$V = \frac{q_i q_j}{\varepsilon r_{ij}}$ Gaussian units

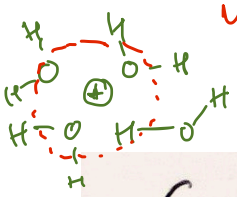
$V = \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij} \varepsilon}$ SI units

Energy in Kcal/mol
distance Å
charge multiples of electron charge

$V \cong 332 \frac{q_i q_j}{\varepsilon r}$

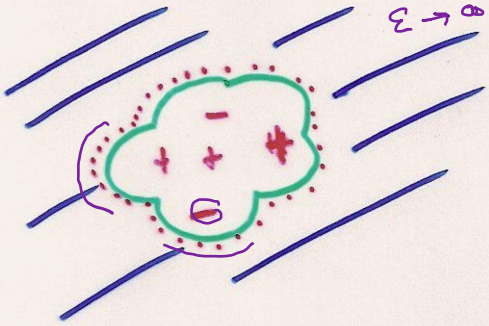
Continuum solvent models

CCB 422/522, Spring 2021



Conductor-like Screening Model

Andreas Klamt
J. Chem. Soc. Perkin 1993, 799



charges

q

$$E = E_{gas} + \int z \frac{1}{r_z - r_s} q + \frac{1}{2} \int q \frac{1}{r_s - r_{s'}} q' \qquad \frac{\varepsilon}{\varepsilon - 1}$$

$$= E_{gas} + z B q + \frac{1}{2} q A q$$

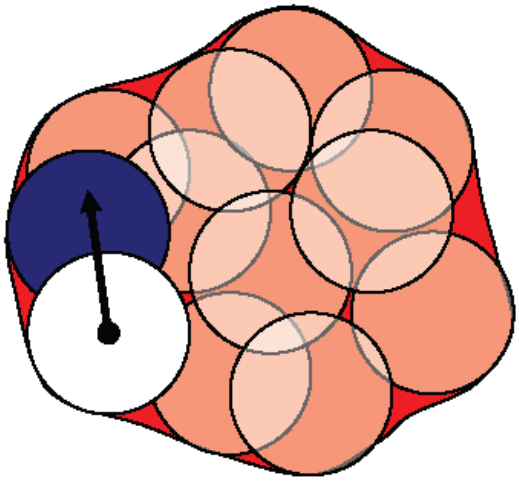
$$\frac{\partial E}{\partial q} = 0 \Rightarrow A q = -Bz \quad \text{or} \quad \boxed{q = -A^{-1} B z}$$

molecule-solvent interaction: $-z B A^{-1} B z \equiv -z \phi^{RF}$

solvent-solvent interaction: $\frac{1}{2} z B A^{-1} A A^{-1} B z = \frac{1}{2} z B A^{-1} B z$

1 The generalized Born model

Simplest model has "high" ε_{ext} outside (white) and "low" ε_{in} where solvent is excluded:



The solvation energy can be computed by quadrature if one adopts the Coulomb field approximation:

$$W = \frac{1}{8\pi}\int \mathbf{E}\cdot\mathbf{D}dV = \frac{1}{8\pi}\left[\int_{in}\frac{q^2}{\varepsilon_{in}r^4}dV + \int_{ext}\frac{q^2}{\varepsilon_{ext}r^4}dV\right]$$

$$\Delta G = W(\varepsilon_{ext}=80) - W(\varepsilon_{ext}=1)$$

$$\Delta G_{GB} = -\frac{1}{2}\left(1-\frac{1}{\varepsilon_{ext}}\right)\frac{q^2}{R_{eff}};\quad or\quad -\frac{1}{2}\left(1-\frac{1}{\varepsilon_{ext}}\right)\frac{q_iq_j}{f^{GB}(R^i_{eff},R^j_{eff},r_{ij})}$$

$$R^{-1}_{eff} = \frac{1}{4\pi}\int_{ext} r^{-4}dV$$

Bashford & Case, *Annu. Rev. Phys. Chem.* **51,** 129 (2000)

$$\left(1-\frac{1}{\varepsilon}\right) \rightarrow \left(1-\frac{e^{-\kappa f^{GB}(d_{ij})}}{\varepsilon}\right)$$

not just water, but salt-water as solvent

↳ comes from Debye-Hückel theory next week's lecture

2 Why explore implicit solvent models?

- simulation speed
- improved sampling — water & counterions; solute (no friction)
- algorithm flexibility — Monte Carlo move set; multiple-copies models; landscape chacterization; simulated annealing; normal mode analysis
- new free energy methods

