Extending the scope of ‘in silico experiments’: Theoretical approaches for the investigation of reaction mechanisms, nucleation events and phase transitions

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Abstract

The investigation of the atomistic mechanisms of processes in complex systems constitutes a major challenge to both theory and experiment. While experimental studies offer a wide variety of insights at the macroscopic scale, the atomistic level of detail often remains elusive. On the other hand, molecular simulation approaches may easily achieve microscopic resolution and hence appear particularly suited for detailed mechanistic analyses. However, the computational effort is typically quite considerable and in many cases special simulation strategies are needed to make simulations possible. This review is dedicated to special approaches for tackling the time/length-scale problem inherent to molecular dynamics simulations. Employing these techniques opened a series of new perspectives. The latter are illustrated with the example of recent simulation studies of the atomistic mechanisms involved in complex processes like crystal nucleation, phase transitions and reactions in solution. Along this line, we discuss the reaction mechanisms for He insertion into C\textsubscript{60} fullerenes, nucleation events and domain morphogenesis in pressure-induced phase transitions in solids and ion aggregation from solution.

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1. Introduction

The dramatic progress in computational materials science, soft matter, physical chemistry and chemical physics is based on two very favorable developments. While computer simulations clearly benefit from increasingly fast hardware, a large part of the success of the computational sciences may be attributed to methods developments. This particularly applies to molecular dynamics simulations that have evolved to a valuable tool for mechanistic studies of atomistic model systems.

Nowadays, advanced molecular dynamics simulation approaches allow tackling complex processes in model systems counting millions of atoms. In such large model systems, the computational demand is not only caused by the evaluation of a specific atomic arrangement, but is also related to the immense configurational manifold arising from the large number of particles. This particularly applies to processes, which involve the crossing of rare intermediate states. Their investigation is complicated by the necessity of scanning a large number of possible arrangements in order to find the transition state(s). In molecular dynamics simulations, this implies long ‘waiting’ times, before the event of interest actually occurs. These waiting periods may easily exceed the scope even of sophisticated hardware by several orders of magnitude, hence making the observation of many processes from direct simulation practically impossible.

In an attempt to circumvent this problem, two major approaches have emerged over the past decades. The most
straightforward ansatz is to enhance the kinetics of rare events by applying elevated temperature, pressure or strong super-concentration of a particular molecular species. While in principle this strategy helps crossing any reaction barrier, the stronger the artificial process acceleration chosen, the more carefully the results have to be considered. Excessive driving may easily lead to the skipping of important intermediates or even cause the system to follow completely different mechanistic routes. Similar limitations are related to the widely used approach of applying external driving forces. This method is based on the choice of a presumed reaction coordinate. The desired process is then induced by artificial potentials or constraints, which are functions of this coordinate. As a consequence, the mechanistic analysis may only be given in terms of predefined models of the reaction coordinate. In principle, this limitation may be overcome by performing several independent investigations based on various mechanistic models. However, in complex systems the number of putative mechanistic routes typically is too large to account for all eventualities.

Many of the limitations described above may be overcome by the transition path sampling method, recently introduced by David Chandler and coworkers [1,2]. This novel approach focuses the molecular dynamics simulations related to a rare event on the relatively short time interval in which the process of interest takes place. In this way, the waiting period required for observation from unconstrained simulations may be completely ignored. In this contribution, we describe methodic developments and applications of the transition path sampling scheme revisiting recent simulation studies of reactions in complex systems, phase transitions and crystal aggregation. Each of these case studies is triggered by the crossing of a major energy barrier larger than \( k_B T \). Apart from rare transition events, we also investigate a different class of slow processes: crystal formation from dilute solution. This process is diffusion controlled, i.e., it is slowed down by random walks over small (but many) energy barriers (Scheme 1, right). While transition path sampling performs excellently for single barrier crossing (Scheme 1, left), the tackling of diffusion-controlled crystal formation requires a different approach. We therefore developed a specialized method for mimicking aggregate growth from dilute solutions.

