$\pi-\pi$ (\(\pi\)-stacking) Interactions: Origin and Modulation

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01-18-11
π-Stacking Geometries: An Electrostatic Tutorial

- Benzene
- Sandwich
- Parallel Displaced
- T-Shaped
- Edge-to-Face
- Hexafluorobenzene
- Hexaaminobenzene
Hunter and Sander Rules: Geometry

Sandwich
Parallel displaced
Edge-to-face

Influence of differing pi electron density

Hunter and Sander Rules applied to Proteins (ala-ala)

Substituent effects parallel stacked

Rotation barriers were measured by line shape analysis in H-NMR

Polar/$\pi$ vs charge transfer

Charge transfer does not contribute significantly to the interaction

Free energy of activation determined from 2D NMR EXSY pulse sequence

Cozzi F.; Siegel, J. S.; et. al. J. Am. Chem. Soc. 1993, 115, 5330
Face-to-face or center-to-edge?

- Rotation barrier determined by 2D EXSY NMR
- Mode of stacking is not well characterized
- Low sensitivity may be a result of decreased favorable electrostatic orientation

MMFF

Parallel Displaced and/or edge-to-face or T-shape

Interaction is strongest when both rings contain e-withdrawing groups?

OMe better fit with $\sigma$(meta)

Other pi-stacking Modes?

“The alternative T-shape orientation is prohibited by the triptycene skeleton.”

T-Shaped geometry?

Double Mutant Cycle: edge-face/T-shaped

\[ \Delta \Delta G_{x,y} = (\Delta G_A - \Delta G_B) - (\Delta G_C - \Delta G_D) \]

\[ = (\Delta G_A - \Delta G_C) - (\Delta G_B - \Delta G_D) \]

NOEs (ROESY)

Double Mutant Cycle: edge-face/T-shaped

Table 5. Aromatic interaction energies (ΔΔΔG in kJ mol⁻¹) in deuterochloroform at 295 K measured using the double mutant cycle in Scheme 1.

<table>
<thead>
<tr>
<th></th>
<th>Y</th>
<th>NMe₂</th>
<th>rBu</th>
<th>H</th>
<th>NO₂</th>
<th>NMe₂[a]</th>
<th>m-X</th>
<th>NO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NMe₂</td>
<td>-0.9 ± 0.5</td>
<td>-1.3 ± 0.5</td>
<td>-1.8 ± 0.6</td>
<td>-4.6 ± 0.5</td>
<td>-1.6 ± 0.5</td>
<td>-1.8 ± 0.6</td>
<td>-4.3 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>-1.1 ± 0.4</td>
<td>-1.6 ± 0.4</td>
<td>-1.4 ± 0.5</td>
<td>-3.4 ± 0.4</td>
<td>-2.0 ± 0.4</td>
<td>-1.4 ± 0.5</td>
<td>-3.1 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>NO₂</td>
<td>-1.4 ± 0.5</td>
<td>-0.1 ± 0.4</td>
<td>-0.2 ± 0.5</td>
<td>+1.2 ± 0.6</td>
<td>-2.4 ± 0.4</td>
<td>-0.2 ± 0.5</td>
<td>-0.5 ± 0.4</td>
</tr>
</tbody>
</table>

ΔΔG(p-X) [kJ mol⁻¹] = 5.2σₓσᵧ - 1.9σₓ + 1.4σᵧ - 1.5  
ΔΔG(m-X) [kJ mol⁻¹] = 2.5σₓσᵧ - 2.3σₓ + 1.5σᵧ - 1.4

Combined (meta and para) equation

ΔΔG [kJ mol⁻¹] = (5.2cosφ)σₓσᵧ - 0.1σₓ + 1.5σᵧ - 1.4

Double Mutant cycle: face-face

Based on NOE and $\Delta\delta$ values

<table>
<thead>
<tr>
<th>X</th>
<th>phenyl</th>
<th>pentafluorophenyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMe$_2$</td>
<td>+1.5</td>
<td>-3.2</td>
</tr>
<tr>
<td>H</td>
<td>+0.3</td>
<td>-3.0</td>
</tr>
<tr>
<td>OMe</td>
<td>+0.9</td>
<td>-2.2</td>
</tr>
<tr>
<td>Cl</td>
<td>0.0</td>
<td>-1.2</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>-1.0</td>
<td>-0.2</td>
</tr>
</tbody>
</table>

$^o$ Values measured in CDCl$_3$ at 293 K, and errors are $\pm 0.7-1.1$ kJ mol$^{-1}$.

Electrostatic or Dispersion?

