of the aglycon and which is amenable to enantioselective synthesis (Scheme I). This approach has culminated in a highly enantio- and stereoselective total synthesis of (-)-calicheamicinone (**1**).

The execution of the synthesis proceeded as summarized in Schemes II and III.[5] Thus lactol **6**, readily prepared from tetronic acid via ketalization and DIBAL reduction, was treated with the allylborane **7** according to the general procedure reported by Brown[6] to give **8** in a highly stereo- and enantioselective manner (95% ee, >98% de).[7] Compound **8** was converted to aldoxime **9** by standard chemistry. Generation of the nitrile oxide with aqueous sodium hypochlorite was accompanied by spontaneous cyclization,[8] resulting in a 4:1 mixture of isoxazoline diastereoisomers, from which the major isomer **10** was isolated by flash chromatography. Addition of lithium (trimethylsilyl)acetylide to **12** at -78 °C proceeded with complete stereoselectivity, delivering the incoming nucleophile from the opposite side to the OMEM group to give, after quenching with acetic anhydride, acetate **13**.[9] Removal of the MEM group[10] followed by Swern oxidation[11] and concomitant aromatization gave the keto isoxazole **15**. Stereocontrolled olefination of **15** proceeded smoothly upon heating with methyl (triphenylphosphoranylidene)acetate, resulting in exclusive formation of the desired geometrical isomer **16**. Coupling of **18** with (*Z*)-(4-chloro-3-buten-1-ynyl)trimethylsilane by palladium (0)-copper(I) catalysis completed the construction of the enediyne moiety,[12] leading to compound **19**. Unmasking of the amino aldehyde functionality was realized by reductive opening of the isoxazole ring with molybdenum hexacarbonyl,[13] furnishing **20**.

The propensity of the aldehyde group of **21** to enolize via the vinylogous amine led us to protect the latter functionality as the phthalimide[14] before proceeding further. Scheme III summarizes the final stages of the synthesis. Ring closure of **23** took place upon exposure to base,[3g,4] leading to a mixture of **24** (wrong stereochemistry at the newly generated center) and lactone **26** (44% total yield, ca. 9:1 in favor of **24**). Taking advantage of proximity effects, we corrected the stereochemistry of the newly generated hydroxy-bearing center by conversion to a mesylate followed by exposure to silica gel leading directly to lactone **26**. The completion of the synthesis was based on chemistry previously developed by Danishefsky[4] and Magnus[3k] on similar compounds.[15] (-)-Calicheamicinone (**1**) ($[\alpha]^{25}_D$ = -472°, *c* 0.21, CH_2Cl_2) exhibited spectral data identical to those reported by Danishefsky et al.[4,16,17]

The described chemistry provides a facile entry into the calicheamicin- and esperamicin-type aglycon skeletons in their optically active forms and opens the way for an eventual total synthesis of these naturally occurring substances. In addition, the efficacy and flexibility of the strategy allow for the construction of rationally designed mimics of these compounds that may prove useful in biotechnology as DNA-cleaving molecules and in chemotherapy as anticancer agents.

Acknowledgment. We thank Drs. Raj Chadha, Dee H. Huang, and Gary Siuzdak, of The Scripps Research Institute, for their X-ray crystallographic, NMR, and mass spectroscopic assistance, respectively. This work was supported financially by a NATO (SERC, U.K.) fellowship (to A.L.S.), by the National Institutes of Health, and by The Scripps Research Institute.

Supplementary Material Available: A listing of selected physical data (R_f, $[\alpha]_D$, IR, ^1H and ^{13}C NMR, and HRMS) for compounds **8**, **10**, **13**, **15**, **19**, **21**, **23**, **24**, **26**, and **1** and X-ray crystallographic data for compound **13** (20 pages). Ordering information is given on any current masthead page.

(5) All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

(6) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535.

(7) The enantiomeric excess was determined by analysis of the ^1H NMR spectrum of the (+)-MTPA ester of compound **11** and comparison with the enantiomeric series, which has also been prepared.

(8) For an excellent review of nitrile oxide cycloaddition reactions, see: Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, Chapter 3, pp 291-392.

(9) Confirmation of the stereochemistry at the acetylenic center came from X-ray analysis of compound **13**.

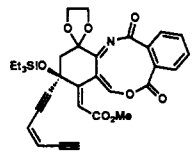
(10) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(12) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811.

