Influence of solutes on Ps formation. Possible applications for determination of the carcinogenicity of chemical compounds and PET

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Field of PAS applications is very wide - from solids to liquids. Studies of solids are associated with their usage as construction materials (we need to know what the defects are therein, in which concentrations. We want to know porosity, sorption properties, behavior of materials under irradiation etc.).

Most of PAS applications related to liquids lie in the field of biology and medicine.

Discarding social factors, in our life (for mankind) there are two sources of danger -- radiation and exposure to harmful chemically active substances. Actually, these factors are interconnected with each other, because radiation (at moderate doses) leads to the formation of chemically active species in a human body.

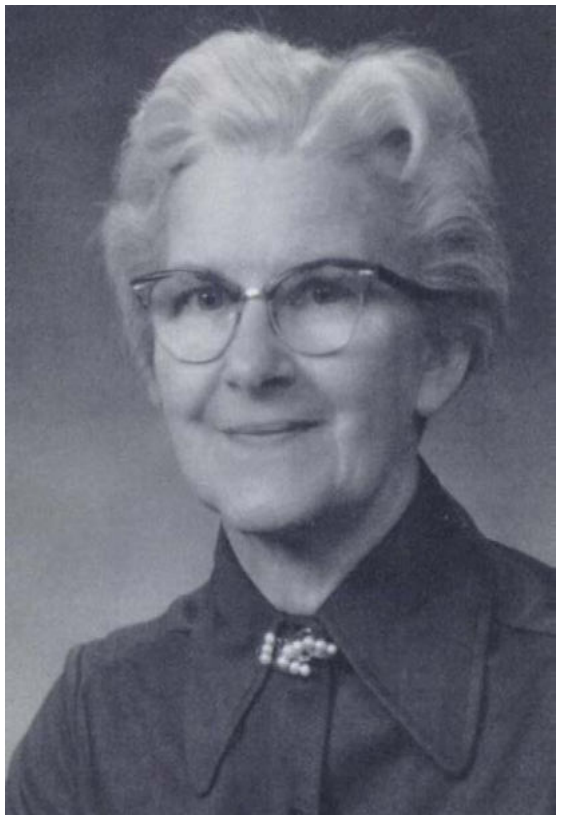
PAS in some sense, combines both these factors. Production of positrons is inevitably related with irradiation, as well as with formation of radiolytic products (which are usually chemically active). If the Ps atom is formed, it lives in a liquid for several ns and during this time Ps may participate in chemical reactions with both solutes and track products.

From this rather general consideration, it becomes clear that PAS can be useful for studying the impact of carcinogenic compounds and radioprotectors on living organisms.

Below we'll consider how various substances (including dissolved oxygen O2) affect the Ps formation and its lifetime. We shall also look for the relationship between Ps inhibition parameters and carcinogenic/anticarcinogenic properties of solutes.

The main source of cancer is chemical carcinogens. When these substances enter a living organism, they cause formation of tumors. These malignant tissues consist of uncontrollably dividing cells that can grow up into neighboring tissues and organs (and form metastases).

Being in cells, carcinogens cause genetic changes (violations in the structure of DNA, loss of some parts of chromosomes etc.) As a result, hereditary changes (mutations) occur. This is the beginning of the oncological process.



Elizabeth C. Miller
Univ. of Wisconsin Medical Center

More then 60 years ago James and Elizabeth Miller established that the main distinctive feature of carcinogens is their strong electrophilicity.

Being in a cell (in the aquatic environment), some carcinogens (**genotoxic carcinogens**) dissociate, forming chemically active derivatives containing an electrophilic group.

This group may form a strong covalent chemical bond with a DNA molecule. So accuracy of its replication (and reproduction of the cell genome) is disrupted $\Rightarrow$ mutations occur, cancer appears.

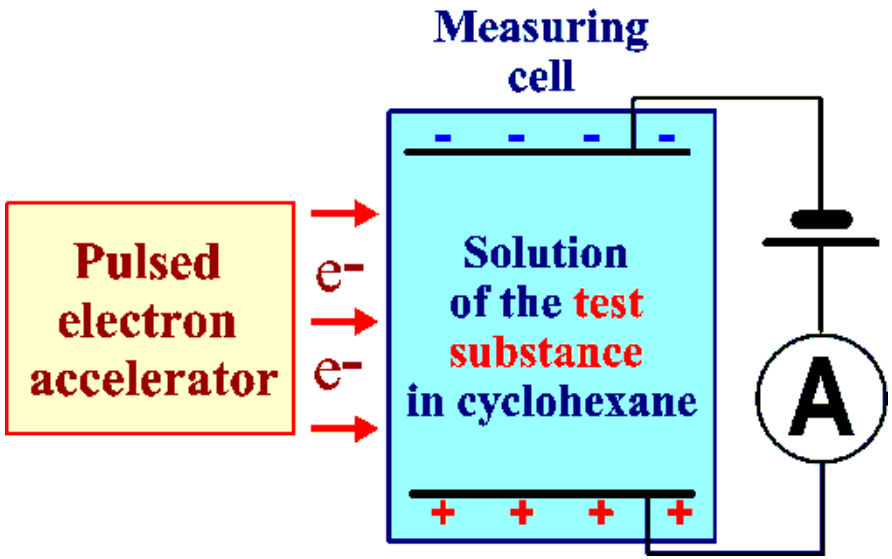
Other carcinogens (**protocarcinogens**) acquire carcinogenic (electrophilic) properties as a result of their metabolic activation (a sequence of biochemical transformations within the body).

Nowadays there are many methods for testing carcinogenic properties of chemical compounds:

- Epidemiological (on people);
- Biomarker method
- Experiments on animals (mice, rats, fishes)
- Tests for mutations of bacteria (Ames test, fruit flies, plants);
- Quantitative Structure-Activity Relationship; QSAR;
- Physicochemical methods

Unfortunately, none of them (including even epidemiological tests on humans) cannot answer for sure whether a given substance is a carcinogen or not. Various methods have to be applied in combinations (battery of tests) to draw a final conclusion. Animal testing (while the most reliable) is very expensive and time consuming. So it is difficult to cover all compounds that we encounter throughout our lives (industrial wastes, food, medicine, cosmetics). Moreover, these compounds can enter a body in combinations with other compounds, and the results are difficult to predict. Thus, development of fast and relatively cheap physicochemical methods for carcinogens screening is important.