Crystal structure: X=NO2; CH3

NMR experiments in CDCl$_3$

<table>
<thead>
<tr>
<th>entry</th>
<th>group</th>
<th>$\Delta G^\circ_{\text{fold}} \pm (10%)^a$ methyl ester (3)</th>
<th>$\Delta G^\circ_{\text{fold}} \pm (10%)^b$ isopropylester (2)</th>
<th>$\Delta G^\circ_{\text{fold}} \pm (10%)^c$ phenyl ester (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO$_2$</td>
<td>0.11</td>
<td>-0.51</td>
<td>-0.21</td>
</tr>
<tr>
<td>2</td>
<td>CN</td>
<td>0.06</td>
<td>-0.64</td>
<td>-0.30</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>-0.06</td>
<td>-0.46</td>
<td>-0.23</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>0.02</td>
<td>-0.54</td>
<td>-0.26</td>
</tr>
<tr>
<td>5</td>
<td>CH$_3$</td>
<td>-0.04</td>
<td>-0.44</td>
<td>-0.27</td>
</tr>
<tr>
<td>6</td>
<td>OH</td>
<td>-0.03</td>
<td>-0.47</td>
<td>-0.23</td>
</tr>
<tr>
<td>7</td>
<td>NH$_2$</td>
<td>-0.06</td>
<td>-0.34</td>
<td>-0.18</td>
</tr>
</tbody>
</table>

Benzene Dimer (Sandwich, T-Shaped, and Parallel Displaced)

Decomposition of energetic components: Perturbation Theory

\[ E_{A-B} = E_{\text{elec}} + E_{\text{ind}} + E_{\text{vdw}} \]
\[ E_{\text{vdw}} = E_{\text{disp}} + E_{\text{rep}} \]

van der Waals (Lennard-Jones)

\[ V_{LJ} = 4\varepsilon \left\{ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^{6} \right\} \]

<table>
<thead>
<tr>
<th>structure</th>
<th>total</th>
<th>E\text{elec.}</th>
<th>E\text{exch.}</th>
<th>E\text{ind.}</th>
<th>E\text{disp.}</th>
</tr>
</thead>
<tbody>
<tr>
<td>sandwich</td>
<td>-0.974</td>
<td>6.034</td>
<td>-0.330</td>
<td>-6.527</td>
<td></td>
</tr>
<tr>
<td>T-shaped</td>
<td>-2.244</td>
<td>4.866</td>
<td>-0.670</td>
<td>-4.366</td>
<td></td>
</tr>
<tr>
<td>parallel-displaced</td>
<td>-2.799</td>
<td>8.652</td>
<td>-0.900</td>
<td>-7.895</td>
<td></td>
</tr>
</tbody>
</table>

Total Interaction energy and Dispersion

$E_{\text{int}}$ traces a dispersive-like potential with increasing distance.

Substituent effects

![Substituent effects image]

**TABLE 3: Interaction Energies Relative to the Benzene Dimer for Heterodimers of Benzene with Monosubsituted Benzenes [Estimated CCSD(T)/aug-cc-pVTZ Results]**

<table>
<thead>
<tr>
<th>X</th>
<th>S</th>
<th>T</th>
<th>T(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>OH</td>
<td>-0.37</td>
<td>0.04</td>
<td>-0.05</td>
</tr>
<tr>
<td>CH₃</td>
<td>-0.47</td>
<td>0.07</td>
<td>-0.33</td>
</tr>
<tr>
<td>F</td>
<td>-0.49</td>
<td>-0.15</td>
<td>0.24</td>
</tr>
<tr>
<td>CN</td>
<td>-1.25</td>
<td>-0.63</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Substituent Effects

Type I

Type II


NO₂, CN, Cl, OH, NH₂

δΔE (kcal/mol)

MP2/aVTZ
CCSD(T)/aVDZ'

δΔE es vs. δΔE tot
δΔE es,ind vs. δΔE tot

δΔE tot

CCSD(T)/aVDZ'

linear fit: R=0.956
linear fit through (0,0): R=0.804

δΔE es vs. δΔE tot
δΔE es,disp + exch vs. δΔE tot
Substituent effects in parallel-displaced: energy profiles

All groups have a lower global minimum than benzene
Energy decomposition

Dispersion: lowest change for F due to low polarizability, followed by OH then CN
Induction: slightly favors CN
Exchange: minima represent minimal e-density in center of ring, dominates in CN
Electrostatics: Positive at large displacements due to overlap of electronegative group with negative electrostatic potential

Revisiting the “molecular torsion balance”

Experiments performed in C₆D₆ compared to that of Wilcox’s in CDCl₃

Desolavation and ESP:

\[ \log K = c_1 \alpha_2^H \beta_2^H + c_2 \]

\[ \alpha = E_{\text{max}} / 52 \text{ kJ mol}^{-1} = 4.1(\alpha_2^H + 0.33) \]

\[ \beta = -E_{\text{min}} / 52 \text{ kJ mol}^{-1} = 10.3(\beta_2^H + 0.06) \]

Diederich, F.; et. al Angew. Chem. Int. Ed. 2004, 43, 5056
Desolvation or $E_{\text{elec}}/E_{\text{rep}}$ Modulation?