(13) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877.

(14) Reaction of **21** with phthaloyl chloride appears to occur first preferentially at the oxygen atom of the vinylogous amide system, resulting in **22**. The use of polar solvents seems to increase the proportion of reaction at the nitrogen atom. Hydrolysis of the enol ester and activation of the intermediate phthalamic acid gave the required phthalimide **23**.



22

(15) Direct treatment of diol **29** under the Mitsunobu conditions described by Danishefsky (see ref 4) for introduction of the thioacetate gave predominantly a dihydropyran byproduct; this was avoided by first protecting the secondary hydroxyl group.

(16) We thank Professor S. Danishefsky for providing us with IR and ^1H NMR spectra of calicheamicinone (**1**).

(17) For some recently reported attempts at enantioselective synthesis of calicheamicinone, see: (a) Yamashita, D. S.; Rocco, V. P.; Danishefsky, S. J. *Tetrahedron Lett.* **1991**, *32*, 6667. (b) Rocco, V. P.; Danishefsky, S. J.; Schulte, G. K. *Tetrahedron Lett.* **1991**, *32*, 6671.

Self-Assembling Metal Rotaxane Complexes of α-Cyclodextrin

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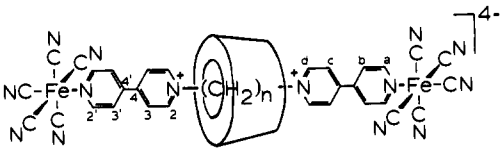
Received December 2, 1991

Rotaxanes are chemical species in which a cyclic molecular bead is threaded by a linear chain bearing bulky end units, which prevent the complex from dissociating into its cyclic and linear molecular components.[1] We report herein the rapid self-assembly of a series of stable α-cyclodextrin (α-CD) rotaxanes by the reaction of the labile $[Fe(CN)_5OH_2]^{3-}$ ions with prethreaded 1,1″-(α,ω-alkanediyl)bis(4,4′-bipyridinium) dicationic ligands $(bpy(CH_2)_nbpy^{2+}$, where n = 8-12). The stability of the α-CD/ligand inclusion complex allows for the quantitative preparation of the rotaxane **1** in aqueous solution, the formation of which may be conveniently monitored by ^1H NMR spectroscopy.



1

Several examples of symmetrical rotaxanes based on the cyclic oligosaccharide α-cyclodextrin, threaded by alkyl chains bearing cationic aromatic N-heterocycle[2,3] or cobalt amine[4,5] end groups, have been reported. The preparation of an asymmetrical zwit-

(1) Schill, G. *Catenanes, Rotaxanes, and Knots*; Academic Press: New York, 1971.

(2) Yonemura, H.; Saito, H.; Matsushima, S.; Nakamura, H.; Matsuo, T. *Tetrahedron Lett.* **1989**, *30*, 3143-3146.

(3) Saito, H.; Yonemura, H.; Nakamura, H.; Matsuo, T. *Chem. Lett.* **1990**, 535-538.

(4) (a) Ogino, H. *J. Am. Chem. Soc.* **1981**, *103*, 1303-1304. (b) Ogino, H.; Ohata, K. *Inorg. Chem.* **1984**, *23*, 3312-3316.

(5) Yamanari, K.; Shimura, Y. *Bull Chem. Soc. Jpn.* **1983**, *56*, 2283-2289.

