

Fluxionality of Catalytic Clusters: When It Matters and How to Address It

Huanchen Zhai[†] and Anastassia N. Alexandrova^{*,†,‡,§}

[†]Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, United States

[‡]California NanoSystems Institute, Los Angeles, California 90095, United States

1. INTRODUCTION

Small clusters secured at a given size, for example, via deposition on surfaces of semiconductors, can be remarkable catalysts. In the so-called “non-scalable” regime, where every atom and every electron counts in catalyst tuning,^{1–4} the opportunities for design are vast and intellectually attractive. At the same time, these systems are incredibly complex to characterize. In particular, in the nonscalable regime, clusters have shapes that are far from being idealized cuts out of the bulk, especially in the presence of adsorbates (reactants, intermediates, products of the reaction) and the support. Instead, cluster shapes can be highly diverse and hardly ever obey our intuition, which is uncomfortably weak in this case.

One problem then is to identify the most stable structure, the global minimum. Many efficient Global Optimization (GO) algorithms, including Generic Algorithm (GA),^{5–8} Particle Swarm Optimization (PSO),^{9,10} Simulated Annealing (SA),¹¹ and Basin Hopping (BH)^{12,13} have been shown to be successfully applied to small cluster systems, when combined with different level ab initio electronic structure methods. In addition, the GO algorithms can be further accelerated by using potential energy surface fitting techniques^{14–16} or empirical potentials,^{17,18} where the latter can be particularly useful for significantly larger clusters.¹⁹ However, even if the global minimum is found, just the global minimum may tell only part of the story.

Potential energy surfaces of clusters are typically rich in low-energy local minima. Many of these isomers are energetically accessible at the elevated temperatures of catalysis, to the degree that thermodynamic equilibration is kinetically possible. For example, the gas-phase Pt₈ cluster has ca. 30 distinct isomers (local minima) within the vicinity of the global minimum that can be populated at 700 K.¹⁴ Of course, it is possible that some isomers are protected kinetically by high barriers, especially when the supporting surface provides strong and selective interactions with certain isomers. Regardless, several isomers should be suspected to be present in the catalytic system. This calls for a statistical ensemble representation of the catalyst. Furthermore, the most stable isomer may not be the most catalytically active. After all, it is intuitive that less-stable species are more likely to be reactive. For example, consider catalytic Au clusters versus stable and inert bulk Au. Thus, if there exists a relationship between the catalytic efficiency of a cluster isomer and its relative stability, then it is more likely to be inversely proportional than otherwise. In summary, even if the global minimum of a cluster is found, the utility of this isomer alone in describing size-specific catalytic activities is likely limited. A cartoon illustration of this point is shown in Figure 1.

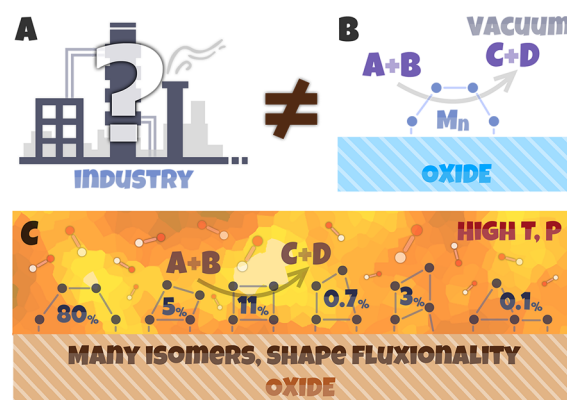


Figure 1. Conditions of catalysis (A) do not imply a single rigid cluster isomer facilitating a single catalytic event in vacuum (B), but instead, realistic coverage, temperature T , pressure p , access to many cluster isomers (% in C indicating probabilities for occurrences), and fluxionality all have an influence on catalyst activity. Thus, a statistical ensemble representation of the catalyst isomers under catalytic thermal conditions is necessary.

The situation is further complicated by the fact that isomers may interconvert from one to another under the influence of increased temperature and because of the changing amount and chemical nature of adsorbates^{20,21} (for example, reactants versus reaction intermediates). This phenomenon is called fluxionality, and it is the topic of the present article.

