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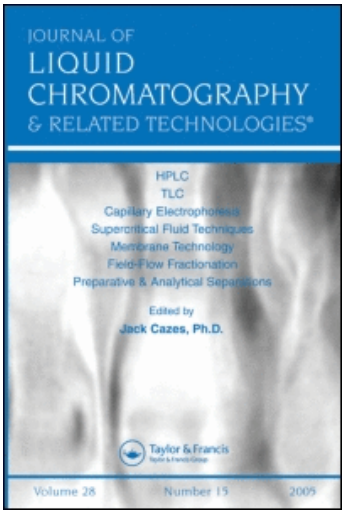

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JOURNAL OF LIQUID CHROMATOGRAPHY, 9(2&3), 313-340 (1986)

CHROMATOGRAPHIC OPTICAL RESOLUTION ON POLYSACCHARIDES AND THEIR DERIVATIVES

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Summary

Cellulose and other polysaccharides have been known to exhibit chiral recognition properties for along time. Microcrystalline cellulose triacetate, cellulose triacetate with a particular morphology, was found to have excellent chiral properties over ten years ago. Recently, a new kind of packing material, utilizing cellulose esters has been developed, to resulting in numerous examples of optical resolution. The history of utilizing polysaccharides for the purpose of optical resolution will be briefly described and the typical examples of successful optical resolutions will be summarized.

Though the mechanism of chiral recognition by polysaccharide derivatives is not known, much interesting information was obtained, the participation of crystalline lattice, the morphology and the ability of chiral recognition, the nature of the adsorptive interaction,etc. will be discussed.

Introduction

In 1980, Professor Blaschke authored a thorough review[1)] in which chromatographic optical resolution on cellulose, starch and cellulose

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acetate were introduced as chiral adsorbents. After that, research activity in the field was vigourous and, recently, a very different type of cellulosic packing material has been developed and become commercially available.[2] Not only their ability of a chiral recognition, but also their ready availability and chemical stability make cellulosics one of the most potentially useful chiral adsorbents. From the viewpoint of the mechanism of a chiral recognition, they show many interesting properties though their complete mechanism of chiral activity remains obscure. We wish to briefly summarize the history and the application of polysaccharides and their derivatives and then refer to some details of recent successful resolutions on cellulose esters with some mechanistic considerations.

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Cellulose and Starch

Around 1950, amino acids were found to give two spots in paper chromatography in some places[3,4,5,] and that was the first indication of chiral recognition by cellulose. Dalgliesh advocated "three point" attachment models[6] including hydrogen bond formation by the hydroxyl groups of cellulose and made an assumption concerning the effect of introducing a substituent on the benzene ring of phenylalanine; its validity has not been examined yet. The optical resolution of an amino acid or its derivative was performed on paper[7,8], on thin layer[9,10,11] and on a powderous cellulose column [12,13,14]. Other than amino acids, catechin (1) and epicatechin [15], some synthetic alkaloids[16,17], a chiral nickel complex (2)[18], $\alpha\alpha'$- diaminodicarboxylic acids (e.g.3)[19] were also resolved on cellulose. Recently Gübitz et.al. showed it was possible to realize high performance chromatography using small (ca.7μm) particles of cellulose.[12]

Yuasa et.al. studied extensively the optical resolution of aliphatic amino acids as well as aromatic amino acids on microcrystalline cellulose[20] and some other polysaccharides; they attempted to give mechanistic insights.[13] They showed, the protection of the hydroxyl groups of cellulose with BrCN resulted in the loss of a chiral recognition and the deprotection in the recovery of it.[13] They also showed upon treatment with aq NaOH (which causes the rearrangement of the naturally occurring cellulose polymorph (cellulose I) to unnatural one (cellulose II)), the cellulose lost its chiral

recognition. It is interesting that, so far, no efficient optical resolution has been performed on regenerated cellulose (usually cellulose II).

A system was developed in which an amino acid analyzer is directly combined with a cellulose column to analyze the enantiomeric composition of each amino acid in a mixture.[14]

Starch was utilized by Krebs et.al. and by Musso et.al. with good results for optically active biphenyls bearing polar substituents (e.g.,4) and the analogue (e.g.,5). The nickel complex 2 was resolved on starch as well as on cellulose. (scheme 1)
As the eluent, aqueous fluids are frequently employed and the addition of a salt assists the adsorption of the substrate onto starch to improve the efficency of resolution.

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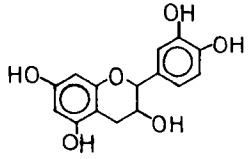
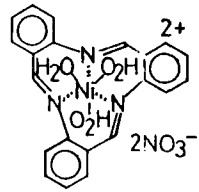
Derivatives of Polysaccharides

It seems that various derivatives of cellulose have been examined as a chiral adsorbents in several laboratories. Carboxy cellulose and cellulose (2.5) acetate are published examples. "Carboxy cellulose", which is obtained by oxidizing the primary hydroxyl of cellulose with N_2O_4 to a carboxyl group was reported to be effective in the resolution

Scheme 1 Examples of compounds resolved on cellulose or starch.



1 catechin



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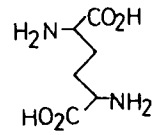

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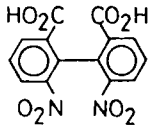
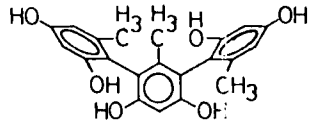


4 (1M Na citrate)



5 (PH 7 Na phosphate buffer)

of 1.2-diaminopropane[21] However the result is questionable. Though the enantiomers of the biphenyl derivative (6) were isolated first by the column chromatography on cellulose (2.5) acetate, the efficiency was very low.[22] The nature of the cellulose acetate which was obtained from Fa. M. Woelm under the designation "Acetylcellulose zur Racematspaltung" is not known and might be something essentially similar to "MCCTA" discussed below. The remarkable success by Hesse and Hagel utilizing "MCCTA" followed it. Their result so strongly impressed the importance of the particular morphlogy of "MCCTA" that research activities were mainly focussed on its use. After about a decade, the relation between the supermolecular structure of cellulose triacetate and the ability of chiral recognition was investigated and, as the result, a new kind of useful packing material was developed.

