Conformational Studies Using Molecular Mechanics on Model Peptides with 1-Aminocycloalkane 1-Carboxylic Acid Residues

Shashidhar N. Rao,* Ming Fai Chan,† and Vitukudi N. Balaji††

Searle Research and Development, 4901 Searle Parkway, Skokie, IL 60077, U.S.A.

†P. O. Box 500826, San Diego, CA 92150-0826, U.S.A.

††MOLARK, 1642 Orchard Wood Road, Encinatas, CA 92024, U.S.A.

(Received October 3, 1995)

Peptides with conformationally restricted 1-aminocyclopropane-1-carboxylic acid (Acc^3) moieties were previously shown to exhibit preference for γ-turn structures in the solution phase and solid phase. We present conformational energy calculations on model compounds containing 1-aminocycloalkane carboxylic acid with 4, 5, and 6-membered rings using molecular mechanics methods. The low-energy models adopt conformations characteristic of a variety of regular structures, such as the α-helix, γ-turn, and polyproline-II-type three- and four-fold helices. The energetically most favored models adopt the γ-turn (2.2_7 helix) conformation in the model peptide of 1-aminocyclobutane-1-carboxylic acid (Acc^4), similar to Acc^3 peptides, while they adopt the α-/3_{10}-helical conformation (of either handedness) in the corresponding compounds with cyclopentane (Acc^5) and cyclohexane (Acc^6). The salient features of our investigations are qualitatively consistent with the crystal structures of peptide analogs containing Acc^4, Acc^5, and Acc^6 and the previously reported solution phase and conformational studies on peptides containing Acc^5. Our results have implications for the design of γ-turn and α-/3_{10}-helical peptidomimetics.

Peptidomimetic design is deemed to be an important step in the development of orally bioavailable and metabolically stable drug candidates from peptide leads.[1—4] Incorporation of conformational restriction in the peptide main-chain, together with side-chain modifications (e.g. steric bulk, electrostatic and hydrogen bonding characteristivs), is one of the strategies employed in developing 3-D pharmacophore models for peptide ligands. Such models form a basis for designing drug candidates with altered metabolic stability and improved oral bioavailability. Aminocycloalkane carboxylic acids represent an interesting combination of main-chain and side-chain modifications in the design of peptidomimetics.[4] A number of compounds incorporating these conformationally constrained molecules have been synthesized and evaluated in biological assays.[5] For example, methanoglutamate which is related to 1-aminocyclobutane-1-carboxylic acid, has been shown to play key role in neurophysiology and neuropathology, via its action at the excitatory amino acid receptors like NMDA (*N*-methyl-D-Aspartate).[6,7] Also, 1-aminocyclopentane-1-carboxylic acid derivatives have been incorporated in the design of anaphylatoxin-receptor ligands.[8]

We have previously presented theoretical investigations on model peptides with 1-aminocyclopropane-1-carboxylic acid (Acc^3) moieties as a part of an overall study of peptidomimetics structures using computational approaches.[9] In continuation of those investigations, we have explored the conformational characteristics of model peptides containing 1-aminocycloalkane-1-carboxylic acids with 4- (Acc^4), 5- (Acc^5), and 6 (Acc^6)- membered rings. Specifically, we have undertaken molecular mechanics studies on the structures and conformations of the model peptides **1**—**3** (Fig. 1a) and have compared the salient conformational features of our calculations with those of the model dipeptides with Acc^3, α-aminoisobutyric acid and diethyl glycine.[10,11] Our results indicate that the energetically most favored models adopt the γ-turn conformation (2.2_7 helix) in the model peptide of 1-aminocyclobutane-1-carboxylic acid (Acc^4) as in Acc^3 dipeptides,[9] while they adopt the α-/3_{10}-helical conformation (of either handedness) in the corresponding compounds with cyclopentane (Acc^5) and cyclohexane (Acc^6). Thus, our findings have implications for the design of γ-turn and α-/3_{10}-helical peptidomimetics.

Methods and Nomenclature

Compounds **1**—**3** (Fig. 1a) were model built from first principles using the program MOL_BUILD (obtained by courtesy of MOLARK, 1642 Orchard Wood Road, Encinitas, CA 92024. USA). Their starting geometries, generated using crystallographically observed average bond lengths and bond angles, were then energy minimized using molecular mechanics methods. All the molecular mechanics computations carried out in this study were done with a force field similar to MM2[12] using the program MOL_MEK (obtained by courtesy of MOLARK, vide supra) executed on IBM RS/6000, SGI, SUN, and VAX platforms. In this program, the molecular mechanics energies are evaluated in kcal/mole (1 kcal mol^{-1} = 4.18 kJ mol^{-1}) using the functional form in MM2.[12] The force field was developed with parameters derived from geometries consistent with X-ray crystal structure analyses and ab initio optimizations on model peptides (Balaji, et al. manuscript in preparation). Specifically, the

