Développement d'une Méthode de Chimie Quantique Mêlant Plusieurs Niveaux de Théorie : Applications à l'Etude des Etats Electroniques de Macromolécules

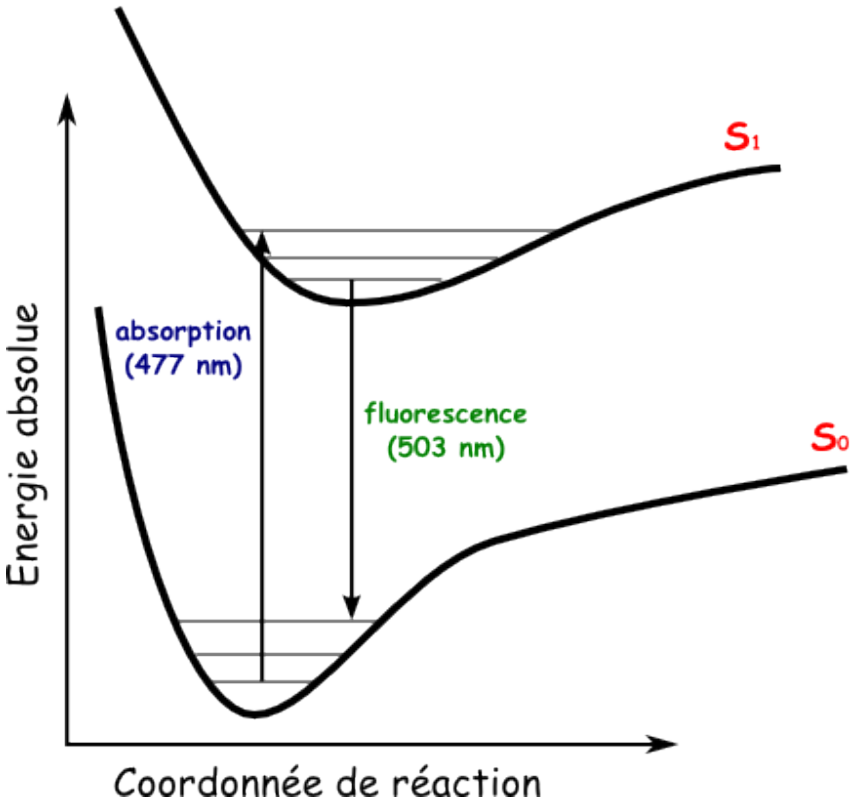
Pierre-François Loos

Equipe de Chimie et Biochimie Théoriques,
UMR 7565 CNRS-UHP, Institut Jean Barriol (FR CNRS 2843),
Faculté des Sciences et Techniques, Nancy-Université, B.P. 239,
France

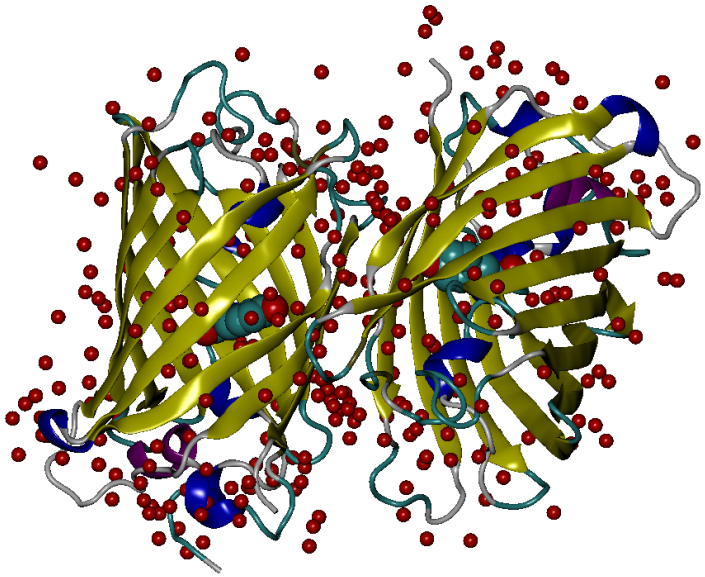
13 Juin 2008

Green Fluorescent Protein (GFP)[1]

Excitation et émission



PDB ID : 1GFL[2] — *Aequorea victoria*

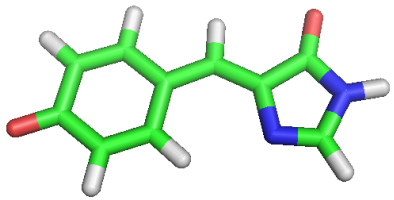


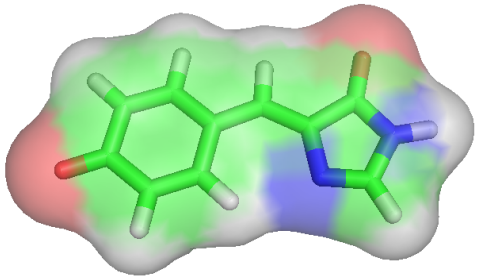
[1] Zimmer, *Chem. Rev.* **2002**, *102*, 759.
[2] Yang et al. *Nat. Biotechnol.* **1996**, *14*, 1246.

Système modèle & effets de solvant

Chromophore de la GFP[1] : état **B**

Modèle SCRF : solvatation implicite





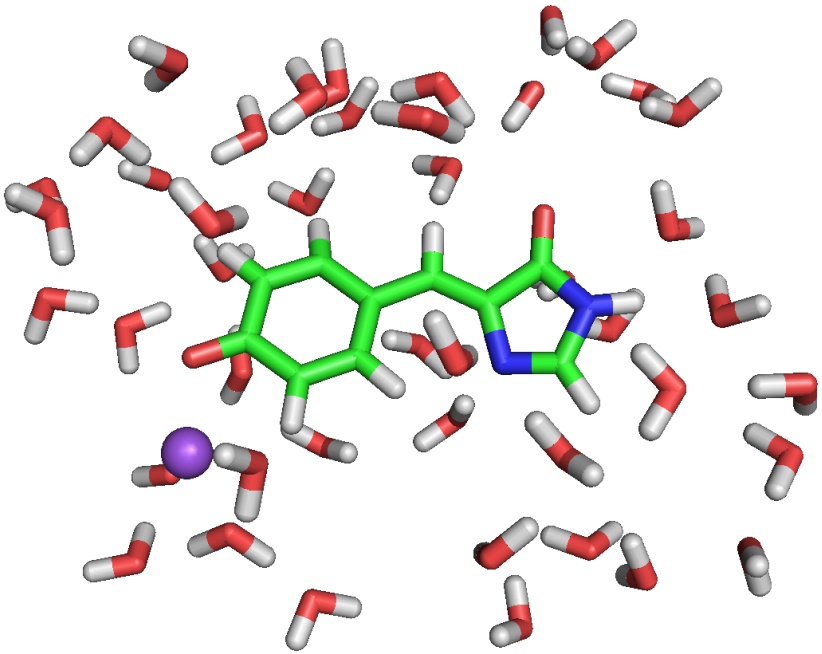
Méthodes	Etat **B**
SAC-CI[3]	558
TD-B3LYP[4]	403
SAC-CI(Onsager)[3]	549
TD-B3LYP(PCM)[4]	417
Exp	**477**

[3] Das et al. *J. Comput. Chem.* **2003**, *24*, 1421

Méthodes hybrides

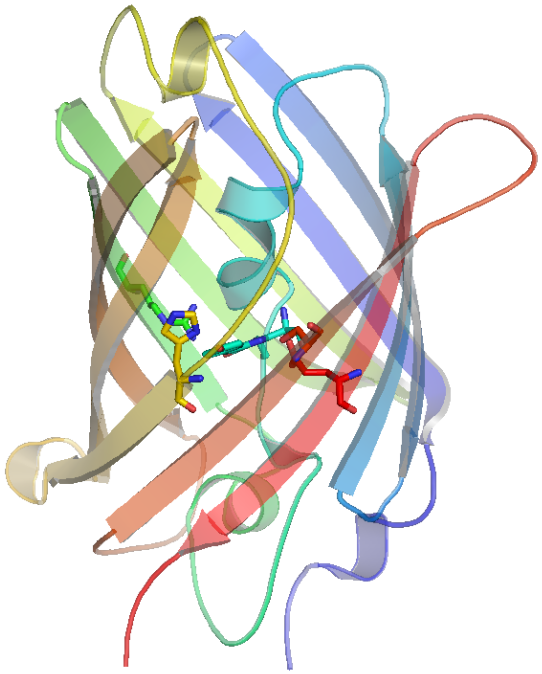
QM:MM : solvatation explicite

CASPT2/TIP3P[5] : **B** (434 nm)

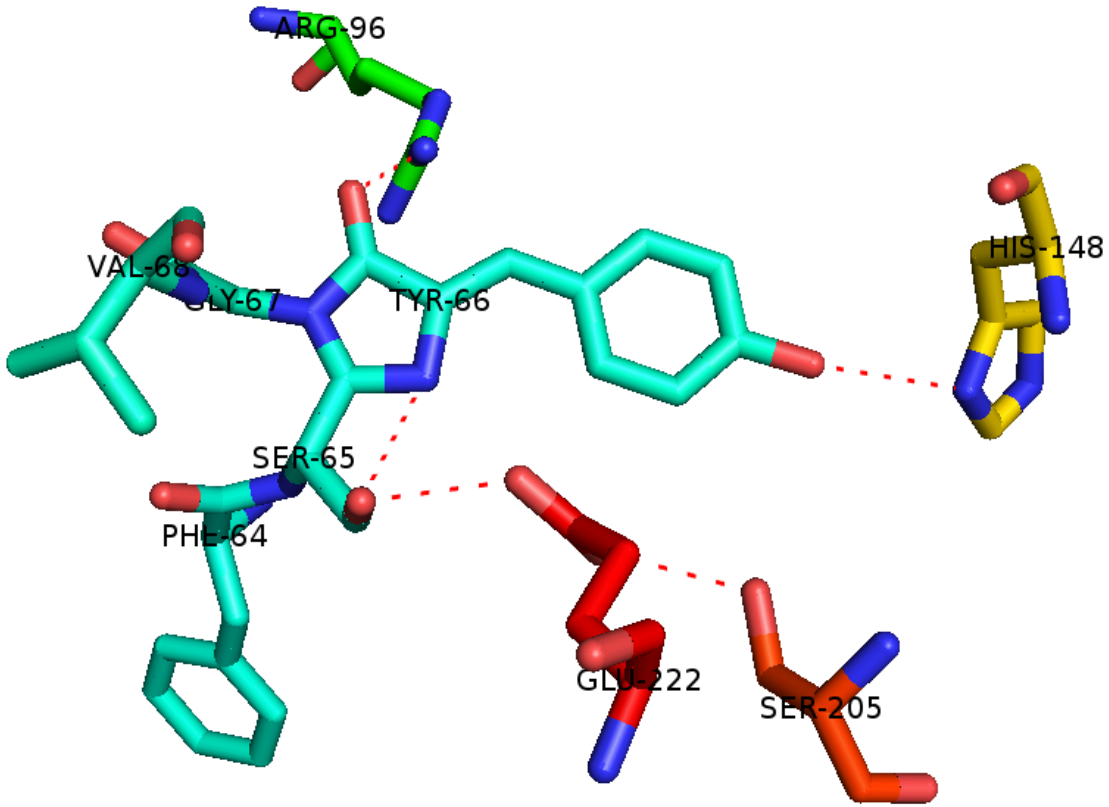


QM/MM : environnement biologique

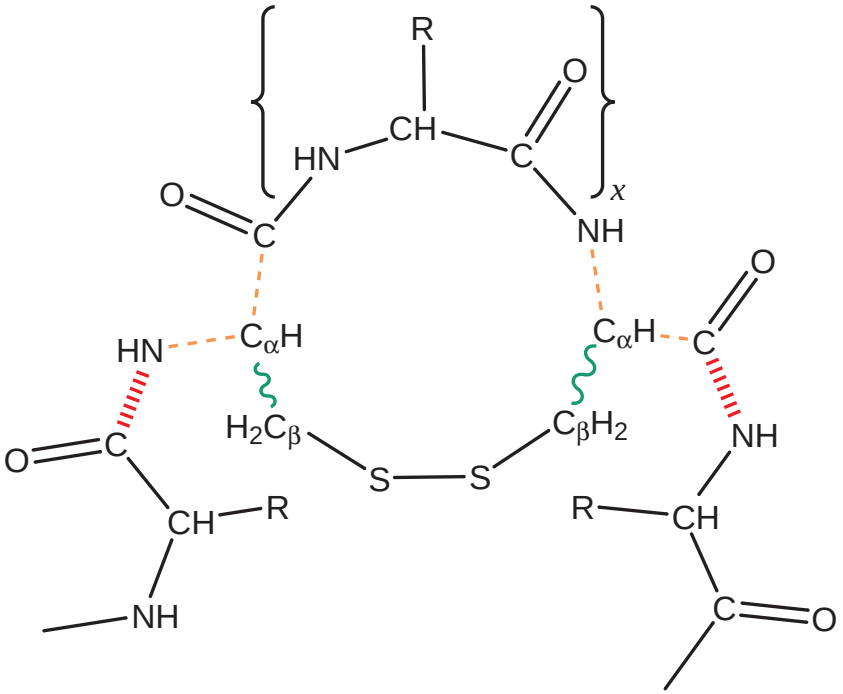
CASPT2/CHARMM[5] : **B** (442 nm)

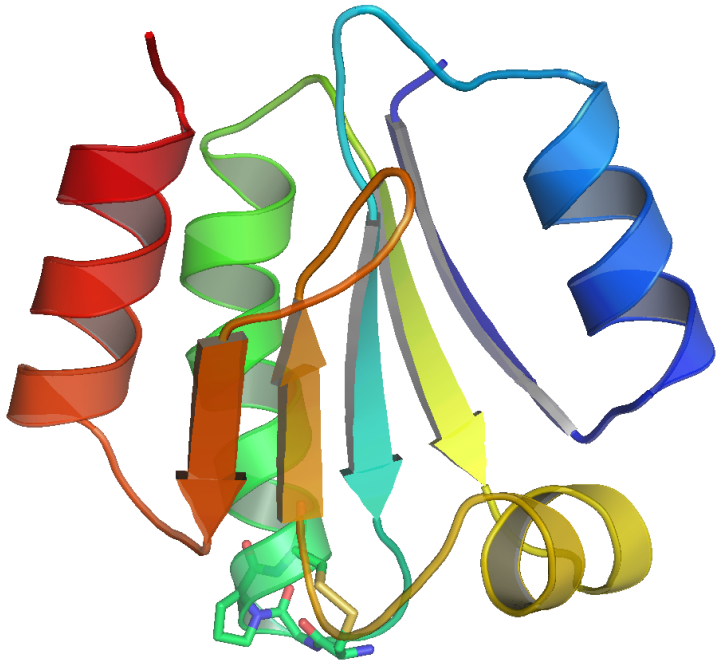


Site actif de la GFP : liaisons covalentes protéine-chromophore



QM/MM, ou l'art de la partition

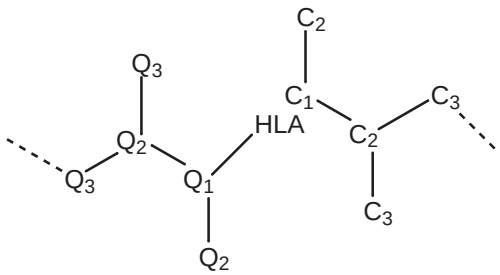




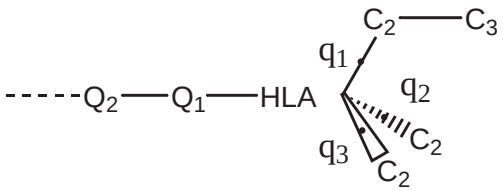
Thioredoxin[6] (1TOF)

[6] Dumont et al. *Chem. Phys. Lett.*, in press; Dumont et al. *J. Phys. Chem. B*, en révision; Dumont et al. *J. Chem. Theor. Comput.*, soumis.

