On the Competition between Scavenging and Recombination in Solutions of Macromolecules

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This paper is concerned with the competition between recombination of a radical pair and radical attack on targets such as macromolecules or nanoparticles in solution, which are large on the molecular scale. The difference in scale between radicals and targets causes the kinetics to be transient over a long period. The specific novel feature of the analysis is the effect of the initial spatial correlation of the radicals on the kinetics of attack on the targets. The main results are (i) a simple modification of the Smoluchowski rate coefficient for scavenging and (ii) the probability of *multiple* hits on the same target. Both effects arise from the clustering of the radicals. The latter is of particular interest in radiation biology, because multiple hits result in complex damage. The analysis is validated against results from random flights computer simulation; excellent agreement is obtained.

1. Introduction

Clustering and complexity are important features of damage caused by ionizing radiation. These features have their origin in the physical structure of the radiation track. Most of the energy of a high-energy electron, for example, is lost in relatively small energy loss events,[1] producing low-energy secondary electrons that cause further damage close to the location of the primary event. Each primary event results in a cluster of molecular fragments, many of which are radicals. These clusters have a spectrum of sizes, shapes and numbers of fragments, whose detailed origin and characterization is a subject of continuing investigation.[2] In solution the radical fragments diffuse and react with one another when they encounter each other in the course of their Brownian motion.

We have developed an efficient modeling method, the IRT (independent reaction times) method, that permits the simulation of diffusion kinetics in the track. This technique has been described in detail[3,4] and has been successfully applied to the modeling of radiation chemistry in water,[5] and in unravelling the short time recombination, which is mainly between fragments in the same cluster, and longer time kinetics where cluster overlap becomes important.[5]

Several important phenomena arise when radiolytic fragments in solution attack larger entities, such as macromolecules,[6] colloidal particles[7] or surfaces.[8] Important consequences of radiolytic radical attack are damage to biomolecules such as DNA,[9] and the radiation enhancement of corrosion.[10,11] In particular, it has been recognized for some time that an important feature of radiation damage to DNA from a biological point of view is complexity of the damage, involving more than one damaged site in proximity.[12] Some of this complex damage comes from the direct effect of the radiation, in which ionization and excitation events take place within the target molecule, and some arises indirectly through the attack of free radicals—predominantly the OH radical—generated by interaction of the radiation with the surrounding water. It is difficult to distinguish between these two processes, but the extent of the indirect effect can be estimated by the addition of scavengers such as dimethyl sulfoxide (DMSO), which may intercept the OH radicals before they can diffuse to the DNA.[13] The result of such experiments is that, in a mammalian cell, about two-thirds of the damage can be scavenged and may be inferred to arise from radical attack.[12]

Complex indirect damage comes from multiple radical attacks in spatially correlated locations. The temporal and spatial correlation of the attacks arises because of the spatial correlation of the initial locations of the radical fragments, which are born from the same primary event of the radiation track. Experiments can distinguish between single and some multiple attacks, for example experiments on solutions of plasmid DNA, where it is possible to distinguish single and double strand breaks.[14]

The essential problem of interest is therefore a small cluster of free radicals generated close to a target that is large on the molecular scale, such as a DNA molecule or a nanoparticle. The free radicals diffuse and may react with one another, they may attack the target, or they may do neither and escape. The aim of this paper is to develop a theory for the diffusion kinetics of a simple model system of this type. The theory must be capable of dealing simultaneously with the transient nature of both the radical recombination and the attack on the target particle, and it must also be able to calculate the probability of multiple hits. Although there have been several attempts to formulate models in the past, mainly applied to DNA, none fulfills all these requirements apart from direct computer simulation of the random trajectories of the diffusing radicals.[15−17]

Milligan et al.[13] have measured yields of single and double strand breaks induced by the γ-irradiation of aqueous solutions of plasmid DNA in the presence of the hydroxyl radical scavenger DMSO. The competition for OH between DNA and scavenger was analyzed by competition kinetics to infer a rate coefficient for the OH + DNA reaction. Although the competition plots with constant DMSO concentrations were essentially straight lines, the inferred OH + DNA rate coefficient was found to vary strongly with the concentration of DMSO. The origin of this variation is the transient nature of the scavenging reaction: the OH + DNA reaction must be described by a time-dependent rate coefficient. According to the Smoluchowski theory,[18] the second-order rate coefficient for a diffusion-

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controlled reaction with a spherical target is as follows:

$$k = 4\pi a D' \left\{ 1 + \frac{a}{\sqrt{\pi D' t}} \right\} \quad (1)$$

where a is the reaction radius and D' is the relative diffusion coefficient of the two reacting species. The rate coefficient thus decreases with time toward an asymptotic limit of $4\pi a D'$. The typical lifetime of the transient in the rate coefficient is proportional to the square of the reaction radius $\tau \sim a^2/D'$. If the target particle is much larger than the diffusing radical, as is a DNA molecule or a nanoparticle, the transient will persist to much longer times than for reactions between small molecules and cannot be ignored. The dependence of the inferred OH + DNA rate coefficient on target concentration is a consequence of this time dependence.

Van Rijn et al.[19] have addressed this problem by treating DNA molecules as spheres of radius a that react with OH radicals in a diffusion-controlled manner. In this model, OH radicals are generated uniformly in space with a constant production rate p and are removed by bimolecular reaction with a scavenger whose concentration is assumed to be homogeneous and constant, and by reaction with the target particles. Following the usual Smoluchowski approach, the motion of the radicals is considered to be diffusive and to obey a diffusion equation in a coordinate system centered on a single isolated target molecule. Furthermore, the OH concentration profile c, built up by these processes, is assumed to be stationary under steady-state irradiation conditions, and is governed by the diffusion equation

$$D' \left\{ \frac{\mathrm{d}^2 c}{\mathrm{d}r^2} + \frac{2}{r} \frac{\mathrm{d}c}{\mathrm{d}r} \right\} + p - \sigma \mathrm{c} = 0 \qquad r \geq a \quad (2)$$

where r is the radial distance from the center of the typical spherical target, D' is the relative diffusion coefficient of the OH radical and the target and σ is the pseudo-first-order rate constant for scavenging (the scavenging capacity). With appropriate boundary conditions, the solution of eq 2 is given by

$$c(r) = c_0 \left\{ 1 - \frac{a}{r} \exp(-(r-a)/L) \right\} \quad (3)$$

where $c_0 = p/\sigma$ is the stationary OH bulk concentration, and $L = \sqrt{D'/\sigma}$ is the diffusion length, a measure of the distance traversed by an OH radical, in the absence of DNA, before capture by a scavenger. The reaction rate is obtained from eq 3 by means of Fick's first law, giving the following expression for the rate constant, which depends on scavenger concentration:

$$k'_{\mathrm{DNA}} = 4\pi a D' \left(1 + \frac{a}{L} \right) \quad (4)$$

Although this expression for the inferred rate coefficient represents an important improvement on simple competition kinetics, the result does not take into account a number of effects, notably the competition with radical recombination, but also the competition of other target particles that may be in the vicinity. The use of Smoluchowski theory assumes that the targets are far enough apart (i.e., their concentration is sufficiently low) that the radical concentration profile around any one target is not perturbed by the presence of a neighboring target.