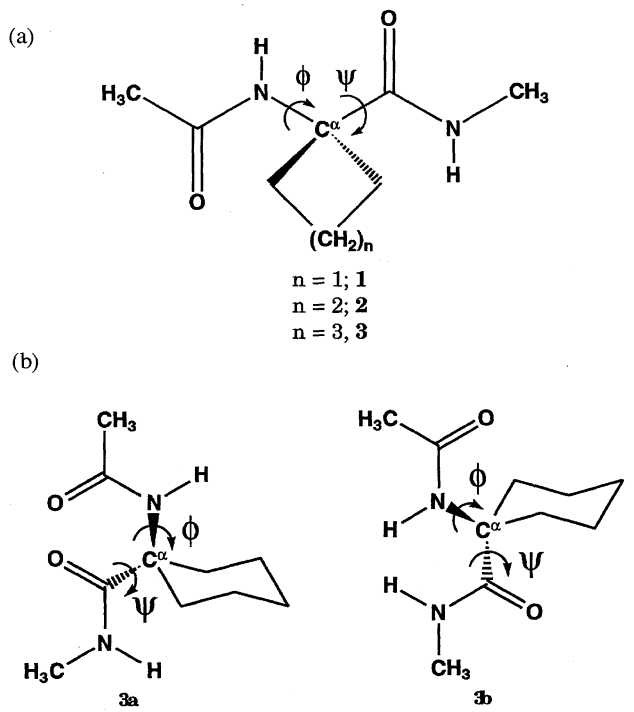

Fig. 1. Schematic representation of the model compounds containing Acc[4] (**1**), Acc[5] (**2**), and Acc[6] (**3**) along with the definition of the conformational parameters, ϕ and ψ (a). The two chair forms of Acc[6] are schematically illustrated in (b).

out-of-plane bending parameter (k_b) was set to 1.0 for the angle N–C$^{\alpha}$, N–H, and N–C (corresponding to the amide nitrogen) and k_b was set to 0.8 for the angles C–N, C–C$^{\alpha}$, and C=O (corresponding to the amide sp^2 carbon) in the MM2 parameter set.[12] Further, the values of V_1, V_2, and V_3 were set to 0.0 for the torsions around the N–C$^{\alpha}$ and C$^{\alpha}$–C bonds. Multiple conformations were then generated for each of the compounds as a function of the torsions ϕ(C–N–C$^{\alpha}$–C) and ψ(N–C$^{\alpha}$–C–N). For compound **2**, these conformers were generated for two different envelope puckers of the cyclopentane. In the case of **3**, two chair conformations (interconvertible through a ring flip) of the cyclohexane were considered separately (Fig. 1b). In one of them, the acetamido group is in an axial orientation (**3a**), while in the other it is equatorial (**3b**). The molecular mechanics energies were evaluated and minimized for each of the conformations, by allowing all the degrees of freedom ***except*** ϕ and ψ. The minimizations at all the grid points were done with a dielectric of 4.0, until an rms gradient of 0.001 kcal mol^{-1} Å^{-1} was achieved. This value of the dielectric constant taken together with the force field employed is more consistent with the ϕ and ψ values in the structures of proteins, peptides and peptidomimetics.[9—11,13]

The results of the calculations are plotted in ϕ–ψ space, wherein isoenergy contours are drawn at 1 kcal mol^{-1} intervals relative to the global minimum (Figs. 2, 3, and 4). The thickness of the contours decreases as the value relative to the global minimum increases. Contours with values of up to 5 kcal mol^{-1} relative to the global minimum are shown. The global minimum is marked 1 in a dark square with the secondary minima marked as 2, 3 etc. Conformational spaces with energies larger than 6 kcal mol^{-1} relative to the global minimum are shown as dark squares. In the (ϕ,ψ) map of **2**, the energy at each grid point in the ϕ–ψ space corresponds to the lower of the energy values obtained for the two

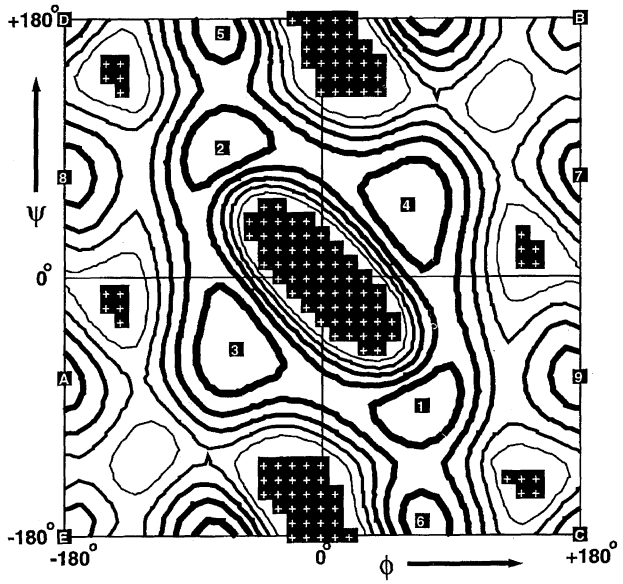

Fig. 2. Energy plot for **1** in (ϕ,ψ) space (minima in Table 1).