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"Microcrystalline Cellusose Triacetate (MCCTA)"

The key to the success of Hesse and Hagel[23] was the use of microcrystalline cellulose triacetate (hereinafter referred to as "MCCTA") which is the product of the heterogeneous acetylation of microcrystalline cellulose.[20] In Fig 1-a is shown the reported chromatogram of Tröger's base (7) on "MCCTA". "MCCTA" belongs to the metastable polymorph called cellulose triacetate (CTA) I and it gives the more stable polymorph, CTA II, upon dissolution and reprecipitation. Fig. 1-b is the chromatogram on CTA II thus obtained from acetone solution. Interestingly, the ability of chiral recognition is essentially lost while the small reversed enantioselectivity was recognised this was explained on the basis of the loss of crystallinity by dissolution. That led "to the conclusion that sorption is not achieved by Tröger's Base simply adhering to one glucose ester moiety, but by insertion between two such moieties(Fig 2)" and they advocated the concept of "inclusion chromatography".[24]
Since this report, it has been accepted for a long time that crystallinity is an essential requirement for a chiral recognition.

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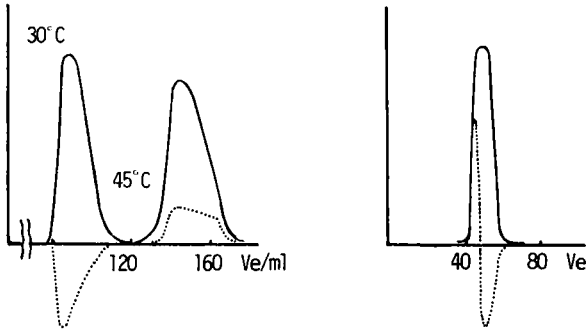

Fig.1-a Fig.1-b
Chromatograms of Trogers base (a) on "MCCTA" and (b) on CTA from acetone. two 16 cm columns, eluent, ethanol. —uv, ·····optical rotation.

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which is obtained by oxidizing the primary hydroxyl of cellulose with N_2O_4 to a carboxyl group was reported to be effective in the resolution of 1.2-diaminopropane[21] However the result is questionable. Though the enantiomers of the biphenyl derivative (6) were isolated first by the column chromatography on cellulose (2.5) acetate, the efficiency was very low.[22] The nature of the cellulose acetate which was obtained from Fa. M. Woelm under the designation "Acetylcellulose zur Racematspaltung" is not known and might be something essentially similar to "MCCTA" discussed below. The remarkable success by Hesse and Hagel utilizing "MCCTA" followed it. Their result so strongly impressed the importance of the particular morphlogy of "MCCTA" that research activities were mainly focussed on its use. After about a decade, the relation between the supermolecular structure of cellulose triacetate and the ability of chiral recognition was investigated and, as the result, a new kind of useful packing material was developed.

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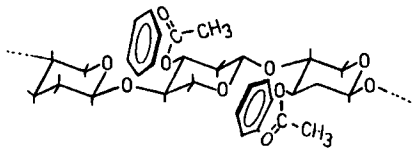

Fig. 2, Mechanism proposed by Hesse and Hagel.

metastable polymorph called cellulose triacetate (CTA) I and it gives the more stable polymorph, CTA II, upon dissolution and reprecipitation. Fig. 1-b is the chromatogram on CTA II thus obtained from acetone solution. Interestingly, the ability of chiral recognition is essentially lost while the small reversed enantioselectivity was recognised this was explained on the basis of the loss of crystallinity by dissolution. That led "to the conclusion that sorption is not achieved by Tröger's Base simply adhering to one glucose ester moiety, but by insertion between two such moieties(Fig 2)" and they advocated the concept of "inclusion chromatography".[24)]
Since this report, it has been accepted for a long time that crystallinity is an essential requirement for chiral recognition.

The optical resolution of diphenylmethanes (8), dioxa [12] paracyclophane (9), and 2-phenylcycloalkanones (10) were described (scheme 2).[25)] Then this adsorbent was widely used in several groups, especially extensively studied by Mannschreck et.al. and by Markgraf et.al.. Mannschreck and his coworkers thoroughly utilized MCCTA to resolve or enantiomerically concentrate compounds having theoretically interesting molecular structures, e.g., nonplanar adjacent π-bond systems as (11),[26)] (12),[28)] (17),[30)] and (27),[31)] helically condensed aromatic hydrocarbons as (13),[26,27)] cyclophanes as (15), and diazilidines as (18) and the kinetic studies of the configurational (conformational) mobility of those molecules were enabled by that. Chiral stannanes[34)] e.g.(16) and, in the attempt to apply the HPLC technique to chromatography on MCCTA, trans-1,2-diphenylcyclopropane (14)[32)] were also resolved. A method was established to determine enantiomeric purity or specific rotation in spite of incomplete separation[29,38)]. The optical resolution of racemic drugs was attempted by Markgraf et.al. to attain resolution of several barbiturates (19) and

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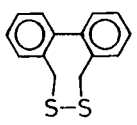
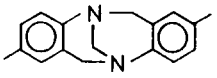
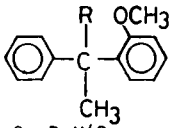
Scheme 2 Examples of compounds resolved on cellulose 2.5acetate (compound 6) and on "MCCTA".[68]



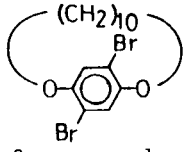
6



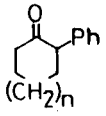
7 α=1.9



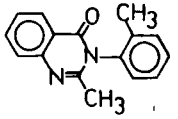
8 R=H(Br, no res.)



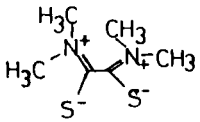
9 comp. rsl. on 40cm col.



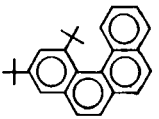
10 a, n=1 α=1.6
b, n=2



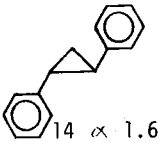
11 α=2.8(CH3OH)



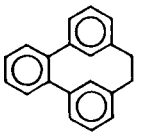
12 enr.



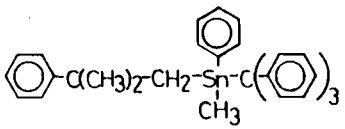
13 α=1.4



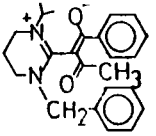
14 α 1.6



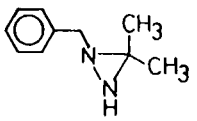
15 comp. rsl. on 30cm col



16 enr.



17 enr.



18 comp. rsl.

