

# L'attaque de l'électron masqué (de basse énergie)

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École Normale Supérieure de Lyon,  
Lyon, France.

19<sup>th</sup> September 2008

## The murderer: the electron



- Secondary electrons<sup>1</sup> of low-energy<sup>2</sup> (< 30 eV)

<sup>1</sup>L. Sanche *Radiat. Phys. Chem.* **1989**, 34, 15.

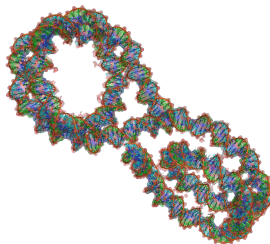
<sup>2</sup>L. Sanche *Eur. Phys. J. D* **2005**, 35, 367.

## The murderer: the electron



- Secondary electrons<sup>1</sup> of low-energy<sup>2</sup> (< 30 eV)

## The victim: the supercoiled DNA



- Dry DNA (only structural H<sub>2</sub>O and counteractions)

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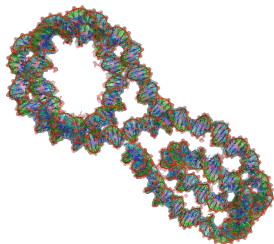
## The murderer: the electron



- Secondary electrons<sup>1</sup> of low-energy<sup>2</sup> ( $< 30$  eV)

⇒ **Single-strand breaks** (SSB) and **double-strand breaks** (DSB)

## The victim: the supercoiled DNA



- Dry DNA (only structural H<sub>2</sub>O and counteranions)

<sup>1</sup>L. Sanche *Radiat. Phys. Chem.* **1989**, 34, 15.

<sup>2</sup>L. Sanche *Eur. Phys. J. D* **2005**, 35, 367.

## The pieces of evidence

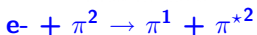
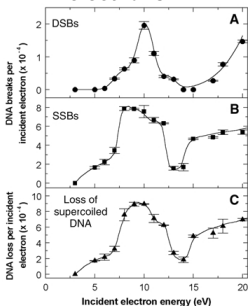
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<sup>3</sup>Boudaïffa et al. *Science* **2000**, *287*, 1658.

<sup>4</sup>Martin et al. *PRL* **2004**, *93*, 068101.

## The pieces of evidence

"Resonant formation of DNA strand breaks by low-energy (3-20 eV) electrons"<sup>3</sup>

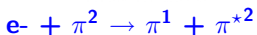
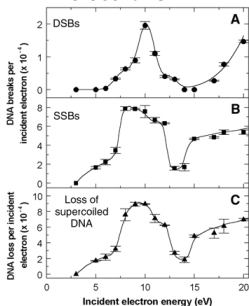


<sup>3</sup>Boudaïffa et al. *Science* **2000**, *287*, 1658.

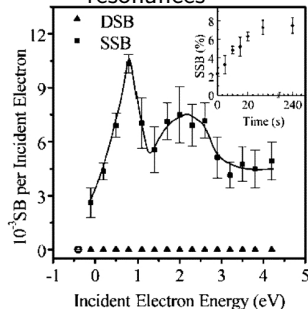
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"Resonant formation of DNA strand breaks by low-energy (3-20 eV) electrons"<sup>3</sup>



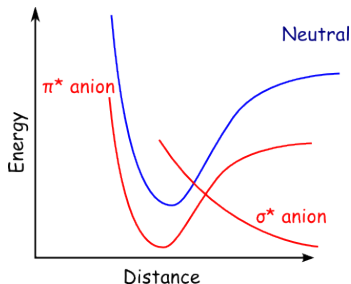
"DNA strand breaks induced by 0-4 eV electrons: the role of shape resonances"<sup>4</sup>



<sup>3</sup>Boudaïffa et al. *Science* **2000**, *287*, 1658.

