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Isosteres of peptides: boron analogs as dipolar forms of α-amino acids – a theoretical study

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ABSTRACT: Modification of peptides to produce peptidomimetics is of great interest, with the aim of designing potent, selective, and metabolically stable analogs having certain conformational properties. Organoboranes have been reported in the literature with a wide range of therapeutic applications. One of the therapeutically important class of molecules is amine-carboxyboranes derived from amino acids by replacement of the Cα atom of an amino acid/peptide by boron. The conformational preferences of these peptides, with respect to backbone ω, φ, and ψ torsion angles, have been investigated by theoretical calculations. The amide bond in these molecules has the same geometry in the ground and transition states as the natural peptides. However, the boron isosteres of glycine and alanine peptides are less structured than their natural derivatives, but are distinguished by structures with a positive value for the φ angle, which is normally disfavored for natural peptides. This property could be used to build peptides with a geometry not usually seen in natural peptides. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: boron isostere of Cα atom of peptides; *ab initio* calculations; PES and peptide conformations

INTRODUCTION

Boron has been used extensively in amino acids and peptides as an isosteric replacement to modify their conformational properties and to improve their stability. These organoboranes have a wide range of therapeutic applications.[1] The replacement of the carbonyl group in peptides by B—OH leads to 'peptide boronic acids' (**1**, Scheme 1) and 'peptide boronamides' (**2**, Scheme 1). These molecules are among the most potent serine protease inhibitors with therapeutic applications in various diseases via inhibition of thrombin, proteasome, dipeptidyl peptidase IV, chymotrypsin, leucocyte elastase, pancreatic elastase, Hepatitis C virus NS3 protease, and penicillin-binding protein.[2–6] These molecules have been studied by both X-ray crystallography and NMR.[7,8]

We have reported in a series of papers the remarkable effects of the isosteric replacement of the C═O and N—H groups of peptides by boron, on the electronic properties, the geometry, and conformations of peptides.[9–13] The replacement of the N—H group by B—H causes a shift in the ω torsion from 180° in natural peptides to 90° in the boron isostere. It has been observed that modifying the B—H bond as B—OH and further as B—OCH_3 is able to induce a change in the conformation of the peptide backbone from a random coil-like state to a more ordered secondary structure. Further, these peptides also exhibit conformations in the 'disallowed regions' of the Ramachandran map. The isosteric replacement of the C═O group by B—OH retains the geometry and barrier of the 'ω angle' making it an important surrogate for the peptide bond with the distinct advantage of being stable to proteolytic enzymes.[9]

BH_2^- and BH^- are isoelectronic with CH_2 and CH, respectively, and this property has been exploited in the design of boron analogs of amino acids, for example $R_3N{\cdot}BH_2CO_2H$.[14] These molecules are termed as 'amine-carboxyboranes' or boron analogs of dipolar forms of α-amino acids. The molecule $[CH_2\underline{N}Me_2{\cdot}\underline{B}H_2\text{-}\underline{C}O\underline{N}HEt]_2$ has good anti-neoplastic activity[15] and can be viewed as a peptide with the Cα atom replaced by boron. *N*-[(Trimethylamine-boryl-carbonyl]-L-tryptophan methyl ester (**3**, Scheme 1) and *N*-[(Trimethylamine-boryl)-carbonyl]-L-histidine methyl ester (**4**, Scheme 1) are peptides derived by replacing the Cα atom by boron, and exhibit anti-tumor activity.[16] The boron atom, in these molecules, is tetravalent and the amine is generally primary, secondary, or tertiary. The amine-carboxyboranes derived from amino acids and peptides containing these moieties exhibit anti-cancer activity through various mechanisms that involves inhibition of various

