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Carbohydrate Amino Acids: The Intrinsic Conformational Preference for a β-Turn-Type Structure in a Carbopeptoid Building Block

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Abstract: Infrared ion-dip spectroscopy coupled with DFT and ab initio calculations are used to establish the intrinsic conformational preference of the basic structural unit of a peptide mimic, a *cis*-tetrahydrofuran-based "carbopeptoid" (amide−sugar−amide), isolated at low temperature in the gas phase. The carbopeptoid units form a β-turn-type structure, stabilized by an intramolecular NH → O═C hydrogen bond across the sugar ring, thus forming a 10-membered, C_{10} turn. Despite the clear preference for C_{10} β-turn structures in the basic unit, however, the presence of multiple hydrogen-bond donating and accepting groups also generates a rich conformational landscape, and alternative structures may be populated in related molecules. Calculations on an extended, carbopeptoid dimer unit, which includes an alternating amide−sugar−amide−sugar−amide chain, identify conformers exhibiting alternative hydrogen-bonding arrangements that are somewhat more stable than the lowest-energy double β-turn forming conformer.

1. Introduction

A key factor in the development of peptide mimics that might be used to provide successful peptidic drugs is the control of their conformation. One approach to this exploits the synthesis of so-called "carbopeptoid" mimics,[1] polymers constructed from carbohydrate amino acids to adopt a specific target conformation presenting secondary folding characteristics that resemble those in a protein.[2]

Solution studies of oligomers based upon sterically controlled tetrahydrofuran (THF) sugar−amide scaffolds (Scheme 1) provide support for the existence of β-turn-type structures, stabilized by intramolecular NH → O═C hydrogen bonding (Scheme 2) across the THF ring.[3−6]

Solution NMR and IR studies of the *cis*-THF-based monomer units **1** and **2** provide strong evidence for the existence of such a 10-membered turn in the acetyl protected monomer **2** and provide some indication that the unprotected monomer **1** may also exist as a β-turn. Evidence for repeating β-turn structure in the fully acetylated tetramer **4** has been provided by an NOE-NMR investigation in $CDCl_3$ and dimethyl sulfoxide (DMSO) solutions, coupled with the results of a molecular mechanics calculation based upon the CHARMM force field.[4] Molecular dynamics simulations with the GROMOS96 force field suggest, however, that a repeating β-turn motif in the acetylated tetramer **4** is transient, appearing ∼15% of the time in $CHCl_3$ solution and less frequently in DMSO.[7] The near IR spectrum of another carbopeptoid tetramer based on an acetonide bridged *trans*-THF building block **5**, in a chloroform solution, gave no indication of NH → O═C bonding.[3] On the other hand, NMR and IR investigations of the (longer) octameric carbopeptoid based on acetonide bridged unit **5** indicated that it resembles a π helix, exhibiting repeating 16-membered (C_{16}) turns stabilized by NH → O═C hydrogen bonds, which span one additional THF-amide unit as compared to the 10-membered β-turn.[3] To date, however, there has been no direct experimental evidence for NH → O═C hydrogen-bonded stabilization in the isolated carbopeptoids free of any solvent interactions, which may perhaps offer a better model of the peptide mimic structure in a biological environment,[8] for example, when it is bound to a protein.

Ion dip vibrational spectroscopy coupled with density functional and ab initio theoretical calculations provides a powerful

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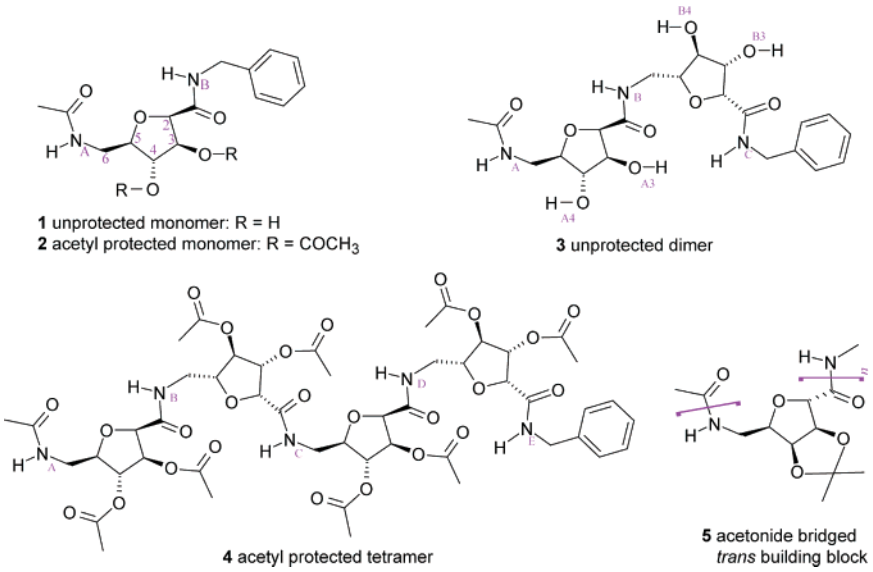
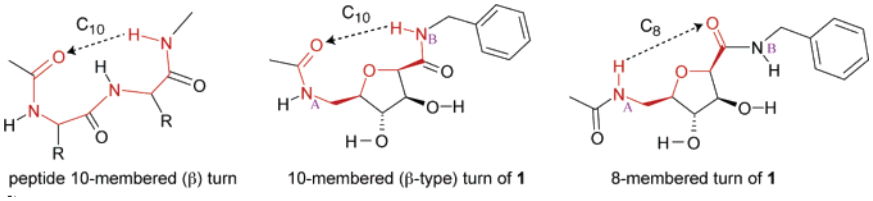
Scheme 1