George Bakale's approach to detection of the carcinogenic compounds (1981)

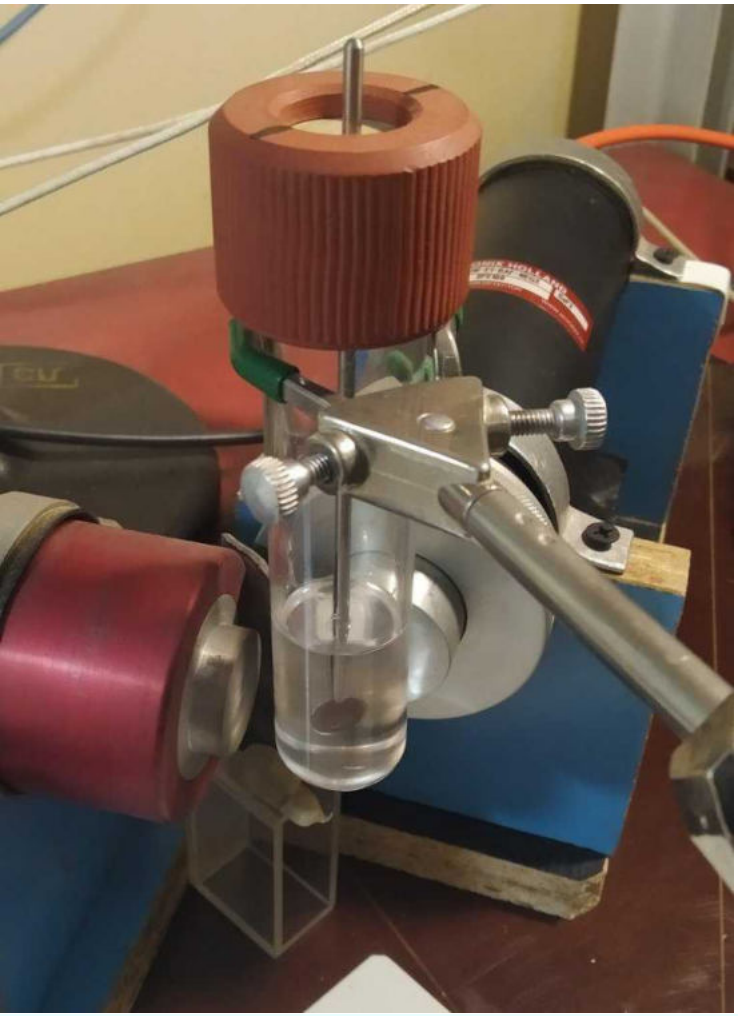


To implement Bakale's method, a complex pulsed radiolysis setup is required. One needs an electron accelerator (for an energy of several MeV) and a cumbersome γ-shielding.

G. Bakale (Case Western Reserve University, Ohio) proposed to measure electrophilicity of a chemical compound using the pulse radiolysis setup. He dissolved different chemicals in cyclohexane and measured their reaction rate constants with track electrons, $k(e^- + S)$.

Bakale came out to conclusion that if k is $>3*10^{11}$ M^{-1} s^{-1} (the trapping reaction rate constant for CCl4) this compound is carcinogenic with 85% probability.

The PALS setup is much cheaper and compact than the pulsed radiolysis one, and does not require huge γ-protection.



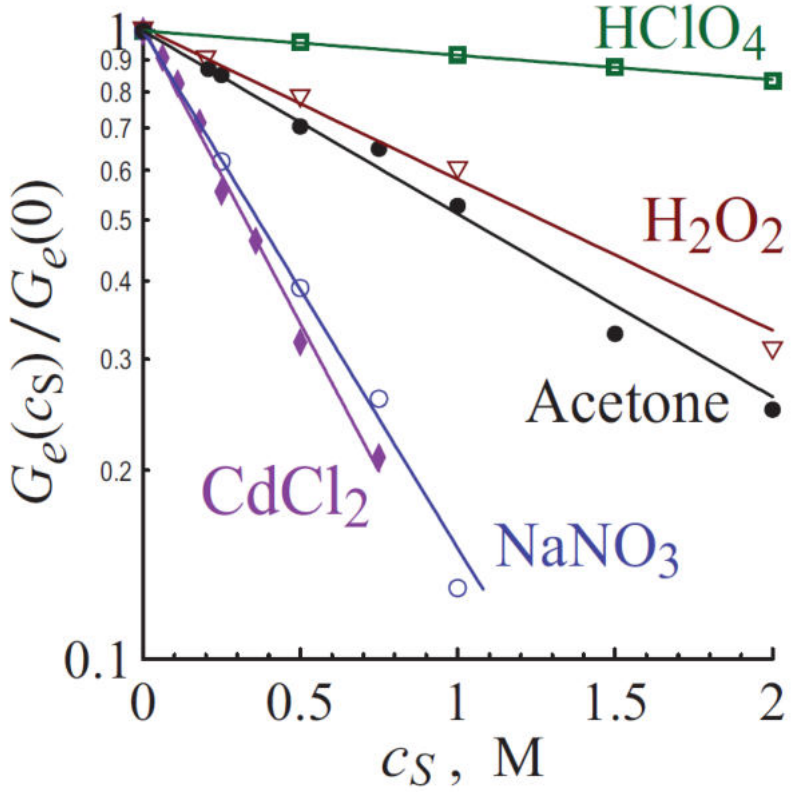
In PAS the radioactive nuclei (e+ source) play the role of an “accelerator”. High-energy e+ are implanted into the medium under study, form tracks and generate secondary e-.

If we dissolved in the medium a substance, we want to test, which captures track electrons, the Ps yield will decrease (it is the inhibition effect).

Thus, we can measure Ps inhibition coefficients (or e- trapping rate constants) and correlate them with the degree of carcinogenicity of these solutes. So with a help of PALS we may proceed with screening of carcinogens.

=> it is necessary to understand well the mechanism of Ps formation!

