Solvent effects on the stability of simple secondary amides†

Kathleen M. Morgan* and Daniel A. Kopp

Department of Chemistry, The College of William & Mary, PO Box 8975, Williamsburg VA 23187-8795. E-mail: kmmorg@chem1.chem.wm.edu; fax: (757) 221 2715

Received (in Gainesville, FL) 8th April 1998, Accepted 11th October 1998

Enthalpies of solution for *N*-methylpropionamide and 2-pyrrolidone in water, propan-1-ol, acetone and toluene were measured by calorimetry. Heats of vaporization were determined for the amides by ebulliometry, and enthalpies of solvation from gas phase were obtained. Enthalpies of solvation were the same for the two nearly-isomeric amides in polar, protic solvents, but in acetone and toluene dimerization of 2-pyrrolidone caused differences in enthalpies of solvation. For *N*-methylpropionamide, solvation enthalpy from the gas phase is highly correlated with the ability of the solvent to donate hydrogen bonds, but not well correlated with the ability of the solvent to accept hydrogen bonds, the polarity/polarizability of the solvent, or solvent relative permittivity.

Introduction

Understanding the factors which influence rotation around the amide C–N bond in simple model systems can give insight into the protein folding process. In planar conformations, delocalization of electrons from the nitrogen to the carbonyl group increases the C–N bond order, restricting rotation compared to a normal sigma bond. The specific origins of these interactions have been studied in considerable detail.[1] In secondary amides, substituents are known to affect both the barrier height and the equilibrium constant between planar conformations.[2–6] The (*Z*) conformation, with the *N*-alkyl group eclipsing the carbonyl group, is more stable than the (*E*) conformation, in which the *N*-hydrogen eclipses the carbonyl group. In *N*-methylacetamide (NMA), a common model of the peptide bond, the population of the (*Z*) conformation was found experimentally to be 98.5%, and *N*-methylformamide has 91% (*Z*) conformation.[4]

There are many studies of tertiary amides which show that solvent affects the C–N rotational barrier but has a negligible effect on the equilibrium population of conformers.[3,7] Very few studies are available for secondary amides due to the difficulty in measuring the highly unbalanced equilibrium population of conformers. The few available data suggest that the same conclusions apply,[2,4,5,8] yet additional data are needed to further explore these trends. The goal of this study is to evaluate quantitatively and comparatively how solvent affects the energies of stable (*E*) and (*Z*) secondary amides. Enthalpies of solution for *N*-methylpropionamide and 2-pyrrolidone are measured by calorimetry, then are converted to enthalpies of solvation from the gas phase. This technique has been applied successfully in evaluating the influence of solvent on the anomeric effect.[9]

Results

Selection of amide model compounds

Two amides were chosen for this study: *N*-methylpropionamide (**1**) and 2-pyrrolidone (**2**). *N*-Methylpropionamide is known to exist exclusively in the natural (*Z*) conformation about the amide bond,[2] thus is more convenient for this study than *N*-methylacetamide since no correction is needed to account for the (*E*) conformation. *N*-Methylpropionamide is also nearly isomeric with 2-pyrrolidone, the least strained lactam in which the ring forces the unfavorable (*E*) conformation to be adopted. An estimate of the lactam strain energy is 1.1 kcal mol^{-1}.[10] Thus 2-pyrrolidone is a reasonable model for the (*E*) conformation of *N*-methylpropionamide.

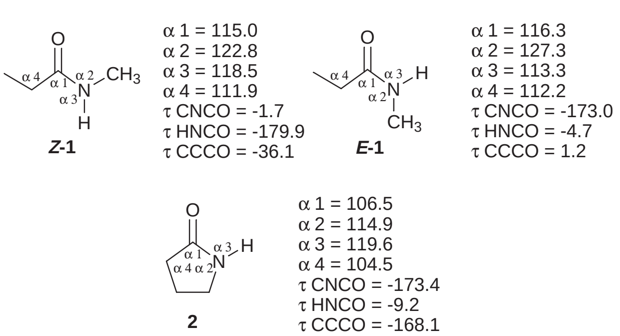

Fig. 1 Selected structural parameters of (*Z*)- and (*E*)-*N*-methylpropionamide and 2-pyrrolidone (B3LYP/6-31G*).

