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Measuring Screw-Sense Preference in a Helical Oligomer by Comparison of ^{13}C NMR Signal Separation at Slow and Fast Exchange

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Supporting Information

ABSTRACT: While an unequal population of rapidly interconverting left- and right-handed conformers of a helical oligomer can be detected by circular dichroism, precise quantification of a conformer ratio has not previously been achieved. We demonstrate, using a set of labeled peptide analogues, that simple analysis of peak separation in their ^{13}C NMR spectra at slow and fast exchange allows an accurate value for the ratio of helical conformers to be obtained. The method reports the ratio of conformers at the site of the label and can therefore be used to investigate local variations in helical conformational control.

Biological signal transduction depends on the communication of molecular conformational change, which enables the function of membrane-bound receptors and allosteric proteins.[1] The challenge of achieving conformational control in synthetic structures has stimulated the development of foldamers: extended molecules with well-defined conformational properties.[2,3] Many foldamers are helical, with a preferred helical screw sense often arising from the presence of chiral monomers within the oligomeric structure.[3]

A preference for helicity should be distinguished from a preference for a single screw-sense (i.e. *M* vs *P*): several classes of foldamers, including those built from aromatic amides[4] and ureas,[5] isocyanides,[6−8] isocyanates,[9−11] and achiral amino acids,[12−15] adopt helical conformations despite being constructed of achiral monomers; they are *conformationally* helical, but *configurationally* achiral. Where screw-sense inversion is slow, as in the polyisocyanides, kinetic control over the growing helical chain may be used to induce a preferred orientation.[7,8] Where screw-sense inversion is fast, a thermodynamic conformational influence is required,[16] and the work of Green showed that high levels of thermodynamic control of helicity can result even from very weak chiral influences;[17] monomers containing a stereogenic center bearing ^{1}H and ^{2}H, for example.[10] Screw-sense control has also been achieved by binding to chiral ligands[8,18] or by incorporating a single terminal chiral controller which, if its stereochemistry can be inverted, allows reversible switching of the helicity of the foldamer,[11,19] with the potential to mimic biological signal transfer mechanisms.[20]

Whatever mechanism of control is employed, its usefulness depends on how effectively screw-sense control is achieved; in other words the quantified preference of the foldamers for *M* or *P* helicity. This figure, which could be termed the "helicity excess" of the foldamer, has rarely been determined accurately. Circular dichroism can yield data on relative helical preferences by calibration against known or modeled spectra,[21] and when *M* and *P* conformers interconvert slowly, NMR can be used to quantify the ratios of diastereoisomeric conformers.[22]

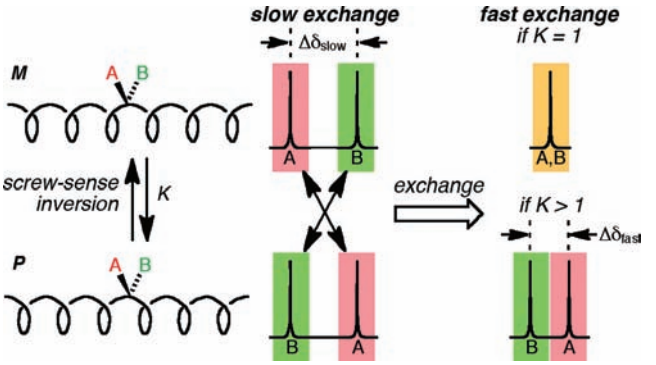

Figure 1. Diastereotopic groups within helical oligomers and their NMR signals in the fast and slow exchange régimes.

Here we demonstrate that comparison of the ^{13}C NMR spectra of a set of ^{13}C-labeled helical foldamers in the slow and fast exchange régimes provides a simple new method for the accurate determination of their helical excess. Line-shape analysis allows both the kinetics and the thermodynamics of screw-sense inversion to be quantified, and the use of multiple ^{13}C labels makes possible the measurement of localized screw-sense preference at specific sites along the helix.