Mark et al.[20] addressed the problem of competition between targets by adding an extra term to eq 2, representing the rate at which radicals are consumed by other targets in the neighborhood of the one being considered. In addition, rather than assume that the reaction between OH and DNA is fully diffusion controlled, Mark et al. used a radiation boundary condition. An alternative method, by modifying the outer boundary condition to allow for the presence of other particles, was suggested by Verberne.[21]

Although these treatments have identified some of the important problems that arise when radicals attack large targets, the problems of most interest have not been addressed. In particular, even though the treatment is applied under steady-state radiolysis, the radicals are created in clusters, and so each target may be hit by more than one radical from the same cluster. This feature must depend strongly on the clustering of the radicals. Because complexity of damage is of great interest in radiation biology, it is important that theory can deal with the possibility of multiple hits and spatial correlations; a treatment that assumes the initial distribution of radicals to be homogeneous in space is unlikely to be able to do this. In previous work the only effects of clustering considered have been modifications of the radical yield to allow for the radical recombination kinetics, which is also determined by the clustering. For example, Verberne[21] used an empirical formula derived by Warman, Asmus and Schuler[22] for the transient OH radical yield.

This paper presents a first attempt to develop a consistent theory that deals with both these points. A simple model is used, in which two identical radicals are produced in close proximity to one another in a sea of large spherical target particles, assumed to be homogeneously distributed throughout the solution. The radicals are given the characteristics of OH radicals (diffusion coefficient, etc.) and the larger particles are assumed to be spherical for simplicity. Because the diffusion coefficient is inversely related to the hydrodynamic radius of the particle, large target particles diffuse much more slowly than small radicals and are assumed to be stationary on the time scale of the recombination kinetics.

The radicals may react either by recombination with one another or by reacting with the target particles. No additional scavenger has been included, and all reactions are considered to be diffusion controlled. Another important assumption of the current model is that a target particle may react with several radicals without change in size or reactivity. Thus, it is assumed that the rate parameters for reaction between a radical and a target is not affected by any previous attack on the same target, at least on the time scale of the kinetics considered.

Although this model may seem crude, especially when applied to DNA, on the time scales involved, the detailed structure of the target is relatively unimportant. The competition between the many reactive sites on the surface means that they cannot be considered in isolation, and it is not wholly unreasonable to treat the target particle as a single entity. Of course, in a study of the accessibility and competition of different reactive sites, a much more detailed model would be necessary. This has only been attempted in computer simulations so far.[15,17,23]

The recombination between the radicals and the attack on the target particles are both assumed to be diffusion controlled. This assumption is also less crude than it may seem. The OH + OH reaction is known to be close to diffusion control at ambient temperatures,[24] and OH reactions with stable molecules are often fast. The closeness of a reaction to diffusion control may be measured by the dimensionless parameter $\upsilon a/D'$, where D' is the relative diffusion coefficient, a the encounter distance and υ is a parameter with the dimensions of velocity that measures the reactivity of the surface. For molecules with similar

reactivities υ, the larger the encounter distance the closer the reaction is to diffusion control, because when the target is large, successive re-encounters are much more likely within the time scale of the transient than for a small target where the radical is more likely to escape. Because each encounter is equally likely to lead to reaction, escape following an encounter is much less likely for a large target than for a small one.

Section 3 presents a highly simplified model of the kinetics of the model system based on the time-dependent geminate survival probability and a competing transient reaction with target particles. This model uses normal homogeneous kinetics for the reactions with the target molecules. Both radical decay and the decay of unattacked target particles are compared with the results from random flights (Brownian dynamics) simulations. This oversimplified kinetic model fails because it cannot deal with the problem of multiple hits, motivating a more detailed analysis of the radical attack.

In section 4 a new theory is formulated that takes into account the correlation between the initial location of the radicals in modeling the radical attack on a target particle. In this section the radical attack on the target is considered in isolation; i.e., the radicals are clustered but are not permitted to recombine with one another. The mathematical formulation is based on the IRT method, which is exact for this model system. Even in the absence of the competing recombination reaction the spatial correlation is found to have an important effect on the kinetics of radical attack.

In section 5 the reaction scheme is extended to include radical recombination. The IRT method is an approximation for this system, but it does permit the analysis of the effect of correlation between the initial locations of the radicals. The results are compared with Monte Carlo random flights simulations and the agreement is found to be excellent, indicating that the multiple hit problem can be treated adequately in terms of correlations in the initial distribution of particles.

2. Random Flights Simulation

The approximations in the main part of this paper are assessed by comparison with Monte Carlo random flights simulations of the trajectories of the diffusing particles. These simulations provide a method of solving the multibody diffusion problem to any required degree of accuracy by judicious choice of time steps and number of realizations. Considerable efforts have been made to develop this type of simulation, with particular reference to boundary behavior, which have been discussed elsewhere.[25−28] Thus only a brief discussion is given here together with any alterations to the general method relevant to the application.

In the simulation, time is discretized in such a way that small steps are taken if the particles are close together but larger steps may be taken if there is little chance of an encounter. At each time step, δt, a particle takes a random flight sampled from a spherical normal distribution with mean zero and variance $2D\delta t$ in each direction. Suitable modifications may be made to allow for interparticle forces if necessary. If two particles encounter each other during δt, a reaction is counted. An encounter is determined in two ways: either the two particles are found to be within the encounter distance of each other at the end of the time step, in which case an encounter must have occurred, or the survival probability is calculated for each pair of particles conditional on their relative separations at the start and end of the time step.[27] The simulation continues until all reactions have taken place or until a given cutoff time has elapsed. The whole process is repeated many times (at least 10^4, typically 10^5) allowing time-dependent reaction probabilities to be accumulated. The statistical significance of the result depends on the number of realizations.

