Insights from Theory into Structure and Stability of Guanine Quadruplexes

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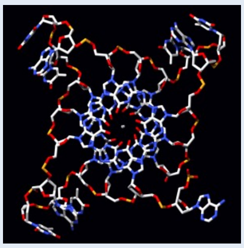
VU UNIVERSITY AMSTERDAM

Outline



1. Resonance-Assistance in B-DNA
2. Cooperativity in Guanine Quartets and Quadruplex
3. Ion Selectivity at the Internal Cavity Site of G-Quadruplexes

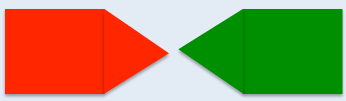
Kohn-Sham DFT Approach

DFT with ADF:

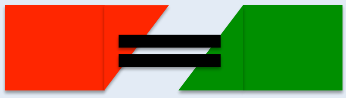
- Level → BLYP-D3(BJ)/TZ2P
- Accuracy → ca. kcal/mol, trends better
  Benchmarked for S22 and DNA
- Solvent → **CO**nductor-like **S**creening **MO**del

Angew. Chem. Int. Ed. **2009**, *48*, 3285

Energy Decomposition Analysis



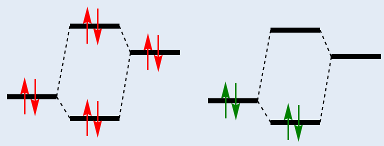
Energy Decomposition Analysis



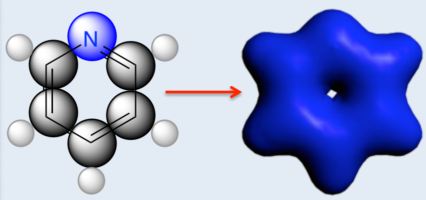
$\Delta E_{\text{deformation}}$

$\Delta V_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{oi}} + \Delta E_{\text{disp}}$

δ+ ⇨ ⇦ δ−



Voronoi Deformation Density from atoms



$\sum_B \rho_B(\mathbf{r})$ to $\rho^{molecule}(\mathbf{r})$

$Q_A^{VDD} < 0$ → A **gains** electrons

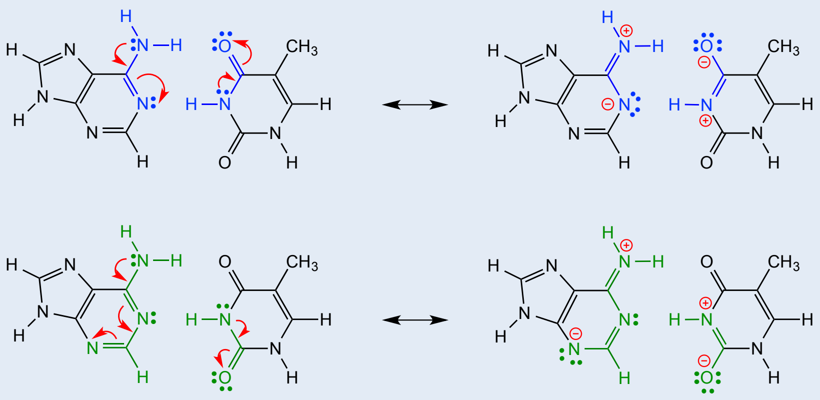
$Q_A^{VDD} > 0$ → A **loses** electrons

$$Q_A^{VDD} = -\int_{\substack{\text{Voronoi} \\ \text{cell of A}}} \left(\rho^{molecule}(\mathbf{r}) - \sum_B \rho_B(\mathbf{r}) \right) d\mathbf{r}$$

J. Comput. Chem **2004**, 25, 189

Importance of Resonance-Assistance

In Watson-Crick Base Pair AT



I.B-DNA: Energy Decomposition Analysis

	AT	GC
ΔE_{Bond}	−13.0	−26.5
ΔE_{prep}	2.3	4.1
ΔE_{int}	−15.3	−30.6

I.B-DNA: Energy Decomposition Analysis

	AT	GC
ΔE_{Bond}	−13.0	−26.5
ΔE_{prep}	2.3	4.1
ΔE_{int}	−15.3	−30.6
ΔE_{Pauli}	39.2	52.1
ΔV_{elstat}	**−32.1**	**−48.6**
ΔE_{oi}	**−22.4**	**−34.1**

