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Molecular docking study for the prediction of enantiodifferentiation of chiral styrene oxides by octakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin

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ABSTRACT

A molecular docking study, using molecular mechanics calculations with AutoDock and semi-empirical PM3 calculations, was used to help predict the enantiodiscrimination of mono-substituted styrene oxides by octakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin (DIACTGCD), through the differences in the interaction energies and inclusion geometries. The small differences in the binding free energy values ($\Delta\Delta G$) obtained from AutoDock do not show any significant enantiodifferentiation, whereas structure re-optimization with the PM3 algorithm results in larger binding energy differences ($\Delta\Delta E$). All DIACTGCD–styrene oxide inclusion complexes have binding energies in the range of −13.62 to −3.83 kcal mol^{-1}, indicating that the host–guest interactions involved are hydrophobic and van der Waals forces between the C=O acetyl group, the O2/O3/O4 atoms of DIACTGCD and the substituents/epoxide group of styrene oxides. The effect of the same substituent position on the inclusion geometry is similar for all styrene oxides entirely embedded at or near the central DIACTGCD cavity. The degrees of enantiodiscrimination are: $o > m > p$ for Cl-, CH_3- and CF_3-enantiomers and $o > p > m$ for Br-, F- and NO_2-enantiomers. The molecular docking results suggest that the complexation between styrene oxides and DIACTGCD depends on the type and position of the substituents on the aromatic ring. The high discriminatory ability exhibited by DIACTGCD against enantiomeric styrene oxides could potentially serve as a chiral selector, for example in chromatographic separation.

1. Introduction

α-, β- and γ-Cyclodextrins (CDs) are torus-like macrocycles comprised of six, seven and eight D-glucopyranose units, respectively [1]. CDs and their derivatives form inclusion complexes with a wide variety of guest molecules, including isomers and enantiomers, and have been widely used as a chiral stationary phase (CSP) in chromatography for chiral separations (reviewed in [2–9]). The enantioseparation of CD derivatives strongly depends on the CD cavity size, the type and the degree of substitution of the substituents on the primary hydroxyls O6-H and on the secondary hydroxyls O2-H and O3-H of the glucose units of CD [4]. Amongst the CD CSPs, permethylated β-CD and 6-*O*-*tert*-butyldimethylsilyl-β-CD derivatives are extensively applied in enantiomeric gas chromatography (GC), whereas 6-*O*-*tert*-butyldimethylsilyl-γ-CD derivatives are rare and deserve further investigations [8].

Enantiopure styrene oxides are of interest because they are used as chiral building blocks for the synthesis of a variety of pharmaceutical products and as intermediates for the synthesis of more complex chiral organic compounds [10,11].

Over the past 20 years, there have been many molecular modeling studies on the chromatographic separations of enantiomers aimed at both the rationalization and prediction of experimental results. Two comprehensive reviews by Lipkowitz have been published for the five types of CSPs [12] and for type III CSPs, particularly on CDs [13]. For the CD inclusion complexation, different host CDs and guest enantiomers have been investigated by various molecular modeling methods, e.g. molecular mechanics, molecular dynamics and Monte Carlo [12,13]. The given examples are for rationalization of the GC separation on 6-*O*-*tert*-butyldimethylsilyl-β-CD-based CSPs [14–16] and for prediction of chiral separations of β-CD and its derivatives as chiral selectors [17–20]. However, a general explanation and guideline for the prediction of the existent or observed enantioselectivity cannot be established.

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In this study, we perform molecular docking simulations, using (i) a molecular mechanics method with AutoDock and (ii) the semi-empirical Parametric Model 3 (PM3) method, to systematically investigate and predict enantiorecognition of styrene oxides by octakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin (DIACTGCD). Because DIACTGCD has a slightly larger cavity size and is less symmetric, it may better anchor and discriminate chiral guests when compared with the corresponding derivative of β-CD.

