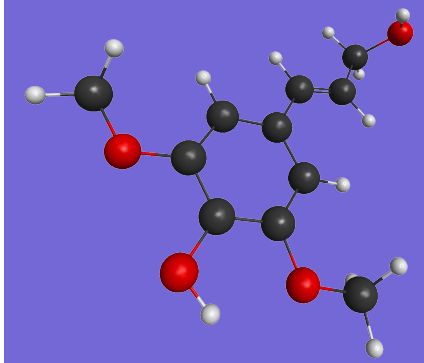
Workshop on Implication of Biomolecules Damage in Cancer Therapy and Progression

Transient Anion States of Potential Radiosensitizers

Márcio T. do N. Varella

Universidade Federal do Paraná

Curitiba, October 18th 2018



Molecular Physics and Modelling Group

Interactions with electrons, positrons and photons

http://fig.if.usp.br/~mvarella/

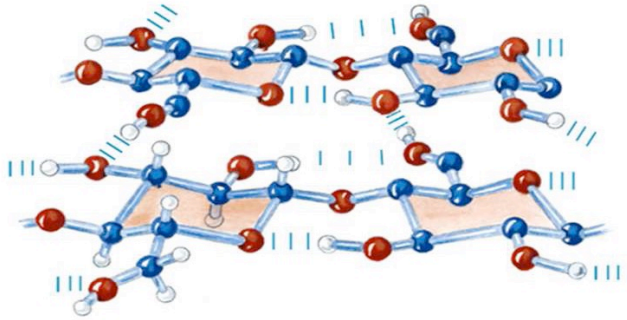
Electronic Transients

Technological applications

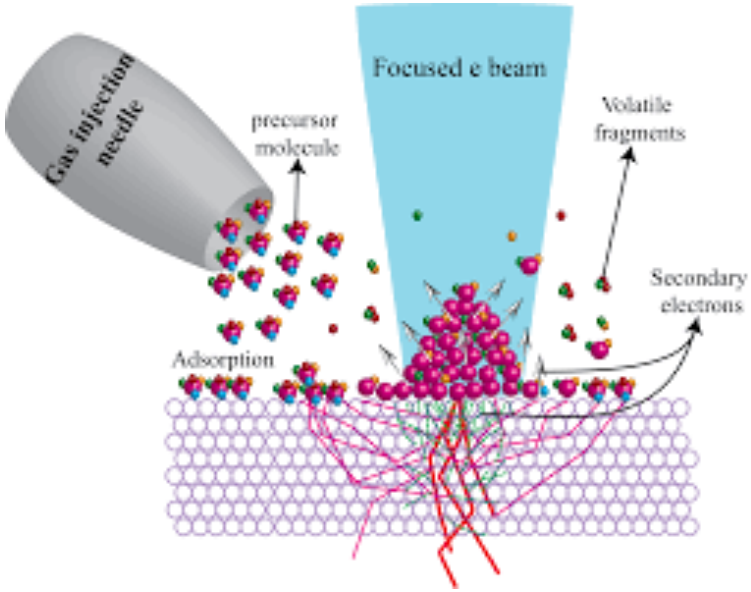
- Plasma-based processing (microelectronics)
- Plasma-assisted ignition
- Plasma-based pre-treatment of sugarcane biomass
- FEBID

Scientific applications

- Astrophysics and Atmospheric Physics (Ionosphere)
- Pre-Biotic molecules
- Radiation damage to biomolecules
- Radiosensitizers

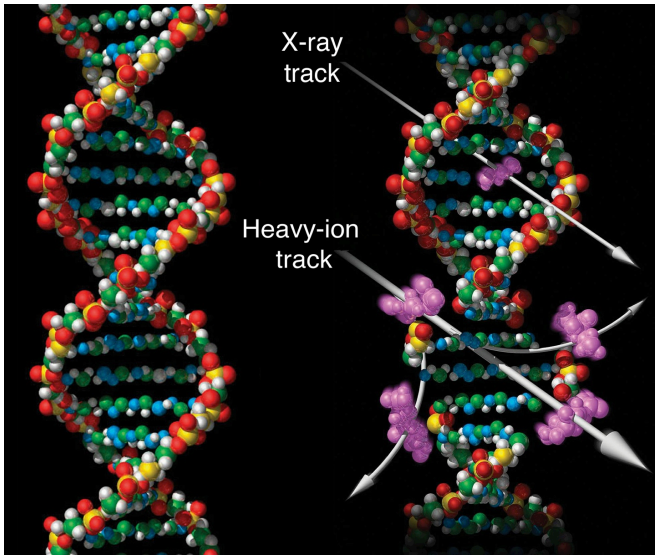


Cellulose Chains
(Biomass Pretreatment)



FEBID: Focused Electron
Beam Induced Deposition

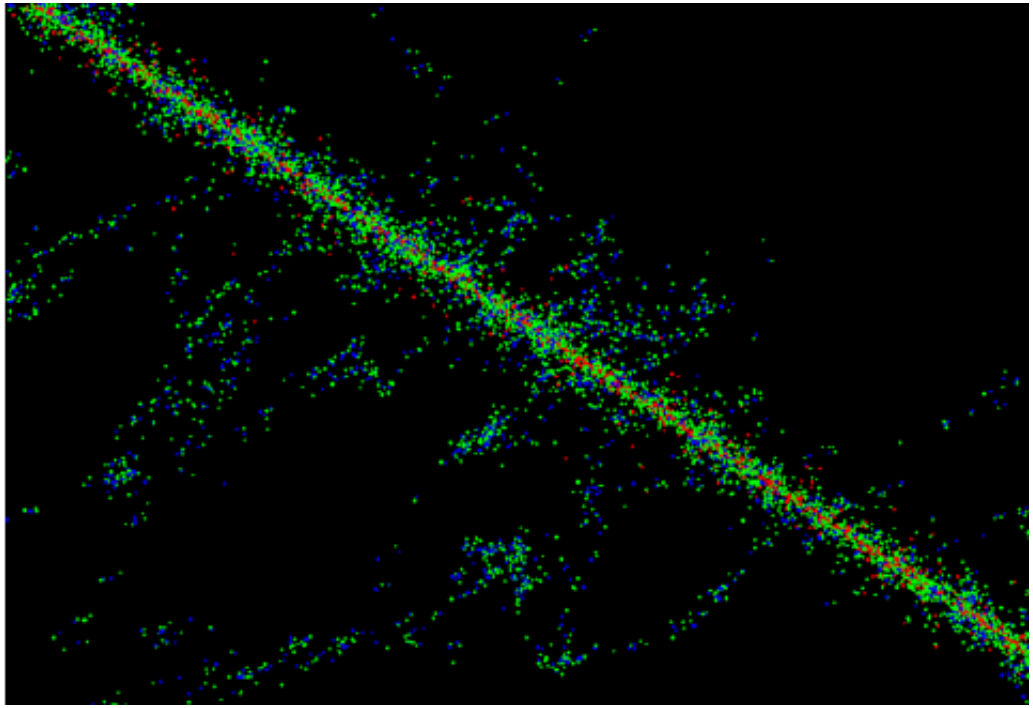
https://rageshkumartp.wordpress.com/



Radiation/Heavy Ion
DNA Damage

http://quantumdiaries.org/author/brookhaven/

Energy Deposition: Secondary Electrons



Proton Track

- Primary Ionization (proton)
- Secondary Ionization (electron)

Douglass, Phys. in Med. & Biol., 60 3217 (2015)

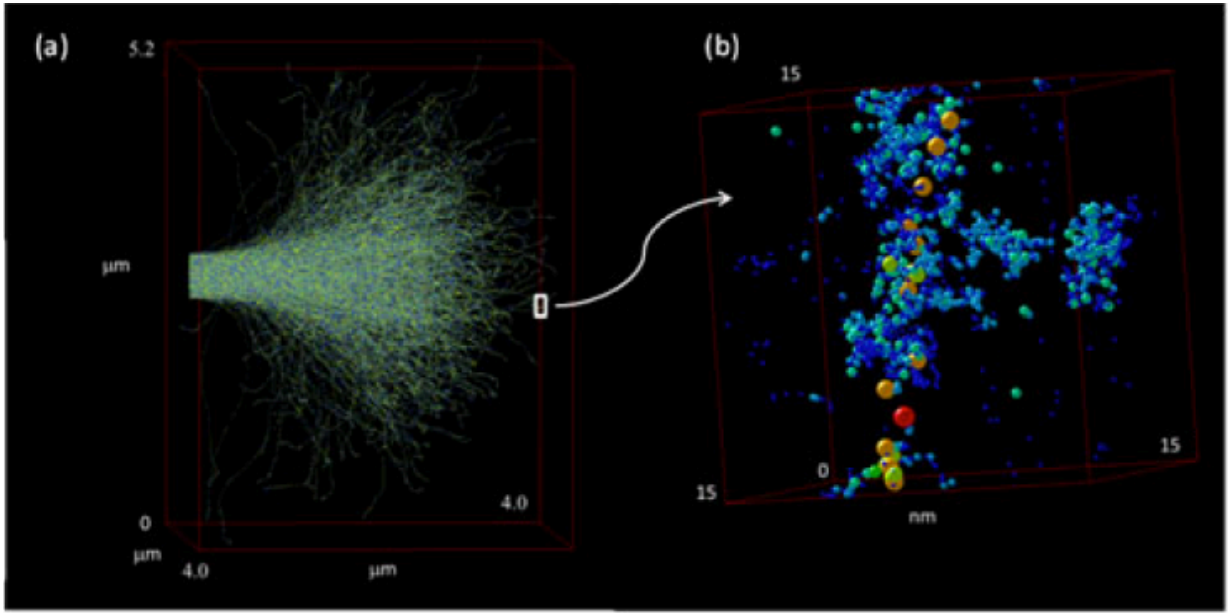
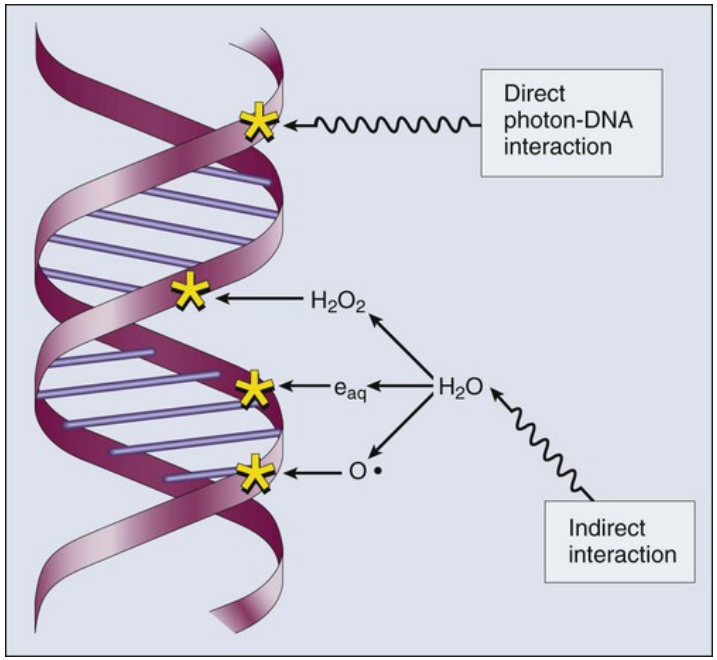


Fig. 14. An example of single electron tracks simulation in liquid water. (a) 1000 electrons with 10 keV incident energies slowing down by successive collisions (coloured balls). (b) Nanovolume detail close to the end of a selected track. The colour of the balls indicates the type of interaction: ●, elastic scattering; ●, rotational excitation; ●, vibrational excitation; ●, electronic excitation; ●, neutral dissociation; ●, ionisation; ●, electron attachment.

