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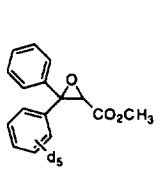
A direct chromatographic separation of enantiomers chiral by virtue of isotopic substitution[1]

William H. Pirkle * and Kevin Z. Gan
School of Chemical Sciences, University of Illinois, Urbana, IL 61801, USA

Abstract: An unprecedented isotope effect on π–π face to edge interaction was observed in the separations of the enantiomers of the pivalamide of α,α′-phenyl-(phenyl-d_5)-methylamine **3a**, and the *p,p′* disubstituted analogs on **CSP 2**. The configuration of the more retained enantiomer of its *p,p′*-dibromo derivative is assigned as *R* through dynamic NMR studies of a mixture of enantiomerically enriched sample of this compound and the chiral selector. The protonated aromatic group is more strongly held in the binding cleft of the chiral selector than is the deuterated aromatic group.

Introduction

Kimata *et al.* recently reported the reversed-phase chromatographic separation of diastereomers chiral because of isotopic substition.[2] The key step in this work was the separation of the racemic diastereomers, **1**, on four achiral C-18 columns connected in series. Eighteen recycles were employed to demonstrate a separation factor of 1.0057 in 65% methanol. The enantiomers of each racemic diastereomer were then separated on a polysaccharide-derived chiral stationary phase, these separations occurring owing to the configurational differences at a second stereogenic center and not because of the isotopic substitution. Kimata *et al.*[2] express the view that, because of the greater distances involved, intermolecular recognition of isotopic chirality by a chiral stationary phase will be even more difficult than the diastereomer separation they report.



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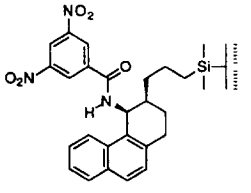
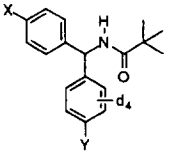


CSP 2



3a X = H, Y = D
3b X = Y = Br
3c X = Y = Trimethylsilylethynyl

Results and discussion

We now describe the first direct chromatographic separation of enantiomers chiral *only* by virtue of isotopic substitution. The chiral stationary phase, shown as **CSP 2**,[3] was designed to have a cleft-like binding site in which aromatic groups are held by simultaneous face to face and face to edge π–π interactions.[3] For example, the enantiomers of the pivalamide of α-methylbenzylamine separate on **CSP 2** with a separation factor of about six at 25°C and the introduction of certain *para*-substituents (eg. bromo, trimethylsilylethynyl) further increases the separation factors of the enantiomers by enhancing the strength of the π–π face to face interaction.[4] It seemed that the isotope effect on these π–π

* Corresponding author.

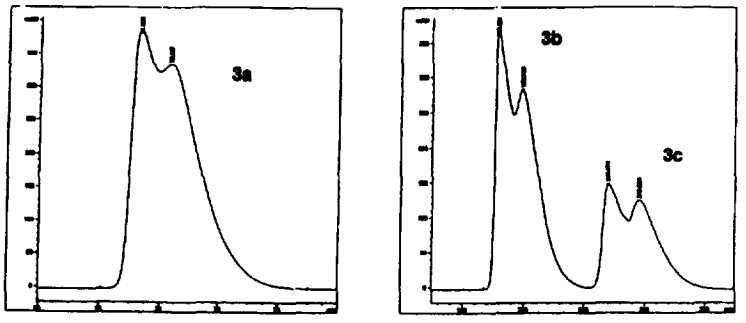


Figure 1. Chromatogram showing the enantioseparations of **3a–c** on **CSP 2** (10% MeCN in CO_2, 1.0 ml/min, 29°C). The retention times are 71.3 min and 72.3 min for **3a**, 196.8 and 199.8 min for **3b**, 213.9 and 219.0 min for **3c**.

interactions might be great enough to allow this CSP to differentiate between the labeled and unlabeled aryl groups in the enantiomers of the pivalamides of benzhydrylamines **3a–c**.

Three 250×4.6 mm (3*S*,4*R*)-Whelk-O 1 columns[5] were coupled in series and used with 10% acetonitrile in carbon dioxide as a mobile phase. A mixture containing the three racemates, **3a–c**, was chromatographed at 29°C. One pass through the three columns afforded perceptable separations of the enantiomers of each racemate (Figure 1). Because these pivalamides tend to afford slightly broadened bands and because the SFC system used is not equipped for recycle chromatography, the separations of these enantiomers are not baseline. However, the observed separation factor, 1.025, is larger than that reported by Kimata *et al.*[2] for their diastereomers. Greater retentions but similar separation factors are observed for the enantiomers of the analogs having *p,p'*-dibromo or *p,p'*-ditrimethylsilylethynyl substituents, just as one might have expected if the separations hinge only on the isotopic effect on the relative strengths of the π–π interactions. Co-injection with the fully protonated achiral analogs show them to co-elute with the more retained enantiomer of the corresponding deuterated racemate. This is suggestive (but not compelling proof) that the enantiomer which places its protonated phenyl into the cleft of **CSP 2** is preferentially retained. To the extent that the face to edge π–π interaction resembles hydrogen bonding by the aromatic protons directed toward the π-electrons of the naphthyl portion of the CSP, this elution order would be expected. Hydrogen bonds involving hydrogen are stronger than those involving deuterium.[6] However, the shorter bond length of C–D bonds means that a deuterated aromatic group is slightly smaller than the corresponding proton-bearing group and, consequently, might penetrate more deeply into the cleft of the CSP, thus resulting in an increase in the strength of the π–π interactions. Such an eventuality would reverse the elution order, as the enantiomer placing its deuterated group into the cleft would be preferentially retained.

