Conformational Choices for the Stereochemically Constrained γ-Amino Acid Residue Gabapentin: Theoretical Studies and Correlation With Experimental Results

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ABSTRACT:

Gabapentin (1-aminomethylcyclohexaneacetic acid, Gpn) is an achiral, conformationally constrained γ amino acid residue. A survey of available crystal structures of Gpn peptides reveals that the torsion angles about the $C^{\gamma}—C^{\beta}$ (θ_1) and $C^{\beta}—C^{\alpha}$ (θ_2) bonds are overwhelmingly limited to gauche, gauche *(g^+g^+/g^-g^-) conformations. The Gpn residue forms C_7 and C_9 hydrogen bonds in which the donor and acceptor atoms come from the flanking peptide units. In combination with α amino acid residues αγ and γα segments can adopt C_{12} hydrogen bonded structures. The conformational choices available to the Gpn residue have been probed using energy calculations, adopting a grid search strategy. Ramachandran ϕ–ψ maps have been constructed for fixed values of θ_1 and θ_2, corresponding to the* gauche *and* trans *conformations. The sterically allowed and energetically favorable regions of conformational space have been defined and experimental observations compared. C_7 and C_9 hydrogen bonded conformational families have been identified using a grid search approach in which θ_1 and θ_2 values are varied over a range of ±10° about ideal values at 1° intervals. The theoretical analysis together with experimental observations for 59 Gpn residues from 35 crystal structures permits definition of the limited range of conformational possibilities at this γ amino acid residue. © 2009 Wiley Periodicals, Inc. Biopolymers (Pept Sci) 92: 426–435, 2009.*

Keywords: gabapentin; γ-amino acid; conformational analysis; grid search; hydrogen bonds

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INTRODUCTION

The realization that hitherto unanticipated hydrogen bonded structures can be readily generated in hybrid polypeptide sequences incorporating backbone homologated β and γ amino acid residues has led to an upsurge of interest in the stereochemistry of hybrid peptides.[1–4] The insertion of additional atoms into polypeptide backbones increases the number of degrees of torsional freedom, expanding the range of accessible conformational space. Several theoretical studies have examined the energetics of regular helical structures in both homo oligomeric and hybrid sequences containing β and γ amino acids.[5–8] The generation of well defined structures in homo oligomers of β and γ amino acids and in hybrid α, β, γ sequences is facilitated by the use of residues in which rotation about individual bonds are restricted. The use of the β

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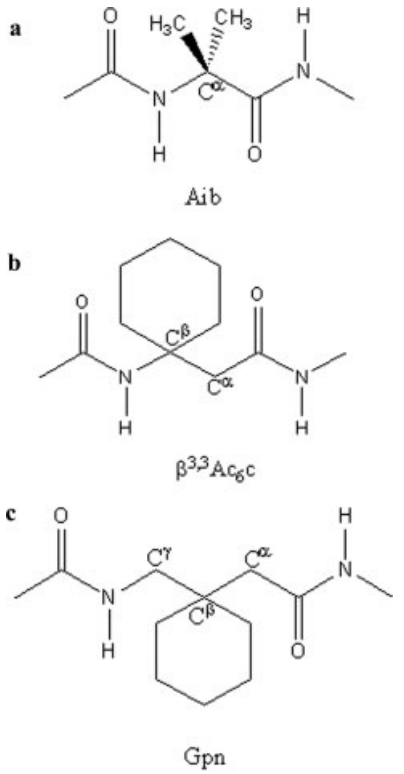

FIGURE 1 Geminally disubstituted α, β, and γ amino acid residues. (a) α-aminoisobutyric acid (Aib), (b) 1-aminocylohexaneacetic acid ($\beta^{3,3}$Ac$_6$c), and (c) 1-aminomethylcyclohexaneacetic acid (gabapentin, Gpn).

residues, 2-aminocyclopentanecarboxylic acid (ACPC) and 2-aminocyclohexanecarboxylic acid (ACHC) permitted the unambiguous crystallographic characterization of the novel 12 and 14 helical structures in oligomeric β peptides.[9–11] Backbone substitution yields useful residues in which accessible conformational space is restricted. Synthetic routes to multiply substituted chiral β and γ amino acids have been developed.[12] For purposes of exploring conformational space it is advantageous to employ readily available achiral, substituted β and γ residues. The use of symmetrical, geminal disubstitution is a device that has proved extremely successful in the generation of well defined, folded peptides in α amino acid sequences. Indeed, the achiral $C^{\alpha,\alpha}$-disubstituted amino acid residue, α-aminoisobutyric acid (Aib, Figure 1) is probably one of the best characterized residues in peptide crystal structures.[13–19] In extending this approach to hybrid peptides, we have examined the achiral β residue, 1-aminocyclohexaneacetic acid ($\beta^{3,3}$Ac$_6$c, Figure 1)[20] and the γ residue, 1-aminomethylcyclohexaneacetic acid (gabapentin, Gpn, Figure 1).[21,22] Gabapentin (trade name Neurontin®) is a very widely used antiepileptic and pain-relieving drug, which is readily available in bulk quantities. The synthesis and crystallographic characterization of a large number of model peptides containing the Gpn residue has permitted the identification of novel hydrogen bonded conformations and new types of helical hydrogen bonding patterns in regular hybrid αγ sequences.[22–25] The availability of experimentally established values for the backbone torsion angles in Gpn provides an opportunity to develop theoretical conformational analysis of conformational possibilities and compare the results of the computational approach to that obtained experimentally. The results of such an analysis are discussed.

