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Conformational Switching in Heterochiral α,β^{2,3}-Hybrid Peptides in Response to Solvent Polarity

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The ability of α,β^{2,3}-hybrid peptides with a heterochiral backbone to exist in a helical, extended, or partially folded state depending on the solvation conditions employed was investigated. The preference was found to be directly dictated by C_α–C_β torsions in the β-residues.

Introduction

The requirement of a specific molecular conformation is central to every protein function, and its dependence on accessible ϕ/ψ torsions and secondary interaction possibilities clearly show that the parameters that regulate the folding phenomena are multifaceted. The design of synthetic models of peptides and proteins with comparable conformations and properties has been a fascination for researchers working in this field.[1] Given that a fine balance between entropic and enthalpic factors is necessary to obtain a well-defined conformation, especially in solution, there have been intense efforts since the early 1990s to use residue preorganization,[2] metal coordination,[3] and cross-linking[4] as strategies to create conformationally unique molecular systems. After early work from the laboratories of Seebach[5] and Gellman,[6] this field has grown tremendously during the last couple of decades, and the group of molecules that can adopt well-defined conformations in solution are now collectively known as "foldamers".[2,7] The development of small oligomeric systems capable of switching from one well-defined conformational state to another in response to variations in the chemical environment is equally important. Apart from giving a closer look at solvation effects on backbone torsions, these oligomeric systems could find application in the design of stimuli-responsive functional molecules/materials. During our studies on the conformational characteristics of a new group of α,β^{2,3}-peptides, we realized that creation of such "switchable foldamers" is indeed possible and our observations are delineated below.

Previously, we reported a group of α,β^{2,3}-hybrid peptides with $(\alpha,\beta)_n$ composition that can adjust their C_α–C_β torsions in response to intramolecular hydrogen-bonding possibilities.[8] It was also possible to initiate sequential unwinding of helical turns in their homologous $(\alpha,\beta)_n\alpha$ oligomers by increasing solvent polarity.[9] In fact, the stereochemistry and substitution pattern at C_α and C_β restrict the rotamer preference to either *gauche* or *anti*, which in turn translates into a helical or extended conformation in such systems; such a preference is tunable by adjusting the chemical environment or temperature. As the next step, we chose to alter the torsions around specific residues by introducing the opposite stereoisomer of the β^{2,3}-residue at the respective locations (Figure 1). Excitingly, this study not only led to molecules that respond to changes in their chemical environment by adopting different but well-defined conformations, but it also gave an understanding on the key backbone torsions that dictate these preferences. Peptides **1**–**3** used in this study were prepared by HATU {1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate} mediated solution-phase peptide synthesis, and structure elucidation was done by using a combination of ^{1}H NMR, ^{13}C NMR, COSY, TOCSY, and ROESY spectroscopy and HRMS. They can be considered

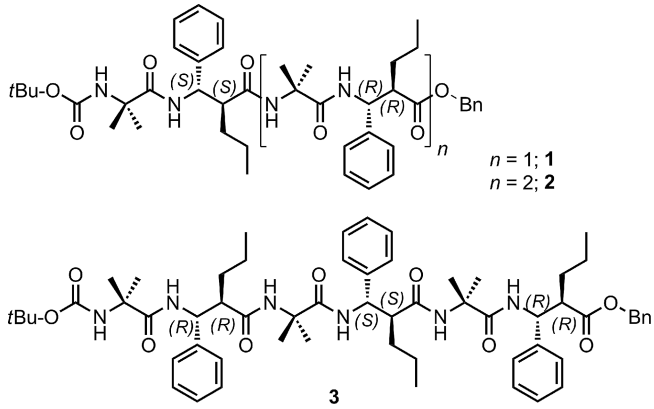

Figure 1. Chemical structures of heterochiral α,β^{2,3}-hybrid peptides **1**–**3** chosen for this study.

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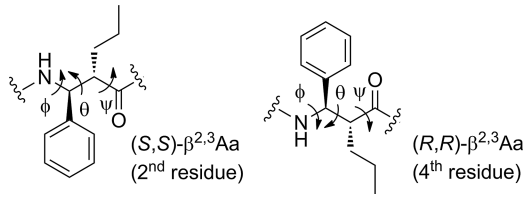
as the simplest members of α,β[2,3]-hybrids with alternation of chirality in β-residues.

