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Tris(4-t-butylphenylcarbamate)s of Cellulose and Amylose as Useful Chiral Stationary Phases for Chromatographic Optical Resolution

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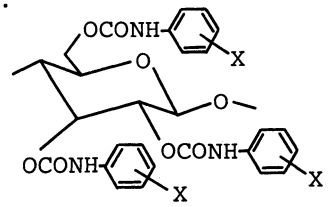
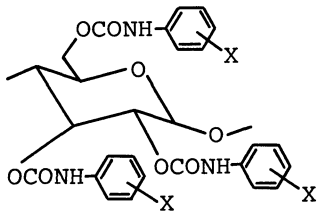
Cellulose tris(4-t-butylphenylcarbamate) and amylose tris(4-t-butylphenylcarbamate) were adsorbed on macroporous silica gel and used as chiral stationary phases for high-performance liquid chromatography to separate racemic compounds. The carbamates, particularly cellulose derivative, exhibited remarkable optical resolving power, and resolved racemic drugs such as chloroquine and nicardipine which were not resolved on other phenylcarbamate derivatives of cellulose and amylose.

We reported that tris(phenylcarbamate) derivatives of polysaccharides such as cellulose and amylose can be supported on silica gel and be used to resolve optical isomers as chiral stationary phases for high-performance liquid chromatography (HPLC).[1] The chiral recognition abilities of these derivatives depend greatly on the species and position of substituents introduced on the phenyl groups of the carbamate derivatives.[2] The derivatives of cellulose and amylose with a high optical resolving power are inclined to form strong hydrogen bond between urethane bonds of the phenylcarbamate derivatives and racemates. In this study, novel phenylcarbamate derivatives, cellulose tris(4-t-butylphenylcarbamate) (1a) and amylose tris(4-t-butylphenylcarbamate) (2a) were synthesized and their chiral recognition abilities were chromatographically estimated. The optical resolving abilities of tris(4-isopropylphenylcarbamate)s (1b and 2b) were also evaluated.



X =

1a: 4-$(CH_3)_3C$
1b: 4-$(CH_3)_2CH$
1c: 4-CH_3
1d: 3,5-$(CH_3)_2$



X =

2a: 4-$(CH_3)_3C$
2b: 4-$(CH_3)_2CH$
2c: 4-CH_3
2d: 3,5-$(CH_3)_2$

The phenylcarbamate derivatives were prepared by the reaction of microcrystalline cellulose (Avicel, Merck) or amylose (Nacalai Tesque, Mw= 16000) with an excess of 4-t-butylphenyl isocyanate or 4-isopropylphenyl isocyanate in