In the present contribution, we will address both types of slow processes indicated in Scheme 1. Along this line, different approaches to molecular dynamics simulations are demonstrated by reviewing recent studies which may be taken as exemplary for the discussed specific aspects of slow processes. Tackling single barrier crossing events (left-hand side of Scheme 1) by means of transition path sampling molecular dynamics simulations is illustrated by the example of pressure-induced helium incorporation in \( C_{60} \) fullerenes. The perspectives of assessing unbiased mechanistic investigations by means of transition path sampling are then demonstrated with the example of solid–solid phase transitions. Going far beyond classical nucleation theory, our simulations allow the study of coexisting nucleation centers leading to single crystal fragmentation in multiple domains. Finally, the limitations of the transition path sampling method are illustrated by our work on crystal nucleation from solution, and a recently developed aggregate growth model is discussed as an alternative. The latter uses the specific character of diffusive processes during ion aggregation corresponding to energy profiles as indicated on the right-hand side of Scheme 1.

2. Transition path sampling of reactions in complex systems

The basic concepts of the transition path sampling approach may be illustrated by the example of rare reaction events. While there are a large number of such studies in the literature [3–17], in this section the focus is set to our recent work on helium incorporation in \( C_{60} \) fullerenes [13]. Despite its apparent simplicity, the formation of endohedral fullerenes may be taken as exemplary for the crossing of a large reaction barrier in a complex system.

The manifold of possible mechanisms for the insertion of noble gas atoms in fullerenes may be divided into two classes. Provided a sufficiently large momentum, single noble gas atoms may directly pass through one of the 5 or 6 rings of the fullerene. Such ring permeation was investigated by both high-energy bombardment experiments [18,19] and theory [20,21]. The related energy barrier of about 10 eV may be reduced drastically by preparing a high-pressure/high-temperature setup in an autoclave. From such experiments of fullerenes in a helium atmosphere, Saunders et al. observed the formation of He at \( C_{60} \) by crossing a reaction barrier of only 3.5 eV [22]. This change in activation energy must be related to a change in the helium incorporation mechanism. Saunders et al. therefore proposed that some bonds of the \( C_{60} \) molecule could temporarily break and thus open a ‘window’ which would facilitate the diffusion of a gas atom into the fullerene [22,23].

In order to explore how such a window actually looks like, Patchkovskii and Thiel investigated as many as 21 different insertion pathways on the basis of minimum energy path calculations [24]. However, the corresponding
reaction barriers were estimated as 9 eV or higher, indicating that none of the investigated pathways turned out to be realistic. The manifold of possible windows of C\textsubscript{60} is quite large: Patchkovskii and Thiel prepared reaction routes according to 5- or 6-ring permeation after dissociation of 0, 1 or 2 C–C bonds, respectively. Considering the temporary breaking of more bonds increases the manifold of pathways even further. For complex systems it is generally quite inefficient to scan for all possible reaction routes, and applying the transition path sampling scheme becomes particularly favorable. The transition path sampling iterations may be started from an arbitrarily chosen reaction route. In the course of the trajectory sampling process, this pathway will be rectified without any bias from predefining a reaction coordinate or using strong thermodynamic driving.

Mimicking the autoclave setup of Saunders et al., we performed a mixed quantum/classical molecular dynamics study of a single C\textsubscript{60} molecule in a gas bath of 1000 helium atoms. An initial helium insertion trajectory was prepared according to 6-ring permeation without window formation. While we already knew that this insertion route is unfavorable, we used the path sampling algorithm to explore the evolution of helium insertion trajectories to the preferred mechanism. Along this line, the reaction barrier changed from 10 to 5 ± 1 eV and the trajectories converged to the window mechanism. The latter involves the opening of three C–C bonds to facilitate the incorporation of a helium atom.

This example reflects a process that requires the crossing of a ‘rough’ landscape of free energy barriers as illustrated in Fig. 1. As a prerequisite to transition path sampling iterations, a starting trajectory of the rare event is needed. The initial route does not need to be a favorable one and is typically prepared artificially. During the path sampling iterations, a snapshot is taken from the preceding transition pathway and slight changes are incorporated. The modified configuration is then propagated in both directions of time and the resulting trajectory is checked for the process of interest. In case the desired event takes place, the new trajectory is chosen for generating further ones. Harvesting in an iterative manner leads to a manifold of dynamical pathways, each reflecting a possible transition route.

