Gas-phase data and computations suggest $K^+$ ion is selectively (de)solvated by multiple aromatic rings; implication for ion channels and transmembrane transport.
Solvent effects on weak intermolecular forces

1. The "classic" hydrophobic effect

\[ X\cdot (H_2O)_m + Y\cdot (H_2O)_n \rightarrow X\cdot Y + (H_2O)_{m+n} \]

\[ \Delta H^\circ_a \geq 0; \; \Delta S^\circ > 0 \]

2. Enthalpy-Entropy compensation

\[ \Delta G^\circ = \Delta G_{\text{complexation}} + \Delta G_{\text{solvation}} \]

\[ \Delta H^\circ_a = \Delta H_{\text{complexation}} + \Delta H_{\text{solvation}} \quad \text{typically} < 0 \]

\[ \Delta S^\circ = \Delta S_{\text{complexation}} + \Delta S_{\text{solvation}} \]

\[ S(X\cdot Y) - S(X) - S(Y) \quad \text{typically} > 0 \]

\[ H_s(X\cdot Y) + H_{\text{solv-solv}} - H_s(X) - H_s(Y) \]

If binding is tight, \( |\Delta S_{\text{complex}}| \) is large
If binding is loose, \( |\Delta S_{\text{complex}}| \) is small

Main source of enthalpy-entropy compensation
Enthalpy-entropy compensation: Case Studies

Case II: Porphyrin hosts with variable guests in nonpolar solutions

Hayashi et al, *JACS*, 1997, 119, 7281

Table 1. Binding Constants and Thermodynamic Parameters for Porphyrin–Quinone Complexes (in toluene)

<table>
<thead>
<tr>
<th>Porphyrin</th>
<th>4a</th>
<th>4b</th>
<th>4c</th>
<th>4d</th>
<th>4e</th>
<th>4f</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_b$ (M$^{-1}$)</td>
<td>(2.2 ± 0.1) x 10$^2$</td>
<td>(8.6 ± 0.1) x 10$^2$</td>
<td>(3.7 ± 0.1) x 10$^3$</td>
<td>(1.3 ± 0.1) x 10$^4$</td>
<td>(3.5 ± 0.1) x 10$^4$</td>
<td>(6.1 ± 1.1) x 10$^5$</td>
</tr>
<tr>
<td>$\Delta H^\circ$ (kcal/mol)</td>
<td>-8.1 ± 0.3</td>
<td>-9.6 ± 0.3</td>
<td>-10.7 ± 0.3</td>
<td>-12.2 ± 0.4</td>
<td>-14.0 ± 0.4</td>
<td>-22.7 ± 0.3</td>
</tr>
<tr>
<td>$T\Delta S^\circ$ (kcal/mol)</td>
<td>-4.9 ± 0.3</td>
<td>-5.5 ± 0.2</td>
<td>-5.9 ± 0.3</td>
<td>-6.7 ± 0.4</td>
<td>-7.8 ± 0.3</td>
<td>-14.7 ± 0.3</td>
</tr>
<tr>
<td>$\Delta G^\circ$ (kcal/mol)</td>
<td>-3.2 ± 0.1</td>
<td>-4.0 ± 0.1</td>
<td>-4.9 ± 0.1</td>
<td>-5.6 ± 0.1</td>
<td>-6.2 ± 0.1</td>
<td>-7.9 ± 0.2</td>
</tr>
</tbody>
</table>

Figure 3. X-ray crystal structure of 1-4 complex. The solvent molecules are omitted for clarity: (a) top view of one molecular structure and (b) side view for one molecular structure.

Figure 4. Comparison of thermodynamic parameters between 1-4 and 2-4 complexes in toluene at 298 K. (a) $-\Delta G^\circ$, (b) $-\Delta H^\circ$, and (c) $-\Delta S^\circ$.

