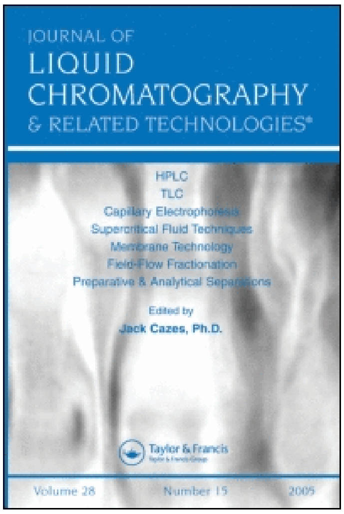

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THE FIRST CHROMATOGRAPHIC RESOLUTION AND ELECTRONIC EFFECTS OF MULTIFUNCTIONAL CARBON COMPOUNDS ON CELLULOSE-BASED ADSORBENTS

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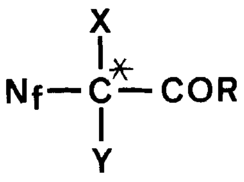
ABSTRACT

Direct chromatographic resolution of some tri- and tetrafunctional chiral carbon compounds **1**-**6** has been studied. Among the columns examined, CHIRALCEL OB exhibited fairly satisfactory resolution ability. The electronic effects associated with the presence of plural functional groups for chiral recognition by the OB adsorbent is discussed.

INTRODUCTION

Despite the potential value of compounds containing a carbon atom bearing more than two different labile groups, *i.e.*, multifunctional carbon (1) compounds, from the viewpoints of chirality and stereoisomerism, this class of compounds has received little attention. The carbon atom surrounded by such functionalities (structure **A**) necessarily presents a new type of asymmetric center (2). Thus, the steric and electronic factors of each functional group, and further, particlularly the combined effects derived from the presence of plural functional groups, are of great interest since they are attached directly to the asymmetric carbon atom. The optically active multifunctional carbon compounds also have the potential to serve as chiral auxiliaries and useful chirons for the synthesis of optically active natural products, in addition to their value as models for spectroscopic studies. We have recently succeeded in the first synthesis (3) and chemical resolution (3,4) of compounds possessing different labile ligands on a carbon atom including ester carbonyl, halogen, nitrogen-containing, and sulfur- or oxygen-containing functionalities.

In our previous work, the resolution method involved MPLC separation of the corresponding diastereomeric phenethyl esters. However, this procedure is time-consuming, and further, not applicable to all of the multifunctional carbon compounds prepared because of their high reactivity (5) and unexpectedly low polarity (6). We therefore turned our attention on the direct chromatographic resolution. We anticipated electronic effects associated with the multifunctionality which would inevitably influence the diastereomeric circumstances under chromatographic conditions, although there have so far appeared no reports on such effects.



$$\mathrm{Nf-\overset{X}{\underset{Y}{\overset{*}{C}}}-COR}$$

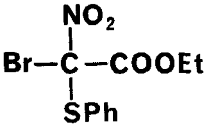
$X = F, Br$

$Y = OR', SR', SOR'$

$N_f = NR'_2, NO_2, N_3$

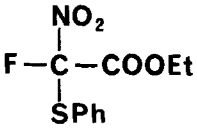
$R = R'', OR'', NR''_2$

A



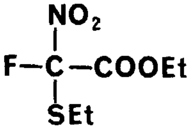
$Br-C(NO_2)(SPh)-COOEt$

1



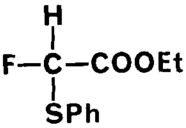
$F-C(NO_2)(SPh)-COOEt$

2



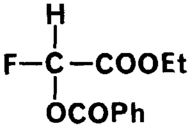
$F-C(NO_2)(SEt)-COOEt$

3



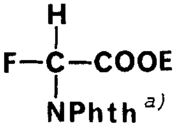
$F-C(H)(SPh)-COOEt$

4



$F-C(H)(OCOPh)-COOEt$

5



$F-C(H)(NPhth^{a)})-COOEt$

6

a) phthalimidyl

The polyfunctionalized carbon compounds introduced here are to serve as the first and yet the best models for studying both steric and total electronic effects of those molecules possessing plural functional groups on a chiral center.