Approches Link-Atom

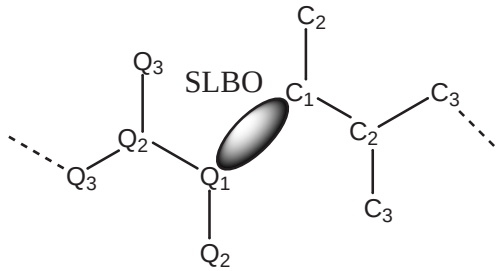


HLA[7]

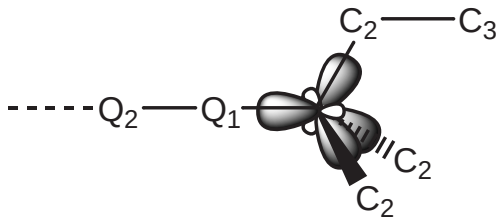


RCD[8]

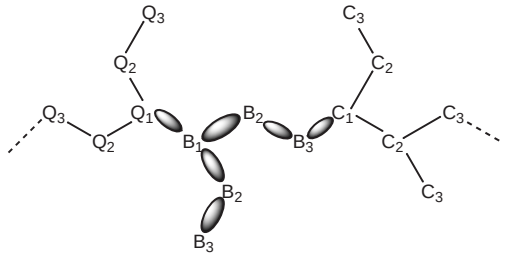
Approches par orbitales localisées



LSCF[9]



GHO[10]

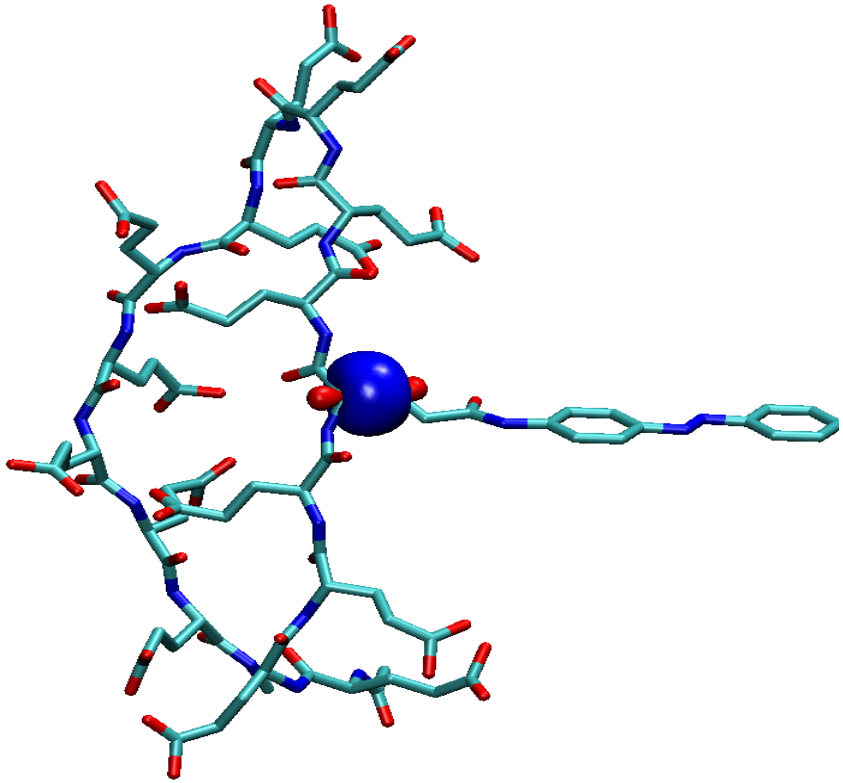


EFP[11]

[7] Maseras et al. *J. Comput. Chem.* **1995**, *16*, 1170.
[8] Lin et al. *J. Phys. Chem. A* **2005**, *109*, 3991.
[9] Assfeld et al. *Chem. Phys. Lett.* **1996**, *263*, 100.
[10] Pu et al. *J. Phys. Chem. A* **2004**, *108*, 632.
[11] Kairys et al. *J. Phys. Chem. A* **2001**, *104*, 6656.

Calcul LSCF/MM

- Local Self-Consistent Field : partie quantique



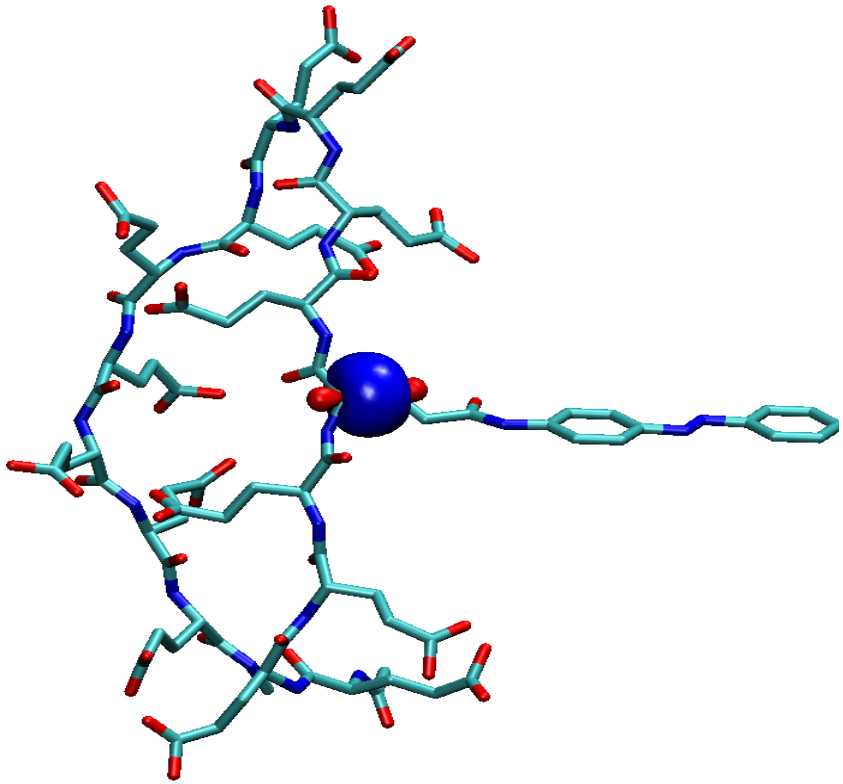
Calcul LSCF/MM

- Local Self-Consistent Field : partie quantique
  - Optimisation sous contrainte de la fonction d'onde :

$$\mathbf{F}\cdot\mathbf{C} = \underbrace{\mathbf{S}\cdot\mathbf{C}\cdot\mathbf{E}}_{\text{variationelle}} + \underbrace{\mathbf{S}\cdot\mathbf{L}\cdot\Lambda}_{\text{gelée}}$$

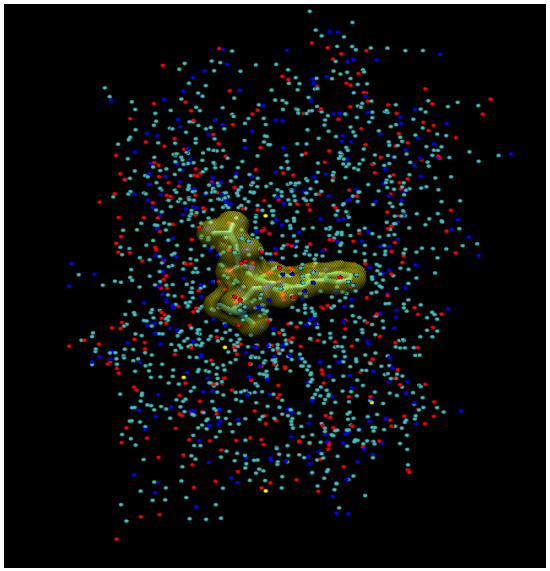
  - Frontière QM/MM *Strictly Localized Bond Orbital* (SLBO) $\Longleftrightarrow$

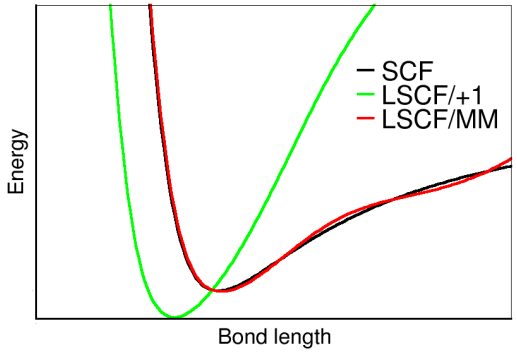
$$|I_I\rangle = \sum_{\mu\in\{X,Y\}} I_{\mu I}|\mu\rangle$$



Calcul LSCF/MM

- Local Self-Consistent Field : interface QM $\rightleftharpoons$ MM





[12] Ferré et al. *J. Comput. Chem.*, **2002**, *23*, 610.

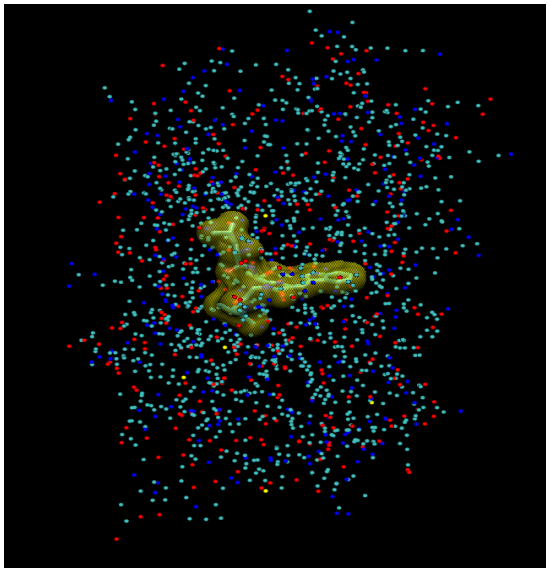
Calcul LSCF/MM

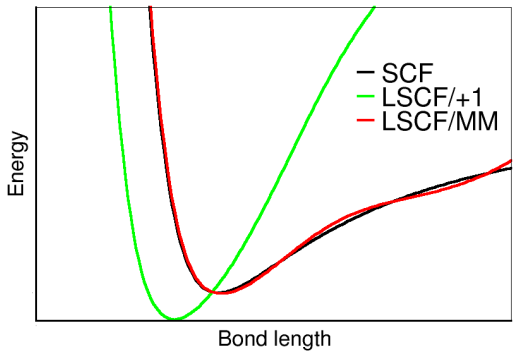
- Local Self-Consistent Field : interface QM $\rightleftharpoons$ MM
  - Electronic Embedding : polarisation explicite de la fonction d'onde

$$\sum_{A \in \mathrm{MM}} \sum_{\mu\nu} P^{T}_{\mu\nu} \left\langle \mu \left| \frac{q_A}{|\mathbf{r} - \mathbf{R_A}|} \right| \nu \right\rangle$$

  - Atome Y quanto-classique :
    - quanto : base gaussienne QM + charge nucléaire (+1)
    - classique : paramètres non-liés (charge, vdw) + certains liés
  - Potentiel de liaison frontière[12] :

$$E_{X_I Y_I} = \left(A + Br + Cr^2\right) e^{Dr} + \frac{E}{r}$$

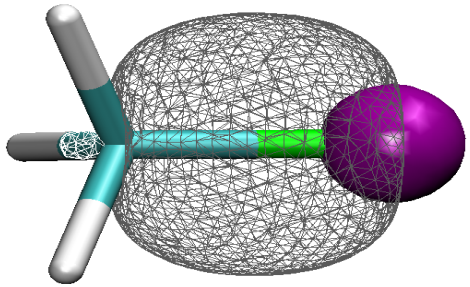




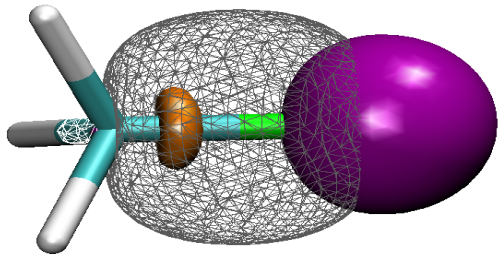
[12] Ferré et al. *J. Comput. Chem.*, **2002**, *23*, 610.

Comment s'affranchir du potentiel frontière ?

- Prise en compte des e- de cœur de l'atome frontière (1 e- SLBO + 2 e- de cœur)
- Augmentation de la charge nucléaire (+3)



FCO[13]

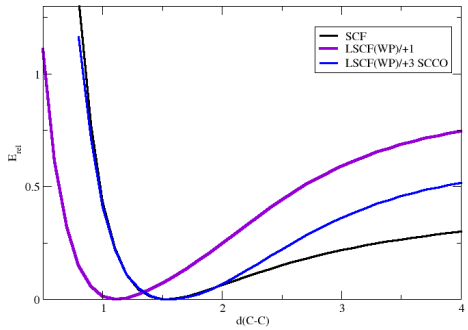


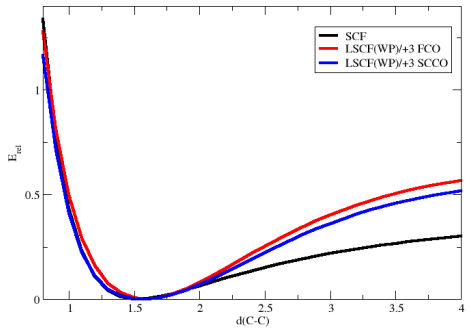
SCCO[14]

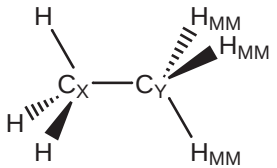
[13] Fornili et al. *Chem. Phys. Lett.* **2006**, *427*, 236.
[14] Loos et al. *Comput. Lett.* **2007**, *4*, 473.

