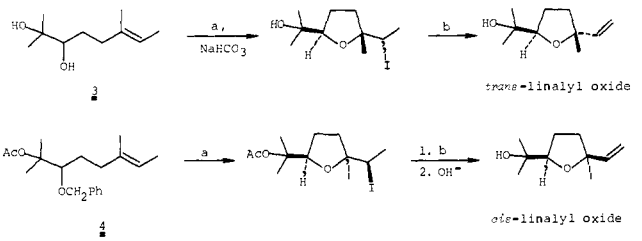
Scheme II[a]




[a] (a) $I_2$, $CH_3CN$, 0 °C. (b) KO-*t*-Bu, DMF, 25 °C.

on the internal consistency of obtaining the opposite stereochemical preference on cyclizing alcohols and benzyl ethers. On cyclization of the disubstituted olefins (examples 10–13), we saw no evidence of tetrahydropyran products, although they would be easily distinguishable by $^1H$ or $^{13}C$ NMR spectroscopy.[7] The fact that cyclization is successful even when the double bond is deactivated by conjugation with an ester group further establishes the versatility of the approach (examples 14–16).

Our success with the synthesis of cis-2,5-disubstituted tetrahydrofurans prompted us to attempt the stereoselective formation of 2,2,5-*tri*substituted analogues, which also appear as subunits of many of the polyether ionophores. As initial targets in this regard, we chose the linalyl oxides, since both isomers are known and well characterized.[8] Previous syntheses have involved nonstereoselective epoxidation and cyclization of linalool or geraniol.[8,9] As illustrated in Scheme II, iodocyclization of the diol **3**[10] and elimination of HI leads to the trans isomer in 70% overall yield. $^1H$ NMR (250 MHz) spectroscopy showed a trans/cis ratio of 20:1 and gave no indication of tetrahydropyran formation from attack by the tertiary hydroxyl. Most importantly, the cis isomer is produced with a selectivity of 13:1 on cyclization of the benzyl ether acetate **4**,[11] followed by elimination and ester hydrolysis (70% overall yield). In comparison to the formation of disubstituted tetrahydrofurans, in this case the initial cyclization step reverses more rapidly, and even the unsubstituted benzyl group allows sufficient equilibration between the isomeric oxonium ions before it is lost.

Further studies on the generality of this approach and its application to more complex polyethers are currently being pursued.

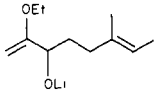
**Acknowledgment.** Support of this research by the National Institutes of Health (Grant CA-16616) and the National Science Foundation (departmental equipment Grant CHE 79-03763) is gratefully acknowledged. We also thank Dr. Alex Kos and Professor Paul v. R. Schleyer for their help and interest in the structure of the oxonium ion intermediates.

(7) Chemical shift values listed in: Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley: New York, 1972; p 256, give $\delta$ 1.8 for the $CH_3C(1)$ < moiety (tetrahydrofuran isomers) and $\delta$ 1.2 for the $CH_3C(OR)$< moiety (tetrahydropyran isomers). The cis and trans products from example 10 (see Table I) show resonances of $\delta$ 1.86 and 1.89, respectively, and the cis and trans products from example 12 show resonances at $\delta$ 1.85 and 1.87, respectively, for the relevant methyl group.

(8) Felix, D.; Melera, A.; Seibl, J.; Kovâts, E. sz. *Helv. Chim. Acta* **1963**, *46*, 1513–1536.

(9) Klein, E.; Farnow, H.; Rojahn, W. *Liebigs Ann. Chem.* **1964**, *675*, 73–82. Ohloff, G.; Schulte-Elte, K.-H.; Willhalm, B. *Helv. Chim. Acta* **1968**, *47*, 602–626. Kametani, T.; Nemoto, H.; Fukumoto, K. *Bioorg. Chem.* **1978**, *7*, 215–220.

