

Molecular dynamics simulation of chiral chromatography

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Abstract

Molecular dynamics (MD) has been used to simulate the liquid chromatography process. The flow speed was arbitrarily increased to save computer time. Then the average translational motion is still relatively slow and does not perturb the interaction of the solute with the stationary phase. The CHFCIBr molecule was used as model chiral system, with water as a solvent. The MD technique with a standard potential provided realistic all-atomic simulations of the separation ratios and enabled to test the sensitivity of the process to solvent polarity and temperature. Low temperature and non-polar solvent favored the separation.

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1. Introduction

The development of methods for chiral separation on an analytical as well as on a preparative scale has attracted great attention during the past two decades. Typical applications of the chromatographic techniques involve enantiomer purity control in synthesis, check for racemization processes, pharmaceutical quality control, and pharmacokinetic studies [1]. Therefore, it appears useful to model the chiral recognition also at the molecular level [2] and to understand the flow and diffusion mechanisms with the aid of the molecular dynamics simulation techniques. This is difficult because of the size of the systems and time scales involved in the separation. Molecular-level simulations are strongly limited by the integration time step [3] which should be shorter than time periods of internal molecular motions. On the other hand, macroscopic processes are relatively slow and require performing excessively long simulations.

However, due to development of computers and advanced simulation techniques, such as the implementation of the periodic boundary conditions [4], some simulations of the macroscopic processes on realistic systems can be done at least on a smaller scale [5]. Even the detection of

chiral molecules by chiral single walled nanotubes was proposed lately on the basis of a theoretical model [6]. In this work, we investigate the potential of common molecular dynamics (MD) techniques for an all-atomic simulation of the chiral chromatography separation. The CHFCIBr molecule is used as a simplified chiral model of the solute while the stationary phase is simulated with CHFCIBr or methane molecules fixed in space.

2. Method

Standard [4] molecular dynamics potential energy was considered as

$$W = \sum_{i=1 \dots N} \sum_{j=i+1 \dots N} \left(\frac{q_i q_j}{r_{ij}} + \epsilon_{ij} \left(2 \left(\frac{\sigma_{ij}}{r_{ij}} \right)^9 - 3 \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right) \right) D(r_{ij}) + \sum_{i=1 \dots n_a} k_b (r_b - r_b^0)^2 + \sum_{i=1 \dots n_a} k_a (\alpha_a - \alpha_a^0)^2 \quad (1)$$

where N is the number of atoms, $r_{ij} = |\mathbf{r}_i - \mathbf{r}_j|$ is the distance between atoms i and j , q_i is the partial charge, $\epsilon_{ij} = 2\sqrt{\epsilon_i \epsilon_j} \sigma_i \sigma_j / (\sigma_i^6 + \sigma_j^6)$ and $\sigma_{ij} = (\sigma_i^6 + \sigma_j^6) / 2$ are the van der Waals parameters, $D(x)$ is a damping coefficient ($D(x) = 1$ for $x < c - s$, $D(x) = 0$ for $x > c$, $D(x) = (c - x) / s$ for $x \in (c - s, c)$, $c = 7 \text{ \AA}$, $s = 4 \text{ \AA}$). The Verlet propagation [7] was implemented with the periodic boundary conditions (a $3.6 \times 3.6 \times 3.0 \text{ nm}$ box) for an NVT ensemble.

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The integration step was 2 fs and for the flow velocity of 33 m/s approximately 1.7×10^7 MD steps were needed to simulate a 1 μm solvent flow. Two independent programs (graphical, Pascal-based operating in Windows, and a performance-oriented one in Fortran, operating in Linux, both available upon request) were used for the MD simulations. General performance of the programs was successfully tested by comparison with the Tinker program package (Appendix A).

A typical arrangement mimicking the chromatographic column can be seen in Fig. 1. Here, the column stationary phase is modeled by 64 *R*-enantiomers of the CHFCIBr molecule. The molecules are regularly spaced and oriented; additionally, a symmetry plane was imposed on the molecular grid so that chirality [8] of the stationary system stemmed exclusively from the internal asymmetry of CHFCIBr. For control purposes an achiral column was constructed in a similar way, using methane molecules instead of CHFCIBr (not shown). The moving phase consisted of the H_2O solvent and a solute enantiometric mixture, which was modeled again by CHFCIBr. The chiral separation was measured by counting the *S*- and *R*-isomers passing through the box wall in the direction of the flow (e.g. from top to bottom). The flow was enforced arbitrarily via an average movement correction for the water molecules. The solute was dragged by the solvent. Other schemes, such as addition of a gravitation force to the potential (1) did not provide stable dynamics.

