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Short Communication

Concerning the role of face-to-edge π–π interactions in chiral recognition

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ABSTRACT

A simplified chiral recognition mechanism involving face-to-edge π–π interaction is advanced to account for chromatographic data previously rationalized by invoking two competing, opposite sense chiral recognition mechanisms.

INTRODUCTION

Accumulation of evidence from a variety of sources often leads to general acceptance of a reaction mechanism. Mechanistic hypotheses have played an invaluable role in advancing the understanding of chemical processes, including processes involving chiral recognition. It is widely understood that mechanistic hypotheses can be disproven, but never proven.

To be generally accepted, a mechanism must be in accord with all relevant experimental data and should comply with the Occam's razor maxim. This maxim, attributed to William of Occam, a fourteenth-century English philosopher, cautions against excessive and unjustifiably elaborate assumptions. In the present paper, we simplify a rationalization presented earlier to explain chromatographic data obtained from a homologous series of racemates on several related chiral stationary phases (CSPs).

DISCUSSION

In several papers published in the mid 1980s [1–3], we described a curious relationship between enantioselectivity, the length of the alkyl substituent in a type 1 analyte, the length of the tether connecting the chiral selector to the support, and the orientation of the selector with respect to the tether. This relationship is illustrated in Fig. 1.

To rationalize the unusual α *versus* n curves obtained from normal-phase chromatography (α is the separation factor for enantiomers and n is the number of methylene units in the alkyl substituent), two

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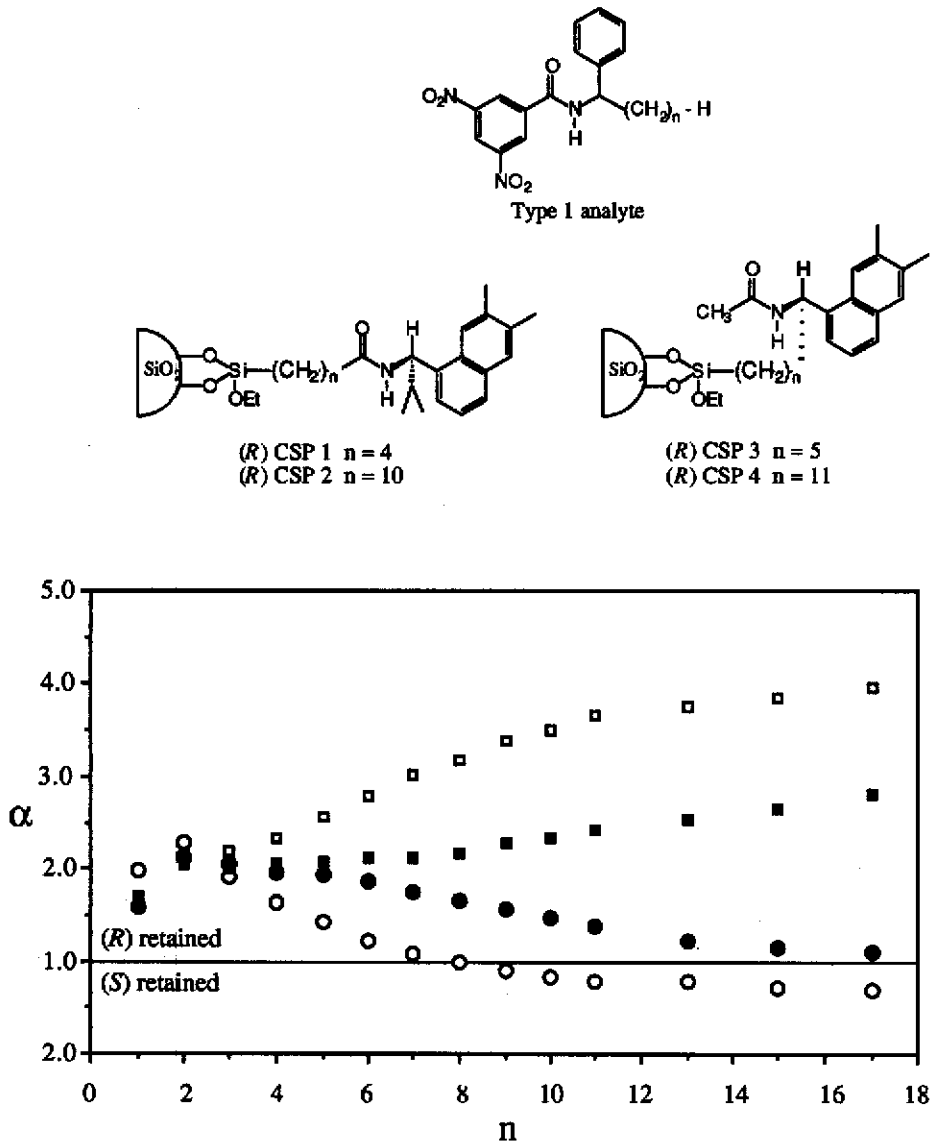