Table 1 Results of calculations: 2-pyrrolidone, (*E*)- and (*Z*)-*N*-methylpropionamide (B3LYP/6-31G*)

	E/Hartrees	ZPE/ kcal mol^{-1}	C_v(298)/cal mol^{-1} K^{-1}	Dipole moment/D
(*Z*)-*N*-Methyl-propionamide	−287.83794	82.55	25.54	3.52
(*E*)-*N*-Methyl-propionamide	−287.83420	82.44	25.58	3.74
2-Pyrrolidone	−286.63010	69.98	19.64	3.90

Ab initio calculations (B3LYP/6-31G*) show that there are several structural differences between (*E*)-*N*-methylpropionamide (***E*-1**) and the model 2-pyrrolidone as shown in Fig. 1. Parameters for (*Z*)-*N*-methylpropionamide (***Z*-1**) are also included. The angles within the ring are compressed in **2**, and the CCCO dihedral angle is substantially different. While some of these differences are large, ***E*-1** has two additional hydrogens whose steric interference causes the molecule to open up, even compared to ***Z*-1**. Table 1 shows other results of the calculations: energies and dipole moments, and unscaled zero-point energies and heat capacities from frequency calculations. The calculated energies show that at room temperature *N*-methyl-

---

† Supplementary material is available (SUPPL. NO. 57449, pp. 2) from the British Library. For details of the Supplementary Publications Scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC Web page (http://www.rsc.org/authors). The supplementary data is also available on the RSC's web server (http://www.rsc.org/suppdata/perkin2/1998/2759/).

Table 2 Properties of the solvents used in this study[a]

	Relative permittivity	H-bond donation	H-bond acceptance	π* (polarity/polarizability)	$E_T(30)$	Cohesive energy density/cal cm^{-3}
Water	78.30	1.17	0.47	1.07	63.1	550.2
Propan-1-ol	20.45	0.84	0.90	0.52	50.7	144.0
Acetone	20.56	0.08	0.43	0.71	42.2	94.3
Toluene	2.38	0.00	0.11	0.54	33.9	79.4
NMA	191.3	0.47	0.80	1.01	52.0	
2-Pyrrolidone	28.2[b]	0.36	0.77	0.85	48.3	

[a] Relative permittivity and $E_T(30)$ values are from reference 15; Cohesive energy density data are from reference 16; and the remaining data are from the review by Marcus (reference 14). [b] *CRC Handbook of Chemistry and Physics*, 78th edn., CRC Press, New York, 1998.

propionamide adopts the (*E*) conformation about 2% of the time, in reasonable agreement with experiment. Note that the calculations represent the vacuum phase and the experiment was done in solution; however the medium is known to have little effect on the equilibrium constant. The calculated dipole moment for ***Z*-1** (3.52 D) compares favorably to the value determined experimentally for **1** (3.59 D).[11]

Choice of solvents

The four solvents studied are water, propan-1-ol, acetone and toluene, chosen to represent a wide range of properties as shown in Table 2. Propan-1-ol and acetone have the same relative permittivity but very different hydrogen bonding properties. Toluene was chosen because the active sites in some peptidyl–proline *cis–trans* isomerases are known to be rich in aromatic residues.[12] Some empirical properties of these solvents are shown in Table 2. Columns 3–5 are the α, β and π* parameters from the linear solvation energy relationship described by Kamlet, Taft and co-workers.[13] The α, β and π* values tabulated were reported by Marcus.[14] Reichardt's solvatochromic $E_T(30)$ values are included,[15] as are values for cohesive energy density.[16] In addition, parameters are included for 2-pyrrolidone, and since data could not be found for *N*-methylpropionamide, the parameters for *N*-methylacetamide (NMA) are included instead.

Enthalpies of solution: amide (l)→amide (solution)

The enthalpies of dissolving pure liquid amide into pure solvent, to a concentration of approximately 0.01 M, were measured by calorimetry using an automated system described previously.[17] Each measurement was repeated several times to ensure accuracy. The results are shown in Table 3. The enthalpy of solution of *N*-methylpropionamide in water agrees with the value reported by Wadsö, within experimental error.[18] In the earlier study, enthalpies were measured as a function of concentration and were extrapolated to 0.01 M.