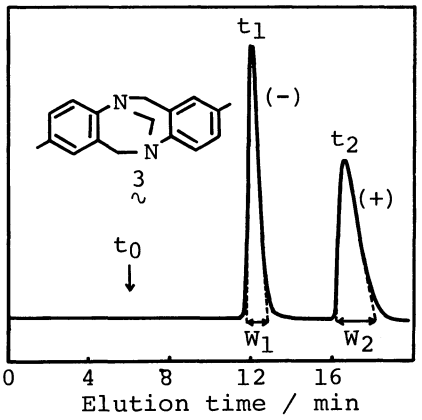
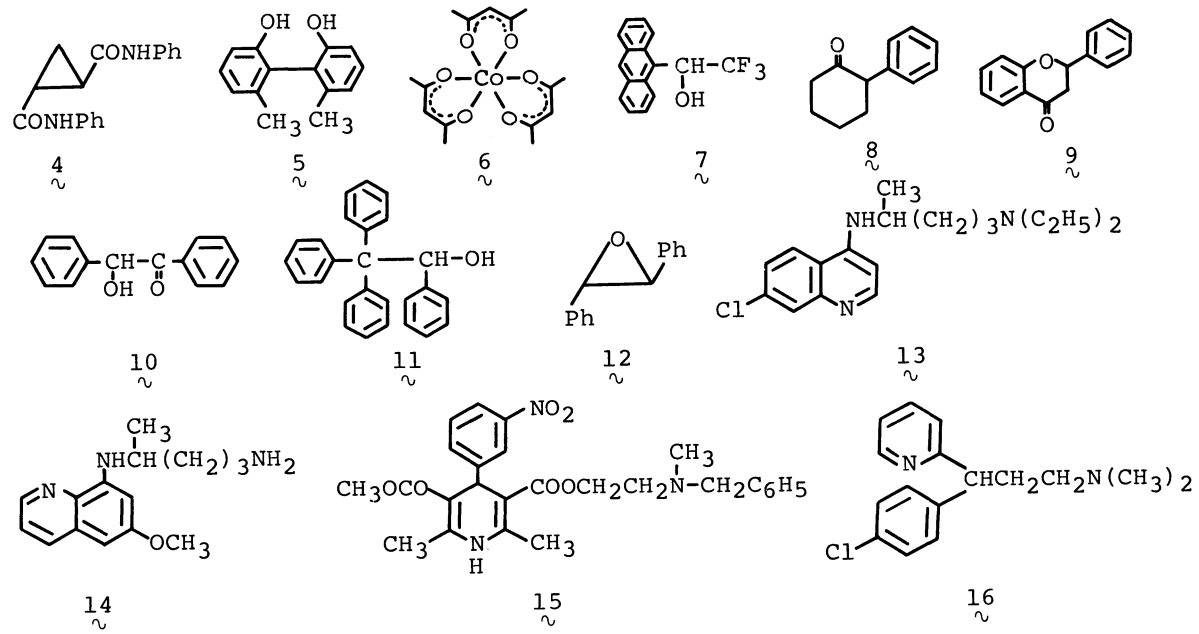


Fig. 1. Chromatographic resolution of Tröger base (3) on a 1a column.

Table 1. Optical resolution of racemates (3-12) on 1a and 2a

Racemate	1a			2a		
	k_1'	α	Rs	k_1'	α	Rs
3	1.07(-)	1.74	3.09	1.34(+)	1.32	1.64
4	1.26(-)	2.24	4.37	0.93(+)	1.16	
5	1.55(-)	1.50	2.47	1.59(-)	1.08	
6	0.33(+)	2.50	3.51	0.48(-)	~1	
7	1.18(-)	1.75	3.70	0.93(-)	1.12	
8	1.13(-)	1.22	1.42	1.39(+)	1.43	2.40
9	1.40(+)	1.45	2.56	1.17	1.00	
10	2.03(-)	1.08		3.67(-)	1.17	1.69
11	0.79(+)	1.36	1.76	1.16(+)	1.14	0.88
12	0.45(+)	1.27	0.84	0.59(-)	~1	



pyridine at 100 °C and were isolated as methanol-insoluble fractions. Elemental analyses and ^{1}H NMR spectra indicated that hydroxy groups of cellulose and amylose were almost quantitatively converted to urethane bonds. Each derivative (0.75 g) was dissolved in tetrahydrofuran (12 ml) and adsorbed on macroporous silica gel (Nucleosil 4000-7), which was treated with 3-aminopropyltriethoxysilane in benzene at 80 °C. The packing materials thus obtained were packed in a stainless steel tube (25 cm x 0.46 (I.D.) cm) by a slurry method. Chromatographic resolution was accomplished on a JASCO TRIROTAR-II chromatograph equipped with UV (JASCO UVIDEC-100-III) and polarimetric (JASCO DIP-181C) detectors. Most optical resolution was carried out with a hexane-2-propanol (90:10, 0.5 ml/min) mixture at 25 °C. 1,3,5-Tri-t-butylbenzene was used to estimate dead time (t_0).

Figure 1 shows the chromatogram of the resolution of Tröger base (3) on a 1a column. The (-)-isomer eluted at t_1 and the (+)-isomer at t_2. Capacity factors, k_1' (=$(t_1-t_0)/t_0$) and k_2' (=$(t_2-t_0)/t_0$), were 1.07 and 1.86, respectively.

