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Citation: *The Journal of Chemical Physics* **148**, 244704 (2018); doi: 10.1063/1.5030114

View online: <https://doi.org/10.1063/1.5030114>

View Table of Contents: <http://aip.scitation.org/toc/jcp/148/24>

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Enhancement of reaction rate in small-sized droplets: A combined analytical and simulation study

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(Received 19 March 2018; accepted 11 June 2018; published online 27 June 2018)

Several recent mass spectrometry experiments reveal a marked enhancement of the reaction rate of organic reactions in microdroplets. This enhancement has been tentatively attributed to the accumulation of excess charge on a surface, which in turn can give rise to a lowering of activation energy of the reaction. Here we model the reactions in droplets as a three-step process: (i) diffusion of a reactant from the core of the droplet to the surface, (ii) search by diffusion of the reactant on the surface to find a reactive partner, and finally (iii) the intrinsic reaction leading to bond breaking and product formation. We obtain analytic expressions for the mean search time (MST) to find a target located on the surface by a reactant in both two- and three-dimensional droplets. Analytical results show quantitative agreement with Brownian dynamics simulations. We find, as also reported earlier, that the MST varies as R^2/D , where R is the radius of the droplet and D is the diffusion constant of the molecules in the droplet medium. We also find that a hydronium ion in the vicinity can substantially weaken the bond and hence lowers the activation barrier. We observe a similar facilitation of bond breaking in the presence of a static dipolar electric field along any of the three Cartesian axes. If the intrinsic reaction is faster compared to the mean search time involved, it becomes primarily a diffusion-controlled process; otherwise the reaction cannot be accelerated in the droplet medium. The air-droplet interface provides a different environment compared to the interior of the droplet. Hence, we might also expect a completely different mechanism and products in the case of droplet reactions. *Published by AIP Publishing.* <https://doi.org/10.1063/1.5030114>

I. INTRODUCTION

Geometry and dimensionality of a reaction system are known to play an important role in determining the yield as well as the rate of the reaction; especially in bi-molecular reactions where search for a reactive partner is usually involved. The reaction rate is usually independent of the volume of the reaction system when the volume of the reaction system is large. However, in the case of a small finite volume (V), the rate constant acquires $1/\sqrt{V}$ dependence.^{1–3} This behavior remains a relatively unexplored area of theoretical research.

Recently several unusual results have been reported for reactions in small droplets that seem to have far reaching consequences.⁴ Electrospray (ES) and other spray-based ambient ionization techniques show an unusual increase in the reaction rate and yield.^{5–9} Studies using microdroplet fusion mass spectrometry also reveal that rates of several chemical reactions exhibit many-fold increase in charged microdroplets compared to the same in bulk solution.^{10–13} However, the enhancement of the chemical reaction rate in microdroplets seems to be system specific; not all reactions show the same trend. Reactions that involve acid/base catalysis or cleavage of reactive polar

groups are shown to be accelerated.¹⁴ The restricted environment of the microdroplet can give rise to the enhancement. This also depends on certain physical properties, for example, temperature, concentration, pressure, and density. It has also been reported that neutral water exhibits auto-ionization with a non-uniform distribution of hydronium and hydroxide ions between the core and surface of the water microdroplet.^{15–17} Although the nature of the air-water interface still remains somewhat controversial,^{18–20} it is broadly accepted that the air-water interface is charged much more than the droplet interior. This heterogeneous distribution of surface charge might play an important role in the acceleration of the reaction rate by the acid/base catalytic effect¹⁰ and through formation of a large electric field.²¹ Also the surface-to-volume ratio increases with decreasing microdroplets size. As a result, the surface charge and catalytic effects are facilitated in microdroplets.

There exist several studies of interfacial reactions that are determined by transport. In these cases, reactants find specific targets through diffusion on the surface in order to react. It plays a huge role in heterogeneous catalysis,^{22,23} ligand binding to DNA/proteins,²⁴ and reactions on micellar/vesicular surfaces.²⁵ In the case of interfacial reactions, the first step is excursion of the reactant from the bulk. This step is controlled by several factors like hydrophobicity of the solute and its affinity for the surface. Depending on the hydrophilic/hydrophobic character, reactants/products can accumulate at or near the droplet surface.

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The second step is the search for the successful reaction partner and environment, now by means of surface diffusion. This step is controlled by the geometry and the curvature of the surface. Time-dependent emergence of heterogeneity is a non-trivial problem and has not been addressed yet.

In spite of a number of earlier studies, the field of microdroplet chemistry is still in its infancy and there are many puzzles to be solved. For example, the exact cause for the reaction acceleration in microdroplets is not yet fully understood. What is the mean reaction time in the case of surface-mediated reactions? What is the molecular level difference between the reaction in microdroplets and in bulk? How general is the reaction acceleration in microdroplets? To what extent can reactions be accelerated? And, do new chemical reactions happen at the surface that are not found in bulk solution?

In this work, we address the above-mentioned questions with the help of time-dependent statistical mechanics (mean first passage time calculations), Brownian dynamics simulation in two and three dimensions, and heuristic quantum calculations. The organization of the rest of the paper is as follows. In Sec. II, we introduce a general and minimalistic theoretical model for the problem. In Sec. III, we explain the relative acceleration by means of dimensional analysis. We formulate the problem and derive analytic expressions for the mean search time (MST) in two- and three-dimensional droplets in Sec. IV. Quantum chemical calculations that show weakening of bonds in the presence of ions and large electric fields are presented in Sec. V. In Sec. VI, we present the Brownian dynamics simulation results for target search, and finally, in Sec. VII, we draw some general conclusions based on ours as well as several other studies.

II. ESSENCE OF THE PROBLEM: A MINIMALISTIC THEORETICAL MODEL

We employ a simple scheme in order to build a model for further theoretical calculations, as described in Fig. 1. At the beginning ($t = 0$), the reactants and the targets are randomly distributed in the bulk phase of the droplet. All of them exhibit random walk. The resultant process can be divided into several uncorrelated processes as described below.

- i. Because of the Grotthuss mechanism,²⁶ the transport of protons in liquid water is extremely fast. Hence,

the hydronium ions reach the surface faster than the organic reactant molecules. In general, ions preferentially reside at and near the periphery of the droplet and it has been shown earlier that hydronium ions tend to reside on the interface.^{17,27} So, they exhibit random walk only on the surface of the droplet once they reach there (with occasional and negligible re-entrance in the bulk).

