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Alkanes

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The Last Globally Stable Extended Alkane**

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At low temperatures, linear alkanes C_nH_{2n+2} of moderate length are known to prefer a fully extended (*all-trans*) conformation, in analogy to the simplest case of butane.[1] Owing to weak dispersion interactions between chain segments, this cannot hold up to $n \rightarrow \infty$. Only a finite, quite moderate[1,2] amount of energy is required to bend an extended chain into a hairpin structure by four *trans-gauche* isomerizations. With increasing n, the self-solvation between the two aligned chain segments grows and will win over the deformation energy at some point.[2] The theoretical minimum structure predicted for a given n will depend sensitively on the details of the alkane model.[2] The maximum chain length n_C with an *all-trans* global minimum is a quality indicator for the balance between intra- and intermolecular forces. Values of $n_C \approx 11$ can be found for PM3, 17 for MM2, 21 for OPLS,[3] 24 for MM3, 25 for AMBER, and 59 for AM1.[2] Recent predictions fall in the range 15–17[3] and 15–21.[4] Experimentally, n_C is still unknown. Experimental lower and upper bounds for n_C are valuable for an assessment of very accurate ab initio and empirically modified[4] quantum-chemical descriptions of alkanes. They can be used for the training of molecular mechanics force fields.[5]

Any experimental strategy to determine n_C must involve cold isolated alkanes in the gas phase. Low temperature is essential, as there is an overwhelming number of non-extended conformations that quickly dominate the isomer distribution for long alkane chains with increasing temperature. Already for pentane at room temperature, the *all-trans* conformation is not dominant anymore.[6,7] Owing to the low volatility of long alkanes, a non-equilibrium technique is unavoidable. Supersonic jet expansions generate molecules with rotational and translational temperatures at around 10 K.[8] It is more challenging to lower the vibrational and conformational temperatures by collisions below the point where the global minimum structure starts to dominate.[9] Concerning detection, a characteristic vibration of the *all-trans* structure in the Raman spectrum[10] stands out among the less specific vibrations of folded alkanes. The frequency of this so-called accordion vibration is roughly inversely proportional to n. The chain ends oscillate symmetrically relative to the chain center,[9] maximizing the change in polarizability. At a given temperature, the accordion Raman intensity relative to the conformationally less-sensitive integrated CH stretching manifold should drop as a function of chain length, because more and more single- and multiple-*gauche* conformations will compete: a conformational entropy effect. An accelerated decrease is expected beyond n_C, when energetically competing hairpin structures emerge. The conformational distribution in a supersonic jet will deviate from a Boltzmann distribution, because the strongly populated single-*gauche* alkanes are more likely to relax to the *all-trans* structure than to a hairpin structure requiring three specific *trans-gauche* isomerizations. Therefore, the disappearance of the *all-trans* structure only provides a loose upper bound for n_C.

To obtain a reliable theoretical estimate of n_C, we performed a series of first-principles calculations for $n = 14$–22. The energy difference is rather small in this size range. This requires a high-level treatment, with a balanced description of the torsion potentials as well as the dispersion interactions responsible for the stability of the hairpin. Our approach is based on density-fitted local correlation methods.[11–14] This class of methods offers substantial reductions in the computational cost but also involves approximations that should be carefully considered in this context. There are two main sources of error. One is due to a truncation of the virtual space (domain error); this error is reduced when approaching the complete basis set limit.[15] Furthermore, in local coupled-cluster treatments, orbital pairs separated by at least one bond are by default treated at the MP2 level (weak pair approximation). This behavior can be controlled by distance criteria. We have performed a careful analysis of these effects (see the Supporting Information) and have devised a composite approach to reduce the abovementioned errors.

The cc-pVTZ (VTZ) and aug-cc-pVTZ basis sets (AVTZ)[16,17] were used throughout. The structures of all conformers were optimized at the DF-LMP2/VTZ level of theory. The electronic energy of each structure was then refined by computing:

$$E = E(\text{DF-LMP2-F12/VTZ-F12}) + \Delta E_{\text{sr}}(\text{CC/AVTZ}) + \Delta E_{\text{lr}}(\text{CC/VTZ}) \tag{1}$$

where:

$$\Delta E_{\text{sr}}(\text{CC/AVTZ}) = E_{\text{sr}}(\text{DF-LCCSD(T0)/AVTZ}) - E(\text{DF-LMP2/AVTZ}) \tag{2}$$

$$\Delta E_{\text{lr}}(\text{CC/VTZ}) = E_{\text{lr}}(\text{DF-LCCSD(T0)/VTZ}) - E_{\text{sr}}(\text{DF-LCCSD(T0)/VTZ}) \tag{3}$$

