Letter

Calculating Gibbs free energies of transfer from Gibbs ensemble Monte Carlo simulations

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Abstract. The partitioning of the ternary systems *n*-pentane/*n*-heptane/(helium or argon) at ambient conditions is investigated using configurational-bias Monte Carlo simulations in the Gibbs ensemble. The results demonstrate that this approach yields very precise partition constants and free energies of transfer. Simulations are carried out to study the dependence of the *n*-pentane partitioning with respect to the carrier gas, the system size, and the overall solute concentrations. None of the changes of variables, within the ranges used here, has a significant effect on the alkane partitioning. However, chemical potentials calculated via Widom's ghost particle insertions show a strong number dependence for phases containing relatively few molecules of a given type. This problem originates from the fact that the chemical potential is calculated for a concentration of real particles plus one ghost particle that is systematically larger than the equilibrium concentration. A simple correction term is suggested to account for this problem.

Key words: Alkane-vapor partitioning – Phase equilibria – Free energies

1 Introduction

Over the last 10 years, the Gibbs ensemble Monte Carlo (GEMC) method developed by Panagiotopoulos et al. [1, 2] has been established as the premier tool for the efficient calculations of fluid phase equilibria of single and multi-component systems [3–5]. Thus far, GEMC has been mainly used to determine coexistence curves. However, here we would like to promote its use as an efficient tool for the calculation of Gibbs free energies of transfer [5]. The reliable calculation of Gibbs free energies of transfer, which govern many biological and chemical processes, is one of the most challenging problems for computational chemistry [6]. Thermodynamic integration and free energy perturbation are the traditional routes to obtain Gibbs free energies of transfer from molecular simulations [7–10] (see also Ref. [11] for a very instructive comparison of the different methods for free energy calculations). Both require the construction of a thermodynamical cycle and multiple simulations. In contrast, partition constants and their corresponding free energies of transfer can be obtained directly from a single GEMC simulation.

The goals of this work are to establish GEMC as an efficient and reliable method for the calculation of free energies and to investigate the influence of carrier gas, system size, and solute concentration on the calculated free energies.

2 Simulation details

All simulations were performed using the isobaric version of the Gibbs ensemble [2] at a temperature of 298.15 K and a pressure of 101.3 kPa. The Gibbs ensemble utilizes two (or more) simulation boxes with periodic boundary conditions that are in thermodynamic contact, but do not have a common interface. If the combined system has a composition and density within the two-phase region, then the system will spontaneously phase separate utilizing the two simulation boxes. The following types of moves are employed during our GEMC simulations: volume exchanges with the external pressure bath, molecule swaps between the two boxes, rigid-molecule translations, rigid-molecule rotations, and conformational changes. The configurational-bias Monte Carlo (CBMC) technique [12, 13] with multiple first-bead insertion [14, 15] is employed for molecule-swap and conformational-change moves.

The united-atom TraPPE force field [16] is used to describe all molecular interactions of the alkanes and rare gases. Lennard-Jones 12–6 potentials are used for non-bonded interactions between pseudo-atoms, and the Lennard-Jones parameters are listed in Table 1. Unlike interactions are computed using the Lorentz-Berthelot combining rules $(\sigma_{ij} = (\sigma_{ii} + \sigma_{jj})/2$ and $\epsilon_{ij} = (\epsilon_{ii}\epsilon_{jj})^{1/2})$.

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A spherical potential truncation at 14 Å and analytical tail corrections are used for the Lennard-Jones interactions. To improve efficiency of the potential energy calculations, an additional center-of-mass based truncation [16] is utilized for all types of Monte Carlo moves, and multiple cut-offs are employed for CBMC moves [17]. Alkane pseudo-atoms are connected by bonds with a fixed length of 1.54 Å, C–C–C bond bending is governed by a harmonic potential with a force constant of $k_{bend}/k_B = 62,500$ K rad^2 [18], and torsional motions are controlled by the OPLS united-atom torsional potential [19].