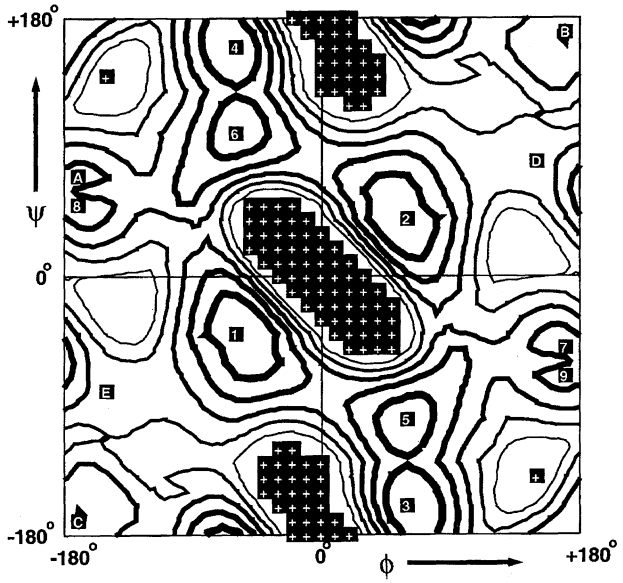

Fig. 3. Energy plot for **2** in (ϕ,ψ) space (minima in Table 2).

puckering forms mentioned above.

The positions and energies of the local minima in each of the four (ϕ,ψ) maps are listed in Tables 1, 2, and 3. The structures corresponding to the minima are called M1_1, M2_1 etc, where the suffixes indicate the molecule number (Fig. 1). The percentages of the conformational space enclosed by the 1 through 5 kcal mol^{-1} contours are listed in Table 4, while Table 5 lists energies of barriers to transitions between the global minimum and secondary minima. The energy minimized structures of the model compounds **1**—**3** are graphically illustrated in Fig. 5(a—d).

Results and Discussion

The (ϕ,ψ) plots of the aminocycloalkane model peptides are all symmetrical about the origin (0°, 0°) since the cycloalkyl rings are unsubstituted, resulting in pairs of global minima (map marks 1 and 2). This symmetry can be broken by introducing different substitutions on the ring systems

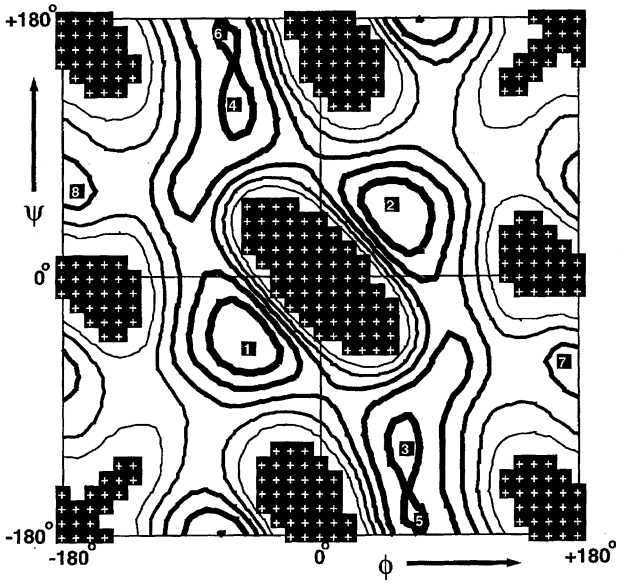

Fig. 4. Energy plot for **3a** (a) and **3b** (b) in their (ϕ,ψ) spaces (minima in Table 3).

Table 1. Energy Minima of **1** in the (ϕ,ψ) Space

Minimum number	ϕ	ψ	Relative energy / kcal mol^{-1}	Map mark
1	±70	∓90	0.00	1:2
2	±60	±50	0.22	3:4
3	∓70	±170	0.40	5:6
4	180	±70	1.53	7:A
5	180	180	2.30	B:E

Table 2. Energy minima of **2** in the (ϕ,ψ) Space

Minimum number	ϕ	ψ	Relative energy / kcal mol^{-1}	Map mark
1	±60	±40	0.00	1:2
2	±60	∓160	0.07	3:4
3	±60	∓100	0.37	5:6
4	±170	∓50	1.23	7:8
5	±170	∓70	1.42	9:A
6	±170	±170	1.96	B:C
7	±150	±80	3.23	D:E

(unpublished data). The percentages of conformational space enclosed by 1 through 5 kcal mol^{-1} contours in Fig. 2 (Acc^4) and 3 (Acc^5) are comparable to those of model dipeptides with Aib[11] and Acc^3.[9] On the other hand, the corresponding values for the cyclohexane dipeptide are smaller (Table 4). However, these percentages are larger than those calculated for the model dipeptide with diethyl glycine.[10,11]

The barriers to conformational transitions from the global minimum to various secondary minima in these plots range from 1.6 to 3.4 kcal mol^{-1} (Table 5). In **1**, these barriers are less than 2 kcal mol^{-1} for transitions to secondary minima, which lie within 1 kcal mol^{-1} of M1 in Fig. 2. Generally,

Table 3. Energy Minima of **3a** and **3b** in the (ϕ,ψ) Space

Minimum number	ϕ	ψ	Relative energy / kcal mol^{-1}	Map mark
3a				
1	±50	±50	0.00	1:2
2	∓60	±120	0.72	3:4
3	±70	∓170	0.22	5:6
3b				
1	±50	±50	0.00	1:2
1	±60	∓100	0.39	3:4
2	∓170	±60	1.34	5:6

Table 4. Percentages of the Total (ϕ,ψ) Conformational Space Enclosed by Isoenergy Contours (1 to 5 kcal mol^{-1}) for Compounds **1**—**3**. For **2**, the Percentages Correspond to the Average over the Plots for Various Puckering Forms of the Cyclopentane

Contour level / kcal mol^{-1}	**1**	**2**	**3a**	**3b**
1	9	6	4	3
2	26	19	16	15
3	43	40	33	28
4	60	64	51	41
5	77	80	64	52

Table 5. Energies of Barriers to Transitions (in kcal mol^{-1}) between the Global Minimum (Map Mark 1) and Secondary Minima in **1**—**3**.

