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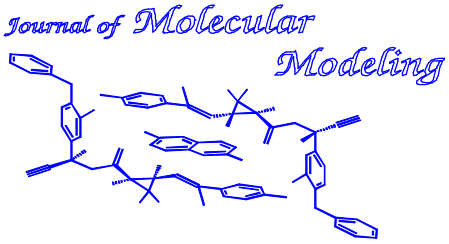

Peptides and Peptoids - A Systematic Structure Comparison

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Abstract

A systematic analysis of the conformational space of the basic structure unit of peptoids in comparison to the corresponding peptide unit was performed based on *ab initio* MO theory and complemented by molecular mechanics (MM) and molecular dynamics (MD) calculations both in the gas phase and in aqueous solution. The calculations show three minimum conformations denoted as $C_{7ß}$, a_D and a that do not correspond to conformers on the gas phase peptide potential energy hypersurface. The influence of aqueous solvation was estimated by means of continuum models. The MD simulations indicate the a_D form as the preferred conformation in solution both in *cis* and *trans* peptide bond orientations.

Keywords: Peptoids, peptides, *ab initio* conformational analysis, molecular dynamic simulations, peptide mimetics, solvation effect

Introduction

It is well known that peptides play an important role in different kinds of biological processes. The main disadvantage for pharmacological application is their proteolytic instability. Therefore, the development of peptide mimetics or peptide analogues with higher stability is of special interest [1-3]. Recently a new class of biopolymers was proposed - the so-called peptoids [4]. The typical structural feature of these compounds is the shift of the amino acid side-chains from the α-carbon of the amino acids to the nitrogen atom of peptide bond. This leads to oligomers or polymers of *N*-substituted glycines (NSGs). The essential advantages of these compounds are their resistance to proteases and the relatively easy synthesis with a wide variety of side chains. However, several structural consequences could be expected from these modified structures as illustrated in Figure 1 [5]:

1. The missing C_a side-chains cause the loss of chirality.
2. The hydrogen bond capacity of the peptide nitrogen responsible for the formation of the typical secondary structure elements gets lost.
3. In order to realize an equivalent orientation of the side-chains to the corresponding peptide, the peptoid chain has to be arranged in the reverse direction.

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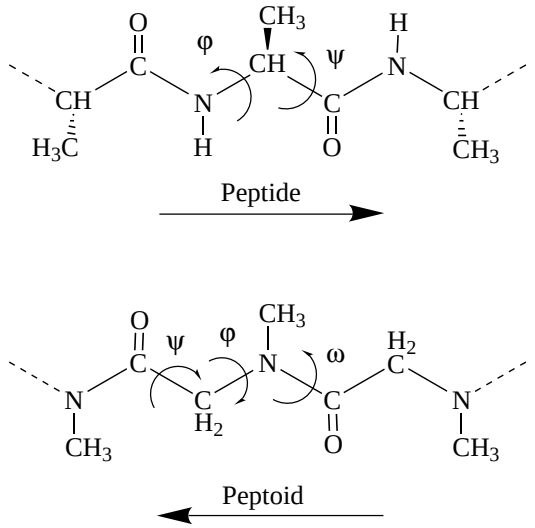

Figure 1. *Comparison between a peptide and a peptoid chain in a corresponding arrangement.*

4. In that arrangement the rotation angles determining the conformation of peptides and peptoids are not in equivalent positions.
5. The occurence of *cis* peptide bonds should increase by *N*-substitution as known for proline-containing peptide bonds.

Therefore, the examination of the conformational space of peptoids should be of special interest to show similarities and differences to the peptide structures. Recently, we presented the results of higher level *ab initio* MO calculations on the peptoid model compound *N,N*-acetylmethylglycine-*N'*,*N'*-dimethylamide, **1** [6]. These results were compared with those calculated on the corresponding peptide analogues of glycine and alanine. In this paper, we want to complement the quantum chemical results by molecular dynamics simulations for the gas phase and aqueous solution based on empirical force fields. Thus, we intend to describe the dynamic behaviour of these compounds.

