

Conformation of Alkanes in the Gas Phase and Pure Liquids

Laura L. Thomas, Theodore J. Christakis, and William L. Jorgensen*

Department of Chemistry, Yale University, 225 Prospect Street, New Haven, Connecticut 06520-8107

Received: July 27, 2006; In Final Form: August 24, 2006

Monte Carlo (MC) statistical mechanics simulations have been carried out for the homologous alkane series of *n*-butane through *n*-dodecane in the gas phase and for the pure liquids at 298 K and 1 atm using the OPLS-AA force field. The study addresses potential cumulative deviations of computed properties and potential conformational differences between the gas phase and pure liquids, for example, from self-solvation in the gas phase. The average errors in comparison with experimental data for the computed densities and heats of vaporization are modest at 0.7% and 6.9%, respectively. Also, the invariant gas and liquid-phase results for average end-to-end distances and percentages of trans conformations for each nonterminal C–C bond assert that the conformer populations are not altered upon transfer from the gas phase to the pure liquid for the *n*-alkanes in this size range. Average end-to-end distances were also computed from the results of conformational searches and corroborated the MC findings. Quantitatively, the OPLS-AA result for the trans population of the C3–C4 bond in *n*-undecane is in close agreement with the findings from ¹³C NMR experiments. Finally, previous work on determining the shortest *n*-alkane that does not have an all-trans global energy minimum has been extended. The smallest *n*-alkane with a hairpin geometry that is lower in energy than the all-trans conformer occurs for C₂₂H₄₆ with OPLS-AA, though with a correction for GG sequences, the true turning point is likely in the C₁₆–C₁₈ range.

Introduction

Despite the status of *n*-alkanes as the simplest series of organic molecules, there is uncertainty regarding their preferred conformations in the gas and liquid phases and, concomitantly, whether a significant change in conformational preference occurs upon transfer from the gas to the pure liquid.^{1–3} It is important to characterize the conformational equilibria present in such paradigmatic systems, as they are among the most fundamental structural units in chemistry and biology.^{4–6} It is also important to understand associated solvent effects, which can have a marked influence on chemical reaction rates and conformational equilibria.⁷ Specifically, the preferred conformations of alkyl chains may directly affect chemical and biological reactivity by altering the spatial arrangements of functional substituents.⁸ Additionally, a better understanding of pure *n*-alkanes may aid in elucidating the structures and properties of more complex systems, such as adsorbed hydrocarbon films,⁵ polymer melts,^{6,9} and the interiors of cell walls.¹⁰

Currently, there remains considerable disparity in the literature regarding the conformational energetics of *n*-alkanes. A variety of experimental gauche–trans energy differences in the gas phase have been reported, ranging from approximately 0.5 to 1.0 kcal/mol for *n*-alkanes.^{1,3,11} The analogous energy difference in the liquid phase has been more consistent, with experimental values in the range of 0.5–0.6 kcal/mol.³ The combination is suggestive of an increase in gauche-containing conformers in solution, which could be explained by packing or internal-pressure arguments. The alternative view would be to expect increased gauche populations in the gas phase owing to self-solvation for larger *n*-alkanes. An electron diffraction study of the alkanes *n*-butane through *n*-heptane by Bartell and Kohl⁴

revealed that the gas-phase conformations often contain gauche dihedral angles, with relatively high populations of conformers with single gauche bonds for *n*-pentane, *n*-hexane, and *n*-heptane. IR measurements for deuterated *n*-tridecane were interpreted to indicate significant alteration of gauche populations in different alkane solvents.¹² However, Menger and D'Angelo⁶ used ¹³C NMR to observe the conformational equilibria of undecane-2,5-di-¹³C in solvents ranging from chloroform to aqueous ethanol; by measuring ³J_{CC}, they obtained the fraction of trans and gauche for the C3–C4 bond. The result was 76% trans in all solvents.⁶ In addition, small-angle neutron scattering (SANS) studies by Dettenmaier⁵ and Goodsaid-Zalduondo and Engelman¹⁰ and Raman studies by Fischer⁹ agree that the influence of intermolecular interactions on individual monomer conformation in the liquid state is negligible and that the conformations of *n*-alkanes in the condensed phase are similar to those populated in isolation. In addition, the gas-phase Raman experiment by Kanesaka and co-workers provided the consistent result that the enthalpy difference between the trans, trans conformer and the single gauche state of *n*-pentane in the gas phase is similar to the value reported for the pure liquid.²

Theoretical investigations have supported both possibilities. For instance, while Monte Carlo (MC) statistical mechanics studies using various force fields indicate that there is no solvation effect for pure alkanes,^{1,13} earlier molecular dynamics studies^{14,15} of *n*-butane and integral equation results¹⁶ predicted that the gauche population should be enhanced upon transfer from the gas phase to the liquid. Additional work has focused on the energetic ordering of conformers using conformational searches or energy-minimized fold motifs.^{17–19} In a novel study, Goodman sought to identify the smallest *n*-alkane for which the global energy minimum is not all-trans in the gas phase.¹⁹ It is expected that favorable intramolecular van der Waals interactions, resulting from the alignment of adjacent chains in

* Author to whom correspondence should be addressed. E-mail: william.jorgensen@yale.edu.

long *n*-alkanes, will allay the energetic cost of forming the gauche bonds necessary to align the chains. Cooperative folding effects, such as “adjacent gauche stabilization”, which may also be attributed to favorable intrachain van der Waals interactions, have likewise garnered attention including high-level quantum mechanical investigations.^{11,20} The associated deviations from the simple rotational isomeric states model of Flory are significant for polymer modeling.²⁰