For the current application, a number of target particles are positioned at random in a cubic cell of edge 10^3 nm. Two radicals are located at the center of the cell a few angstroms apart. The radical trajectories were followed, as outlined above, using a diffusion coefficient of 2.8×10^{-9} m^2 s^{-1} (a value appropriate for OH). The target particles were assumed to be much larger than the radicals, and consequently their diffusion coefficients were so much smaller that they were assumed to remain stationary. An encounter between two radicals was assumed to occur at a distance of 0.13 nm. The encounter distance between a radical and a target was set at 50 nm.

The values chosen for the above parameters were based on the experiment of Milligan,[13] in which the kinetics of the reaction between the OH radical and pUC18 plasmid DNA (2686 base pairs) was investigated. The cubic cell size was chosen so that over the lifetime of the simulation (10 μs) the root-mean-square distance traversed by the radical ($\sqrt{6Dt}$) was significantly less than the distance to the cell boundary. This means that it is unlikely in any given realization that the radical would pass through the cell wall. However, a periodic boundary condition was also applied to account for the rare occasions when a radical does diffuse out of the cube.

3. Homogeneous Theory

This section outlines an attempt to apply "normal" diffusion kinetics to this system, using the Smoluchowski time-dependent rate coefficient for the reactions of radicals with target particles, and a time-dependent rate coefficient for recombination derived from the survival probability of a radical pair in the absence of competition. In the case of a single radical pair the time-dependent geminate survival probability $\Omega(t)$ is well-known; however, for larger clusters it is envisaged that a simulated decay might be used, or alternatively the radical decay could be described by an approximate parametric form, such as that of Hummel[29,30] and Warman et al.[22] for track kinetics.

The radical recombination rate in the absence of traps is described using a time-dependent rate coefficient

$$\lambda(t) = -\frac{\mathrm{d}(\ln \Omega(t))}{\mathrm{d}t} \tag{5}$$

Equivalently, the concentration of surviving radicals [R] obeys the transient rate equation

$$\frac{\mathrm{d}[\mathrm{R}]}{\mathrm{d}t} = -\lambda(t)[\mathrm{R}] \tag{6}$$

showing that $\lambda(t)$ is effectively a time-dependent rate coefficient for the recombination of radicals in the absence of additional scavenger.

A simple description of the competition kinetics is summarized in the following scheme.

$$\mathrm{R} + \mathrm{R} \xrightarrow[\lambda(t)]{} \mathrm{RR} \tag{7}$$

$$\mathrm{R} + \mathrm{D} \xrightarrow[k_{\mathrm{D}}(t)]{} \mathrm{E} \tag{8}$$

$$\mathrm{R} + \mathrm{E} \xrightarrow[k_{\mathrm{D}}(t)]{} \tag{9}$$

In this scheme D represents target particles that have not yet been hit by a radical, and E represents target particles that have

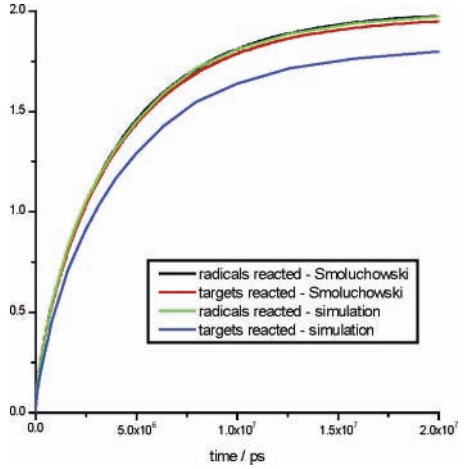

Figure 1. Normal kinetics applied to two radicals in a sea of scavengers compared with random flights simulation. Recombination of radicals is explicitly excluded. The following parameters were applied: radical separation, 5 Å; scavenger concentration, 10^{-10} Å^{-3}; radical diffusion coefficient, 0.28 Å^2 ps^{-1}; radical−target encounter distance, 500 Å.

been hit by one or more radicals. The same rate coefficient is used for both.

For convenience the concentrations are denoted as follows: [R] = x, [D] = y. [E] = $y_0 - y$. The rate coefficient k_D is assumed to be the Smoluchowski time-dependent rate coefficient for reaction between a radical and a target,[18] given by $k_D = k(1 + \gamma/\sqrt{t})$, where the steady-state rate constant k is $4\pi aD'$, and $\gamma = a/\sqrt{\pi D'}$, a being the reaction radius and D' the relative diffusion coefficient.

It follows from the kinetic scheme that the radical concentration obeys the rate equation

$$\frac{dx}{dt} = -\lambda x - k_D xy - k_D x(y_0 - y) = -x(\lambda + k_D y_0) \quad (10)$$

which has the solution

$$x = x_0 e^{-\int \lambda dt} e^{-k_D y_0 dt} = x_0 \Omega(t) \exp[-y_0 k(t + 2\gamma\sqrt{t})] \quad (11)$$

and can be evaluated explicitly.

The rate equation for the concentration of virgin target particles is

$$\frac{dy}{dt} = -k_D xy = -k\left(1 + \frac{\gamma}{\sqrt{t}}\right)xy \quad (12)$$

The formal solution of eq 12 is

$$y(t) = y(t_0) \exp\left[-\int_{t_0}^{t} k\left(1 + \frac{\gamma}{\sqrt{t}}\right)x\, dt\right] \quad (13)$$

This integral may be obtained numerically because $x(t)$ is known from eq 11.

The analysis described here was evaluated for an initial concentration of target particles of 0.166 μmol dm^{-3}. For plasmid pUC18 DNA, this corresponds to a nucleotide concentration of approximately 0.9 mmol dm^{-3}, which is within the experimentally accessible range.[13] In the first runs the radical−radical encounter distance was set to zero so that the only permitted reaction for the radicals was attack of the targets. Figure 1 shows the time variation of the expectation number of radical reactions and the expectation number of targets that have reacted, normalized for a radical pair.