Results and Discussion

The solvent-shielded nature of the internal NHs in **1** was clear from [D$_6$]DMSO titration experiments [$\Delta\delta$NH = 0.16–0.24 ppm for NH(2), NH(3) and NH(4); Figure S2, Supporting Information]. Although the splitting pattern of the $C_\beta H$ signals (^{1}H NMR in $CDCl_3$) was expected to give information on its folding preference, heavy overlap of the $^2C_\beta H$ and $^4C_\beta H$ signals made the analysis difficult; its ROESY spectrum was also less useful because of signal overlap. We were, however, successful in getting X-ray quality crystals of this peptide by slow evaporation of its chloroform solution, and diffraction analysis showed it as having a left-handed 11-helical conformation (Figure 2, a). This was facilitated by *gauche* conformation of the $^2C_\beta$ unit with θ = –79.3° (Table 1). Interestingly its $^4C_\beta$ unit is antiperiplanar with $\theta \approx 177.6°$, which suggests that stereochemical differences at that location do not adversely affect the folding ability in $CHCl_3$. Dispersion of signals was very good if the ^{1}H NMR spectrum was recorded in [D$_6$]DMSO. The second and fourth C_βHs appeared as apparent triplets with J values of 9.0 and 9.5 Hz, respectively, which indicated antiperiplanar arrangement in these residues. This was further supported by the ROESY spectrum recorded in the same solvent, which had NOEs only from the adjacent residues (i,i+1 type). These data clearly show the ability of peptide **1** to choose either a fully extended or a fully helical conformation depending on whether the medium is hydrogen bonding or not.

To determine whether the nature of the solvent could dictate the folding profile and packing in the solid state, peptide **1** was subsequently crystallized from 2-propanol by slow evaporation. As anticipated on the basis of hydrogen-bonding effects from 2-propanol, a strand-like conformation was observed in this case (Figure 2, b). Closer analysis of the lattice revealed the existence of a pair of conformational isomers (**I** and **II**, Figure 2, b) that formed parallel β-sheet-like structures stabilized by $^{\mathbf{I}}$CO(3)···$^{\mathbf{II}}$NH(3) hydrogen bonding through the bottom face of **I** and two such secondary interactions [$^{\mathbf{II}}$CO(1)···$^{\mathbf{I}}$NH(1) and $^{\mathbf{II}}$CO(3)···$^{\mathbf{I}}$NH(3)] through the top. Remarkably, the second and fourth C_βHs of conformer **I** chose to have a near antiperiplanar arrangement with θ = 175.7 and 168.7°, respectively, whereas the corresponding values for conformer **II** were θ = –173.8 and 160.1°. Selected backbone torsions in these structures are presented in Table 1. The arrangement if viewed along b axis is shown in Figure 2 (b). The hydrogen-bonding distances and relevant angles in these systems are included in Table 2.

Table 1. Selected backbone torsions from the X-ray structures of peptide **1** crystallized from $CHCl_3$ and 2-propanol; local conformation around individual residues is evident from the θ values.



Solvent	Conformer	Residue	ϕ [°]	θ [°]	ψ [°]
$CHCl_3$	–	2	111.7	–79.3	70.6
$CHCl_3$	–	4	–129.1	177.6	130.5
*i*PrOH	**I**	2	103.6	175.7	120.6
*i*PrOH	**I**	4	–94.6	168.7	113.3
*i*PrOH	**II**	2	108.9	–173.8	–121.8
*i*PrOH	**II**	4	–101.3	160.1	130.6

Table 2. Hydrogen-bonding distances and angles observed in the crystal structures of peptide **1**.

Condition	Type		H···O [Å]	∠N–H···O [°]
$CHCl_3$	Boc-C=O···NH(3)	Intra	2.192	161.9
	CO(1)···NH(4)		2.162	164.1
*i*PrOH	$^{\mathbf{II}}$CO(1)···$^{\mathbf{I}}$NH(1)	Inter	2.212	145.7
	$^{\mathbf{II}}$CO(3)···$^{\mathbf{I}}$NH(3)		2.266	144.4
	$^{\mathbf{I}}$CO(3)···$^{\mathbf{II}}$NH(3)		2.153	155.7