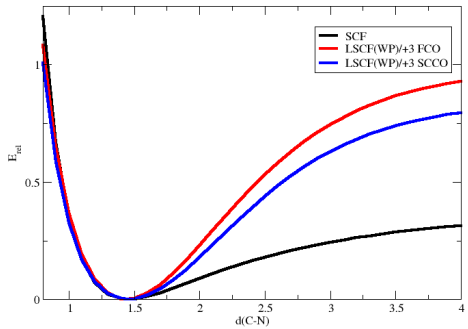
Profils de dissociation des différents types de liaisons

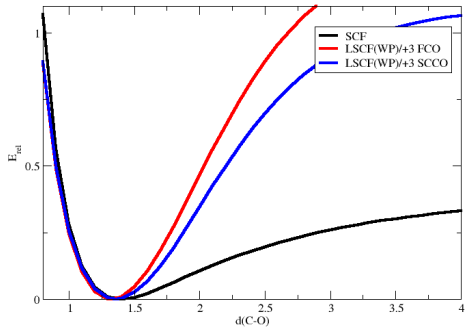
Ethane (C-C)

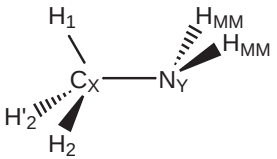


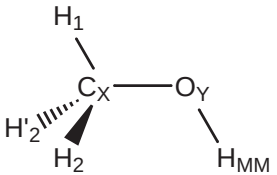












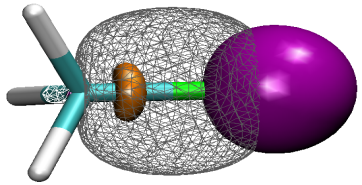
Méthylamine (C-N)

Méthanol (C-O)

Orbitale de cœur gelée (FCO) ou auto-cohérente (SCCO) ?

- SCCO plus diffuse que FCO

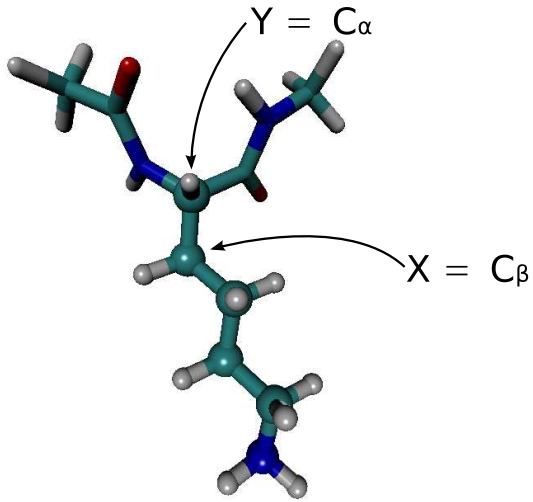
- Délocalisation partielle de la SCCO vers l'atome X



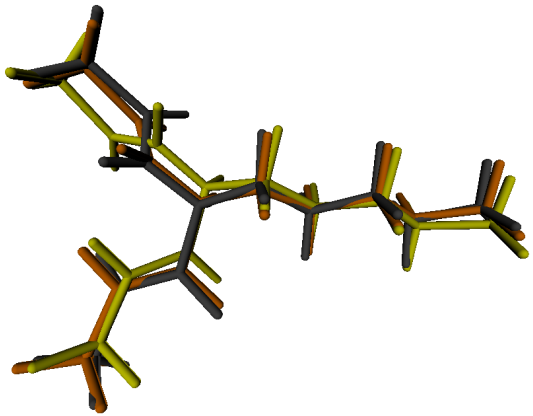
- SCCO évite la determination de la FCO !
- Performances géométriques et énergétique quasi-identique

Tripeptide Ace-Lys-NMe

- QM : HF/6-311G**
- MM : Amber *ff99* + RESP
- SLBO et FCO : ELMO[15]



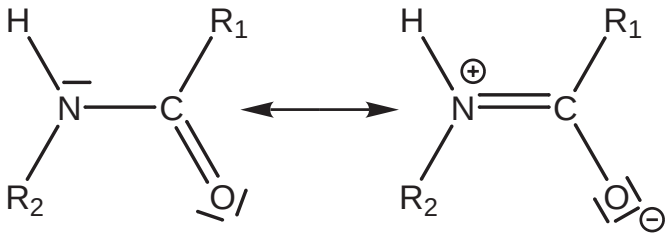
	d(C_α-C_β)	ΔE
FBP	1,519(-0,017)	239,0(3,6)
FCO	1,573(0,037)	237,6(2,2)
SCCO	1,589(0,053)	238,0(2,6)



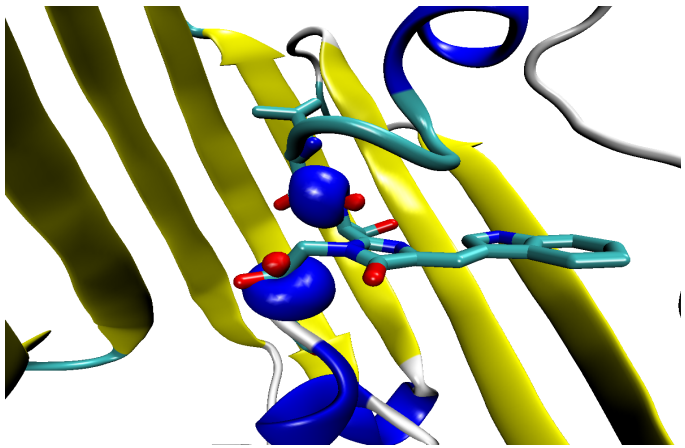
[15] Stoll et al. *Theor. Chem. Acc.* **1980**, *57*, 169; Fornili et al. *J. Mol. Struct. (THEOCHEM)* **2003**, *632*, 157.

Traitement de la liaison peptidique[16]

- Prise en compte de 2 e- de valence pour l'atome d'azote
- Permet de représenter le doublet de l'azote
  $\Longrightarrow$ augmentation de la charge nucléaire (+5) de l'atome d'azote frontière



Formes mésomères

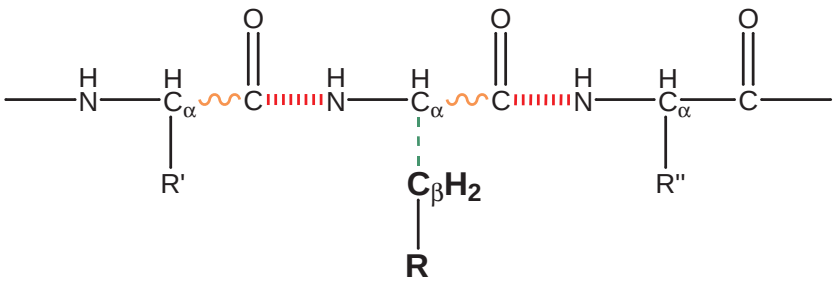


Enhanced Cyan Fluorescent Protein (1OXD)

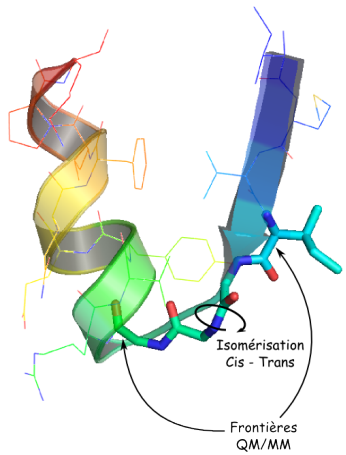
[16] Loos et al. *AIP Conf. Proc.* **2007**, *963*, 308.

Une alternative intéressante aux partitions communes

- Partition naturelle pour les polypeptides et protéines
- Utilisable quelque soit le champ de force (traitement des charges classiques)
- Description symétrique de l'acide aminé
- Densité convenable à la jonction



Différents localisations

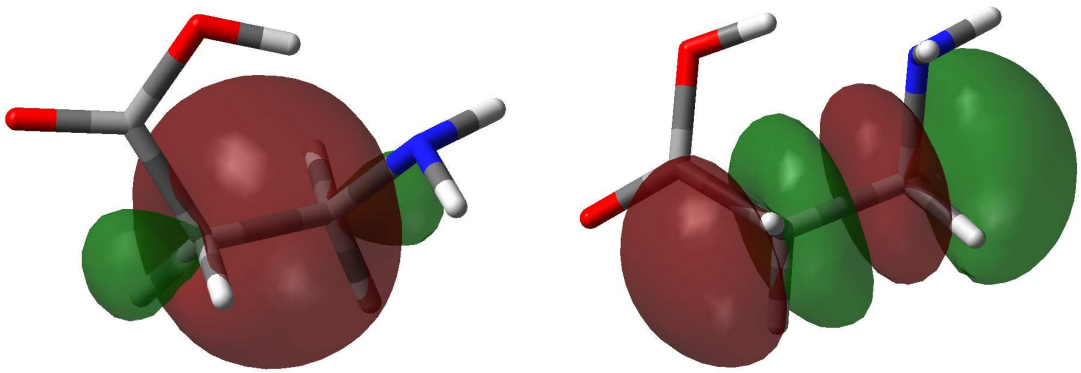


DHFR (1DRE) : C_α-C(=O)[17]

[17] Loos et al. *Theor. Chem. Acc.* **2007**, *118*, 165.

Vers une SLBO aut-cohérente : SCSLBO[18]

$$\mathbf{F}^I = \begin{pmatrix} F^I_{11} & F^I_{12} \\ F^I_{12} & F^I_{22} \end{pmatrix} = \begin{pmatrix} \langle I_I|\hat{F}|I_I\rangle & \langle I^\star_I|\hat{F}|I_I\rangle \\ \langle I_I|\hat{F}|I^\star_I\rangle & \langle I^\star_I|\hat{F}|I^\star_I\rangle \end{pmatrix}$$



SLBO $|I_I\rangle$ SLABO $|I^\star_I\rangle$

$$|I_I\rangle_{\text{new}} = C^I_1 \cdot |I_I\rangle_{\text{old}} + C^I_2 \cdot |I^\star_I\rangle_{\text{old}}$$
$$|I^\star_I\rangle_{\text{new}} = -C^I_2 \cdot |I_I\rangle_{\text{old}} + C^I_1 \cdot |I^\star_I\rangle_{\text{old}}$$

[18] Loos et al. *J. Chem. Theor. Comput.* **2007**, *3*, 1047.

Comment obtenir une SLABO ?

- idem que SLBO : rotation dans l'espace des MOs virtuelles
- Projection PB $\rightarrow$ GB :

$$|l_I^\star\rangle = \sum_{\mu\nu}^{\mathrm{GB}} |\mu\rangle \left(\mathbf{S}^{-1}\right)_{\mu\nu} \langle\nu|l_I^\star\rangle_{\mathrm{PB}}$$

- "Sens chimique" :

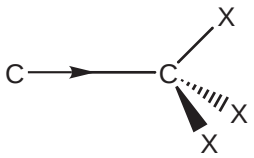
$$\text{SLBO} : |l_I\rangle = l_{X_I I}|h_I^{X_I}\rangle + l_{Y_I I}|h_I^{Y_I}\rangle$$

$$\text{SLABO} : |l_I^\star\rangle = N_I^\star \left(l_{X_I I}|h_A^{X_I}\rangle - l_{Y_I I}|h_I^{Y_I}\rangle\right) = l_{X_I I}^\star|h_A^{X_I}\rangle + l_{Y_I I}^\star|h_I^{Y_I}\rangle$$

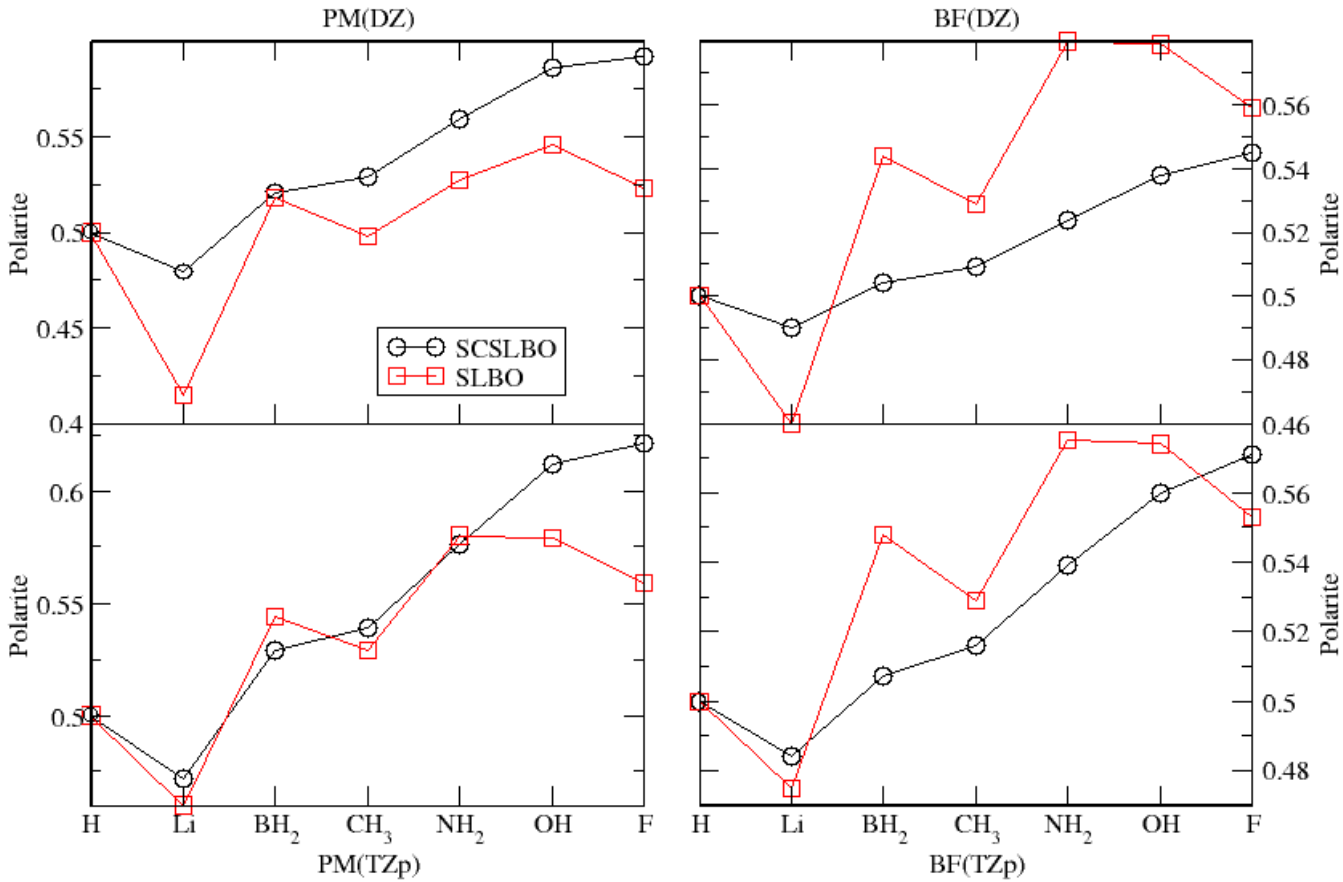
- Méthode de Head-Gordon et collaborateurs[19]

[19] Subotnik et al. *J. Chem. Phys.* **2005**, *123*, 114108.

