Hydrazino Peptides as Foldamers: An Extension of the β-Peptide Concept

Robert Günther and Hans-Jörg Hofmann*

Contribution from the Institute of Biochemistry, Faculty of Biosciences, Pharmacy, and Psychology, University of Leipzig, Talstrasse 33, D-04103 Leipzig, Germany

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Abstract: Replacing the C^{β} atoms in the β-amino acid constituents of β-peptides by nitrogen atoms leads to hydrazino peptides. A systematic conformation analysis of blocked hydrazino peptide oligomers of the general type **I** at the HF/6-31G*, MP2/6-31G*, and DFT/B3LYP/6-31G* levels of ab initio MO theory and on the basis of molecular mechanics reveals a wide variety of secondary structures, as for instance various helices and sheet- and turnlike conformers. Some of them are closely related to secondary structure types found in β-peptides; others represent novel types. Thus, a very stable, novel helix with 14-membered hydrogen-bonded pseudocycles, which occupies a conformation space different from that of helices with 14-membered rings found among the most stable conformers in β-peptides, is indicated. The most important secondary structure elements are characterized by interactions between peptidic NH and CO groups. The additional hydrazino $N^{\alpha}H$ group takes part in special structuring effects but is of lesser importance for secondary structure formation. The influence of environmental effects on the existence and stability of the various structure types is discussed. Due to the wide variety of structural possibilities, hydrazino peptides might be a useful tool for peptide and protein design.

Introduction

There are considerable efforts to improve the pharmacological properties of natural peptides by structure modification of the amino acid constituents.[1] A very important point for the utility of such modified peptides as peptidomimetics is the realization of well-defined three-dimensional structures mimicking the essential features of their natural counterparts. Among the numerous possibilities of peptide structure alteration, the replacement of α-amino acids by β-amino acids is a well-known principle documented by numerous studies in the last three decades.[2] A very interesting idea is the synthesis of peptide sequences completely from β-amino acids (β-peptides).[3−6] Extensive studies from Seebach's[3] and Gellman's[4] groups demonstrate the formation of stable secondary structures, as for instance various helix, sheet, and turn types. In particular, helix formation, which was first observed in β-peptides in the 1980s,[5] might be surprising since a higher conformational flexibility could be expected in β-amino acid oligomers due to the additional methylene group in each monomer constituent. In the meantime, the conformation space of β-peptides has been

* Corresponding author. Fax: ++49-341-97-36749. E-mail: hofmann@rz.uni-leipzig.de.

(1) (a) Hruby, V. *J. Life Sci.* **1982**, *31*, 189. (b) Toniolo, C. *Int. J. Pept. Protein Res.* **1990**, *35*, 287. (c) Spatola, A. F. In *The Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; Vol. 7, p 267. (d) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (e) Kirshenbaum, K.; Zuckermann, R. N.; Dill, K. A. *Curr. Opin. Struct. Biol.* **1999**, *9*, 530. (f) Stigers, K. D.; Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714.

(2) (a) Bestian, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 278. (b) Schmidt, E. *Angew. Makromol. Chem.* **1970**, *14*, 185. (c) Glickson, J. D.; Applequist, J. *J. Am. Chem. Soc.* **1971**, *93*, 3276. (d) Chen, F.; Lepore, G.; Goodman, M. *Macromolecules* **1974**, *7*, 779. (e) Yuki, H.; Okamoto, Y.; Taketani, Y.; Tsubota, T.; Marubayashi, Y. *J. Polym. Sci., Polym. Chem. Ed.* **1978**, *16*, 2237. (f) Narita, M.; Doi, M.; Kudo, K.; Terauchi, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3553. (g) Kovacs, J.; Ballina, R.; Rodin, R. L.; Balasubramanian, D.; Applequist, J. *J. Am. Chem. Soc.* **1965**, *87*, 119. (h) Pavone, V.; Lombardi, A.; Yang, X.; Pedone, C.; Di Blasio, B. *Biopolymers* **1990**, *30*, 189. (i) Di Blasio, B.; Lombardi, A.; D'Auria, G.; Saviano, M.; Isernia, C.; Maglio, O.; Paolillo, L.; Pedone, C.; Pavone, V. *Biopolymers* **1993**, *33*, 621. (j) Pavone, V.; Lombardi, A.; Saviano, M.; Di Blasio, B.; Nastri, F.; Fattorusso, R.; Maglio, O.; Isernia, C. *Biopolymers* **1994**, *34*, 1505. (k) Pavone, V.; Lombardi, A.; Saviano, M.; Nastri, F.; Fattorusso, R.; Maglio, O.; Isernia, C.; Paolillo, L.; Pedone, C. *Biopolymers* **1994**, *34*, 1517.

(3) (a) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913. (b) Seebach, D.; Ciceri, P. E.; Overhand, M.; Jaun, B.; Rigo, D.; Oberer, L.; Hommel, U.; Amstutz, R.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 2043. (c) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015. (d) Hintermann, T.; Seebach, D. *Chimia* **1997**, *51*, 244. (e) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1998**, *81*, 932. (f) Seebach, D.; Abele, S.; Sifferlen, T.; Hänggi, M.; Gruner, S.; Seiler, P. *Helv. Chim. Acta* **1998**, *81*, 2218. (g) Abele, S.; Seiler, P.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1559. (h) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed. Engl.* **1999**, *111*, 1595. (i) Sifferlen, T.; Rueping, M.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 2067. (j) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1. (k) Gademann, K.; Ernst, M.; Seebach, D.; Hoyer, D. *Helv. Chim. Acta* **2000**, *83*, 16.

(4) (a) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071. (b) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. *Nature (London)* **1997**, *387*, 381. (c) Krauthäuser, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1997**, *119*, 11719. (d) Chung, Y. J.; Christianson, L. A.; Stanger, H. E.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 10555. (e) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (f) Appella, D. H.; Barchi, J. J.; Durell, S.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 2309. (g) Applequist, J.; Bode, K. A.; Appella, D. H.; Christianson, L. A.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 4891. (h) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Richards, M. R.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 1, 7574. (i) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 6206. (j) Barchi, J. J.; Huang, X.; Appella, D. H.; Christianson, L. A.; Durell, S. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 2711. (k) Chung, Y. J.; Huck, B. R.; Christianson, L. A.; Stanger, H. E.; Krauthäuser, S.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 3995.

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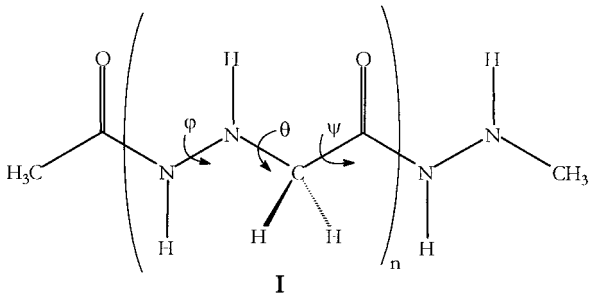
systematically examined by employing quantum chemical and empirical force field methods illustrating the wide variety of secondary structure possibilities and their peculiarities in relation to α-peptide structures.[5c,7] Extensive molecular dynamics studies describe folding phenomena in these oligomers.[8] Even in γ-peptides, characteristic folding patterns were found.[9]

In the search for further useful structural variations, the replacement of the C^{α} and C^{β} atoms of the β-amino acid constituents by heteroatoms could be an attractive extension of the β-peptide concept. In fact, oligomers of aminoxy acids, which have an oxygen atom instead of the β-carbon atom, exhibit also characteristic elements of secondary structure. The most stable one differs from the preferred ones in β-peptides.[10] Another idea might be the introduction of nitrogen atoms for the C^{β} atoms leading to hydrazino peptides composed of α-hydrazino acids ($H_2N^{\beta}-N^{\alpha}H-CH(R)-COOH$). These hydrazino peptides, which could be considered as β-azapeptides derived from β-peptides, offer a wide variety of possibilities for structure modifications at C^{α} and the two nitrogen atoms of their constituents in analogy to the well-known azapeptide[11] and peptoid[12] concepts in α-peptides. Moreover, the additional $N^{\alpha}H$ group might be responsible for novel types of secondary structure.

