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Conformational dynamics for catalysis beyond the Sabatier limit

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ABSTRACT: Conformational changes occur throughout biology and are implicated in numerous phenomena, including in enzyme catalysis where their role remains controversial. Conformational dynamics have also been observed in small-molecule catalysis, yet a lack of systematic study means that their influence is poorly understood. Here, we highlight how advances in chemical reaction network mathematics, alongside the translation of the Sabatier Principle from heterogeneous to homogeneous catalysis, now enable the behavior of conformationally dynamic catalysts to be understood from first principles. We demonstrate that for common classes of reaction mechanism, catalyst conformational dynamics can in principle cause large rate enhancements relative to each of the catalyst's individual conformations, as well as rate enhancements of orders of magnitude above the Sabatier limit. This quantitative understanding reveals how particular features of a catalyst or reaction mechanism govern catalytic rate, which allows us to propose general design principles that might be exploited by future conformationally dynamic catalysts. The understanding that conformational dynamics can allow a catalyst to overcome otherwise fundamental rate limits should have broad implications across chemistry and biology.

Introduction

Conformational dynamics are important throughout biology¹ as an enabling feature of allosteric regulation,² cellular signalling,³ energy transduction,⁴ and molecular machinery.^{5,6} They also underlie numerous models of enzyme catalysis^{7–11} and have been implicated in the evolution of new protein functions^{12,13} and disease¹⁴ (Figure 1a). Changes in the shape of a molecule span orders of magnitude in time and space, and range from single-bond vibrations to global changes in macromolecular structure.^{15–18} Large amplitude dynamics are a consequence of Brownian motion and occur when the secondary interactions responsible for the shape of a molecule¹⁹—such as attractive noncovalent interactions or repulsive steric interactions—can be reorganized without a significant energy barrier or free energy cost. These weak interactions are more likely^{19,20} to occur as the number of atoms, functional

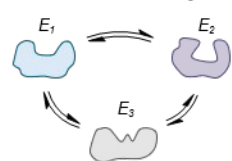
groups, and rotatable bonds in a molecule increase. Accordingly, conformational changes increase in both likelihood and number as molecules increase in size,²⁰ yet even simple small molecules can undergo consequential and well-defined conformational (e.g. methylcyclohexane²¹) or configurational (e.g. benzophenone imines²²) changes. As well as spontaneous conformational changes, thermodynamically unfavorable^{23–25} or kinetically inaccessible^{25,26} conformational changes are also known to take place, with the requirement that they are driven by (i.e. coupled to) a free energy releasing process^{27,28} (such as exergonic chemical reactions, photon absorption and relaxation, or redox events).

Inspired by the desirable outcomes of enzyme catalysis, chemists have sought to incorporate certain features of enzymes into their own catalyst designs²⁹ (Figure 1b). Consequently, attractive noncovalent interactions,^{30–33} rationally designed active-site

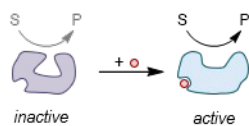
microenvironments,^{34–36} and even electric fields^{37–39} are now employed to improve catalyst activity and selectivity. Yet the inclusion of conformational dynamics remains conspicuously absent in homogenous catalyst design, despite a widely reported^{7–11} importance in enzyme catalysis. Conformational changes have been observed in well-known metal- and organo-catalyst scaffolds,^{40–48} but their complexity and a concomitant difficulty in characterization often cloud their influence. Progress towards understanding and harnessing conformational dynamics in homogeneous catalysis has therefore largely taken place on a case-by-case basis.^{40,48} It is clear that a systematic study that provides insight into the underlying principles and mechanisms, as well as an analysis of current precedents, could benefit future catalyst design across both chemistry and biology.

In this Perspective, we quantitatively demonstrate how, why, and in which circumstances, spontaneous conformational dynamics can lead to catalytic rate enhancements. Our approach rests on the chemical reaction network mathematics^{49–52} developed in the context of ‘catalysis-driven’ or ‘chemically fueled’ molecular machinery^{5,53–55} (Figure 1c). By modelling these networks according to the Sabatier Principle—whose translation from heterogeneous^{56–58} to homogeneous catalysis is an emerging field^{59–72} of research—we demonstrate how numerous common

a Conformational dynamics in biology



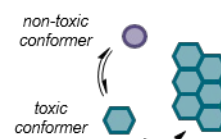
Enzyme catalysis
May contribute to enhanced rate and selectivity



Allosteric catalysis
Signalling, regulation, and systems behaviour

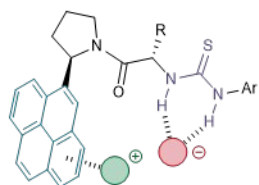


Molecular machinery
Directional motion and performance of work



Disease
Implicated in Alzheimer's, Parkinson's, others

b Emulating the properties of enzymes: conformational dynamics require systematic study

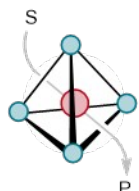


Attractive non-covalent interactions

Frequent use in catalysis

Systematically studied

Well-understood physics

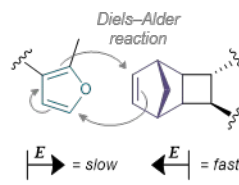


Active site microenvironments

Frequent use in catalysis

Systematically studied

Emerging quantitative insight



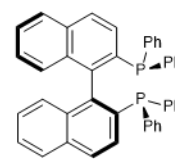
Electric fields

Emerging use in synthesis

Systematically studied

Well-understood physics

artificial catalysts often designed to be rigid



Conformational dynamics

Rarely intentionally used

Limited systematic study

Limited quantitative insight

c This Perspective: how do conformational dynamics affect catalytic rate?

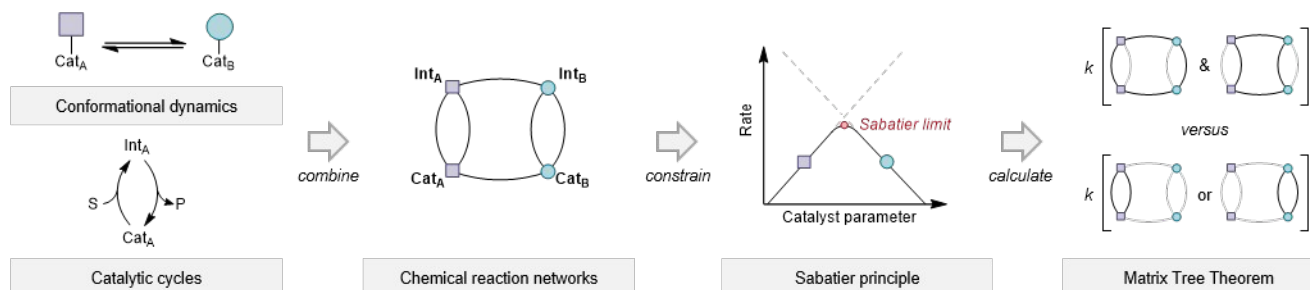


Figure 1. Introduction. a) Conformational dynamics have a wide-ranging importance in biology. b) Chemists seek to understand and emulate the catalytic properties of enzymes. Most of the characteristic phenomena of enzyme catalysis, such as attractive noncovalent interactions, active-site microenvironments, and even electric fields, have been the subject of systematic study. In contrast, the systematic study of conformational dynamics in catalysis is limited. c) This Perspective: a quantitative understanding of conformationally dynamic catalysis enabled by both nonequilibrium chemical reaction network mathematics and the Sabatier principle.

reactions are amenable to conformationally dynamic rate enhancement. We uncover the importance, and lack of importance, of particular features of both the catalyst and the reaction mechanism in relation to rate enhancement, results which may also have relevance for the study of enzyme catalysis. Our findings, alongside an analysis of artificial catalyst precedents, allow us to propose a number of design principles that might be exploited by future dynamic catalysts. We end by discussing conformational dynamics in enzyme catalysis and the future of conformationally dynamic catalysis.

Principles of conformational dynamics in homogeneous catalysis

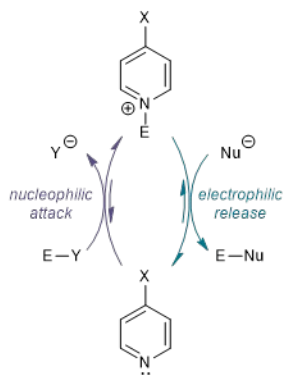
The Sabatier Principle in homogeneous catalysis

The principles underlying conformational dynamics in homogeneous catalysis can be best understood through a simple model reaction. Consider an illustrative homogeneous chemical reaction: the reaction of an electrophile + nucleophile $\rightarrow$ product + leaving group, which can be abbreviated as $E-Y + Nu^- \rightarrow E-Nu + Y^-$. The reaction can be catalysed by a pyridine nucleophilic catalyst⁷³⁻⁷⁵ in a simple two-step catalytic cycle involving nucleophilic attack of pyridine into the electrophile, followed by electrophilic release

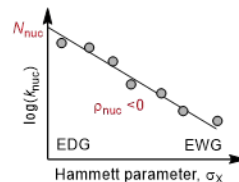
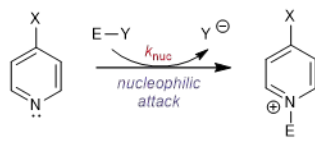
of the electrophile (E^+ , from the pyridinium) by the nucleophile to form the coupled product (Figure 2ai). By substituting the pyridine catalyst with an X group and varying the electron donating ability of that group, a Hammett plot^{76–79} can be constructed for each of the two elementary steps of the catalytic cycle. Electron rich X groups favour nucleophilic attack^{76,77,78} (the Hammett plot for this step has a negative gradient: $\rho < 0$, Figure 2aii), while electron

a Linear Free Energy Relationships: nucleophilic catalysis case study

i General catalytic cycle



ii Nucleophilic attack elementary step

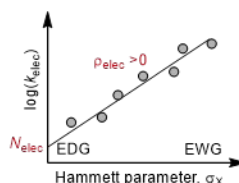
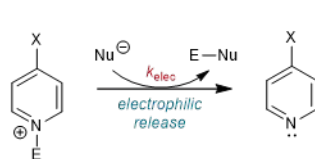


