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$n \rightarrow \pi^*$ Interactions in Helices

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Introduction

Helices are prevalent molecular structures in natural and synthetic polymers, including peptides and proteins. The topology of helices brings atoms that are nearby in a sequence into close proximity in a three-dimensional structure. This proximity can be reinforced by hydrogen bonds, like those in an α or 3_{10} helix. Other helices, however, lack hydrogen bonds (*e.g.*, polyproline type-I and type-II, and poly(L-lactic acid)), and do not have a clear basis for their conformational stability.

We have proposed that a quantum mechanical interaction stabilizes common helices - an $n \rightarrow \pi^*$ interaction between backbone carbonyl groups [1,2]. This interaction is between a lone pair (n) of the oxygen (O_{i-1}) of one carbonyl group and the antibonding orbital (π^*) of the subsequent carbonyl group ($C'_i{=}O'_i$) [3-5]. Here, the structures of natural and synthetic helices are analyzed from this perspective.

Results and Discussion

Models of $AcAlaNH_2$ in an α, 3_{10}, and polyproline type-I and type-II helix, and a model of an Ac(L-lactic acid)OH helix were created based on the ω, ϕ, and ψ backbone dihedral angles listed in Table 1. These models are depicted in Figure 1. A key aspect of these helices is that $r_{O\cdots C=O}$ is near or within the sum of the van der Waals radii of oxygen and carbon (3.22 Å) and $\angle_{O\cdots C=O}$ is close to the Bürgi–Dunitz trajectory for the approach of a nucleophile to a carbonyl group (~109°). Accordingly, the parameters indicate that $n \rightarrow \pi^*$ interactions make a significant contribution to the conformational stability to each of these helices. The energy of the interaction is 0.3 kcal/mol in $AcProNH_2$, and is enhanced with thiocarbonyl groups [6,7].

This analysis has numerous implications. For example, the data provide a new view of the α helix, which is the most prevalent structural element in folded proteins. This view is depicted in Figure 2 [1]. In addition, the data establish a physicochemical basis for the conformational stability of polyproline type-I and type-II helices, and the helical structure of poly(L-lactic acid) [2,5].

Table 1. Structural parameters of common helices with backbone carbonyl groups.[a]

Helix	ω	ϕ	ψ	$r_{O\cdots C=O}$	$\angle_{O\cdots C=O}$
A	180°	–60°	–45°	2.91 Å	97.9°
3_{10}	180°	–49°	–26°	2.73 Å	116.1°
polyproline type-I[b]	0°	–75°	150°	3.35 Å	127.5°
polyproline type-II	180°	–75°	160°	3.18 Å	89.4°
poly(L-lactic acid)[c]	180°	–64°	154°	2.86 Å	94.4°

[a] *ω: C^{α}_i–C'_i–N_{i+1}–C^{α}_{i+1}, ϕ: C'_{i-1}–N_i–C^{α}_i–C'_i, ψ: N_i–C^{α}_i–C'_i–N_{i+1};* [b] *In the polyproline type-I helix, $O\cdots C{=}O$ refers to $O'_i\cdots C'_{i-1}{=}O'_{i-1}$;* [c] *In poly(L-lactic acid), N_i and N_{i+1} are replaced with oxygens.*

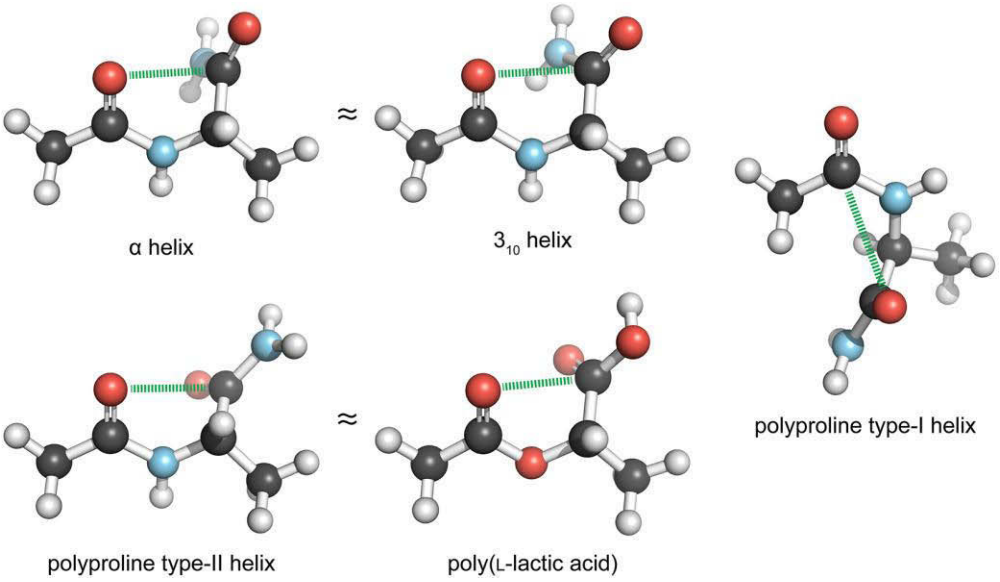

Fig. 1. n→π Interactions (hatched lines) between backbone carbonyl groups in common helices. The depicted models are $AcAlaNH_2$ or Ac(L-lactic acid)OH with structural parameters listed in Table 1.*

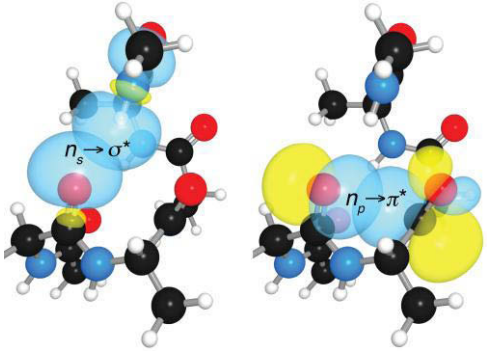

Fig. 2. A new view of the α helix. The s-rich lone pair (n_s) forms the canonical i→i+4 hydrogen bond; the p-rich lone pair (n_p) forms an i→i+1 n→π interaction. The depicted model is $AcAla_4NH_2$ in an α helix.*

We conclude that the n→π* interaction must be considered along with other noncovalent interactions when examining and considering the structure, stability, engineering, and design of common helices, and that n→π* interactions be included in relevant computational force fields.

Acknowledgments

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