To verify that the population of ***E*-1** remains essentially zero on the timescale of the calorimetry experiment, solutions of *N*-methylpropionamide were studied by NMR. *N*-Methylpropionamide was dissolved in D_2O, acetone-d_6, and toluene-d_8, and room temperature spectra were acquired within ten minutes of mixing, 30 minutes to an hour later, then three hours later. In all cases, only the resonances for ***Z*-1** were observed.

Aggregation of amides and lactams

The enthalpies of solution are not simple quantities for two reasons, both due to aggregation. First, the numbers in Table 3 represent the process of dissolving a pure liquid, and it is known that (*Z*)-amides and (*E*)-amides have different liquid structures.[19] The (*E*) conformation of the lactam predisposes it to form hydrogen-bonded cyclic dimers. Amides of the (*Z*) conformation instead tend to oligomerize at high concentration, overall a less favorable process. The boiling points of the two molecules support this distinction: 209 °C (**1**) and 245 °C (**2**). The differences in the intrinsic stabilities of the liquids can be factored out if one instead takes an isolated gas-phase molecule and dissolves it. These values are easily obtained by combining enthalpies of vaporization with the enthalpies of solution.

Table 3 Enthalpies of solution (cal mol^{-1})[a]

Solvent	*N*-Methylpropionamide **1**	2-Pyrrolidone **2**
Water	−3575 ± 20 (5)[b]	−2162 ± 61 (6)
Propan-1-ol	94 ± 13 (5)	1185 ± 75 (5)
Acetone	1090 ± 18 (5)	883 ± 40 (5)
Toluene	2728 ± 20 (5)	1241 ± 46 (3)

[a] The uncertainty interval is 2 s, twice the standard deviation from the mean. [b] Number of runs.

In addition, (*E*)-lactams aggregate in non-polar solvents to a greater extent than (*Z*)-amides,[19] even at the relatively dilute concentration of the calorimetry experiment. For example, 2-pyrrolidone is known to dimerize in carbon tetrachloride with $K_{\text{dimer}} = 142 \pm 20\ \text{M}^{-1}$[20] and $\Delta H_{\text{dimer}} = -7.0$ kcal mol^{-1}.[21] The dimerization of **2** in toluene was examined using infrared spectroscopy, and at 0.01 M, 2-pyrrolidone has $K_{\text{dimer}} = 60\ \text{M}^{-1}$: about half the lactam molecules are involved in a dimer, and half are free. The value in Table 3 for the lactam in toluene represents the enthalpy of solution *plus* dimer formation, and is thus not especially useful. Dimers of caprolactam are known to form favorably in acetone,[22] so solvation with dimerization is expected to occur for 2-pyrrolidone in acetone as well.

Enthalpies of solvation: amide (g)→amide (solution)

Enthalpy of solvation factors out the aggregation of liquid amide and lactam. The heat of vaporization combined with the heat of solution gives the heat of solvation, that is, the energy of an isolated molecule in the gas phase being dissolved in a medium of interest:

$$\begin{array}{lcll}
\text{amide (l)} & \rightarrow & \text{amide (sol'n)} & \Delta H\ \text{solution} \\
\text{amide (g)} & \leftarrow & \text{amide (l)} & -\Delta H\ \text{vaporization} \\
\hline
\text{amide (g)} & \rightarrow & \text{amide (sol'n)} & \Delta H\ \text{solvation}
\end{array}$$

The heat of vaporization of **1** is known, 15.51 ± 0.06 kcal mol^{-1}, determined calorimetrically by Wadsö[23] and is used in the following analysis. The enthalpy of vaporization for 2-pyrrolidone was not readily available, thus values were determined by ebulliometry for both **1** and **2**. The data were analyzed as described in the Experimental section, and $\Delta H_{\text{vap}}(298)$ was found to be 16.0 ± 0.3 kcal mol^{-1} for **1** and 17.6 ± 0.3 kcal mol^{-1} for **2**. To correct the ebulliometric data to 298 K, gas-phase heat capacities were required, and were calculated using harmonic vibrational frequencies. This analysis neglects the low-frequency torsional modes present in the amides. Qualitatively, these modes would increase the gas-phase heat capacities, hence lower the ΔH_{vap} slightly. The value for **1** obtained by ebulliometry would then be in better agreement with the value obtained by Wadsö. Since the low frequency modes in cyclic **2**

Table 4 Enthalpies of solvation from the gas phase (kcal mol^{-1}), *N*-methylpropionamide and 2-pyrrolidone