<sup>4</sup>Martin et al. *PRL* **2004**, *93*, 068101.

## A through-bond electron transfer process<sup>5</sup>



<sup>5</sup>Barrios et al. *JPCB* **2002**, *106*, 7991; J. Simons *Acc. Chem. Res.* **2006**, *39*, 772.

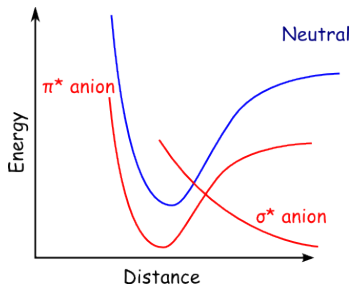
<sup>6</sup>Li et al. *JACS* **2003**, *125*, 13668; Gu et al. *JACS* **2006**, *128*, 9322.

<sup>7</sup>Theodore et al. *Chem. Phys.* **2006**, *329*, 139; Gu et al. *Angewandte* **2007**, *46*, 1.

<sup>8</sup>Liang et al. *JCC* **2008**, in press.



## A through-bond electron transfer process<sup>5</sup>



$\pi^*$  orbital ?  
phosphate or base<sup>5</sup> ?

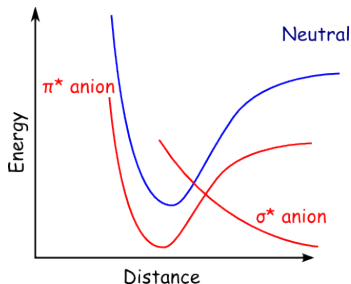
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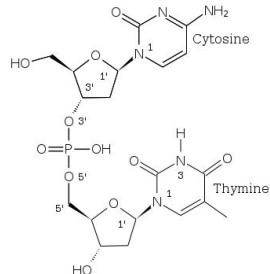
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### Pyrimidines or purines ?



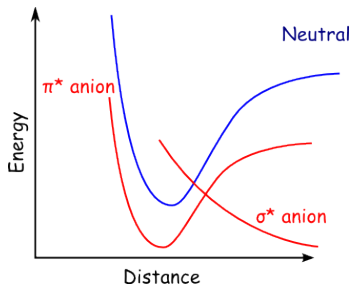
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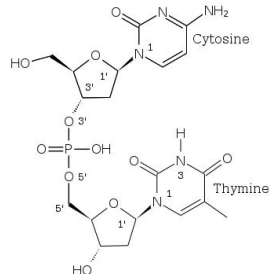
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## A through-bond electron transfer process<sup>5</sup>



$\pi^*$  orbital ?  
phosphate or base<sup>5</sup> ?

Pyrimidines or purines ?



$\sigma$  bond ?  
 $C_{3'}-O_{3'}$  or  $C_{5'}-O_{5'}$ <sup>6</sup> ?  
 $C_{1'}-N_1$  or  $N_3-H$ <sup>7</sup> ? Other<sup>8</sup> ?

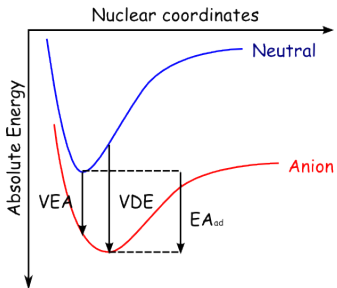
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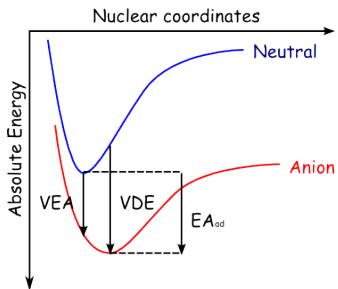
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## Requirement for an electron capture