- ii. In the second step, that is, after bulk excursion, the reactant molecules diffuse in order to find the targets that reside on the surface of the droplet.
- iii. Once the reactants find any of the targets, reactions occur with a finite reaction probability and reaction time.

We assume that the time scales of these three processes are not correlated and differ in several orders of magnitude from each other. So, the total reaction time can be expressed as a sum of times required for the different processes,

$$\tau_{total} = \tau_{b \rightarrow s}^{targets} + \tau_{b \rightarrow s}^{reactants} + \tau_{s \rightarrow T}^{reactants} + \tau_{reaction}. \quad (1)$$

Here, “b,” “s,” and “T” stand for the bulk, surface, and target, respectively. The first term on the right-hand side of Eq. (1) is assumed to be negligible compared to the other terms. Hence, we shall neglect this term in subsequent calculations and analyses. In this model, we neglect reactions that occur in the bulk phase. In Sec. VI, we show that the search time in bulk is significantly higher than that of the surface.

III. DIMENSIONAL ANALYSIS: ENHANCEMENT OF RATE ON SURFACE

In order to obtain a scaling factor of the reaction rate on the surface as compared to the bulk, we perform a simple analysis, as described below. Let the radius of the droplet be “ R ” and the number density of the target molecules be ρ_{bulk} in the bulk. Hence, the total number of target molecules in a spherical domain of radius “ R ” can be expressed as

$$N = \frac{4}{3}\pi R^3 \rho_{bulk}. \quad (2)$$

We define a shell of width “ Δ ” around the surface, and we identify a particular molecule as a surface molecule if its distance from the centre of the droplet lies in the range from $R - \Delta$ to R . The reactant molecules exhibit random walk and eventually reach the surface. Hence, the number density of

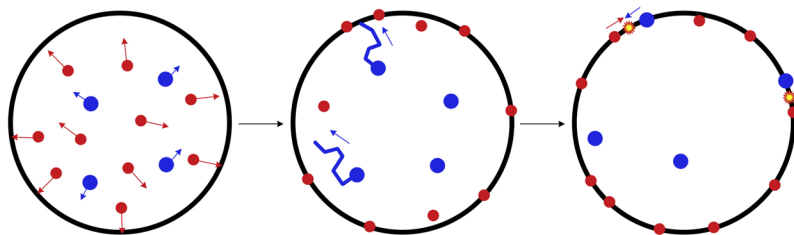


FIG. 1. The basic scheme of a theoretical model of a surface mediated reaction. First the reactants (blue) and the targets (red) are randomly distributed in the bulk portion of the droplet. Because of the huge diffusion constant of the targets (hydronium ions), almost all of them reach the surface in a short time, while the reactants still exhibit slower random walk in the bulk. Eventually the reactants reach the surface, find the reactive targets, and react with a finite probability associated with this process.

the same target molecules on the surface can be expressed as

$$\rho_s = \frac{N}{V_s} = \frac{\frac{4}{3}\pi R^3 \rho_{bulk}}{4\pi R^2 \Delta} = \frac{1}{3\Delta} R \rho_{bulk}, \quad (3)$$

where ρ_s is the number density of the targets on the surface. We assume that the random walkers are free from any external forces. In this case, that is, in a diffusion-controlled process, the rate constant (k) is given by the following Smoluchowski expression:^{3,28}

$$k = 4\pi D R \rho_s = \frac{4\pi}{3\Delta} D R^2 \rho_{bulk}. \quad (4)$$

From Eq. (4), it is clear that there is a modulation of the rate constant on the surface by a factor ($\frac{R}{3\Delta}$) compared to the same in bulk ($4\pi D R \rho_{bulk}$). As $\Delta \ll R$, the analysis predicts a large increment in the value of k .

We now present a theoretical analysis using methods of time-dependent statistical mechanics which provide a quantitative expression for the dependence of rate on the size of the droplet.

IV. THEORETICAL FORMULATION: MEAN REACTION TIME

Diffusion of the reactant molecules inside the solvent medium is a necessary prerequisite in order to find the proper target, in the case of any reaction occurring inside a solution.² Diffusion-controlled processes/reactions are studied extensively in the past to explain certain types of reactions, namely, annihilation ($A + B \rightarrow 0$), coalescence ($A + B \rightarrow B$), fluorescence quenching, growth kinetics, etc.^{1,29–36} Here, we model a general chemical reaction in aqueous microdroplets by using time-dependent statistical mechanics. By this means, we find the mean reaction time (that is, the sum of mean search time of the target by the reactants and the time taken to react).

The reaction can be written schematically as follows:



The rate law of this process is given by

$$\frac{dC_R(t)}{dt} = -k(t)C_T C_R(t). \quad (5)$$

Here, $C_R(t)$ is the time-dependent concentration of reactant molecules, $k(t)$ is the time-dependent rate constant, and C_T is considered as a time-invariant concentration (which is present in excess) of target molecules. Under these conditions, the rate law resembles that of a pseudo first-order reaction.³⁷ The general solution of Eq. (5) can be written as

$$S(t) = \frac{N(t)}{N(0)} = \frac{C_R(t)}{C_R(0)} = \exp\left\{-C_T \int_0^t k(t') dt'\right\}. \quad (6)$$

Here, $C_R(0)$ is the initial concentration of reactant molecules. $S(t)$ is known as the survival probability, which is the fraction of molecules unreacted at time t . In the short time limit, the rate constant is time-independent and the survival probability is exponential. However, in the long time limit, $S(t)$ becomes non-exponential and possesses a slowly decaying tail.