There are some natural peptides with single α-hydrazino acid constituents, e.g. linatine and negamycin. First attempts of peptide modification by α-hydrazino acids providing bioactive peptides have been done in the early 1970s.[13] However, the difficulties to obtain pure α-hydrazino enantiomers have probably prevented more extensive studies in this field. In recent years, these difficulties have been overcome. Now, peptides with single α-hydrazino amino acids are accessible[14] and even a solid-phase synthesis for hydrazino peptides by N-electrophilic amination has been elaborated.[15] Thus, a systematic examination of the possibilities of secondary structure formation in hydrazino peptides and its peculiarities could be useful. For this purpose, we employ quantum chemical and molecular mechanics methods which have provided an overview on the conformational aspects in the parent β-peptides.[7]

Computational Methods

The dihydrazide derivative $h(N^{\beta}\text{-Ac})Gly-N^{\beta'}H-N^{\alpha'}H-Me$ (**I**) with $n = 1$ derived from α-hydrazinoacetic acid $hGly{=}H_2N^{\beta}-N^{\alpha}H-CH_2-COOH$, the hydrazino analogue of glycine, and oligomers with $n = 2-5$ in **I**, where the $-CO-N^{\beta}H-N^{\alpha}H-$ structure element replaces the peptide bond (N^{β}-coupling), were considered in theoretical conformational analyses as model compounds for hydrazino peptides. In a first step, the blocked monomer **I** with $n = 1$ was examined to describe the intrinsic conformation possibilities of the single constituents of hydrazino peptides and to look for those conformers which might be suited for the formation of characteristic secondary structures. Even for $n = 1$, a systematic investigation of the complete conformational space characterized by the rotation angles φ, θ, and ψ within a grid of small angle intervals is rather tedious at a higher level of ab initio MO theory. Here, we followed a strategy similar to that already employed in our previous study on β-peptides.[7b] Starting conformations with values of 180, 120, 60, and 0°, respectively, for the central torsion



I

(n=1-5)

angle θ were selected. Compounds such as hydrazine, 1,2-diformylhydrazine, and N,N′-diacetylhydrazide, respectively, could be considered as models for the hydrazide part in the hydrazino peptides. According to several higher level ab initio MO conformation studies,[16] these molecules prefer values of about −90° and, alternatively, 90° for the backbone rotation angle around the NN bond. Therefore, these values were assigned to the torsion angle φ in the blocked hydrazino

(5) (a) Fernández-Santín, J. M.; Aymamí, J.; Rodríguez-Galán, A.; Muñoz-Guerra, S.; Subirana, J. A. *Nature (London)* **1984**, *311*, 53. (b) Fernández-Santín, J. M.; Muñoz-Guerra, S.; Rodríguez-Galán, A.; Aymamí, J.; Lloveras, J.; Subirana, J. A. *Macromolecules* **1987**, *20*, 62. (c) Navas, J. J.; Alemán, C.; Muñoz-Guerra, S. *J. Org. Chem.* **1996**, *61*, 6849. (d) López-Carrasquero, F.; García-Alvarez, M.; Navas, J. J.; Alemán, C.; Muñoz-Guerra, S. *Macromolecules* **1996**, *29*, 8449. (e) Alemán, C.; Navas, J. J., Muñoz-Guerra, S. *Biopolymers* **1997**, *41*, 721. (f) García-Alvares, M.; Martinez de Barduya, A.; León, S.; Alemán, C. *J. Phys. Chem.* **1997**, *101*, 1A, 4245. (g) García-Alvarez, M.; León, S.; Alemán, C.; Campos, J. L.; Muñoz-Guerra, S. *Macromolecules* **1998**, *31*, 124. (h) De Ilarduya, A. M.; Alemán, C.; García-Alvarez, M.; López-Carrasquero, F.; Muñoz-Guerra, S. *Macromolecules* **1999**, *32*, 3257.

(6) (a) Diederichsen, U.; Schmitt, H. W. *Eur. J. Org. Chem.* 1998, 827. (b) Gung, B. W.; Zhu, Z. *J. Org. Chem.* **1997**, *62*, 6100. (c) Gung, B. W.; Zhu, Z., Stalcup, A. M.; Cottrell, C. E. *J. Org. Chem.* **1999**, *64*, 2176. (d) Bode, K. A.; Applequist, J. *Macromolecules* **1997**, *30*, 2144. (e) DeGrado, W. F.; Schneider, J. P.; Hamuro, Y. *J. Pept. Res.* **1999**, *54*, 206.

(7) (a) Wu, Y.-D.; Wang, D.-P. *J. Am. Chem. Soc.* **1998**, *120*, 13485. (b) Möhle, K.; Günther, R.; Thormann, M.; Sewald, N.; Hofmann, H.-J. *Biopolymers* **1999**, *50*, 167. (c) Wu, Y.-D.; Wang, D.-P. *J. Am. Chem. Soc.* **1999**, *121*, 9352. (d) Rao, S.; Balaji, V. M.; Ramnarayan, K. *Pept. Res.* **1992**, *5*, 343.

(8) (a) Daura, X.; van Gunsteren, W. F.; Rigo, D.; Jaun, B.; Seebach, D. *Chem.−Eur. J.* **1997**, *3*, 1410. (b) Daura, X.; Jaun, B.; Seebach, D., van Gunsteren, W. F.; Mark, A. E. *J. Mol. Biol.* **1998**, *280*, 925. (c) Daura, X.; van Gunsteren, W. F.; Mark, A. E. *Proteins: Struct., Funct., Genet.* **1999**, *34*, 269. (d) Seebach, D.; Schreiber, J. V.; Abele, S.; Daura, X.; van Gunsteren, W. F. *Helv. Chim. Acta* **2000**, *83*, 34. (e) Daura, X.; Mark, A. E.; van Gunsteren, W. F. *Comput. Phys. Commun.* **1999**, *123*, 97.

(9) (a) Hintermann, T.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983. (b) Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8560.

(10) (a) Yang, D.; Ng, F.-F.; Li Z.-J.; Wu, Y.-D.; Chan, K. W. K.; Wang, D.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9794. (b) Yang, D.; Qu, J.; Li, B.; Ng, F.-F.; Wang, X.-C.; Cheung, K.-K.; Wang, D.-P., Wu, Y.-D. *J. Am. Chem. Soc.* **1999**, *121*, 589. (c) Wu, Y.-D.; Wang, D.-P.; Chan, K. W. K.; Yang, D. *J. Am. Chem. Soc.* **1999**, *121*, 11189.

(11) (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. (b) Hess, H.-J.; Moreland, W. T.; Laubach, G. D. *J. Am. Chem. Soc.* **1963**, *85*, 4041. (c) Gante, J.; Krug, M.; Lauterbach, G.; Weitzel, R.; Hiller, W. *J. Pept. Sci.* **1995**, *2*, 201. (d) André, F.; Boussard, G.; Bayeul, D.; Didierjean, C.; Aubry, A.; Marraud, M. *J. Pept. Res.* **1997**, *49*, 556. (e) Benatalah, Z.; Aubry, A.; Boussard, G.; Marraud, M. *Int. J. Pept. Protein Res.* **1991**, *38*, 603. (f) Lecoq, A.; Boussard, G.; Marraud, M. *Tetrahedron Lett.* **1992**, *33*, 5209. (g) André, F.; Marraud, M.; Tsouloufis, T.; Tzartos, S. J.; Boussard, G. *J. Pept. Sci.* **1997**, *3*, 429.

(12) (a) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9367. (b) Möhle, K.; Hofmann, H.-J. *Biopolymers* **1996**, *38*, 781. (c) Möhle, K.; Hofmann, H.-J. *J. Peptide Res.* **1998**, *51*, 19. (d) Kirshenbaum, K.; Barron, A. E.; Goldsmith, R. E.; Armand, P. A.; Bradley, E. K.; Truong, K. T. V.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4303. (e) Armand, P.; Kirshenbaum, K.; Goldsmith, R. E.; Farr-Jones, S.; Barron, A. E.; Truong, K. T. V.; Dill, K. A.; Mierke, D. F.; Cohen, F. E.; Zuckermann, R. N.; Bradley, E. K. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4309.

(13) Niedrich, H.; Köller, G. *J. Prakt. Chem.* **1974**, *316*, 729.

(14) Aubry, A.; Mangeot, J.-P.; Vidal, J.; Collet, A.; Zerkout, S.; Marraud, M. *Int. J. Pept. Protein Res.* **1994**, *43*, 305.

(15) Bonnet, D.; Samson, F.; Rommens, C.; Gras-Masse, H.; Melnyk, O. *J. Pept. Res.* **1999**, *14*, 270.

