

Molecular simulation study of the bonded-phase structure in reversed-phase liquid chromatography with neat aqueous solvent

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Abstract

The dramatic loss of retention in reversed-phase liquid chromatography when switching to 100% aqueous solvent and stopping flow (depressurizing) has long intrigued separation scientists. Recent experimental evidence suggests that the observed loss of retention is due to the loss of pore wetting with subsequent loss of solvent penetration in the porous matrix. One of the prevalent explanations of this phenomenon has been that the bonded phase chains, typically octadecyl silane bound to porous silica, would undergo significant conformational changes, viz. collapse, under pure aqueous conditions. As a definitive means toward elucidating the conformation of bonded-phase chains under pure aqueous conditions, configurational-bias Monte Carlo simulations in the Gibbs ensemble were carried out for a system of dimethyl octadecyl silane of intermediate coverage bound to the (1 1 1) face of β -cristobalite and immersed in pure water. The results of two sets of simulations, which were started from two entirely different starting configurations as a validity check toward reaching the same equilibrium distribution of states, show that chains are neither clustering together nor laying on the surface but rather have a broad distribution of orientations and of conformational states. The interface between the bonded and solvent phases is rough on a molecular level, and clusters of water molecules are sometimes found to adsorb at the silica surface. This computational study lends further evidence that the driving force for the loss of retention when switching to pure aqueous conditions and depressurizing is not the collapse of bonded-phase chains.

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1. Introduction

Csaba Horváth, a pioneer of high performance liquid chromatography (HPLC), contributed many important insights into the mechanism of reversed-phase liquid chromatography (RPLC) [1,2]. In RPLC the solvent is typically a water/methanol or water/acetonitrile mixture and the retentive (stationary) phase is a hydrophobically-modified surface of silica. Horváth published many papers on the theory of RPLC, most notably the solvophobic theory of RPLC [3–6], in which various experimental parameters were utilized to construct a thermodynamic theory of the driving force for retention. This work built upon Oktay Sinanoğlu's "solvophobic theory" of liquids [7]. Horváth's papers were beautifully con-

structed and offered chromatographic guidance through the shear choice of parameters. Unfortunately, liquid-state theories that aim to provide quantitative properties, are often too complex to be useful [8,9]. However, the solvophobic theory of Horváth and coworkers stood for many years as the most successful, if not the most recognized theory of RPLC.

One problem in RPLC that Horváth and coworkers did not appear to explain, is the loss of retention when changing the experimental conditions from solvent mixtures with organic modifiers to pure aqueous conditions when columns are depressurized. The problem has been known for a number of years [10–14] but thought to originate with a "chain collapse" mechanism [15], whereby the bonded-phase chains would loose their open (swollen) structure and simply coat the surface. Only very recently has the thermodynamic origin of this retention loss been described as a wettability problem where the solvent does not enter the porous particle structure because the contact angle and surface energy do not allow

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penetration at a certain pressure [16]. Similar situations are widely recognized in colloid and surface chemistry [17,18] as they constitute one of the most basic aspects of capillarity [19]. The evidence for the loss of retention based on the loss of pore wetting and subsequent loss of solvent penetration in pores is rather convincing [12,14] when pore size and pressure are included as experimental variables. However, the “chain collapse” mechanism [10,11,13] where chain conformations such as clustering or chains laying on the surface were thought to be the origin of retention loss have not been proven or disproven by spectroscopic means. Hence it remains part of the folklore of chromatographic research.

The most common ideas about the mechanism of RPLC have come from retention measurements and spectroscopic experiments [20] yet these offer only limited insight into the mechanism for a number of reasons. First, retention measurements are purely thermodynamic, and macroscopic thermodynamics is not capable of pinning down molecular driving forces but rather only functions as a bookkeeping system. Second, spectroscopic measurements appear to be excellent at giving structural details of various parts of this problem, for example, elucidating *trans/gauche* ratios at various chain positions via infrared [21] and Raman spectrometry [22], however, these signals are necessarily averaged over many chains and do not offer individual chain detail.

With the development of advanced computational methodologies and accurate force fields [23–25], particle-based simulations have become a valuable tool for studying chromatographic separation processes [26–37]. Since in molecular simulations, the specific location (using a classical description of phase space) of each atom is known throughout the simulation, and the surface area and coverage are controllable, microscopic insight into structural details can be gained directly through the analysis of the configurations produced from simulation. This allows the direct analysis of structures and the distribution of positions for chains, solvent molecules, and solute when present.

In this paper, we will discuss the results of a Monte Carlo simulation study of a dimethyl octadecyl/silica model system in a pure water environment. In addition, we will present simulation data for an isolated *n*-octadecane chain in either neat water or neat methanol. The aim of this work is to show that there is no significant collapse of medium-length alkyl chains due to a pure water environment. Thereby, offering molecular-level evidence that leads away from the chain collapse mechanism as an explanation for the retention loss in RPLC with pure aqueous solvent.

