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The docking of chiral analytes on proline-based chiral stationary phases: A molecular dynamics study of selectivity

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ABSTRACT

Molecular dynamics simulations are employed to examine the selectivity of four proline-based chiral stationary phases in two solvent environments, a relatively apolar *n*-hexane/2-propanol solvent and a polar water/methanol solvent. The four chiral surfaces are based on a BOC-terminated diproline, a TMA-terminated diproline, a TMA-terminated triproline and a TMA-terminated hexaproline. This range of chiral selectors allows an analysis of the impact of oligomer length and terminal group on selectivity while the two solvent environments indicate the impact of solvent hydrogen bonding and polarity. The selector–analyte interactions are examined for six closely related analytes that each have an aromatic moiety, a hydrogen, and an alcohol group directly bonded to the stereocenter. The analytes differ in the nature of the aromatic group (phenyl or anthracyl), in the attachment point (to the central ring or a side ring in the anthracyl), and in the fourth group bonded to the carbon (CH_3, CF_3, or C_2H_5). For each of the 48 solvent + selector + analyte systems, selectivity factors are calculated and, when possible, compared to experiment. The docking mode for these proline-based selectors is analyzed.

1. Introduction

Polyproline stationary phases have successfully resolved a number of racemates [1–4] including chiral aliphatic alcohols, esters, aromatic and aliphatic amides. These chiral stationary phases (CSPs) are stable in a wide range of solvents including *n*-hexane/2-propanol, water/methanol and chloroform, and the selectivity of some polyproline CSPs has been measured in multiple solvent environments [1–4]. The selectivity of a monoproline CSP was first examined in 1991 [5] but CSPs based on proline oligomers were first prepared and examined by Li et al. in 2005 [1]. In the past decade, several experimental studies have been performed to improve the enantioselective properties of these proline-based CSPs [2–8]. Modifications include chain length [2], the identity of the group terminating the proline chain [3], and the presence of side chains [1].

In bulk solution, polyproline chains adopt two distinct helical conformations known as PPI and PPII which differ in the amide linkage: when all backbone amide dihedrals are cis (they adopt an angle of close to 0°), the structure is compact and is referred to as PPI. On the other hand, when they adopt angles of close to 180° (trans amides), the helical structure is more extended and is named PPII. It is well known that solvent polarity can trigger a switch between PPI and PPII [9]. In biological systems, PPII is a well-known helical structure that occurs for sequences of amino acids that include other amino acids beyond proline [9–11].

Surface-bound polyprolines have conformational distributions that reflect the steric constraints of the interface and interactions with other nearby surface bound moieties, such as end-caps, silanols, and other surface-bound polyprolines. Huang [2] studied the effect of increasing the proline chain length on enantioselectivity and showed that the progression is not systematic but that, generally, longer chains are more selective. The conformational balance of surface-bound proline oligomers, from dimers to hexamers, has previously been studied using Molecular Dynamics (MD) simulations [12,13]. For a given proline chain, conformations intermediate between PPI and PPII were observed. The MD simulations also considered [12,13] two solvents – *n*-hexane/2-propanol and water/methanol – and the impact of the terminal group. The conformational balance was found to be highly impacted by all three factors (chain length, terminal group, and solvent). As a result, the characteristics of the proline oligomers, including the accessibility of hydrogen bonding sites, are different under different conditions.

In this article, we use molecular dynamics (MD) simulations to examine the selectivity of four polyproline selectors: TMA–$(Pro)_n$–$N(CH_3)$-tether with $n = 2$, 3, 6 and BOC–$(Pro)_2$–$N(CH_3)$–tether. These selectors, shown in Fig. 1, allow an analysis of the impact of chain length and terminal group

