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How to Conceptualize Catalytic Cycles? The Energetic Span Model

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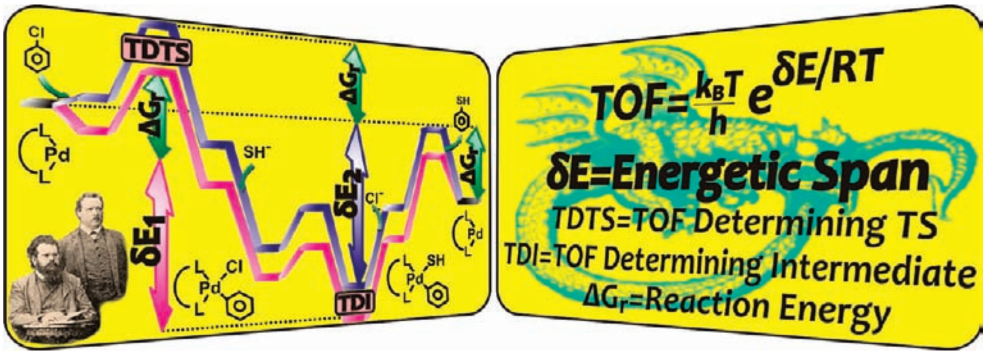

A computational study of a catalytic cycle generates state energies (the *E*-representation), whereas experiments lead to rate constants (the *k*-representation). Based on transition state theory (TST), these are equivalent representations. Nevertheless, until recently, there has been no simple way to calculate the efficiency of a catalytic cycle, that is, its turnover frequency (TOF), from a theoretically obtained energy profile. In this Account, we introduce the energetic span model that enables one to evaluate TOFs in a straightforward manner and in affinity with the Curtin–Hammett principle. As shown herein, the model implies a change in our kinetic concepts.

Analogous to Ohm's law, the catalytic chemical current (the TOF) can be defined by a chemical potential (independent of the mechanism) divided by a chemical resistance (dependent on the mechanism and the nature of the catalyst). This formulation is based on Eyring's TST and corresponds to a steady-state regime.

In many catalytic cycles, only one transition state and one intermediate determine the TOF. We call them the TOF-determining transition state (TDTS) and the TOF-determining intermediate (TDI). These key states can be located, from among the many states available to a catalytic cycle, by assessing the degree of TOF control (X_{TOF}); this last term resembles the structure–reactivity coefficient in classical physical organic chemistry. The TDTS–TDI energy difference and the reaction driving force define the energetic span (δE) of the cycle. Whenever the TDTS appears after the TDI, δE is the energy difference between these two states; when the opposite is true, we must also add the driving force to this difference. Having δE, the TOF is expressed simply in the Arrhenius–Eyring fashion, wherein δE serves as the apparent activation energy of the cycle.

An important lesson from this model is that neither one transition state nor one reaction step possess all the kinetic information that determines the efficiency of a catalyst. Additionally, the TDI and TDTS are not necessarily the highest and lowest states, nor do they have to be adjoined as a single step. As such, we can conclude that a change in the conceptualization of catalytic cycles is in order: in catalysis, there are no rate-determining *steps*, but rather rate-determining *states*.

We also include a study on the effect of reactant and product concentrations. In the energetic span approximation, only the reactants or products that are located between the TDI and TDTS accelerate or inhibit the reaction. In this manner, the energetic span model creates a direct link between experimental quantities and theoretical results. The versatility of the energetic span model is demonstrated with several catalytic cycles of organometallic reactions.

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1. Introduction: Creating a "Language" for Catalytic Cycles

A catalytic cycle is a wheel with many individual chemical steps spinning in a coordinated manner at a common "speed". In a reaction which is first-order in the catalyst and in steady state, this "speed" is defined by the turnover frequency (TOF) of the cycle, given in eq 1 as the number of cycles (N) per catalyst concentration (C) per time (t):[1,2]

$$\mathrm{TOF} = \frac{N}{[C]t} \tag{1}$$

The TOF determines the efficiency of the catalyst, and hence, it is important to interrogate this property and produce insight that may allow control and design of better catalysts.

The manner by which this can be achieved has occupied our thoughts for some years, and since we are computational chemists, we used quantum chemistry to seek a winning recipe.[3,4] However, the connection between computational and experimental results is not always obvious, as the languages of these disciplines are different. This recognition motivated us to create a bridge between computational chemistry and experiment in a manner that will allow efficient exploitation of both approaches.

In recent papers[5−8] we studied the popular palladium catalyzed cross-coupling.[1,2,9−12] One objective was to tackle a specific problem that interested experimentalists, namely, to establish the chain length (n) that generates the most efficient catalyst in the family of the bidentate-phosphine ligands, L = $Ph_2P(CH_2)_nPPh_2$. The computed energy profiles for two such catalysts are shown in Figure 1. Inspection of the two profiles shows that while the catalyst with $n = 3$ has lower transition states, it also features deeper lying intermediates. As such, once all mechanisms were computed, an important fact emerged: the computed energy profile gave no clue about the identity of the better catalyst!

