Temperature-Dependent Changes in the Folding Pattern of a Simple Triamide

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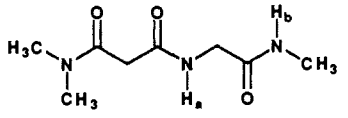
We describe the conformational behavior of triamide **1**[1] in methylene chloride solution. Triamide **1** has several alternative folding patterns available to it, but at low temperatures in this relatively non-interactive solvent, one highly ordered conformation predominates. The non-covalent forces at work in **1** include amide–amide hydrogen bonding, one of the principal conformation-specifying factors in proteins. The examination of oligoamides under conditions in which conformation is determined by a relatively small number of internal non-covalent interactions is the basis of our effort to understand the interplay of the non-covalent forces that influence protein secondary and tertiary structural stability.[2]



1

Insight on the conformational behavior of triamide **1** in CD_2Cl_2 is provided by the temperature dependences of the amide proton NMR chemical shifts (Figure 1). The data for **1** are juxtaposed with the data for diamides **2** and **3**,[1] which model respectively the six- and seven-membered-ring hydrogen bonds available to the triamide. Also shown are the data for a 1:1 mixture of *N*-methylacetamide and *N*,*N*-dimethylacetamide, indicating the inherent chemical shift temperature dependence for a non-hydrogen bonded amide proton (intermolecular hydrogen bonding is minimal under these conditions[3]). It is immediately clear that the folding patterns experienced by **1** in CD_2Cl_2 include conformations other than those involving the six- and seven-membered-ring amide–amide hydrogen bonds.

In a very weakly hydrogen bonding solvent, both the absolute value and the temperature dependence of the amide proton chemical shift provide structural information.[2,4] Under these conditions, the rate at which an amide proton exchanges among its various hydrogen bonded and non-hydrogen bonded states is usually rapid on the NMR time scale. Therefore, the lone signal observed for a given amide proton represents a weighted average of the signals for that proton in its alternative environments, with more time in a hydrogen bonded state moving the signal further downfield.[5] The substantial difference between the observed amide proton chemical shifts for diamides **2** and **3** at all temperatures indicates that much more intramolecular hydrogen bonding occurs in **2** than in **3**. This qualitative conclusion is confirmed by the infrared spectra of these two diamides in dilute CH_2Cl_2 solution at room temperature: the N–H stretch region for diamide **2** is dominated by a broad hydrogen bonded N–H signal (3310 cm^{-1}), with only a small signal for a free N–H (3450 cm^{-1}); for diamide **3**, the free N–H stretch is strong (3450 cm^{-1}) and the broad hydrogen bonded N–H signal is weak (3360 cm^{-1}).[6]

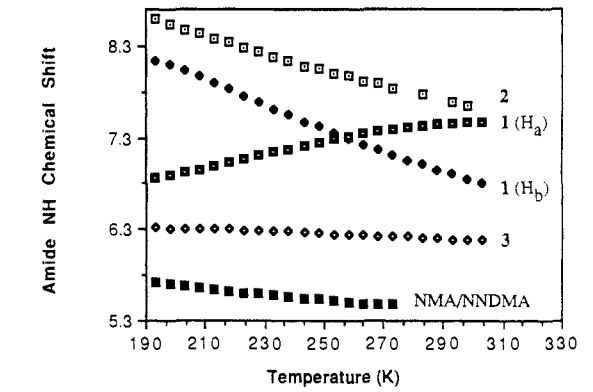
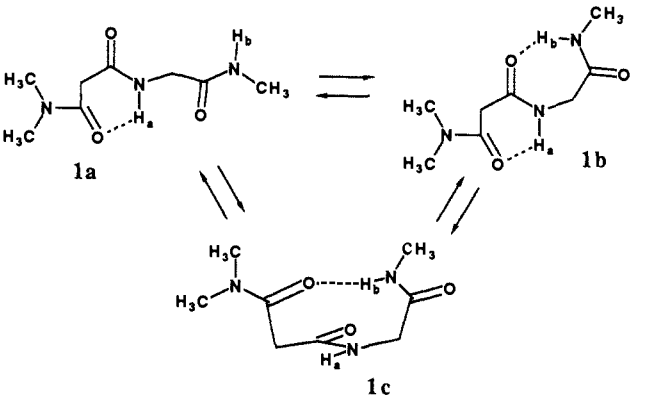
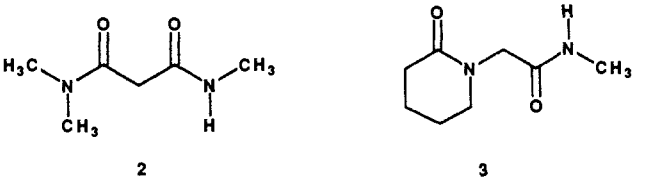


Figure 1. Temperature dependences of the amide proton–proton chemical shifts for diamides **2** (□) and **3** (◆); triamide **1**, H_a (■) and H_b (♦); and a 1:1 mixture of *N*-methylacetamide and *N*,*N*-dimethylacetamide (■) in CD_2Cl_2. All amides present at 1 mM. Chemical shifts referenced to residual $CHDCl_2$ (5.320 ppm). Spectra obtained on a Bruker AM-500.