Previously, the OPLS all-atom (OPLS-AA) force field was tested in MC simulations only for the alkanes ethane, propane, butane, isobutane, and cyclohexane.^{13c} In the current study, the coverage has been extended to the *n*-alkanes butane through dodecane to explore the possibility that the condensed-phase effects on the conformational equilibria may not be revealed until larger systems are considered and also to see if there are cumulative homologation errors for computed properties using the model. Gas- and liquid-phase Monte Carlo simulations have been carried out, and the calculated densities and heats of vaporization, properties indicative of molecular size and intermolecular interactions, are compared to experimental values. In addition, the preferred conformations of the *n*-alkanes in the gas and liquid phases have been characterized by calculating the average end-to-end distances of the monomers. The MC results have been corroborated by additionally performing conformational searches, which were used to provide Boltzmann-weighted end-to-end distances in the gas phase. Percentages of trans conformations for all dihedral angles for the alkanes in the gas and the liquid are also reported. Finally, the work of Goodman¹⁹ on the shortest *n*-alkane not having an all-trans global minimum has been extended using the OPLS-AA force field. This was achieved by generating energetically favorable, folded conformers for several long *n*-alkanes, followed by energy minimizations and comparison to the all-trans state.

Computational Methods

Gas-Phase Simulations. Gas-phase Metropolis Monte Carlo statistical mechanics simulations were carried out for *n*-butane through *n*-dodecane at 25 °C using the BOSS program and the OPLS-AA force field.^{13c,21} The original OPLS-AA torsional parameters for alkanes from 1996^{13c} were modified, as reported in 2001,²² and only the modified parameters have been used by us since then. All internal degrees of freedom were sampled. In the MC algorithm used in BOSS, a random set of bond lengths, bond angles, and dihedral angles is chosen for variation upon an MC move. The default, which was used here, is to vary a maximum of 15 internal degrees of freedom of each type. In addition, the BOSS “flip” option was used to enhance the sampling of alternative conformational states. The flip command attempts a large dihedral flip every sixth attempted variation of a dihedral angle. In this set of simulations, all C–C–C dihedral angles were allowed to flip with a value of $\pm 120^\circ$. Otherwise, the typical range is $\pm 15^\circ$ for attempted variations of dihedral angles or $\pm 2^\circ$ for improper dihedral angles. As an example, for the MC simulation of heptane in the gas phase, the overall acceptance rate was 44% for new configurations and 17% for attempted moves that included a flip. Each system, consisting of one molecule, was equilibrated for 1×10^6 configurations, and the thermodynamic properties were averaged over 2×10^6 configurations. During the averaging period, molecular coordinates were saved every 1000 configurations, effectively providing 2000 “molecular snapshots” spaced 1000 configurations apart. The end-to-end distances of these 2000 structures, measured from terminal carbon to terminal carbon,

were averaged to find the mean end-to-end distance. The reported trans conformer percentages are from the full gas-phase MC simulations with averaging for every configuration.

Pure Liquid Simulations. Monte Carlo simulations of the pure alkane liquids were carried out in the NPT ensemble at 25 °C and 1 atm with Metropolis sampling of all internal and intermolecular degrees of freedom. In each case, a cubic, periodic box of 267 monomers was generated and force-field cutoffs of 12 Å were used, along with quadratic smoothing and a standard correction for the Lennard-Jones interactions neglected beyond the cutoff.¹³ Basically, if any C–C distance between two molecules is within the cutoff, the entire molecule–molecule interaction is evaluated and included in the total energy. Initially, each liquid was equilibrated for 8×10^6 configurations, and averaging took place over 12×10^6 configurations. However, examination of the output from these simulations showed that there was limited variation in monomer orientation for the higher alkanes; they had not melted well from their initially ordered structures. Thus, the final configuration from each of these simulations was used as input to an NVT MC simulation covering 4×10^6 configurations at 1000 °C to randomize the coordinates. Subsequently, the C₄–C₉ liquids were reequilibrated in the NPT ensemble at 25 °C and 1 atm for 25×10^6 configurations, and then a final 25×10^6 configurations of averaging were executed. For *n*-decane, *n*-undecane, and *n*-dodecane, the reequilibration covered 75×10^6 configurations, and the final averaging took place over 25×10^6 MC steps. In the NPT simulations, attempts to alter the volume were made every 390 configurations. The coordinates of the simulation cells were output every 1×10^6 configurations during the last 25×10^6 configurations, and the end-to-end distances of all 267 monomers per snapshot were calculated. Thus, the average end-to-end distances reported for the liquid phase are the result of averaging over 6675 molecular structures for each alkane. Statistical uncertainties for computed properties were computed from the fluctuations in the averages over blocks of 10^6 configurations.

Conformational Searches. Internal coordinate Monte Carlo conformational searches were carried out for each of the *n*-alkanes to identify unique conformers and their energies.²¹ This process involved the generation of 10 000 starting structures, followed by energy minimization and subsequent identification of unique conformers by energy, RMS deviation between structures, and internuclear distances.²¹ The terminal carbon end-to-end distance was then computed for each structure, and the Boltzmann-weighted end-to-end distance was calculated for each *n*-alkane using eq 1:

$$\langle d_{e-to-e} \rangle = \frac{\sum_j g_j d_j e^{-\beta E_j}}{\sum_j g_j e^{-\beta E_j}} \quad (1)$$

where $\langle d_{e-to-e} \rangle$ is the average end-to-end distance, as determined by summing the product of the degeneracy g_j , the end-to-end distance d_j , and the Boltzmann factor for each conformer j , and then dividing by the partition function. E_j is the energy of each conformer j , and $\beta = 1/kT$, where k is the Boltzmann constant and T is the temperature (298 K). The degeneracies, g_j , were determined by considering the symmetry and mirror images of each conformer.²³ Dihedral angles (φ) around individual bonds were classified as syn-periplanar ($\varphi = 330-30^\circ$), (+)-synclinal ($\varphi = 30-90^\circ$), (+)-anticlinal ($\varphi = 90-150^\circ$), anti-periplanar ($\varphi = 150-210^\circ$), (–)-anticlinal ($\varphi =$