Since computational chemistry produces an energy landscape of the cycle, we needed an energy representation (E-representation) of the TOF, rather than the rate constants-based one (k-representation) which is used by experimentalists (Figure 2).

A mathematical derivation for the TOF of simple "serial" catalytic cycles (as in Figure 3) has been published 50 years ago by Christiansen,[13] who calculated the TOF from the rate constants using linear algebra. However, this formulation which used the k-representation led to equations too complex to grasp.[6,13−15] In addition, this k-representation of the TOF is less convenient for making links to quantum-mechanical (QM) studies. As such, our first goal became to generate a straightforward mathematical model for TOF calculations based on the E-representation.

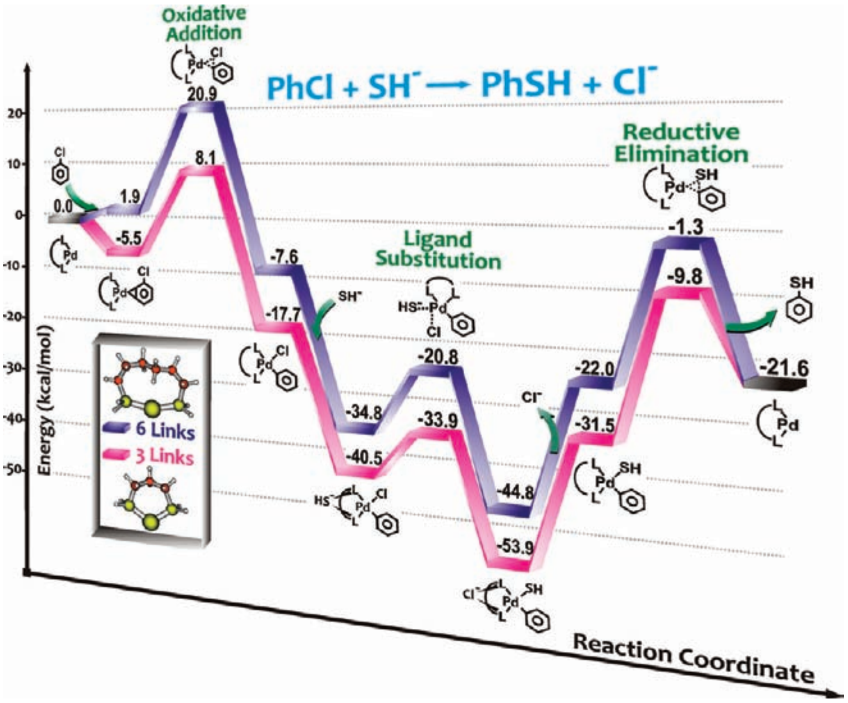

FIGURE 1. Mechanisms for a cross-coupling reaction catalyzed by $Pd[PH_2(CH_2)_nPH_2]$, with $n = 3$ and 6. All energies are gas-phase values with ZPE corrections.[5,6] A shorter chain ($n = 3$) produces low-energy transition states, but also low-energy intermediates, compared to $n = 6$. Which one is more efficient?

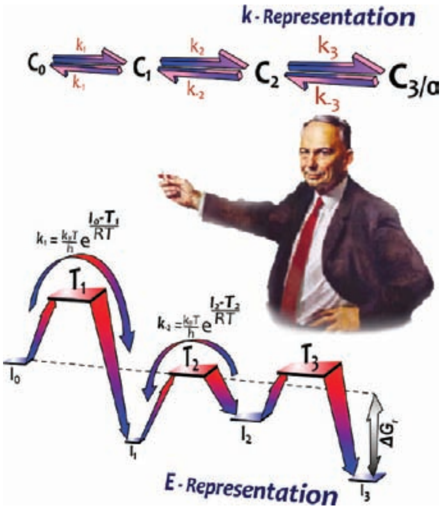

FIGURE 2. Two languages: Rate constant (*k*) representation versus energy (*E*) representation. The *k*-representation is mostly used by experimentalists, while the *E*-representation by theoreticians. Eyring's transition state theory serves as translator.

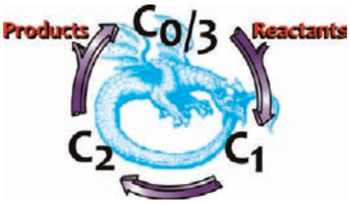

FIGURE 3. Scheme of a simple "serial" catalytic cycle along with the Ouroboros, the alchemical dragon biting its own tail, symbolizing the periodicity of the cycle.

2. The Energetic Span Concept

The energetic span (δE) term was coined by Amatore and Jutand.[16] Starting from the active species (C_a, the intermediate preceding the determining transition state) and according to Arrhenius, the rate of reaction is

$$r = [C_a]A\,e^{-E_a/RT} \tag{2}$$

Since the concentration of the active species is given by their Boltzmann distribution relative to the lowest intermediate (C_0), we have

$$[C_a] = [C_0]\,e^{-\Delta E/RT} \tag{3}$$

Inserting eq 3 into eq 2 we get

$$\begin{aligned} r &= [C_0]A\,e^{-(E_a+\Delta E)/RT} \\ E_a + \Delta E &= \delta \mathrm{E} \end{aligned} \tag{4}$$

where δE is defined as the energy difference between the summit and trough of the cycle (Figure 4).

