STSM Visit Report for project Ref. 945:

Molecular Mechanisms of DNA Alterations Induced by Low Energy Electrons -Quantum Chemical Modelling as a Support for Electron Attachment Experiments

HOST:	**GUEST:**
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Purpose of the visit

The main goal of visit of Dr Dabkowska was to support by means of quantum chemical methods the electron attachment experiments to DNA constituents, already initiated and successfully proceeded in the group of Prof Illenberger.

Specifically, our collaborative attention has been focused on studies related to molecular mechanism of DNA alterations induced by slow energy electrons.

Fundamental questions which were addressed by us were the following: (1) what is the nature of anions supported by different nucleic acids' building blocks (whether these are bound or metastable states), (2) what are the most plausible sites for excess electron attachment (another words – what are the binding energies of anions based of different moieties), and, the most challenging: (3) what can be a possible sequence of transformations leading from the attachment of an electron to the cleavage of DNA.

Description of the work carried out during the visit

Quantum chemical calculations on metastable, weakly, or non-typically bound anionic states are known to be very tedious and extremely time-consuming. At the same time, having good computational resources, it is possible to conduct several projects in parallel. Therefore, during the stay in FU Berlin, I have been working simultaneously on five projects:

(1) Modelling the sequence of transormations of single nucleotide (thymine-deoxyriboze-protonated phosphate) leading from binding of an excess electron by nucleic acid base to the cleavage of sugar-phosphate bond.

(2) Determining energy profiles for breaking of the C-O bond in dimethylated phosphate

(3) Characteristics of metastable anion of acetylated riboze, using the stabilization methodology (in this way one can obtain only the binding energies, but not the lifetimes of metastable states)

(4) Investigation of the possibilities of binding an additional electron by CF_3COOH

(5) Description of a nature of anionic state of C_2F_4 – this molecule posses negative electron affinity, but the parent anion has been observed experimentally by Illenberger's group in cluster experiments.

Only first three projects have been directly connected with DNA, however, we decided to expand our pool of models, as we believed, these additional systems gave us the opportunity of gaining some insight into the nature of binding additional electrons by closed-shell systems.

Description of the main results obtained

Ad (1) Modelling the sequence of transormations of single nucleotide (thymine-deoxyriboze-protonated phosphate) leading from binding of an excess electron by nucleic acid base to the cleavage of sugar-phosphate bond.

We propose a mechanism of DNA single strand breaks induced by low-energy electrons. Density functional theory calculations have been performed on a nucleotide of thymine to identify barriers for the phosphate-sugar O-C bond cleavage. Attachment of the first excess electron induces barrier-free intermolecular proton transfer to thymine. The resulting neutral radical of hydrogenated thymine binds another excess electron, and the excess charge is localized primarily on the C6 atom. A barrier of less than 5 kcal/mol is encountered for proton transfer from the C2' atom of the adjacent sugar unit to the C6 atom of thymine. The proton transfer is followed by a barrier-free sugar phosphate C-O bond cleavage. The rate of the C-O bond cleavage in the anion of hydrogenated nucleotide of thymine is estimated to be in a range $8.2 \times 10^{7} - 7.5 \times 10^{9}\ s^{-1}$, which makes the proposed mechanism very probable in DNA. The process proceeds through bound anionic states, not through metastable states with finite lifetimes and discrete energy positions with respect to the neutral target. The results suggest that even ballistic, almost thermal, electrons may cleave the DNA backbone.

Figure 1. Proposed mechanism of the DNA strand break induced by excess electrons.