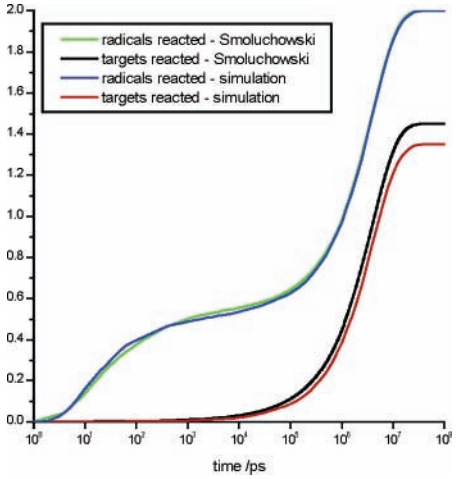

Figure 2. Normal kinetics applied to two radicals in a sea of scavengers compared with random flights simulation. Recombination of radicals is included. Refer to Figure 1 for parameter values.

These results immediately bring out an important defect in this kinetic model. Figure 1 shows that in this model the number of targets reacted is essentially the same as the number of radicals scavenged. If the radicals start close to one another, the number of targets that have reacted should be less than the number of radical−target reactions because of the possibility that both radicals may have hit the same target. For comparison, the results generated by the random flights simulation method described in section 2 are also shown. The interesting point to note is that, although the number of radical−target reactions predicted by normal kinetics agrees well at all times with the simulation, the analysis seems to overestimate the number of targets that have reacted.

The essential problem with this simple kinetics scheme is that the treatment of scavenging is unable to account for effects arising from the correlation of the radical positions, notably the possibility of multiple hits on the same particle. On the other hand, the simulation explicitly models the positions and trajectories of the diffusing radicals, so that if a pair is generated close to a target there is a significant probability that both radicals will react with it. In such cases, the number of targets that have reacted will be smaller than the number of radical reactions. In the simple kinetic model of this section the radical−target distances are implicitly assumed to be independent, and therefore the probability of the two radicals hitting the same target in an infinite sea of targets is effectively zero.

In a second set of tests, recombination of radicals was permitted to occur in competition with scavenging. The results are shown in Figure 2 together with those from the computer simulation. Once again, and for the same reasons, the formulation correctly predicts the time variation of the number of radical reactions while overestimating the number of targets that have reacted.

In sections 4 and 5, a new formulation is developed to describe the time variation of the number of radical reactions as well as the number of targets that have reacted for both the case in which recombination is not allowed (section 4) and that in which it is allowed (section 4). These will also be compared with the simulation results.

4. Two Radical Analysis without Recombination

4.1. Number of Radicals Reacted. This section introduces an idealized model of the scavenging rate for a pair of identical radicals that recognizes the correlation between the initial

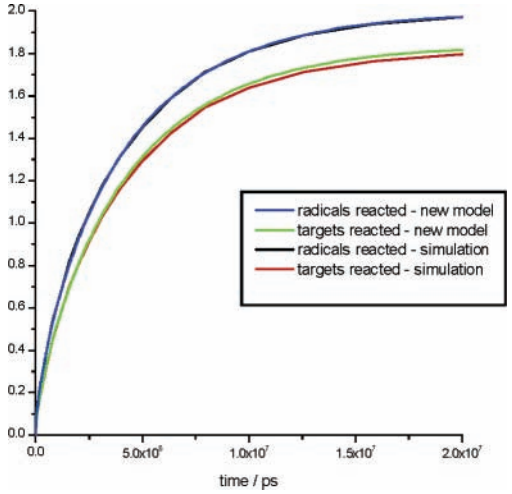

Figure 3. New model applied to two radicals in a sea of scavengers compared with random flights simulation. Recombination of radicals is excluded. Refer to Figure 1 for parameter values.

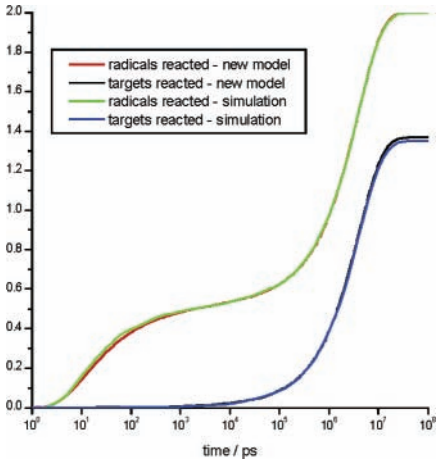

Figure 4. New model applied to two radicals in a sea of scavengers compared with random flights simulation. Recombination of radicals is included. Refer to Figure 1 for parameter values.

positions of the radicals. Additional complications that arise from the competition with recombination are initially removed; these will be considered in the next section. One additional simplification is made, that the radicals are the same distance from each spherical target. This simplification is obviously limiting but may be justified because the typical initial radical−radical distance will generally be much smaller than the distance to the center of the target. In addition, the simulations can be used to test the approximation and indicate that reactions with the target particles are insensitive to the initial radical−radical distance, as long as the radicals are close to one another. The results are be shown later in Figures 3 and 4. This assumption renders the mathematics of the model and its results much simpler. A fuller analysis, in which this approximation is lifted, will be presented in a subsequent paper.

We start by considering a system that consists of two radicals initially located at points equidistant from the center of a sphere of radius R in which is placed a single target molecule at a random position, sampled from a uniform distribution within the sphere. The possibility of radical recombination is ignored and the variables T_1 and T_2 are defined to be the times at which radical 1 and radical 2 react with the target particle, respectively. The joint probability distribution function for these two random times is denoted $Q(t,u) \equiv P(T_1>t,T_2>u)$. In the following the symbol P represents the probability of some event, and the symbol P is a probability density.

In spherical polar coordinates the function $Q(t, u)$ has the explicit form (using the known solution for the geminate survival probability in three dimensions):[31−34]

$$Q(t,u) = \frac{4\pi}{V}\int_a^R r^2\left(1-\frac{a}{r}\,\mathrm{erfc}\left[\frac{r-a}{\sqrt{4D't}}\right]\right)\left(1-\frac{a}{r}\,\mathrm{erfc}\left[\frac{r-a}{\sqrt{4D'u}}\right]\right)\mathrm{d}r \quad (14)$$

where the variable of integration r is the radical-target separation, V is the volume of the sphere, a is the reaction radius for reaction between radical and target and D' is the relative diffusion coefficient. The radicals are assumed to diffuse independently of one another. If the target is stationary, this equation is exact within the diffusion equation formalism.