Blanco *et al.*, Eur. Phys. J. D 67, 199 (2013)

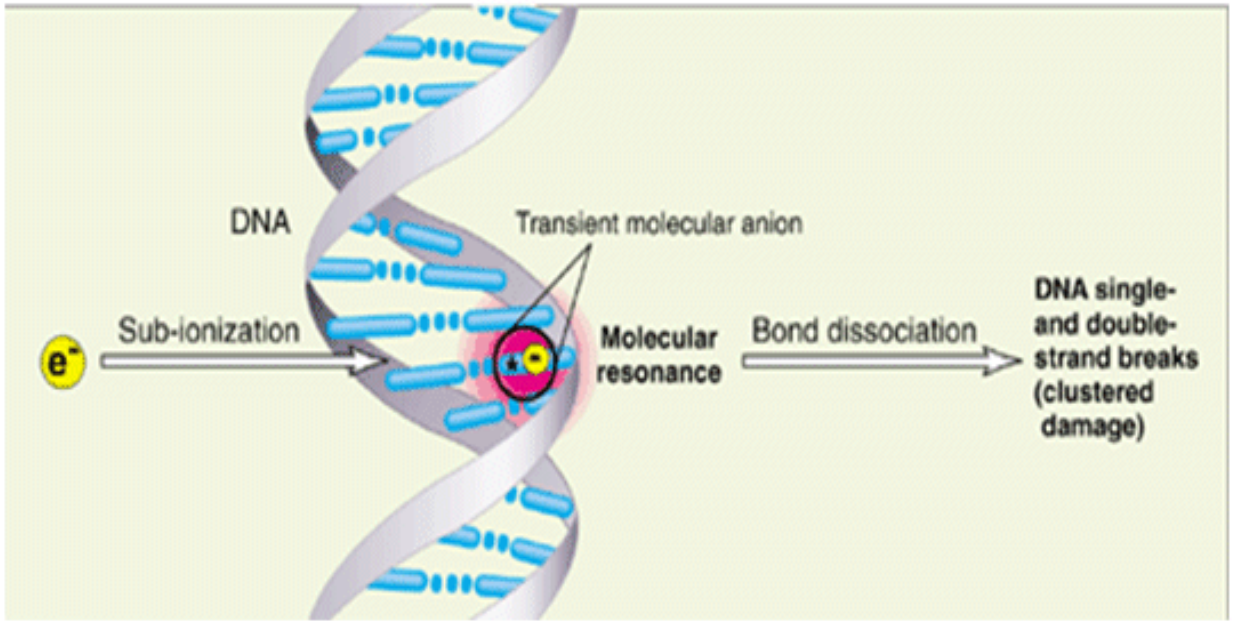
Radiation / Heavy Particle Damage



Radiation Damage: mostly indirect (OH radicals, electrons, etc.)

https://clinicalgate.com/basics-of-radiation-therapy-2/

Electron-Induced Damage: Transient Anions

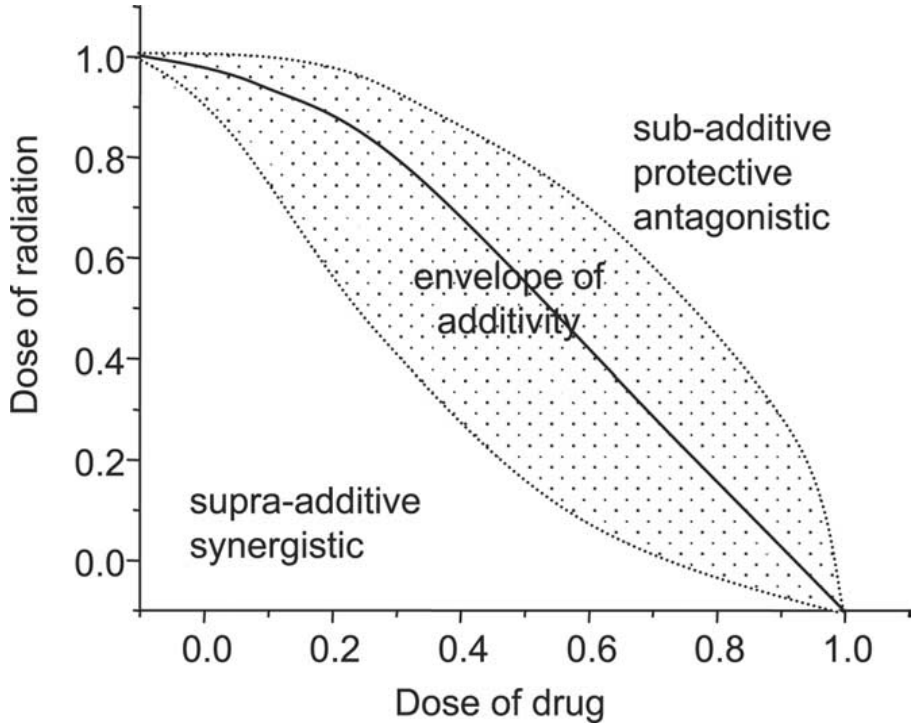


http://www.isa.au.dk/networks/eipam/radam-research.html

Radiosensitizers

"Radiosensitizers are intended to enhance tumor cell killing while having much less effect on normal tissues"

P. Wardman, *Chemical Radiosensitizers for Use in Radiotherapy*, Clin. Oncol. **19**, 397 (2007).

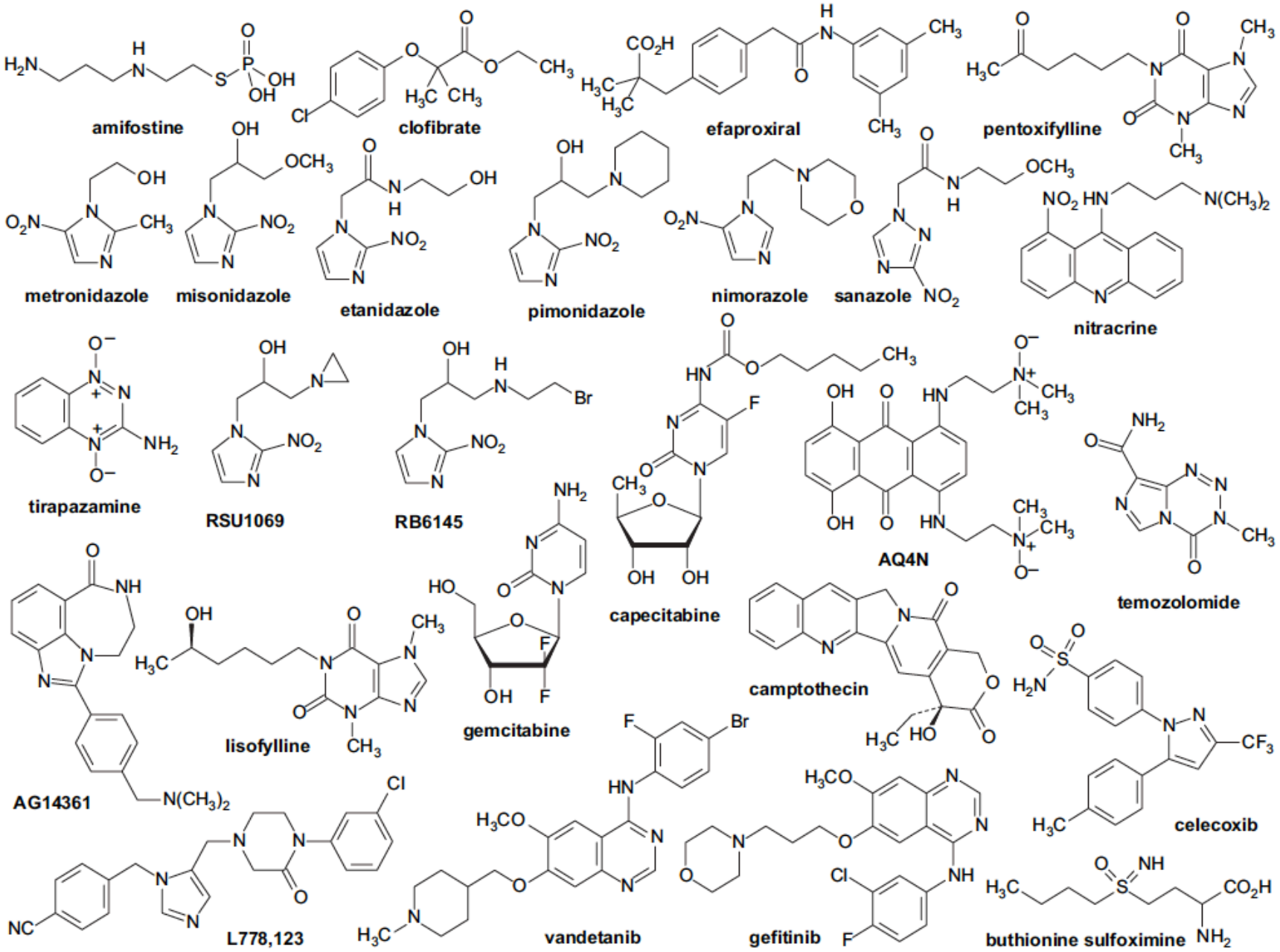


Wilson *et al.*, Semin. Radiat. Oncol. **16**, 2 (2006)

Wardman's tip for dummies: "Radiotherapy is free-radical therapy"

P. Wardman, Clin. Oncol. 19, 397 (2007).

Fig. 1 — Some of the drugs discussed in the text (those asterisked at first mention).