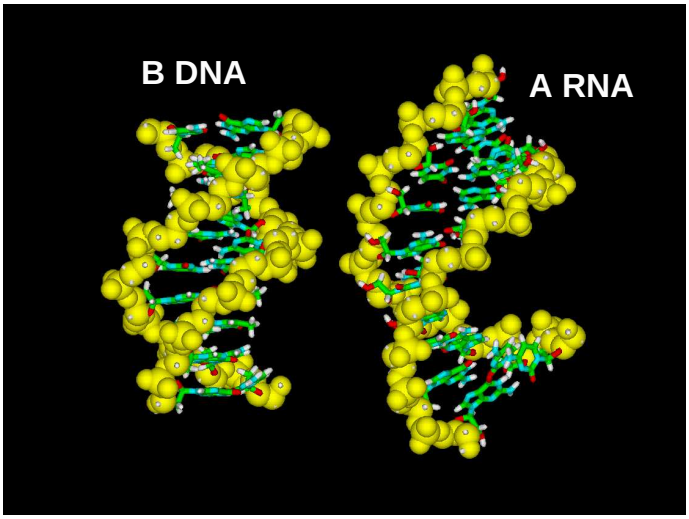
traditional:

$$\Delta G = \int_0^1 \langle \frac{\partial V}{\partial \lambda} \rangle_\lambda \, d\lambda$$

also feasible:

$$G \approx < H_{MM} > + H^{tr} - TS_{chain} + < G_{sol} >^{elec} + < G_{sol} >^{nonp}$$

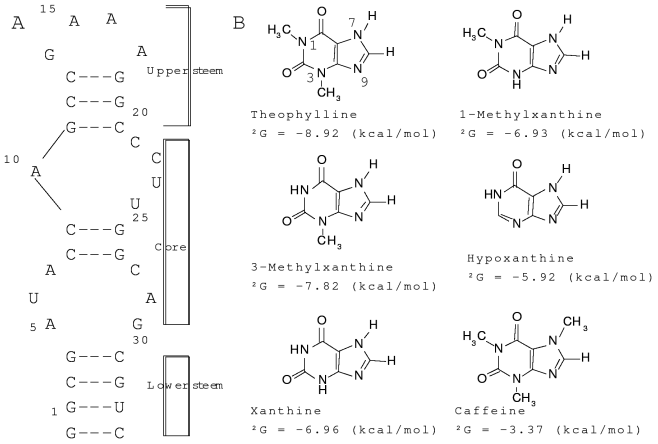
3 B-A energy differences for r,d(CCAACGTTGG)$_2$

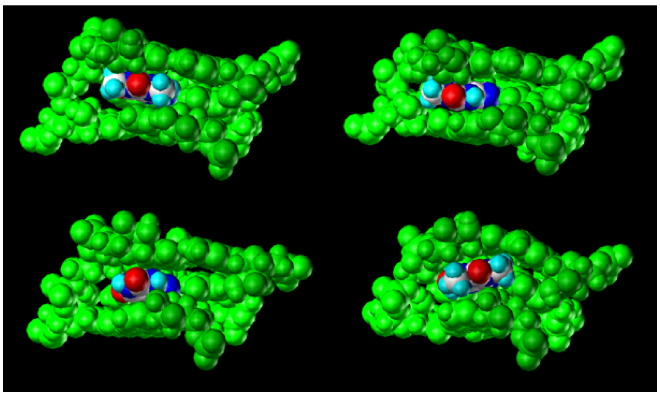


	DNA	RNA
Couomb	-293.0	-266.9
PB	286.6	240.2
GB	288.1	242.2
vdW	-7.7	18.7
bad	-7.0	17.6
$-T\Delta S$	2.9	0.5
total	-21.0	9.8
0.1M salt	5.2	3.4
1.0M salt	6.0	3.9

Srinivasan, Cheatham, Kollman, Case, JACS 120, 9401 (1998)

4 Application: theophylline binding to an RNA aptamer





Gouda, Kuntz, Case & Kollman, *Biopolymers* **68**:16 (2003)

compound	$\Delta G(MM-PBSA)$	$\Delta G(TI)$	$\Delta G(exp)$
theophylline	-9.3		-8.9
theophylline	0.0	0.0	0.0
3-methylxanthine	3.3	1.0	1.1
xanthine	7.0	1.6	2.0
1-methylxanthine	4.4	1.8	2.0
hypoxanthine	8.6		3.0
caffeine	6.7	6.6	5.5