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Note

Resolution of optical isomers by liquid chromatography

WILLIAM H. PIRKLE and DAVID L. SIKKENGA
School of Chemical Sciences, University of Illinois, Urbana, Ill. 61801 (U.S.A.)
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The direct chromatographic resolution of enantiomers upon a solid chiral stationary phase has, with some signal exceptions, been an elusive goal. Early workers (for a review, see ref. 1) were sometimes successful in obtaining partial optical resolution on adsorbants made of naturally occurring chiral materials like starch or quartz. More recent methods (for a review, see ref. 2) include the use of Sephadex gels[3], ligand-exchange columns containing metal ions[4], the use of cyclic ether host molecules attached to a support[5], and chiral charge transfer agents adsorbed upon a silicic acid support[6,7]. Almost all attempts at the direct resolution of optical isomers via liquid chromatography (LC) have been empirical in approach rather than rationally devised. Notable exceptions are the works of Dotsevi *et al.*[5] and of Baczuk *et al.*[8]. In general, there is yet little understanding of the structural requirements demanded of a chiral stationary phase if it is to effectively distinguish between enantiomers.

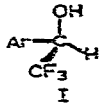
This paper describes a rationally planned direct chromatographic resolution which, although hardly optimized, affords preparatively useful amounts of two sulfoxides in enantiomeric purities unobtainable by any other presently known synthetic or resolution scheme.

RATIONALE

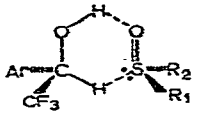
Studies of the perturbing effects of chiral type I solvating agents upon the NMR spectra of enantiomeric solutes have demonstrated that these fluoroalcohols afford diastereomeric solvates with a variety of solutes[9–12]. In the presence of chiral I, the time-averaged spectra of the solute enantiomers can differ if simultaneous two-point solvent–solute interactions cause the population of a rather specific type of conformation.

For example, with sulfoxides, the significant solvate conformers have been suggested to have the structures shown in IIa and IIb[12]. These solvates have intrinsically nonidentical PMR spectra owing to the stereochemically dependent shielding of the sulfoxide substituents by the aromatic group of fluoroalcohol I. The absolute configuration of many sulfoxides can be established in this manner[12].

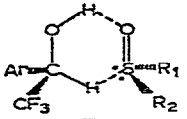
Although it is unnecessary to invoke stability differences between the diastereomeric solvates to account for spectral behavior, such differences could arise from



I



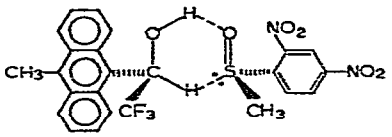
II a



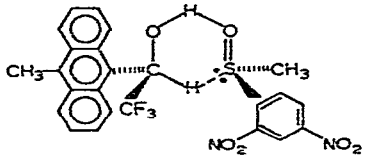
II b

the stereochemical dependence of the interaction of either sulfoxice substituent with the aryl or trifluoromethyl groups of I.

Such stability differences were expected when the aromatic substituent of I was 9-anthryl, a good π base, and one substituent of the sulfoxide was a good π acid such as 2,4-dinitrophenyl or 4-nitrophenyl. In such an instance, solvate IIIa, by virtue of π–π interaction, could simultaneously experience three bonding interactions, whereas solvate IIIb could experience but two. Indeed, mixtures of 2,2,2-trifluoro-1-(10-methyl-9-anthryl)ethanol IV* and methyl 2,4-dinitrophenyl sulfoxide, V, are red, indicating π–π complexing. The intensity of this coloration is inversely temperature dependent, demonstrating reversible complexation.



III a



III b

The expected stability difference has been demonstrated by an NMR method[13] Addition of small increments of the achiral shift reagent Eu(fod)$_3$ to either racemic or optically enriched sulfoxide V dissolved in a carbon tetrachloride solution of *R*(−)IV occasions a greater time-averaged downfield shift for the *S* enantiomer of the sulfoxide. The shape of the curve obtained by plotting the chemical shift difference between the sulfinyl methyl resonance of the sulfoxide enantiomers *vs.* the mole ratio of Eu(fod)$_3$ to sulfoxide is qualitatively relatable to the stability difference between the diastereomeric solvates, IIIb being the least stable. Comparable results were obtained with 4-nitrophenyl sulfoxide, VI[13].

Differential stability of the diastereomeric solvates has been demonstrated in yet another manner. Saturation of a carbon tetrachloride solution of *S*(+)IV with an excess of racemic sulfoxide V causes preferential dissolution of one enantiomer, the filtrate showing a 7% excess of the enantiomer exhibiting a low field sense of nonequivalence by PMR. Crystallization of racemic V from carbon tetrachloride solutions of *S*(+)IV preferentially retains the same enantiomer in solution.

* The synthesis and resolution of alcohols IV and VII are to be reported elsewhere.

CHROMATOGRAPHIC STUDIES

Use of a stationary phase consisting of chiral IV covalently bonded to an inert support is the obvious approach to the direct chromatographic separation of the optical isomers of V or VI, since the preceding rationale predicts not only that such separation will occur but also predicts the elution order of the enantiomers. The preparation of such a support is under way. An alternate and more rapidly consumated approach* is to use a solution of a chiral type I anthryl carbinol to elute the optical isomers of V or VI at dissimilar rates from a column of achiral adsorbant. The latter approach is not as elegant as the first, since it requires eventual separation of the alcohol from the sulfoxide. Moreover, the presence of the carbinol in the eluent introduces some problem in determining when the sulfoxide is emerging from the column. However, the experiment can be performed with readily available materials.