Linear free energy relationship (Hammett equation)

$$k_{\text{nuc}} \propto \exp(N_{\text{nuc}} + \rho_{\text{nuc}} \sigma_X)$$

electron donating groups (EDG) favour nucleophilic attack

iii Electrophilic release elementary step

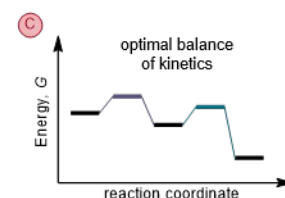
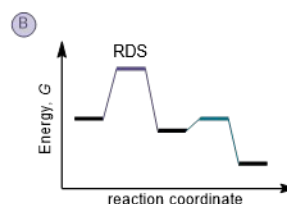
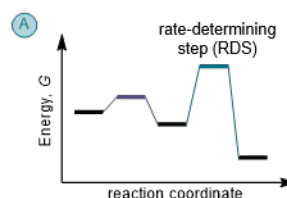
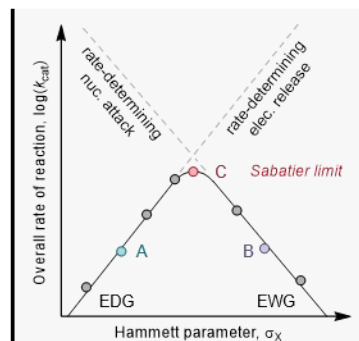
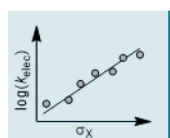
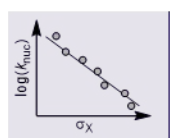


Linear free energy relationship (Hammett equation)

$$k_{\text{elec}} \propto \exp(N_{\text{elec}} + \rho_{\text{elec}} \sigma_X)$$

electron withdrawing groups (EWG) favour electrophilic release

b How the Sabatier principle arises in homogeneous catalysis



- A electrophilic release = RDS
increase rate by increasing σ_X
- B nucleophilic attack = RDS
increase rate by decreasing σ_X
- C optimal σ_X , maximum rate

Figure 2. The Sabatier principle in homogeneous catalysis. a) i) A simplified general mechanism, consisting of only two elementary steps, for nucleophilic catalysis by an X-substituted pyridine catalysis. E–Y = electrophile, Y = leaving group, Nu = nucleophile, E–Nu = product. ii) The nucleophilic attack elementary step is governed by an (illustrative) linear free energy relationship (Hammett equation). iii) The electrophilic release elementary step is governed by an (illustrative) oppositely-sloped Hammett equation. b) A Sabatier volcano arises from the superposition of the two oppositely sloped linear free energy relationships. One slope of the volcano is bound by rate-determining nucleophilic attack (point B), the other by rate-determining electrophilic release (point A). The peak of the volcano is the Sabatier limit (point C), which, due to an optimal balance of kinetics, represents the fastest rate of the catalyzed reaction.

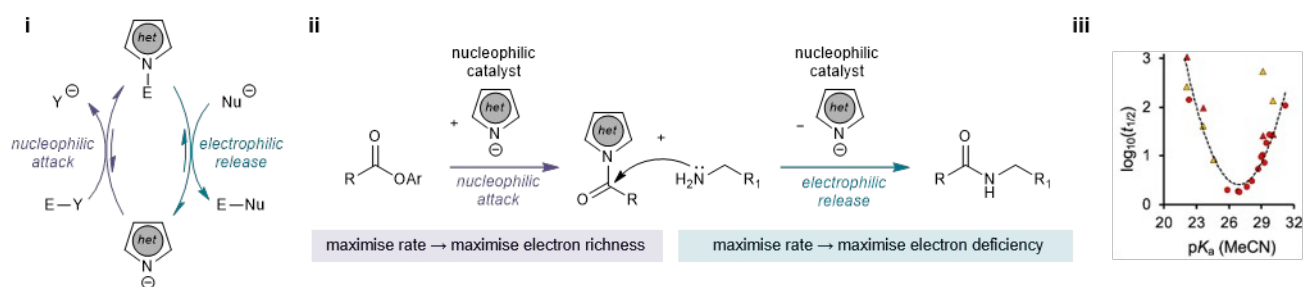
poor X groups favour electrophilic release^{76,77,79} ($\rho > 0$, Figure 2aiii). Because the overall rate of the reaction depends on the rate constants of each elementary step (see Supplementary Information, Section 1.1 for the analytical expression), the overall rate dependence on the X group electron richness—and

therefore on the catalyst electron richness at the active site—can be described by a superposition of each oppositely sloped Hammett plot.⁸⁰ This superposition results in a volcano-shaped curve referred to as a Sabatier volcano (Figure 2b).^{59–67}

This volcano plot was constructed using the Hammett equation, and so the overall rate (y axis) depends on the electron richness of the catalyst (x axis). However, there is no physical reason that other linear free energy relationships (such as the Taft equation,⁸¹ or the Brønsted equation⁸²) cannot be used to construct a Sabatier volcano.^{59-67,71,72,80} Accordingly, compound variables derived from techniques such as multi-variate linear regression, or calculated variables such as those provided by density functional theory, may also serve as the Sabatier volcano x-axis. When the rate of a reaction (i.e. the logarithm of the rate constant) can be shown to depend linearly on multiple variables, three- or higher-dimensional Sabatier volcanoes might result.⁶⁵ In this Perspective, we have chosen to focus on Hammett-derived Sabatier volcanoes for narrative simplicity, and because Hammett studies are both widely understood and frequently performed by chemists. However, it is likely that the results, discussions, and conclusions presented here can be generalised to many different types of Sabatier volcanoes.

The representative pyridine example serves as a qualitative illustration of how the Sabatier principle can arise in nucleophilic catalysis. Dale et al.⁸³ (Figure 3a) and Kluga et al.⁸⁰ report experimental examples that are analogous to the general example in Figure 2. Although the authors do not explicitly discuss the Sabatier principle, kinetic analysis demonstrates that the reactions exhibit volcano-shaped rate profiles. The origin of each volcano-shaped rate profile is reported to arise due to different regimes in which nucleophilic attack, or electrophilic release, are rate-

a Experimental example of a Sabatier volcano in homogeneous catalysis (Ref. 83)

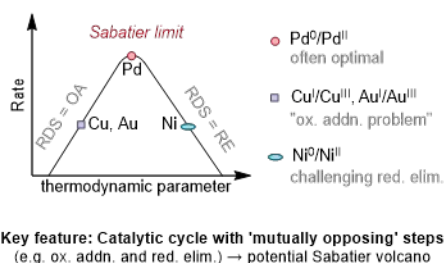


b Other catalytic reactions reported to be governed by the Sabatier principle

i Reported reaction classes

- **cross couplings**^{59,61,66}
Suzuki, Kumada, Negishi, Stille, Hiyama, etc.
- **hydrogenations**⁸⁵; **hydrofunctionalizations**⁶⁵
- **nucleophilic (Lewis base) catalysis**
cyclopropanation,⁸⁰ ester amidation,⁸³ esterification? phosphorylation? Baylis-Hillman? cycloadditions? Benzoin/Stetter reaction? etc.
- **others?** Lewis acid? Brønsted acid/base? redox?

ii A focus on cross couplings



iii Mechanistic rationale

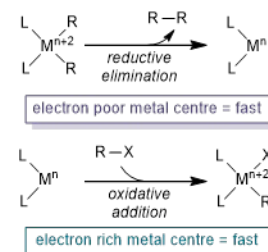


Figure 3. Sabatier principle precedents. a) i) Simplified mechanism of nucleophilic catalysis of ester amidation by an anionic heteroarene catalyst. ii) Nucleophilic attack is faster for electron rich heteroarene catalysts, which are typically those with a low pK_a . Electrophilic release is faster for electron poor heteroarene catalysts, which are typically those with a high pK_a . iii) A Sabatier volcano arises from these two opposing effects. The Sabatier volcano is constructed from pK_a -dependent linear free energy relationships, rather than the Hammett equation. The Sabatier volcano is inverted due to the y-axis dependence on the logarithm of the reaction half-life, rather than the logarithm of the catalytic rate constant. Graph reproduced with permission from Reference 83, Copyright ©. b) i) Other classes of catalytic reaction are reported to be governed by the Sabatier principle. Due to mechanistic similarities, additional classes of reactions may be similarly governed (text followed by a question mark: e.g. 'esterification?'). ii) iii) The Sabatier principle arises in cross-couplings due to the opposing demands of electron rich catalyst = fast oxidative addition (OA) and electron poor catalyst = fast reductive elimination (RE).

determining. It is reported in both cases that the optimal catalyst for the reaction occupies the peak of the volcano. Because Hammett analyses on the catalyst are less common than the corresponding substrate Hammett analysis, and because the Sabatier principle is only recently emerging as a concept in homogeneous catalysis, further experimental examples⁸⁴ are limited.

It is clear, however, that the same reasoning applies to numerous other classes of reactions in homogeneous catalysis. Theoretical reports from Corminboeuf⁵⁹⁻⁶⁵ and others⁶⁶⁻⁷² have revealed that certain metal-catalysed cross couplings,^{59,61,66} hydrogenations,⁸⁵ and hydrofunctionalizations,⁶⁵ as well as other⁶⁵ common reactions, are also governed by the Sabatier principle (Figure 3b). Due to mechanistic similarities, it is possible that other classes of reactions such as Lewis acid,⁸⁶ Brønsted acid⁸⁷/base⁸⁸, and redox catalysis^{89,90} are similarly governed. The unifying feature of these examples is the existence of a pair of 'mutually opposing' steps in

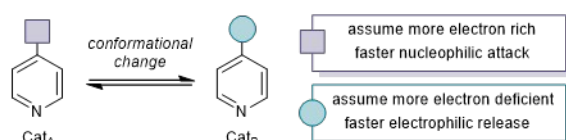
the catalytic cycle (e.g. steps opposing in electronic demand, such as nucleophilic attack and electrophilic release; oxidative addition and reductive elimination; deprotonation and protonation), in which the rate of one step can usually only be improved at the expense of the other.

