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Tris(chloro- and methyl-disubstituted phenylcarbamate)s of Cellulose as Chiral Stationary Phases for Chromatographic Enantioseparation

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Four types of tris(chloro- and methylphenylcarbamate)s of cellulose were prepared and their chiral recognition abilities were evaluated as chiral stationary phases (CSPs) for HPLC. It has been established that simultaneous introduction of both electron-donating and electron-withdrawing groups improved enantiomer resolving power of CSP in some cases compared with those possessing only electron-donating or electron-withdrawing substituents.

Phenylcarbamate derivatives of polysaccharides such as cellulose and amylose show high chiral recognition abilities for a variety of racemic compounds as CSP for high performance liquid chromatography (HPLC).[1-5] Their chiral recognition depends greatly on the type and position of substituents introduced on the phenyl groups of the carbamate derivatives.[2] The introduction of electron-donating or electron-withdrawing substituents at 3- or 4-position tends to improve the optical resolution abilities of CSPs.[2,4] 2-Substituted derivatives showed a low chiral recognition. Thus, 3,5-dimethylphenylcarbamates of cellulose and amylose which have been commercialized[6] belong to one of the most widely used CSPs for HPLC enantioseparation. Cellulose tris(3,5-dichlorophenylcarbamate) also shows high chiral recognitions, but this cannot be applied to practical use due to exceptionally high solubility in most of chromatographic eluents.[3,4] Tris(3,5-dimethylphenylcarbamate) and tris(3,5-dichlorophenylcarbamate) of cellulose were blended and coated on silica gel, but the CSP did not lead to the substantial improvement of chiral properties.[7]

In this report, a new class of disubstituted phenylcarbamate derivatives (**1a-d**) of cellulose were prepared for the first time by introducing both electron-donating methyl group and electron-withdrawing chloro group onto the phenyl moieties and their chiral recognition abilities were evaluated and compared with those of dimethyl-, dichloro- and monosubstituted phenylcarbamate derivatives.

The chloro and methyl disubstituted derivatives were prepared by the reaction of

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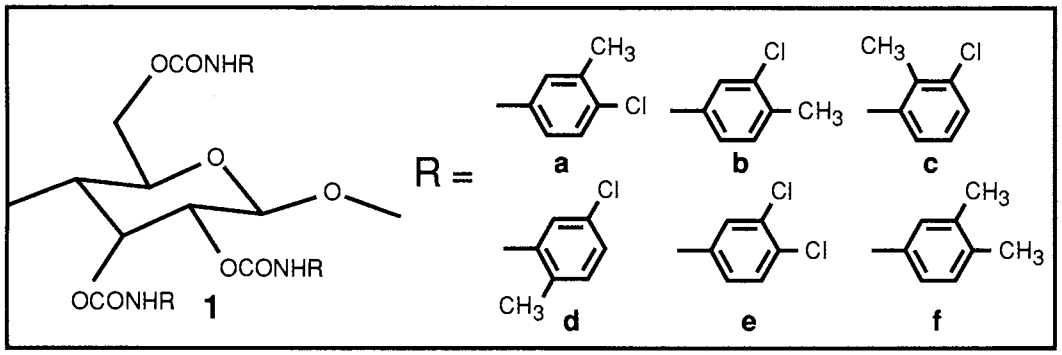

cellulose (Avicel, Merck) with corresponding isocyanates. An overnight reaction with isocyanate in dry pyridine at *ca.* 90°C led to almost 100% conversion of hydroxy groups to carbamates. The degree of substitution of hydroxy groups was determined by elemental analysis and ^{1}H NMR spectroscopy. Packing materials were prepared in the same way as before[2] using macroporous silica gel (Daiso Gel, particle size 7 μm, pore size 100 nm), and were packed in a stainless steel tube (25 cm x 0.46 cm (i.d.)). Capacity factors (k') and separation factor (α) in chromatographic analysis were also estimated in the same manner as previously reported[2] using a hexane-2-propanol (90 : 10) mixture as an eluent. 1,3,5-Tri-*t*-butylbenzene was used as a non-retained compound to estimate dead time.