Effets de substituants : HF/6-31G* et HF/6-311G**



$$P_I = \frac{qc_X}{2} = \sum_{\mu \in c_X} \sum_{\nu} l_{\mu I} l_{\nu I} S_{\mu\nu}$$

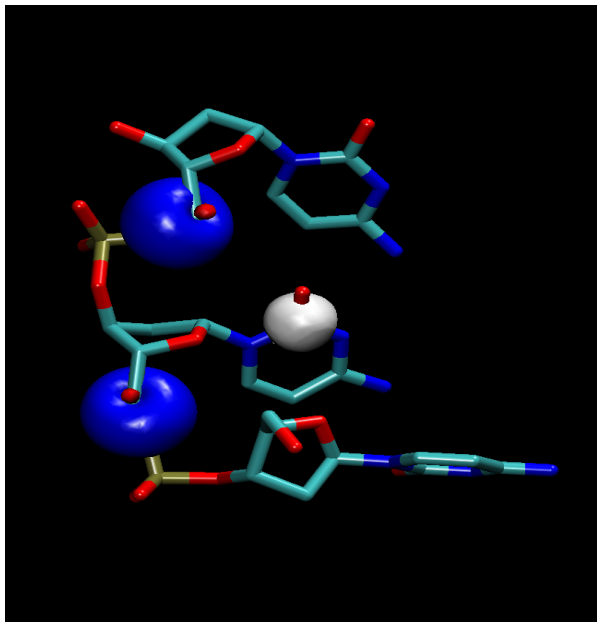


Energie d'ionisation de cœur

- Permet d'obtenir des informations sur la structure et la nature des molécules[1]
- Etudes expérimentales sur des macromolécules[2]

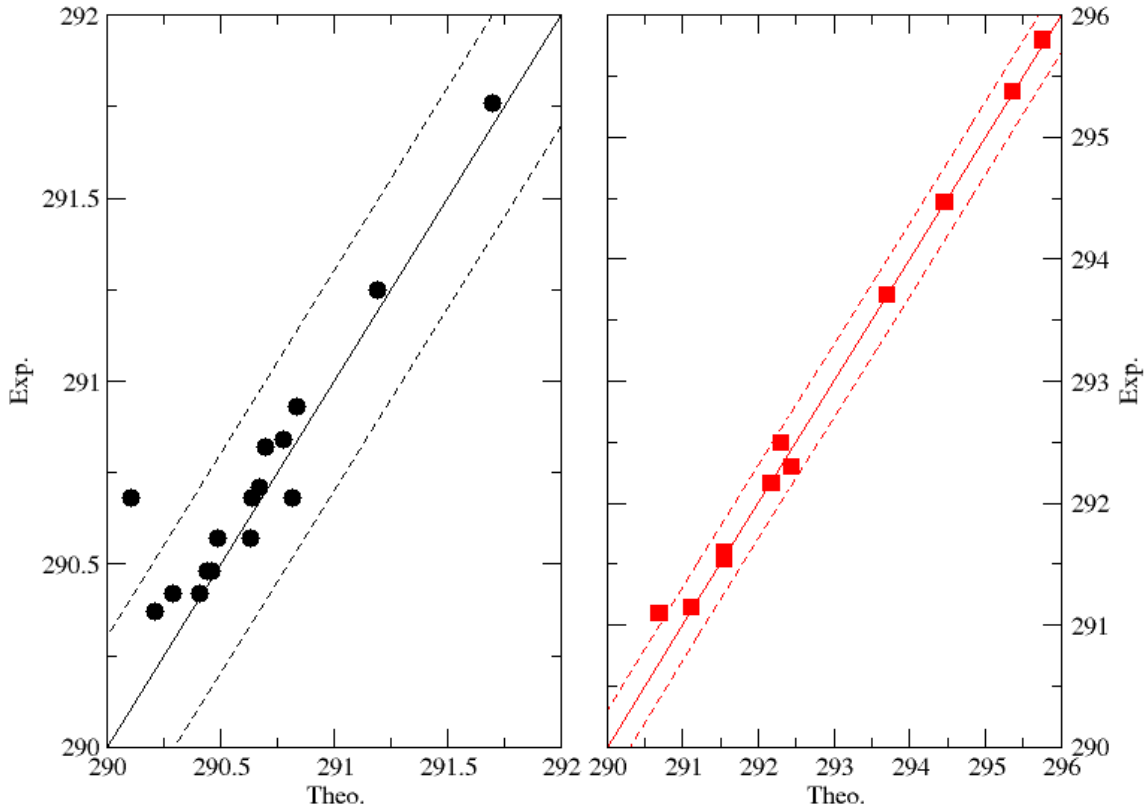
Etudes théoriques

- Etats excités $\Longrightarrow$ effondrement variationel et contrainte d'orthogonalité [3]
- Systèmes macromoléculaires $\Longrightarrow$ calculs LSCF/MM



[1] Schwarz et al. *Angew. Chem. Int. Ed.* **1974**, *13*, 454.
[2] voir par exemple : Gordon et al. *J. Phys. Chem. A* **2003**, *107*, 8512.
[3] Ferré et al. *J. Chem. Phys.* **2002**, *117*, 4119.

Molécules organiques : PBE0(BF)/6-311++G**//B3LYP/6-311++G** (RMSD = 0,16 eV)



atomes C, H
RMSD = 0,09 eV

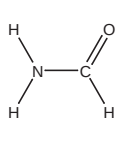
atomes C, H, N, O
RMSD = 0,19 eV

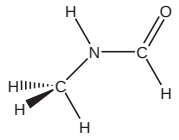
Déviation maximale
Th. vs Th. & Exp. vs Th.

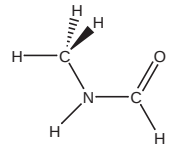
- Ref.[1]-This work: $\simeq 0.3$ eV
- Exp.[2]-This work: $\simeq 0.2$ eV
- Exp.-Ref.: $\simeq 0.2$ eV

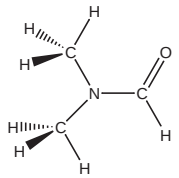
$\Longrightarrow$ Détermination précise des énergies d'ionisation de cœur (C 1s)

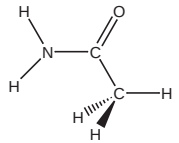
Etats de cœur ionisés de la liaison peptidique : PBE0/6-311++G**//B3LYP/6-311++G**

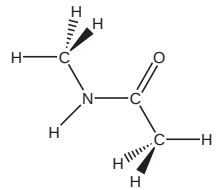

Formamide

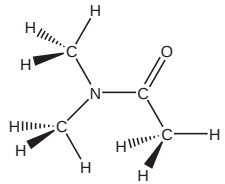

trans N-méthylformamide

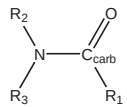

cis N-méthylformamide


N,N-diméthylformamide


Acétamide


N-méthylacétamide

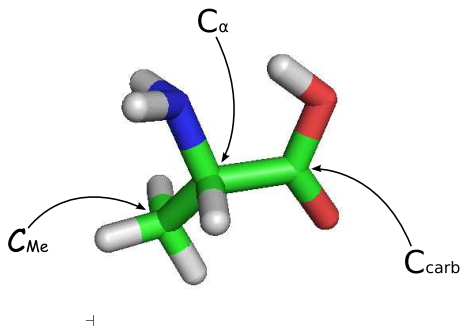

N,N-diméthylacétamide



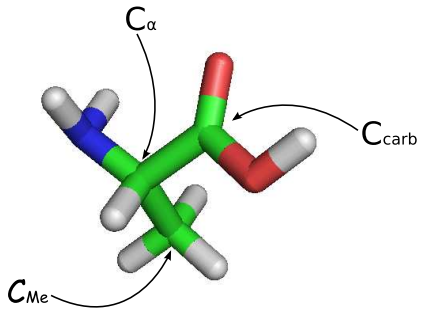
Numérotation des atomes

[1] Chong et al. *J. Phys. Chem. A* **2002**, *106*, 356.
[2] Joly et al. *J. Atomic Data and Nuclear Data Tables*, **1984**, *31*, 433.

Conformations: $\Delta E < 1$ kcal/mol



Conf. 1



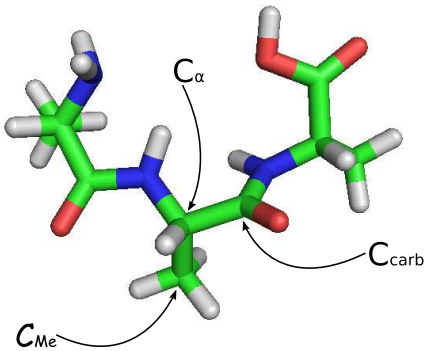
Conf. 2

Energie d'ionisation C 1s (eV) : Alanine

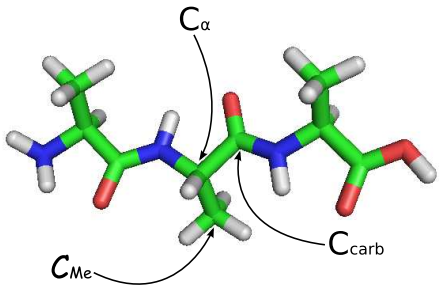
	Conf. 1	Conf. 2	Exp.[2]
C_α	292.45(-0.15)	292.16(+0.14)	292.30
C_{carb}	294.60(+0.70)	294.92(+0.38)	295.30
C_{Me}	291.11(+0.09)	290.89(+0.31)	291.20

[2] Powis et al. *J. Phys. Chem. A* **2003**, *107*, 25.

Ala-Tripeptide: conformation en hélice α et en brin β



hélice α



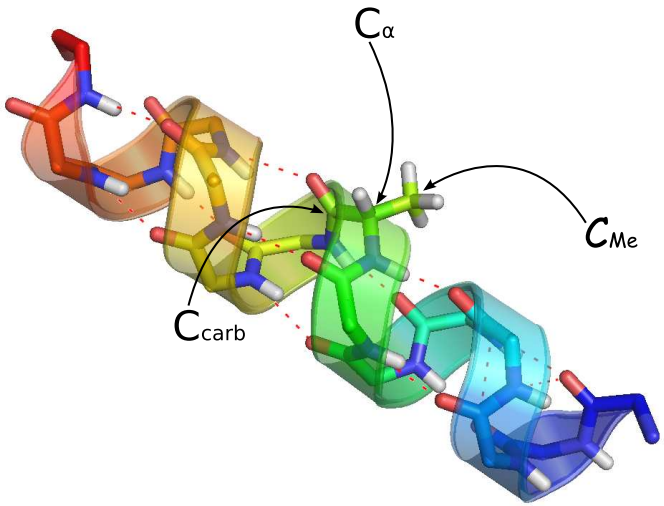
brin β

Energies d'ionisation C 1s (eV) : Ala-Tripeptide

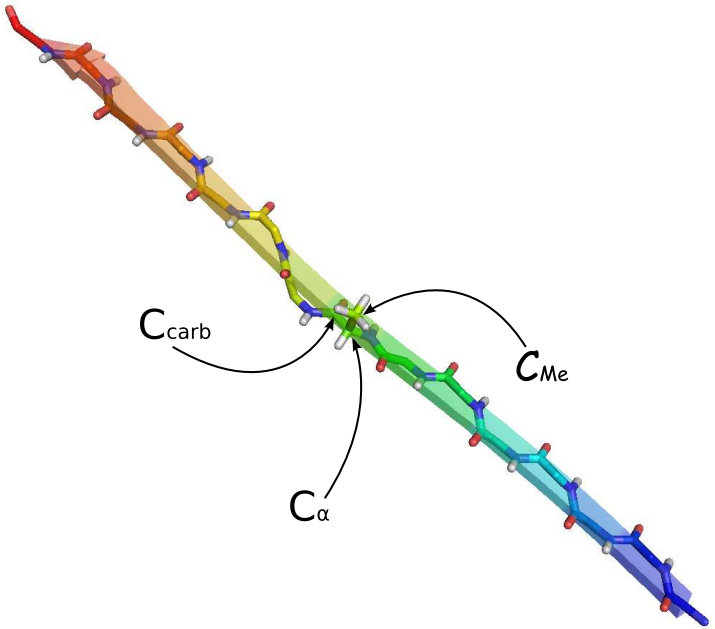
	hélice α	brin β	
C_α	291.87	292.00	$\simeq$ 0.3-0.4 eV
C_{carb}	293.69	293.87[3]	$\simeq$ 2.0 eV
C_{Me}	290.50	290.62	$\simeq$ 0.3-0.4 eV

[3] C_{carb} N-methylacetamide 293.37 eV

Poly-Ala-pentadecapeptide

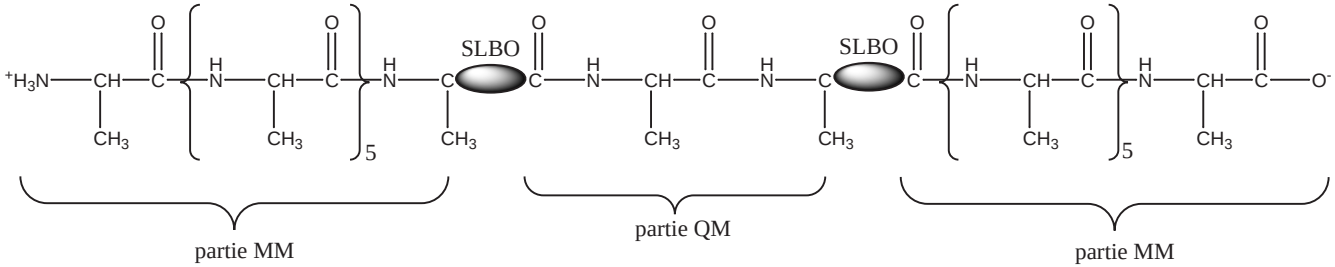


hélice α



brin β

Partition QM/MM du poly-Ala-pentadecapeptide

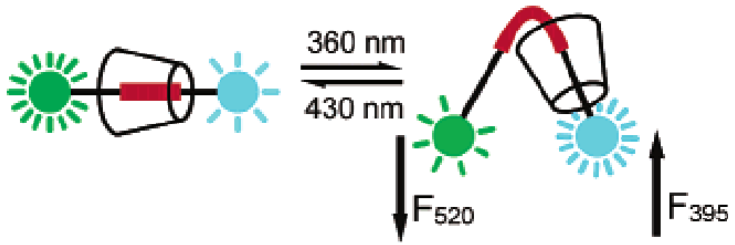


Energies d'ionisation C 1s (eV) : Pentadecapeptide

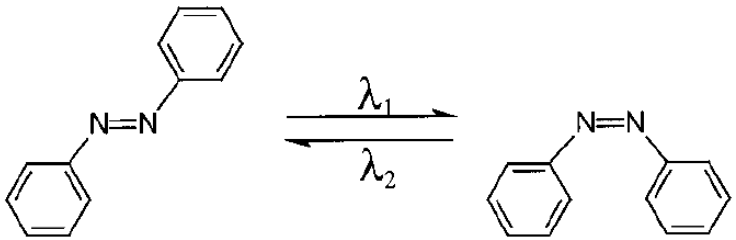
	PBE0/Amber		PBE0/Amber*	
	Hélice α	Brin β	Hélice α	Brin β
C_α	-0.26	-0.62	+0.05	+0.08
C_{carb}	-0.09	-0.76	+0.63	+0.23
C_{Me}	-0.71	-0.32	+0.47	+0.11

Applications industrielles et technologiques des dérivées de l'azobenzène

- Colorant en 'absorption' : 60-70% de la production mondiale[1]



Isomérisation photoréversible : TAB $\rightleftharpoons$ CAB



[7] Loos et al. *J. Chem. Theor. Comput.* **2008**, *4*, 637.

