



Resolution and Determination of the Enantiomeric Purity and Absolute Configurations of α -Aryl- α -hydroxymethanephosphonates

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Abstract: The enantiomers of each of a series of α -aryl- α -hydroxymethanephosphonates have been found to be easily separable by liquid chromatography on a chiral stationary phase, CSP 1, and to elute in the order expected from mechanistic considerations. The *dextro*- enantiomer of each of the compounds listed in Table 1 is preferentially retained by the (3*R*, 4*S*)-WHELK-O 1 stationary phase and is assigned the (+)-(*R*)-configuration. The presence of an *ortho*- substituent interferes with the recognition process, reduces the separation factor for the enantiomers, and possibly alters their elution order. Copyright © 1996 Elsevier Science Ltd

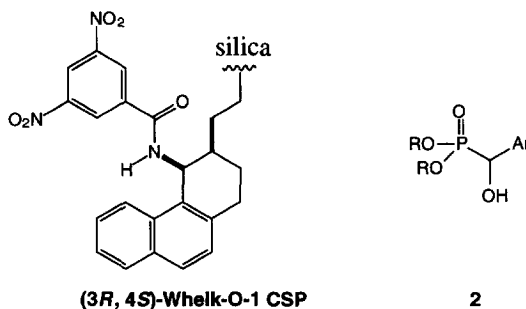
INTRODUCTION

Owing to their potential for biological activity, many organo phosphonates have been prepared and evaluated. Among these are the analogs of α -amino acids and α -hydroxy acids, compounds in which stereochemistry may be a matter of concern. Enantiomerically enriched mixtures of several of these have been prepared.^{1,2} The enantiomeric purity of these mixtures has varied considerably, these having been determined by indirect NMR methods.³ Consequently, a relatively general and convenient means for obtaining enantiomerically enriched samples of these compounds is of interest. The direct chromatographic separation of enantiomers on a chiral column is often a means of accomplishing this goal, providing as well a means of determining enantiomeric purity. Potentially, such chromatographic separations are both predictable and capable of being used to assign absolute configurations. The predominant mode of action of the chiral selector used in chiral stationary phase 1 (now known as the WHELK-O 1) has been studied and is understood to the point that the latter potential can sometimes be realized.⁴

RESULTS AND DISCUSSION

The addition of disubstituted phosphites to aldehydes offers a short, convenient, and inexpensive route to racemic α -hydroxyphosphonates, these being useful precursors to other types of phosphorus-containing compounds. When derived from arylaldehydes, these hydroxy

phosphonates contain a π -basic site and a hydrogen bond acceptor site on the stereogenic center. These structural features lead one to anticipate that **CSP 1** will differentiate between the enantiomers of these compounds⁵. The Table below provides data obtained from the separation of the enantiomers of a series of α -aryl- α -hydroxymethane phosphonates, **2**, obtained by the base-promoted addition of diethyl (or dimethyl) phosphite to a number of arylaldehydes, on **CSP 1**.



The enantiomers of each compound in the Table were base-line separated, retention and separation factors increasing with increasing π -basicity of the aryl substituent. Methyl phosphonates show somewhat greater retention and enantioselectivity than their ethyl counterparts. The signs of rotation of the enantiomers were determined as they eluted using an in-line polarimetric detector set at 365 nm. At 589 nm, the rotations have the same signs but rather smaller magnitudes.

Initially, the phosphinyl oxygen was considered to be more likely to undergo hydrogen bonding to the amide N-H of the selector than is the hydroxyl oxygen. Moreover, the more retained enantiomer was expected to be the one which, while undergoing the simultaneous face to face and face to edge π - π and the hydrogen bond interactions, presents its methine hydrogen to the π -cloud of the naphthyl portion of the selector, affording a weak additional hydrogen bond. Consequently, the (*R*)-enantiomers of these phosphonates were expected to be the more retained on the (*3-R, 4-S*) **CSP 1**.⁶ Several compounds in the Table previously have been assigned the (*R*)-(+)-configuration³ and, indeed, the *dextro*- enantiomer of each of the phosphonates in the Table is more retained. In view of this, it seems reasonable to similarly assign the configurations of the remaining entries in this Table.

