1. 基礎研究

Mechanism of Positronium Formation. Positron Radiation Chemistry. Application for Revealing of Carcinogens and Fight Against Cancer

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Such terms as α- or γ-radiation and α- or γ-radiolysis are known long ago to any radiation chemist. However, the terms "β^+-radiolysis" and "positron radiation chemistry"— which is a branch of radiation chemistry, studying chemical processes initiating by fast positrons, are up to date exotic. Their affinity with usual radiation chemical processes becomes apparent first of all in similarity of the positronium (Ps) and radiolytic hydrogen formation mechanisms. In water and aqueous solutions these are following intratrack reactions [1]:

$$(H_2O, H_2O)^+ + e^- \Rightarrow H_2 + 2OH, \quad (1)$$

$$e^+ + e^- \Rightarrow (3/4)o\text{-Ps} + (1/4)p\text{-Ps}. \quad (2)$$

(Of course the reaction (2) of thermalized positrons and electrons occurs in terminal parts of the positron tracks, in terminal blobs. To determine the overall Ps yield it is enough to measure the *ortho*-Ps yield only).

The dissolved electron scavengers S compete with reactions (1) and (2), thus, inhibit the H_2 and Ps formation:

$$e^- + S \Rightarrow S^-. \quad (3)$$

As a result, the relative yields of H_2 and *ortho*-Ps equally decrease with increasing concentration of S, c_S [2]. For instance, the *ortho*-Ps yield, $I_{o\text{-Ps}}$, decreases according the following asymptotic equation:

$$I_{o\text{-Ps}} = I^0_{o\text{-Ps}}/(1 + q_S c_S). \quad (4)$$

Here $I^0_{o\text{-Ps}}$ is the yield of *ortho*-Ps in the pure solvent and q_S is the inhibition coefficient of Ps formation by S:

$$q_S = (k_S/k) \cdot (V_0/n_0) \quad (5)$$

In Eq. 5 k and k_S are the rate constants of the reactions (2) and (3), respectively, V_0 is the spheroidal volume of the terminal blob of the positron track, initially containing n_0 ion-electron pairs.

These chemical properties of e^+ and Ps together with their short lifetimes make them convenient probes for investigation of not only early radiation chemical processes, but some effects useful for other disciplines as biology and medicine. In this paper we give an example of possible application of positron radiation chemistry for revealing of carcinogens and for fight against cancer diseases.

One of the major causes of cancer among humans are chemical carcinogens that enter the body through food additives, cosmetics, drugs, industrial pollutants etc. New products and technologies have led to newer potential chemical carcinogens, so that in the European Community alone ~100 such compounds need to be screened every day. Hence, it is needed to develop faster and cheaper methods of testing. The suggested positron method for fast detection of potentially carcinogenic compounds may answer the demands [1].

1 The method is based on the two following discoveries:

The first is the result of extensive investigations James and Elizabeth Miller [3]. They established that an overwhelming majority of chemical carcinogens were strong electrophiles (substances with high electron affinity). Because electrophilicity is a chemical property, methods of physics and chemistry became relevant and applicable to this field.

The second important development was the suggestion by George Bakale that a pulse radiolysis setup attached to an electron accelerator could be used to measure electrophilicity of chemical compounds [4], and indeed with his group he was able to establish that most chemical carcinogens [say S] dissolved in liquid cyclohexane have highest reaction rate constants with track electrons, $k(e^- + S) > 3\times10^{11}\ M^{-1}s^{-1}$. The reaction rate constants of carcinogens with track electrons turned out to be diffusion controlled (accordingly the thermodynamic barrier in the electron–solute interaction was absent) and it is this feature which