Four ternary systems containing n-pentane as the solute (minor component), n-heptane as the liquid solvent, and helium or argon as the carrier gas, were studied in this work. The systems differ with respect to carrier gas, system size, and solute concentration (Table 2). All systems were equilibrated for at least 50,000 Monte Carlo cycles (one cycle consists of N randomly selected moves) and the results were computed from production periods of 100,000 cycles for the smaller systems and of 25,000 cycles for the larger systems; 1,000 cycles require 75 and 530 minutes of CPU time on an Intel Pentium II. Statistical uncertainties were calculated by breaking the production periods into five blocks.

The Gibbs free energies of transfer from vapor (helium or argon) to liquid (alkane) phase are calculated directly from the number densities [20]

$$\Delta G_t = RT \, \ln \left(\frac{\rho_t^{vap}}{\rho_t^{liq}} \right) \qquad (2.1)$$

where R and T are the molar gas constant and the temperature, and the index t denotes the type of molecule. The chemical potentials are computed on-the-fly during the insertion part of the molecule-exchange moves. For simulations in the Gibbs ensemble, Widom's formula for ghost particle insertions [21] has to be modified to account for the fluctuations in the volume and the number of particles as suggested by Smit and Frenkel [22]

$$\mu_{t,b} = -k_B T \ln \left(\Lambda_t^{-3} \left\langle \frac{V_b}{N_{t,b}+1} \, \exp\left[-\frac{U_{t,b}^+}{k_B T} \right] \right\rangle_T \right) \qquad (2.2)$$

Table 1. Lennard-Jones parameters for the TraPPE force field

pseudo-Atom	ϵ/k_B [K]	σ [Å]
CH$_3$	98	3.75
CH$_2$	46	3.95
Ar	116	3.39
He	4	3.11

Table 2. Composition of the four systems

Atom/molecule	System A	System B	System C	System D
He	210	0	840	840
Ar	0	210	0	0
n-Pentane	2	2	8	1
n-Heptane	140	140	560	560

where the indices t and b denote the molecule type and the simulation box for the insertion, Λ, V, N, and U^+ are the thermal de Broglie wavelength, the volume, the number of particles, and the interaction energy of the ghost particle with all other particles present in the simulation box. The angular brackets denote an ensemble average. In the special case of CBMC insertions of chain molecules the exponential has to be replaced with $\langle W^+ \rangle / W_{ideal}$ where W^+ and W_{ideal} are the Rosenbluth weights of the ghost chain and of an ideal chain (the reference state)[1] [13,23].

3 Results and discussion

The Gibbs free energies of transfer and the specific densities obtained from the four simulations are summarized in Table 3. Comparison of systems A and B shows that replacing helium with argon as the carrier gas does not change the partitioning of the alkanes. Of course, argon has a higher affinity for the liquid alkane phase, and its free energy of transfer is about 6 kJ/mol less positive than that of helium. Studying the influence of the carrier gas is of importance, because oil-vapor partitioning experiments are often performed with air or nitrogen as the carrier gas. However, experiments also show little difference in solute partitioning with helium or nitrogen as the carrier gas. Systems A and C have identical overall composition, but system C contains four times as many molecules (see Table 2). Again, we see no differences outside the statistical uncertainties in the free energies of transfer and the specific densities. Changing the solute concentration by a factor of 8 (systems C and D) also does not affect the partitioning, but it should be noted that the solute mole fraction in the more concentrated system C are already less than 0.01 in the liquid and vapor phases.

The Gibbs free energies of transfer for n-pentane and n-heptane are in very good agreement for all four systems studied here; their values are about -12.7 and -18.3 kJ/mol, respectively. The statistical uncertainties are remarkably small, with 0.35 kJ/mol being the largest value. This suggest that the GEMC technique can yield Gibbs free energies of transfer with relative statistical error smaller than 2%. This level of statistical error appears to be a major improvement compared to the errors encountered in more traditional free energy calculations [24].