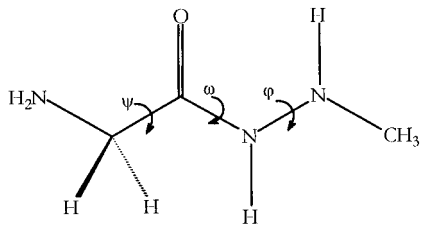
(16) (a) Riggs, N. V.; Radom, L. *Aust. J. Chem.* **1986**, *39*, 1917. (b) Schmitz, B. K.; Euler, W. B. *J. Mol. Struct. (THEOCHEM)* **1992**, *257*, 227. (c) Reynolds, C. H.; Hormann, R. E. *J. Am. Chem. Soc.* **1996**, *118*, 9395. (d) Thormann, M.; Hofmann, H.-J. *J. Mol. Struct. (THEOCHEM)* **1999**, *469*, 63. (e) Chakravorty, S.; Reynolds, C. H. *J. Mol. Graphics* **1999**, *17*, 315. (f) Alemán, C.; Puiggalí, J. *J. Org. Chem.* **1999**, *64*, 351.

peptide monomer. Finally, the torsion angle ψ was set to values of 180, −120, −60, 0, 60, and 120°, respectively. The above-mentioned quantum chemical studies indicated a remarkable dependence of the pyramidality at the hydrazine/hydrazide nitrogen atoms on the NN torsion angle. This configuration aspect at both nitrogens, N^{α} (hydrazino) and N^{β} (peptidic), in the α-hydrazino acid constituents deserves special attention because of chirality. Thus, a wider variety of conformers could be realized, even if nitrogen inversion might reduce the importance of such effects. Nevertheless, to obtain the information on the conformers as completely as possible, the two possibilities of pyramidality of the two nitrogen atoms were considered in additional calculations for each (φ, θ, ψ) angle combination. The conformations obtained in this way cover the complete conformation (and configuration) space of the hydrazino peptide monomer **I**. They were the starting points for complete geometry optimizations at the HF/6-31G* level of ab initio MO theory.[17] Numerous studies have shown this level sufficient to provide a reliable picture of the conformational properties in peptides.[18] To get information on a possible influence of correlation effects arising from the hydrazide structure, the optimizations were repeated at the MP2/6-31G* and DFT/B3LYP/6-31G* levels of ab initio MO theory.[17,19] The quantum chemical grid search was supplemented by a complete molecular mechanics conformational search employing the CHARMm23.1 force field[20] with grid intervals of 30° for the backbone torsion angles. Conformers from this search, which were not found so far at the HF/6-31G* level, were reoptimized for verification. Finally, conformations with rotation angles of conformers determined in unsubstituted and substituted β-peptide monomers of the general type Ac−NH−CH(R_2)−CH(R_1)−CO−NHMe with R_1 and R_2 = H and/or Me in our previous study,[7b] which were not confirmed for the hydrazino peptide monomer by the two described procedures, were also considered in geometry optimizations. All stationary points estimated at the HF/6-31G* level were characterized by frequency analyses. Because of the interest in periodic secondary structures, a systematic HF/6-31G* conformation search for the blocked hydrazino dipeptide **I** (n = 2) was started from grid points with φ = 90° or, alternatively, −90° and always the same combinations of ±60° intervals between 0 and 180° for θ and ψ in both amino acids. Although starting from periodic structures, nonperiodic conformers could also be obtained from this search. HF/6-31G* and DFT/B3LYP/6-31G* geometry optimizations of hydrazino peptide trimers, tetramers, and pentamers **I** with n = 3−5, respectively, were focused on periodic structures as they are suggested by the conformers found in the (φ, θ, ψ) conformation space of the monomers and dimers (vide infra). Since the results for the various trimer, tetramer, and pentamer structures are in close agreement, only the data of the pentamers are presented and discussed.

The solvent influence on the secondary structures was estimated by employing two quantum chemical continuum models, the Onsager self-consistent-reaction field (SCRF) and the polarizable continuum model (SCI-PCM) formalisms.[21] Although peptide and protein structures might essentially be influenced by specific solute−solvent interactions, such continuum calculations provide a general idea of the trends of solvent influence, even if the quantitative aspect of the data should not be overestimated. In the Onsager SCRF calculations, the geometries of the various structures were optimized at the HF/6-31G* level. The molecular radii necessary for such calculations were determined from the Conolly surfaces on the basis of the HF/6-31G* gas-phase geometries. These geometries were also the basis for the single-point SCI−PCM calculations, which do not need the molecular radii. An isodensity value of 0.001 was used in these calculations. Calculations in the presence of a solvent were for water with a dielectric constant of ϵ = 78.4. The quantum chemical calculations were performed employing the Gaussian94 and Gaussian98 software packages (Gaussian Inc., Pittsburgh, PA 15106). The molecular mechanics conformation search employed the QUANTA97 software (Molecular Simulations, Inc., San Diego, CA 92121).

Results and Discussion

Conformation of Dihydrazide I (n = 1). At first, the possibility of cis peptide bonds in hydrazino peptides has been examined in a conformational analysis on the backbone fragment **II** varying systematically ψ and φ for starting values of ω = 0 and 180°, respectively, and considering the alternative pyramidal arrangements at both nitrogen atoms. The calculations indicate the trans orientation is distinctly preferred. Thus, all conformation studies are based on this structure.Table 1 informs on the geometry and stability of 12 conformer families in the dihydrazide **I** (n = 1) obtained in the conformation search at the



II

HF/6-31G* level of ab initio MO theory. The results of the correlation energy methods, MP2/6-31G* and DFT/B3LYP/6-31G*, are in good agreement. Thus, only the energy data from these calculations are listed in Table 1. The geometry information is available in Table S1 of the Supporting Information. For each conformer in this table, there is an energetically equivalent mirror image with opposite signs of the values for the torsion angles φ, θ, and ψ. The greater diversity of the basic conformer types in comparison with β-peptides comes from the above-mentioned possibility of pyramidal alternatives of the two nitrogens. It is further increased by consideration of the alternative hydrazine conformers in the terminal hydrazide part described by the torsion angle φ_2. With respect to the central torsion angle θ, typical values of about ±60, ±120, and 180° for gauche, skew, and anti-periplanar conformations are preferred, with the gauche conformations being favored. The torsion angle φ corresponds to that for hydrazine (±90°) within a range of about ±30° in most conformer families. As in α- and β-peptide monomers, conformers that are characterized by hydrogen-bonded rings denoted by C_x, where x means the number of atoms in the pseudocycle, predominate. The hydrogen-bonding patterns for the most stable conformer in each family are indicated in Table 1. They may be considered as part of a general scheme of hydrogen bond formation in hydrazino peptide sequences illustrated in Figure 1. The structures of some

(17) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; J. Wiley: New York, 1986.

