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STACKING OF AMIDE DIPOLES AS AN ALTERNATIVE TO HYDROGEN BONDS IN CHIRAL RECOGNITION RATIONALES

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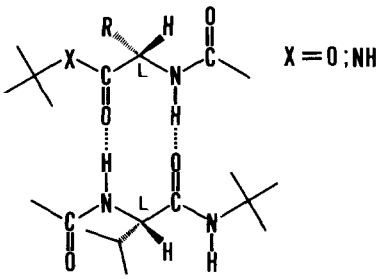
Abstract: Face-to-face stacking of N-acylated amino acid esters (or amides) is suggested to occur owing to electrostatic attraction between amide dipoles. Diastereomers of the resultant transient dimers may differ in stability and these stability differences may allow chromatographic separation of the enantiomers of the N-acylated amino acid derivatives. The dipole-stacking model allows rationalization of the results of Hara et al.[2] and of Gil-Av et al.[4]

Dolbashi and Hara have recently reported the separation of enantiomeric N-acetyl amino acid tert-butyl esters (or amides) on an achiral silica column.[1] This was accomplished through the use of a chiral mobile phase additive (CMPA), S-N-(acetyl)valine tert-butylamide. The S enantiomers of the solutes are selectively retained and the observed separations were attributed to the formation of diastereomeric dimers, pictured in 1, where the associative interactions are bidentate NH···O=C hydrogen bonds. The authors believe the diastereomers to differ in stability, this stability difference being, in some unspecified manner, responsible for the observed separations. However, the authors admit difficulty in determining "what factors impart additional stability to one of the associated enantiomers."

Such stability differences are almost certainly present (although not rigorously necessary for the separation to occur on silica[2]) for Hara has earlier reported[3] that the S-enantiomers of N-acylated-O-tert-butylated amino acids are more strongly retained on an S-N-(formyl)valylaminopropylsilanized-silica column than are their R-counterparts.

It is difficult to see why the diastereomers of the type of hydrogen-bonded dimer proposed by Hara would differ significantly in stability. The "edge-to-edge" approach imparts such distance between the R and H substituents on the chiral centers as to preclude effective interaction between these substituents. From our studies of chiral recognition mechanisms, we have come to believe that electrostatic attraction between amide dipoles can lead to "face-to-face" stacking of certain types of amides. By assuming that hydrogen-bonding interactions are largely incidental and that dipole stacking is responsible for the stability difference of the diastereomeric dimers, one can nicely rationalize Hara's data. For the "head-to-tail" S-S dimer shown in 2, dipole interaction could lead to a "stack" in which the small aminyl hydrogens are "internal". Similar stacking of the R-S dimer necessitates having a large substituent "internal" and would raise the energy of the R-S dimer relative to the S-S (or R-R) dimer owing to the resulting steric repulsion. The combination of small N-acylating agents and bulky O-derivatizing groups was found to



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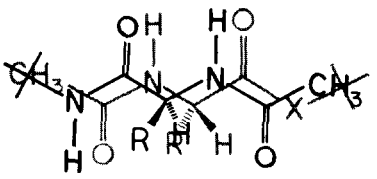

2

Note: For the sake of clarity, the relative positioning of the two components in 2 is shifted somewhat from the presumed "best" stacking arrangement.

optimize Hara'a amino acid-derived CMPA's and CSP's. This large-small derivatization pattern is consistent with either the "head-to-tail" stacking we propose or Hara's "head-to-tail" hydrogen-bonded model. We presume that by lessening the extent of "head-to-head" interaction, this derivatization pattern lessens the degree to which these interactions attenuate the magnitude of the observed chiral recognition (i.e., the time-averaged chromatographic separability factor).

Finally, we note that the elution orders noted by Gil-Av for gas chromatographic separation of the enantiomers of N-acylated amines on stationary N-lauroyl-α-(1-naphthyl)-ethylamine may also be rationalized by the dipole-stacking model. In the instances where elution orders were established, the S-S interaction is more favorable than the R-S interaction. The former, by the dipole-stacking model, has the smaller groups (on the chiral centers) "internal".

The suggestion that dipole stacking may be involved in the aforementioned chiral recognition processes in no way disproves prior models. However, a growing number of researchers are concerned with the details of chiral recognition mechanisms and we present these alternative rationalizations for their consideration.

Notes and References

1) A. Dobashi and S. Hara, Tetrahedron Lett. 1983, 1509.

2) When CMPA is used, there is always a problem in determining the origin of a separation of enantiomers. If one forms diastereomeric complexes in solution, they may have different association constants and this may dominate the separation mechanism. For example, the least strongly complexed solute enantiomer (in solution) might then be more strongly adsorbed and be the last to elute. Alternatively, the CMPA may "load" the surface of the adsorbent and act as a de facto chiral stationary phase, the most strongly complexed solute enantiomer then being the last to elute. Finally, the diastereomeric complexes may have intrinsically different chromatographic mobilities that override any stability differences.

3) A. Dobashi, K. Oka, and S. Hara, J. Am. Chem. Soc. 1980, 102, 7122, and references therein.

4) S. Weinstein, B. Feibush, and E. Gil-Av, J. Chromatogr. 1976, 126, 97. These workers present a detailed chiral recognition model to account for their observed elution orders.

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