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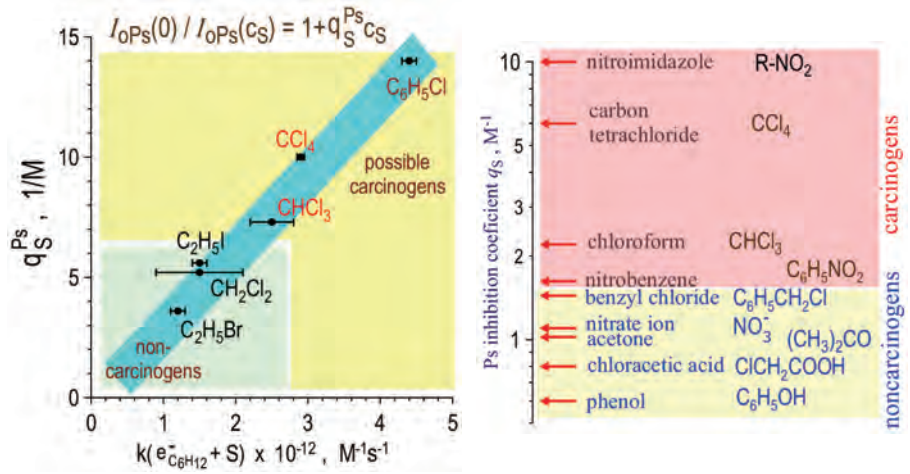

Figure 1. Left: Inhibition coefficients q_S of Ps formation in cyclohexane by different scavengers S of quasi-free track electrons against the reaction rate constant $k(e^- + S)$. Right: Inhibition coefficients q_S of Ps formation by different track electron scavengers dissolved in ethanol[1)].

expedites the process and thus proves to be efficacious.

Though the Bakale's method has obtained a high appreciation among other physicochemical methods, it is necessary to remark that the total number of appropriate pulse radiolysis setups in the whole world is very limited and this method is not able to provide the needed rate of analysis. This consideration served us as a motive to suggest the positron method as, in principal, simpler, faster, cheaper and widely available.

2 Essence of the positron method

As it is seen from Eq. 5 for a specific solvent the inhibition coefficient q_S of an electron scavenger S is proportional to its reaction rate constant with the blob electron: $q_S \sim k_S = k\,(e^- + S)$.

From Eq. 4 it is evident that effective electron scavengers could completely inhibit the process of Ps formation. Therefore, one may suppose that the change of Ps formation probability in irradiated by fast positrons solvent (modeling intracellular milieu) after introducing there a test substance S, could serve as a measure of carcinogenic properties of the solute S. Being effective acceptors of track electrons chemical carcinogens should strongly inhibit Ps formation. The experimental data support the above assumptions.

3 The positron diagnostics in action

Fig. 1(Left) demonstrates a rather good correlation between inhibition coefficients q_S of Ps formation in cyclohexane by different scavengers S of quasi-free track electrons against the reaction rate constants $k(e^-_{c\text{-}C_6H_{12}} + S)$. The strongest Ps inhibitors ($q_S > 6\ M^{-1}$), being the most effective electron scavengers, $k(e^-_{c\text{-}C_6H_{12}} + S) > 3 \cdot 10^{12}\ M^{-1}s^{-1}$, are really carcinogens according to biological data.

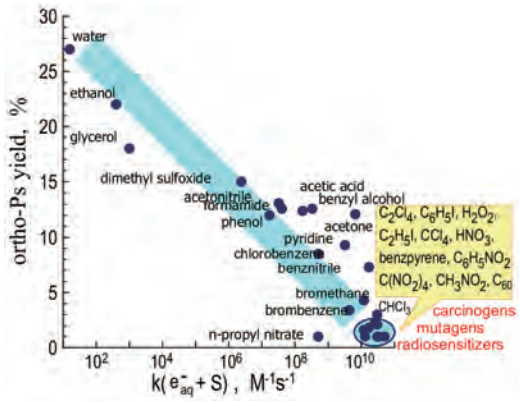

Figure 2. *o*-Ps yields (in %) in chemical compounds, S, vs. their reaction rate constants, $k(e^-_{aq} + S)$ $M^{-1}s^{-1}$, with hydrated electrons, e^-_{aq}. The chemicals were not dissolved in a solvent, but were taken "as is" (as a monophase substance).