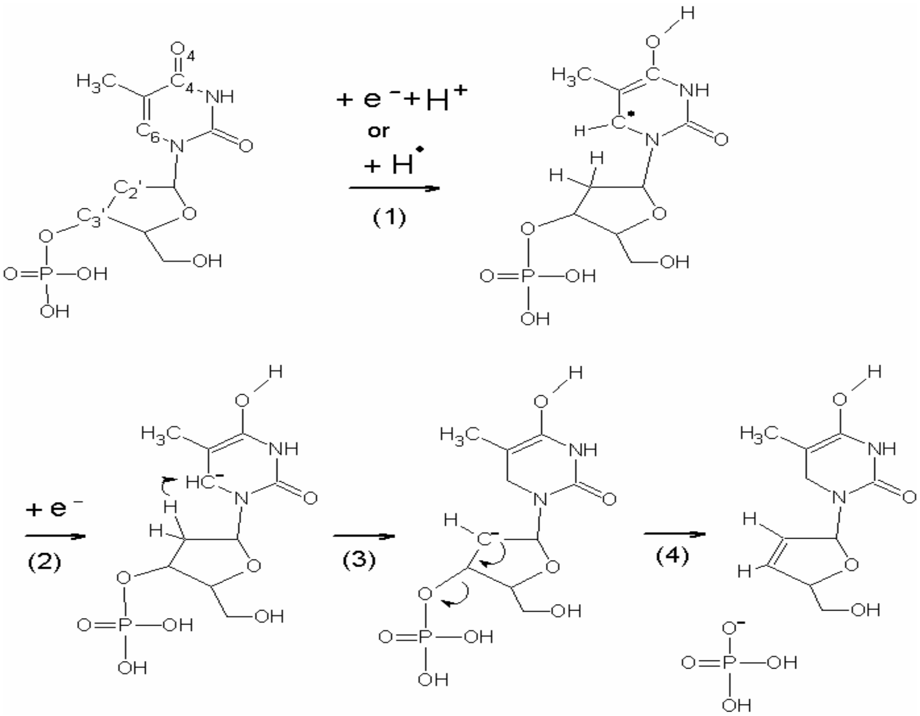
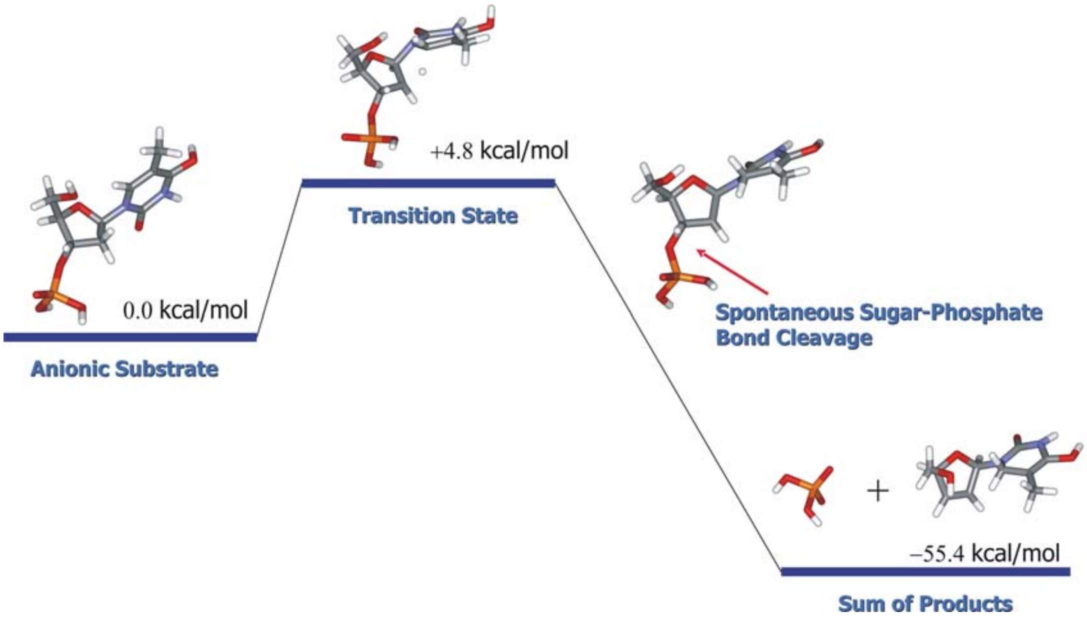


