Different Folding Patterns of Two Similar Triamides: A Sharp Contrast in Their Intramolecular Amide−Amide Hydrogen-Bonding Propensity

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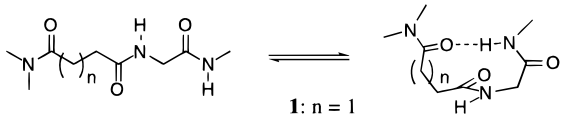
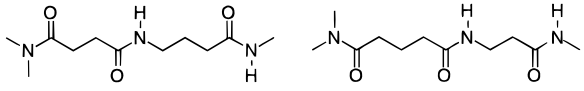
Recently we reported the folding pattern of a succinyl (**1**) and a glutaric (**2**) glycine derivative in chloroform.[1] Both triamides **1** and **2** display a strong preference to fold in the temperature range of 213−323 K. An intramolecularly hydrogen (H)-bonded conformation through a 10- and an 11-membered ring was identified, respectively, by means of IR and ^{1}H NMR spectroscopy.



The strong folding tendency of these triamides is somewhat surprising since Gellman has reported that there is little internal hydrogen bonding in diamides derived from pimelic and suberic acids,[2] which are analogs of triamides **1** and **2**, respectively. This difference between the diamides and the triamides is intriguing. It suggests that the 10- and 11-membered ring hydrogen bonds in the triamides are strongly promoted by the central amide group. To explore the conformational directing effect of the central amide function, we have prepared triamides **3** and **4**, both of which are capable of forming an intramolecular hydrogen bond through a 12-membered ring. In this study, we find a sharp contrast in the conformational behavior of these two very similar triamides.[10]



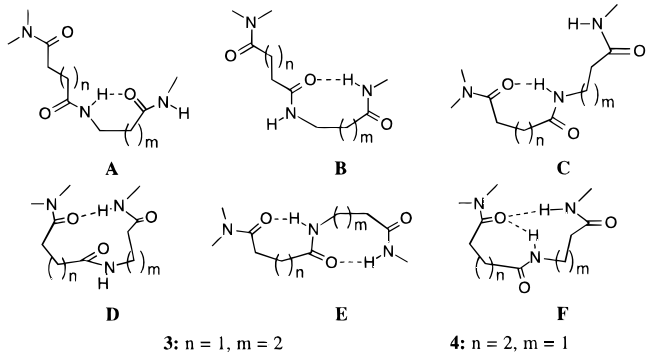
3 **4**

There are two NH groups and three C═O groups in each triamide. Each NH may form an H-bond to either of the two C═O groups, which would form 6−12-membered rings (A−D). These four structures plus a possible bicyclic form (E) and a bifurcated form (F) give a possibility of six H-bonded conformations. These expected conformations are displayed in Chart 1.

Variable temperature IR and NMR experiments on triamides **3** and **4** were performed in $CDCl_3$ at 1 mM concentration.[3] Variable concentration IR spectroscopy shows that there is little change in the ratio of H-bonded to non-H-bonded NH stretching in the range of 1−10 mM indicating the absence of intermolecular hydrogen bonds.

The data displayed in Figures 1 and 2 suggest that a significant population of triamide **3** contains an intramolecular amide−amide hydrogen bond, while a much smaller population of triamide **4** has such an intramolecular H-bond. The most direct evidence for this conclusion comes from the IR spectra in Figure 1, which show a strong absorption at ∼3320 cm^{-1} for triamide **3** but a negligible absorption for triamide **4** in this region that is assigned to intramolecularly hydrogen-bonded NH stretching.[1,2] In addition, at 213 K, the broad peak at ∼3320 cm^{-1} for triamide **3** has greatly increased in intensity, while the broad peak at ∼3310 cm^{-1} for triamide **4** changes only slightly with temperature.

Chart 1



Consistent with the IR results, the variable temperature ^{1}H NMR data show a clear difference in the temperature dependence of NH proton chemical shifts between triamide **3** and triamide **4**. The chemical shifts of the NH protons are plotted as a function of temperature in Figure 2. At room temperature the two NH protons of triamides **3** and **4** were distinguished by a two-dimensional ^{1}H NMR experiment (COSY). At lower temperatures, they can be identified by their coupling patterns. The terminal NH proton (a quartet) of triamide **3** shows a large temperature dependence with a reduced temperature coefficient ($\Delta\delta$NH/ΔT)[4] of −11.8 ppb/K indicating a large change in the NH proton's chemical environment with temperature. The influence of solvent and substrate structure on the NH proton chemical shifts has been discussed in the literature.[4−6] In a nonpolar organic solvent, such as chloroform or methylene chloride, model peptides such as those currently used in our experiments are expected to show a chemical shift around 6 ppm for non-hydrogen-bonded NH protons and around 8 ppm for intramolecularly amide−amide H-bonded NH protons.[1,2] Therefore, a large change in NH proton chemical shifts is an indication of the changes in the population of hydrogen-bonded conformations.

