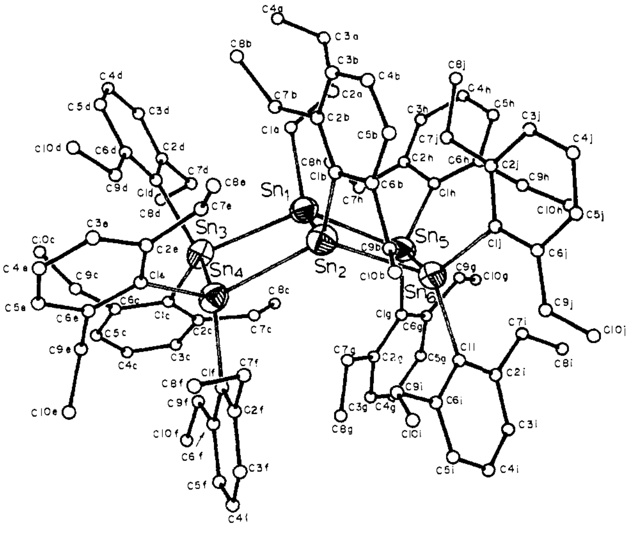

Figure 1. Crystal structure of **1**: Tin atoms are represented by thermal vibration ellipsoids drawn to encompass 50% of their electron density, and carbon atoms are represented by small spheres of arbitrary size for purposes of clarity. Butyl carbon atoms are labeled 1a-4a, and the aryl ligand carbons are each labeled with a number (from 1 to 10) with a literal subscript (b-j) identifying their particular ligand. Bond lengths (Å): Sn_1-Sn_2 2.818 (1), Sn_1-Sn_3 2.832 (1), Sn_1-Sn_5 2.835 (1), Sn_2-Sn_4 2.931 (1), Sn_2-Sn_6 2.925 (1), Sn_3-Sn_4 2.924 (1), Sn_5-Sn_6 2.899 (1), Sn-C 2.214 (8)-2.230 (9). Bond angles (deg): $Sn_3Sn_1Sn_2$ 91.6 (1), $Sn_1Sn_2Sn_4$ 90.2 (1), $Sn_2Sn_4Sn_3$ 87.5 (1), $Sn_4Sn_3Sn_1$ 90.1 (1), $Sn_2Sn_1Sn_5$ 92.9 (1), $Sn_1Sn_5Sn_6$ 88.9 (1), $Sn_5Sn_6Sn_2$ 89.4 (1), $Sn_6Sn_2Sn_1$ 88.7 (1), $Sn_3Sn_1Sn_5$ 133.3 (1), $Sn_4Sn_2Sn_6$ 130.8 (1).

state, as demonstrated by its dramatic reversible thermochromic behavior, being pale yellow at −196 °C and orange-red at room temperature. In addition, the ultraviolet absorption maxima at 309 nm (ϵ_{max} = 37 900) and at 360 nm (ϵ_{max} = 13 690) in methylcyclohexane are similar to those attributed to σ-delocalization in short-chain linear polystannanes.[3b] With regard to its mechanism of formation, it is likely that the aryllithium reagent, **2**, can serve to reductively remove either a chloro or aryl substituent to form a radical (or anionic) intermediate which can then react with the *n*-butyl bromide (produced from the reaction of the aryl bromide with *n*-butyllithium) to form **1**.[9]

In conclusion, the view provided by the structure of **1** will aid in identifying the steric features of the ligands which will be required for the successful development of new synthetic routes for the construction of polycyclic polystannane frameworks. Further studies concerning the physical properties of **1** and the synthesis of other derivatives are currently in progress.

Acknowledgment. We thank Dr. Cynthia Day of Crystalytics Co. for the structural analysis of **1** and the Office of Naval Research for financial support. The high resolution mass spectrum of **1** was provided by Dr. Catherine Costello of the facility supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann), from the Division of Research Resources.

Supplementary Material Available: Detailed information concerning the spectroscopic and crystallographic analysis of **1**, including listings of atomic coordinates and temperature factors, bond lengths, bond angles, and anisotropic temperature factors and an ORTEP representation of **1** (23 pages). Ordering information is given on any current masthead page.

