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CONFORMATIONAL ANALYSIS OF THE COVALENT PIRKLE CHIRAL STATIONARY PHASES.†

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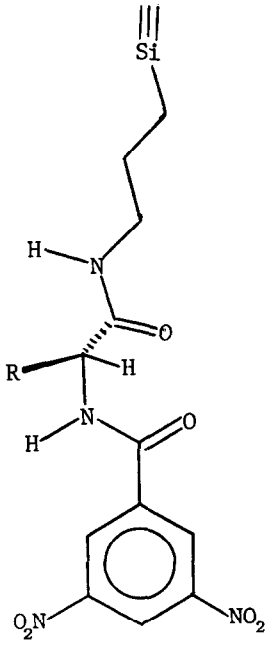
Summary: The multidimensional potential energy surface for a model Pirkle chiral stationary phase is computed with MM2. Five minimum energy conformations are located, the minimum energy reaction pathway between the three lowest energy forms is described and the ability of these chiral phases to act as templates is discussed.

By placing a racemic mixture on a chromatographic column that is composed of suitable chiral substances one should, in principle, allow the enantiomers to migrate through the column at different rates and be individually collected at the other end of the column. Although this technique has long been recognized as feasible[1] and chiral chromatographic columns have been developed,[2] it is only recently that they have been marketed[3] and incorporated into the bench-chemist's ritual. The most popular and perhaps most versatile columns are those developed by Pirkle et al.[4] These chiral stationary phases (CSP) are derived from N-3,5-dinitrobenzoylamino acids and are attached by a propylene chain to a silica surface,[5] 1.

To understand, from first principles, how these chromatographic columns work, we have initiated a research program that uses modern computational chemistry to help design improved versions of chiral surfaces for enantiomer resolution.[6] This application of computational chemistry is called "column design" because it borrows tools and ideas used in the pharmaceutical industry for "drug design".

†Part 2 of a series entitled **Column Design.**

Precisely how the Pirkle CSP's discriminate between enantiomers is not known; clearly there is a difference between the two diastereomeric complexes formed upon adsorption and, several enlightening chiral recognition models have been put forth.[7] These models depend, in part, on the templating ability of the CSP which, in turn, depends on the allowed molecular conformations of these amino acid derivatives. In this paper we present a preliminary study on the conformational analysis of the covalent Pirkle columns. More specifically we present the multidimensional potential energy surface for the alanine derivative (R = Me) of 1 computed by the Allinger MM2 force field.[8] To make this a computationally tractable problem we use 2 as a suitable model for 1. In 2 we have truncated the propylene chain, assumed planar amides in the Z configuration, and, have replaced the NO_2 groups with CHO functionality because force field parameters for aromatic nitro groups do not yet exist.

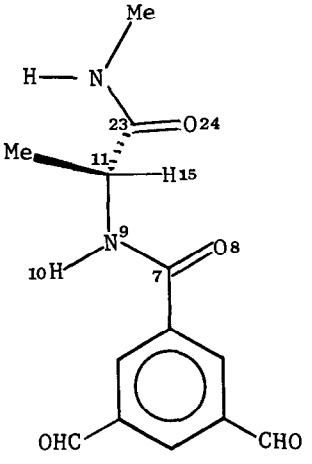


1

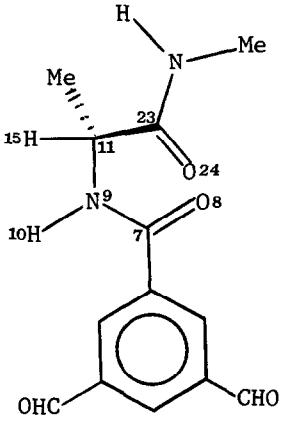
$\omega = H_{15}C_{11}N_9C_7$

$\delta = O_{24}C_{23}C_{11}N_9$

9



2 syn



2 anti

The two unique degrees of freedom that characterize the templating ability of the Pirkle CSP's are depicted in 2 as torsion angles δ and ω. In figure 1 we present contours for full 360° rotations around δ and ω for the S enantiomer of 2. Several important points are to be noted. First, there exist five low energy conformers. The global minimum is located at $\delta = 140°$, $\omega = 200°$. A degenerate set of conformers that are 0.30 kcal mol^{-1} less stable than the global minimum are to be found at $\delta = 120°$, $\omega = 40°$ and $\delta = 120°$, $\omega = 340°$. Finally, a second set of conformers can be found at $\delta = 20°$, $\omega = 320°$ and $\delta = 220°$, $\omega = 300°$ with an energy 0.75-0.79 kcal mol^{-1} above the global minimum. Under normal chromatographic conditions all conformers are expected to be populated.

