Homogeneous Catalysts with a Mechanical (“Machine-like”) Action

Introduction

According to collision theory, when two or more reactant molecules or atoms collide with each other in an uncatalyzed process, they momentarily form an unstable, high-energy species known as the transition state (Figure 1a). This moiety exists for only an exceedingly brief period of time, after which its constituent atoms or molecules disengage to yield either the original reactants back ("elastic collision"), or they generate new chemical species known as the products of the reaction ("reactive collision"). The outcome of such a collision is determined by its energy. Products are formed if the collision is sufficiently energetic to overcome a certain threshold energy, known as the activation energy ($E_a$; Figure 1b). If this threshold is not overcome, the collision is unsuccessful and the reactants are reformed. The lower the threshold energy ($E_a$), the greater will be the proportion of reactive collisions. If $E_a$ is close to zero, then virtually every collision will result in a reaction.

The overall rate of a chemical reaction is given by the Arrhenius equation [Eq. (1)], which relates reaction rate ($k$) to the frequency with which the reactant molecules collide with each other (the pre-exponential term $A$, known as the collision frequency), and the proportion of those collisions that are sufficiently energetic to result in product formation (expressed in kcalmol$^{-1}$ or kJmol$^{-1}$). The reaction could be considered to display an energy-dependent character and course.

$$k = A \exp\left(-\frac{E_a}{RT}\right)$$

The least-favored of these steps will determine the character and course of the reaction. In reactions where the activation energy is large, there will be many collisions, of which only a small proportion will be successful. That is, step ii will be disfavored relative to step i, meaning that the reaction will be dominated by the exponential term in Equation (1). The overall rate, $k$, will then depend on the thermodynamics of the collision and the activation energy that must be overcome in the transition state (expressed in kcalmol$^{-1}$ or kJmol$^{-1}$). The reaction could be considered to display an energy-dependent character and course.

Figure 1. Schematic depiction of an uncatalyzed chemical reaction as: a) a collision between two molecules, A and B, leading to a chemical reaction in which products are formed, and b) the energy profile followed during the collision, showing the minimum threshold energy needed for product formation (termed: the activation energy, $E_a$).
However, in reactions in which the activation energy is small, virtually every collision will result in a reaction. That is, step ii will be favored relative to step i, meaning that the reaction will be dominated by the pre-exponential term in Equation (1). The overall rate, \( k \), will then depend on the collision frequency of the reactants. In other words, the reaction rate will depend most fundamentally on the mechanics of reactant collision (expressed in s\(^{-1}\) or s). Since frequency is intrinsically a measure of time and not of energy, we will term such reactions time-dependent so as to distinguish them from reactions governed by \( E_a \).

These distinctions reflect, in broad terms, the two fundamental transformational processes that are recognized in science: 1) thermodynamics, which describes transformations due to an energy differential, and 2) mechanics, which describes transformations due to physical cause-and-effect sequences that play out over time.[2] While the field of thermodynamics has been extensively developed in chemistry, mechanics is substantially less developed.[2]

Most uncatalyzed reactions in the liquid phase at ambient temperature are undoubtedly energy-dependent. However, time-dependent processes are known. One example in this respect is the reaction of \( \text{H}^+ \) and \( \text{OH}^- \). When an \( \text{H}^+ \) ion encounters an \( \text{OH}^- \) ion, they react rapidly to form \( \text{H}_2\text{O} \) (\( k = \text{ca.} \ 10^{-10} \text{s} \)). This occurs, essentially, without regard to the energy of the encounter, because the \( E_a \) threshold for this reaction is exceedingly low. Such reactions are said to be diffusion-controlled, because they are governed by the rate at which the reactant species diffuse to each other in solution. In other words, the overall reaction rate is dependent on the frequency with which \( \text{H}^+ \) and \( \text{OH}^- \) encounter each other (“collide”) in solution and this is a function of their speed of diffusion.

Catalysts are species that intervene in, and accelerate chemical reactions without themselves being changed. Catalytic action involves, firstly, binding the reactants and, secondly, bringing them into collision while bound to the catalyst. In binding the transition state, catalysts decrease the activation energy of the reaction.

Figure 2 schematically illustrates how a catalyst would typically intervene in the processes depicted in Figure 1. As can be seen, the catalyst will generally first bind the two reactants \( \text{A} \) and \( \text{B} \), and then bring them into collision with each other. The transition state, thus formed, is stabilized by binding to the catalyst, thereby lowering the threshold activation energy that must be overcome, \( E_a^{\text{cat}} \), relative to its uncatalyzed equivalent, \( E_a^{\text{uncat}} \) (Figure 2b).

How does a catalyst lower the activation energy? Upon binding, a catalyst typically polarizes or stretches bonds within the reactant, thereby making these bonds more conducive to reaction. This process is known as activation and is illustrated in Figure 3 for a representative reactant, di-oxygen \( \text{O}_2 \). As can be seen, catalysts usually stretch bonds by either withdrawing electron density from reactant bonding molecular orbitals or increasing it in anti-bonding molecular orbitals.

A typical catalyst then further facilitates collisions between the bound reactants in which the orientations of the activated reactants are relatively ideal for reaction; that is, the threshold activation energy of the collision (\( E_a \)) is relatively low. The activation provided to the reactants by the catalyst is then sufficient for them to react with each other when brought into physical contact. The catalyst may create such “low-threshold-energy” collisions by constraining the reactants to approach each other along trajectories that are energetically favorable. By contrast, collisions in uncatalyzed reactions typically involve random approach trajectories, including some highly inopportune ones that have very high energy thresholds. Reaction is therefore less likely without a catalyst than with one.
As in an uncatalyzed reaction, the overall rate of the catalyzed reaction depicted in Figure 2a is also dependent on the collision frequency \((A)\) and the rate at which collisions overcome the activation energy \((E_a)\) to form products. However, the reaction process differs in two important aspects, from the uncatalyzed process depicted in Figure 1a:

1) As shown in Figure 2b, the activation energy \((E_a)\) is typically much lower in a catalyzed reaction than in its equivalent uncatalyzed counterpart. This makes step ii in Figure 2a more favorable than it would be in the equivalent uncatalyzed reaction, meaning that the reaction is more likely to depend on step i. In other words, the fact that catalysts diminish \(E_a\) increases the likelihood that the reaction will be controlled by the catalyst-mediated collision frequency. If some uncatalyzed reactions are known to be time-dependent in liquid phases at ambient temperature, then a comparatively greater number of such reactions should be governed by their collision frequency when catalyzed.