To establish the actual elution order, samples enriched in each enantiomer of the *p–p'*-dibrominated analog, **3b**, were obtained by chromatography of 100 mg of the racemate on **CSP 2**. Two preparative columns[5] in series were used with 20% THF in hexane, the sequential order being changed manually to achieve a recycle effect. After four such recycles at 0°C, the initially eluted fraction (5 mg) contained a 1.18:0.68 ratio of the enantiomers and the most retained fraction (5 mg) contained a 0.85:1.20 ratio of enantiomers. The 400 MHz NMR spectrum of **3b** shows the AA'BB' pattern of the aromatic protons as two doublets at 7.45 and 7.06 ppm. The NMR spectrum of a sample of four mg of racemic **3b** mixed with an equimolar amount of the same enantiomer of the chiral selector used to prepare **CSP 2** shows two separate AA'BB' multiplets. At 22°C, the four doublets are noted at 6.95, 7.00, 7.40, and 7.45 ppm. The dinitrobenzamide **N–H** signal of the selector is observed at 6.50 ppm. When this experiment is repeated using the pivalamide sample enriched in the less retained enantiomer, the intensities of the two sets of AA'BB' multiplets differ, the more intense pair of doublets being noted at 7.02 and 7.44 ppm. The remaining pair of doublets are noted at 6.96 and 7.40 ppm. At 0°C, these signals have shifted to 6.95 and 7.45 ppm and 6.86 and 7.34 ppm respectively. The dinitrobenzamide

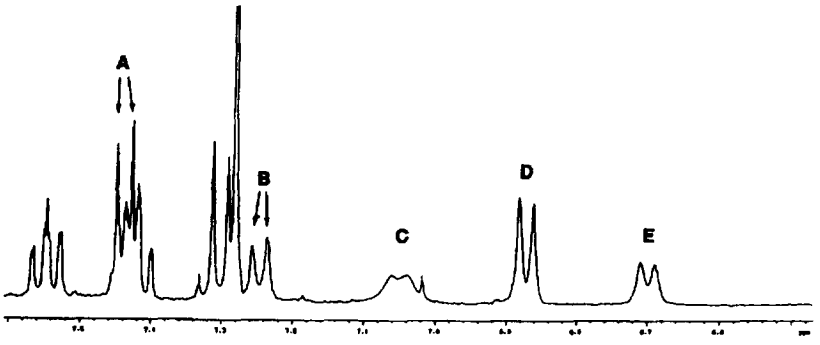


Figure 2. Aromatic region of the ^{1}H NMR spectrum (taken at −20°C) of 1:1 mixture containing **3b** enriched in the enantiomer less retained on **CSP 2** and the chiral selector used in **CSP 2**. **A** and **D**: Downfield and upfield doublet of the least retained enantiomer of **3b**, respectively; **B** and **E**: Downfield and upfield doublet of the more retained enantiomer of **3b**, respectively; **C**: Amide *N*–H of the chiral selector of **CSP 2**.

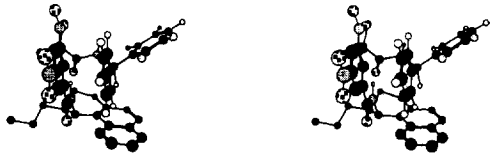


Figure 3. A stereo view of how the chiral selector of **CSP 2** is envisioned to interact with the most retained enantiomer of **3a**. The fully protonated phenyl ring is involved in simultaneous face to face and face to edge π–π interactions with the dinitrobenzoyl and the naphthyl portion of the selector respectively. The dinitrobenzamide *N*–H forms a hydrogen bond to the carbonyl oxygen of the pivalamide. Nonessential hydrogen atoms were omitted for clarity.

N–**H** signal is now at 6.73 ppm. At −20°C, these signals occur at 6.88 and 7.44 ppm, 6.70 and 7.24 ppm, and 7.05 ppm respectively (Figure 2). By lowering the temperature, the extent of association is increased. As this occurs, the dinitrobenzamide N–**H** signal moves downfield (increased extent of hydrogen bond formation) and the AA′BB′ multiplets of the more strongly retained enantiomer (the minor enantiomer) are shielded more heavily than are those of the less retained enantiomer. The same conclusion is reached when the fraction enriched in the more retained enantiomer (assigned the *R* configuration) is similarly examined.

The NMR data show that the enantiomer which places the proton-bearing aromatic ring in the cleft of the selector is preferentially retained. This is consistent with the participation of these protons in a hydrogen bond-like interaction with the π-electrons of the naphthyl portion of the selector. A presumption of the approximate structure of this complex is shown in Figure 3.

An alternate rationalization, that the deuteriated ring is better solvated and that this reduces the ability of this ring to participate in the π–π interactions, is also conceivable. However, since a number of other polar modifiers were also added to the carbon dioxide with no significant change in the separation factors of the enantiomers of any of the three racemates, this rationalization of the observed elution order is largely discounted. Changes in the extent of solvation of the aromatic groups would be expected to change the separation factors. Interestingly, the magnitude of the separation factors are, within experimental error, independent of temperature between 30°C and −15°C. This suggests that the value of $\Delta\Delta S$ is essentially zero, just as one might expect for systems chiral only because of isotopic substitution.

Kimata *et al.* opined that, because of the difficulty encountered in their separation of diastereomers, based as it was on *intramolecular* effects, the separation of enantiomers chiral because of isotopic substitution would be even more difficult since such a separation must necessarily be based on *intermolecular* effects. The present work demonstrates that such separations need not be as difficult

as imagined and provides some suggestion as to the nature of face to edge π–π interactions. It seems likely that longer capillary columns coated with the polysiloxane version of **CSP 2** might provide enough theoretical plates to afford baseline separations of the enantiomers of these pivalamides in a straight forward manner.

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