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Direct Optical Resolution of Carboxylic Acids by Chiral HPLC on Tris(3,5-dimethylphenylcarbamate)s of Cellulose and Amylose[1)]

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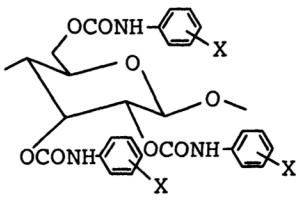
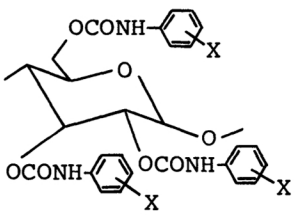
A variety of racemic carboxylic acids have been for the first time directly resolved by normal-phase, high-performance liquid chromatography using a hexane-2-propanol eluting system containing a small amount (≈1%) of a strong carboxylic acid, like formic acid, trichloroacetic acid, and trifluoroacetic acid.

Carboxylic acids are the most important class of chiral compounds and their optical resolution has been extensively carried out by recrystallization of diastereomeric salts.[2)] Recently, direct optical resolution of carboxylic acids by high-performance liquid chromatography (HPLC) on chiral stationary phases (CSP) has been realized; ligand-exchange chromatography with cuprous ion,[3,4)] inclusion chromatography with cyclodextrin[5)] and ion-pair chromatography with proteins[6)] and alkaloids[7)] have been used with aqueous mobile phases. However, as far as we know, no efficient optical resolution of carboxylic acids has been attained by normal-phase HPLC on CSP with organic mobile phases such as a hexane-2-propanol mixture.



CDMPC (X=3,5-Me_2)



ADMPC (X=3,5-Me_2)

In this letter, we wish to report the first, efficient, optical resolution of a variety of carboxylic acids by normal-phase HPLC on the CSP cellulose tris(3,5-dimethylphenylcarbamate) (CDMPC)[8)] and/or amylose tris(3,5-dimethylphenylcarbamate) (ADMPC)[9)] using hexane-2-propanol eluting systems containing a small amount of a carboxylic acid such as formic acid, trichloroacetic acid or trifluoroacetic acid. The present chromatographic systems should prove to be valuable for obtaining optical isomers of carboxylic acids and for determining their optical purities. The preparation of CDMPC and ADMPC phases supported on macroporous silica gel and chromatographic conditions were reported previously.[8,9)]

Figure 1 shows the chromatogram of the resolution of mandelic acid on CDMPC

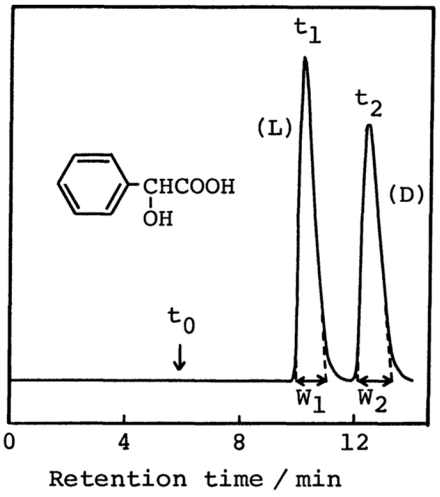


Fig. 1. Optical resolution of mandelic acid on a CDMPC column. (Eluent, hexane-2-PrOH-CF_3COOH (80:20:1))

Table 1. Effect of the acids added in eluent (hexane-2-propanol) on optical resolution of mandelic acid by cellulose tris(3,5-dimethylphenylcarbamate)[a)]

Acid	k_1'	α	Rs
none	not eluted		
CH_3COOH[b)]	not eluted		
CH_3CH_2COOH	2.02	1.37	≈0
CH_3COOH	1.28	1.34	0.47
HCOOH	0.74	1.37	1.19
$CHCl_2COOH$	0.50	1.60	1.62
CCl_3COOH	0.55	1.66	1.74
CF_3COOH	0.75	1.51	1.98

a) Chromatographic conditions: column, 25 x 0.46 (id)cm; eluent, hexane-2-propanol-acid (80:20:1); flow rate, 0.5 cm^3 min^{-1}; temp 25 °C. (L)-(+)-Isomer eluted first. b) Eluent, hexane-CH_3COOH (95:5).

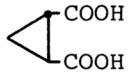
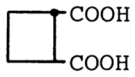
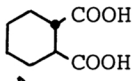
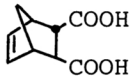
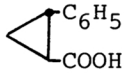
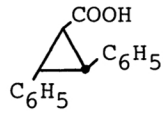
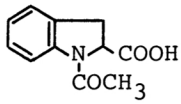
using a hexane-2-propanol eluting system containing 1% of trifluoroacetic acid. Dead time (t_0) of this column was estimated with 1,3,5-tri-tert-butylbenzene. Chromatographic parameters were determined as follows; capacity factor $k_1'=(t_1-t_0)/t_0$, separation factor $\alpha=(t_2-t_0)/(t_1-t_0)$, and resolution factor $Rs=2(t_2-t_1)/(W_1+W_2)$.

HPLC resolution of racemic carboxylic acids was influenced greatly by the eluting systems used. As an example, the results of resolution of mandelic acid on a CDMPC column are summarized in Table 1. The acid was not eluted from the column when a mixture of hexane-2-propanol (80:20) which is a typical eluting system for normal-phase HPLC was employed. The same was true for the hexane-CH_3COOH (95:5) eluting system. By the addition of a small amount (≈1%) of a carboxylic acid to a hexane-2-propanol (80:20) mixture base-line separation of racemic acids was attained. Strong acids such as formic acid, dichloroacetic acid, trichloroacetic acid, or trifluoroacetic acid were more effective than the weak acids, and larger separation factor and resolution factor were observed. The presence of a stronger acid in the eluting system may depress the dissociation of mandelic acid. The acid may also weaken the adsorption of mandelic acid on the silica gel which was used as a support of CDMPC. These are probably the reasons for the effectiveness of the strong acids. A similar acid effect was observed in the resolution of N-benzyloxycarbonylasparagine on the same column.