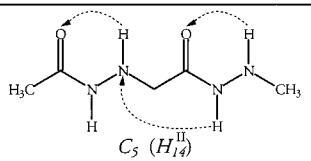
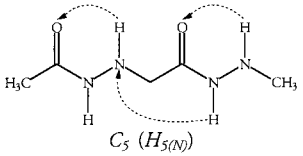
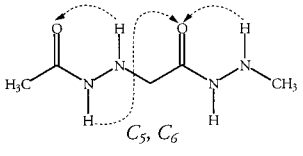
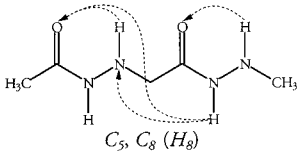
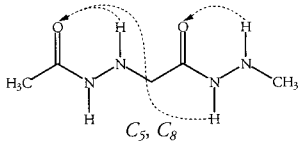
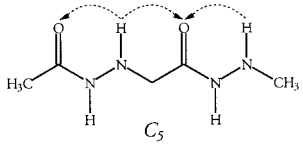
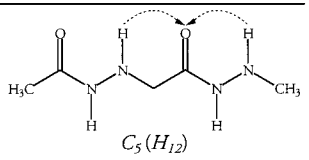
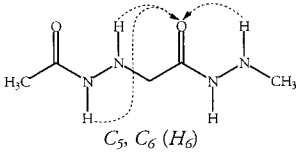
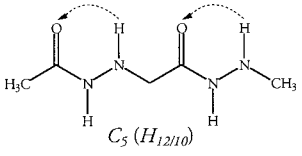
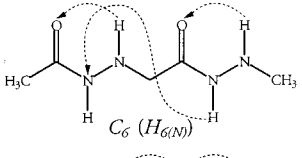
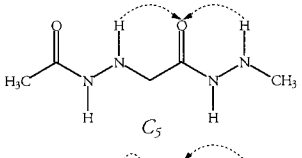
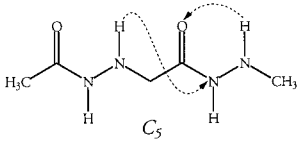
(18) (a) Head-Gordon, T.; Head-Gordon, M.; Frisch, M. J.; Brooks, C. L., III; Pople, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 5989. (b) Böhm, H.-J.; Brode, S. *J. Am. Chem. Soc.* **1991**, *113*, 7129. (c) Gould, I. R.; Kollman, P. A. *J. Phys. Chem.* **1992**, *96*, 9255. (d) Rommel-Möhle, K.; Hofmann, H.-J. *J. Mol. Struct. (THEOCHEM)* **1993**, *285*, 211. (e) Gould, I. R.; Cornell, W. D.; Hillier, I. H. *J. Am. Chem. Soc.* **1994**, *116*, 9250. (f) Brooks, C. L., III; Case, D. A. *Chem. Rev.* **1993**, *93*, 2487. (g) Schäfer, L.; Newton, S. Q.; Cao, M.; Peeters, A.; Van Alsenoy, C.; Wolinski, K.; Momany, F. A. *J. Am. Chem. Soc.* **1993**, *115*, 272. (h) Van Alsenoy, C.; Cao, M.; Newton, S. Q.; Teppe, B.; Perczel, A.; Csizmadia, I. G.; Momany, F. A.; Schäfer, L. *J. Mol. Struct. (THEOCHEM)* **1993**, *286*, 149. (i) Frey, R. F.; Coffin, J.; Newton, S. Q.; Ramek, M.; Cheng, V. K. W.; Momany, F. A.; Schäfer, L. *J. Am. Chem. Soc.* **1992**, *114*, 5369. (j) Endredi, G.; Perczel, A.; Farkas, O.; McAllister, M. A.; Csonka, G. I.; Ladik, J.; Csizmadia, I. G. *J. Mol. Struct. (THEOCHEM)* **1997**, *391*, 15. (k) Möhle, K.; Gussmann, M.; Rost, A.; Cimiraglia, R.; Hofmann, H.-J. *J. Phys. Chem.* **1997**, *101A*, 8571.

(19) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *37B*, 785.

(20) (a) Momany, F. A.; Rone, R. J. *J. Comput. Chem.* **1992**, *13*, 888. (b) Momany, F. A.; Rone, R. J.; Kunz, H.; Frey, R. F.; Newton, S. Q.; Schäfer, L. *J. Mol. Struct.(THEOCHEM)* **1993**, *286*, 1.

(21) (a) Miertus, S.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1981**, *55*, 117. (b) Pascual-Ahair, J. L.; Silla, E.; Tomasi, J.; Bonaccorsi, R. *J. Comput. Chem.* **1987**, *8*, 778.

Table 1. Torsion Angles and Relative Energies of Conformers of Dihydrazide **I** ($n = 1$) Obtained at HF/6-31G*, MP2/6-31G* and DFT/B3LYP/6-31G* Levels of ab Initio MO Theory[a]

Conf.	φ	θ	ψ	φ_2	ΔE HF	ΔE MP2	ΔE B3LYP	Type[b]
M1a	86.9	78.5	20.0	85.9	**0.0**[c]	**0.0**[d]	0.6	 C_5 (H^{II}_{14})
M1b	86.2	78.4	30.6	-82.2	0.3	0.4	0.9	
M1c	86.8	77.8	23.6	-102.6	5.1	5.8	5.8	
M1d	86.8	77.9	28.3	122.8	5.2	6.2	5.9	
M2a	85.1	165.5	-13.7	-85.0	0.9	1.4	1.3	 C_5 ($H_{5(N)}$)
M2b	85.1	162.7	-25.3	81.9	1.2	1.6	1.5	
M2c	85.9	166.6	-16.8	107.2	5.9	7.3	6.4	
M2d	86.0	165.6	-23.8	-117.9	6.0	7.3	6.4	
M3a	78.0	73.6	159.8	-83.8	1.6	1.8	1.9	 C_5, C_6
M3b	78.3	73.0	161.7	84.6	1.7	1.8	2.0	
M3c	78.0	72.2	163.5	107.2	6.2	7.2	6.5	
M3d	77.9	71.8	162.9	-110.3	6.2	7.4	6.6	
M4a	-113.1	69.0	18.5	-86.3	1.9	0.3	**0.0**[e]	 C_5, C_8 (H_8)
M4b	-122.4	79.4	19.5	-84.4	2.2	1.8	1.8	
M4c	-122.6	79.9	14.9	80.7	2.3	1.5	2.0	
M4d	-114.3	68.3	10.1	79.7	2.4	0.7	0.5	
M4e	-117.1	78.0	23.0	-123.5	5.4	6.0	5.9	
M4f	-119.9	79.2	21.2	108.1	5.5	5.6	5.7	
M5a	78.5	-130.8	42.7	87.2	2.0	1.0	→**M4a**	 C_5, C_8
M5b	79.5	-133.4	54.6	-76.0	2.9	1.8	→**M4d**	
M5c	78.5	-131.6	44.8	-98.0	6.1	6.0	5.2	
M5d	78.5	-131.8	46.8	136.1	6.4	6.6	5.2	
M6a	81.5	-171.4	-150.8	83.6	1.7	3.1	2.7	 C_5
M6b	81.2	-170.2	-153.4	-84.7	2.1	3.2	2.8	
M6c	81.1	-170.2	-154.0	-108.6	6.9	8.8	7.7	
M7a	-58.8	102.7	-146.9	86.7	2.6	2.6	3.0	 C_5 (H_{12})
M7b	-62.8	106.4	-151.7	-73.4	3.6	3.3	3.8	
M7c	-57.2	103.8	-145.8	-93.3	7.0	7.1	3.8	
M7d	-56.6	102.3	-144.5	152.8	7.3	8.1	7.6	
M8a	119.7	62.6	-175.5	-83.1	3.2	4.5	4.2	 C_5, C_6 (H_6)
M8b	121.1	62.6	-176.2	82.7	3.2	4.6	4.3	
M8c	119.4	62.4	-176.7	-112.7	7.4	9.6	8.5	
M9a	-90.5	55.3	89.0	-84.5	3.9	2.4	3.9	 C_5 ($H_{12/10}$)
M9b	-96.5	58.9	93.8	80.9	4.1	3.2	4.2	
M9c	-91.9	50.9	79.1	-151.1	7.6	6.6	7.3	
M10a	-87.0	-84.1	71.4	-85.7	3.8	3.5	4.1	 C_6 ($H_{6(N)}$)
M10b	-87.1	-86.0	70.1	106.6	9.1	3.5	4.2	
M11	94.2	167.2	139.5	-84.2	6.1	7.7	6.7	 C_5
M12	103.6	177.6	-61.2	-87.4	11.4	12.7	11.9	 C_5

[a] Energies in kcal/mol, angles in deg. [b] C_x: Hydrogen-bonded cycle with x atoms. H_x: Basic unit of a periodic structure with hydrogen-bonded C_x turns. $H_{x/y}$: "Mixed" helix. [c] $E_T = -563.804\,670$ au. [d] $E_T = -565.445\,522$ au. [e] $E_T = -567.168\,126$ au.