2. Molecular models

For the investigation of the structural properties of an RPLC stationary phase in contact with a pure water solvent, the following model system is utilized. The simulated system consists of three separate simulation boxes that are in thermodynamic contact but do not share a direct physical interface.

The first simulation box contains the stationary phase and is elongated along the *z*-axis (see Fig. 1), the second and third boxes contain pure liquid water and a helium vapor, respectively. The dimensions of the first box were fixed throughout the simulations at the following values: 20, 26, and 90 Å for the *x*-, *y*-, and *z*-axis, respectively. As is customary in molecular simulations, the simulation boxes are surrounded by periodic replicas in all three directions, i.e. the simulation box is the “unit” cell of an infinitely replicated system [23–25]. A five-layer slab of β -cristobalite silica with exposed (1 1 1) surfaces parallel to the *x*–*y* plane of the simulation box represents the solid support material [38]. A previous study [38] has shown that bonded phase surface coverages predicted using the (1 1 1) β -cristobalite surface gave very good agreement with experiment. However, the agreement was poor using random silica surface models or the (1 0 0) face of β -cristobalite. The initial surface density of dangling hydroxyl groups on this substrate is approximately 4.6 vicinal silanol groups per nm² (7.6 $\mu\text{mol}/\text{m}^2$). The bonded phase consists of dimethyl octadecyl silanols (C₁₈ chains) that are bound randomly (with no chain overlap in the starting geometry) to both surfaces of the silica slab. There are nine chains bound to each of the cristobalite surface, i.e. the coverage is about 1.8 C₁₈ chains per nm² (2.9 $\mu\text{mol}/\text{m}^2$) which is an intermediate value for typical RPLC systems. The second box contains initially about 1300 water molecules and acts as a reservoir that can provide a suitable number of water molecules (as dictated by the thermodynamic requirement of equal chemical potential) for the stationary phase box. The third box functions as a transfer medium and contains a vapor consisting of 30 helium atoms. The second and third boxes are in contact with a pressure reservoir, i.e. their volume is allowed to fluctuate throughout the simulation (see below).

For the model RPLC system, the united-atom version of the Transferable Potentials for Phase Equilibria (TraPPE-UA) force field [39–42] was used to model the bonded phase, the dangling vicinal silanol groups, and helium, while the TIP4P model [43] and a zeolite force field [44,45] were used for water and silica, respectively. The TraPPE-UA model utilizes pseudo-atoms located at the carbon positions to represent entire methyl or methylene groups, thereby reducing the number of interaction sites and computer time needed to simulate the system. A spherical potential truncation at a distance of 10 Å is employed throughout the simulations with analytical tail corrections for Lennard–Jones interactions (accounting for repulsive and dispersive interactions) and an Ewald summation technique, with $\kappa \times L = 5$, $K_{\text{max}} = 5$ and tin-foil boundary conditions is used in the calculation of long-range electrostatic interactions [23].

For the investigation of the chain conformation of an isolated *n*-octadecane molecule in pure solvent environments, a single simulation box is utilized. In addition to a single *n*-octadecane molecule, this box contains either 900 water or 900 methanol molecules, i.e. the number of solvent molecules is sufficient that the two ends of the C₁₈ do not affect each other (through the periodic boundaries) but is well below the