I.B-DNA: Energy Decomposition Analysis

	AT	GC	
ΔE_{Bond}	−13.0	−26.5	
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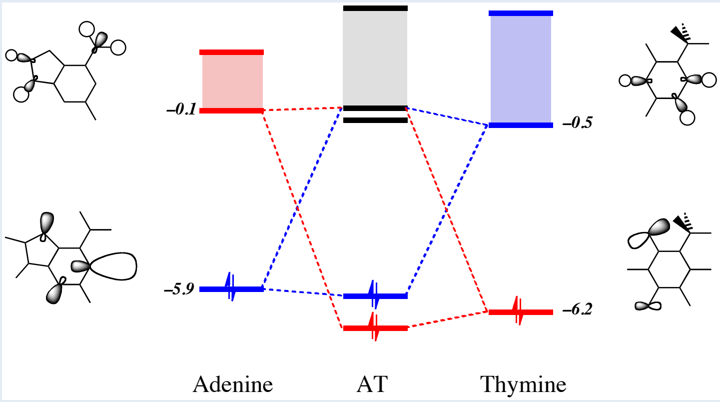
ΔE_{Pauli}	39.2	52.1	
ΔV_{elstat}	**−32.1**	**−48.6**	
ΔE_{oi}	**−22.4**	**−34.1**	
ΔE_{σ}	−20.7	−29.3	
ΔE_{π}	**−1.7**	**−4.8**	RAHB

I. B-DNA: MO diagrams of AT and GC

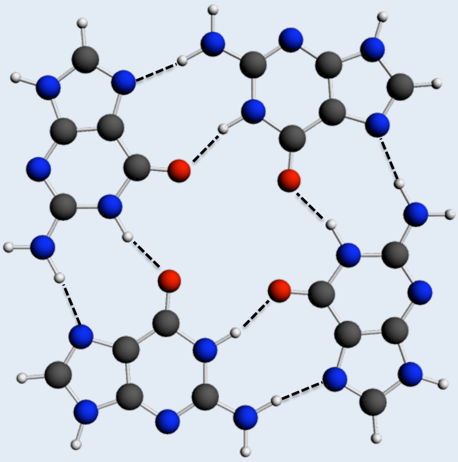


I. B-DNA: Conclusions on RAHB

- Electrostatic interaction
- Orbital interaction
  - Charge transfer in σ system
  - Some assistance by π delocalisation

But also in G-DNA

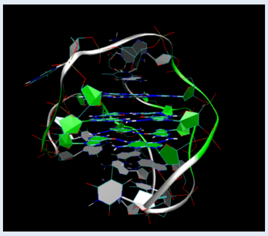
2. G-DNA: Guanine quartet



2. G-DNA: In Telomeres

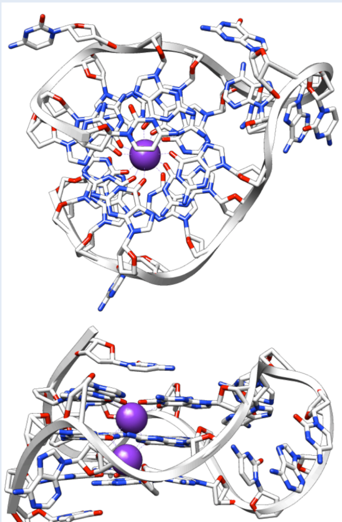
Nobel Prize in Medicine 2009

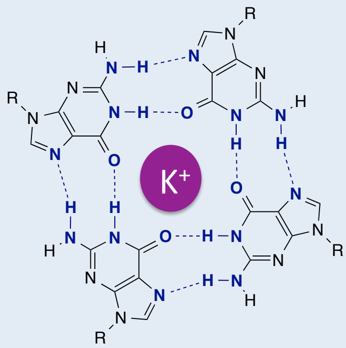
for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase



Blackburn Greider Szostak

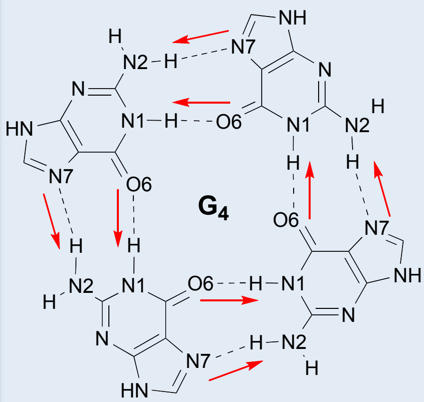
2. G-DNA: In Telomeres

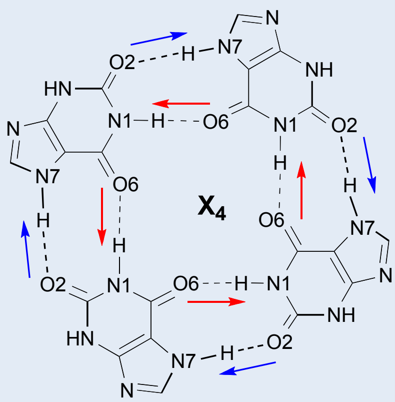

Balasubramanian et al.