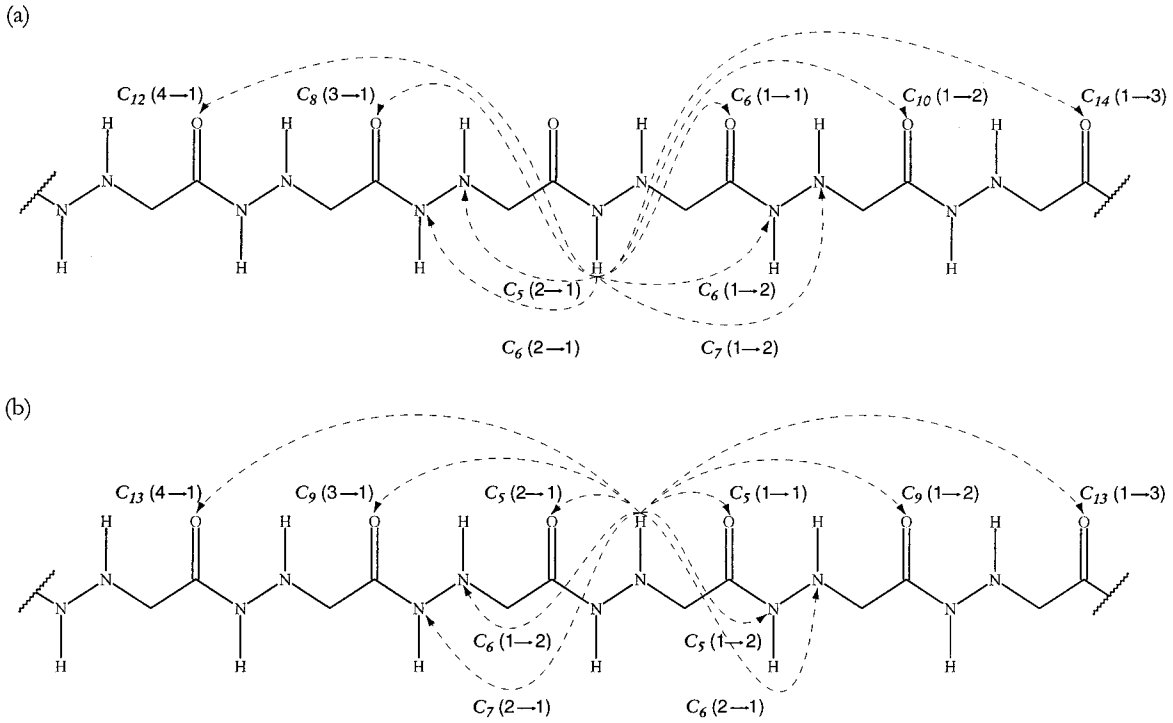


Figure 1. Various possibilities of hydrogen bonding in hydrazino peptides for secondary structure formation: (a) hydrogen bonding from a peptidic $N^{\beta}H$ group to peptidic CO and other peptidic and hydrazino NH groups; (b) hydrogen bonding from a hydrazino $N^{\alpha}H$ group to peptidic $N^{\beta}H$ and CO groups and to other hydrazino $N^{\alpha}H$ groups.

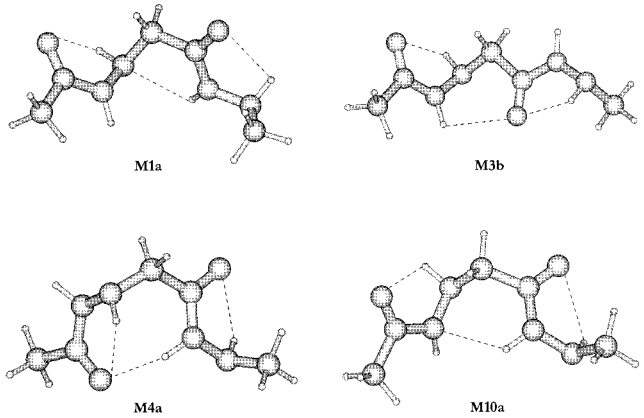


Figure 2. Selected conformers of the hydrazino peptide monomer **I** with different hydrogen-bonding patterns.

conformers selected from Table 1 are visualized in Figure 2. Analogy with conformers found in β-peptides[7] exists for several rather stable C_6 and C_8 conformers, e.g. **M3**−**M5** and **M8**, with forward and backward formation of the hydrogen-bonded rings between the peptidic $N^{\beta}H$ and CO groups along the sequence. These C_6 and C_8 rings could be regarded as analogues of the so-called C_5 conformer in α-peptides, which is the parent conformation in β-strands there, and the C_7 conformer, respectively, a model compound for γ-turns in peptides and proteins. However, some peculiarities in hydrazino peptides arise from the $N^{\alpha}H$ group, which participates in several types of hydrogen bonds (Figure 1). This group may serve as a proton donor to realize hydrogen-bonded cycles of the same size but different type in forward and backward directions with peptidic CO groups, e.g. C_5, C_9, etc. As a proton acceptor, hydrogen bonds between the nitrogen atom and the NH groups of peptide bonds and other $N^{\alpha}H$ groups could be thought of. In fact, the most stable conformer **M1a** shows two types of C_5 rings, the one with backward formation of the hydrogen bond between $N^{\alpha}H$ as proton donor and the preceding peptidic CO group and the other with the nitrogen atom of this group as proton acceptor and the peptidic NH of the following amino acid (Table 1, Figure 2). There are further structures of high stability in Table 1 with such characteristics, which cannot be compared with the above-mentioned C_5 rings in α-peptides. There are even conformers showing both the typical peptidic CO···HN interactions and the effects involving $N^{\alpha}H$, e.g. **M3a** and **M4a**. However, according to our conformation studies on oligomers of **I** up to $n = 5$, the hydrazino $N^{\alpha}H$ group is not involved in hydrogen-bonded rings larger than C_5. Obviously, geometry factors generally favor the interactions between peptidic structure elements in the rings of larger size. The proton donor capability of the peptidic $N^{\beta}H$ is anyway preferred over that of the $N^{\alpha}H$ group, which could be seen in a comparison of the electron densities at both nitrogen atoms or the electrostatic potentials around these groups. Most conformers of Table 1 are confirmed when considering solvation influence (Table 2). There are, however, changes of the stability order. Thus, C_8 conformers of family **M4**, e.g. **M4b**^{s},**c**^{s}, are now most stable followed by conformers of family **M2** and only then by conformers of family **M1** with the most stable conformers in vacuo. The torsion angles estimated for the conformers of family **M4** are supported by X-ray data obtained for four α-peptide derivatives with a single hydrazino acid constituent.[14] It is interesting to find structures in the conformer pool of the dihydrazide **I** that represent the basic units of helical secondary structures with hydrogen-bonded pseudocycles larger than C_6 and C_8, respectively, although the structural prerequisites for hydrogen bond formation are not yet fulfilled at the blocked monomer level (e.g. **M1** and **M7**).[7,12b−e]

Conformation of Oligomers of I ($n = 2-5$). The monomers of Table 1 may serve as starting points for estimating the formation of periodic and nonperiodic secondary structures in hydrazino peptide oligomers. Obviously, the same and different C_6 conformers can be oligomerized since hydrogen bonding is realized in forward direction within the same amino acid (1 →

Table 2. Torsion Angles and Relative Energies of Conformers of Dihydrazide **I** ($n = 1$) Obtained at the HF/6-31G* Level of the SCRF Solvation Model[a]

conf	φ	θ	ψ	φ_2	ΔE	type[b]
M1a^s	81.9	83.9	15.3	87.4	1.0	C_5 (H^{II}_{14})
M1b^s	81.2	82.6	21.6	−82.2	1.5	
M1c^s	79.5	85.6	13.5	−119.4	1.7	
M1d^s	79.4	85.2	16.3	117.4	1.4	
M2a^s	81.8	165.7	−19.3	−84.9	0.8	C_5 ($H_{5(N)}$)
M2b^s	82.4	162.9	−25.1	84.2	0.6	
M2c^s	79.6	162.0	−24.7	111.9	0.6	
M2d^s	79.6	161.8	−27.4	−125.0	0.9	
M3a^s	86.2	72.1	155.6	−82.7	5.4	C_5, C_6
M3b^s	84.7	71.6	156.8	83.3	5.5	
M3c^s	130.3	67.5	158.8	120.6	6.7	
M3d^s	134.4	67.8	156.4	−115.8	6.5	
M4b^s	−117.4	96.6	1.9	−85.4	0.4	C_5, C_8 (H_8)
M4c^s	−119.8	92.1	1.8	83.4	**0.0**[c]	
M4d^s	−105.6	89.6	−10.1	83.1	1.9	
M4e^s	−117.1	99.0	−3.7	−132.0	1.6	
M4f^s	−117.1	100.1	−5.0	104.2	1.4	
M5a^s	80.9	−123.1	36.4	89.1	1.2	C_5, C_8
M5c^s	86.3	−118.5	34.2	−102.8	2.0	
M5d^s	86.2	−119.6	36.7	134.4	2.1	
M6a^s	84.3	−174.1	−139.2	84.3	3.0	C_5
M6b^s	84.1	−174.1	−140.8	−83.9	3.0	
M6c^s	87.4	−178.9	−126.1	−107.6	3.6	
M7a^s	−60.3	100.1	−139.1	86.8	3.3	
M7b^s	−63.3	101.5	−140.7	−71.2	4.1	C_5 (H_{12})
M7c^s	−63.4	101.9	−133.1	−92.7	4.8	
M7d^s	−98.7	77.1	−88.8	153.5	4.0	
M8a^s	129.8	63.4	175.2	−82.0	3.7	C_5, C_6 ($H_{6(N)}$)
M8b^s	128.4	62.1	176.8	82.0	3.6	
M8c^s	139.8	63.1	173.5	−121.1	3.9	
M11^s	120.1	166.8	158.4	−81.6	6.0	C_5
M12^s	107.7	−179.9	−78.6	−86.2	8.4	C_5

[a] Energies in kcal/mol, angles in deg. [b] C_x: Hydrogen-bonded pseudocycle with x atoms. H_x: Basic unit of a periodic structure with hydrogen-bonded C_x turns. $H_{x/y}$: "Mixed" helix. [c] $E_T = -563.811\,617$ au.