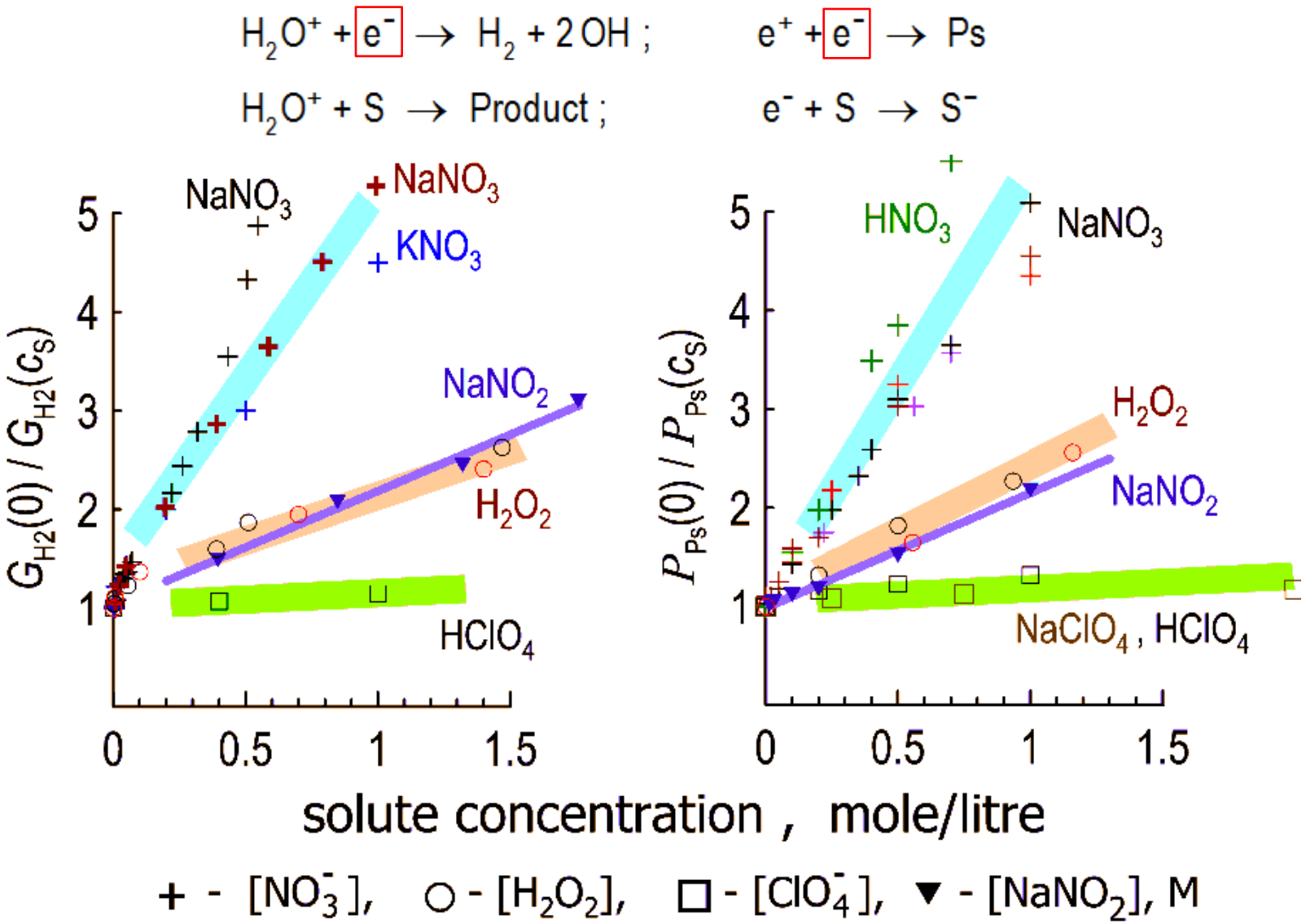
Basing just on PALS experiments, we cannot unambiguously state what does the scavenger (solute) trap – e- or e+?
So it is necessary to involve other data, for example, on the yields of radiolytic H2 or solvated electron



<= EXPONENTIAL suppression of the yield of the hydrated (solvated) e-, $G(e_s)$, indicates that the scavenger reacts with pre-solvated e- (this reaction usually takes place at picosecond times).

Because the same scavengers suppress Ps formation in the same amount, we conclude that the pre-solvated track e- is the Ps precursor.

The above statement is confirmed by the data on the concentration dependencies of the (reciprocal) yields of radiolytic H2 and Ps (track e- is the common precursor of H2 and Ps)



Two-stage model, used for interpretation of the PALS experiments in solutions

"Pico-second" stage:

$e^-_{qf} + e^+_{qf} \Rightarrow$ **quasifree-Ps ;** $e^-_{qf} + S \Rightarrow S^-$ - electron trapping

e^-_{qf} and $e^+_{qf} \Rightarrow$ solvation; $e^+ \Rightarrow 2\gamma$-annihilation

P_{qf} is the quasifree-Ps formation probability. It takes into account competition between all the above reactions.

"Nano-second" stage:

qf-Ps => 2γ-annihilation, Ps bubble formation (o-Ps, p-Ps)

AMOC + theoretical estimations: Ps "bubble" formation time ≈50 ps ($\lambda_b \approx 20$ ns^{-1}). During this time qf-Ps seeks for a preexisting trap, growth of the equilibrium Ps bubble proceeds rather fast.

ortho-Ps => pick-off 2γ-annihilation from the bubble state,

ortho-Ps oxidation, ortho-to-para-Ps-conversion;

e+ may reappear after ortho-Ps oxidation;

para-Ps => 2γ self-annihilation; para-Ps oxidation & para-to-ortho conversion are neglected.

It is simple, but rather general case of the e+/Ps annihilation kinetics in liquid solutions (with e- scavenger/oxidizer/converter):

e+ reappearence due to oxidation

quasifree Ps formation

annihilation

Ps bubble formation

oxi-dation

o-p-conversion

$$
\begin{aligned}
\text{e}^+ \quad & \dot{n}_+(t) = -\lambda_+ n_+ + \lambda_{ox} n_o, \qquad n_+(0) = 1 - P_{qf}, \\
& \dot{n}_{qf}(t) = -\lambda_q n_{qf}, \qquad n_{qf}(0) = P_{qf}, \qquad \lambda_q = \lambda_{qf} + \lambda_b, \\
\text{qf-Ps} \quad & \dot{n}_o(t) = \frac{3\lambda_b}{4} n_{qf} - \lambda_o n_o, \qquad n_o(0) = 0, \qquad \lambda_o = \lambda_{po} + \frac{\lambda_{opc}}{4} + \lambda_{ox}, \\
\text{o-Ps} \quad & \dot{n}_p(t) = \frac{\lambda_b}{4} n_{qf} + \frac{\lambda_{opc}}{4} n_o - \lambda_p n_p, \qquad n_p(0) = 0, \qquad \lambda_p = \lambda_{2\gamma} + \lambda_{po}.
\end{aligned}
$$

p-Ps

Ps bubble formation

ortho-to-para-conversion

p-Ps self-annihilation

This model may be easily generalazed for the case when Ps oxidation results not in «free» e+ production, but e+ complex/cluster formation.

$$n_{\mathrm{qf}}(t) = P_{\mathrm{qf}} e^{-\lambda_q t}, \quad n_o(t) = \nu\left(e^{-\lambda_o t} - e^{-\lambda_q t}\right), \quad \nu = \frac{3P_{\mathrm{qf}}}{4}\frac{\lambda_{\mathrm{b}}}{\lambda_q - \lambda_o},$$