The method depends on the fact that a pair of groups rendered diastereotopic by virtue of their location within a helical structure will give rise to anisochronous signals when the screw-sense inversion of the helix is slow on the time scale of their chemical shift separation, $\Delta\delta_{slow}$, in Hz (Figure 1). The value of $\Delta\delta_{slow}$ is independent of the ratio of the two screw-sense conformers. However, when the screw-sense interconversion becomes fast on the time scale of their chemical shift separation—at higher temperature for example—a new averaged pair of anisochronous signals arises with peak separation $\Delta\delta_{fast}$. $\Delta\delta_{fast}$ must be 0 if the *M* and *P* conformers of the helix are equally populated, for example in the absence of a chiral controlling influence. In the general case, the ratio $\Delta\delta_{fast}/\Delta\delta_{slow} = ([P] - [M])/([P] + [M]) = (K - 1)/(K + 1)$, where $K = [P]/[M]$ (provided anisochronicity is temperature-independent). The quantity $\Delta\delta_{fast}/\Delta\delta_{slow}$ can be termed "helicity excess" (by analogy with "enantiomeric excess" = $([R] - [S])/([R] + [S])$).

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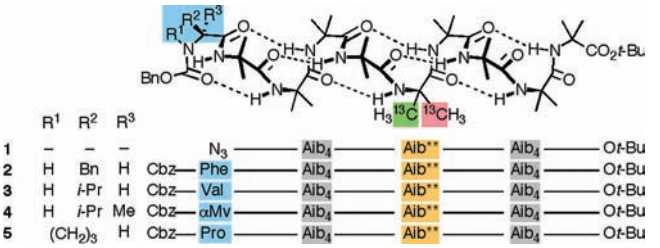

Figure 2. ^{13}C-Labeled Aib$_9$ oligomers shown as a *P* helix with an N-terminal cap.

In connection with our work on the control and switching of helical structures built from aminoisobutyric acid (Aib)[14,15,19] we chose to explore and illustrate the utility of this method by investigating the degree of screw-sense control exerted by an *N*-terminal chiral amino acid on a chain of nine Aib residues. Homo-oligomers of Aib are known to adopt 3_{10} helical conformations in solution,[13,23] and both CD and ^{1}H NMR spectroscopy have shown that an *N*-terminal amino acid exerts a measurable, but unquantified, level of screw-sense control in solution.[24]

The challenge in determining the helicity excess by our proposed method is to choose a reporter group with a peak separation $\Delta\delta_{slow}$ which allows both slow and fast régimes to be explored at temperatures compatible with solubility of the oligomer in a suitable solvent. Typical separations of the diastereotopic ^{1}H signals in Aib oligomers and their analogues are insufficiently large to make slow exchange accessible;[14,15] thus, we turned instead to the ^{13}C signals of selectively ^{13}C-labeled compounds **1**−**5** (Figure 2). Dynamic NMR studies of the ^{13}C spectra of achiral Aib oligomers[25−27] and other helices[28] have previously been used to determine kinetic parameters associated with their screw-sense inversion.

Labeled compounds **1**−**5** were synthesized by ligating two N_3Aib$_4$O*t*-Bu tetramers[14] through a doubly ^{13}C-labeled Aib made by Strecker reaction of acetone-$^{13}C_2$ (details in Supporting Information [SI]).[29] The location of the ^{13}C labels in the middle of the helix was chosen to avoid specific direct interactions with the helix termini − especially the chiral controller at the N-terminus. The labeled methyl groups are of course diastereotopic as a result of the presence of this chiral controller, irrespective of helicity, but by locating them at a distance from the controller we ensure their anisochronicity results only from their interactions with the helix itself. This synthetic approach gave **1**, which was reduced and coupled with Cbz-L-phenylalanine, Cbz-L-valine, Cbz-L-α-methylvaline, and Cbz-L-proline to yield peptides **2**−**5**. Titrations of the peptides **1**−**5** in $CDCl_3$ with DMSO and comparison of circular dichroism spectra (see SI) indicated that **2**, **3**, and **5** adopt preferentially a left-handed (*M*), and **4** a right-handed (*P*) 3_{10} helical conformation in solution.[30]