Solvent	*N*-Methylpropionamide **1**	2-Pyrrolidone **2**
Water	-19.1 ± 0.1	-19.8 ± 0.3
Propan-1-ol	-15.4	-16.4
Acetone	-14.4	-16.7
Toluene	-12.8	-16.4
Self	-15.5	-17.6

Table 5 Correlation of solvent parameters with measured enthalpies of solvation for *N*-methylpropionamide

Parameter	r^2 for a linear fit
Relative permittivity: $(\varepsilon - 1)/(2\varepsilon + 1)$	0.48
H-bond donating ability	0.83
H-bond accepting ability	0.12
π^* polarity/polarizability	0.56
$E_T(30)$	0.94
Cohesive energy density	0.90

are less important than in **1**, the ΔH_{vap} used for **2** does not include this correction.

Table 4 presents the enthalpies of solvation from the gas phase for *N*-methylpropionamide and 2-pyrrolidone. In addition to the entries for the four solvents studied by calorimetry, there is an entry for "self". This value is the negative of the heat of vaporization, representing the process of taking a gas-phase molecule and dissolving it in a solution of itself.

Discussion

In the two polar protic environments, the enthalpies of solvation for the (*E*) and (*Z*) molecules are the same. Initially this result is surprising since the dipole moments differ by 0.4 D. However, these results are in agreement with experiments[2,4,5] and calculations[4,24–26] for aqueous solvation of (*E*)- *versus* (*Z*)-NMA. The calculations show that the electron distribution of the solvated amide is dependent on conformation,[4,24,25] thus the two conformations are polarized differently by the medium.[26] The results in water and propanol also suggest that 2-pyrrolidone **2** is a valid model for ***E*-1**, despite differences in structure shown in Fig. 1 and the slight difference in molecular formula.

In toluene and acetone, solvation of **2** is more favorable than **1** because the lactam aggregates under the experimental conditions. The differences in the enthalpies reflect the favorable association of 2-pyrrolidone in solvents which do not donate H-bonds, assuming the (*E*):(*Z*) equilibrium constant for **1** is the same in all solvents. Thus the tabulated values for 2-pyrrolidone represent solvation including some percentage of dimerization. In toluene, where half the lactam molecules have dimerized, the difference of 3.6 kcal mol^{-1} would predict a dimerization enthalpy of approximately -7.2 kcal mol^{-1}, in line with that observed in carbon tetrachloride.[21]

The magnitudes of the solvent/amide interactions quantitatively agree with expectations. Water is a polar solvent and a good hydrogen bond donor and acceptor, and stabilizes the amide group the most. Toluene interacts weakly with the amide and shows the least favorable solvation enthalpy. These trends can be interpreted more explicitly comparing the enthalpies of solvation for *N*-methylpropionamide to the solvent parameters shown in Table 2, and results are shown in Table 5. The self-solvation term for the amide was included in this analysis, and the solvent parameters for *N*-methylacetamide were used in this case because those for *N*-methylpropionamide are unavailable. The fit of the data is not changed significantly if this point is omitted from the analysis.

The ability of the solvent to donate a hydrogen bond to the amide oxygen is strongly correlated with enthalpies of solvation. *Ab initio* calculations on the complexation of water with *N*-methylformamide[24] and NMA[24,27] show that hydrogen bonds formed to the amide oxygen are stronger by at least 1 kcal mol^{-1} than those formed at the nitrogen. The ability of the solvent to accept the N–H hydrogen bond is poorly correlated with the measured enthalpies of solvation. Both of these correlations are supported by Wolfenden's measurements of vapor–water distribution coefficients for acetamide, *N*-methylacetamide and *N,N*-dimethylacetamide.[28] He found that mono *N*-methylation has a small effect on the hydrophilicity of the amide. The greater importance of hydrogen bonding from solvent to the amide oxygen was also observed by Spiro and co-workers, who studied NMA in various solvents using ultraviolet resonance Raman spectroscopy.[29] In contrast, Krikorian studied solvent effects on secondary amide and lactam dimerization and found that hydrogen bonding from the N–H group to solvent is stronger than the ability of the carbonyl oxygen to accept a proton.[20]

The polarity/polarizability of the solvent was not found to be a strong predictor of solvation enthalpy. This is in agreement with recent calculations on the solvent effect on electronic polarization of *N*-methylacetamide. In water, polarization effects were shown to account for 10–15% of the solvent–solute interaction energy *via* either hybrid QM(3-21G)/MM or AM1/MM simulations.[30]

The relative permittivity of the medium is often used as a simple model of the solvent environment. The amide solvation enthalpies are correlated weakly with relative permittivity, as represented by the Kirkwood function. This is not surprising, since discrete solvent–solute interactions are not well modeled by a solvent continuum alone. The high correlation with the solvatochromic parameter $E_T(30)$ is not unexpected, since this parameter represents an amalgam of all solvent properties.