RESULTS AND DISCUSSION

Review of Experimental Results

Figure 2a defines the degrees of backbone torsional freedom in α and γ residues. The homologation of the backbone results in two additional degrees of torsional freedom about the C^{γ}—C^{β} (θ_1) and the C^{β}—C^{α} (θ_2) bonds. The conven-

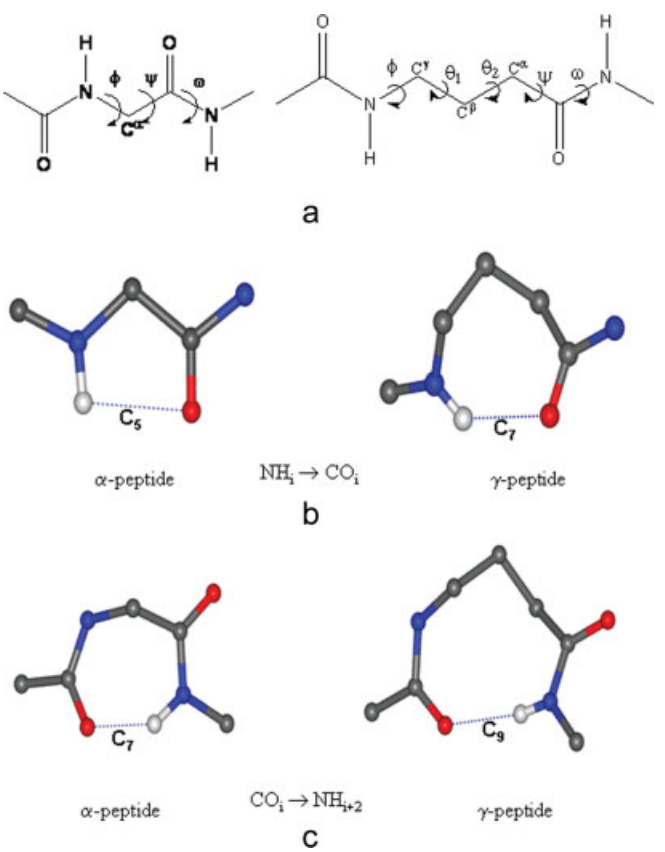

FIGURE 2 (a) Definition of backbone torsion angles for an α amino acid residue (left) and a γ amino acid residue (right). (b) Single residue hydrogen bonded turns formed between the NH and CO groups of the same residue, in α peptides (left) and γ-peptides (right). (c) $CO_i \cdots HN_{i+2}$ hydrogen bonded turns in α peptides (left) and γ peptides (right).

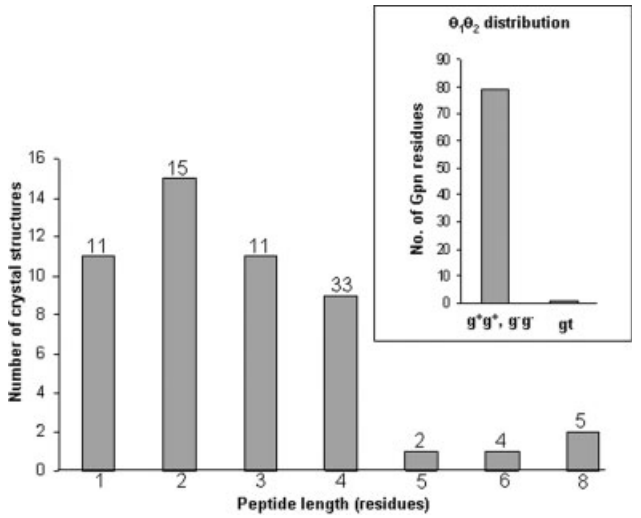

FIGURE 3 Histogram showing the distribution of peptide length in crystallographically characterized Gpn containing sequences. The numbers shown above the bars indicate the number of Gpn residues in each case. The inset shows the distribution of θ_1 and θ_2 values in the 81 characterized Gpn residues. Number of crystal structures = 35. For achiral peptides crystallizing in centrosymmetric space groups both combinations of signs for θ_1 and θ_2 have been considered. The total number of independent residues is 59, in which 22 are determined in centrosymmetric crystal structures.

tional Ramachandran analysis of α amino acid residue conformations requires consideration of only two torsional variables, ϕ and ψ, while a similar analysis for a γ residue would involve four torsional variables ϕ, θ_1, θ_2, and ψ. The dihedral angle nomenclature θ_1, θ_2,...,θ_n suggested for ω-amino acids[26] allows the torsional variables to be sequentially numbered from the N-terminus end of a peptide chain. The use of a single Greek letter and an Arabic numeral as a subscript is preferred to the use of multiple Greek letters, especially for authors and readers who are not familiar with classical languages. Comparison of the structures of Aib and Gpn suggests that symmetrical substitution at C^{β} in the latter should impose a significant limitation on the range of sterically accessible values for θ_1 and θ_2 in a manner analogous to the ϕ, ψ restriction established for Aib. Crystallographic studies on short Gpn containing peptides have established the occurrence of the C_7 and C_9 hydrogen bonded conformations illustrated in Figures 2b and 2c.[7] These two internally hydrogen bonded structures are conformational features determined only by the torsion angles at a single residue. As seen in Figures 2b and 2c, the C_7 and C_9 conformations for a γ-residue may be considered as backbone expanded analogs of the C_5 and C_7 (γ-turn) structures characterized for α-residues. The C_5 (α) and C_7 (γ) structures involve a hydrogen bond between NH of the i^{th} residue and the CO of the same residue. In contrast, the C_7 (α) and C_9 (γ) structures involve the $CO_i \cdots NH_{i+2}$ hydrogen bond. The C_5 hydrogen bond in α peptides has been largely involved in sequences which adopt fully extended conformations as exemplified in homo oligomers of the $C^{\alpha,\alpha}$-dialkyalted residues, $C^{\alpha,\alpha}$-diethylglycine (Deg), and $C^{\alpha,\alpha}$-dipropylglycine (Dpg).[27–30]