In order to obtain $S(t)$ and the mean reaction time, we solve Eq. (7)³⁸ for this system for the position and time-dependent probability $P(\mathbf{r}, t)$,

$$\frac{\partial P(\mathbf{r}, t)}{\partial t} = D[\nabla^2 - \beta F \nabla] P(\mathbf{r}, t). \quad (7)$$

Here, $F = \nabla U(r)$ is the force term, which is given as the gradient of potential energy $U(r)$, ∇^2 is the standard Laplacian operator, D is the diffusion coefficient, and β is the inverse of ($k_B T$). In the context of the present problem, $P(\mathbf{r}_0, t)$ can be thought of as the probability of a pair of particles to remain unreacted at time t given that their initial relative separation is \mathbf{r}_0 . The time-dependent survival probability can be obtained from $P(\mathbf{r}_0, t)$ by integrating over the spatial coordinates with an initial distribution of particles $w(\mathbf{r}_0)$,

$$S(t) = \int d\mathbf{r}_0 P(\mathbf{r}_0, t) w(\mathbf{r}_0). \quad (8)$$

Here $P(\mathbf{r}_0, t)$ must satisfy two conditions—(i) $P(\mathbf{r}_0, 0) = 1$, that is, in the beginning, the reactants remain unreacted; and (ii) $P(\mathbf{r}_0, \infty) = 0$, which depicts the certainty of reaction (i.e., annihilation/coalescence) in the infinite time limit. On the other hand, in order to obtain an expression for the time constant, we need to integrate $-t \frac{\partial}{\partial t} P(\mathbf{r}_0, t)$ with respect to time from 0 to ∞ ,

$$\tau(\mathbf{r}_0) = - \int_0^\infty dt t \frac{\partial}{\partial t} P(\mathbf{r}_0, t). \quad (9)$$

$\tau(\mathbf{r}_0)$ is known as the mean first passage time (MFPT) for a particle provided that the source is at \mathbf{r}_0 . Mean first passage time (MFPT), $\langle \tau \rangle$, for the entire system of particles with a certain spatial distribution $w(\mathbf{r}_0)$ can be expressed as^{1,39–41}

$$\int_0^\infty dt S(t) = \langle \tau \rangle = \int d\mathbf{r}_0 \tau(\mathbf{r}_0) w(\mathbf{r}_0). \quad (10)$$

Integrating Eq. (7) with respect to time (from 0 to ∞), by using the definition of $\tau(\mathbf{r}_0)$ given in Eq. (9) and by the consideration of the boundary conditions imposed on $P(\mathbf{r}_0, t)$, the following adjoint equation for $\tau(\mathbf{r}_0)$ can be obtained:^{1,42,43}

$$D \nabla [\nabla - \beta F] \tau(\mathbf{r}_0) = -1. \quad (11)$$

This equation can be analytically solved for certain forms of the force term (for example, simple harmonic motion) and an expression for the MFPT can be obtained. For simplicity, here we assume a free diffusion ($F = 0$). Below we separately treat two- and three-dimensional systems to obtain an expression for the mean reaction time.

A. Mean reaction time in a 2D droplet

In Fig. 2, we describe the model system in 2D. The reactant (at A, at $t = 0$) diffuses to a point B with a diffusion constant D_b in time τ_b . From B, it again diffuses with a surface diffusion constant D_s in order to find the target (CE) fixed at the north pole of the circle with an angular span of 2δ in time τ_s . If $\tau_R (= 1/k_{\text{intrinsic}})$ is the time required to react with the target,

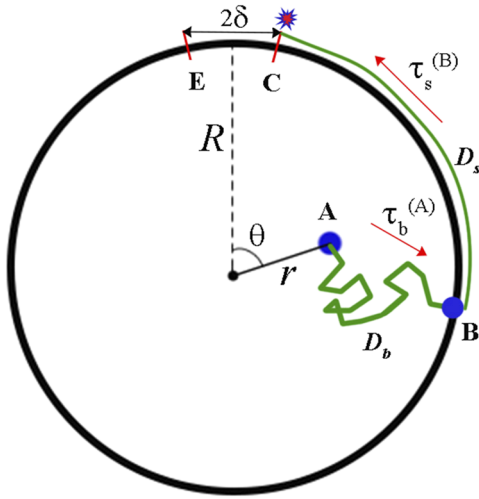


FIG. 2. The model system for reaction in a 2D droplet. R is the radius of the droplet. D_b and D_s are the diffusion coefficients of the reactant (blue dot) in the bulk and on the surface, respectively. Here, A is the source and the reactant exhibits random walk inside the bulk in order to reach a point B on the surface. From B, it again exhibits random walk to find the static target (either C or E) where it finally reacts (or annihilates). The target is a patch on the periphery of the surface with an angular span of 2δ . τ_b and τ_s are, respectively, the time required to reach at the surface starting from the bulk and to reach the target from a point on the surface.

the mean reaction time can be approximated as a sum of three different processes,

$$\langle \tau \rangle \approx \langle \tau_b \rangle + \langle \tau_s \rangle + \langle \tau_R \rangle$$

or

$$1/k_{tot} \approx 1/k_{b \rightarrow s} + 1/k_{s \rightarrow T} + 1/k_{intrinsic}. \quad (12)$$

Here we assume that τ_b and τ_s are not correlated; that is, the time required to reach the surface has no effect on the time required to reach the target starting from any point on the surface. We also assume that once a reactant molecule reaches the surface, it cannot diffuse back to the bulk. We write the adjoint backward equations in plane polar coordinates in the following way:^{30,40}

$$D_b \left\{ \frac{\partial^2}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r} \right\} \tau_b(r) = -1, \quad \tau_b(R) = 0, \quad (13)$$

$$D_s \left\{ \frac{1}{R^2} \frac{\partial^2}{\partial \theta^2} \right\} \tau_s(\theta) = -1, \quad \tau_s(\delta) = 0 = \tau_s(2\pi - \delta). \quad (14)$$

We solve Eq. (13) and arrive at the expression for $\tau_b(r)$. If we assume a uniform distribution of reactants in the circular area, then we can obtain the mean first passage time from the bulk to the surface in the following fashion:⁴⁴

$$\langle \tau_b \rangle = \frac{\int_0^R dr r \tau_b(r)}{\int_0^R dr r} = \frac{R^2}{8D_b}. \quad (15)$$

The solution of Eq. (14) with the appropriate boundary conditions yields

$$\tau_s(\theta) = -\frac{R^2}{2D_s} \theta^2 + \frac{\pi R^2}{D_s} \theta - \frac{R^2 \delta}{D_s} \left(\pi - \frac{\delta}{2} \right). \quad (16)$$

