Experimental Observations of Non-covalent Interaction Using Molecular Torsion Balances

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Introduction:

Non-covalent interactions govern many chemically and biologically relevant processes. Chemically, these interactions are vital for the determination of material properties and contribute to the selectivity of asymmetric processes.[1] In the field of biology, non-covalent interactions contribute to the secondary and tertiary structure of proteins and the docking and binding of enzymes.[1] Although non-covalent interactions are invoked for these processes, their presence is often difficult to quantify.

Chemical synthesis allows for the simplification of these previously complex systems by providing simple manifolds for the isolation of these non-covalent interactions. Unimolecular systems provide further simplification, by allowing rigid orientations and geometric control. Additionally, tethers can facilitate the measurement of weak intramolecular interactions due to lowering of entropic contributions.[1] Synthetically derived systems can further exploit rotational barriers to study the equilibrium between several discrete rotational states. These synthetic tools have been deemed Molecular torsion balances by Wilcox *et al.* and have been employed in numerous model systems for the experimental study of interactions that have been previously difficult to quantify.[4] Instead, differences in rotational ground state conformations can be probed upon installation of various functionality responsible for non-covalent interactions. The change in population of these ground states is then related to the free energy gained by the non-covalent interaction of interest.[1]

Molecular Torsion Balances:

Oki, through his study of rotational barriers of the triptycene scaffold, realized modification of various functional groups at the Y and Z position could be implemented to measure non-covalent interactions.[2] Oki, successfully probed CH-Lone pair interactions inspiring Gung to conduct additional studies of lone pair-π and π-π stacking interactions using the triptycene scaffold.[2,3]

Scheme 1. Oki's triptycene Balence

Anti
(Unfolded)

Syn
(Folded)
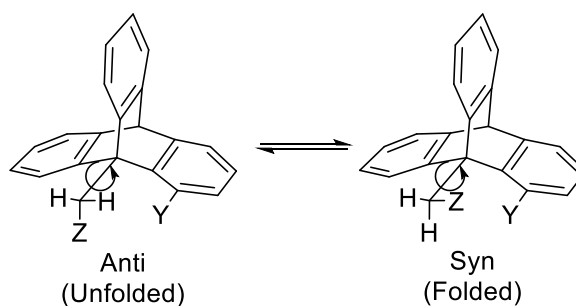
Wilcox *et al.* developed a new balance based on the Tröger base (Scheme 2) which allows for the alignment of the A and B ring in a face to edge manner. This balance was used to evaluate CH-π interactions and edge to face π-stacking.[4] Diederich further explored these Tröger base-derived balances to study fluorine carbonyl interactions and used double mutant cycles to increase the accuracy and test the validity of his results.[5]

Scheme 2. Wilcox's Tröger base derived Balence

Folded   Unfolded
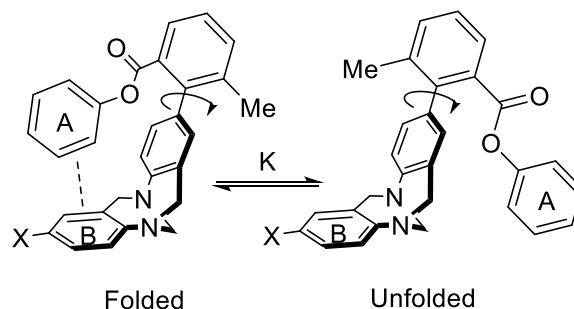
Shimizu developed a bicyclic N-arylsuccinimide balance (Scheme 3) that forces the A and B rings in an offset face to face geometry.[6] This scaffold has been used by Shimizu and coworkers to measure CH-π, lonepair-π, and face to face aromatic stacking. Notably, this balance has been also used to study Ag-π and cationic-π interactions.[6] The field of molecular torsion balances has furnished many experimental values for previously unquantifiable non-covalent interactions. Many research groups are currently designing new balances to probe such interactions

Scheme 3. Shimizu Balance

$X=CH$,N , N^+H, N^+Me
$Y=CH$, N , N^+H, N^+Me
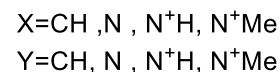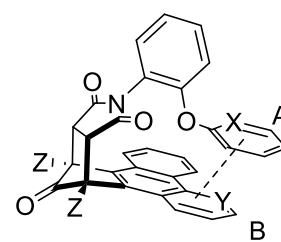
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