Types of Chemical Radiosensitizer

An early pioneer in this field, G. E. Adams, divided radiosensitizers into five categories [15,16]:

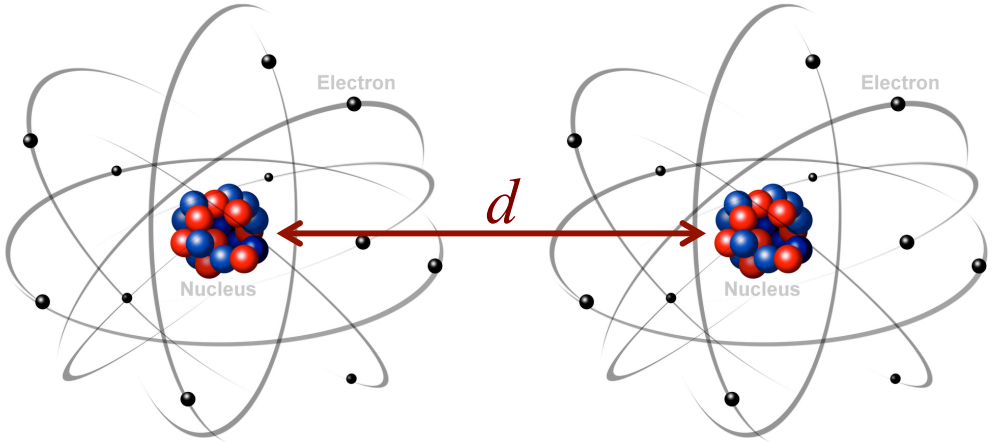
- 'Suppression of intracellular-SH [thiols] or other endogenous radioprotective substances.
- Radiation-induced formation of cytotoxic substances from the radiolysis of the sensitizer.
- Inhibitors of post-irradiation cellular repair processes.
- Sensitization by structural incorporation of thymine analogues into intracellular DNA.
- Oxygen-mimetic sensitizers, for example the electron-affinic drugs ...'.

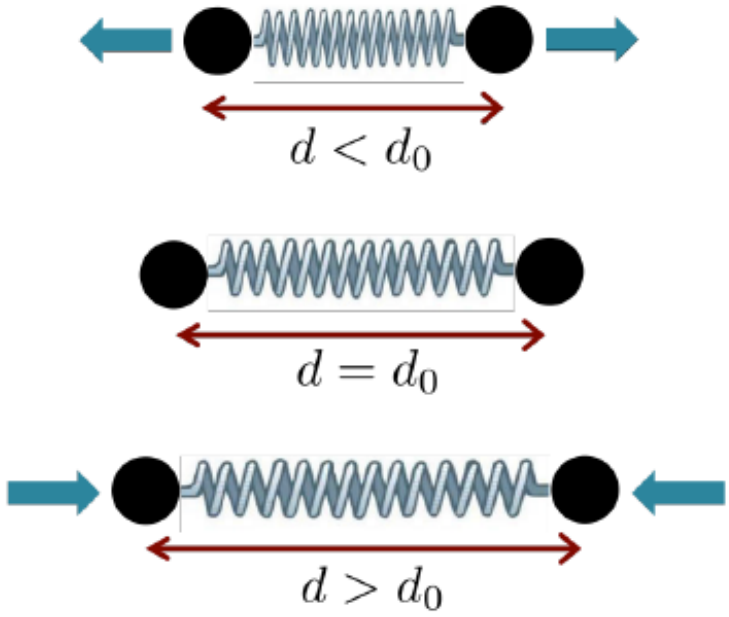
P. Wardman, Clin. Oncol. 19, 397 (2007).

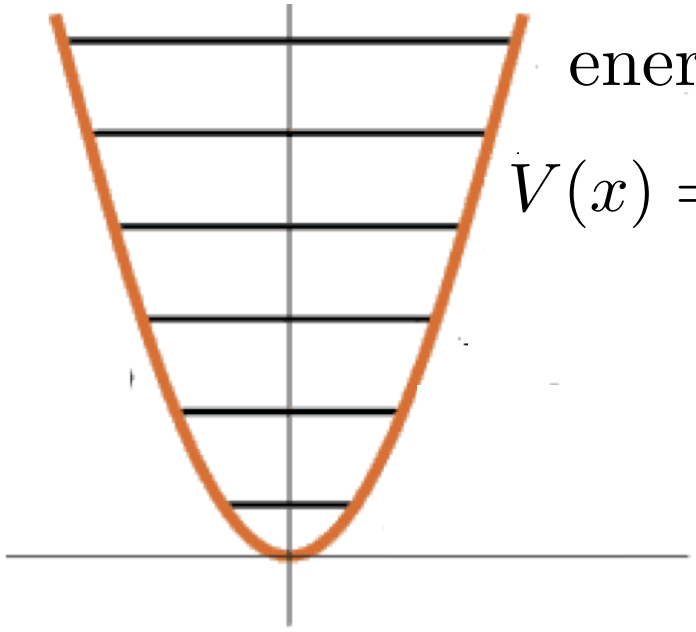
Electron-induced dissociation reactions often produce radicals

$$AB + e^- \longrightarrow AB^- \longrightarrow A^\bullet + B^-$$

Breaking Bonds







energy

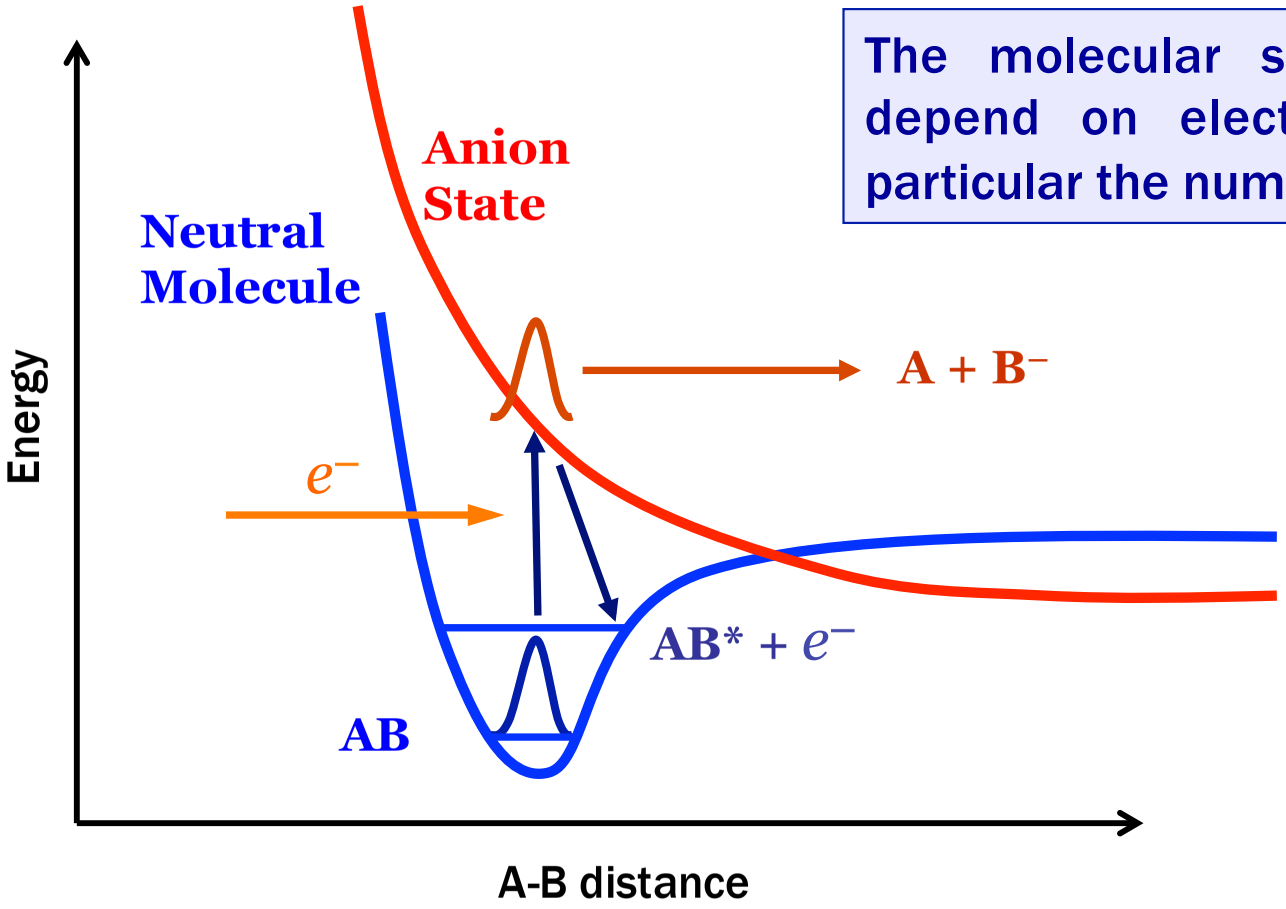
$$V(x) = \frac{1}{2}\, k_e\, x^2$$

deformation

$$x = (d - d_0)$$

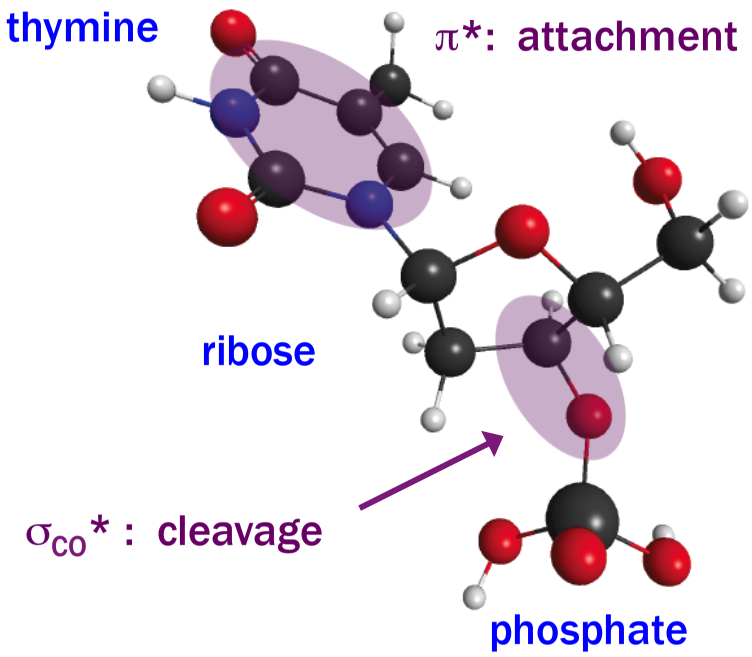
Breaking Bonds

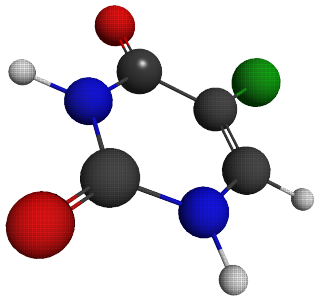
The molecular spring constants (k_e) depend on electronic properties, in particular the number of electrons.