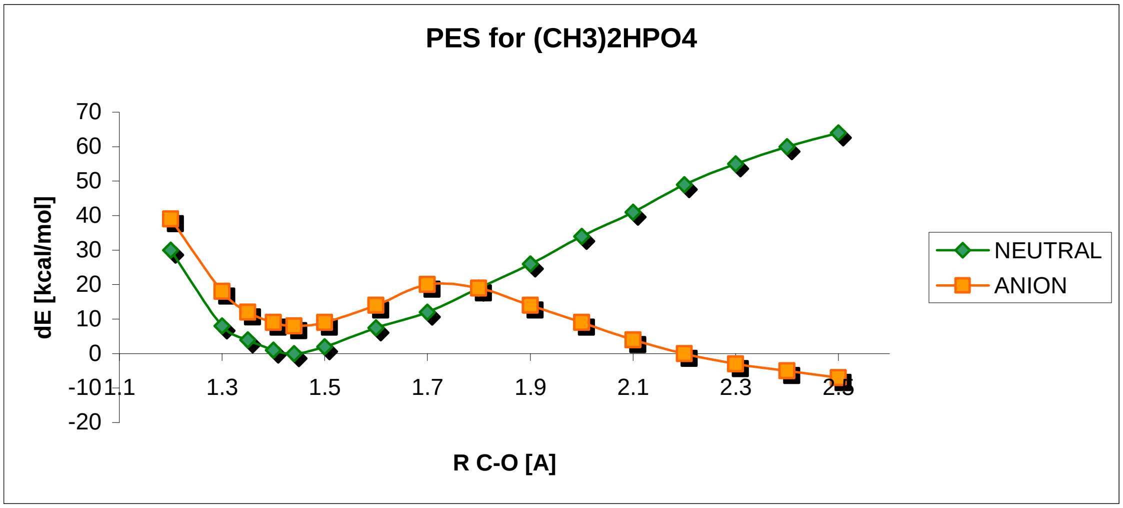
Figure 2. B3LYP/6-31++G** free energies for a rupture of sugar-phosphate bond in the neutralized thymidine nucleotide



Ad (2) Determining energy profiles for breaking of the C-O bond in dimethylated phosphate

We have explored several possible pathways for dissociation of dimethyl phosphate induced by an attachment of an electron. The most plausible path (being presented in Fig.3) does not correspond to the most probable dissociation channel being determined by Illenberger at al. for a very similar component - dibutyl-phosphate. Further investigations are necessary.

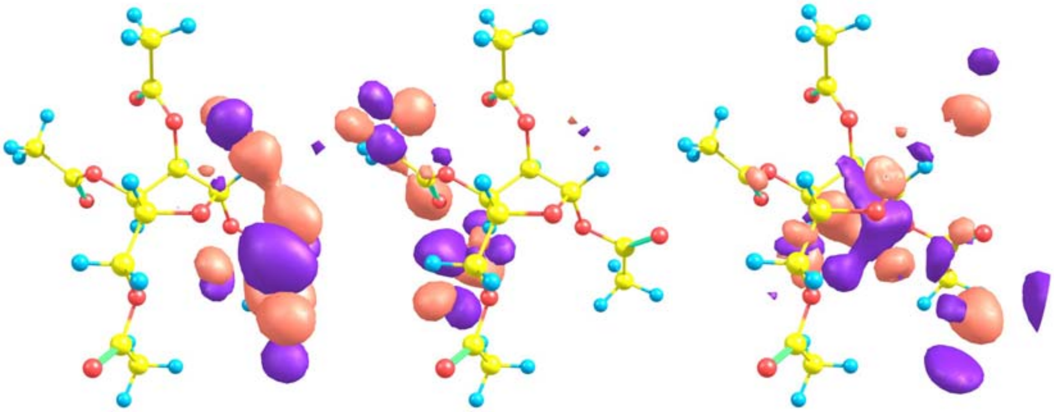
Figure 3. Energy profile for CO distance in neutral and anionic $(CH_3)_2$ H PO_4.



Ad. (3) Characteristics of metastable anion of acetylated ribose, using the stabilization methodology

Metastable states are not electronically stable, and as such, they cannot be treated with standard quantum chemistry methods based on energy optimizations. Stabilization approach is the simplest (yet, very tedious) method providing us with the values of discrete binding energies of such states. Applying such method (by putting an extra charge on the atoms where an excess electron can be bound and electronically stable and then extrapolating it to the region of unstable anionic states) we were able to detect the position of the resonances for several matastable states of our system. (Fig. 4) These values (from 2-9 eV) correspond quite well with the values obtained from dissociative electron experiments. Also, the location of the SOMO orbitals suggests that one of the main dissociation channel is de-acethylation (at about 2 eV), while the resonance at about 5 eV is responsible for cleavage of the ribose ring. However, we were unable (so far) to detect with theoretical chemistry one more resonance state, observed experimentally at 0 and about 0.9 eV.