The peak of a Sabatier volcano is known as the Sabatier limit.^{65,91} It is typically occupied by a 'Goldilocks' catalyst that is well-adapted to both elementary steps, without necessarily being the most active catalyst for an individual elementary step. For example, palladium (Pd^0/Pd^{II}) catalysts are reported^{59,61,66} to occupy the Sabatier limit in certain cross-coupling reactions, despite copper (Cu^I/Cu^{III}) catalysts often exhibiting superior rates of reductive elimination, and nickel (Ni^0/Ni^{II}) catalysts often exhibiting superior rates of oxidative addition (Figure 3b). Because the Sabatier principle appears to result in a fundamental limit^{59-67,91} to the rate of important reactions in homogeneous catalysis, it is interesting to consider whether or not it can be overcome.

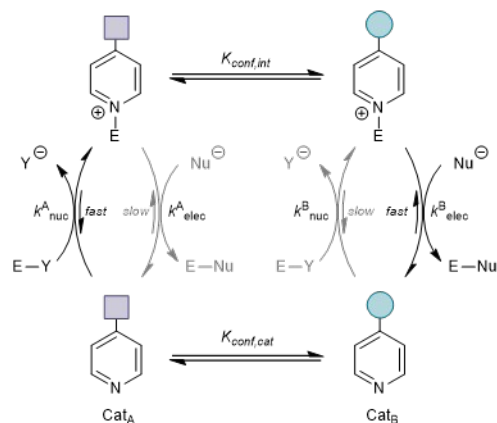
Conformational dynamics appear to accelerate catalysis

Let us introduce catalyst conformational dynamics to the model reaction. In the place of the X group, the pyridine is substituted by a group that undergoes a spontaneous, well-defined, and reversible conformational change between two conformers: Cat_A (square) and Cat_B (circle) (Figure 4a). The catalytic cycle for the reaction is now a four-state chemical reaction network^{5,27,28,49-55} in which the vertical edges represent chemical reactions and the horizontal edges represent conformational changes (Figure 4b). In the field of molecular machinery, these networks are referred to as 'chemomechanical' cycles.⁵³⁻⁵⁵ Assuming that

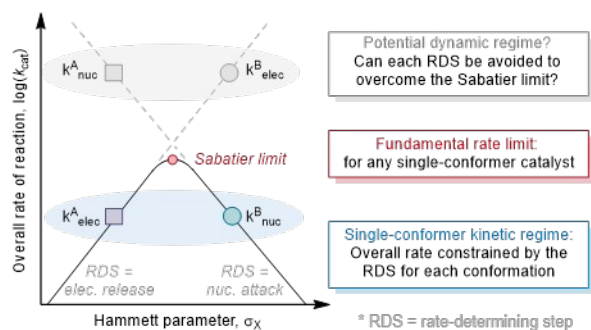
a Introducing a conformational change



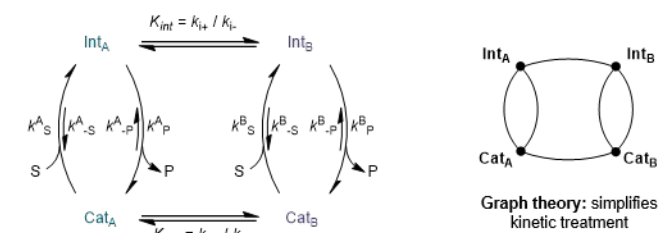
b Effect of conformational change on catalytic cycle



c Different conformers and the Sabatier principle



d Generalising the model



Graph theory: simplifies kinetic treatment

e The Sabatier principle constrains the model

$$k_S^A = \Gamma \exp(N_S + \rho_S \sigma_A) \quad k_S^B = \Gamma \exp(N_S + \rho_S \sigma_B) \quad k_P^A = \Gamma \exp(N_P + \rho_P \sigma_A) \quad k_P^B = \Gamma \exp(N_P + \rho_P \sigma_B) \quad k_j^i = k_j^i \exp(-\Delta G_j / RT)$$

Sabatier principle constrains $k_j^i \rightarrow$ rate constants are now dependent variables

f Mathematical approach: relative fluxes through cycles determine the effects of conformational dynamics on rate

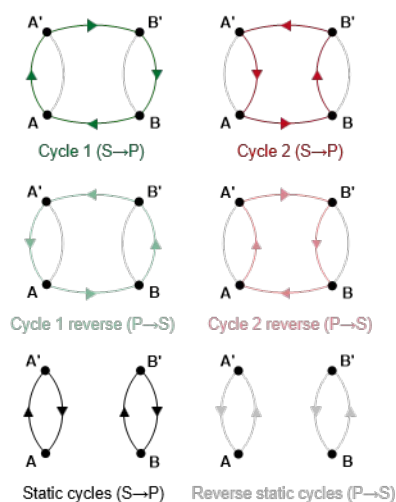


Figure 4. Analyzing conformationally catalysis. a) The pyridine catalyst exhibits a conformational change between an electron rich conformer (square) and an electron poor conformer (circle). b) The inclusion of catalyst conformational dynamics causes the previously two-step catalytic cycle to become a four-state chemical reaction network. Each conformer has a faster rate for one of the two elementary steps. c) In the kinetic regime of panel

b, it appears that conformational dynamics has provided a new route for the catalysed reaction, one in which the rate-determining steps for each conformation are avoided. The rate of the new catalytic cycle appears to exceed the Sabatier limit. d) A generalized representation of the four-state chemical reaction network in panel b. e) Constraining the rate constants of the network in panel d using the Sabatier principle—which makes the previously independent variables dependent—results in tractable mathematics. f) Solutions to the dynamics of the chemical reaction network arise from the constraints of the Sabatier principle and a combination of graph theory and nonequilibrium chemical reaction network mathematics.^{5,27,28,49–55} S = substrate/reactant, P = product.

square conformer Cat_A has a more electron rich 'active site' than circle conformer Cat_B—simply due to a difference in the arrangement of its constituent atoms in space—it follows that nucleophilic attack is faster for Cat_A and electrophilic release is faster for Cat_B. In short, each conformer favors a different elementary step of the catalytic cycle. In the language of the Sabatier Principle, this means that the electron rich conformer Cat_A occupies the lefthand slope of the Sabatier volcano in Figure 4c (defined by rate-determining electrophilic release), while the electron poor conformer Cat_B occupies the righthand slope of the volcano in Figure 4c (rate-determining nucleophilic attack).

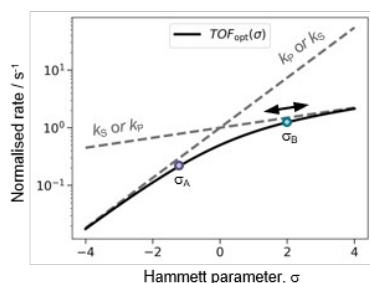
Neither Cat_A or Cat_B alone are optimal catalysts because neither conformer is situated at the Sabatier limit: the maximum rate of the catalyzed reaction. However, it is clear from Figure 4b that sufficiently rapid conformational changes between the two states provides access to a new route through the reaction network: one in which the rate-determining steps for Cat_A (electrophilic release) and Cat_B (nucleophilic attack) appear to be avoided. In other words, it appears that the most favorable conformer for each elementary step can be kinetically selected for,^{54,69} resulting in a faster rate for the conversion of reactants to products than either conformer is capable of in isolation. This kinetic selection can be thought of as two consecutive dynamic kinetic resolutions,^{54,69} one for each elementary step, which together result in accelerated catalysis.

Quantitative validation of conformationally dynamic rate enhancement

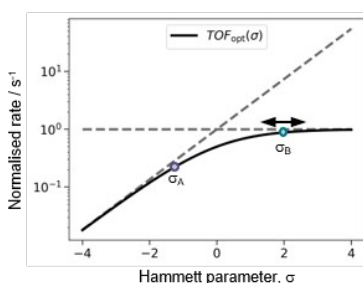
The intuition that conformational dynamics can cause rate enhancement was validated by the mathematical approach summarized in Figure 4d–f. We focus the discussion in this

a Does the Sabatier Principle govern the reaction?

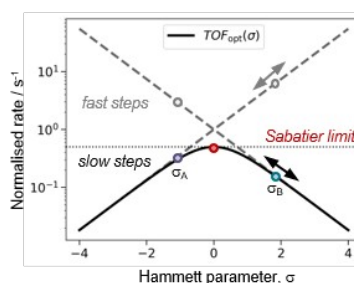
i No: ρ_S and ρ_P are the same sign



ii No: ρ_S and/or ρ_P equal zero



iii Yes: ρ_S and ρ_P are opposite signs



TOF_{dynamic} is always slower than the fastest TOF_{static}

Analytical result: True in all cases in which ρ_S and ρ_P are the same sign, or one is zero

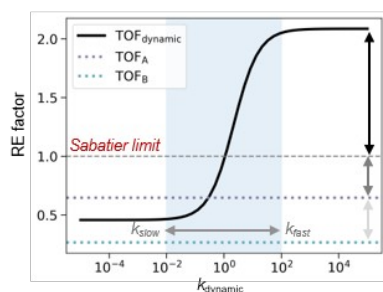
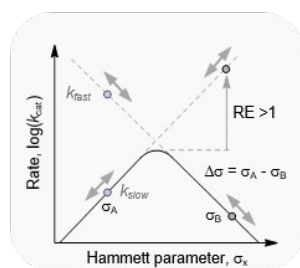
Best strategy to maximise rate: Static catalysis and traditional synthetic methodology techniques

TOF_{dynamic} can exceed TOF_{sabatier}

Rationale for rate enhancement: avoid slow steps; follow fast steps with rate constants beyond the Sabatier limit

b Sabatier-controlled reactions: the rate of conformational dynamics is important for rate enhancement (RE)

i Effect of k_{dyn} for an arbitrary volcano ($\Delta\sigma = 3$)

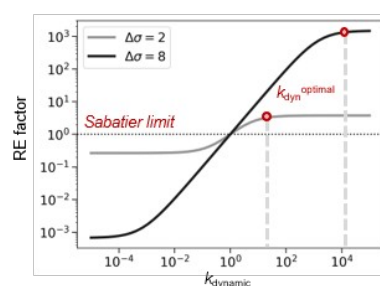


TOF_{dyn} > TOF_{Sabatier} > TOF_{static}

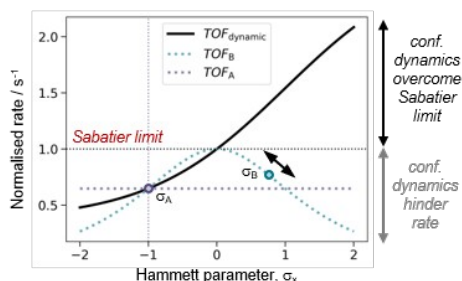
TOF_{Sabatier} > TOF_{dyn} > TOF_{static}