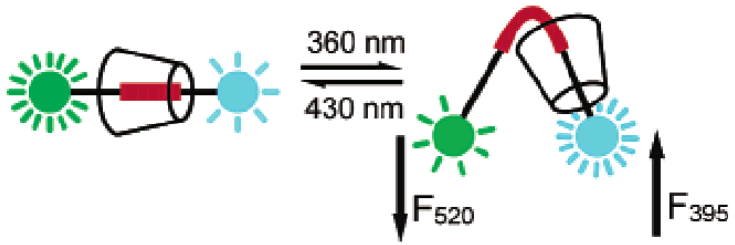
[1] Zollinger, H. In *Color Chemistry, Syntheses, Properties and Applications of Organic Dyes and Pigments*; Wiley-VCH, Weinheim, 3 ed., 2003.

[2] Natansohn et al. *Chem. Rev.*, **2002**, *102*, 4139.

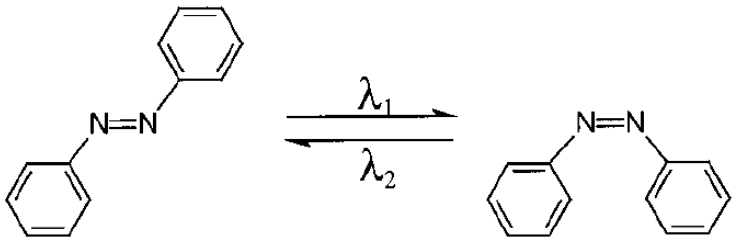
[3] Qu et al. *Org. Lett.*, **2004**,*6*, 2085.

Applications industrielles et technologiques des dérivées de l'azobenzène

- Colorant en 'absorption' : 60-70% de la production mondiale[1]
- Périphériques de stockage[2]
- Moteurs moléculaires[3]



Isomérisation photoréversible : TAB $\rightleftharpoons$ CAB



[7] Loos et al. *J. Chem. Theor. Comput.* **2008**, *4*, 637.

[1] Zollinger, H. In *Color Chemistry, Syntheses, Properties and Applications of Organic Dyes and Pigments*; Wiley-VCH, Weinheim, 3 ed., 2003.

[2] Natansohn et al. *Chem. Rev.*, **2002**, *102*, 4139.

[3] Qu et al. *Org. Lett.*, **2004**,*6*, 2085.

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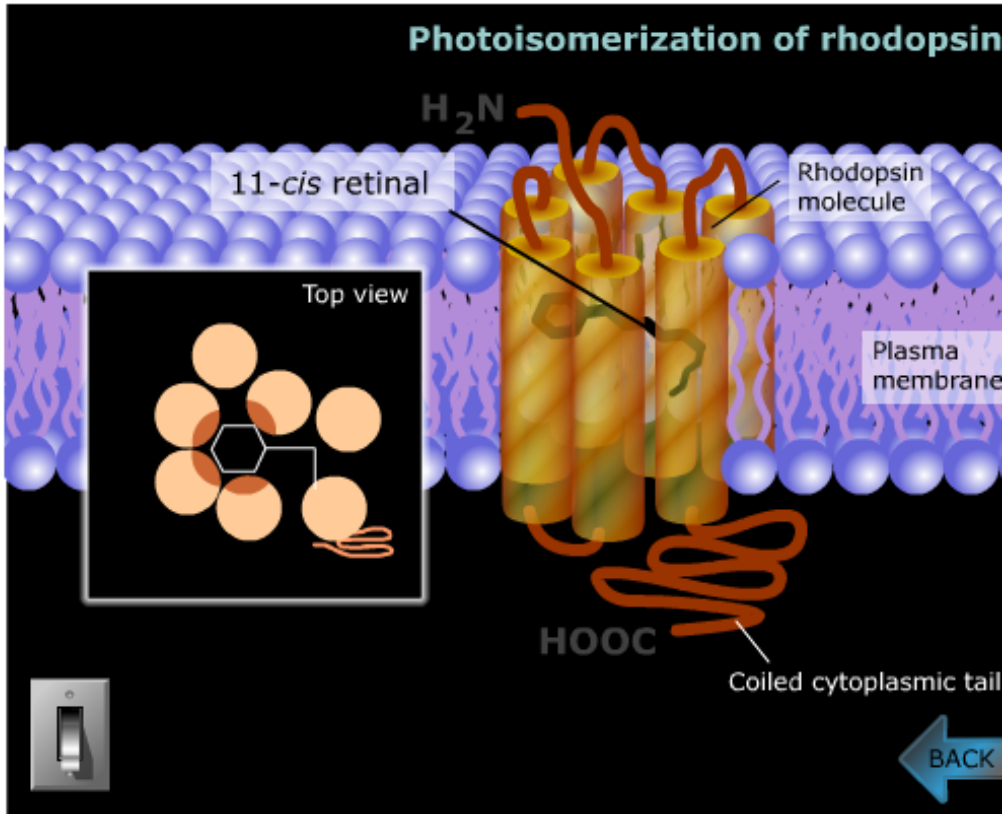
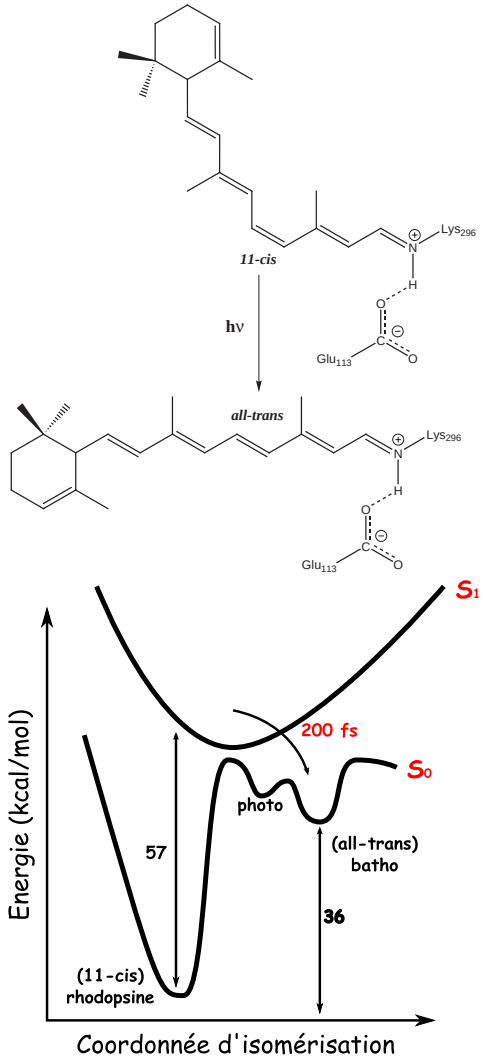
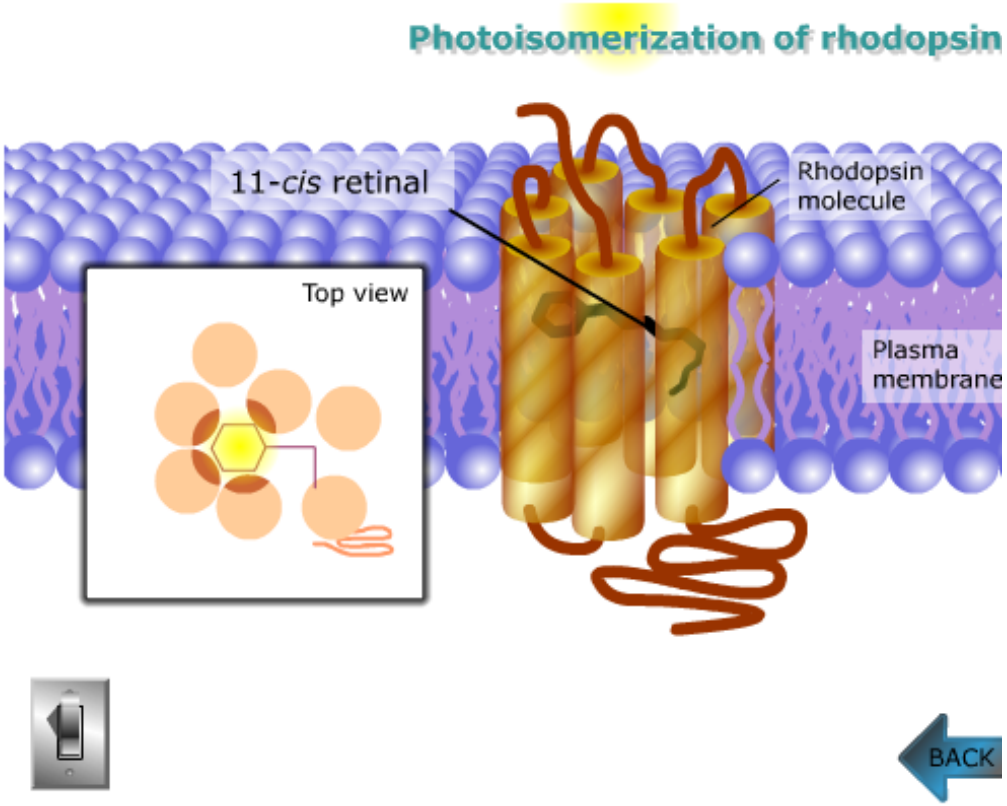
Energie lumineuse $\rightleftharpoons$ Energie mécanique

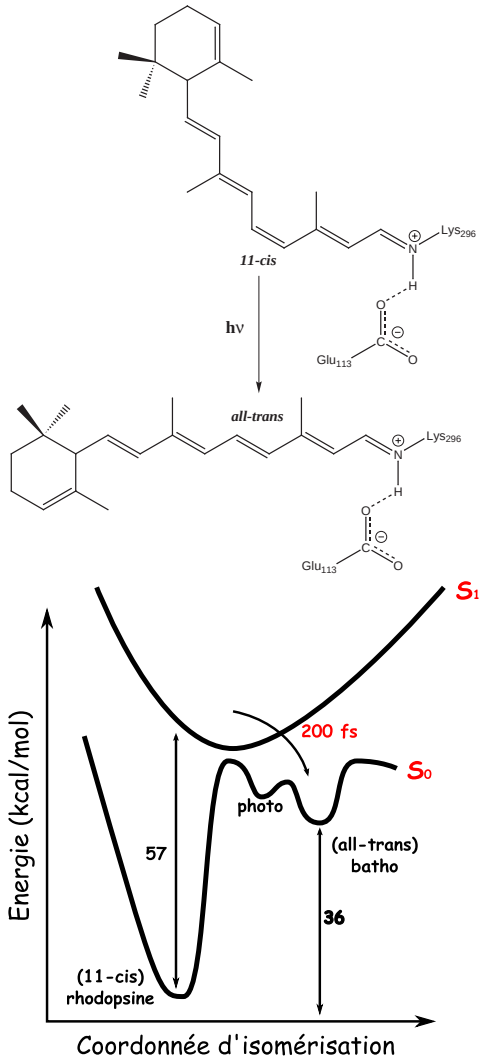




http://www.blackwellpublishing.com/matthews/rhodopsin.html

Energie lumineuse ⇌ Energie mécanique





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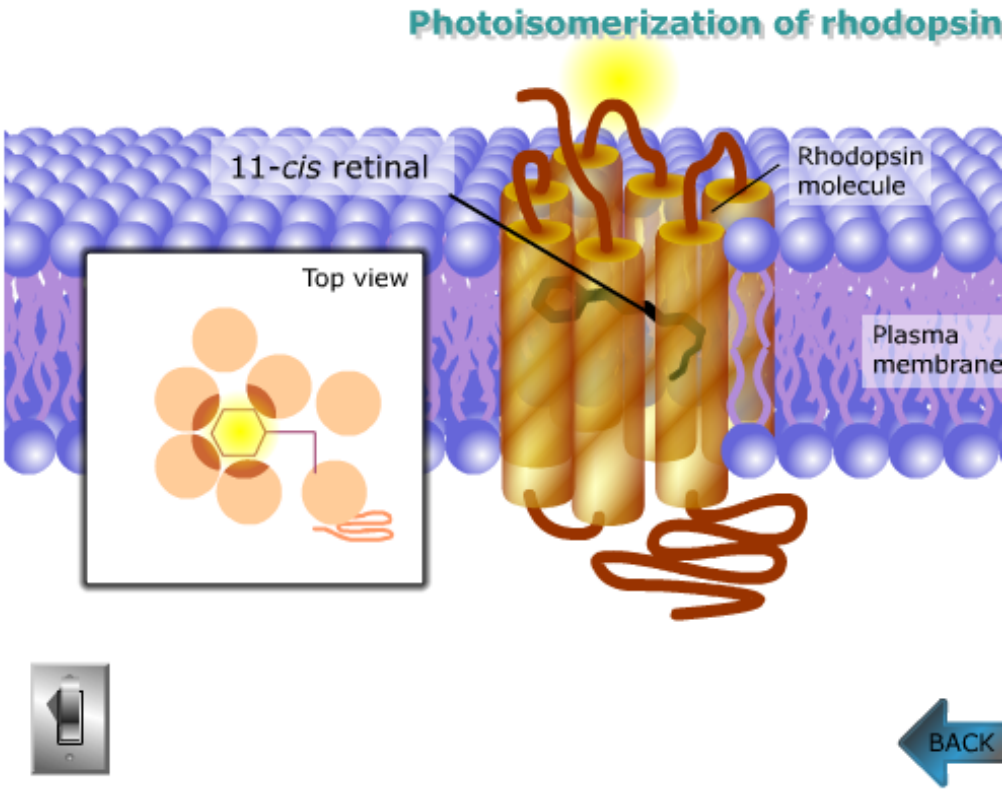
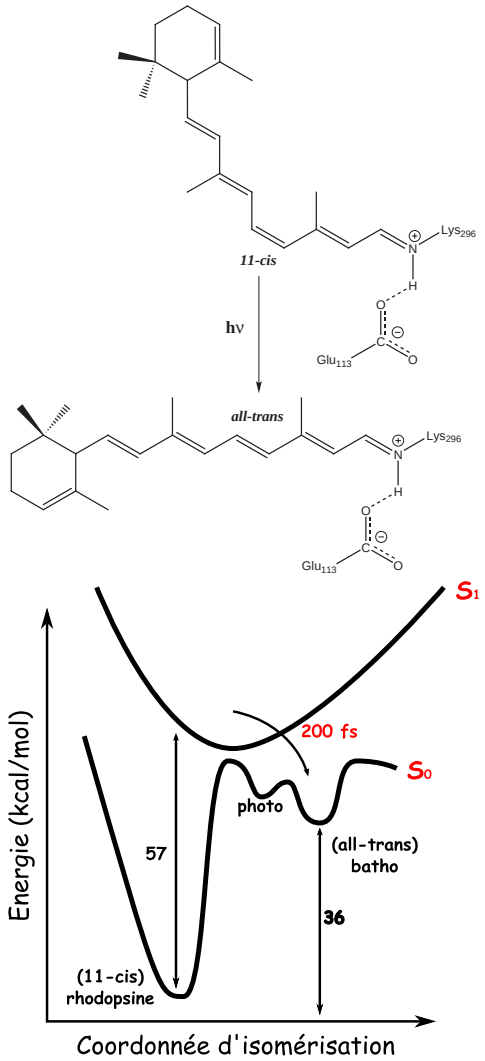
Energie lumineuse $\rightleftharpoons$ Energie mécanique





