the corresponding diazirines by 5.6, 12.6, 7.1, 9.5, and 1.9 kcal/mol, respectively, even though all of these groups have similar χ_{BE} values. The larger effect for the first four groups is attributed to π-acceptor stabilization of the diazomethanes. Thus there are major effects of the substituents on which isomer is more stable that are largely attributable to the influences of electronegativity and conjugation on the diazomethane stabilities.[9]

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Supplementary Material Available: Tables of geometries, dipole moments, and Mulliken atomic charges of diazomethanes and diazirines (Tables 2–6) (9 pages). Ordering information is given on any current masthead page.

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[9] **Note Added in Proof.** Prof. Schleyer has kindly sent us a preprint of ref 4c, which reports calculations on **1** and **2** for R = H and F at a higher level of theory than reported here. In agreement with their results we also find diazomethane to be 6.4 kcal/mol more stable than diazirine at the MP4/6-31G*//MP2/6-31G* level. Thus these results suggest that our essential conclusions are unchanged at higher levels of theory.

New Results on Protein Folding from Simulated Annealing

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The prediction of the native states of proteins from their primary sequences entails the solution of two basic types of problems. First, one must model the interaction energies of the peptides and the solvent with adequate fidelity; second, one must locate the low-lying energy states that dominate at biological temperatures. Model potentials that are capable of reproducing the low-energy states of peptide fragments with ideal structural motifs have been described recently by Rey and Skolnick[1] and by Honeycutt and Thirumalai.[2,3] Studies by these groups have mainly focused on simulating and understanding folding pathways of protein models. Although the pathways and mechanics of folding are of great interest and represent yet another basic problem, our goals are to rigorously address the first two problems to ensure that the folded state can be reliably located. The purpose of the present work is to describe the application of a new simulated annealing method to locate the global minimum conformation and analyze the thermodynamic properties of a 22-residue model of a peptide structure. The ideal structural motif for the model chosen is an α-helical hairpin.

Our method uses the continuum potential and peptide model described by Rey and Skolnick for their Brownian Dynamics (BD) simulations of protein folding.[1] We have combined simulated annealing[4] with the optimal histogram method of Ferrenberg–Swendsen[5] to analyze the density of states and specific heat of this continuous space model.[6] Unlike molecular dynamics (MD) based methods that require substantial computing resources, we found the energy minimization problem tractable on a modest desktop personal computer. Our implementation reproduces the low-energy helical hairpin states previously observed[1] and also reveals the existence of a lower, qualitatively different family of states not generated by the other methods (see Figure 1). Our results also indicate that the development of structure is associated with a peak in the specific heat vs temperature plot (see Figure 2), supporting the notion that appreciable structure forms before folding to the final state.

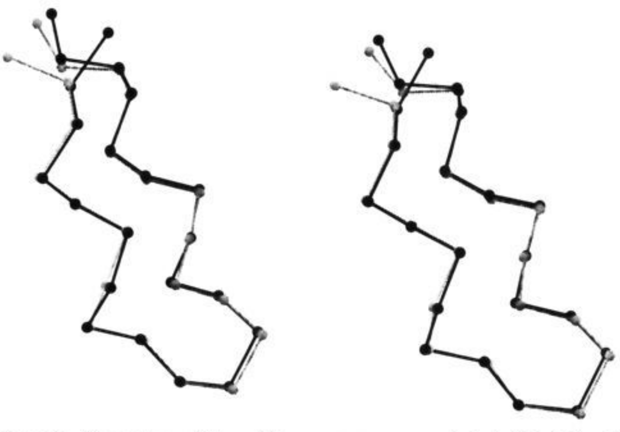

Figure 1. Stereoview of the minimum-energy scrunch state (black) and the higher energy α-hairpin state (gray) for a 22-bead protein model.