Although the resonance dispersion of **1** in $CDCl_3$ was poor at room temperature, a noticeable improvement was observed upon performing the experiment at 313 K. Pleasingly, the helicity remained unperturbed, as indicated by a clear apparent doublet for $^2C_\beta H$ with $^3J_{C_\beta H,C_\alpha H}$ and $^3J_{C_\beta H,NH}$ values of 4.8 and 9.6 Hz, respectively (Table 3). The C-terminal β-residue at the same time preferred an *anti* conformation with $^3J_{C_\beta H,C_\alpha H} = {}^3J_{C_\beta H,NH} \approx 8.8$ Hz. A stepwise increase in the temperature to 328 K led to little change in the position of the signals or the splitting pattern (Figure 3, a). The experiments were then repeated with [D$_8$]toluene to access higher temperatures. As evident from the data presented in Table 3, the spectral characteristics did not show much variation till 368 K, and then they were comparable to those obtained from $CDCl_3$, which further

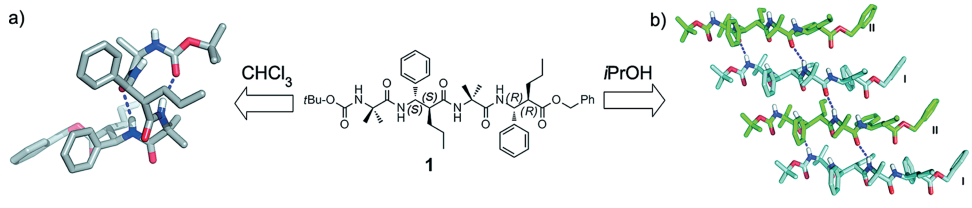


Figure 2. X-ray crystallographic structures of **1** based on diffraction analyses of its crystals grown from (a) chloroform and (b) 2-propanol.[10] Nonrelevant hydrogen atoms and the co-crystallized solvent molecule are omitted for clarity.

confirmed its conformational integrity and stability. Given that all $C_\beta H$ signals were well dispersed in [D_8]toluene (Figure 3, b), we could obtain the crucial NOE information that was not possible from $CDCl_3$ because of signal overlap. The characteristic $^2C_\beta H \rightarrow {}^4NH$ NOE indicative of an 11-helical conformation from the experiment performed in a [D_8]toluene/$CDCl_3$ (4:1) mixture is presented in Figure 3 (d). Interestingly, the behavior in CD_3CN was slightly different (Figure 3, c, see also Figure S5 and Table S2 in the Supporting Information). The $^4C_\beta H$ signal in this case appeared as an apparent triplet with equal J values of 9.5 Hz in the temperature range of 298 to 348 K and showing *anti* conformational preference around this residue as in previous cases. At the same time, broad appearance of the $^2C_\beta H$ signal made its J value assessment difficult for experiments performed in the temperature range of 298 to 318 K. Fortunately, this signal was well resolved with a dd pattern with J values of 7.5 and 9.5 Hz for experiments done at 328 and 348 K. The intermediate J value for $^2C_\beta H$ and a consistent and large $^3J_{C_\beta H,C\alpha H}$ for $^4C_\beta H$ under this condition suggested a considerable degree of rotational transitions in the first half of the molecule with minimum disturbance in the C terminus.

Table 3. Results from a temperature-dependent ^{1}H NMR study of tetrapeptide **1** in $CDCl_3$ and [D_8]toluene; $C_\beta H$ splitting pattern [apparent triplet: app. t, or doublet of doublets: dd] gives a direct picture of C_α–C_β torsion in these systems.

T [K]	$CDCl_3$			T [K]	[D_8]Toluene		
	$^4C_\beta H$ (app t) $J_1 = J_2$ [Hz]	$^2C_\beta H$ (dd) J_1 [Hz]	J_2 [Hz]		$^4C_\beta H$ (app. t) $J_1 = J_2$ [Hz]	$^2C_\beta H$ (dd) J_1 [Hz]	J_2 [Hz]
298	–[a]	–[a]	–[a]	298	8.0	–[a]	–[a]
313	8.8	4.8	9.6	318	8.0	5.0	9.0
328	8.8	4.8	9.6	328	8.0	5.5	9.0
				368	8.0	5.5	8.5

[a] J values could not be deciphered in these cases owing to signal overlap/poor splitting pattern ($J_1 = {}^3J_{C_\beta H,C_\alpha H}$; $J_2 = {}^3J_{C_\beta H,NH}$).