^{13}C NMR spectra were acquired for each peptide **1**−**5** at temperatures from −60 °C to +23 °C. Figure 3 shows data points from the portions of the NMR spectra containing the ^{13}C-enriched signals of **1**−**4** in CD_3OD and of **2** in CD_3CN at a range of temperatures between −40 and 0 °C. To facilitate line-shape modeling, data points arising from peaks due to natural abundance ^{13}C signals from the remaining 16 methyl groups of the oligomers were excised from the traces. For each set of spectra as a function of temperature, the remaining data points were subjected to global nonlinear least-squares fitting to a model assuming doubly degenerate exchange with unequal populations and Arrhenius kinetics. The fit was performed by iteration on the

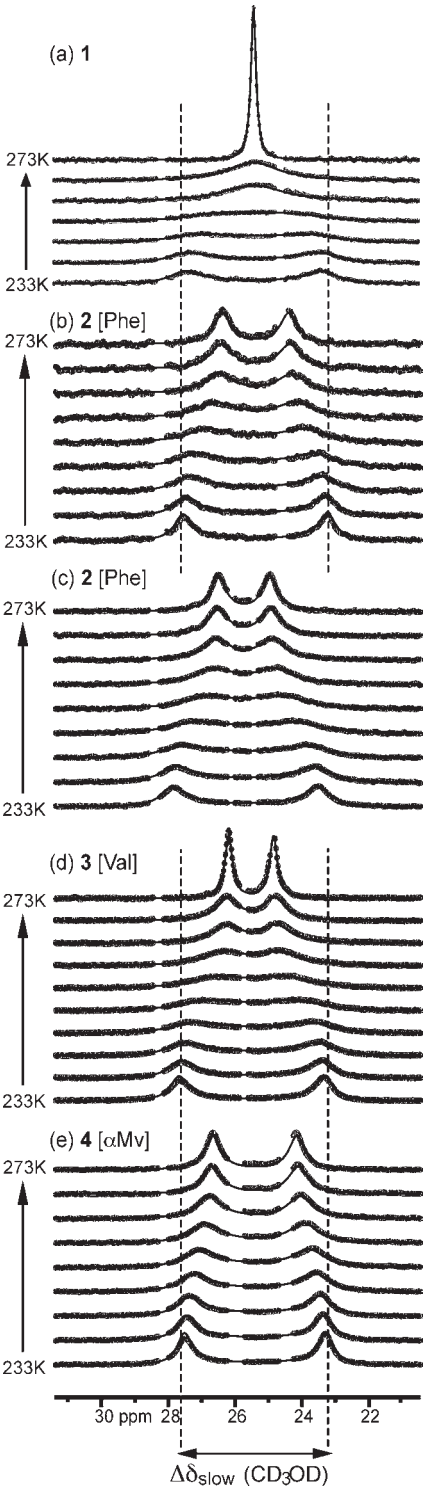

Figure 3. Experimental data (gray dots) and fitted spectra (black lines) for portions of the ^{13}C spectra of labeled CbzXxxAib$_9$O*t*-Bu oligomers at a range of temperatures between 233 and 273K. (a) **1** in CD_3OD; (b) **2** CD_3OD; (c) **2** in CD_3CN; (d) **3** in CD_3OD; (e) **4** in CD_3OD. Gaps in the experimental data appear where interfering signals from unenriched species were excised. Dotted vertical lines for the spectra in methanol indicate the positions and separations of the peaks at the slow exchange limit calculated in the fitting process.

limiting chemical shift difference, $\Delta\delta$, the average chemical shift, δ, the temperature coefficient $d\delta/dT$ of the shift, the natural