Scheme 2



means of investigating the gas-phase structures of peptides[9−11] and carbohydrates (including oligo-saccharides),[8,12] and its success encourages extension of this strategy to investigate carbohydrate amino acid peptide mimics. The incidence of any localized hydrogen-bonded interactions involving N−H or O−H modes, to which fully resolved near-infrared spectra are extremely sensitive, should readily be detected. In this way, infrared spectral analysis supported by reference to ab initio and density functional theoretical computation can establish overall molecular structure and, in the present case, determine whether β-turn forming NH → O═C hydrogen bonds are present in the intrinsically favored conformation(s) of carbopeptoid structural units.

The results of applying this strategy to a structural investigation of the "free" and acetylated ("protected") carbopeptoid building blocks, **1** and **2**, are presented in this Article, together with a computational study of the conformational landscape of the more extended carbopeptoid dimer unit, **3** (Scheme 1), a penta-peptide mimic.

2. Methods

2.1. Calculations. Starting structures of molecules **1**−**3** for higher-level calculations were produced using the MacroModel molecular modeling program (v. 8.5, Schrodinger Inc.).[13] Conformational searches were performed using the Monte Carlo Multiple Minimum (MCMM) conformation searching routine[14] followed by energy minimization using the MMFFs force field[15] included with the MacroModel package. The pucker of the sugar ring was not constrained in the searches, nor were constraints placed on exocyclic bonds with the exception of the amides, which were constrained to a trans geometry in molecules **2** and **3** (but allowed to rotate in molecule **1**). For molecule **1**, an initial conformational search of 1000 MCMM steps was performed followed by MMFFs energy minimization. All conformers from this search with energies lying within 50 kJ mol^{-1} of the global minimum (a total of 26 different structures) were saved and used as starting structures for higher-level calculations. A second conformational search on molecule **1**, consisting of 10 000 MCMM steps followed by MMFFs energy minimization, was subsequently performed. From the second search, all structures within 20 kJ mol^{-1} of the global minimum were examined, and those exhibiting types of interactions not found in the previous search were selected as additional starting structures for higher level calculations, resulting in a further 10 starting conformations of **1**. The correlation between relative energies computed with the MMFFs forcefield and

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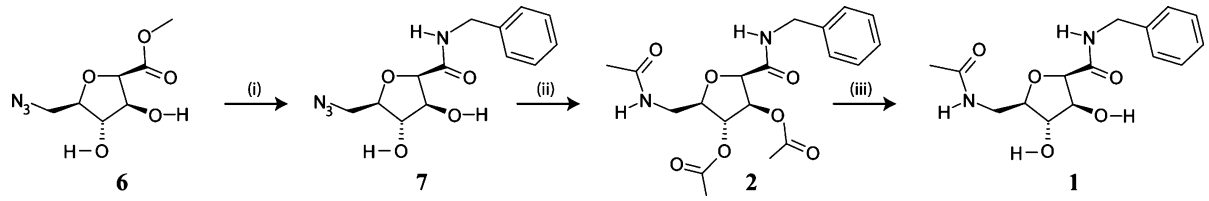
Scheme 3 [a]



[a] (i) $PhCH_2NH_2$, MeOH (57%); (ii) H_2, 10% Pd/C, dioxane:H_2O (2:1); then Ac_2O, pyridine (72%); (iii) K_2CO_3, MeOH (84%).

those from subsequent ab initio calculations (see Supporting Information Figure S3) suggests that MMFFs force field with 16 kJ mol^{-1} cutoff is adequate to identify low-energy conformations for this type of molecule; none of the higher energy structures selected (beyond the 16 kJ mol^{-1} cutoff) had energies within 10 kJ mol^{-1} of the global minimum at the MP2/6-311+G(d,p)//B3LYP/6-31+G(d) level, giving us reasonable confidence that the chosen energy cutoff levels did not result in missed low-energy conformations.