2) As shown in step i of Figure 2a, the collision frequency \((A)\) in a catalyzed system is dependent on the rate of reversible catalyst–reactant binding and the rate at which the catalyst then mediates collisions between bound reactants. In a molecular catalyst, collisions would typically be created when the catalyst framework undergoes a conformational change. This is different to the uncatalyzed reaction shown in step i of Figure 1a, the collision frequency of which depends only on the rate at which the reactants diffuse to, and collide with each other in solution. In other words, time-dependent catalytic reactions need not be diffusion-controlled. Moreover, they must necessarily display a catalyst–reactant intermediate in their rate expression, since the formation and processing of this intermediate comprises the slowest step of the reaction process.

While a dependence on collision frequency is formally recognized in uncatalyzed chemical reactions, it is less well known in homogeneous catalysis. Indeed, to the best of our knowledge, the distinction that must necessarily exist between energy- and time-dependent actions in molecular catalysis has not been explored in any detail. Such processes should be very different. A time-dependent action should, for example, rely on the spatial and temporal factors involved in achieving reactant collision. By contrast, an energy-dependent catalytic action will not be limited by the collision frequency and will, instead, be governed by the thermodynamic efficiency of the collisions it mediates; that is, by the extent to which it diminishes the activation energy of reactant collision (Figure 2b).

In this work we will consider this distinction. We will examine several non-biological molecular catalysts, the actions of which appear to be controlled by their collision frequency, including [1.1]ferrocenophane hydrogen reduction catalysts, Co diporphyrin dioxygen reduction catalysts, and Mn−O cubane water oxidation catalysts. Drawing on these examples, we will discuss the nature of “mechanical” catalytic actions. The incidence of “mechanical” actions in the catalysts of biology, enzymes, will be considered here only insofar as they may influence the development of bioinspired molecular catalysts. A recent edited volume by the authors considers mechanical actions in biological catalysis in greater detail.

For convenience and continuity in argument, we will use the terms collision and collision frequency to describe reactive contact between reactant functionalities in the liquid phase. We acknowledge that collision is a gas-phase term and the liquid-phase equivalent is, more correctly, termed an encounter.

Reactions Governed by their Collision Frequency are not Formally Subject to Transition-State Theory

Perhaps the most critical distinction between reactions (both catalyzed and uncatalyzed) that are governed by their collision frequency rather than by their activation energy relates to their fundamental character. The latter are formally described by transition-state theory, while the former are not. To explain this aspect, we need to go back in history.

In the 1930s, Henry Eyring of Princeton University developed transition-state theory by applying quantum mechanics to the general theory of gas phase reactions, known at the time as Hinshelwood–RRK theory. It is not well known that Hinshelwood–RRK theory, which was an elaboration of collision theory, involves two so-called “limits” and that transition-state theory, in fact, conforms to only one of these limits. The limits are:

1) The high-pressure limit, in which the rate of reaction is governed by the activation energy of the transition state and the system is subject to a thermodynamic equilibrium, and

2) The low pressure limit, in which the rate of reaction is governed by the frequency of reactant collisions and the system operates under non-equilibrium conditions (as demonstrated by a depletion in the Boltzmann distributions during reaction).

In order to employ quantum mechanics, Eyring had to make the assumption that the reactants, the products, and the transition state were all in equilibrium with each other. However, this situation only exists in the high-pressure limit of Hinshelwood–RRK theory, at which the rate of reaction is governed by the activation energy of the transition state. It does not apply in the low-pressure limit, at which reactions are governed by the collision frequency.

Thus, a critical distinction between catalyzed or uncatalyzed reactions governed by their collision frequency rather than by their \(E_a\), is that they are not formally subject to transition-state theory. This is because the key issue involves
achieving collision and this need not be influenced by the energy landscape about the collision.

We will discuss the meaning of this later. Suffice to say at this stage, that these implications are potentially significant, especially since nonequilibrium processes have been relatively unknown and unstudied in chemistry to date. Moreover, the distinction between a time- and an energy-dependent process is demonstrated to be more than mere intellectual semantics. It has a real and a rather important basis.

**Dynamism in Reactant Binding Induces a Mechanical Action in Heterogeneous Catalysis**

How, then, does one recognize and distinguish a catalytic action that is mechanical from one that is not? What is materially different between them? In particular, what physical feature causes the action of a catalyst to be governed by the collision frequency not $E_a$?

A possible insight into this question can be found in a technique employed in heterogeneous catalysis to distinguish catalysts governed by their collision frequency from those controlled by their $E_a$. In the 1950s, Balandin and others noticed a distinctive relationship between the relative rates at which formic acid is decomposed in the gas phase by various metal catalysts and the strength of catalyst–formate binding.\[4–6\] This relationship is depicted in Figure 4.

![Volcano plot](image)

**Figure 4. Volcano plot for the decomposition of formic acid by a range of heterogeneous metal catalysts.**

As can be seen, the reaction rate initially rises with increasing binding strength (quantified as the heat of adsorption of formate), after which it falls, giving a characteristic volcano-like shape. Such graphs are therefore termed “volcano plots”. They are common to a wide range of catalyzed reactions and are routinely used to optimize the heterogeneous catalysts employed in industrial chemical transformations.