From our point of view, the most difficult question is that of the interdependence and the interaction between the catalyzed reaction and cluster isomer interconversion. Clusters covered with reactants may have a different preferred shape or an ensemble of shapes than those covered with reaction intermediates or products. However, does it mean that the cluster rearranges in the course of the reaction step, that is, part of the reaction coordinate? Alternatively, does it mean that the clusters interconvert from one to another within the given free-energy well (say that of the reactants) and, once a particularly catalytic isomer forms in this process of equilibration, the reaction proceeds with a very small barrier? If the latter is the case, then, once the next reaction intermediate is formed, the clusters may again re-equilibrate in the new free-energy well. The generally longer lifetime in the wells should allow for this. At the moment, there is a controversy and a general lack of clarity on this question. How can we begin thinking about it?

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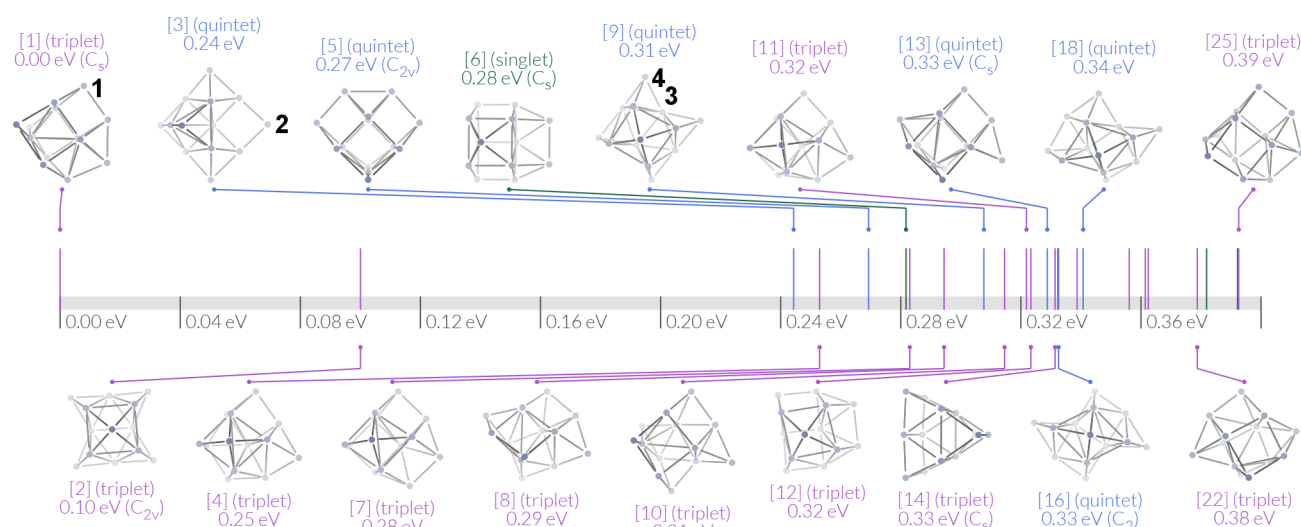


Figure 2. Global and local minima of Pt_{13} in the gas phase, found within 0.4 eV from the global minimum, using the neural network accelerated search. All relative energies are at DFT/PBE level of theory. Notice the difference in the coordination geometries of the representative binding sites on these clusters, labeled 1, 2, 3, and 4. Reprinted with permission from ref 16. Copyright 2016 American Chemical Society.

In fact, some experience can be drawn from the field of enzymatic catalysis, where an understanding has recently emerged that proteins, being large, sluggish, and flexible, usually sample their conformational space slowly as compared to the reaction rate. Therefore, the direct coupling of the protein motion with the reaction coordinate has a very low probability. What is feasible instead is that, as proteins undergo their native dynamics, they once in a while assume the right conformation that is very close to the transition state of the catalyzed reaction. The barrier thus becomes smaller and easily crossed. This point of view is strongly advocated by Warshel and co-workers,²² whereas the opposite was advocated by Karplus,²³ both recipients of the Nobel Prize in Chemistry in 2013. To what degree can this be viewed as a parallel to cluster catalysis? Of course, clusters are smaller than proteins and thus might be more capable of coupling their degrees of freedom in the reaction step. However, the masses of late-transition-metal atoms are still much larger than those of typical reacting molecules consisting of light main-group elements. Next, clusters are held together by delocalized bonds, which lack directionality and thus contribute to the fluxionality of cluster shapes. These bonds may be additionally weakened by the bound adsorbates. On the other hand, protein tertiary structures are also held together by weak H-bonds, as well as hydrophobic and other weak interactions, yet their conformational changes are sufficiently hindered to not couple directly to the reaction dynamics. Supporting surfaces additionally stabilize cluster geometries and should deter fluxionality. Taking these considerations together, it is not obvious that intracuster degrees of freedom should be part of the reaction coordinate. Additional work needs to be done to show whether cluster catalysts assume “aka-Warshel” or “aka-Karplus” scenarios, and whether a general theoretical framework for this can even be made. Several studies, including our own, have been reported, and the theory of fluxionality in cluster catalysis has begun to be constructed. In this Viewpoint, we will now tackle the problem of cluster fluxionality one aspect at a time, in the order of increasing complexity, and we will introduce the advanced theoretical methods that have been or should be developed in the near future, to enable the much-needed studies.