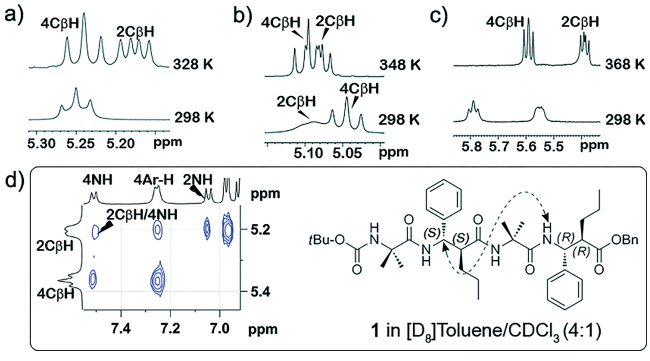


Figure 3. Relevant regions of the variable-temperature (VT) NMR spectra of **1** in different solvents showing the nature of the $C_\beta H$ signals: (a) $CDCl_3$, (b) [D_8]toluene, and (c) CD_3CN (complete VT NMR spectra are given in Figures S3–S5, Supporting Information); (d) expanded region of the ROESY spectrum of **1** in [D_8]toluene/$CDCl_3$ (4:1) showing the long-range NOEs.

Given that solvation effects are crucial in the selection of conformation in the solid and solution states, we set out to follow the transition from one conformation to another upon changing the polarity of the chemical environment. Towards this, the ^{1}H NMR spectra of **1** in $CDCl_3$ after incremental additions of [D_6]DMSO were recorded (0–100% [D_6]DMSO), and changes in the signal positions and their splitting patterns were systematically analyzed. A significant downfield shift in all NH signals along with separation of the $^2C_\beta H$ and $^4C_\beta H$ signals was seen on using 20% [D_6]-DMSO (Figure 4). Whereas the $^2C_\beta H$ signal was broad, likely because of rotamer equilibria, the $^4C_\beta H$ signal came as an apparent triplet in support of an *anti* conformation across $^4C_\alpha$–C_β under this condition. A further increase in the [D_6]DMSO content was found to affect the signals of NH(1), NH(2), NH(3), and $^2C_\beta H$ to a greater extent than the signals of NH(4) and $^4C_\beta H$, which suggests enhanced conformational transitions in the first three residues. A broad $^2C_\beta H$ signal in experiments involving 50–80% [D_6]-DMSO and its emergence as a separate apparent triplet in 100% [D_6]DMSO, if correlated with continuous downfield shifts of the signals of NH(1), NH(2), and NH(3), suggest that the $^2C_\beta$–C_α torsion equilibrates more towards the *anti* form upon increasing solvent polarity. This happens in response to enhanced hydrogen bonding with the solvent in the unfolded state.

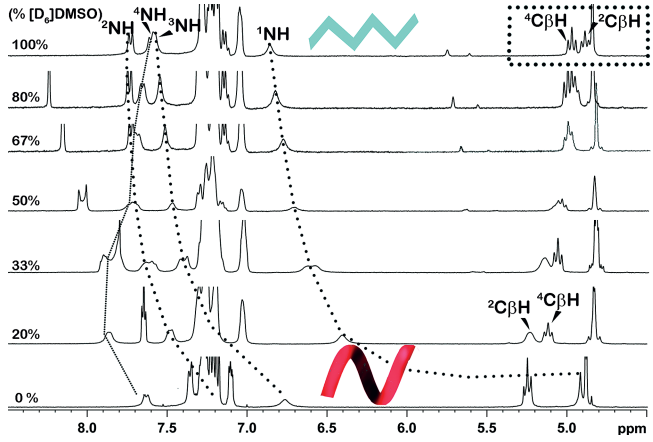


Figure 4. Relevant regions of the ^{1}H NMR spectra of **1** in different proportions of [D_6]DMSO and $CDCl_3$; percentage of [D_6]DMSO is indicated on the left-hand side. Two apparent triplets corresponding to the second and fourth $C_\beta H$ ($^3J \approx 9.0$ Hz) in the dotted box indicate a completely extended conformation for **1**.

Peptide **1**, in the folded state, has two intramolecular hydrogen-bonding interactions (i,i+3 C=O···HN). Its unfolding through *gauche* to *anti* shift across $^2C_\beta$–C_α with solvent polarity shows the interplay and compromise between entropy and enthalpy changes as these intramolecular secondary interactions give way to intermolecular ones. Although realization of this in a segment as short as a tetrapeptide itself is exciting, we moved ahead to witness similar conformational preferences in its higher oligomers. On the basis of the structure of **1**, we anticipated that stereochemical inversion at the C-terminal β-residue would have only a minimum influence on the stability of the helix. Hence, only peptides **2** and **3** were chosen for detailed analysis. Resonance dispersion in their ^{1}H NMR spectra was good, which