Based on various physical studies,\[4–6\] it was concluded that the formate ion is an intermediate in this reaction, which has the mechanism $(K=k_i/k_{-i})$ shown in Equations (2) and (3).

$$
\text{HCOOH} \rightarrow \text{HCOO}^- + \text{H}^+ \quad (2)
$$

$$
\text{H}^+ + \text{HCOO}^- \rightarrow \text{CO}_2 + \text{H}_2 \quad (3)
$$

The importance of these equations is that they, effectively, depict the two general steps involved in a catalyzed reaction: steps i and ii of Figure 2a. Note that the right-hand side of Equation (2) is identical to the left-hand side of Equation (3). Thus, Equation (2) describes the rate at which the reactants are bound and brought into collision with each other on the catalyst (step i in Figure 2a). That is, Equation (2) describes all of the processes involved in catalyst-mediated collision. Equation (3) describes the rate at which such collisions, once achieved, are converted into products (step ii in Figure 2a). That is, Equation (3) depicts the process of overcoming the threshold activation energy ($E_a$).

The trends shown in Figure 4 represent these underlying processes. Thomson and Webb summarize it as follows:\[7\] on the left side of the plot, Equation (2) is rate-limiting (reactant binding and collision) and its rate increases with binding strength (since this increases the likelihood that the reactants will be bound and available for catalyst-mediated collisions). On the right side of the plot, Equation (3) is rate-limiting (overcoming $E_a$ to form products) and its rate decreases with binding strength (because stronger binding increases $E_a$). At the peak of the volcano plot the two processes are balanced and their rates are identical.

Fahrenfort, van Reyen, and Sachtler have put it thus:\[6\] “[the reason for the shape of the volcano plot is that] on one side of the maximum [the right-hand side], the activation energy becomes unfavorably high; on the other side [the left-hand side], the frequency factor [collision frequency] drops to low values”.

The critical point that comes out of volcano plots is that catalytic reactions are governed by their collision frequency when the individual catalyst–reactant binding contacts are weak and dynamic. In other words, when the reactant functionalities bind and release the catalyst rapidly and dynamically, they are attached so briefly that there is little time for them to collide with each other. Achieving collision then becomes the key impediment that must be overcome in the catalytic process; that is, the collision frequency becomes low and rate-determining.

In such time-dependent catalysts, binding and collision of the type shown in Equation (2) is the slower process and therefore rate-limiting overall. Thus, their rate expressions must necessarily contain a rapidly equilibrating catalyst–reactant intermediate of the type shown in Equation (2), since the formation and processing of this intermediate is the slowest step.

The key implication is that a mechanical action in a catalyst originates in the physical feature of dynamic reactant
binding. To find homogeneous catalysts with a mechanical action, one should therefore look for examples in which the reactants dynamically interact with the catalyst.

**Nonbiological Homogeneous Catalysts**

**Ferrocenophane hydrogen reduction catalysts**: To check the above deduction, we reviewed the scientific literature in search of non-biological homogeneous species through which the use of dynamic, weak binding interactions leads to time-dependent catalysis. Such catalysts are extremely rare: only a few potential examples could be found. While a dependence on collision frequency is highly probable in several of them, data is not available to unequivocally demonstrate it in most of them. A clear example of an abiological time-dependent catalyst was found, however, in the proton reduction catalyst \([1.1]\text{ferrocenophane}\) \(1\) (Scheme 1).

This species converts strong acids (\(H^+\)) to dihydrogen (\(H_2\)) in the presence of a sacrificial reductant. The mechanism of the catalysis involves simultaneous homolytic cleavage of transient Fe–H species during conformational flexing of the catalyst as shown in Scheme 1. Theoretical calculations indicate that the bound \(H^+\) ions in intermediate \(2\) are effectively atomic hydrogen (\(H\)) with most of their positive charge resident on the metal. A collision between two such highly reactive atomic hydrogen atoms, of the type shown in \([2]_{\text{TSC}}\) must, consequently, involve an exceedingly low \(E_a\) for \(H_2\) formation.

The key feature of catalysis by \(1\) is weak and dynamic proton binding. The ferrocenes in \(1\) are very weakly basic (\(pK_a = -6.5\), \(pK_a = -7.1\)). During the infrequent periods of ferrocene–H\(^+\) binding, the protons participate in a rapid, dynamic equilibrium involving Fe–H and agostic Cp ring C–H isomers as shown in Scheme 2. Density functional theory (DFT) calculations indicate that the \(\cdot\)Fe–H state is of higher energy and its lifetime is exceedingly short; too short to be measured at ambient temperature. As such, it must be considered to be the activated form of the bound reactant. Recently, \(2\) could be directly observed by \(^1H\) NMR spectroscopy at \(-122^\circ\text{C}\).

This confirmed that both iron atoms became protonated and that the exchange processes were too rapid to be resolved by NMR spectroscopy. The effect of this dynamic and transient reactant binding is to make it difficult for the catalyst to create collisions between bound reactants. Indeed, this becomes the major obstacle and the controlling factor in the catalytic process. The reasons for this are as follows.

Catalysis by \(1\) involves, in effect, two highly dynamic processes: 1) reactant binding by the catalyst and 2) conformational flexing by the catalyst. Reactive collisions can only occur if protons are simultaneously bound and activated at both ferrocene Fe ions (event I) at the instant that conformational flexing brings the catalyst into a structure (event II), which complements the transition state (shown in an exaggerated form as \([2]_{\text{TSC}}\) in Scheme 1). However, events I and II occur only very briefly and with relatively long time intervals between them. Moreover, they occur independently of each other. To have any chance of a reactive collision, catalyst flexing must therefore be synchronized with reactant binding. In other words: the ferrocene groups must undertake rapid conformational flexing about a structure that complements the reaction transition state. That is, the arrangement of the ferrocene catalytic groups must be such that vigorous conformational motion is available to bring simultaneously activated H substrates into reactive collisions with each other in the very brief time periods that both Fe atoms bear activated protons. For this reason, the structure and conformational dynamics of this class of catalyst are critical to achieving a catalytic effect.