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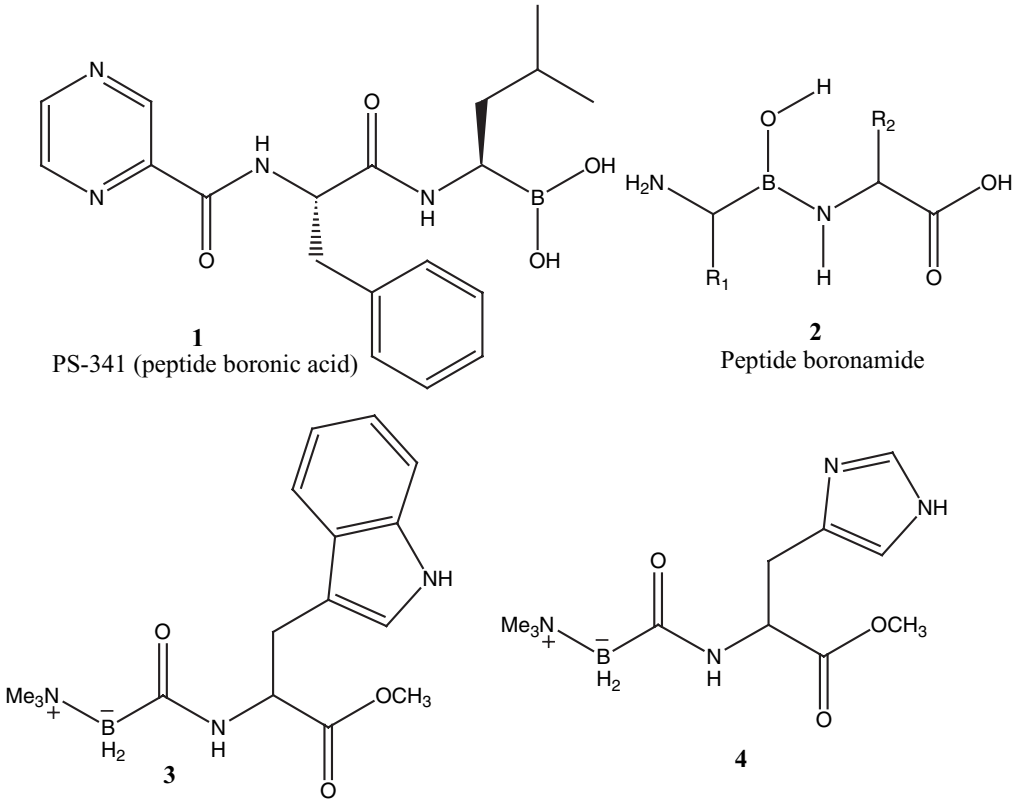
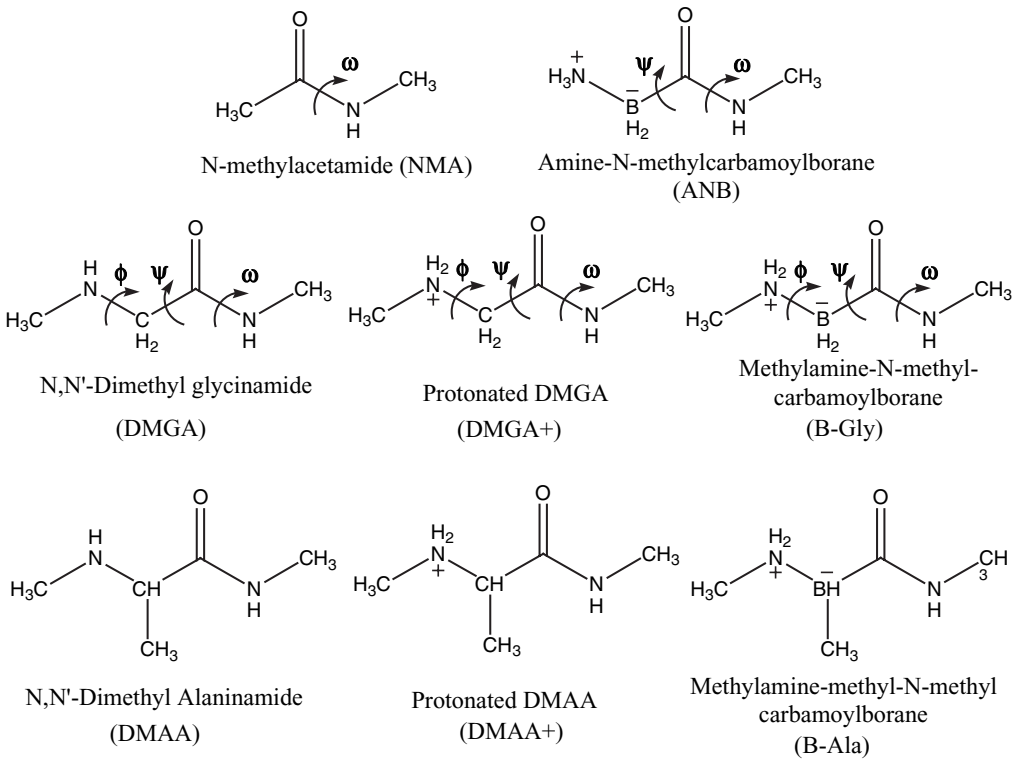


Scheme 1.



Scheme 2.

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enzymes like topoisomerase II phosphorylase, phosphoribosylpyrophosphate amidotransferase, inosine monophosphate dehydrogenase, and dihydrofolate reductase.[1] The simplest of the amine-borane complexes – $NH_3{\cdot}BH_3$ has been extensively investigated by both experimental and theoretical methods.[17–19] There are few reports on experimental and theoretical studies on 'amine-carboxy boranes' like $NH_3{\cdot}BH_2CO_2H$.[20] However, there are only limited literature reports of 'amine-carboxyboranes' that resemble peptides. The synthesis of these 'amine-carboxyboranes' is straight forward and has been reported in the literature.[14,15]

In this paper, we report the geometry, conformations, and electronic properties of peptides where the Cα atom is replaced by boron using *ab initio* and density functional methods. *N*-Methylacetamide (NMA, Scheme 2) is a well-established peptide model to study the backbone ω angle of peptides.[21] Amine-*N*-methylcarbamoylborane (ANB, Scheme 2) represents the minimum structure to study the ω angle in the amine-carboxyborane analog of NMA. Replacing the ammonium group by methylamine in ANB leads to methylamine-*N*-methyl-carbamoylborane (B-Gly) which is an isostere of DMGA [*N*,*N*′-Dimethyl glycinamide] or DMGA+ [protonated DMGA], the corresponding natural peptides (Scheme 2). The natural peptides DMGA and DMGA+ and their boron isostere B-Gly are achiral. The smallest peptide with chirality at the Cα centre is *N*,*N*′-Dimethyl alaninamide, in its neutral and protonated state DMAA and DMAA+, respectively (Scheme 2). The boron analog of these peptides is B-Ala (Scheme 2).