The insightful Amatore–Jutand equation (eq 4) is accurate only when the energy of the reaction (ΔG_r) approaches zero, in which case the forward rate also approaches zero.

FIGURE 4. The original approximate energetic span (δE) definition:[16] the energy difference between the summit and trough of the cycle, following Arrhenius and his mentor Boltzmann.

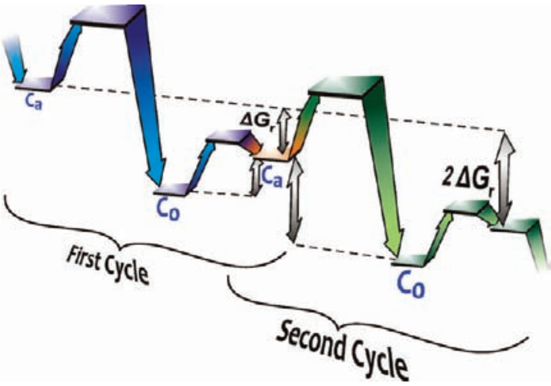

FIGURE 5. Two cycles in the continuous series of turnovers of a catalytic reaction. Is C_a in equilibrium with C_0 of the first or of the second cycle? The Ouroboros nature of catalysis does not allow one to define a Boltzmann distribution unless $\Delta G_r = 0$.

The reason lies in the "Ouroboros-like" nature of a catalytic cycle: once one turnover is completed, the catalyst restarts a new cycle, wherein the starting-point is now below the original one by the reaction energy, ΔG_r. In this case, do we apply the Boltzmann distribution (eq 3) with respect to C_0 of the first or the second cycle (see Figure 5)? We must take this cyclic nature into account, but how?

3. Accurate TOF Calculation

Based on Eyring's transition state theory, we can move between the *k*- and *E*-representations of each chemical step using eq 5 (Figure 2):

$$\begin{aligned} k_i &= \frac{k_B T}{h}\,e^{-\Delta G_i^{\neq}/RT} = \frac{k_B T}{h}\,e^{(I_{i-1}-T_i)/RT} \\ k_{-i} &= \frac{k_B T}{h}\,e^{-\Delta G_{-i}^{\neq}/RT} = \frac{k_B T}{h}\,e^{(I_i-T_i)/RT} \end{aligned} \tag{5}$$

Herein, I_i and T_i symbolize the standard-state Gibbs energies of the *i*th intermediate or transition state. Applying

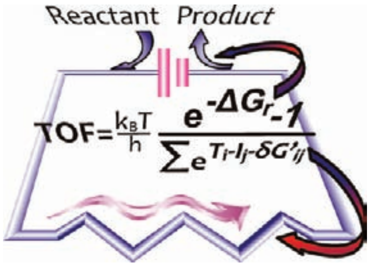

FIGURE 6. Equivalent to Ohm's law, the TOF is given as the chemical current determined by the potential (function of the reaction energy) divided by the resistance (function of the mechanism).

eq 5 to Christiansen's *k*-formulation[13] results in a much simpler formula for serial catalytic cycles (Figure 3) of *N* steps, due to cancellation of terms. These derivations were explained in the original literature,[6,14] and here we show the final form:

$$\mathrm{TOF} = \frac{k_\mathrm{B}T}{h}\frac{\mathrm{e}^{-\Delta G_\mathrm{r}/RT}-1}{\sum\limits_{i,j=1}^{N}\mathrm{e}^{(T_i - I_j - \delta G'_{i,j})/RT}} = \frac{\Delta}{M} \tag{6}$$

with

$$\delta G'_{i,j} = \begin{cases} \Delta G_r & \text{if } i > j \\ 0 & \text{if } i \leq j \end{cases} \tag{7}$$

By analogy to Ohm's law, eq 6 represents the TOF as *a catalytic-flux law* (Figure 6).[17] The TOF is given as the forward chemical current of the reaction, determined by the potential divided by the resistance. The potential of the process is Δ, a function of the energy of the reaction (ΔG_r); the "−1" term provides thermodynamic consistency for the case with $\Delta G_\mathrm{r} = 0$, for which the TOF is zero, or in the case of an endothermic reaction where the current flows backward and the TOF is negative. The resistance to the chemical flow is given by *M*, corresponding to the sum of exponentials of Gibbs energy differences between all the combinations of intermediates (I_j) and transition states (T_i).

The term $\delta G'$ which appears in the *M* expression derives directly from the translation of the *k*- to the *E*-representation. Thus, $\delta G'_{i,j} = \Delta G_\mathrm{r}$ whenever the *i*th TS follows the *j*th intermediate in the forward direction, or zero if the TS precedes the intermediate (eq 7). $\delta G'$ resolves the dilemma of Figure 5: as we are correcting this with the $\delta G'$ function, it does not matter if we consider the TS that appears before or after the intermediate. Applying eq 6 to the cross-coupling profile of Figure 1 (using *E* + ZPE gas phase values and room temperature[5,6]), we obtain the relative TOF values as TOF($n = 3$)/TOF($n = 6$) = 1.45. Despite their very different energy landscapes, both processes are virtually isokinetic! In addition, having large effective barriers, the two cycles have TOF values too low (10^{-16} h^{-1}) to qualify as efficient catalysts.