The following force field parameters were used, with distances (d) in Å, angles (α) in degrees, force constants (k) for distances in kcal/mol/Å², for angles in kcal/mol/rad². Chiral phase (CHFCIBr): $d(\text{C-H}) = 1.087$, $d(\text{C-F}) = 1.353$, $d(\text{C-Cl}) = 1.782$, $d(\text{C-Br}) = 2.004$, $k(\text{C-H}) = 346.4$, $k(\text{C-F}) =$

450.0, $k(\text{C-Cl}) = 250.0$, $k(\text{C-Br}) = 180.0$, $\alpha(\text{HCF}) = 109.6$, $\alpha(\text{HCCl}) = 111.1$, $\alpha(\text{HCBr}) = 111.3$, $\alpha(\text{FCCl}) = 105.0$, $\alpha(\text{FCBr}) = 108.5$, $\alpha(\text{ClCBr}) = 110.8$, all angle force constants were set to 41.7 kcal/mol/rad², $q_{\text{H}} = 0.2811$; $q_{\text{C}} = -0.1445$; $q_{\text{F}} = -0.3621$; $q_{\text{Cl}} = 0.1132$; $q_{\text{Br}} = 0.1128$. Additionally, to prevent racemization during the long simulation runs, arbitrary bonds (H-F, H-Cl, H-Br, F-Cl, F-Br, Cl-Br) were introduced to the moving phase. For the solvent (H_2O), $d(\text{OH}) = 1.090$, $k = 356.4$, $\alpha(\text{HOH}) = 105.0$, $k = 41.7$, $q_{\text{H}} = 0.417$; $q_{\text{O}} = -0.834$. The van der Waals parameters were: H: $\epsilon = 0.02$, $\sigma^3 = 26.865$; C: $\epsilon = 0.054$, $\sigma^3 = 64$; F: $\epsilon = 0.054$, $\sigma^3 = 54$; Cl: $\epsilon = 0.054$, $\sigma^3 = 74$; Br: $\epsilon = 0.054$, $\sigma^3 = 84$; O: $\epsilon = 0.054$, $\sigma^3 = 64$.

3. Results and discussion

A principle obstacle for all-atomic simulations is the different time scale of the intermolecular motions and of the macroscopic flow processes. Molecular bonds, for example, undergo many oscillations before a molecule changes noticeably its position in the liquid phase. However, the coupling between the translational and vibrational motions is very weak. Therefore we suppose that the flow speed can be increased to a higher value than is common in a laboratory. Although higher flow speed might influence the overall efficiency, it cannot be avoided for simulation in real time. On the other hand, as the average translation speed of the solution is still much smaller than the molecular motions, principal interactions between the solute and the stationary phase are not perturbed during the MD simulation.

Particularly, the flow velocity of 33 m/s was used for the simulation recorded in the left hand part of Fig. 2. This velocity is bigger than in usual HPLC experiments, but still much smaller than flows achieved in the gas chromatography [9]. Then a sufficient flow path (9 μm) could be simulated in a reasonable real time. About seven weeks of CPU time (1 AMD 64 bit 2.5 GHz processor) were needed for the simulations. Dependence of the enantiomeric excess ($N_{\text{R}} - N_{\text{S}}$) on the path exhibited longer-path (longer-time) oscillations and simulations for shorter paths were not reliable. For the path of 9 μm , however, we clearly see that the enantiomeric separation does happen and that the separation efficiency given by an average slope of the dependence can be estimated. The simulation with the flow velocity of 3 m/s displayed at the right hand side of Fig. 2 could be done for shorter distances only. However, it clearly exhibits similar characteristics to the dependence obtained with the higher speed. Particularly, the *R* and *S* enantiomers start to separate. The right hand part of Fig. 2 also indicates that the separation with the lower flow might be more efficient, in agreement with the experimental experience, although this could not be verified for longer times.