TABLE 1: Relative Conformational Energies for Alkanes

conformer ^a	ΔE (kcal/mol)			
	OPLS-AA	MM2 ^b	MP4SDQ ^c	MP2:CC ^d
Butane				
G	0.80	0.86	0.74	0.63
Pentane				
TG	0.94	0.90	0.74	0.62
GG	1.89	1.62	1.30	0.99
GG'	3.29	3.36	3.29	2.85
Hexane				
TTG	0.93	0.88	0.72	
TGT	1.05	0.93	0.73	0.60
TGG	1.97	1.62	1.30	0.93
GTG	1.82	1.70	1.44	
GTG'	1.92	1.89	1.56	1.32
GGG	2.88	2.30	1.84	1.27
TGG'	3.31	3.21	3.12	
TGG'	3.38	3.24	3.21	2.74
GGG'	4.20	3.94	3.87	3.12
GGG'	4.38	4.24	3.90	
GG'G	5.62	5.58	5.92	

^a Notation as in ref 11; ΔE relative to all-trans conformer; bold-faced G for dihedral angle near $\pm 95^\circ$. ^b Reference 11. ^c Reference 11; MP4SDQ/6-31G(d)//HF/6-31G(d). ^d Reference 20; MP2:CC \approx CCSD(T)/cc-pVQZ.

210–270°), or (–)-synclinal ($\varphi = 270$ –330°). A degeneracy of 1 was assigned to the conformer with all dihedrals in the trans (anti-periplanar) conformation. All other symmetric conformers, in addition to all asymmetric conformers with superimposable mirror images, were given a degeneracy of 2. The remainder of the geometrical isomers were assigned $g_j = 4$. The end-to-end distances determined in this fashion were compared with the analogous results from the MC simulations.

Results and Discussion

Conformational Energetics. Results from energy minimizations with the OPLS-AA force field are compared with reference values in Table 1 for *n*-butane, *n*-pentane, and *n*-hexane. The OPLS-AA and MM2 force fields give very similar results, with an average discrepancy of only 0.15 kcal/mol for the 15 relative energies. The OPLS-AA results are also similar to the MP4SDQ/6-31G(d) values with an average difference of 0.35 kcal/mol. The principal contributor to the differences arises from the GG form of pentane being 0.4–0.6 kcal/mol higher in relative energy with OPLS-AA. This effect carries over to the TGG, GGG, and GGG' conformers of hexane. Since the results for gauche butane and TG and GG' pentane are nearly identical with the two force fields, the difference for GG pentane can be attributed to the treatment of the 1,5-nonbonded interaction between the methyl groups. For OPLS-AA, the associated Lennard-Jones parameters were obtained by fitting primarily to reproduce densities and heats of vaporization for liquid alkanes.^{13c}

The MP2:CC results,²⁰ which are presumably the most accurate, consistently find gauche structures to be relatively more favorable than the other methods. For gauche butane, the OPLS-AA result of 0.80 kcal/mol is close to the MP4 value of 0.74 kcal/mol, but it is 0.17 kcal/mol above the 0.63 kcal/mol from the MP2:CC calculations.²⁰ Thus, it can be expected that MC or MD calculations for alkanes with the OPLS-AA force field will yield lower populations of gauche-containing conformers than the best estimates. The difference is quantified below.

Thermodynamics. The molecular volumes and heats of vaporization calculated via the MC simulations at 25 °C and 1

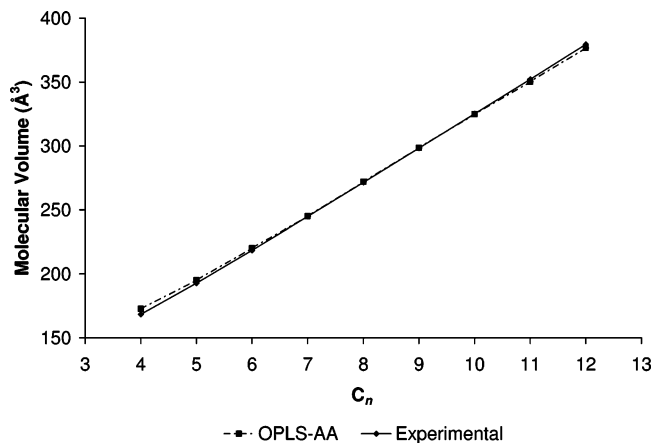


Figure 1. OPLS-AA and experimental molecular volume vs number of carbons for the *n*-alkanes butane through dodecane at 25 °C and 1 atm. The average error between theory and experiment is 0.7%.

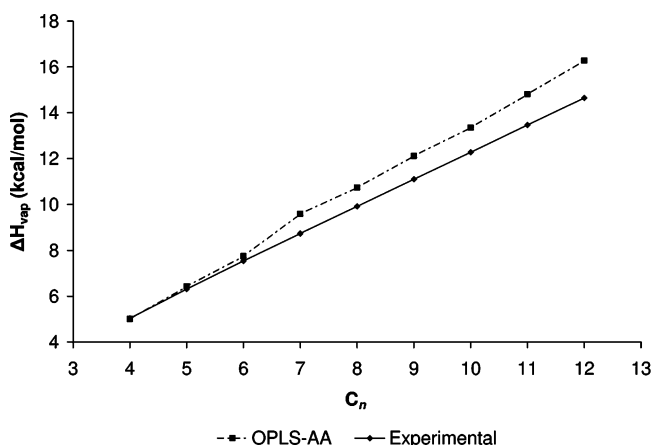


Figure 2. OPLS-AA and experimental heats of vaporization vs number of carbons for the *n*-alkanes butane through dodecane at 25 °C and 1 atm. The average error between theory and experiment is 6.9%.