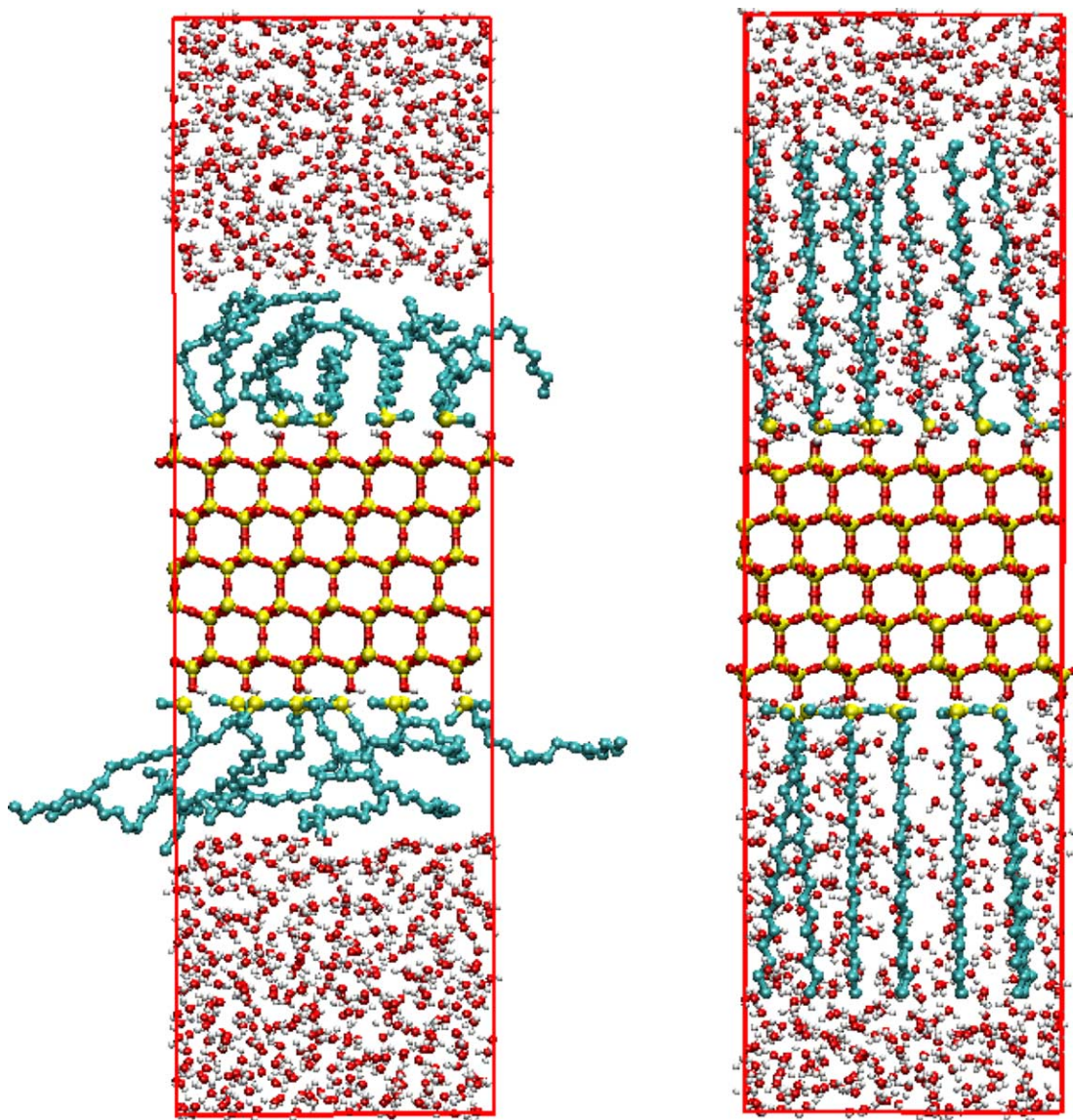


Fig. 1. The side view (y - z plane) of the two starting structures after the water insertion step. Left: the EQ starting geometry where the chains are pre-equilibrated in vacuum. Right: the AT starting structure where the chains are solvated in the all-trans geometry.

actual number of solvent molecules required to reach the extremely low solubility limit of such a long alkane in water or methanol. Again, the volume of this box is allowed to fluctuate in contact with a pressure reservoir. The TraPPE-UA force field [39–42] is used for the alkane chain and the methanol solvent and the TIP4P model [43] is used for water. As for the RPLC system, tail corrections and Ewald summation are employed but a longer cut-off distance at 14 Å is used.

3. Simulation details

A combination of the configurational-bias Monte Carlo (CBMC) algorithm [40,46,47] and the constant-pressure Gibbs ensemble Monte Carlo (GEMC) method [48–50] was used here to investigate the model RPLC system. The GEMC

technique allows for the simulation of multiple phases in thermodynamic contact, each in its individual, periodically replicated simulation box without an explicit physical interface. Volume moves are performed separately for each phase to reach mechanical equilibrium with an external pressure bath (but not for the simulation box that contains the stationary phase because the solid silica support is considered to be rigid). CBMC particle transfer moves are used to equilibrate the chemical potentials of the aqueous solvent species between the three phases. The third box containing the helium vapor phase is used because the sampling efficiency of indirect liquid \rightarrow vapor \rightarrow liquid particle transfer moves is significantly greater than that of direct liquid \rightarrow liquid transfer moves [37,51].

The simulations for the solvated n -octadecane chain were carried out in the isobaric–isothermal ensemble [52]. The

conformational degrees of freedom of the alkane chain were sampled using a combination of coupled-decoupled CBMC moves [40] (to re-grow parts of the chain including one chain end) and self-adapting fixed-endpoint CBMC moves [53] (to re-grow interior segments of the chain).

The simulations for the RPLC system and the solvated *n*-octadecane chain were both carried out at a temperature of 323.15 K, but an external pressure of 0.1015 MPa was used for the RPLC system while a slightly elevated pressure of 1.015 MPa was used for the solvated *n*-octadecane chain. For each of the two RPLC set-up protocols (see below), two independent simulations were carried out, while four independent simulations were used for the solvated *n*-octadecane chain. Statistical uncertainties were estimated from the results of the independent simulations. Finally, the lengths of the simulations are measured by the number of Monte Carlo (MC) cycles (one MC cycle equals *N* moves, where *N* is the total number of particles in the system).