The sampling of transition pathways reflects a Monte-Carlo simulation in trajectory space and—after convergence—the likeliness of a specific reaction mechanism may directly be related to its occurrence in the manifold of transition routes. The mechanistic analysis is not biased from predefinitions, but may instead be derived as a direct result from the simulations. This feature makes transition path sampling a very powerful tool for investigating reaction mechanisms from molecular dynamics simulations [25].

In many cases, less preferred mechanisms are related to considerably larger barriers and appear only extremely rare during conventional transition path sampling. However, the analysis of all reaction routes may be accomplished from biasing transition path sampling [17]. Along this line, we first explore the preferred reaction route. After its characterization the favored route is avoided by biasing the sampling of trajectories. As a consequence, the pathways then evolve to an alternative mechanism. Repeating this procedure allows assessing all possible reaction routes. This issue and other technical aspects like systematic strategies for the preparation of initial transition trajectories are reviewed in Ref. [25].

Transition path sampling may be combined with all variations of molecular dynamics simulations, including classical, mixed quantum/classical and ab-initio approaches. The study of complex processes like reactions in solution typically requires large numbers of atoms. In such cases, assessing the reaction coordinate is far from trivial and unbiased simulation approaches like transition path sampling are particularly appealing. While chemical intuition allows guessing the most relevant degrees of freedom for many reactions, the example of helium incorporation in fullerene molecules shows the limitations of relying on intuition only. This problem is even more eminent when other types of rare events in complex systems are investigated for which less experience is available. Unlike chemical reactions, much less is known about the atomistic mechanisms of phase transitions and crystal aggregation processes. This particularly applies to the very early stage of nucleation events as discussed in the following.

3. Exploring the atomistic mechanisms of phase transitions

The majority of theoretical approaches to the investigation of solid–solid transformations are based on static models, in which the atomic configurations are interpolated from a limiting structure to the other. The commonly used models imply a concerted movement involving all atoms. Indeed, the typical setup is that of the smallest possible
common cell (usually a single unit cell) with periodic boundary conditions. Therein, the atomic positions are continuously modified as a function of an interpolation variable. The underlying interpolation scheme is based on a predefined geometric model, which may be derived from a prejudiced choice of the respective orientation of the crystal. While such approaches allow the investigation of the mechanisms describing the overall displacement of the atoms, the direct observation of local processes like nucleation and growth remains elusive.

Second-order phase transitions imply very small atomic displacements and proceed continuously. While this picture directly corresponds to the collective atomic displacement inherent to unit cell transformation models, a dramatically different situation is encountered in first-order phase transitions. Reconstructive phase transitions imply strain and may involve large atomic displacements. Unlike second-order phase transitions, the space groups of the two crystalline structures connected by a reconstructive phase transition are in general not in the relation of a group and a direct subgroup, thereby preventing classical Landau theory to be applied [26]. As a consequence, first-order phase transitions do not exhibit collective atomic displacements and are instead characterized by nucleation and growth.

Despite this fact, a large number of studies rely on geometric models in terms of a pseudo-second-order approach. Therein the collective interpolation models are assumed to hold locally. Depending on the nature of the investigated material, the atomic arrangement may change smoothly from one phase domain to the other and ‘pseudo-second-order’ approaches can be applied. However, in case of sharp phase interfaces this picture represents a conceptual mistake, which can seriously bias the mechanistic analysis. It is reasonable to assume that the latter issue becomes of increasing relevance the more the phase transition is dominated by first-order characteristics.

The investigation of the atomistic mechanisms of first-order phase transitions constitutes a major challenge to both theory and experiment. First-order phase transitions are connected to very local events and a detailed mechanistic analysis requires in-situ methods allowing investigations at the atomic level and of fs-to-ps resolution in the time scale. Molecular dynamics simulations, in principle, offer such insights and are hence particularly appealing for mechanistic studies such as the exploration of nucleation processes.

In analogy to the formation of energetically unfavorable reaction intermediates, nucleation processes are also triggered by the crossing of activation barriers. At the very early stage of domain formation, the nuclei comprise very few atoms and practically the whole nucleus consists of phase interfaces. Unlike the stable phase domains, the respective interfaces reflect unfavorable atomic arrangements and account for an increase in free energy. This disfavoring is compensated only after crossing the nucleation barrier, i.e., when the gain in free energy caused by the formation of phase domains of lower chemical potential becomes dominant.