Scheme I





2 **3**

There are two particularly striking features of the NMR data shown for triamide **1** in Figure 1. First, H_a apparently experiences an *increasing* amount of hydrogen bonding as the temperature rises. Second, H_b is predominantly hydrogen bonded at the lowest temperatures. Comparison with the data for diamide **3** demonstrates that this large amount of internal hydrogen bonding for H_b at low temperatures cannot result from the seven-membered-ring interaction. The NMR data for **1** are consistent with a conformational equilibrium involving the three folding patterns shown in Scheme I. According to our hypothesis, conformation **1a** is the major form at room temperature, but **1b** and **1c** are also present in significant amounts. As the temperature falls, conformation **1c** becomes dominant. We draw **1c** with a single nine-membered-ring hydrogen bond, but we cannot rule out the possibility of a bifurcated hydrogen bond, involving the central amide carbonyl as a second acceptor. The increasing proportion

(1) All new amides were prepared by standard methods, which will be presented in a full paper. The NMR, IR, and high-resolution mass spectroscopic data for each new compound are consistent with the proposed structure.

(2) Gellman, S. H.; Adams, B. R. *Tetrahedron Lett.* **1989**, *30*, 3381.

(3) The chemical shift temperature dependence data shown in Figure 1 were obtained with 1 mM amide solutions. When a 5 mM solution of **1** was examined, little variation was observed in the behavior of H_b, relative to the 1 mM sample, over the entire temperature range. Below 253 K, however, the 5 mM H_a signal showed increasing downfield deviations relative to 1 mM; we attribute these deviations to the onset of intermolecular amide–amide hydrogen bonding at low temperatures.

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(5) (a) Connors, K. A. *Binding Constants*; Wiley Interscience: New York, 1987; Chapter 5. (b) Laplanche, L. A.; Thompson, H. B.; Rogers, M. T. *J. Phys. Chem.* **1965**, *69*, 1482.

(6) All IR spectra obtained at 1 mM in CH_2Cl_2 at room temperature. As discussed in ref 2, there is little or no intermolecular amide–amide hydrogen bonding under these conditions. In that reference, we reported that we could not detect any free N–H stretch for diamide **2** by IR; using a more sensitive spectrometer, we have now found a small free N–H signal. Under these conditions, the IR spectrum of **1** shows a non-hydrogen bonded N–H stretch at 3440 cm^{-1} and a hydrogen bonded N–H stretch at 3320 cm^{-1}.

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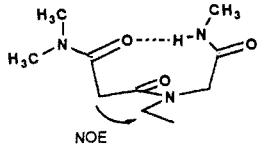
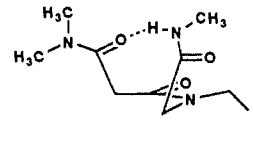
of **1c** as temperature decreases indicates that **1c** is enthalpically superior to **1a** and **1b**. The balance of non-covalent forces in **1** is sufficiently fine, however, that the entropic advantage of **1a** (and perhaps **1b**) becomes an important factor at higher temperatures.

The conformational equilibrium proposed in Scheme I is supported by the behavior of triamide **4**,[1] in which H_a of **1** is replaced by an ethyl group. This triamide has no option for a six-membered-ring hydrogen bond. IR spectroscopy shows triamide **4** to be virtually locked in an intramolecularly hydrogen bonded conformation in CH_2Cl_2 even at room temperature: the hydrogen bonded N-H stretch (3320 cm^{-1}) is dominant, and a tiny free N-H signal at 3445 cm^{-1} is just barely discernable in a 1 mM solution.[7] The proton NMR spectrum of **4** in CH_2Cl_2 shows that, despite the tertiary amide moiety, one conformer is predominant (>85%). Molecular models suggest that either stable rotamer about the central C-N bond (e.g., **4a** or **4b**) could allow a nine-membered-ring amide-amide hydrogen bond. We detect a positive NOE between the indicated methylenes, which implies that the major form has the *Z* conformation about the this C-N bond.