A similar 10 000 step MCMM/MMFFs search was used to identify candidate conformations for molecule **2**. All conformations with energies within 50 kJ mol^{-1} of the global minimum were saved and examined. Despite this initial filtering, there were too many different conformers for it to be feasible to perform ab initio calculations on all of them, so a subset of conformers was selected, based upon the relative energies determined from the molecular mechanics calculation, with the goal of examining a variety of structures through further, higher level calculations. The conformers selected for the carbopeptoid building block **2** included all those within 16 kJ mol^{-1} of the global minimum (32 conformers) as well as a few higher energy structures (4 conformers) which displayed different types of hydrogen-bonded interaction. None of the higher energy structures selected (beyond the 16 kJ mol^{-1} cutoff) had energies within 10 kJ mol^{-1} of the global minimum at the MP2/6-311+G(d,p)//B3LYP/6-31+G(d) level, again giving us reasonable confidence that the chosen energy cutoff levels, although low, were adequate to identify the most stable conformations.

For the double building block (or penta-peptide mimic) **3**, the X-cluster program (Schrodinger, Inc.)[16] was used to cluster all structures with relative energies lying within 19 kJ mol^{-1} of the global minimum (50 structures) into families based on RMS distances of all atoms, excluding the terminal methyl and phenyl groups. The lowest-energy member of each of these families (22 in toto at the clustering level chosen) was selected for further calculations; some additional structures from low-energy families were also selected to confirm correct identification of the lowest-energy structures in each family. The potential energy surface for dimer **3** is extremely complicated, and, while the global minimum conformation may not have been identified using this computational procedure, effort was made to identify the most stable double β-turn conformer; all double β-turn conformers among the catalogued structures (those within 50 kJ mol^{-1} cutoff) were selected for high-level calculations.

Each of the selected structures was subsequently optimized using hybrid method density functional theory at the B3LYP/6-31+G(d) level, and their single point energies were evaluated using perturbation theory at the MP2/6-311+G(d,p) level. This resulted in 31, 26, and 29 unique conformers for molecules **1**, **2**, and **3**, respectively. Harmonic vibrational frequencies were calculated at the B3LYP/6-31+G(d) level for 23 of the 31 remaining conformer of **1**. Because of the computational expense for the (much larger) protected monomer molecule **2** and the dimer, molecule **3**, the frequency calculations were restricted to 10 of each of their conformers. These included all those with energies lying within 12 kJ mol^{-1} of the minima determined from the MP2 perturbation theory calculations. All B3LYP and MP2 calculations were done using the Gaussian 03 suite of programs.[17] The relative energies of conformers presented in this report were all obtained from single point MP2/6-311+G(d,p) calculations and include a correction for zero-point vibrational energy from the harmonic B3LYP/6-31+G(d) frequency calculations. Calculated infrared frequencies are scaled by 0.9734 for comparison with experimental frequencies. This scaling factor has been found to provide good agreement for weakly bonded OH stretches in mono- and disaccharides.[12] However, the use of a constant scaling factor, and indeed the harmonic approximation, is less good for more strongly perturbed stretches. Nevertheless, a consistent scaling factor was used for simplicity, and matches between calculated and measured infrared spectra were determined on the basis of patterns of IR bands, rather than absolute position, especially for the more perturbed modes.

2.2. Synthesis. The tetrahydrofuran-based protected **2** and unprotected **1** carbopeptoids were prepared from the azido ester **6**.[6] Reaction of **6** with benzylamine gave the azido amide **7** (Scheme 3). Catalytic hydrogenation of azide **7** to the corresponding amine, followed by acetylation, afforded the protected derivative **2**, which on treatment with potassium carbonate in methanol underwent ester exchange to give the unprotected carbopeptoid **1**. Supplementary synthetic information is available in the Supporting Information.

