

CHEMISTRY



# The conformational preference of s-cis amides.

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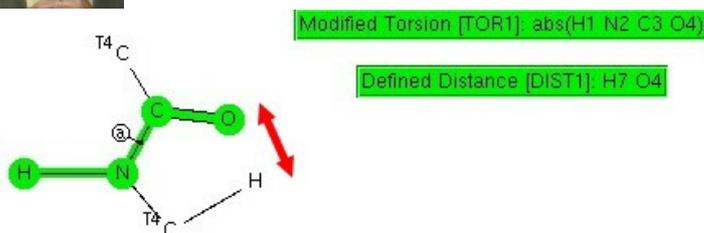
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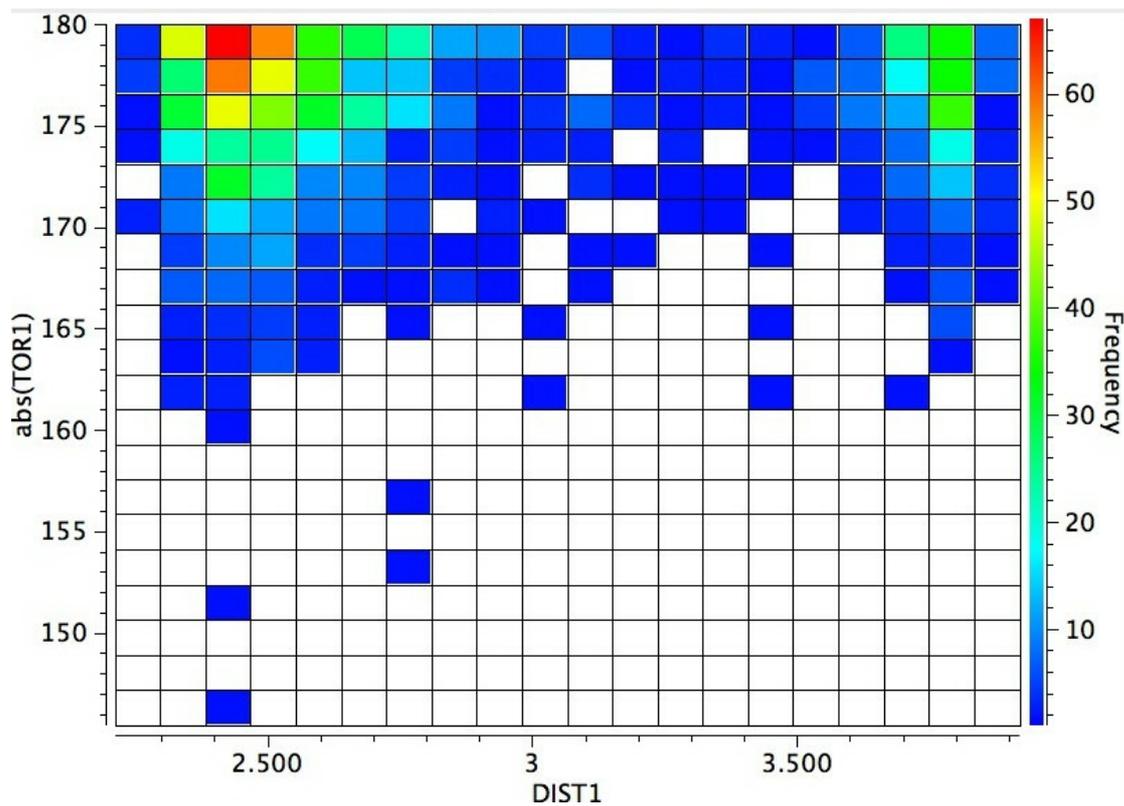
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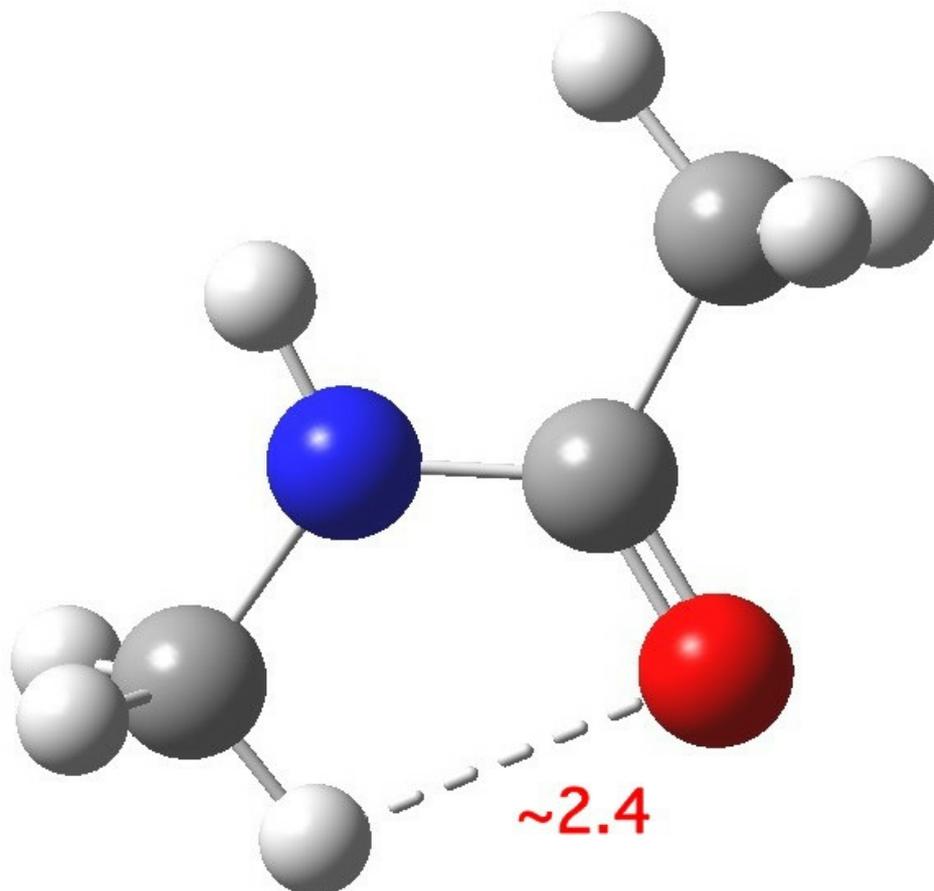
Amides with an H-N group are a component of the [peptide linkage](#) (O=C-NH). Here I ask what the conformation (it could also be called a configuration) about the C-N bond is. A search of the following type can be defined:



The dihedral shown is for H-N-C=O (but this is equivalent to the C-C-N-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  $T \leq 175\text{K}$ ,  $R$ . **The search results in 619 hits (January 2013 version of the CCDC database), and these are displayed below.**

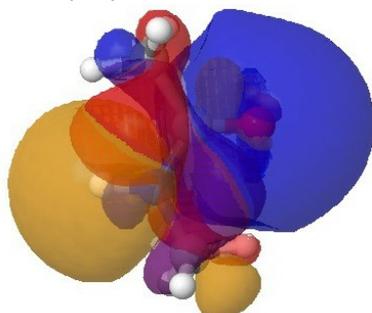


The horizontal axis reveals the highest concentration (red) at  $\sim 2.4\text{\AA}$  due to a syn-co-planar alignment of the C-H bond with the plane of the C=O bond in the s-cis conformer (the significantly smaller hot-spot at  $\sim 3.9\text{\AA}$  may be due to an anti-co-planar alignment of this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

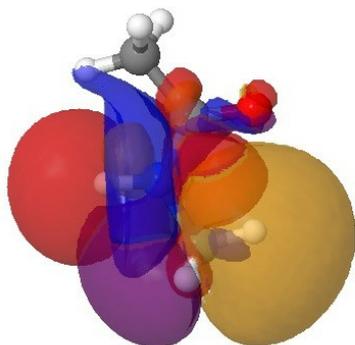


The vertical axis shows a clear preference for a dihedral of  $179^\circ$  (in fact no hits with a dihedral of less than  $140^\circ$  were found) and this can only arise from the *s-cis* conformation in which the H-N bond is oriented antiperiplanar to the axis of the C=O bond. This preference can be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

1. Antiperiplanar interaction between the N-H as donor and the C=O as a  $\sigma$ -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)



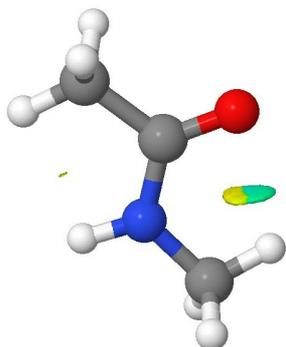
H-N/C=O. Click for 3D



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  $\sim 8$  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.