Disulfide Bonds: Basis for Structure and Function

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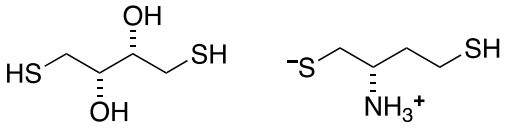
Approximately 20% of human proteins, including mucins, have disulfide bonds between cysteine residues. The reactivity of disulfide bonds and their component thiols can be manipulated by through-bond and through-space electronic effects. For example, a cationic amino group makes dithiobutylamine (DTBA) superior to the venerable dithiothreitol (DTT) as a biochemical reducing agent. Similarly, small-molecule dithiols with a low thiol pK_a and high disulfide reduction potential are efficacious organocatalysts of oxidative protein folding. In proteins, the reactivity of thiols and disulfide bonds is controlled by interactions between the sulfur lone pairs (n) and antibonding orbitals of main-chain carbonyl groups (π*). These S···C=O n-to-π* interactions modulate the acid–base and redox equilibria of the CXXC-motif in enzymes that mediate redox homeostasis, are endemic to vicinal disulfide bonds, and are apparent in cystinyl linkages between β-strands. The anticancer activity of epidithiodiketopiperazine natural products relies on a disulfide bond with the strongest n-to-π* interaction observed to date. The wavelength of the maximal absorbance of a disulfide bond can vary from 250 to 500 nm. This wavelength derives from stereoelectronic effects and is predictable using quantum chemistry. A sinusoidal equation, analogous to the Karplus equation, relates the absorbance maximum (λ_{max}) and the C–S–S–C dihedral angle (θ): $\lambda_{max}(\theta) = A - B \cdot \sin|\theta| + C \cdot \sin 2|\theta|$. This equation enables the value of θ to be predicted from that of λ_{max}. Collectively, these findings highlight the underlying quantum chemistry of disulfide bonds in natural contexts and provide guidance in biomolecular design and manipulation.



DTT **DTBA**