<= The above equations are solved analytically and may be used in the fitting program

$$n_+(t) = (1 - P_{\mathrm{qf}})e^{-\lambda_+ t} + \nu\frac{\lambda_{\mathrm{ox}}}{\lambda_+ - \lambda_o}\left(e^{-\lambda_o t} - e^{-\lambda_+ t}\right) - \nu\frac{\lambda_{\mathrm{ox}}}{\lambda_q - \lambda_+}\left(e^{-\lambda_+ t} - e^{-\lambda_q t}\right),$$

$$n_p(t) = \frac{P_{\mathrm{qf}}}{4}\frac{\lambda_{\mathrm{b}}}{\lambda_q - \lambda_p}\left(e^{-\lambda_p t} - e^{-\lambda_q t}\right) + \nu\frac{\lambda_{opc}/4}{\lambda_p - \lambda_o}\left(e^{-\lambda_o t} - e^{-\lambda_p t}\right) - \nu\frac{\lambda_{opc}/4}{\lambda_q - \lambda_p}\left(e^{-\lambda_p t} - e^{-\lambda_q t}\right).$$

Usually the short-lived components I_0 and I_1 cannot be resolved in conventional deconvolution, so they are combined in one component, which is incorrectly identified as the p-Ps formation probability. As a result, a wrong conclusion is made about violation of the "1-to-3" ratio of p-Ps and o-Ps formation probabilities

$$I_0 = P_{\mathrm{qf}}\frac{\lambda_{\mathrm{qf}}}{\lambda_q} - \frac{P_{\mathrm{qf}}}{4}\frac{\lambda_p\lambda_{\mathrm{b}}}{\lambda_q(\lambda_q - \lambda_p)} + \nu\frac{\lambda_p\lambda_{opc}/4}{\lambda_q(\lambda_q - \lambda_p)} + \nu\frac{\lambda_+\lambda_{\mathrm{ox}}}{\lambda_q(\lambda_q - \lambda_+)} - \nu\frac{\lambda_{\mathrm{po}}}{\lambda_q},$$

$$I_1 = \frac{P_{\mathrm{qf}}}{4}\frac{\lambda_{\mathrm{b}}}{\lambda_q - \lambda_p} - \nu\frac{\lambda_{opc}/4}{\lambda_p - \lambda_o} - \nu\frac{\lambda_{opc}/4}{\lambda_q - \lambda_p},$$

$$I_2 = 1 - P_{\mathrm{qf}} - \nu\frac{\lambda_{\mathrm{ox}}}{\lambda_+ - \lambda_o} - \nu\frac{\lambda_{\mathrm{ox}}}{\lambda_q - \lambda_+},$$

$$I_3 = \nu\frac{\lambda_p\lambda_{opc}/4}{\lambda_o(\lambda_p - \lambda_o)} + \nu\frac{\lambda_+\lambda_{\mathrm{ox}}}{\lambda_o(\lambda_+ - \lambda_o)} + \nu\frac{\lambda_{\mathrm{po}}}{\lambda_o}.$$

Interaction of positronium with dissolved oxygen in liquids†‡

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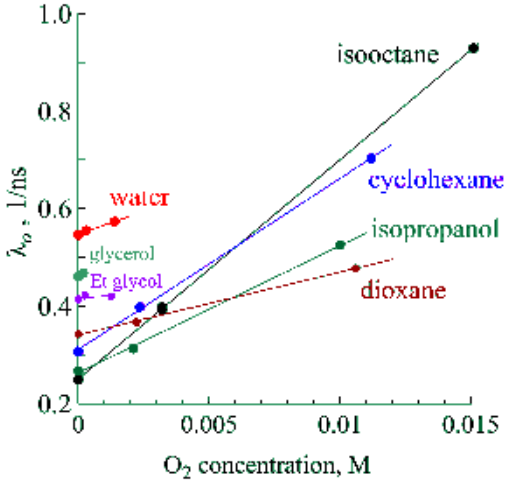
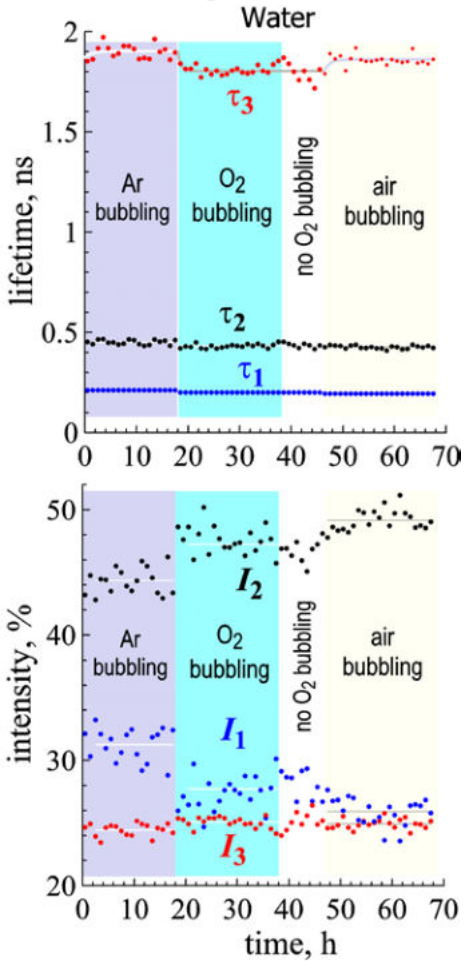
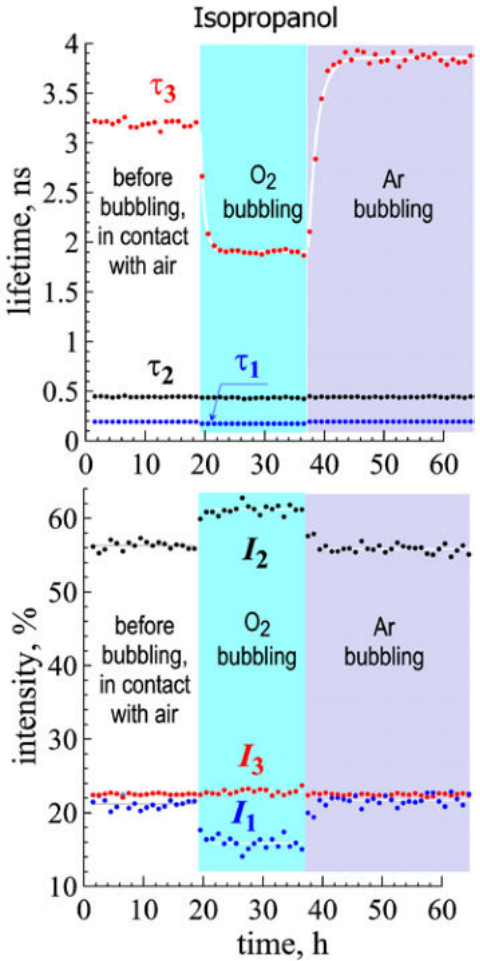
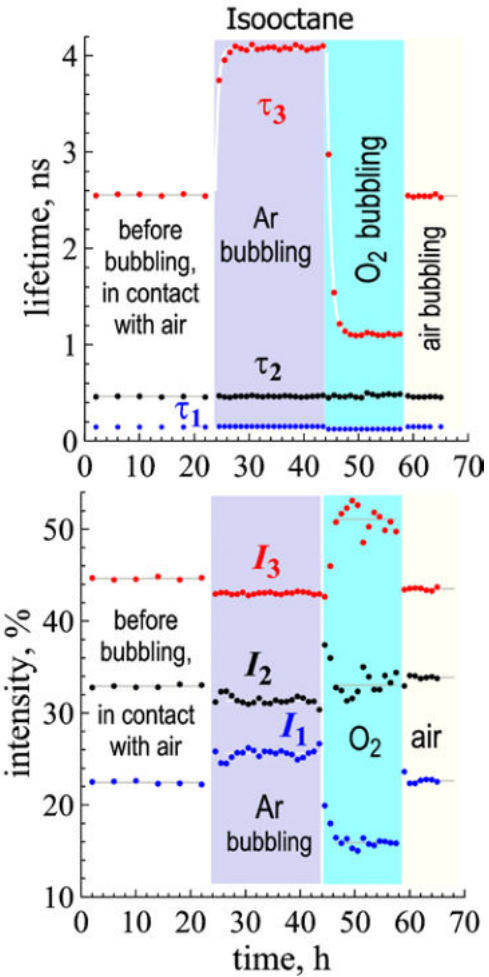
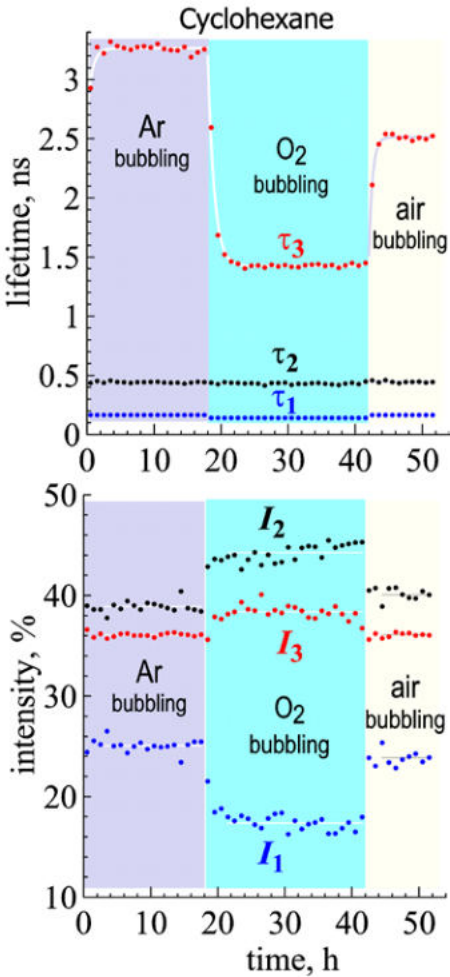