1 interaction). Examples are given in the Tables 3 and 4, which summarize data for a selection of periodic and nonperiodic dimer ($n = 2$) and pentamer ($n = 5$) conformers of **I**. One of the periodic H_6 pentamers can be seen in Figure 3. Such structures are typically sheet- or ladderlike. Even if hydrogen bonding in C_8 pseudocycles of **I** is organized in backward direction between three amino acids (3 → 1 interaction), it can be seen that oligomerization of the same or different C_8 rings is always possible keeping all monomer torsion angles. Most interesting of the various H_8 structures are oligomers from the conformer

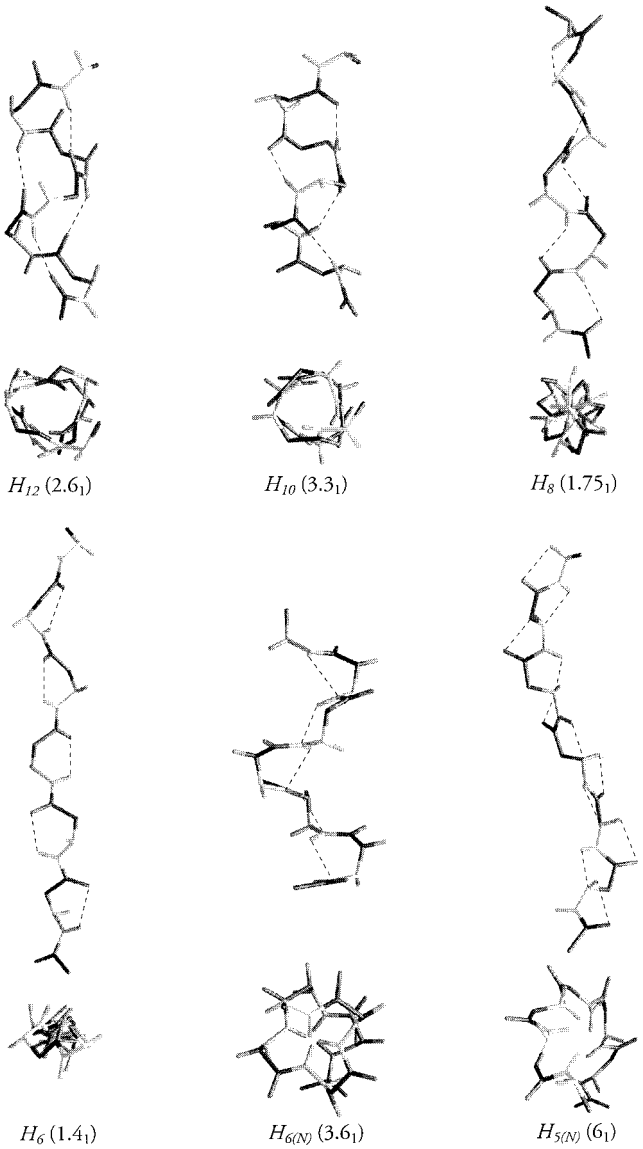


Figure 3. Various periodic secondary structures found for the hydrazino peptide pentamer **I**.

family **M4** (Tables 1 and 2), which have been found to be rather stable in a polar environment. The sheet- or stairlike H_8 pentamer prototype derived from **M4a** is shown in Figure 3. It is equivalent to the theoretically predicted and experimentally

Table 3. Torsion Angles and Relative Energies of Selected Periodic and Nonperiodic Minimum Conformations of the Dimer **I** ($n = 2$) Obtained at the HF/6-31G* Level of ab Initio MO Theory[a]

conf	φ	θ	ψ	ΔE	type[b]	conf	φ	θ	ψ	ΔE	type
D1	83.6	70.3	41.9	**0.0**[c]	C_{10}	**D6**	−95.0	61.7	92.1	5.2	C_5, C_5
	70.8	67.4	49.26		(H_{10})		72.1	65.3	178.8		($H_{12/10}$)
	81.5						87.1				
D2	86.3	76.2	22.5	0.7	C_5, C_5	**D7**	−69.0	98.5	−145.6	5.8	C_{12}
	85.4	75.2	23.7		(H^{II}_{14})		−65.3	95.9	−131.1		(H_{12})
	86.1						−68.8				
D3	−117 .7	79.6	22.9	3.1	C_8, C_8	**D8**	98.9	61.9	−128.6	7.7	C_{10}
	−125 .0	80.5	17.8		(H_8)		−92.2	60.1	96.3		($H_{10/12}$)
	−85.0						81.2				
D4	−90.2	−82.2	72.5	3.6	C_{10}	**D9**	−83.9	−84.8	67.5	8.7	C_6, C_6
	67.0	76.1	137.9				−87.0	−84.2	70.1		(H_6(N))
	−82.5						−86.1				
D5	84.9	161.3	−26.1	3.7	C_5, C_5	**D10**	125.4	−58.6	150.5	14.1	(H^{I}_{14})
	81.7	162.3	−25.0		($H_{5(N)}$)		128.6	−62.0	147.7		
	81.9						85.3				

[a] Energies in kcal/mol, angles in deg. [b] C_x: Hydrogen-bonded pseudocycle with x atoms. H_x: Dimer unit of a helix with hydrogen-bonded C_x turns. $H_{x/y}$: "Mixed" helix. [c] $E_T = -825.614\,018$ au.

Table 4. Torsion Angles of Selected Minimum Conformations of the Pentamer **I** ($n = 5$) Obtained at the HF/6-31G* Level of ab Initio MO Theory[a]

conf	type[b]	φ	θ	ψ	conf	type	φ	θ	ψ
P1	H_6	120.6	62.8	−178. 2	**P2**	H_8	−117. 9	80.6	20.3
		117.3	62.5	−179. 8			−120. 9	81.6	19.2
		116.9	62.2	179.4			−120. 8	81.2	19.9
		116.8	62.2	−178. 1			−123. 3	83.5	15.1
		77.4	72.2	156.8			−113. 0	69.9	16.7
		83.4					−86.4		
P3	H_{10}	83.2	68.5	38.6	**P4**	H_{12}	−71.1	95.1	−139 .0
		76.6	66.3	68.0			−70.9	91.4	−127 .9
		67.0	58.1	62.5			−69.1	90.7	−127 .8
		71.1	64.0	57.0			−69.6	91.4	−130 .6
		67.9	65.7	47.8			−65.8	94.6	−128 .7
		81.5					−68.9		
P5	H^{I}_{14}	126.5	−48.6	130.1	**P6**	H^{II}_{14}	84.0	80.7	17.7
		134.9	−50.2	137.0			79.5	69.2	28.3
		129.5	−43.3	133.2			76.9	70.5	29.4
		126.9	−49.9	140.2			72.9	72.1	28.9
		131.3	−59.4	152.0			75.8	70.4	34.6
		84.5					82.7		
P7	$H_{5(N)}$	84.9	161.0	−26.3	**P8**	$H_{6(N)}$	−84.7	−84.6	69.1
		81.7	160.3	−25.8			−85.2	−84.1	70.4
		81.7	160.0	−25.5			−85.9	−84.1	71.2
		81.6	160.4	−25.5			−85.3	−84.4	69.1
		81.7	162.2	−24.8			−86.6	−84.1	69.7
		81.9					−85.7		
P9	$H_{10/1\,2}$	76.2	68.2	−109. 2	**P10**	$H_{12/10}$	−94.7	61.8	94.5
		−93.9	61.0	92.2			77.1	72.2	−118 .3
		78.8	73.6	−118. 6			−96.7	56.8	93.2
		−94.6	49.3	87.0			83.6	71.2	−121 .1
		100.5	57.7	−167. 2			−86.8	53.7	87.3
		−70.0					−81.9		

[a] Angles in deg. [b] H_x: Pentamer of a periodic structure with hydrogen-bonded C_x turns. $H_{x/y}$: "Mixed" helix.

