Chinese Chemical Letters Vol. 11, No. 4, pp. 347–350, 2000

Molecular Dynamic Study for Chiral Discrimination of α-Phenylethylamine by Modified Cyclodextrin in Gas Chromatography

Meng Yan NIE, Liang Mo ZHOU*, Qing Hai WANG, Dao Qian ZHU

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116012

Abstract: A molecular dynamic method in conjunction with a statistic test has been utilized to model chiral recognition of α-phenylethylamine on heptakis (2,6-di-*O*-butyl-3-*O*-butyryl)-β-cyclodextrin in gas chromatography. The modelling data correlated with the chromatographic elution order, and indicated that the preferred site of α-phenylethylamine is the interior of cavity.

Keywords: Molecular modelling, modified cyclodextrin, chiral recognition.

Introduction

After the introduction of modified cyclodextrins (CDs) as a new type of chiral stationary phases, great progress has been made in enantioselective gas chromatography, which has raised many questions about the mechanism of chiral recognition and intermolecular interactions[1]. Theoretical computational methods in conjunction with modelling procedures have been extensively used to investigate the nature of binding processes responsible for inclusion complex formation[2,3]. It is of interest to couple the ability of molecular dynamics as the basis of a computational method to describe chirally discriminating complexes between analytes and cyclodextrins to predict their chromatographic behavior. Furthermore, in enantioselective chromatography, the elution order of the separated optical antipodes can only be assigned by coinjection of optically pure reference substances. But, the information about the absolute configuration of the separated enantiomers or reference substances is not available in some cases. It is very necessary to construct an interaction model to predict the chromatographic elution sequences of the enantiomers. The object of the present work is to demonstrate a general strategy to construct the chiral discrimination model to predict the elution sequences on modified cyclodextrin chiral stationary phases (CD CSPs).

Computational Methods

All energy minimizations and molecular dynamics (MD) trajectories were performed on a PII233 personal computer using MM2 and MD programs of CS Chem3D Pro

(CambridgeSoft Corporation).

The molecular structure of heptakis (2,6-di-*O*-butyl-3-*O*-butyryl)-β-CD (DBBBCD) was derived from the crystal structure of β-CD[4]. Using the tools of Chem3D, the structures of both enantiomers of *N*-trifluoroacetyl-α-phenylethylamine (α-PEA) were built. All the obtained geometries were optimized based on standard bond lengths and angle parameters using MM2 force field. Minimization was terminated when the gradient root mean square was below 0.001 kcal/mol/Å.

The DBBBCD molecule was fixed so that the *x*-axis is perpendicular to the plane occupied by seven *O*(4) atoms of the glucosidic linkages between glucose residues of the macrocycle, and the positive direction of *x*-axis points at the C-2 and C-3 substituents of DBBBCD. Similar with the docking procedures, the complexes were achieved by insertion of the enantiomers into DBBBCD cavity. Twelve pairs of complexes were obtained when the enantiomers approach DBBBCD from the infinity and pass through the cavity along *x*-axis in 2Å translation step size. Each complex was subjected to a geometry optimization to remove the internal strain in the complexes resulting from the docking process. During the geometry optimization of the complexes, the minimization was terminated when the gradient root mean square was less than 0.1 kcal/mol/Å.

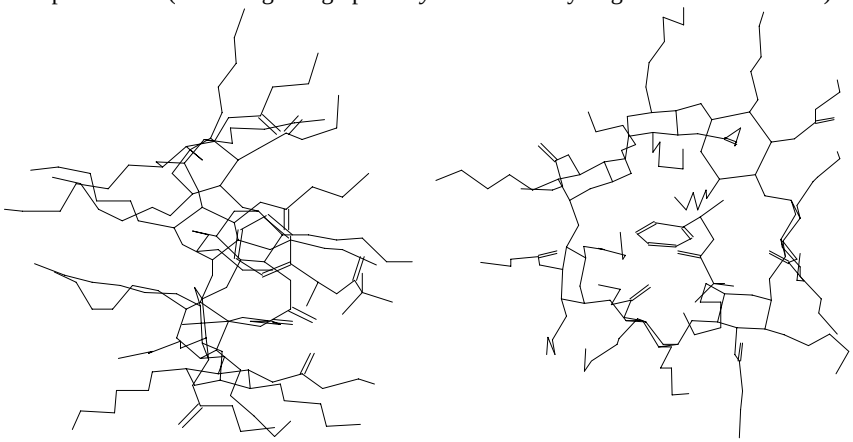
With the optimized geometries as the initial structures, the molecular dynamic simulations were carried out in vacuum. The simulation temperature has been chosen to be 413 K, which corresponds to the average temperature of the gas chromatographic separation process[5,6]. To maintain the temperature at 413 K during the simulations, the system was coupled to an external heat bath, whose heating/cooling rate was 2.512 kcal/atom/ps. An integration step of 2 fs was used, a structure was recorded every 50 fs, and translational and rotational kinetic energies were removed every 0.2 ps. During the MD trajectories, the data were collected every 0.5 ps within the period from 10 to 20 ps. In principle, the interaction energies were evaluated from the Boltzmann weighted average of all the interaction energies collected. Here, the mathematical average of all the energy values collected from each trajectory was used as a measure of complex stability. Since the Boltzmann weighting of the interaction energies was not performed, a statistical procedure (*t* test) was applied for the comparison of the average energies calculated between the enantiomers.

