Conformational Study of Succinic and Glutaric *β*-Alanine Derivatives: Resistance of *β*-Alanine Amides To Form Intramolecular Hydrogen Bonds

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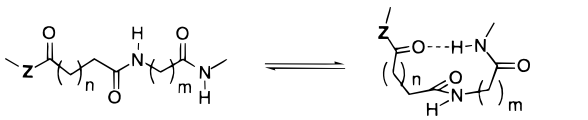
Recently, two groups have independently reported the synthesis of oligomers *β*-amino acids which form helical conformation.[1,2] Seebach and co-workers synthesized a hexamer of chiral *β*-amino acids and found that its conformation in pyridine to be helical with 14-membered rings intramolecularly hydrogen bonded from the CO group of residue *i* to the NH group of residue *i* + 3. Gellman et al. have synthesized a series of oligomers of optically active *trans*-2-aminocyclohexanecarboxylic acid (*trans*-ACHC).[2] The hexamer shows a robust helical conformation both in crystalline form and in methanol solution. The oligomers of *trans*-ACHC have a restricted rotation at the C_α-C_β single bond. Hence their helical conformation is stable. However, other polymers of *β*-amino acids should experience more conformational freedom than the corresponding peptides of α-amino acids. In fact, there are conflicting reports regarding both solution and solid state conformations of poly(*β*-amino acids). Goodman and co-workers studied the conformation of poly[(*S*)-*β*-aminobutyric acid] in hexafluoroisopropyl alcohol (HFIP) by circular dichroism, ultraviolet, and infrared spectroscopy.[3] They suggested a *β*-associated conformation for the polymer in HFIP. The solid state structures of poly(α-alkyl-*β*-l-aspartate) have been studied by two independent groups, and conflicting conclusions have been reached.[4]

We wish to report our results from a conformational study of the diacid derivatives of *β*-alanine that can form *turns* through intramolecular hydrogen bonds. Our results suggest that, unlike α-amino acids, polymers of *β*-alanine do not favor the folded conformations.



Stretched form ⇌ Head-to-tail folding

		Z = NH	Z = O
Glycine derivatives:	n = 1, m = 1	**1a**	**1b**
	n = 2, m = 1	**2a**	**2b**
β-Alanine derivatives:	n = 1, m = 2	**3a**	**3b**
	n = 2, m = 2	**4a**	**4b**

We have recently reported a conformational study of two polyamides made from glycine and succinic or glycine and glutaric acid (**1a** and **2a**).[5a] Both triamides **1a** and **2a** have a tendency to fold in a head-to-tail fashion into a intramoleculary hydrogen bonded 10- and 11-membered ring, respectively. However, triamide **4a**, which is built from *β*-alanine and glutaric acid, prefers a stretched conformation even in nonpolar solvent, chloroform.[5b] To examine the extent to which *β*-alanine derivatives resist formation of an intramolecular hydrogen bond, we have studied the conformational preference of triamide **3a** and a series of diamide esters **1b-4b**. These results enable us to compare the glycine derivatives (**1** and **2**, *m* = 1) directly with that of the *β*-alanine derivatives (**3** and **4**, *m* = 2) for their ability to form intramolecular amide−amide hydrogen bond.

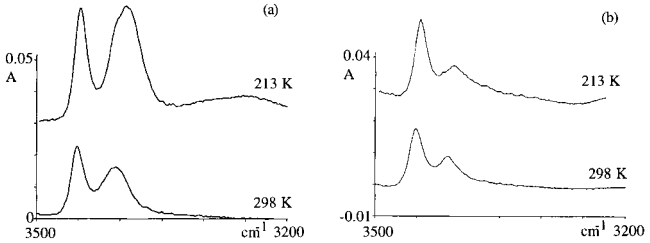


Figure 1. NH stretch region of the IR spectra at 213 K and 298 K for (a) succinylglycyl *N*-methylamide methyl ester, **1b**, and (b) glutarylglycyl *N*-methylamide methyl ester, **2b**. The sharp band at 3448−3452 cm^{-1} is assigned to the free NH stretch and the broad band at 3393−3405 cm^{-1} to the amide NH intramolecularly hydrogen-bonded to the ester carbonyl group.

Thus, both glycine and *β*-alanine derivatives of succinic and glutaric acid are prepared, which allow the formation of 10−12-membered rings through intramolecular hydrogen bonding. In each case, we found that the glycine derivatives favor the folded conformation to a greater extent than the *β*-alanine derivatives.