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[9] Other *n*-butyltin derivatives have been isolated from the reaction of $SnCl_2$ with sterically hindered lithium reagents prepared from *n*-butyllithium, see: (a) Cardin, C. J.; Cardin, D. J.; Norton, R. J.; Parge, H. E.; Muir, K. W. *J. Chem. Soc., Dalton Trans.* **1983**, 665. (b) Bigwood, M. P.; Corvan, P. J.; Zuckerman, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 7643.

Interactions between Amides in Solution and the Thermodynamics of Weak Binding

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Interactions between amides have been widely investigated owing to the connection to protein structure and stability.[1] Among classic studies,[2,3] infrared work has revealed decreasing aggregation for secondary amides along the solvent series $CCl_4 > C_6H_6 > CHCl_3, CH_2Cl_2 >$ dioxane >> water.[3] In fact, Klotz and Franzen quantified the negligible self-affinity of *N*-methylacetamide (NMA) in water by measuring a free energy of association of +3.1 kcal/mol.[3c] As reported here, modern theoretical methods have now been applied to obtain the first free energy profiles or "potentials of mean force" (pmf's) for the association of amides and the corresponding predicted K_a's.

Monte Carlo statistical mechanics simulations were carried out for two NMA molecules plus 250 chloroform or 310 water molecules in periodic boxes in the NPT ensemble at 25 °C and 1 atm. The computational details are the same as for prior pmf determinations.[4,5] In particular, statistical perturbation theory[6] was used to obtain the free energy changes as the two solutes were perturbed apart in increments of 0.2 Å with the N···O distance as the reaction coordinate. The OPLS potential functions were used for NMA[7,8] and chloroform[9] along with the TIP4P model of water.[10] Thus, all atoms are explicit except hydrogens on carbon, and Coulomb and Lennard-Jones interactions are included between the interaction sites. Feathered cutoffs were used to truncate the intermolecular interactions beyond 12 Å in chloroform and 8.5 Å in water.[4,5] Bond lengths and bond angles were not varied, while the torsional motion about the central C-N bond of NMA was sampled.[8] Otherwise, the motion of the solutes was unconstrained so all intermolecular arrangements were accessible at the set values of the reaction coordinate. Each of the 16 simulations then entailed equilibration for at least 6×10^5 configurations starting from equilibrated solvent boxes and the amides in a hydrogen-bonding orientation, followed by averaging for 2×10^6 configurations.

The resultant pmf's are shown in Figure 1. In chloroform, a single free energy well is found with a depth of −3.5 kcal/mol for the minimum at r(N···O) = 2.8 Å. Plots of configurations clearly show that the amides are hydrogen bonded (Figure 2, top). However, in water the amides exhibit no net attraction owing to the competition with hydrogen bonding to the solvent. In fact, plots of configurations reveal that at short separations the amides

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(1) Schulz, G. E.; Schrimer, R. H. *Principles of Protein Structure*; Springer-Verlag: New York, 1979.

(2) (a) Schellman, J. A. *Compt. Rend. Trav. Lab Carlsberg, Ser. Chim.* **1955**, *29*, 223. (b) Davies, M.; Thomas, D. K. *J. Am. Chem. Soc.* **1955**, *60*, 763, 767. (c) Kauzmann, W. *Adv. Protein Chem.* **1959**, *14*, 1. (d) Nemethy, G.; Scheraga, H. A. *J. Phys. Chem.* **1962**, *66*, 1773. (e) Kresheck, G. C.; Klotz, I. M. *Biochemistry* **1969**, *8*, 8.