In case that α is not given but the chromatogram is, the possibly minimum was calculated assuming Vo = 0 and printed as α>X.XX.

their precursors, cyanoacetic esters (20), while thalidomide, warfarin(78), and pheniramine were not resolved (scheme 3). J. C. Jochims et.al. reported the resolution of a cumulenic tetraene (21) and Schlögl, of an aromatic allene (22), dibenzospirononane (23), cyclophanes, biphenyls,a ferrocene, and 2,7-methanoaza [10] annulenes(e.g.24) and a ferrocene (25) (scheme 4). Though it is apparent that compounds bearing (an) aromatic group(s) in the close vicinity of the chiral center have a better chance of successful resolution, some aliphatic compounds e.g., hexobarbital(19 R^1=c-C_6H_{11}, R^2=CH_3), spiroketals 26,(the secretion of Andrena bees[44]), and

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brominated hexa-2.4-dienes (27)[31] were resolved or enriched and the enantiomeric enrichment was observed even for a hydrocarbon and an aliphatic ketone (28)[25] (scheme 5).

At that time, another type of cellulose acetate, which is called "crosslinked acetyl cellulose", was sometimes utilized. This material, commercially available from Macherey-Nagel Co., seems to be cellulose (2.5) acetate[45] and have characteristics similar to those of "MCCTA" but we do not know the nature. trans-Diphenylcyclopropane (14) and the pyrazoline (29) were each completely resolved on a 25 cm column and that enabled the mechanism of the extrusion reaction from 29 to 14 to be clarified. Recently the resolution of some drugs(e.g.,30) and mandelic esters (31) were reported[47] (scheme 6).

A polar eluent e.g., aqueous ethanol is usually employed in chromatography with this kind of adsorbents and concerning the reported data, a nonpolar eluent seldom gave a good result.[25]

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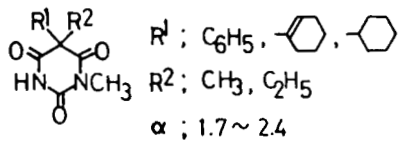
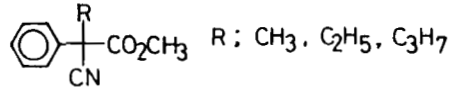
Cellulose Triacetate II

In spite of its excellent ability for a chiral recognition, "MCCTA" seems to have a few limitations. The most important one is that it loses its ability for chiral recognition upon dissolution. That makes it impossible to use a solvent for the purpose of preparing a packing material with improved efficiency. Another one is that the methods of such a trisubstitution reaction of cellulose under a heterogeneous condition is established only for a few derivatives. Contrary to CTA I ("MCCTA"), the stable polymorph CTA II has none of these problems. Postulating that CTA II should also have an excellent ability for chiral recognition in its crystalline state, study in this field was initiated in our group. The preparation of fine crystalline powder of CTAII was, nevertheless attained and trans-stilbene oxide (32) and Tröger's Base (7) were resolved with it.[48,50] In Fig 3 are shown chromatograms of 7 on a 25 cm column packed with "MCCTA" and the CTA II powder. While there are striking differences between them, an essentially comparable resolution efficiency was attained. In Table 1 are summarized some data; the most striking differences between the two kinds of CTA are in the enantioselectivity and in the magnitudes of relative retention, k', especially that of benzene. Though the latter phenomenon could be attributed to the polar nature of the adsorptive interaction of CTA II (see section 3-7), no total explanation for these differences is found.

Scheme 3 Barbiturates and cyanoacetic esters resolved on "MCCTA".

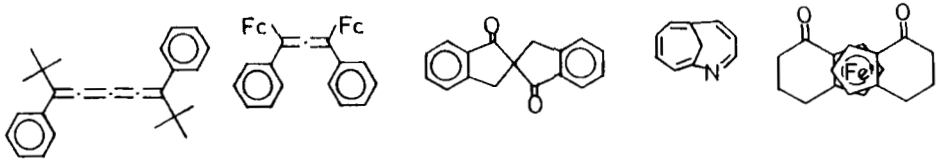


19



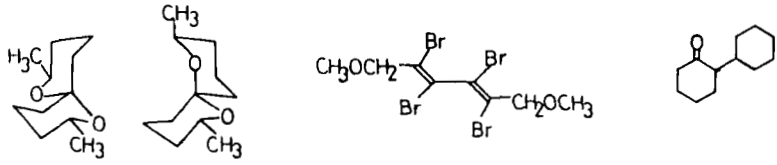
20

Scheme 4 Examples of compounds resolved on "MCCTA"



21, $\alpha > 3$ (pentane) 22, $\alpha = 1.4$ 23, $\alpha = 2.1$ 24, $\alpha = 1.4$ 25, $\alpha = 1.09$

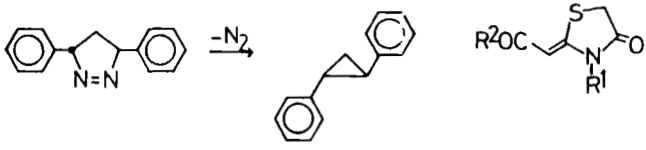
Scheme 5 Examples of aliphatic compounds resolved on "MCCTA".



t,t-26 t,c-26 27 enr. 28 enr.

1.23 1.16

Scheme 6 Examples of compounds resolved on "cross linked cellulose acetate".



30

R1	R2	R3	
CH_2	C_2H_5	2.26	
C_2H_5	C_2H_5		
(on two 25cm col.)			

29 1.7 14 1.6

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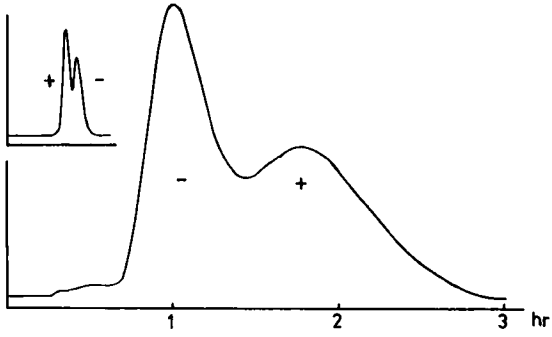

Fig.3 Chromatogram of Troger's base on crystalline CTA II (upper) and "MCCTA"(lower) eluent ethanol,0.2ml/min; column 25cm

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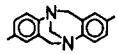
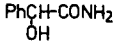
Later it was suggested by some experiments that, contrary to our presumption, the crystallinity of CTA II is not directly related to the ability of chiral recognition. For example, we later examined the effect of utilizing a macroporous support that was applied by Y. Okamoto et. al. to their polymer, optically active poly triphenylmethyl-methacrylate[51] This led them to an appreciable improvement in column efficiency. Though crystalline CTA II supported on macroporous silica gel was obtained, it showed that crystallinity is totally not beneficial to the ability of chiral recognition (fig 4). It was then found that hexane - 2-propanol mixture as the eluent resulted in a more satisfactory resolution of many substrates than alcoholic fluids. The chromatograms of trans-stilbeneoxide (32) on a variety of CTA II are shown in Fig 4. In spite of the somewhat reduced magnitude of (separation factor), the higher column efficiency and the shorter analysis time are quite advantageous in a practical sense. In addition, the supported packing material is easier to prepare and handle.