If V is very large, it is permissible to take the limit $R \to \infty$ in all terms of the integral except for the constant term in the integrand. This is possible because of the asymptotic properties of the complementary error function, which guarantee that the error is exponentially small. The explicit solution of eq 14 is then

$$Q(t,u) = 1 - \frac{4\pi a^3}{3V} - \frac{4\pi a D'}{V}(t+u) - \frac{8\pi a^2}{V}\sqrt{\frac{D'(t+u)}{\pi}} \quad (15)$$

The most important new feature of the formulation is already present in this equation for Q: the two reaction times are not independent; they are correlated with one another. This correlation must now be carried through to a system with an arbitrary number of scavengers using the IRT approximation.

If there are N scavengers in the sphere, independently and identically distributed (i.e., each scavenger is assumed to have a constant probability density in the sphere and the position of a scavenger is assumed to be unaffected by the positions of any others), then the probability of radical 1 surviving to time t and radical 2 surviving to time u (ignoring recombination) is $Q(t,u)^N$, i.e.

$$P(T_1>t,T_2>u|N) = Q(t,u)^N \quad (16)$$

The interpretation of this equation is that for radical 1 to survive to time t and radical 2 to time u the inequality defining Q must be obeyed separately for each of the N targets. Note that the pair of correlated distances between the two radicals and each target have been assumed to be identical; however, because the targets have been assumed to be stationary, this is the only additional approximation at this point. It is important to realize that although the two reaction times with a given target are not independent, the pair of reaction times with one target are assumed to be independent of the pair of reaction times with any other target, and each pair of reaction times has the same probability distribution because of the uniform distribution of targets.

To introduce the concentration of targets, it is supposed that the number of targets in the sphere is Poisson distributed with mean cV where c is the target concentration. This assumption is good for dilute solutions. Hence

$$P(T_1>t,T_2>u) = \sum_{N=0}^{\infty}\frac{(cV)^N}{N!}\mathrm{e}^{-cV}Q(t,u)^N = \mathrm{e}^{-cV(1-Q(t,u))} \quad (17)$$

It is now convenient to change the notation, by defining

$$v(t+u) = V(1 - Q(t,u)) = \frac{4}{3}\pi a^3 + 4\pi a D'(t+u) + 8a^2\sqrt{\pi D'(t+u)} \quad (18)$$

and noting that $v(t+u)$ has the dimensions of volume and is a function of one time variable, $t + u$. Equation 17 now becomes

$$P(T_1>t,T_2>u) = e^{-cv(t+u)} \quad (19)$$

We now consider the number of radicals remaining as a function of time. For both radicals to survive to time t, an event whose probability is denoted P_2, it is necessary that both $T_1 > t$ and $T_2 > t$. Hence

$$P_2 = e^{-cv(2t)} \quad (20)$$

For one radical only to remain, probability P_1, we require either $T_1 < t$, $T_2 > t$ or $T_1 > t$, $T_2 < t$. By symmetry, these events have equal probabilities. They may be found by considering the density of T_1 joint with the probability that $T_2 > u$, denoted loosely

$$P(T_1=t,T_2>u) = -\frac{\partial}{\partial t}e^{-cv(t+u)} = c\frac{\partial v}{\partial t}e^{-cv(t+u)} \quad (21)$$

Integrating over t we obtain

$$P(T_1<t,T_2>u) = -\int_0^t \frac{\partial}{\partial t'}e^{-cv(t'+u)}\,dt' = e^{-cv(u)} - e^{-cv(t+u)} \quad (22)$$

Hence, substituting $u = t$,

$$P(T_1<t,T_2>t) = e^{-cv(t)} - e^{-cv(2t)} \quad (23)$$

by symmetry the probability $P(T_1>t,T_2<t)$ has the same value, hence,

$$P_1 = 2(e^{-cv(t)} - e^{-cv(2t)}) \quad (24)$$

For no radicals to remain, probability P_0, it is necessary that both $T_1 < t$ and $T_2 < t$. First consider the density that $T_2 = u$ joint with the probability that $T_1 < t$, obtained by differentiation of eq 22

$$P(T_1<t,T_2=u) = -\frac{\partial}{\partial u}(e^{-cv(u)} - e^{-cv(t+u)}) \quad (25)$$

integrating over u, and setting $u = t$,

$$P(T_1<t,T_2<u) = e^{-cv(0)} - e^{-cv(t)} - e^{-cv(u)} + e^{-cv(t+u)} \quad (26)$$

$$P(T_1<t,T_2<t) = e^{-cv(0)} - 2e^{-cv(t)} + e^{-cv(2t)} \quad (27)$$

Now zero-time reactions must be considered; these occur when the two radicals are generated in a location overlapping one of the targets, corresponding in this simple model to the direct effect. Because the radicals have been assumed to be equidistant from each target at time zero, either both react or none reacts. The expression for P_2 ($P_2(0) = e^{-cv(0)}$) automatically includes this effect, but it has not yet been included in P_0, which has been obtained by integrating over reactions that take place at times $t > 0$. P_0 must be increased by $1 - e^{-cv(0)}$ to allow for this effect. Thus,

$$P_0 = 1 - 2e^{-cv(t)} + e^{-cv(2t)} \quad (28)$$

The system of probabilities is now normalized.

4.2. Number of Radicals Remaining. The expectation number of radicals remaining is given by

$$2P_2 + P_1 = 2e^{-cv(t)} \quad (29)$$

The expectation number of radicals that have reacted is therefore given by $2(1 - e^{-cv(t)})$. The analytic result shown for the mean number of radicals having reacted by time t is identical to that obtained from the simple kinetic analysis in section 3 and is in good agreement with the random flights simulations, as illustrated in Figure 3.

4.3. Ordered Reaction Times. The exact agreement with normal kinetics despite the correlation in the initial positions of the two radicals is necessary because the two radicals diffuse independently of one another. In the absence of recombination, each radical will react with a stationary target with a rate given by the Smoluchowski theory. The *marginal* distributions of the two radical−target reaction times are therefore the same as given in section 3. However, the two reaction times in the new formulation are not independent of one another, which is the point of departure from the theory of section 3.