Results and Discussion

Chromatographic separation processes are characterized by the reversible binding between the stationary phase and the analyte. During the chiral separation, both enantiomers are expected to interact with CD molecules in a dynamic equilibrium, and the diastereomeric complexes with various stabilities and lifetime are formed between the enantiomers and cyclodextrin. The differences in complex stability determine the retention times of the optical antipodes and thus the chiral discrimination. Therefore, the most realistic simulation of this reversible process can not be obtained by consideration of a single diastereomeric complex but by analysis of a variety of diastereomeric complex geometries. A comparison of the inclusion complexes should not be limited to the geometry with the lowest energy but instead include all complexes within a certain energy range. It is usually suggested that both exterior and interior binding modes are possible for

enantioselective chromatographic separation on CD CSPs. Thus, our initial structures for MD simulations included exterior binding, partial inclusion complexation and interior binding modes. However, upon providing the kinetic energy to the systems, the enantiomers of exterior binding modes were pushed away from the CD molecules in less than 5 ps, and the MD simulations were not further investigated. Similarly, the enantiomers of partial inclusion complexation modes were fast expulsed from the CD cavity in less than 10 ps, and the equilibration phases were not be reached. Only six pairs of complexes with the aromatic ring of α-PEA embedded within the CD cavity can be maintained up to the end of MD trajectories, which indicated that the preferred site of α-PEA is the interior of the cavity of DBBBCD (as shown in **Figure 1**).

Figure 1. Structure of the *R*-α-PEA-DBBBCD complex from the MD trajectories over 20ps at 413 K (the orthogonal graphs on *y*-axis and all hydrogen atoms are omitted).



From these six trajectories, the average interaction energies of inclusion complexes were evaluated by mathematically averaging all the energy values collected, and were summarized in **Table 1**. From this table, it is obvious that the *R*-enantiomer of α-PEA is able to form more stable diastereomeric complex with DBBBCD than *S*-enantiomer, which is consistent with the chromatographic retention order (the capacity factor for *R*-enantiomer is greater than *S*-enantiomer on DBBBCD CSP[4]). In addition, from the differences in average interaction energy ($\Delta \overline{E}_{R\text{-}S}$), the chiral discrimination effect for α-PEA is different within the different domains of the cavity of DBBBCD molecule.

Table 1. The averages ($\overline{E}$) of the interaction energy with the confidence interval CI (α=0.05) for the complexes between α-PEA and DBBBCD. (Units: kcal/mol)

No.	R-α-PEA-DBBBCD complex		S-α-PEA-DBBBCD complex		$\Delta \overline{E}_{R\text{-}S}$
	$\overline{E}$	CI of $\overline{E}$	$\overline{E}$	CI of $\overline{E}$	
1	1995.84	1993.83 ~ 1997.86	1997.93	1994.79 ~ 2001.08	- 2.09
2	1993.62	1990.56 ~ 1996.68	2002.73	2000.70 ~ 2004.77	- 9.11
3	1983.88	1980.13 ~ 1987.63	2002.23	2001.16 ~ 2003.30	-18.35
4	1983.00	1981.33 ~ 1984.67	1998.49	1996.29 ~ 2000.69	-15.49

5	1982.33	1980.00 ~1985.65	1992.77	1987.93 ~ 1997.61	-10.44
6	1992.29	1990.75 ~1993.83	1994.13	1990.23 ~ 1998.04	- 1.84

Acknowledgments

Financial support from the NSFC (Project No.29775025) is gratefully acknowledged.

References

1. W.A. König, *Gas Chromatographic Enantiomer Separation with Modified Cyclodextrins*, Hüthig Buch Verlag, Heidelberg, **1992**.
2. K.B. Lipkowitz, *Chem. Rev.*, **1998**, *98*, 1829 and references cited therein.
3. T. Beier, H.D. Höltje, *J. Chromatogr. B*, **1998**, *708*, 1.
4. C. Betzel, W. Saenger, B.E. Hingerty, G.M. Brown, *J. Am. Chem. Soc.*, **1984**, *106*, 7545.
5. L.M. Zhou, X.L. Liu, Z.S. Li, Q.H. Wang, D.Q. Zhu, D.H. Hu, *Chin. J. Chem.*, **1996**, *14*, 348.
6. L.M. Zhou, M.Y. Nie, Q.H. Wang, D.Q. Zhu, H.Q. Shen, *Chin. J. Chem.*, **1999**, *17*, 363.

Received 19 November 1999