Derivatives of cellulose

Thus the "spell" of crystallinity was broken and a variety of cellulose derivatives supported on a carrier were examined extensively by us[50,54,55] and by Y. Okamoto et.al.[56,57,58,59]. Until now, cellulose triesters e.g., benzoate (CTB)[49,52,58], trisphenylcarbamate (CTPc)[59], nitrate, methycarbamate[59], cinnamate (CTCi), propionate, and the related derivatives are known to exhibit good chiral recognition.

Table 1. Comparison between MCCTA(CTA I) and CTA II

compound	column	k_1'	k_2'	α
	I	2.61 (-)	5.36 (+)	2.05
	II	0.59 (+)	0.91 (-)	1.53
	I	7.82 (+)	11.3 (-)	1.45
	II	0.94 (-)	1.23 (+)	1.31
	I	2.08	3.08	1.48
	II	0.80		1.0
	I	10.3		
	II	0.46		

column: 25cm x 0.46cm , I: packed with CTA I, II: packed with CTA II.
eluent: ethanol

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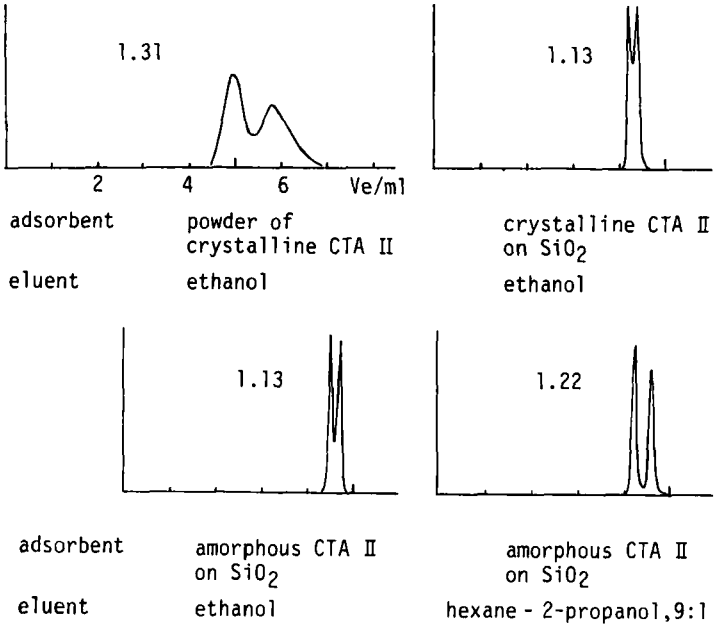
In contrast, cellulose ethers showed much poorer ability and no apparent peak separation was observed except tribenzyl and substituted tribenzyl ethers.[64] Some examples of optical resolutions on the typical adsorbents are shown in Table 2. The results are summarized as follows.[60] (1) Every derivative has its own selectivity for substrates. In other words, no generally useful "best one" can be chosen. (2) Sometimes the difference in substrate selectivity is attributed to the lengths of the substituents on cellulose. For example, Tröger's Base is resolved on CTCi, CTPc, and tris-p-substituted benzoates (except p-F) but neither on CTB, tris-4- fluorobenzoate, tris-3-chlorobenzoate, nor tris-3,5-dichlorobenzoate(see also section 3-6). (3) A conformationally flexible substituent on cellulose was apt to give poor results. Cellulose tris phenylacetate showed only a poor ability as compared to CTPc. (4) Aliphatic esters and nitrate tend to show a common enantioselectivity while aromatic derivatives the reverse one for the same substrate.

Derivatives of Other Polysaccharides

Study of polysaccharide derivatives other than cellulosics was expected to give some information regarding the mechanism of chiral recognition on cellulose derivatives. Those studied in our group and by Y. Okamoto et.al. were described in scheme 7 and some results were shown in Table 3 and scheme 13 [61,54,57,59]. Though more or less ability of



sample t-stilbene oxide; column 25 cm x 4.6 mm i.d.; flow rate 0.2 ml/min.

Fig. 4 Improvement in column efficiency and in choice of eluent.

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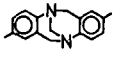
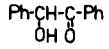
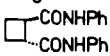
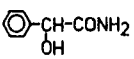
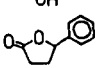
Table 2. Optical resolution (α) on cellulose derivatives.

substrate	No	substituent on cellulose					
		$COCH_3$	NO_2	CO⬡	CH_2⬡	CONH⬡	COCH=CH⬡
	32	1.22-	1.61-	1.47+	1.0	1.32+	1.15+
	7	1.31+	1.33+	1.0 -	1.34+	1.32+	2.82+
	33	1.05-	1.0 -	1.12+	1.0	1.0 +	1.08-
	10a	1.07+	1.14+	1.47-	1.0	1.14-	1.26-
	34	1.13-	1.22-	2.06+	1.0	1.25+	1.52-
	35	1.08	1.10	1.0	1.0	1.0	1.0
	36	1.39+		1.17-	1.0		1.07-

Signs indicate the optical rotation of the first elute in the eluent. The values of α vary depending on factors. The details will be reported elsewhere.[67]

Scheme 7 Polysaccharides examined.