0002-7863/92/1514-3136$03.00/0

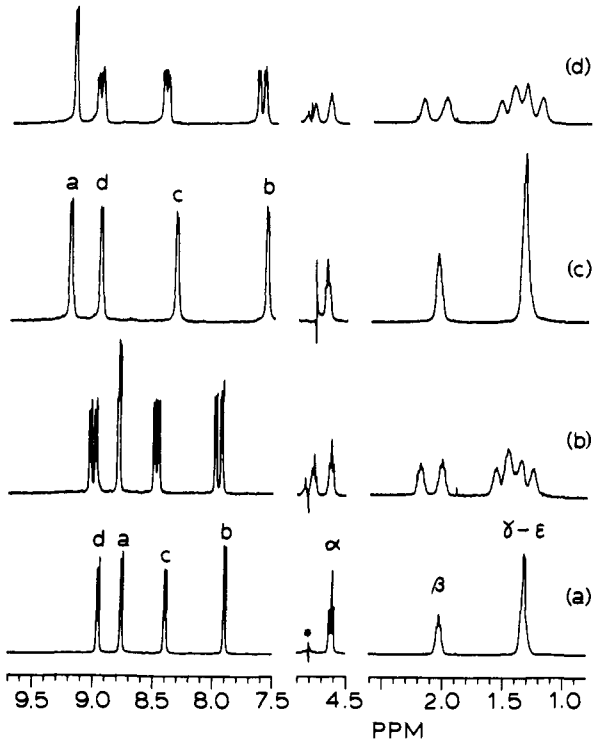


Figure 1. The 400-MHz ^{1}H NMR spectra (in D_2O vs TSP) of the bpy$(CH_2)_9$bpy protons on (a) the free bpy$(CH_2)_9$bpy^{2+}, (b) the (bpy-$(CH_2)_9$bpy·α-CD)$^{2+}$ inclusion complex, (c) the $[(NC)_5Fe$(bpy-$(CH_2)_9$bpy$)Fe(CN)_5]^{4-}$ complex, and (d) the $[(NC)_5Fe$(bpy-$(CH_2)_9$bpy·α-CD)$Fe(CN)_5]^{4-}$ rotaxane complex. The proton labels a–d refer to the aromatic protons in **1**, and the α–ε labels indicate the positions of the aliphatic protons with respect to the quaternary nitrogens.

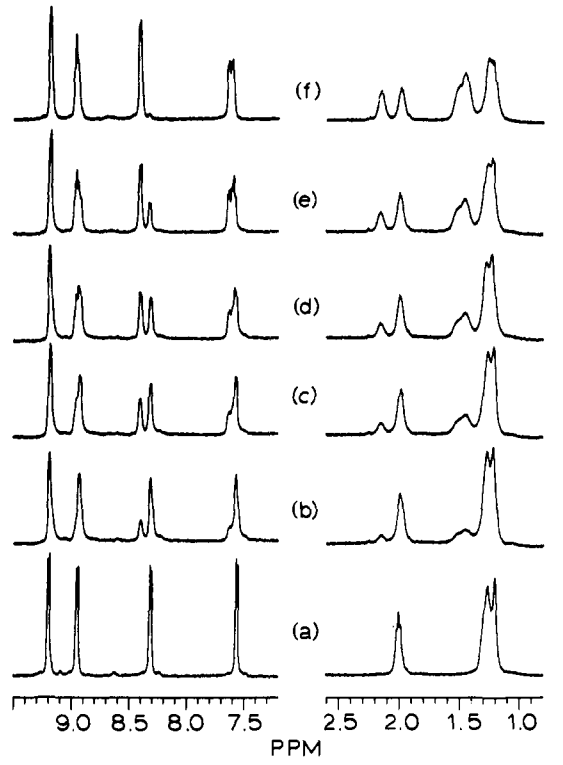


Figure 2. (a) The 400-MHz ^{1}H NMR spectrum (in D_2O vs TSP) of bridging ligand protons on the $[(NC)_5Fe(bpy(CH_2)_{10}bpy)Fe(CN)_5]^{4-}$ complex and spectra recorded (b) 2 min, (c) 4 min, (d) 6 min, (e) 14 min, and (f) 30 min after the addition of a 2-fold excess of α-cyclodextrin. The final spectrum (f) corresponds to the rotaxane complex.

terionic α-CD rotaxane, bearing dimethyl(ferrocenylmethyl)ammonium and naphthalene-2-sulfonate end units, has recently been described.[6] The preparations of these metal rotaxane complexes have generally involved the reaction of a semirotaxane (bearing one end unit) with a second metal complex or organic end unit. Stoddart and co-workers have recently advanced elegant strategies for the self-assembly of rotaxanes comprising a tetracationic cyclophane bead, polyether threads, and triisopropylsilyl end units.[7]