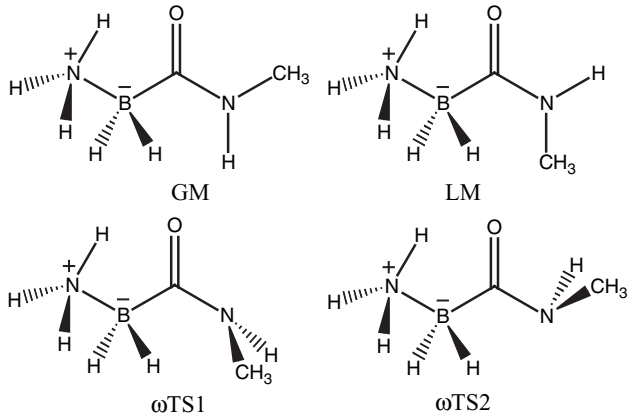

Figure 1. Minima and transition states for rotation of ω angle on PES of ANB

COMPUTATIONAL DETAILS

Ab initio molecular orbital[22] and density functional theory[23] calculations have been carried out using the Gaussian 03W (revision C.01)[24] package running on a 3.0 GHz Pentium IV processor with 1 GB RAM. The stability of all wavefunctions was checked at the HF,[25] Becke's three parameter exchange functional and the gradient corrected functional of Lee, Yang, and Paar (B3LYP).[26–28] Second-order Møller-Plesset MP2(full)[29,30] calculations were also carried out with the 6-31+G* basis set for all ground and TS structures.

The ω and ψ angles in ANB are defined by the sequences B—CO—N—C and N—B—CO—N, respectively. The ψ angle was fixed in an 'extended conformation' (180°) as observed in a crystal structure of a structurally related molecule $Me_3N{\cdot}BH_2CO_2H$ (angle N—B—CO—O).[31] With ψ of 180°, a scan in increments of 30° of the ω torsion angle was carried out at the HF/6-31+G* level of theory. Conformations with an ω value of 0° and 180° were found to be the lowest in energy. Now, for each conformation with ω value of 0° and 180°, respectively, a ψ scan in increments of 30° was run at the HF/6-31+G* level of theory. The minima and saddle points for rotations about the ω torsion were thus identified. All these conformations were further optimized at the B3LYP and MP2 levels of theory with the same basis set, and the conformations confirmed by frequency calculations, which returned one imaginary frequency for each transition state and all positive frequencies for each ground state.

Table 1. Energies (a.u.) and relative energies (kcal mol^{-1}) of various minima and transition states on the PES of ANB at the HF, B3LYP, and MP2 levels of theory with the 6-31+G* basis set

			HF/6-31+G*		B3LYP/6-31+G*		MP2(full)/6-31+G*		
	NIMAG	PG	a.u.[a]	rel.[b]	a.u.[a]	rel.[b]	a.u.[a]	rel.[b]	ω[c]
GM	0	C_1	−289.3250963	0.0	−291.1376045	0.0	−290.2187843	0.0	177°
LM	0	C_1	−289.3214552	2.3	−291.1357007	1.2	−290.2098186	5.6	−8°
ωTS1	1	C_1	−289.2872459	21.5	−291.1016941	22.5	−290.1834600	22.2	56°/−56°
ωTS2	1	C_1	−289.2910572	19.1	−291.1041077	21.0	−290.1863951	20.3	124°/−124°

NIMAG = number of imaginary frequency, PG = point group, GM = global minimum, LM = local minimum.
[a] Zero-point vibrational energy corrected values.
[b] Relative energy in kcal mol^{-1}.
[c] Torsion angle in degrees.

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The NBO[32–34] analysis was carried out on the global minimum (GM) energy structure of ANB, optimized at the MP2(full)/6-31+G* level using MP2 density, to quantitatively estimate the second-order interactions as $E_{ij} = -2F_{ij}/\Delta E_{ij}$, where E_{ij} is the energy of the second-order interaction; $\Delta E_{ij} = E_i - E_j$ is the energy difference between the interacting molecular orbitals i and j; and F_{ij} is the Fock matrix element for the interaction between orbitals i and j. The atomic partial charges of the global minima of ANB and NMA, optimized at the MP2(full)/6-31+G* level using MP2 density, were calculated by the 'ESP fit' method of Merz–Singh–Kollman.[35]

For each of the molecules – DMGA, DMGA+, B-Gly, DMAA, DMAA+, and B-Ala, starting with an ω value of 180°, the minima in the ϕ and ψ space was searched by incrementing the ϕ, ψ angles in 30° steps, to generate a total of 144 conformations. Each conformation was geometry optimized first at the HF/3-21G level of theory with 'constraints' on the initial ϕ, ψ angles. A Ramachandran map of the 144 conformations was constructed and conformations within 5.0 kcal mol^{-1} of the GM were identified. These low energy conformations were further optimized without constraints at the B3LYP/6-31+G* level of theory.