4. Set-up protocol

In previous molecular dynamics simulations of model RPLC systems, two main protocols for the chain/solvent equilibration were followed and lead to results with rather different final structures. These include the simulations by Klatte and Beck et al. [29] where the bonded phase was first sampled in vacuum followed by solvent addition once equilibrium was thought to be established for the chain part. In the study by Klatte and Beck, the chains were found to “collapse” on the flat substrate (no explicit silica structure with dangling hydroxyl groups was utilized) and the solvent did not enter the chain structure. In an earlier simulation study by Schure [27], the chains were started in the all-trans conformation and solvent was added to all solvent accessible regions prior to chain equilibration. Chains were found to possess a wide range of conformational diversity which was determined by surface coverage: single chains bound to silica did not sit flat but were not found in extended positions under considerable methanol solvent content. Pure water was not run in these simulations. Only for a system with a single chain bound to silica without solvent, the chain was found to adsorb to the silica surface. Both of these studies used the molecular dynamics (MD) simulation technique where the hard degrees of freedom (e.g., vibrational modes) and the mean collision time limit the finite time step that can be used for the integration of the equations of motion. Thus, since model RPLC systems are rather complex with thousands to millions of pair interactions, these MD simulations were limited to a total run length of less than 10 ns which might not be a sufficient amount of time to sample equilibrium structures of solvated long chain molecules or the spatial distribution in mixed solvents.

In the work described here, the Monte Carlo technique is used that allows for specific moves that can efficiently sample types of motion that are characterized by separate physical

time scales [23–25]. To avoid the problems encountered in the previous studies where the outcomes appear to be biased by the starting structures and whether or not the chains are pre-equilibrated in vacuum prior to addition of solvent molecules, the present work employs two different set-up protocols that try to mimic the earlier MD simulations. Thus, an important validation test for the present simulations is to demonstrate that equivalent structures are reached after equilibration.

As a first step, the dimethyl octadecyl silanol chains are randomly chemisorbed to the substrate, i.e. a dangling surface silanol group is picked at random and if an all-trans C₁₈-chain can be placed at this position without steric overlap with any previously placed C₁₈-chain, then the chemisorption placement is accepted. This process is continued until the desired surface coverage is reached (nine chains per surface in the present work). This random chemisorption procedure implies that the relative spacing of the C₁₈-chains on the two surfaces present in the simulation box can be different and that therefore the properties of the two surfaces do not need to be identical.

Starting from a set of randomly chemisorbed C₁₈-chains, the first simulation protocol, denoted as EQ (for “equilibrated”) in the following discussion, allows the bonded phase to equilibrate the chain conformations in vacuum. This initial equilibration process yields a rather disordered chain structure that is characterized by a large number of conformational defects, significant tilt of the chain long axis, and an average distance of the terminal methyl group from the substrate of about 10 Å. Once equilibration of the chain in vacuum has been achieved, the chain structure is “frozen” and a slab of liquid water is placed between the two C₁₈-covered surfaces (to avoid the need to overcome a nucleation barrier in the narrow pore). Thereafter, the water layer in the RPLC box is brought into thermodynamic contact with the reservoir (through particle transfer moves). The starting protocol EQ is complete, once the average number of water molecules in the RPLC box has stabilized. From then on, all moves described in the previous section are used to sample the configurational space of the RPLC system.

The second starting protocol proceeds as follows. Immediately following the initial placement of the randomly chemisorbed molecules, a slab of liquid water is added and allowed to equilibrate with the water reservoir, i.e. water is added while the chains remain frozen in their original all-trans starting conformation. This method is referred to as AT (“all trans”). Again, the starting protocol is complete, once the average number of water molecules in the RPLC box has stabilized.

The resulting starting geometries for protocols EQ and AT are shown in Fig. 1. It is clearly evident that chains in the all-trans conformation allow for ample interchain spacing that is filled up with water molecules, whereas pre-equilibration in vacuum has resulted in a disordered, but densely packed chain region that is very unfavorable toward water penetration.

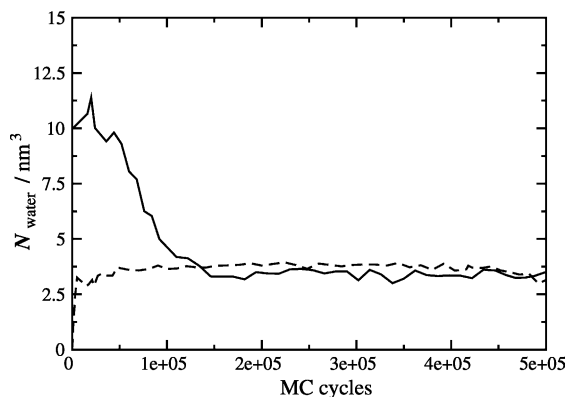


Fig. 2. The evolution of the number density of water molecules within 5 Å from the substrate (averaged over intervals of 10^4 MC cycles) as a function of the number of MC cycles. Solid and dashed lines depict the results averaged for the simulations starting from protocols AT and EQ, respectively.