The $[bpy(CH_2)_nbpy]Br_2$ bridging ligands[8] form stable inclusion complexes with α-cyclodextrin by threading the 4,4′-bipyridinium group through the α-CD cavity such that the hydrophobic alkyl chain resides within the cavity and the cationic bipyridinium end groups extend from either end.[9] The symmetry-related bpy-$(CH_2)_n$bpy^{2+} proton resonances in the ^{1}H NMR spectrum of the free ligand (Figure 1a) are split into two sets of peaks upon formation of the inclusion complex (Figure 1b). This splitting of the peaks (in addition to induced chemical shifts, as seen for the majority of rapidly exchanging inclusion complexes) results from the asymmetry in the α-CD cavity, and the slow inclusion and release of the ligand on the NMR time scale.[3]

The pentacyanoferrate(II) group, which has a very strong affinity for aromatic N-heterocycles,[11] may be introduced as the bulky end units by means of a rapid ligand substitution reaction of the self-assembled α-CD/ligand complex with the $[Fe(CN)_5OH_2]^{3-}$ ion (using solid $Na_3[Fe(CN)_5NH_3]\cdot 3H_2O$, which rapidly aquates in solution[11]) in aqueous solution ($k_f \approx 3000$ M^{-1} s^{-1} at 25 °C, $I = 0.10$ M (NaCl)[10]), yielding the rotaxane complex **1**. Coordination of the iron centers to the free or α-CD included forms of the ligand results in the formation of a strong MLCT transition in the visible spectrum ($\lambda_{max} = 540$ nm, $\epsilon = 1.18 \times 10^4$ M^{-1} cm^{-1} for **1**, $n = 12$) and ^{1}H NMR chemical shifts of the pyridine protons ortho (downfield shift) and meta (upfield shift) to the coordinated nitrogen (parts c and d of Figures 1).[11] The ^{1}H NMR spectrum of the rotaxane (Figure 1d) again exhibits two sets of ligand proton peaks, indicating that the complexed ligand is also included in the α-CD cavity.[12]

The rotaxane complex $[(NC)_5Fe(bpy(CH_2)_nbpy\cdot\alpha\text{-CD})Fe(CN)_5]^{4-}$ also forms spontaneously upon addition of α-cyclodextrin to a solution containing the bridged dimer, $[(NC)_5Fe(bpy(CH_2)_nbpy)Fe(CN)_5]^{4-}$. The formation of the rotaxane by this route may be monitored by ^{1}H NMR (Figure 2). A relatively slow dissociation of a $[Fe(CN)_5]^{3-}$ moiety ($t_{1/2} \approx 5$ min at 25 °C), followed by the formation of the semirotaxane $[(bpy(CH_2)_nbpy\cdot\alpha\text{-CD})Fe(CN)_5]^-$ and then rapid recomplexation by $[Fe(CN)_5OH_2]^{3-}$, yields the rotaxane. The self-assembly of the metal rotaxane complex will occur, therefore, irrespective of the order of the addition of the α-CD, bridging ligand, and $[Fe(CN)_5]^{3-}$ components. The α-CD inclusion of the bridging ligand enhances the stability of the resulting bond with the pentacyanoferrate(II) end group ($k_d = 1.5 \times 10^{-3}$ s^{-1} at 25 °C).

Analogous bridging ligands, in which pyrazine has replaced 4,4′-bipyridine, have also been prepared and lead to similar ro-

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(7) (a) Anelli, P. L.; Spencer, N.; Stoddart, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 5131–5133. (b) Philp, D.; Stoddart, J. F. *Synlett* **1991**, 445–458. (c) Stoddart, F. *Chem. Br.* **1991**, *27*, 714–718. (d) Anelli, P. L.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer, A. E.; Philp, D.; Pietraszkiewicz, M.; Prodi, L.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Vicent, C.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 193–218.

(8) Attalla, M. I.; McAlpine, N. S.; Summers, L. A. *Z. Naturforsch.* **1984**, *39B*, 74–78.

(9) The $[(bpy(CH_2)_nbpy\cdot\alpha\text{-CD})]^{2+}$ inclusion complex stability constants (K_{CD}) increase with the length of the alkyl chain; $K_{CD} = 70$ M^{-1} for $n = 8$, 2600 M^{-1} for $n = 10$, and >4500 M^{-1} for $n = 12$ (determined by ^{1}H NMR titrations in D_2O at 25 °C).[10]

(10) Wylie, R. S.; Macartney, D. H. Manuscript in preparation.

(11) Macartney, D. H. *Rev. Inorg. Chem.* **1989**, *9*, 101–151 and references therein.