Hence, the mean first passage time of surface search, considering a uniform distribution of reactants along the periphery, becomes

$$\langle \tau_s \rangle = \frac{\int_{\delta}^{2\pi-\delta} \tau_s(\theta) d\theta}{\int_{\delta}^{2\pi-\delta} d\theta} = \frac{R^2}{D_s} \frac{\left(\frac{1}{3} \pi^3 - \pi^2 \delta + \pi \delta^2 - \frac{1}{3} \delta^3 \right)}{\pi - \delta}. \quad (17)$$

In the $\delta \rightarrow 0$ limit, that is, in the case of a point target, $\langle \tau_s \rangle = \frac{\pi^2 R^2}{3D_s}$. Hence, the expression of mean first passage time to search a point target fixed at the north pole reduces to

$$\langle \tau \rangle_{search}^{2D} = \frac{R^2}{8D_b} + \frac{\pi^2 R^2}{3D_s}. \quad (18)$$

Equation (18) is one of the key results of this paper which was earlier obtained by Voituriez *et al.*³⁰ It embodies several important features. First is the proportionality of the time to the square of the radius. As we show later, this R^2 dependence is preserved in three dimensions also. Second, the time is inversely proportional to the respective diffusion constants. The R^2/D dependence of mean first passage time had been discussed in several pioneering studies by Zwanzig,^{1,29} Szabo,⁴¹ Tachiya,^{35,42} Periasamy,⁴⁵ and others.^{30,40}

If the concentration of H_3O^+ ions (that is, the targets) is substantially high so that the targets (or reactive partners) are distributed over the entire periphery, the mean search time reduces essentially to $\frac{R^2}{8D_b}$, where surface searching is not required or the time taken for surface search is negligible compared to $\langle \tau_b \rangle$.

In order to incorporate the concentration dependence of the targets on the droplet surface, one can add another $(n - 1)$ targets on the surface at various positions along with that at the north pole. These additional targets make the target concentration increase by n -fold. Another way to realise the same is by increasing the angular span of the target patch on the north pole from 2δ to $2n\delta$.

B. Mean reaction time in a 3D droplet

In the case of 3D reaction systems, the model and scheme remain the same but with an additional degree of freedom. Again, we decouple the “search time” into two parts: (i) time taken to go to the surface ($r = R$ for any θ and ϕ), τ_b , and (ii) time taken to search the surface for a target patch fixed at the north pole ($\theta \in [0, \delta]$ for any ϕ), τ_s . Here θ is the zenith angle which can vary from δ to π ($\theta = \pi$ being the farthest from the target) and ϕ is the azimuthal angle that spans from 0 to 2π . Clearly the adjoint equation that involves τ_b should only depend on radial coordinates as follows:

$$D_b \left\{ \frac{\partial^2}{\partial r^2} + \frac{2}{r} \frac{\partial}{\partial r} \right\} \tau_b(r) = -1, \quad \tau_b(R) = 0. \quad (19)$$

On the other hand, the same kind of equation for surface search should only involve θ dependence as the target can be found for any values of ϕ ,

$$\frac{D_s}{R^2} \left[\frac{\partial^2}{\partial \theta^2} + \cot \theta \frac{\partial}{\partial \theta} \right] \tau_s(\theta) = -1, \quad \tau_s(\delta) = 0. \quad (20)$$

The solution of Eq. (19) yields the mean first passage time from the bulk to the surface,⁴⁰ considering a uniform initial distribution, as

$$\langle \tau_b \rangle = \frac{\int_0^R dr \, r^2 \tau_b(r)}{\int_0^R dr \, r^2} = \frac{R^2}{15D_b}. \quad (21)$$

We solve Eq. (20) using the condition that $\tau_s(\delta) = 0$ in order to obtain the following expression of $\tau_s(\theta, \delta)$:⁴⁶

$$\tau_s(\theta, \delta) = 2 \frac{R^2}{D_s} \ln \left| \frac{\sin \frac{\theta}{2}}{\sin \frac{\delta}{2}} \right|. \quad (22)$$

As described above, the mean search time can be obtained by integrating over the angular coordinates by considering a uniform initial distribution of reactants on the surface as follows:

$$\begin{aligned} \langle \tau_s(\delta) \rangle &= \frac{\int_0^\delta d\theta \sin \theta \tau_s(\theta, \delta)}{\int_0^\delta d\theta \sin \theta} \\ &= -\frac{R^2}{D_s(1 + \cos \delta)} \left[4 \ln \left| \sin \left(\frac{\delta}{2} \right) \right| + \cos \delta + 1 \right]. \end{aligned} \quad (23)$$

In the case of Eq. (23),^{46,47} we can obtain an asymptotic expression for the point target, that is, in the $\delta \rightarrow 0$ limit. Hence, in 3D, the mean search time for an infinitesimally small target can be expressed as

$$\langle \tau \rangle_{search}^{3D} = \frac{R^2}{15D_b} + \frac{R^2}{D_s} \left[2 \ln \left(\frac{2}{\delta} \right) - 1 \right]. \quad (24)$$

Equations (18) and (24) provide the mean search time in order to find a reactive target. The reaction consumes a finite time to occur. And there is a finite probability for the occurrence. *Not every visit to the target might result in a reaction.* In order to incorporate this correction, one needs to solve the diffusion equations with respect to the additional constraint, that is, $\frac{\partial \tau_s}{\partial \theta} \Big|_{\theta=\delta} = \frac{\lambda}{D_s} \tau_s$.^{41,42} In the limit of $\lambda \rightarrow \infty$ (also known as the Smoluchowski limit), the problem reduces to the absorptive boundary condition, which means the reactants react whenever they come in contact.