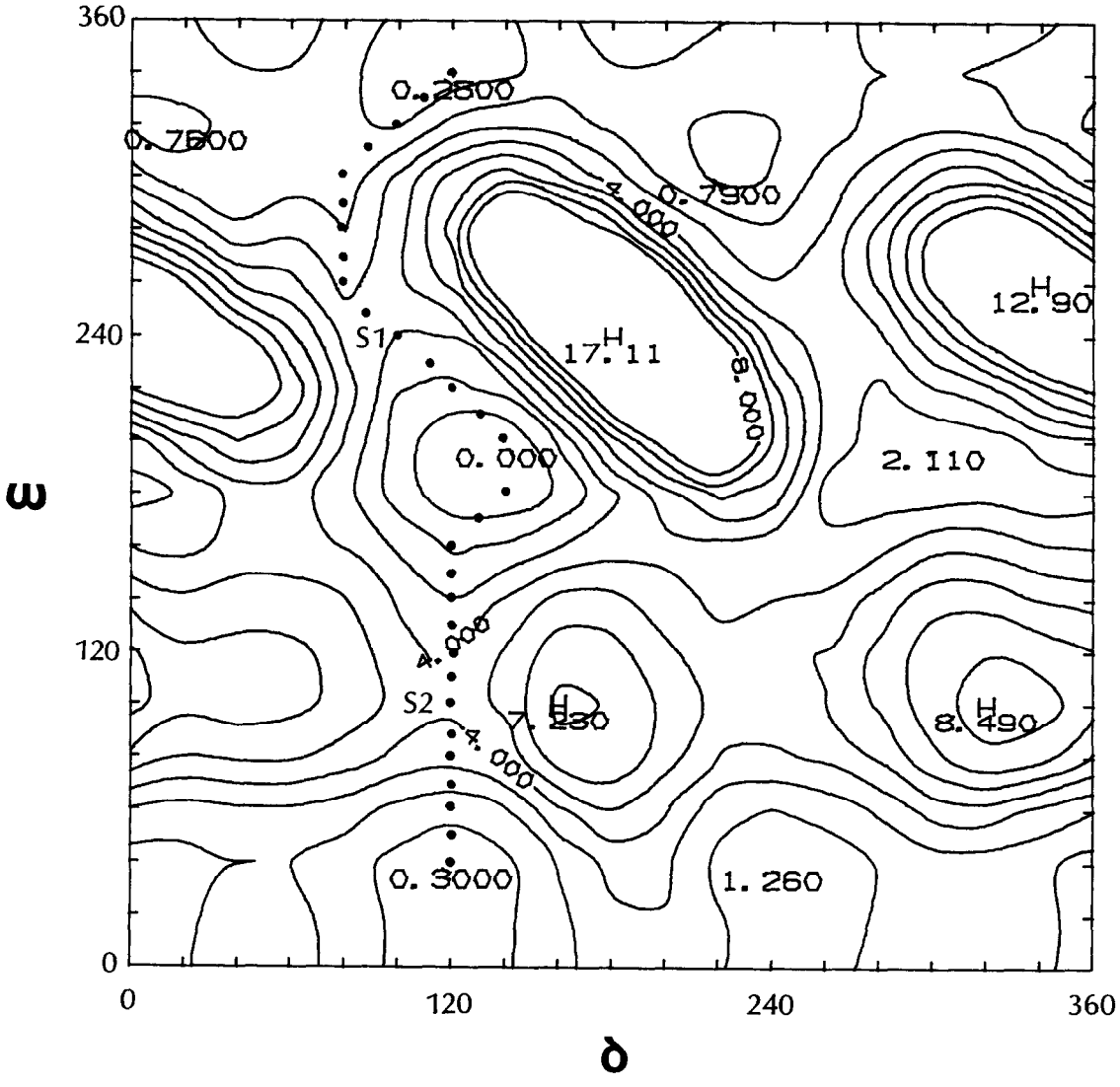


Figure 1. Potential energy surface for 2 as a function of δ and ω. Contours are in units of 1 kcal mol^{-1}, with the global minimum arbitrarily set to zero. Actual data is an equally spaced square array of data points 20° apart. Contour lines above 8 kcal mol^{-1} are not shown. High points are designated with H. The dotted line is the minimum energy reaction pathway connecting the global minimum (anti) with the energetically degenerate syn forms. Saddle points along this path are designated as S1 and S2.

Next, the interconversion of these conformations will be rapid; the barriers are under 5 kcal mol^{-1}. The minimum energy reaction pathway (MERP) connecting the global minimum with the next most stable structures is depicted with a dotted line in the figure. The saddle point labeled S1 is a 2.96 kcal mol^{-1} barrier and that labeled S2 is a 4.25 kcal mol^{-1} barrier.

Finally, we mention that the chiral recognition models developed by Pirkle invoke the syn conformation ($\omega = 0^{o}$) where the methine hydrogen at the chiral carbon adapts an orientation in alignment with the C=O of the benzoyl amide group.[9] Based on MM2 we find that the preferred orientation is in the anti form ($\omega = 180^{o}$). Although large regions of conformational space are forbidden to the covalent CSP there are many regions accessible for templating purposes, and, the syn rotamer is perfectly reasonable. It is intruiging to speculate that the mechanism of enantiomer differentiation takes place not from the most stable molecular conformation, but rather, from an energetically less stable structure. A detailed discussion of conformations allowed with other R groups on the Pirkle CSP will be presented in a forthcoming paper.

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