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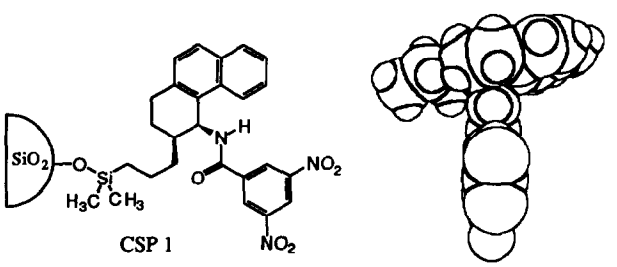
Use of Simultaneous Face to Face and Face to Edge π-π Interactions to Facilitate Chiral Recognition

William H. Pirkle* and Christopher J. Welch[1]

School of Chemical Sciences, University of Illinois, Urbana, IL 61801

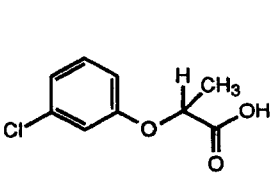
Abstract: A recently developed HPLC chiral stationary phase exhibits a general ability to resolve the enantiomers of compounds possessing both an electron rich conjugated π-system and a hydrogen bond acceptor located near the stereogenic center.

Despite their importance, chromatographic enantioseparations[2,3] are often sought and conducted without much real understanding of how the chiral stationary phase distinguishes between enantiomers. We are striving to better understand the mechanistic details of "chiral recognition" and thereby design highly enantioselective selectors of broad scope. CSP 1, recently designed specifically for resolution of the enantiomers of naproxen and related α-aryl propionic acids,[4,5] possesses structural features conducive to wider applicability. The chiral selector used in CSP 1 can be viewed as a semirigid framework holding a π-acidic 3,5-dinitrobenzamide group perpendicular to a π-basic polynuclear aromatic group. The amide N-H serves as a hydrogen bond donor and is situated in the cleft formed by the two aromatic systems. These are capable of simultaneous face to face and face to edge π-π interaction with an aromatic group present in the analyte. Presumably, the face to face interaction undergone by the analytes aromatic substituent enhances its ability to simultaneously participate in the face to edge interaction.

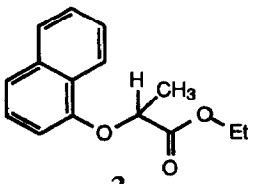


CSP 1

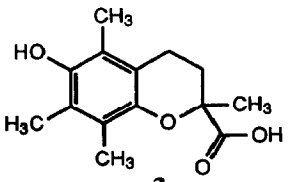
Many classes of chiral compounds possess the "complimentary functionality" needed for chiral recognition by CSP 1. Typically, the enantiomers of a compound having an aromatic substituent and a hydrogen bond acceptor on or near a stereogenic center can be separated chromatographically on CSP 1.



1
$k'_1 = 1.04$
$\alpha = 1.31$
95:5:0.5 hex./IPA/HOAc



2
$k'_1 = 2.75$
$\alpha = 2.53$
95:5:0.5 hex./IPA/HOAc



3
$k'_1 = 5.87$
$\alpha = 1.20$
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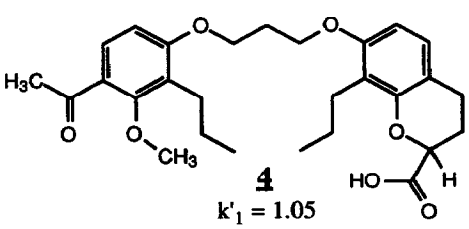
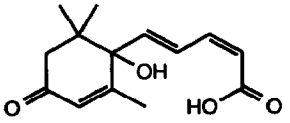
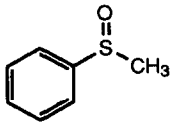


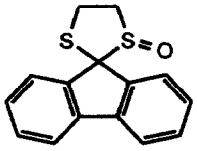
4
$k'_1 = 1.05$
$\alpha = 1.12$
80:20:0.5 hex./IPA/HOAc



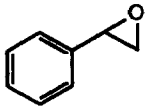
5
$k'_1 = 0.41$
$\alpha = 1.37$
80:20:0.5 hex./IPA/HOAc



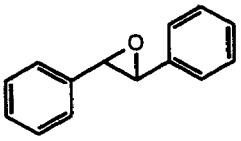
6
$k'_1 = 3.83$
$\alpha = 1.24$
7:2:1 hex./IPA/CH_2Cl_2



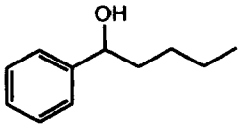
7
$k'_1 = 3.29$
$\alpha = 2.14$
7:2:1 hex./IPA/CH_2Cl_2



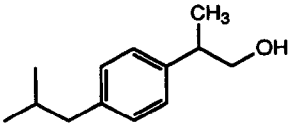
8
$k'_1 = 1.37$
$\alpha = 1.37$
99:1 hex./IPA