$$AB + e^- \longrightarrow AB^- \longrightarrow A^\bullet + B^-$$

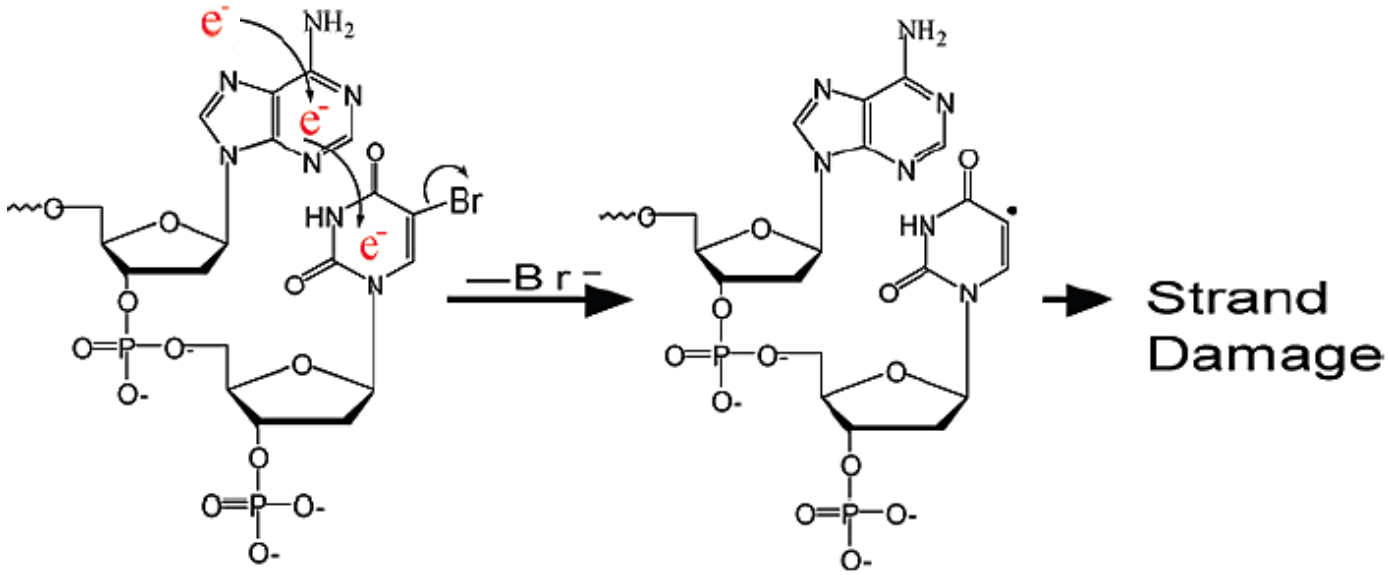
Halouracils





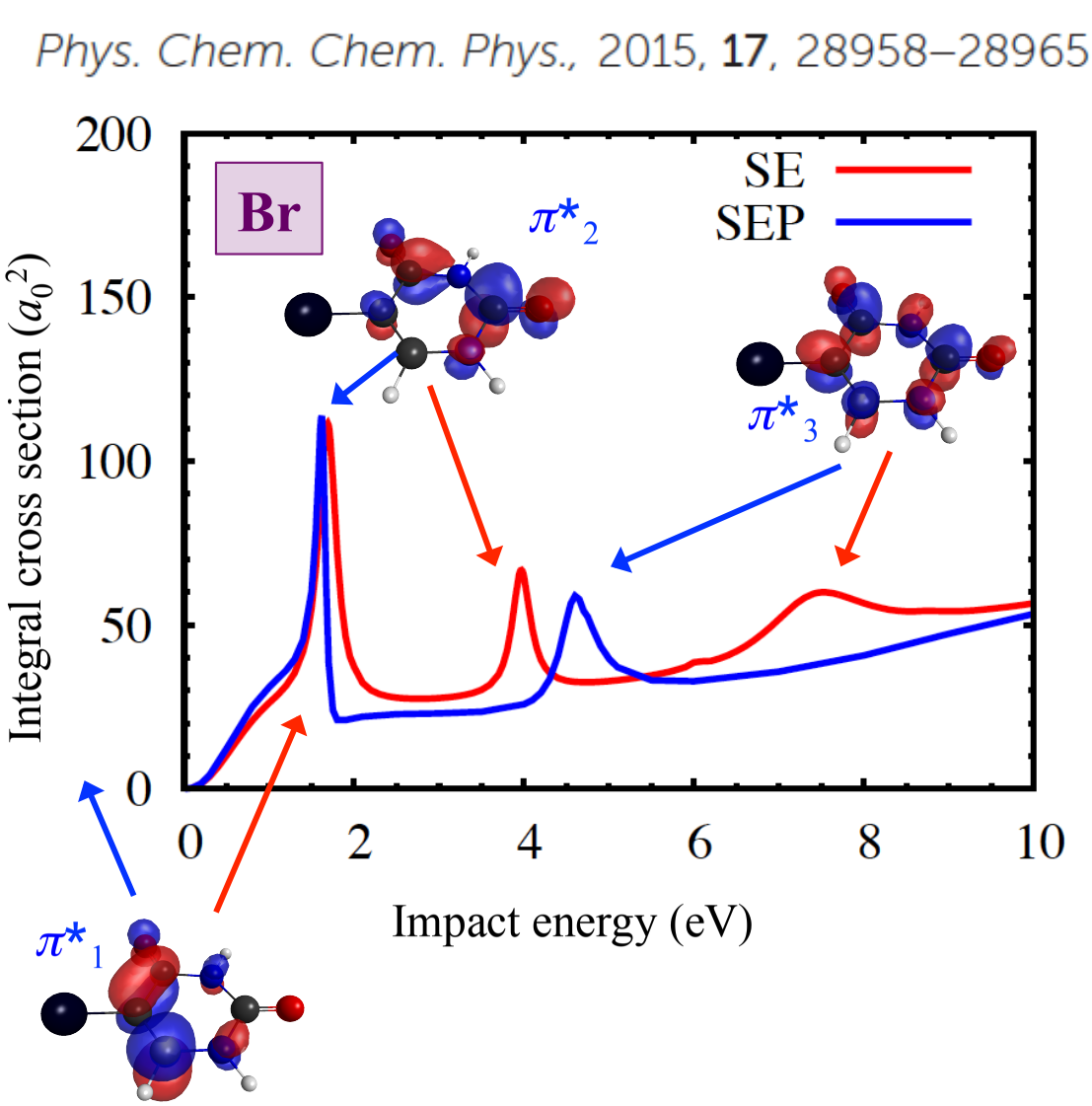
5-bromo-uracil

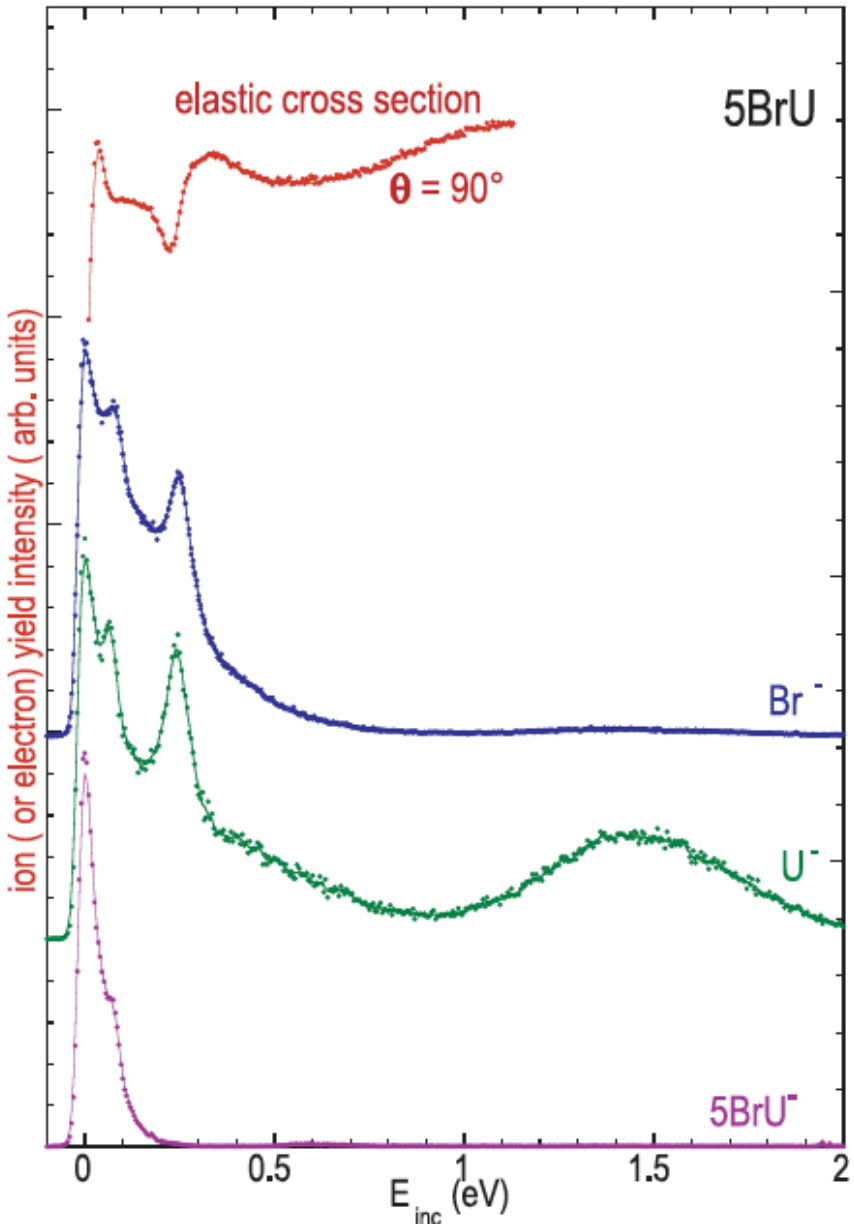
Release of Br^- produces reactive uracilyl radicals.



Adapted from Wang and Lu, JACS **132**, 14710 (2010)

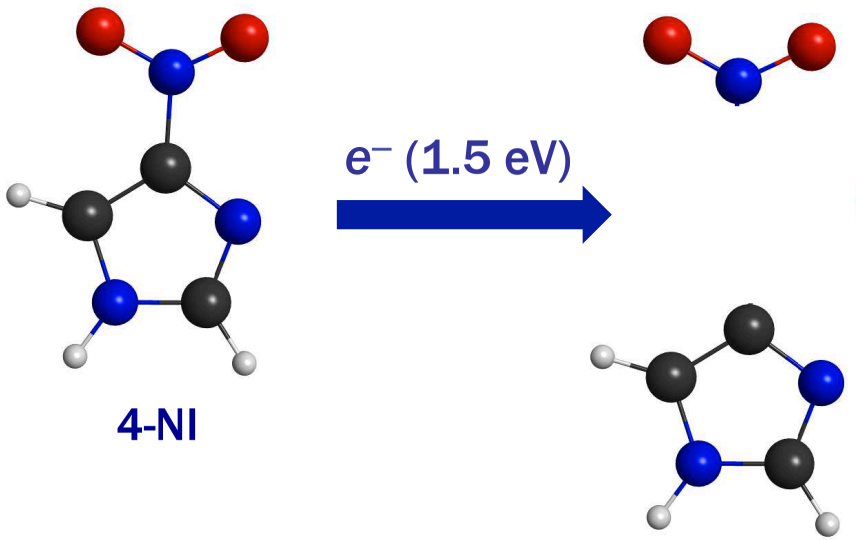
Transient anion states of 5-Br-Uracil



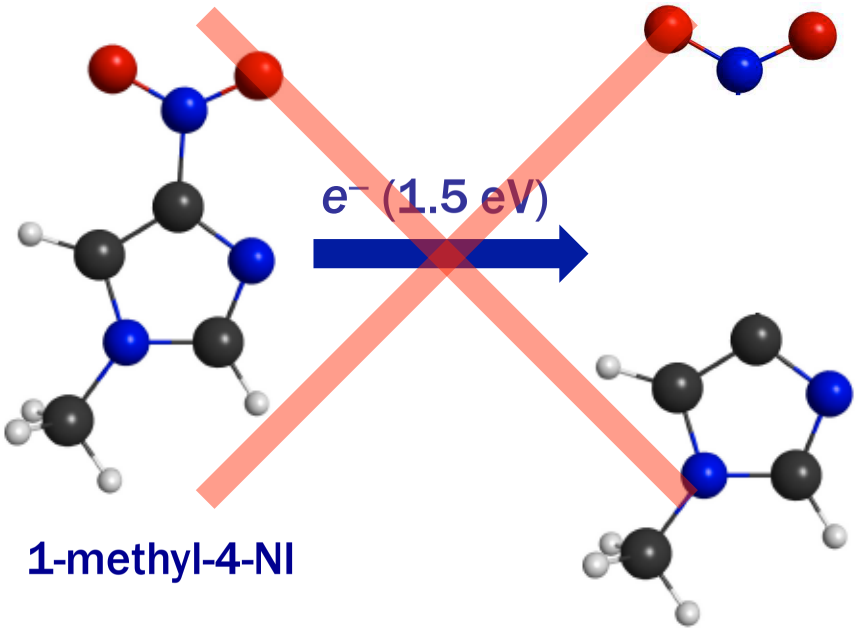


Abouaf & Dunet, EPJD 35, 405 (2005).