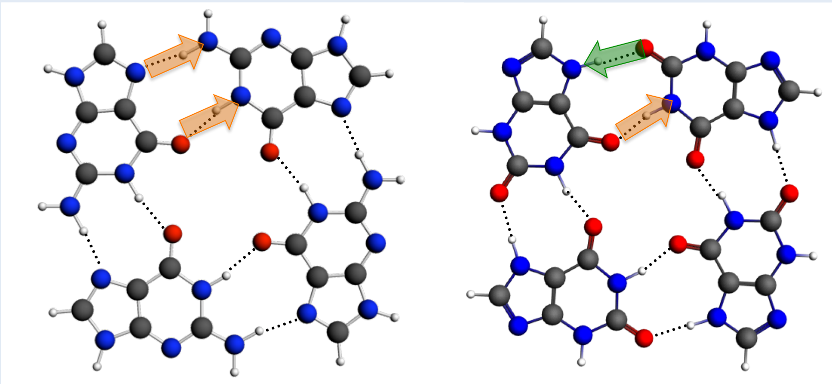
$$4*\Delta E(G_2) < \Delta E(G_4)$$

2. G-DNA: Guanine and Xanthine





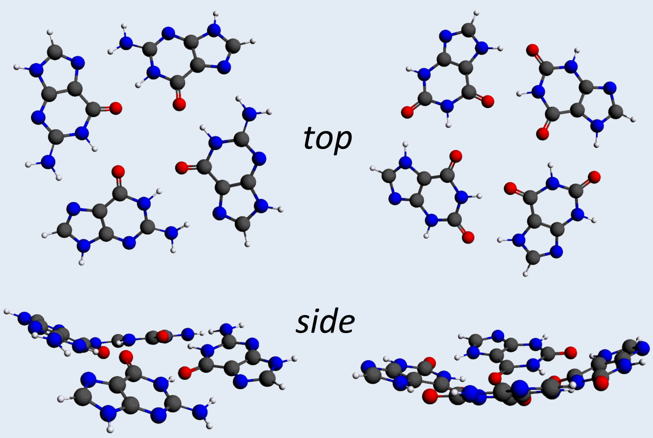
2. G-DNA: Guanine and Xanthine



$4 \bullet \Delta E(G_2) < \Delta E(G_4)$ $4 \bullet \Delta E(Xan_2) = \Delta E(Xan_4)$

Chem. Eur. J. **2011**, *17*, 12612

2. G-DNA: Guanine and Xanthine



G_4 (in S_4) X_4 (in C_4)

Chem. Eur. J. **2011**, *17*, 12612

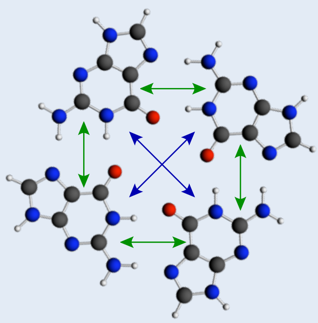
2. G-DNA: Guanine and Xanthine

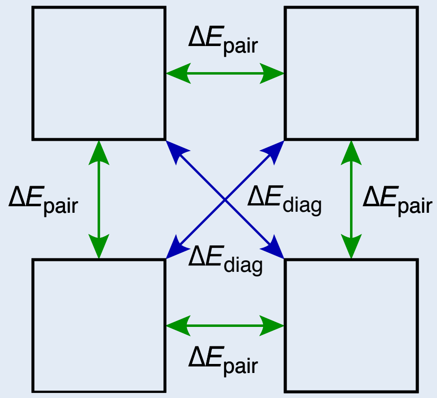
Quartet	Symmetry	ΔE_{bond}
G_4	S_4	**−79.8**
	C_{4h}	−79.1
X_4	C_4	**−66.5**
	C_{4h}	−65.5