Table 5. Relative Energies of Selected Minimum Conformations of the Pentamer **I** ($n = 5$)[a]

type[b]	HF/6-31G*[c]	PCM/HF/6-31G*// HF/6-31G*	SCRF/HF/6-31G*[d]	DFT/B3LYP/6-31G*
H_6	22.1 (14.9)	8.8	19.1	23.9
H_8	11.0 (19.7)	7.3	**0.0**[e]	7.8
H_{10}	6.2 (10.7)	12.6	8.3	3.8
H_{12}	14.7 (18.8)	22.3	2.0	9.6
H^{I}_{14}	34.1 (19.5)	30.4	17.2	23.5
H^{II}_{14}	**0.0**[f] (10.2)	**0.0**[g]	3.3	**0.0**[h]
$H_{5(N)}$	16.2 (8.9)	8.5	20.2	16.3
$H_{6(N)}$	28.7 (10.2)	19.3	28.7	29.5
$H_{10/12}$	10.9 (1.6)	18.9	20.7	4.3
$H_{12/10}$	10.2 (3.9)	21.0	19.0	1.6

[a] Energies in kcal/mol. [b] H_x: Pentamer of a periodic structure with hydrogen-bonded C_x turns. $H_{x/y}$: "Mixed" helix. [c] Dipole moments (in Debye) in parentheses. [d] Dielectric constant $\epsilon = 78.4$. [e] $E_T = -1611.066\,470$ au. [f] $E_T = -1611.050\,401$ au. [g] $E_T = -1611.118\,572$ au. [h] $E_T = -1620.495\,977$ au.

confirmed most stable secondary structure in oligomers of aminoxy acids, which have oxygen instead of the N^{α} nitrogen in their monomer constituents.[10] The corresponding C_8 conformers have also been predicted in β-peptides[7a,b] and indicated in 1-(aminomethyl)cyclopropanecarboxylic acid oligomers, where both C_8 ring alternatives occur.[3g,j]

Whereas the C_6 and C_8 oligomers of hydrazino peptides correspond to β-peptide oligomers, further periodic secondary structure types in hydrazino peptides can be derived from all C_5 monomer structures. Such structures are impossible in β-peptides since the hydrazino nitrogen atom N^{α} is now involved in the hydrogen bonds. Thus, oligomerization of **M2b** and **M10a** leads to the helical structures $H_{5(N)}$ and $H_{6(N)}$ (Tables 3 and 4), which are visualized as pentamers in Figure 3. In $H_{5(N)}$, the hydrazino nitrogen is employed as proton acceptor and proton donor at the same time, whereas the peptidic nitrogen fulfills these functions in $H_{6(N)}$. The indices 5(N) and 6(N) in the symbols for the two special helices denote the size of the pseudocycles as in all other periodic structures and the fact that only nitrogen atoms are involved in hydrogen bonding. Although these structures are interesting, these two helices are distinctly less stable in comparison to other structures (Table 5) and their existence might, therefore, be improbable. Nevertheless, C_5 interactions could be a stabilizing factor in higher oligomers. This is striking when considering the most interesting monomer with C_5 structure elements, the very stable conformer **M1a** (Table 1). Oligomerization of this monomer provides a novel H_{14} helix (Tables 3 and 4, Figure 4), which does not have a counterpart in β-peptides. The 14-membered hydrogen-bonded pseudocycle with a hydrogen bond in forward direction between the peptidic NH group of amino acid *i* and the CO group of amino acid $i + 2$ can only be formed in the trimer, where the structural prerequisites for hydrogen bonding are fulfilled (1 →3 interaction, Figure 1), but the conformation is already present in the monomer and dimer structures (**M1a** and **D2** in Tables 1−3). In comparison to the well-known H_{14} alternative in β-peptides[3a,c,4a,e,5] with torsion angles of $\varphi \approx \pm 150°$, $\theta \approx \mp 60°$, and $\psi \approx \pm 130°$, the novel helix occupies a different

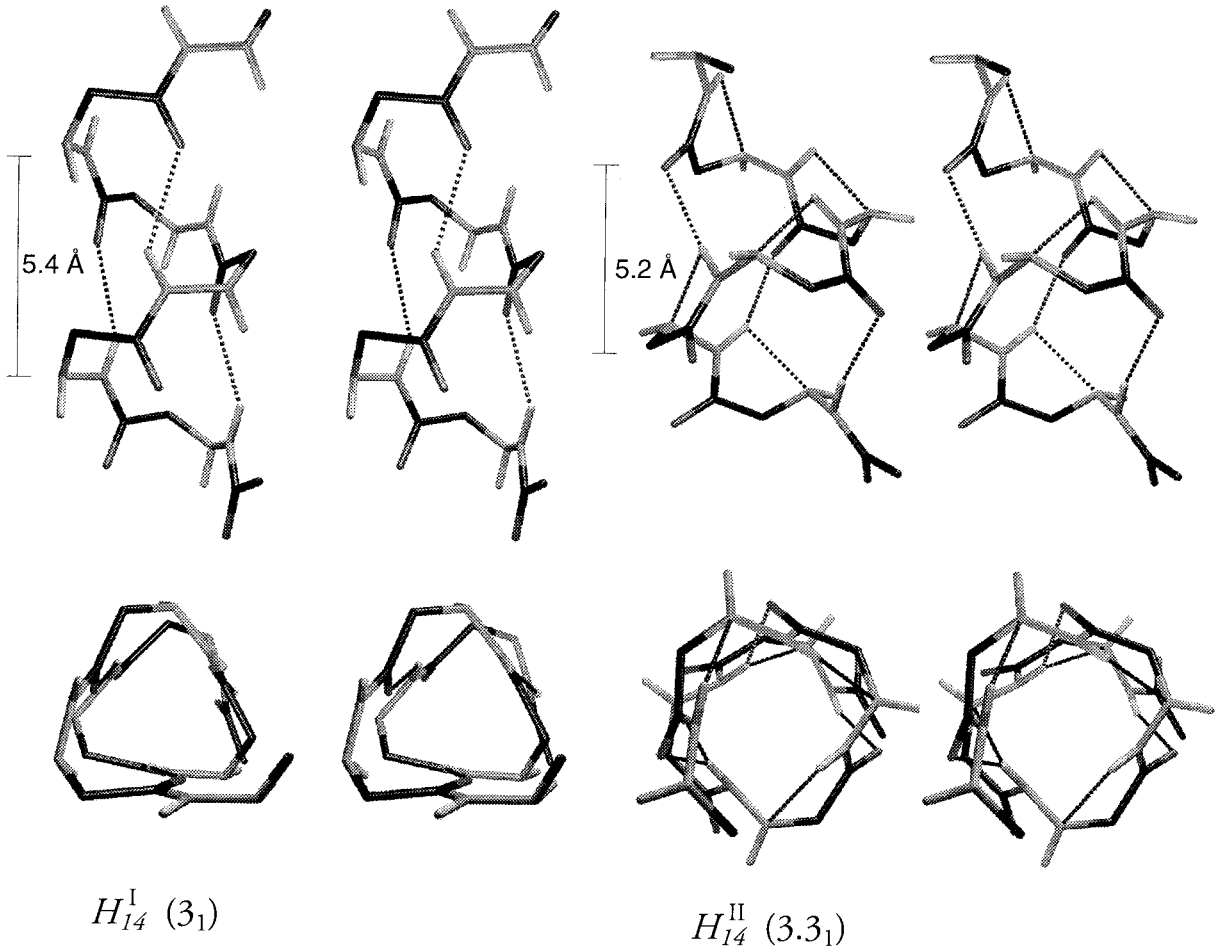


Figure 4. Stereoview of the two hydrazino peptide helix alternatives, H_{14}^{I} and H_{14}^{II}, with 14-membered hydrogen-bonded pseudocycles.