This is a good point to mention the technical difficulties to compute accurate Gibbs energies for the proper use of the model (i.e., eq 6). The above cross-coupling example is based on internal energies, but since the cycles (Figure 1) have the same molecularity, there is no significant loss of accuracy on the *relative* TOFs (see section 9).

4. The Energetic Span Approximation

Equation 6 can be simplified. For exothermal reactions ($\Delta G_\mathrm{r} < 0$) the "−1" term in the numerator can be neglected. More important, the denominator is usually (but not always!) dominated by a single term of the summation. In these conditions, eq 6 can be shortened to

$$\mathrm{TOF} = \frac{k_\mathrm{B}T}{h}\mathrm{e}^{-\delta E/RT} \tag{8}$$

where now we define δE, the energetic span, as

$$\delta E = \begin{cases} \boldsymbol{T}_\mathrm{TDTS} - \boldsymbol{I}_\mathrm{TDI} & \text{if TDTS appears after TDI} \quad \text{(a)} \\ \boldsymbol{T}_\mathrm{TDTS} - \boldsymbol{I}_\mathrm{TDI} + \Delta G_\mathrm{r} & \text{if TDTS appears before TDI} \quad \text{(b)} \end{cases} \tag{9}$$

Two fundamental terms appear in eq 9: the TDTS (TOF-determining transition state) and the TDI (TOF-determining intermediate). These species are the TS and the intermediate that maximize the energetic span within the cyclic constraints according to eq 9a and b, and thereby gauge the kinetics of the cycle.

Let us point out that this approximate derivation of the catalytic efficiency can be thought of as an extension of the Curtin−Hammett principle[18] (CHP). The CHP was formulated to treat selectivity of reactions, wherein several intermediates are in fast pre-equilibrium, followed by larger barriers to produce different products. The product ratio is determined solely by the energy difference of the transition states for the competing processes.

Additionally, we point out that in some communities the TDI is described by the term "resting state" (as it is the most populated intermediate), while the TDTS is termed as "the rate-limiting TS". However, we prefer to use the terms TDI and TDTS, which are functional and neutral terms describing the fact that these species determine together the TOF of a cycle. Thus, from eq 8, δE (given in Gibbs energies) serves as the *apparent activation energy of the cycle.*[19] As such, the smaller the energetic span, the faster the reaction.[20−24]

Let us apply the energetic span approximation to the cross-coupling of Figure 1. For $n = 3$, the TDI is the Pd$\{$-[$PH_2(CH_2)_3PH_2$]PhCl$\}^+Cl^-$ species (here, it is the lowest intermediate on the graph). The TDTS occurs at the reductive elimination TS, *even though it is not the highest state of the graph*! As the TDTS appears after the TDI for this example, we must employ eq 9a, obtaining TOF $= 1.2 \times 10^{-16}$ h^{-1}. For $n = 6$, the TDI is the same state as for $n = 3$, but the TDTS is the oxidative addition; consequently, eq 9b defines the energetic span here and leads to TOF $= 1.2 \times 10^{-16}$ h^{-1}. The TOFs ratio is then 1:1, which is close to the value obtained by the full equation (eq 6).

From the above example, it is apparent that the TDTS is not necessarily the highest state (as in the $n = 3$ ligand), nor the one that appears with the highest activation energy (as with the $n = 6$ ligand). There is no single step that controls the kinetics; instead, the kinetics is determined by two state As shown later (Figure 11), the energy graph can be drawn in a manner that makes the TDTS the highest point (or the TDI the lowest), since the starting point of the cycle is arbitrary. However, this kind of cyclic consideration may not be immediately apparent, while eq 9a and b gives a straightforward TOF result and spares this conceptual difficulty.

The utility of finding the TDTS/TDI is exemplified in the work of Carvajal et al. on the undesired alkene isomerization byproduct (from a terminal to an internal double bond), formed during the rhodium-catalyzed hydroformylation process.[28] The full cycle was computed using a small model ligand (Figure 7), which provided the identities of the TDI and TDTS. Having this information, determining the relative TOFs for the much larger complexes (Cb and Cc in the figure) required the computations of only these two determining states, thus saving much computational time. This quick estimate enabled identification of the catalysts that led to the smallest amount of olefin isomerization.

An analogous approach was used in a QM/MM (quantum mechanics/molecular mechanics) analysis[7] of the Pd cross-coupling reaction using the small PH_3 ligand as model.[5,6] To screen the activity of numerous large phosphine ligands, only the TDTS and the TDI were considered, as all the other states do not affect the TOF. The results showed that medium sized electron withdrawing phosphines or bulky ones are the most efficient for this reaction. Of course, this practice should be qualified, since changing the model catalyst may also change the identity of the TDI and TDTS, or even change the mechanism.