Figure 3 summarizes the presently available structures of Gpn containing peptides and provides the observed distribution of the experimentally determined θ_1 and θ_2 values. It is immediately evident that the *gauche*, *gauche* conformation in which both θ_1 and θ_2 adopt the same sign for the two torsion angles is overwhelmingly favored with 80 out of 81 residues falling in this category. The sole exception is the *gauche*, *trans* conformation observed for the Gpn residue in an octapeptide β-hairpin Boc-Leu-Phe-Val-Aib-Gpn-Leu-Phe-Val-OMe, (unpublished results) in which the Aib-Gpn segment adopts a C_{12} conformation (Figure 4c) that permits chain reversal together with registered hydrogen bonds between the antiparallel β-strands. In addition to the increased number of backbone torsional variables, Gpn residue poses an additional conformational problem. Since Gpn is a 1,1-disubstituted cyclohexane, two distinct conformational states are possible, in which the aminomethyl and carboxymethyl groups interchange between axial and equatorial orienta-

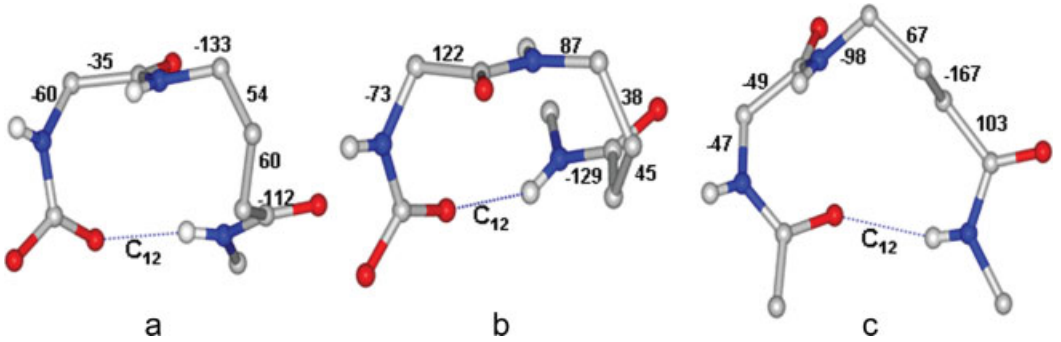

FIGURE 4 Three types of $\alpha\gamma$ hybrid turns. The backbone torsion angles (deg) are indicated.

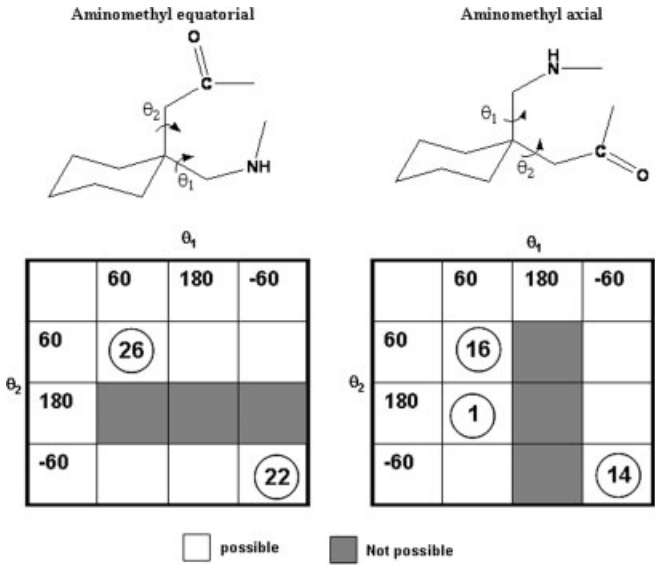

FIGURE 5 Nine possible combinations of the torsion angles θ_1 and θ_2 for the two conformational isomers of the Gpn residue. Sterically disallowed combinations for the Gpn residue are shaded dark. The number of examples that are crystallographically characterized are shown in circles in the respective cells. In the case of achiral structures both the combinations, (+60°, +60°) and (−60°, −60°) are indicated (21 achiral structures in aminomethyl equatorial and 11 in aminomethyl axial).