(10) Prepared from 3-methyl-3-buten-2-ol by vinyl ether exchange and Claisen rearrangement, ethoxyvinyllithium addition to give intermediate i, hydrolysis, and reaction with methyllithium.[4]




i

(11) Prepared from i by benzylation, hydrolysis, methyllithium addition, and acetylation.[4]

# A Widely Useful Chiral Stationary Phase for the High-Performance Liquid Chromatography Separation of Enantiomers

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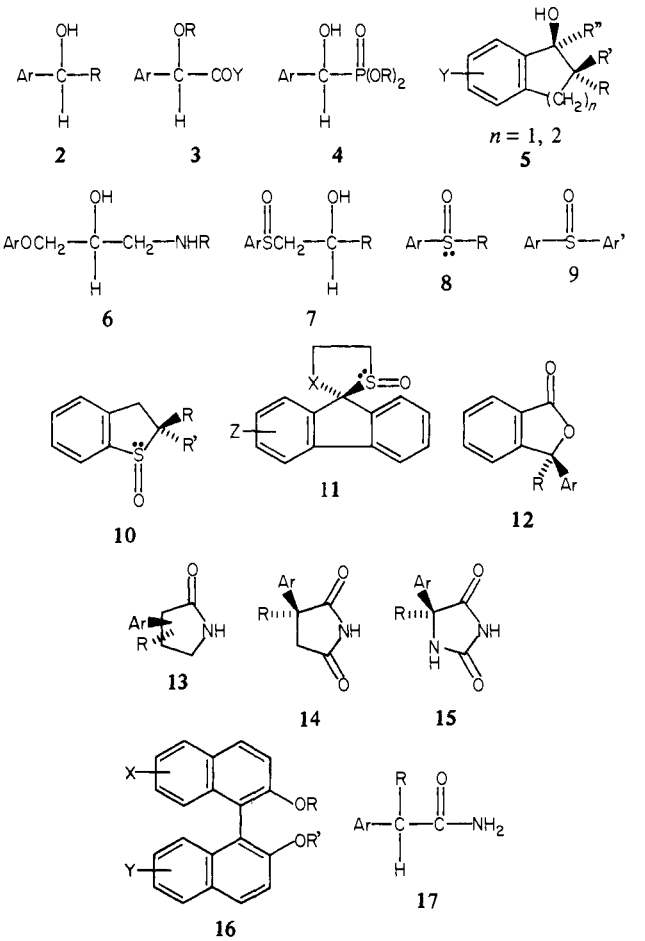
*Received November 17, 1980*

With the heightened interest in stereochemistry that today pervades most branches of chemistry, biochemistry, and pharmacology, the need for better methods of ascertaining enantiomeric purities and absolute configurations is obvious to many. An almost ideal solution to such problems would be the direct HPLC separation of the enantiomers of interest upon a column packed with a suitable chiral stationary phase (CSP). While no CSP will ever separate all enantiomers, considerable progress has been made in our laboratories in devising relatively "broad spectrum" CSP's for HPLC applications.[1,2] Although our initial fluoroalcohol CSP's are not yet widely available, we can now describe an ionically bonded CSP that shows even greater generality than does the fluoroalcohol CSP's and is extremely simple to prepare. Owing to its availability, its scope, and its myriad potential applications, this CSP should find wide and immediate acceptance. This preliminary paper is intended solely to document the widespread utility of this ionically bonded CSP. Later papers will describe the effects of structural variations within each solute category, relationships between absolute configuration and elution order, and relevant chiral recognition rationales.




(1) Pirkle, W. H.; House, D. W. *J. Org. Chem.* **1979**, *44*, 1957.

(2) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, 192, 143.