5. Degree of TOF Control

The degree of rate control (X_{rc}) belongs to the family of structure–reactivity coefficients used in physical organic chemistry to describe the influence of various factors (substituents, solvents, equilibrium constants, etc.) on rates.[29] Campbell defined X_{rc}[30,31] as the normalized influence of a certain rate constant on the overall rate of the reaction, where all the other rate and equilibrium constants are held constant. Thus,

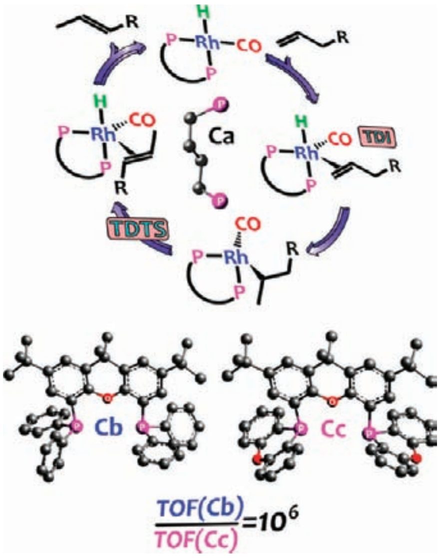

FIGURE 7. Simplified alkene isomerization reaction cycle occurring during alkene hydroformylation catalyzed by a rhodium complex.[28] The cycle was computed with the small Ca ligand, for which the TDI and TDTS were identified. Calculating only these two states enabled the conclusion that the complex Cb leads to much more extensive isomerization compared with Cc.

$$X_{\mathrm{rc},i} = \frac{k_i\,\partial r}{r\,\partial k_i}\bigg|_{K_m, k_{n\neq i}, -i} = \frac{\partial \ln r}{\partial \ln k_i}\bigg|_{K_m, k_{n\neq i}, -i} \qquad (10)$$

Knowing from eqs 8 and 9 the connection between the *k*- and *E*-representations, we derived the notion of "degree of rate control" in catalytic cycles using state energies, and termed it the degree of TOF control (X_{TOF}):[6,14]

$$X_{\mathrm{TOF},i} = \left|\frac{1}{\mathrm{TOF}}\frac{\partial \mathrm{TOF}}{\partial E_i}\right| \qquad (11)$$

where E_i can be a transition state or an intermediate Gibbs energy. The meaning of X_{TOF} is simple: the bigger its value, the higher the influence of the corresponding state (TS or intermediate) on the TOF. Equation 10 shows that the condition of fixed equilibrium constants makes Campbell's $X_{\mathrm{rc},i}$ equal to our $X_{\mathrm{TOF},i}$ (eq 11) for transition states. However, the new concept in eq 11 is the treatment of the effects of intermediates ($X_{\mathrm{TOF},I}$) and TSs ($X_{\mathrm{TOF},T}$) on equal footing.[32] As eq 11 is normalized, the sum of all the $X_{\mathrm{TOF},T}$ or $X_{\mathrm{TOF},I}$ is one.′ We can define the TDI and TDTS as the states that have X_{TOF} closest to one. These states are the ones that maximize δE (eq 9), and hence, the use of X_{TOF} values is a quick method for identifying the TDTS and TDI and for deciding whether there are more states that determine the kinetics of the cycle.

Applying eq 11 to eq 6, we can write the degree of TOF control explicitly in the *E*-representation:

$$
\begin{aligned}
X_{\mathrm{TOF},T_i} &= \frac{\sum_j \mathrm{e}^{(T_i - I_j - \delta G'_{i,j})/RT}}{\sum_{ij} \mathrm{e}^{(T_i - I_j - \delta G'_{i,j})/RT}} \\
X_{\mathrm{TOF},I_j} &= \frac{\sum_i \mathrm{e}^{(T_i - I_j - \delta G'_{i,j})/RT}}{\sum_{ij} \mathrm{e}^{(T_i - I_j - \delta G'_{i,j})/RT}}
\end{aligned}
\tag{12}
$$

If we apply eq 12 to the Pd cross-coupling of Figure 1, we obtain for the shorter chain that only one TS and one intermediate have a significant X_{TOF}; these are the TDI and TDTS species already described. However, for the ligand with $n = 6$, along with a single TDI there are two influential transition states: the oxidative addition with $X_{\mathrm{TOF},T} = 0.7$ and the reductive elimination with $X_{\mathrm{TOF},T} = 0.3$. This explains why for $n = 6$, the TOF calculated with the exact eq 6 is 30% smaller than the energetic span approximation (eq 8).