Species like \(1\) and \(4\), which rapidly and dynamically oscillate about a structure that complements the transition state, are therefore highly active catalysts of proton reduction (Schemes 1 and 3). However, complex \(5\), which also flexes about a suitable structure but does so only slowly because of

**Scheme 1. Hydrogen reduction catalysis by [1.1]ferrocenophane, 1.**

![Scheme 1](image1)

**Scheme 2. Dynamic proton binding by ferrocene.**

![Scheme 2](image2)

**Scheme 3. Hydrogen reduction catalysis by other ferrocenophanes.**

![Scheme 3](image3)
the steric constraints of the additional Me groups, is entirely inactive as a catalyst (Scheme 3). Moreover, 6 and 7, which do not flex about a structure that complements the transition state, yield no catalytic effect (Scheme 3). The same is true for diferoxyethane 8 (Scheme 3) and monomer ferrocene in open solution; they also have a low likelihood of mediating a collision between simultaneously bound protons. Their collision frequency is, consequently, zero.

Catalyst 1 is therefore governed by the spatial and temporal fluctuations that lead to reactive collisions. In other words, it is a mechanical catalyst. This terminology is particularly apt, since 1 exhibits numerous characteristics common to mechanical processes in general. For example, like essentially all mechanical devices, the movements and actions of the components of 1 must be synchronized in order to realize an effect. That is, the catalytic groups must act in a concerted, coordinated manner or, more correctly, a convergent manner.

The catalytic action of 1 is, indeed, intrinsically machine-like. That is, when the processes of catalyst flexing and binding are synchronized, protons are dynamically bound, activated, and carried, repeatedly, along specific, unchanging, near-optimum pathways into reactive collisions with each other. These collisions occur within a structure that complements the desired outcome, namely the transition state. The process is driven by the mechanical impulse of conformational flexing. The products are then dynamically ejected and new reactants taken up for the next cycle. This binding, collision, and ejection process is arguably analogous to a mechanical device.

The action of 1 therefore generates products because its mechanical action and spatial arrangement at the point of collision is such that H₂ is formed. This is not the case for 5–8 and free ferrocene in open solution.

In terms of its general catalytic properties, [1.1]ferrocenophane can be, firstly, characterized as being a highly structure-sensitive catalyst. That is, small changes in its structure drastically affect its catalytic properties. In other words, structural modifications that decrease the rate of flexing (as in 5) or that diminish the population of the required conformational exchange during flexing (as in 6–8) rapidly and nonlinearily destroy the catalytic effect. This is because they severely diminish the extent of synchronization. In the same way, minor changes in the structure of a single cog within a machine may cause disproportionate, nonlinear losses in its efficiency.

A second feature is that the ferrocene Fe atom, which is not known to be a catalytic species in any other reaction, is transformed into a potent catalyst in 1. This transformation is wholly the result of the optimum conformational dynamics of 1. Without that, the ferrocene Fe atom cannot catalyze proton reduction because it binds and activates protons too transiently. This is confirmed by the fact that 1 progressively loses its activity in solution as it is cooled. At −122°C, Fe–proton binding is still rapid and dynamic, but conformational flexing is halted on the NMR timescale.

In conclusion, we should note that [1.1]ferrocenophane is remarkably active and long-lived for a homogeneous catalyst. Individual molecules of 1 have been shown to turn over 1000000 H₂ molecules, on average, without any noticeable loss of activity. When bound to polystyrene and coated on a p-type silicon photocathode, 1 turns over an estimated five molecules of H₂ per second, over five days of continuous operation. The sheer durability of 1 can only be due to its excellent selectivity, which prevents the formation of nonfunctional intermediates and avoids deactivation. Production of such vigor and high fidelity is typical of a machine—in this case, a “molecular machine”.

The physical chemistry of complex 1 during catalysis: Finally, it is worthwhile asking: is the activation energy of 1 low and does it display a catalyst–reactant intermediate in its rate expression? These features were said to be characteristic of mechanical catalysis.

The former question is not simple to answer. The problem is that the standard assumptions which underlie most methods for determining Eₐ are not appropriate to reactions governed by the collision frequency. For example, the Eyring equation that is widely used in this respect, is based on transition-state theory, which, as mentioned earlier, does not formally apply in these cases.

An alternative approach is to use an Arrhenius plot, in which the natural logarithm of the reaction rate (ln k) is plotted against the reciprocal of the temperature (1/T). According to Equation (1), such a plot should yield a line graph, the slope (−Eₐ/R) of which gives the activation energy and the intercept of which corresponds to the logarithm of the collision frequency, ln A.

A referee has argued that all of the above points regarding ideal spatial arrangement, the bringing together of reaction partners, and conformational movements in 1, can be described using the Eyring equation in combination with Michaelis–Menten kinetics (involving substrate–catalyst binding as a pre-equilibrium). For this reason, the referee argues that it is redundant to invoke a mechanical description of catalysis by 1. The authors respectfully disagree with this assertion. Transition-state theory may, indeed, describe the optimum equilibrium thermodynamics of reactant collision. That is, it may elucidate the ideal approach pathways and trajectories leading to the energetically most optimum collision between the bound reactants. However, it does not describe the nonequilibrium actions of a molecular catalyst that consistently and repeatedly achieves highly optimum collision thermodynamics. In such cases, the course of the reaction becomes determined by other, external factors that are unrelated to the thermodynamic efficiency of collision, including: 1) the frequency and rapidity of catalyst conformational flexing and 2) the extent to which it is synchronized with dynamic reactant binding. These factors control the frequency of collision, which becomes the chief determinant of reaction. Turnover in such species is then a function of the mechanics of reactant encounter, not its thermodynamics. In mapping the equilibrium energy hypersurface about reactant collision, transition-state theory does not describe nonequilibrium systems which, under an external impulse, repeatedly track only along the valleys on the surface.
quency ($A$) is unaffected by, and independent of, temperature and, moreover, that $E_a$ constitutes the most significant barrier to reaction.\cite{15} This is, of course, not true in a reaction that depends on the collision frequency. For example, an Arrhenius plot for the reaction of $\text{H}^+$ and $\text{OH}^-$ will yield the temperature dependence of the collision frequency, not the activation energy. As such, techniques based on the Arrhenius relationship generally describe the temperature dependence of the slowest step of the reaction. In a molecular catalyst, this is not the step of overcoming the threshold $E_a$ in the transition state. It would, instead, be the step of binding and subsequent flexing of the catalyst leading to reactant collision.

How then does one determine the $E_a$ for a mechanical catalyst? At this stage, we are, frankly, unaware of a suitable method for doing so.