In this paper we present the results on the first chromatographic resolution of chiral carbon compounds with multifunctionalities **1**-**6** using macroporous silica gel coated with cellulose derivatives (8-11).

GENERAL EXPERIMENTAL PROCEDURE

High performance liquid chromatographic resolutions of compounds **1**-**6** were carried out with CHIRALCEL OA(cellulose triacetate) (9-11), OB(cellulose tribenzoate) (9-11), OC(cellulose tris(phenylcarbamate)) (8,9,11), and OK(cellulose tricinnamate) (10,11). The chromatography was performed at 25°C using Jasco BIP-I liquid chromatograph equipped with a Uvidec-100V variable-wavelength spectrophotomeric detector(254nm). As exemplified in

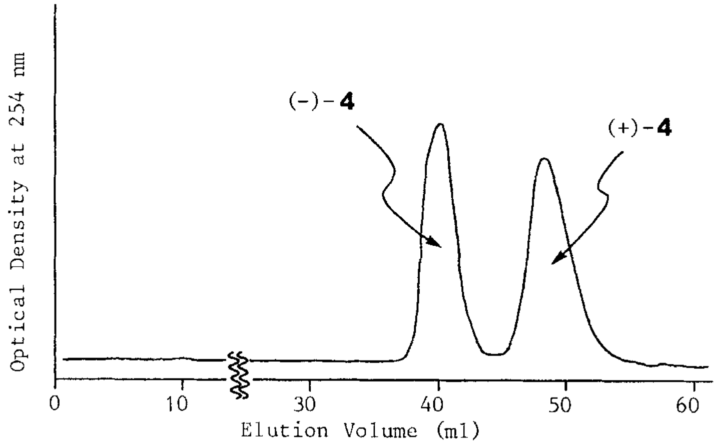


Figure
Chromatographic Resolution of the Compound **4** (Run 15 in the TABLE)

the figure for ethyl fluoro(phenylthio)acetate **4**, some of the compounds were resolved completely under appropriate conditions. Columns, chromatographic conditions (12), and the resolution results are shown in the Table.

RESULTS

Dramatic effects of these compounds on the chiral recognition by the cellulose-based adsorbents were observed, of which the essential points can be summarized as follows.

1) Among the four columns tested, only CHIRALCEL OB exhibits significant resolution ability for most of the compounds. OA, OC, and OK have, in general, little or no ability for resolution of this kind of compounds except for **4** (13).

2) The trifunctional carbon compounds **4**, **5**, and **6** are resolved much more effectively on the OB adsorbent than the nitro group-containing tetrafunctional carbon compounds **1**, **2**, and **3**.

3) For those compounds which have a hydrogen on the asymmetric

TABLE

Optical Resolution of Multifunctional Carbon Compounds on Cellulose-Based Adsorbents

Run	Compound	Colunm[a)]	Eluent[b)]	Flow Rate ml/min	$\underline{k}_1'$[c)]	α[d)]	R_s[e)]
1	1	OA	A	0.5	0.41	1.00	
2		OB	B	1.0	6.86	1.09	~0.5
3		OB	A	1.0	1.33	1.00	
4		OC	A	0.5	0.56	1.00	
5		OC	B	1.0	2.07	1.00	
6		OK	A	1.0	3.46	1.00	
7	2	OA	A	0.5	0.61	1.00	
8		OB	B	1.0	6.32	1.00	
9		OC	A	0.5	0.41	1.00	
10	3	OA	B	1.0	2.20	1.00	
11		OB	B	1.0	4.15	1.09	~0.5
12		OC	B	1.0	4.09	1.00	
13		OK	B	1.0	3.24	1.00	
14	4	OA	A	1.0	0.87	1.12	0.59
15		OB	B	1.0	11.48	1.21	1.32
16		OB	A	1.0	1.89	1.15	0.62
17		OC	A	1.0	0.85	1.0(sh)	
18		OK	A	1.0	2.24	1.45	2.87
19	5	OA	A	1.0	1.12	1.18	0.91
20		OB	B	1.0	13.91	1.27	2.06
21		OB	A	1.0	1.84	1.00	
22		OC	A	1.0	1.06	1.00	
23		OK	A	1.0	2.39	1.00	
24	6	OA	A	1.0	7.26	1.00	
25		OB	B	1.0	41.91	1.31	1.25
26		OB	A	1.0	9.58	1.19	1.07
27		OC	A	1.0	9.83	1.00	
28		OK	A	1.0	19.14	1.00	