A glass column (56 cm × 9 mm) was packed with deactivated silica gel** and a shorter glass column (5 cm × 9 mm) was packed with activated silica gel***. The columns were connected such that the eluting solvent flowed from the pump through the longer column, through a UV detector, through the short column and then back to the pump in a recycle loop. Forty milliliters of 0.16 *M* *R*(−)2,2,2-trifluoro-1-(9-anthryl)ethanol, VII, in carbon tetrachloride was recycled through the apparatus for 2 h to allow equilibration. Then a 30-mg sample of racemic 2,4-dinitrophenyl methyl sulfoxide, V, dissolved in 1 ml of carbon tetrachloride with 60 mg of *R*(−)VII (to aid solubility) was injected onto the long column. The recycling of the solution of *R*(−)VII was resumed (150 ml/h). The yellow sulfoxide forms the red π complex in the presence of VII and can be seen to move slowly down the column. The elution of the red sulfoxide–carbinol π-complex (monitored at 510 nm) was first noted 11.3 h after injection. The short column with the active silica gel traps the sulfoxide while allowing the less polar VII to pass through and recycle. After 1.2 h of trapping, the short column was removed from the system, eluent now being recycled directly onto the long column. After an additional 2 h, the three sulfoxide fractions (high R_F in the short column, mid-R_F in the top 10 cm of the long column, low R_F in the bottom 40 cm of the long column) were recovered by washing the silica containing each of the fractions with diethyl ether to afford a mixture of carbinol VII and the sulfoxide. Each of these fractions was then chromatographed on silica gel with methylene chloride, the polar sulfoxide being easily separated from the carbinol. The purified sulfoxide fractions were dried under reduced pressure, weighed, and specific rotations were determined. Finally *R*(−)VII was added to each fraction to allow 100 MHz NMR determination of optical purities and absolute configurations. This information is derived from relative areas and relative chemical shifts of the singlet methyl resonances for each optical isomer (Fig. 1). The results are summarized in Table I. The proposed solvation model allows assignment of the *S* configuration to the levorotatory optical isomer[12,13].

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* Previous attempts to chromatographically resolve enantiomers using chiral eluents have met with little success[14].

** Ventron large-pore silica gel (58 μm) was deactivated by adding 11 g water to 20 g silica gel with agitation.

*** Brinkmann silica gel (50–200 μm) was used as obtained.

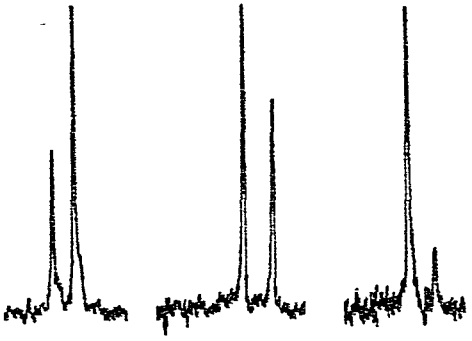

Fig. 1. The S-methyl resonances of the low-R_F (left), mid-R_F (middle), and high-R_F (right) fractions of partially resolved sulfoxide V in the presence of $R(-)$ VII.

TABLE I

SPECIFIC ROTATIONS AND OPTICAL PURITIES OF THE THREE SULFOXIDE FRACTIONS

Fraction	*Weight** *(mg)*	$[\alpha]^{25°}$ *(concentration, g/100 ml CH_2Cl_2)*	*Optical purity (by NMR) (%)*
High R_F	5.4	+58.7 (0.6)	68
Mid R_F	12.1	+15.7 (1.3)	20
Low R_F	17.3	−30.7 (1.7)	28

* The total weight of the three fractions is 4.8 mg more than the 30 mg injected. We believe this is due to entrained solvent since the sulfoxide samples were not heated during drying to avoid possible racemization. Entrained solvent will cause some inaccuracy in the observed specific rotations but not in the NMR optical purity determinations.

We view the chromatographic separation as consisting of competition between the silica support and the mobile carbinol for the sulfoxide

$$\underset{\text{Stationary}}{\text{Silica–Sulfoxide}} \rightleftarrows \underset{\text{Mobile}}{\text{Sulfoxide–Carbinol}}$$

The more strongly solvated sulfoxide enantiomer will be preferentially "lifted" from the silica and will therefore elute faster. The high R_F fraction is enriched in the sulfoxide enantiomer showing a lowfield sense of nonequivalence in accordance with this picture.

Similarly, methyl 4-nitrophenyl sulfoxide, VI, has been partially resolved using this method to give samples of both enantiomers of 30% optical purity. Again the elution order is in accordance with the model presented. The complex formed between the colorless sulfoxide, VI, and VII is light yellow and visual detection of the moving band is more difficult.

Another possible mechanism of resolution is an intrinsic difference in the chromatographic behavior of the diastereomeric complexes. This possibility cannot be rigorously eliminated. However, the two mechanisms can be differentiated once the synthesis of a support covalently bonded to chiral IV has been achieved.

No concerted effort was made to improve the efficiency of the silica columns employed in this study. On these columns, the polar sulfoxide underwent severe band broadening and showed a propensity to "tail". Because of these problems, a more complete chromatographic study of this system is being deferred until the covalently bonded chiral packing has been prepared. Despite the limitations of the present approach, it has synthetic utility. The two partial resolutions reported here cannot be obtained using conventional methods. The nitro groups interfere with the Grignard reagent used in the Anderson synthesis[15]. Other reported methods (for a recent review, see ref. 16) typically give sulfoxides of much lower optical purity.

ACKNOWLEDGEMENT

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