The enthalpy of solvation is most favorable in solvents with a large cohesive energy density, a measure of the cost to make the solute cavity. For the solvents in this study, the cohesive energy density and hydrogen bonding ability are correlated, thus the cost to make the cavity appears to be more than compensated for when solvent–amide hydrogen bonding is substantial. True has studied gas-phase amide rotational barriers and concludes that the rotational barrier is greater in the condensed phase than the gas phase because the bulkier transition state needs an enlarged solvent cavity, and must overcome the internal pressure of the solvent.[31] Since a rotational barrier depends on the relative stability of ground state *versus* transition state, perhaps the importance of ground-state effects on rotational barriers should be considered more thoroughly.

Conclusions

The enthalpy of solvation of *N*-methylpropionamide in five media is highly correlated with the ability of the solvent to donate a hydrogen bond to the amide oxygen. The enthalpies of solvation are poorly correlated with the ability of the solvent to accept the N–H hydrogen bond from the amide, with the solvent relative permittivity, and with the polarity/polarizability of the medium. In polar protic media, where solute–solute aggregation is minimal, the enthalpies of solvation are the same for *N*-methylpropionamide and 2-pyrrolidone, a stable model of the amide in the (*E*) conformation.

Experimental

Preparation of reagents

N-Methylpropionamide and 2-pyrrolidone were purchased from Aldrich and were purified by vacuum distillation from 4 Å molecular sieves. Purity was ⩾99.5% by analytical GC. Purified samples were kept in sealed storage bulbs under nitrogen.

For calorimetry measurements, a pre-weighed spherical ampoule was evacuated then refilled with nitrogen, then

Table 6 Heats of vaporization

	N-Methylpropionamide **1**	2-Pyrrolidone **2**
ΔH_{vap} (298 K)	16.0 ± 0.3 kcal mol^{-1}	17.6 ± 0.3 kcal mol^{-1}
Temperature range/K	368.1–473.5	391.0–484.5
Pressure range/mm Hg	7.9–551.2	7.1–274.2
r^2 for linear fit	0.999	0.998
Slope	−6967.3	−7481.3
Intercept	21.09	21.13
C_p(1)/cal mol^{-1} K^{-1}	44.5	40.5
C_p(g)/cal mol^{-1} K^{-1}	27.0	21.2
Number of data points	19	14

approximately 0.1 g of amide was added *via* pipette. After degassing, the ampoule was flame-sealed under vacuum and was reweighed to determine the mass of amide.[32] A Mettler analytical balance, reproducible to 5×10^{-6} g was used for all weighings.

Deionized water used for calorimetry was distilled under nitrogen. Other solvents were purchased from Aldrich (HPLC grade) and were used with no further purification. Solvents were transferred *via* cannula into 2 L solvent-resistant plastic dispensers fitted with gas-tight closures and were stored under nitrogen. Solvent was discharged under a stream of nitrogen into the calorimetry cell immediately prior to the experiment.

Calorimetry experiments

An automated isoperibol submarine calorimetry system previously described was used to measure enthalpies of solution.[17] A dry glass vessel was flushed with nitrogen then was charged with approximately 100 mL of solvent. An ampoule containing amide was placed in the ampoule holder and the system was assembled. The temperature was recorded every ten seconds after the reaction vessel had reached equilibrium, and after approximately ten minutes the ampoule was broken. Temperature was recorded for 30 additional minutes. Temperature was measured to 1×10^{-4} °C using a Hewlett-Packard quartz probe. An electrical calibration followed each run to measure the effective heat capacity of the system. The constant temperature bath was set at 25.10 °C and was constant to $\pm 3 \times 10^{-4}$ °C over the course of each run. Each measurement was performed several times to ensure reproducibility. The uncertainty interval is given as twice the standard deviation of the mean, following the suggestion of Rossini.[33]

Dimerization equilibria

The dimerization of 2-pyrrolidone in toluene was determined following the example of Affsprung.[21] Spectra were obtained using a Perkin-Elmer 1600 Series Fourier Transform infrared spectrometer. A calcium fluoride solution cell with 0.5 cm path length was used. The spectrum of the solvent blank was subtracted from each solution. Solutions were prepared by adding 100 µL of **2** to toluene-d_8 in a 1 mL volumetric flask. Toluene-d_8 was added to give a final volume of 1 mL. Subsequent dilutions were made from this stock solution, taking 100 µL and diluting to 1 mL.