Table 2. Bond length (Å) and bond angles (degrees) of minima and TS of ANB optimized at the MP2(full)/6-31+G* level of theory

Parameter	GM	LM	ωTS1	ωTS2
NB	1.625	1.625	1.629	1.639
BC	1.621	1.623	1.616	1.601
CO	1.264	1.264	1.240	1.244
CN	1.353	1.355	1.450	1.451
NC	1.453	1.452	1.475	1.474
BH	1.210	1.211	1.211	1.208
NBC	100.8	100.8	102.6	102.9
BCO	121.1	120.4	121.3	123.2
OCN	119.3	119.1	117.8	120.3
CNC	122.4	124.3	111.8	111.1
BCNC (ω)	177.0	−8.0	56.0/−56.0	124.0/−124.0
NBCN (ψ)	172.1	−178.8	171.7	−179.1

Table 3. The bond lengths (Å) of GM of ANB at MP2(full)/6-31+G* level of theory and of $Me_3N{\cdot}BH_2CO_2H$ and $Me_3N{\cdot}BBr_2CO_2Et$

Parameter	GM of ANB	$Me_3N{\cdot}BH_2CO_2H$	$Me_3N{\cdot}BBr_2CO_2Et$
NB	1.625	1.589	1.605
BC(O)	1.621	1.593	1.626
CO	1.264	1.229	1.222

RESULTS AND DISCUSSION

The conformations of the minima and various transition states for ANB are shown in Fig. 1 and the absolute and relative energies at the HF, B3LYP, and MP2(full) levels of theory with the 6-31+G* basis set are given in Table 1.

Minima and TS of ANB

The structures of the minima and transition states for rotation about the ω angle are shown in Fig. 1 and the absolute and relative energies at the HF, B3LYP, and MP2(full) levels of theory with the 6-31+G* basis set are given in Table 1. There are two minima on the PES of ANB. The major difference between the two minima is in the value of ω, which is 177° in the GM and −8° in the local minimum (LM) structure. In both minima, ψ has a preferred value of 180°. Both minima exhibit an intra-molecular hydrogen bond between the carbonyl *O* (as the acceptor) and the amine *NH* (as the donor). The corresponding minima in the ω space of NMA is 180° (GM) and 0° (LM).[21] Thus, both ANB and NMA have the same preference for a *trans* arrangement around the ω angle. Though the GM and LM of ANB are separated by 5.6 kcal mol^{-1}, the interconversion between them is governed by the transition states for ω rotation (ωTS1 and ωTS2). The two transition states for rotation around the ω angle are differentiated by the arrangement of the lone pair of electrons on the amide nitrogen. In ωTS1, the lone pair of electrons on nitrogen is

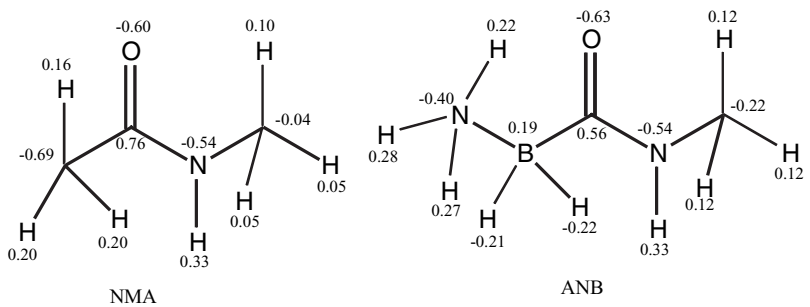

Figure 2. ESP-fitted partial atomic charges calculated using the Merz–Singh–Kollman scheme, of NMA and ANB optimized at MP2(full)/6-31+G* level of theory