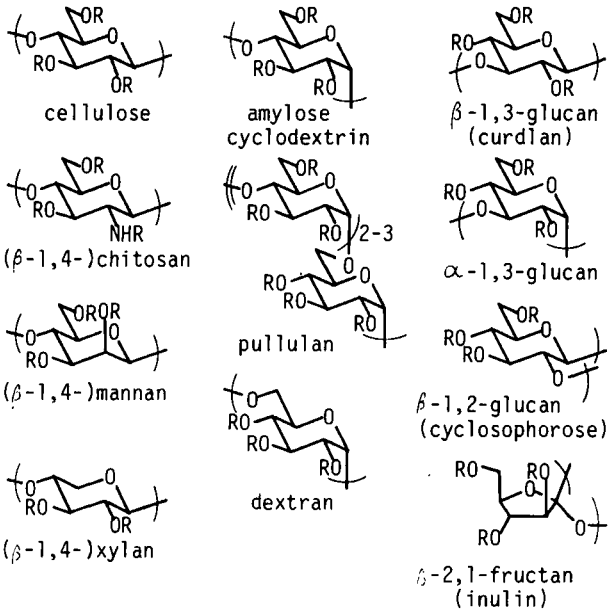


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Table 3. Optical resolution on polysaccharide derivatives.

substrate	XB	MB	ACi	ß1,3GA	1,3GA
32	1.17+	1.13+	1.31+	1.60+	3.42+
7	1.0	1.0	1.0	1.0	large+
33	1.0	1.0	1.0	1.65+	1.09+
10a	1.17-	1.09-	1.19-	1.43+	1.0 +
34	1.0	1.0	1.0	1.41+	1.0
35	1.0	1.0	1.0	1.42+	1.0-
36	1.11-	1.24-	1.08-		1.0-

XB, xylan dibenzoate; MB, mannan tribenzoate; ACi, amylose tricinnamate; ß1,3GA, ß-1,3-glucan(curdlan)triacetate; 1,3GA, -1,3-glucan triacetate; Compare with cellulose derivatives on table 2.67)

chiral recognition was found with polysaccharide triesters, no general principle governing adsorption behavior was found. Among 1,4-glycans, derivatives of chitosan, whose skeleton is identical to that of cellulose, reasonably showed an ability approaching that of cellulose, while the enantioselectivity for the same compound was not identical to that of the corresponding cellulose derivative. It is noteworthy that benzoates of cellulose, amylose, xylan, and mannan usually showed the same enantioselectivity and cinnamates too; that seems rather strange considering the differences in the molecular chain conformation and in the configurations of the hydroxyl groups of the α-polysaccharides. The fact that the benzoate of pullulane, which has an 1.6-linkage randomly distributed every three to four α-1.4-linkages did not show any apparent peak separation indicates that a high degree of structural regularity is one requirement for a chiral recognition. It must be noted that making a natural polysaccharide which often has branches, minor sugar(s) and/or minor linkage(s) the subject of the study the intrinsic behavior of the ideal polysaccharide derivative can hardly be concluded. Actually, an amylose derivative showed somewhat different behavior depending on the starting material. This is also conceivable about xylan, mannan etc.. Interesting behaviors were shown by 1.3-glucan derivatives[62]. While curdlan (ß-1.3-glucan) triacetate showed an excellent ability which may be possibly due to its helical conformation; the ability was too unstable to be practically employed. Though only a few compounds were resolved on α-1, 3-glucan triacetate, the compounds gave a very large α. Chiral recognition on phenylcarbamates of cellulose, chitosan, amylose, xylan, dextran, curdlan, and innulin were reported by Y. Okamoto et.al. (scheme 13) and the importance of the polymeric nature of these substances was suggested, based on the comparison with ß-cyclodextrin derivatives[57,59].

Totally, we think the chiral adsorption behaviors of polysaccharide derivatives are still the subject of further careful examination.

Physical Factors Affecting Chiral Recognition

The decrease in the degree of substitution of the cellulose ester resulted in the deterioration of a chiral recognition. Interestingly, factors undescribable with an organochemical structure were found to have profound effects on characteristics of chiral recognition. Those

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factors are the molecular weight (average M.W. and M.W. distribution) of a cellulose derivative, the solvent used in depositing the cellulosic on the support, the nature of the support, and so on.

In our group, cellulose derivatives with M.W. ($\overline{Mn}$) less than 100 were mainly studied and it sometimes happened that a substrate resolved well on higher M.W. cellulosic was not resolved on a lower M.W. material, and vice versa. In addition, the effect of molecular weight is dependent on the substrate and on the adsorbent e.g., in the case of cellulose triacetate, benzoin (33) and 2-phenylclohexanone (28) etc. for example showed the marked tendency to result a larger α on a higher molecular weight CTA, mandelamide (35), binaphthol and pantoyl lactone (37) etc. the inversed tendency, and trans-stilbene oxide (32), Tröger's Base (7) etc. were relatively insensitive to the molecular weight. CTA of too small M.W. ($\overline{Mn} < 2000$) showed little ability to recognize chirality. So far as shown, in case of aromatic derivatives of cellulose, a higher molecular weight one usually resulted a larger (Fig 6).

Conditions under which a cellulosic material was deposited on a support, especially the solvent used to dissolve the cellulosic, left some effect on the adsorption behavior and also in that case, the effect was dependent on the substrate. There is no observation indicating that liquid crystal formation plays any role in chiral recognition, though many cellulose derivatives are well known to form a mesophase under certain conditions.

Though we have not found any reasonable explanation for these complicated adsorption behaviors, a brief discussion will be given below under, "Some Mechanistic Insights."

Application of Supported Cellulosic Columns

The application of these columns has been extensively studied by us and by Y. Okamoto et.al.. Some of these results will be summarized. Some interpretations for our results regarding the molecular structure of substrates will be attempted from some view points.

The first question is whether the resolved substrates are limited to aromatic compounds. Though an aromatic one generally has a better chance of successful resolution, many nonaromatic compounds were successfully resolved(scheme 8, Fig.5). The resolution of α-BHC reported by Y.Okamoto et al. is also noteworthy.

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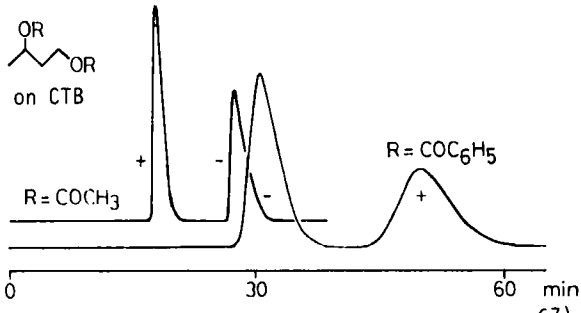

Fig. 5 Chromatograms of 1,3-butanediol esters.[67]
+,- optical rotation in the eluent.