Vapor pressure measurements

A semi-micro ebulliometer was used for the measurements.[34] Approximately 1 mL of amide and a Teflon-coated stir bar were introduced into the oven-dried apparatus. Pressure was regulated using a mercury manostat. After changing the pressure, the temperature of the vapors was recorded after the sample was at reflux. Temperature was measured to hundredths of a degree using a Hewlett-Packard 2804A quartz thermometer, calibrated against a water triple-point cell. Pressure was measured using a Bourdon gauge (Wallace and Tiernan), and was read to the nearest 0.1 mm Hg. Data are provided in the Supplementary Material, Tables 7S and 8S.

Vapor pressure–temperature data were fit to the Clausius–Clapeyron equation using a linear least-squares program since the data are perfectly linear in the range studied. The enthalpy of vaporization at the midpoint of the temperature range was calculated from the slope of the line, then was corrected to 298 K using the appropriate heat capacities as shown in eqn. (1).

$$\Delta H_{vap}(298) = \Delta H_{vap}(T_{mid}) + (298.15 - T_{mid})(C_p(g) - C_p(l)) \quad (1)$$

Gas-phase heat capacities (constant volume) were obtained from B3LYP/6-31G* frequency calculations, and were scaled by 0.98.[35] Constant pressure heat capacities were obtained from $C_p = C_v + R$, where R is the gas constant. The heat capacity of liquid **2** is known experimentally[36] and agrees well with that calculated by a group additivity scheme.[37] The liquid-phase heat capacity is also available for *N*-methylpropionamide[36] but this does not agree well with the additivity scheme. The additivity scheme was compared to known heat capacities for seven simple amides[36] and the scheme was found to overestimate C_p by 1.08. The subset of four *N*-alkylamides had the same average deviation. Thus C_p(l) for **1** was calculated by additivity, then scaled by 1.08. Table 6 contains the data used in calculating heats of vaporization. The estimated uncertainty for the heats of vaporization is ±0.1 kcal mol^{-1}, and the error from the temperature correction is estimated to be ±0.2 kcal mol^{-1}, thus the overall uncertainty is ±0.3 kcal mol^{-1}.

Calculations

Calculations were performed using Gaussian 94[38] on an IBM RS6000 workstation. Electron correlation was needed to obtain optimized structures which correctly reproduce the slight nonplanarity of the amide nitrogen, and the more economical B3LYP/6-31G* was chosen over MP2/6-31G*. A frequency calculation was done for each structure at the same level of theory as the geometry optimization to obtain pertinent information and to ascertain that the structure is a minimum on the energy surface. Complete structures of 2-pyrrolidone and the two conformers of *N*-methylpropionamide are available in the Supplementary Material. Attempts to find other conformations of **1** having other values for the CCCO dihedral angle were unsuccessful.

In a recent study, Glendening and Hrabal calculated simple amides at the B3LYP/6-31+G* level of theory.[1] The inclusion of diffuse functions is often useful in the description of molecules with lone pairs.[39] However, the scale factor for zero-point energies is well established for B3LYP/6-31G*,[35] but not B3LYP/6-31+G*. The structures of (*E*) and (*Z*)-**1** and **2** were optimized at the higher level of theory and small differences were observed, thus it is believed that the B3LYP/6-31G* level of theory is appropriate for the molecules studied.

Acknowledgements

This research was supported by an award from Research Corporation. D. A. K. thanks Merck for a summer research fellowship. K. M. M. thanks Professor K. B. Wiberg for helpful discussions, and Dr. Henry Castejon for assistance with heat capacity calculations. The workstation used to run the Gaussian calculations was purchased with a grant from The Jeffress Memorial Trust and new faculty start-up from The College of William & Mary.