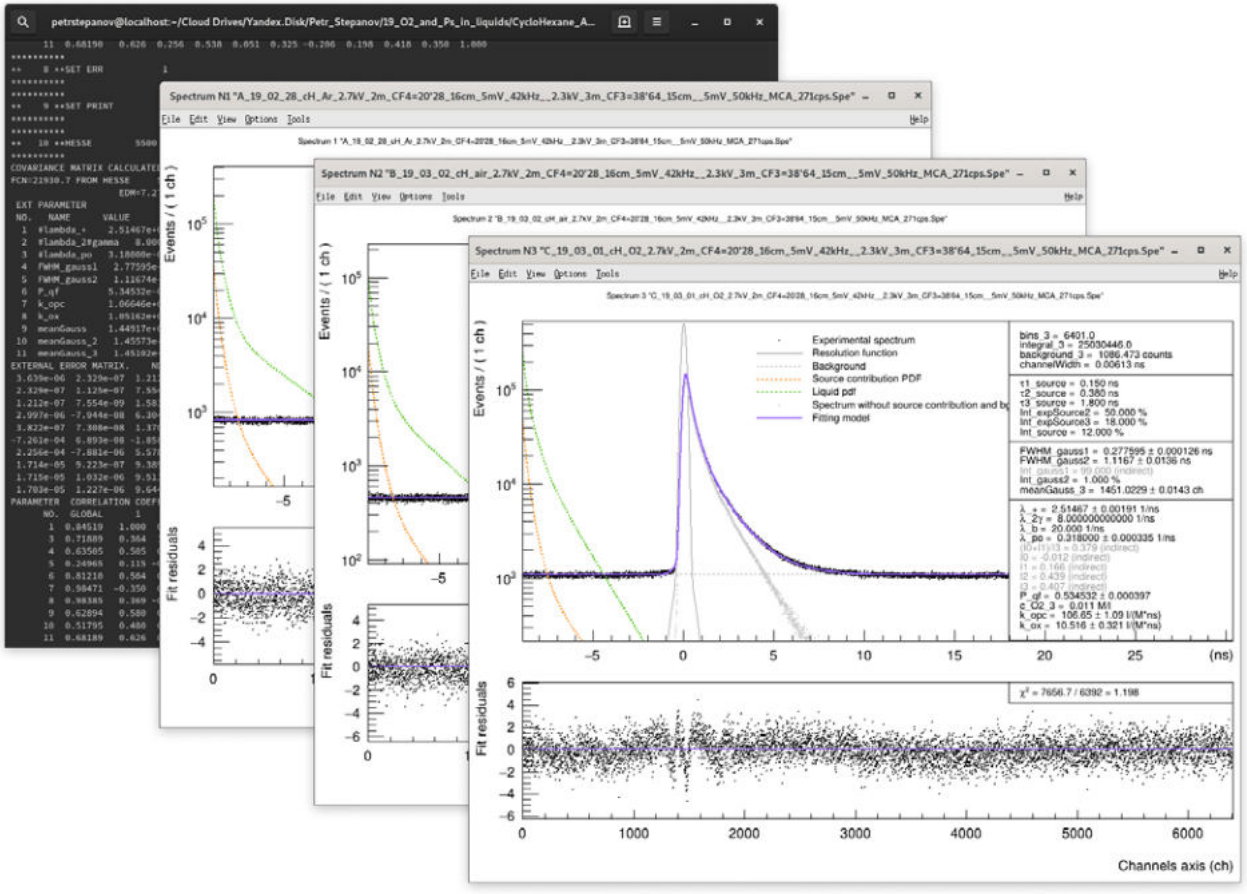






All LT spectra were analyzed by means of the proposed model with a help of the developed RooPositron software

The program is written in object-oriented C++ using CERN ROOT libraries. Fitting is performed via RooFit package functionality.