V. QUANTUM CHEMICAL EXPLANATION OF THE INTRINSIC RATE ENHANCEMENT

In Sec. IV, we concentrated on the mean search time. But the third term in Eq. (12) has not been considered. However, the third term is crucial in order to depict the whole process as a diffusion-controlled process. If the intrinsic reaction rate is faster than the mean search time, diffusion becomes the rate-determining process. On the other hand, if the activation barrier of the reaction is high, the intrinsic reaction time becomes the rate-determining step and diffusion becomes less important. However, because of the R^2 dependence of mean search time, in the case of larger droplets, diffusion plays a pivotal role. We note that not all reactions can be accelerated in microdroplet reactions.¹⁴

In this section, we study the effect of the presence of excess charge in the neighborhood in the bond dissociation energy of ether bonds and estimate the activation barrier in methoxyethane by performing quantum chemical calculation using second-order Møller–Plesset (MP2) perturbation theory⁴⁸ with an aug-cc-pVTZ⁴⁹ basis set. All the calculations are done using the Gaussian 09 software package.⁵⁰ To begin with, we first optimize the geometry of methoxyethane with a hydronium ion. Then, with the optimized structure of methoxyethane, we scan along the Me–O bond (shown in Fig. 3) in order to get the potential energy surface (PES) in the presence and absence of hydronium ions. In Fig. 3, we show the PES along the Me–O bond scan coordinate both in the presence and absence of hydronium ions. It is clear from the figure that the presence of hydronium weakens the bond and facilitates the bond breaking process. In the presence of hydronium ions the bonds (Me–O) dissociation energy (D_e) becomes $\sim 30\%$ less than that observed in the absence of hydronium ions (Fig. 4).

Here, we investigate an exemplary reaction in order to obtain the intrinsic reaction rate. We study the acid hydrolysis of ethyl methyl ether. It is a well-known two-step process. The first step is the protonation of the ether oxygen, and the second step is the nucleophilic substitution by a water molecule. Out of these two, the second step is the rate-determining step (Fig. 5). This step is associated with an activation barrier of ~ 19.6 kcal/mol. From this value, we can calculate the rate constant of this process by using the rate expression obtained from transition state theory [Eq. (25)],⁵¹

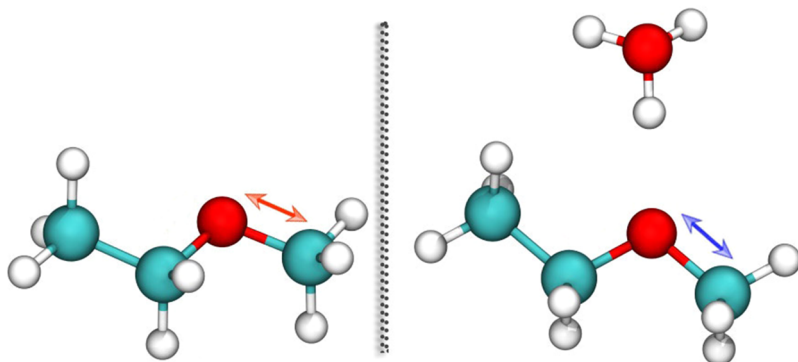


FIG. 3. Definition of scan coordinates along Me–O without hydronium ions (red arrow) and in the presence of hydronium ions (blue arrow). The potential energy surface along this reaction coordinate is generated by relaxed scans of the O–Me bond with 0.1 Å grids.

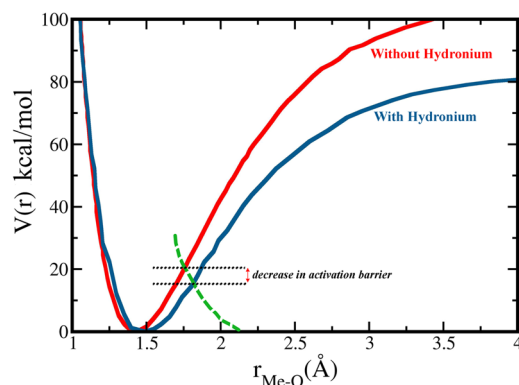


FIG. 4. Potential energy scan using second-order Møller–Plesset (MP2) perturbation theory with the aug-cc-pVTZ basis set in the presence and absence of hydronium ions. The scan coordinate is along the Me–O bond. All the data sets are fitted to the Morse potential form and shown by solid lines. The green dashed line schematically (and not exact) represents the potential energy surface of the products. Because of the lower bond dissociation energy, the crossing point (tentatively the location of the transition state on the potential energy surface) becomes of lower energy. Hence the activation barrier is reduced by more than ~ 4 –5 kcal/mol.

$$k = \frac{k_B T}{h} e^{-\left(\frac{\Delta G^\ddagger}{k_B T}\right)}. \quad (25)$$

According to the above equation, $k = 0.027 \text{ s}^{-1}$ for this reaction.

It is known that a large electric field of the order of millions of volts per centimetre exists near the droplet–air interface. In order to investigate the influence of such a strong electric field gradient on the rate of bond breaking, we perform gas-phase model quantum calculations using DFT with B3LYP functional and 6-311G + (d, p) basis set⁵² with a static dipolar electric field acting on the molecule from the positive X direction to obtain the effects of the field. Previous studies show that the presence of an external

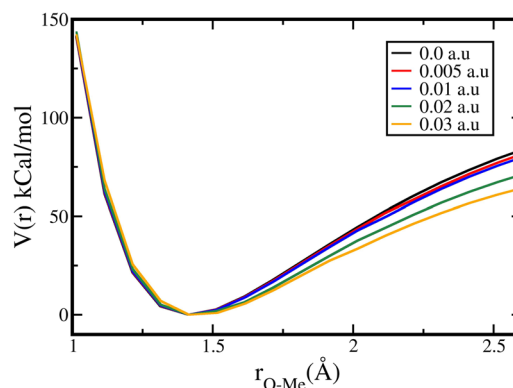


FIG. 6. Potential energy plots of ethyl methyl ether as a function of O–Me bond distance with various electric fields along the positive X direction. The units of the electric fields are given in atomic units ($1 \text{ a.u.} = 5.14 \times 10^9 \text{ V/cm}$). The bond dissociation energy decreases as the strength of the electric field is increased which in turn facilitates the bond breaking and hence accelerates the intrinsic reaction. [The data are scaled to zero with respect to the minima for comparison.]

electric field can activate small unreactive molecules like hydrogen.^{53,54}

We again perform relaxed coordinate scans (starting from 1 Å to 5 Å with 0.1 Å increments) for the O–Me bond present in ethyl-methyl ether; that is, the system is optimized at each point of the scan. The corresponding plots with various strengths of electric fields (0.0 a.u., 0.005 a.u., 0.01 a.u., 0.02 a.u., and 0.03 a.u.) are shown in Fig. 6. From this figure, it is clear that the presence of a static electric field can substantially weaken the O–Me bond in ethyl-methyl ether. Because of this weakening, the activation barrier decreases further and the reaction acquires additional acceleration.