Methods

In the *ab initio* MO calculations we performed geometry optimizations for selected peptoid structures at the MP2/6-31G*, HF/6-31G* and HF/3-21G* levels. A detailed description of the methodical aspects of these calculations can be found in Ref. 6. The molecular mechanics (MM) treatments and molecular dynamics (MD) simulations were based on the CHARMm22 force field as it is part of the QUANTA 4.1 molecular modeling package [7]. In this force field all parameters for the peptoids are available. For the MD simulations in the gas phase and in aqueous solution we used different charge models. In the gas phase charges calculated according to Gasteiger and Marsili [8] yield a potential surface in good agreement with the *ab initio* results. A greater charge polarization is considered by application of the CHARMm template charges in aqueous solution. Therefore, the increase of the dipole moments for neutral solutes in aqueous solution by about 20-30 % [9,10] is taken into account.

Starting from the different minimum conformations the MD simulations were performed at 300K in the microcanonical ensemble. The peptoid was solvated by 206 TIP3P water molecules in a cubic box of 18.9 Å length using periodic boundary conditions. A switching function based on groups truncated the nonbonded interactions between 8.0 and 9.4 Å. The SHAKE algorithm was used to constrain the XH bond lengths and consequently time steps of 1 or 2 fs in the numerical integration procedure could be employed. The whole system was heated and equilibrated for 23 ps and trajectories running for another 200 ps with the coordinates saved every 0.1 ps were used for analysis.

For the calculation of free energy differences ($\Delta\Delta A$) between different minimum conformations, we used MD simulations with holonomic internal coordinate constraints [11] and thermodynamic perturbation theory (TPT) [12,13]. Simulations of 40 ps were performed with ϕ and ψ constrained at 10 different pairs of ϕ_i and ψ_i, respectively, along a given path.

Results and discussion

First, we want to give a short review of the *ab initio* results. Our calculations showed only three minimum conformations and their symmetric counterparts on the potential hypersurface of the model peptoid independent of the basis set level (Figure 2). The torsion angles of these conformers and the energetic relations between them are summarized in Table 1. The most stable conformations are the $C_{7ß}$ and α_D forms with comparable stability. These conformations could be interpreted as mixed structures of peptide minimum conformations. In the case of peptides, conformations with intramolecular hydrogen bonds are usually the most stable conformers on the potential hypersurfaces (e.g. the C_7 form), but this opportunity gets lost in the peptoids. Thus the $C_{7ß}$ form represents a compromise between the C_7 and another peptide conformation, the ß form. The steric requirements of the methyl group at the peptide nitrogen lead to an extension of the original ring structure, although attractive interactions between the methyl hydrogens and carbonyl oxygen still occur. The α_D form could be derived from the fully extended peptide conformation. The dihedral ϕ has changed, but ψ still remains near 180°. The third conformer of 1 corresponds to the α helical conformation of peptides, but is distinctly more unstable than the other two conformers. This is interesting because the α form was not obtained as a minimum