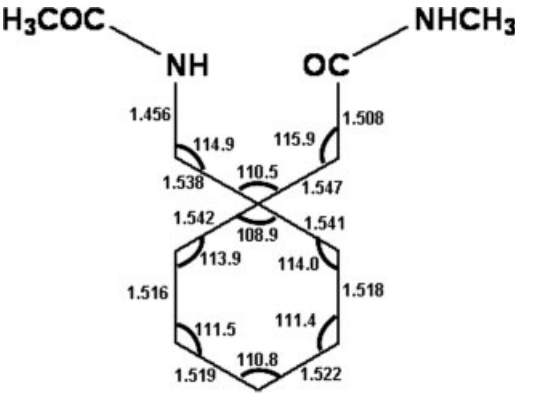

FIGURE 6 Average geometry of the Gpn residue, used in the computational studies.

tions. The availability of several crystal structures has permitted an examination of the distribution of these two conformations of the cyclohexane ring and the relationship, if any, to the backbone torsion angles θ_1 and θ_2. Figure 5 summarizes the experimentally observed conformations of the cyclohexane ring for the various values of θ_1 and θ_2. Inspection of models reveals that for substituents in an axial orientation, the fully extended values of the torsion angles θ_1 or θ_2 ($\approx 180^\circ$) is sterically disallowed because of the unfavorable 1,3-diaxial interactions present in the chair conformation. Thus, when the carboxymethyl substituent is axial, the *trans* conformation for θ_2 is sterically disallowed, whereas when the aminomethyl group is axial, the *trans* value for θ_1 is not permissible. From Figure 5 it is clear that almost all observed conformations cluster in regions with $\theta_1 \approx \theta_2 \approx \pm 60^\circ$. There are no examples as yet in peptides where the Gpn residue exhibits a *gauche*, *gauche* (g^+g^-) conformation where the signs of θ_1 and θ_2 are opposite. The only examples reported

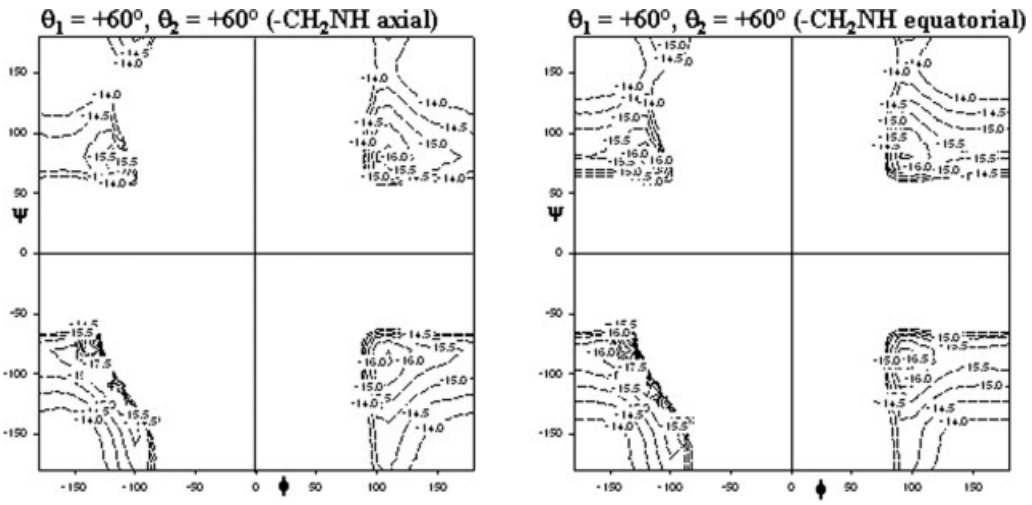

FIGURE 7 Energy contour maps for Ac-Gpn-NHMe, with an axial orientation of the aminomethyl group (left) and with an equatorial orientation of the aminomethyl group (right) on the cyclohexane ring.