The experimental alkane-air free energies of transfer are -13.7 (n-pentane) and -19.5 kJ/mol (n-heptane) [25, 26]. Obviously, agreement between simulation and experiment is not perfect and the deviation of about 1 kJ/mol is clearly larger than the statistical uncertainties. We attribute this difference to inaccuracies of the TraPPE

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[1]Using configurational-bias insertions the chemical potential of an articulated molecule can also be computed with respect to an *isolated* molecule as the reference state, that is using $\langle W^+ \rangle / \langle W_{isolated} \rangle$. An isolated chain is characterized by its bonded (say, bending and torsion) and non-bonded (say, Lennard-Jones) intramolecular interactions. Whereas no interactions are taken into account when an ideal chain is constructed.

Table 3. Gibbs free energies of transfer and specific densities

Property	System A	System B	System C	System D
ΔG (He) [kJ/mol]	7.48_{15}	–	7.56_{17}	7.53_{11}
ΔG (Ar) [kJ/mol]	–	1.35_{15}	–	–
ΔG (C$_5$) [kJ/mol]	-12.75_{24}	-12.64_{13}	-12.71_{20}	-12.52_{33}
ΔG (C$_7$) [kJ/mol]	-18.24_{35}	-18.18_9	-18.26_{14}	-18.24_{22}
ρ_{liq} [g/ml]	0.6845_9	0.6848_{12}	0.6843_6	0.6849_6
ρ_{vap} [g/ml]	0.00060_6	0.00191_9	0.00060_2	0.00058_4

Table 4. Chemical potentials (calculated from equations 2.2 and 3.1) and average numbers of molecules

Property	Equation	System A	System B	System C	System D
μ_{liq}(He)/k_B [K]	2.2	-2753_{12}	–	-3158_9	-3147_8
μ_{vap}(He)/k_B [K]	2.2	-3809_5	–	-3809_2	-3807_3
μ_{liq}(Ar)/k_B [K]	2.2	–	-4470_{14}	–	–
μ_{vap}(Ar)/k_B [K]	2.2	–	-4839_2	–	–
μ_{liq}(C$_5$)/k_B [K]	2.2	-6435_{88}	-6419_{45}	-6616_{86}	-6826_{56}
μ_{vap}(C$_5$)/k_B [K]	2.2	-6532_7	-6530_4	-6626_{12}	-7034_8
μ_{liq}(C$_7$)/k_B [K]	2.2	-6143_{201}	-5908_{90}	-6047_{136}	-5986_{88}
μ_{vap}(C$_7$)/k_B [K]	2.2	-6024_{38}	-6020_{12}	-6026_{16}	-6023_3
N_{liq}(He)		0.03	–	0.12	0.12
N_{vap}(He)		209.97	–	839.88	839.88
N_{liq}(Ar)		–	0.36	–	–
N_{vap}(Ar)		–	209.64	–	–
N_{liq}(C$_5$)		0.67	0.65	2.65	0.31
N_{vap}(C$_5$)		1.33	1.35	5.35	0.69
N_{liq}(C$_7$)		114.8	114.2	460.5	459.7
N_{vap}(C$_7$)		25.2	25.8	99.5	100.3
μ_{liq}(He)/k_B [K]	3.1	-3807	–	-3832	-3817
μ_{vap}(He)/k_B [K]	3.1	-3810	–	-3809	-3807
μ_{liq}(Ar)/k_B [K]	3.1	–	-4871	–	–
μ_{vap}(Ar)/k_B [K]	3.1	–	-4840	–	–
μ_{liq}(C$_5$)/k_B [K]	3.1	-6708	-6698	-6712	-7253
μ_{vap}(C$_5$)/k_B [K]	3.1	-6649	-6695	-6677	-7302
μ_{liq}(C$_7$)/k_B [K]	3.1	-6146	-5911	-6048	-5987
μ_{vap}(C$_7$)/k_B [K]	3.1	-6035	-6031	-6029	-6026

force field. In calculations of vapor-liquid coexistence curves, it has already been noted that the TraPPE force field yields too high vapor pressures (and densities), while yielding very good agreement in liquid densities and critical temperatures [16]. Too high vapor densities are consistent with the too small (in magnitude) Gibbs free energies of transfer observed in this work.