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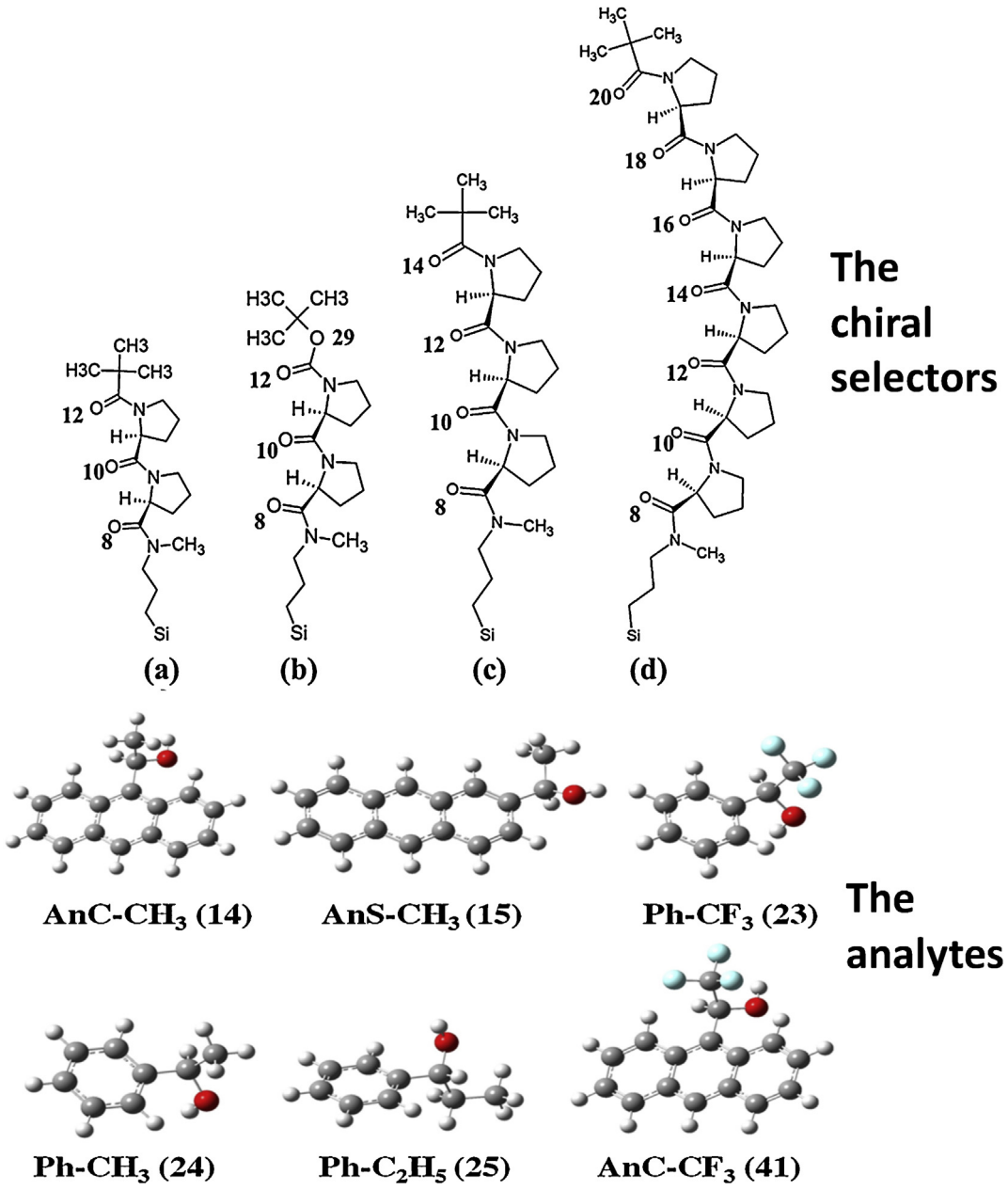

Fig. 1. The chiral selectors and B3LYP/6-311G(d,p) optimized structures of the analytes. The chiral selectors are: (a) TMA–$(Pro)_2$–$N(CH_3)$–tether; (b) BOC–$(Pro)_2$–$N(CH_3)$–tether; (c) TMA–$(Pro)_3$–$N(CH_3)$–tether; and (d) TMA–$(Pro)_6$–$N(CH_3)$–tether. The atom numbering of the carbonyl oxygens is shown and will be used throughout. For convenience, analytes are identified according to the groups on the chiral carbon. The chiral carbon is always bonded to a hydroxyl group, a hydrogen, an aromatic group, and either a methyl, an ethyl, or a trifluoromethyl group. "AnC" indicates an attachment to a central carbon in anthracyl, "AnS" indicates an attachment to a side carbon in anthracyl, and Ph represents attachment to a phenyl ring. Numbers in brackets correspond to the analyte numbering from the Li group [2].

on selectivity. Six chiral analytes have been chosen based on the results of experimental resolutions, where some are well resolved and others unresolved by these selectors, and on structural similarities. Our goal is to provide insights into the mechanism of selectivity via comparisons between the analytes. These analytes are α-methyl-9-anthracenemethanol (AnC-CH_3), 1-anthracen-2-yl-ethanol (AnS-CH_3), α-(trifluoromethyl) benzyl alcohol (Ph-CF_3), 1-phenylethanol (Ph-CH_3), 1-phenyl-1-propanol (Ph-C_2H_5), and 1-(9-anthryl)-2,2,2-trifluoroethanol (AnC-CF_3) and are included in Fig. 1. Every analyte has an aromatic moiety, a hydroxyl group, a hydrogen, and an alkyl or a fluoroalkyl group attached to the chiral carbon. The selected analytes are also relatively small, with limited flexibility that reduces the number of possible docking arrangements. Two solvent environments have been chosen, *n*-hexane/2-propanol and water/methanol to examine the role of solvent polarity. Molecular dynamics simulations are undertaken for each solvent + selector + analyte combination (48 systems in total).

Despite the experimental work on polyproline stationary phases, not much is known about the underlying mechanism of enantioseparation. According to the three point interaction model [14–18], for the enantioseparation to happen, three simultaneous interactions are needed to differentiate between enantiomers. Such interactions often include hydrogen bonding, π–π stacking, CH–π interaction, and steric interactions. For poly-proline stationary phases, however, the selectors lack any aromatic moiety, and can only act as hydrogen bond acceptors. Also, the analytes under consideration only hydrogen bond through a single donating site, an alcohol group directly bonded to the stereocenter. As a result, it is expected that the complex interactions of the