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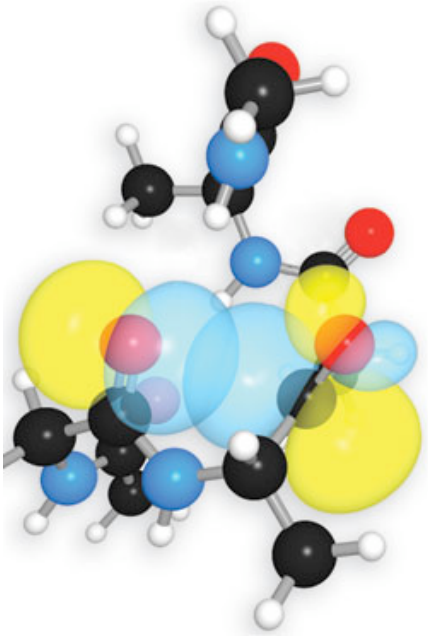
# Another Force To Stabilize Proteins

## Structural Biology: Unappreciated interaction is widespread, research shows

**Celia Henry Arnaud**



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SHORT-RANGE The $n \rightarrow \pi^*$ interaction occurs when a lone pair of electrons on the carbonyl oxygen in one amino acid overlaps the π antibonding orbital of the carbonyl group in the adjacent amino acid. The light blue and yellow represent the phases of the relevant orbitals. (Black = C, red = O, blue = N, white = H)

The hydrogen bond has company. Another noncovalent interaction along the protein backbone might help proteins fold and maintain their three-dimensional structures, according to a new study in *Nature Chemical Biology* (DOI: 10.1038/nchembio.406). Protein modelers may need to incorporate this interaction in their algorithms.

Ronald T. Raines and coworkers at the University of Wisconsin, Madison, have studied the so-called *n* to pi-star ($n \rightarrow \pi^*$) interaction in a variety of systems for several years. They have now teamed up with Derek N. Woolfson and coworkers at the University of Bristol, in England, to show, using protein database searches, that this interaction occurs in nearly every protein. In the $n \rightarrow \pi^*$ interaction, one of the lone pairs of electrons on a carbonyl oxygen in one amino acid overlaps with the π antibonding orbital of the carbonyl group in the adjacent amino acid.

"Because it's a main-chain interaction, it doesn't matter what the side chains are," Raines says. Any amino acid can form an $n \rightarrow \pi^*$ interaction, but proline's ring structure makes it especially suited because of the constraints imposed by the distance and angles necessary for orbital overlap.

"What's neat about this is that it's short-range," Raines says. "In the α-helix, the hydrogen bond is between the first and fifth residues." In contrast, the $n \rightarrow \pi^*$ interaction is between adjacent residues. The $n \rightarrow \pi^*$ interaction is typically weaker than a hydrogen bond, however. In addition, Raines, Woolfson, and coworkers find evidence for these interactions in

nearly every type of secondary structure and even in seemingly unstructured regions of proteins.

Raines thinks this interaction has been ignored for so long because of how people have tended to represent and think about protein structure. "If you look at the α-helix without considering quantum mechanics, you would never think of the $n \rightarrow \pi^*$ interaction," he says.

"At a practical level, the work suggests that some geometric aspects are not properly accounted for in standard molecular mechanics force fields," says William F. DeGrado, a professor of biochemistry and biophysics at the University of Pennsylvania. "We might have to wait to see how significant this particular missing piece is in the overall picture" of protein modeling, he says. "But it is already clear that they have identified an important feature that will spark new interest and investigations."

The work is notable for its willingness to make bold claims about the ubiquity of the $n \rightarrow \pi^*$ interaction, according to Neville Kallenbach, a chemistry professor at New York University. "This is risky, but changing the mainstream of current thinking has to be," he says. "One still can't be sure that $n \rightarrow \pi^*$ interactions are the exclusive explanation for the geometrical correlations that they find. It is worth finding out."

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