2. Computational methods

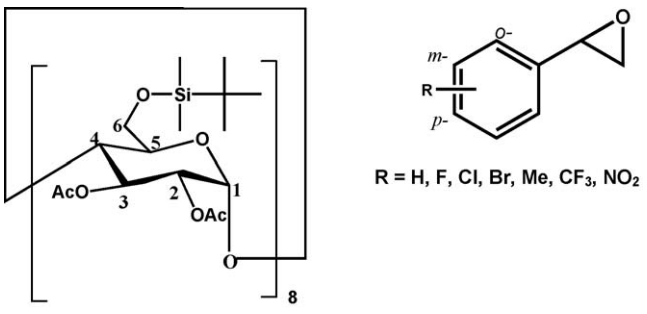
To simplify the calculations, we assumed that the guests bind primarily within the DIACTGCD cavity and hence that the enantiorecognition is mainly attributed to the distinction in structures and interaction energies of the inclusion complexes. However, it should be noted that this assumption is still controversial because some chiral separations may occur when a cavity is not available, i.e., chiral recognition by interaction with the outer CD surface, in the interstices between CD molecules. This is an analogy to the interactions with linear dextrins that have been reported recently [21–23].

2.1. Structure optimization of host DIACTGCD and guest styrene oxides

The starting atomic coordinates of DIACTGCD non-H-atoms were taken from the X-ray crystal structure of octakis(2,3,6-tri-*O*-methyl)-γ-CD [24]; all methyl C-atoms were replaced at the O2 and O3 positions with acetyl groups and at the O6 positions with *tert*-butyldimethylsilyl groups. All H-atoms were added. The structures obtained were then optimized using the PM3 method implemented in Gaussian 03 [25]. Styrene oxide (SO) and its 18 derivatives (hereafter, the abbreviations used are, for example, *o*-Br, *m*-Br and *p*-Br standing for *ortho*-, *meta*- and *para*-bromostyrene oxides, respectively) were optimized at the calculation level HF/6-31G** with Gaussian 03 [25]. The optimized structures of host and guests were used for the molecular docking calculations. The chemical structures and atom labeling of DIACTGCD and styrene oxides are given in Scheme 1.

2.2. Molecular docking simulations

Molecular docking simulations were carried out with the automated docking program, AutoDock 4.0.1 [26]. A Lamarckian Genetic Algorithm (LGA) in combination with a grid-based energy evaluation method were used for pre-calculating grid maps according to the interatomic potentials of all atom types present in the host and guest molecules, including the 12-6 Lennard–Jones potentials for van der Waals interactions and Coulomb potentials for electrostatic interactions. A grid map of dimensions



Scheme 1. Chemical structures of DIACTGCD and styrene oxide derivatives. Atomic numbering is given for the CD skeleton.

Table 1
Binding free energies at 298 K of the complexes between DIACTGCD and 19 styrene oxides obtained from molecular docking with AutoDock [26]. Units are in kcal mol^{-1}.

Analyte	%Frequency	ΔG[a]	$\Delta\Delta G$[b]
SO			
R	100	−4.18	0.00
S	100	−4.18	
o-F			
R	96	−1.25	0.28
S	100	−1.53	
m-F			
R	100	−2.63	−0.16
S	94	−2.47	
p-F			
R	84	−1.70	−0.03
S	100	−1.67	
o-Cl			
R	98	−3.91	−0.05
S	100	−3.86	
m-Cl			
R	100	−3.26	0.05
S	97	−3.31	
p-Cl			
R	86	−3.47	−0.01
S	68	−3.46	
o-Br			
R	100	−4.33	−0.06
S	99	−4.27	
m-Br			
R	85	−2.36	−0.07
S	100	−2.29	
p-Br			
R	100	−3.35	−0.05
S	99	−3.30	
o-Me			
R	100	−2.37	0.08
S	100	−2.45	
m-Me			
R	100	−0.38	−0.05
S	100	−0.33	
p-Me			
R	78	−1.80	0.02
S	97	−1.82	
o-CF_3			
R	100	−1.50	−0.24
S	81	−1.26	
m-CF_3			
R	66	−1.19	0.22
S	99	−1.41	
p-CF_3			
R	94	−1.27	−0.10
S	70	−1.17	
o-NO_2			
R	90	−2.26	0.11
S	99	−2.37	
m-NO_2			
R	74	−1.54	−0.08
S	91	−1.46	
p-NO_2			
R	94	0.04	0.02
S	50	0.02	

[a] Binding free energies derived from AutoDock 4 with standard errors of ~2.5 kcal mol^{-1}.
[b] Binding free energy difference between the complexes of the (*R*)- and (*S*)-enantiomers, $\Delta\Delta G = \Delta G_R - \Delta G_S$; negative/positive value means the elution order: (*S*) > (*R*)/(*R*) > (*S*).