Supplementary Material: Vapor pressure/temperature data for *N*-methylpropionamide (Table 7S) and 2-pyrrolidone (Table 8S); Gaussian archive entries for geometry optimizations (2 pages).

References

1 K. B. Wiberg and K. E. Laidig, *J. Am. Chem. Soc.*, 1987, **109**, 5935; C. L. Perrin, *J. Am. Chem. Soc.*, 1991, **113**, 2865; Q.-P. Wang, A. J. Bennet, R. S. Brown and B. D. Santarsiero, *J. Am. Chem. Soc.*, 1991, **113**, 5757; K. B. Wiberg and C. M. Breneman, *J. Am. Chem. Soc.*, 1992, **114**, 831; K. B. Wiberg, C. M. Hadad, P. R. Rablen and J. Cioslowski, *J. Am. Chem. Soc.*, 1992, **114**, 8644; K. B. Wiberg and P. R. Rablen, *J. Am. Chem. Soc.*, 1993, **115**, 9234; A. Greenberg, D. T. Moore and T. D. DuBois, *J. Am. Chem. Soc.*, 1996, **118**, 8658; D. Lauvergnat and P. C. Hiberty, *J. Am. Chem. Soc.*, 1997, **119**, 9478; E. D. Glendening and J. A. Hrabal, II, *J. Am. Chem. Soc.*, 1997, **119**, 12940.

2 L. A. LaPlanche and M. T. Rogers, *J. Am. Chem. Soc.*, 1964, **86**, 337.

3 W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, 1970, **70**, 517.

4 A. Radzicka, L. Pedersen and R. Wolfenden, *Biochemistry*, 1988, **27**, 4538.

5 T. Drakenberg and S. Forsén, *J. Chem. Soc.*, *Chem. Commun.*, 1971, 1404.

6 D. M. Pawar, A. A. Khalil, D. R. Hooks, K. Collins, T. Elliott, J. Stafford, L. Smith and E. A. Noe, *J. Am. Chem. Soc.*, 1998, **120**, 2108.

7 For example, T. Drakenberg, K.-I. Dahlqvist and S. Forsén, *J. Phys. Chem.*, 1972, **76**, 2178; C. B. LeMaster and N. S. True, *J. Phys. Chem.*, 1989, **93**, 1307; K. B. Wiberg, P. R. Rablen, D. J. Rush and T. A. Keith, *J. Am. Chem. Soc.*, 1995, **117**, 4261, and references cited therein.

8 P. Li, X. G. Chen, E. Shulin and S. A. Asher, *J. Am. Chem. Soc.*, 1997, **119**, 1116.

9 K. B. Wiberg and M. M. Marquez, *J. Am. Chem. Soc.*, 1994, **116**, 2197.

10 G. Pilcher, in *Supplement B: The Chemistry of Acid Derivatives*, ed. S. Patai, Wiley, New York, 1992, vol. 2, ch. 2.

11 R. M. Meighan and R. H. Cole, *J. Phys. Chem.*, 1964, **68**, 503.

12 G. Fischer, *Angew. Chem.*, *Int. Ed. Engl.*, 1994, **33**, 1415.

13 M. J. Kamlet, J.-L. M. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem.*, 1983, **48**, 2877.

14 Y. Marcus, *Chem. Soc. Rev.*, 1993, **22**, 409.

15 C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 2nd edn., VCH, New York, 1988, ch. 7; K. Dimroth, C. Reichardt, T. Siepmann and F. Bohlmann, *Liebigs Ann. Chem.*, 1963, **661**, 1; C. Reichardt, *Liebigs Ann. Chem.*, 1971, **752**, 64.

16 M. R. J. Dack, *Chem. Soc. Rev.*, 1975, **4**, 211.

17 K. B. Wiberg and R. R. Squires, *J. Chem. Thermodyn.*, 1979, **11**, 773; E. J. Martin, Ph. D. Thesis, Yale University, 1984, chs. 2 and 3; L. S. Crocker, Ph. D. Thesis, Yale University, 1989, ch. 2.

18 J. Konicek and I. Wadsö, *Acta Chem. Scand.*, 1971, **25**, 1541.

19 R. B. Homer and C. D. Johnson, in *The Chemistry of Amides*, ed. J. Zabicky, Interscience Publishers, New York, 1970, ch. 3.