The results of optical resolution of ten racemates (**2**-**11**) on the cellulose carbamate derivatives (**1a**-**d**) in this study are summarized in Table 1 together with those on dimethyl- and dichloro-substituted derivatives(**1e**, **1f**)[2] for comparison. The results clearly demonstrated superiority of the chloro and methyl disubstituted derivatives to the dimethyl- and dichloro-substituted derivatives in a few separations; especially, **1a** and **1b** columns showed very high chiral resolving powers and could resolve all 10 racemic compounds almost completely. Introduction of both electron-donating and electron-withdrawing substituents on phenyl groups may enable to prepare CSPs with higher "total" enantioselectivities than those of dimethyl- and dichlorophenylcarbamate derivatives. Moreover, an interesting synergistic effect can be observed for some racemic compounds. For example, neither **1e** nor **1f** can separate the compound **5**,[2] which could be separated both on **1a** and **1b** with high selectivity (α=3.05 and 1.95, respectively). The chloro and methyl disubstituted derivatives are scarcely soluble in hexane with 0-20% of 2-propanol mixture and have longer life time over cellulose tris(3,5-dichlorophenylcarbamate).

Interestingly, the derivatives **1c** and **1d** showed characteristic chiral recognition abilities and could separate several racemic compounds, although tris(2-methylphenylcarbamate) of cellulose showed low chiral resolving power and could resolve only three racemic compounds (**3**, **4**, and **10**) among ten compounds.[2] Enantioseparation exhibited by **1c** and **1d** columns depended on the position of the chloro group. It is also worth to be mentioned that elution order of racemic compounds **6** and **10** reversed when the methyl group was at position 2 (**1c**) or 6 (**1d**) instead of position 4 (**1b**) in 3-chlorophenylcarbamates of cellulose. The same effect is observed for racemic compounds **2**, **7**, **8**, **9**, and **11** in the case when methyl group is substituted in position 2 but not in

position 6. These results suggest that chiral recognition mechanism in these cases may be controlled not only sterically but also electronically.

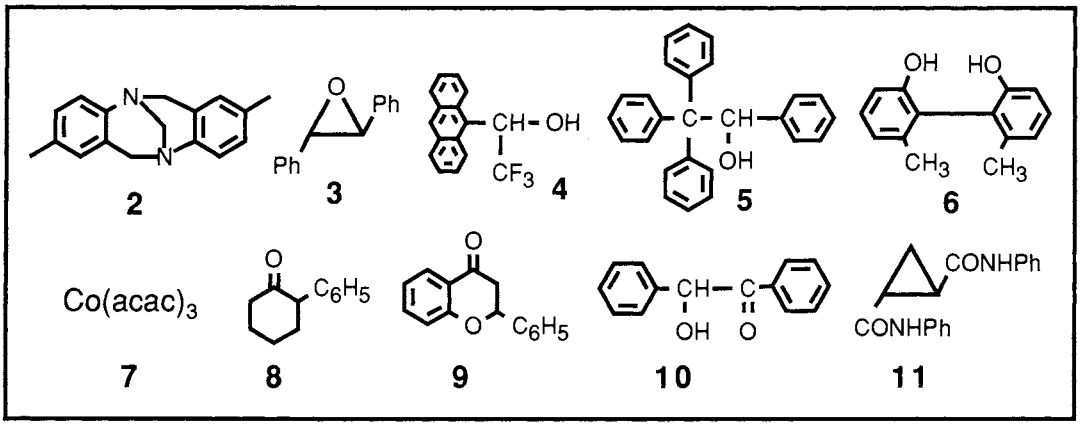

Table 1. Optical resolution of racemates (**2** - **11**) on cellulose derivatives (**1a** - **1f**)[a]

	1a		**1b**		**1c**		**1d**		**1e**[c]		**1f**[c]	
	k'_1	α	k'_1	α	k'_1	α	k'_1	α	k'_1	α	k'_1	α
2	1.10(+)	1.13	0.45(+)	1.25	0.67(-)	≈1	0.80(+)	≈ 1	0.79(+)	1.47	0.87(+)	1.49
3	0.43(+)	3.25	0.77(+)	2.09	0.63(+)	≈1	0.67(+)	1.30	0.38(+)	1.93	0.61(+)	1.13
4	0.80(-)	1.25	0.95(-)	1.20	0.60	1.00	1.53(-)	≈1	0.33(-)	1.21	1.76(-)	2.13
5	0.73(+)	3.05	0.65(+)	1.95	0.97(+)	1.17	1.00	1.00	0.48	1.00	1.55(+)	≈1
6	1.80(-)	1.35	1.45(-)	1.24	1.47(+)	1.25	1.90(+)	1.19	1.34(-)	≈1	1.86(-)	1.87
7	5.86(+)	1.44[b]	2.50(+)	1.67[b]	3.93(-)	≈1[b]	2.87(+)	1.05[b]	1.21(+)	1.63	0.57(+)	1.32
8	1.27(-)	1.26	1.05(-)	1.19	1.58(+)	1.08	2.20(-)	≈1	1.92(-)	1.31	0.95(-)	1.20
9	1.73	1.06	1.36(-)	1.09	1.77(+)	≈1	1.90(-)	1.08	1.29(+)	1.04	1.53(-)	1.42
10	5.00(-)	1.23	3.36(-)	1.27	3.67(+)	1.30	4.76(+)	1.10	3.24(-)	1.10	2.77(+)	1.31
11	2.13(-)	1.54	1.10(-)	2.06	1.50(+)	1.24	1.30(-)	1.20	0.81(+)	1.15	1.27(+)	2.39