TOF_{Sabatier} > TOF_{static} > TOF_{dyn}

ii Effect of $\Delta\sigma$ on k_{dyn} and RE

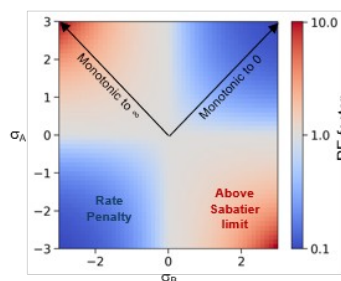


c Sabatier-controlled reactions: the response of TOF_{dynamic} to the properties of each conformer



Best strategy to maximise rate: Conformationally dynamic catalysis; static catalysis is fundamentally limited

Analytical result: True for all symmetrical ($\rho_S = -\rho_P$) Sabatier volcanoes when $\sigma_A < \sigma_{Sabatier} < \sigma_B$



Assumptions for panel c: 1) Conformational dynamics are very fast, 2) Substrate binding is very exergonic, 3) Conformational changes have no thermodynamic bias ($K_{eq} = 1$)

Figure 5. Analytical results. a) i) ii) In the absence of a Sabatier volcano, or in other words, when the Sabatier principle does not govern the reaction, conformational dynamics always result in a catalytic rate penalty versus the fastest conformer in the couple. iii) When the Sabatier principle governs catalysis, conformational dynamics can cause a catalyst to beat the Sabatier limit. b) The rate of conformational dynamics is important for rate enhancement, with RE varying monotonically (sigmoidally) with $k_{dynamic}$. i) There are regimes in which conformational dynamics results in either 1) rate penalties, 2) rate enhancements below the Sabatier limit, or 3) rate enhancements above the Sabatier limit, depending on whether or not the dynamics are rate limiting. ii) As the magnitude of conformationally dynamic RE increases (for example, due to $\Delta\sigma$ increasing), $k_{dynamic}$ must also increase to observe an optimal effect. c) Given certain assumptions, conformational dynamics represents the best strategy for catalyst design in Sabatier-controlled reactions, fundamentally outperforming traditional synthetic methodology techniques. A sweep of σ_B while σ_A is fixed (left, and panel aiii), and a simultaneous sweep of σ_A and σ_B (right), show that in the symmetric case each conformer must sit on opposite slopes of the Sabatier

volcano for rate enhancement to occur. Conformers sitting on the same side of the volcano results in rate penalties.

Section on the most significant insights, while providing mathematical derivations and additional numerical experiments in the Supporting Information in Sections 1.1 and 2, respectively. In the following sections, unless otherwise specified, we refer to steady-state catalysis with an excess of substrate and limited amounts of product (see Supporting Information for other conditions and for a discussion on this choice). Additionally, subscript or superscript S (e.g. ρ_s , or k_A^{+S}) refers to substrate/reactant binding to the catalyst, while subscript or superscript P refers to product release from the catalytic intermediate.

In the context of homogeneous catalysis, emerging theoretical^{70,92,93} and experimental⁹⁴ work has suggested that conformationally dynamic catalysts can outperform each of their constituent conformers in isolation. However, it is unclear in these cases whether conformational dynamics represents the optimal strategy for maximizing rate, or whether similar rate enhancements might be achieved by simpler (and far more synthetically achievable) strategies such as varying the Hammett parameter of the catalyst. Instead, the goal of the following sections is to identify conditions in which the introduction of conformational dynamics allows a catalyst to outperform the best possible static catalyst in Sabatier-controlled reactions (e.g. common cross couplings,^{59,61,66} nucleophilic catalysis,^{80,83} etc.). In other words, we aim to identify scenarios in which conformational dynamics as a strategy can outperform the best-case scenario that traditional synthetic methodology techniques might yield.

Given the constraints in Figure 4e, there is an optimal Hammett parameter $\sigma_X = \sigma_{\text{Sabatier}}$ yielding the largest possible turnover frequency (TOF) that an optimized static catalyst can achieve, $\text{TOF}_{\text{opt}}(\sigma_{\text{Sabatier}})$ (see Supplementary Information, Section 1.1 for the analytical expression and the mathematical definition of optimized conditions). Alternatively, for a dynamic catalyst given any choice of σ_A and σ_B , the eight catalytic cycles in Figure 4f contribute simultaneously to catalysis and define $\text{TOF}_{\text{dynamic}}$, whose analytical expression is provided in the Supplementary Information, Section 1.2.3. We can therefore quantify the rate enhancement (RE) provided by conformational dynamics with respect to the Sabatier limit as the dimensionless factor $\text{RE} = \text{TOF}_{\text{dynamic}} / \text{TOF}_{\text{opt}}(\sigma_{\text{Sabatier}})$. If RE is greater than 1, the dynamic catalyst has beaten the Sabatier limit, if RE is less

than 1, the dynamic catalyst is slower than the fastest possible static catalyst.

For $\text{RE} > 1$, a trivial condition that is nevertheless worth stating is that TOF_{opt} must be bounded. In other words, the catalyzed reaction must be governed by the Sabatier principle. Indeed, if ρ_s and ρ_p have the same sign, or either is zero, as shown in Figure 5a, a static catalyst can in principle either be made arbitrarily fast (same sign) or faster up to the maximum possible rate (if either is zero) by simply optimizing the Hammett parameter (σ_{Sabatier} is undefined). Consequently, in these scenarios conformational dynamics always impedes the rate of catalysis with respect to the best static catalyst in the couple. However, the mathematical approach detailed in the Supplementary Information, Section 1.2 reveals that conformationally dynamic rate enhancement is possible when ρ_s and ρ_p have opposite signs, a condition we assume from now on.

We previously reasoned that conformational changes should be sufficiently rapid for catalytic rate enhancement to occur. In the Supplementary Information, Section 1.2.4, we analytically prove that RE grows monotonically to a plateau as the rate of conformational dynamics increases. The typical behavior of RE as the rate of conformational dynamics varies is shown in Figure 5b. A clear rule of thumb is that RE reaches its maximum value for a particular system when conformational changes are no longer rate-limiting (the ‘non-plateau’ regions essentially span the minimum (k_{slow}) and the maximum (k_{fast}) rates of the individual elementary steps). Since our primary interest here is establishing the conditions under which rate enhancement is possible, we assume from now on that conformational changes are well above that threshold.

To elucidate further factors enabling $\text{RE} > 1$, it is useful to first consider the special, “symmetric”, case where $\rho_s = -\rho_p = \rho$ (symmetrical Sabatier volcano), $K_{\text{cat}} = K_{\text{int}} = 1$ (unbiased conformational changes), $k_X^{-S} \ll k_X^{+S}$ (very exergonic substrate/reactant binding), and $k_X^{+P} \ll k_X^{-P}$ (very exergonic product release). When this is the case, RE has a simple analytical expression, which shows that a necessary and sufficient condition for conformationally dynamic rate enhancement ($\text{RE} > 1$) is that σ_A and σ_B must sit on opposite sides of the Sabatier volcano (e.g., $\sigma_A < \sigma_{\text{Sabatier}} < \sigma_B$), as shown in Figure 5c and analytically derived in the

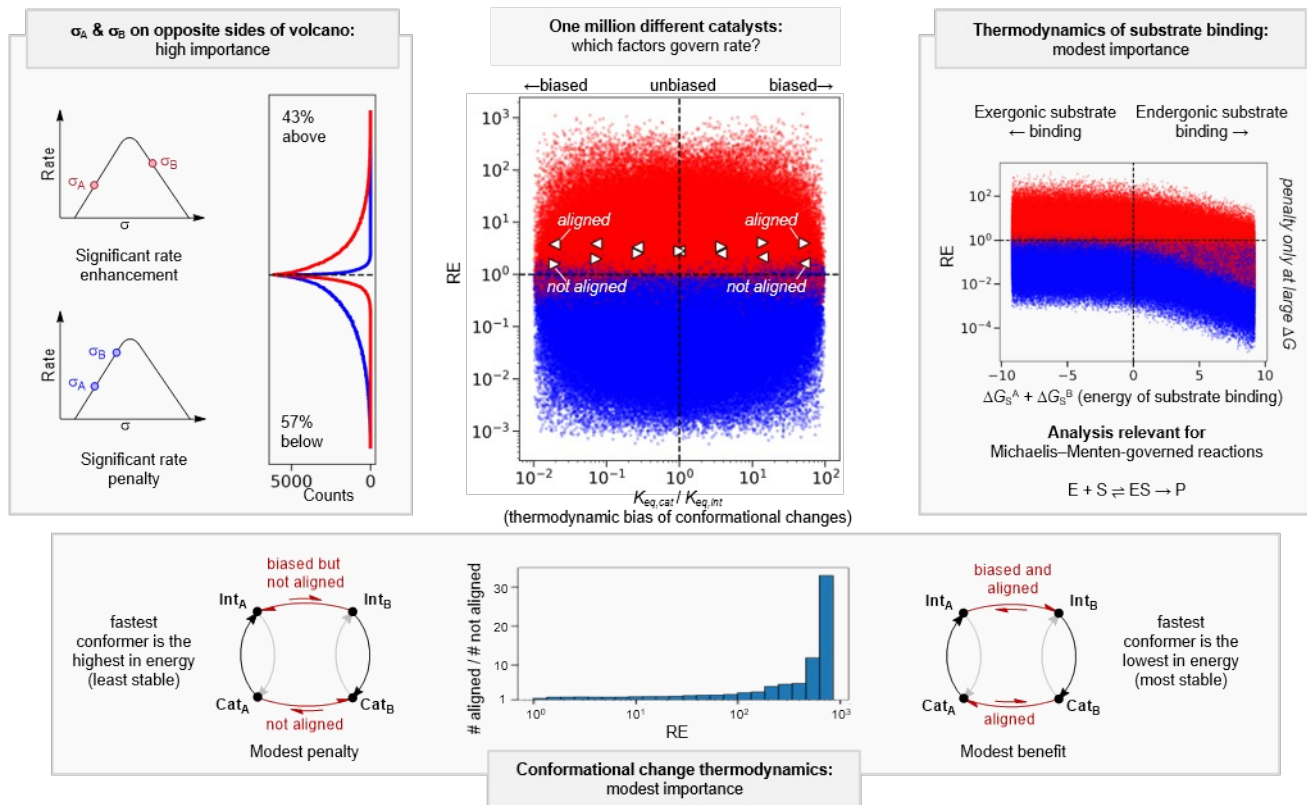
Supplementary Information, Section 1.2.4. This mathematical result confirms the intuition from the previous section that sufficiently fast conformational dynamics provides access to a catalytic pathway that avoids the rate-limiting steps that the two conformers would be subject to when acting as isolated static catalysts. It also shows that $\text{TOF}_{\text{dynamic}}$ is not fundamentally bounded (unlike the TOF of a static catalyst) and can, in principle, be made arbitrarily large. Interestingly, the further σ_A and σ_B are from the optimum σ_{Sabatier} , the higher the rate enhancement will be, despite the fact that the two conformers would be very poor static catalysts if considered in isolation. This situation is loosely reminiscent of the Parrondo Paradox^{95,96} in game theory, according to which a winning strategy (optimizing a static catalyst to be as close as possible to the optimum σ_{Sabatier}) can be beaten by two losing strategies (taking σ_A and σ_B as far as possible from σ_{Sabatier} to inevitably yield poor static catalysts) if the latter are opportunely combined (coupling by conformational dynamics).