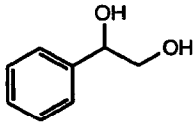
9
$k'_1 = 0.45$
$\alpha = 2.00$
90:10 hex./IPA



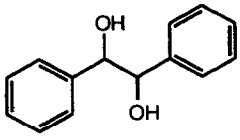
10
$k'_1 = 2.52$
$\alpha = 1.08$
99:1 hex./IPA



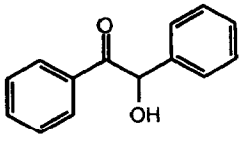
11
$k'_1 = 3.38$
$\alpha = 1.05$
99:1 hex./IPA



12
$k'_1 = 7.54$
$\alpha = 1.08$
98:2:0.5 hex./EtOH/HOAc

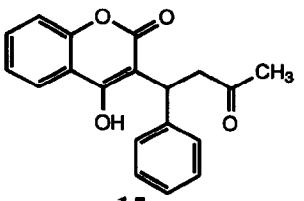


13
$k'_1 = 3.27$
$\alpha = 1.32$
95:5:0.5 hex./EtOH/HOAc

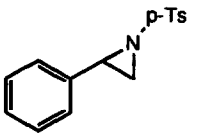


14
$k'_1 = 0.86$
$\alpha = 1.97$
80:20:0.5 hex./IPA/HOAc

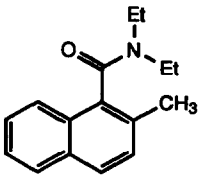
Figure 1: Examples of compounds which are resolved on CSP 1. k'_1 = retention factor for initially eluted enantiomer. α = chromatographic separation factor. Mobile phase as indicated. All separations were conducted at a flow rate of 1.00 ml/min.



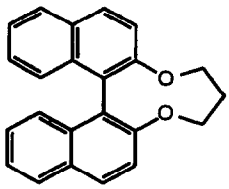
15
$k'_1 = 2.85$
$\alpha = 2.00$
80:20:0.5 hex./IPA/HOAc



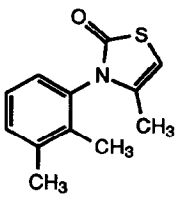
16
$k'_1 = 2.75$
$\alpha = 2.53$
90:10 hex./IPA



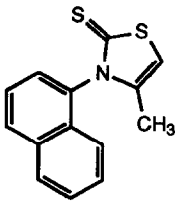
17
$k'_1 = 0.46$
$\alpha = 2.17$
EtOAc



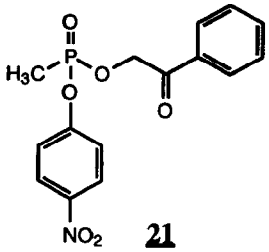
18
$k'_1 = 2.26$
$\alpha = 1.11$
90:10 hex./IPA



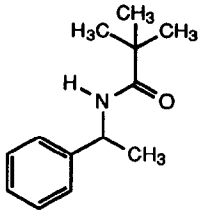
19
$k'_1 = 1.73$
$\alpha = 1.64$
70:30 hex/IPA



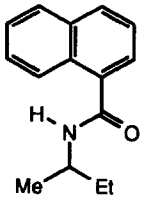
20
$k'_1 = 1.91$
$\alpha = 2.13$
70:30 hex/IPA



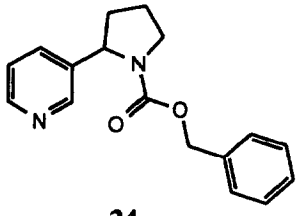
21
$k'_1 = 1.11$
$\alpha = 1.15$
5:5:1 hex./CH_2Cl_2/CH_3CN



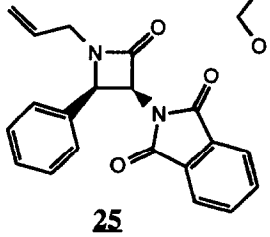
22
$k'_1 = 0.16$
$\alpha = 5.56$
EtOAc



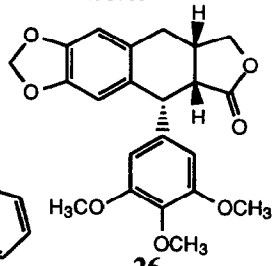
23
$k'_1 = 14.97$
$\alpha = 1.12$
80:20 hex./IPA



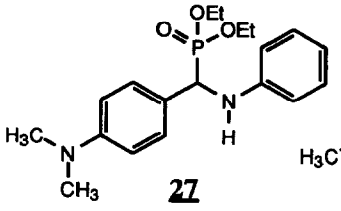
24
$k'_1 = 0.37$
$\alpha = 1.38$
75:25 CH_2Cl_2./MeOH