As has been noted for other analytes having *ortho*-substituents on the aromatic ring being used as the π -basic site, enantioselectivity is reduced, presumably because the *ortho*-substituent alters the conformational disposition of the aryl group relative to the groups on the stereogenic center. An *ortho*-substituent approximately *syn* to the methine hydrogen would interfere sterically with entry of the aryl group into the cleft-like active site of **CSP 1**, thus reducing the retention of the (otherwise) more retained enantiomer and reducing the separation factor of the enantiomers. For example, ethyl (or methyl) phosphonates having *ortho*-chloro, methyl, nitro or hydroxyl

Table 1. Chromatographic Separation of the Enantiomers of Some α -Hydroxy α -arylmethanephosphonates on the (3*R*, 4*S*)-Whelk-O-1.

R	Ar	Mobile Phase (hexane/2-propanol)	k'_1	α
Et	Ph	95/5	3.29	1.21
Et	4-methylphenyl	95/5	3.65	1.21
Et	2-naphthyl	80/20	1.88	1.63
Et	1-naphthyl	80/20	1.62	1.33
Et	2-fluorenyl	80/20	2.27	1.76
Et	2-naphthyl	95/5	4.24	1.56
Et	1-naphthyl	90/10	3.50	1.30
Et	2-fluorenyl	90/10	4.88	1.68
Et	4-bromophenyl	90/10	1.81	1.33
Et	4-chlorophenyl	90/10	1.59	1.30
Me	4-bromophenyl	90/10	3.19	1.39
Me	4-chlorophenyl	90/10	2.95	1.37
Et	4-nitrophenyl	95/5	7.16	1.18
Et	4-chlorophenyl	95/5	3.61	1.27
Et	4-methoxyphenyl	95/5	7.14	1.27
Et	2-fluorenyl	95/5	9.57	1.60
Et	4-isopropyl phenyl	95/5	3.67	1.24
Me	phenyl	90/10	6.24	1.41
Me	4-(dimethylamino)phenyl	80/20	7.76	1.77
Me	4-fluorophenyl	80/20	1.56	1.35
Me	4-methoxyphenyl	80/20	4.19	1.42
Me	3-methoxyphenyl	80/20	3.17	1.55
Me	2,4,6-trimethylphenyl	80/20	1.05	1.20
Me	4-chlorophenyl	95/5	1.75	1.44
Me	biphenyl	80/20	3.13	1.55

substituents show separation factors of 1.01 to 1.09. Even when separation of the enantiomers is barely discernible from the chromatogram (254 nm detection), the polarimeter reported

unmistakable rotations (365 nm). With the exception of the *ortho*-hydroxy-substituted phosphonate, the (+)-enantiomers of these *ortho*-substituted compounds are preferentially retained on the (3*R*, 4*S*) CSP 1. Because *ortho*-substituents may possibly alter the recognition process, no claim is presently made concerning the relationship between elution order and analyte stereochemistry for these compounds.

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REFERENCES AND NOTES

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4. Pirkle W.; Welch C. *J. Chromatography*, **1994** 683, 347 and references therein.
5. Additional discussion of the mechanism(s) by which CSP 1 differentiates between enantiomers is to be found in: Pirkle, W.; Koscho, M.; and Wu, Z. *J. Chromatography* **1996**, 726, 91.
6. The column used in these studies is a Regis Technologies 4.6 x 250 mm (*S,S*)-Whelk-O 1. The absolute configuration of the selector used in the (*S,S*)-Whelk-O 1 is incorrectly designated and should properly be (3*R*, 4*S*). It is the configuration at C-4 which determines elution order. Hence, the incorrect designation should not lead to confusion concerning expected elution order. The (*S,S*) assignment was originally made for the CSP bearing an eleven-carbon tethering moiety. The use of a three-carbon tether improves performance but causes a priority inversion at C-3, necessitating a change in the stereochemical descriptor.

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