The second question above relates to the presence of a catalyst–reactant intermediate in the rate expression of \( \mathbf{1} \). This is expected for catalysts governed by their collision frequency, since they are limited by the formation and processing of this intermediate.

The kinetics of homogeneous catalysts involving a rate-limiting, rapidly equilibrating, catalyst–reactant intermediate has been extensively developed in the field of biochemistry, which terms it Michaelis–Menten kinetics.\cite{15} One method of confirming the presence of such kinetics in a system involves seeing whether the experimental data fits a so-called Lineweaver–Burke plot, that is, a graph of \( 1/k \) versus \( 1/[\text{reactant}] \) as a straight line with a slope \( K_m/k_{\text{max}} \) and an intercept \( 1/k_{\text{max}} \) \((k = \text{rate}, \ k_{\text{max}} = \text{maximum rate}, \ K_m = \text{the Michaelis constant})\).\cite{15}

To the best of our knowledge, only one kinetic study of \( \mathbf{1} \) has been reported.\cite{12} This study employed the acid BF$_3$H$_2$O, and produced kinetic data that does indeed conform to a Lineweaver–Burke plot (with \( K_m \approx 0.2 \mu \text{M} \)\).\cite{12} While the significance of this result was not appreciated until very recently, \( \mathbf{1} \) does therefore appear to display a kinetically observable rapidly equilibrating catalyst–reactant intermediate.

**Cobalt–diporphyrin oxygen reduction catalysts**: Another likely example of a time-dependent homogeneous catalyst is the co-facial dicobalt–diporphyrin \( \mathbf{9} \) first described by Collman (Scheme 4).\cite{16} Compound \( \mathbf{9} \) catalyzes the four-electron reduction of $\text{O}_2$ to H$_2$O at potentials negative of 0.71 V (vs. NHE) and below pH 3.5, when adsorbed on a graphite electrode.\cite{14} Under identical conditions, the equivalent diporphyrin \( \mathbf{10} \), which contains a single extra -CH$_2$- group in its tethers, catalyzes the two-electron formation of $\text{H}_2\text{O}_2$.\cite{16,17}

The same is true for the corresponding and other Co–porphyrin monomers, which also generate $\text{H}_2\text{O}_2$\cite{16,17}.

A similar effect is observed for the dicobalt porphyrins \( \mathbf{12} \) and \( \mathbf{13} \), which also facilitate exclusively 4-electron dioxygen reduction despite a difference of almost 1 Å in their average Co–Co separations (Scheme 5).\cite{16,17} The aryl linkers in \( \mathbf{12} \) and \( \mathbf{13} \) constrain the Co ions to rapidly and repeatedly flex longitudinally along a binding pocket in which the metal ions eclipse each other (Scheme 6). This is critically necessary in this class of catalyst, since a capacity for “slippage” away from an eclipsed arrangement during flexing diminishes the extent of four-electron reduction.\cite{16,17} The important role of rapid, longitudinal flexing in these catalysts has led to the proposal of a so-called “Pac-Man” catalytic mechanism, which is named after a 1980s video game icon that employed a rapid and repeated biting motion (Scheme 6).\cite{16,17}

Extensive studies have revealed that, for O–O bond cleavage to occur in this class of catalyst, the O–O molecule must be simultaneously bound to, and activated by both Co centers in the cleft between the porphyrins.\cite{18} One of the Co centers needs only to act as a Lewis acid, as demonstrated by the fact that \( \mathbf{11} \), the mono-Co analogue of \( \mathbf{9} \), is also a four-electron reduction catalyst (Scheme 4).\cite{19} During the time that the diporphyrin binds dioxygen, the activation preferred by the Co ions is likely ideal for spontaneous O–O cleavage. This presumably occurs via a transition state in which the two O atoms are pulled apart along longitudinal...
trajectories that are optimum for O–O scission. The structure of the diporphyrin conformer that binds the O$_2$ during this process must necessarily complement the transition state for O–O bond cleavage. The population of this conformer at any one time will depend on the conformational properties of the Co diporphyrin. It is clearly high for 9, 11, 12, and 13, but low for 10.

It therefore appears that four-electron dioxygen reduction in the Co diporphyrins requires a very specific and rather unique confluence of circumstances. Each O atom in the O=O molecule must be simultaneously bound to a different Co center at the instant that conformational flexing of the diporphyrin framework pulls them apart.

The aryl linkers in 12 and 13 are ideal for maintaining an eclipsed structure, whilst allowing for the necessary oscillation in the Co–Co distance during flexing. In contrast, 9 depends on the shortness of its linkers to achieve satisfactory flexing about a face-to-face orientation. Lengthening the linkers, as in 10, increases the flexibility, thereby diminishing the population of the face-to-face conformer and destroying its selectivity for the necessary, longitudinal conformational change. The likelihood of the required, coordinated, synchronized interplay is then too low in 10 (or in monomeric Co porphyrins), to yield substantial four-electron reduction. Instead, a slower two-electron reduction, involving O$_2$ bound to a single Co center at the instant of reduction, is favored.[14]

The extreme sensitivity of the catalytic effect to this minor structural change is consistent with dynamism in one or both of the individual Co–O binding contacts. In 10, the dioxygen (or its peroxide intermediate) must be attached too briefly to both Co centers simultaneously to be present when they are also correctly arrayed and on the optimum trajectory for O–O bond cleavage. At any one instant therefore, effectively no molecules of 10 simultaneously have the dioxygen attached to both Co ions and the porphyrins flexing out of a face-to-face arrangement. That is, the collision frequency is zero. The term collision frequency refers here to the rate per unit time at which the dioxygen O atoms disengage from each other.

By contrast, the catalytic rates for 9, 11, 12, and 13, which also depend upon and are set by the collision frequency, are clearly substantial. This is undoubtedly due to the fact that these catalysts vigorously oscillate in a longitudinal manner, about the ideal, face-to-face conformer. In other words, they flex rapidly about a structure that complements the transition state for O–O cleavage.