atm, and the corresponding experimental values, are reported as functions of the number of carbon atoms in Figures 1 and 2 and in Table 2. Comparison with the experimental values yields average errors for the computed quantities of 0.7% for the volumes or densities and 6.9% for the heats of vaporization. For the heats of vaporization (Figure 2), the negligible deviation from the experimental values through *n*-hexane increases to an 11% error at dodecane. So, a slight decrease in the OPLS-AA ϵ values for the Lennard-Jones potentials for carbon or hydrogen could be considered. Overall, the agreement between the calculated and experimental thermodynamic quantities is satisfying in view of the limited, prior testing for liquid alkanes.^{13c}

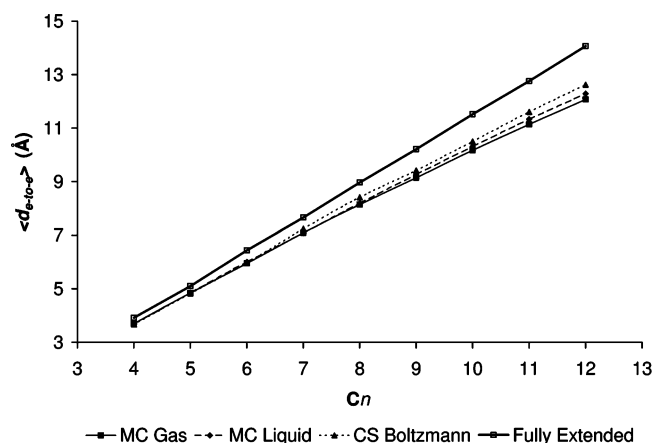
Calculated and experimental values of the constant pressure heat capacities and isothermal compressibilities for the alkanes are given in Table 3. The intermolecular contribution to the heat capacity, $C_p(\text{inter})$, is calculated from fluctuations in the total intermolecular energy during the liquid-phase MC simulations. The full heat capacity for the liquid, $C_p(\text{l})$, is then determined from $C_p(\text{l}) = C_p^\circ + C_p(\text{inter}) - R$, where C_p° is the experimental heat capacity for the ideal gas.^{13c} The isothermal compressibility, κ , is computed from the volume fluctuations: $\kappa = (\langle V^2 \rangle - \langle V \rangle^2) / k_B T \langle V \rangle$. Such fluctuation properties converge much more slowly than simple averages such as for the total energy and volume. In view of this, the results in Table 3 are reasonable. The computed and observed C_p values are in good accord and the compressibilities are in the correct range, though convergence problems are apparent in the oscillatory behavior with increasing alkane size.

TABLE 2: OPLS-AA and Experimental Molecular Volumes (\AA^3), Densities (g cm^{-3}), and Heats of Vaporization (kcal mol^{-1}) for Liquid *n*-Alkanes at 25 °C and 1 Atm

liquid	<i>V</i>		<i>d</i>		ΔH_{vap}	
	calcd	exptl	calcd	exptl	calcd	exptl
<i>n</i> -butane	172.8 ± 0.3	168.5	0.5585 ± 0.0010	0.5729 ^a	5.00 ± 0.04	5.04 ^a
<i>n</i> -pentane	195.1 ± 0.3	192.8	0.6140 ± 0.0008	0.6214 ^a	6.43 ± 0.05	6.32 ^a
<i>n</i> -hexane	220.3 ± 0.2	218.5	0.6495 ± 0.0007	0.6548 ^a	7.75 ± 0.06	7.54 ^a
<i>n</i> -heptane	245.1 ± 0.4	244.9	0.6788 ± 0.0010	0.6795 ^a	9.58 ± 0.06	8.74 ^a
<i>n</i> -octane	272.0 ± 0.2	271.5	0.6973 ± 0.0006	0.6986 ^a	10.73 ± 0.07	9.92 ^a
<i>n</i> -nonane	298.7 ± 0.4	298.4	0.7131 ± 0.0009	0.7138 ^a	12.12 ± 0.08	11.1 ^a
<i>n</i> -decane	324.9 ± 0.4	325.3	0.7271 ± 0.0008	0.7264 ^a	13.35 ± 0.09	12.28 ^a
<i>n</i> -undecane	350.4 ± 0.2	352.2	0.7408 ± 0.0004	0.737 ^b	14.81 ± 0.09	13.46 ^c
<i>n</i> -dodecane	376.8 ± 0.3	379.6	0.7506 ± 0.0005	0.7452 ^a	16.28 ± 0.09	14.65 ^a

^a Reference 24. ^b Reference 25. ^c Reference 26.**TABLE 3: OPLS-AA and Experimental Heat Capacities ($\text{cal mol}^{-1} \text{deg}^{-1}$) and Isothermal Compressibility Coefficients (atm^{-1}) for Liquid *n*-Alkanes at 25 °C and 1 Atm**

liquid	<i>C_p</i> ^o	<i>C_p(l)</i>		$10^6 \kappa$	
		calcd	exptl	calcd	exptl
<i>n</i> -butane	23.54 ^a	37.0 ± 1.1		352 ± 29	
<i>n</i> -pentane	28.69 ^a	42.4 ± 1.3	39.96 ^a	227 ± 20	221 ^a
<i>n</i> -hexane	34.08 ^a	46.7 ± 1.1	46.72 ^a	136 ± 10	169 ^c
<i>n</i> -heptane	39.48 ^a	61.0 ± 2.7	53.77 ^a	161 ± 18	146 ^c
<i>n</i> -octane	44.88 ^a	58.4 ± 1.2	60.74 ^a	90 ± 7	130 ^c
<i>n</i> -nonane	50.29 ^a	69.2 ± 2.2	68.01 ^a	97 ± 10	119 ^a
<i>n</i> -decane	55.70 ^a	81.7 ± 3.4	75.18 ^a	116 ± 14	111 ^c
<i>n</i> -undecane	61.53 ^b	78.9 ± 1.8		63 ± 5	104 ^c
<i>n</i> -dodecane	66.52 ^a	87.1 ± 2.5	89.86 ^a	67 ± 7	100 ^c