2. CLUSTER ISOMER DIVERSITY

The first important aspect is the fluxionality of cluster catalysts within any minimum on the reaction profile. The theoretical treatment of this aspect is largely accessible via existing technologies: global optimization methods that thoroughly explore free-energy surfaces of clusters, finding both the global and all the low-energy local minima. Many isomers of small clusters have energies similar enough to the global minimum to be populated simply thermally, at elevated temperatures of catalysis (e.g., 700 K). For example, in Figure 2, we show all the isomers of the Pt_{13} cluster in the gas phase, without any reactants bound to it, that were found within 0.4 eV from the global minimum.¹⁶ This cluster attracted special attention because it is close to 1 nm in size and is supposedly the minimal closed polyhedron that can be cut out of bulk Pt. However, it can be seen that there is a disturbing number and diversity of structures, all of which should have a chance to exist in the given temperature range. It is therefore insufficient to consider just one isomer, even though for Pt_{13} , for example, it might seem logical. Instead, it is necessary to describe a cluster of a given size as a statistical ensemble, where isomers are populated according to their free energies and subject to Boltzmann statistics.

Notice also that at different temperatures, different isomers would have different electronic, vibrational, and rotational entropies, and thus, their relative free energies and hence populations would change as a function of T . In Figure 3, we show the probabilities of the lowest-energy five isomers of Pt_{13} that exist at 200, 300, 500, 700, 1000, and 1500 K.¹⁶ Strong variations can be observed, indicating that the populations of different isomers can grow or drop at higher temperatures, and consequently, different ensemble-averaged properties are expected.

Any one of the accessible isomers can play a role in catalysis. Notice also that there are numerous ways in which any given reactant could bind to available isomers. Consider, for example, four representative binding sites of the Pt_{13} clusters, labeled 1, 2, 3, and 4 in Figure 2. The Pt atom of the site 1 is coordinated to three other Pt atoms, and as such, it is rather undercoordinated, suggesting high affinity for the incoming gas phase species.^{24,25}

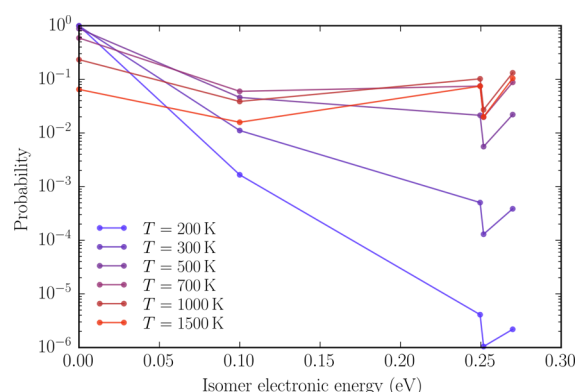


Figure 3. Probabilities of occurrence of the first 5 low-energy isomers of Pt_{13} (all having different relative electronic energies show on the abscissa) at different temperatures. Energies and harmonic frequencies were evaluated using the PBE functional. Reprinted with permission from ref 16. Copyright 2016 American Chemical Society.

Site 2 is even more undercoordinated. Site 3, on the other hand, has a very high coordination number of 7. Site 4 is 3-fold coordinated, just like site 1, but the difference is in the nature of the Pt atoms to which it is coordinated: they belong to the triangular faces on the cluster, rather than the square ones as on site 1 in the global minimum. Every one of these sites would have different affinity to small molecules.²⁶ In recent work by Sautet, Loffreda et al., it was shown that the generalized coordination number, $\overline{\text{CN}}$,^{27,28} is a very good descriptor of a site's affinity to small molecules on extended surfaces with and without defects. $\overline{\text{CN}}$ is the count of the nearest-neighbor atoms of the site, but they are counted in such a way that their contributions are weighted by their own number of neighbors. This descriptor was found predictive of the outcomes of new experiments. It instructs us that sites 1, 2, 3, and 4 in Figure 2 would exhibit very different chemistries. The chance of a given site to promote catalysis would depend both on the intrinsic reactivity of this site and its likelihood to exist in the population of isomers at the given T .