Since polar media could also be considered as appropriate models of intracellular milieux surrounding DNA

molecules, measurements have been carried out also in ethanol solutions. The obtained results are shown in Fig. 1(Left). The electrophilic molecules with large Ps inhibition coefficients, $q_S > 2\ M^{-1}$, are carcinogens too.

Probably more visual results are obtained when a chemical is not dissolved in some solvent, but is taken as a pure substance. It is seen in Fig. 2 that Ps is not formed practically in most substances that are identified as carcinogens in animal-tests. In these substances Ps formation probability does not exceed 2 %–3 %. This fact may be of a practical importance since there is no need to dissolve somewhere a test substance, prepare a series of its solutions and to measure therein the *ortho*-Ps yield. It may be enough to do only one measurement instead of many.

4 Anticarcinogens and Ps antiinhibitors

It may appear that the positron method only simplifies, accelerates and reduces the price of carcinogen detecting. However, such conclusion is not true. The positron method gives new opportunities in investigation and understanding of mechanism of carcinogenic action. We illustrate this by the following example.

To chemical compounds which effectively react with free electrons, belong anthracene and phenanthrene. According to criterion of Bakale they should be ranked among carcinogens. However, biologic data do not confirm it. Moreover, biologists regard them as anticarcinogens[5]. These substances, when present in an organism, conceal a harmful effect of carcinogens. The given example shows that the Bakale's criterion is not always sufficient.

Now let ask ourselves: What influence on Ps formation exerts the presence of anthracene and phenanthrene in solutions of Ps inhibitors? The answer is: just the same as in animal organism. In the presence of these compounds the inhibitors in solutions (including carcinogens) lose their ability to decrease the Ps yield[6].

We see that the positronium antiinhibitors in solutions act as anticarcinogens when they occur in an animal organism. This fact, if it will be confirmed, may be used for detection of anticarcinogenic properties of substances.

The cause of specific action of anthracene and phenanthrene on Ps yield is understood rather well. In contrast to Ps inhibitors like CCl_4, which retain accepted blob electrons due to irreversible subsequent transformations as, for example,

$$e^- + CCl_4 \Rightarrow CCl_3 + Cl^-, \qquad (6)$$

that gives strongly electrophilic anion Cl^-, electron attachment to phenanthrene occurs through the formation of a comparatively long-lived excited state ($C_{14}H_{10}^{-*}$). The last only weakly retains the accepted electron and immediately pass it to the positron nearby. Therefore, the intercept of track electrons by phenanthrene molecules does not affect deeply the Ps formation probability. But the addition of sufficient concentration of phenanthrene to the solution of carbon tetrachloride prevents the irreversible capture of intrablob electrons by CCl_4 molecules. As a result the Ps yield in the ternary system –[solvent + CCl_4 + *c*-$C_{14}H_{10}$]– is practically the same as in the pure solvent. It seems even very effective electron acceptors with low electron affinity (EA) at the level of phenanthrene (EA $\sim$ 0.1 eV) are not able to form a strong covalent bond with a DNA molecule and produce in such a way its mutation.

5 Conclusion

The results presented, encourage further study of the positron method for detection of carcinogenic and anticarcinogenic properties of substances. It seems to be simpler, faster, cheaper and widely available in comparison with other competing physicochemical methods. Further application of the positron radiation chemical method should contribute to a better understanding of the primary processes of carcinogenesis.

The above results to a large extent were predetermined by fruitful collaboration with Japanese radiation chemists. Y. Katsumura, Y. Ito, T. Hirade, Y. Kobayashi and M. Domae made valuable contribution to the development of the Ps formation blob model, which is the base of the suggested method. We also thank Prof. Y. Tabata for inspiring attention to our investigations.

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