^a Reference 24. ^b Reference 26. ^c Reference 27.**Figure 3.** OPLS-AA average end-to-end distance vs number of carbons for the *n*-alkanes butane through dodecane at 25 °C and 1 atm calculated from MC simulations in the gas and liquid phase and from the Boltzmann-weighted results of a conformational search. The end-to-end distances of the fully extended (all-trans) conformers are included for reference.

Conformational Equilibria. The end-to-end distances obtained from MC simulations in the gas and liquid phase and from the conformational searches (Boltzmann-weighted for 25 °C) are provided in Figure 3 and in Table 4, along with the end-to-end values from energy minimizations for the all-trans conformers. The results in Figure 3 clearly indicate that the *n*-alkanes are relatively extended, but not all-trans, in both the gas and liquid phases. The gas-phase MC and liquid-phase MC results agree to within ca. 1.0%, so there is no condensed-phase effect for these alkanes. The trans populations for each dihedral angle, listed in Table 5, are also notably invariant in the 75–80% range except for butane at 69%. The statistical uncertainties in the trans populations can be gauged by the differences in

TABLE 4: OPLS-AA Average End-to-End Distances (\AA) from Monte Carlo Simulations in the Gas and Liquid Phases at 25 °C and 1 Atm and from Conformational Searches

liquid	MC gas	MC liquid	con. search ^a	all-trans ^b
<i>n</i> -butane	3.70 ± 0.01	3.69 ± 0.00	3.67	3.92
<i>n</i> -pentane	4.85 ± 0.01	4.85 ± 0.00	4.83	5.10
<i>n</i> -hexane	5.95 ± 0.01	6.01 ± 0.01	5.97	6.44
<i>n</i> -heptane	7.09 ± 0.01	7.08 ± 0.01	7.24	7.66
<i>n</i> -octane	8.14 ± 0.02	8.20 ± 0.01	8.42	8.97
<i>n</i> -nonane	9.14 ± 0.02	9.27 ± 0.01	9.42	10.21
<i>n</i> -decane	10.17 ± 0.02	10.31 ± 0.01	10.50	11.52
<i>n</i> -undecane	11.14 ± 0.03	11.33 ± 0.01	11.61	12.76
<i>n</i> -dodecane	12.08 ± 0.03	12.29 ± 0.02	12.63	14.07

^a With Boltzmann weighting for 25 °C. ^b From energy minimizations.

results for symmetry-equivalent dihedral angles; they amount to ca. 1% for the gas-phase populations and 2% in the liquids. Additionally, the conformational search results are in good accord with the MC results. For *n*-heptane through *n*-dodecane, the end-to-end lengths and trans populations from the conformational searches are only slightly higher than those obtained from the gas-phase MC simulations. The difference for the end-to-end lengths amounts to 5% for the largest alkanes; this likely arises from only populating the precise energy minima using the conformational search structures (effectively at 0 K), while the MC simulations sample geometries in all regions of each conformational energy well (at 298 K).

There is good accord with the ^{13}C NMR data of Menger and D'Angelo for the dihedral distribution about the C3–C4 bond in *n*-undecane at 25 °C.⁶ The observed $^3J_{\text{CC}}$ was found to be 3.6 ± 0.1 Hz in four solvents, chloroform, diethyl ether, ethanol, and 13% aqueous ethanol. This translates to a trans population of $76 \pm 5\%$ independent of the medium, while the OPLS-AA results in Table 5 are 82% and 84% trans for the C3–C4 and C8–C9 bonds in pure liquid *n*-undecane and 78% and 82% in the gas phase. Klauda et al., who reported the MP2:CC energetics in Table 1,^{20a} also performed MD simulations for alkane liquids using a CHARMM force field that was modified to be consistent with the MP2:CC results. For liquid *n*-decane and *n*-tridecane, they obtained average trans populations for the rotatable bonds of 69–70% at 39 °C, which on the basis of the results below should correspond to 71% at 25 °C; so, their results appear to be a little lower than the experimental findings of Menger and D'Angelo. Furthermore, for liquid heptane at 39 °C, Klauda et al. reported an average population of trans conformers for the four rotatable bonds to be 66.6% with the modified force field (C27r), 71.0% for the older version (C27), and 75.2% with AMBER99.^{20a} For comparison, an MC simulation for heptane in the gas phase was run here at 25 °C (Table 5) and then was run at 39 °C; the resultant average trans populations are 77.7% and 76.3%, respectively, using OPLS-

TABLE 5: Average trans Conformer Populations (%) from Monte Carlo Simulations in the Gas and Liquid-Phases at 25 °C and 1 Atm

dihedral	φ_1^g/φ_1^l	φ_2^g/φ_2^l	φ_3^g/φ_3^l	φ_4^g/φ_4^l	φ_5^g/φ_5^l	φ_6^g/φ_6^l	φ_7^g/φ_7^l	φ_8^g/φ_8^l	φ_9^g/φ_9^l
<i>n</i> -butane	69/69								
<i>n</i> -pentane	76/78	76/73							
<i>n</i> -hexane	75/77	83/85	75/73						
<i>n</i> -heptane	75/73	80/82	80/78	75/76					
<i>n</i> -octane	75/75	80/84	79/81	81/84	74/75				
<i>n</i> -nonane	75/76	80/84	81/78	80/85	80/81	75/79			
<i>n</i> -decane	75/78	79/81	79/84	78/82	79/81	82/81	76/77		
<i>n</i> -undecane	74/79	82/82	77/83	81/81	79/79	81/83	78/84	75/74	
<i>n</i> -dodecane	74/80	80/83	80/79	78/80	80/78	80/80	79/81	80/83	75/81

AA. Thus, OPLS-AA yields average trans populations that appear to be 10% higher than from the new C27r force field and 5% higher than from the ^{13}C NMR data.