2.3. Spectroscopy. The carbopeptoid units **1** and **2** were vaporized by heating ca. 40 mg samples of each monomer in a 200 °C oven attached to the expansion side of a pulsed nozzle (General Valve, pulsed at 10 Hz). The vaporized molecules were entrained and cooled in the expanding pulse of gas (Ar and/or Xe), backing pressure of 3.5 (Xe) to 6 (Ar) bar. The pulsed expansion was skimmed, after which its path was crossed with one or two laser beam(s) in the extraction region of a linear time-of-flight mass spectrometer (Jordan). Resonant two photon ionization (R2PI) spectra were recorded using the frequency doubled output of an Nd:YAG-pumped dye laser (Spectra Physics GCR 170 at 355 nm/LAS 205, pulsed at 10 Hz). For the IR ion-dip (IRID) experiments, this laser was tuned onto successive transitions of interest and used as the probe laser, while 150 ns prior to the probe laser pulse, an IR burn pulse was scanned. The IR radiation ($\sim$3000−4000 cm^{-1}, 0.4 cm^{-1} bandwidth, 4−5 mJ $pulse^{-1}$) was generated by difference frequency mixing the fundamental of a Nd:YAG laser (Powerlite Precision 8000) and that of a pumped dye laser (ND6000, Continuum) in a $LiNbO_3$ crystal. When both lasers are in resonance with the same ground state (i.e., the same conformation), this results in a dip in the ion signal measured by the probe laser because population has been transferred out of the monitored ground state by the burn laser. The signal monitored by the probe then corresponds to the IR spectrum of each selected conformer.

3. Results and Discussion

3.1. Calculations. Figure 1 shows a selection of the lowest-energy conformers examined for the unprotected monomer unit **1** including the two most stable structures identified, Ia and Ib. They both exhibit a 10-membered (C_{10}) β-turn H-bond, as do several other low-energy structures, differing from Ia or Ib primarily by the torsion of the phenyl ring and the pucker of the sugar ring (see the Supporting Information).

The lowest-energy structure of **1** that does not form a hydrogen-bonded β-turn, conformer Ic, lies significantly higher in energy (11 kJ mol^{-1} above the global minimum, conformer

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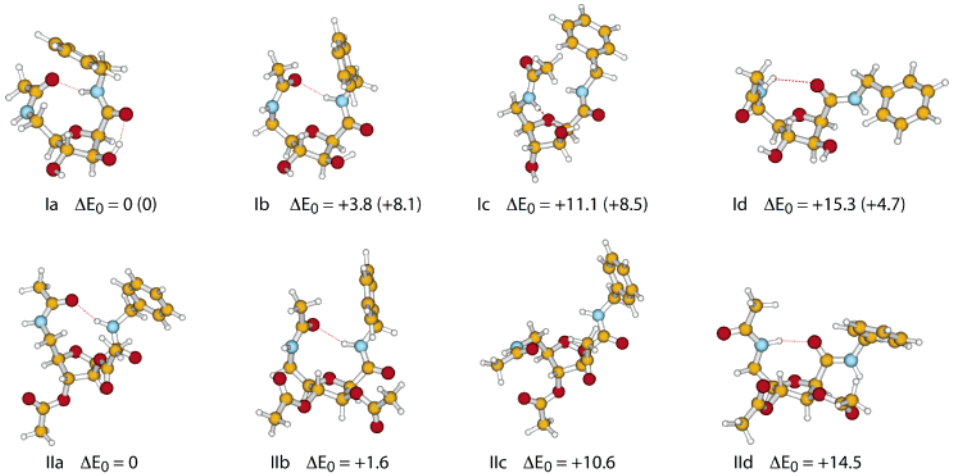

Figure 1. A selection of low-energy structures of the carbopeptoid monomer units **1** and **2** with their relative energies in kJ mol^{-1} calculated at the MP2/6-311+G(d,p)//B3LYP/6-31+G(d) level of theory. Relative energies of the methylated analogues of **1** are given in parentheses. Conformers Ia and Ib (IIa and IIb), the two most stable conformers identified for **1** (**2**), each exhibit a C_{10} β-turn. Conformers Ic and IIc are the lowest-energy structures that do not form β-turns.

Ia) and is unlikely to be populated in the molecular beam. Several other conformers lying at energies slightly above Ic exhibit different hydrogen-bonded interactions, for example, an alternative cross-ring bond that creates an eight-membered, C_8 turn (see Scheme 2); conformer Id is the most stable structure of this type. In view of their high energy, significant population of the C_8 conformers is improbable for the unprotected monomer unit **1** (although the corresponding conformers of the extended dimer **3** are quite stable, see later discussion).