While the partitioning itself seems to be very robust and not affected by changes in the system size, we would like to note here some problems that were encountered with respect to the chemical potentials calculated using the modified Widom expression given in Eq. (2.2). The calculated chemical potentials are listed in Table 4. At first hand, it might be puzzling to note striking discrepancies in the calculated chemical potentials for vapor and liquid phases. Let us focus on the calculated chemical potentials for helium because the statistical uncertainties are much smaller in this case than for the articulated alkanes. Comparing systems A, C, and D, we notice that the chemical potentials of helium in the vapor phase are in agreement for both system sizes. However, the values for the liquid phase differ by $1050\,k_B$ K (system A) and $650\,k_B$ K (systems C and D) from the results for the vapor phase. Remember that the partitioning itself was not affected by the same change in system size (see Table 3). Similar discrepancies are also obvious for argon and n-pentane. What is the origin for these discrepancies? Widom's formula [21] and its

modification for the Gibbs ensemble [22] were derived to calculate the (excess) chemical potential from the ratio of the $N+1$ and N particle partition functions in the limit of large N. However, the average numbers of helium (or argon) atoms in the liquid phase are extremely small, and the same is of course also true for n-pentane, the solute (see Table 4). Thus in these cases, we are clearly outside the range of validity of Eq. (2.2), that is the test insertion of, say, an additional helium atom results in a significantly higher helium concentration than the corresponding equilibrium value. This biased concentration appears in the number density part, $V_b/(N_{t,b}+1)$, of Eq. (2.2). In contrast, the energetic part, $U_{t,b}^+$, is dominated by the interactions with the liquid solvent. To account for this number dependence of the chemical potential, we suggest adding a number-dependent correction term to the computed chemical potential as follows

$$\mu_{t,b}^{\text{m}} = \mu_{t,b} - k_B T \ln\left(\Lambda_t^{-3} \frac{\langle N_{t,b}\rangle + 1}{\langle N_{t,b}\rangle} \right) \qquad (3.1)$$

where $N_{t,b}$ is the average number of particles of type t in box b. The modified chemical potentials are also listed in Table 4. Again, focusing on helium, since the average numbers of helium atoms in the vapor phase are large (>200), the correction term is obviously very small. However, the corrections are large for the chemical potentials in the liquid phase, and the modified chemical

potentials of helium for the vapor and liquid phases are now in satisfactory agreement for systems A, C, D (and also for argon in system B).

Here we should strongly emphasize that the Widom-type Eq. (2.2) suggested by Smit and Frenkel is and remains the correct way to calculate chemical potentials in GEMC simulations. Only in the (possibly pathological) cases studied here that are characterized by extremely small numbers of gas atoms in the liquid phase and solute molecules in both phases, and that are therefore outside of the validity of Eq. (2.2) might one experiment with ad hoc correction terms as suggested in Eq. (3.1). Nevertheless, the GEMC simulations and the resulting partitionings are reliable despite the apparent discrepancyes in the chemical potentials. Finally, this number dependence of the chemical potential should not be confused with the system-size dependence of the excess chemical potential that originates from the larger amount of reversible work that is required to insert a molecule into a smaller system [27]. For example, while the system size (total number of molecules) changes by an insignificant amount between systems C and D, the number of pentane solutes changes by a factor of 8 and the number-dependence problem in the chemical potential of n-pentane is more pronounced for system D.

4 Conclusions

The Gibbs free energies of transfer are calculated for the ternary systems n-pentane/n-heptane/(helium or argon) by performing GEMC simulations. This approach allows us to compute Gibbs free energies of transfer for articulated molecules, such as the alkanes, with a precision of about 0.2 kJ/mol. Neither replacing helium with argon as the carrier gas, nor increasing the system size from 350 to 1400 solvent plus carrier gas molecules, nor changing the solute mole fraction from 0.001 to 0.01 significantly alters the partitioning of the alkanes. However, chemical potentials calculated via Widom's ghost particle insertions have to be viewed with caution because of the extremely small numbers of solute molecules in both phases and of carrier gas atoms in the liquid phase.

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