Figure 5. Enthalpy-entropy compensation plot for 1 and 2 with a series of 4 in toluene at 298 K. All plots in the graph refer to the entries in Tables 1 and 2.
Enthalpy-entropy compensation: Case Studies

Case I: β-Cyclodextrin (n=7) with variable guests in aqueous solution

Table 1. Complex Stability Constant (K) and Thermodynamic Parameters in kcal/mol for 1:1 and/or 1:2 Inclusion Complex Formation of Naphthalene Derivatives with α-, β-, and γ-Cyclodextrins in Water at 25 °C

<table>
<thead>
<tr>
<th>Host</th>
<th>Guest</th>
<th>Stoichiometry (n)</th>
<th>log K</th>
<th>-ΔG</th>
<th>-ΔH</th>
<th>TΔS</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>2-naphthalenesulfonate (2)</td>
<td>1</td>
<td>2.56</td>
<td>3.49</td>
<td>0.78</td>
<td>2.71</td>
</tr>
<tr>
<td>α</td>
<td>2,7-naphthalenedisulfonate (4)</td>
<td>1</td>
<td>0.98</td>
<td>1.34</td>
<td>5.99</td>
<td>-4.65</td>
</tr>
<tr>
<td>α</td>
<td>1-naphthaleneacetate (7)</td>
<td>1</td>
<td>2.94</td>
<td>4.01</td>
<td>0.74</td>
<td>3.27</td>
</tr>
<tr>
<td>β</td>
<td>1-naphthalenesulfonate (1)</td>
<td>1</td>
<td>3.40</td>
<td>4.64</td>
<td>1.49</td>
<td>3.15</td>
</tr>
<tr>
<td>β</td>
<td>2-naphthalenesulfonate (2)</td>
<td>1</td>
<td>5.37</td>
<td>7.33</td>
<td>7.01</td>
<td>0.32</td>
</tr>
<tr>
<td>β</td>
<td>2,6-naphthalenedisulfonate (3)</td>
<td>1</td>
<td>3.20</td>
<td>4.39</td>
<td>2.79</td>
<td>1.70</td>
</tr>
<tr>
<td>β</td>
<td>2,7-naphthalenedisulfonate (4)</td>
<td>1</td>
<td>2.44</td>
<td>3.33</td>
<td>6.76</td>
<td>-3.42</td>
</tr>
<tr>
<td>β</td>
<td>2,3,6-naphthalenetrisulfonate (5)</td>
<td>1</td>
<td>2.22</td>
<td>3.03</td>
<td>3.09</td>
<td>-0.06</td>
</tr>
<tr>
<td>β</td>
<td>4-aminoo-1-naphthalenesulfonate (6)</td>
<td>1</td>
<td>1.70</td>
<td>2.32</td>
<td>2.18</td>
<td>0.06</td>
</tr>
<tr>
<td>β</td>
<td>1-naphthaleneacetate (7)</td>
<td>1</td>
<td>4.35</td>
<td>5.93</td>
<td>1.11</td>
<td>4.82</td>
</tr>
<tr>
<td>γ</td>
<td>2-naphthalenesulfonate (2)</td>
<td>1</td>
<td>1.58</td>
<td>1.58</td>
<td>4.18</td>
<td>-2.60</td>
</tr>
<tr>
<td>γ</td>
<td>2,7-naphthalenedisulfonate (4)</td>
<td>1</td>
<td>2.59</td>
<td>4.11</td>
<td>5.73</td>
<td>-1.62</td>
</tr>
<tr>
<td>γ</td>
<td>4-aminoo-1-naphthalenesulfonate (6)</td>
<td>1</td>
<td>1.31</td>
<td>1.79</td>
<td>6.70</td>
<td>-4.91</td>
</tr>
</tbody>
</table>

* Determined calorimetrically in buffered aqueous solution at pH 7.20 (0.1 M sodium phosphate); average of more than three independent runs.
* Guest/host ratio.

Figure 1. Free energy (-ΔG), enthalpy (-ΔH), and entropy changes (TΔS) for the inclusion complexation of naphthalene derivatives 1–7 with β-cyclodextrin in a buffered aqueous solution (pH 7.20) at 25 °C.