6. Influence of Reactant and Product Concentrations

The influence of reactant/product concentrations is less pronounced than that of state energies, but not negligible. Moreover, because experimentalists use concentration changes as a technique for deciphering the kinetics, it is essential to analyze concentration effects. A simple extension of the energetic span approximation allows us to determine which reactants and products affect the TOF:

$$
\mathrm{TOF} = \frac{k_{\mathrm{B}}T}{h}\,\mathrm{e}^{-\delta E/RT} \prod \frac{[R]}{[P]}\Bigg|_{\text{from TDI to TDTS}} \tag{13}
$$

Herein, eq 8 was multiplied by the concentration of all reactants consumed between the TDI and the TDTS, and divided by the concentrations of all products generated in the same section. As such, high concentrations of reactants entering the cycle between the TDI and the TDTS accelerate the reaction, and products exiting the cycle in this portion inhibit the reaction. All other species have negligible influence, as long as their concentrations remain at "ordinary" levels (huge amounts or only traces of reactants and products outside this active section will also impact the kinetics). As can be seen from eq 13, a change of a reactant or product concentration has a linear influence, while a determining state energy affects the TOF exponentially. The full derivation of the TOF including concentrations can be found in refs 14 and 33.

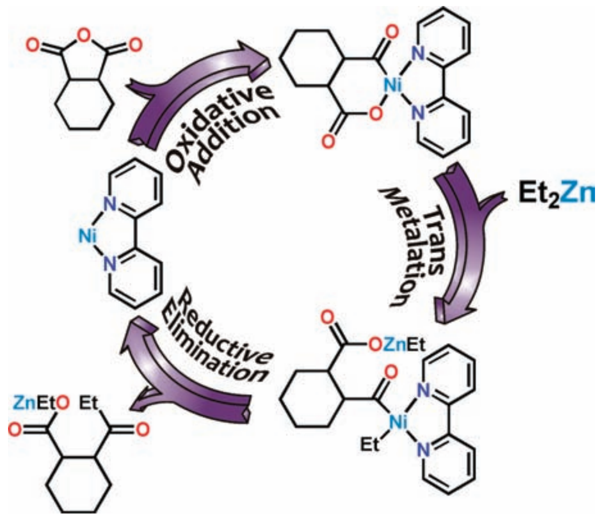

FIGURE 8. Cross-coupling reaction of an anhydride with an organozinc reactant catalyzed by a Ni-bipy complex, as appeared in the original experimental paper. Adapted with permission from reference 34. Copyright 2007 American Chemical Society.

7. Nickel Cross-Coupling: An Example of the Insight of the Model

A representative application is the cross-coupling reaction of an anhydride with an organozinc reactant, catalyzed by a nickel complex (Figure 8). This system was studied experimentally by Johnson et al.[34] and was found to exhibit a nontypical kinetic profile: The rate of the reaction was insensitive to the anhydride, and the TOF grew linearly with the Et_2Zn concentration until a critical concentration, beyond which the TOF remained constant.

The natural conclusions reached by the Johnson group were as follows:

(I) The oxidative addition step is not rate-determining, since an anhydride concentration change should have affected the TOF.

(II) At low Et_2Zn concentration, transmetalation must be the rate-determining step, since it follows first order kinetics on the diethyl-zinc reagent.

(III) At high Et_2Zn concentration, the TOF is independent of the concentration, and thus, the reductive elimination, being the only step left, must be rate-determining.

The energetic span model was used to test these conclusions. Thus, a reaction mechanism was proposed, and a full reaction profile was computed (Figure 9),[35] leading to the following observations:

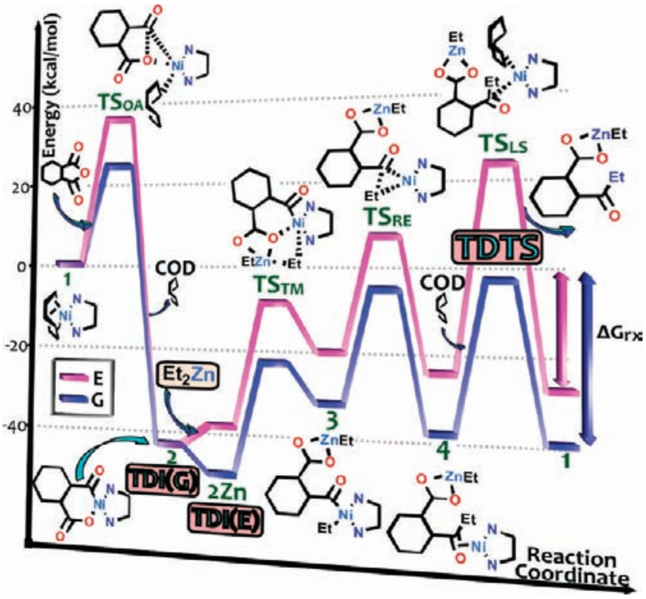

FIGURE 9. Energy (*E*, in purple) and free energy (*G*, in blue) computed profiles for the Ni cross-coupling.[35] The TDTS is the ligand substitution (TS_{LS}). The TDI is either intermediate **2** (in the *E* profile) or the encounter complex **2Zn** (in the *G* profile).

(I) Cyclooctadiene (COD), used in the experiment as a labile ligand, has an important function of lowering the oxidative addition (TS_{OA}). This effect was not observed in the reductive elimination (TS_{RE}) because of steric prohibition. If the Ni does not bind to COD at the end of the cycle, the oxidative addition of the next turnover will be much slower.