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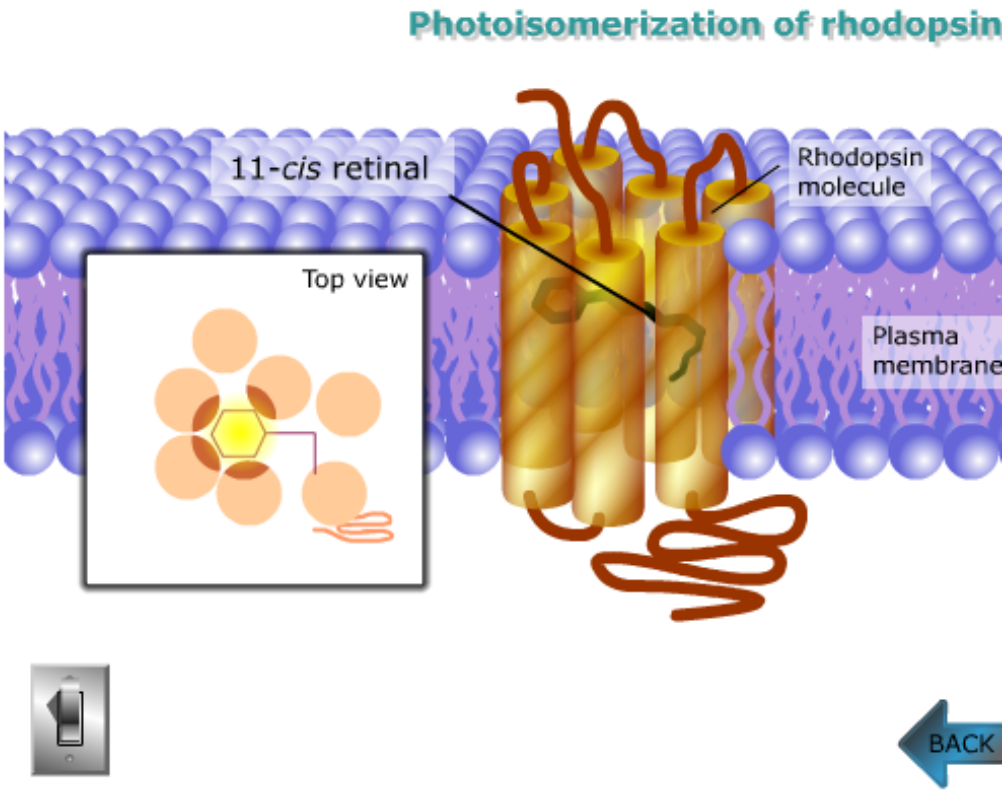
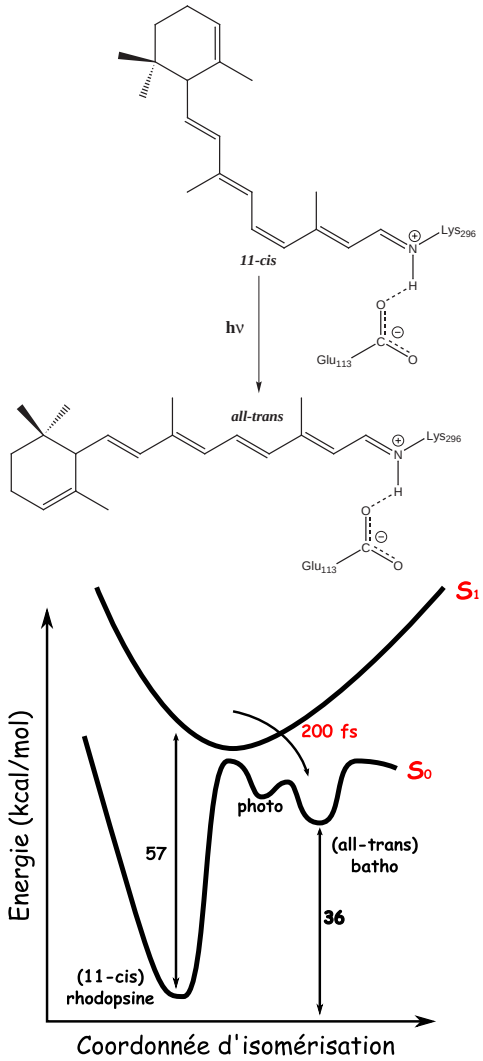
Energie lumineuse $\rightleftharpoons$ Energie mécanique





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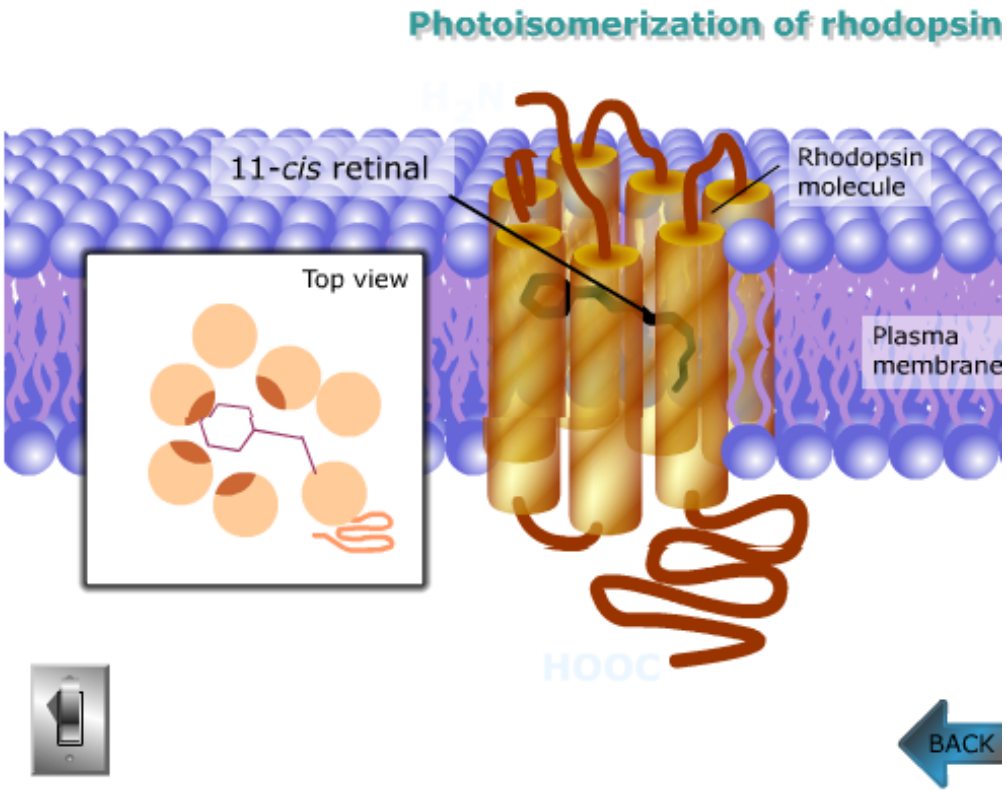
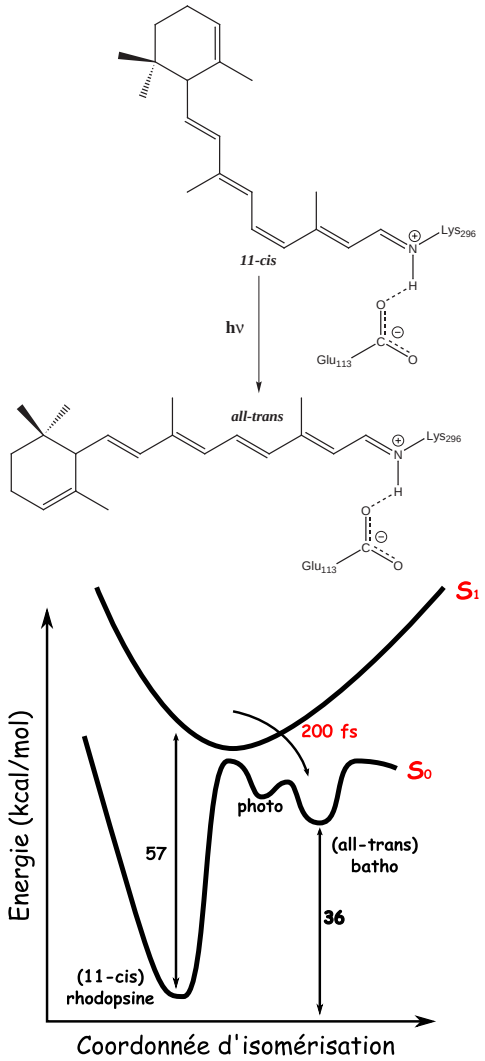
Energie lumineuse $\rightleftharpoons$ Energie mécanique





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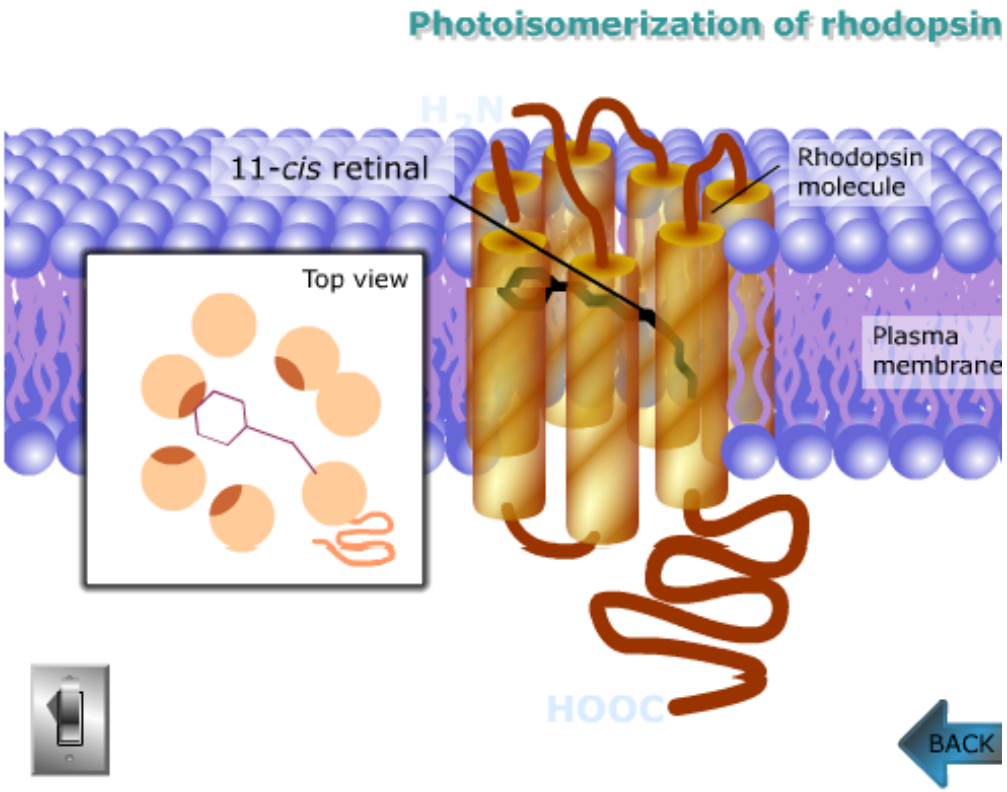
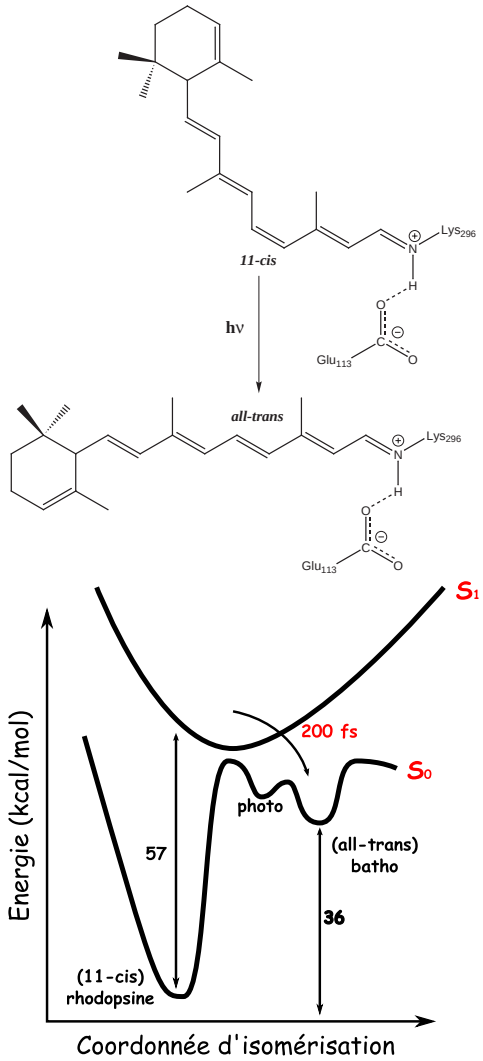
Energie lumineuse $\rightleftharpoons$ Energie mécanique





