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Predictable chromatographic separations of enantiomers: aryl allenic acids and their derivatives

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Abstract

Designed to distinguish between the enantiomers of compounds having certain rather common structural features, the chiral selector used in chiral stationary phase (CSP) 1 columns is broadly applicable. The validity of the chiral recognition mechanism used to design the selector is supported by NMR and chromatographic studies and one can honestly claim to have a relatively good understanding of when and how this selector will differentiate between enantiomers. Consequently, one can often confidently predict not only that this column will separate the enantiomers of a given compound but also specify the relation between absolute configuration and elution order. A recent paper describing the use of a chiral allenic acid to aid in assigning absolute configurations by exciton-coupled circular dichroic measurements focused our attention on these allenes. A priori, these aromatic allenic acids appeared to contain structural features which would allow enantioseparation on CSP 1. Accordingly, a series of chiral allenic acids and their ester and amide derivatives were prepared for chromatographic study. Indeed, the enantiomers of the acids and esters are readily resolved, eluting in the expected order. The amides resolve more poorly for reasons that are clearly defined. Relevant data and mechanistic explanations are presented to convey an understanding of how CSP 1 differentiates between enantiomers.

Keywords: Enantiomer separation; Chiral stationary phases, LC; Allenic acid

1. Introduction

Typically, those who wish to chromatographically separate the enantiomers of some substance through the use of a chiral stationary phase (CSP) seek a suitable CSP by trial and error. This is particularly true of those who utilize CSPs derived from biopolymers. Such CSPs typically contain multiple types of binding sites and are of such mechanistic complexity as to presently defy a detailed understanding of how they differentiate between enantiomers. In contrast, brush-type CSPs have been prepared using low-molecular-weight selectors which have been designed to contain only those interaction sites which are essential for the differentiation of the enantiomers. These work for relatively well-defined reasons and are commercially available.

As a case in point, the recent report by Nakanishi et al. [1] concerning the synthesis, resolution and application of a chiral aryl allenic acid as an auxiliary stereogenic center for exciton-coupled circular dichroism (ECCD) studies prompted us to prepare a series of these allenic acids and their derivatives. Our goal in this was to demonstrate that it is possible to predict when the enantiomers of members of a previously unstudied class of com-

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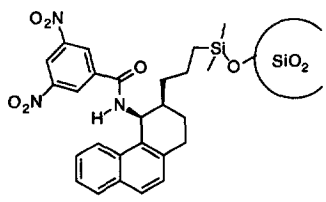
pounds can be separated on a CSP and to correctly anticipate the order in which the enantiomers will elute. This requires that one recognize those structural features in the analyte which can be utilized in a chiral recognition process and then choose a CSP which has the appropriate 'structural complementarity' to utilize those features. In other words, one must understand the manner in which the CSP differentiates between enantiomers and determine whether the enantiomers in question have the requisite interaction sites to be differentially accommodated by the CSP. With the knowledge of the spatial arrangement of the interaction sites on the CSP and the manner in which the analyte is retained, one is able to assign the absolute configuration of the enantiomers of the analyte based on the elution order.



(3*R*,4*S*) WHELK-O 1

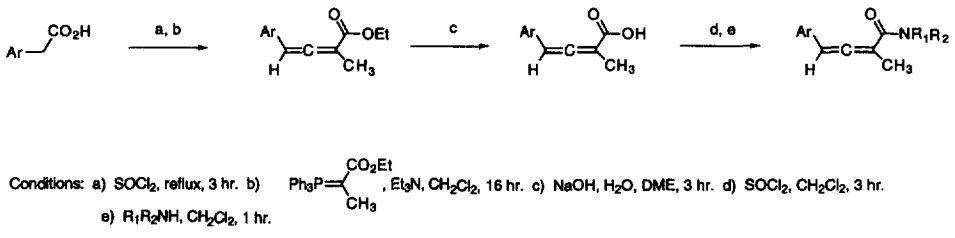
Fig. 1. Synthetic chiral stationary phase used in this study (CSP 1).