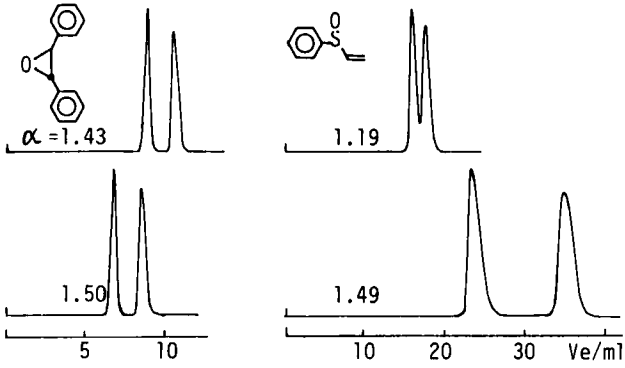

Fig. 6 Molecular weight dependence of resolution.
upper, on CTB $[\eta]$ =0.07. lower, on CTB $[\eta]$ =0.35.
$[\eta]$ was measured in CH_2Cl_2-CH_3OH 9:1 at 25°C.

The second is whether a polar functional group such as hydroxyl had better be protected. This problem was thoroughly investigated in a case study of alcohols.[64] As a conclusion, we emphasize an alcoholic substrate can be frequently resolved as it is when it has some other functional group(s). For example, α-arylethanols were usually resolved on CTB with a high efficiency (The levorotatory enantiomer elutes first as a rule.) while chiral recognition was deteriorated by the acetylation or the methylation of the hydroxyl group or by the halogen substitution. This suggests hydrogen bond formation plays an important role in chiral recognition (scheme 9). The same behavior was oberved for 40 and 49 on

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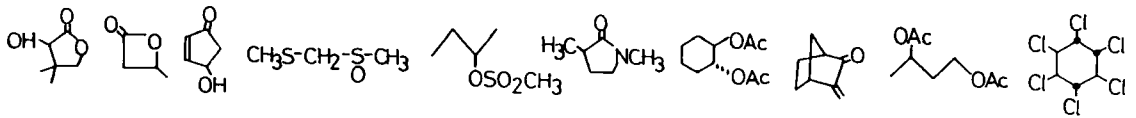
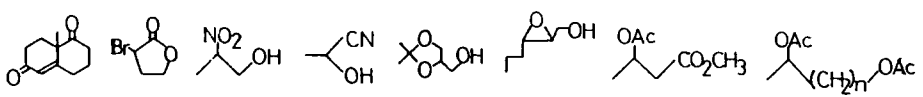
Scheme 8 Aliphatic compounds resolved on cellulosic columns.[67]

Rs 1.0 on a 25 cm column



No	37	39	40	41	42	43	44	45	46	38
α	1.22	1.31	1.23	1.61	1.21	1.21	1.44	1.41	1.80	
adsorbent	(CTA)	CTA	CTA	CTB	CTB	CTB	CTB	CTB	CTB	CTPc [56]

Rs 0.7 – 1.0 on a 25cm column



No	47	48	49	50	51	52	53	46 n	c 3	d 4
α	1.09	1.07	1.16	1.17	1.15	1.10	1.15		1.20	1.15
adsorbent	CTPc	CTA	CTA	CTA	CTB	CTB	CTB		CTB	CTB

CTA, 59 on CTB, etc. However it must be noted the reverse is also sometimes observed (60, 62, 64, on CTB). As to katalization, 4-phenyl-1,3-dioxane(58b) was resolved on CTB as efficiently as the diol(58a) while the acetonide of phenyl-1,2-ethanediol(85a) was not further resolved. 2-Phenylpropionic acid behaved similarly, i.e., on CTB, the acid itself was resolved (α=1.28) while the methylester was not. Phenethylamine whose acetamide was resolved on CTB with a high efficiency (α=1.69) gave a vague chromatogram because of a considerable tailing, and in such a case, an eluent containing an amine which was employed by Y. Okamoto et.al. to resolve ß-blockers 80, 81 may be useful.

The third is if discrimination between saturated alkylgroups is possible. Though it seems rather difficult, still the almost complete resolution of 2-butyl methanesulfonate (42) and the partial resolution of butylmethyl and ethyl 2-propyl sulfoxides were attained.

The fourth is if a conformationally more rigid substrate has a better chance of successful resolution. The answer is rather "no". One reason is that cyclization of an acyclic molecule sometimes makes resolution impossible e.g., neither trans-1-phenylcyclohexane-2-ol (63) nor its derivatives were resolved while 59a and 60b were. The similar situation was observed for 64 and 65 in comparison with the acyclic molecules 60b and 66 respectively (scheme 10). Another is that the increase in the number of the free rotating bonds between two functional groups of a substrate molecule is not necessarily detrimental to the efficiency of chiral recognitions (Scheme 9, Scheme 11) It is conceivable that a particular conformation should be required for a substrate molecule under adsorption and a molecule which can not take such a conformation refuses chiral recognition. The last is what is the difference of substrate selectivities of a variety of cellulose derivatives.

Though very few can be explained, an apparent correlation between the length of the substituents on cellulose and the size effent of the rigid structure of a substrate molecule was found in comparison between CTB and CTCi. As a general tendency, moleules with a very rigid structure, e.g. aromatic cyclic amides, were resolved efficiently on CTCi and one with a less rigid stucture e.g., monocylic amides and acyclic compounds with an aromatic substituent, on cellulose

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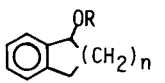
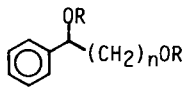
Scheme 9. Resolution of arylalcohols on CTB.

54	a	b	c
R	H	Ac	CH_3
	1.61	1.20	1.0

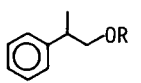


55	56a	56b
n	1	2	2
R	H	H	Ac
	1.82	1.75	1.0

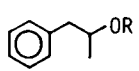
57
1.22



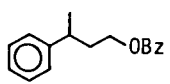
	85a	85b	58a	58b
n	1	1	2	2
R	H	Ac	H	R,R= CH_2
	1.34	1.0	1.29	1.33



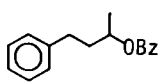
59	a	b
R	H	Ac
	1.18	1.0



60	a	b
R	H	Ac
	1.0	1.60



61
1.64

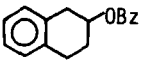


62
1.63

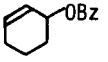
Scheme 10

Comparison between cyclic vs. acyclic substrates on CTB.

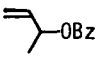
63
R= H, Ac
no res.



64
α = 1.16

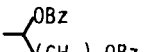


65
no res.