The lack of independence is shown clearly by considering the ordered reaction times. The first reaction removes the system from the state containing two radicals, and the probability distribution of the first reaction time is therefore given by $P_2 = \exp(-cv(2t))$. If the two reaction times were independent, this would be $\exp(-2cv(t))$. Comparing the two exponents,

$$v(2t) = \frac{4}{3}\pi a^3 + 8\pi a D' t + 8a^2\sqrt{2\pi D t} \quad (30)$$

$$2v(t) = \frac{8}{3}\pi a^3 + 8\pi a D' t + 16a^2\sqrt{\pi D t} \quad (31)$$

The first term corresponds to zero-time reaction, and it is evident that $2v(0)$ in the second expression is twice as large as it should be. The assumption of independence overestimates the chance of zero-time reaction because, even if one radical survives, it gives the other radical a chance to react, whereas in the model system, if one radical survives zero-time reaction the other must do so as well.

The second term corresponds to the normal Smoluchowski steady-state rate constant, which operates in the limit of long times when all memory of any initial proximity to the target has been wiped out, either by reaction or by diffusion. At long times all memory of the initial correlation between the radicals will be lost, and so it is not a surprise that this term is common to the two formulations.

The third term is much more interesting, however, because this represents the transient in the rate coefficient that arises from the tendency of the radicals generated close to the target to react quickly, before the steady state is achieved. In the new formulation this term is a factor of $\sqrt{2}$ smaller than Smoluchowski, suggesting that the effect of the correlation in initial positions is to reduce the transient term in the Smoluchowski rate coefficient for the first reaction by a factor of $\sqrt{2}$; i.e., the

rate coefficient for the first reaction should be

$$k_{\mathrm{corr}} = 4\pi a D'\left(1 + \frac{a}{\sqrt{2\pi D' t}}\right) \tag{32}$$

The result of eq 30 is particularly interesting for a number of reasons. A similar result, which arises simply from the small-number statistical weighting, was reported some time ago for steady-state scavenging.[35] This paper shows that the use of $\nu(2t)$ also applies when the scavenging rate coefficient is time-dependent, giving the reduction in the transient term observed in eq 32. In addition, the rate coefficient for the first scavenging also controls the total scavenging yield in this simple system, because once one radical has been scavenged, the only possible fate for the other radical is also to be scavenged.

The first radical-target reaction is slower than predicted by Smoluchowski theory because, if one radical is initially far from the nearest target, the other radical must also be, whereas the assumption of independence essentially gives it a second chance to be close to a target. This is a more subtle version of the effect already remarked for the zero time reaction. (Conversely, if one radical is close to the nearest target, the other is too; however, the probability distribution for the nearest radical−target distance varies as r^2 so that the correlation in large separations is more important.)

Given that the first reaction is slower than that predicted on the assumption of independence, but that the radical decay is identical, the second radical−target reaction must be faster than predicted by Smoluchowski theory. This is indeed the case, and the difference arises because if the first reaction takes place in the transient, the second radical will still be nearby (on the scale of the target). The second radical is then much more likely to react with the same target as the first radical than would be expected if the two reaction times were independent, and this will take place faster than diffusion to a second possible target. The theory must therefore be capable of distinguishing a second reaction with the same target from a reaction with a different target. In other words, once both radicals have reacted, have they both reacted with the same target or with different targets? This question does not arise with normal scavenging, because reaction generally modifies the scavenger so that it is no longer reactive, but it is an important problem for targets such as DNA, where complexity of damage needs to be modeled correctly.

4.4. Number of Targets Hit. The number of targets that have reacted is not the same as the number of radicals that have reacted because sometimes both radicals hit the same target. It is therefore necessary to find the probabilities of hitting the same target and different targets separately.

The joint density of T_1 and T_2 is

$$p(t,u) = \frac{\partial^2}{\partial t \partial u} \mathrm{e}^{-c\nu(t+u)} = -c\frac{\partial^2 \nu}{\partial t \partial u}\mathrm{e}^{-c\nu(t+u)} + c^2 \frac{\partial \nu}{\partial t}\frac{\partial \nu}{\partial u}\mathrm{e}^{-c\nu(t+u)} \tag{33}$$

where ν is a function of $t + u$. The concentration dependence of the two terms in this equation suggests that the first term corresponds to the reaction of both radicals with the same scavenger, whereas the second term corresponds to reaction with different scavengers.

This claim may be justified as follows. The joint probability density that radical 1 reacts at time t and radical 2 at time u with the *same* target is given by

$$\begin{aligned} p_{\mathrm{same}}(t,u) &= \sum_{N=1}^{\infty} \frac{\partial^2 Q}{\partial t \partial u}(t,u) Q(t,u)^{N-1} N \mathrm{e}^{-cV} \frac{(cV)^N}{N!} \\ &= cV \frac{\partial^2 Q}{\partial t \partial u}(t,u) \mathrm{e}^{-cV(1-Q)} \\ &= -c\frac{\partial^2 \nu}{\partial t \partial u}\mathrm{e}^{-c\nu(t+u)} \end{aligned} \tag{34}$$

In the first equality of eq 34, the second derivative represents the joint density of the two reaction times with a given target. The factor Q^{N-1} represents the probability that no other target is hit by radical 1 before t or by radical 2 before u. The factor of N is the number of ways of choosing one target from N. The final term is the Poisson probability for the number of targets in the volume.

The joint probability density that radical 1 reacts at time t and radical 2 at time u with a *different* target is given by

$$\begin{aligned} p_{\mathrm{diff}}(t,u) &= \\ &\sum_{N=2}^{\infty} \frac{\partial Q}{\partial t_1}(t_1,u)|_{t_1=t} \frac{\partial Q}{\partial t_2}(t,t_2)|_{t_2=u} Q(t,u)^{N-2} N(N-1)\mathrm{e}^{-cV}\frac{(cV)^N}{N!} \\ &= (cV)^2 \frac{\partial Q}{\partial t}(t,u)\frac{\partial Q}{\partial u}(t,u)\mathrm{e}^{-cV(1-Q)} \\ &= c^2 \frac{\partial \nu}{\partial t}\frac{\partial \nu}{\partial u}\mathrm{e}^{-c\nu(t+u)} \end{aligned} \tag{35}$$

In the first equality of eq 34, the first factor is the probability density for radical 1 to react with a particular target at time t joint with radical 2 not hitting this target before time u. The second factor is a similar density for radical 2 to hit a different target. The third factor is the probability that the remaining $N - 2$ targets are not hit by radical 1 before t or by radical 2 before u. The factor of $N(N - 1)$ is the number of ways of choosing the two targets to be hit, and the final term is the Poisson distribution, as before.