In contrast to triamide **3**, the change in the terminal NH proton chemical shifts of triamide **4** is small over the same temperature range, Figure 2b. The IR and NMR data suggest that there is little intramolecular hydrogen bonding in triamide **4**. Diamide **5**, which is identical to the right half of triamide **4**, was also found to not fold in methylene chloride.[7b] By analogy to diamide **5**, conformations B and E can be eliminated from consideration. To help distinguish between D and F, diamide **6**, which is identical to the left half of **4**, was subjected to a variable temperature ^{1}H NMR study. An NH chemical shift temperature dependence of −5.3 ppb/K was obtained in chloroform for diamide **6**[8] which indicates that conforma-

(1) Gung, B. W.; Zhu, Z. *J. Org. Chem.* **1996**, *61*, 6482.
(2) Gellman, S. H.; Dado, G. P.; Liang, G.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164.
(3) For advantages of using $CDCl_3$ over CH_2Cl_2, see footnote 8 in ref 1.
(4) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, 512.
(5) Stevens, E. S.; Sugawara, N.; Bonara, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048.
(6) Winningham, M. J.; Sogah, D. Y. *J. Am. Chem. Soc.* **1994**, *116*, 11173−11174.
(7) (a) Gellman, S. H.; Adams, B. R.; Dado, G. P. *J. Am. Chem. Soc.* **1990**, *112*, 460. (b) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054−1062.

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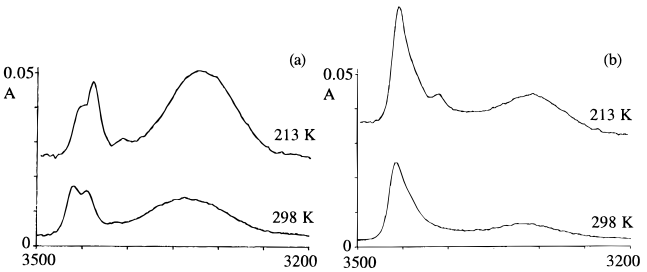


Figure 1. NH stretch region of the IR spectra at 213 and 298 K. Data are collected in $CDCl_3$ at 1 mM concentration. (a) Triamide **3**: the band at 3454−3460 cm^{-1} is assigned to the free terminal NH stretch, the band at 3440−3446 cm^{-1} to the free internal NH stretch, and the broad band at 3324−3338 cm^{-1} to the intramolecularly hydrogen-bonded NH. (b) Triamide **4**: the sharp band at 3452−3458 cm^{-1} is assigned to the free NH stretch and the broad band at 3304−3319 cm^{-1} to the intramolecularly hydrogen-bonded NH.

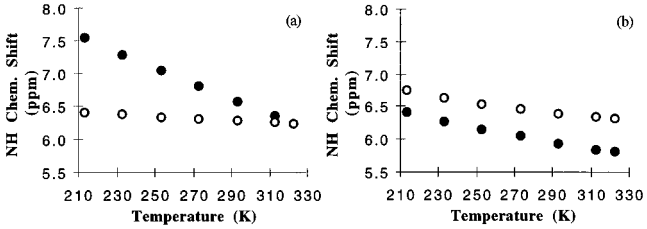
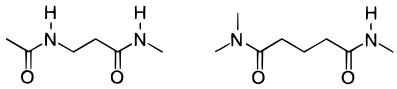


Figure 2. Amide proton NMR chemical shifts as a function of temperature. Data are collected in $CDCl_3$ at 1 mM concentration. (a) Triamide **3**: internal NH (○, $\Delta\delta NH/\Delta T = -1.5$ ppb/K) and terminal NH (●, $\Delta\delta NH/\Delta T = -11.8$ ppb/K). (b) Triamide **4**: internal NH (○, $\Delta\delta NH/\Delta T = -3.8$ ppb/K) and terminal NH (●, $\Delta\delta NH/\Delta T = -5.5$ ppb/K).

tion C, which is identical to the intramolecularly hydrogen-bonded **6**, should be enthalpically favored to a small degree. However, the internal NH proton of triamide **4**, which can form the same 8-membered ring as **6** through C, shows a $\Delta\delta NH/\Delta T$ of only −3.8 ppb/K. This reduced temperature constant is comparable to that of the NH proton of *N*-methylacetamide (NMA; −3.3 ppb/K at 1 mM in $CDCl_3$) indicating that the involvement of the internal NH proton of triamide **4** in hydrogen bonding is minimal.