made signal assignment easy. The $^{2}C_{\beta}H$ signals of these peptides were broad doublets in support of specific folding around this residue. Surprisingly, both $^{4}C_{\beta}H$ and $^{6}C_{\beta}H$ gave apparent triplets with equal J values ($^{3}J_{C_{\beta}H,C_{\alpha}H} = {}^{3}J_{C_{\beta}H,NH}$ = 8.0–8.5 Hz) showing preference for *anti* conformation across the associated C_{α}–C_{β} bonds. Overall, this implied that the 11-helical structure exists only in the first half of the molecule, which is followed by an extended strand-like conformation from the fourth residue onwards, and this makes it a unique hybrid of helix and strand! In strong support of this, the ROESY (500 MHz, $CDCl_3$) spectra of these peptides showed only one nonsequential NOE corresponding to the $^{2}C_{\beta}H \rightarrow {}^{4}NH$ interaction (Figure 5, c,d). The absence of other long-range NOEs once again suggested that the remaining part of the molecule adopts an extended conformation.[9]

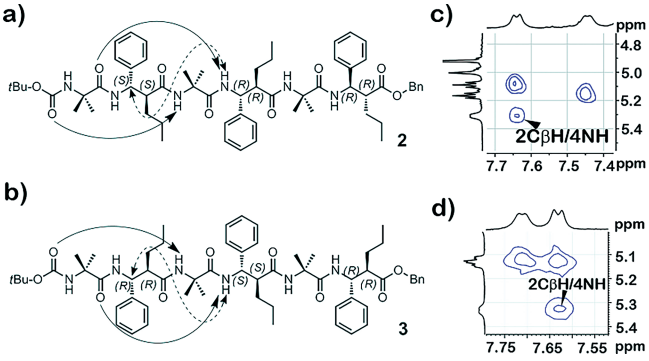


Figure 5. (a,b) Chemical structures of α,β-peptides **2** and **3**. Dotted arrow lines in the chemical structure indicate nonsequential NOEs in the ROESY ($CDCl_3$) spectrum. Hydrogen-bonding interactions proposed on the basis of the NMR spectroscopy data are indicated with solid arrow lines. Relevant regions in the ROESY ($CDCl_3$) of (c) **2** and (d) **3**.

Their response to solvent polarity was also remarkable, and ^{1}H NMR spectral changes could be directly used to follow the transition from a partially folded conformation to a fully extended conformation. Initial solvent titration experiments revealed that the signals of NH(1), NH(3), and NH(5) of **2** and **3** undergo larger downfield shifts than the signals of NH(2), NH(4), and NH(6) on incremental additions of [D_6]DMSO (up to 30% v/v in $CDCl_3$; Figures S6, Supporting Information). More than their solvent-exposed nature, we believe that [D_6]DMSO induces some degree of unfolding, and this could be the reason why NH(3), which is normally associated with intramolecular $i,i+3$ hydrogen-bonding interactions, suffers a greater shift. The signal of $^{2}C_{\beta}H$ continued to be broad in the [D_6]DMSO concentration range of 0 to 25% (Figure 6). In the case of **3**, the signal of $^{2}C_{\beta}H$ merged with those of $^{4}C_{\beta}H$ and $^{6}C_{\beta}H$ at 50% [D_6]DMSO, and on increasing the concentration further (75% [D_6]DMSO) we could see two distinct apparent triplets in a 1:2 ratio; for **2**, all these signals were in the same place with significant signal overlap. These observations tend to indicate that the 11-helical segment in the N-terminal region of **2** and **3** unwinds at a lower [D_6]DMSO concentration than that required for **1**.

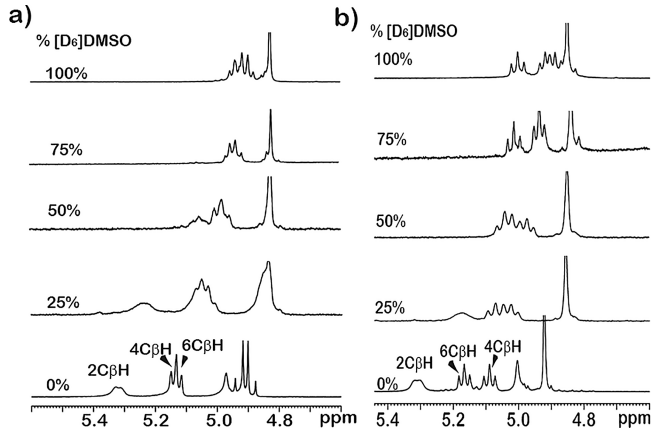


Figure 6. Solvent-induced conformational transition in hexapeptides **2** (a) and **3** (b) in varying proportions of $CDCl_3$ and [D_6]-DMSO; appearance of $^{2}C_{\beta}H$ as an apparent doublet in $CDCl_3$ and the change in its splitting pattern with increasing amount of [D_6]-DMSO are shown.