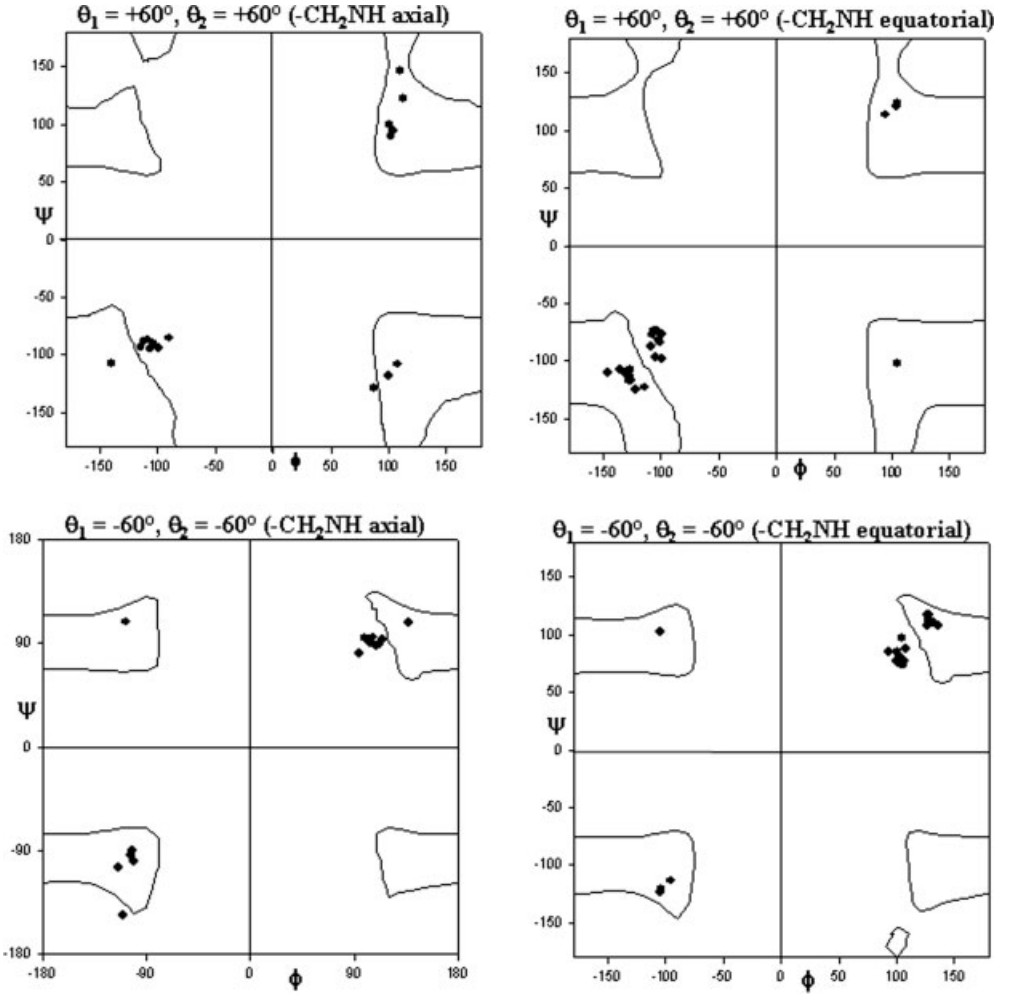

FIGURE 8 Experimentally observed ϕ, ψ values of the Gpn residue plotted onto the theoretically calculated map, for the conformation in which the aminomethyl group is in axial orientation (left) and in which the aminomethyl group is in equatorial orientation (right). Plots are shown for the residue conformations with the torsion angles θ_1 and θ_2 adopting g^+g^+ and g^-g^-.

of the g^+g^- conformation for Gpn are in the amino acid derivatives gabapentin hydrochloride,[21] *E*-4-*tert*-butylgabapentin, *E*-4-*tert*-butylgabapentin hydrochloride, and *E*-4-*tert*-butylgabapentin hydrobromide.[31] A notable feature of Figure 5 is that the observed distribution of g^+g^+/g^-g^- Gpn residue conformation does not appear to be strongly correlated to the orientation of the aminomethyl or the carboxymethyl groups with respect to the cyclohexane ring.

Theoretical Conformational Maps for the Gpn Residue

To probe the conformational space accessible to Gpn residue, Ramachandran steric and energy maps were generated for *N*-acetyl-Gpn-*N′*-methylamide (Ac-Gpn-NHMe). The residue geometry used is summarized in Figure 6. This was obtained by averaging the experimentally determined parameters for 59 crystallographically-independent Gpn residues. The ϕ–ψ maps were generated for fixed values of the torsional variables θ_1 and θ_2. Computations were carried out for both the aminomethyl axial and aminomethyl equatorial orientations with respect to the cyclohexane ring. Figure 7 shows representative conformational energy maps generated for *gauche*+, *gauche*+ (g^+g^+) values for θ_1 and θ_2 for the cases in which the aminomethyl group adopts axial and equatorial orientations. These maps representing the energetically-favorable regions of ϕ–ψ space were obtained primarily by nonbonded energy values (hydrogen bond contributions not being taken into account at this stage). Minima are observed in all four quadrants. It is evident that the energetically-favorable regions of ϕ–ψ space are limited. Figure 8 provides a distribution of the observed experimental values for ϕ and ψ at the Gpn residue,