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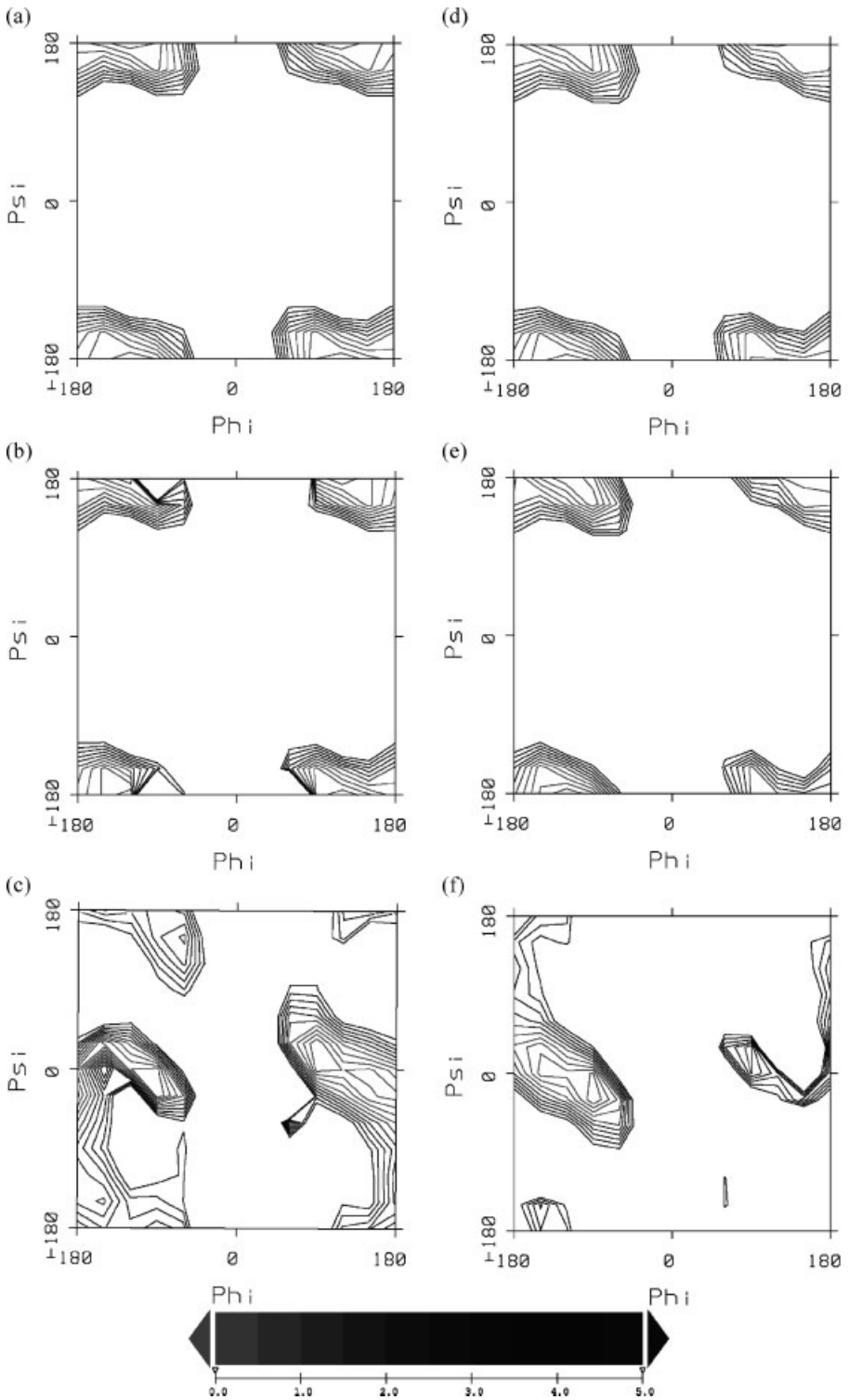

Figure 3. Ramachandran map for (a) B-Gly, (b) DMGA+, (c) DMGA, (d) B-Ala, (e) DMAA+, and (f) DMAA. The energy values associated with the contours are color coded according the scale given at the bottom

syn-periplanar to the carbonyl group while in ωTS2 it is *anti*-periplanar. The transition states for rotation around the ω angle of ANB resemble those of NMA.[21]

The geometric parameters of the minima and all transition states of ANB at the MP2(full)/6-31+G* level of theory are given in Table 2. There is a increase of about 0.1 Å in the C—N bond length in the transition states for rotation about the ω angle compared to the ground states. The crystal structures of two related molecules, $Me_3N{\cdot}BH_2CO_2H$[31] and $Me_3N{\cdot}BBr_2CO_2Et$[36] have been reported, and Table 3 compares the bond lengths in these two crystal structures with the GM of ANB

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optimized at the MP2(full)/6-31+G* level of theory. The NB and BC(O) bond lengths in ANB are in good agreement with those in the crystal structures. The CO bond in ANB is slightly longer in length than that in the crystal structures. A hydrogen bond between the carbonyl *O* and *NH* group of amine is present in ANB, but no hydrogen bond is seen in both crystal structures, this hydrogen bonding might be responsible for the small stretching of the CO bond in ANB. The BH bond length in ANB is 1.21 Å, which is close to that in $PhPH_2{\cdot}BH_3$ (1.212 Å)[37] and in the borane-pyrrole dimer (1.140 Å).[38]

Rotation barrier in ANB

The barrier to rotation about the ω angle in natural peptides ranges from 16.0 to 25.0 kcal mol^{-1}. The ω rotation barrier in ANB at the MP2(full)/6-31+G* level of theory is found to be between 20.3 and 22.2 kcal mol^{-1}, which is comparable to that in natural peptides. The rotation barrier in amide systems (e.g., NMA, urea, and guanidines) has been attributed to second-order orbital interactions namely, $n_o \rightarrow \sigma^*_{C-N}$ (delocalization from lone pairs on oxygen into the sigma anti-bonding orbital of the C—N bond, i.e., negative hyperconjugation) and $n_N \rightarrow \pi^*_{C-O}$ (delocalization from the lone pair on nitrogen to the *pi* anti-bonding orbital of carbonyl) leading to electron delocalization over the amide bond.[39,40] The energy $E^{(2)}$ associated with negative hyperconjugation, that is, $n_o \rightarrow \sigma^*_{C-N}$ is 26.7 kcal mol^{-1} (occupancy of n_O is 1.911 and σ^*_{C-N} is 0.046) and that with $n_N \rightarrow \pi^*_{C-O}$ is 104.4 kcal mol^{-1} (occupancy of n_N is 1.759 and π^*_{C-O} is 0.238) for the GM of ANB at the MP2(full)/6-31+G* level of theory. The energy associated with negative hyperconjugation, that is, $n_o \rightarrow \sigma^*_{C-N}$ is 32.8 kcal mol^{-1} and that with $n_N \rightarrow \pi^*_{C-O}$ is 98.5 kcal mol^{-1} for the global energy minimum structure of NMA. The NBO results show that the amide bond has the same geometry and energetics in NMA and ANB.