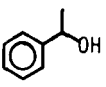
66
α = 1.21

Scheme 11 Diol dibenzoates on CTB.

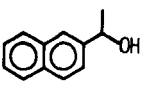


No.	67	68	69	70
n	1	2	3	4
α	1.14	1.74	1.44	1.83

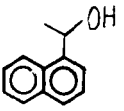
Scheme 12 Optical resolution of -arylethanols on CTB and on CTCi — Size selectivity —.



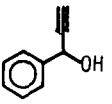
54



71



72



73

	54	71	72	73
on CTB	1.61	1.16	1.37	1.08
on CTCi	1.0	1.14	1.21	1.21

tribenzoate. Such a comparison can more clearly be seen among structurally related compounds. A typical case follows. On CTB a variety of α- phenylalcohols were resolved efficiently while not on CTCi and the condensation of an additional aromatic ring on the phenyl group (i.e., α and ß-naphthyl ethanols(71), (72)) or the addition of a rigid group to the chiral center (e.g., 1-phenyl-2-propynol 73) reduces the efficiency of the resolution on CTB while it enables the resolution on CTCi (scheme 12). Many similar cases were found and, furthermore, substition at the 4-position of the benzoyl group of CTB with a methyl group (i.e., cellulose tri-p-toluate) resulted in a substrate selectivity rather similar to that of CTCi.

Some group specificity, for example, aromatic thionophosphate on CTA[55], sulfoxides on CTB and on CTPc[55], α-phenylalcohols on CTB,

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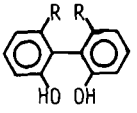
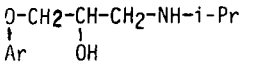
Scheme 13 Typical compound well resolved on cellulose (C), amylose (A), chitosan (Ch), xylan (X), dextran (D), and inulin (I) phenylcarbamates (Pc).[57]

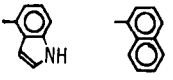
/ CPc, APc



R= OH / CPc, APc

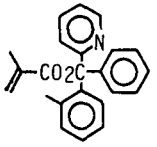
R= NO_2 / CPc



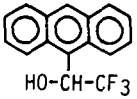
Ar= 

/ CPc

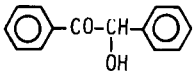
(81) (82)



/ APc



/ ChPc, XPc



/ XPc

$M(acac)_3$ M=Co,Cr / IPc

lactones and lactams on CTA and on CTB, aryloxypropionic esters on CTB and on CTCi, etc., were observed and the size selection may more or less contribute to the group specificity.

Though some insights into the scope of the method were given, still quite little is predictable now.

From a practical viewpoint, it must be emphasized that many materials useful as pharmaceuticals, and agrochemicals, and a precursor for these were successfully resolved(scheme 14). Many barbiturates and cyclic imides having an aromatic substituent (e.g., 19 R^1=Ph R^2=CH_3, 74, 75)which are central depressant were resolved efficiently on CTCi. Many insecticidal organophosphates and thionophosphates e.g.,76, 77 were resolved on CTA, on OTB, or on CTPc. Aryloxypropionic acid derivatives

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e.g.79, many of which have herbicidal activities were resolved on CTB and on CTCi. Though not as efficiently as those, arylpropionic acid derivatives e.g.,80, some of which are topical antiinflammatories, and the corresponding nitriles were also resolved(e.g.,83). Y. Okamoto et.al. showed some ß-adrenergic blockers, 81 and 82, were resolved on CTPc and Daicel researchers also some others(scheme 13). As to a chiral intermediate, the resolution of pantoyl lactone (37), a 2,3-isopropylideneglycerol derivative (84), esters of 1,3-butanediol, (46, 70), phenethylalcohol(54), and phenyl ethanediol (85a) are noteworthy. 4-Hydroxy-2-cyclopentenone which was resolved on CTA is the key intermediate for a variety of prostanoids in the synthetic approach recently established by Noyori et.al.[65] Some optically active compounds which have been utilized seldom because of their inaccessibility may be given chances for supply and use. For example ß-propiolactone(39), a 3-butene- 2-ol ester (66), and sulfoxides e.g.,86, 87 may be the case. The resolution of hexahelicene(88) and the related compounds[58] shown by Y. Okamoto et al. may be helpful for the research in this field. These cellulosic adsorbents are being utilized in researches of structurally novel or biologically interesting compounds here and there and the reports may appear in the near future.

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Some Mechanistic Insights

Supermolecular structures ; As refered to above (in chapter 3-2), no evidence for the participation of crystalline region in a chiral recognition was obtained in the case of CTA II. A similar result was also obtained on CTA I. In Fig.7 are shown the X-ray diffraction spectra of so called "MCCTA" and that crystallized upon heat treatment(220°C)and the chromatograms of mandelamide on them. Regardless to its name, "MCCTA" is not very crystalline actually and crystallization rather reduced its adsorptivity to result in a poor optical resolution. Thus so far as the term of crystallinity is defined by X-ray diffraction peaks, its critical importance in chiral recognition is no longer accepted. If so some other explanation for the low efficiency of the reprecipitated CTA in the experiment by Hesse and Hagel[23] should be required. The ordinary explanation based on the size and the shape of the particles of a packing material was excluded and the importance of the permeability of a substrate molecule in the

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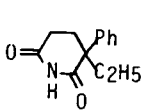
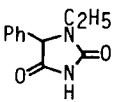
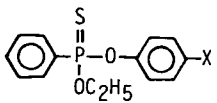
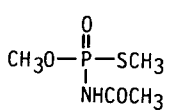
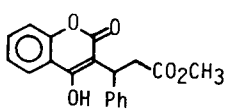
Scheme 14 Drugs, synthetic intermediates, etc. resolved on cellulosic columns.