Overall, the close agreement between the end-to-end distances and trans populations in the gas phase and the pure liquids supports the position that there are no significant solvent effects on the conformational equilibria for these *n*-alkanes. Any difference between the present gas-phase and pure liquid results is at the statistical limit of the calculations, though there is a small hint (1–2%) of longer end-to-end distances and larger trans populations in the liquids. However, at this point, the results indicate that self-solvation does not occur to any noticeable extent for *n*-alkanes of these lengths in the gas phase. Of course, relative to the all-trans conformer, the alkanes do become progressively more compact as a function of chain length. The average end-to-end distance for *n*-heptane reflects that it populates an average of close to one gauche bond per monomer (4 bonds \times 20–25% gauche/bond), while for dodecane the average number of gauche bonds per monomer is about 2 at 25 °C.

Higher *n*-Alkanes. To probe the phenomenon of self-solvation further, conformational searches for longer *n*-alkanes, $\text{C}_{14}\text{H}_{30}$ – $\text{C}_{34}\text{H}_{70}$, were performed to seek the transition from a linear global minimum (all-trans) to a nonlinear one. However, these finite-length conformational searches for one molecule in isolation failed to return any conformers with energies lower than the all-trans state for $\text{C}_{14}\text{H}_{30}$, $\text{C}_{18}\text{H}_{38}$, $\text{C}_{26}\text{H}_{54}$, or $\text{C}_{34}\text{H}_{70}$. Nevertheless, the conformational searches did show a tendency for other low-energy conformers to become more globular as a function of chain length. Thus, the “four-twist turn” hairpin motif proposed by Goodman¹⁹ (Figure 4, left), consisting of a GGTGG series of dihedral angles involving the central eight atoms of the chain, was imposed on several long *n*-alkanes, and these folded structures were then energy-minimized. $\text{C}_{22}\text{H}_{46}$ was the first *n*-alkane in which the hairpin motif was energetically

favored over the all-trans conformer using the OPLS-AA force field. The energy difference is 0.3 kcal/mol, while it is 1.3 and 2.2 kcal/mol favoring all-trans for C_{18} and C_{16} . However, in Table 1 it appears that OPLS-AA overestimates the energy of GG sequences by 1 kcal/mol, so the true turning point is likely in the C_{16} – C_{18} range. Similar analyses carried out by Goodman identified $\text{C}_{18}\text{H}_{38}$, $\text{C}_{25}\text{H}_{52}$, and $\text{C}_{26}\text{H}_{54}$ as the shortest *n*-alkanes with folded global minima for the MM2*, MM3*, and AMBER* force fields, respectively.¹⁹

Some additional investigations with OPLS-AA revealed that at C_{30} a double-hairpin conformer containing two GGTGG sequences (Figure 4, middle) becomes lower in energy than the all-trans alternative by 0.4 kcal/mol. This double hairpin is compact with the three chains in a bundle; however, the alternative single hairpin is 3.3 kcal/mol lower in energy than the bundle. The solvent-accessible surface areas using a probe with a 1.4-Å radius are 1126, 808, and 791 Å² for the all-trans conformer, single-hairpin, and double-hairpin bundle for $n\text{-C}_{30}\text{H}_{62}$. There is an alternative double-hairpin with one GGTGG and one G'G'TG'G' sequence that forms three parallel strands such as an S, but its energy is 1.7 kcal/mol higher than for the double-hairpin bundle. Another motif that was studied can be called the broken paperclip. It contains one GGTGG sequence for the inner turn and the outer turn is formed by a GGTTTTG'G' run (Figure 4, right). It becomes lower in energy than the all-trans form by 0.5 kcal/mol at C_{33} , and it is preferred by 1.1 kcal/mol at C_{34} . Progressing to C_{58} , one can find other highly folded conformers such as the M and the full paperclip in Figure 5; the relative energies with OPLS-AA are 0.0, 2.6, 9.7, and 11.7 kcal/mol for the single hairpin, the paperclip, the M, and the all-trans conformer, respectively. Conformers that are not substantially folded are uncompetitive in this size range. These examples illustrate that there are many folded structures for higher *n*-alkanes that are lower in energy than extended structures. In view of their significantly reduced surfaces areas,