We are now in a position to calculate the probabilities of hitting the same target twice and different targets by time t.

$$P_{\mathrm{same}}(t) = 1 - \mathrm{e}^{-c\nu(0)} - \int_0^t \int_0^t c\frac{\partial^2 \nu}{\partial t' \partial u}\mathrm{e}^{-c\nu(t'+u)}\,\mathrm{d}t'\,\mathrm{d}u \tag{36}$$

$$P_{\mathrm{diff}}(t) = \int_0^t \int_0^t c^2 \frac{\partial \nu}{\partial t'}\frac{\partial \nu}{\partial u}\mathrm{e}^{-c\nu(t'+u)}\,\mathrm{d}t'\,\mathrm{d}u \tag{37}$$

The expression given in eq 36 includes the possibility of zero-time reaction.

Although the sum of these two terms is given by eq 28, the two terms separately must be found by numerical integration. It is not necessary, however, to perform the whole two-dimensional integral numerically. In both cases the integrand is a function of the single variable $t' + u$. Hence it is necessary to find integrals of the general form

$$\int_0^t \int_0^t f(t'+u)\,\mathrm{d}t'\,\mathrm{d}u \tag{38}$$

With the change of variable $x = t' + u$, integrals of the form shown in eq 38 are easily transformed to single integrals of the form

$$\int_0^{2t} x f(x)\,\mathrm{d}x - 2\int_t^{2t} (x - t) f(x)\,\mathrm{d}x \tag{39}$$

which are more efficient to evaluate numerically.

The long time limits of these probabilities, however, may be found analytically to be

$$P_{\text{same}}(\infty) = 1 - e^{-4\pi a^3 c/3} + e^{-4\pi a^3 c/3} e^{4ca^3} \operatorname{erfc}(\sqrt{4ca^3}) \quad (40)$$

$$P_{\text{diff}}(\infty) = e^{-4\pi a^3 c/3} - e^{-4\pi a^3 c/3} e^{4ca^3} \operatorname{erfc}(\sqrt{4ca^3}) \quad (41)$$

The expectation number of targets that have reacted at time t is given by $P_1 + P_{\text{same}} + 2P_{\text{diff}}$. Figure 3 shows a comparison between the time dependence of the predicted number of targets that have reacted and the number observed in the simulation. The two plots are in very good agreement, implying that the new theory has correctly identified the most important correlation missing from the simple kinetic description of this model system.

In the next section, this analysis is repeated with the more realistic stipulation that recombination of radicals is allowed.

5. Two Radical Analysis with Recombination

The situation where radical scavenging by targets competes with radical recombination is more complicated, because it is necessary to start with the joint probability distribution of the recombination time and the two times at which each target would have been hit by the two diffusing radicals. This joint distribution must be constructed from the IRT approximation, in which the recombination time is assumed to be independent of the scavenging times and depends only on the initial separation of the two radicals. As in the last section, the scavenging is treated as if the two radicals were equidistant from each target.

5.1. Number of Radicals Reacted. As before, the expected number of radicals remaining as a function of time is determined from the probabilities of all the possible states of the system. The probability of both radicals remaining is given by

$$P_2(t) = e^{-c\upsilon(2t)}\Omega(t) \quad (42)$$

The first term in eq 42 represents the probability of both radicals surviving reaction with the targets, whereas the second term, $\Omega(t)$, is the probability that the radicals have survived recombination.

Equation 42 makes the assumption that the recombination time is independent of the time for reaction of each radical with a target. This is not actually the case. However, as discussed earlier, previous workers[3,36,37] have shown that errors made by this assumption of independent reaction times leads to insignificant errors in the overall kinetics of the system, and this will be verified by simulation later in this section (Figure 4).

We now consider P_1, the probability that only one radical remains. Such a state can only be produced by reaction with a target because recombination necessarily removes both radicals. With the random time for recombination T_R and the times for the two radicals to react with targets T_1 and T_2, respectively, the required probability is for the event that one and only one of the two radicals has been scavenged. This event requires one of the two scavenging times to be less than t, the other to be greater than t and the recombination time to be greater than the time at which the first scavenging occurred.

$$P_1(t) = P(T_1<t,T_2>t,T_R>T_1) + P(T_1>t,T_2<t,T_R>T_2) \quad (43)$$

By symmetry, the two terms on the right-hand side are equal, hence

$$P_1 = 2P(T_1<t,T_2>t,T_R>T_1) \quad (44)$$

First consider the more general function of three variables

$$P(T_1>t,T_2>u,T_R>s) = e^{-c\upsilon(t+u)}\Omega(s) \quad (45)$$

Differentiating with respect to t gives a density for T_1 jointly with the distributions of T_2 and T_R.

$$P(T_1 = t,T_2>u,T_R>s) = -\frac{\partial}{\partial t} e^{-c\upsilon(t+u)}\Omega(s) = c\upsilon'(t+u)e^{-c\upsilon(t+u)}\Omega(s) \quad (46)$$

where the prime denotes differentiation with respect to the argument. Demanding that no recombination occur before the scavenging time (i.e., setting $s = t$) and integrating from 0 to the current time t,

$$P(T_1<t,T_2>u,T_R>T_1) = \int_0^t c\upsilon'(t'+u)^{-c\upsilon(t+u)}\,\Omega(t')\,dt' \quad (47)$$

Finally set $u = t$ to obtain

$$P_1(t) = 2P(T_1<t,T_2>t,T_R>T_1) = 2\int_0^t c\upsilon'(t'+t)e^{-c\upsilon(t'+t)}\,\Omega(t')\,dt' \quad (48)$$

Now consider P_0, the probability that no radicals remain. Either the radicals have recombined or they have both reacted with targets, and in the latter case they may have reacted with the same target or with different targets.

$$P_0 = P(T_R<t,\min(T_1,T_2)>T_R) + P(T_1,T_2<t,T_R>\min(T_1,T_2)) \quad (49)$$

Denoting the density of the recombination time by

$$\omega(t) = -\frac{d}{dt}\Omega(t) \quad (50)$$

the first term in eq 49 is

$$P(T_R<t,\min(T_1,T_2)>T_R) = \int_0^t \omega(s)e^{-c\upsilon(2s)}\,ds \quad (51)$$

and the second term is

$$P(T_1,T_2<t,T_R>\min(T_1,T_2)) = 2\int_0^t\int_0^t \frac{\partial^2}{\partial t_1 \partial t_2} e^{-c\upsilon(t_1+t_2)}\Omega(t_2)\,dt_2\,dt_1 \quad (52)$$

in which it has been assumed that $T_2 < T_1$ and the factor of 2 accommodates the case $T_2 > T_1$.