- *G_4 stronger bound than X_4*
- *C_{4h} symmetry applicable*

Chem. Eur. J. **2011**, *17*, 12612

2. G-DNA: Cooperativity





Synergy = $\Delta E_{int} - (4{*}\Delta E_{pair} + 2{*}\Delta E_{diag})$

2. G-DNA: Cooperativity

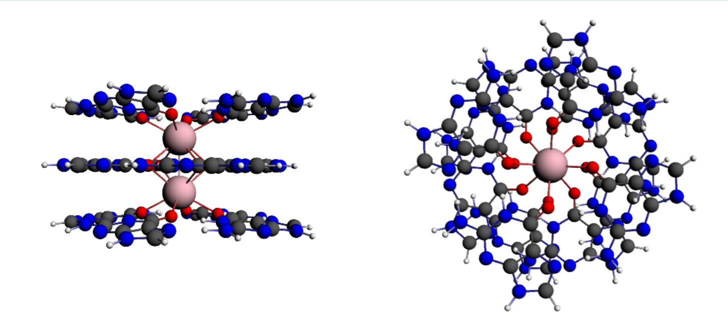
Quartet	ΔE_{int}	ΔE_{sum}	$\Delta E_{int} - \Delta E_{sum}$
G_4	−89.1	−68.3	
G_4 no π	−75.4	−61.2	
X_4	−72.6	−71.1	
X_4 no π	−64.6	−62.2	

2. G-DNA: Cooperativity

Quartet	ΔE_{int}	ΔE_{sum}	$\Delta E_{int} - \Delta E_{sum}$
G_4	−89.1	−68.3	**−20.8**
G_4 no π	−75.4	−61.2	**−14.3**
X_4	−72.6	−71.1	−1.5
X_4 no π	−64.6	−62.2	−2.4

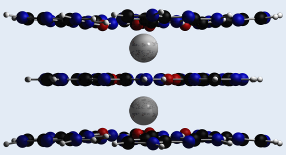
- *cooperativity*
- *even when* ***π*** *electrons do* ***NOT*** *cooperate!*

2. G-DNA: G_4 –K^+– [B_4] – K^+–G_4



$$\Delta E_{int} = \underbrace{[\Delta E(G_{12}K_2^{2+}) - \Delta E(G_8K_2^{2+})]}_{\text{Quartet}} - 4*\underbrace{[\Delta E(G_9K_2^{2+}) - \Delta E(G_8K_2^{2+})]}_{\text{Base}}$$

2. G-DNA: G_4 –K^+– [B_4] – K^+–G_4

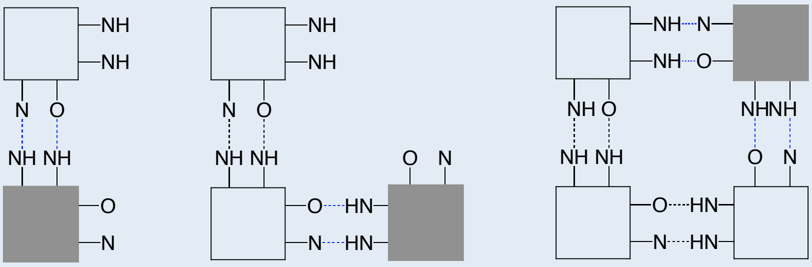


$G_4K^+[G_4]K^+G_4$

	Quartet	ΔE_{int}	ΔE_{sum}	Synergy
$G_4 - K^+ - [G_4\ ] - K^+ - G_4$	G_4	–72.7	–54.8	–17.9

Cooperativity under “natural” conditions

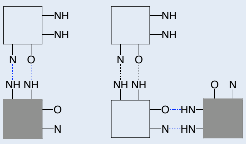
2. G-DNA: Building up G_4



G_2 G_3 G_4

2. G-DNA: Building up G_4

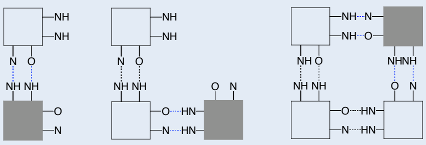
	G_2 (G+G)	G_3 (G_2+G)
ΔE_{oi}	−16.4	−18.3
ΔE_{Pauli}	30.7	30.0
ΔV_{elstat}	−26.2	−29.9
ΔE_{disp}	−4.2	−4.4
ΔE_{int}	−16.1	−22.7