There have been a large number of efforts in the past to closely monitor conformational transitions by using peptide sequences designed on the basis of either relevant segments from proteins or rational means. Temperature, pH, concentration, ionic strength, solvents, and pressure are some of the variables that were found to be influential in bringing about transition from one conformational state to another.[11] Peptides with appropriate alternation of polar and nonpolar residues are known to adopt specific conformations owing to their tendency towards an amphipathic arrangement and have been widely used for accessing different conformations.[12] In line with this, Dado and Gellman elegantly used methionine side-chain oxidation as a tool to fine-tune polarity characteristics and were successful in identifying a redox-switchable 18-residue peptide.[13] Studies on the effect of N-terminal hydrophobicity on the α-helix to β-sheet transition in α-peptides,[14] redox-switching of the Ac-SIRKLEYEIEELRLRIG-NH_2 peptide between extended and helical conformations by making use of its differential affinity towards Cu^{II}/Cu^{I} ions,[15] photoswitching of peptide conformation with a built-in azobenzene unit,[16] chain-length-dependent 10- or 14-helical preferences in *trans*-2-aminocyclohexane carboxylic acid oligomer,[17] solvent-driven α- and 3_{10}-helical preferences of an *N*-acylated homoheptapeptide isopropylamide based on L-α-methylvaline in the crystalline state,[18] partially unwound helical structure in hexameric oligourea containing a selenourea moiety proximate to the positive pole,[19] partially unwound helical structure of a four residue γ-peptide analogue having a carbamate–urea hybrid sequence,[20] and zigzag tap-like conformation stabilized by α- and γ-turns in a hybrid octapeptide of leucine with a 8-amino-2-quinolinecarboxylic acid derivative[21] are some selected examples showing the active interest in understanding and manipulating folding preferences of peptides and peptide mimetics. Fülöp et al. have previously shown that oligomers based on *cis*-2-aminocyclopentanecarboxylic acid (*cis*-ACPC) have a tendency to adopt an extended conformation, unlike their

analogues based on *trans*-ACPC.[22] The idea of chirality alternation has also been experimented by the Fülöp group by using some selected *cis*- and *trans*-ACPC oligomers. Among these, heterochiral *cis*-ACPC peptides were found to assume a H10/12 helical structure. At the same time, the heterochiral *trans*-ACPC oligomer existed as a polar strand.[23] As mentioned before, we recently reported the sequential unwinding of helical turns in peptides with $(\alpha,\beta)_n\alpha$ composition through incremental changes in solvent polarity/temperature.[9] The present work is in continuation of our efforts in this direction and shows that heterochiral sequences of this class of peptides are good candidates for accessing partially folded conformations. The ability of peptide **1** to exist in either a helical or extended state depending on the chemical environment points towards the potential use of such hybrid peptides in the design of stimuli-responsive materials.

Conclusions

The ability of proteins to shift from one specific conformation to another in response to biological triggering events is responsible for the high degree of regulation in every cellular function. Simulation of such transitions by using small oligomers is an extremely important subject owing to its direct application in the design of new functional systems. Such studies are also of special significance, as they can shine light onto the intricacies of protein folding. Herein, we presented a group of α,β[2,3]-peptides with a heterochiral backbone; these peptides not only assume specific conformations depending on the solvent but also respond to a change in polarity by shifting from one conformation to another. The helical and extended structural preferences of tetrapeptide **1** in $CDCl_3$ and [D_6]DMSO, respectively, was retained in its crystals grown from solvents of comparable polarities. Using a similar design strategy, we accessed two hexapeptides capable of adopting a half helix–half strand structure. Realization of a combination of two extreme conformations in a segment as short as a hexapeptide is remarkable and can be used as a model system to understand the fine balance between enthalpic and entropic factors during conformation selection.

Acknowledgments

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[10] CCDC-906802 (for **1**, grown from $CHCl_3$) and -945946 (for **1**, grown from *i*PrOH) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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