Table 2. Separation factors (α) on tris(alkylphenylcarbamate) derivatives of cellulose and amylose

Racemate	Cellulose derivatives				Amylose derivatives			
	1a	1b	1c[a)]	1d[a)]	2a	2b	2c	2d[b)]
3	1.74(-)	1.17(+)	1.48(+)	1.32(+)	1.32(+)	1.09(-)	1.00	1.58(+)
4	2.24(-)	2.14(-)	1.35(-)	3.17(+)	1.16(+)	1.32(+)	1.44(+)	2.01(+)
5	1.50(-)	1.39(-)	1.30(-)	1.83(-)	1.08(-)	1.19(-)	1.54(-)	2.11(-)
6	2.50(+)	2.46(+)	1.75(+)	~1(+)	~1(-)	1.23(-)	1.29(-)	~1(-)
7	1.75(-)	1.59(-)	1.52(-)	2.59(-)	1.12(-)	~1(-)	1.00	1.15(+)
8	1.22(-)	1.15(-)	1.20(-)	1.15(-)	1.43(+)	1.24(+)	~1(+)	~1(-)
9	1.45(+)	1.23(-)	1.16(+)	1.41(-)	1.00	1.00	1.15(+)	1.12(+)
10	1.08(-)	1.13(-)	1.12(-)	1.58(+)	1.17(-)	~1(-)	1.00	1.21(-)
11	1.36(+)	1.47(+)	1.37(+)	1.34(+)	1.14(+)	1.32(+)	1.57(+)	1.98(+)
12	1.27(+)	1.43(+)	1.55(+)	1.68(-)	~1(-)	~1(+)	1.38(+)	3.04(+)

a) Data in Ref. 2. b) Data in Ref. 3.

Separation factor α ($=k_2'/k_1'$) and the resolution factor Rs ($=2(t_2-t_1)/(W_1+W_2)$) were obtained 1.74 and 3.09, respectively.

In Table 1 are shown the results of the optical resolution of 3, trans-cyclopropanedicarboxylic acid dianilide (4), 2,2'-dihydroxy-6,6'-dimethylbiphenyl (5), cobalt(III) tris(acetylacetonate) (6), 1-(9-anthryl)-2,2,2-trifluoroethanol (7), 2-phenylcyclohexanone (8), flavanone (9), benzoin (10), 1,2,2,2-tetraphenylethanol (11), and trans-2,3-diphenyloxirane (12). Most compounds except for 10 and 12 were completely resolved on 1a. However, 2a showed relatively low optical resolving power and only 8 and 10 were better resolved than on 1a. These two columns sometimes exhibited the opposite elution order of enantiomers as clearly observed for 3, 4, and 8.

Table 2 shows the α values for 3-12 in the resolution on the cellulose derivatives (1a-d) and the amylose derivatives (2a-d). In this table, the data for 4-methyl (1c,2c) and 3,5-dimethyl (1d,2d[3)]) derivatives[2)] of cellulose and amylose are also shown for comparison. The novel cellulose derivatives 1a and 1b, particularly 1a, exhibited noticeable resolving power and several compounds were resolved more effectively than on 1d which is considered to be one of the most practically useful chiral stationary phases derived from cellulose.[2)] The stereoselection of 1a and 1d was quite different and opposite elution order with high α values were observed for 3, 4, 9, and 12. On the other hand, optical resolving power of 2a was rather low compared with that of 2d and only 8 was better resolved on 2a.