Given the decisive role of the solvent in the HPLC chromatography [10] it is pleasant to see that the modeling is extremely sensitive to the solvent properties, too. This can be documented in Fig. 3 where the previous simulation is compared to the dependence obtained for non-polar

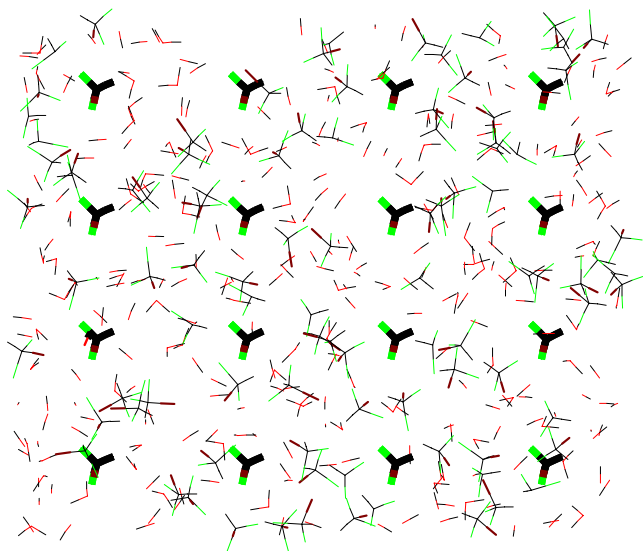


Fig. 1. The model system consisting of a solid phase (thick, 64 *R*-CHFCIBr molecules), solvent (429 H_2O), 48 *R*- and 48 *S*-CHFCIBr solute molecules. Periodic boundary conditions were imposed for a $3.6 \times 3.6 \times 3.0$ nm box.

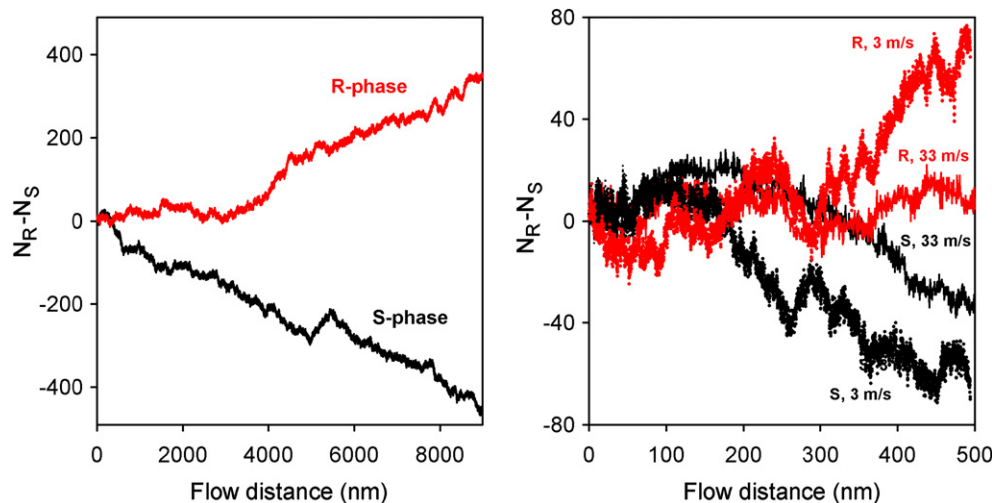


Fig. 2. Left: The simulated chiral separation for the system from Fig. 1. The separation is given as the difference of the number of the *S*- and *R*-CHFCIBr molecules passed through the column. At the flow distance of 9000 nm, a total of 350 000 *S*- and *R*-enantiomers passed. The speed of the solvent was 33 m/s. Right: Comparison of initial stages of the separation for solvent speeds of 3 and 33 m/s.

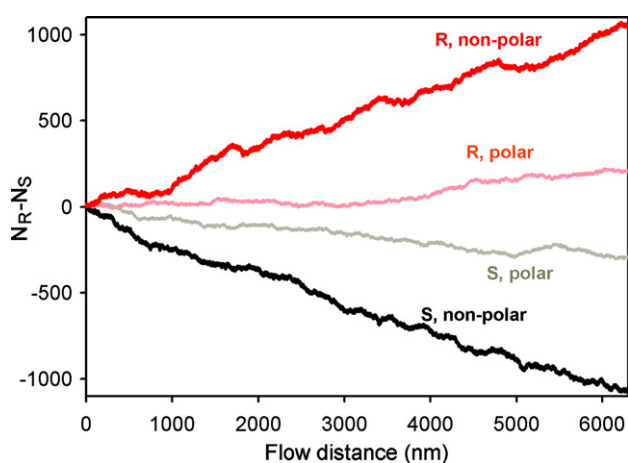


Fig. 3. Comparison of the chiral flows of the system displayed in Fig. 1 for polar (water) and non-polar solvent. The non-polar medium was modeled also by water, with all-atomic partial charges set to zero.