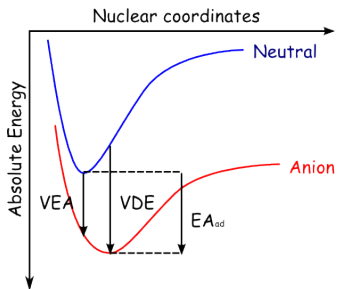


## Requirement for an electron capture



- **VEA: Vertical Electron Affinity**
- **EA<sub>ad</sub>: adiabatic Electron Affinity**
- **VDE: Vertical Detachment Energy**

## Requirement for an electron capture



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- **VDE: Vertical Detachment Energy**

**Electron capture**  $\iff$  **VEA**, **EA<sub>ad</sub>** and **VDE** should be  $> 0$

## Single nucleotide: 2'-deoxycytidine-3'-monophosphate (3'-dCMPH)

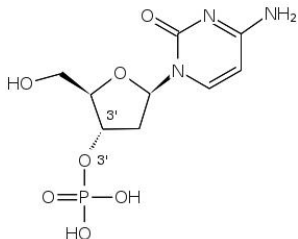
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<sup>9</sup>Gu et al. *JACS* **2006**, *128*, 1250.

<sup>10</sup>Gu et al. *JACS* **2006**, *128*, 9322.

## Single nucleotide: 2'-deoxycytidine-3'-monophosphate (3'-dCMPH)

### ■ Electron affinities<sup>9</sup> (eV)



<b>EA<sub>ad</sub></b>	<b>0.15</b>
<b>VEA</b>	<b>0.00</b>
<b>VDE</b>	<b>0.87</b>

Level of theory: B3LYP/6-311+G\*

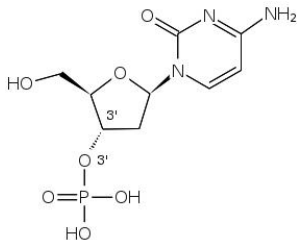
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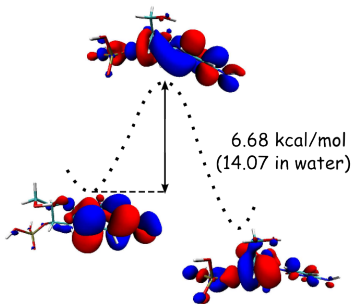
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- Energetic barrier of the C<sub>3'</sub>-O<sub>3'</sub> bond cleavage<sup>10</sup> (kcal/mol)



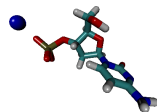
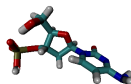
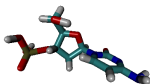
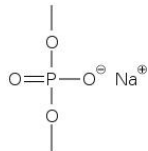
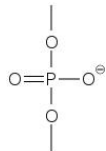
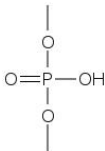
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## Adiabatic electron affinities wrt protonation state

$EA_{ad}$  (eV)

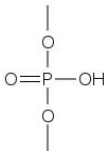


<sup>11</sup>IEF-PCM model using water solvent and UA0 radii.

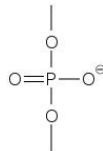
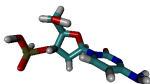


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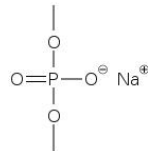
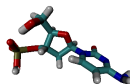
$EA_{ad}$  (eV)  
Gas phase



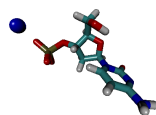
0.15



-2.18



Na-attached

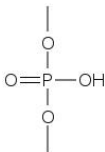


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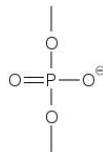
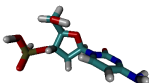


## Adiabatic electron affinities wrt protonation state

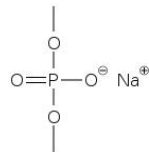
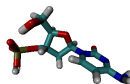
**EA<sub>ad</sub> (eV)**  
 Gas phase  
 Aqueous solution<sup>11</sup>