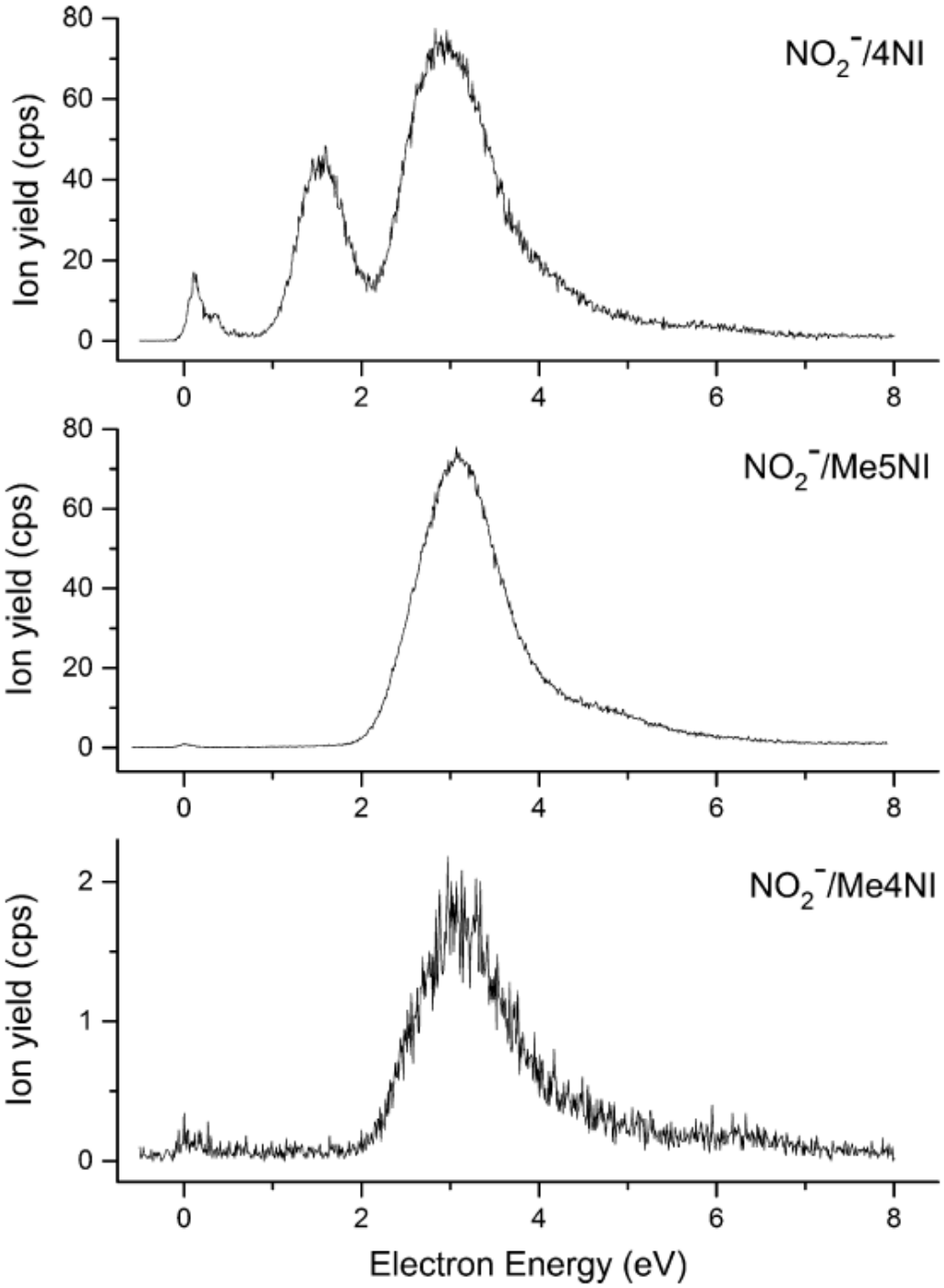
Nitroimidazoles



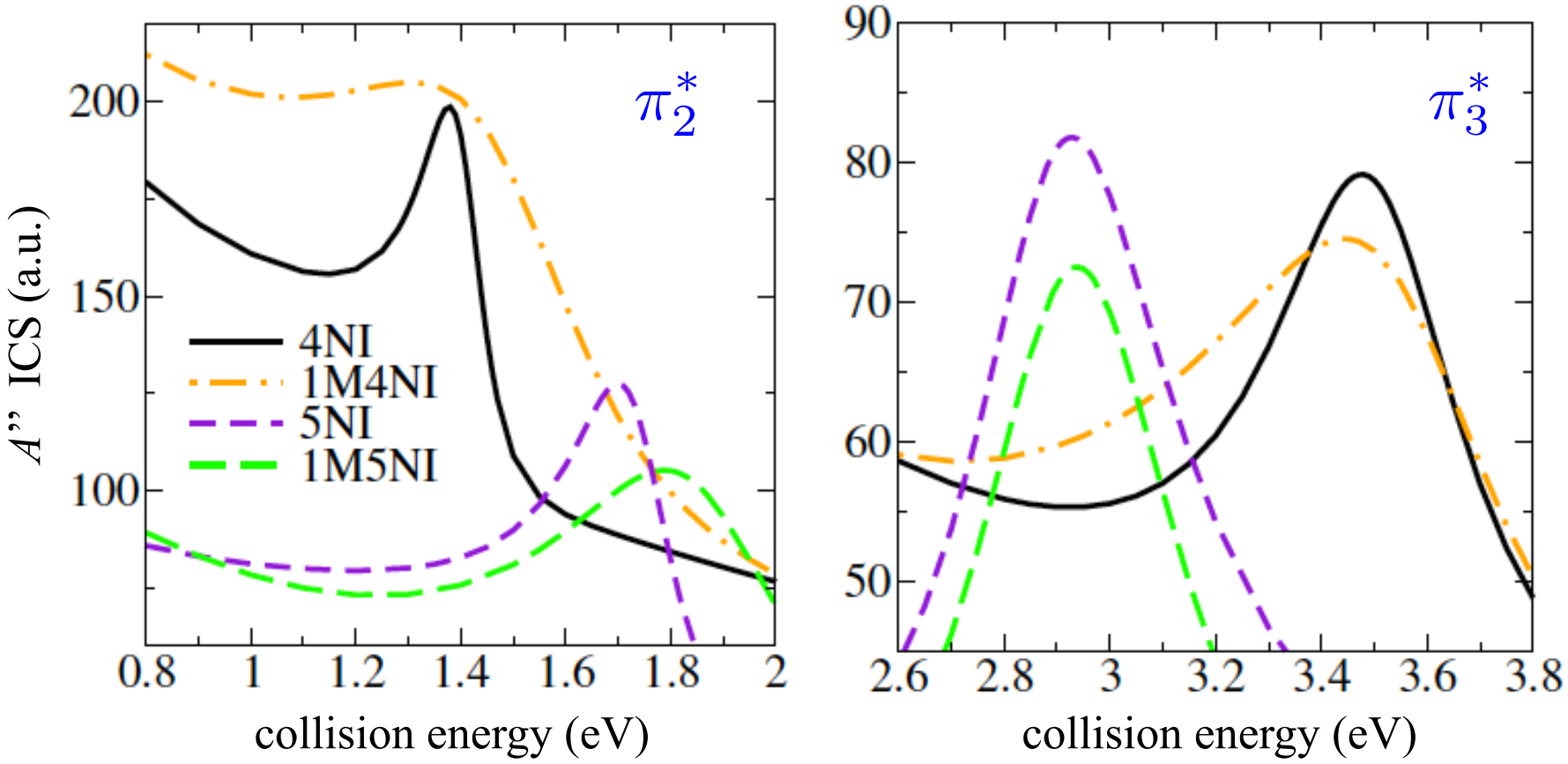
4-NI



1-methyl-4-NI



Tanzer *et al.*, Angew. Chem. 53 12240 (2014)



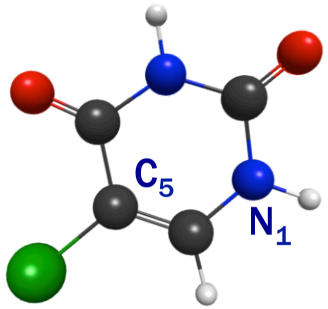
	π_1^*	π_2^*	π_3^*
4NI	−0.29	1.41 (0.14)	3.50 (0.45)
1M4NI	−0.26	1.49 (0.61)	3.56 (0.65)
5NI	−1.02	1.74 (0.24)	2.93 (0.45)
1M5NI	−0.79	1.86 (0.52)	2.93 (0.49)

resonance positions (widths) in eV

Methylation reduces the π_2^* lifetimes by a factor of 4 (2) in 4NI (5NI) .