In four-electron dioxygen reduction by 9, 11, 12, and 13 we again see the distinctive features of a mechanical action, albeit in the form of the reactant being pulled apart, rather than being put together into a new moiety.

Thus, we again have two dynamic and independent processes that must be synchronized: 1) transient O$_2$ binding at both Co ions simultaneously and 2) catalyst conformational flexing along a very specific and well-defined pathway. These processes can only be synchronized by constraining the catalyst to flex, vigorously and longitudinally, about a face-to-face structure that complements the desired transition state. When this is achieved, as in 9, 11, 12, and 13, the catalytic groups act in a concerted, coordinated, and convergent manner.[15] When it is not, as in 10 or in monomeric Co porphyrins, the collision frequency declines rapidly and nonlinearly to zero.

The whole process is driven by the mechanical impulse of conformational flexing. The system is machine-like in that it dynamically takes up reactant molecules, and then mechanically pulls them apart within a structure that complements the desired outcome. It does so in a highly repeatable and very specific way.

The process therefore involves synchronized mechanical actions the spatial and temporal features of which lead to the formation of products. These products, effectively, derive from an advantageous confluence of circumstances in which everything that was needed to create them occurred simultaneously and in the necessary spatial arrangement and orientation. These conditions originate in the conformational and binding constraints of the Co diporphyrins.

A final important point is that, in common with [1.1]ferrocenophile 1, the need for synchronized, convergent (mechanical) actions in the Co diporphyrins derives, fundamentally, from dynamism in the individual Co–O binding contacts. These contacts are clearly weak and transient, forming and releasing constantly. That does not mean however, that the overall strength of dioxygen binding by 9, 11, 12, or 13 need be weak. In fact, cooperative molecular recognition effects can cause overall binding to be much stronger than the individual binding contacts. Thus, for example, the dioxygen binding affinity of 9 ($K_{O_2}=10^{10.0\pm 0.3}$ atm$^{-1}$), is several orders of magnitude larger than that of comparable monomeric Co porphyrins.[16] This undoubtedly reflects the cooperative influence of molecular recognition.

### Biological Homogeneous Catalysts

A question that arises in light of the above discussions is whether any of the homogeneous catalysts of biology, that is, enzymes, employ a mechanical action? This topic will be examined in detail elsewhere,[2] so that we will consider it here only in respect of the possible implications for developing bio-inspired molecular catalysts.

Several characteristics of catalysis by certain enzymes are reminiscent of “mechanical” homogeneous catalysts. For example, enzymes are known to generally employ the lowest activation energies of any class of catalyst.[17] Of course, we do not know whether the reported $E_a$ for each enzyme truly reflects the energy threshold that must be overcome in substrate collision; this would be the case only if the enzyme was an energy-dependent catalyst. If an enzyme were a time-dependent catalyst, its reported $E_a$ would actually relate to the energy requirement of conformational flexing leading to substrate collision. Nevertheless, the reported data for enzymatic $E_a$’s are generally notably lower than those of abiological catalysts.
Some recent studies also indicate that the activities of certain enzymes are governed by conformational fluctuations in their protein framework,[20] rather than by the activation energy involved in substrate collision. For example, NMR studies on cyclophilin A and triosephosphate isomerase have detected conformational fluctuations within the active site that occur on a timescale that correlates with the microscopic rate of substrate turnover.[31,32] These conformational changes are currently believed to facilitate other parallel processes, such as gating and solvent exclusion of the active site.[22,23]

Enzymes are, moreover, widely considered to employ concerted (convergent) catalytic actions involving very particular spatial arrangements and conformational movements in their active site.[2,20] As we have seen, this is also true for abiological homogeneous catalysts that employ a mechanical action.

Indeed, as first noted by Pauling,[24] a characteristic feature of enzymes is that their active sites are often structurally complementary to their reaction transition states. This appears to also be true for non-biological, homogeneous catalysts that involve a mechanical action, such as 1, 4, 9, and 11–13. That property arose in those cases, because the individual catalyst–reactant binding contacts were weak and transient. Reactive collisions could therefore only ever occur if the catalyst vigorously flexed about a structure that complements the transition state. The individual binding contacts between enzymes and their substrates are, however, also often weak and transient, comprising of hydrogen-bonding, ion-pairing, hydrophobic–hydrophilic, or van der Waals interactions. A mechanical action therefore offers a potential explanation for the fact that enzyme active sites often structurally complement their transition states.

There seem to be many more such correlations. For example, many enzymes are extremely structure-sensitive catalysts, with even minor changes in the spatial arrangement of their active site leading to large, nonlinear decreases (> 10^2-fold) in their catalytic activity.[20,26] An extreme structure sensitivity is also a feature of non-biological mechanical homogeneous catalysts that depend on vigorous and very specific conformational dynamics for their catalytic effect.

As noted earlier, highly efficient conformational dynamics in abiological mechanical systems may transform transiently binding and activating groups into potent catalysts (e.g., the Fe ions in 1 or the free porphyrin ring in 11). In the absence of the necessary conformational dynamics, such groups are typically entirely inactive in open solution, because they bind and activate their reactants too briefly.

This could conceivably also be the case with the amino acid residues that serve as powerful catalytic groups in many enzymes. Of all the available monomers and oligomers of amino acids, only artificial 1-prolines[26] have been reported to be catalytically active outside of enzymology, in open solution.

Another distinctive and characteristic feature of many enzymes is that they display Michaelis–Menten kinetics, which involves a rate-limiting, rapidly equilibrating, catalyst–reactant intermediate (known as the Michaelis complex).[15] As noted earlier, abiological mechanical homogeneous catalysts necessarily also display such a catalyst–reactant intermediate in their rate expressions. A mechanical action therefore offers a potential explanation for the origin of Michaelis–Menten kinetics in biology.

Finally: the concept of a “mechanical” catalytic action has been raised before in enzymology, but not explored in detail. For example, Moss and others have explicitly described enzymes as machine-like “specialized combining centers”[27,28] while Williams has characterized enzymatic action as being akin to a mechanical device.[29] In other cases, more oblique allusions have been used. For example, Benkovic and Hammes-Schiffer describe catalysis by enzymes in terms of “coupled protein motions”[20] while Menger has proposed a spatiotemporal hypothesis for enzymic action.[30] The archetypal spatiotemporal system is, however, a mechanical device, which operates by coupling one action to another (e.g., the interlocking cogs in a mechanical watch). Machines are critically dependent on the spatial pathways followed by their components and the precise times at which they do so. The high activities and specificities of enzymes are consistent with “molecular machines”.