The presence of the benzyl moiety (used as a chromophore in these experiments) rather than a second methyl terminus does not change the global minimum conformation, but it might influence the overall conformational landscape. Replacement of the benzyl group in **1** by a methyl group does indeed alter the relative conformational energies among conformers with differing benzyl group orientations; conformer Id, for example, becomes the second most stable conformer. However, the relative energies of conformers with similar benzyl group orientations are little changed, and the general ordering of relative energies among stable conformers, shown in parentheses in Figure 1, is largely retained.

A similar distribution of conformers is found for the acetyl protected monomeric unit **2** (Figure 1). Again, the two most stable conformers, IIa and IIb, each exhibit C_{10} β-turn structures and are of similar energy. The most stable conformation that does not have a C_{10} β-turn, conformer IIc, lies at an energy 11 kJ mol^{-1} above the global minimum, close to the energy gap for the unprotected monomer. The second most stable non-β-turn conformer is conformer IId; this conformation is stabilized by a C_8 turn, similar to conformer Id. Once again, non-β-turn conformers are unlikely to be populated in the molecular beam.

The monomer units are capable of forming different types of β-turn analogue structure, as measured by the overall bend in the chain of the backbone. Conformer Ia, for example, is a βIII-type turn, while the structure of conformer IIb lies closest to a βII′-turn, see Figure 2. This effects the "angular propagation" of the continuing backbone chain; in conformers Ia and IIa, for example, the terminal methyl group is oriented into the page, but it points out of the page in conformers Ib and IIb, see Figure 1.

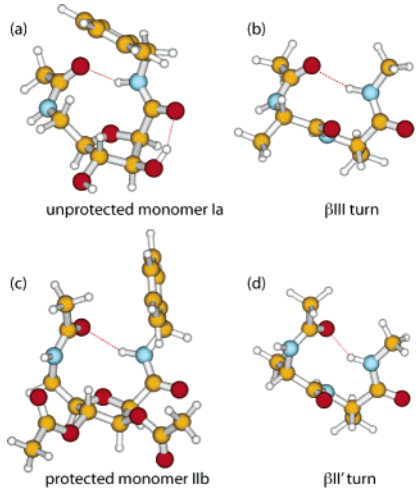

Figure 2. Comparisons between β-turn structures of (a) and (c), the carbopeptoid monomer units, **1** and **2**, and (b) and (d), the computed β III and β II′ structures of the alanine tripeptide.

The most stable structure calculated for the extended, unprotected dimeric structure **3**, conformer IIIa, is shown in Figure 3. It does not display a repeated, double β-turn interaction. Instead, an $NH_B \rightarrow N_A$ hydrogen bond (linking the central and terminal units) is followed by a "head-to-tail" $NH_A \rightarrow O{=}C$ hydrogen bond, creating a C_{14} turn, see Figure 3. In contrast to the monomer units, **1** and **2**, the lowest-energy conformer exhibiting a repeating C_{10} β-turn structure, IIIc, is calculated to lie 10 kJ mol^{-1} above the most stable conformation found. Conformer IIIc features two successive βIII-type turns, which overlay well with conformer Ia of the monomer.

Despite the preference for non-β-turn-type structure in the dimer **3**, in even longer carbopeptoid chains, it is likely that regular extensible hydrogen-bonding patterns such as repeated β-turns will be favored by co-operative dipole alignment. NMR investigations of the acetylated tetramer **4** and of other extended carbopeptoid chains indicated the existence of such repeating turn structures.[4,5]

3.2. Spectroscopy. R2PI spectra of **1** and **2** and the associated IRID spectra, recorded in the N−H and O−H stretch region, are shown in Figures 4 and 5. Both the R2PI and the IRID

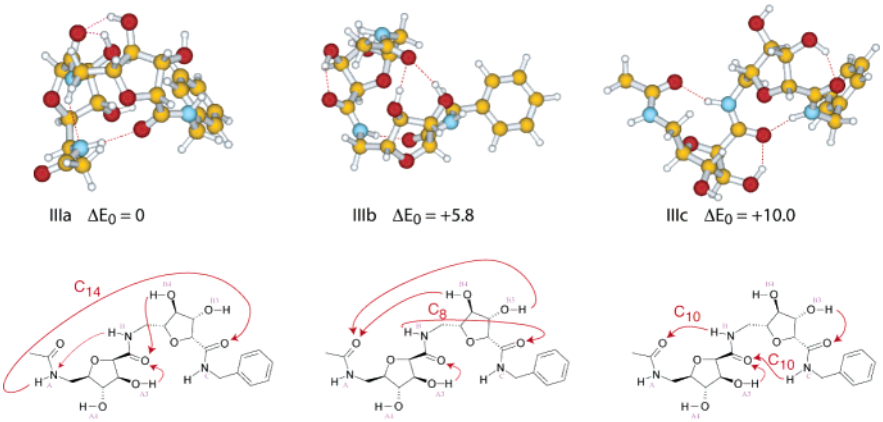

Figure 3. Three low-energy conformations of the carbopeptoid dimer **3** with relative energies (kJ mol^{-1}) calculated at the MP2/6-311+G(d,p)//B3LYP/6-31+G(d) level of theory. The top row shows 3-D molecular representations, while the cartoons below highlight the stabilizing hydrogen-bonding interactions, indicated by the red arrows. The lowest-energy conformer found that displays a repeating C_{10} β-turn motif is conformer IIIc.