It has been seen in state-of-the-art experiments by Anderson, Heiz, Schneider, Vajda, and others that small clusters exhibit nonlinear trends in catalytic activity as a function of cluster size. Certain sizes, such as Pd_7 on TiO_2 for CO oxidation,²⁹ are particularly active. In view of the considerations presented so far though, what is even the size-specific catalytic activity of a given cluster? We have to admit that this property must be an ensemble average over all or most of the thermally accessible

isomers of the catalytic cluster. This isomers-ensemble-averaged property can be significantly different from that of a single isomer, such as the correctly identified global minimum and that of a single binding site.

In our recent work, we embraced this complexity to the extent currently technically possible. For example, we considered the intrinsic properties of clusters, the size-specific catalytic activity, and the stability against sintering on the support, within the ensemble representation. The superposition approximation suggested by Ballard et al.³⁰ was used, which considers the energetic and entropic effect of each isomer k as an additive term Z_k in the partition function Z

$$Z = \sum_k Z_k, P_k = \frac{Z_k}{Z}$$

This can be a reasonable starting point of the theoretical framework for the ensemble representation. In Figure 4A, we show the application of this approach to the equilibrium properties of the Pt_9 and Pt_{13} clusters.¹⁶ It has been demonstrated that not only the zero-point energies (from vibrational degrees of freedom) but also different spin multiplicities and point-group symmetries can make significant contributions to entropy and change the probability of isomer occurrence. This indicates that electronic, vibrational, and rotational degrees of freedom are all important in this description

$$Z_k = Z_{\text{elec},k} Z_{\text{vib},k} Z_{\text{rot},k}$$

In addition, Figure 4B shows that at higher temperature, the role of some isomers with higher energy can also be important.¹⁶ The calculated heat capacity, which is sensitive to the isomer structure, can be different if fewer isomers are included.

Our previous studies also showed that averaging over a set of different cluster isomers can be important for explaining sintering effects. For example, the averaged occurrence probability of Pt–Zn clusters of different sizes and compositions, which have been obtained from a Monte Carlo sintering simulation, illustrate that a high concentration of Zn in the initial population would improve the sintering resistance of mixed Pt–Zn clusters deposited on MgO and TiO_2 .³¹ Application of this algorithm to Pt–Pd deposited on TiO_2 , has shown that at high temperatures the 1:1 Pt/Pd clusters have considerably more accessible isomers than clusters of other Pt/Pd proportions, which leads to their greater (entropic) stabilization against sintering (Figure 5), in excellent agreement

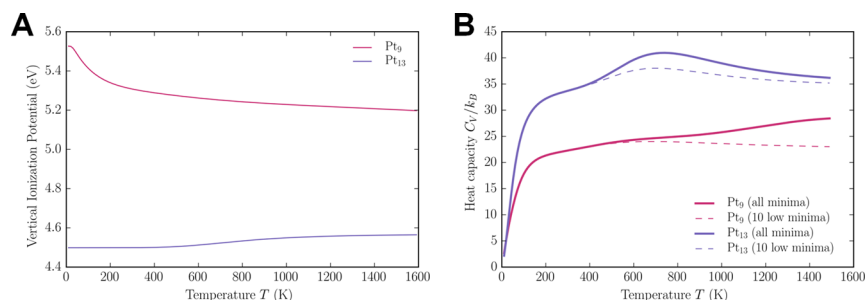


Figure 4. (A) Ensemble-averaged vertical ionization potential of Pt_9 (red) and Pt_{13} (blue), evaluated at different temperatures. (B) The heat capacity contribution from the electronic, vibrational, and rotational degrees of freedom for isomer ensemble of Pt_9 (red) and Pt_{13} (blue), when all local minima found within 0.4 eV from the global minimum (solid line), and only the first 10 low energy isomers (dashed line) are considered. Reprinted with permission from ref 16. Copyright 2016 American Chemical Society.

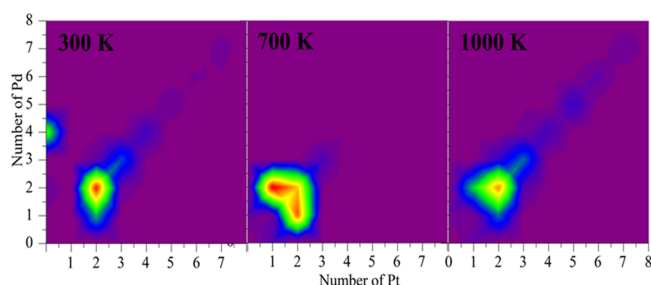


Figure 5. Ensemble-averaged occurrence probability of Pt–Pd clusters of different sizes, over 1000 different initial configurations on TiO_2 , from a sintering simulation. Reprinted with permission from ref 32. Copyright 2014 American Chemical Society.

with the experiment.³² We note that in these studies, the temperature effect has been included via both the Monte Carlo sintering algorithm and the statistical ensemble treatment of cluster isomers for different sizes and compositions.