(12) The 100-MHz ^{13}C NMR spectrum of the $[(NC)_5Fe(bpy(CH_2)_9bpy\cdot\alpha\text{-CD})Fe(CN)_5]^{4-}$ complex is also indicative of rotaxane formation, with pairs of peaks for the aromatic carbons (ppm vs TSP): 158.68 and 158.55 (C2′), 154.15 and 154.03 (C4), 145.52 and 145.03 (C2), 140.90 and 140.73 (C4′), 126.68 and 126.33 (C3), 121.54 and 121.49 (C3′), and separate peaks for each of the aliphatic carbons; 62.31, 62.14, 32.52, 32.35, 32.23, 31.81, 31.73, 27.85, and 27.72.

taxane complexes.[13] Substituted pyridine and pyrazine ligands form stable coordination complexes with a number of redox-active d^6 metal centers, such as $[M(CN)_5]^{n-}$ and $[M(NH_3)_5]^{m+}$ with iron, cobalt, ruthenium, and osmium. Using these preassembled α-CD/ligand complexes, a great variety of symmetrical and asymmetrical α-cyclodextrin metal rotaxanes may be prepared. Kinetic and spectroscopic investigations of the ligand-substitution and electron-transfer reactions involving these α-CD metal rotaxanes are ongoing in our laboratory.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support in the forms of operating and equipment grants (D.H.M.) and a postgraduate scholarship (R.S.W.).

(13) The $[(NC)_5Fe(pyz(CH_2)_npyz\text{-}\alpha\text{-}CD)Fe(CN)_5]^{4-}$ rotaxanes are best prepared by reacting the $Fe(CN)_5OH_2^{3-}$ ions with the prethreaded $(pyz\text{-}(CH_2)_npyz\text{-}\alpha\text{-}CD)^{2+}$ complex, as the rate of dissociation of a $[Fe(CN)_5]^{3-}$ group from the $[(NC)_5Fe(pyz(CH_2)_npyz)Fe(CN)_5]^{4-}$ dimer is an order of magnitude slower than for the bipyridinium complex.

On the Use of AM1 Calculations for the Study of Intramolecular Hydrogen Bonding Phenomena in Simple Amides

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The manner in which networks of nonbonded interactions control spatial arrangements between or among molecules (e.g., enzyme–substrate interactions, host–guest chemistry) and the juxtaposition of segments of a single molecule with respect to one another (e.g., the folding of natural and synthetic polymers) is of considerable interest to both experimentalists and theoreticians.[1] Our experimental efforts in this area have involved the folding of small oligoamides in organic solvents.[2] Because of the structural simplicity of these model systems, they provide an opportunity to evaluate the accuracy with which computational methods reproduce the balance of noncovalent forces (including solvation forces) that controls intramolecular hydrogen bond formation.

On the basis of IR and variable-temperature NMR measurements, we have proposed that triamide **1** in dilute methylene chloride solution experiences substantial temperature-dependent changes in its folding pattern.[2a] Our data indicate that the form favored at low temperature (i.e., the most enthalpically stable folding pattern) is I, in which only H_b is involved in an intramolecular hydrogen bond. Novoa and Whangbo have recently reported AM1 calculations that predict the global energy minimum to be II; III is also predicted to be energetically favorable.[3,4] In

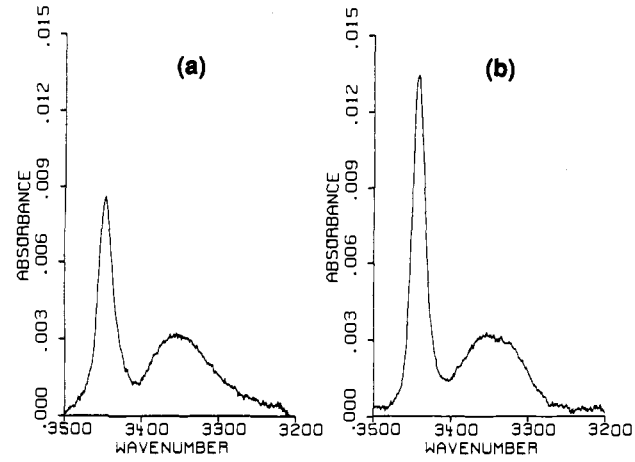
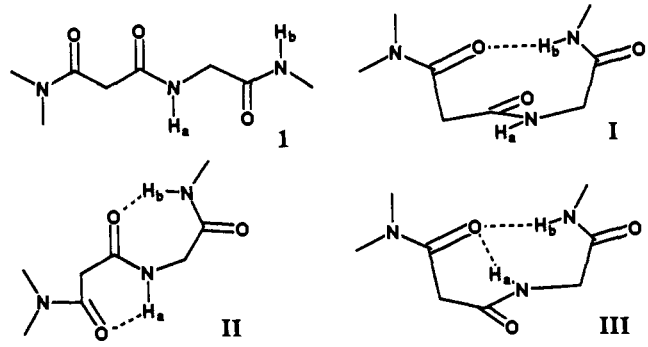
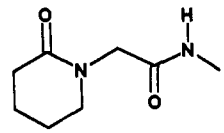