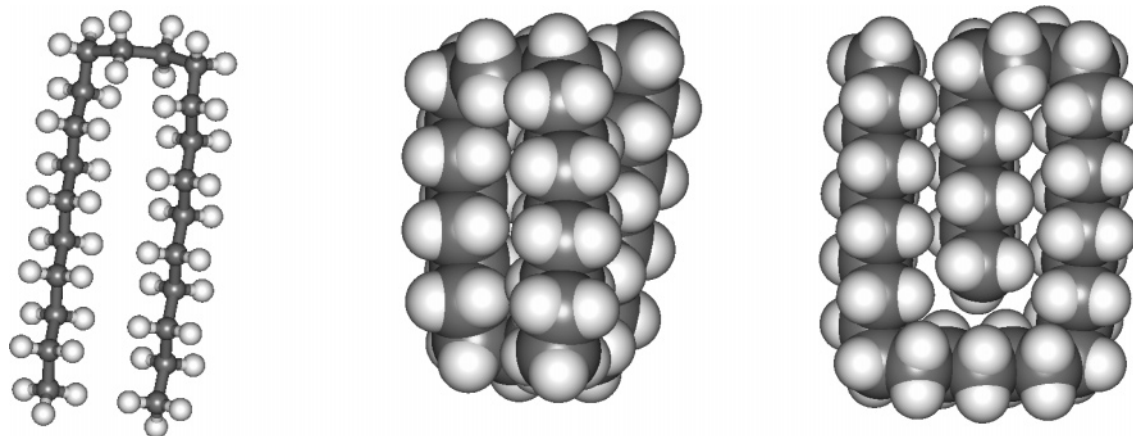


Figure 4. Left: The hairpin conformer for $n\text{-C}_{22}\text{H}_{46}$ in a ball-and-stick rendering. Middle: The double-hairpin bundle conformer for $n\text{-C}_{30}\text{H}_{62}$ in a space-filling image. Right: The broken paperclip conformer for $n\text{-C}_{34}\text{H}_{70}$. All are lower in energy than the all-trans conformers.

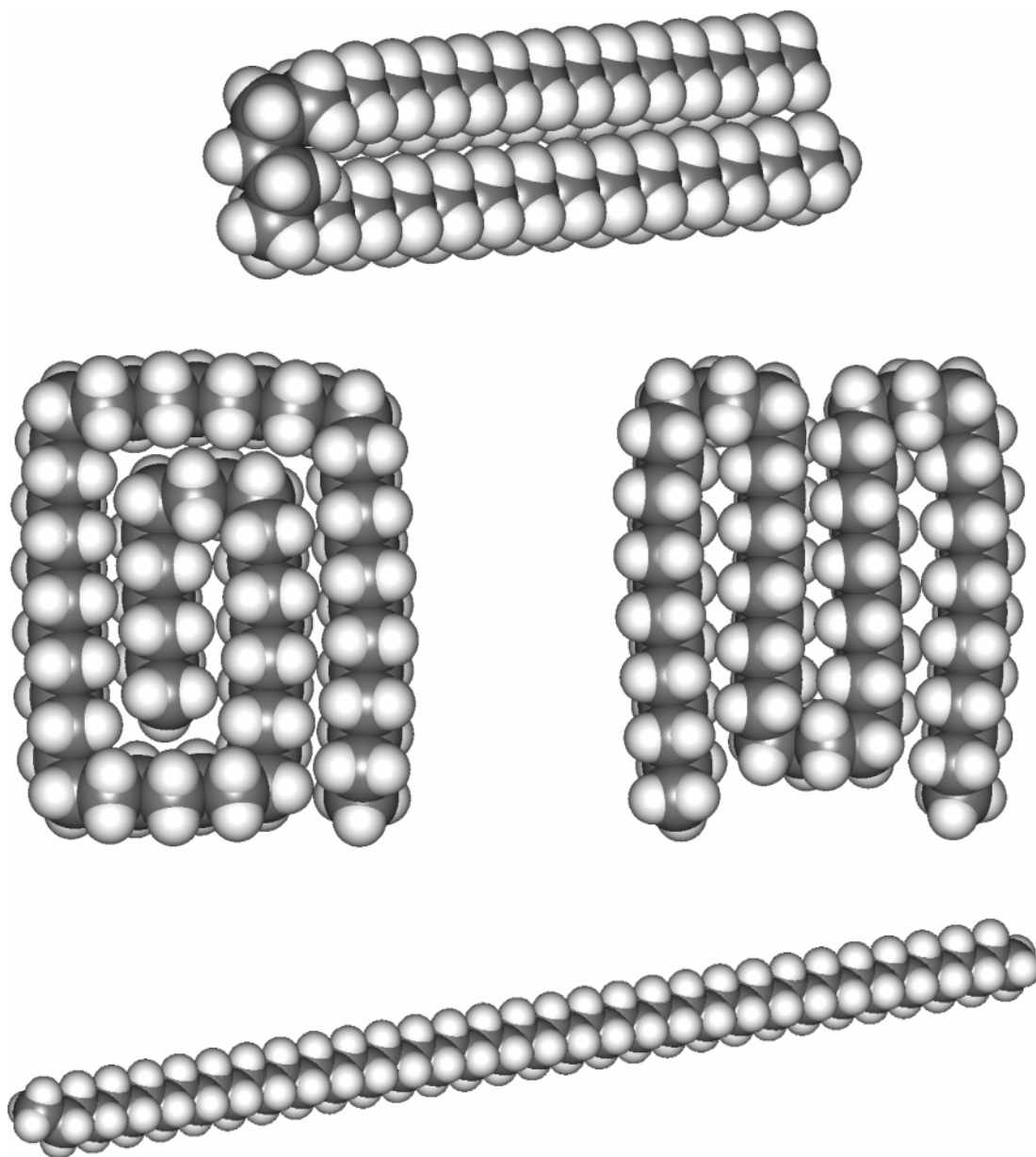


Figure 5. Four conformers of n -C₅₈H₁₁₈. Top: The single hairpin. Left: The paperclip. Right: The triple-hairpin M. Bottom: All-trans. Their relative energies from the OPLS-AA force field are 0.0, 2.6, 9.7, and 11.7 kcal/mol, respectively.

it can be expected that the folded structures would be relatively less well solvated in nonpolar solvents than the more extended conformers. Of course, these effects are immersed in the plethora of conformers that are populated for the higher alkanes, so detection of the solvent perturbations would be difficult.