The second term may be simplified by changing the order of integration:

$$P_0 = \int_0^t \omega(s)e^{-c\upsilon(2s)}\,ds + 2\int_0^t \Omega(t_2)\int_{t_2}^t \frac{\partial}{\partial t_1}\frac{\partial}{\partial t_2} e^{-c\upsilon(t_1+t_2)}\,dt_1\,dt_2 \quad (53)$$

which simplifies further to

$$P_0 = -2\int_0^t \Omega(t_2)c\upsilon'(t+t_2)e^{-c\upsilon(t+t_2)}\,dt_2 + e^{-c\upsilon(0)} - \Omega(t)e^{-c\upsilon(2t)} \quad (54)$$

This expression for P_0 has been obtained by integrating over the densities of the scavenging time, which do not include the

point at zero. Thus it is necessary to add the probability that the two radicals are scavenged at zero time, i.e., $1 - e^{-c\upsilon(0)}$. Thus

$$P_0 = 1 - \Omega(t)e^{-c\upsilon(2t)} - 2\int_0^t \Omega(t_2)c\upsilon'(t+t_2)e^{-c\upsilon(t+t_2)}\,dt_2 \quad (55)$$

Having obtained expressions for P_0, P_1 and P_2, the expectation number of radicals that have reacted by time t is evaluated as $2P_0 + P_1$. The time-dependence of this expectation is shown in Figure 4 together with the corresponding simulation results. The agreement is excellent.

5.2. Number of Targets Reacted. As in the last section, the probability of hitting the same target or different targets is first considered. Following eqs 47 and 48,

$$P_{\text{same}} = -2c\int_0^t\int_0^{t_1} \upsilon''(t_1+t_2)e^{-c\upsilon(t_1+t_2)}\Omega(t_2)\,dt_2\,dt_1 \quad (56)$$

$$P_{\text{diff}} = 2c^2\int_0^t\int_0^{t_1} [\upsilon'(t_1+t_2)]^2 e^{-c\upsilon(t_1+t_2)}\Omega(t_2)\,dt_2\,dt_1 \quad (57)$$

These integrals must be evaluated numerically. However, as in the last section, it is not necessary to evaluate the whole two-dimensional integral numerically. Both integrals have the form

$$P = \int_0^t\int_0^{t_1} f(t_1+t_2)\,\Omega(t_2)\,dt_2\,dt_1 \quad (58)$$

With the substitution $x = t_1 + t_2$, it can be shown that each integral is equivalent to the following pair of one-dimensional integrals, which may be evaluated numerically with greater efficiency

$$P = \int_0^{2t} f(x)\,G(x/2)\,dx - \int_t^{2t} f(x)\,G(x-t)\,dx \quad (59)$$

where $G(x) = \int_0^x \Omega(t)\,dt$. It may be necessary to create a table of values of G, which corresponds to the integral of the survival probability. However, if the initial distance between the radicals is fixed, or if a parametric form of the radical decay is used, this integral may be evaluated explicitly.

Once the single integrals in eq 59 have been evaluated numerically, the expectation number of targets that have reacted at any time may be evaluated as $P_1 + 2P_{\text{diff}} + P_{\text{same}}$. Figure 4 shows the time dependence of this number and its comparison with computer simulation. The agreement is excellent, indicating that the additional assumptions that the recombination time is independent of the times to hit the targets, and that the scavenging is treated as if the radicals are effectively coincident at time zero, do not seriously affect the kinetics.

6. Discussion

The modified version of diffusion kinetics based on the IRT method presented in the last two sections is in good agreement with the results of the random flights simulations reported here. The novel feature of the analysis is the application of the independent pairs approximation *after* the initial configuration is laid down, i.e., with all the initial correlations between the interparticle distances present. The simple kinetic scheme of section 3 makes the independence assumption earlier in the analysis, and so loses track of these initial correlations. The good agreement between the new theory and simulation implies that these correlations between distances in the initial distribution are the most important correlations, at least as far as the kinetics are concerned.

The theory permits the derivation of an explicit time-dependent rate coefficient for the first radical attack, given in eq 32, which is very similar to the Smoluchowski theory except that the transient part of the rate coefficient has been reduced by a factor of $\sqrt{2}$ by the correlation between the two radical-target distances. The same rate coefficient applies whether there is geminate recombination or not. The second radical attack cannot be described by a time-dependent rate coefficient, partly because its rate depends on when the first attack took place, but the theory gives a solution for the kinetics of the second attack that can be evaluated by a simple numerical integration.

At this point, we address what appears to be a major shortcoming of the analysis: it has effectively been assumed that the radicals start from a coincident position (equidistant from each target). This has been done to simplify the analysis. Although this assumption appears extreme, it is only a potential problem on the time scale of the geminate recombination, which is generally faster than the attack on the target. The simulation results presented in Figures 1−4 are for a system in which the radicals are not coincident but are initially located a fixed distance apart (5 Å). The initial separation of the radicals has no significant effect on the kinetics of attack on target particles as long as the separation is small relative to the scale of the largest particle.

This work is a first attempt at addressing the problem of the kinetics of multiple hits. The system addressed in this paper, comprising two identical geminate radicals, is very simple. There are not many experimental examples of such systems, although there are some, for example, the photolysis of hydrogen peroxide. For application in real radiation chemical systems it will be very important to extend this work to larger clusters. The analysis presented here can be applied to any spur containing two identical radicals, regardless of its other contents, for example, spurs arising from the dissociation of two water molecules, which contain two OH radicals. Before larger numbers can be dealt with, further development is necessary. We have already done some work to generalize the approach to noncoincident radicals, to chemical scavengers, which are removed by reaction (as opposed to macromolecular scavengers, which are not), and to larger clusters of radicals. We expect to report this work in a future publication. Most spurs in low LET radiation chemistry are sufficiently spatially extended[5] that the effects described here will be rather small. However, in the tracks of high LET radiation, radicals are clustered more closely and in larger numbers. We expect the correlation effects described here to be much more important for these large clusters. There are indications that scavenging yields in heavy ion tracks are lower than predicted by models using conventional scavenging rate coefficients, for example for the Fricke dosimeter,[38] and the correlation effects described here could be the origin of these anomalies. If corrections of the type described in this paper can be found for these larger systems, they will be very useful in improving the analysis of the chemistry of heavy ion tracks.

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