Although consideration of the simplified, symmetric conditions discussed above can help derive insightful analytical results, most experimental systems will not match these assumptions. It is therefore important to establish how the results derived for the simplified model change as those assumptions are relaxed. To do so, we computed RE for a large number of dynamic catalysts, obtained by randomly sampling the space of independent parameters that define the rate constants in Figure 4d-e (Figure 6a). While a detailed description of our procedure and a statistical analysis can be found in the Supplementary Information, Section 2, Figure 6 presents the data for one million model dynamic catalysts and highlights the key results.

a Numerical approach: randomize the value of every variable (except k_{dyn}) for 10^6 different catalysts, then measure rate



b Numerical results: which factors govern conformationally dynamic rate enhancement?



c Influence of $\Delta\sigma$ and $\Delta\rho$

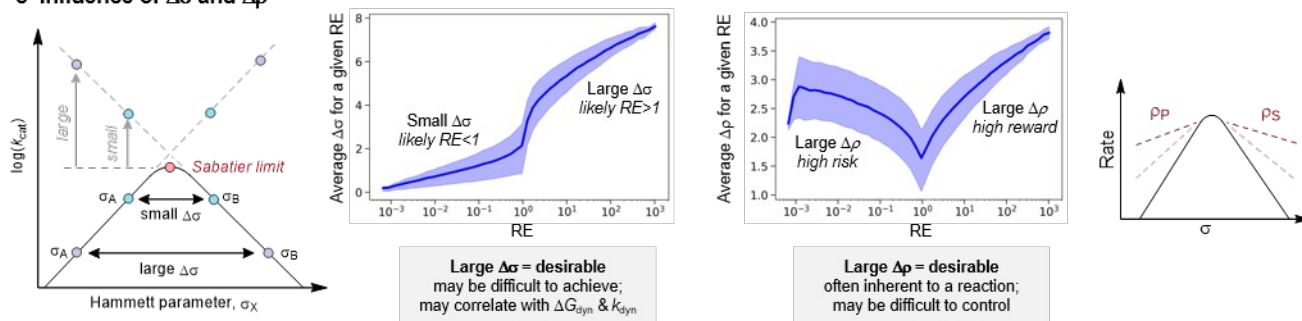


Figure 6. Numerical results. a) The numerical approach consists of randomizing every possible variable (except k_{dyn} , which is kept large, and excepting the fact that the overall reaction must be exergonic) for the dynamic catalyst and measuring the rate. b) The overall rate of one million random conformationally dynamic catalysts, shown relative to the Sabatier limit for each catalyst. Beating the Sabatier limit is a common event (43% of catalysts). Red points represent catalyst conformers on either side of the Sabatier volcano, while blue points represent conformers on the same side of the Sabatier volcano, a property that is highly important for dynamic rate enhancement (left). The central scatter plot is shown relative to the ratio of the equilibrium constants for the conformational changes. Values of the x-axis variable away from 1 should be read as biased conformational change thermodynamics, while values close to 1 represent unbiased thermodynamics. Right arrows on the right-hand side of the graph (and vice versa) indicate the thermodynamic and kinetic biases are aligned (bottom), while the opposite arrows indicate the thermodynamic biases oppose the kinetic biases. The y-axis value of each arrow represents the (arithmetic) mean RE value for every aligned or not aligned catalyst at each x-axis point. c) Influence of $\Delta\sigma$ and $\Delta\rho$. Large $\Delta\sigma$ = desirable may be difficult to achieve; may correlate with ΔG_{dyn} & k_{dyn} . Large $\Delta\rho$ = desirable often inherent to a reaction; may be difficult to control.

Conformational change thermodynamics are found to play a role in dynamic rate enhancement (bottom). Endergonic substrate/reactant binding is found to elicit a modest rate penalty (right). c) $\Delta\sigma$ and $\Delta\rho$ are shown to have strong effects on dynamic rate enhancement.

The numerical approach shows that the analytical result derived previously for the simplified, symmetric scenario remains a good design principle for the general case: in the vast majority of cases, dynamic catalysts where the σ_A and σ_B of each conformer sit on opposite sides of the Sabatier volcano (red markers) yield $RE > 1$, or in other words, beat the Sabatier limit. Likewise, when both conformers sit on the same side of the Sabatier volcano (blue markers), the resulting dynamic catalyst is likely to be suboptimal with respect to the Sabatier limit (Figure 6b, left).

The numerical results also demonstrate that the thermodynamics of the conformational changes have a modest importance (Figure 6b, bottom). When the thermodynamics are aligned with the kinetics—in other words, when the fastest catalyst conformer for each elementary step is also the most thermodynamically stable—conformationally dynamic rate enhancement is typically larger than the opposite case. For very large rate enhancements, it is rare that the conformational change thermodynamics are not aligned with the kinetics. This suggests a potential causal role^{97,98} for conformational change thermodynamics in catalytic rate enhancement, which is important because ground states are often amenable to rational design, more so than transition states.

Whether or not the first (substrate binding) step of the catalytic cycle is endergonic (which is related to the catalyst resting state) is also revealed to play a role. The fraction of conformationally dynamic catalysts with $RE > 1$ does not change (in a statistically significant manner) as the first step becomes increasingly exergonic. However, as the first elementary step becomes more endergonic (for both conformers), conformationally dynamic rate enhancement becomes more unlikely, which can be seen by the downward slope of the scatter plot in Figure 6b, right. This result is relevant for catalytic reactions that follow Michaelis–Menten kinetics,⁹⁹ because it describes a scenario analogous to $E + S \rightleftharpoons ES \rightarrow E + P$ (i.e. reversible substrate (S) binding to an enzyme (E), followed by practically irreversible reaction and product (P) release). We note that the first elementary steps in both conformers must become highly endergonic for a significant penalty to conformationally dynamic rate enhancement. Accordingly, rate enhancement is possible even when

both conformers only weakly bind the substrate/reactant.

Additionally, how significant the conformational changes are—i.e. how large the difference in electron richness between each conformer is, or $\Delta\sigma$ —controls dynamic rate enhancement. As $\Delta\sigma$ grows, the fraction of dynamic catalysts with $RE > 1$ grows monotonically (Figure 6c, left). This suggests that maximizing $\Delta\sigma$ (or whichever thermodynamic parameter has been used to construct the Sabatier volcano) is an important design principle in conformationally dynamic catalysis. Accordingly, it is evident that small, rapid, and otherwise incidental changes to a catalyst's structure—such as bond vibrations and minor rotations—are unlikely to cause large dynamic rate enhancements. This is because each conformation is not sufficiently different. Conformational changes must instead be significant enough to exert a strong influence on the catalyst's electronics (or other property), such that each conformer is faster for a different one of the catalytic cycle's elementary steps.

It is important to note that $\Delta\sigma$ often cannot be maximized without consequence. This is because $\Delta\sigma$ likely correlates with the thermodynamic favorability of the conformational change, or ΔG_{dyn} . For pairs of conformers with large $\Delta\sigma$ (such as, presumably, *cis*-azobenzene and *trans*-azobenzene), one conformer is often thermally inaccessible (here, *cis*-azobenzene¹⁰⁰). Because a large ΔG_{dyn} necessarily reduces the rate of conformational dynamics (since $\Delta G_{dyn}^\ddagger$ must be greater than or equal to ΔG_{dyn}), any potential dynamic rate enhancement would be inhibited.

Finally, the mechanism of the catalyzed reaction also contributes to potential dynamic rate enhancement. Catalytic cycles which consist of elementary steps with strong dependencies on electron-richness⁷⁶—i.e. where each elementary step has a steep, oppositely sloped Hammett plot, or large $\Delta\rho$ —exhibit the greatest potential magnitude of conformationally dynamic rate enhancement (Figure 6c, right). This comes with risks, however, as steep volcanoes (large $\Delta\rho$) also increase the magnitude of dynamic rate penalties should σ_A and σ_B exist on the same side of the Sabatier volcano. Catalytic cycles whose mechanisms consist of elementary steps with only shallow Hammett slopes (small $\Delta\rho$), or those where either ρ_S or ρ_P approach zero, will likely prove poor candidates for dynamic rate enhancement because the magnitude of any benefits will be small.

This section has demonstrated how general design principles for conformationally dynamic catalysis result from a simple kinetic treatment based on chemical reaction network mathematics. These general design principles—as well as others that are likely to be discovered in the future—must then be applied to specific catalytic systems in order to result in useful new catalyst designs. We envisage that our general approach will serve as a complement to the chemical intuition and advanced atomistic simulations that usually underlie the design of specific catalyst structures. The results likely also generalise to catalysts with cooperating^{101,102,103} ligands; in these examples, metal ligands can exchange during a catalysed reaction through spontaneous binding and release, a process that is mathematically equivalent to a conformational change. A strength of this approach (vs. conformational dynamics) is that each component can be simple, and that ‘dynamic rate enhancement’ may occur even if every component is rigid. A weakness may be that intermolecular ligand exchanges are inherently slower than intramolecular conformational changes. The results may also generalize to catalysts that diffuse back-and-forth between different microenvironments.