Conclusions

Monte Carlo simulations of n -butane through n -dodecane have been carried out to investigate potential differences in conformer distributions between the gas-phase and pure liquid environments and also to uncover any systematic errors for computed densities and heats of vaporization using the OPLS-AA force field. The average errors for the computed densities and heats of vaporization are 0.7% and 6.9%. Though the errors are small, particularly in view of the limited prior testing, the latter result suggests that a small reduction in the Lennard-Jones ϵ parameters for alkanes could be considered for the force field. The results for the average end-to-end distances and trans conformer populations revealed no evidence for a shift in

conformer populations upon transfer from the gas phase to the pure liquids for n -alkanes through dodecane. Quantitatively, the present results for the trans population of the C3–C4 bond in n -undecane were in close agreement with the findings from ¹³C NMR experiments. In addition, C₂₂H₄₆ has been identified as the shortest n -alkane that does not have the all-trans conformer as the global energy minimum in the gas phase using the OPLS-AA force field. A variety of topologically interesting, low-energy, folded conformers exist for higher alkanes that reflect self-solvation in the gas phase. Reduction in the populations of such structures in solution can be expected, though it would be challenging to detect.

Acknowledgment. Support from the National Science Foundation (CHE-0446920) and National Institutes of Health (GM032136) is gratefully acknowledged. Gratitude is also expressed to Dr. J. Tirado-Rives for numerous helpful discussions.

References and Notes

- (1) For a review, see: Jorgensen, W. L. *J. Phys. Chem.* **1983**, *87*, 5304–5314.
- (2) Kanesaka, I.; Snyder, R. G.; Strauss, H. L. *J. Chem. Phys.* **1986**, *84*, 395–397.
- (3) Jorgensen, W. L. *Chemtracts: Org. Chem.* **1989**, *2*, 97–99.
- (4) Bartell, L. S.; Kohl, D. A. *J. Chem. Phys.* **1963**, *39*, 3097–3105.
- (5) Dettenmaier, M. *J. Chem. Phys.* **1978**, *68*, 2319–2322.
- (6) Menger, F. M.; D'Angelo, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 8241–8242.
- (7) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2003.
- (8) Gottlich, R.; Kahrs, B. C.; Kruger, J.; Hoffmann, R. W. *Chem. Commun. (Cambridge)* **1997**, 247–251.
- (9) Fischer, E. W.; Strobl, G. R.; Dettenmaier, M.; Stamm, M.; Steidle, N. *Faraday Discuss.* **1979**, *68*, 26–45.
- (10) Goodsaid-Zalduondo, F.; Engelman, D. M. *Biophys. J.* **1981**, *35*, 587–594.
- (11) Tsuzuki, S.; Schafer, L.; Goto, H.; Jemmis, E. D.; Hosoya, H.; Siam, K.; Tanabe, K.; Osawa, E. *J. Am. Chem. Soc.* **1991**, *113*, 4665–4671.
- (12) Casal, H. L.; Yang, P. W.; Mantsch, H. H. *Can. J. Chem.* **1986**, *64*, 1544–1547.
- (13) (a) Jorgensen, W. L.; Binning, R. C., Jr.; Bigot, B. *J. Am. Chem. Soc.* **1981**, *103*, 4393–4399. (b) Jorgensen, W. L.; Madura, J. D.; Swenson, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 6638–6646. (c) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *118*, 11225–11236.
- (14) Ryckaert, J. P.; Bellemans, A. *Faraday Discuss.* **1978**, *66*, 95–106.
- (15) Weber, T. A. *J. Chem. Phys.* **1978**, *69*, 2347–2354.
- (16) Pratt, L. R.; Hsu, C. S.; Chandler, D. *J. Chem. Phys.* **1978**, *68*, 4202–4212.
- (17) Morley, S. D.; Abraham, R. J.; Haworth, I. S.; Jackson, D. E.; Saunders, M. R.; Vinter, J. G. *J. Comput.-Aided Mol. Des.* **1991**, *5*, 475–504.
- (18) Goto, H.; Osawa, E.; Yamato, M. *Tetrahedron* **1992**, *49*, 387–396.
- (19) Goodman, J. M. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 876–878.
- (20) (a) Klauda, J. B.; Brooks, B. R.; MacKerell, A. D., Jr.; Venable, R. M.; Pastor, R. W. *J. Phys. Chem. B* **2005**, *109*, 5300–5311. (b) Klauda, J. B.; Pastor, R. W.; Brooks, B. R. *J. Phys. Chem. B* **2005**, *109*, 15684–15686.
- (21) Jorgensen, W. L.; Tirado-Rives, J. *J. Comput. Chem.* **2005**, *26*, 1689–1700.
- (22) Price, M. L. P.; Ostrovsky, D.; Jorgensen, W. L. *J. Comput. Chem.* **2001**, *22*, 1340–1352.
- (23) Smith, R. P.; Mortensen, E. M. *J. Chem. Phys.* **1961**, *35*, 714–721.
- (24) *Techniques of Chemistry, Vol. II: Organic Solvents, Physical Properties and Methods of Purification*, 4th ed.; Riddick, J. A., Bunger, W. B., Sakano, T. K., Proskauer, E. S., Toops, E. E., Jr., Eds.; Wiley: New York, 1986.
- (25) Hust, J. G.; Schramm, R. E. *J. Chem. Eng. Data* **1976**, *21*, 7–11.
- (26) Rossini, F. D.; Pitzer, K. S.; Arnett, R. L.; Braun, R. M.; Pimentel, G. C. *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*; American Petroleum Institute: Carnegie Press: Pittsburgh, PA, 1953.
- (27) Diaz Pena, M.; Tardajos, G.; Menduina, C.; Arenosa, R. L. *J. Chem. Thermodyn.* **1979**, *11*, 67–71. Diaz Pena, M.; Tardajos, G.; Arenosa, R. L.; Menduina, C. *J. Chem. Thermodyn.* **1979**, *11*, 951–957.