

The conformational preference of s-cis amides.

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April 17, 2023

CHEMISTRY



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DATE RECEIVED:

June 10, 2015

DOI:

10.15200/winn.143118.81278

ARCHIVED:

May 09, 2015

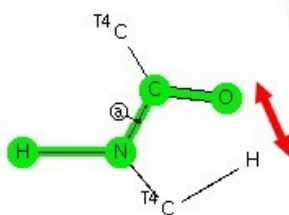
CITATION:

Henry Rzepa, The conformational preference of s-cis amides., *The Winnower* 2:e143118.81278, 2015, DOI: [10.15200/winn.143118.81278](https://doi.org/10.15200/winn.143118.81278)

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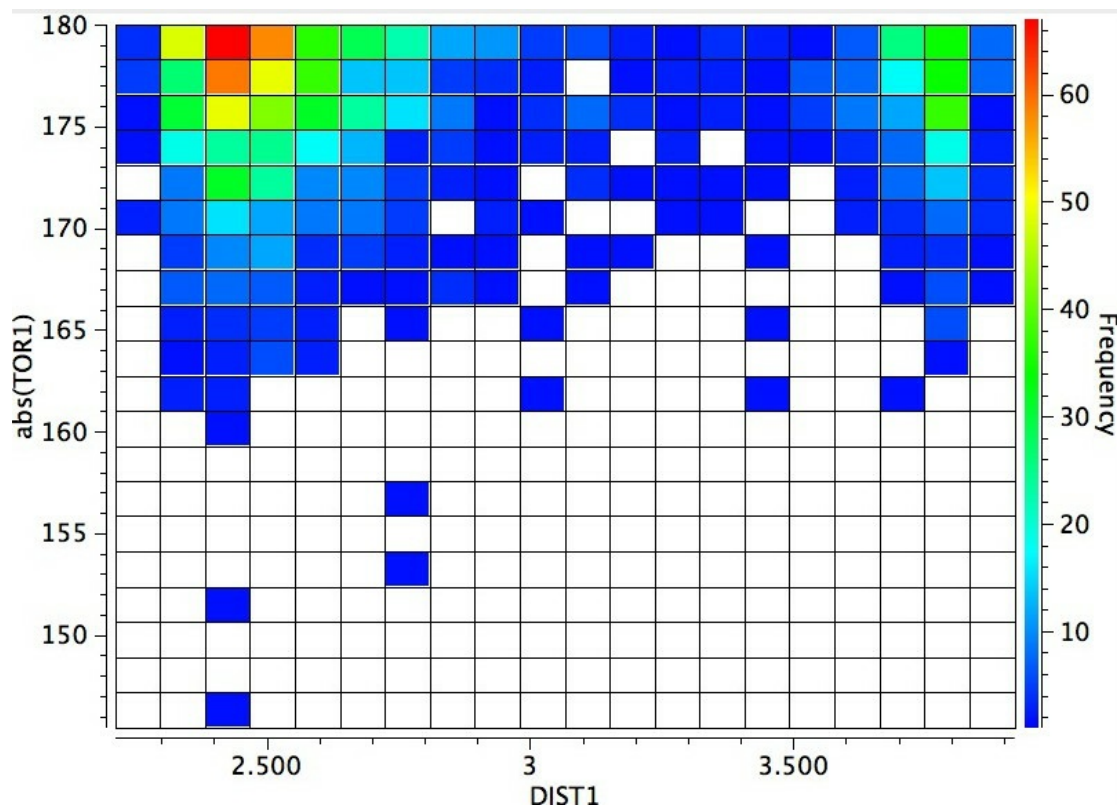
Amides with an H-N group are a component of the [peptide linkage](#) ($\text{O}=\text{C}-\text{NH}$). Here I ask what the conformation (it could also be called a configuration) about the C-N bond is. A search of the following type can be defined:



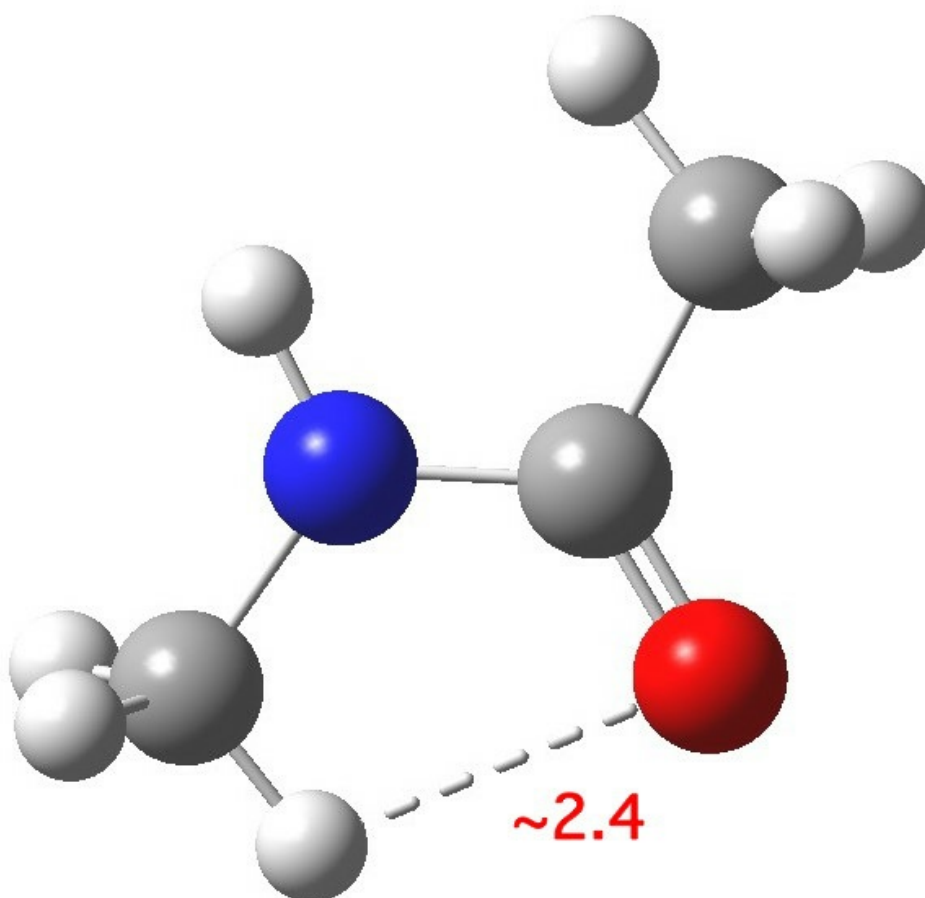
Modified Torsion [TOR1]: $\text{abs}(\text{H1 N2 C3 O4})$