Partial atomic charges of ANB

The partial atomic charges calculated by fitting the electrostatic potential of ANB and NMA optimized at MP2(full)/6-31+G* level of theory using the Merz–Singh–Kollman scheme is shown in Fig. 2. It can be seen that substitution of the CH_3 group in NMA by $NH_3{\cdot}BH_2$ in ANB causes a slight decrease in the positive charge on the carbonyl carbon, while the atomic charges of the other atoms of the amide group remain unaffected. Thus, the carbonyl carbon remains the preferred site of attack by a nucleophile in ANB.

PES of glycine derivatives B-Gly, DMGA+, and DMGA

The Ramachandran (ϕ, ψ) map for glycine derivatives are given in Fig. 3. The minima in the ϕ and ψ space for B-Gly, DMGA+, and DMGA are given in Table 4. For B-Gly, there are two minima which are mirror images of each other and with the same energy. The structures correspond to $\phi = 113^\circ$ and $\psi = -177^\circ$ (Fig. 4a) and $\phi = -113^\circ$ and $\psi = 177^\circ$ (Fig. 4b) and can be described by the regular secondary structure motif. A similar situation exists for DMGA+, which is isoelectronic with B-Gly. The two minima of DMGA+ correspond to structures with $\phi = 110^\circ$ and $\psi = -175^\circ$ (Fig. 4c) and $\phi = -110^\circ$ and $\psi = 175^\circ$ (Fig. 4d), which are also mirror images of each other. These four structures are characterized by extended values of the ψ angle and have an intra-molecular hydrogen bond between the carbonyl *O* (as acceptor) and the *NH* of the methylamine group (as donor). One minimum energy structure of both B-Gly and DMGA+ has a positive ϕ value which is not favored for natural peptides.

The neutral form – DMGA exhibits a variety of structures. There are three local minima besides the two global minima. The global minima correspond to structures with $\phi = 90^\circ$ and $\psi = 20^\circ$ (Fig. 4e) and $\phi = -90^\circ$ and $\psi = 20^\circ$ (Fig. 4f). These figures describe

Table 4. Torsion angles (degrees), relative energies (kcal mol^{-1}), and secondary structure features of minima of glycine peptides B-Gly, DMGA+, and DMGA

	ϕ	ψ	Rel. E (kcal mol^{-1})	Structural feature (ideal values of the torsion angles)
B-Gly	113°	−177°	0.0	Positive ϕ, extended ψ conformation
	−113°	177°	0.0	Extended ψ conformation
DMGA+	110°	−175°	0.0	Positive ϕ, extended ψ conformation
	−110°	175°	0.0	Extended ψ conformation
DMGA	90°	20°	0.0	Positive ϕ, 3rd residue of Type I′ beta turn (90°, 0°)
	−90°	20°	0.0	3rd residue of Type I beta turn (−90°, 0°)
	165°	−20°	0.2	Folded ψ
	−69°	150°	2.4	Poly-L-Pro-II helix (−79°, 150°)
	−160°	−140°	2.5	Extended conformation

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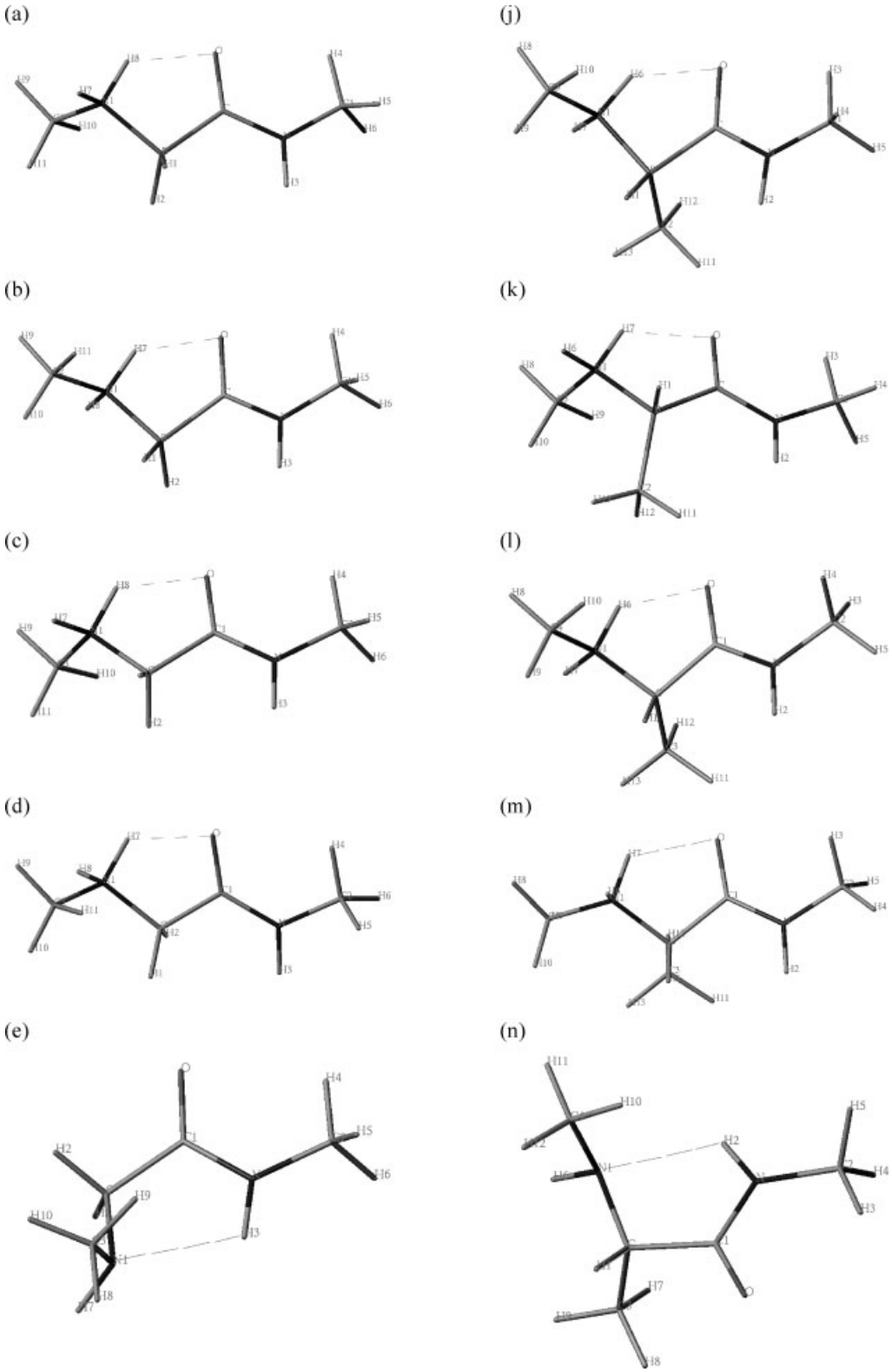