(3) (a) Klemperer, W.; Cronyn, M. W.; Maki, A. H.; Pimentel, G. C. *J. Am. Chem. Soc.* **1954**, *76*, 5846. (b) Tsuboi, M. *J. Chem. Soc. Jpn. Pure Chem. Sect.* **1955**, *76*, 376. (c) Klotz, I. M.; Franzen, J. S. *J. Am. Chem. Soc.* **1962**, *84*, 3461. (d) Susi, H.; Timasheff, S. N.; Ard, J. S. *J. Biol. Chem.* **1964**, *239*, 3051. (e) Spencer, J. N.; Garrett, R. C.; Mayer, F. J.; Merkle, J. E.; Powell, C. R.; Tran, M. T.; Berger, S. K. *Can. J. Chem.* **1980**, *58*, 1372. (f) Krikorian, S. E. *J. Phys. Chem.* **1982**, *86*, 1875.

(4) Jorgensen, W. L.; Buckner, J. K.; Huston, S. E.; Rossky, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 1891.

(5) Buckner, J. K.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 2507.

(6) Zwanzig, R. W. *J. Chem. Phys.* **1954**, *22*, 1420.

(7) Jorgensen, W. L.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1988**, *110*, 1657.

(8) Jorgensen, W. L.; Swenson, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 569, 1489.

(9) Jorgensen, W. L.; Nguyen, T. B.; Boudon, S. *J. Am. Chem. Soc.* **1989**, *111*, 755.

(10) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926.

0002-7863/89/1511-3770$01.50/0

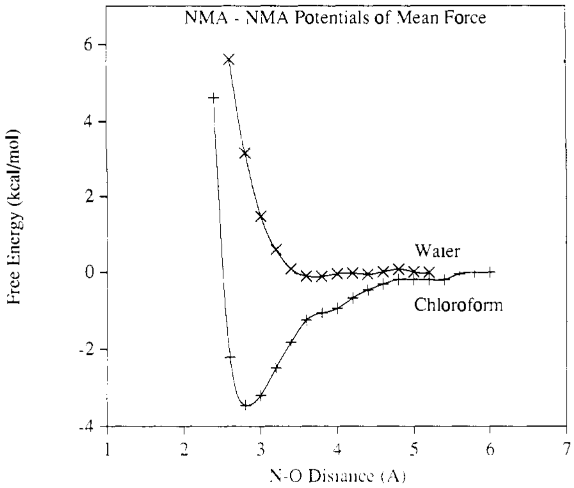


Figure 1. Computed potentials of mean force for the association of two NMA molecules in chloroform and water. The statistical uncertainties ($\pm 1\sigma$) at the ends of the curves starting from the middle are ca. ±0.2 kcal/mol.

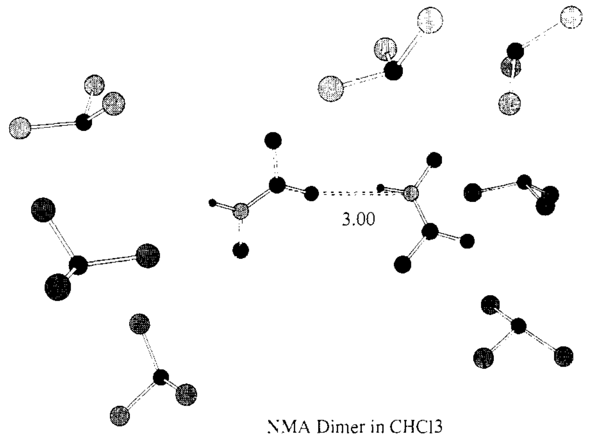
do not form a hydrogen bond (Figure 2, bottom); rather, stacked geometries are common with a favorable dipole alignment that exposes the amides' edges to minimize loss of hydrogen bonding to water. However, the potential energy for just the NMA–NMA interaction at 3.0 Å averages only −3.5 kcal/mol which is not enough to overcome the more optimal hydration that occurs at larger separations. For comparison, the average intersolute energy at 3.0 Å in chloroform is −7.5 kcal/mol.