Column 1 Lists the Map Marks Corresponding to the Secondary Minima in the (ϕ,ψ) Maps

Map mark	**1**	**2**	**3a**	**3b**
2	1.67	3.05	2.89	3.08
3	1.54	2.26	2.89	2.10
4	1.67	3.05	2.36	3.08
5	1.67	2.26	2.36	3.08
6	1.59	3.05	2.89	2.11
7	3.36	2.60		
8	3.36	3.05		
9	3.36	2.60		
10	3.36	3.05		

the transition barriers are higher between the pairs of global minima than between M1 (or M2) and secondary minima lying within 1 kcal mol^{-1}. As earlier,[9—11] the transitions via the origin are energetically very expensive, being at least 10 kcal mol^{-1}.

The global minimum in the (ϕ,ψ) plot of the Acc^4 peptide **1** lies in the γ-turn region. This conformational preference is similar to that of the model peptide with Acc^3.[9] Three pairs of secondary minima correspond to the α-/3_{10}-, polyproline-II (PPII)-type-three- and four-fold helical conformations,[14,15] and are destabilized by less than 0.5 kcal mol^{-1} (Fig. 2). Conformations corresponding to $(\phi,\psi) \approx (180°\pm20°, \pm70°\pm10°)$ (henceforth referred to as ζ-

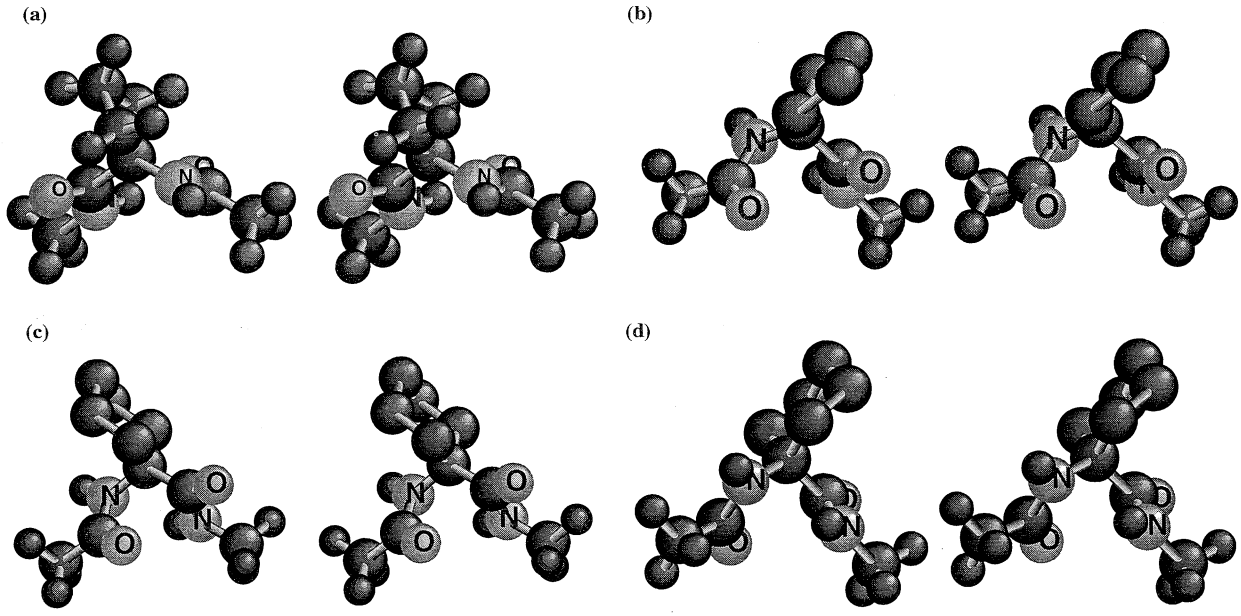

Fig. 5. Computer graphics illustrations of four low energy minima M1_**1** (a), M1_**2** (b), M1_**3a** (c) and M1_**3b** (d). Nitrogen and oxygens are labelled N and O, respectively. The large and small dark spheres represent carbon and hydrogen atoms, respectively.

structure) are destabilized by ca. 1.5 kcal mol^{-1} relative to M1. The fully extended conformations corresponding to $(\phi,\psi) \approx (180°\pm20°, \pm180°\pm10°)$ are destabilized by at least 2.3 kcal mol^{-1}. This destabilization is significantly less than that seen in Acc[3] model dipepetides, where these conformations were higher than the global minimum by at least 6.5 kcal mol^{-1}.