The competition of these two energy terms may be denoted in terms of classical nucleation theory whose implementation to specific systems typically relies on a series of simplifications. Along this line, the transformation is assumed to originate in a single nucleus and the manifold of possible transition states is reduced to a single configuration, i.e., the critical nucleus. In the mainframe of classical nucleation theory, the shape of the nuclei must be predefined and is usually taken to be spherical. The energy cost related to the formation of phase interfaces is then computed on the basis of prejudiced phase morphologies.

Many of the limitations related to this approach to first-order phase transitions may be overcome by employing the transition path sampling method. In this field, constant temperature/constant pressure molecular dynamics simulations—combined with the transition path sampling technique—opened a series of new insights into nucleation and growth events. It allows direct evidence on the nucleation processes and the structure of the underlying phase interfaces without any of the predefinitions described above. Since 2004, a series of transition path sampling molecular dynamics simulations of phase transitions have been reported in the literature [27–35]. While the latter comprise many types of first-order phase transitions (boiling, melting, etc.), in the present contribution we shall focus on two exemplary studies only.

The perspectives for the investigation of local nucleation events may be very nicely illustrated from our work on pressure-induced solid–solid transformations of NaCl [29]. This study revealed that nucleation events of structural transitions in solids may occur as locally as one could imagine: by the displacement of a single atom. The transformation of the NaCl model system from the NaCl-type structure to the CsCl-type structure is illustrated in Fig. 2. Therein the phase interfaces may be identified as layers of ions in which the ions are arranged in coordination polyhedra known from the α-TII-type structure.

Extending our studies of pressure-induced phase transitions to further alkali halides, we always observed particularly pronounced first-order characteristics reflected by sharp phase fronts and very local nucleation events. Such phase transitions are related to large hystereses effects and high activation barriers. For this class of systems, conventional molecular dynamics simulation approaches relying on artificial driving forces have to be considered with caution. Too strong driving causes the transformation to overrun nucleation and subsequent phase growth and reflect a collective (second-order type) collapse of the system [30,34]. On the other hand, transition path sampling studies may be implemented without artificial driving forces at all. Only by benefiting from this feature could we obtain such detailed insights like material-dependent domain morphogenesis and polysynthetic twinning arising from coexisting nuclei as described in the following.
While the overall mechanism of the pressure-induced phase transition of KF is identical to the one found for NaCl, striking differences emerge in the characteristics of nucleation and growth. In NaCl, layers of ions are shifted by half of the Na–Na distance under fast formation of a two-dimensional interface that propagates orthogonal to the shifting layers at a slower pace. In KF, the overall rearrangement of ionic layers is the same; however, they are not moved as an entity, but by subsequent displacement of columns of ions. In contrast to the rectangular phase domains observed for NaCl, in KF cylindrical domain shapes are preferred. Moreover, the density of nucleation centers is particularly high and even in small simulation boxes of a few (nm)$^3$ multiple nucleation centers are observed.

The transformation from the CsCl-type structure to the NaCl-type structure is illustrated in Fig. 3. The sequence of snapshots clearly shows the evolution of coexisting nuclei and the formation of initially separate domains. As a consequence of the system’s symmetry, the shuffling of ionic layers may occur along several equivalent directions. This may lead to domains of different orientations resulting in a mismatch that prevents the coalescence of domains. After completion of the phase transition, the system is hence fragmented in grains. Fig. 3 shows the formation of such a polycrystal. The corresponding grain boundaries arise from the contact of two domains, which accounts for the formation of a mirror plane at the interface.

In macroscopic crystals, phase transitions are known to start from several nuclei and phase growth from multiple centers is an important phenomenon. Indeed, many mechanic properties are triggered by polycrystallinity, and the study of grain boundaries reflects a central topic in materials science. There is a large manifold of routes leading to grain boundary formation, and our studies cannot account for all of them. Nevertheless, focusing on grain formation during pressure-induced phase transitions, our example illustrates the perspectives of exploring the underlying mechanisms from molecular dynamics simulations.