‘water’ where the atomic partial charges were set to zero. This model enabled us to perform the simulation in a reasonable time and estimate the role of the solvent polarity on the separation. Clearly, the separation efficiency increases about four-times; otherwise general characteristics, such as the longer-path oscillations, remain the same.

Finally, in Fig. 4, we can look at the influence of the temperature on the simulated chromatographic process. As expected, the coldest temperature (300 K) provides the most efficient separation, as the interaction between the solute and the chiral stationary phase is least disturbed. The highest temperature (400 K) probably leads to the poorest separation. However, for 400 K, rather large fluctuations of the separation curve from a linear dependence appear. Still, we can estimate that the separation rate is roughly proportional to the temperature within the investigated range. This is true also for the total achiral flow (bot-

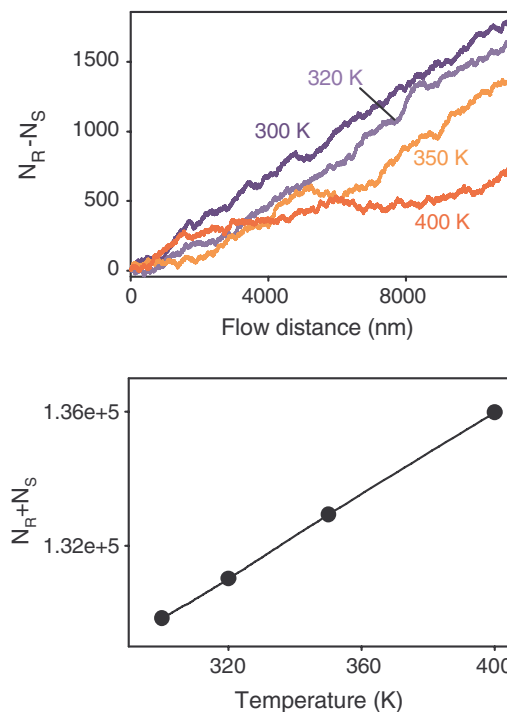


Fig. 4. (Top) chiral flows simulated for four different temperatures, and (bottom) the dependence of the total (non-chiral) flow at 5000 nm on the temperature.

tom part of Fig. 4) that nearly linearly increases with the temperature, in agreement with the experimental experience [10]. The simulation predicts that the flow of the *R*-enantiomer is by about 1% faster than for the *S*-form on the *R*-stationary phase. Thus such a separation would be possible on common HPLC columns [1]. For example, with a 15 cm column 1.5 mm retardation would be achieved.

Regarding future prospects of the HPLC simulations, they seem to be limited by the system size and short

simulation time, similarly as other usual MD tasks. Methodically, nothing hinders a more realistic modeling of the solvent, solute, and the stationary phase geometries. In the near future, however, we expect that the modeling can provide rather basic chromatographic characteristics than rationally-designed stationary phases, for example. The limited force field quality, which is also common for all MM and MD studies, might be another bottleneck in a wider application of the method. On the other hand, the unique ability of MD to simulate and statistically sample long-time processes in a realistic environment (concentration, temperature, pressure) makes it potentially highly suitable also for computational models of the transport processes, including the chromatography.

4. Conclusions

The all-atomic molecular dynamics technique was used for the first time for the modeling of the chiral chromatographic processes. Several characteristics observed in common experiments were thus obtained. Since rather extensive computer time was required for the simulation of the macroscopic flow processes including HPLC, a simplified model system and an arbitrary flow speed were adopted. For the fast flows and the CHFCIBr model the chiral separation could be modeled and detected by the MD technique in reasonable real times. Moreover, the roles of the flow speed, solvent polarity and the temperature during the separation process could be simulated.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.cplett.2007.12.015](https://doi.org/10.1016/j.cplett.2007.12.015).

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