In the (ϕ,ψ) plot of Acc[5] containing peptide, **2**, the global minimum conformation corresponds to the α-/3_{10}-helical conformation of either handedness (Table 2). This conformational preference is similar to that of the Aib model peptide,[10,11] but is in contrast to the preferences of the cyclobutane compound **1** and model peptides with Acc[3].[9] The regions corresponding to the left- and right-handed γ-turn and PPII-type three- and four-fold helical conformations have two pairs of symmetry related minima, which are destabilized by less than 0.4 kcal mol^{-1} (Fig. 3). Two other pairs of secondary minima occur in the rgion of $(\phi,\psi) \approx (180°\pm20°, \pm70°\pm10°)$, and are destabilized by more than 1.2 kcal mol^{-1} relative to the global minimum. Extended conformations with $(\phi,\psi) \approx (180°\pm20°, \pm180°\pm10°)$ are destabilized by about 2 kcal mol^{-1}.

In the (ϕ,ψ) plots of the Acc[6] peptides **3a** and **3b** (Figs. 4a and 4b, respectively), the global minima also correspond to the α-/3_{10}-helical conformation of either handedness (Tables 3a and 3b). The energy of the global minimum of **3a** is lower than that of **3b** by 1.3 kcal mol^{-1}. In Fig. 4a, two pairs of secondary minima corresponding to the three- (M2 and M3) and four-fold (M4 and M5) helical conformations are destabilized by less than 1 kcal mol^{-1} (Table 3a). In Fig. 4b, the four-fold helical conformations are significantly destabilized (by more than 3 kcal mol^{-1} relative to the global minimum of **3b**). Here too, although two pairs of symmetry related secondary minima are found (Table 3b), the corresponding conformations are destabilized by at least 1.6 kcal mol^{-1} relative to the global minimum of **3**. For both the cyclohexane chair conformations of the Acc[6] peptide, the β-structure conformation is destabilized by more than 5 kcal mol^{-1}.

Conformational studies on model peptides with Acc[6] were previously reported by[16,17] using a rigid rotor approach, wherein all the bond lengths and angles were fixed at the crystallographic averages. By contrast, we have allowed all degrees of freedom, except ϕ and ψ, to vary during the molecular mechanics calculations. Furthermore, the force field employed in the previous calculations[16] did not satisfactorily account for the occurrence of certain crystallographically observed conformations in peptides with Aib residues.[11] Comparing the (ϕ,ψ) maps in Figs. 4a and 4b with those reported previously,[16,17] we have found that the positions of the energy minima are very similar. However, the two sets of maps differ significantly in that the barriers to conformational transitions between the global minimum and secondary minima are significantly lower (Table 5) in Figs. 4a and 4b compared to those reported previously (> 8 kcal mol^{-1}). Also, the percentage occupancy by the 5 kcal mol^{-1} isoenergy contour is correspondingly lower in the previous work.[16,17]

How do the results of our investigations compare with the X-ray crystallographic analyses of Acc[4], Acc[5], and Acc[6] containing compounds ? In all the energy refined models of **1**, the bond angle τ(N–C$^{\alpha}$–C) is larger (ca. 115°) than the standard tetrahedral value of ca. 110° in a normal peptide, due to the strain introduced by the cyclobutyl ring at C$^{\alpha}$. On the other hand, this bond angle varies from 107° to 116° in the crystal structures of Acc[4] containing compounds[18—23] where the cyclobutane ring is flatter than the somewhat puckered form obtained in the energy minimized models. Further, the crystal structure values are influenced by intramolecular interactions with ring substituents. In the energy refined models of **2** and **3**, the bond angle τ(N–C$^{\alpha}$–C) is closer to

the tetrahedral value of ca. 110°, since the cyclopentyl and cyclohexyl moieties do not impose rigid constraints characteristic of either the cyclopropyl or cyclobutyl ring systems.

The backbone torsion angles reported for the Acc^4 residues in single crystals are located in the α- or 3_{10}-helical regions ($\phi \approx \pm 53° \pm 6°$, $\psi \approx \pm 40° \pm 4°$). Table 6 lists these conformational parameters in some of the crystal structures. It should be noted that in many of the crystal structures, the cyclobutane ring is locked in conformationally restricted ring systems. The experimentally observed values are qualitatively consistent with the energetically accessible conformational space, as determined from our conformational analyses of model peptides with Acc^4 and its derivatives. Interestingly, the global minimum conformation for the model peptide with unsubstituted cyclobutane (γ-turn, Fig. 2) has not yet been observed in an Acc^4 peptide. This can be rationalized by the following factors: (a) the crystallographically observed conformations are influenced by crystal packing forces which have not been considered in the present study. (b) The conformations of Acc^4 in the crystal structures would be influenced by intermolecular interactions. Since our studies have been confined to model peptides to determine the inherent conformational preferences in Acc^4 peptides, such interactions have not been considered. Nevertheless, it is significant that the crystallographically observed conformations of Acc^4 are found in the space enclosed by the 2 kcal mol^{-1} contours of the (ϕ,ψ) space.