G_2 G_3

2. G-DNA: Building up G_4

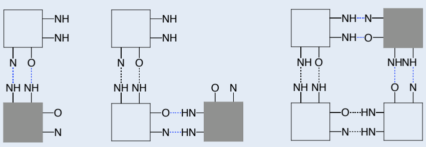
	G_2 ($G+G$)	G_3 (G_2+G)	G_4 (G_3+G)
ΔE_{oi}	−16.4	−18.3	−42.1
ΔE_{Pauli}	30.7	30.0	60.9
ΔV_{elstat}	−26.2	−29.9	−60.6
ΔE_{disp}	−4.2	−4.4	−8.6
ΔE_{int}	−16.1	−22.7	−50.3



G_2 G_3 G_4

2. G-DNA: Building up G_4

	G_2 ($G+G$)	G_3 (G_2+G)	G_4 (G_3+G)	$[G_2 + G_3 + G_4] - 4G_2 - 2G_{2diag}$
ΔE_{oi}	−16.4	−18.3	−42.1	−10.8
ΔE_{Pauli}	30.7	30.0	60.9	−1.4
ΔV_{elstat}	−26.2	−29.9	−60.6	−8.6
ΔE_{disp}	−4.2	−4.4	−8.6	0.0
ΔE_{int}	−16.1	−22.7	−50.3	−20.8

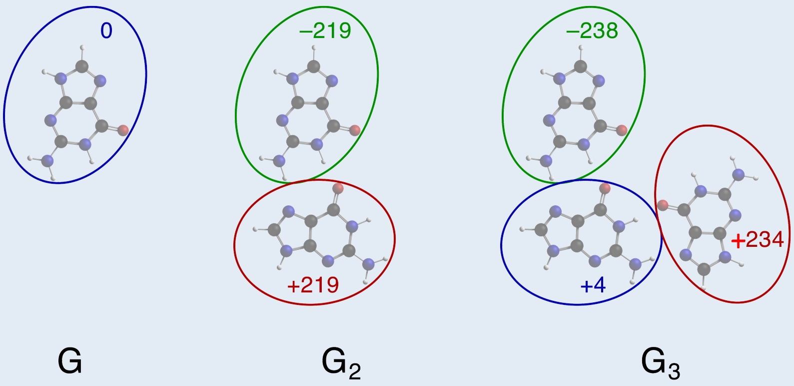


G_2 G_3 G_4

2. G-DNA: Building up G_4

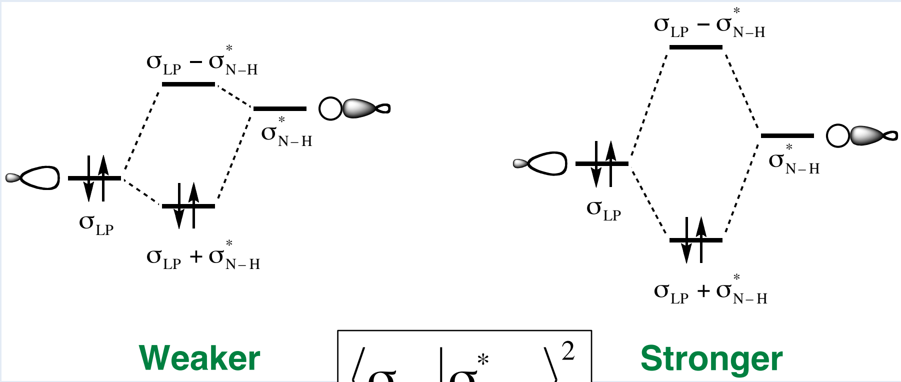
	G_2 (G+G)	G_3 (G_2+G)	G_4 (G_3+G)	[G_2 + G_3+ G_4] $-4G_2 -2G_{2diag}$
ΔE_{oi}	−16.4	−18.3	−42.1	−10.8
ΔE_{Pauli}	30.7	30.0	60.9	−1.4
ΔV_{elstat}	−26.2	−29.9	−60.6	−8.6
ΔE_{disp}	−4.2	−4.4	−8.6	0.0
ΔE_{int}	−16.1	−22.7	−50.3	−20.8
ΔE_{σ}	−14.6	−16.0	−35.9	−7.8
ΔE_{π}	−1.8	−2.3	−6.2	−3.0