VI. BROWNIAN DYNAMICS SIMULATION

We next employ the Brownian dynamics simulation technique to numerically obtain the mean search time (MST) of a target by reactants uniformly distributed inside a droplet in two and three dimensions.⁵⁵ We use the well-known Brownian diffusion equation (26) in order to propagate the particle positions as follows:

$$\vec{r}_i(t + \Delta t) = \vec{r}_i(t) + \frac{\vec{F}_i(t)}{\zeta} \Delta t + \vec{R}_i(\Delta t). \quad (26)$$

We note that the hydrodynamics interactions are neglected in Eq. (26). Here $\vec{r}_i(t)$ is the position of the i^{th} particle at time t and $\vec{r}_i(t + \Delta t)$ is the position after Δt time. $\vec{F}_i(t)$ is the total force experienced by the i^{th} particle at time t . ζ is the coefficient of friction given by Stokes' law as $\zeta = 6\pi\eta r_H$, where η is the coefficient of viscosity and r_H is the hydrodynamic radius of the molecule.^{3,56} The Stokes-Einstein formula relates the coefficient of friction to the temperature of the system and the diffusion coefficient of the molecule as $D = \frac{k_B T}{\zeta}$. $R_i(\Delta t)$ is the random displacement in the form of white noise with a mean value of zero and a covariance of $\frac{2k_B T}{\zeta} \Delta t$. The Brownian dynamics simulations are performed using an in-house code in reduced units. We use the following parameters in the simulation for ethyl-methyl ether: $\sigma = 6.4 \text{ Å}$, $\epsilon = 1 \text{ kcal/mol}$, $m = 60.1 \text{ g mol}^{-1}$, $T = 298 \text{ K}$, and $D = 7.71 \times 10^{-6} \text{ cm}^2/\text{s}$.⁵⁷

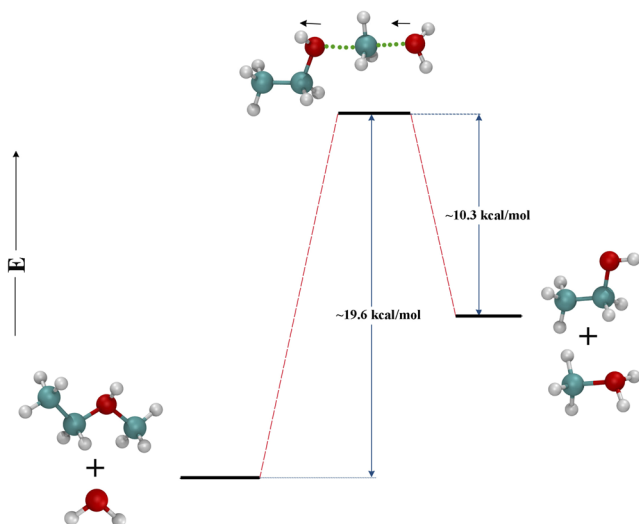


FIG. 5. Energetics of the rate-determining step of ethyl-methyl ether hydrolysis in an acidic medium. One water molecule (here, acting as a nucleophile) attacks the methyl carbon and produces an ethanol molecule along with a protonated methanol. The energy barrier of this process is calculated to be $\sim 19.6 \text{ kcal/mol}$.

TABLE I. Mean search time for 2D and 3D droplets of three different radii. The total search time is represented as the sum of two search times, that is, from the bulk to the surface and from the surface to the target. The results obtained show a quantitative match with the analytical expressions.

Radius of the droplet (nm)	Mean first passage time (from bulk to surface), $\langle\tau_b\rangle$ ns		Mean first passage time (from surface to target), $\langle\tau_s\rangle$ ns		Mean search time (ns) $\langle\tau\rangle_{\text{search}} = \langle\tau_b\rangle + \langle\tau_s\rangle$	
	Simulation	Theory	Simulation	Theory	Simulation	Theory
Two-dimensional circular droplet						
3.2	1.69	1.66	20.62	21.82	22.31	23.48
6.4	6.62	6.64	86.98	87.24	93.6	93.88
12.8	25.6	26.6	348.14	349.14	373.74	375.74
Three-dimensional spherical droplet						
3.2	0.84	0.88	35.2	39.5	36.04	40.38
6.4	3.42	3.59	142.5	158.1	145.9	161.7
12.8	13.4	14.2	620.5	632.4	633.9	646.6

Here σ and ϵ are Lennard-Jones parameters for length and energy, respectively.

We have taken 1000 non-interacting particles that are uniformly distributed inside a circular (in the case of 2D) and spherical (in the case of 3D) droplet. Hence, the particles are non-interacting, that is, freely diffusing. We obtain the mean search time of a target of angular span 2δ by the particles, as described in Fig. 2.

Similar to the analytical treatment, we decouple the search time into the time required for two uncorrelated processes. In the first step, a particle reaches any part on the surface by means

of bulk diffusion, irrespective of the position of the target. In the second step, particles on the surface exhibit surface diffusion with a higher diffusion coefficient (approximately twice) than that of the bulk in order to reach a target. The mean search time can be expressed as the sum of these two time scales. In Table I, we provide the results for 2D and 3D droplets of three different radii. The target patch is taken to be 2.0 \AA wide on the surface.

The survival probabilities obtained from simulations show non-exponential characteristics. $S(t)$ for core-to-surface diffusion is found to be bi-exponential with two distinct time