2. Experimental

The analytes used in this study were prepared using literature methods [1,2] outlined in the Scheme 1. All chromatographic solvents were HPLC grade from EM Science. Chromatography was carried out at ambient temperature using a commercial version of CSP 1 (i.e. a (3*R*,4*S*) Whelk-O 1 brush-type HPLC column (250×4.6 mm, 5 μm spherical silica particles of 100 Å pore size) available from Regis Technologies, Morton Grove, IL). To facilitate comparison of all the data, all experiments were carried out at a nominal flow-rate of 2.00 ml/min and a mobile-phase of hexanes–2-propanol–acetic acid (95:5:1). Elution was monitored by ultraviolet (254 nm) and polarimetric detectors in series. The latter was used (in stopped-flow experiments) to determine the relative rotations of the enantiomer in the flow cell at six wavelengths ranging from 636 nm to 365 nm. Tri-*tert.*-butylbenzene was used as the void volume marker.

3. Results and discussion

From extensive studies it is clear that CSP 1 (Fig. 1) functions largely as it was designed to do [3,4]. This chiral selector, originally designed to resolve the enantiomers of naproxen and other NSAIDs [5–7], has been shown to be useful for the chromatographic enantioseparation of many compounds [8]. CSP 1 contains a cleft-like binding site which preferentially binds that enantiomer which, without departing substantially from a low-energy conformation, can undergo simultaneous face-to-face and face-to-edge π–π interactions as well as a hydrogen bonding interaction with the CSP. Without restating old material, analytes containing a π-basic group and a hydrogen bond acceptor site near a stereogenic center are candidates for enantiodifferentiation by this CSP. The biphenylallenic acid recently used by Nakanishi et al. [1] as an auxiliary stereogenic center to aid in the assignment of absolute configuration by EECD clearly meets these criteria. Even without the aid of models, it can be seen that the (*R*)-enantiomer



Scheme 1.

of this compound (and its ester and amide derivatives) would be selectively retained by the (3*R*,4*S*) enantiomer of CSP 1. In fact, one expects the same for a whole series of aryl allenic acids and their ester and amide derivatives as generalized by structures 1–3 (Fig. 2). Fig. 3 presents a stereoview of the manner in which the more retained enantiomer of 2-methyl-4-phenyl-2,3-butadienoic acid (compound 2d) was expected to fit into the cleft of CSP 1. The allenic system is considered to be a part of the π-basic system and the vinyl hydrogen of the more retained enantiomer is presumed to be involved in an edge-to-face π–π interaction with the naphthyl portion of the CSP. Implicit in this drawing is the presumption that the allene has no 'appendages' which prevent either enantiomer from entering the cleft and no functionality to 'divert' an essential interaction to a 'non-essential' site.

It has been established that both the (*S*)-biphenylallene acid and its ethyl ester have positive CD bands in the 240–280 nm range, leading one to expect positive plain dispersion curves at wavelengths longer than this. In other words, the (*S*)-enantiomers should be dextrorotatory in the 365–636 nm range. As expected, the enantiomers of all the acids, esters and N-alkyl amides used in this study resolve readily and elute in the expected order, (*S*)-(+) before (*R*)-(−). The relationships between the sign of rotation and the elution order for the N,N-dialkyl amides were not established as the enantiomers of these compounds are not especially well separated on CSP 1. The polarimetric detector was used (in stop-flow experiments) to determine the relative rotations of the enantiomer in the flow cell at six wavelengths (633, 589, 546, 435, 405 and 365 nm). This was done to ensure that the signs of the rotations are not wavelength dependent (over this range) and that plain dispersion curves obtain. The latter were judged to be dependable gauges of the absolute configurations of the enantiomers. The separations of the acids and esters are facile. Large

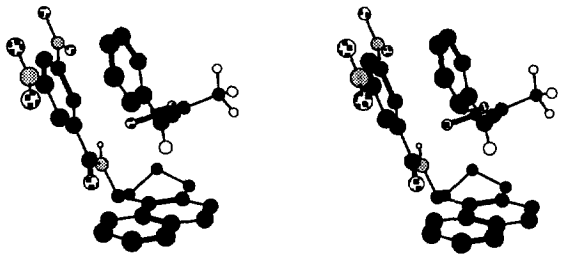


Fig. 3. Proposed chiral recognition model. Computer-generated stereo model of the proposed complex between (−)-(*R*)-2d and CSP 1. All ring hydrogens and the alkyl tether of CSP 1 have been omitted for clarity.

separation factors and high chromatographic efficiencies are afforded (Tables 1 and 2) and the optical rotations of the enantiomers are substantial.

Our proposed chiral recognition model raises several other expectations. Increasing the π-basicity of the aryl-substituent should increase the strength of both the face-to-face and edge-to-face π–π interactions, thus increasing enantiodiscrimination. Electron donating groups on the aryl-substituents do indeed increase the separation factors. Compound 11, where the vinyl hydrogen, thought to undergo a face-to-edge π–π interaction with the naphthyl portion of the selector has been replaced with an ethyl group, does not resolve on CSP 1, presumably because the ethyl group sterically impedes the entry of the (*R*)-enantiomer into the cleft of the selector.