X-ray crystal structures of peptides with 1-aminocyclopentane carboxylic acid moieties have been reported.[24—29] Most of the conformations in the Acc^5 residues in the crystal structures correspond either to the right- or left- handed $\alpha/3_{10}$-helical region of the (ϕ,ψ) space (Table 7), and are enclosed within the 2 kcal mol^{-1} contour of Fig. 3. In cases where this moiety occurs either at the N-terminus or the C-terminus of the peptide with protecting groups, the observed (ϕ,ψ) values correspond to regions of other minima (e.g. left- or right-handed polyproline-II type four-fold helical) in the conformational space. However, it should be pointed out that the conformations of the end protected moieties are likely to be influenced by crystal packing forces, which have not been included in our calculations. Analyses of the X-ray crystal structure data on peptides with 1-aminocyclohexane carboxylic acid moieties[16,30—35] indicate that the experimentally observed conformations (Table 8) lie within 2 kcal mol^{-1} of the global minimum conformation for **3**. The cyclohexane ring in all the crystal structures was

Table 6. Values of Conformational Parameters ϕ and ψ in Crystal Structures of Compounds Containing 1-Aminocyclobutane-1-carboxylic Acid Residues

Refcode	ϕ	ψ	Ref.
JATDUD	−48	−43	23
	48	43	
JATFAL	−51	−44	23
	51	44	
KIDHUA	60	28	18

Table 7. Values of Conformational Parameters ϕ and ψ in Crystal Structures of Compounds Containing 1-Aminocyclopentane-1-carboxylic Acid Residues

Refcode	ϕ	ψ	Ref.
GIPJAQ	−58	−38	24
	−60	−31	
JAGSOZ	61		26
JAGSUF	−58		26
JAGTIU	−62	−34	26
JAGTOA	64	32	26
JAVFAN	64	32	25
POBJEV	58	26	35
SUKMAM	52	38	28, 29
	57	26	
	62	25	
	−52	−49	
SUKMIU	−59	−30	28, 29
	−56	−29	
	−54	−32	
	−60	−27	
	−65	−39	
	59		
SUKMOA	−61	−37	28, 29
	−53	−35	
	−60	−24	
	−62	−43	
	52	33	

Table 8. Values of Conformational Parameters ϕ and ψ in Crystal Structures of Compounds Containing 1-Aminocyclohexane-1-carboxylic Acid Residues

Refcode	ϕ	ψ	Ref.
DEPCOQ	59	37	34
DIDZEV	48	43	33
DIDZIZ	−68	−15	33
FALRUF	61	30	16
	61	25	
	−50	−46	
FALSAM	62	29	16
GARFOU	54	47	31
GARFUA	−57	−46	31
GARGAH	51	39	31
GARGEL	54	42	31
GARGOV	48	39	31
KAMDEH	−74	−24	30
	49	50	
POBJIZ	52	35	
SACXID	59	32	32
	55	32	
	72	11	
	−54	−48	
SACXOJ	−58	−29	32
	−55	−25	
	−60	−35	
	−56	−50	
SACXUP	−53	−52	32
	−56	−38	
	−69	−32	
	44	55	

found in the standard chair conformation. Here too, most of the conformations of the Acc^6 moieties correspond either to the right- or left-handed $\alpha/3_{10}$-helical region of the (ϕ,ψ) space. Thus, the results of our calculations on the model dipeptides **2** and **3** are in qualitative agreement with the X-ray data.

Synthetic, NMR and conformational studies have recently been reported[36] on a somatostatin analog containing Acc^5. Three of the four "possible conformations" reported by those investigations for the Acc^5 residue lie within a 2 kcal mol^{-1} contour in the (ϕ,ψ) map of Fig. 3. The remaining reported conformation with (ϕ,ψ)=(176°, 119°) lies in a region in the (ϕ,ψ) map (Fig. 3) that is destabilized by around 4 kcal mol^{-1} relative to the global minimum. These energy values are qualitatively consistent with the calculated differences in the corresponding energies of the conformations of the somatostatin analog with Acc^5 based on NMR observations.[36] This consistency is despite the fact that our studies have not explicitly taken into account the solvation effects present in the experimental studies. Thus, our results are in qualitative agreement with the NMR results.

How are the results of our calculations affected by the possibilities of hydrogen bonding interactions of the N–H and C=O groups in the model peptides with solvent molecules? In our computational protocol we have employed a dielectric constant of 4.0. This values is considered to mimic an effective physiologic solvent environment in the absence of explicit solvation. Here the intramolecular hydrogen bonding interactions are somewhat deemphasized, effectively accounting for the corresponding interactions with a solvent environment. Furthermore, qualitative agreement with the experimental data is a testimony to the robustness of the computational technique employed. Thus, the essential conclusions of our studies in terms of conformational preferences will not be significantly affected by the lack of consideration of explicit solvation.

The (ϕ,ψ) map of **1** is qualitatively similar to the corresponding map for model peptides with Acc^3.[9] The conformational constraints imposed by both the cyclopropane and cyclobutane rings lead to stabilization of the γ-turn structure. On the other hand, the (ϕ,ψ) maps of **2** and **3** are qualitative similar to that of the Aib model dipeptide reported previously.[10,11] The global minima in all these plots correspond to the α-/3_{10}-helical conformation while secondary minima are found in similar positions. All the (ϕ,ψ) maps examined here are distinctly different from the corresponding map for the model peptide with diethyl glycine.[9,11] While the fully extended β-structure is the global minimum for the latter, this conformation is energetically significantly destabilized in **1**—**3** due to the relatively unfavorable steric interaction between the hydrogens on C^β and the oxygen of the N-terminal side carbonyl group. In the case of **3**, there are additional steric interactions between the C^γ hydrogens and the C-terminal side N–H group. In the absenece of constraints of cyclization, as in the model peptide with diethyl glycine, these interactions are relieved through torsional variations in the ethyl groups.[9,11]