5. Results and discussion

5.1. Equilibration of model RPLC system

Figs. 2 and 3 depict the evolution of the number density of water molecules near the silica substrate and of the height of the terminal methyl group of the C_{18} -chains above the substrate. These are two of the properties that were used to monitor whether the simulations with the two different set-up protocols equilibrate and reach configurations with similar properties. As should be expected, substrate-bound water is initially absent from the simulations using protocol EQ. As these simulations proceed, some water molecules quickly migrate to the substrate and form hydrogen bonds with dangling silanol groups (the migration is greatly facilitated by special CBMC moves that allow the water molecules to “jump” directly to surface-bound sites instead of having to follow a slow diffusion process through the nonpolar bonded phase). In the case of the AT set-up protocol, the initial surface water density is high because the chains in their all-trans confor-

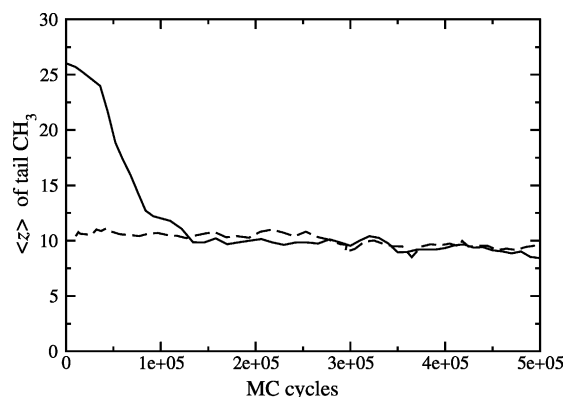


Fig. 3. The evolution of the position of the terminal methyl group (averaged over intervals of 10^4 MC cycles) as a function of the number of MC cycles. The distance of the tail methyl group from the substrate. Solid and dashed lines depict the results averaged for the simulations starting from protocols AT and EQ, respectively.

mation do not cover the substrate very well and leave many exposed silanol groups. As the AT simulations proceed, the chains become more disordered and water is expelled from the substrate and from between the chains.

The different approaches to equilibration taken by the EQ and AT simulations are also evident from the height of the terminal methyl group (see Fig. 3). The terminal groups of the all-trans chains extend to about 26 Å above the substrate, whereas the large degree of conformational disorder and chain tilt leads to a height of only about 11 Å for the chains initially equilibrated in vacuum. During the full equilibration process, disordered chain conformations and large chain tilts are also realized for the simulations started with protocol AT. In contrast, the height of the terminal methyl group does not change much for runs EQ. The fact that the simulations started from either protocol AT or EQ converge after about 1.5×10^5 MC cycles to very similar substrate water densities and terminal methyl heights despite their rather different trajectories, clearly demonstrates that the efficient MC techniques used here facilitate the study of fully equilibrated RPLC systems.

5.2. Chain conformation and water penetration in model RPLC system

Snapshots of the configurations taken after 5×10^5 MC cycles for two simulations using the EQ and AT set-up protocols are compared in Fig. 4. In both cases, the most striking feature is the large degree of conformational disorder for the bonded phase, i.e. large fraction of gauche defects and large non-uniform chain tilt. This leads to a chain/water surface that is relatively rough on a molecular level, and to hydrogen-bonded “threads” of water molecules that can extend into the bonded-phase (see left side of the lower surface of run EQ in Fig. 4). Also in both cases it is seen that a few water molecules are present near the silica substrate. Further analysis shows that the surface-bound water molecules often exist in clusters with two to four molecules, i.e. a cooperative effect makes substrate regions where already one or two water molecules are located more attractive for additional water molecules because these additional water molecules cannot only form hydrogen bonds with dangling silanol groups but also with other substrate bound water molecules. Nevertheless, throughout these simulations we did not observe a complete “thread of water” extending from the mobile phase to the substrate as has been previously hypothesized [12].