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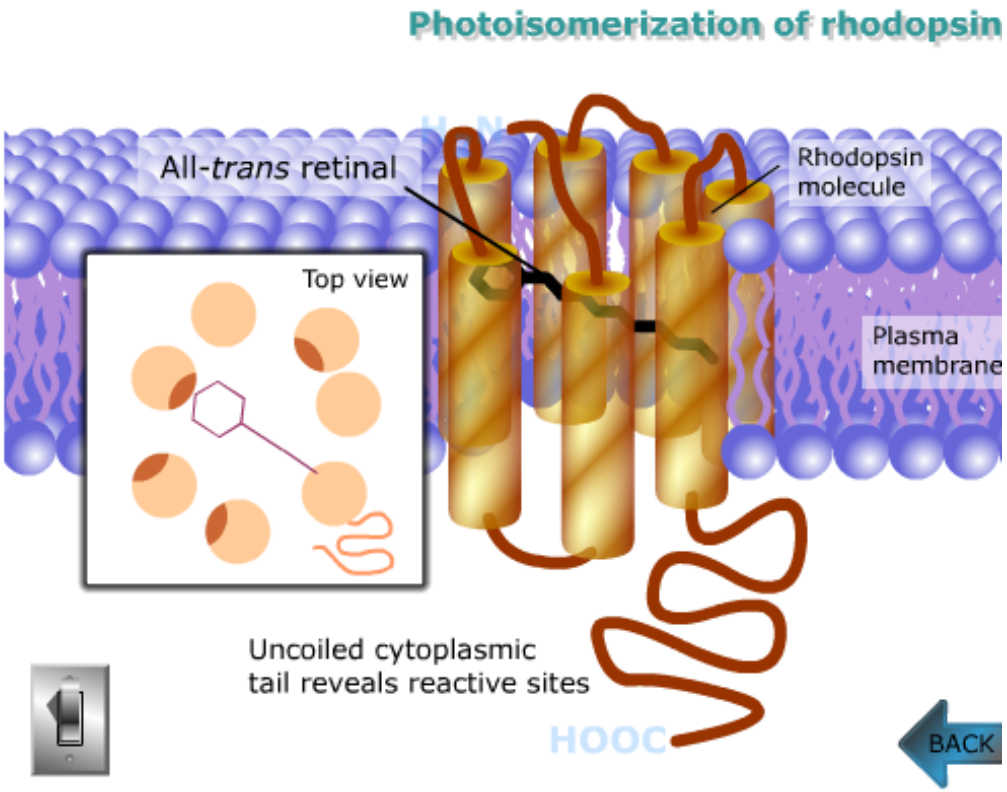
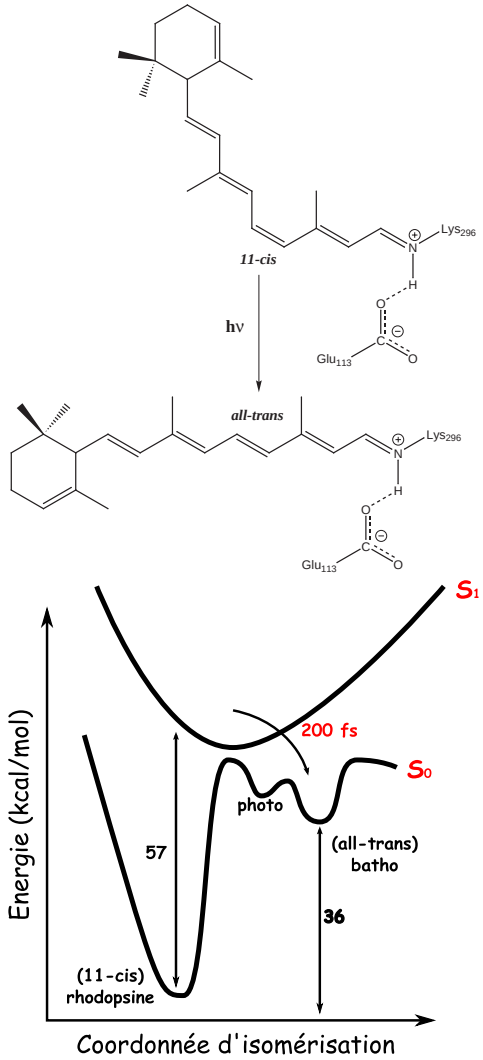
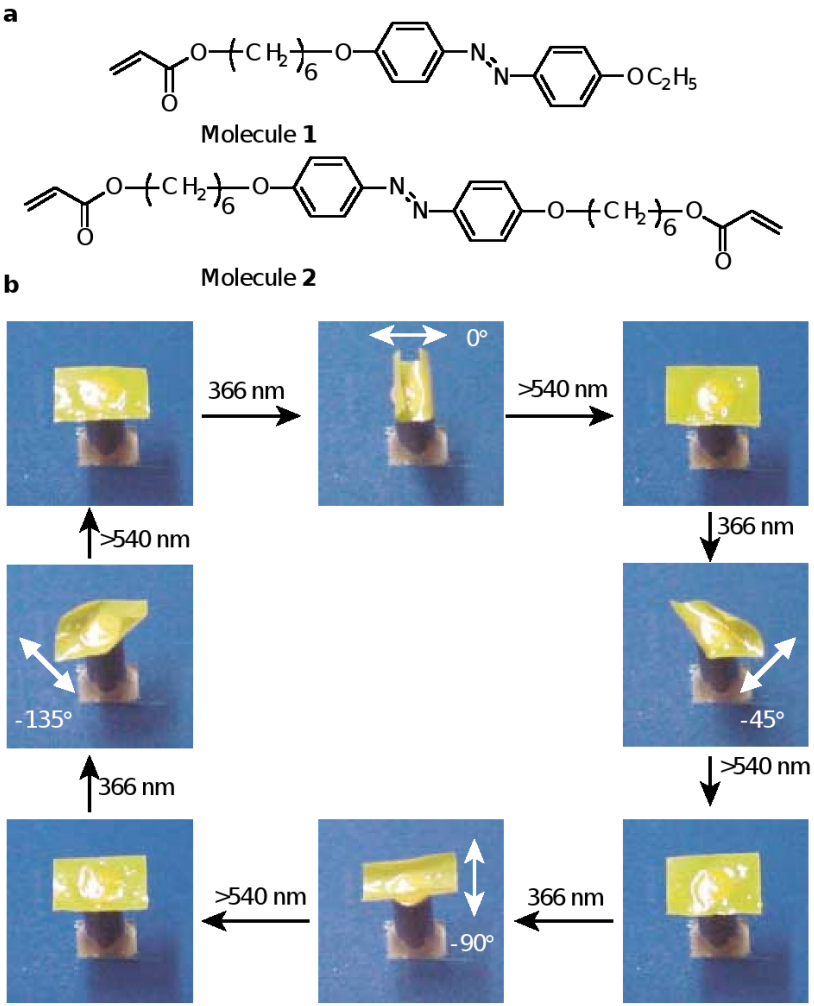
Energie lumineuse $\rightleftharpoons$ Energie mécanique

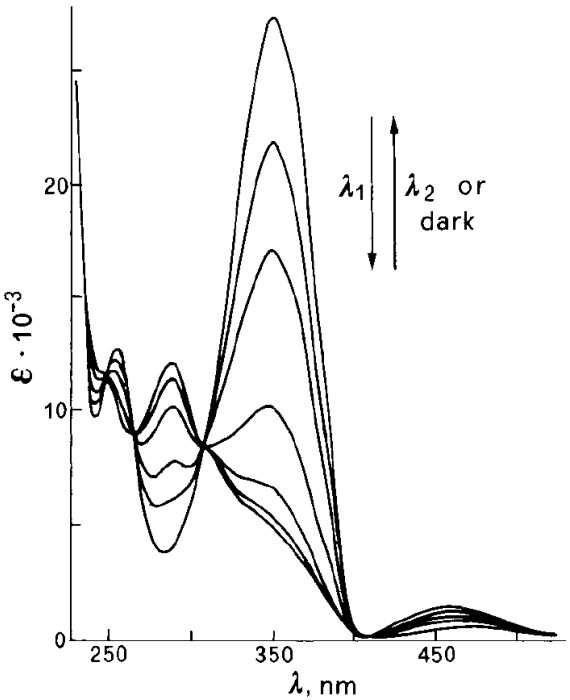




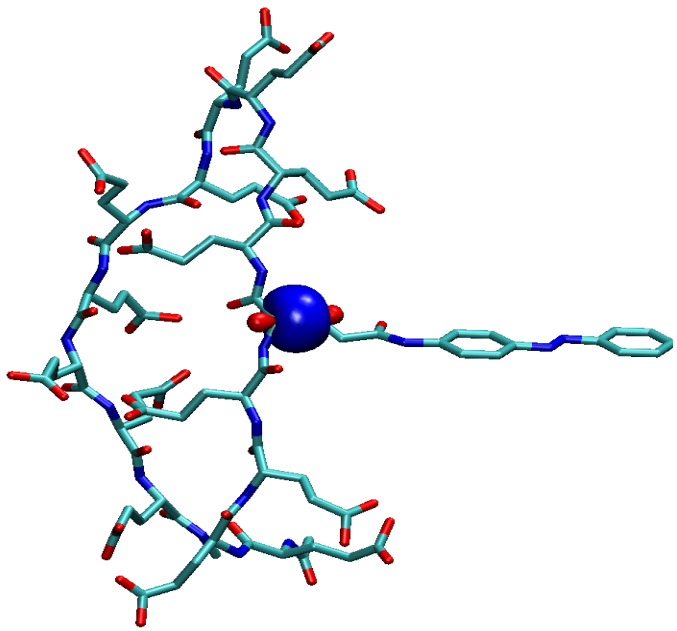
Yu, Y.; M. Makoto, M.; T. Ikeda, T. *Nature*, **2003**, *425*, 145.



Spectre UV-vis : TD-DFT



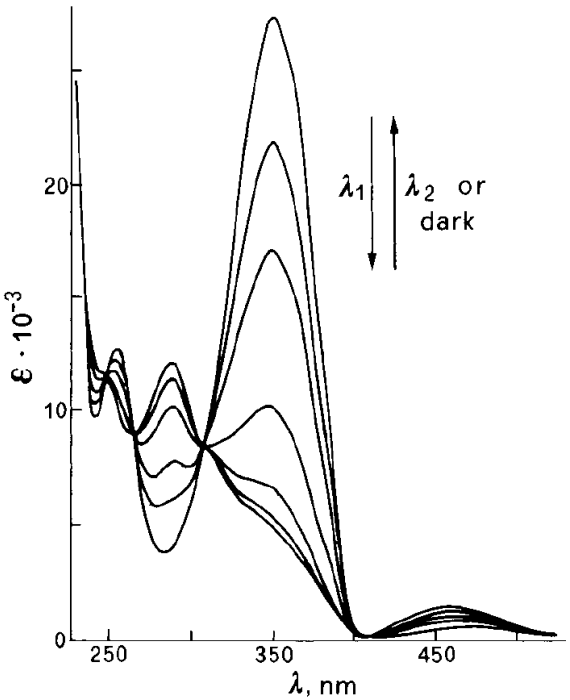
Système macromoléculaire : calculs MM



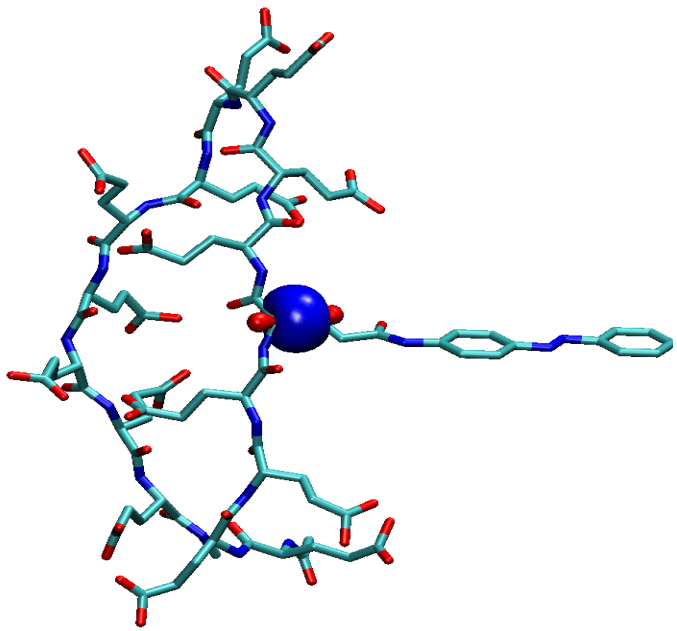
[6] Briquet et al. *Chem. Phys. Lett.*, **2006**, *417*, 190.

Spectre UV-vis : TD-DFT

- Géometries: B3LYP/6-311G(d)
- Spectre UV-vis : TD-DFT PBE0/6-311+G(d)[6]



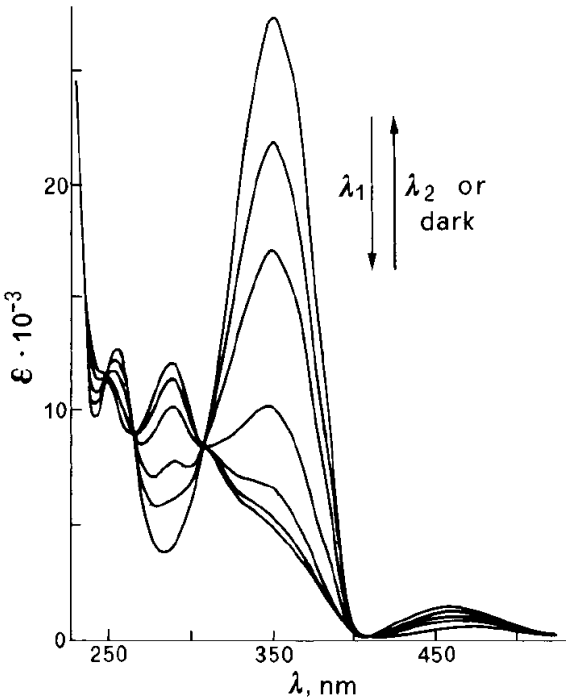
Système macromoléculaire : calculs MM



[6] Briquet et al. *Chem. Phys. Lett.*, **2006**, *417*, 190.

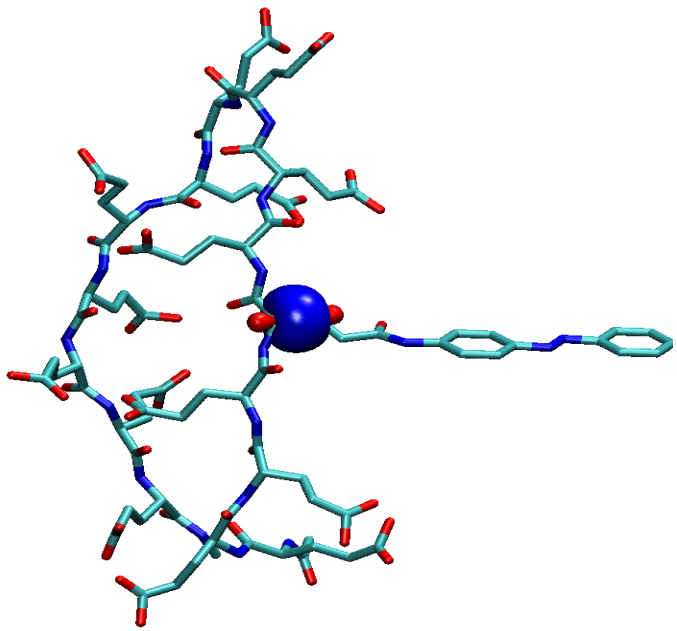
Spectre UV-vis : TD-DFT

- Géometries: B3LYP/6-311G(d)
- Spectre UV-vis : TD-DFT PBE0/6-311+G(d)[6]



Système macromoléculaire : calculs MM

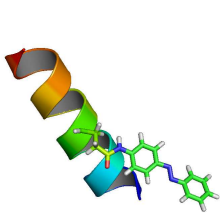
- Champ de force : Amber *ff99*
- GLU protoné
- N et C-*terminus*: groupement NME et ACE



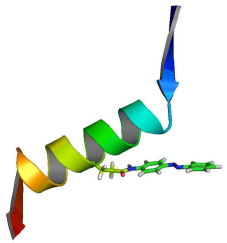
[6] Briquet et al. *Chem. Phys. Lett.*, **2006**, *417*, 190.