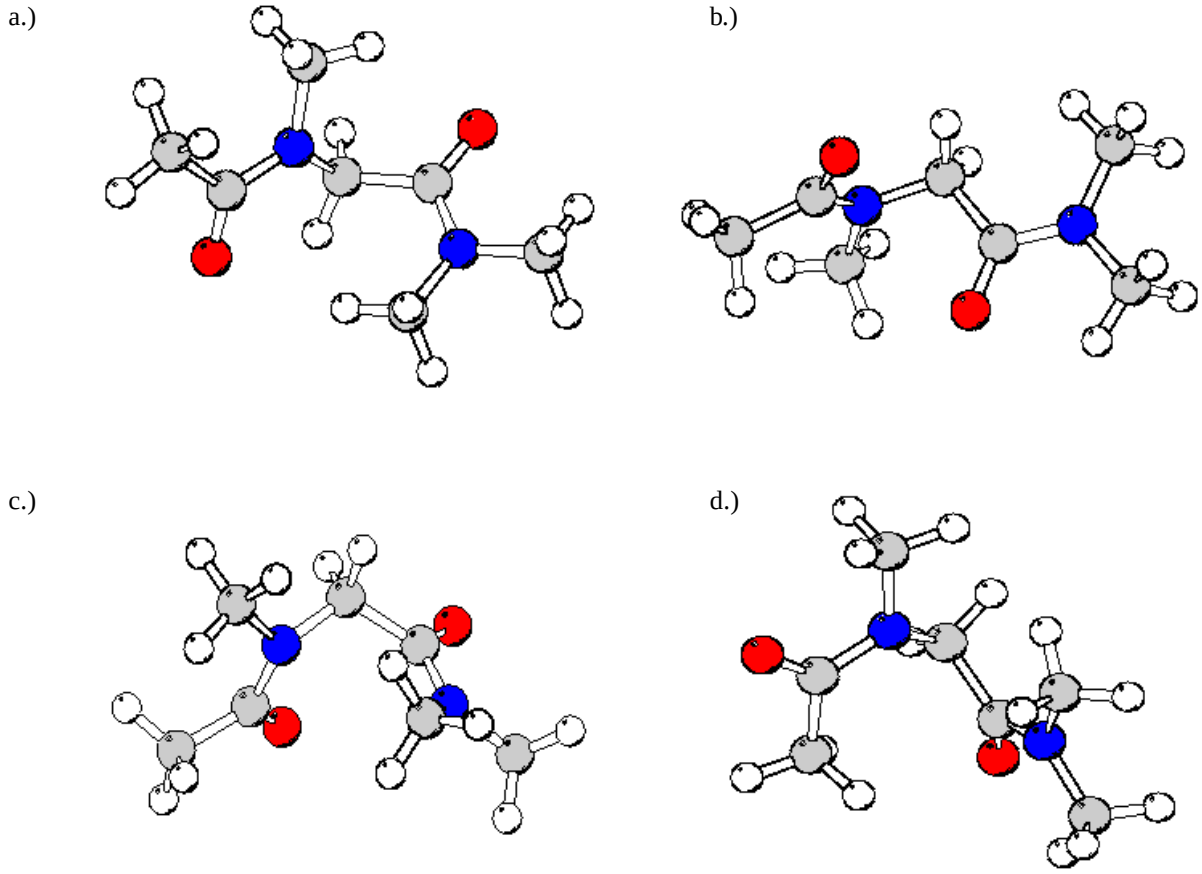

Figure 2. *Sketch of the three trans conformers (a) $C_{7ß}$,(b) α_D, (c) α and (d) the cis α conformation of the model peptoid* ***1***.

structure on the gas phase potential hypersurface of peptides, but appears only in an aqueous environment [14-18].

Further calculations were performed on peptoid structures with a *cis* orientation of the peptide bond since such arrangements get more importance in tertiary amide bonds. The three conformers above-mentioned were also obtained in the *cis* peptoids without essential geometry distortions. At the different *ab initio* approximation levels the *cis* α_D form is always the most stable conformation. The *cis* $C_{7ß}$ form is considerably destabilized, whereas the *cis* α form is even more stable than the corresponding *trans* orientation due to the additional interactions between the carbonyl oxygens and the hydrogen atoms of the different methyl groups (see Figure 2d).

The estimation of the solvation influence on the peptoid conformers by means of a quantum chemical polarizable continuum model (PCM) and a self-consistent reaction field model (SCRF) shows that all gas phase minimum structures remain stable and the α_D form is always the most stable solution conformation. Also the *trans* α helical conformation gets additional stabilization. The $C_{7ß}$ form and the *cis* form are destabilized in solution.