The enantiomers of the aryl allenic amides (Table 3) separate much more poorly than those of the corresponding acid and ester derivatives, the enantiomers of the acids separating better than those of the esters. This can be explained in terms of the low-energy conformations of these analytes and the geometry necessary for the analyte to fit into the binding cleft of CSP 1. There are two relatively low-energy conformations about the single bond between the allene and the carbonyl carbon, the s-*cis* and s-*trans* (Fig. 4). It has been shown for non-aromatic allenic esters that the s-*trans* conformation

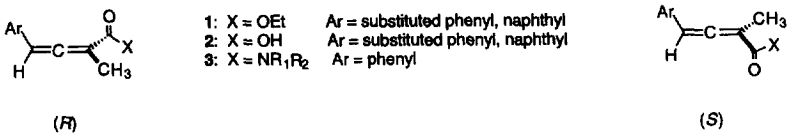
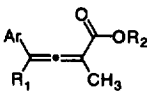


Fig. 2. General structure of compounds used in this study.

Table 1
Retention and separation factors for aryl allenic esters

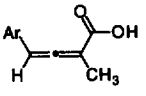


Compound	Ar	R_1	R_2	k_1'	k_2'	α	R_S
1a	α-naphthyl	H	Et	1.84	10.46	5.68	18.52
1b	β-naphthyl	H	Et	1.84	6.37	3.46	14.16
1c	4-biphenyl	H	Et	1.33	4.16	3.13	11.83
1d	phenyl	H	Et	0.79	2.55	3.23	9.80
1e	*p*-Me-phenyl	H	Et	0.93	3.58	3.85	12.25
1f	*p*-MeO-phenyl	H	Et	1.64	5.39	3.29	13.15
1g	*p*-I-phenyl	H	Et	0.85	2.11	2.48	6.93
1h	*p*-Br-phenyl	H	Et	0.79	1.90	2.41	6.51
1i	*p*-Cl-phenyl	H	Et	0.74	1.76	2.38	6.01
1j	*p*-F-phenyl	H	Et	0.72	1.68	2.33	5.99
1k	*p*-NO_2-phenyl	H	Et	2.20	3.50	1.59	5.62
1l	phenyl	Et	Et	0.69	0.69	1.00	0.00
1m	phenyl	H	Me	0.87	2.52	2.90	8.70
1n	phenyl	H	i-Pr	0.69	2.55	3.70	10.47
1o	phenyl	H	*t*-Bu	0.43	1.39	3.23	5.13

Mobile phase: hexanes–2-propanol–acetic acid (95:5:1). Flow-rate: 2 ml/min.

is slightly preferred in the crystalline state and it is reported that the s-*cis* conformation is slightly preferred in solution [9]. Either of these conformations present a favorable hydrogen bonding situation for the acids and the esters, one presents the carbonyl oxygen to the selector whereas the other presents the alkoxy oxygen. One might suggest that the acids

Table 2
Retention and separation factors for aryl allenic acids

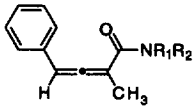


Compound	Ar	k_1'	k_2'	α	R_S
2a	α-naphthyl	1.99	14.90	7.49	18.81
2b	β-naphthyl	1.95	8.18	4.19	16.17
2c	4-biphenyl	1.53	5.44	3.56	12.48
2d	phenyl	0.90	3.53	3.92	8.58
2e	*p*-Me-phenyl	1.04	4.45	4.28	12.44
2f	*p*-MeO-phenyl	1.88	6.80	3.62	12.73
2g	*p*-I-phenyl	1.07	3.04	2.84	8.70
2h	*p*-Br-phenyl	1.01	2.70	2.67	8.11
2i	*p*-Cl-phenyl	0.92	2.46	2.67	7.79
2j	*p*-F-phenyl	0.90	2.31	2.57	6.32
2k	*p*-NO_2-phenyl	2.94	5.04	1.71	6.04

Mobile phase: hexanes–2-propanol–acetic acid (95:5:1). Flow-rate: 2 ml/min.

populate the s-*trans* conformation to a greater extent than the esters because of steric interference of the alkyl group of the ester. The amides are expected to