- In-depth control of the convolution operation.
- Fitting models support evaluation of the indirect parameters as functions of regular model parameters.
- Simultaneous fitting of multiple spectra with various channel widths.
- Plotting functionality and output of raster and vector images, output plots as ASCII.


Bowling Green State University

By authority of the Board of Trustees and upon recommendation of the faculty of the

Graduate College

hereby confers upon

Petr Stepanov

the degree of

Doctor of Philosophy

with all the rights, privileges, and honors pertaining thereto.
In witness whereof, this diploma is given at Bowling Green, Ohio
this sixteenth day of May, 2020.

Ps oxidation and o-to-para conversion reaction rate constants were obtained. Ps oxidation by O2 turned out to be about 5-10 times **less favorable** than Ps ortho-para conversion (stimulated by paramagnetic O2)

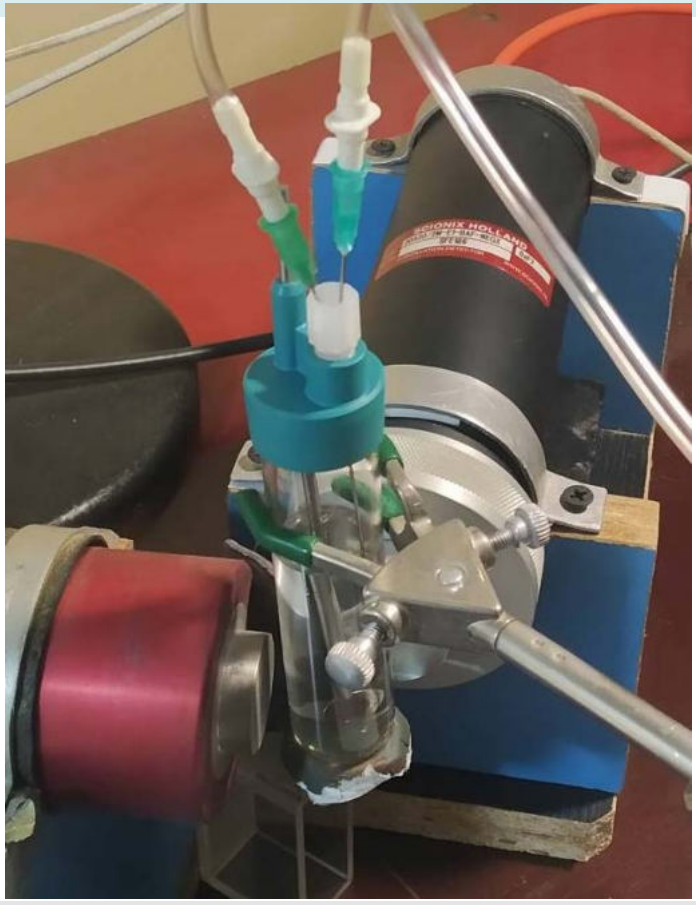
Table 5.3: Parameters of the model Eqs. (5.5-5.10) obtained as a result of fitting of the LT spectra of liquids with different O_2 contents, $\lambda_{qf} = \lambda_+$, $\lambda_b = 20$ ns^{-1}, $\lambda_{2\gamma} = 1/0.16$ ns^{-1} (in accordance with the magnetic quenching experiments [74, 75]), $\tau_+ = 1/\lambda_+$, $\tau_{po} = 1/\lambda_{po}$. Statistical uncertainties of the fitting parameters are indicated in parenthesis.

Liquid	$\lambda_+ = \lambda_{qf}$; ns^{-1}	τ_+ ns	λ_{po} ; ns^{-1}	τ_{po} ns	P_{qf}	k_{opc}, 10^{10}M^{-1}s^{-1}	k_{ox}, 10^{10}M^{-1}s^{-1}	$k_{opc}/4 + k_{ox}$, 10^{10}M^{-1}s^{-1}
i-octane	2.430(1)	0.412(1)	0.252(1)	3.968(4)	0.639(2)	9.62(9)	2.37(3)	4.78(5)
c-hexane	2.568(2)	0.389(1)	0.320(3)	3.125(10)	0.542(1)	12.6(2)	1.02(4)	4.17(5)
i-propanol	2.509(1)	0.399(1)	0.276(2)	3.622(10)	0.340(2)	9.8(1)	0.35(5)	2.82(5)
water	2.516(8)	0.397(4)	0.556(1)	1.799(2)	0.451(3)	1(1)	1.1(4)	1.3(8)

The proposed model naturally explains the extremal behavior of the S(t) parameter ("juvenile broadening") observed in AMOC experiments.

LT spectra **in H2O** with/without dissolved O2 show small difference. This is due to very low O2 solubility in water. That is why pure water is often used as a "reference" medium for testing the operation of the PAL spectrometers.

According to Miller's approach, strong electrophiles must efficiently inhibit Ps formation



Originally we planned to measure Ps inhibition of the substances in c-hexane (as was done by G.Bakale) and compare our results with his, but…

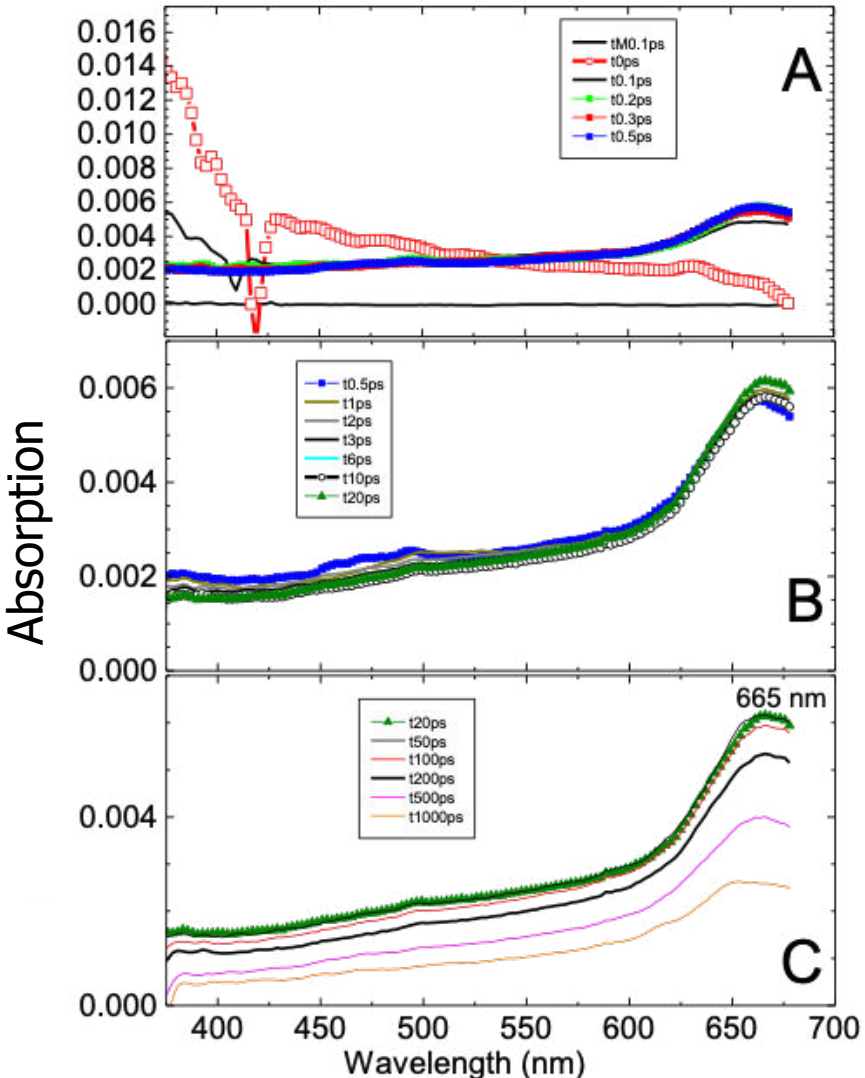
For removing dissolved oxygen we used permanent Ar bubbling