These findings demonstrate that ensemble representation is the right way forward, at least for the cluster systems that we have had a chance to consider. We further note that, despite the nontrivial attempt to resolve the problem, we are far from the ideal solution.

First, in conditions of catalysis, cluster shapes will be greatly influenced by the bound adsorbates. For example, Raybaud et al. demonstrated that the Pt_{13} cluster on alumina completely restructures in the presence of H, becoming more globular (Figure 6A).³³ In contrast, highly symmetric Au_{20} essentially melts when covered with CO molecules, as was found in the joint experimental and theoretical (molecular dynamics) study by Rousseau et al. (Figure 6B).³⁴ Therefore, one would wish to include the appropriate coverage in the discoveries of relevant cluster populations. We note also that the coverage of clusters with reactants/intermediates and the structures of a cluster catalyst are interdependent.^{35,36} Therefore, global optimizations would need to be carried out in the presence of reactants/intermediates, to ensure self-consistency between geometries and coverage, at the given chemical potentials of adsorbates in the gas phase. In our most recent studies, concerning dehydrogenation of alkanes on Pt clusters on alumina,³⁷ we find only when the composition of a cluster ensemble is expanded to include all thermally relevant isomers, and at relevant high coverages with reactants, that we reproduce various experimentally observed properties, such as size-dependent catalytic activity and selectivity.

In multistep reactions, the nature of the adsorbates will change in the course of the catalyzed reaction, from the reactants, to intermediates, to products. These species will compete for the binding sites and, once bound, will influence the cluster shape. In the end, the system will reach a

thermodynamic equilibrium between the number and nature of adsorbates (in the average sense) and the accessible cluster geometries. At this dynamic equilibrium, adsorption/desorption events, reaction steps, and cluster isomerizations will continue to occur. A tractable way of describing this complexity theoretically could be the consideration of the ensemble present only in the minimum on the reaction profile that is most kinetically relevant. With the recent developments in our laboratory, we aim to approach the realistic description of this picture of the cluster catalyst, using a blend of first-principle calculations, GPU-accelerated global optimization algorithms, short-cuts for site activity assessments, classical thermodynamics, and statistical modeling. The field is hungry for efficient algorithms and also their applications.

3. CLUSTER ISOMERIZATION: FLUXIONALITY INDEPENDENT OF THE CATALYZED REACTION

The picture described so far relies purely on the properties of low-energy minima as the main determinant of the nature of cluster catalysts. However, it is possible that some of the isomers are separated from other minima by large free-energy barriers, and this may cause either kinetic trapping in just one or few isomers of the cluster or hindered accessibility of the given isomer, which cannot be reached upon thermal equilibration. Thus, the relevant questions to ask are the following: “How likely are the clusters to interconvert between geometries within the lifetime of a reactant complex or reaction intermediate?” and “How likely is the system to exhibit significant anharmonic effects, where the accurate shape of the free-energy profile, but not only that in the vicinity of the minima, matters?” There has been a report suggesting that the interconversion for pure Pt clusters in the gas phase can be kinetically hindered (by barriers of ca. 1 eV), and clusters can be viewed as a glass-like state, locked in different irregular isomeric forms. On the other hand, a report on Pt clusters deposited on C nanotubes asserted easy interconversion.³⁹ For Au clusters (other than Au_{20}), the interconversion is rapid even at 300 K.^{40,41} Several reported observations support that clusters of a given composition with a fixed number of adsorbates (which can be zero) may reshape from one isomer to another at elevated T .^{2,40,42,43} It was shown by Landman and Parks⁴² in their joint theory-experimental work that, upon coadsorption of CO and H_2O on gas-phase clusters of Au, the barriers to interconversion can decrease to ~ 0 eV (Figure 7). This work is highly instructive as it shows that the binding of small molecules can completely change the isomerization free-energy landscape. On the other hand, the presence of the support would provide certain stabilization of the isomers. Among Pt, Pd, and Ni clusters on MgO under conditions of ethylene hydrogenation at 300 K, Pt clusters were shown to