Figure 4. Preferred conformations of B-Gly: (a) $\phi = 113°$, $\psi = -177°$ and (b) $\phi = -113°$, $\psi = 117°$; DMGA+: (c) $\phi = 110°$, $\psi = -175°$ and (d) $\phi = -110°$, $\psi = 175°$; DMGA: (e) $\phi = 90°$, $\psi = 20°$, (f) $\phi = -90°$, $\psi = 20°$, (g) $\phi = 165°$, $\psi = -20°$, (h) $\phi = -69°$, $\psi = 150°$, and (i) $\phi = -160°$, $\psi = -140°$; B-Ala: (j) $\phi = -100°$, $\psi = 168°$ and (k) $\phi = 94°$, $\psi = -167$; DMAA+: (l) $\phi = -97°$, $\psi = 165°$ and (m) $\phi = 157°$, $\psi = 156°$; DMAA: (n) $\phi = -85°$, $\psi = -21°$, (o) $\phi = 180°$, $\psi = -25°$, (p) $\phi = 81°$, $\psi = 26°$, (q) $\phi = -65°$, $\psi = 135°$, and (r) $\phi = -151°$, $\psi = -152°$

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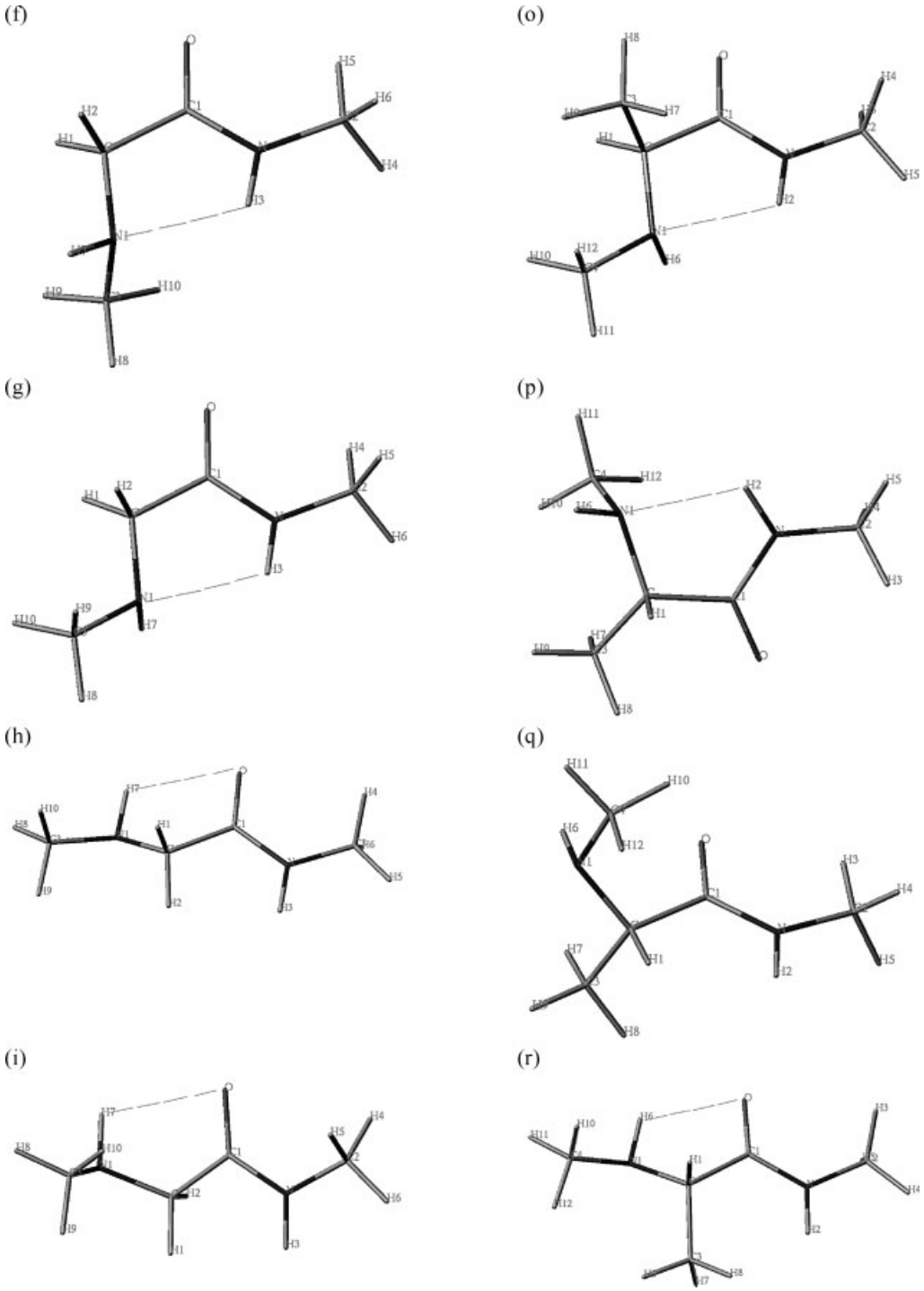