In summary, conformationally dynamic catalysts can beat the Sabatier limit by orders of magnitude. In other words, the maximum rate that a homogeneous catalyst can achieve is not fundamentally constrained⁵⁹⁻⁶⁷ by the Sabatier limit, and consequently there is a beyond-Sabatier-regime^{57,58,68,69,94} that has yet to be explored. Best in class homogeneous catalysts are usually arrived at after long campaigns¹⁰⁴ of catalyst optimization and trial and error. Here, we demonstrate that this approach is not optimal for reactions governed by the Sabatier principle, which includes important transformations such as common cross coupling reactions^{59,61,66} and nucleophilic catalysis.^{80,83} Instead, simply randomizing the parameters of a conformationally dynamic catalyst (akin, perhaps, to randomly choosing a dynamic catalyst) has a high likelihood of outperforming the best catalyst that traditional synthetic methodology and catalyst optimization can afford (Figure 7). The implications of this result are profound: are we, as chemists, betting on the horse with the worst odds?

Implications for catalyst design: are we betting on the horse with the worst odds?

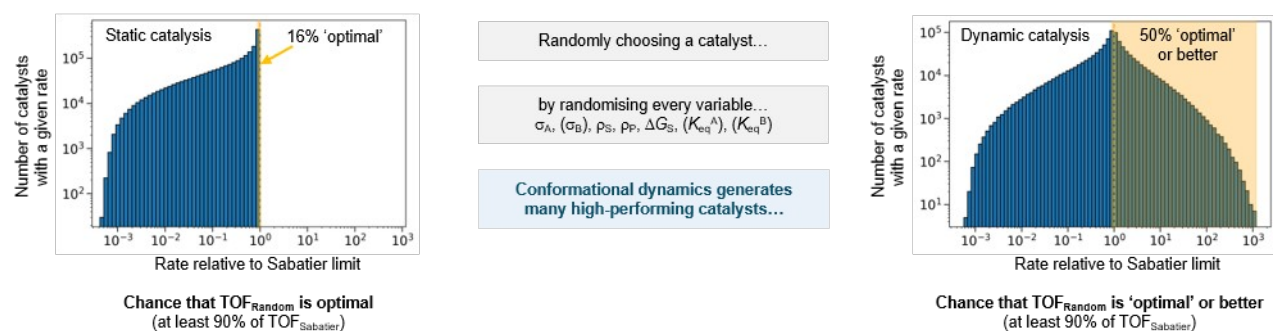


Figure 7. A comparison between the approach of traditional synthetic methodology for reactions governed by the Sabatier principle, which is to optimize the structure of a static catalyst in order to reach the Sabatier limit, and the outcome of randomly selecting the variables for a conformationally dynamic catalyst. Conformational dynamics frequently overcome the otherwise fundamental rate limit. The comparison is not entirely fair because σ_A and σ_B , as well as other pairs of variables, likely cannot be independently randomized. The comparison is, however, a succinct demonstration of the large potential benefits that conformationally dynamic catalysis could one day bring to synthetic chemistry.

Precedents and design principles

In the model presented so far, the dynamic catalyst's conformational changes have been referred to in a structureless and general sense (i.e. square $\rightleftharpoons$ circle, $A \rightleftharpoons B$). This has been intended to demonstrate that catalytic rate enhancement is possible provided that each conformer exhibits at least one different property (such as electron richness), and provided that this property can influence the transition states of the catalyzed reaction through linear free-energy relationships. Structure-specific and interaction-specific arguments, we hope to have made clear, are not necessary.

Nonetheless, an analysis of precedents may aid in the design of new conformationally dynamic catalysts. Established functional groups and motifs are known to exhibit simple, large-amplitude, sufficiently rapid, and well-defined conformational changes (Figure 8, see Box for a discussion on the definition of 'conformational dynamics'). The key characteristics of these groups are the presence of secondary structural interactions that can be rearranged without a significant energy barrier or a significant free energy cost. In other words, the conformational change exhibits a thermally accessible $\Delta G^\ddagger$ and ΔG , respectively. Specific examples include amide/carbonyl rotamers,¹⁰⁵ hemilabile metal ligands,⁴¹ metal-ligand coordination dynamics,⁴¹ reversible π -interactions,^{43,44} cyclic-molecule 'ring flipping',⁴⁶ supramolecular shape changes,^{45,106} and rearrangements to hydrogen bonding networks such

as those in peptides.^{47,94,105} Single-bond and multi-bond rotations^{18,48} can also result in different catalyst conformations, and it is likely that numerous other motifs can, and do, result in well-defined conformational changes.

Figure 9 depicts a selection of examples from the small-molecule catalysis literature. In Figure 9a, xantphos acts as a hemilabile metal ligand with multiple well-defined conformations,^{40,41} a property that has led to it being referred to as "shapeshifting".⁴⁰ Xantphos is commercial, structurally simple, and commonly used by chemists; incidentally, its palladium complexes are also widely regarded¹⁰⁷ to be some of the best general cross-coupling catalysts. Could this be because of conformational dynamics? More research is required, but it is clear that conformational dynamics may be operating 'under the radar' in common catalytic reactions.

In Figure 9b, a hemi-labile *P,N*-ligand changes conformation between bidentate and monodentate in a gold-catalyzed cross-coupling reaction. The conformational changes occur during catalysis and are reported⁴² to be concerted with the elementary steps of the reaction (incidentally, this means that the reaction cannot be described by our square model, which requires orthogonal conformational and chemical steps). The existence of a Sabatier volcano can be inferred from the reported⁴² kinetic data, with the 'optimal' catalyst close to the peak of the volcano. Figure 9c shows the conformational changes of JohnPhos during a nickel catalyzed cross-coupling

reaction. The hemi-labile ortho-arene group is reported⁴³ to undergo reversible η^2 -coordination at the metal center. During catalysis, calculations indicate that the catalyst is conformationally dynamic, with oxidative addition occurring in an η^2 -coordinated state, transmetallation in a de-coordinated state, and reductive elimination again in a coordinated state.

Figure 9d shows a nucleophilic pyridine catalyst (analogous to the model catalyst in Figure 2) undergoing a conformational change upon formation of an acyl-pyridinium catalytic intermediate.⁴⁴ An intramolecular $n \rightarrow \pi^*$ interaction causes the linearly extended pendant group to contract in the pyridinium state, with the conformational change reported to result in a greater-than-expected projection of chirality. In Figure 9e, a supramolecular coordination cage undergoes a reversible conformational change^{45,106} in order to effectively bind a guest molecule, with kinetic analysis demonstrating⁴⁵ that binding occurs through a conformational selection mechanism. Metal-ligand dynamics at the vertices induce a global conformational change from an S_4 -symmetry irregular tetrahedron to a T -symmetry regular tetrahedron. Because some supramolecular catalysts are known to operate through Michaelis-Menten kinetics,^{99,108} they may help to inform the debate^{7-11,109-112} on the role of conformational changes in enzyme catalysis. Figure 9f shows a metal-ligand complex exhibiting chair-boat conformational changes during catalysis. The selectivity-determining step is reported⁴⁶ to occur in the boat conformation, while the rate-determining step occurs

Selected motifs and groups that can exhibit conformational dynamics

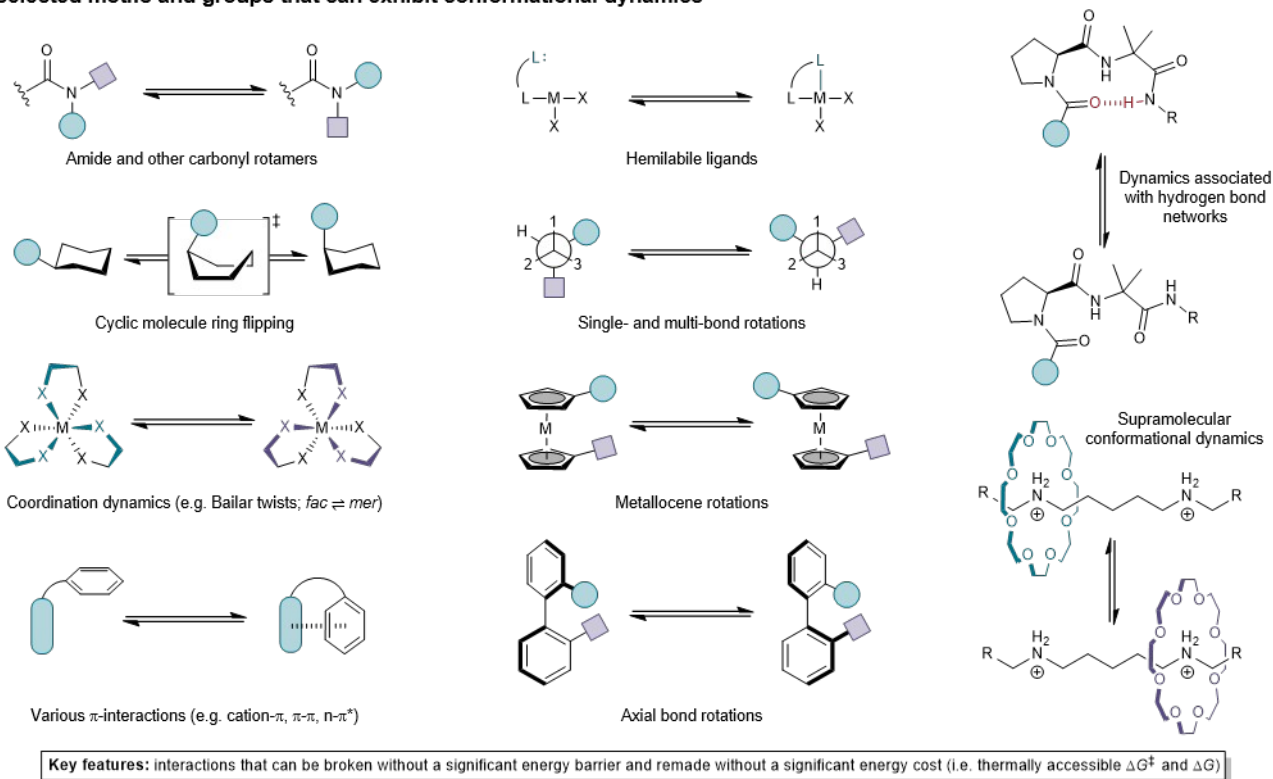


Figure 8. Selected motifs and groups that can exhibit conformational dynamics. Here, conformational dynamics are defined as incessant stochastic processes in which the shape of the molecule changes (see Box for discussion).