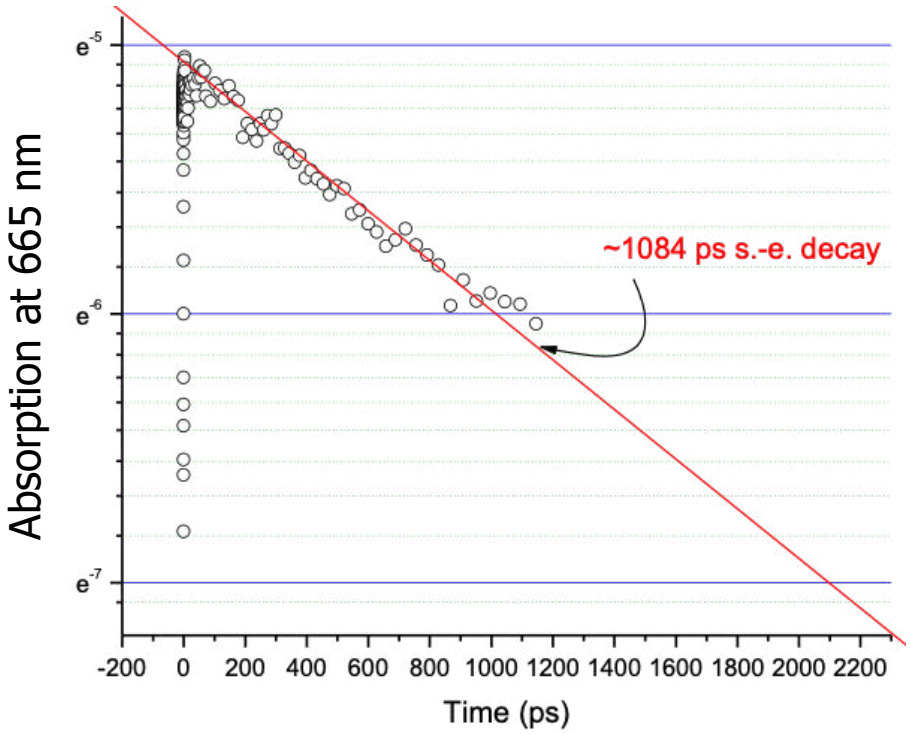
We have to use **dioxane** as a solvent (instead of c-hexane) because:

-- dioxane solutions are not so volatile as c-hexane, so it was possible to use Ar-bubbling for removing dissolved oxygen;

-- Ps yield in dioxane is very high (52%) => easy to measure inhibition.

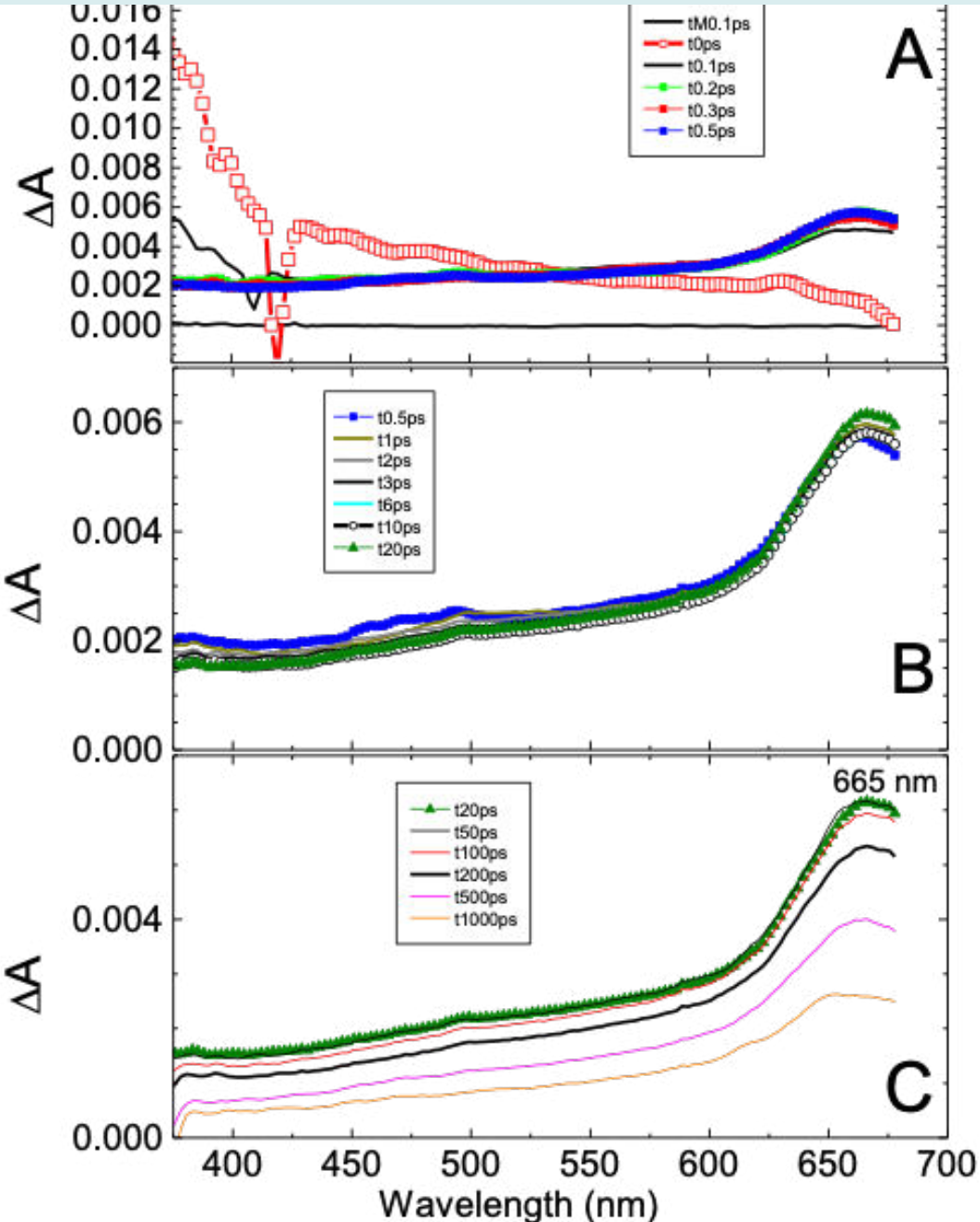
Aleksandr N. Tarnovski (BGSU, Ohio) using femtosecond photolysis setup measured optical absorption spectra (at 0,1 ps to 1 ns times) of the solvated e- in dioxane. He obtained that the e- solvation time is very short – about 0.1-0.2 ps (like in liquid H2O)