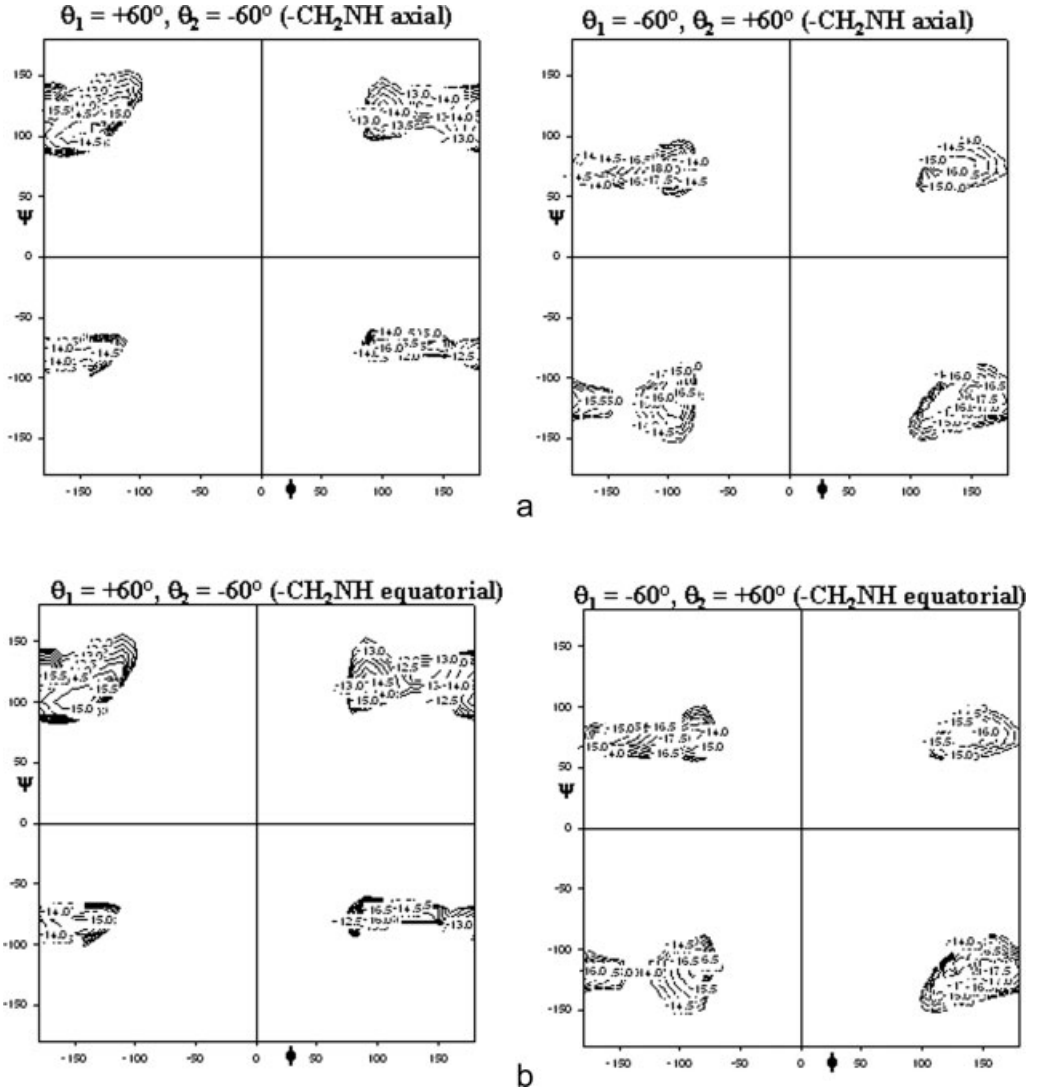

FIGURE 9 Energy contour maps for the torsion angle combination $\theta_1 = +60^\circ$, $\theta_2 = -60^\circ$, and $\theta_1 = -60^\circ$, $\theta_2 = +60^\circ$, for the two chair conformations of Gpn residue. (a) aminomethyl group axial, (b) aminomethyl group equatorial.

for both the g^+g^+ and g^-g^- combinations and for the equatorial and axial orientations of the aminomethyl group. For simplicity, only the contours corresponding to the energy -14 kcal mol^{-1} are shown. The experimental observations cluster in the vicinity of the minimum energy regions. The observation that the clusters appear to be positioned just outside the favorable regions may be attributed to the fact that the computations have been carried out for a fixed geometry of the Gpn residue. Slight distortions of bond angles can compensate for unfavorable steric overlap.

Figure 9 shows the conformational energy maps obtained for the cases where θ_1 and θ_2 are both *gauche* but adopt opposite signs of the torsion angles. Maps have been computed for both axial and equatorial orientations of the aminomethyl group. There is a significant reduction in the extent of energetically-favorable ϕ–ψ space for the g^+g^+/g^-g^- combinations. As noted in the preceding section, under review of experimental results, the only examples of crystallographically characterized g^+g^-/g^-g^+ combinations are in the case of amino acid derivatives.[21,31]

For the Gpn residue, fully extended conformations about the $C^\gamma—C^\beta$ (θ_1) and $C^\beta—C^\alpha$ (θ_2) bonds are disfavored because of the steric overlap between the backbone atoms and the methylene groups of the cyclohexane ring (Figure 10a). For the axial substituents, the θ value of 180° is sterically disallowed because of unfavorable 1,3-diaxial interactions (Figure 10b). Computations of conformational energies in ϕ–ψ space were therefore carried out for the combinations