(II) To restart the catalyst, the COD replaces the product in a ligand substitution (TS_{LS}). This transition state was found to be the TDTS.

(III) Since current computational methods overestimate the entropic factors,[35−40] an accurate Gibbs energy could thus be estimated to lie between the computed values of the energy (*E*) and Gibbs energy (*G*) profiles.

(IV) In the *G* profile, the TDI is the Ni^{II} complex **2**, while in the *E* profile the TDI is the encounter pair **2Zn**.

Let us apply the model, including concentrations, for this Ni catalyst. According to eq 13 and considering the position of the TDTS and the two TDIs, we can express the TOF in both the energy and Gibbs energy profiles as[41]

$$\mathrm{TOF}\,(E) = \frac{k_{\mathrm{B}}T}{h}\,\mathrm{e}^{-\left[E(\mathrm{TS_{LS}}) - E(\mathrm{2Zn})\right]} \qquad (14\mathrm{a})$$

$$\mathrm{TOF}\,(G) = \frac{k_{\mathrm{B}}T}{h}\,\mathrm{e}^{-\left[G(\mathrm{TS_{LS}}) - G(2)\right]}\,[\mathrm{Et_2Zn}] \qquad (14\mathrm{b})$$

As stated before, the most accurate energy values are between the computed *E* and *G* values, and the resulting TOF should be some combination of eq 14a and b. At low Et_2Zn concentration, eq 14b defines the TOF and the kinetics have order one dependence on the zinc reagent, while at high concentration eq 14a describes the TOF wherein the reaction is independent of the diethyl-zinc concentration. Figure 10 shows the fit of the so computed TOF to the experimentally determined points.

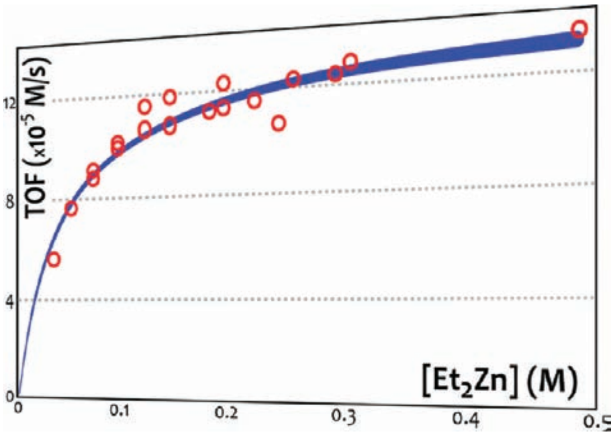

FIGURE 10. TOF of the Ni cross-coupling versus concentration of Et_2Zn. Red circles are the experimental values;[34] the blue line corresponds to the fitting using eq 14.[35]

It is apparent from this analysis that there is no meaning for the rate-determining *step* term in catalytic cycles, as the rate-determining *states* (TDI and TDTS) define the kinetics of a catalytic cycle.

8. Reviewing Kinetic Terminology for Catalytic Cycles

Although a lot of the concepts discussed above have been "in the air" for a long time (e.g., the CHP[18]), some wrong usages are still rooted in daily practice. Let us show now how the above concepts help in restoring the correct *kinetic paradigm*.[6,7,14,32,33,35] Thus, eqs 8 and 9 demonstrate the following:

1. One Transition State Does Not Determine the Kinetics of the Cycle. As the TDTS is only half of the story, stating that a catalyst that lowers the rate-determining TS will provide a faster reaction is incorrect, since the catalyst may change also the energy of the TDI or even its identity.[21,24,42]

2. The Determining States Are Not Necessarily the Highest TS or the Lowest Intermediate. Because of the condition that the TDI and TDTS must be the ones that maximize the energetic span (eq 9), the determining states may be different from the extreme state of the energy graph (Figure 11).[26,27]

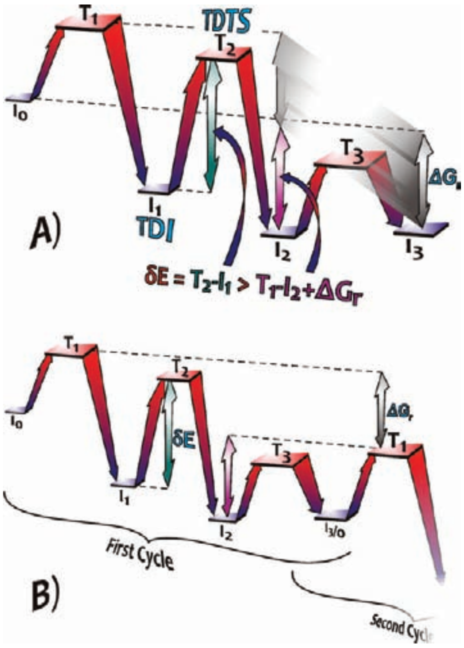

FIGURE 11. (A) Energy profile of a model catalytic cycle. T_1 and I_2 are the maximum and minimum energy states. Nevertheless, as T_1 precedes I_2, eq 9b shows that the activation energy would be reduced by the reaction energy term. T_2 and I_1 are not extreme states in this representation, but as T_2 follows the intermediate, we must use eq 9a, which reveals that combination of I_1 and T_2 maximizes δE and these states result the TDI and TDTS. (B) The condition of eq 9b can be rationalized by recognizing that since the cycle "flows forward", we cannot take I_2 and go backward to T_1. Instead we must consider I_2 along with the T_1 in the following turnover, energetically equivalent to $T_1 - I_2 + \Delta G_r$. Note that if we start the cycle at the TDI, then the TDTS will always be the highest point.