Inoue et al, JACS, 1993, 115, 475
Enthalpy-entropy compensation: Summary

Assuming a constant (linear) relation between $\Delta S$ and $\Delta H$:

$$T\Delta S^\circ = \alpha \Delta H^\circ + T\Delta S_0^\circ$$

$$\Delta G^\circ = (1-\alpha)\Delta H^\circ - T\Delta S_0^\circ;$$

$$\Delta \Delta G^\circ = (1-\alpha)\Delta \Delta H^\circ$$

Case I (naphthalenesulfonate-cyclodextrin complexation): $\alpha = 0.90$

Case II (porphyrin-quinone complexation): $\alpha = 0.62$
Enthalpy-entropy compensation: Solvent effects

Case IV: Cyclophane host with pyrene guest in variable solutions: 
\[ \Delta H_{\text{comp}}, \Delta S_{\text{comp}} \text{ remains constant} \]

Observations:

1) host-guest complex formation is enthalpically driven (in most cases)
2) enthalpy-entropy compensation is in effect \((\alpha = 0.72)\)

Cases where \(\Delta S^o > 0\): possibly due to release of caged solvent
\((\Delta H^o > 0 \text{ as well, due to differences in van der Waals})\)
**π-π interactions**


<table>
<thead>
<tr>
<th>X</th>
<th>$K_s$(CDCl₃, 298 K), M⁻¹</th>
<th>$\Delta G^\circ$, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>290</td>
<td>3.35</td>
</tr>
<tr>
<td></td>
<td>570</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>138</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>2.7</td>
</tr>
</tbody>
</table>

due to differences in binding modes (see next slide)


- aromatic rings have permanent quadrupole moment
- van der Waals interactions favor maximum coplanar overlap, but direct stacking results in electronic repulsion
- π-electrons in aromatic systems are delocalized, but electropositive nuclei (σ-framework) generate local electric field
\( \pi-\pi \) interactions: X-ray crystal structures

**Tyrosine–guanosine stacking complex**

Electron-donating substituents (-OR) Increase **edge-to-face** interactions!

---

**Figure 1.** (a) X-ray structure of 1 and (b) X-ray structure of the complex between 1 and 5.

Hamilton and van Engen, *JACS*, **1987**, 109, 5035

Guanosine binding site of ribonuclease \( T_1 \). Guanosine is shown in bold.

Rules for predicting $\pi-\pi$ interactions:

1) $\pi-\pi$ orbital repulsion dominates in face-to-face stacking

2) $\pi-\sigma$ orbital attraction dominates in edge-to-face stacking

3) $\pi-\sigma$ orbital attraction results in an offset stacking

Electronic effects:

- $\pi$ orbital electron density is affected as a function of the substituents, but effect is averaged and has no significant effect on orientation

- $\sigma$-framework is polarized by electronegative substituents, with substantial consequences for interacting $\pi$ systems

Hunter and Sanders, JACS, 1990, 112, 5525
Hunter–Sanders Rules for \( \pi-\pi \) interactions

Hunter and Sanders, *JACS*, 1990, 112, 5525

Figure 1. The four basic aromatic crystal packings. The short axes are indicated in each case.

Figure 9. Interaction between two idealized \( \pi \)-atoms as a function of orientation: two attractive geometries and the repulsive face-to-face geometry are illustrated.

Edge-to-face binding interaction

\((C-H \cdots \pi \text{ interaction})\)

Edge-to-face interactions in a quinone receptor:

Molecular Recognition of Apolar Organic Molecules

Surface complementarity as a driving force in nonpolar solvents: Cram et al., *J. Am. Chem. Soc.* 1985, 2574

Complexation is entropically driven, but stabilized by vdW forces

![calix[4]resorcinarene](image_1)

Complexation with $\text{CS}_2$:

<table>
<thead>
<tr>
<th>R</th>
<th>$K_a$ (CDCl$_3$, 250 K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>0.82</td>
</tr>
<tr>
<td>Et</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>13.2</td>
</tr>
</tbody>
</table>

"cavitand" - cavity-bearing ligand
Encapsulation of Guest Molecules

Encapsulation: process by which guest cannot dissociate from host without major changes in conformation of bond restructuring (i.e., entry and exit cannot occur by simple diffusion)

2. "Cryptophane" inclusion complex with halogenated solvent molecules:

Canceill et al., J. C. S. Chem. Commun. 1985, 361;
Canceill et al., Angew. Chem. 1989, 28, 1246.