Diederich: $(\alpha - \alpha_S) = 1.7$
Wilcox: $(\alpha - \alpha_S) = 0.3$

\[ \Delta \Delta G = - (\alpha - \alpha_S) \beta + c \]

grey: $R^1 = H$
black: $R^1 = \text{CF}_3$
Desolvation counters

\[(\alpha - \alpha_s)\]

<table>
<thead>
<tr>
<th>Y</th>
<th>Solvent</th>
<th>Theory</th>
<th>Experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF₃</td>
<td>Benzene</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>CF₃</td>
<td>Chloroform</td>
<td>1.4</td>
<td>1.3</td>
</tr>
<tr>
<td>H</td>
<td>Benzene</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>H</td>
<td>Chloroform</td>
<td>-0.2</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

\[\Delta \Delta G = -(\beta - \beta_s)\alpha + c\]

Based on \((\alpha + \alpha_s)\) between CDCl₃ and C₆D₆, a large sensitivity difference is not anticipated.

Sandwich interaction in [4+2] cycloaddition

1a: R = H  
1b: R = Me  
1c: R = OMe  
1d: R = Br

2a: R = H  
2b: R = Me  
2c: R = OMe  
2d: R = Br

3b: R = Me  
3c: R = OMe  
3d: R = Br

Substituent effects on ESP

Molecular Electrostatic Potential (Multipole Expansion)

\[ V(r) = \sum_{A}^{\text{nuclei}} \frac{Z_A}{|r - R_A|} - \int \frac{\rho(r')}{|r - r'|} \, dr' \]

ESP vs \( \rho \)
“net result at a given point of the integrated effects of all of the electrons and nuclei, whereas \( \rho(r) \) of course represents only the electronic density at that point.”

Are substituent effects on ESP manifested by polarization of \( \pi \)-electron density?

**Procedure**

\[ \text{optimize geometry} \rightarrow \text{evaluate esp on grid} \rightarrow \text{map esp onto e-density isosurface} \]

Compare ESP\(_A\) and ESP\(_B\) with Hodgkin index (H\(_{AB}\))

\[ H_{AB} = \frac{2 \int \rho_A \rho_B \, dv}{\int \rho_A^2 \, dv + \int \rho_B^2 \, dv} \]


Examples

Application of Method: Cation/\pi & Anion/\pi

Cation/\pi

\[-E_{int} = -1.04E_{int}(HX + C_{6}H_{5} - H\_2) - 0.46\]
\[r = 0.90\]

\[-E_{int}(H-X\cdots Na\_\text{Na}) + E_{int}(C_{6}H_{5}\cdots Na\_\text{Na}) - E_{int}(H-H\cdots Na\_\text{Na})\] (kcal mol\(^{-1}\))

\[E_{int} = 0.73E_{\text{additive}} + 0.41\]
\[r = 0.92\]

Anion/\pi

\[E_{int} = -0.98\text{ESP} - 7.27\]
\[r = 0.99\]

ESP (kcal mol\(^{-1}\)) above the Ring Centroid

Additive Interaction Energy (\(E_{int}^{\text{additive}}\), kcal mol\(^{-1}\))

Sandwich: minus one pi-surface?

Is all the variation in structure that accounts for the observed $E_{\text{int}}$ be derived from the just the substituent?

Attributed to Dispersion ($\sim -0.5$ kcal)

Substituent Additivity

Dispersion forces are likely contributing

Edge-to-Face aryl-aryl interactions

Wheeler, S. E.; Houk, K. N. *Molecular Physics* 2009, 107, 749
Global vs local dipole moment

Global dipole moment is insignificant relative to individual dipoles

Edge-ring-substituted  Face-ring-substituted

Wheeler, S. E.; Houk, K. N. *Molecular Physics* 2009, 107, 749
Conclusions

- Electrostatic-only (rather than donor-acceptor) considerations illustrate much of the observed experimental results (stacking orientation and substituent effects)

- Substituent effects generally follow that predicted by the polar/π model in the absence of significant dispersion contributions

- Gas phase calculations: dispersion forces are considered to be the principle contributor to the overall interaction

- Relative role of desolvation and dispersion forces in solution (e.g. CHCl₃ and C₆D₆) is inconclusive

- Origin of electrostatic interaction may primarily result from through-space interactions with the substituents for the majority of stacking configurations