conformation space indicated by torsion angles of $\varphi \approx \pm 80°$, $\theta \approx \pm 70°$, and $\psi \approx \pm 30°$. Here, the torsion angle φ is close to the ideal hydrazine rotation angle. It could be interesting to look for the H_{14} structure alternative of the β-peptides in hydrazino peptides. The basic conformer is not among the monomers of Table 1 but can be indicated at the dimer level (**D10** in Table 3). It is maintained in all higher oligomers (Table 4). In the following paragraphs, the β-peptide-like H_{14} conformer and the novel H_{14} helix in hydrazino peptides are denoted by H_{14}^{I} and H_{14}^{II}, respectively. Figure 4 visualizes these two important helix types in a stereoview. Whereas the H_{14}^{I} helix belongs to the most stable secondary structures in β-peptides, its stability is remarkably lower in hydrazino peptides (Tables 3 and 5). The main reason for this seems to be the considerable deviation of the rotation angle φ from the optimum value for hydrazine-like conformers. In the β-peptide H_{14}^{I} helix, this angle is closer to that of the s-trans arrangement of hydrazine. A search for the novel helix type H_{14}^{II} in β-peptides was not successful. Starting the optimization of a β-peptide sequence from the corresponding rotation angles provides a periodic H_{10} helix in this conformation space, which has already been obtained as a rather stable conformer in our systematic conformation search in β-peptides.[7b] The reduction of the size of the hydrogen-membered pseudocycle is caused by steric effects arising from one of the hydrogens at the C^{β} atoms of the β-amino acid constituents. This H_{10} helix with hydrogen-bonded cycles in forward direction between the peptidic NH group of amino acid i and the CO group of amino acid $i + 1$ appears in hydrazino peptides at the dimer level (**D1** in Table 3), where the structural prerequisites for the hydrogen bond formation are fulfilled (1 $\rightarrow$ 2 interaction; cf. Figure 1). The H_{10} helix proves to be very stable in the higher oligomers, too (Tables 4 and 5, Figure 3). Obviously, H_{14} and H_{10} helices can principally be formed in two independent conformational regions in hydrazino peptides and β-peptides. Whether the two helix types appear in both regions depends on the actual structure. Thus, the two different H_{14} helices, H_{14}^{I} and H_{14}^{II}, can be seen in hydrazino peptides but only one of them in β-peptides (H_{14}^{I}). The H_{10} helix is only indicated in one conformational region, which is the same in β-peptides and hydrazino peptides and involves also the H_{14}^{II} helix. H_{10} helices in the other conformation space change into the corresponding H_{14}^{I} helix there. Another helix type found in β-peptides exhibits C_{12} rings formed in backward direction between peptidic CO and NH groups of the amino acids $i + 2$ and i ($3 \rightarrow 1$ interaction; cf. Figure 1).[4b,e,g,h] The basic conformer for this H_{12} helix is among the hydrazino peptide monomers of Table 1 (**M7b**), although the prerequisites for hydrogen bond formation are only fulfilled at the dimer level (**D7** in Table 3). The H_{12} pentamer helix is shown in Figure 3.

All characteristic helix types for the hydrazino peptides are confirmed at the B3LYP/6-31G* level of DFT theory. The DFT geometry data are available in the Tables S2 and S3 of the Supporting Information. According to both approximations, the novel H_{14}^{II} helix is most stable followed by H_{10}, H_8, and H_{12} (Table 5). The energy data in Table 5 show a considerable influence of a polar medium. Helix H_{14}^{II} remains rather stable, H_8 gains considerable stability, but the stability of the H_{10} helix decreases such as in β-peptides as suggested by the smaller helix dipole moment due to a less parallelity of the hydrogen bonds to the helix axis (Table 5). The energy data provided by the

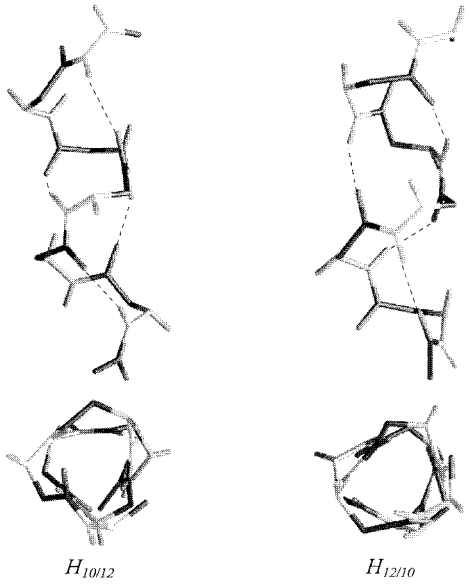


Figure 5. "Mixed" helix alternatives in the hydrazino peptide pentamer **I** with alternating C_{10} and C_{12} hydrogen-bonded rings.

two solvation models, SCRF and SCI−PCM, are contradictory and might only be considered as a qualitative trend estimation of solvent influence. In any case, both models indicate considerable stability differences between the corresponding helices in β-peptide and hydrazino peptide models. In particular, the preference of the H_{14}^{I} helix in β-peptides cannot be confirmed in hydrazino peptides, which distinctly prefer the H_{14}^{II} alternative with a proper hydrazine rotation angle. This helix competes with the periodic H_8 conformer in a polar environment, which is the most stable secondary structure type in oligomers of aminoxy acids.[10] All conformation data indicate a great influence of the hydrazine structure element on the type and stability of hydrazino peptide secondary structures.

An unusual "mixed" helix type with alternating C_{12} and C_{10} rings has been found in β-peptides.[3e,7b,c] Such mixed helices, for which basic conformers can be recognized among the monomers in Table 1 (**M9**), are also predicted for hydrazino peptides. The geometry and energy data for the corresponding dimer (**D6**, **D8**) and pentamer (**P9**, **P10**) alternatives are given in the Tables 3−5. Figure 5 visualizes this helix type for the two alternatives with C_{10}/C_{12} and C_{12}/C_{10} orders of the pseudocycles. In a polar environment, these helices should be disadvantaged in comparison to the periodic helices because of compensating effects on the helix polarity due to the opposite directions of the hydrogen bonds in the alternating pseudocycles (cf. dipole moments in Table 5).

Amino acid dimers are of particular importance, since they are able to induce turn structures, which are necessary to reverse the direction of a sequence. Such reverse turns can be realized on the basis of periodic and nonperiodic structures. Most of the well-known β-turns in α-peptides exhibit a C_{10} ring with a hydrogen bond in backward direction from the NH group of amino acid $i + 3$ to the CO group of amino acid i ($4 \rightarrow 1$ interaction).[22] Blocked hydrazino peptide and β-peptide dimers possess the structural prerequisites for C_{10} but also for C_{12} ring formation. They offer, therefore, access to two different types

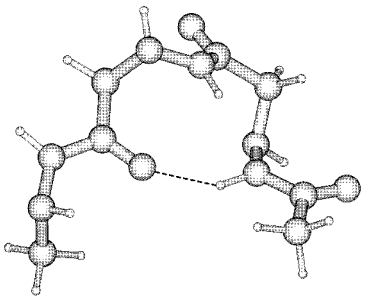


Figure 6. Hydrazino peptide C_{10} turn in the dimer minimum conformation **D4** (cf. Table 3).

of turns with the hydrogen bonds in forward (C_{10}, $1 \rightarrow 2$ interaction) and backward (C_{12}, $3 \rightarrow 1$ interaction) directions. Figure 6 shows the blocked nonperiodic dimer **D4**, which belongs to the most stable dimer conformers (Table 3), as a representative example for a hydrazino peptide turn with a C_{10} ring. Recently, such C_{10} turn structures were experimentally found in tripeptides of 1-(aminomethyl)cyclohexanecarboxylic acid.[3f,j]

Conclusions

The conformation analyses on hydrazino peptide oligomers show a wide variety of secondary structure elements, as for instance various helices and sheet- and turnlike structures. Whereas some of them correspond to secondary structure types found in β-peptides, others represent novel types. Most interesting is a very stable helix with 14-membered hydrogen-bonded pseudocycles located in a conformation space different from that of helices with 14-membered rings found among the most stable conformers in β-peptides. Secondary structure formation in hydrazino peptides is determined by the peptidic NH and CO groups. The hydrazino $N^{\alpha}H$ group takes part in some structuring effects, but its importance for secondary structure formation is distinctly smaller. The wide variety of well-defined secondary structure types and the considerable potential for structural modification make hydrazino peptides a useful tool for peptide and protein design.

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Supporting Information Available: Tables of the torsion angles in various conformers of the blocked hydrazino peptide monomer **I** ($n = 1$) estimated at the MP2/6-31G* and DFT/B3LYP/6-31G* levels and of the blocked hydrazino peptide pentamer **I** ($n = 5$) at the SCRF/HF/6-31G* and DFT/B3LYP/6-31G* levels (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) (a) Venkatachalam, C. M. *Biopolymers* **1968**, *6*, 1425. (b) Richardson, J. S. *Adv. Protein Chem.* **1981**, *34*, 167. (c) Richardson, J. S.; Richardson, D. C. In *Prediction of Protein Structure and the Principles of Protein Conformation*; Fasman, G. D., Ed.; Plenum Press: New York, 1989; p 1. (d) Chou, P. Y.; Fasman, G. D. *J. Mol. Biol.* **1977**, *115*, 135. (e) Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1. (f) Levitt, M. *J. Mol. Biol.* **1976**, *104*, 59. (h) Möhle, K.; Gussmann, M.; Hofmann, H.-J. *J. Comput. Chem.* **1997**, *18*, 1415.