Figure. 4. Singly occupied molecular orbitals of metastable states at 1.9 eV, 2.0 eV, and 8.7 eV respectfully.



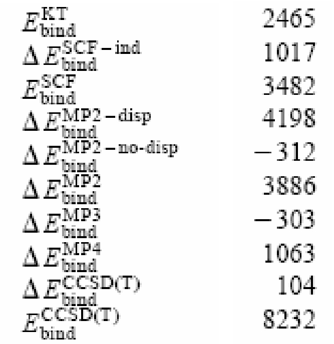
Ad (4) Investigation of the possibilities of binding an additional electron by CF_3COOH

Anion supported by the closed-shell molecule CF_3COOH had been detected experimentally in cluster experiments. However, this project appeared to be very problematic, as the values of electron affinities in this case drastically depend on the chosen quantum chemistry method. We have obtained positive adiabatic electron affinity at the B3LYP/6-311++G** +0.6 eV, and strongly negative (-1.3 eV) at the MP2 level, with the same basis set. Therefore, in the nest step, we need to utilize a method with higher order of electron correlation (for instance CCSD(T)) to obtain decisive result.

Ad. (5) Description of a nature of anionic state of C_2F_4

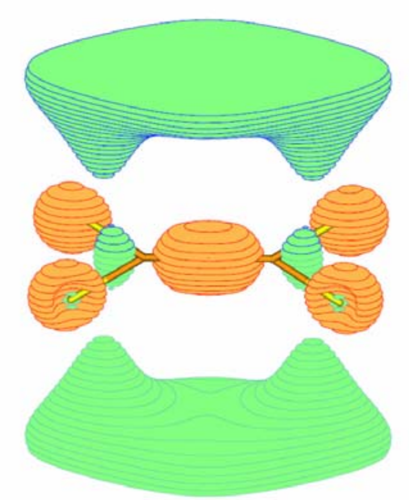
Adiabatic electron affinity determined theoretically at MP2/aug-cc-pVDZ level is slightly negative, but the parent anion has been observed experimentally by Illenberger's group in cluster experiments. Taking into account that the first non-vanishing moment of neutral molecule (in its equilibrium geometry) was a quadrupole moment, we decided to use specially designed basis set, to allow the possibility of binding an electron to a very diffuse orbital of B_{2u} symmetry (here, we have have supplemented the aug-cc- pVDZ basis set with two-term sets of diffuse s, four-term p, and 6-term d functions on C atoms). In fact, we were able to detect an anionic state, whose characteristics allow us to call it a quadrupole-bound anion. (Table 1 and Fig.5). However this data, as presented below, needs to be further verified, by exploring the molecule with broken symmetry as well as excluding the basis set dependences.

Table 1. Electron binding energies (in cm^{-1}) for anion of C_2F_4. (For the definitions of particular contributions, please use Chem. Phys. 279, 2002, 101)



$E_{\text{bind}}^{\text{KT}}$	2465
$\Delta E_{\text{bind}}^{\text{SCF-ind}}$	1017
$E_{\text{bind}}^{\text{SCF}}$	3482
$\Delta E_{\text{bind}}^{\text{MP2-disp}}$	4198
$\Delta E_{\text{bind}}^{\text{MP2-no-disp}}$	−312
$\Delta E_{\text{bind}}^{\text{MP2}}$	3886
$\Delta E_{\text{bind}}^{\text{MP3}}$	−303
$\Delta E_{\text{bind}}^{\text{MP4}}$	1063
$\Delta E_{\text{bind}}^{\text{CCSD(T)}}$	104
$E_{\text{bind}}^{\text{CCSD(T)}}$	8232

Figure 5. Excess electron density distribution in anion supported by C_2F_4



Future collaboration with host institution

During my stay in Berlin, I have successfully applied for Marie Curie Individual Fellowship, which provides me with 24 months' postdoctoral position in the group of my EIPAM host. This fellowship will start from November 2006.

Projected publications/articles resulting or to result from the grant

The publication resulting form the project (1) is being ready for submission to the Journal of Physical Chemistry. The results of the remaining projects will be finalized into the publications during my MC postdoctoral stay in the group of prof. Illenberger.

Other comments