The first term in Equation (1) corresponds to the DF-

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LMP2-F12/3*A(loc)[18] energy using the VTZ-F12 basis set.[19] Through the use of explicit correlation, we are able to significantly reduce the basis set as well as the domain error in the underlying LMP2 calculation. The two remaining terms include higher-order correlation effects through the use of density fitting CCSD with noniterative perturbative triples (DF-LCCSD(T0)). In calculations with the sr (short-range) subscript, the default pair distances are used. In this way, only short-range contacts are treated at the highest level. Although the largest corrections are found for such pairs, the distance criterion needs to be increased to treat interactions between the parallel chains at the coupled-cluster level. This is done in the calculations with the lr(long-range) subscript, where the distance criterion for strong pairs is increased. The scaled zero point vibrational energy DF-LMP2/VTZ values (scaling factor of 0.978)[20] are then added to the electronic energy values obtained with Equation (1), together with thermal corrections (100 K). Further details relative to the distance criteria used and the overall computational procedure, together with benchmark calculations for the pentane system, can be found in the Supporting Information.

The results are shown in Figure 1. It should be noted that the energy difference varies very slowly with increasing size. This means that very small errors in the calculations might shift the energetic crossover point significantly. Taking into account the approach chosen, the largest error should be in determining the zero-point corrections. It is difficult to assess the latter accurately, but an estimated uncertainty of ±1 carbon atom or about 2 kJ mol^{-1} in the energy difference appears reasonable. This leads to a prediction of $n_C = 17 \pm 1$.

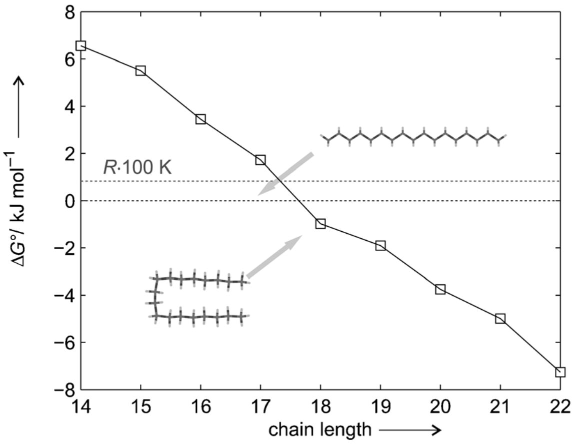

Figure 1. Calculated Gibbs energy difference $\Delta G^\circ = G^\circ_{\text{hairpin}}(100\text{ K}) - G^\circ_{all\text{-}trans}(100\text{ K})$ versus chain length using the energy expression given in Equation (1), together with the scaled DF-LMP2/VTZ zero-point and thermal corrections (100 K).

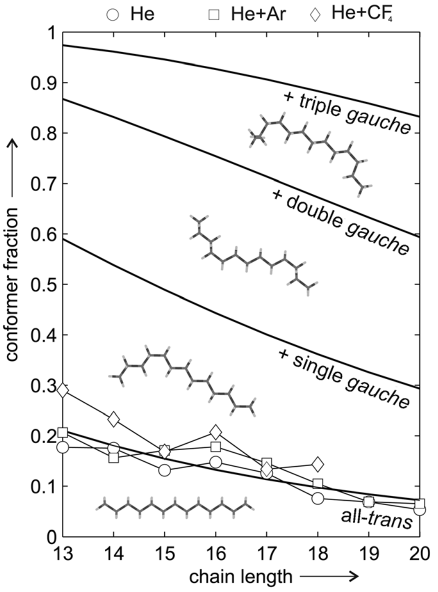

Figure 2. Cumulative abundance of *all-trans*, single-, double-, and triple-*gauche* conformations as a function of chain length *n* for a conformational temperature of 100 K. The *all-trans* fraction is determined semi-empirically (see the Supporting Information) and formally corresponds to a temperature of 100 K (He), 100 K (He + Ar), and 95 K (He + CF_4).