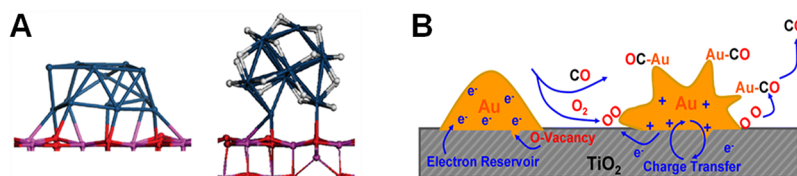


Figure 6. (A) Shape of a Pt_{13} particle on the (100) surface of γ -alumina in the absence (left) and presence (right) of gaseous hydrogen pressure, with 20 hydrogen atoms chemisorbed. Adapted with permission from ref 33. Copyright 2013 Elsevier. A dramatic change of shape is observed, even for this one isomer, accessed via molecular dynamics simulations.³⁸ (B) Schematics of the results of the molecular dynamics simulations of the Au_{20} cluster on TiO_2 after coverage with CO. Reprinted with permission from ref 34. Copyright 2013 American Chemical Society.

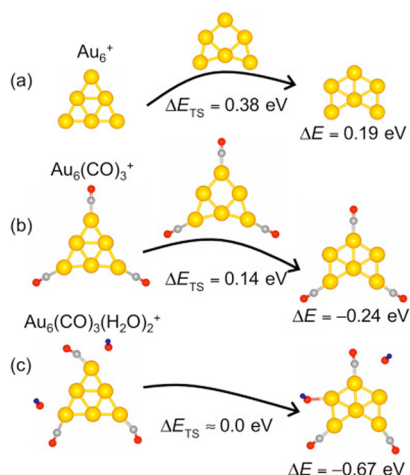


Figure 7. Atomic structures of Au_6^+ cluster complexes and transition-state energies obtained from first-principle calculations. (a) Bare clusters exhibiting a transition between the triangular ground state $\text{Au}_6(t)^+$ and the incomplete hexagonal isomer $\text{Au}_6(ih)^+$ at $\Delta E = 0.19$ eV with a barrier of 0.38 eV. (b) The same transition in the presence of three CO ligands occurs with a barrier of 0.14 eV. (c) For the coadsorption complex $\text{Au}_6(\text{CO})_3(\text{H}_2\text{O})_2^+$, the transition occurs with a negligible barrier. Reproduced with permission from ref 42. Copyright 2015 Elsevier.

deactivate the least,⁴⁴ indicating their higher relative stability in the presence of hydrocarbons and hydrogen. However, adsorbates can also cause cluster dissociation, as is sometimes the case with clusters of Au in the presence of CO.³⁸

In view of these reports, the likely conclusion can be that the majority of cluster minima are generally easily accessible within a given well on the reaction profile at high temperatures and coverage. Hence, the description based on superposition of local minima and harmonic approximation that we have been using so far in our laboratory is a good first-order approximation, particularly because it showed results in agreement with the experiment, at least for the limited number of systems to which it has been applied. However, a suggestion could be made for the future work in this domain. If, among the cluster isomers constituting the relevant ensemble, a few are identified as the main players in the catalytic process, then a thorough exploration of the free-energy surfaces in the vicinity of these isomers should be performed. That would reveal whether or not any isomer of interest is kinetically inaccessible, and thus whether or not the system would be able to use the catalytic power of the binding sites on this isomer. If the barriers to isomerization leading to the isomer of interest are relatively low, compared to the barriers to the catalyzed reaction, then the isomer-ensemble picture has stronger ground to stand on.

4. FLUXIONALITY OF CLUSTERS DURING A REACTION STEP

The hardest issue to address is the possible isomerization of cluster catalysts concurrent with the catalyzed reaction (i.e., being part of the reaction coordinate). Because cluster shapes change upon binding different adsorbates,^{38,45,46} one shape might be preferred in the reactant state and another in the next reaction intermediate or product.^{38,45,47} However, this does not immediately imply that isomerization and the chemical step happen simultaneously. Because the minima on the free-energy profile of the catalyzed reactions are in fact described by

ensembles of many isomers, it is the ensemble and not the single isomer that is different in the well of the intermediate from that in the well of the reactant. The two most stable cluster isomers in the two ensembles may or may not be connected by a direct reaction pathway. It is conceivable that instead, every one of many possible reaction paths would connect minima that are geometrically close, so that there would be no dramatic and costly rearrangement of the catalyst during the reaction step. Cluster isomerization would precede and/or follow the reaction step, making the process effectively stepwise. In other words, the system would re-equilibrate to populate various accessible minima within each well on the reaction profile. This scenario would be computationally more tractable and it is therefore seducing. Let us not create a bias on this ground, though.