The restricted conformational preferences of peptides with 1-aminocycloalkane-1-carboxylic acid moieties can be utilized in the design of peptidomimetics which are resistant to proteolytic degradation. The substrates of some digestive enzymes (e.g. serine and aspartyl proteases) are characterized by active site conformations which include extended β-structure and β- and γ-turns.[1,37,38] Such conformations are typically essential for good substrate binding, implying that an inhibitor with a constrained conformation (e.g. α-helix as induced by the incorporation of Acc^5 and Acc^6 moieties) different from the active site conformation could be useful for imparting resistance to proteolysis. The implementation of unnatural amino acids in altering the metabolic stability to proteolytic enzymes has been reported recently.[39—41] In addition to small organic compounds, unnatural amino acids have also recently been incorporated into site-directed mutagenesis studies of enzymes and protein probes.[42—47] Thus, 1-aminocycloalkane-1-carboxylic acid moieties can be utilized in the selective stabilization and destabilization of secondary structural motifs, such as α-helix, extended β-structure and β- and γ-turns in enzymes and proteins.

Conclusions

Molecular mechanics calculations on model compounds with three 1-aminocycloalkane carboxylic acids have been presented. The energetically most favored structures for the cyclobutane compound have the γ-turn (2.2_7 helix) conformation of either handedness, as was also noted for the corresponding model peptides with cyclopropane. This compound can adopt the α-/3_{10}-helical conformation more easily than the corresponding model dipeptide with cyclopropane. The theoretically derived models are consistent with the X-ray crystallographic data on compounds with Acc^4 and its derivatives. Our calculations demonstrate that the Acc^5 and Acc^6 moieties lead to the stabilization of α- and 3_{10}-helical conformations, particularly since the transition barriers to other conformations are greater than 2 kcal mol^{-1}. This is qualitatively consistent with the predominance of these conformations for the Acc^5 and Acc^6 moieties in the crystal structures of peptides containing them. All the three model peptides could be accommodated in PPII-type three- and four-fold helical conformations with energy penalties of less than 1 kcal mol^{-1}. Thus, the incorporation of aminocycloalkane derivatives can form the basis of rational strategies for the design of conformationally restricted peptides and peptidomimetics with γ-turn, α-/3_{10}-helical and PPII-type helical structures.

The authors thank the Searle Research and Development (Drug Design) and Immuno Pharmaceutics Inc., for computational, graphics and document builder facilities.

References

1) S. S. Abdel-Meguid, Inhibitors of aspartyl proteinases, *Med. Res. Rev.*, **13**, 731 (1993).