Defined Distance [DIST1]: H7 O4

The dihedral shown is for $\text{H}-\text{N}-\text{C}=\text{O}$ (but this is equivalent to the $\text{C}-\text{C}-\text{N}-\text{C}$ dihedral, which is also often called the [dihedral angle](#) associated with the peptide group). I have also added a distance, from a C-H to the carbonyl oxygen. Other search constraints include $\text{T} \leq 175\text{K}$, R . **The search results in 619 hits (January 2013 version of the CCDC database), and these are displayed below.**

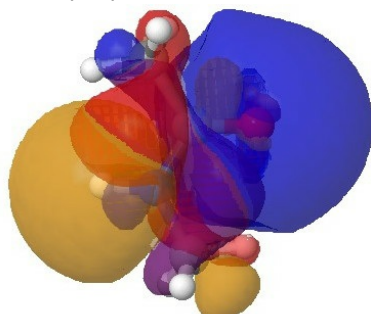


The horizontal axis reveals the highest concentration (red) at $\sim 2.4\text{\AA}$ due to a syn-co-planar alignment of the C-H bond with the plane of the C=O bond in the s-cis conformer (the significantly smaller hot-spot at $\sim 3.9\text{\AA}$ may be due to an anti-co-planar alignment of this C-H bond).

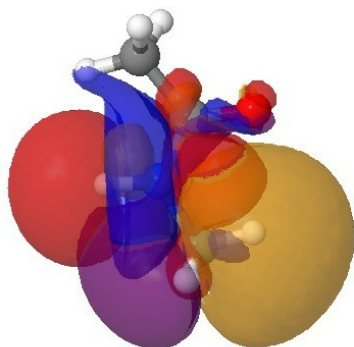


The vertical axis shows a clear preference for a dihedral of 179° (in fact no hits with a dihedral of less than 140° were found) and this can only arise from the **s-cis** conformation in which the H-N bond is oriented antiperiplanar to the axis of the C=O bond. This preference can be rationalised by filled/empty NBO-orbital interactions, which include:

1. Antiperiplanar interaction between the N-H as donor and the C=O as a σ -acceptor ($E(2) = 4.1$ kcal/mol)
2. Antiperiplanar interaction between the N-H as acceptor and C-H as donor ($E(2) = 4.7$ kcal/mol)



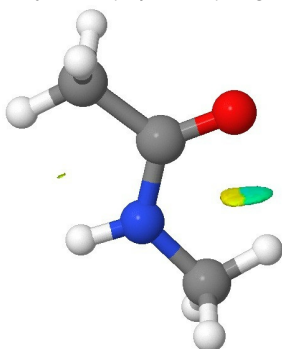
H-N/C=O. Click for 3D



Click for 3D.

This latter overlap conspires to bring the C-H hydrogen close to the oxygen ($\sim 2.35\text{\AA}$, DIST1 in the diagram above). So one might be entitled to ask: is this a hydrogen bond? There are (at least) two ways of testing this.

1. The NBO E(2) interaction energy between the oxygen in-plane lone pair and the H-C as acceptor is 0.8 kcal/mol. For hydrogen bonds, such E(2) energies more or less resemble the actual H-bond strengths, *i.e.* a strong H-bond has an E(2) energy of ~ 8 kcal/mol; and a medium O...H-C hydrogen bond weighs in at around 3 kcal/mol. So this one is very weak. This is due to poor overlap resulting from the **small ring size** (5).
2. The NCI (non-covalent-interaction) surface does reveal a feature in the CH...O region, but the colour coding (which indicates how attractive/repulsive this is) is both pale blue (attractive) and yellow (repulsive). Again this is only consistent with a very weak overall H-bond.



NCI surface. Click for 3D.

I end by reminding that the s-cis H-N-C=O conformation is a very common feature in **peptides** (the CCDC database comprises mostly small molecules, not larger peptides and proteins) arising from really quite subtle orbital interactions.