We need to ask three critical questions. (i) Is the interconversion of clusters fast enough for the full thermodynamics equilibration to happen in the lifetime of a typical reaction intermediate? (ii) Is the rate of isomerization comparable to the rate of the catalyzed reaction step? (iii) If the rates are comparable, does the isomerization dynamically couple to the reaction coordinate, or can it be separated out? It might seem obvious that if the rates are similar, coupling would be unavoidable, and cluster reorganization should be part of the reaction coordinate. However, again in the very different field of enzymatic catalysis, Warshel et al.²² demonstrated that even when protein structural changes in the vicinity of the enzyme active site and the chemical steps happen with similar rates, the coupling between the two is minimal, and reaction happens in a sequential manner (as in Figure 8). The chemical step in this

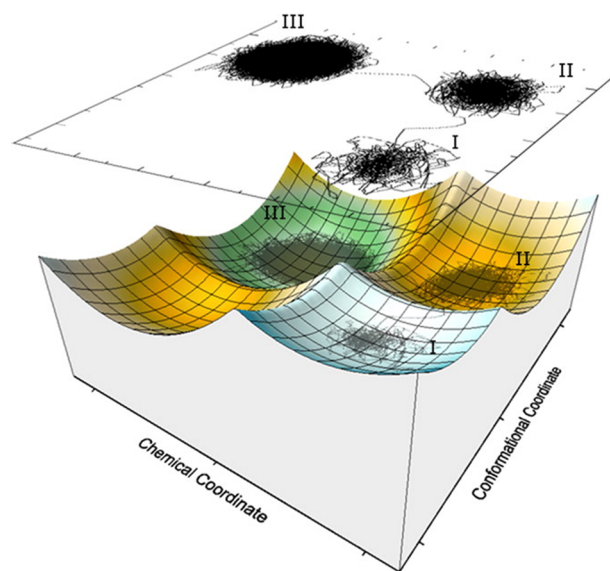


Figure 8. Illustration of how catalyst isomerization (going along the conformational coordinate from state I to state II) precedes the chemical step (II to III). Even though a concerted path across the diagonal exists, it is a higher-barrier path. Reprinted from ref 22.

case keeps essentially no memory of the conformational step. The differences in the barriers as small as 1 kcal/mol were shown to be sufficient to completely decouple the two steps. Although enzymes are very different objects, these findings made us aware that question (iii) might have a nontrivial answer.

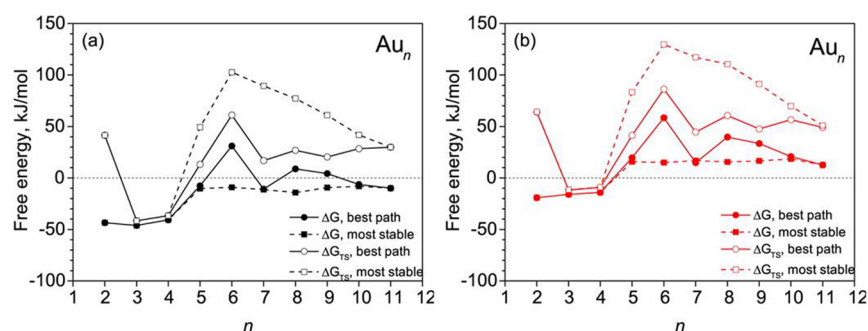


Figure 9. Change in free energy, ΔG , upon H_2 adsorption on the neutral gold clusters calculated at $T = 0$ K (a) and $T = 298.15$ K (b) for the most stable configurations (filled squares) and configurations leading to the best dissociation path (filled dots). Free energy of the lowest transition state for H_2 dissociation, ΔG_{TS} , calculated relative to the sum of free energies of the noninteracting H_2 and gold clusters for the most stable configurations (open squares) and configurations leading to the best dissociation path (open dots). Reprinted with permission from ref 45. Copyright 2015 American Chemical Society.