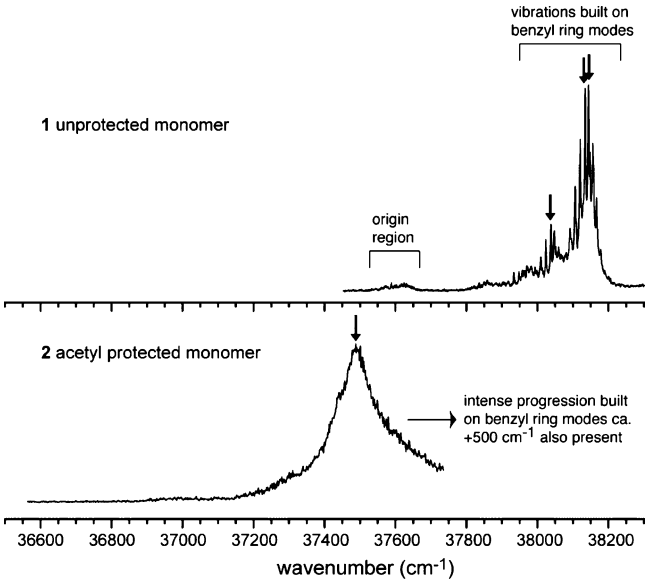

Figure 4. R2PI spectra of the carbopeptoid monomer units, **1** and **2**. Vertical arrows indicate wavenumbers at which IRID spectra were measured.

spectra of the unprotected monomer unit **1** are well resolved, and the IRID spectrum clearly shows the expected four bands (corresponding to two O−H stretches and two N−H stretches).[18] Virtually identical IRID spectra were recorded at several UV probe wavelengths (indicated by the vertical arrows in Figure 4), suggesting that UV bands correspond to the same conformation, that is, suggesting the population of one predominant conformer in the molecular beam expansion. The R2PI spectrum of the acetylated carbopeptoid monomer unit **2** was not well resolved, and its IRID spectrum was measured with the UV probe set to the R2PI maximum. The IRID spectrum, displaying the two bands expected from N−H stretches, indicates the population of a single predominant conformer at the probe wavelength, although there may be a hint of a minor contribution from a second conformer (see later discussion). The overall shape of the R2PI spectrum of molecule **2** closely resembles that of the better resolved R2PI of molecule **1**, which suggests that it too has only a single conformer.

(18) An overtone of the amide I band with low intensity is also distinguishable at ~3420 cm^{-1}.