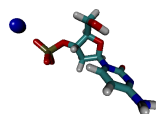
**0.15**  
**2.07**



**-2.18**  
**1.93**

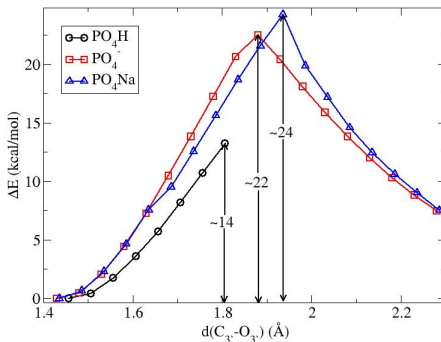


**Na-attached**  
**1.94**

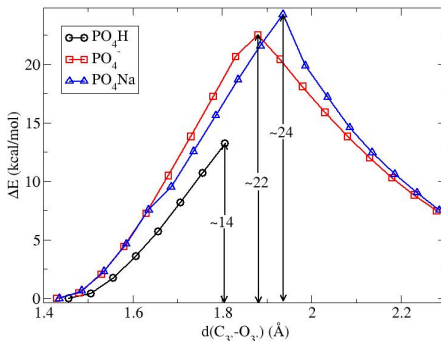


<sup>11</sup>IEF-PCM model using water solvent and UA0 radii.

## Barrier of the $C_3'-O_3'$ bond cleavage wrt protonation state in aqueous solution



## Barrier of the $C_{3'}-O_{3'}$ bond cleavage wrt protonation state in aqueous solution



**A key question:** modulation due to the environment ?

## The Local Self-Consistent Field method

- Optimization of the WF under constraint<sup>12</sup>

$$\mathbf{F} \cdot \mathbf{C} = \underbrace{\mathbf{S} \cdot \mathbf{C} \cdot \mathbf{E}}_{\text{variational}} + \underbrace{\mathbf{S} \cdot \mathbf{L} \cdot \mathbf{A}}_{\text{frozen}}$$

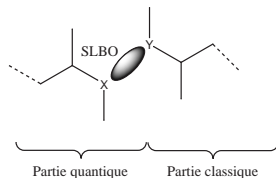
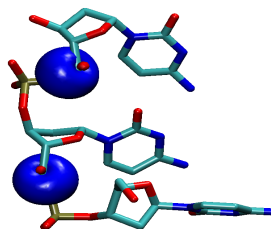
- QM/MM boundary<sup>13</sup>  
*Strictly Localized Bond Orbital (SLBO)*  $\iff$

$$|I_I\rangle = \sum_{\mu \in \{X, Y\}} I_{\mu I} |\mu\rangle$$

$\implies$  Localization criteria  
(transferability principle)

<sup>12</sup>Assfeld et al. *Chem. Phys. Lett.* **1996**, 263, 100.

<sup>13</sup>Ferré et al. *J. Comput. Chem.*, **2002**, 23, 610.

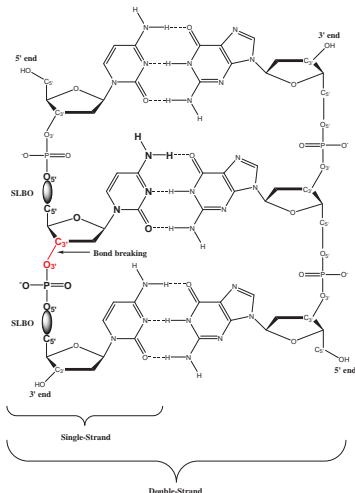


## LSCF/MM calculation

- **Electrostatic Embedding:**  
polarization of the WF

$$\sum_{A \in \text{MM}} \sum_{\mu\nu} P_{\mu\nu}^T \left\langle \mu \left| \frac{qA}{|\mathbf{r} - \mathbf{R}_A|} \right| \nu \right\rangle$$

- **Self-consistent core orbitals<sup>14</sup>:**
  - any additional parameters for the QM/MM frontier<sup>15</sup>
  - proper treatment of the electronic attachment
  - No ponctual charges redistribution



<sup>14</sup>Loos et al. *Comput. Lett.* **2007**, *4*, 473.