2. G-DNA: Electrostatic interaction



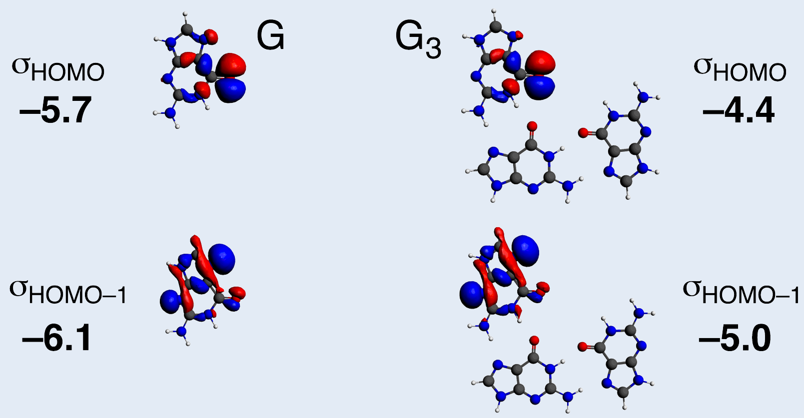
In mili-electrons

2. G-DNA: MO-diagram



$$\propto \frac{\langle \sigma_{LP} | \sigma^{*}_{N-H} \rangle^{2}}{E_{\sigma_{LP}} - E_{\sigma^{*}_{N-H}}}$$

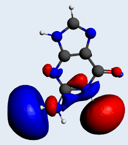
2. G-DNA: Donor orbitals G_4 (eV)

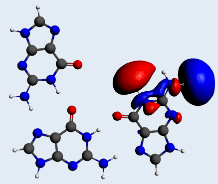


2. G-DNA: Acceptor orbitals G_4 (eV)

σ_{LUMO+2}

0.1



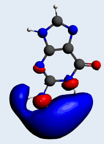


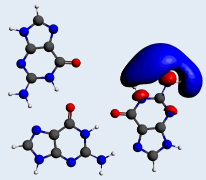
σ_{LUMO+3}

–0.1

σ_{LUMO}

–1.1





σ_{LUMO}

–1.2

2. G-DNA: Cooperativity G_4

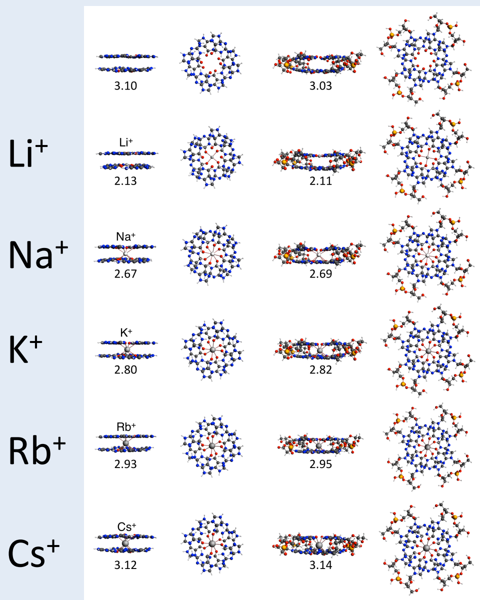
- about 20 kcal/mol
- in gas phase, stack and telomere
- not due to RAHB!
- due charge separation in σ system

due to covalent component in hydrogen bonds

3. Ion Selectivity: why K^+ is preferred?

- by **the size of the cavity** and the relatively fit of cations
  - Williamson et al. Cell (1989)
- on the different free **solvation energies of cations** competing for the channel site
  - Hud et al. Biochemistry (1996) & Leszczynski JPCA(2002)