4a



4b

The observation that conformation **1c** (with or without the bifurcated hydrogen bond) is enthalpically superior to **1b** in a solvent that offers little or no hydrogen bonding competition demonstrates that the most stable folding patterns of oligoamides need not have the maximum pairing of hydrogen bond donors and acceptors. This conclusion is interesting in the context of protein tertiary structure, because one of the factors that specifies the compact, folded conformation of a globular protein is thought to be the drive to satisfy the hydrogen bonding potential of the largest possible number of the amide groups that are buried in the relatively nonpolar core of the macromolecule.[8]

We speculate that conformation **1c** is enthalpically more favorable than conformations containing hydrogen bonds in smaller rings because of the more linear N-H--O angle allowed by the larger ring. Ab initio calculations suggest that optimum amide-amide hydrogen bond strength is achieved when the N-H--O arrangement approaches linearity.[9] In protein crystal structures, deviations from hydrogen bond linearity are often observed, but it is impossible to know the extent to which such deviations result from competing non-covalent interactions within the biopolymer.[10] The conformational equilibrium observed for triamide **1** in nonpolar solution provides an opportunity to examine competition among hydrogen bonds of different geometries. These studies also suggest that multi-state conformational equilibria in oligoamides can be elucidated by comparisons with related molecules in which the number of conformational options is reduced.

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(7) The amide proton chemical shift temperature dependence measured for triamide **4** in CD_2Cl_2 is also consistent with nearly complete hydrogen bonding at all temperatures. The amide proton chemical shift occurs at 7.85 ppm at 298 K and at 8.36 ppm at 193 K, varying approximately linearly in between.

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Fluorine-Substituted Ferracyclopentadiene Complexes with an Unprecedented Fluorine Bridge between Boron and Carbon

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We recently reported the preparation of complexes **1a**,**b**, shown in Scheme I, which are derivatives of the well-known complex $Fe_2(\mu\text{-}CH_2)(CO)_8$.[1] Pettit has shown that the latter compound readily reacts with alkynes to form binuclear allyl complexes,[2] and it was thus of interest to determine if complex **1** would incorporate alkynes in a similar fashion. However, as reported herein, this reaction takes a most surprising course, to yield fluorine-substituted ferracyclopentadiene complexes that form by fluoride donation from BF_4^- and which have been crystallographically shown to possess an unprecedented fluorine atom bridge between carbon and boron atoms. Furthermore, it has been found that the fluorine substituent is readily abstracted by the BF_3 group when this complex is treated with nucleophiles.

Complex **1** rapidly reacts with PhC≡CH to give the fluorinated ferracyclopentadiene complexes **2a**,**b**,[3a] Scheme I, which were isolated as microcrystalline solids and have been crystallographically characterized, Figure 1 (**2b**).[3b] These complexes are derivatives of the well-known family of binuclear ferracyclopentadiene complexes (ferroles) prepared by the reaction of alkynes with iron carbonyls.[4,5] The surprising feature of this structure is the fluorine substituent on the ferracyclopentadiene ring and its bonding to both C(9) and the B atom in a bridging fashion [C(9)-F(1)-B(1) = 126.4 (4)°]. The short C(9)-F(1) distance of 1.329 (5) Å implies the presence of a C-F single bond (1.32-1.39 Å)[6] whereas the F(1)-B(1) distance of 1.528 (8) Å is quite long, especially when compared to the 1.37 (1) Å average bond length for the remaining three B-F bonds. The molecule appears best described as having a covalently bonded C-F group interacting in a donor-acceptor fashion with the Lewis acid BF_3, but to our knowledge, this is the first example of any type of compound with a fluorine atom bridging between carbon and boron atoms.

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(3) (a) **2b**: IR (CH_2Cl_2) ν_{CO} = 2078 (m), 2049 (vs), 2017 (m), 1997 (m), 1614 (w) cm^{-1}; ^1H NMR (CD_2Cl_2) δ 7.94 (d, 1 H, J_{HF} = 15.8 Hz, C*H*), 7.32, 7.21 (m, 5 H, Ph) 6.62 (q, 1 H, C*H*, J_{H-F} = 1.2 Hz), 1.50 (s, 9 H, Bu^t); ^{13}C NMR (CD_2Cl_2) δ 210.1,209.0, 206.4, 205.6 (*C*O), 184.6 (dd, 4.1 Hz), 175.3 (d, $^1J_{CH}$ = 173.9 Hz, *C*H), 161.9 (*C*F), 149.8, 128.9, 128.5, 127.9 (Ph), 102.3 (d, $^1J_{CH}$ = 173.9 Hz, *C*H), 99.0, 60.3 (*C*(Me)$_3$, 28.6 (C(*C*H$_3$)$_3$). (b) $P2_1/c$, a = 21.188 (6) Å, b = 8.552 (2) Å, c = 13.429 (4) Å, β = 94.13 (2)°, V = 2427.0 (11) Å^3, Z = 4, $R(F)$ = 4.22%, R(wF) = 4.39% for 2360 reflections ($F_o \geq 5\sigma(F_o)$).

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