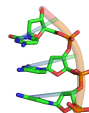
<sup>15</sup>Fornili et al. *CPL* **2006**, *427*, 236.



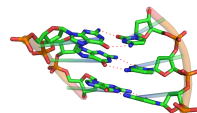
## From single nucleotide to double-stranded DNA



3'-dCMPH



C-C-C



CG-CG-CG

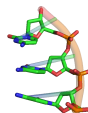
Level of theory: B3LYP/6-311+G\*/Amber *ff99* for nucleic acids

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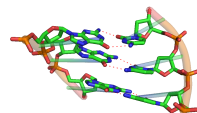
$EA_{ad}$  (eV)



3'-dCMPH  
0.15



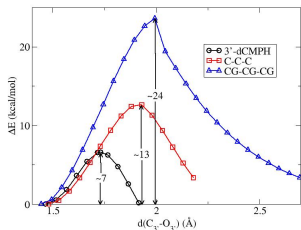
C-C-C  
0.32



CG-CG-CG  
0.92

Level of theory: B3LYP/6-311+G\*/Amber *ff99* for nucleic acids

## From single nucleotide to double-stranded DNA



**EA<sub>ad</sub> (eV)**  
**ΔE (kcal/mol)**

3'-dCMPH

**0.15**

**6.69**

C-C-C

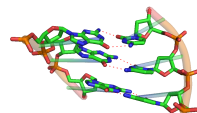
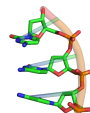
**0.32**

**≈ 13**

CG-CG-CG

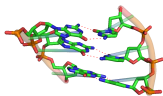
**0.92**

**≈ 24**



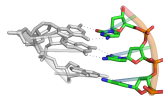
Level of theory: B3LYP/6-311+G\*/Amber *ff99* for nucleic acids

## Switch off the electrostatic embedding<sup>16</sup>

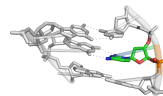


Embedding

Full



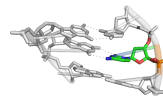
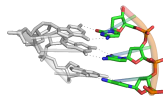
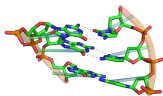
Only SS



None

<sup>16</sup>Loos et al. *JCTC* **2008**, 4, 637; Dumont et al. *JCTC* **2008**, 4, 1171.

## Switch off the electrostatic embedding<sup>16</sup>



**Embedding**  
**EA<sub>ad</sub> (eV)**

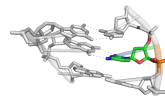
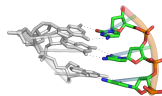
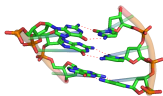
Full  
**0.92**

Only SS  
**0.32**

None  
**-0.24**

<sup>16</sup>Loos et al. *JCTC* **2008**, 4, 637; Dumont et al. *JCTC* **2008**, 4, 1171.

## Switch off the electrostatic embedding<sup>16</sup>

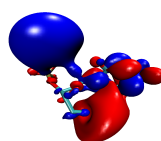
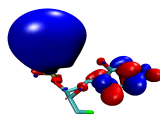
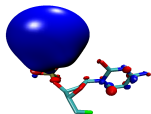


Embedding  
EA<sub>ad</sub> (eV)

Full  
0.92

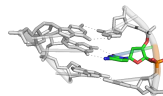
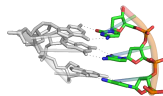
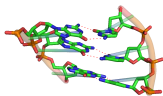
Only SS  
0.32

None  
-0.24



<sup>16</sup>Loos et al. *JCTC* 2008, 4, 637; Dumont et al. *JCTC* 2008, 4, 1171.

