1'[c]	α	k_1'[c]	α
8	0.31(+)	ca. 1		0.88(+)	1.73	3.25	0.87(+)	1.65	0.97(+)	1.32
9	0.25(+)	1.54	1.03[d]	0.51(+)	1.81	3.06	0.56(+)	1.84	0.74(−)	1.68
10	0.65(−)	1.42	1.40[d]	0.34(−)	1.27		0.28(−)	1.38	2.13(−)	2.59
11	0.09(+)	ca. 1		0.44(+)	ca. 1		0.40(+)	1.29	1.37(+)	1.34
12	0.79(+)	ca. 1		1.70(+)	1.05		1.62(+)	1.11	2.36(−)	1.83
13	0.34(+)	1.47	1.20	1.72(+)	2.36	6.94	0.76(+)	1.82	0.42(+)	ca. 1
14	1.66(−)	1.09		3.62(−)	1.21	1.90	2.65(−)	1.26	1.17(−)	1.15
15	0.51(−)	ca. 1		2.01(−)	1.18	1.64	1.55(−)	1.20	1.47(−)	1.41
16	1.60(−)	1.28	1.69	3.77(−)	ca. 1		3.08(−)	1.21	2.43(+)	1.58
17	0.20(−)	ca. 1		0.68(+)	1.63	2.46	0.59(+)	1.41	0.83(+)	3.17
T_a[e]	9.13 min			22.6 min			15.0 min		8.40 min	

a) Eluent: hexane–2-propanol (90:10), 0.5 ml min^{-1}. b) Ref. 2. c) The sign in parentheses shows optical rotation of first-eluted enantiomer. d) Eluent: hexane–2-propanol (98:2). e) Retention time of acetone.



For a comparison, capacity factors and separation factors on 3,5-dichloro- and 3,5-dimethylphenylcarbamates are also shown. Chiral recognition abilities depended greatly on the substituents. Although difluoro derivative (**2**) showed a somewhat similar chiral recognition ability to dichloro derivative (**3**), bis(trifluoromethyl) derivative (**1**) showed quite a different chiral recognition ability. Except for derivative **1**, chiral recognition seems to depend on the inductive effect of the substituents. The racemic compounds carrying the hydroxyl group, **10**,**11**, and **12**, were more retained on **4** than on **2** and **3**. In contrast, carbonyl compounds, **13**, **14**, and **15**, were more retained on **2** and **3** than on **4**. Similar results have been observed for 4-substituted phenylcarbamates of cellulose.[2] These results may be ascribed to the interaction shown in Fig. 2. When the substituent is electron-withdrawing, the hydrogen bonding between NH and a carbonyl group is likely to be enhanced; if the substituent is electron-donating, the hydrogen bonding between CO and a hydroxyl group may be enhanced. Therefore, a change in the capacity factor may be associated with a change in the polarity of the urethane moiety induced by the substituent. This is supported by ^1H NMR spectroscopy. The chemical shifts of the N–H proton moved to a lower magnetic field in the order **4**, **2**, and **1**. Therefore, the elution time of acetone which is probably adsorbed on N–H

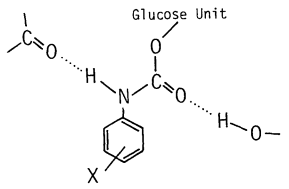


Fig. 2. Adsorbing site of phenylcarbamate derivatives.

group is expected to increase in the order **4**, **2**, and **1**. However, the elution time of acetone on **1** was especially shorter. Shorter elution times on **1** were also observed for other racemates. The bulky trifluoromethyl groups at the 3- and 5-positions may prevent the racemates from adsorbing on urethane bonds.

Table 2 shows the results of the optical resolution on amylose tris(3,5-disubstituted phenylcarbamate)s. The same substituents effect on the retention time of acetone was also observed, although the effect was less pronounced compared with that on cellulose derivatives. A similar substituent effect was observed for the retention times of hydroxy (**10**—**12**) and carbonyl compounds (**13**—**15**).