Bioinspired Homogeneous Catalysts

While detailed, confirmatory experimentation is therefore still required, the evidence available at present suggests that the catalytic action of at least some enzymes may be determined by their collision frequency. In that case, we wondered whether it would be possible to emulate the catalytic feats of an enzyme using a model species that employed a mechanical action? Such a model would necessarily have to exhibit:

I) An active site capable of facilitating reactive collisions by rapid conformational flexing about a shape that is complementary to the transition state of the reaction.
II) Highly dynamic individual catalyst–reactant binding contacts, involving a continuous attachment and release of reactant functionalities.

Mn-Oxo cubanes—a model of the photosystem II water-oxidizing complex (PSII-WOC): Only one homogeneous catalyst is known to sustainably facilitate water oxidation: the water-oxidizing complex (WOC) of photosystem II (PSII), which is found in all photosynthetic organisms and operates at 1.00 V versus Ag/AgCl (1.20 V vs. SHE). An atomic model of the resting oxidation state of the PSII-WOC core, isolated from the cyanobacterium Thermosynechococcus sp., has recently been derived from single-crystal X-ray diffraction (XRD) data.[31] Although the low-XRD resolution (3.2 to 3.6 Å) lead to differences in data interpretation, one model[32] indicates an inorganic core comprised of a cubical Mn,Ca cluster, with four metal atoms in a symmetrical het-
erocubane arrangement of Mn₃Ca, connected to a single Mn atom (Figure 5).[33] Four O atoms have been proposed to link the CaMn₄O₄ cluster, which is compatible with Mn EXAFS and EPR studies.[34]

The absence of evolutionary diversity in the PSII-WOC implies that combinatorial biosynthesis in nature has produced a single catalyst capable of oxidizing water. This conclusion has implications for research and has informed attempts to model this catalyst.

One model system of the PSII-WOC are the cubane Mn₄O₄L₆ complexes[14] (L/C₀ = (p-R-C₆H₄)₂PO₂/C₀; R = H, OMe; Scheme 7). These species comprise a flexible, cubical Mn–O arrangement, the structural motif of which is analogous to that proposed to be present in the active site of the PSII-WOC (Figure 5).[35] They also spontaneously self-assemble from Mn2⁺.[35] Under suitable conditions, 14 will, moreover, sequentially abstract 4H atoms (4H⁺ + 4e–) to yield the “pinned butterfly” 15, with associated release of two H₂O molecules (Scheme 7).[36] This process is readily reversible, indicating that the oxygen bridges in 14 are dynamically formed from water.

UV illumination of 14 in the gas phase leads to the spontaneous release of O₂ (and a Ph₂PO₂⁻ ligand, thereby forming the “butterfly” complex 16; Scheme 7).[37] The quantum efficiency for this process at 350 nm was found to approach 100% for 14 (R = OMe).

A potential catalytic cycle therefore exists for 14 (the framed question mark in the middle of Scheme 7). Such a cycle had, however, never been realized in practice.

Of particular interest to us was the likely mechanism for the step of photolytic O₂ release (14 → 16), which is depicted in Scheme 8.[38] Theoretical calculations suggested that the key catalytic step involves the photoinduced loss of a ligand.[39] The remaining cubane framework is then able to flex, causing the two highly reactive, coordinatively unsaturated, corner O atoms to collide with each other (Scheme 8).[39] Given the high quantum efficiency of this process for 14 (R = OMe), this collision must readily overcome the activation energy threshold, thereby resulting in reaction. However, the flexing process that creates the collision and subsequently sees the release of the O₂ product, was calculated to require 96–126 kJ mol⁻¹ of energy overall.[39]

Thus, in the gas phase at least, indications existed to suggest that 14 may facilitate a mechanical process, albeit only for a single turnover.[39] Moreover, 14 appeared to display both of the required features I and II described earlier, and needed for a mechanical catalyst, namely: it creates successful, reactive collisions between the corner O atoms by rapid conformational flexing after photorelease of a Ph₂PO₂⁻ ligand (as observed in the gas phase), and in its self-assem...
Based on these considerations, it seemed to us that 14 offered a potential bio-inspired catalyst that may employ a mechanical action. In that case, we wondered whether it would be capable of facilitating active water oxidation in aqueous solution, if suitable conditions for continuous turnover could be found. Such conditions would necessarily provide for the disassembly of the cubane by photolytic ligand release prior to O₂ formation (14 → 16), as well as its subsequent reassembly to take up the free ligand, along with two water molecules (16 → 15 → 14; Scheme 7). As 14 (and 14+) are strongly hydrophobic and therefore entirely insoluble in aqueous medium, we examined the use of Nafion as a catalyst support. Nafion offers an interface of hydrophobic and hydrophilic domains.

**Nafion-doped with Mn–Oxo cubane is an efficient photoelectrocatalyst of water oxidation**: In experiments we found that when 14+ (R = OMe) is doped, by ion exchange, into a thin Nafion layer deposited on a glassy carbon disk electrode that is then immersed in H₂O, poised at 1.00 V (vs Ag/AgCl), and illuminated with light (EM 1.5), a substantial and sustained photocurrent is generated (Figure 6).[39] The photocurrent appears when the light is turned on (up arrows in Figure 6). It disappears when the light is turned off (down arrows in Figure 6). Under constant illumination, the current persists over a continuous 65 h of testing.