The dynamic behaviour of the peptoid structure was analyzed on the basis of the MD trajectories. The results are presented as Ramachandran-like plots for the torsion angles ϕ and ψ in Figures 3a-d. Because of the missing chirality, these plots are symmetric. Whereas the symmetry of the gas phase plots is clearly visible, the time evolution of the solution trajectories is not sufficient to overcome the corresponding barriers to get into the alternative conformation range, so that these plots should be regarded as complete after symmetric reflection. When discussing the MD results, it should be remembered that the empirical force field overestimates the stability of the α helical conformation in relation to the other two conformers in the gas phase (Table 1). The gas phase trajectory plots for the *trans* (Figure 3a) and *cis* (Figure 3b) peptoid orientations indicate smaller fluctuations of the torsional angles due to larger steric restrictions in comparison to peptide analogues. The $C_{7ß}$ and α_D forms could be considered as dynamically stable with a slight energetic preference of $C_{7ß}$, whereas the α helical conformation disappears. Free energy calculations provide a free energy difference of $\Delta\Delta A$ ($C_{7ß} \rightarrow \alpha_D$) = 2.9 kJ/mol. Contrary to this, the α helical conformation is the preferred one in the *cis* peptoids. In that case, the α_D form represents the second conformer and the $C_{7ß}$ minimum disappears. The dynamics study shows that the highest energy conformers change into the more stable conformers.