3. Ion Selectivity: systems studied



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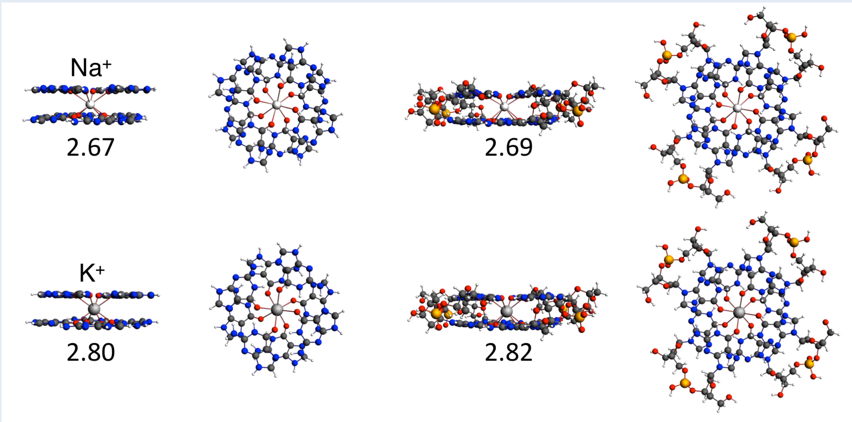
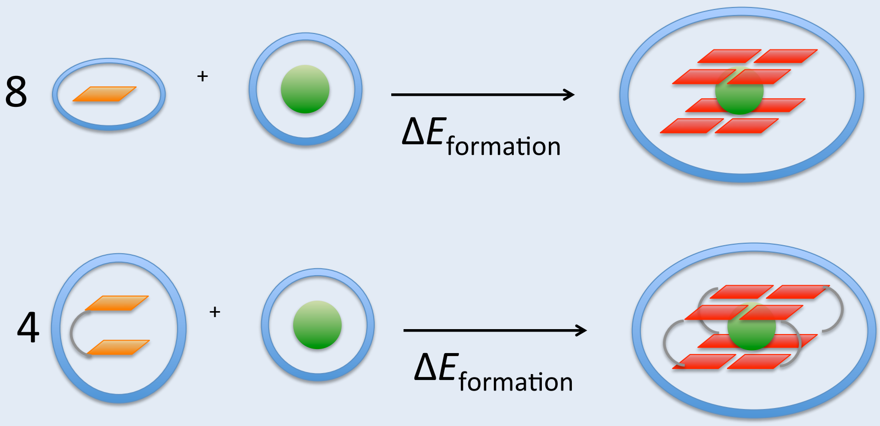


3. Ion Selectivity: Energy of formation



3. Ion Selectivity: ΔE_{form} for G_4-M^+-G_4

System	M^+	$D[O–M^+]$	ΔE_{form}
parallel	-	3.10	-84.4
	Li^+	2.13	-122.9
	Na^+	**2.67**	**-138.4**
	K^+	**2.80**	**-138.8**
	Rb^+	2.93	-132.7
	Cs^+	3.12	-124.7

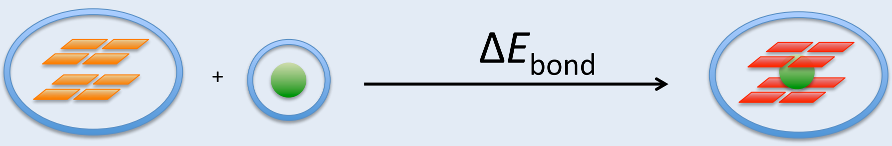
3. Ion Selectivity: ΔE_{form} for GQ-M^+

System	M^+	$D[O–M^+]$	ΔE_{form}
GQ-M^+	-	3.03	-62.5
	Li^+	2.11	-100.2
	Na^+	**2.69**	**-114.5**
	K^+	**2.82**	**-115.4**
	Rb^+	2.95	-111.1
	Cs^+	3.14	-103.1

3. Ion Selectivity: ΔE_{form} for GQ-M^+

System	M^+	$D[O–M^+]$	ΔE_{form}
GQ-M^+	-	3.03	-62.5
	Li^+	2.11	-100.2
	Na^+	**2.69**	**-114.5**
	K^+	**2.82**	**-115.4**
	Rb^+	2.95	-111.1
	Cs^+	3.14	-103.1
GQ_{4Na}-M^+	-	3.09	-67.6
	Na^+	**2.70**	**-119.1**
	K^+	**2.83**	**-120.4**

3. Ion Selectivity: Partioning ΔE_{Bond}



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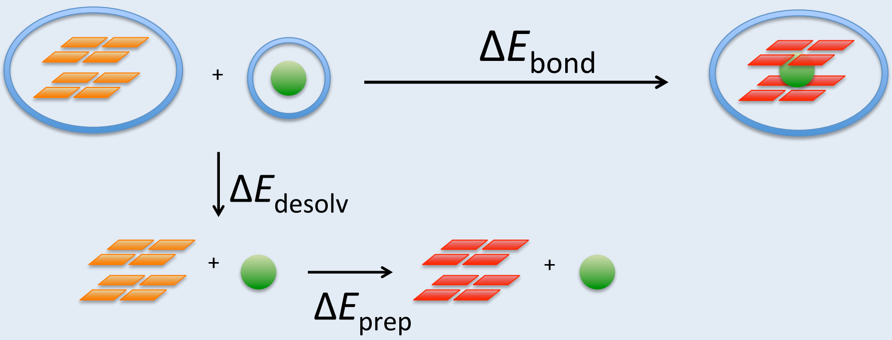