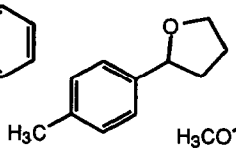
25
$k'_1 = 1.75$
$\alpha = 2.10$
MeOH



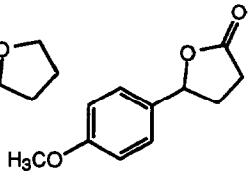
26
$k'_1 = 0.94$
$\alpha = 1.69$
MeOH



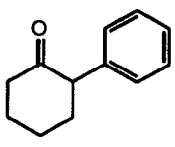
27
$k'_1 = 1.35$
$\alpha = 3.53$
90:10 hex./IPA



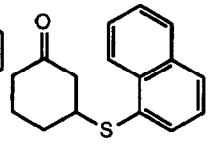
28
$k'_1 = 1.17$
$\alpha = 1.68$
80:20 hex./IPA



29
$k'_1 = 5.66$
$\alpha = 1.29$
80:20 hex./IPA



30
$k'_1 = 3.41$
$\alpha = 1.81$
90:10 hex/IPA



31
$k'_1 = 7.82$
$\alpha = 1.12$
98:2 hex./IPA

Resolution of a number of profens (α-aryl propionic acids) on CSP 1 was previously reported.[5] The esters and amides of profens also resolve, as do the structurally related α-aryloxy propionic acids and their ester and amide derivatives (Figure 1; compounds **1** and **2**). Other chiral carboxylic acids [e.g. the antioxidant, trolox (**3**), the experimental psoriasis drug, SC 41930 (**4**) and the plant hormone, abscisic acid (**5**)[6]] are also resolved with this CSP. Aryl sulfoxides fit the general pattern (*e.g.* **6** and **7**) as do α-aryl epoxides (*e.g.* **8** and **9**), aryl alkanols (*e.g.* **10** and **11**), and aryl diols (*e.g.* **12** and **13**). The enantiomers of benzoin, **14**, and warfarin, **15**, are well resolved as are the enantiomers of *N*-tosyl-α-aryl aziridines (e.g. **16**).[7] Atropisomers such as the naphthamide, **17**,[8] the ß-binaphthol derivative, **18**, and *N*-arylthiazolinones (or the oxygen analogs, e.g. **19** and **20**) resolve on CSP 1 as do chiral phosphonates such as **21**. The enantiomers of virtually any amide, carbamate, or urea derivative of an α-aryl aminoalkane (*e.g.* **22**) are readily separated on CSP 1, separation factors of 2 to 15 being observed. The enantiomers of a great many aliphatic and heterocyclic amines can be resolved after acylation with an achiral reagent (*e.g.* **23**, **24**). The ß-lactam, **25**, the lignan, **26**, the amino phosphonate, **27**, the tetrahydrofuran, **28**, and the lactone **29** are all readily resolved. A variety of chiral ketones having their carbonyl group near an aryl substituent and a stereogenic center also resolve nicely on CSP 1 (e.g. **28** - **30**). These examples are provided as guides to aid potential users and are illustrative, not "best case" examples. A more detailed account concerning mechanism and elution order will be forthcoming. In view of the generality, durability, high chromatographic efficiency, and the ability to tolerate a variety of temperatures, mobile phases, and large sample loads, CSP 1[9] is regarded as being the most useful CSP to yet emerge from our research.

Acknowledgements: We thank Dorothy Honda of G.D. Searle & Co. for providing a sample of compound **4**, Dr. Eric Jacobsen of Harvard University for providing samples of compounds **11** and **16**, Dr. Gary Schuster of the University of Illinois at Urbana-Champaign for providing a sample of Compound **18**, Dr. Ildilko Kovach of the Catholic University of America for providing a sample of compound **21**, and Dr. Stephen Hanessian of the University of Montreal for providing a sample of compound **26**. Chromatographic solvents have been provided by EM Science. The work has been partially funded by grants from the National Science Foundation and from Eli Lilly and Co.

References:

1) present address: Regis Technologies, Inc., Morton Grove, IL 60053.

2) Allenmark, S., *Chromatographic Enantioseparation, Methods and Applications*, Ellis Horwood, New York, 1991.

3) Krstulovic´, A., *Chiral Separations by HPLC: Applications to Pharmaceutical Compounds*, John Wiley & Sons, New York, 1989.

4) Pirkle, W.H.; Welch, C.J.; Lamm, B., *J. Org. Chem.*, **1992**, *57*, 3854.

5) Pirkle, W.H.; Welch, C.J., *J. Liq. Chromatogr.*, **1992**, *15*, 1947.

6) Welch, C.J., *Chirality*, **1993**, *5*, 569.

7) Li, Z.; Conser, K.R.; Jacobsen, E.N., *J. Amer. Chem. Soc.*, **1993**, *115*, 5326.

8) Pirkle, W.H.; Welch, C.J.; Zych, A., *J. Chromatogr.*, **1993**, *648*, 101.

9) These columns are now available as the Whelk-O 1 CSP from Regis Technologies, Inc., Morton Grove, IL.

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