0002-7863/81/1503-3964$01.25/0 

Table I. Separation of Enantiomers Upon CSP 1

| compd | Ar | R | R′ | R″ | Y | X | Z | Ar′ | *n* | $\alpha$[a] | $k_1'$[b] | IPA[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | Ph | Me | | | | | | | | 1.05 | 5.4 | 1 |
| | 1-Naph | Me | | | | | | | | 1.14 | 5.1 | 5 |
| | 9-Anth | Me | | | | | | | | 1.30 | 6.8 | 5 |
| 3 | Ph | H | | | OMe | | | | | 1.08 | 5.1 | 5 |
| | 1-Naph | H | | | OMe | | | | | 1.10 | 13.0 | 5 |
| | Ph | H | | | $NH_2$ | | | | | 1.11 | 4.5 | 10 |
| | Ph | *i*-Pr | | | $NH_2$ | | | | | 1.30 | 9.6 | 5 |
| 4 | Ph | Et | | | | | | | | 1.08 | 9.5 | 5 |
| | 1-Naph | Et | | | | | | | | 1.19 | 10.0 | 10 |
| | 9-Anth | Et | | | | | | | | 1.28 | 15.0 | 10 |
| 5 | | Me | Me | H | H | | | | 1 | 1.02 | 9.8 | 0.25 |
| | | Me | Me | H | H | | | | 2 | 1.04 | 7.2 | 0.25 |
| | | H | H | H | 7,8-benzo | | | | 2 | 1.17 | 19.0 | 1 |
| | | H | H | Me | 7,8-benzo | | | | 2 | 1.40 | 8.9 | 1 |
| 6 | 1-Naph | *i*-Pr | | | | | | | | 1.07 | 11.8 | 5 |
| | *o*-allyl Ph | *i*-Pr | | | | | | | | 1.08 | 4.0 | 5 |
| | *o*-allyloxy Ph | *i*-Pr | | | | | | | | 1.09 | 10.8 | 5 |
| 7 | Ph | Me | | | | | | | | 1.00 | 9.8 | 5 |
| | Ph | Me | | | | | | | | 1.04 | 14.9 | 5 |
| | 2-Naph | Me | | | | | | | | 1.21 | 11.6 | 10 |
| | 2-Naph | Me | | | | | | | | 1.08 | 19.6 | 10 |
| | 9-Anth | Me | | | | | | | | 1.38 | 17.0 | 10 |
| | 9-Anth | Me | | | | | | | | 1.22 | 30.2 | 10 |
| 8 | Ph | Me | | | | | | | | 1.05 | 12.9 | 5 |
| | 1-Naph | Me | | | | | | | | 1.09 | 19.0 | 5 |
| | 9-Anth | Me | | | | | | | | 1.16 | 25.4 | 10 |
| 9 | *p*-tolyl | | | | | | | Ph | | 1.07 | 5.2 | 5 |
| | | | | | | | | *o*-Me $C_6H_4$ | | 1.07 | 5.2 | 5 |
| 10 | | Me | H | | | | | | | 1.06 | 14.9 | 5 |
| | | Me | $CH_2OMe$ | | | | | | | 1.09 | 9.2 | 5 |
| | | $CH_2OMe$ | Me | | | | | | | 1.08 | 11.8 | 5 |
| 11 | | | | | H | $CH_2$ | H | | | 1.13 | 5.8 | 20 |
| | | | | | H | S | H | | | 1.09 | 6.4 | 20 |
| | | | | | 2-OH | S | H | | | 1.30 | 20.7 | 20 |
| 12 | Ph | H | | | | | | | | 1.04 | 17.7 | 5 |
| | *p*-anisyl | H | | | | | | | | 1.06 | 8.0 | 10 |
| | 1-Naph | Me | | | | | | | | 1.38 | 7.3 | 5 |
| 13 | 3-Ph | H | | | | | | | | 1.18 | 9.0 | 10 |
| | 5-Ph | H | | | | | | | | 1.03 | 5.8 | 10 |
| 14 | Ph | H | | | | | | | | 1.13 | 10.7 | 10 |
| | *p*-anisyl | H | | | | | | | | 1.24 | 34.0 | 10 |
| 15 | Ph | H | | | | | | | | 1.13 | 10.7 | 10 |
| | Ph | Et | | | | | | | | 1.29 | 35.4 | 5 |
| | 2-Naph | Me | | | | | | | | 1.39 | 25.2 | 10 |
| 16 | | H | H | H | H | H | | | | 1.33 | 17.4 | 5 |
| | | Me | H | H | H | H | | | | 1.53 | 3.8 | 5 |
| | | H | H | H | 6,7-$Me_2$ | 6,7-$Me_2$ | | | | 2.00 | 12.1 | 5 |
| | | Me | H | H | 6,7-$Me_2$ | 6,7-$Me_2$ | | | | 3.03 | 3.3 | 5 |
| 17 | Ph | *i*-Pr | | | | | | | | 1.08 | 9.2 | 5 |
| | 1-Naph | Me | | | | | | | | 1.10 | 2.46 | 5 |

[a] The chromatographic separability factor of the enantiomers, $\alpha$, is the ratio of the capacity ratios of the enantiomers. [b] $k_1'$ is the capacity ratio for the initially eluted enantiomer. [c] This is the volume percentage of isopropyl alcohol in hexane used as a mobile phase. Flow rates of 2 mL/min were typically used for the 4.6-mm × 250-mm columns.