4. Exploring the atomistic mechanisms of aggregation processes

Compared to the picosecond scale of a molecular dynamics study, most crystallization processes are extremely slow and appear inaccessible to atomistic simulation. Depending on the system, this issue may be related to two different phenomena (see also Scheme 1). (i) Crystal nucleation from the melt or from solutions of high concentration is typically related to a large activation barrier. This causes nucleation to occur only rarely, while the event itself happens on a much faster time scale. However, many solute/solvent combinations exhibit very low saturation concentrations. In such systems (ii), aggregation processes are mainly controlled by diffusion. The investigation of aggregation processes hence constitutes a double challenge to molecular simulations.

In full analogy to other phase transitions, we successfully adopted the transition path sampling approach to explore the crystallization of NaCl from the melt [35]. The solidification process was found to be initiated by the formation of a small aggregate of ‘solid-like’ motifs consisting of $[\text{NaCl}_6]^{5-}$ or $[\text{ClNa}_6]^{5-}$ octahedra (no preference for either species could be observed). Interestingly, such motifs of the bulk crystal also occur in the liquid state. However, in the melt, the octahedra only
reflect temporary features. Our definition of ‘solid-like’ particles was therefore based on demanding permanent coordination polyhedra. At the very initial growth stage, the solid nuclei comprise only 1–2 octahedra. Subsequent aggregate growth occurs on a picosecond scale and after only about 20 ps the whole simulation cell (540 ions) was transformed to the crystalline structure [35]. Circumventing the waiting time for spontaneous nucleation, crystallization from the melt is sufficiently fast to be sketched by transition path sampling molecular dynamics simulations.

We furthermore studied the formation of NaCl aggregates from a supersaturated aqueous solution [36]. This allowed insights into the structure of an ‘embryonic’ crystal formed from salt solution. The core of this [Na\textsubscript{x}Cl\textsubscript{y}]\textsubscript{aq}\textsuperscript{x/C0} aggregate in aqueous solution is formed by an entirely non-hydrated sodium ion. In fact, all nucleation trajectories exhibited at least one sodium ion having no or at most one water molecule in its first coordination sphere. Non-hydrated chloride ions could not be observed in the small aggregates obtained from the simulations. The non-hydrated sodium ion was found to be 6-fold coordinated by chloride ions, arranged as a slightly distorted [NaCl\textsubscript{6}]\textsuperscript{2–} octahedron. These formations nicely agree with the ion arrangement in the crystal structure and appear to be a common feature of the aggregate core.

In a few simulation runs the growth of these motifs of the crystalline structures is observed [36]. However, this process requires ion diffusion to the aggregate and the overall growth rate is extremely small compared with the few hundred picosecond time sketches of our molecular dynamics simulations. Ion migration is intrinsically slow and cannot be accelerated by transition path sampling. Such diffusion processes typically do not occur in phase transitions in pure systems (such as crystallization from the melt). In multinary systems, diffusion-controlled domain growth, however, implies an important limitation to the scope of transition path sampling simulations.

Moreover, the study of nucleation processes from solution is often complicated by the need to tackle very large simulation systems. Depending on the concentration of the compound to crystallize, a considerable number of solvent molecules must be included in the simulation model. In our work on the aggregation of NaCl from a slightly supersaturated aqueous solution, this ratio was relatively favorable: the simulation model of an aqueous solution comprised 35 Na\textsuperscript{+} and 35 Cl\textsuperscript{–} ions and 275 water molecules [36]. Nevertheless, upon aggregate formation the ion concentration in the solution decreases, which changes the solute/solvent ratio. Larger simulation models in principle can reduce this effect; however, this requires slow ion diffusion processes. In the course of the aggregation event, locally, ions are removed from the solution. This phenomenon temporarily (in small model systems, even permanently) hinders further aggregate growth. While the computational demand related to the investigation of nucleation events in the small system described above was already considerable, the investigation of the crystallization of compounds of lower solubility implies dramatically larger numbers of solvent molecules. For such systems, both transition path sampling and free energy approaches are quite ineffective and there is a strong motivation for the development of alternative methods.
Making specific use of the characteristics related to crystallization processes of compounds of low solubility, we developed an atomistic simulation scheme for investigating crystal growth from solution [37]. Our method reflects an iterative scheme that combines a Monte-Carlo-type approach for the identification of ion adsorption sites and—after each growth step—structural optimization of the ion cluster and the solvent by means of molecular dynamics simulation runs. An important approximation of our method is based on assuming full structural relaxation of the aggregates between each of the growth steps. This concept only holds for compounds of low solubility, for which sufficient time given between the association events and dissociation processes may be neglected. To illustrate our method, we studied the growth of CaF$_2$ aggregates from aqueous solution, which may be taken as a prototype for compounds of very low solubility (in water).