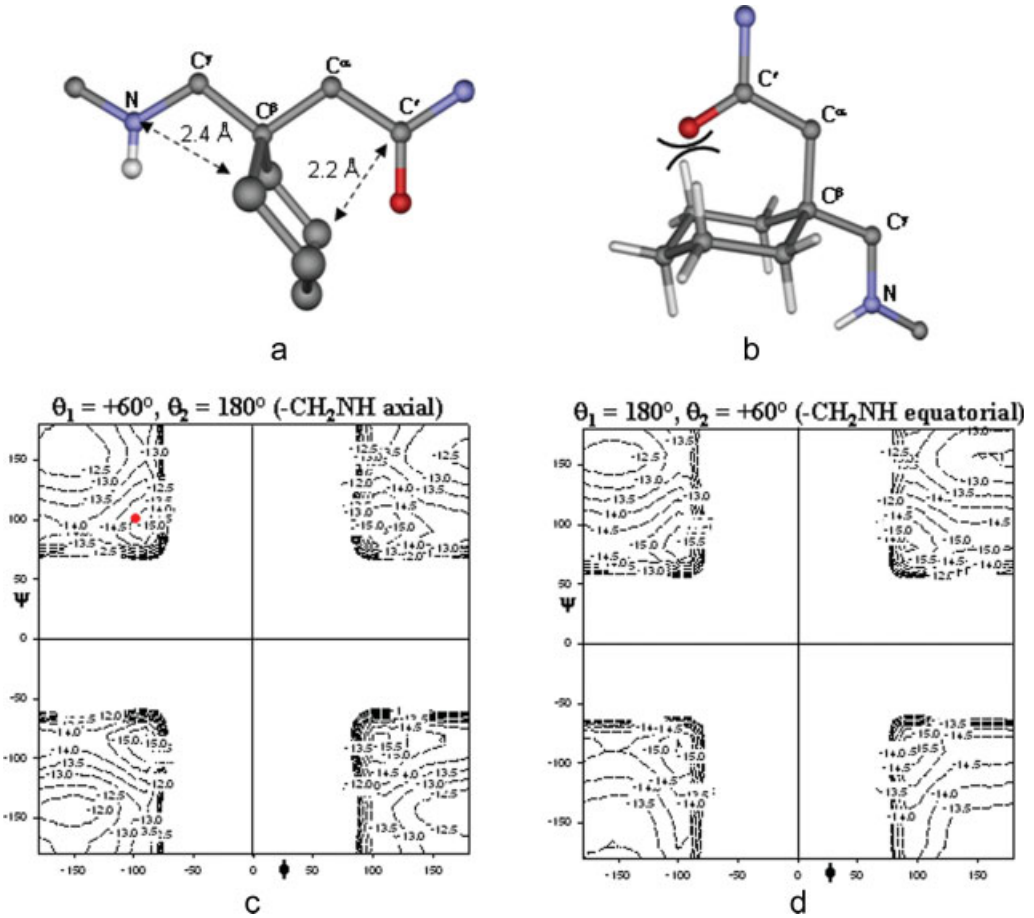

FIGURE 10 (a) Steric clash in the fully extended conformation of Gpn residue. The distances indicated are between the hydrogen atoms of the cyclohexane ring and the backbone atoms, and are independent of the values of ϕ and ψ. (b) The 1,3-diaxial interaction in the fully extended conformation of Gpn residue. (c) Energy contour map for the Gpn conformation with $\theta_1 = 60^\circ$, $\theta_2 = 180^\circ$ (aminomethyl group axial) and (d) Energy contour map for the conformation with $\theta_1 = 180^\circ$, $\theta_2 = 60^\circ$ (aminomethyl group equatorial). The only experimental point determined in these cases is shown in the contour plot in figure (c).

g^+t and tg^+. The results are summarized in Figures 10c and 10d. Thus far, the only crystallographically-characterized example of a gt/tg conformation is the case of the Gpn residue in the octapeptide hairpin Boc-Leu-Phe-Val-Aib-Gpn-Leu-Phe-Val-OMe (Figure 4c; unpublished results).

Hydrogen Bonded Conformations

Thus far the exploration of conformational space for the Gpn residue was based only on the consideration of non-bonded interactions. Internal hydrogen bonds in peptides can, of course, provide additional stability for specific residue conformations. Computations were therefore carried out to identify sterically allowed regions of conformational space where C_7 or C_9 hydrogen bonds could be formed at the Gpn residue. The values of θ_1 and θ_2 varied at 1° intervals over a range of $\pm 10^\circ$ from the ideal values ($+60^\circ$, -60°, and 180°). Conformations with the best hydrogen bond energies are listed in Table I. Computations were carried out for both the aminomethyl axial and equatorial orientations. It should be noted that the orientations of substituents with respect to the cyclohexane ring does not directly affect the strength of the hydrogen bond, but determines whether a particular value of θ_1 or θ_2 is sterically allowed or energetically favorable. For C_7 hydrogen bonds, it is clear that out of the four listed possibilities, only two regions of the ϕ–ψ space correspond to distinct backbone conformations. These correspond to the g^+g^+ and the g^-g^- cases, the other two being the mirror image

Table 1 C_9 and C_7 Hydrogen Bonds at Different θ Values, Calculated for the Equatorial Orientation of Aminomethyl Group

θ_1, θ_2	Torsion Angles (°), C_9 Hydrogen Bonds	E (kcal mol^{-1}) (Hydrogen Bond)	Torsion Angles (°), C_7 Hydrogen Bonds	E (kcal mol^{-1}) (Hydrogen Bond)
g^+, g^+	$\phi = -120, \psi = -70$ $\theta_1 = 69, \theta_2 = 68$	−4.446	$\phi = 100, \psi = 90$ $\theta_1 = 50, \theta_2 = 50$	−2.762
g^-, g^-	$\phi = 120, \psi = 70$ $\theta_1 = -69, \theta_2 = -68$	−4.444	$\phi = -120, \psi = -80$ $\theta_1 = -50, \theta_2 = -50$	−2.60
g^-, g^+	$\phi = 120, \psi = -70$ $\theta_1 = -51, \theta_2 = 66$	−4.448	$\phi = -150, \psi = 70$ $\theta_1 = -70, \theta_2 = 70$	−4.273
g^+, g^-	$\phi = -120, \psi = 70$ $\theta_1 = 51, \theta_2 = -66$	−4.446	$\phi = 140, \psi = -60$ $\theta_1 = 69, \theta_2 = -69$	−4.279
t, g^-	$\phi = -80, \psi = 0$ $\theta_1 = 170, \theta_2 = -62$	−2.537	None	
t, g^+	$\phi = 80, \psi = 0$ $\theta_1 = -170, \theta_2 = 61$	−2.530	None	

conformations. Crystallographic studies have provided several examples of C_7 hydrogen bonds, with g^+g^+ or g^-g^- conformations of Gpn.[21,22] The only examples of a C_7 hydrogen bond in g^-g^+/g^+g^- is in the case of the amino acid derivatives Gpn hydrochloride, *tert*-butylgabapentin, *tert*-butylgabapentin hydrochloride, and *tert*-butylgabapentin hydrobromide.[21,31]

For the C_9 hydrogen bonded structure, three distinct conformations emerge corresponding to the g^+g^+/g^-g^-, g^+g^-/g^-g^+, and tg^+/tg^- cases. Of these the tg^+/tg^- conformations appear to have significantly poorer hydrogen bond energies. C_9 conformations have been extensively observed in Gpn peptides and all the 21 examples characterized thus far adopt the g^+g^+/g^-g^- conformations. The absence of the conformations g^-g^+ and g^+g^-, where the signs of θ_1 and θ_2 are opposite, may be a consequence of the significantly reduced sterically accessible regions of (ϕ,ψ) space.