Passage[3] of a THF solution of (*R*)-*N*-(3,5-dinitrobenzoyl)-phenylglycine[2] through a prepacked $\gamma$-aminopropyl silanized column[4] of silica affords ionically bonded CSP **1** that is not leached from the support at significant rates so long as relatively nonpolar organic mobile phases are used. Using hexane containing isopropyl alcohol to adjust polarity, such chiral columns have been found to separate the enantiomers of solutes within classes **2–17**. The quality of the separations is such as to allow accurate determination of enantiomeric purity upon submilligram quantities, the limiting factor being detection sensitivity. Solute categories **2–17** all bear aromatic substituents, making ultraviolet detection of small quantities straightforward. Absolute configurations can be determined either by comparison to known reference compounds or ultimately deduced from chiral recognition models and observed elution orders. Preliminary indications are that elution orders will consistently correlate to absolute configuration within solute classes.

In terms of affinity, chiral recognition requires a minimum of three simultaneous interactions between the CSP and at least one solute enantiomer, at least one of these interactions being stereochemically dependent. The present CSP utilizes a combination of $\pi$ acidity, hydrogen bond receptor sites, hydrogen bond donor sites, and steric interactions for chiral differentiation purposes. The aromatic groups common to classes **2–17** are used as $\pi$-basic sites to complement the $\pi$ acidity of CSP **1**.

Figure 1 shows two such resolutions conducted upon a modified

(3) The following procedure has been used successfully with the commercial columns mentioned in ref 4. At a flow rate of 2 mL per min, the following solutions were sequentially pumped through a 25-cm × 4.6-mm column of $\gamma$-aminopropyl silanized silica: 2 mL of triethylamine in 40 mL of dry THF, 20 mL of dry THF, 2 g of (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine in 40 mL of dry THF, 20 mL of dry THF, and finally 10% isopropyl alcohol in hexane (until the base line stabilizes).

(4) We have used commercial amino columns supplied by Regis Chemical Co., Morton Grove, IL 60053 (5 $\mu$m Spherisorb), the DuPont Company, Analytical Instruments, Wilmington, DE 19898 (7 $\mu$m Zorbax), the Anspec Co. Inc., Warrenville, IL 60555 (10 $\mu$m Merck Lichrosorb), and the J. T. Baker Chemical Co., Phillipsburg, NJ 08865 (5 $\mu$m irregular). The various columns produce similar but not identical results. The most important variable is the efficiency of the original unmodified column.

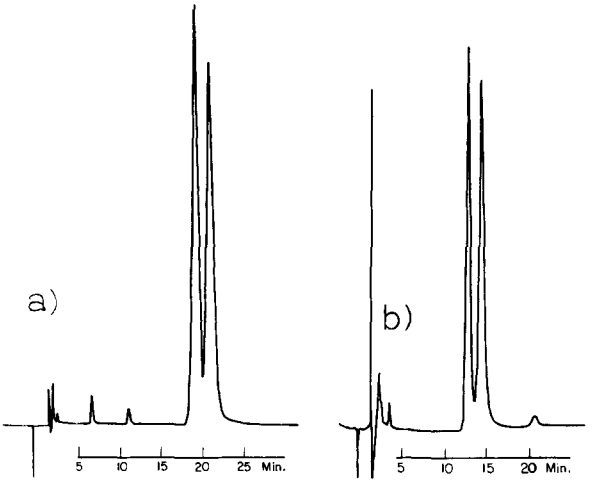



**Figure 1.** Separation of the enantiomers of (a) racemic phenyl isopropyl sulfoxide and (b) 1,2,3,4-tetrahydro-4-hydroxyphenanthrene upon a CSP **1** modified Regis 5-$\mu$m $NH_2$ column using 5% isopropyl alcohol in hexane.

Regis column,[5] the examples being selected to show excellent separation even when the magnitude of $\alpha$, the enantiomer separability factor, is relatively modest. Table I provides additional examples of $\alpha$ values and capacity factors (for the initially eluted enantiomer) for representative members of each of the solute classes. For most solute classes, considerably more solutes have been resolved upon CSP **1** than are included in Table I. In general, increasing the $\pi$ basicity of the Ar portion of the solute increases $\alpha$ as does use of the higher homologues of R and R′. Since the examples in Table I are typically lower homologues, they are closer to being "worst case" examples than "best case" examples. In general, no prior derivatization of the solutes in Table I is required. However, the propranolol analogues **6** were N acylated with lauroyl chloride to reduce the basicity of the nitrogen and shorten elution times. Owing to the presence of two chiral centers in the $\beta$-hydroxy sulfoxides **7**, four stereoisomers of each compound may be formed. In most such cases, CSP **1** allows separation of all

**Acknowledgment.** This work has been supported by the National Science Foundation. Several of the type **12** compounds were prepared by Joel Hawkins.