Solvated e- disappears most probably due to recombination with parent ion. Its lifetime is 1 ns. We used this value to obtain (S+e-) reaction rate constants.

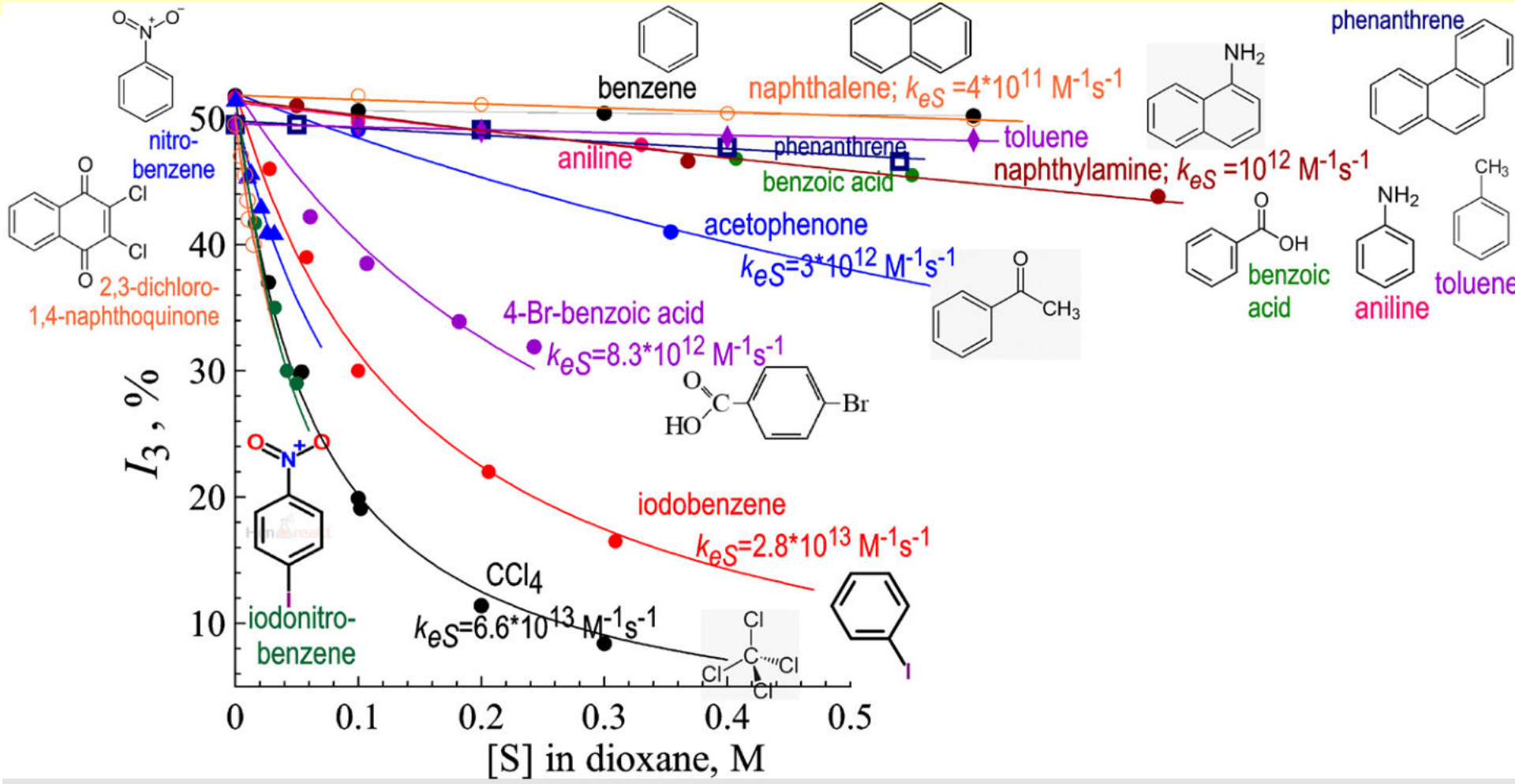
Maximum of the e^-_{solv} absorption spectra is at 665 nm (=1.87 eV)



So e^-_{solv} binding energy is high enough (much more then thermal energy, 1/40 eV). => e^-_{solv} is low mobile (it is not a Ps precursor) and our scheme of the Ps formation still holds:

1) only presolvated track e- is a Ps precursor;
2) we may use the above mathematical model for obtaining the $S+e^-_{quasifree}$ reaction rate constants.

Ps inhibition in dioxane solutions of aromatic/phenolic compounds



1) strong Ps inhibitors are strong carcinogens;
2) strong Ps inhibitors are strong Ps quenchers;
3) nitro-group (and halogens?) scavenges track e- very efficiently. Amino-group, -COOH, -CH3 as well as the benzene ring are much less effective.

Conclusions :

1) PAS may be used for fast detection of carcinogenic compounds. This approach is much easier, cheaper (and setup is compact) then application of the huge pulse radiolysis apparatus;

2) The positron method is based on the correlation between the carcinogenicity of the testing substance and its e- trapping rate constant. It is a consequence of the Millers' observation that (almost all) carcinogens are strong electrophiles. This correlation is confirmed by our present measurements (but nature of e- in PAS and pulse radiolysis is different);

3) It is believed that non-polar solvents better simulate the intracellular milieu (since there are many organic compounds within a cell). Water therein is “structurized” by these organic molecules, so its hydration ability is reduced. That is why G. Bakale conducted his experiments in cyclohexane. We chose dioxane to reduce volatility of the studied solutions, but keeping large Ps yield;

4) We got some indications that Ps antiinhibitors are at the same time anticarcinogens.


2007, near Lublin