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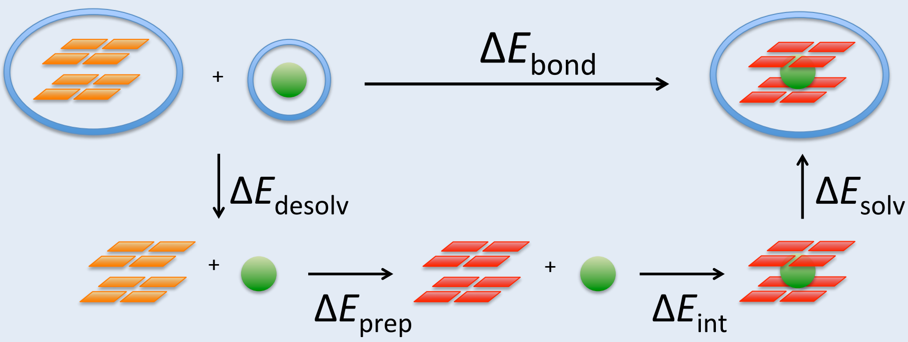
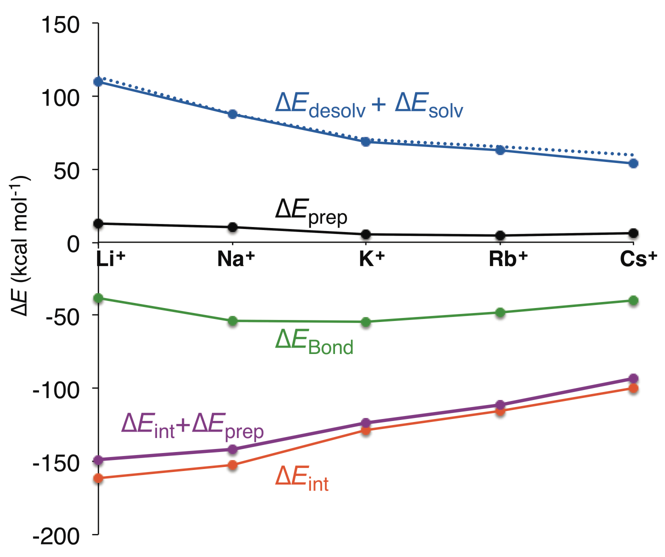
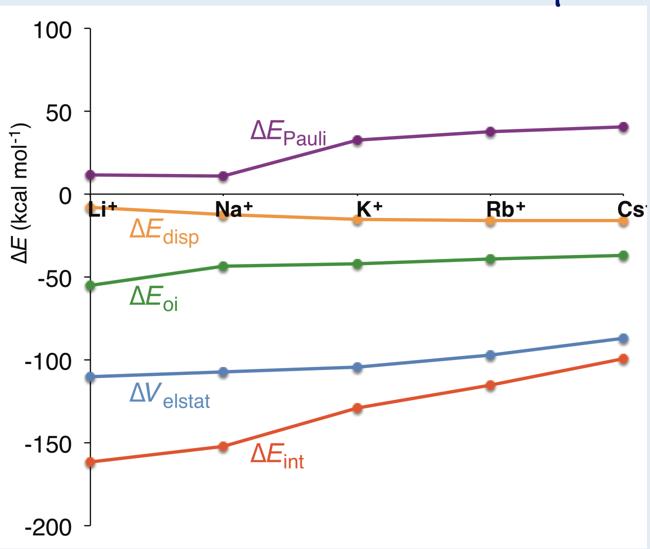


3. Ion Selectivity: Partioning for G_4-M^+-G_4



3. Ion Selectivity: Energy Decomposition for G_4-M^+-G_4



3. Ion Selectivity: Why K^+ is preferred

- *Desolvation/solvation for Na^+ is larger than for K+*
  - Follows trend of desolvation of the cations
- *Na^+ has a better interaction than K^+*
  - 2/3 electrostatics and 1/3 orbital interaction

Steric effects responsible for smaller ΔE_{int} for K^+.
But Deformation less for K+

Acknowledgements

F. Zaccaria Guillaumes G. Paragi H. Zijlstra N. Smits L. Wolters L.

YOUR KIND ATTENTION

Further reading on G-DNA

- ***CEJ* 2011, *17*, 12612**
- *CEJ* **2014**, *20*, 9494
- *PCCP*, **2015**, *17*, 1585
- *ChemOpen*, **2015**, *4,* 318
- ***PCCP*, 2016, *18*, 20895**

http://www.few.vu.nl/~guerra/