The chemical shifts of NH proton of 1a-d and 2a-d in ^{1}H NMR spectra were similar to each other. This suggests that the polarity of the carbamate groups (-NHCOO-) is similar in these derivatives.[2)] Therefore, different chiral recognition observed in Table 2 is rather ascribed to steric reason. 3,5-Dimethyl group and 4-t-butyl group appear to show quite different sterical effect. 3,5-Dimethyl groups may more depress the interaction of NH proton of the carbamate group with a solute because of the steric hindrance. The lower chiral recognition of 2a may be due to the disturbance of the ordered structure of the amylose derivative on the surface of silica gel because of the existence of t-

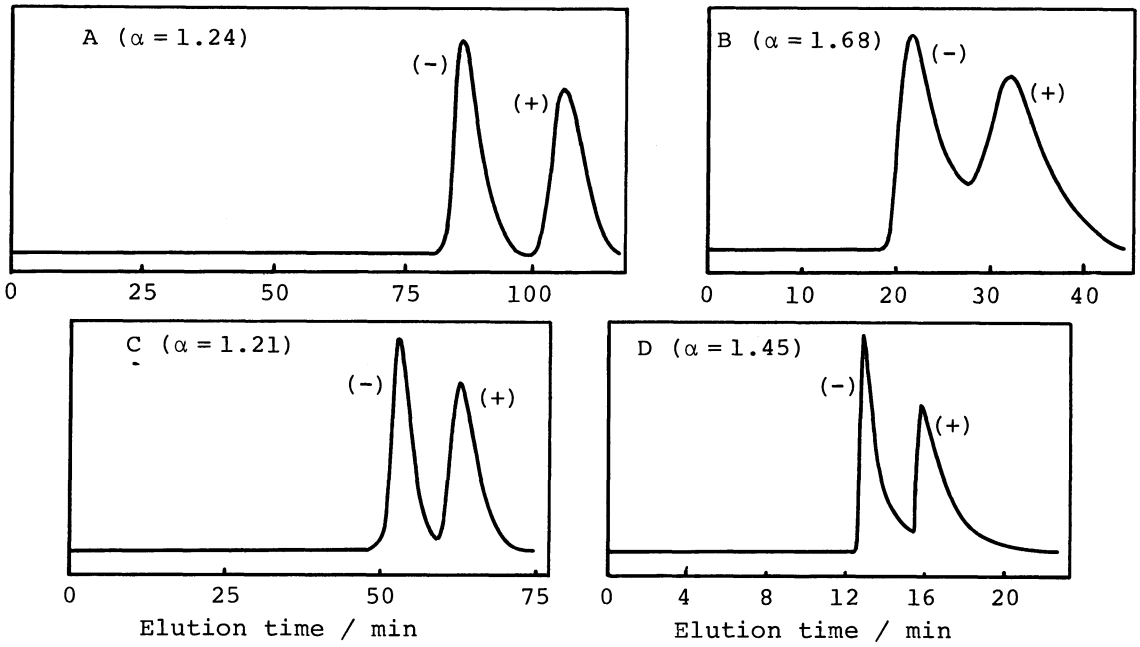


Fig. 2. Optical resolution of 13 (A), 14 (B), and 15 (C) on 1a and 16 (D) on 2a. Eluent: A: hexane-2-propanol-$HNEt_2$ (96:2:2) B: hexane-2-propanol-$HNEt_2$ (80:20:0.1) C,D: hexane-2-propanol (90:10)

butyl group.

4-t-Butyl derivatives 1a and 2a effectively resolved several racemic drugs which could not be resolved on other polysaccharide derivatives (Fig. 2). For example, 1a resolved drugs of anti-malarial chloroquine (13) and primaquine (14). Nicardipine (15) which is an important drug as calcium antagonist was almost completely resolved on 1a. These drugs were not resolved on 1d and 2d which showed high resolving abilities for many racemic compounds including drugs. Chlorpheniramine (16) was more effectively resolved on 2a than 1d and 2d. A phenylcarbamate ($C_2H_5(CH_3)CHCH_2OCONHPh$) of a racemic primary alcohol ($C_2H_5(CH_3)CH$-CH_2OH) was unable to resolve with the all cellulose tris(phenylcarbamate) derivatives.[4] However, this racemate was completely resolved on 1a (α= 1.29, Rs= 1.03). These 4-t-butylphenylcarbamate derivatives were quite stable under the conditions with the eluent of hexane containing 20 % of ethanol or 2-propanol.

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References

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