20 S. E. Krikorian, *J. Phys. Chem.*, 1982, **86**, 1875.

21 H. E. Affsprung, S. D. Christian and J. D. Worley, *Spectrochim. Acta*, 1964, **20**, 1414.

22 J.-S. Chen, *J. Chem. Soc.*, *Faraday Trans.*, 1994, **90**, 717.

23 P. Starzewski, I. Wadsö and W. Zielenkiewicz, *J. Chem. Thermodyn.*, 1984, **16**, 331.

24 W. L. Jorgensen and J. Gao, *J. Am. Chem. Soc.*, 1988, **110**, 4212.

25 P. Cieplak and P. Kollman, *J. Comput. Chem.*, 1991, **12**, 1232.

26 S. W. Rick and B. J. Berne, *J. Am. Chem. Soc.*, 1996, **118**, 672; D. J. Tannor, B. Barten, R. Murphy, R. A. Friesner, D. Sitkoff, A. Nicholls, M. Ringnalda, W. A. Goddard, III and B. Honig, *J. Am. Chem. Soc.*, 1994, **116**, 11875.

27 D. A. Dixon, K. D. Dobbs and J. J. Valentini, *J. Phys. Chem.*, 1994, **98**, 13435.

28 R. Wolfenden, *Biochemistry*, 1978, **17**, 201.

29 Y. Wang, R. Purrelle, S. Georgiou and T. G. Spiro, *J. Am. Chem. Soc.*, 1991, **113**, 6368.

30 J. Gao and M. Freindorf, *J. Phys. Chem. A*, 1997, **101**, 3182.

31 C. Suarez, C. B. LeMaster, C. L. LeMaster, M. Tafazzoli and N. S. True, *J. Phys. Chem.*, 1990, **94**, 6679, and references therein.

32 Ampoule technique is described in detail by Crocker (ref. 17). To seal the ampoule, the sample within is frozen in liquid nitrogen, and the upper part of the ampoule is heated with a heat gun to remove any sample that could otherwise char during sealing. A gas/oxygen torch is used to cleanly seal the ampoule at the constriction. The ampoule is held so that the glass naturally separates, without the formation of a long glass fiber which would complicate determination of the sample mass were the fiber to break. The sealed ampoule and stem are weighed, and the mass of the sample is determined by difference. In the data analysis, a buoyancy correction is made because the empty ampoule is weighed in air while the ampoule containing sample is evacuated.

33 F. D. Rossini, "Assignment of Uncertainties to Thermochemical Data" in *Experimental Thermochemistry*, ed. F. D. Rossini, Interscience, New York, 1956.

34 K. M. Morgan, Ph. D. Thesis, Yale University, 1994, ch. 5; S. R. Hoover, H. John and E. F. Mellon, *Anal. Chem.*, 1953, **25**, 1940; G. W. Thomson, in *Techniques in Organic Chemistry*, *Volume 1*, *Part 1. Physical Methods in Organic Chemistry*, 3rd edn., ed. A. Weissberger, Interscience Publishers, Inc., New York, 1959, ch. IX.

35 J. B. Foresman and A. Frisch, *Exploring Chemistry with Electronic Structure Methods*, 2nd edn., Gaussian, Inc., Pittsburgh, 1995–1996, ch. 4; C. W. Bauschlicher, Jr. and H. Partridge, *J. Chem. Phys.*, 1995, **103**, 1788.

36 E. S. Domalski and E. D. Hearing, "Condensed Phase Heat Capacity Data" in *NIST Standard Reference Database Number 69*, eds. W. G. Mallard and P. J. Linstrom, August 1997, National Institute of Standards and Technology, Gaithersburg MD, 20899 (http://webbook.nist.gov).

37 R. C. Reid, J. M. Prausnitz and T. K. Sherwood, *The Properties of Gases and Liquids*, 3rd edn., McGraw-Hill Book Company, New York, 1977, ch. 5; C. F. Chueh and A. Swanson, *Chem. Eng. Progr.*, 1973, **69**, 83; A. C. Swanson, *Can. J. Chem. Eng.*, 1973, **51**, 596.

38 Gaussian 94 (Revision D.4), M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1995.

39 J. B. Foresman and A. Frisch, *Exploring Chemistry with Electronic Structure Methods*, 2nd edn., Gaussian, Inc., Pittsburgh, 1995–1996, ch. 5.

Paper 8/02717J