(5) This type of chiral column is now available from Regis Chemical Company.[4]

# *Book Reviews**

**The Chemistry of Functional Groups, Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues.** Edited by S. Patai. John Wiley & Sons, New York. 1981. xiii + 1142 pp. Two Volumes, $288 for the set.

This Supplement continues the practice of bringing up-to-date selected topics from earlier volumes and filling in gaps with new chapters. It is a supplement to three earlier volumes: "The Ether Linkage" (1967), "The Hydroxyl Group" (1971), and "The Thiol Group" (1974). At least 15 of the 24 chapters cover new topics, from crown ethers, enol ethers, and allene oxides through structural chemistry, stereodynamics, and mass spectroscopy to electrochemistry, thermolysis, and oxidation and reduction. These authoritative reviews will be tremendously useful, as the previous ones have been.

There are some shortcomings that could be eliminated in future volumes to everyone's benefit. The typesetting differs from one chapter to the other. By itself, this might not be worth noticing, but in one volume, the boldface type differs so little from the normal that it is a source of annoyance and potential confusion in the reference citations. The effect is accentuated because editorial control has not extended to the bibliographies, which as a result use varying styles (abbreviations for names of Journals, inversion of names, etc.). Another problem is that only a few of the chapters contain a statement of the cut-off date for the literature reviewed ("to end of 1977", "through late 1978", etc.). There should be a clear editorial direction to all contributors to provide this important information to the readers. Another point of inconsistency is in the content of the chapters: some of them discuss the properties of the compounds corresponding to the title (e.g., enol ethers), whereas others say nothing at all, but discuss only preparation and reactions (e.g., cyclic ethers). Perhaps the contributors were not made aware of what should or should not be included in their chapters.

The second volume contains an author index and a thorough subject index to both.

**Modern Synthetic Methods, 1980. Band 2.** Edited by R. Scheffold (Universität Bern). Verlag Sauerländer, Aarau, Switzerland. 1980. 358 pp. SF 38.00.

This book details the seminars of four well-known chemists at the International Seminar on Modern Synthetic Methods, 1980, held at Interlaken, Switzerland.

The first section, given by L. Eberson, gives a brief description of electrochemical principles as applied to organic synthesis. This section is well written and easily understood and should be quite useful for the beginner in this rapidly growing area of electroorganic synthesis. The remainder of the article is devoted to specific examples of synthetically useful reactions. The entire article is well referenced and anyone wishing to become acquainted with synthetic organic electrochemistry will find this chapter a useful starting point for further study.

The second section, by Seebach and Hungerbühler, outlines the chemistry of tartaric and malic acid derivatives with the goal of developing a variety of chiral synthons. The bonus of this chapter lies at the end where detailed experimental procedures are provided for a large variety of chiral synthons.

A. Vasella in the third chapter reviews the more recent literature on the application of carbohydrates as chiral starting materials for natural product synthesis. This section is an excellent complement to B. Fraser-Reid's recent review on the same subject.

Finally, the last chapter by A. Fischli provides a brief up-to-date review of some recent applications of enzymatic transformations as applied to organic synthesis.

Overall, the book provides a large variety of timely chemical formations with numerous references and would, therefore, be an asset to a synthetic chemist's personal library.

**Peter G. M. Wuts,** *University of Michigan*

**The Conformational Analysis of Heterocyclic Compounds.** By Frank G. Riddell (University of Sterling). Academic Press, London and New York. 1980. ix + 153 pp. $39.50.

The author's earlier review of this subject in 1967 has undoubtedly contributed to its growth since then to the point that he has been able to expand the review into a book, and even then not claim to be complete. An instructive introduction sets the subject in perspective by reviewing the origins of conformational analysis, examining the terminology critically, and pointing out the complexities involved when one tries to understand the contributing factors. One of the difficulties, or at least points of difference from carbocyclic systems, is connected with the unshared electron pairs on heteroatoms, the steric requirements of which are not easily assessed, and which allow inversions to take place that are not possible for carbon. There are six other chapters, beginning with one, Special Conformational Considerations for Heterocycles, which discusses methods of investigation as well as bond lengths, nonbonded interactions, hydrogen bonding, etc. The remaining chapters take up rings by size, from four-membered to seven-membered and larger. The discussion includes nitrogen, oxygen, sulfur, and phosphorus as heteroatoms. The whole is a balanced mix of theory and descriptive fact and is nicely written.

*Unsigned book reviews are by the Book Review Editor.