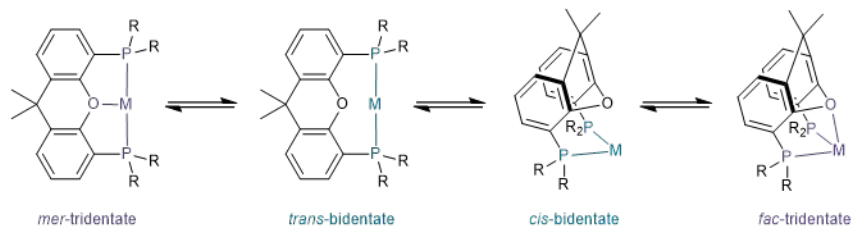
in the chair conformation. Finally, Figure 9g shows a nucleophilic histidine catalyst with a pendant oligopeptide group.⁴⁷ The oligopeptide-histidine catalyst exists as a conformational ensemble prior to catalysis, and it is likely that these conformational changes also occur during catalysis. This list is not meant to be exhaustive, and we encourage readers to consider other examples—for example, certain ligands are known to “stretch and bend” in metal-catalysed alkyne metathesis and the elementary steps of the catalytic cycle may exhibit ‘Sabatier-like’ properties.¹¹³

In each of these examples—to the best of our knowledge—exhaustive kinetic analyses have not established a causal link between observed mid-reaction conformational changes and catalytic rate enhancement. In other words, it is unknown whether the reported conformational dynamics simply occur as a coupled result of the catalyzed reaction (similarly to the way in which local solvent molecules rearrange following a chemical reaction), or whether the conformational dynamics *cause* rate acceleration. One example in which an exhaustive kinetic analysis has been performed is the example of a conformationally dynamic carboxylate organocatalyst reported by Leigh and co-workers,⁹⁴ which exists as

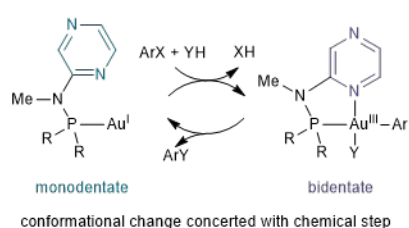
two discrete supramolecular conformations (Figure 9h). By synthesizing ‘static’ analogues of each of the catalyst’s two conformations, the authors demonstrate that the conformationally dynamic catalyst is significantly faster than either of its conformers in isolation. The authors therefore conclude that the conformational dynamics of the catalyst *cause* rate acceleration. Kinetic modelling revealed that each conformer is better able to catalyze a different one of the two elementary steps of the reaction, meaning that rate enhancement occurs through a similar mechanism to the model presented throughout this Perspective.

It is important to note that observations of mid-catalysis conformational changes are not sufficient evidence of ‘beneficial dynamics’ or ‘enhanced catalysis’. In fact, we highlight numerous scenarios in this Perspective where conformational dynamics can significantly impede the rate of the catalyzed reaction. Claims of beneficial conformational dynamics should therefore be made following a detailed kinetic analysis, which should aim to provide

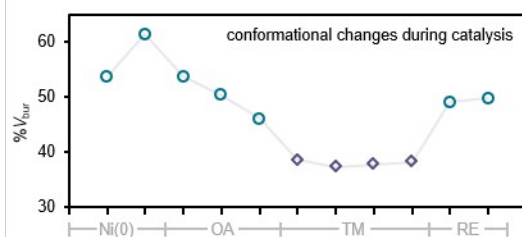
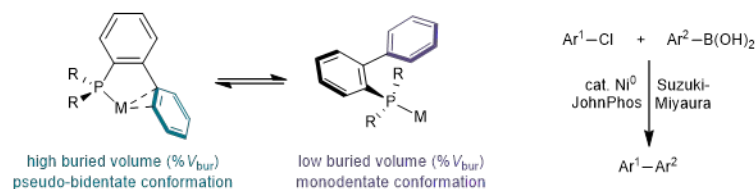
a Xantphos and other POP-type ligands (Ref. 40,41)



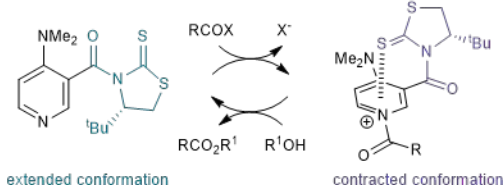
b Hemilabile gold ligands (Ref. 42)



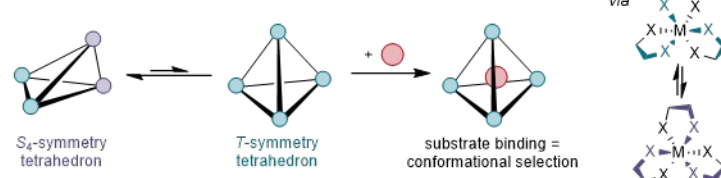
c JohnPhos and other Buchwald-type phosphine ligands (Ref. 43)



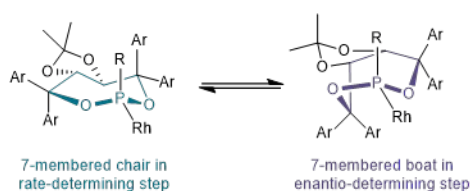
d Yamada pyridine catalysts (Ref. 44)



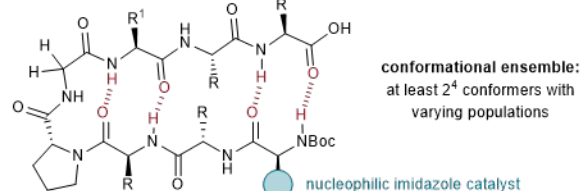
e Supramolecular substrate binding (Ref. 45,106)



f Cyclic ligand dynamics (Ref. 46)



g Peptide conformational ensembles (Ref. 47)



h Experimental evidence that conformational dynamics can cause catalytic rate enhancement (Ref. 94)

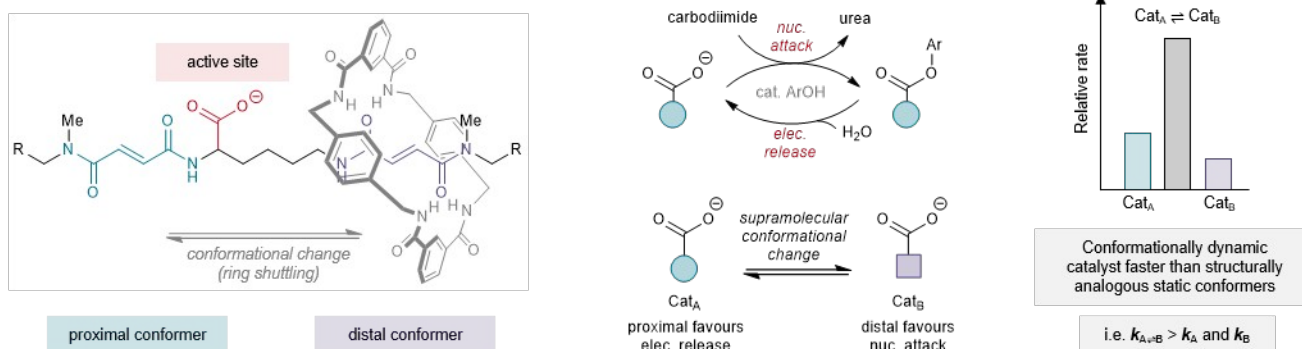


Figure 9. Examples. a) “Shapeshifting” xantphos, b) A hemilabile *P,N* ligand undergoes conformational changes during Au^I catalysis, c) Metal complexes of Buchwald-type phosphine ligands such as JohnPhos can exist in different conformations with different steric (quantified by % V_{bur}) and electronic properties. During a nickel-catalysed Suzuki–Miyaura cross coupling reaction, Ni(CyJohnPhos) is reported to undergo conformational dynamics. Tick marks on the x-axis of the graph indicate points along the reaction coordinate at which conformational calculations were performed. M = metal, OA = oxidative addition, TM = transmetalation, RE = reductive elimination. Graph adapted with permission from Reference 43, Copyright © 2022 American Chemical Society. d) A pyridine catalyst undergoes a conformational change during nucleophilic catalysis, e) A supramolecular coordination cage has been reported to bind guests through conformational selection, f) Calculations indicate that a cyclic ligand adopts one conformation during the enantio-determining step of a hydroboration reaction, and another conformation in the rate-determining step, g) Oligo-peptide catalysts

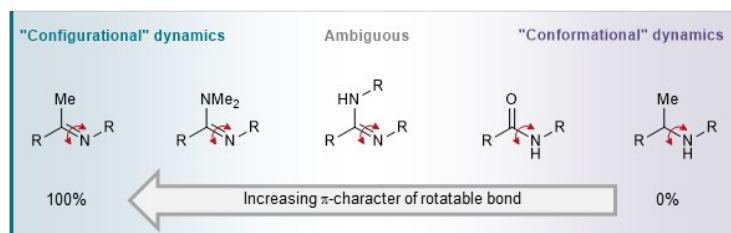
typically exist as spontaneously interconverting ensembles of conformations, h) An experimental report of causality in conformationally dynamic rate acceleration.

Box 1. Semantics issues concerning the dynamics of molecules:

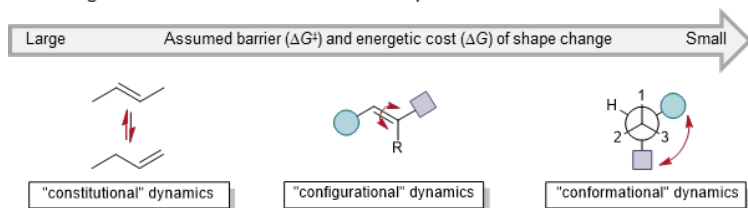
'Conformations' are defined¹¹⁶ as stereoisomers that can be interconverted by rotation(s) around *formal* single bonds, 'configurations' are defined¹¹⁶ as stereoisomers that are not conformations, and 'constitutions' are defined¹¹⁶ as isomers that are not stereoisomers. Panel i below demonstrates how these definitions can result in ambiguities. For example, where should one draw the line between the 'configurational dynamics' of imine isomerization and the 'conformational dynamics' of amide rotation? This ambiguity is compounded by the fact that additional terms such as 'fluxional'¹¹⁶ and 'flexible'⁴⁸ have been used in the literature to refer to either conformational, configurational, or constitutional dynamics.