While the overall configurations of the modeled [Ca$_x$F$_y$]$_{30}$ aggregates varied considerably, a series of common features may be identified. The latter are predominantly observed in the inner core of the aggregates. In the initial stage of aggregate growth, practically all ions have to be considered as part of the aggregate surface. However, in agglomerates of around 20 ions one can already observe the formation of regular structures. The more the aggregates grow, the more clearly one can distinguish a structured inner core from the more irregular outer regions of the ion clusters. In Fig. 4, an aggregate of 80 ions is shown. At this stage of the growth process, one can clearly identify a nanometer-sized domain with an ordered structure. As observed in NaCl, in CaF$_2$ also self-organization of the ions is directly connected with the formation of characteristic motifs of the crystal structure of the bulk crystal (fluorite).

5. Conclusion

The examples discussed in this contribution may be taken as case studies representing new perspectives for the investigation of different types of slow processes from molecular dynamics simulations. In many topics of computational physics, chemistry, bioscience and materials science the time/length-scale problem reflects one of the key obstacles. Indeed, without appropriate simulation approaches, the investigation of slow processes may demand years if not decades of calculation times.

The dramatic progress in hardware development clearly pushes the limits to larger systems and longer simulation times. However, advanced simulation approaches as discussed here can boost computational efficiency by many orders of magnitude. A particularly successful story of this kind is related to the transition path sampling method. This approach extended the scope of molecular dynamics simulations to processes that were believed to be elusive so far. Apart from reactions in complex systems, this includes phase transitions and phase separation processes. The quickly increasing number of related studies will surely make transition path sampling a standard method of investigation in the near future.

The perspectives of such simulations are quite appealing: the virtual laboratory allows in-situ investigations at fs resolution and at the atomistic level of detail. For all of the fields discussed in this contribution, molecular dynamics simulations provided new insights into the underlying mechanisms. This includes the identification of intermediates that are typically ignored when writing down reaction equations. For example, in textbooks crystal formation from solution is denoted as

$$A + B \rightarrow AB \downarrow.$$  

The arrow in the reaction equation effectively conceals the most interesting aspect of the process, i.e., the reaction mechanism. While the most important types of intermediates are surely reflected by the transition-state regime, molecular dynamics simulations may also reveal pre-nucleation events and domains growth after crossing a transition state. This extended picture may be written as

$$A + B \rightarrow \text{aggregation} \rightarrow \text{self-organization} \rightarrow \text{transition state(s)} \rightarrow \text{domain growth} \rightarrow AB \downarrow.$$  

The full understanding of crystal formation from solution requires the characterization of each of these processes. Moreover, there is a large variety of possible implementations of a single reaction mechanism. Rather than taking a single critical nucleus as the transition state, we must consider a manifold of transition-state structures. Transition states represented by single nuclei were shown to vary considerably in shape and size [31,34]. Nevertheless, this does not necessarily imply that methods based

![Fig. 4. Snapshot of a [Ca$_{28}$F$_{54}$]$^{4+}$ aggregate as obtained from the aggregation model reported in Ref. [36]. Calcium and fluoride ions are illustrated in green and blue, respectively. Only two water molecules of the dilute aqueous solution are shown. The dashed lines indicate ion–water (yellow) and water–water (cyan) interactions which stabilize the aggregate surface and its solvent structure.](image-url)
on classical nucleation theory and predefined reaction coordinates are intrinsically incorrect. Indeed, it appears reasonable to assume a good choice of the reaction coordinate to lead to a transition-state structure that might well represent the nucleation process. In such cases, the characteristics of the manifold of transition-state structures are approximated by a single ‘average’ critical nucleus.

As it is difficult to judge the accuracy of a reaction coordinate model a priori, it is appealing to use approaches like transition path sampling [1–3], Wang-Landau sampling [38] and metadynamics [39] which are free of predefinitions. Moreover, many phase transitions involve multiple nucleation centers and may not be characterized by the picture of a critical nucleus at all [28,33].

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