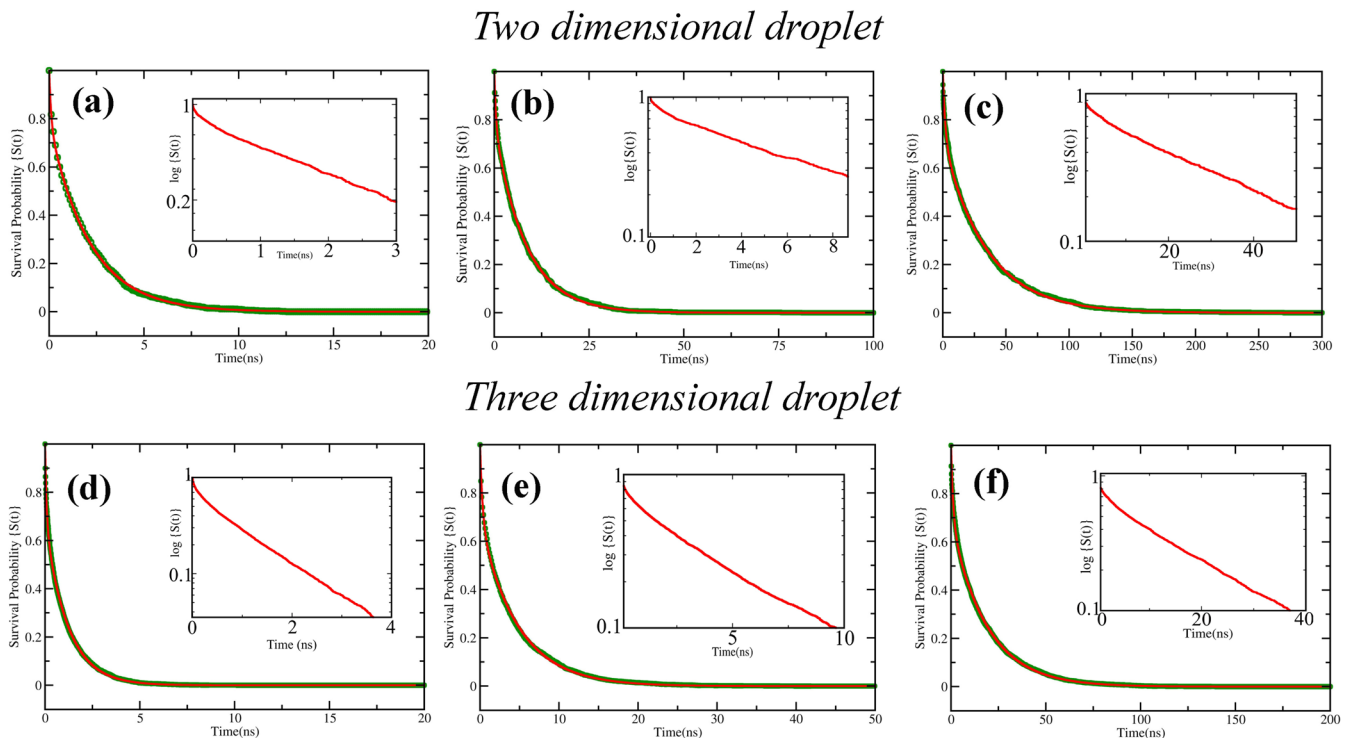


FIG. 7. Survival probability of bulk excursion against time for 2D and 3D droplets of three different radii. (a)–(c) are for $R = 3.2 \text{ nm}$, 6.4 nm , and 12.8 nm , respectively, for a two-dimensional droplet. (d)–(f) are for $R = 3.2 \text{ nm}$, 6.4 nm , and 12.8 nm , respectively, for a three-dimensional droplet. In the insets, the corresponding semi-logarithmic plots are shown.

TABLE II. Multi-exponential fitting parameters of the survival probability vs time plots in two- and three-dimensional droplets.

Radius of the droplet (nm)	Correlation coefficient	a_1	τ_1 (ns)	a_2	τ_2 (ns)
2D BD simulation of bulk excursion					
3.2	0.9996	0.22	0.103	0.78	2.14
6.4	0.9997	0.23	0.460	0.77	8.28
12.8	0.9996	0.29	1.984	0.71	34.58
3D BD simulation of bulk excursion					
3.2	0.9995	0.31	0.079	0.69	1.18
6.4	0.9994	0.31	0.326	0.69	4.81
12.8	0.9996	0.31	1.14	0.69	18.923

TABLE III. Multi-exponential fitting parameters for survival probability of surface search in two- and three-dimensional droplets.

Radius of the droplet (nm)	Correlation coefficient	a_1	τ_1 (ns)	a_2	τ_2 (ns)
2D BD simulation of surface search					
3.2	0.9998	0.19	1.13	0.81	25.01
6.4	0.9994	0.18	4.37	0.82	103.73
12.8	0.9998	0.20	23.57	0.80	423.70
3D BD simulation of surface search					
3.2	0.9995	0.10	11.45	0.90	37.90
6.4	0.9994	0.09	56.78	0.91	151.3
12.8	0.9996	0.08	100.01	0.92	592.86

scales. The plots are shown in Fig. 7 for both 2D and 3D droplets. In Table II, we show the fitting parameters of the marked non-exponential decay of survival probability with time in the case of two- and three-dimensional droplets.

A particle that is already present on the surface further undergoes surface diffusion (associated with a larger coefficient of diffusion) to find a target. We show the survival probability plots of surface search in the case of 2D and 3D droplets in Fig. 8 and provide the corresponding fitting parameters in Table III.

If the reactive partner (or trap) resides inside the droplet, the adjoint equation cannot be decoupled into radial and angular parts. In that case, the first passage time becomes dependent on both r and θ . Hence, the corresponding adjoint equation in

2D becomes

$$D \left[\frac{\partial^2}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r} + \frac{1}{r^2} \frac{\partial^2}{\partial \theta^2} \right] \tau(r, \theta) = -1, \quad (27)$$

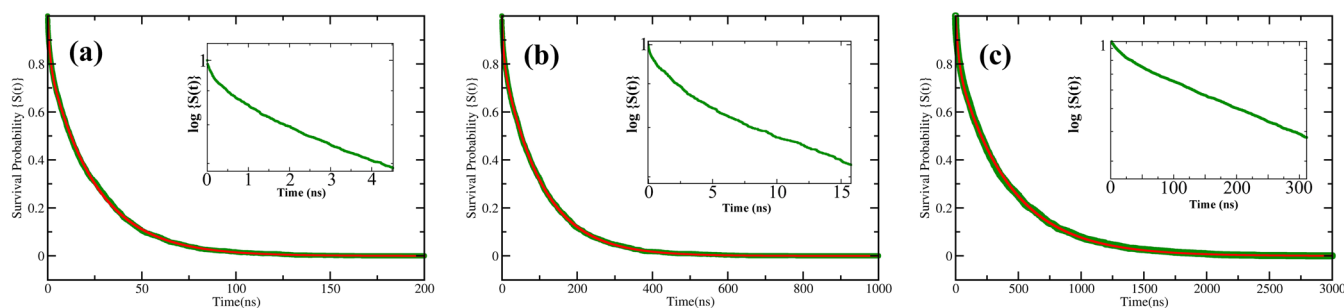
$$\tau(r, \theta) = 0 \quad \text{when } r = r' \text{ and } \theta \in [\delta, 2\pi - \delta],$$