Fig. 1. Enantioselectivities observed for type 1 analytes on CSPs 1 (○), 2 (●), 3 (□) and 4 (■).

chiral recognition processes were proposed. A "dipole stacking" process was suggested to selectively retain one enantiomer while a "hydrogen bonding" process selectively retains the other. Both processes involve "face-to-face" approaches of the analytes and the CSP owing to π–π interactions between the π-basic naphthyl groups in the CSPs and the π-acidic 3,5-dinitrobenzoyl groups in the analytes. Both processes invoked steric interaction between the alkyl substituents of the analytes and the tethers and/or silica as the alkyl substituents were intercalated between adjacent strands of bonded phase. These steric interactions were suggested to become more severe as the alkyl substituents became longer or the tethers became shorter. These steric interactions were suggested to be nonidentical for the enantiomers and to depend upon the orientation of the selector with respect to the tethers. Both processes were predicated upon the presumption that the aromatic substituent (phenyl, *p*-anisyl,

α-naphthyl, β-naphthyl) in the analytes behaved as if it were effectively larger than the alkyl group and that this size difference (and the consequent differential steric interactions with the CSP) was the source of the chiral recognition.

A confluence of events and observations leads us to reconsider the earlier data in terms of face-to-edge bonding interactions between aromatic systems. By invoking such an interaction, the earlier observations can be rationalized more simply and, in our view, more plausibly.

There is ample precedent for attractive face to edge interaction between aromatic rings. Such arrangements are found in the crystal structures of proteins [4], peptides [5] and small molecules [6], and have been the subject of theoretical calculations [7]. Moreover, in other chiral recognition studies, we are encountering chromatographic and nuclear magnetic resonance spectroscopic data which can be rationalized in terms of such interactions. Contemplation of an attractive interaction between the face of the aryl substituent of the analyte and the edge of the naphthyl group of CSPs 1–4 leads to the conclusion that a single chiral recognition process will suffice to rationalize the data.

Fig. 2 shows the simplified postulate in which the previously invoked face-to-face π–π interaction and the hydrogen bond between the analyte's dinitrobenzamide N–H and the carbonyl oxygen of the CSP are retained. As before, both selector and analyte are shown in presumed low energy conformations in which the methine hydrogens on the stereogenic centers are approximately eclipsed with the carbonyl oxygens and approximately in the plane of the naphthyl and dinitrobenzoyl rings, respectively. These are held to be relatively low energy conformations which are significantly populated prior to complexation. In the case of the homochiral (*i.e.* the *R*:*R* or *S*:*S*) complex, π–π and hydrogen bonding interactions lead to a structure where the face of the analyte's aryl substituent is presented to the edge of the CSPs naphthyl ring, a bonding interaction ensuing. This arrangement also positions the methine hydrogen of the CSP such that it may simultaneously undergo weak hydrogen bonding to the π cloud of the aryl ring of the analyte. In addition, the analyte's alkyl substituent is directed more or less parallel to the CSP's acyl substituent. In acyl-tethered CSPs 1 and 2, this orientation of the alkyl group is viewed as an intercalative orientation where the resultant steric difficulties reduce retention (relative to the non-intercalating antipode) as the alkyl substituent is lengthened or the tether is shortened. Since the analyte enantiomer involved in the homochiral complex is normally the more retained, the reduction in enantioselectivity noted as the alkyl substituent is lengthened or the tether is shortened is explained, as is the eventual inversion of elution order on CSP 1.

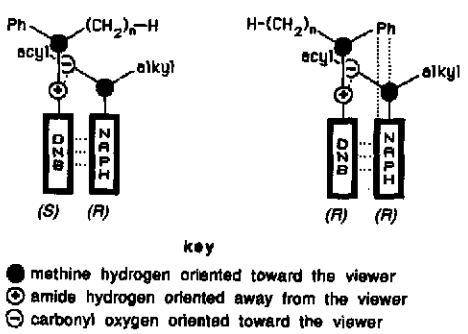

Fig. 2. Schematic representation of the two diastereomeric adsorbates proposed to account for chiral recognition of type 1 analytes on CSPs 1–4. The homochiral (*R*:*R*) adsorbate allows for simultaneous hydrogen bonding, face-to-face π–π interaction, and face-to-edge π–π interaction.

In the corresponding heterochiral complex, the aryl substituent of the analyte is directed toward the acyl group of the CSP. The alkyl substituent of the analyte is oriented more or less alongside the alkyl group of the CSP where, in CSPs 3 and 4, this constitutes an intercalative arrangement. Since the heterochiral analyte enantiomer is the least retained, increasing the length of the alkyl group or shortening the length of the alkyl tether in CSPs 3 and 4 increases enantioselectivity by decreasing the retention of the least retained enantiomer relative to its non-intercalating antipode. The effect is most profound on the short-tethered CSP 3.