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Table 1. Kinetic and Thermodynamic Parameters from ^{13}C NMR Spectra of 1−5 and Corresponding Values for Helical Ratios in CD_3OD

cmpd	E_a/kJ mol^{-1}[a]	K^{253K}	ΔH^{253K}/kJ mol^{-1}	h.r.^{253K}[b]	$\Delta\delta_{slow}{}^{213K}$/ppm[c]	$\Delta\delta_{fast}{}^{296K}$/ppm[c]	h.r.^{296K}[d]
1	35.2 ± 0.1	1	0	50:50	4.36	0	50:50
2	32.8 ± 1.1	2.56 ± 0.06	−1.0 ± 1.0	72:28	4.42	1.74	70:30
2[e]	35.5 ± 0.3	2.04 ± 0.01	−1.5 ± 0.2	67:33	4.33	1.34	65:35
						0.91[f]	60:40[f]
3	34.3 ± 0.2	1.96 ± 0.02	−1.0 ± 0.2	66:34	4.40	1.33	65:35
4	38.7 ± 0.4	3.53 ± 0.03	−1.5 ± 0.3	78:22	4.40	2.31	76:24
5	−	−	−	−	4.46	1.73	69:31

[a] Activation energy for conversion of minor to major helix conformer. [b] Ratio of major to minor helix conformer calculated from the modeled value of K^{253K}. [c] Observed chemical shift difference at the temperature indicated. [d] Ratio of major to minor helix conformer calculated from the ratio of $\Delta\delta_{fast}{}^{296K}$ to $\Delta\delta_{slow}{}^{213K}$. [e] In CD_3CN. [f] At 334 K (70 °C).

logarithm ln A of the pre-exponential factor for the major to minor conversion, the activation energy E_a for that process, the enthalpy difference ΔH between major and minor partner, and the entropy difference ΔS between the two. The analytical expression for the exchanging spectrum was determined by automated steady-state solution of the Bloch equations, modified for exchange and assuming negligible saturation, using the program Mathematica;[31] the results obtained were in exact agreement with those of Gutowsky and Holm[32] but cast in a slightly more convenient form, with a lower highest order of term and, hence, slightly greater numerical accuracy. In the case of the achiral peptide, ΔH and ΔS were fixed at zero. Values at 253 K (−20 °C) for E_a, ΔH, and K, also expressed as a helical ratio (h.r.), are shown in Table 1.

The peak separation $\Delta\delta_{slow}$, and indeed the location δ, of the two signals arising from the labeled diastereotopic methyl groups at slow exchange in each oligomer was essentially independent of the terminal residue, changing only with solvent. This result validates the assumption that the labels experience a local environment determined solely by the helix which flanks them, and are not affected by the nature of the helix terminus.

The activation energy for helical inversion, E_a, varied a little with helix structure and with solvent, and was comparable with (if slightly lower than) that corresponding to the reported rate of inversion of an Aib hexamer, octamer, or decamer in CD_2Cl_2.[25,27] Inversion of a 3_{10} helix can occur via a "zipper" mechanism,[27] and with the typical strength of a hydrogen bond being approximately 21 kJ mol^{-1},[33] values in the region of 35 ± 3 kJ mol^{-1} are consistent with the simultaneous breakage of 1−2 hydrogen bonds at the transition state for helix inversion.

Consistent with previous reports,[25,27] the peaks of **1**, devoid of a chiral residue, coalesced at high temperature to a single signal. For the rest, raising the temperature led, as expected, to broadening followed by resharpening to a new pair of signals separated by a new chemical shift difference, $\Delta\delta_{fast}$. The average chemical shift δ was again independent of the N-terminal residue, consistent with the assumption that chemical shift is not directly affected by the terminal residue, but only by the local helical environment.

