

TABLE I. Entropy of an ensemble of 100 independent three-dimensional harmonic oscillators. Values from the stochastic dynamics simulation are compared to analytical results. (Exact method [Eq. (3)] and Schlitter's approximation [Eq. (5)].)

Method	S_{sho} J K ⁻¹ mol ⁻¹
SD simulation:	
full covariance matrix	33.449
only diagonal elements	36.897
Analytical calculations:	
Exact using Eq. (3)	36.9782
Schlitter using Eq. (5)	36.9784

from leaving their initial position with a force constant of 25 kJ mol⁻¹ nm⁻². They were given initial velocities according to a Maxwell–Boltzmann distribution at 300 K. A 1 ns stochastic dynamics simulation with a friction coefficient of 10 ps⁻¹ at a temperature of 300 K was performed using the GROMOS simulation package.^{10,11} The time step was set to 0.01 ps.

This setup yields a system of 300 independent, one-dimensional classical harmonic oscillators whose entropy can be calculated analytically using Eq. (3) (exact expression) or Eq. (5) (Schlitter's approximation).

Taking the generated trajectory the entropy can be calculated using the covariance matrix [Eq. (10)]. When using the full covariance matrix the entropy will be slightly lowered because of spurious correlations that arise from the finite numerical accuracy and finite simulation length. These correlations are in this case an artifact and unwelcome when comparing to analytical results for truly independent oscillators with zero correlations. The spurious correlations are omitted by using only the diagonal elements of the covariance matrix in the calculation. The results are summarized in Table I.

The exact result [Eq. (3)] is slightly smaller than the result from Schlitter's approximation [Eq. (5)], showing that the latter approximation is always an upper bound to the exact value. The results of the simulation ignoring spurious correlations agree well with the analytical results.

IV. SIMPLE MANY-PARTICLE SYSTEMS

A. The ideal gas

For the ideal gas it is possible to calculate the entropy analytically, either through classical statistical mechanics or using Schlitter's approximation (see Appendix A).

The molar entropy of an ideal gas with a volume of 22.41/mol was calculated for a range of temperatures using both methods (see Table II). Clearly Schlitter's method gives an upper bound to the exact value. The ideal gas represents the worst case for the harmonic approximation used in Schlitter's formula explaining the relatively large errors. The error is only slightly decreasing with increasing temperature.

B. The Lennard-Jones fluid

The Lennard-Jones fluid is used as a more realistic test system for which numerical values for the entropy are still available for comparison. A system of 256 argon atoms us-

TABLE II. Molar entropy of an ideal gas (mass 16 amu) in J K⁻¹mol⁻¹ at different temperatures. Exact analytical values obtained using Eq. (A3) are compared to analytical values using Schlitter's approximation, Eq. (A4).

T K	S_{ideal} J K ⁻¹ mol ⁻¹	Error	
	exact	Schlitter	
	Eq. (A3)	Eq. (A4)	
100	690.774	810.044	17.2%
200	699.419	818.689	17.1%
300	704.476	823.746	16.9%

ing the parameters of the GROMOS96 force field¹⁰ version 43A1 ($\epsilon/k_B = 119.8$ K, $\sigma = 0.341$ nm) was set up in a cubic box with an edge length of 2.3 nm (reduced density $\rho^* = 0.834$). The system was simulated (time step = 2 fs) at constant volume (volume = 12.2 nm³) and constant temperatures: $T = 200, 300, 400$ K. At each temperature the systems were simulated for 200 ps and the entropy calculated over the whole 200 ps trajectory. The entropy was calculated ignoring correlations ($S_{\text{lj,nc}}^{\text{sim}}$) and with all correlations included ($S_{\text{lj,cr}}^{\text{sim}}$).

The numerical results obtained from the simulations are compared to numerical results which were obtained by calculating the entropy of an ideal gas ($S_{\text{id}}^{\text{exact}}$) exactly and afterwards correcting for the interaction between the particles. This correction, the residual entropy of a Lennard-Jones fluid ($S_{\text{corr}}^{\text{eos}}$), was calculated numerically using a polynomial fit to the equation of state of the Lennard-Jones fluid.¹²

Table III shows the results. In the case of complete neglect of any correlation between the particles ($S_{\text{lj,nc}}^{\text{sim}}$), the entropy of the Lennard-Jones fluid is very similar to the entropy of an ideal gas ($S_{\text{id}}^{\text{exact}}$). Taking the correlation into account, the entropy ($S_{\text{lj,cr}}^{\text{sim}}$) is drastically lowered. This again illustrates that for the ideal gas the harmonic approximation is poor.

The difference between the entropy $S_{\text{lj,cr}}^{\text{sim}}$ from the simulation including all correlations and the corrected entropy $S_{\text{lj}}^{\text{exact}}$ calculated numerically from the equation of state is also given in Table III and ranges between 6.9% and 3.7%. The difference is significantly smaller than in the case of the ideal gas.

V. ENTROPY CALCULATIONS FOR A β -HEPTAPEPTIDE IN SOLUTION

The ensemble of harmonic oscillators and the Lennard-Jones fluid are highly idealized test systems in which a number of important aspects of more realistic systems are not addressed, e.g., presence of internal degrees of freedom of a molecule. Therefore, the formula was applied to a peptide in solution which has been extensively studied and characterized.⁵ A β -heptapeptide in methanol was simulated at different temperatures. The peptide undergoes reversible folding in the simulations and the ratio of folded to unfolded structures decreases with increasing temperature from 49 to 1 at 298 K to 1 to 3 at 360 K. For 298 and 340 K, 200 ns trajectories, and for 350 and 360 K, 50 ns trajectories, were available. The first three simulations were done in a rectan-