3,5-Difluorophenylcarbamate of cellulose (**2**) can more effectively resolve some racemic β-blockers than cellulose tris(3,5-dimethylphenylcarbamate).[5] Pro-

Table 2. Optical Resolution and Retention Time of Acetone on Amylose Tris(3,5-disubstituted phenylcarbamate) Derivatives[a]

Racemate	**5**(3,5-F_2)			**6**(3,5-Cl_2)[b]		**7**(3,5-Me_2)[b]	
	k'_1	α	R_s	k'_1	α	k'_1	α
8	0.78(+)	1.13		0.84(+)	1.34	0.53(+)	1.58
9	0.32(+)	1.30	0.70	0.50(+)	1.32	0.42(+)	3.04
10	0.39	1.00		0.37	1.00	1.30(+)	1.15
11	0.48(+)	1.64	1.83	0.88(+)	2.25	2.65(+)	1.98
12	2.03	1.00		1.10(+)	ca. 1	2.46(−)	2.11
13	2.58(−)	1.08		0.63(+)	ca. 1	0.25(−)	ca. 1
14	2.19(−)	ca. 1		1.26(−)	ca. 1	0.61(−)	ca. 1
15	1.40(+)	1.50	2.36	1.62(+)	1.10	0.93(+)	1.12
16	3.53(−)	ca. 1		6.08(+)	ca. 1	3.14(−)	1.21
17	0.83(+)	1.51	1.76	0.59(−)	1.11	3.25(+)	2.01
T_a[c]	12.2 min			10.4 min		8.16 min	

a) Eluent: hexane–2-propanol (90:10), 0.5 ml min^{-1}. b) Ref. 3. c) Retention time of acetone.

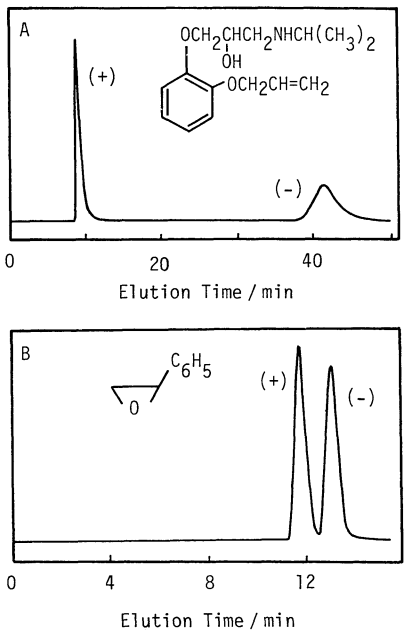


Fig. 3. Optical resolution on cellulose tris(3,5-difluorophenylcarbamate) (**2**). A: oxyprenolol (Eluent: hexane–2-propanol (90:10)), B: styrene oxide (Eluent: hexane–2-propanol (98:2)).

pranolol (α=2.77) and oxyprenolol (Fig. 3A,α=6.81) were resolved with larger α values. However, the α value of 1.49 for alprenolol on **2** was inferior to that of cellulose tris(3,5-dimethylphenylcarbamate). Pindolol and atenolol did not show any distinct peaks because of slow elution. Styrene oxide, which was not resolved on other polysaccharide phenylcarbamate derivatives, was completely resolved (Fig. 3B, α=1.20).

As shown in Table 1, **2** was especially useful for the separation of carbonyl compounds. Other carbonyl compounds, like 3-methylcyclopentanone (α=1.06) and β-butyrolactone (α=1.08), which were not resolved on other polysaccharide derivatives at all, were resolved into two peaks with hexane–2-propanol (90:10) as an eluent. Another advantage of **2** compared with **3** is the fact that solubility of **2** in hexane–2-propanol is lower than that of **3**. Therefore, the column packed with **2** was not damaged by an eluent system containing 10% 2-propanol in hexane which could not apply to the column packed with **3**.

References

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