In the present study, a simple conformational analysis using fixed internal geometries and classical potentials for nonbonded and hydrogen bonded interactions has been used. A reviewer of this manuscript, in an interesting comment, noted that "the theoretical methods employed are the good old methods of Ramachandran from the 60s of last century. In that time, these methods had some merits, but nowa-days better methods are accessible, which are much more reliable with respect to conformational data on torsion angles and, above all, energy differences." The original Ramachandran approach of using a hard sphere steric overlap criterion as a filter for disallowed conformations has indeed stood the test of time. Energy refinements are overwhelmingly dominated by contributions from the nonbonded interactions, with the other terms having a much smaller effect on the computed total energy. More sophisticated (modern) conformational calculations are not of great value for molecular design purposes. The present analysis is really intended to serve as a guide for eliminating large tracts of conformational space which are energetically inaccessible. Within the "allowed regions" only small energy differences ($\leq$3 kcal mol^{-1}) separate different conformational states. Such differences can be readily overcome by solvation in solution and by intermolecular interactions in the solid state. Conformational energy calculations can be valuable in peptide design, by identifying specific regions of structure space within which intramolecular hydrogen bonds can be formed between backbone amide groups. In the area of peptide and protein folding, simple steric overlap criterion and estimate of nonbonded energies are sufficient to delineate inaccessible regions of conformational space. The "molecular designer" can then explore the possibilities of intramolecular hydrogen bonds within the framework of sterically allowed regions. Figure 9 in Ref. 25 provides a summary of experimentally observed hydrogen bonded conformations for the Gpn residue in *gauche–gauche* conformations.

Experimental and theoretical studies establish that the γ amino acid residue gabapentin (Gpn) is limited with respect to the range of accessible conformations despite the addition of two torsional variables. For the Gpn residue, *gauche, gauche* conformations (g^+g^+/g^-g^-) are predominantly observed. *Trans* conformations for θ_1 and θ_2 and structures in which θ_1 and θ_2 are *gauche* but adopt opposite signs (g^+g^-/g^-g^+) are exceedingly rare. C_7 and C_9 hydrogen bonded structures can be formed, which are determined only by the conformational parameters ϕ, θ_1, θ_2, ψ at the Gpn residue. While these conformations may be considered as expanded versions of the C_5 and C_7 structures in α residues, the C_7 conformation provides a bending of the backbone,

whereas the C_5 conformation corresponds to a fully extended situation. The limitations imposed by the cyclohexyl substituents at the central C^{β} atom clearly restrict the range of conformational possibilities. When Gpn is placed adjacent to α residues C_{12} hydrogen bonded structures can be formed in $\alpha\gamma/\gamma\alpha$ segments, which may be considered as backbone expanded analogs of conventional two-residue turns in $\alpha\alpha$ segments.[32] The present study describes the nature of sterically and energetically allowed Gpn backbone conformations. Together with the growing body of information on the conformational properties of α and β residues, these studies make it possible to design hybrid peptides containing amino acids with a variable number of backbone atoms.

METHODS

Database Analysis

An analysis of the Cambridge Structural Database (CSD, Version) provided crystal structures of 6 derivatives and 27 peptides containing the Gpn residue. A total of 59 Gpn residues were extracted from 35 crystal structures (33 compounds), out of which 20 belong to centrosymmetric space groups and 15 belong to noncentrosymmetric space groups. For achiral peptides crystallizing in centrosymmetric space groups, both signs of torsion angles for the Gpn residue were considered, which results in 81 examples of the residue conformations.

Energy Calculations

The calculations were performed on model compound Ac-Gpn-NHMe, using the contact criteria originally employed for the formulation of the Ramachandran map,[33,34] to identify allowed conformations. Allowed conformations in the two-dimensional ϕ–ψ space were generated for nine combinations of θ_1 and θ_2, which are (+60°, +60°), (+60°, −60°), (−60°, −60°), (−60°, +60°), (+60°, 180°), (−60°, 180°), (180°, +60°), (180°, −60°), and (180°, 180°), by systematically varying the backbone torsion angles. The calculations were performed for both the conformational isomers of the Gpn residue, which differ in the relative orientation of the aminomethyl and carboxymethyl substituents on the cyclohexane ring, which allowed ϕ–ψ space for six combinations of θ_1 and θ_2 in each case. The internal parameters for the Gpn residue used for the computations are shown in Figure 6, which were obtained by averaging the crystallographically determined values. The energy computations were carried out in a similar way for the nine combinations of θ_1 and θ_2 for both the axial and equatorial orientations of the aminomethyl group, by varying ϕ and ψ from −180° to +180° at 10° interval. Calculations were carried out also for the C_7 and C_9 hydrogen bonded conformations of the Gpn residue. For this, in addition to ϕ and ψ, the values of θ_1 and θ_2 were also varied at 1° intervals over a range of ±10° from the ideal values. The criteria used for identifying the hydrogen bond interactions are, N···O distance between 2.6 and 3.3 Å and angle H—N···O < 40°. Both the hydrogen bond and nonbonded energy values were computed using the functions and values of the parameters given by Ramachandran and Sasisekharan,[33] with the 6-exp form of function being used for the latter.

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