The resolution of mandelic acid and N-benzyloxycarbonylphenylglycine was examined on ten cellulose tris(phenylcarbamate) derivatives[8)] having substituents, 4-CF_3, 4-F, 4-Br, H, 4-C_6H_5, 4-C_2H_5, 4-CH_3, 4-CH_3O, 3,4-$(CH_3)_2$, or 3,5-$(CH_3)_2$, on the phenyl groups. In the case of both racemic mixtures, CDMPC exhibited the highest resolving power (α=1.37 for mandelic acid; α=1.50 for N-benzyloxycarbonylphenylglycine) when a hexane-2-propanol-HCOOH (80:20:1) mixture was the eluting system. ADMPC also possessed resolving ability for these two racemic compounds showing α=1.13 for mandelic acid and α=1.68 for N-benzyloxycarbonylphenylglycine.

Various mono- and dicarboxylic acids were completely resolved on the CDMPC and/or ADMPC columns by using a mixture of hexane-2-propanol-HCOOH (80:20:1) as the eluting system (Table 2). Most compounds were better resolved on the CDMPC than on ADMPC. Simple aliphatic acids like 2-methylbutyric acid did not show two HPLC peaks although a polarimetric detector for HPLC indicated partial resolution.

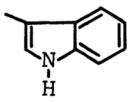
Table 2. Resolution of various carboxylic acids on CDMPC and ADMPC columns[a)]

Racemate	CDMPC				ADMPC			
	Eluent[b)]	k_1'	α	Rs	Eluent[b)]	k_1'	α	Rs
	B	2.56(-)	1.14	1.24	A	1.70(+)	1.13	1.07
	B	3.09(-)	1.13	1.06	A	2.43(+)	1.12	1.02
	B	2.41(-)	1.08		A	1.89	1.00	
	B	2.89(-)	2.07	6.74	A	2.37(-)	1.14	1.23
	A	0.63(-)	1.59	2.18	A	0.58(+)	1.31	1.02
	B	1.30(+)	2.60	6.82	A	1.64(-)	1.07	
	C	1.20(+)	1.33	1.71	C	1.19(+)	1.27	1.50
$C_6H_5OCHCOOH$ CH_3	A	0.89(-)	2.48	5.44	A	0.56(-)	1.33	1.00
$C_6H_5CHCOOH$ OCH_3	A	1.08(+)	1.60	2.90	A	0.99(-)	≈1	
$C_6H_5CHCOOH$ CH_3	D	2.56(-)	1.20	1.34	D	1.72	1.00	
$C_6H_5CHCOOH$ C_2H_5	D	2.03(-)	1.38	2.77	D	1.91	1.00	
$C_6H_5CHCOOH$ $C_6H_5CHCOOH$	C	0.69(-)	1.56	0.97	C	0.80(-)	1.68	2.63
OH $C_6H_5-C-COOH$ CH_3	A	1.05(-)	1.13	0.53	A	2.80(+)	1.26	2.22

a) Chromatographic conditions: see Table 1. The sign in parentheses represents optical rotation of the first-eluted isomer. b) A: hexane-2-propanol-HCOOH (90:10:1); B: hexane-2-propanol-HCOOH (95:5:1); C: hexane-2-propanol-HCOOH (80:20:1); D: hexane-2-propanol-HCOOH (98:2:1).

N-Benzyloxycarbonyl amino acids (CBZ-NHCH(R)COOH) except for the phenylalanine derivative were almost completely resolved on the CDMPC column (Table 3). In all cases the L-isomers eluted first. The α values in Table 3 except for that for N-benzyloxycarbonylphenylalanine are greater than those observed in resolution with aqueous mobile phases.[4,7] Most of the derivatives were also resolved on the ADMPC column with comparable or slightly low separation factors. However, phenylglycine (α=1.68) and phenylalanine (α=1.11) derivatives were better resolved on the ADMPC column.

Table 3. Optical resolutin of CBZ-NHCH(R)COOH on the CDMPC column[a)]

R	k'_1	α	Rs
C_6H_5	1.87	1.50	2.61
CH_3	0.68	2.12	2.15
$CH(CH_3)_2$	0.46	4.24	6.29
$CH_2CH_2CH_3$	0.58	2.42	3.79
$CH_2CH(CH_3)_2$	0.55	2.11	3.23
$CH_2CH_2CH_2CH_3$	0.53	1.79	2.54
$CH_2C_6H_5$	1.19	≈1	
$CH_2CH_2SCH_3$	0.98	1.52	2.26
	3.10	1.16	0.94
CH_2OH	1.22	1.39	1.74
CH_2COOH	1.13	1.27	1.12
CH_2CONH_2	2.08	1.40	1.49

a) Chromatographic conditions: see Table 1. (L)-Isomers eluted first.

As reported in this letter, the combination of CDMPC or ADMPC with the eluting system of hexane-2-propanol containing a small amount of a strong carboxylic acid is very valuable for the resolution of various carboxylic acids and may be used for obtaining optically active acids and determining their optical purities. The chiral column was quite stable during the present work.

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