

## A SCALE QUANTIFYING THE STRENGTH OF INTRAMOLECULAR HYDROGEN BONDS FROM IR SPECTROSCOPY

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Intramolecular hydrogen bonds are of fundamental importance in chemistry, existing in a range of systems from small medicinal molecules to the macromolecules of DNA, proteins, and plastics. The strengths of these hydrogen bonds have important consequences on the structure, and consequently the function of such chemical systems. However, the strength of intramolecular hydrogen bonds cannot be either directly measured experimentally or computed theoretically through dissociation, like those in regular intermolecular hydrogen bonds. Computational approaches, such as the rotational bond method, can approximate these energies but rely on a series of assumptions that limit their application. This work proposes a scale based on the spectral-energy relationship first studied by Badger and Bauer to estimate the strength of intramolecular hydrogen bonds from the measured experimental infrared (IR) bands of the respective vibrations. A single regression between energy and shifts in vibrational frequency was derived for hydrogen bonds incorporating O, N, and F atoms. The linear regression between energy and underlying frequency was established at the MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ levels of theory and validated at both higher levels of electron correlation (CCSD(T)) and by using experimental IR spectra and zero-point energies. Our results reproduce the intramolecular hydrogen bond energies of enolones and amino alcohols obtained by the rotational bond method within 1 kcal/mol. We subsequently used our approach to estimate the hydrogen bond strengths of a variety of systems for which the experimental frequencies for the respective intra-molecular hydrogen bonds have been reported. Our results quantify the strengthening of the hydrogen bond in amino-ethanols under fluorination by over 2 kcal/mol and yield hydrogen bond strengths of about 4 kcal/mol in helical poly-peptides, making it possible, for the first time, to quantify the strengths of these elusive interactions in systems of biological importance.