a) OA, OB, OC, and OK represent CHIRALCEL OA, OB, OC, and OK, respectively(25 X 0.46(i.d.)cm). b) A : n-hexane / 2-propanol = 9 / 1, B : n-hexane. c) $\underline{k}_1'$ (capacity factor for less retained enantiomer) = (retention volume - dead volume) / dead volume. d) α (separation factor) = $\underline{k}_2'$ (capacity factor for more retained enantiomer) / $\underline{k}_1'$. e) R_s (resolution factor) = 2 X (distance of the two peak position) / (sum of bandwidths of the two peaks).

center (compounds 4, 5, and 6), the OB adsorbent exhibits chiral recognition more effectively in n-hexane than in the protic medium (n-hexane/2-propanol).

DISCUSSION

These results are difficult to explain merely in terms of steric effects. Since the fluorine atom is considered to be comparable to hydrgen in steric bulkiness (14), the shape of structures 4, 5, and 6 must be much closer sterically to a symmetrical, i.e., achiral molecule than that of the other three. Electronic effects of the whole molecule, or of each heteroatom-containing substituent on the chiral center, presumably participate in the formation of diastereomeric complexes between the racemic molecules and the chiral adsorbents.

It is easily understandable that CHIRALCEL OB is more effective for these polyfunctionalized compounds since the column is known (11) to exhibit chiral recognition ability particularly effective for those racemates which have polar functional groups such as carbonyl, nitro, and phenyl groups. The carbonyl groups of cellulose tribenzoate(OB) possessing permanent dipole moments seem to interact strongly with the polar site of our molecules through proper alignment of both dipoles in a linear configuration (7). If the carbonyl group of the OB adsorbent were to interact selectively with the nitro group, which has much larger dipole moment than the other functional groups in these molecules, this adsorbent should exhibit more resolution ability for those nitro group-containing compounds. The result is, however, opposite to this expectation. Therefore, the dipole interaction probably occurs in this case between the adsorbent and the dipole of the whole molecule of racemates, and not between the adsorbent and individual functional groups. Indeed, trifunctional carbon compounds 4, 5, and 6 seem to have larger dipole moments as a whole molecule than the nitro group-containing tetrafunctional carbon compounds where the nitro group is contributing to reduce totally the dipole moment of molecule.

To our knowledge, this result presents the first example for a chiral adsorbent to discriminate between the electronic features of enantiomers through the whole molecule, rather than the individual functional groups in it. As for the eluent effect, there must be the hydrogen-bonding interaction (7,15). Chiral recognition ability is known (16) to be affected by hydrogen bond formation between 2-propanol and racemates or adsorbents, and actually the hydrogens on the asymmetric carbon in **4**, **5**, and **6** must be acidic enough to be compared to that of chloroform (17).

The optically active multifunctional carbon compounds offer interesting subject of investigation, e.g., relationship between stereostructure and optical rotation, steric aspect of reaction mechanisms, or chiral auxiliary. Further studies of the steric and electronic effects caused by the geminally functionalized structures are under way.

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(5) For example, α-bromo-α-nitroacetate produces dibromonitro- and nitroacetates on standing.

(6) Most of the multifunctional carbon compounds were purified by silica gel column chromatography employing the solvent system of n-hexane/ether = 10/1~5/1. Since all of the functional groups in structure **A** have dipole moments large enough to interact with adsorbents and solvents (7), the rather low polarity of the multifunctional carbon compounds is noteworthy.

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(12) The dead volume(V_0) of the columns was estimated to be 3.2 ml with 1,3,5-tri-t-butylbenzene as a non-retained compound.
(13) The compound **4** seems to possess also the structural features generally required for chiral recognition by the adsorbents OA, OC, and OK. See references (10) and (11).
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(17) The protons on the asymmetric carbons of **4**, **5**, and **6** appear at considerably low fields, 6.09, 6.70, and 6.41ppm, respectively, in their ^1H NMR spectra. Also the central carbon signals for those compounds appear at much lower fields(94.2, 95.3, and 81.1ppm, respectively) than that of chloroform in their ^{13}C NMR spectra.