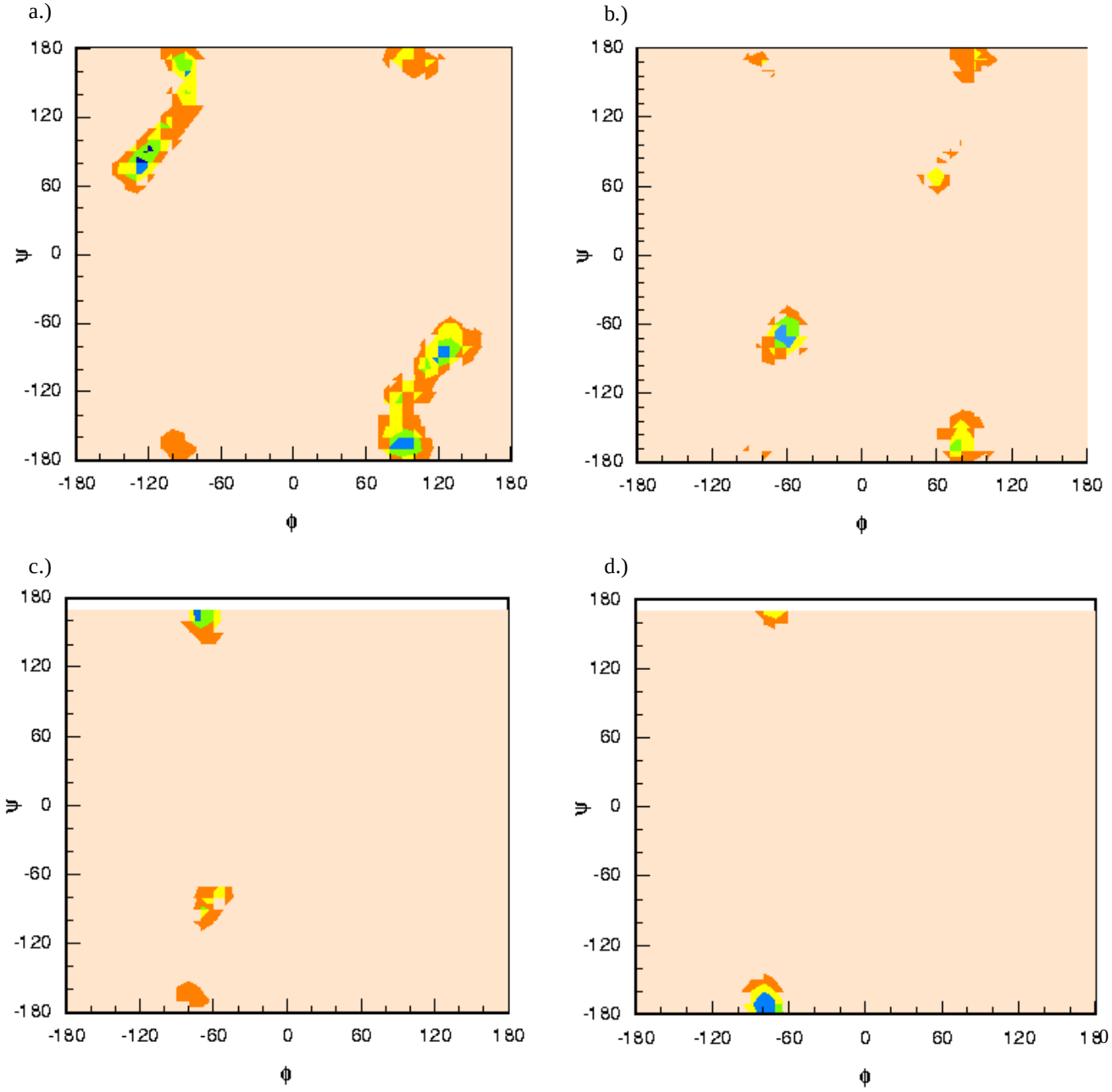

Figure 3. *Ramachandran-like plots of the gas phase trajectories for a) the trans and b) the cis peptoid and the trajectories in solution for c) the trans and d) the cis peptoid.*

When embedding the peptoid in a water box distinct differences occur with respect to the gas phase results as can be seen in Figures 3c and 3d. Independent of the peptide bond orientation, the α_D form is the preferred conformation in solution, whereas the $C_{7ß}$ form disappears. Only a small amount of the *trans* α helical conformation can additionally be found in the trajectories indicating the higher probability of helical structures in aqueous solution as also found for peptides. Free energy calculations indicate a preference of the α_D form by about 6 kJ/mol over the α helical conformation.

Conclusions

The results of MD simulations on the basic structure unit of peptoids reflect essential features of the *ab initio* MO conformational analysis. However, the higher energy conformers disappear on dynamic conditions and change into more stable conformers. In aqueous solution, the α_D conformer predominates and only a small amount of the α helical conformation was additionally indicated. In any case, some struc-

Table 1. *Relative energies and dihedral angles (ϕ, ψ) of the trans and cis conformers of the peptoid basic unit* ***1*** *at various levels of theory [a].*

	trans			***cis***		
	$C_{7ß}$	α_D	α	$C_{7ß}$	α_D	α
ΔE(MP2/6-31G*)	0.0[b](0.0)[c]	2.0 (1.2)	24.2 (24.7)	14.7 (15.5)	7.9 (7.5)	17.2 (17.9)
ϕ	-128.2	74.2	-54.7	-153.8	72.4	-62.4
ψ	77.0	-175.6	-47.2	62.5	172.1	-51.2
ΔE(HF/6-31G*)	5.4	0.0[d]	27.3	20.9	8.3	23.3
ΔG	5.9	0.0	25.5	18.0	6.6	21.1
ϕ	-128.4	79.2	-60.0	-153.2	76.9	-67.2
ψ	79.8	-174.6	-42.7	59.1	171.2	-48.7
ΔE(HF/3-21G)	0.0[e]	4.9	35.0	24.4	11.2	27.3
ϕ	-114.1	85.1	-53.3	-148.4	76.9	-57.5
ψ	96.6	-178.0	-47.3	60.6	170.3	-51.0
ΔE(CHARMm)[f]	0.0	3.2	10.5	7.3	4.9	3.1
ϕ	-120.6	94.0	-65.5	-135.9	83.4	-62.2
ψ	82.6	-164.1	-68.7	73.5	-176.4	-66.6

[a] Energies in kJ·mol^{-1}, angles in degrees.
[b] E_T = -533.453074 a.u.
[c] MP2/6-31G//HF/6-31G* single point energies in parentheses; E_T = -533.447244 a.u.*
[d] E_T = -531.869079 a.u.
[e] E_T = -528.910625 a.u.
[f] Gasteiger- Marsili charges; cf. Ref. 8.

tural differences appear in the peptoid structures when compared with the corresponding peptides which should be considered when replacing peptide units by peptoid ones.

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