a) Eluent: hexane-2-propanol (90 / 10), 0.5 ml min^{-1}. b) Eluent: hexane-2-propanol (98 / 2).
c) Taken from Ref. 2.

From practical point of view, it may be important to examine chiral resolving abilities of the new derivatives for racemic drugs. Examples of chromatographic enantioseparations of some pharmacologically important compounds on **1a** are illustrated in Fig. 1. CSP **1a** could completely resolve isradipine and nicardipine which are important drugs as calcium antagonist, and could not be resolved on cellulose tris(3,5-dimethylphenylcarbamate).[5] β-Adrenergic agent, acebutolol was also more effectively resolved on **1a** than cellulose tris(3,5-dimethylphenylcarbamate) (α=1.12).[8] The derivative **1b** also resolved isradipine (α=1.15).

Some other chloro- and methyl-di- or trisubstituted phenylcarbamates of cellulose and amylose will also be expected to show efficient chiral recognition abilities. These systems are under more detailed study.

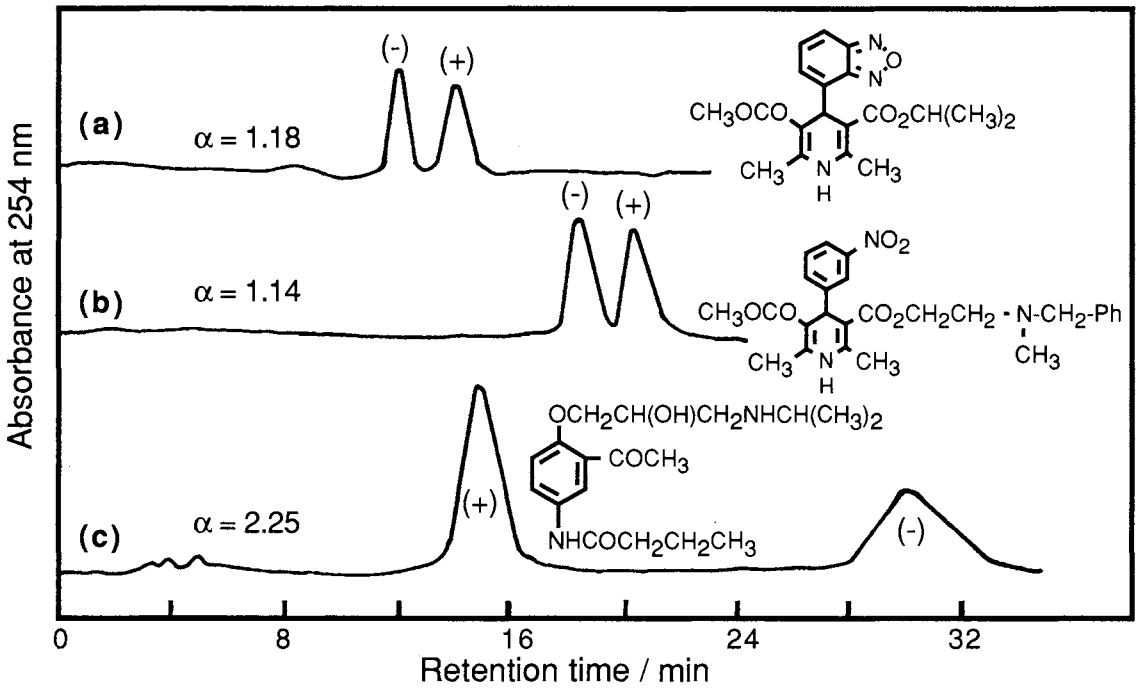

Fig. 1. Chromatographic separation of isradipine (a), nicardipine (b), and acebutolol (c) on cellulose tris(3-methyl-4-chlorophenylcarbamate) (**1a**).
Eluent; hexane-2-propanol (90 / 10), flow rate; 1.0 ml min^{-1}.

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