Géométries QM/MM des Poly(acide L-glutamique) + TAB

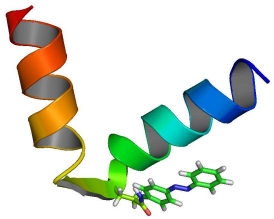
- Structure α



Hélice α

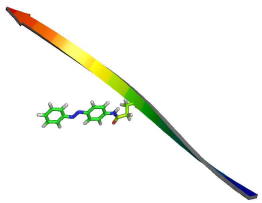


β-α-β

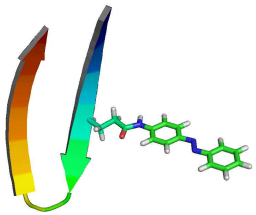


α-β-α

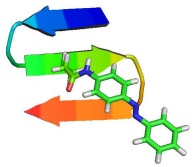
- Structure β



Brin β

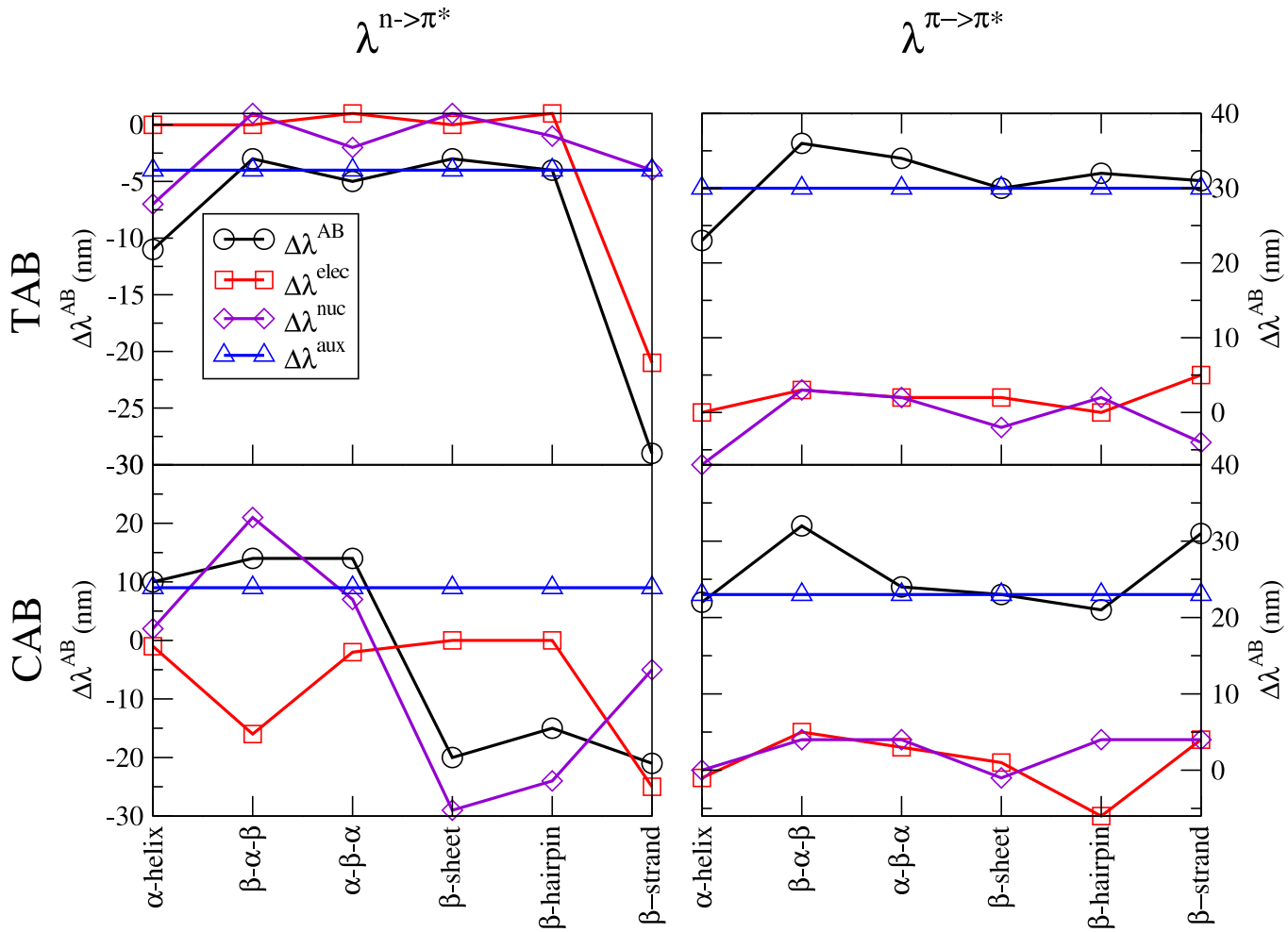


Epingle β



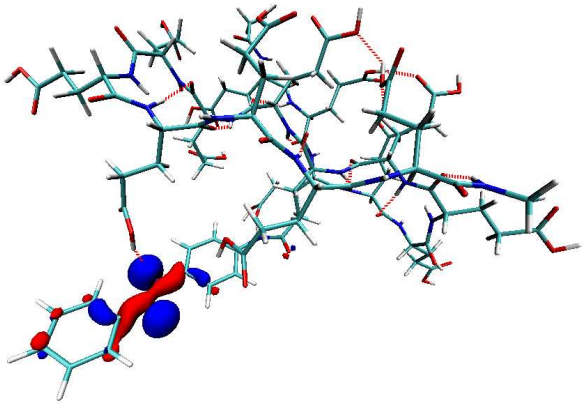
Feuillet β

$$\Delta\lambda^{\mathrm{AB}} = \Delta\lambda^{\mathrm{elec}} + \Delta\lambda^{\mathrm{nuc}} + \Delta\lambda^{\mathrm{aux}}$$

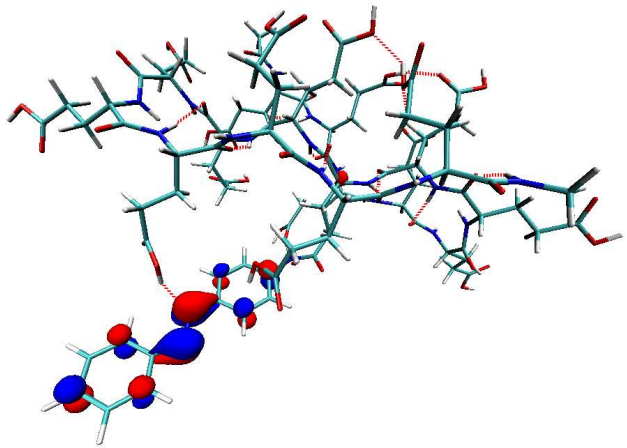


Orbitales frontières de la transition $n \longrightarrow \pi^\star$

Orbitale non-liante (n)

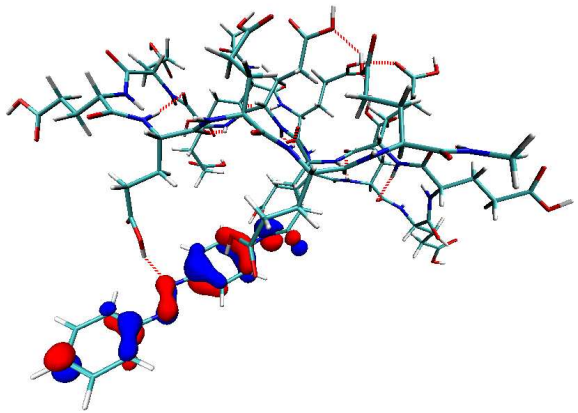


Orbitale anti-liante ($\pi^\star$)

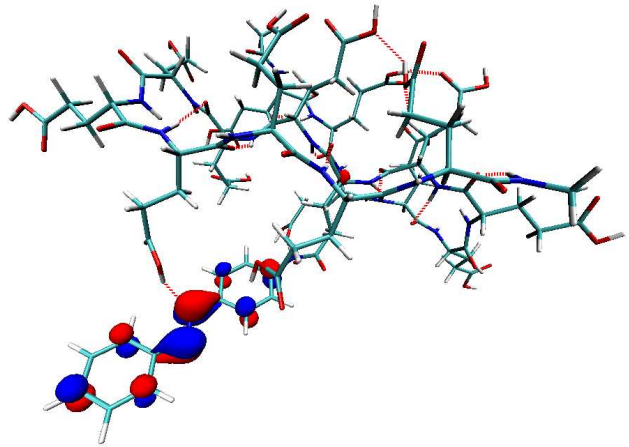


Orbitales frontières de la transition $\pi \longrightarrow \pi^\star$

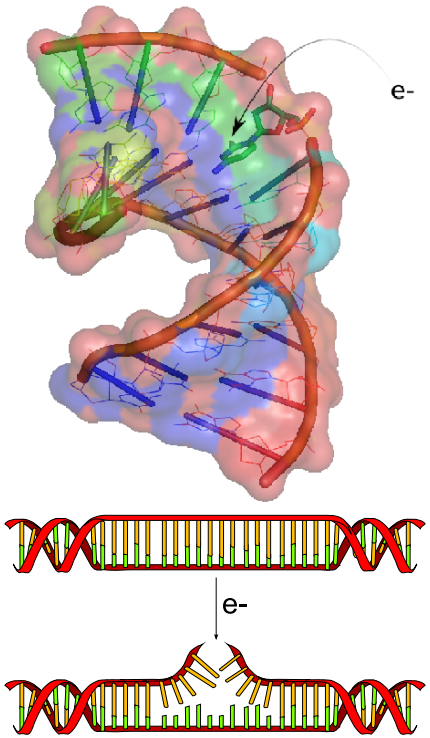
Orbitale liante (π)



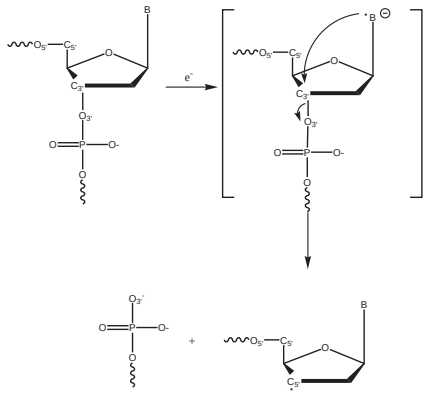
Orbitale anti-liante ($\pi^\star$)



Lésion simple-brin de l'ADN[1]

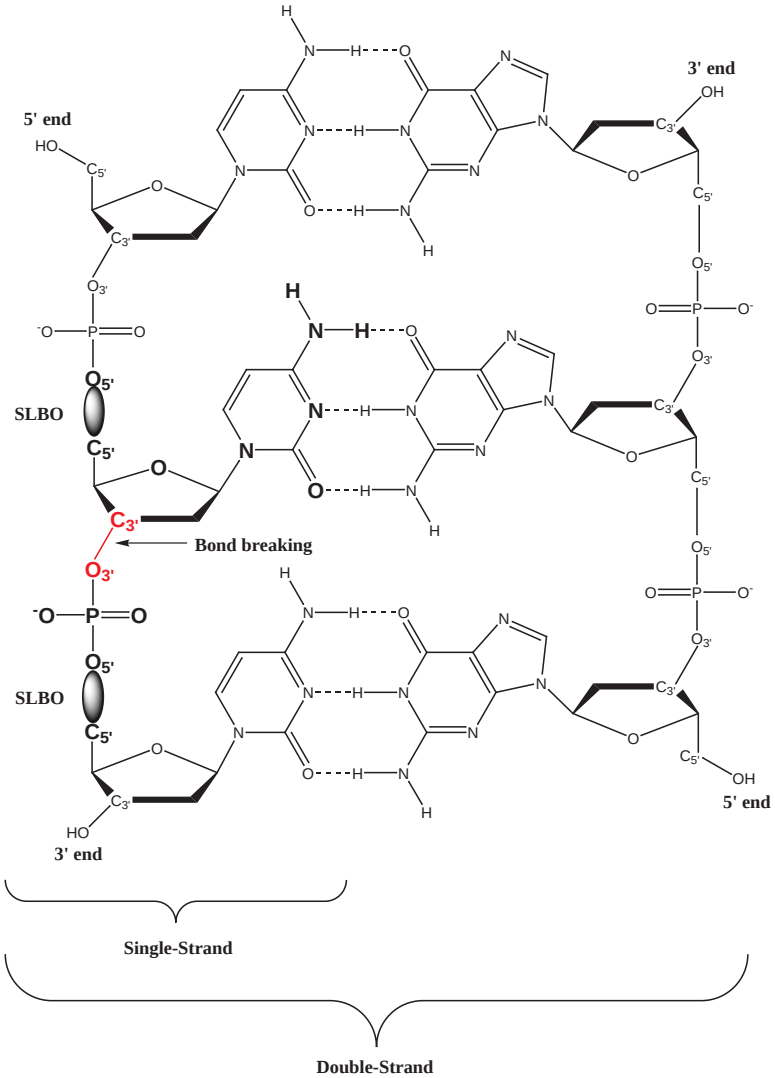


Mécanisme proposé



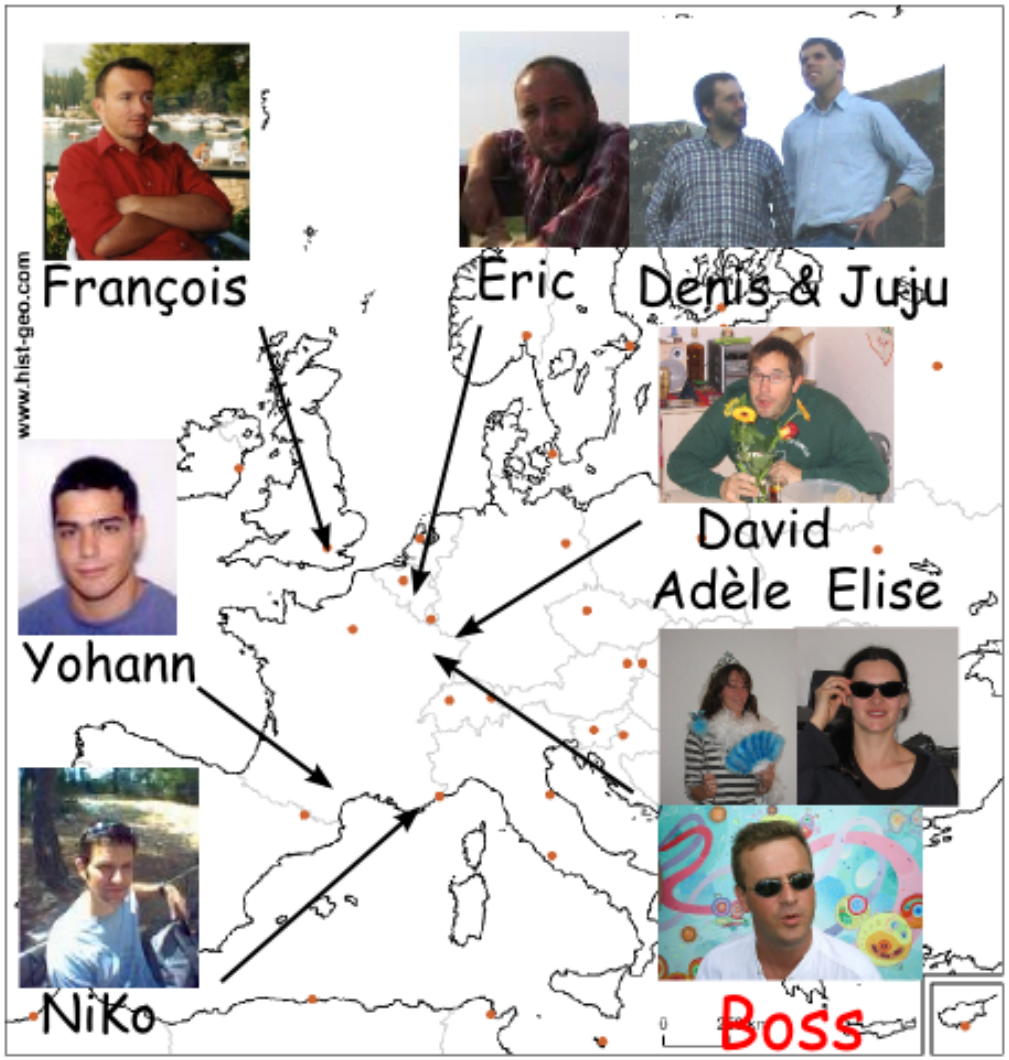
[1] Boudaiffa et al, *Science*, **2000**,*287*, 1658.

Partition QM/MM



Conclusions

Perspectives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