From the value of K we established that the maximal control of helix orientation among the residues we studied arose from an N-terminal α-methylvaline residue, which gave a 78:22 ratio halfway along the helix. The helical ratio can also be estimated simply by dividing $\Delta\delta_{fast}$ by $\Delta\delta_{slow}$, and acquiring spectra at −60 C and at +21 °C gave us sharp signals from which we obtained these values. The resulting helical ratios at 296 K are

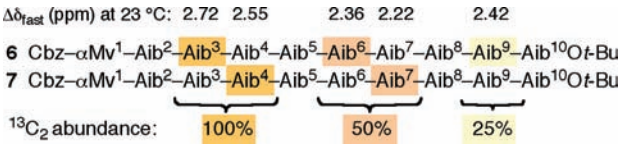

Figure 4. Limiting chemical shift differences $\Delta\delta_{fast}$ for ^{13}C-labeled Cbz-αMv-Aib$_9$O*t*-Bu oligomers, with the locations of $^{13}C_2$ labels within each molecule identified by differing enrichments.

shown in the last column of the table and are in essentially perfect agreement with those derived by line-shape modeling if the effects of the difference in temperature are taken into account. Increasing the temperature of **2** in MeCN beyond 296 K led to a further, approximately linear, diminution of the estimated helical ratio with temperature, dropping from 70:30 at 21 °C to 60:40 at 70 °C.

The values for helicity ratios determined by these methods apply only at the position of the label. It is to be expected that, due to a small but finite chance of a helix reversal at each position in the oligomer, there will be a slow decay of helical preference moving along the chain away from the helical controller. A previous study[14] estimated a 3.5% loss of helical preference per Aib residue. To investigate the effect of the position of the ^{13}C reporter on $\Delta\delta_{fast}$, and hence probe the dependence of the local helical ratio on the position in the chain, we made two compounds **6** and **7** bearing labels respectively at residues 3, 6, and 9 and at residues 4 and 7 of the peptide (Figure 4). In order to identify the location of the label within each peptide, Aib residues nearest the N terminus (position 3 or 4) were labeled at 100% abundance, the next positions (6 and 7) at 50% abundance, and position 9 at 25% abundance. Figure 4 gives values for $\Delta\delta_{fast}$ at 23 °C.

A decay of $\Delta\delta_{fast}$ as the label was moved along the chain was clearly evident, except with the label at residue 9, which is too close to the chain terminus to give reliable information about helix conformation. Fitting the values of $\Delta\delta_{fast}$ (other than that of residue 9) to an exponential decay[14] returned a value for the fidelity of transmission of helical preference of 0.975, or in other words a rate of decay of 2.5% per Aib residue. Repeating the study at 30 and 40 °C also gave decay rates of 2.5%. As expected, on decreasing the temperature, the sets of peaks from the ^{13}C labels of **6** and **7** coalesced to a single pair of signals with $\Delta\delta_{slow}$ = ∼4.30 ppm, confirming that the change in peak separation ($\Delta\delta_{fast}$) on moving along the chain is due to a diminishing screw-sense preference and does not directly result from position in the helix.

In summary, the method we outline elucidates the substrate-dependence of helical control with finer detail than is possible by

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circular dichroism, quantifying the screw-sense ratio at a specific site in a helical structure. The results show that, while Aib oligomers transmit a helical preference highly effectively, a single amino acid in fact induces a relatively weak screw-sense preference, giving rise to a maximum among those studied here of about 3:1 with α-methylvaline as the controller. The method is in principle applicable in stereochemically and kinetically comparable situations and offers the prospect of the straightforward determination of helicity excess in a wide range of foldamers.

■ ASSOCIATED CONTENT

Supporting Information. Details of the synthesis and characterization of all peptides, NMR and circular dichroism spectra, and full details of line-shape modeling. This material is available free of charge via the Internet at http://pubs.acs.org

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(30) Recent CD and NMR data suggest, contrary to literature reports (ref 24a), that, while an *N*-terminal L-α-methylvaline induces *P* helicity in an Aib oligomer, an N-terminal secondary L-amino acid induces *M* helicity. Further clarification of this effect is under way and will be published shortly.

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