Figure 1. N–H stretch region FT-IR spectral data for 1 mM diamide **2** in CH_2Cl_2, after subtraction of the spectrum of pure CH_2Cl_2 at the same temperature: (a) 23 °C (absorption maxima at 3447 and ca. 3355 cm^{-1}); (b) −69 °C (absorption maxima at 3442 and ca. 3350 cm^{-1}). Samples prepared and data obtained on a Nicolet 740 spectrometer as described in ref 2c. Control experiments indicate that little or no aggregation of **2** occurs under these conditions.

II and III, both H_a and H_b are engaged in intramolecular hydrogen bonds, which is not consistent with our data concerning the most enthalpically stable folding pattern of **1**.[2a] We point out here that comparison of the AM1 results with experimental observations and with ab initio calculations suggests that the semiempirical methodology does not accurately predict the energetics of intramolecular N—H··O=C hydrogen bond formation in solution.





Our folding hypothesis for **1** was derived in part from the behavior of diamide **2**, which can form a seven-membered-ring hydrogen bond that is similar to the seven-membered-ring hydrogen bond available to H_b of **1**.[2a,5] Since only one intramolecular N—H··O=C pairing is available to **2**, deducing this

(1) For leading references see: (a) Rebek, J. *Acc. Chem. Res.* **1990**, *23*, 399. (b) *Cyclophanes*; Diederich, F., Ed.; The Royal Society of Chemistry: Cambridge, 1991. (c) Jorgensen, W. L. *Acc. Chem. Res.* **1989**, *22*, 184. (d) Kollman, P. A.; Merz, K. M. *Acc. Chem. Res.* **1990**, *23*, 246. (e) Dill, K. A. *Biochemistry* **1990**, *31*, 7133. (f) *Prediction of Protein Structure and the Principles of Protein Conformation*; Fasman, G. D., Ed.; Plenum Press: New York, 1989.

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(3) Novoa, J. J.; Whangbo, M.-H. *J. Am. Chem. Soc.* **1991**, *113*, 9017.

(4) Similar computational predictions for **1** and **2** have been made on the basis of AMBER/MacroModel calculations, using a continuum solvation model for CH_2Cl_2: Smith, D. A.; Vijayakumar, S. *Tetrahedron Lett.* **1991**, *32*, 3613, 3617. For a critical evaluation of these computational results, see: Gellman, S. H.; Dado, G. P. *Tetrahedron Lett.* **1991**, *32*, 7737.

(5) The seven-membered-ring hydrogen bond available to **2** is closely related to the "C_7" folding pattern available to peptides, which has been the subject of considerable experimental and theoretical investigation. For leading references, see: (a) Böhm, H.-J.; Brode, S. *J. Am. Chem. Soc.* **1991**, *113*, 7129. (b) Perczel, A.; Angyan, J.; Kajtar, M.; Viviani, W.; Rivail, J.-L.; Marcoccia, J.-F.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1991**, *113*, 6256. (c) Head-Gordon, T.; Head-Gordon, M.; Frisch, M. J.; Brooks, C. L.; Pople, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 5989. (d) Roterman, I. K.; Lambert, M. H.; Gibson, K. D.; Scheraga, H. A. *J. Biomol. Struct. Dynam.* **1989**, *7*, 421. (e) Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1. (f) Maxfield, F. R.; Leach, S. J.; Stimson, E. R.; Powers, S. P.; Scheraga, H. A. *Biopolymers* **1979**, *18*, 2507.

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