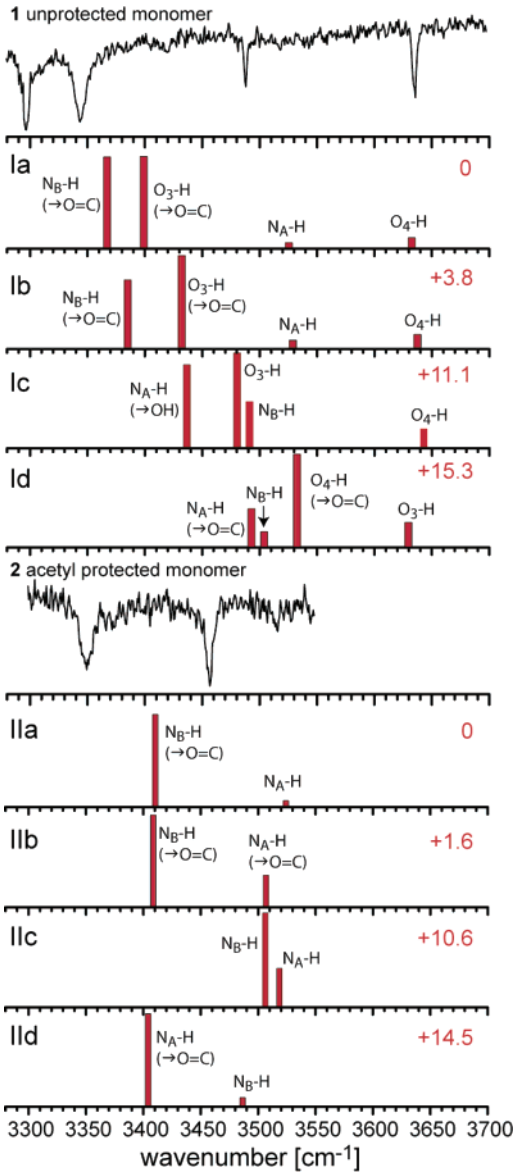

Figure 5. Experimental and computed IRID spectra of the carbopeptoid monomer units, **1** and **2**, with calculated relative energies of low-lying conformers in kJ mol^{-1}.

The two low-energy, C_{10} β-turn conformers of the carbopeptoid unit **1**, Ia and Ib (and others illustrated in the Supporting

Information), each have similar stretching motions: one weakly H-bonded (weakly perturbed) O−H stretch (O_4−H), one relatively free N−H stretch (N_A−H), an O−H stretch that is strongly perturbed (through an $O_3H \rightarrow O{=}C$ hydrogen bond), and an N−H stretch that is strongly perturbed by an $N_BH \rightarrow O{=}C$ hydrogen bond, linking the terminal amide groups across the sugar ring. The latter interaction completes the 10-membered β-turn. These common interactions generate a characteristic vibrational signature, as can be seen in the close similarity of the near IR spectra calculated for each of the two β-turn forming conformers, see Figure 5, frames Ia and Ib; their vibrational patterns are both in good agreement with the experimental IRID signature. In contrast, the O−H and N−H stretches in the low energy non-β-turn forming structures, conformers Ic and Id (as well as others illustrated in the Supporting Information), are involved in different types of interactions and exhibit quite different spectral patterns that do not look at all like that of the measured spectrum. The good match between band patterns of measured and calculated infrared spectra for conformers Ia and Ib and lack of match for higher-energy conformers gives us added confidence that important low-energy conformations were not missed in the original conformational search procedure used to identify possible conformations. Thus, the experimental IRID spectrum can be assigned to a β-turn conformational structure associated with conformer Ia, or possibly Ib, although Ia is the more favored in view of its lower relative energy.

In the protected monomer unit **2**, the O−H groups of molecule **1** are replaced by acetyl protecting groups whose stretching motions lie at much lower wavenumbers; only the two N−H stretch modes remain in the IR region scanned, see Figure 5. The band at 3455 cm^{-1} indicates a slightly perturbed N−H vibration, but the band displaced to lower wave number at 3350 cm^{-1} indicates a much stronger interaction. The pattern of the measured IR ion dip spectrum matches well that calculated for all conformers containing one NH group, which acts as a hydrogen-bond donor, including conformers IIa, IIb, and IId. Conformer IIc does not have an NH acting as a hydrogen-bond donor; consequently, its calculated spectrum does not resemble the measured spectrum, and significant population of this conformer can be ruled out. Distinguishing among other possible conformers is more difficult. The spectral data alone do not permit an unequivocal conformational assignment due to the similarity of the calculated spectral patterns. When the large energy difference between the β-turn and the non-β-turn structures is taken into account, however, assignment to one (or more) of the β-turn conformer(s) is, again, strongly favored. The low-lying conformer IIb provides the closest match with experiment (see Figure 5), because the higher wavenumber N−H band appears at 3455 cm^{-1}, ~35 cm^{-1} below that of the corresponding N−H band measured for monomer **1**. The shift to lower wavenumber as well as the increased intensity of the band both suggest an N−H group that is involved in a more perturbing interaction than the corresponding "free" N−H group in the unprotected monomer **1**. The integrated intensities of the experimental bands of molecule **2** provide a reasonable match with the calculated relative intensities of conformer IIb, although band patterns and relative positions (here, analyzed in comparison to molecule **1**) are a more reliable indicator of conformation than band intensities because experimental factors such as saturation of the infrared transition can alter measured IRID intensities. In conformer IIb of the protected monomer **2**, the N_AH group is weakly bonded to the carbonyl oxygen of the neighboring acetyl protecting group, while the other group, N_BH, is involved in the (more strongly perturbing) $N_BH \rightarrow O{=}C$ β-turn forming a hydrogen bond. It is possible that conformer IIa is also present in the molecular beam contributing to the broad R2PI spectrum displayed in Figure 4;[19] note the possible blending of the more strongly shifted (and broadened) N_B−H band at 3350 cm^{-1}. The weak IRID feature at 3515 cm^{-1} might be associated with an N−H mode, but it lies at too high wavenumber to correspond to a "free" NH. Much more probable is its association with an overtone of the amide I band, also visible in the IR spectrum of the unprotected monomer **1** at 3420 cm^{-1}.