The NH stretch regions of the IR spectra at 213 K and 298 K for the glycine derivatives **1b** and **2b** are shown in Figure 1. The IR spectra and the variable temperature ^1H NMR data are collected in $CDCl_3$ at 1 mM concentration. There is an intense peak at 3400 cm^{-1} in the NH stretch region of the IR spectrum of **1b** in addition to the free NH peak at 3450 cm^{-1} (Figure 1a), indicating that there is a substantial intramolecular hydrogen bonding in **1b**. The frequency of the NH absorption suggests that it is an NH that is hydrogen bonded to an ester carbonyl group [(NH---O=C(OCH_3)R] because an NH that is hydrogen bonded to an amide carbonyl group usually absorbs at ∼3300 cm^{-1}.[5−8]

Consistent with the IR spectra, the VT NMR data in Figure 2a also shows a chemical shift change for the terminal NH proton of **1b** with temperature. Therefore, there is a substantial amount of head-to-tail folding for the succinic (mono methyl ester) glycine *N*-methylamide **1b** in chloroform. This is quite remarkable considering the fact that an ester carbonyl group is a weaker hydrogen bond acceptor than an amide carbonyl group,[7] and the fact that there is little internal hydrogen bonding in a diamide derived from pimelic acid, which is analogous to **1a**.[7]

Similar pattern is observed for the glutaric (mono methyl ester) glycine methyl amide **2b** except that the

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(7) Gellman, S. H.; Dado, G. P.; Liang, G.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164.

(8) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228−4245.

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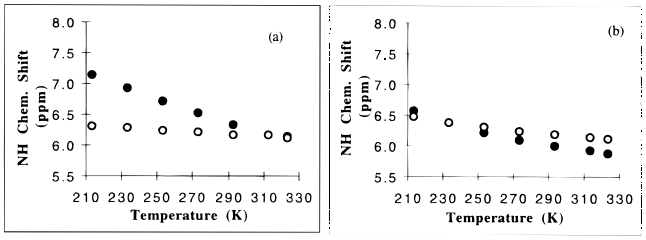


Figure 2. Amide proton NMR chemical shifts of as a function of temperature. (a) Succinylglycyl *N*-methylamide methyl ester, **1b**. Internal NH (○, $\Delta\delta$ NH/$\Delta T = -1.7$ ppb/K). Terminal NH (●, $\Delta\delta$ NH/$\Delta T = -9.4$ ppb/K). (b) Glutarylglycyl *N*-methylamide methyl ester, **2b**. Internal NH (○, $\Delta\delta$ NH/$\Delta T = -3.1$ ppb/K). Terminal NH (●, $\Delta\delta$ NH/$\Delta T = -6.0$ ppb/K).

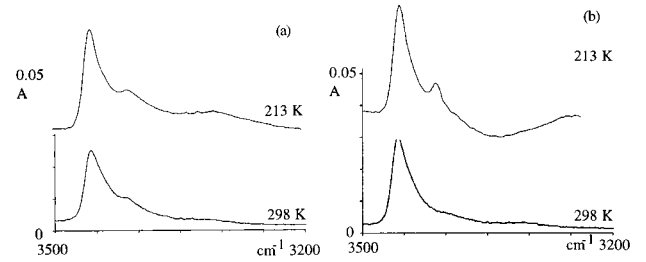


Figure 3. NH stretch region of the IR spectra at 213 K and 298 K. (a) Succinyl-β-alanyl *N*-methylamide methyl ester, **3b**. The sharp band at 3453−3457 cm^{-1} is assigned to the free NH stretch. (b) Glutaryl β-alanyl *N*-methylamide methyl ester, **4b**. The sharp band at 3453−3458 cm^{-1} is assigned to the free NH stretch.

population of the hydrogen bonded conformation is not as great. The absorption at 3400 cm^{-1} for **2b** is lesser (Figure 1b), and the temperature dependency of the terminal NH chemical shift is also smaller ($\Delta\delta$ NH/$\Delta T = -9.4$ ppb/K for **1b** and $\Delta\delta$ NH/$\Delta T = -6.0$ ppb/K for **2b**, Figure 2). The fact that a smaller population of folded conformation is observed for **2b** than for **1b** is consistent with entropic effects. A more negative entropy term is expected for an 11-membered ring formation than for a 10-membered ring formation.