This section will leave more questions than answers. Works that address fluxionality during the reaction are few, and the scope is limited due to the high computational cost, among other factors. Fabris et al.³⁸ studied Au clusters deposited on CeO_2 (111) with O vacancies, for the catalysis of CO oxidation. They found that cluster fluxionality in this case facilitates the reaction. Au_2 on ceria dissociates in the presence of CO, but Au_3 survives. The structural flexibility of these small clusters activates dynamical effects that prevent cluster dissociation while boosting reactivity. In this case, there is a pronounced adjustment of the cluster shape upon binding different adsorbates, CO or O_2 . Because the cluster is very small, the structural changes that would seem minor on a large cluster are very visible here (triangular, bent, or nearly linear geometries are all distinct). Flexing of the Au–Au–Au angle is also unavoidable during every reaction step. This flexibility allows the system to catalyze the reaction, and also to regenerate afterward. Although there is a small number of isomers in this small cluster and the ensemble is simple, this example represents a limit at which reaction step fluxionality is obvious.

Once the cluster becomes larger, structural changes in the reaction step might appear minor (imagine flexing a single Au–Au–Au angle in the Au_{20} cluster, for instance). In such cases, complete reorganization of the cluster during the reaction will be much less likely. Reactants are generally light as compared to multiple late-transition metal atoms of the cluster. Therefore, it is likely that the reaction and isomerization dynamics happen on different time scales: the reaction would be too quick to wait for the cluster to reorganize. Taketsugu et al. studied the catalytic dissociation of H_2 on neutral, positively, and negatively charged gold clusters Au_n^q ($n = 2–11$; $q = 0, \pm 1$), using the global reaction route mapping (GRRM) technique combined with the anharmonic downward distortion following (ADDF) and artificial force-induced reaction (AFIR) methods.⁴⁵ In their work, they considered different cluster isomers and indeed found that the most active isomers are not the most stable ones. Instead, isomers only moderately higher in energy than the global minimum (in their work they considered isomers within 20 kJ/mol range) are dramatically more active. An example of this exploration for the neutral clusters is given in Figure 9. This work uses sophisticated automated techniques for reaction path identification and yet does not find any reaction pathways that would include isomerization as part of the reaction coordinate. Of course, these are gas-phase clusters under conditions of low coverage. It is hard to say how the situation would change in

more realistic conditions. We also notice that the ensemble representation in this work is incomplete in a statistical sense, in that the overall activity of the cluster of a given size is not averaged over different isomers, subject to their occurrence probabilities at a given temperature. Nevertheless, Taketsugu et al. give us an important fundamental message and a hope: ensembles matter, but cluster reorganization might be decoupled from the reaction step.

5. SUMMARY

Cluster catalysts are incredibly complex and dynamical. We hope to have shown that it is essential to consider them as statistical ensembles, in order to reproduce experimentally observable properties, such as electronic spectra, heat capacity, resistance to deactivation, and size-specific catalytic activity, and to correctly describe the mechanisms of catalyzed reactions. The key elements in the ensemble description are the following: (i) the recovery of the global and thermally accessible local minima on the free-energy surface, including entropic effects, in the presence of appropriate coverage with reacting species; (ii) testing the kinetic accessibility of these relevant isomers and the ease with which they can interconvert within a given well on the free-energy profile of the catalyzed reaction; (iii) assessment of the possibility of the dynamic coupling between cluster isomerization and reaction step, as well as testing the quality of the approximation that the two processes occur sequentially.

Cluster fluxionality can be understood in different ways, and in our view, it is important to distinguish the intrinsic fluxionality of clusters due to elevated temperatures and high coverage, and possible fluxionality as part of the reaction coordinate. The former can and should be addressed with currently available global optimization methods, supplemented with statistical thermodynamics. The latter is much harder to address. There is a need for an updated algorithmic paradigm. In Warshel's work on enzymes, the reason the problem became tractable is that the authors found a suitable collective coordinate corresponding to the particular (known) way of protein conformational change. They then applied the renormalization-group approach to address system dynamics, and they showed the lack of dynamic coupling. What could be the collective coordinate that would describe cluster isomerization? At this point, we feel that we need to catch up both in method development and in the conceptual understanding of the dynamics of cluster catalysis. It is not safe to assume that

clusters would necessarily flux in the course of the reaction step, but neither it is yet safe to assume that they would not.

The awareness of the community about the huge implications of the complexity and fluxionality of cluster catalysts is growing in the recent years. From the theory community, we express our commitment to catching up with the fundamental understanding, making our algorithms more sophisticated, and taking advantage of the available computing resources, to provide a realistic description of fluxional cluster catalysts. Our initial progress in this domain is encouraging.

AUTHOR INFORMATION

Corresponding Author

*E-mail: ana@chem.ucla.edu.

ORCID

Anastassia N. Alexandrova: 0000-0002-3003-1911

Notes

The authors declare no competing financial interest.

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