Shape resonance spectra of uracil, 5-fluorouracil, and 5-chlorouracil

THE JOURNAL OF CHEMICAL PHYSICS **140**, 024317 (2014)

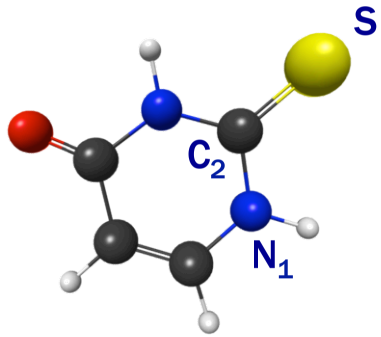


Negative ion states of 5-bromouracil and 5-iodouracil

Phys. Chem. Chem. Phys., 2015, **17**, 17271–17278

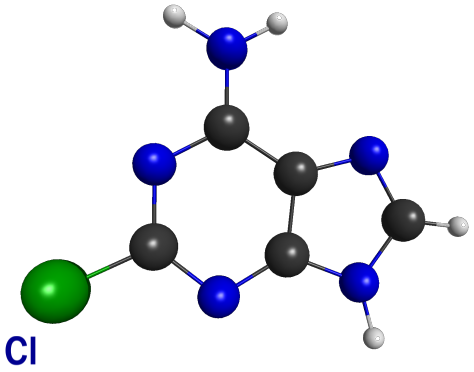
Electron driven reactions in sulphur containing analogues of uracil: the case of 2-thiouracil

Phys. Chem. Chem. Phys., 2014, **16**, 25054–25061



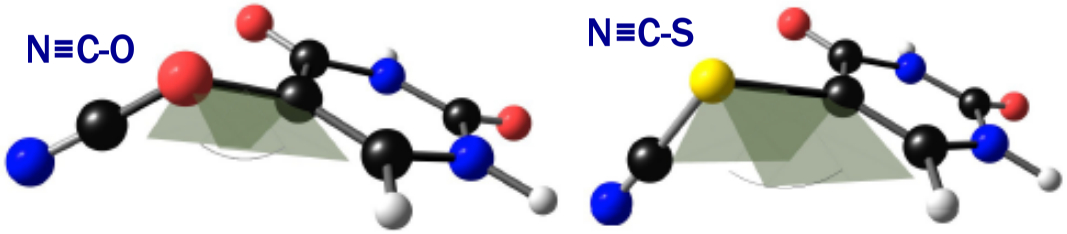
Anion states and fragmentation of 2-chloroadenine upon low-energy electron collisions†

Phys. Chem. Chem. Phys., 2015, **17**, 28958–28965



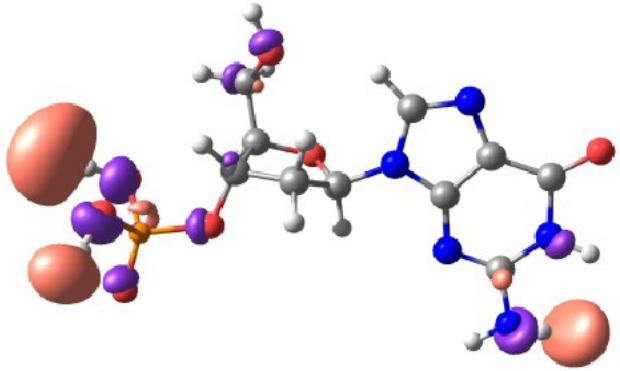
Transient anion spectra of the potential radiosensitizers 5-cyanateuracil and 5-thiocyanateuracil

THE JOURNAL OF CHEMICAL PHYSICS **147**, 214310 (2017)



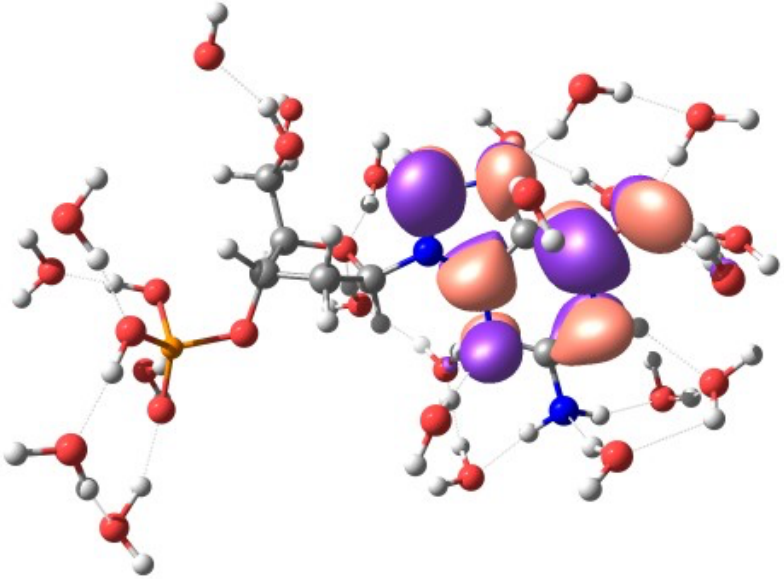
From Gas to Condensed Phase

dGMP$^-$
(Gas Phase)



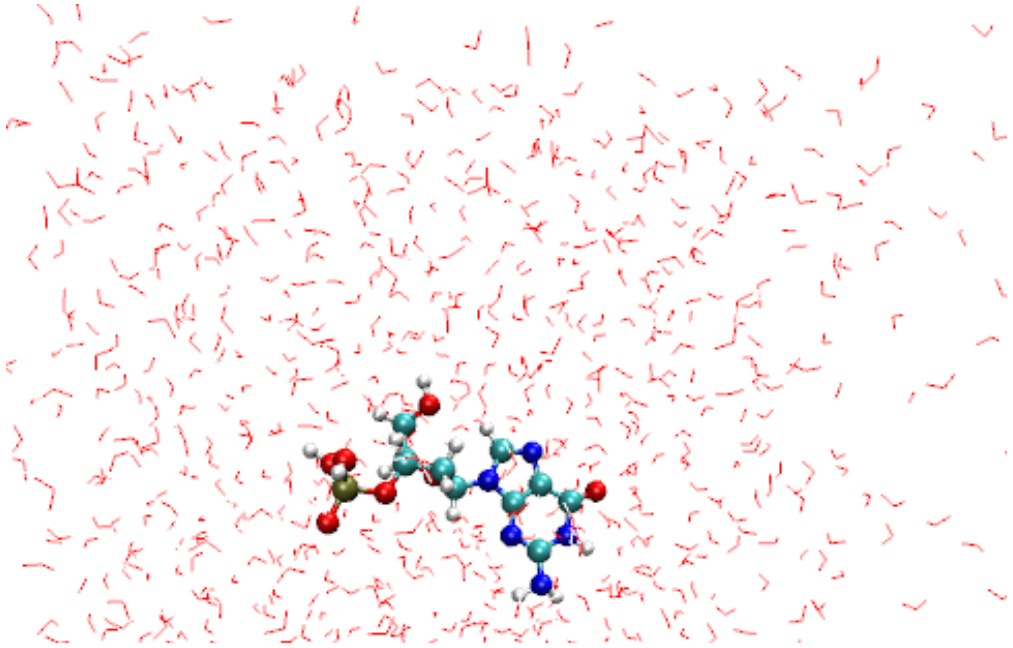
Dipole Bound State
(longer-range interaction)

dGMP$^-$
(+ 1,000 water molecules)

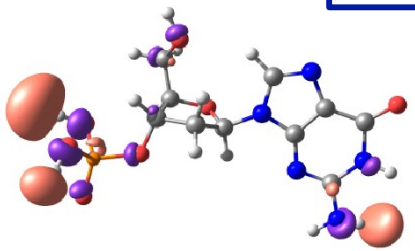


Valence Bound State
(shorter-range interaction)

Electron-induced processes relevant in the gas phase may become irrelevant in water medium.



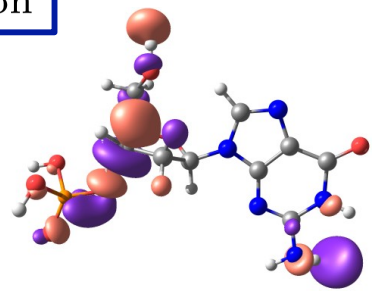
$$\Delta G^{\text{solution}}_{\text{barrier}} = \Delta G^{\text{gas}}_{\text{barrier}} + \Delta G^{\text{TS}}_{\text{solvation}} - \Delta G^{\text{Min}}_{\text{solvation}}$$



min (gas)

$\Delta G^{\text{gas}}_{\text{barrier}}$

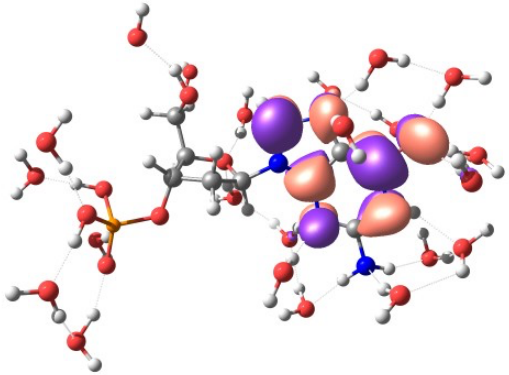
TS (gas)



$\Delta G^{\text{Min}}_{\text{solvation}}$

$\Delta G_{\text{cycle}} = 0$

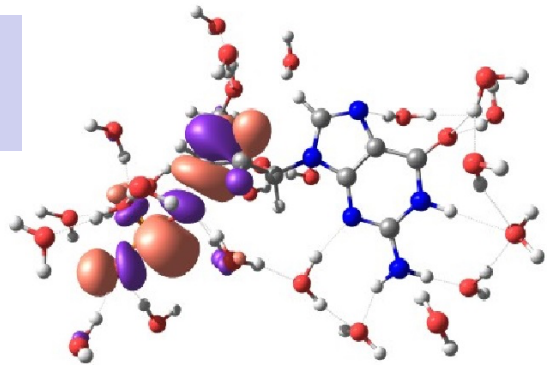
$\Delta G^{\text{TS}}_{\text{solvation}}$



min (solution)

$\Delta G^{\text{solution}}_{\text{barrier}}$

TS (solution)

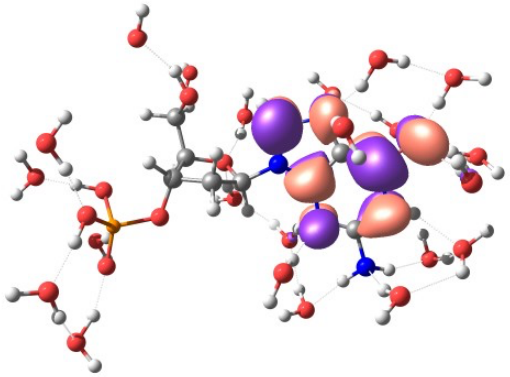


From Gas to Condensed Phase

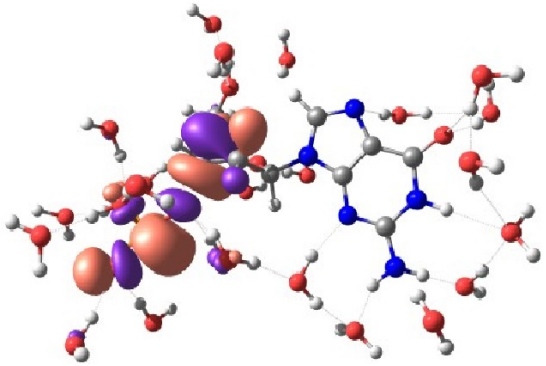
Free energy barrier for dissociation of the guanosine monophosphate anion in water*