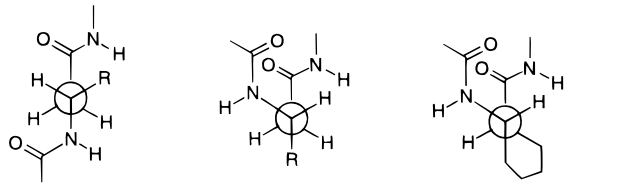
In contrast to **1b** and **2b**, inspection of the IR (Figure 3) and NMR data for the β-alanine derivatives **3b** and **4b** shows negligible signs of intramolecular hydrogen bonding. The temperature dependency of the terminal NH chemical shifts are $\Delta\delta$ NH/$\Delta T = -4.2$ ppb/K for **3b** and $\Delta\delta$ NH/$\Delta T = -3.6$ ppb/K for **4b**. These reduced temperature constants are 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 terminal NH proton of **3b** and **4b** in hydrogen bonding is minimal.

Previously we have reported that triamides **1a** and **2a** strongly prefer the folded conformation[5a] while triamide **4a** prefers the stretched form.[5b] To complete the series, we have also obtained the IR and NMR data for triamide **3a**, a succinic β-alanine monoamide. At lower temperatures, both the IR spectrum and the ^{1}H NMR data show a significant amount of intramolecular hydrogen bonding. The temperature dependency of the terminal NH proton for triamide **3a** is −8.7 ppb/K. It appears that an increased population of the folded conformation is achieved with a stronger hydrogen bond acceptor (compare **3a** with **3b**).

However, the population of intramolecular hydrogen bonded conformation of triamide **3a** is still considerably smaller than the triamides of glycine derivatives **1a** or **2a**. Triamide **1a** assumes almost a complete folded form at all temperatures, and triamide **2a** has a temperature dependency of the NH chemical shift of −13 ppb/K.[5a] On the other hand, triamide **4a**, a glutaric β-alanine derivative, assumes almost none of the folded form.[5b]

By comparison of the succinic and glutaric derivatives of glycine and β-alanine, the glycine derivatives clearly have a greater tendency to form an intramolecular hydrogen bond than the β-alanine derivatives. Entropy certainly plays a role in the conformational preference of these polyamides. β-Alanine derivatives have one more single bond to rotate freely in the stretched form but not in the folded form. However, this entropic consideration alone cannot explain the fact that the folded form of triamide **2a** is about 70% more favorable than the corresponding folded form of **3a** since both triamide **2a** and triamide **3a** have the same chain length and both fold into a 11-membered ring.

On the basis of their studies on single-residue β-peptides, Dado and Gellman have predicted that polymers of β-amino acids may adopt compact and specific folding patterns, because the nearest neighbor hydrogen-bond formation is not a favorable process.[6] The current results show that the β-alanine derivatives **3a,b**, **4a,b** are reluctant to form intramolecular hydrogen bonds not only to the nearest neighbor but also to the next nearest neighbor. Since our experiments are done in a nonpolar organic solvent, chloroform, it would be unlikely for polymers of β-alanine to form turns or helices in polar solvents, such as water and methanol. However, these results are not inconsistent with that of Seebach or Gellman's studies. The following rational should account at least partially for the differences among these β-amino acid derivatives.



A single β-amino acid residue peptide is depicted above in Newman projections along the two sp^3 carbons between the nitrogen atom and the carbonyl carbon. In general, hydrocarbon chains with sp^3 carbons prefer an anti rather than a gauche conformation. However, a gauche or near gauche conformation is required in the *turns* and *helices* of poly β-amino acids. Since β-alanine (R = H) is used in our construction of **3a,b** and **4a,b**, this anti preference is strong, and we observed no intramolecular hydrogen bonding for **3b**, **4a**, and **4b**, and a small amount of intramolecular hydrogen bonding for **3a**.

However, Seebach employed homochiral β-amino acids, and some of the side chain groups are bulky (R = methyl, isopropyl, and isobutyl). As shown in the Newman projections, the steric bulk of the R group should be greater than that of the main chain amide functionality and should drive the dihedral angle $NC_{sp^3}-C_{sp^3}C(=O)$ to a gauche conformation. Gellman's design of poly (*trans*-2-ACHC) excludes entirely the possibility of an anti conformation. The result is a robust helical conformation.

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR spectra for **1b**, **2b**, **3a,b**, and **4b** (9 pages).

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