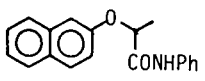


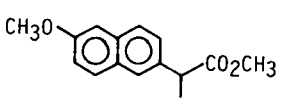


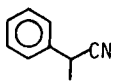


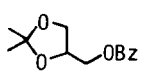


No	74 glutethimide	75 ethotoin	76 X= CN[58]	NO_2	77 oltran	78 warfarin
α	1.31	1.25	1.29	1.40	1.43	1.69
adsorbent	CTCi	CTCi	CTA	CTA	CTPc	CTPc

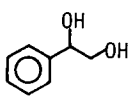


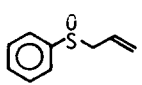


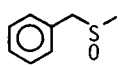


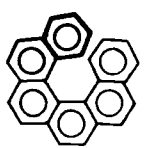


No	79 naproanilide	80 naproxen methyl	83		84
α	1.56	1.18	1.22,	1.19	1.60
adsorbent	CTB	CTCi	CTB	CTA	CTB









No	85	86	87	hexahelicene[58] 88
α	1.34	1.44	1.26	1.34
adsorbent	CTB	CTPc	CTB	CTA

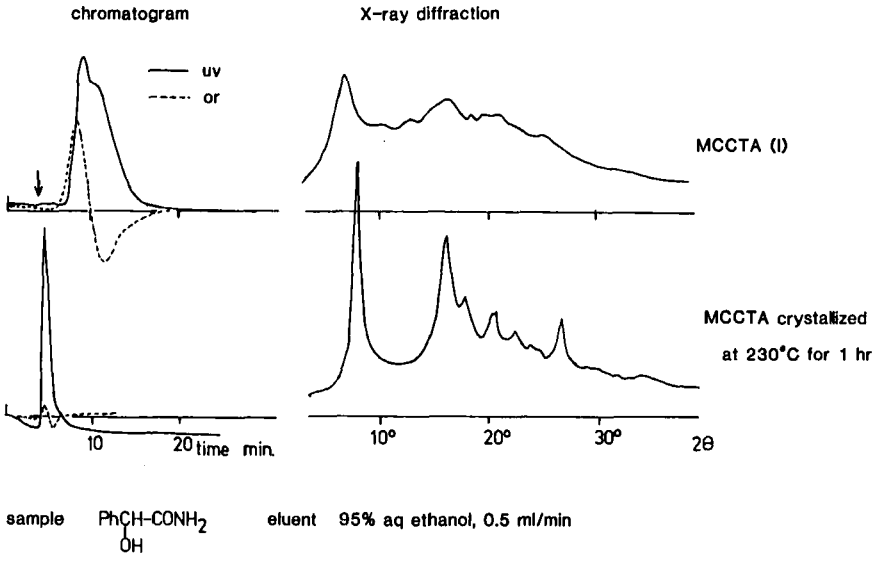


Fig. 7 Crystallinity and chiral adsorption on MCCTA (CTA I).

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particle was pointed out. Adsorption on cellulose derivatives was shown to take place not only on its surface but also on the whole cellulosic material. When the layer of the cellulosic is too thick, adsorption-desorption equilibrium on the whole layer can not be reached within the time required for the chromatographic technique to result in a considerable broadening of the elution peak(s). To this point, some researchers' failure in attaining an efficient optical resolution on cellulose derivatives and the success attained on a very fine precipitate of CTA II and on cellulosics supported on a porous carrier could likely be attributed. Moreover the success by Hesse and Hagel could also be attributed to this morphological reason, i.e., some fine structure naturally occurring could endow "MCCTA" with a high permeability. This point is under investigation now.

Nature of interaction between substrate and cellulosics; Most substrates successfully resolved have a phenyl group(s), carbonyl group, nitro group, sulfonyl group, sulfinyl group, cyano group or hydroxyl group(s). All of them are relatively polar except for a phenyl group, which still has some polarizability. In this respect, the adsorption

behavior was compared between CTB and tribenzyl cellulose on which only a few compounds were resolved. Relative retentions (k') for an achiral compound on CTB and on tribenzyl cellulose were measured respectively and the ratio k'(CTB)/k'(tribenzyl cellulose) was calculated. The value was less than 2 for a saturated hydrocarbon, chlorohydrocarbon, and carbondisulfide, about 2 for aromatic hydrocarbons with nonpolar substituents, and more than 3 for amides, lactones, aliphatic nitro compounds, sulfoxides, and alcohols.[66] Apparently the large affinity of those polar compounds showed for CTB comes mainly from the polar interaction caused by the carbonyl groups of CTB. Considering the observations as above, we emphasize the role of the polar interaction directly or indirectly induced by the carbonyl group of cellulose esters in a chiral recognition.

That is in good accord with the fact that a nonpolar eluent usually gives a better resolution than a polar one as a rule. While Y. Okamoto et.al. suggested polar interactions between a substrate and polysaccharide phenylcarbamates,[59] we think that is not specific to phenylcarbamates, but general to cellulose esters.

In the case of "MCCTA" a space-substrate molecular interaction (inclusion) has been suggested by investigators while Hesse and Hagel's mechanism (Fig 2) itself can hardly be accepted considering the van der Waals radii of the constituent atoms. It is a very interesting problem to find any conformity between those two quite different systems, "MCCTA" and CTA II. Considering that the selectivity of CTA II for substrates was affected by physical factors depending on substrates, it is conceivable that multiple sites recognizing a chirality coexist. Some could be intermolecular, some inter-glucose residue, and some intraglucose residue and each might be affected by molecular orientation and by conformation of every linkage individually to be emphasized or to be averaged out. Such coexistence of multiple sites may result in more chances of successful optical resolution for substrates. On the other hand, the magnitude of α may becomes moderate; that is not necessarily a detriment to a chromatographic method.

Conclusion

The behavior of polysaccharide derivatives summarized in this paper are as confusing as the case of the five blind men and the elephant.

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But considering that the structures of the two dominant polymorphs of cellulose are still the controversial subjects, that may be natural. Cellulose thus will evoke new interests of molecular physics, organic chemistry, analytical chemistry, spectrometry, crystallography, and morphology, etc. Of course, the question of why or hether polysaccharides among variety of natural chiral polymers are appropriate for a chiral recognition will also stimulate investigators.

On the viewpoint of application, the potential of the cellulosic adsorbents is thus becoming distinct. They do not have problems in their availability or in their chemical stability and only the technology of preparative chromatography remains to be established toward the industrial application of this method. Thus, this technology will aid chemists and pharmacologists not only in measuring an optical purity but also in establishing a reasonable synthetic approach to an optically active material as a tool for preparative optical resolution.

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67) Experimental description for our results packing material;20-22% polymer on LiChrospher Si-1000 treated with diphenyldimethoxy silane column;4.6mmi.d.x250mmi.l.
column temp. ; 20 C
values attained on a typical column were cited in this paper. The detailed description will be reported elsewhere.
68) Abbreviations in figures
MCCTA;microcrystalline cellulose triacetate,
CTA, CTB, CTCi, CTPc;cellulose triacetate, tribenzoate, tricinnamate, tris phenylcarbamate respectively
col.;column, res.;resolution, enr;enrichment(no apparent peak separation)

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