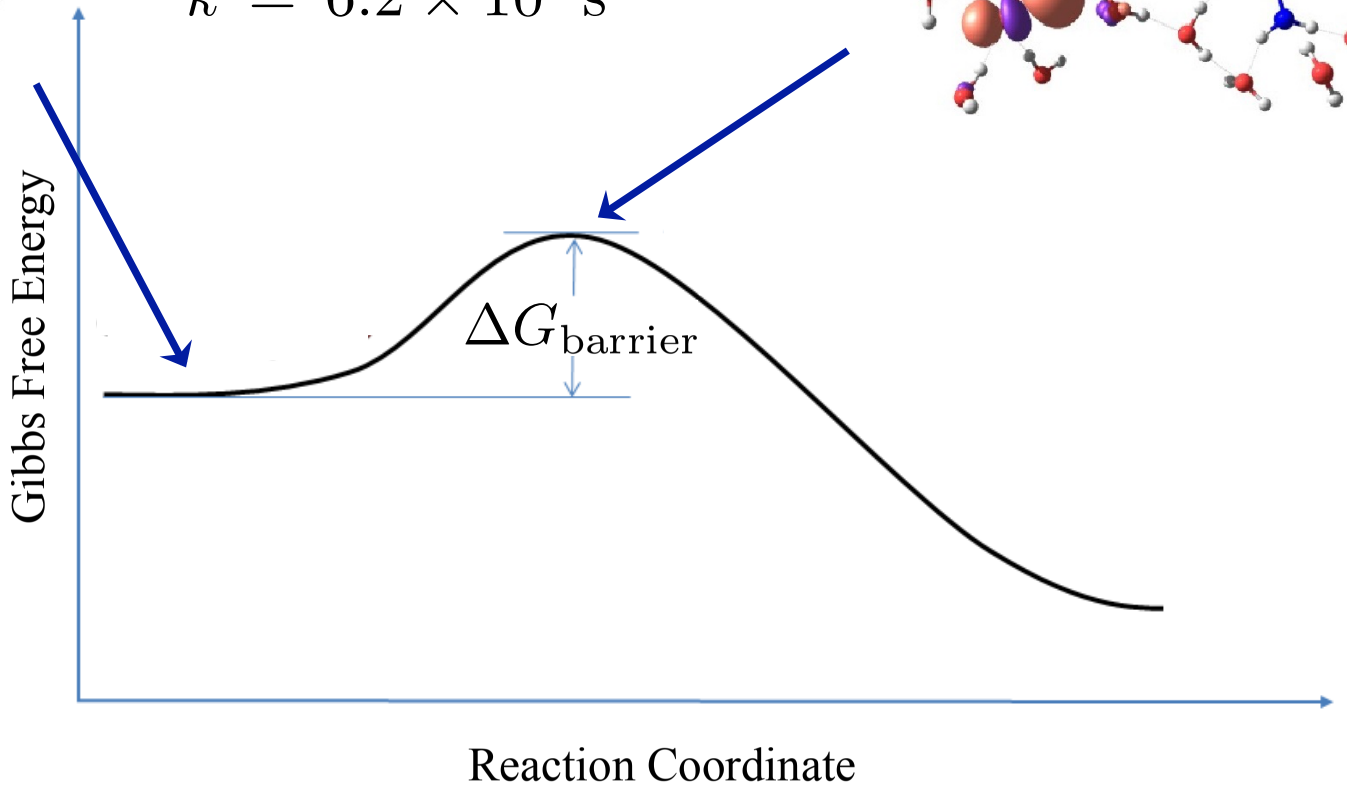
Lucas M. Cornetta, Kaline Coutinho, Sylvio Canuto, and Márcio T. do N. Varella[a]

Eur. Phys. J. D (2016) 70: 176



$$\Delta G = 16\,\text{kcal/mol}\ \ (0.69\,\text{eV})$$
$$k = 6.2 \times 10^2\,\text{s}^{-1}$$

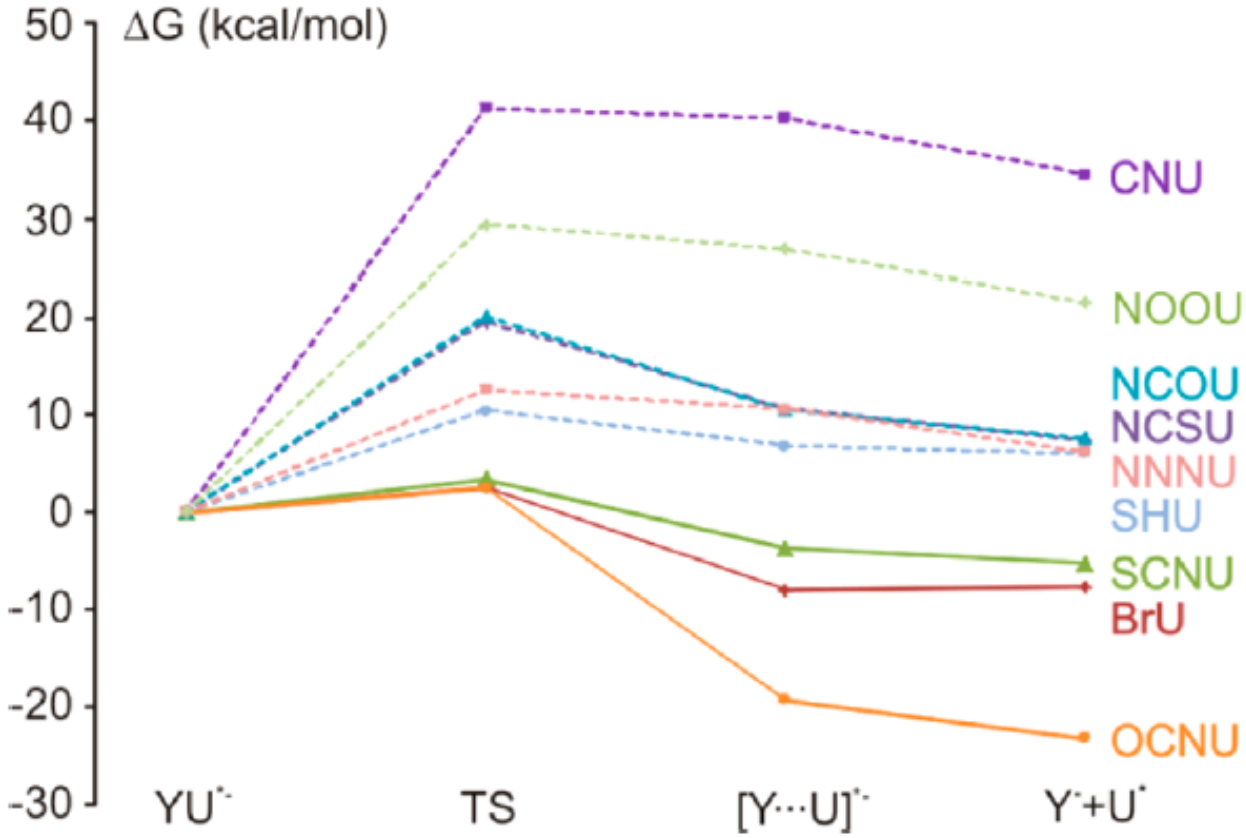




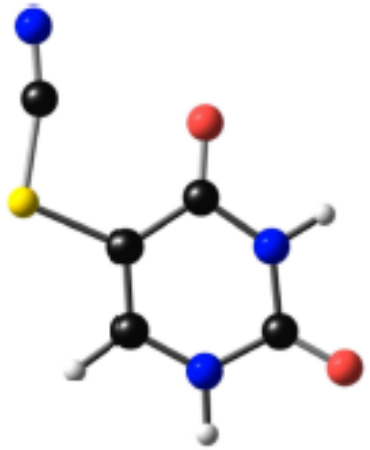
How to Find Out Whether a 5-Substituted Uracil Could Be a Potential DNA Radiosensitizer

Lidia Chomicz,[†] Magdalena Zdrowowicz,[†] Franciszek Kasprzykowski,[†] Janusz Rak,*[,†]
Angela Buonaugurio,[‡] Yi Wang,[‡] and Kit H. Bowen*[,‡]