The pmf's, $w(r)$, can also yield the association constants K_a in the high-dilution limit via eq 1.[11] Such computations have been

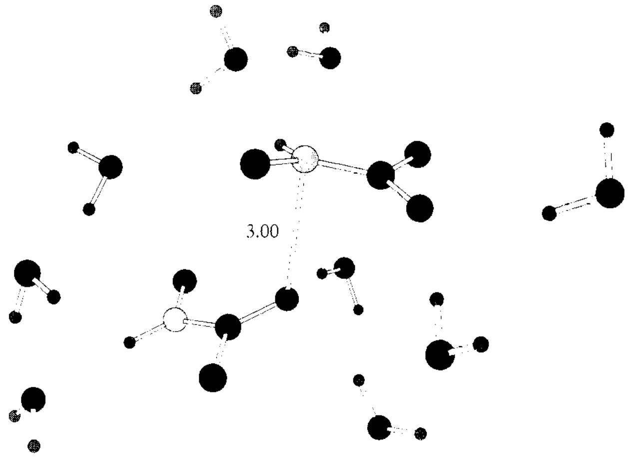
$$K_a = 2\pi \int_0^c r^2 \exp(-w(r)/k_B T) \mathrm{d}r \qquad (1)$$

rare since pmf's have been unavailable.[5,12] For chloroform, the results turn out not to be very sensitive to reasonable choices of the geometric limit to association, c; c = 3, 4, and 5 Å gives K_a = 2.4, 3.8, and 4.0 M^{-1}.[13] The accord with the experimental value[3f] of 2.7–2.8 M^{-1} provides important support for the computational methods, the potential functions, and the pmf. For water, c = 3, 4, and 5 Å gives K_a = 0.0001, 0.04, and 0.12 M^{-1}, while the IR finding is 0.005 M^{-1}.[3c] In this case, there is significant uncertainty in the experimental result[3c,f] and in the appropriate choice for c; however, the qualitative description of the binding is clear.

The discrepancy between the well-depth of −3.5 kcal/mol in chloroform and the free energy of binding (ΔG_b°) of only −0.8 kcal/mol from $-RT \ln K_a$ should also be noted. Of course, it follows from the integration over the pmf in eq 1. In fact, if the pmf in chloroform is scaled, an excellent linear correlation (r = 0.998, σ = 0.19 kcal/mol) is obtained between the well-depth (ΔG_{min}) and ΔG_b°, $\Delta G_{\mathrm{min}} = 1.16 \Delta G_b^\circ - 2.37$. Since a prototypical hydrogen bond is being considered, this result should have some generality. It emphasizes that for typical, measured ΔG_b°'s the corresponding well-depths in the free energy profiles may be several kcal/mol more negative.



NMA Dimer in CHCl3



NMA Dimer in Water

Figure 2. Typical configurations from the simulations of two NMA molecules in chloroform (top) and water (bottom) with r(N···O) constrained to be 3.0 Å. Only a few of the solvent molecules in the vicinities of the solutes are shown. Hydrogens on carbon are implicit.

Overall, the present results illustrate the capabilities of computer simulations to study molecular association in solution.[14] Detailed thermodynamic and structural insights are available along with the opportunity for direct comparisons with experimental binding data.[15]

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(11) (a) Justice, M.-C.; Justice, J.-C. *J. Solution Chem.* **1976**, *5*, 543. (b) Chandler, D.; Pratt, L. R. *J. Chem. Phys.* **1976**, *65*, 2925. (c) Chandler, D. *Faraday Discuss. Chem. Soc.* **1978**, *66*, 184. (d) Shoup, D.; Szabo, A. *Biophys. J.* **1982**, *40*, 33.

(12) Hirata, F.; Levy, R. M. *J. Phys. Chem.* **1987**, *91*, 4788.

(13) Different choices of the reaction coordinate would alter $w(r)$, though K_a would be invariant for appropriate choice of the new integration limit c. Also, proper application of eq 1 requires complete sampling of intersolute geometries at each r. The stability of the computed free energy changes between 1×10^6 and 2×10^6 configurations of averaging and the smoothness of the $w(r)$'s are consistent with the occurrence of adequate sampling.

(14) (a) Jorgensen, W. L. *Acc. Chem. Res.* **1989**, in press. (b) Beveridge, D. L.; DiCapua, F. M. *Ann. Rev. Biophys.* **1989**, in press.

(15) This work was supported by grants from the National Institutes of Health and the National Science Foundation.