In natural peptide structures, β-turn-type I occurs the most frequently, but types II and III are also common.[20] The favored conformations of the monomeric carbopeptoid building blocks, Ia (**1**) and IIb (**2**), correspond best to β-turns of type III and type II′, respectively (see Figure 2 where the structures were compared to those calculated for the alanine tripeptide), although for both monomer units, carbopeptoid building block conformations corresponding to β-turn types I′, II′, and III were also calculated to lie at relatively low energies. Mons and co-workers,[9,10] who have examined the conformations of several capped di- and tripeptides, isolated in the gas phase, have found evidence for multiple varieties of β-turn structure, populated in the gas phase, including types I, II, and II′ and VIa.

In β-turn conformers of small peptides, bands corresponding to the N−H stretches participating in the C_{10} turns have been observed between 3460 and 3370 cm^{-1},[10] significantly higher in wavenumber than the corresponding bands observed here for carbopeptoids **1** and **2**, which appear at ~3300 and 3350 cm^{-1}. This suggests a stronger perturbation of the C_{10} N−H stretches in the carbopeptoids as compared to the peptides. Calculations indicate that this is not due just to shorter or more linear H-bonds in the carbopeptoids; the H···O bond lengths calculated for the β-turn carbopeptoid conformers range between 1.99 Å (Ia) and 2.14 Å (IIb), similar to those calculated for peptides by Mons and co-workers. The N−H···O bond angles, ranging between 150° and 160°, are also similar to or of lower linearity than those calculated for peptides. An alternative explanation for the relatively large shifts to lower wavenumber in the carbopeptoids is the proximity of the oxygen in the furanose ring, which is 2.0−2.2 Å away from the N−H hydrogen, close enough to confer some additional hydrogen-bonding character. Whatever the cause, the strong perturbation of this mode in the carbopeptoids relative to that in peptides is correctly predicted by the calculations, although the scaling factor (which corrects for anharmonicity and deficiencies in the computational method) that is required to reconcile the absolute magnitude of the calculated and experimental shift between the relatively "free" N−H and O−H modes and the strongly perturbed modes increases with the degree of displacement in all of these systems. In other words, the computational methods used, by our group as well as others, systematically underestimate the band shift

(19) The broad R2PI spectrum of the protected monomer likely results from difficulties associated with efficiently cooling the molecule, which are significantly larger than the unprotected monomer.

(20) Creighton, T. E. *Proteins: Structures and Molecular Properties*; W. H. Freeman and Co.: New York, 1984.

to lower wavenumbers associated with more strongly bonded interactions.[21]

4. Conclusions

The *cis*-tetrahydrofuran-based carbopeptoid units, **1** and **2**, provide relatively robust peptidomimetic building blocks, exhibiting β-turn structures when isolated at low temperature in the gas phase. Calculations also indicate a rich conformational landscape, however, presenting structures that are quite flexible and likely to be influenced by interactions with a surrounding environment as well as by intramolecular interactions with neighboring groups. Replacement of the terminal phenyl ring in the unprotected monomer unit **1**, for example, by a methyl group, significantly reduces the gap between the (global minimum energy) β-turn forming conformer and the lowest-energy non-β-turn conformer, although the β-turn conformer remains the most stable structure.

Calculations on the carbopeptoid dimer **3** further exemplify the flexibility of these structures and reveal a fortiori the delicate balance among intramolecular interactions, which can determine conformational choice; unlike the smaller monomer units, the favored conformation of the dimer does not exhibit β-turns. In many ways, this reflects the natural situation: the functional folds of proteins are often only marginally stable, and short amino acid sequences adopt a variety of conformations in peptides and proteins, although within this there are known conformational preferences and structural motifs.

(21) The tripeptide calculations of Mons and coworkers, which show cosmetically better agreement, were scaled by a factor of 0.96 (ref 10). All of the carbopeptoid calculations employed a "weaker" scaling factor of 0.9734, a value which has provided good agreement with experiment in very weakly hydrogen-bonded systems (ref 12), but which results in poorer agreement among bands at lower wavenumber.

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Supporting Information Available: Carbopeptoid conformational and vibrational calculations. Comparison of MMFFs energy and MP2 energies for molecule **1**. Details of synthesis. Complete ref 17. This material is available free of charge via the Internet at http://pubs.acs.org.

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