2) B. Blackburn and T. R. Gadek, *Ann. Rep. Med. Chem.*, **28**,

79 (1993).
3) A. Giannis and T. Kolter, *Angew. Chem., Int. Ed. Engl.*, **32**, 1244 (1993).
4) R. A. Wiley and D. H. Rich, *Med. Res. Rev.*, **13**, 327 (1993).
5) D. Konopinska, G. Rosinski, and W. Sobotka, *Pol. J. Pharmacol. Pharm.*, **44**(5), 505 (1992).
6) W. F. Hood, E. T. Sun, R. P. Compton, and J. B. Monahan, *Eur. J. Pharmacol.*, **161**, 281 (1989).
7) G. B. Watson, M. A. Bolanowski, M. P. Baganoff, C. L. Deppeler, and T. H. Lanthorn, *Eur. J. Pharmacol.*, **167**(2), 291 (1989).
8) P. E. Wiedeman, M. Kawai, J. R. Luly, Y. S. Or, and R. Wagner, World Patent (Patent Index: WO 9211858), 1992.
9) V. N. Balaji, K. Ramnarayan, M. F. Chan, and S. N. Rao, *Pept. Res.*, **7**, 60 (1994).
10) S. N. Rao, K. Ramnarayan, M.F. Chan, and V. N. Balaji, *Protein Pept. Lett.*, **1**, 141 (1994).
11) K. Ramnarayan, M. F. Chan, V. N. Balaji, S. Profeta, Jr., and S. N. Rao, *Int. J Pept. Protein Res.*, **45**, 366 (1995).
12) N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1977).
13) V. N. Balaji, S. Profeta, Jr., and S. W. Dietrich, *Biochem. Biophys. Res. Commun.*, **128**, 109 (1987).
14) V. N. Balaji, Energy calculations on helical polypeptides: Structure of polyglycine II, *Int. J. Quant. Chem.*, **20**, 347 (1981).
15) V. Sasisekharan and V. N. Balaji, *Macromolecules*, **12**, 28, (1979).
16) P. K. C. Paul, M. Sukumar, R. Bardi, A. M. Piazzesi, G. Valle, C. Toniolo, and P. Balaram, *J. Am. Chem. Soc.*, **108**, 6363 (1986).
17) M. Crisma, G. M. Bonora, C. Toniolo, A. Bavoso, E. Benedetti, B. Di Blasio, V. Pavone, and C. Pedone, *Macromolecules*, **21**, 2071 (1988).
18) R. D. Allan, J. R. Hanrahan, T. W. Hambley, G. A. R. Johnston, K. N. Mewett, and A. D. Mitrovic, *J. Med. Chem.*, **33**, 2905 (1990).
19) G. N. Austin, P. D. Baird, H.-F. Chow, L. E. Fellows, G. W. J. Fleet, R. J. Nash, J. M. Peach, R. J. Pryce, and C. H. Stirton, *Tetrahedron*, **43**, 1857 (1987).
20) E. A. Bell, M. Y. Qureshi, R. J. Pryce, D. H. Janzen, P. Lemke, and J. Clardy, *J. Am. Chem. Soc.*, **102**, 1409 (1980).
21) K. K. Chacko, and R. Zand, *Cryst. Struct. Commun.*, **4**, 17 (1975).
22) Y. Gaoni, *Tetrahedron Lett.*, **29**, 1591 (1988).
23) T. Iwamoto, S. Kashino, and M. Haisa, *Acta Crystallogr., Sect. C*, **C45**, 1753 (1989).
24) R. Bardi, A. M. Piazzesi, C. Toniolo, M. Sukumar, and P. Balaram, *Biopolymers*, **25**, 1635 (1986).
25) C. Toniolo, M. Crisma, G. Valle, G. M. Bonora, S. Polinelli, E. L. Becker, R. J. Freer, Rao R. B. Sudhanand, P. Balaram, and M. Sukumar, *Pept, Res.*, **2**, 275 (1989).
26) G. Valle, M. Crisma, and C. Toniolo, *Can. J. Chem.*, **66**, 2675 (1988).
27) J. M. Villalgordo, B. R. Vincent, and H. Heimgartner, *Helv. Chim. Acta*, **73**, 959 (1990).
28) F. H. Allen, J. E. Davies, J. J. Galloy, O. Johnson, O. Kennard, C. F. Macrae, E. M. Mitchell, G. F. Mitchell, J. M. Smith, and D. G. Watson, *J. Chem. Inf. Comput. Sci.*, **31**, 187 (1991).
29) F. H. Allen and O. Kennard, *Chem. Des. Automation News*, **8**, 31 (1993).
30) E. Benedetti, B. Di Blasio, V. Pavone, C. Pedone, A. Santini, M. Crisma, and C. Toniolo, *Acta Crystallogr., Sect. C, Cryst. Struct. Commun.*, **C45**, 634 (1989).
31) G. Valle, M. Crisma, C. Toniolo, N. Sen, M. Sukumar, and P. Balaram, *J. Chem. Soc., Perkin Trans.*, **1988**, 393.
32) V. Pavone, E. Benedetti, V. Barone, B. Di Blasio, F. Lelj, C. Pedone, A. Santini, M. Crisma, G. M. Bonora, and C. Toniolo, *Macromolecules*, **21**, 2064 (1988).
33) R. Bardi, A. M. Piazzesi, C. Toniolo, M. Sukumar, P. A. Raj, and P. Balaram, *Int. J. Pept. Protein Res.*, **25**, 628 (1985).
34) G. Bocelli, *Acta Crystallogr., Sect. C, Cryst. Struct. Commun.*, **C42**, 110 (1986).
35) N. Fabiano, G. Valle, M. Crisma, C. Toniolo, M. Saviano, A. Lombardi, C. Isernia, V. Pavone, B. Di Blasio, C. Pedone, and E. Benedetti, *Int. J. Pept. Protein Res.*, **42**(5), 459 (1993).
36) Z. Huang, A. Probstl, J. R. Spencer, T. Yamazaki, and M. Goodman, *Int. J. Pept. Protein Res.*, **42**(4), 352 (1993).
37) D. Fischer, H. Wolfson, S. L. Lin, and R. Nussinov, *Protein Sci.*, **3**(5), 769 (1994).
38) G. W. Zhou, J. Guo, W. Huang, R. Fletterick, and T. S. Scanalan, *Science*, **265**, 1059 (1994).
39) P. Wipf and H. Heimgartner, *Helv. Chim. Acta*, **70**(2), 354 (1987).
40) S. Reissmann, C. Schwuchow, P. Filatova, N. Krit, W. Siems, G. Heder, U. Schrader, H. Schubert, and B. Mueller, *Collect. Czech. Chem. Commun.*, **53**(11A), 2591 (1988).
41) J. Hlavacek and I. Fric, *Collect. Czech. Chem. Commun.*, **54**(8), 2261 (1989).
42) H. H. Chung, D. R. Benson, V. W. Cornish, and P. G. Schultz, *Proc. Natl. Acad. Sci. U.S.A.*, **90**, 10145 (1993).
43) V. W. Cornish, M. I. Kaplan, D. L. Veenstra, P. A. Kollman, and P. G. Schultz, *Biochemistry*, **33**, 12022 (1994).
44) V. W. Cornish, D. R. Benson, C. A. Altenbach, K. Hideg, W. L. Hubbell, and P. G. Schultz, *Proc. Natl. Acad. Sci. U.S.A.*, **91**, 2910 (1994).
45) J. K. Judice, T. R. Gamble, E. C. Murphy, A. M. de-Vos, and P. G. Schultz, *Science*, **261**, 1578 (1993).
46) D. Mendel, J. A. Ellman, Z. Chang, D. L. Veenstra, P. A. Kollman, and P. G. Schultz, *Science*, **256**, 1798 (1992).
47) C. J. Noren, S. J. Anthonyl-Cahill, M. C. Griffith, and P. G. Schultz, *Science*, **244**, 182 (1989).