Fig. 5 shows the water and carbon number density profiles along the z -axis (i.e. perpendicular to the (1 1 1) face of the supporting cristobalite substrate). These profiles were averaged over the last 2×10^5 MC cycles of the runs. Note that the silica layers are found in the middle of the simulation box here. Hence, the small spikes in water density toward the middle of the figure represent water molecules that are either directly hydrogen-bonded to the substrate or are part of small clusters of water molecules. This is followed by a z -range of about 7 Å where the water density is very low because the

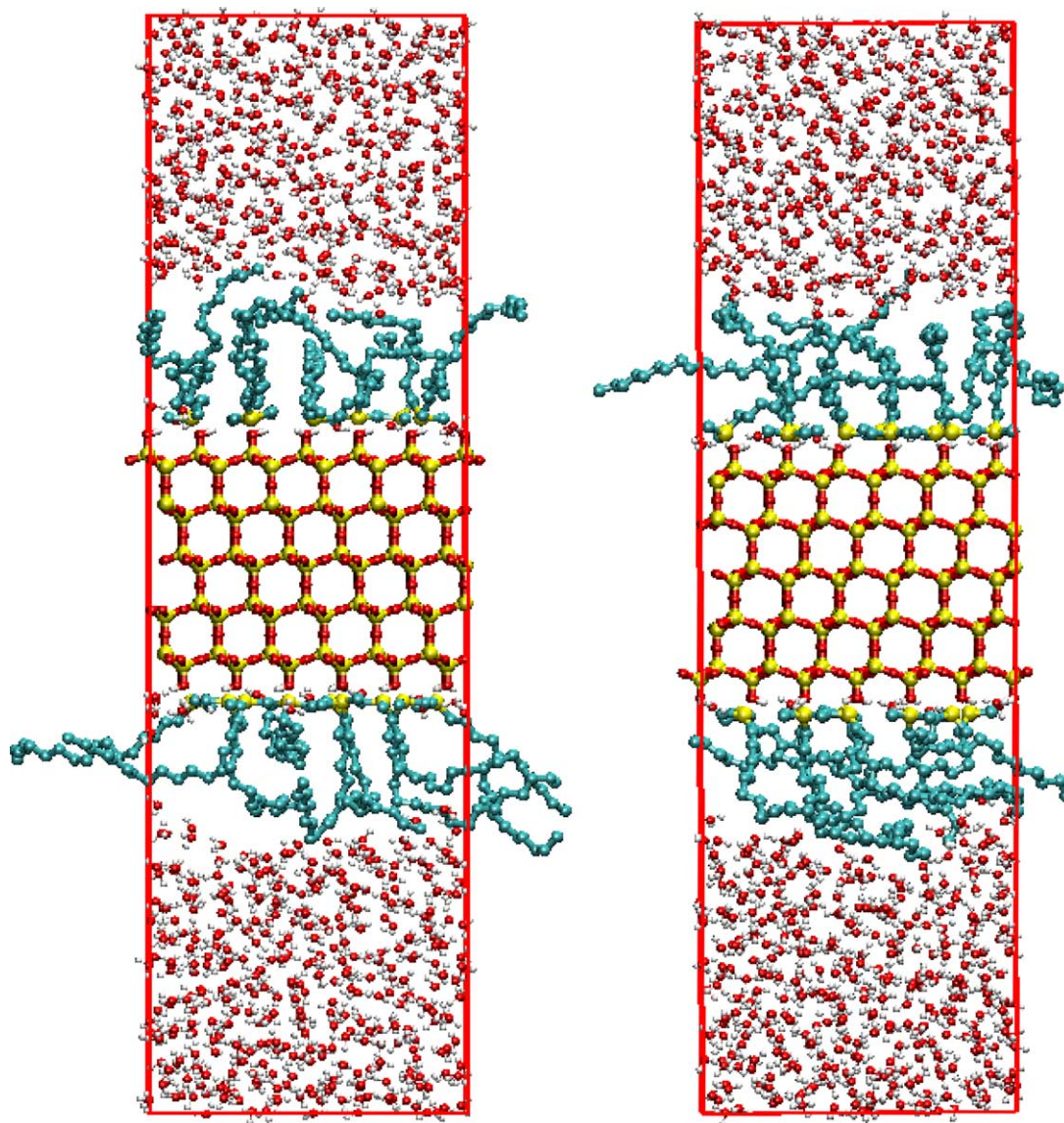


Fig. 4. The side view (y - z plane) of two simulations after 5×10^5 MC cycles. Left: a structure resulting from the EQ starting geometry. Right: a structure resulting from the AT starting geometry.

core of the nonpolar C_{18} phase is a region of unfavorable free energy for water molecules compared to either the mobile phase or the substrate region that both provide ample opportunity for the formation of hydrogen bonds. Following upon the core region of the bonded phase, the water density raises sharply over a span of about 5 \AA and reaches its bulk value. Complementary to the density trend observed for water, the carbon density of the chemisorbed C_{18} -chains is more localized to the surface region. The first peak of the carbon density near the substrate is due to the two methyl groups bound to the base silanol. The subsequent peaks in the carbon density are typical for relatively densely packed chains near a flat substrate with the peak spacing of about 5 \AA reflecting the preferred backbone spacing for linear alkanes [54,55]. To achieve the dense packing requires large chain tilts and the incorporation of many gauche defects in the chain conforma-

tions. These defects have also been detected from infrared [21] and Raman [22] spectrometry. Finally, an important feature of the RPLC structure is that the total number density is depleted at the mobile phase/stationary phase interface, i.e. at the point where the carbon and water oxygen number densities cross, their total density is only about 24 atoms/nm^3 or about 25% below the respective bulk values. This is a microscopic consequence of this type of hydrophobic surface/water interface that would show no wetting on a macroscopic scale.

