N-H---N Hydrogen Bonds in Proteins
(a quantum mechanical study of hydrogen bonding by amino acids)

Sandra Lundell
Department of Chemistry and Biochemistry
Proteins

Proteins are key biological macromolecules that perform a countless number of vital tasks within every organism that forms the basis of life.

The job of a protein can be:

- **Structural** - ex: dystrophin is a major component in muscle tissue.
- **Antibodies** - made by the immune system to recognize and defend against foreign pathogens.
- **Transport** – ex: hemoglobin transports O2 and CO2 throughout the body.
- **Cell-signaling**
- **Enzymes** - Facilitate difficult chemical reactions
- Etc.
The Structure of Proteins

Amino acids are small molecules with the same backbone but with a different side chain.
The Structure of Proteins

Depending on the sequence of amino acids, a protein chain will form different shapes.

The combination of these shapes forms the protein’s final structure.
The role of a protein is directly related to its shape.

If it folds incorrectly into the wrong shape, it will not function properly, causing many diseases.

In many cases, hope for the design of drugs to treat these ailments relies, in part, on understanding the normal, or native, structure of these proteins and what goes awry under disease conditions.

Diseases involving dysfunctional proteins:
- Gaucher disease
- Muscular dystrophy
- Alzheimer’s disease
- Sickle Cell Anemia
- Cancer
- And more

Bonding within the Protein

The sequence of amino acids in a protein chain determines the protein's due to the different types of chemical interactions that occur between the amino acids.

Many types of interactions contribute, including:

- Hydrophobic interactions
- Hydrogen bonds
- Disulfide bonds
- Charge-charge interactions
- Salt bridges
- $n \rightarrow \sigma^*$ interactions
It is well known that N-H---O hydrogen bonds are common within proteins, but what about other types?
N-H---N Hydrogen Bonds

Computer simulations based on quantum mechanics were used to observe chemical bonding between amino acids paired with N-methyl acetamide.

N-methylacetamide (NHC) is very similar to the protein backbone and was used to save time and resources in this study.

NHC (left) and Valine (right) forming an N-H---N hydrogen bond.
Asparagine is a polar amino acid with two nitrogen atoms capable of forming N-H---N bonds.

Three different structures were found of the Asparagine/NHC pair that formed N-H---N bonds.
To verify that the N-H---N interactions could be classified as hydrogen bonds, additional tests were done.

<table>
<thead>
<tr>
<th></th>
<th>R(N···H) (Å)</th>
<th>Θ(N···HN) (deg)</th>
<th>Δr(_{N-H}) (Å)</th>
<th>Δ(\nu) (cm(^{-1}))</th>
<th>NMR (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparagine A</td>
<td>2.27801</td>
<td>140.684</td>
<td>0.00671</td>
<td>-80.03</td>
<td>-2.1846</td>
</tr>
<tr>
<td>Asparagine B</td>
<td>2.37594</td>
<td>140.013</td>
<td>0.00343</td>
<td>-90.93</td>
<td>-1.3409</td>
</tr>
<tr>
<td>Asparagine C</td>
<td>2.42298</td>
<td>153.848</td>
<td>0.00366</td>
<td>-62.44</td>
<td>-0.5834</td>
</tr>
</tbody>
</table>
The stabilization energies (kcal/mol) associated with the delocalization of the ideal Lewis structure provides an indication of the strength of bonds between Asparagine and NHC.

<table>
<thead>
<tr>
<th></th>
<th>Nlp → NHσ*</th>
<th>Olp → NHσ*</th>
<th>COσ → CHσ*</th>
<th>Nlp → COσ*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparagine A</td>
<td>4.59</td>
<td>13.4</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Asparagine B</td>
<td>4.03</td>
<td>1.03</td>
<td>1.41</td>
<td></td>
</tr>
<tr>
<td>Asparagine C</td>
<td>2.96</td>
<td>4.16</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>
- The N-H---N interactions observed between Asparagine and NHC are hydrogen bonds.
- So far, 11 out of 15 amino acids studied have had the same results.

Knowing N-H---N hydrogen bonds exist in proteins expands our understanding of why proteins fold into the shapes they do and will aid in the study of protein-related diseases and finding their cures.