Evidence for Intramolecular Hydrogen Bonding in β-Alanine Derivatives of 2,8-Dimethylphenoxathiin 4,6-Dicarboxylic Acid. Model Studies for Nucleation of Parallel β-Sheets

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In light of recent reports concerning the use of dibenzofuran derivatives[1] as antiparallel β-sheet nucleators and temperature dependence chemical shift coefficients ($\Delta\delta/\Delta T$) to distinguish between intramolecularly hydrogen-bonded and free NH groups,[1-3] we wish to report the results of our FTIR and variable temperature ^{1}H NMR studies, which show that phenoxathiin derivative **1** (Chart 1) nucleates hydrogen bonding in a parallel fashion and does not aggregate through intermolecular hydrogen bonding. Design and synthesis of β-turn nucleators, largely inspired by the need to better understand factors that control protein folding, has remained an active area of research.[1,4-6] The studies, to date, have concentrated on nucleation and propagation of hydrogen bonding in antiparallel β-sheets, with only a limited effort directed toward elucidating the requirements for parallel β-sheet nucleation.[6] Our interest lies in the design and syntheses of protein- and peptide-based polymers that contain hydrogen-bonded sheets as crystalline domains, principally because biopolymers and synthetic polymers are similar in many respects. For example, synthetic polymers, such as nylon-6,6 (**4**) and poly(*p*-phenylene terephthalamide) (**5**) (Chart 1), exist as stacks of parallel hydrogen-bonded sheets.[7] By delineating the factors that control hydrogen bonding in appropriate model systems, we hope to lay the ground work for the design and synthesis of hybrid polymers that synergistically incorporate the useful properties of both naturally occurring biopolymers and synthetic materials.

Compounds **1** and **2** were synthesized from the corresponding carboxylic acids using modifications of literature procedures.[4] Figure 1 shows the N–H stretching region of the FTIR spectra of **1** in CH_2Cl_2 at varying concentrations. The peak at 3429 cm^{-1} corresponds to non-hydrogen-bonded NH_B and that at 3373 cm^{-1} to the hydrogen-bonded NH_A. The extent of hydrogen bonding is concentration independent between 0.86 and 43 mM (Figure 1a–d), suggesting that the 3373 cm^{-1} band results from intra- rather than intermolecular hydrogen bonding. Structures **1a–e** (Chart 2) illustrate the intramolecular hydrogen bonding possibilities available to **1**. To distinguish among these, compound **2**, which potentially can exist as **2a–c** (Chart 2), and compound **3** (a model for examining participation of the ring oxygen in the hydrogen bonding, Chart 1) were synthesized and examined by IR spectroscopy. The IR spectrum of **2** shows only one concentration independent N–H stretching band at 3434 cm^{-1} (Figure 2a–c), with no evidence of either inter- or intramolecular hydrogen bonding, which typically occurs below 3400 cm^{-1}. This suggests that **2** neither aggregates through intermolecular hydrogen bonding nor forms any of the hydrogen-bonded structures shown in **2a–c** throughout the concentration range studied. Similarly, **3** shows only a single N–H stretching band at 3447 cm^{-1}, indicating a free NH (Figure 2d). Thus, the ring oxygen does not participate in the hydrogen bond

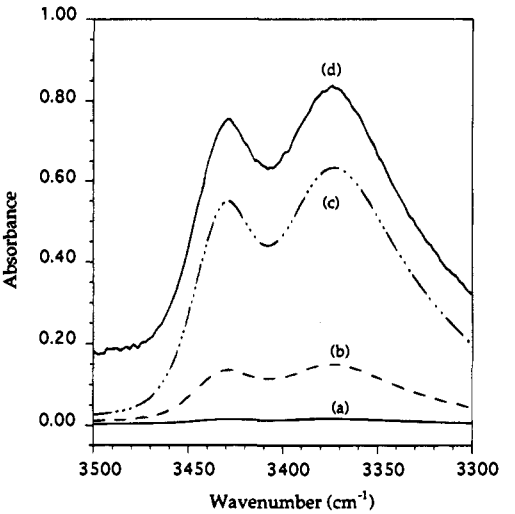


Figure 1. FTIR spectra for the N–H stretching region of **1** in CH_2Cl_2 solutions at room temperature after subtraction of the spectrum of pure CH_2Cl_2: (a) 0.86, (b) 8.6, (c) 43, and (d) 0.86 mM spectrum expanded 50×. All spectra were recorded on a Perkin Elmer 16PC spectrometer.