A computer-generated space-filling molecular model representation of an exploded view of the two diastereomeric adsorbates which more clearly illustrates the face–edge π–π interaction is illustrated in Fig. 3 (the interested reader is also encouraged to constuct space-filling models). For clarity in this depiction, the 3,5-dinitrobenzamide derivative of α-phenylethylamine is used to represent a generic type 1 analyte (bottom structure) and the acetamide

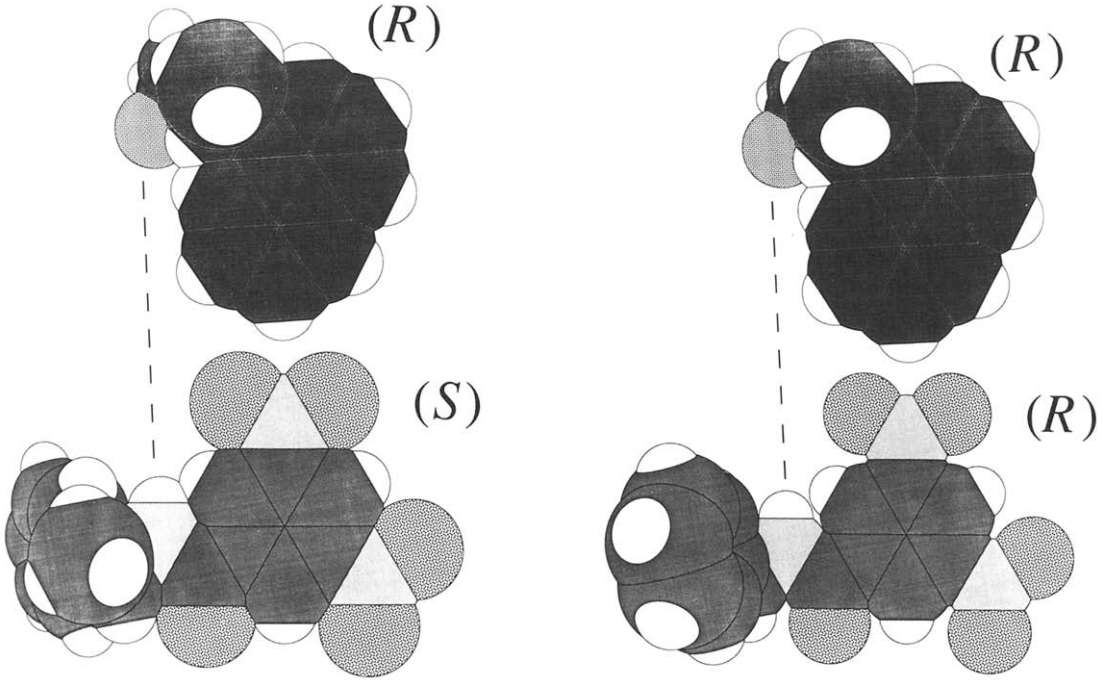

Fig. 3. Exploded view of computer-generated space-filling molecular model representations of the two diastereomeric adsorbates pictured in Fig. 2. The dashed line indicates a hydrogen bond between the upwardly oriented amide hydrogen of the analyte and the downwardly oriented carbonyl oxygen of the CSP. As the distance along this line is decreased by sliding the two structures together within the x–y plane, the proposed face-to-edge π–π interaction of the homochiral (R:R) adsorbate can be visualized.

derivative of (R)-α-naphthylethylamine is used to represent the stationary phase (top structure). A hydrogen bonding interaction between the upwardly oriented DNB amide hydrogen and the downwardly oriented amide carbonyl oxygen of the CSP is indicated by a dashed line. In the postulated adsorbates, the analyte and CSP are closer together than depicted so as to allow the face-to-face geometry necessary if the homochiral (R:R) adsorbate is to simultaneously undergo hydrogen bonding, face-to-face π–π interaction, and face-to-edge π–π interaction.

Some aspects of the original rationalization remain unchanged, the principal refinement stemming from a growing appreciation that aromatic substituents can serve as sites for a variety of bonding as well as steric interactions. By recognizing the occurance of face-to-edge π–π interaction, competing "opposite sense" dipole stacking and hydrogen bonding chiral recognition processes need not be invoked to rationalize the α vs n plots shown in Fig. 1. While multiple adsorption processes are thought to be common (if not universal), the simplest adequate rationalization is, according to Occam, to be preferred. Obviously, those mechanistic model which conform most closely to reality are of the greatest value in the design of improved chiral stationary phases.

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