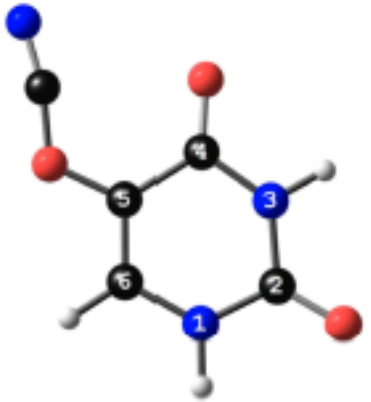
J. Phys. Chem. Lett. 2013, 4, 2853−2857



Free-energy barriers in water

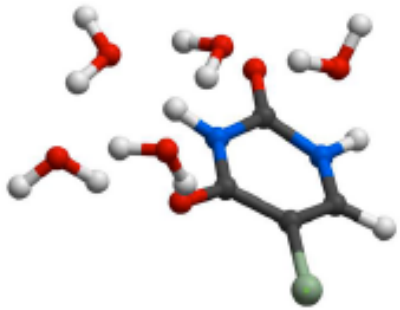


5-SCNU



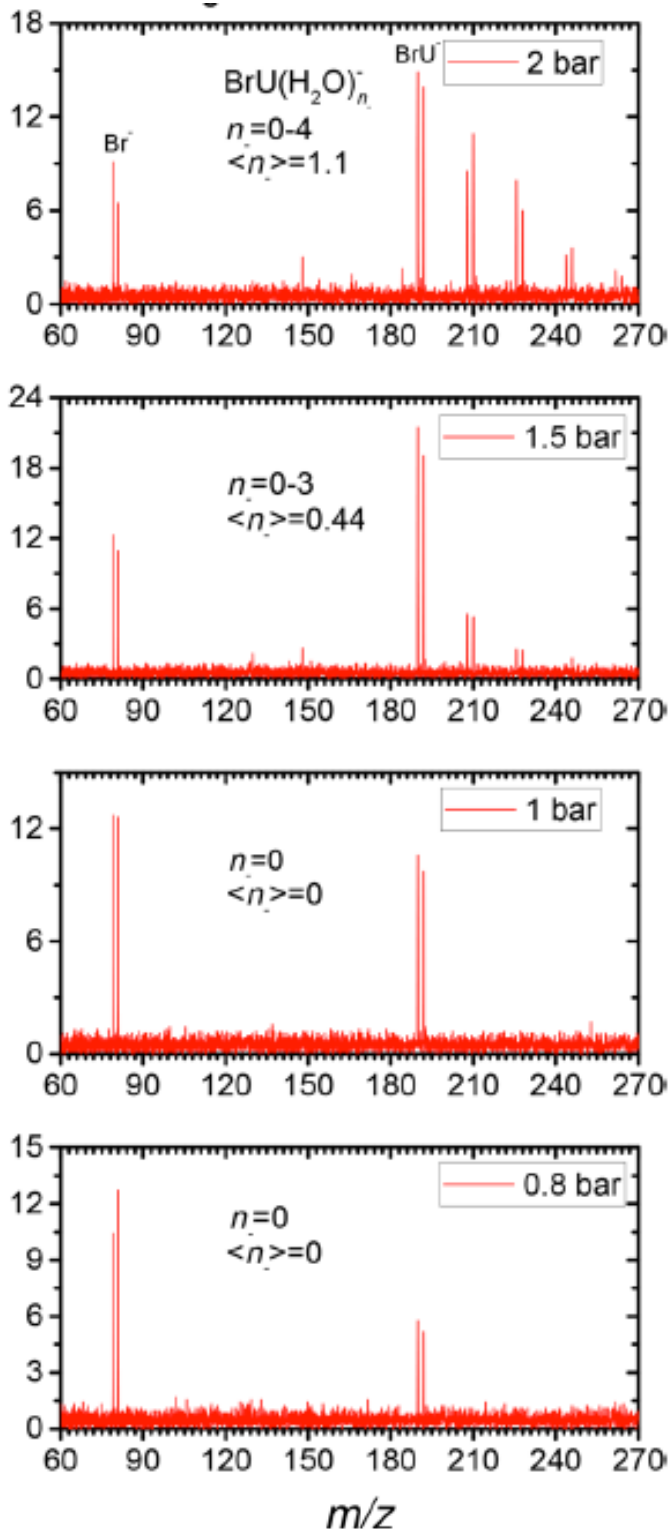
5-OCNU

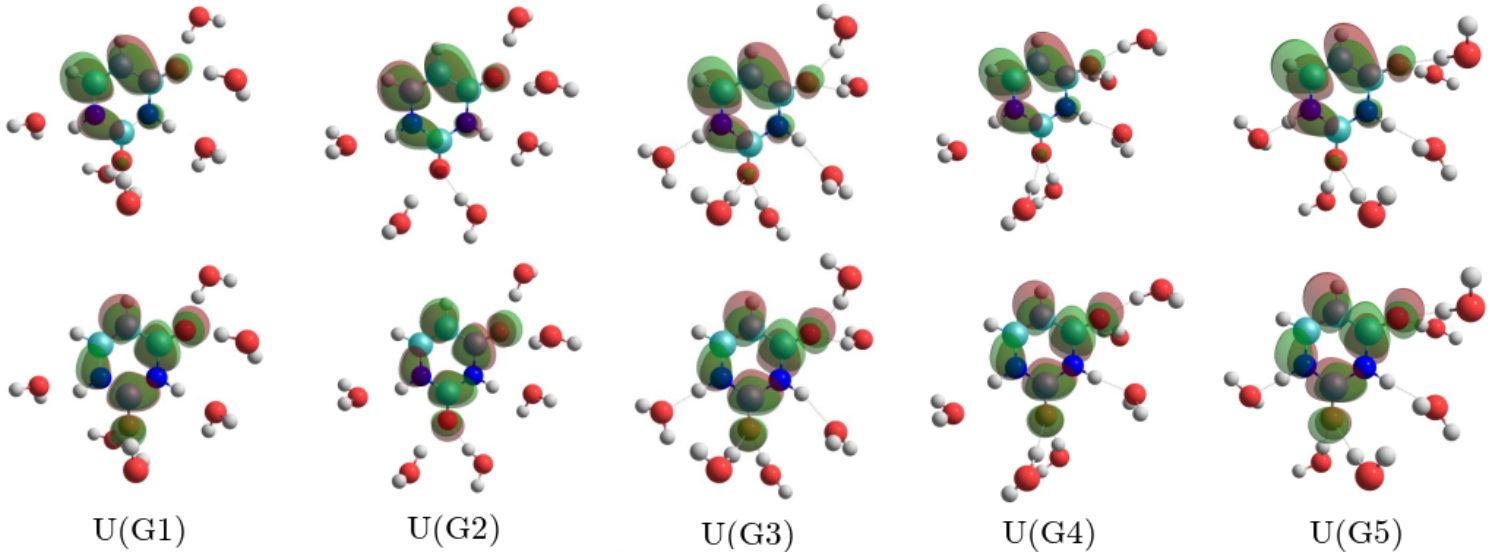
Postulka *et al.*, JPCB 121 8965 (2017)



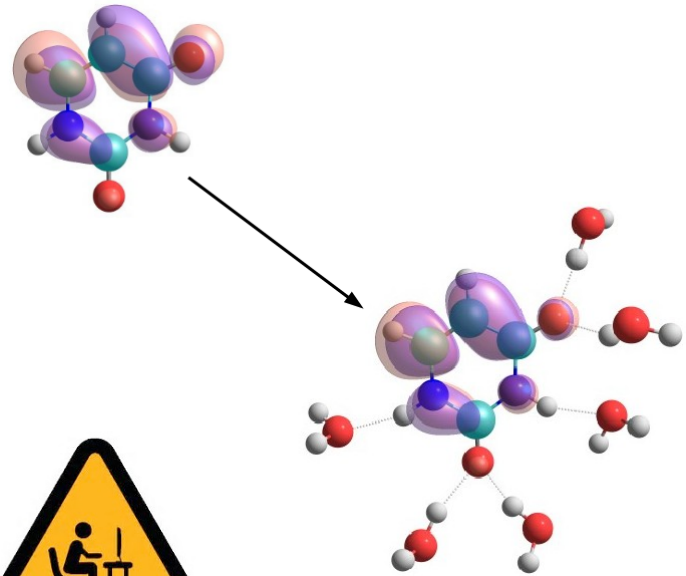
5-Br-Uracil : $(H_2O)_n$

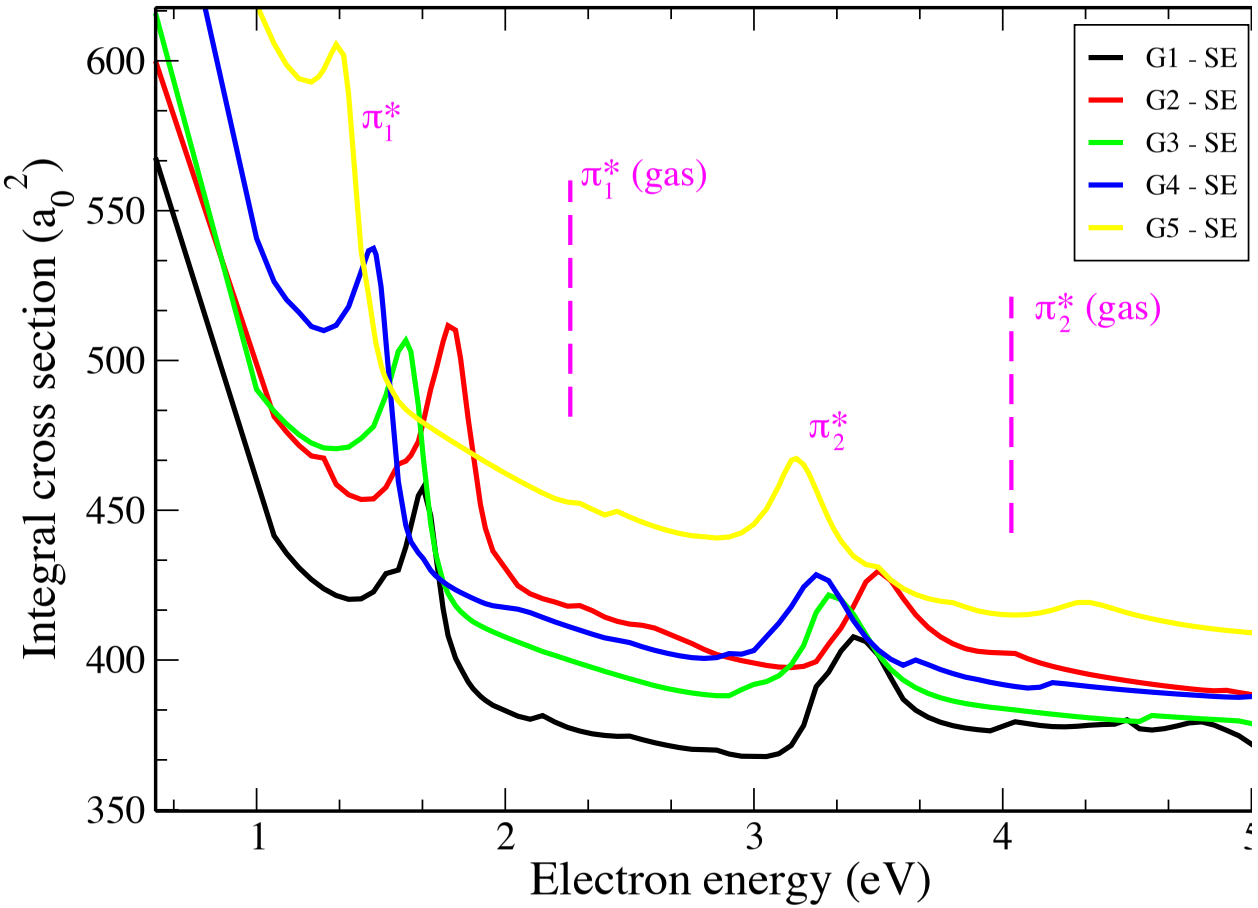
Higher expansion pressures change cluster size, but the Br^- signal is hardly affected.



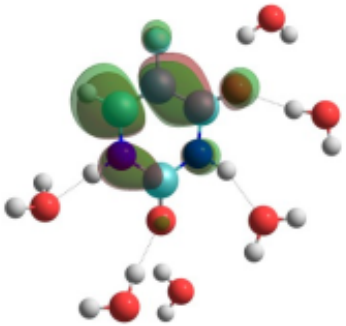


Micro-hydrated Uracil: transient anion states are stabilized.

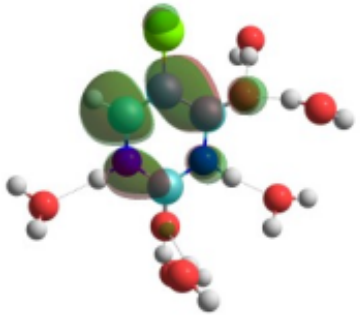




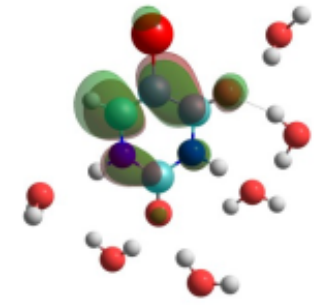
Halouracils



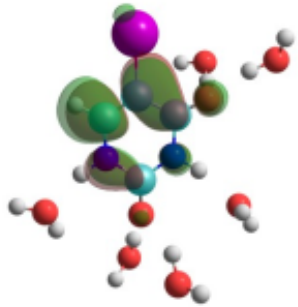
5-FU



5-ClU



5-BrU



5-IU

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Support

FAPESP
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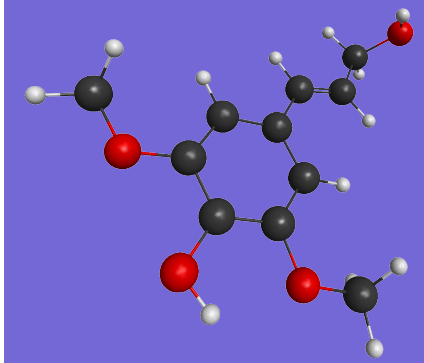
Thanks for your attention!



Molecular Physics and Modelling Group

Interactions with electrons, positrons and photons

http://fig.if.usp.br/~mvarella/