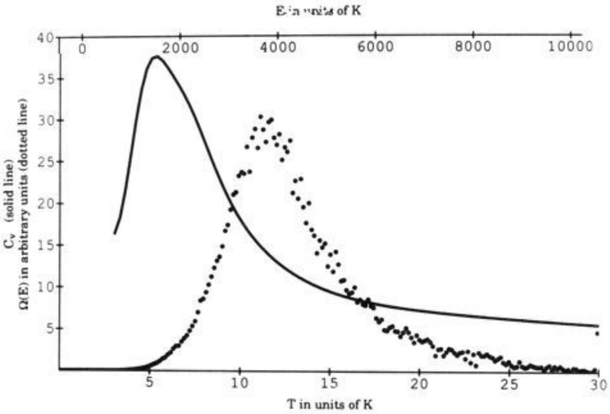

Figure 2. Density of states Ω vs E and specific heat C_v vs T for a schematic 22-bead α-hairpin protein.

We refer to the new states as "scrunch" configurations. Although the minimum-energy configuration obtained in all runs was the scrunch form, the scrunch and helical hairpin forms do overlap in energy, suggesting that a mixture of these configurations contributes to the free energy of the model at nonzero temperatures. At low temperatures the system is dominated exclusively by small fluctuations of the bead positions about the scrunch state. Low-energy states with structural anomalies have also been reported by Honeycutt and Thirumalai for a larger system.[2,3] However, that study was not specific about the relationship of such states to the global minimum configuration nor was it clear that these states have physical significance. It is argued that these states are "metastable" and would presumably interconvert to the expected conformational states given sufficient time. These states, and many others, are proposed to exist within the framework of the metastability hypothesis.[2] Our results, on the other hand, are consistent with the system being thermally equilibrated and indicate that at moderate temperatures (0.5–2 K) a population of structures exists that has minor fluctuations about the ideal α-helical hairpin and scrunch states. These should not be confused with states regarded as being metastable.

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[5] Ferrenberg, A. M.; Swendsen, R. H. *Comp. Phys.* **1989**, Sept/Oct, 101–104.

[6] Specific details of the method can be obtained from the authors.

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Although these scrunch states exist on the continuum model studied by Rey and Skolnick, they have not been previously reported as the ground state.[1] The apparent failure of the BD simulations to locate the scrunch state may be due to the relative inefficiency of dynamics methods for searching conformational space.[7] Alternatively, it may be that the entropy of the scrunch states is so low that they are very improbable at the finite temperatures used in the BD simulations.[1] These configurations are also absent from the more efficient Monte Carlo lattice simulations reported in that same study. This may be due to the truncation of configuration space by the lattice or from differences in the discrete and continuous potentials. Our results suggest that the physical characteristics of the lattice and off-lattice models may not be the same, contradicting the results of that study. However, they are not conclusive, and further investigation is required to determine whether a significant difference exists.

As can be seen in Figure 1, the scrunch configuration has the N-terminal bead twisted from its torsionally favored gauche (−) state into the trans state (nomenclature from ref 1), allowing it to form an additional hydrophobic contact with the interior of the protein at the expense of increased torsional energy. Although the structural difference appears minor, the energy difference is significant (2 K, units from ref 1). The degree to which the scrunch conformation is favored relative to the α-hairpin depends on the relative strengths of the trans and gauche (−) minima, which favor helix formation, and the depth of the phobic–phobic well, which favors formation of a hexagonal close-packed structure. For example, the scrunch state depicted in Figure 1 is 2 K below the accompanying α-helical state. This results in an energy increase of roughly 6 K in torsion, 3 K in the repulsive philic–philic/philic–phobic term, and 2 K in bond angle energy. The bond length energy and helical cooperative energies are virtually unchanged, while the phobic–phobic energy decreases by 13 K.

One of the great advantages to using simulated annealing for this type of optimization problem is that it is based on statistical mechanics and therefore can be used to extract a great deal of chemically relevant information about a system in addition to its ground-state configuration. We have chosen a conservative cooling schedule, so that during the later portion of each sweep, the system is in thermal equilibrium, allowing one to measure equilibrium thermodynamic features of the system. By combining the data for all of the temperature sweeps using the Ferrenberg–Swendsen multiple histogram method,[5] $\Omega(E)$ and $C_v(T)$ have been determined and are shown in Figure 2.