5.3. Conformation of solvated n -octadecane chain

The evolution of the end-to-end length of an n -octadecane chain solvated in either water or methanol is shown in Fig. 6. As can be seen rather clearly, most of the time the chain undergoes only relatively small fluctuations around a predom-

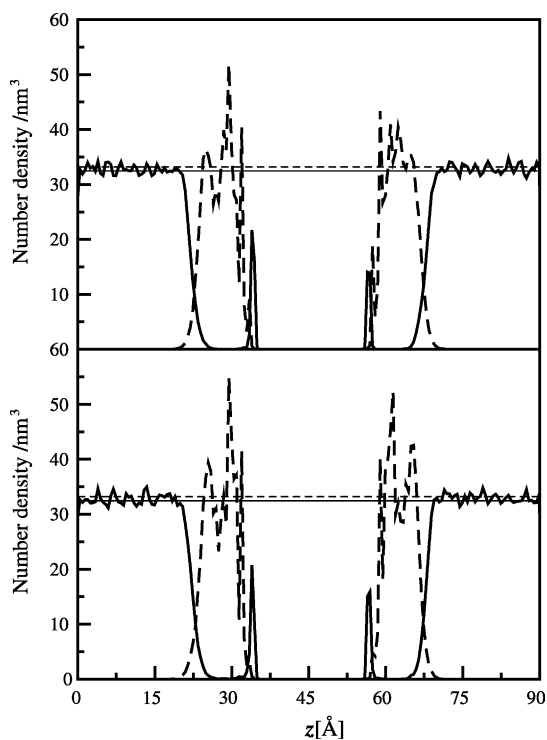


Fig. 5. Average density profiles resulting from the simulations using protocol EQ (top) and AT (bottom). The water oxygen and carbon number densities of the stationary phase are depicted as thick solid and dashed lines, respectively. For comparison, the number densities corresponding to bulk water and *n*-octadecane at $T = 323$ K are shown as thin horizontal lines.

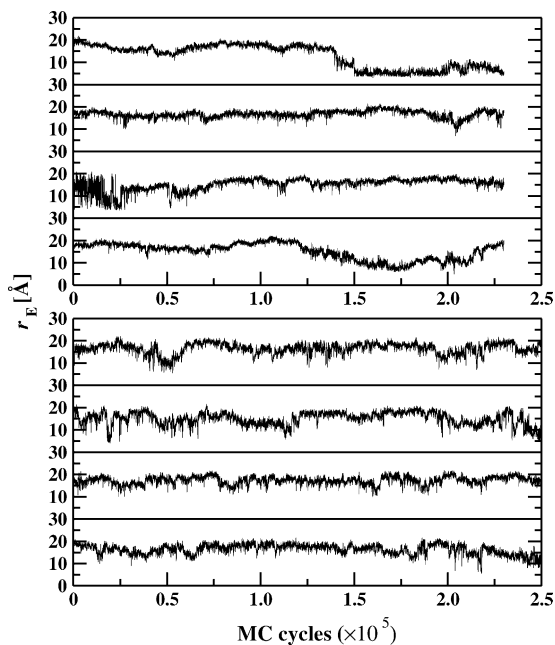


Fig. 6. Evolution of the end-to-end lengths of a single *n*-octadecane chain solvated in neat water (top) and neat methanol (bottom) vs. the number of MC cycles. The data are shown for four independent simulations for each solvent.

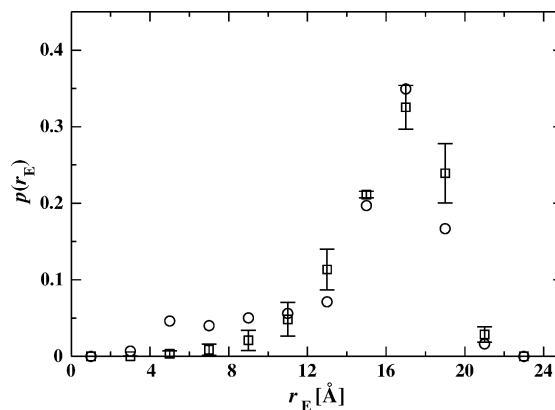


Fig. 7. Distribution of the root mean square end-to-end lengths of a single *n*-octadecane chain solvated in neat water (circles) and neat methanol (squares). For clarity, the error bars are only shown for the chain solvated in methanol.

inantly extended conformation with an end-to-end length of about 17 Å, but occasionally a relatively rapid transition to conformational states with significantly shorter end-to-end distance are observed. Recent molecular dynamics simulations of solvated *n*-cosane chains showed qualitatively similar behavior characterized by relatively infrequent transitions between a coiled and an extended state [56].