## Switch off the electrostatic embedding<sup>16</sup>

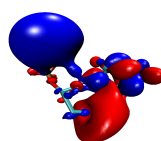
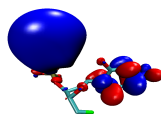
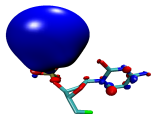


**Embedding**  
**EA<sub>ad</sub> (eV)**

Full  
**0.92**

Only SS  
**0.32**

None  
**-0.24**



**Spin densities**

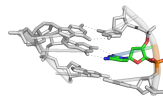
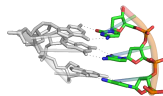
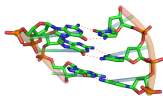
0.92; 0.02; 0.06

0.77; -0.02; 0.25

0.36; 0.27; 0.37

<sup>16</sup>Loos et al. *JCTC* **2008**, 4, 637; Dumont et al. *JCTC* **2008**, 4, 1171.

## Switch off the electrostatic embedding<sup>16</sup>

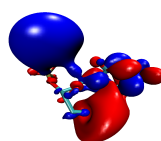
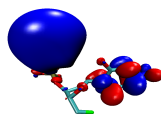
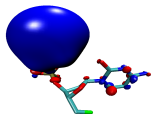


**Embedding**  
**EA<sub>ad</sub> (eV)**

Full  
**0.92**

Only SS  
**0.32**

None  
**-0.24**



**Spin densities**  
**ΔE (kcal/mol)**

0.92; 0.02; 0.06  
**≈ 24**

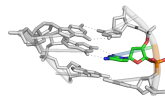
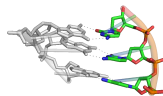
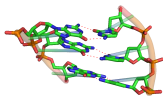
0.77; -0.02; 0.25  
**≈ 19**

0.36; 0.27; 0.37  
**≈ 8**

<sup>16</sup>Loos et al. *JCTC* 2008, 4, 637; Dumont et al. *JCTC* 2008, 4, 1171.



## Switch off the electrostatic embedding<sup>16</sup>

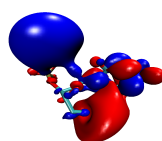
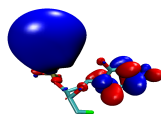
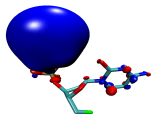


**Embedding**  
**EA<sub>ad</sub> (eV)**

Full  
**0.92**

Only SS  
**0.32**

None  
**-0.24**



**Spin densities**  
**ΔE (kcal/mol)**

0.92; 0.02; 0.06  
**≈ 24**

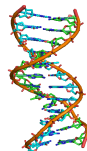
0.77; -0.02; 0.25  
**≈ 19**

0.36; 0.27; 0.37  
**≈ 8**

<sup>16</sup>Loos et al. *JCTC* 2008, 4, 637; Dumont et al. *JCTC* 2008, 4, 1171.

## Conclusions

- Huge modulation once the environment is taken into account:
  - Electron affinities increase (electrostatic effects)
  - and also the barriers of the 3' cleavage
- Other pathways may exist . . .



## Outlooks

- Other bonds<sup>17</sup>: C<sub>5'</sub>-O<sub>5'</sub>?
- Other nucleobases: Thymine and purines<sup>18</sup>
- Helical structures: A-DNA, B-DNA, Z-DNA

<sup>17</sup>Gu et al. *PNAS* **2008**, *130*, 12224.

<sup>18</sup>Schyman et al. *JACS* **2008**, *130*, 12224.

## Nancy

- Elise Dumont and Adèle Laurent



## Namur

- Denis Jacquemin, Julien Preat and Eric Perpète



## LSCF

- Yohann Moreau (Orsay) and Nicolas Ferré (Marseille)



## Boss

- Jean-Louis Rivail and Xavier Assfeld