The peak in C_v vs T near $T = 6$ suggests that the system undergoes a phase transition there. This was further corroborated by examining the conformations during annealing (i.e., the populations of the dihedrals) and the corresponding density of states. Above $T \approx 6$ K little secondary structure is observed. However, when T is below 6 K, large helical fragments and some phobic contacts form and persist over many structural perturbations. Examination of the dihedral angle variance as a function of temperature shows that it undergoes a decrease of 1–2 orders of magnitude over about a 1 K range in the region of the peak in C_v. This phase transition is consistent with the results of Honeycutt and Thirumalai.[2,3] Further analysis of the statistics and reaction coordinates is required to confirm the nature of this phase transition.

Further application of our methodology to study protein models should greatly aid in understanding the behavior of these simplified representations and their physical significance. It is also important to note that our approach should be applicable to a wide variety of problems and systems in computational chemistry, biology, and physics. The determination of the density of states allows the complete characterization of all thermodynamic properties of molecular systems, providing a new route to calculate important quantities such as free energy and entropy.

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Internal Coordination at Tin Promotes Selective Alkyl Transfer in the Stille Coupling Reaction

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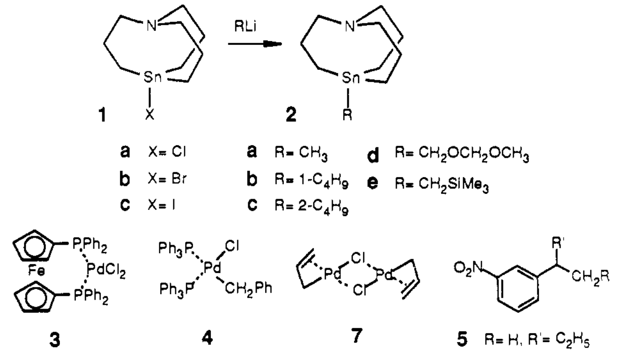
The CH_3–Sn bond in 1-aza-5-stannabicyclo[3.3.3]undecane **2a** is ca. 0.1 Å longer than the CH_2–Sn bonds.[1] The contrasting ^{13}C–^{119}Sn coupling constants (methyl $^1J_{C\text{-}Sn} = 171$ Hz; methylene $^1J_{C\text{-}Sn} = 405$ Hz)[1] also suggest unusual CH_3–Sn hybridization and the possibility of increased reactivity.[2] However, **2** and the precursor halides **1** have been difficult to prepare, and very little is known about this intriguing ring system. We now report that **1a** can be obtained by the hydrozirconation of triallylamine, followed by in situ metal exchange with $SnCl_4$ (one-pot method; 50% isolated).[3] The air-stable alkyl derivatives **2**[3b] (from **1** + RLi) are unusually reactive in Stille coupling with aryl and alkenyl halides. Metal–alkyl exchange occurs at the exocyclic Sn–C bond and solves the problem of selective transfer of a single primary alkyl group from tin.[4]



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(3) (a) A 250-mL flask was purged (N_2) and charged with Cp_2ZrHCl (6.45 g), dry THF (160 mL), and *N*,*N*,*N*-triallylamine (1.10 g). After 3 h of stirring at 23 °C, the solution was cooled to −78 °C, treated with freshly distilled $SnCl_4$ (2.19 g), and allowed to warm to 23 °C over 4 h. After 14 h, the mixture was added to water (400 mL), extracted ($C_2H_5O_2CCH_3$; 200 mL; 100 mL), dried (Na_2SO_4), filtered, and evaporated (aspirator) to give a pale yellow solid (1.44 g). Recrystallization (CH_3OH) gave **1a** (1.18 g, 50%), mp 222–224 °C (lit.[1] mp 240–242 °C). The NMR spectrum matches that reported.[1] (b) New compounds gave satisfactory exact mass and NMR data: δ ^{13}C ($^1J_{C\text{-}Sn}$) [δ ^1H]; endocyclic CH_2Sn, **2b**, 6.9 ppm (376 Hz) [0.60 ppm], **2c**, 5.7 ppm (255 Hz) [0.61 ppm], **2d**, 6.29 ppm (398 Hz) [0.74 ppm]; exocyclic RCH_2Sn, **2b**, 16.3 (214 Hz) [0.38 ppm], **2c**, 27.0 ppm (355 Hz) [0.87 ppm], **2d**, 64.2 ppm (213 Hz) [3.36 ppm].

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