The probability distributions of the end-to-end distances of the solvated *n*-octadecane chains averaged over four independent simulations are depicted in Fig. 7. Whereas the chain solvated in water shows a bimodal distribution with the maximum at about 17 Å and a minor peak at about 6 Å, the distribution for the chain solvated in methanol is unimodal with a peak around 17 Å, albeit this peak is strongly asymmetric with a very extended tail toward shorter distances. For both cases, only about 3% of the chains are found in fully extended all-trans conformations (corresponding to an end-to-end length of about 22 Å). The minor peak for the water-solvated chain corresponds to a coiled conformation where the two methyl groups approach each other closely and are not separated by even one solvent molecule.

The fraction of gauche defects along the chain backbone are compared in Fig. 8. Most evident is that the water-solvated *n*-octadecane chain contains a significantly larger number of gauche defects than the methanol-solvated chain. Averaged over the entire backbone, the former contains about 33% gauche defects, while the latter contains only about 28%. For both solvent media, a significantly larger fraction of gauche defects is observed for the terminal dihedral angle. A striking (albeit given the statistical uncertainties maybe not significant) difference is that the distribution for the water-solvated chain shows a slight increase of gauche defects toward its center, whereas the smallest fraction of gauche defects is observed for the dihedral angles close to the center of the methanol solvated chain. A possible origin for this difference might be that to reach the coiled conformations of the water-solvated chain with the two methyl groups in close contact, requires gauche defects at the center so that the chain can fold back on itself.

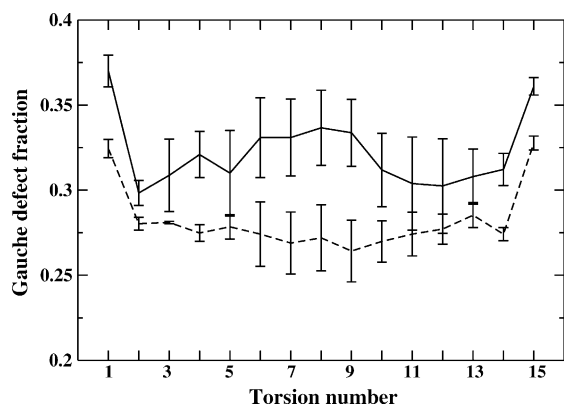


Fig. 8. Fraction of gauche defects as function of dihedral angle for a single *n*-octadecane chain solvated in neat water (solid line) and neat methanol (dashed line).

6. Conclusions

There are a number of aspects which can be learned from these simulations. First, under pure water conditions (and also in vacuum), the C_{18} -chains of the model RPLC system at intermediate surface coverage of $2.9 \mu\text{mol}/\text{m}^2$ are partially collapsed and highly disordered with a large number of gauche defects and a large non-uniform backbone tilt. The chain/water interface shows significant roughness and a substantial density depletion on the molecular scale. The roughness of this interface is not surprising and is probably good from a viewpoint of adding some shape selectivity to the retention process. However, even though the phase is noted to be in a partially collapsed state, it is the lack of water penetration at the outer part of the bonded-chain region that drives wetting phenomena and macroscopically limits the fluid from entering pores of a certain size at a certain pressure. The chain conformation appears not to be the limiting phenomena which reduces the available retentive surface area when solvent mixtures are switched to pure water and when pressure is reduced. It is noticed that a significant amount of water is adsorbed on the silica surface where unprotected surface silanols are available for hydrogen bonding. However, the water concentration in the core region of the bonded phase is very low. Again, for water it is energetically more favorable to form hydrogen bonds and either self-associate or bond to dangling silanols than to stick out into or be isolated in the hydrophobic region.

Simulations of an isolated *n*-octadecane chain solvated in either water or methanol show statistically significant, but not dramatic differences in the chain conformation. For example, the water-solvated chain contains slightly more gauche defects and shows a somewhat bimodal distribution of end-to-end distances with about 10% of the chains being highly coiled with an end-to-end distance of less than 10 \AA . However, the location and shape of the main peak at about 17 \AA are very similar for both the water- and methanol-solvated chains. Overall, the differences are small which

should not be surprising because *n*-octadecane is insoluble in both pure water and in pure methanol under the temperatures and pressures commonly used in RPLC separations. Hence, there is probably little difference between the bonded-phase conformation of RPLC systems in pure water and pure methanol. A more important factor in determining chain conformation is the chain surface concentration. The chain excluded volume drives the chains up away from the surface at higher concentrations and this phenomena has been noted in a number of studies of surface-bonded polymers. Further simulations in particular of model RPLC systems in methanol or mixed aqueous environments would enhance our understanding of this delicate surface region and close the gaps of our knowledge regarding other mysteries of RPLC.

Acknowledgements

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