To access n_C experimentally, supersonic jet expansions of linear alkanes with $n = 13$–20 were characterized by Raman spectroscopy. The expansions were probed 1 mm downstream a 4.0×0.15 mm^2 heated slit nozzle, using 0.5–0.9 bar He as a carrier gas partially doped with Ar or CF_4 to enhance energy transfer. In the range $n = 16$–20, the *all-trans* enhancement amounts to (30 ± 10) % for 4 % CF_4 addition, as derived from the accordion vibration intensity gain relative to the spectral vicinity. The nozzle temperature was kept at about 403 K with substance temperatures between 310 and 393 K to achieve similar mole fractions for all chain lengths. To quantify the *all-trans* fraction in the supersonic jet, we periodically switched between the low-frequency range with the accordion vibration and the CH stretching spectral range. Comparison of the integrated scattering strength for the *all-trans* accordion mode with the sum of all CH oscillators allows for an estimate, based on corresponding B3LYP/6-311++G** predictions (see the Supporting Information). Occasional mode mixing and Fermi resonances in the accordion range are included.[9] Although systematic intensity errors may be in the order of 30 %, an estimate of the relative conformational temperature between different expansions to within 5 K is still possible. For this purpose, we compare to a simplified count of conformations up to five simultaneous *gauche* angles, assuming an average energy penalty of 2 kJ mol^{-1} per *gauche* angle, forbidding neighboring *gauche* angles of opposite sign (*syn*-pentane effect), and including rotational symmetry numbers and enantiomeric degeneracies. 2 kJ mol^{-1} is a compromise between higher-energy single-*gauche*, simple double-*gauche*, and several lower multiple-*gauche* values.[1,5,21] Figure 2 shows that the achievable *all-trans* fraction slowly decays from 20 % at $n = 13$ to less than 10 % at $n = 20$, being somewhat higher when Ar and in particular CF_4 is added to the expansion. The drop is steeper than $1/n$ because of contributions from populated multiple-*gauche* states. Applying the simple isomer count model to the experimental curves yields effective conformational temperatures of 100 K (He), 100 K

(He + Ar), and 95 K (He + CF_4). Approximate fractions of single-*gauche*, double-*gauche*, and triple-*gauche* conformations at 100 K are shown. The absolute conformational temperature is less well-defined. A sensitivity analysis with respect to the average *gauche* energy penalty and preferred isomerization of single torsional angles in the jet collisions suggests that it may be as high as 150 K.

Most competing conformations are seen to involve one or two *gauche* angles in the chain, for which the low-frequency vibrations are spread over a wide spectral range. In Figure 3, they give rise to moderately structured bands in the Raman jet spectra at around $(200 \pm 50)\,\mathrm{cm}^{-1}$ as well as to more local and weakly chain-length dependent bands near $400\,\mathrm{cm}^{-1}$. These non-specific Raman signals contrast to the sharp accordion bands at the low frequency end to which the spectra are scaled. At nearly threefold wavenumber, the next higher order accordion mode is found. The *all-trans* spectrum is simulated with dotted Gaussian line profiles ($4\,\mathrm{cm}^{-1}$ full width at half maximum) underneath the experimental spectrum. For this type of simulation, B3LYP/6-311++G** without any wavenumber-scaling has proved to be successful.[9] With increasing chain length, the non-accordion contribution to the spectrum grows and some bands of intermediate width start to separate from the broad background.

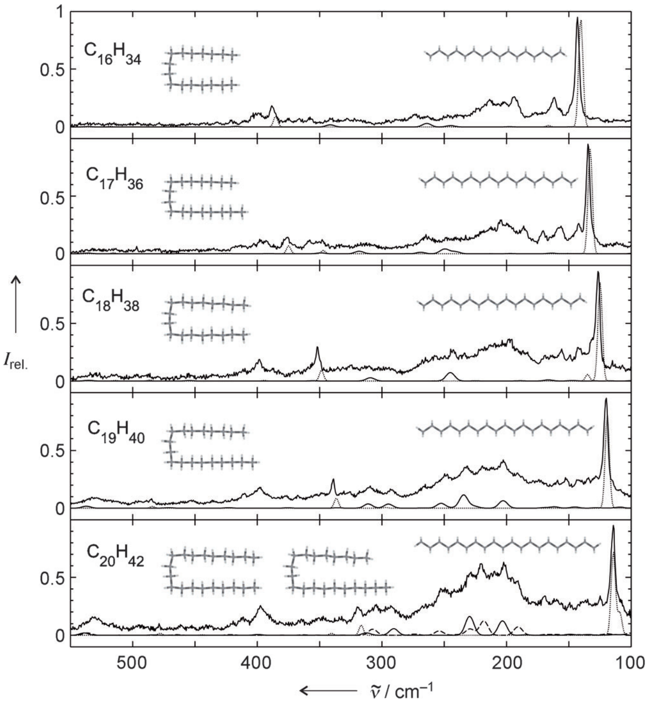

Figure 3. Experimental and simulated low-frequency Raman jet spectra in He expansions of hexadecane to eicosane. The *all-trans* spectrum is shown with dotted lines, and upper bounds of the hairpin conformer are shown with solid and dashed lines (nonsymmetric eicosane). The visually estimated abundance ratios for the scaling of the simulated spectra are (hairpin:*all-trans*) 0.2:1, 0.3:1, 0.3:1, 1:1, and (1 + 1):1 for hexa-, hepta-, octa-, nonadecane, and eicosane, respectively.