Table 3
Retention and separation factors for aryl allenic amides



Compound	R_1	R_2	k_1'	k_2'	α	R_S
3a	methyl	methyl	7.96	8.19	1.03	0.50
3b	methyl	H	10.07	14.65	1.45	6.23
3c	ethyl	ethyl	5.00	5.70	1.14	1.92
3d	ethyl	H	7.10	10.19	1.44	5.42
3e	*n*-propyl	*n*-propyl	4.47	4.85	1.09	1.20
3f	isopropyl	isopropyl	2.76	3.13	1.13	1.29
3g	*n*-butyl	*n*-butyl	4.14	4.47	1.08	1.05
3h	isobutyl	isobutyl	3.10	3.67	1.18	1.84
3i	*n*-pentyl	*n*-pentyl	4.28	4.28	1.00	0.00
3j	*n*-pentyl	H	5.46	7.30	1.34	4.46
3k	*n*-hexyl	*n*-hexyl	4.10	4.10	1.00	0.00
3l	*n*-hexyl	H	5.21	6.94	1.33	4.46
3m	cyclohexyl	cyclohexyl	3.47	3.96	1.14	1.53
3n	methyl	*n*-butyl	5.30	5.61	1.06	0.88
3o	-$(CH_2)_4$-	–	10.30	11.40	1.11	1.58
3p	-$(CH_2)_6$-	–	6.07	6.80	1.12	1.68

Mobile phase: hexanes–2-propanol–acetic acid (95:5:1). Flow-rate: 2 ml/min.

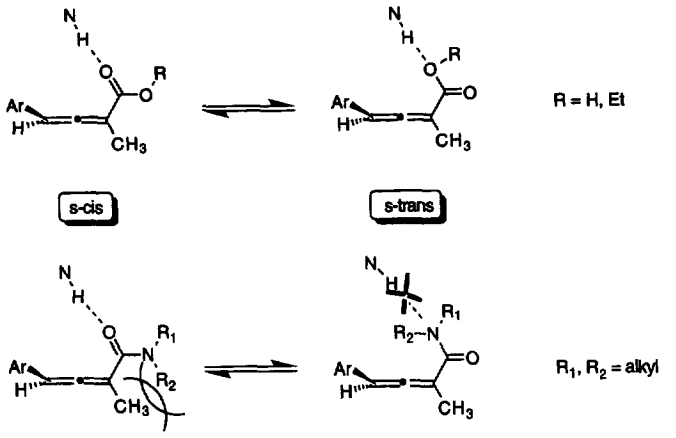


Fig. 4. s-*cis* and s-*trans* conformations of aryl allenic acids, esters and amides. N-H represents the amide of CSP 1 when the aryl group and the vinyl hydrogen of the analyte are undergoing simultaneous face-to-face and edge-to-face $\pi-\pi$ interactions. The curved lines for the amide s-*cis* conformation represent the steric destabilization which would arise from close proximity of the vinyl methyl and the R_2 group on the amide nitrogen.

populate the s-*trans* conformation rather extensively owing to steric repulsion between the allenic methyl group and the alkyl groups on the amide nitrogen which would occur in the s-*cis* conformation. Since the dialkyl amide nitrogen is a poor hydrogen bond acceptor, the s-*trans* conformation does not lead to effective hydrogen bonding with the CSP. Consequently, the CSP loses most of its ability to discriminate the enantiomers of the amide derivatives. The small amount of discrimination that does occur for these amides may arise from a small population of the higher energy s-*cis* conformation. N-Alkyl amides would be expected to more heavily populate the s-*cis* conformation than the N,N-dialkyl amides because of the lesser steric interaction between the amide hydrogen and the vinyl methyl group. Indeed, the enantiomers of the N-alkylated amides do show larger separation factors than the corresponding N,N-dialkylated amides. However, these separation factors are still less than those of the corresponding acids and esters.

4. Conclusion

From a mechanistic point of view, the enantiomers of aryl allene carboxylic acids (and their ester and amide derivatives) were expected to be resolvable on a CSP designed to differentiate between the enantiomers of compounds having aromatic substituents and hydrogen bond acceptor sites on or near a stereogenic center. The allenic compounds meet this description and are readily resolved on CSP 1, the enantiomers eluting in the expected order. The relatively large separation factors observed and the ability of CSP 1 to accommodate large samples lead us to believe that CSP 1 is presently the chiral phase of choice for the preparative chromatographic separation of the enantiomers of this class of aryl allenic acids and their ester derivatives.

Acknowledgments

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