Figure 4. (*Continued*)

the third residue (i + 2) in a Type-I′ β-turn (ideal values: $\phi = 90^\circ$, $\psi = 0^\circ$) and Type-I β-turn (ideal values: $\phi = -90^\circ$, $\psi = 0^\circ$), respectively. The first LM has $\phi = 165^\circ$ and $\psi = -20^\circ$ (Fig. 4g) and is characterized by ϕ with a positive value and a folded ψ conformation. These three structures (the global minima and the first local minimum) are stabilized by an intra-molecular hydrogen bond between the amine *N* (as acceptor) and the *NH* of the amide (as donor). The second LM has $\phi = -69^\circ$ and $\psi = 150^\circ$ (Fig. 4h), which resemble a Poly-L-Pro-II helix (ideal values $\phi = -79^\circ$, $\psi = 150^\circ$). The third LM corresponds to a structure with $\phi = -160^\circ$ and $\psi = -140^\circ$ (Fig. 4i). The second and third local minima exhibit a hydrogen bond between the carbonyl *O* (as acceptor) and the amine *NH* (as donor).

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Table 5. Torsion angles (degrees), relative energies (kcal mol^{-1}) and secondary structure features of minima of alanine peptides B-Ala, DMAA+, and DMAA

	ϕ	ψ	Rel. E (kcal mol^{-1})	Structural feature (ideal values of the torsion angles)
B-Ala	−100°	168°	0.0	Extended ψ conformation
	94°	−167°	1.4	Positive ϕ, extended ψ conformation
DMAA+	−97°	165°	0.0	Extended ψ conformation
	157°	156°	2.0	Positive ϕ, extended ψ conformation
DMAA	−85°	−21°	0.0	3rd residue of Type I beta turn (−90°, 0°)
	180°	−25°	1.5	Folded ψ
	81°	26°	2.2	Positive ϕ, 3rd residue of Type I′ beta turn (90°, 0°)
	−65°	135°	2.3	Poly-L-Pro-II Helix (−79°, 150°)
	−151°	−152°	3.4	Extended conformation

PES of alanine derivatives B-Ala, DMAA+, and DMAA

The Ramachandran maps for alanine derivatives are given in Fig. 3. The conformations (global and local minima) of B-Ala, DMAA+, and DMAA are summed up in Table 5 and the structures are shown in Fig. 4j–r.

B-Ala and DMAA+, in analogy with B-Gly and DMGA+, display structures favoring positive ϕ values and extended values of the ψ angle. All the favored conformations of B-Ala and DMAA+ exhibit an intra-molecular hydrogen bond between the carbonyl *O* (as acceptor) and the *NH* of the methylamine group (as donor). DMAA, in analogy to DMGA, exhibits variety of secondary structures like Type I and I′ β-turn, poly-L-Pro-II helix, in addition to structures with positive ϕ value. The data in Tables 4 and 5 reveal that the conformations of B-Gly and B-Ala, DMGA+ and DMAA+, and DMGA and DMAA pairs are remarkably similar. Thus, the introduction of a chiral center at boron/carbon with a small group does not seem to change the conformational preferences of these peptides, which are stabilized by intra-molecular hydrogen bonds.

CONCLUSIONS

Isosteric replacement of the Cα atom in peptides by boron yields the 'amine-carboxyboranes'. The amide bond in these molecules has the same geometry in the ground and transition states as the natural peptides. However, the boron isosteres of glycine and alanine peptides are less structural than their natural derivatives, but are distinguished by structures with a positive value for the ϕ angle, which is normally disfavored for natural peptides. This property could be used to build peptides with a geometry not usually observed in nature.

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