Spectral simulations of elementary hairpin structures are included in Figure 3 with doubled full width at half maximum. They involve a *gauche-gauche-trans-gauche-gauche* sequence in the middle of the chain with all *gauche* angles carrying the same sign.[2,22] To achieve an attraction between the two parallel chain segments, it is necessary to add a dispersion correction, for which we use Grimme's recent D3 version[23] in combination with the B3LYP/6-311++G** method. The effect is small for an *all-trans* conformation, but dramatic for a hairpin structure. For $C_{20}H_{42}$, we include the two hairpin structures with at least seven adjacent carbon atoms. The simulated hairpin abundance relative to *all-trans* in Figure 3 sets an upper limit to the experimental abundance, assuming a reasonably close reproduction of the band positions and intensities. In this way, a substantial hairpin contribution can be ruled out for $n = 16$–18. For $n = 19$, it is already close to the *all-trans* fraction and for $n = 20$, the hairpin contribution exceeds the *all-trans* contribution, with experimental evidence for both shown hairpin structures. The good wavenumber match between unscaled prediction and experiment follows the B3LYP performance for the *all-trans* structures.[9] It suggests an outstanding stability of the employed folding motif, but we cannot rule out the presence of other suggested variants.[4] The most prominent hairpin Raman modes fall in the range of analogous accordion modes of large cycloalkanes C_nH_{2n}, which are known to prefer the same hairpin motif[24] and to match the position of the linear alkane mode with half the number of carbon atoms.[25]

This leads to a straightforward initial assignment of $C_{18}H_{38}$ as the last alkane which does not prefer a folded state at low temperature, because it is the last chain which shows a negligible quantity of populated hairpin contributions in Figure 3. However, this $n_C = 18$ assignment may just be an upper bound. The conformational equilibrium in the jet is not complete and the *all-trans* structure just needs one torsional change to be populated from the abundant single-*gauche* structures, whereas the hairpin is handicapped by three required changes, lagging behind in population in this kinetically controlled experiment.

It could be argued that $n_C = 17$ is a more likely interpretation based on a quantum-statistical argument. Whereas the *all-trans* structures and the symmetric hairpins have a rotational symmetry number of 2 owing to the Pauli exclusion principle, the odd-numbered chains as well as the nonsymmetric eicosane structure share a symmetry number of 1. This doubles their statistical weight. Furthermore, all hairpins are chiral and have an enantiomeric partner, as opposed to *all-trans*. Therefore, at the moment where the hairpin structures cross the energy of the *all-trans* structure, each of them is statistically favored by a factor of 2 or even 4. Taking this into account, the experimental hairpin contribution for $n = 17$ is less than 8% of what would be expected for the ideal isoenergetic cross-over point, whereas starting with $n = 18$ (15%) this fraction steeply increases up to 25% ($n = 19$) and 33% ($n = 20$). This turning point in statistical abundance could be taken as an indication that $n = 18$ already starts to fold by a significant amount at 100–150 K. Furthermore, the relaxation between structures of similar energy separated by four C–C torsion barriers is notoriously difficult in supersonic jets,[8] possibly delaying the visible onset of folding despite its energetic feasibility.

The effective conformational temperature of 100–150 K involves a smearing out of the structural transition by at least 2 kJ mol^{-1}. This means that even for perfect thermal equilibrium it would be difficult to sequence conformations which are just 2 kJ mol^{-1} apart. In summary, we can firmly state that $n_C = 17$–18, in agreement with the quantum chemical prediction. $n_C = 17$ is actually more likely, because even chain lengths profit somewhat more from folding than odd ones (Figure 1). Nonadecane is definitely a hydrocarbon which prefers a folded state over a fully stretched state when suspended in vacuum under thermal equilibrium conditions at sufficiently low temperature. It has to be verified by experiments that achieve still lower conformational temperatures[26] whether octadecane may instead be named the most elementary organic foldamer.[27]

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