The following evidence supported the contention that the observed photocurrent derived from water oxidation catalysis by the cubane.[39] Gas bubbles generated as a result of the current were collected and shown to be pure O₂. The volume of O₂ matched the cumulative current passing through the electrode. Isotopic-labeling studies confirmed that the O₂ originated in the H₂O electrolyte. When an electrolyte of pure CH₃CN was used, no photocurrent was observed. However, the addition of H₂O to the CH₃CN led to an increasing photocurrent up to 8% water/CH₃CN, at which point saturation occurred (Michaelis–Menten kinetics). The photocurrent varied with pH in accord with that expected for H₂O oxidation, the E₀ of which changes by 59 mV per pH unit. There was no photocurrent without 14+ or with a range of other Mn species in the Nafion layer. The photocurrent declined when 14+ was progressively leached out of the Nafion by competitive ion-exchange. EPR spectroscopy of the doped Nafion indicated that 14+ was taken up intact and disassembled and reassembled during turnover under illumination at 1.00 V (vs. Ag/AgCl).[40]

The reduction in overpotential for H₂O oxidation catalysis was found to be 0.38 V (plus light). A typical Nafion layer on the 3 mm diameter disk electrode was about 7 µm thick and contained mere nanograms of 14+. The average turnover frequency per 14+ at 1.00 V (vs. Ag/AgCl) was, at least, 24 molecules O₂ h⁻¹ over 65 h of continuous operation.[39] Peak turnover frequencies of up to 270 molecules O₂ h⁻¹ were measured.[40] These data make 14+ one of the most active and durable known abiological Mn homogeneous catalysts of H₂O oxidation, to the best of our knowledge.[2]

The action spectrum indicated that the maximum catalytic efficiency occurred at 350 nm illumination, which corresponds to the main MLCT absorption peak of 14. Catalysis was facilitated however upon illumination up to 600 nm in the visible spectrum.[39]

These results are, we believe, significant. They represent one of the first times, as far as we know, that a model complex (of the PSII-WOC in this case) has demonstrated sustained and active catalysis that is similar to its enzyme. The catalysis cannot be said to be identical to the enzyme, since the PSII-WOC is known to turn over without illumination by sunlight, whereas 14+ in Nafion requires illumination. The observed 0.38 V decline in the overpotential for water
oxidation may reflect, in part, the added influence of the light. While $^{14}+^+$ is critical to the catalysis, we cannot yet pronounce unequivocally upon the mechanism (nor, certainly, on its relationship to that in PSII-WOC). However, it is likely that, during the process of doping Nafion from an organocatalytic solution of $^{14}+^+$, the hydrophobic $^{14}+^+$ ions are drawn into the water channels of the membrane, attracted by the sulfonate anions. Subsequent immersion of the electrode in an aqueous electrolyte may then cause the cubane cations to migrate into the hydrophobic pockets of the Nafion polymer. Within these hydrophobic domains, electrochemical, EPR, and other evidence suggests that illumination results in spontaneous photodissociation of one of the phosphinate ligands from the cubane core.$^{[9]}$ This facilitates the release of dioxygen and the formation of the butterfly cubane $^{16}$ according to the gas-phase mechanism shown in Scheme 8. Under the applied potential of 1.00 V (vs. Ag/AgCl), the butterfly $^{16}$ appears to take up two water molecules and cycle through an EPR-detectable pinned butterfly intermediate $^{15}$, to regenerate the cubane by four successive proton-coupled electron transfer steps (4$^+\text{H}^+ + 4e^- $). The $^+\text{H}$ ions thus generated, are likely transported away by the proton channels in the Nafion in much the same way that is believed to occur in the PSII-WOC.

In summary, we have shown that a Nafion membrane doped with miniscule quantities of the cubical model complex $^{14}+^+$ displays a significant photocatalytic effect in the oxidation of water. While we have not demonstrated that $^{14}+^+$ undertakes mechanical catalysis of water oxidation, the evidence available at present does not contradict such a possibility. Moreover, the assumption of a mechanical catalytic action in $^{14}+^{14}+^+$ has led us to develop a new and efficient water oxidation photoelectrocatalyst.

Conclusions

Two fundamental transformational processes are recognized in science: thermodynamics, which describes transformations due to an energy differential, and mechanics, which describes transformations due to physical cause-and-effect sequences, which play out over time.

Thermodynamics and its associated realm of transformations under equilibrium conditions, is, historically, a highly developed field of endeavor in chemistry and catalysis. Kinetics describes the physical interactions that mediate thermodynamic imperatives.

Mechanics, and its associated realm of transformations under non-equilibrium conditions, is, by contrast, underdeveloped.

In this work we have sought to address this imbalance. We have examined the incidence, properties, and fundamental character of mechanical reactions facilitated by selected non-biological homogeneous catalysts. We have shown that, in being governed by their collision frequency rather than by their activation energy, such catalysts rely on spatial and temporal fluctuations in their molecular framework. Such fluctuations must be narrowly constrained to the optimum in order to yield an observable catalytic effect. Necessary conditions include: 1) vigorous conformational oscillation about a molecular structure that complements the transition state of the catalyzed reaction and 2) highly dynamic catalyst–reactant binding contacts. These constraints arise in the fact that multiple, weak, and transient binding contacts allow for catalyst-mediated collisions only if reactant binding is synchronized with catalyst flexing.

When a molecular catalyst employs a mechanical action, it appears to operate somewhat like a machine that is driven by regular conformational flexing to facilitate chemical transformations. Products are generated as a response to the repeated and optimally configured spatial and temporal (mechanical) impulses present.

In seeking to understand, define, and test the principles of mechanical catalysis, we have discovered a new ground-breaking catalyst, Nafion-14+, with potentially important implications for the field of biomimetic chemistry and for attempts to mimic biological catalysis in general.$^{[6]}$ This discovery has been made by working towards homogeneous catalysts with mechanical actions. The fact that it has led to a new catalyst suggests that the approach has potential merit and that we and others should continue with it.

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References

Complex catalytic systems that include metal catalysts have been the subject of extensive research due to their widespread application in various industrial processes. For example, in the context of catalase, a key enzyme in cellular defense mechanisms, several studies have explored its role in hydrogen generation. The saturation current of a catalyst has been reported to be 37 mA, as seen in reference [10].

In the context of coating technology, references [10] and [12] suggest the importance of a coating material for enhancing catalytic activity. The saturation current of a catalyst has been reported to be 37 mA, as seen in reference [10].

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