Current definitions also result in imagery and associations that may not be useful to the reader. For example, 'constitutional dynamics' may evoke a dynamic process which is extremely slow and unfavourable (such as 1-butene $\rightleftharpoons$ 2-butene exchange, panel ii). However, some constitutional dynamics are more rapid and facile than some conformational dynamics (e.g. bullvalene exchange¹¹⁷ vs. BINAP enantiomerisation,¹¹⁸ panel iii). The problem is especially acute regarding the lack of any biological connotations for the terms 'constitutional dynamics' and 'configurational dynamics'. If the overall outcome of the shape change is the same, should we deny these two cases the widely-used term of 'conformational dynamics', which is rich in useful connotations and associations?

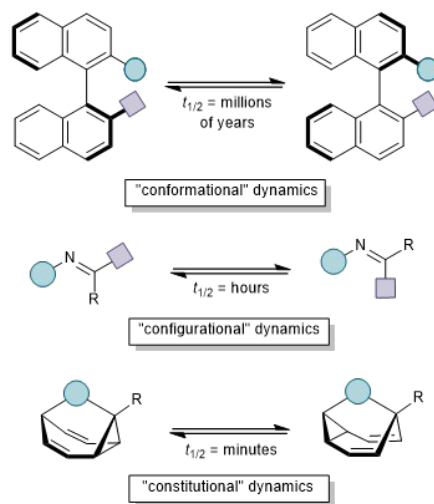
i "Configurational" vs. "conformational" dynamics



ii Existing nomenclature can result in assumptions



iii Examples contradicting these assumptions



We believe that the community would benefit from further discussion on these semantic issues. To begin, we propose three possible solutions: **One**, continue the distinction between 'conformational', 'configurational' and 'constitutional' dynamics. *Pros*: already in use. *Cons*: imprecise and sometimes ambiguous; the latter two terms are rarely used and lack certain connotations. **Two**, use the term 'conformational dynamics' for all such dynamics. *Pros*: rich associations and connotations across fields, single unambiguous term. *Cons*: imprecise by current definitions. **Three**, invent a new term (e.g. 'shapeshifting')⁴⁰ or repurpose another (e.g. 'rearrangement'¹¹⁶, 'steredynamics'¹¹⁷). *Pros*: would be precise. *Cons*: would require broad adoption, currently no useful connotations. In this manuscript we have chosen option two, but we welcome and encourage further discussion.

A final issue is the use of 'dynamics' and 'dynamical' to mean underdamped vibrational motion in physics and physical chemistry, and by controversies^{7-11,109-112,114,115} over whether or not this 'dynamical' vibrational motion causes rate enhancement in enzymes. Here, we define 'dynamics' in the traditional synthetic chemistry sense to mean incessant stochastic exchange processes.

evidence that each of the two or more conformers is a slower catalyst than the dynamic catalyst. In other words, causality must be demonstrated.

Enzyme conformational dynamics

The importance of conformational changes in biology requires little emphasis; their influence on substrate binding, for example, is taught in schools. Conformational changes have also been observed during enzyme catalysis,¹⁰ however, the effects of conformational dynamics over the whole catalytic cycle remain controversial.^{7-11,109-112,114,115} Current models vary, assigning special roles to either 'stepwise conformational selection' (a model analogous to the one presented here),^{7,8,9} electrostatic preorganization,¹⁰⁹⁻¹¹² quantum tunneling,¹¹⁴ and direct energy-transfer from the conformational change to the substrate,¹¹⁵ among others. Accordingly, it is apparent that there is not yet a consensus^{7-11,109-112,114,115} on 1) whether conformational dynamics *cause* rate acceleration, or 2) whether conformational changes simply occur as non-causal coupled motions, and 3) if conformational dynamics do cause rate acceleration, through which mechanism this occurs, and finally 4) the precise definition of "dynamics" in the context of enzyme catalysis.

It is not the scope this Perspective to address these four points. Indeed, the analysis presented here is likely to be too reductive to adequately explain the catalysis of even the simplest enzymes. We do note, however, that enzyme catalysis has begun to be examined^{70,93} theoretically through the lens of the Sabatier principle, and that Sabatier volcanoes have also been observed^{71,72} experimentally in enzyme catalysis.

There is now an extensive literature^{7-11,109-112} of top-down biological experiment and biophysical theory aiming to address the nature of conformational dynamics in enzyme catalysis. Yet bottom-up chemical experiment remains largely absent. We seek to motivate the design, exploitation, and understanding of small-molecule conformationally dynamic catalysts in the hopes that it might also contribute to the understanding of enzyme catalysis.

Conclusion and outlook

The link between conformational dynamics and the catalytic sophistication of enzymes has captivated chemists and biologists for decades. Yet how and why conformationally dynamic rate enhancement occurs in enzymes—or indeed, whether it occurs at all—has generated controversy^{7-11,109-112,114,115} that persists to

the present day. Progress has been hindered by one of the perennial challenges of biology: the untangling of cause and effect in highly complex systems. Approaching the problem from a purely chemical perspective is desirable because simple chemical systems are, in principle, entirely knowable. Conformational dynamics have now been reported^{40-47,94,106} to occur during small-molecule catalysis in a wide range of transformations using a wide range of catalyst scaffolds (Figure 9). However, these conformational changes have rarely been intentionally incorporated into a catalyst, and indeed they are often explicitly avoided⁴⁸ in catalyst design. Accordingly, there has been little systematic study on the role that conformational dynamics might play in small-molecule catalytic rate enhancement.

This Perspective provides a framework for understanding how and why conformational dynamics affect catalytic rate. The approach is built from first principles and relies on chemical reaction kinetics derived from linear free energy relationships (LFERs)^{76,77,81,82} such as the Hammett equation. Application of LFERs over whole catalytic cycles reveals that common catalytic reactions are governed by the Sabatier principle,^{59-72,91} a 'Goldilocks' effect in which the best catalyst is one that is well-adapted to all of the reaction's elementary steps. A combination of chemical reaction network mathematics and nonequilibrium thermodynamics^{5,27,28,49-55} permit conformationally dynamic catalytic cycles to be described quantitatively under these Sabatier principle conditions. Catalytic rate enhancement is found to occur when one conformer is well-adapted to one elementary step of the catalytic cycle, while another is well-adapted to a different elementary step. Conformational dynamics between these two states causes the rate-determining steps in each state to be avoided, allowing each chemical step to be optimized without a trade-off. The result is a large rate enhancement relative to each conformer in isolation, as well as rate enhancements of orders of magnitude above the Sabatier limit, which has been previously regarded^{59-67,91} as a fundamental limit to catalytic rate. The causal relationship between conformational dynamics and catalytic rate enhancement is proven analytically in a simple model case and is evident numerically in more general scenarios. Statistical analysis of the numerical results reveals how certain mechanistic and catalyst-specific factors affect dynamic rate enhancement, with potential relevance for both small-molecule and enzyme catalysis.

A number of general design principles can be identified in conformationally dynamic catalysis: 1) conformational changes can only provide benefits in certain reactions (i.e. multi-step catalytic reactions with 'mutually opposing' elementary steps, where neither step is significantly faster than the other), 2) conformational changes must be faster than the chemical steps, 3) conformational changes must exert a large enough electronic influence, 4) catalyst-designers must aim to design or identify catalyst conformers that, by themselves, are far from optimal and that are individually optimized for one step of the catalytic cycle, and 5) that conformational change thermodynamics are a potentially useful design handle. These general design principles should serve to point researchers towards reactions that are amenable to conformationally dynamic rate enhancement, while narrowing the window of potential dynamic catalyst structures and serving to inform and complement traditional means of catalyst design.

An intriguing implication^{95,96} of these results is that highly active conformationally dynamic catalysts consist of two conformers that, by themselves, are extremely poor catalysts. This means that valuable catalyst structures—that for example exhibit extremely rapid nucleophilic attack, or oxidative addition, but poor overall turnover—are likely to have been ignored as failures and are at risk of continuing to be ignored in the future. It is clear that catalyst structures and conformations that perform individual elementary steps very well should still be regarded as valuable even if their overall catalytic turnover (as static catalysts) is poor.

Further work in this area should aim to identify the presence, or the lack thereof, of the Sabatier principle and the Sabatier limit in as many different classes of homogeneous reactions as possible. Identifying industrially or medicinally relevant reactions that are constrained by the Sabatier limit may help to draw wide attention to the area. Simple groups and motifs that undergo large-amplitude, well-defined, rapid, and consequential conformational changes should continue to be designed and studied. Because conformational dynamics have now been observed^{40-47,103} during catalysis on a number of occasions, rigorous kinetic analyses should aim to prove⁹⁴ whether or not these conformational dynamics *cause* increases in rate or selectivity, or whether they are simply consequential. One strategy, although others surely exist, is to synthesize conformationally static models of each conformer of the catalyst and measure their rates (Ref. 94 is an example of this

approach). Although this approach may be synthetically challenging, and may introduce unintended or compounding effects, some means of obtaining experimental evidence is crucial for the determination of cause and effect. For systems in which isolating (models of) a catalyst's conformers proves impossible, atomistic calculations and kinetic models may provide theoretical evidence of causality. Further theoretical work should aim to study the effects of conformational changes on more complex (3+ steps) catalytic cycles. The effects of energy consuming^{27,28} (driven) dynamics, in contrast to spontaneous dynamics, should also be explored. Experimental evidence of a dynamic catalyst beating an experimentally observed Sabatier limit should represent a major goal for the field.

This Perspective has highlighted how conformational dynamics can accelerate catalysis beyond otherwise fundamental limits. Given the ubiquity of conformational dynamics in biology, it is clear that much exciting research awaits.

ASSOCIATED CONTENT

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Kinetic model. Assumptions and conventions.
Analytical results for static catalysis and dynamic catalysis. Numerical results.

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Notes

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ABBREVIATIONS

RE = rate enhancement, S = substrate/reactant, P = product, RDS = rate-determining step.

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