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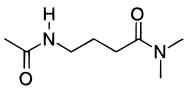
Conformation B is assigned as the most enthalpically favored form for triamide **3** based on the following observations. The internal NH proton of triamide **3** shows a smaller reduced temperature constant ($\Delta\delta NH/\Delta T = -1.5$ ppb/K) than that of NMA. This indicates that the internal NH proton of triamide **3** is partially H-bonded (through either one of the 7-membered rings, A or C) at higher temperatures. As the temperature is lowered, this hydrogen bond of the internal NH is broken to yield other more enthalpically favored conformations which involve a hydrogen bond by the terminal NH. Both conformations B and D involve the terminal NH in a hydrogen bond. To help elucidate the conformational profile of triamide **3**, diamides **7** and **8** were prepared to model conformations A and C.



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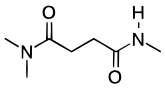

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A variable temperature ^1H NMR study in $CDCl_3$ at 1 mM concentration gives reduced temperature constants of −7.2 and −3.2 ppb/K for **7** and **8**, respectively.[15] A temperature dependence of chemical shift equaling that of NMA for diamide **8** indicates little intramolecular hydrogen bonding in this structure. On the other hand, diamide **7** shows a considerable amount of intramolecular hydrogen bonding. The current results are consistent with a previous study performed in methylene chloride.[2] This information, combined with the VT NMR data of Figure 2, helps to rule out conformations C, E, and F for triamide **3**. Thus conformation A appears to be present at high temperatures. An equilibrium between conformation A and B or D can explain the variable temperature ^1H NMR data. At high temperatures, the smaller ring A is favored due to entropic advantage, while at lower temperatures, the large ring B or D is favored due to optimal hydrogen bond geometry.

The remaining question is whether the intramolecular hydrogen bond involving the terminal NH proton is through conformation B, a 9-membered ring, or D, a 12-membered ring. Conformation B has a free tertiary amide function, and conformation D has a free secondary amide function. The carbonyl stretching frequencies for triamides **1**−**4** at 298 and 213 K are compared. The secondary amide carbonyl group of triamide **3** has a lower frequency (1650 cm^{-1}) than that (average 1659 cm^{-1})[10] of the other three triamides, and the tertiary amide carbonyl group of **3** has a higher frequency (1631 cm^{-1}) than the rest (average 1624 cm^{-1}).[10] Since a carbonyl that is hydrogen bonded should have a lower frequency, these facts are consistent with conformation B being the predominant form at lower temperatures.

A van't Hoff analysis of the ^1H NMR variable temperature data can produce the thermodynamic parameters for the equilibrium between the states in which the terminal NH proton is free and triamdie **3** is in conformation B. An important step in this analysis is to find *temperature-dependent* upper and lower limits of chemical shifts.[7] Following Gellman's lead, we have chosen the chemical shifts of a 1:1 mixture of *N*-methylacetamide and *N*,*N*-dimethylacetamide in $CDCl_3$ at 1 mM concentration as the limiting value for non-hydrogen-bonded states. For the limiting chemical shifts of intramolecularly hydrogen-bonded states, compound **8** from ref 9 is used to produce a ΔH of -1.7 ± 0.5 kcal/mol and a ΔS of -5.9 ± 2 eu.[10] Compound **8** from ref 9 has been shown to be completely intramolecularly hydrogen bonded at all temperatures, and its structure is similar to triamide **3**.[9]

In summary, we have shown that triamide **3** experiences an equilibrium between the 9-membered conformation B and the 7-membered conformation A with conformation B becoming predominant at lower temperatures. We have also shown that triamide **4** does not favor the folded conformation even in chloroform.

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Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectra for compounds **3** and **4**, two-dimensional NMR (COSY) spectrum for **3**, and variable temperature ^1H NMR data for diamides **6**−**8** (9 pages).

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(8) See Supporting Information.
(9) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228−4245.
(10) Zhu, Z. Study of Model Peptide Conformations. Ph.D. Dissertation, Miami University, Oxford, OH, 1996.