where the target has the same angular span of 2δ but now residing at $r = r'$ (and $r' < R$) and D is the relative diffusion coefficient of the reactant molecules. Similarly, in three dimensions, the equation acquires the following form:

$$D \left[\frac{\partial^2}{\partial r^2} + \frac{2}{r} \frac{\partial}{\partial r} + \frac{1}{r^2} \left\{ \frac{\partial^2}{\partial \theta^2} + \cot \theta \frac{\partial}{\partial \theta} \right\} \right] \tau(r, \theta) = -1, \quad (28)$$

$$\tau(r, \theta) = 0 \quad \text{when } r = r' \text{ and } \theta \in [0, \delta] \forall \phi.$$

Two dimensional surface search



Three dimensional surface search

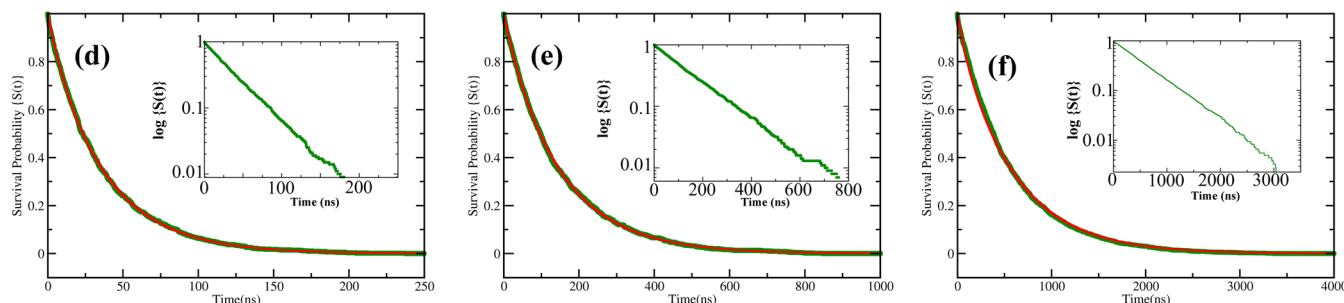


FIG. 8. Plots showing survival probabilities of target search on the droplet surface against time for 2D and 3D droplets of three different radii. (a)–(c) are for $R = 3.2$ nm, 6.4 nm, and 12.8 nm, respectively, for a two-dimensional droplet. (d)–(f) are for $R = 3.2$ nm, 6.4 nm, and 12.8 nm, respectively, for a three-dimensional droplet. In the insets, the corresponding semi-logarithmic plots are shown.

TABLE IV. Comparison between mean search times for the target residing in the bulk of the droplet and on the surface. The search time is always higher when the target is inside the droplet and the difference grows as the size of the droplet increases in both two and three dimensions.

Radius of the droplet (nm)	Mean search time of the surface target (ns)	Mean search time of the bulk target (ns)
Bulk target search in two dimensions		
3.2	22.3	115.8
6.4	93.6	671.5
12.8	373.7	6431.5
Bulk target search in three dimensions		
3.2	36.0	51.9
6.4	145.9	425.7
12.8	633.9	4896.6

We numerically solve these equations using BD simulation as described above and evaluate the mean first passage time to a bulk target starting from uniform distributions of 1000 particles. We take targets of similar dimensions and employ reflective boundary conditions at the surface of the droplets. We compare the results with the ones mediated by surface search and present the results in Table IV.

It is clear that the reactant particles consume more time when the target search is not mediated by a surface search with negligible re-entrance.

VII. CONCLUSION

The aqueous droplets are omnipresent in nature, ranging from atmospheric science to biological systems. For example, they are found in aerosols, micelles, and vesicles. It has been known for a long time that many reactions unfavourable in the bulk become feasible when performed in aqueous droplets. In recent experimental studies, such droplets of various sizes have been created by electrospray. Nam *et al.* recently showed, by examining the phosphorylation of sugar on charged and uncharged microdroplets, that the reason lies in the change in entropy of the reactions.⁵⁸ In microdroplet systems, reactions occur spontaneously because the entropic barrier can be overcome at the surface. This might in turn change the free energy of reaction from a positive to a negative value.^{58,59} This entropic barrier is large in the bulk due to the low probability of encounter between the reactants. An equally important factor is the influence of charges produced during the preparation of the microdroplets.

In this work, we calculate the mean reaction time by considering the entire process as a combination of several uncorrelated events. We show that the mean search time (MST) exhibits an interesting quadratic dependence on the radius of the droplet and inverse proportionality with the diffusion constant. Reduction in the reaction time occurs because of the reduction in the diffusion space from d to $d - 1$ when the reactants diffuse from the bulk to the surface of the droplet. With the help of Brownian dynamics simulations, we show that surface-mediated search is always less time consuming than a sole bulk target search. This contributes to the acceleration when majority of the targets reside on the surface. We

also find that the presence of an ion in the neighbourhood or a static unidirectional dipolar electric field substantially weakens a bond by ~ 5 –10 kcal/mol. The last two can combine to lead to further weakening of the bond. All these factors when combined together give rise to a large net increment in the overall rate of the reactions.

However, we must point out that reactions which are intrinsically slow (that is, where the intrinsic reaction rate becomes the rate-determining step) may not exhibit this accelerated kinetics. Therefore the observation of the acceleration depends on the two combined factors: weakening of the bond and decreased search time on the surface.

Finally, we conjecture that the environment of the air-surface interface sufficiently differs from that in the interior of the droplet and we can expect some reactions in droplets to be completely different from those observed in bulk solution.

ACKNOWLEDGMENTS

We thank the Department of Science and Technology, India, for providing partial funding (Grant No. DST01439) for this project. B.B. thanks the Sir J. C. Bose fellowship. S. Mondal thanks University Grants Commission, India, for providing research fellowship. S. Acharya thanks IISc, Bangalore, for financial assistance. R. N. Zare expresses his gratitude for a visiting professorship at IISc.

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