Chart 1

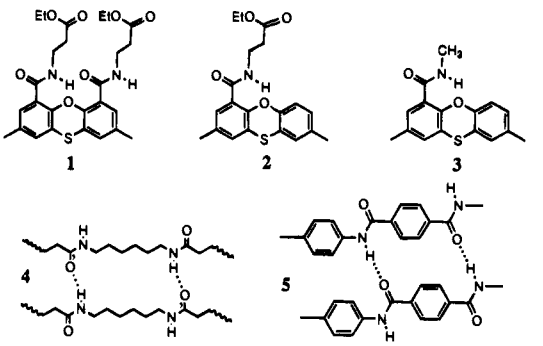
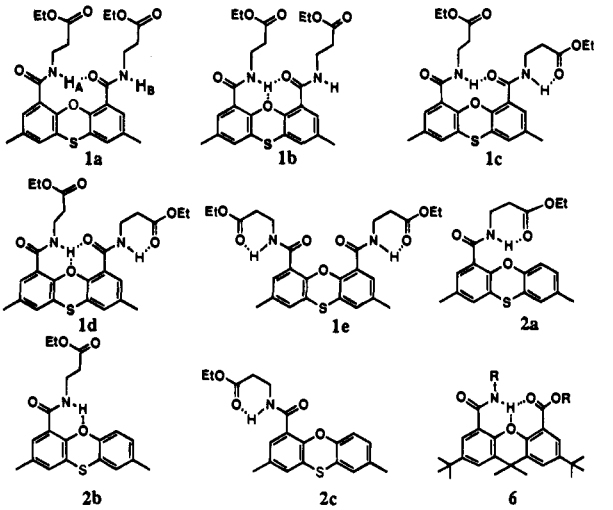


Chart 2



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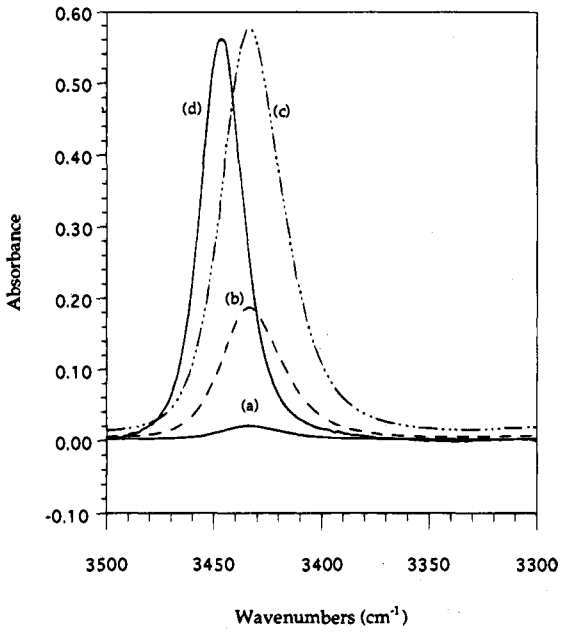
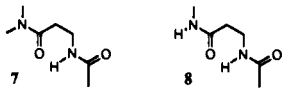


Figure 2. FTIR spectra for the N−H stretching region of **2** and **3** in CH_2Cl_2 at room temperature after subtraction of the spectrum of pure CH_2Cl_2: (a) 1.1 mM **2**; (b) 11 mM **2**; (c) 37 mM **2**; (d) 5.5 mM **3**. Baseline has been corrected for spectrum d. All spectra were recorded on a Perkin Elmer 16PC spectrometer.

Chart 3



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formation. In their independent study, Rebek and co-workers suggested the bifurcated hydrogen-bonded structure **6** (Chart 2).[8] The above results essentially rule out formation of **1b−e** and lead us to conclude that the observed intramolecular hydrogen bonding in **1** is due to formation of the 10-membered hydrogen-bonded structure **1a**. The absence of six-membered ring hydrogen bond formation by these β-alanine derivatives is both consistent with esters being somewhat weak hydrogen acceptors and in agreement with the findings of Dado and Gellman[3a] and Marraud and Neel,[9] who independently showed that the β-alanine derivatives **7** and **8** (Chart 3) did not form the six-membered ring hydrogen bonds.

Temperature dependence chemical shift coefficients, $\Delta\delta/\Delta T$, determined from variable temperature NMR data, have become a standard criterion for distinguishing between hydrogen-bonded and free NH in peptides and related amides.[1-3] A small value of $\Delta\delta/\Delta T$ indicates either a free NH or one that remains hydrogen-bonded throughout the temperature range, while a large value always reflects an initially shielded NH that is transferred to an unshielded environment. However, it appears there is no simple one-to-one correspondence between the magnitude of $\Delta\delta/\Delta T$ and the extent of hydrogen bonding,[10] and care must be exercised in using the numbers. The ^{1}H NMR

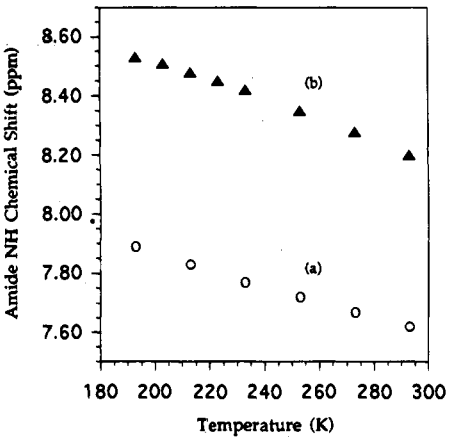

Figure 3. Temperature dependence of amide hydrogen NMR chemical shift for **1** and **2** in CD_2Cl_2 solutions: (a) 2.0 mM **1**; (b) 0.59 mM **2**. The data were obtained on Varian VXR 400 and Varian Unity 500 spectrometers, respectively.

spectrum of **1** at 20 °C shows only one NH peak, indicating fast intramolecular exchange between NH_A and NH_B on the NMR time scale. The plots of chemical shift δ (ppm) vs temperature (T, K) for **1** and **2** are shown in Figure 3a and b, respectively. The $\Delta\delta/\Delta T$ for **1** is −2.7 ppb/K and for **2** is −3.3 ppb/K. However, since the IR data clearly show that **1** is hydrogen-bonded and **2** is not, the small value for **1** indicates that it remains hydrogen-bonded throughout the temperature range. The small $\Delta\delta/\Delta T$ values for both systems reinforce the lack of one-to-one correspondence between structure and magnitudes of $\Delta\delta/\Delta T$.

In conclusion, we have provided IR and NMR evidence for nucleation of hydrogen bonding in a parallel manner by the rigid phenoxathiin **1**, which satisfies the first important criterion for inducing sheetlike structures into polyamides. We further showed that the ring oxygen does not participate in the hydrogen bonding and that the phenoxathiin derivatives do not form aggregates at the concentrations used. Our results also reinforce the need to restrict degrees of freedom through the use of rigid units in efforts to induce the desired hydrogen bonding. An important difference between our results and those obtained using dibenzofuran is that spacers were necessary in the latter for stable hydrogen bond formation. This may be due to the divergent nature of dibenzofuran, which will render difficult hydrogen bonding close to the aromatic nucleus. We are currently investigating the extent to which the nucleated hydrogen bonding propagates and the incorporation of various rigid β-turn mimics in protein-based polymers.

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