3. There Are No Rate-Determining STEPS, but Rate Determining STATES. The rate-determining step (RDS) is a deeply rooted paradigm in the kinetic community, although it has been criticized as not necessary,[43] misleading,[44] or outmoded.[45] Is the RDS a real physical concept for catalytic cycles? Can we answer this question using the energetic span model?

The common, naïve definition of the RDS is "the slowest step of the reaction".[26,44,46] However, in a steady-state regime, all steps proceed at the same rate, and therefore, this definition is flawed.[43,44] The IUPAC definition is (in a simplified form) the step whose rate constant exerts the strongest influence on the overall rate of the reaction, when all the equilibrium constants (K) are held constant (this resembles Campbell's degree of rate control, see eq 10).[27,47,48] However, as we saw in section 5, this actually means a change in a TS energy: *when we were considering rate-determining steps, we in fact meant the rate-determining TS.*[26,27,32]

Besides, from eqs 8 and 9, we know that the influence of the intermediates is equally significant (and easier to study[49,50]). Moreover, as the TDI and TDTS are not necessarily adjoined (as in Figure 12),[26,27] several steps can participate in the shaping of the kinetics.[9,25,51−53] Therefore, *there are no rate determining STEPS, but rate determining STATES!*

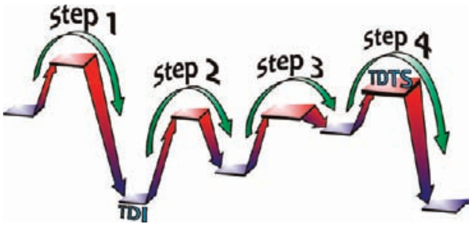

FIGURE 12. Which step is the *rate-determining step*? Step 1, with the highest energy TS? Step 2, having the highest activation energy? Or maybe step 4, containing the TDTS? The answer is neither is right; the kinetics is determined by the TDI and TDTS, and follows the maxim: "*There are no rate-determining STEPS, but rate determining STATES!*"

9. A Word of Caution

The energetic span model permits the kinetic assessment of computationally calculated catalytic cycles. However, it is important to bear in mind the approximations behind this expression and thereby stress the correct usage of δE as a predictor.

The model is derived with three conditions: (i) transition state theory (TST) is valid, (ii) a steady state regime is applicable, and (iii) the intermediates undergo fast relaxation.

For systems where TST is insufficient, for example when having tunneling or other reasons where the transmission coefficient κ is different than one, it is always possible to convert κ to an exponential term and add it to the energy of the TS as a correction.

Steady state can be typically achieved after some turnovers. Some exceptions are systems wherein the reaction is too fast, or where there is a chaotic behavior. Fast relaxation of the intermediates is easily reached in a solvent or under moderate pressure in the gas phase.

Another key point is the fact that TST requires Gibbs energies (G). Computationally, accurate G's are harder to obtain than internal energies (E), since thermal/entropic corrections rely on several approximations, such as harmonic potentials or ideal-gas expressions. Solvation Gibbs energies provide further difficulties, as the entropic factors are strongly diminished if there are strong solute−solvent interactions, up to a point where it is sometimes better to completely neglect the entropic contributions.[35−40] Nevertheless, if we have the same molecularity at the determining states of the reactions, E and G will give similar results (this was considered for the cross-coupling example of Figure 1).

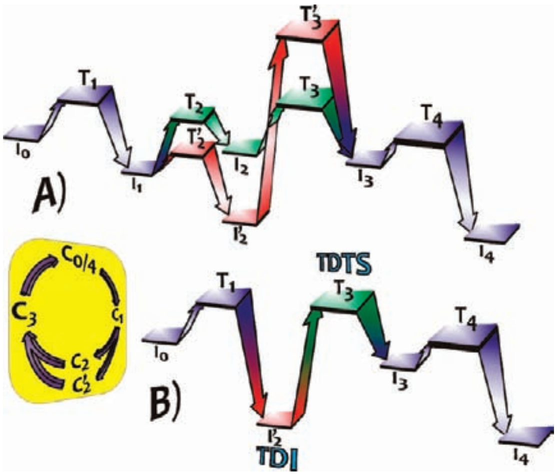

FIGURE 13. (A) Model reaction with two competing mechanisms having shared states. In the red pathway, there is a very low intermediate (I'_2) but also a very high TS (T'_3), making this way a dead end. The reaction will proceed through the green mechanism, but it has to take into account I'_2 as the TDI. (B) The actually followed cycle. The energetic span model can be now applied.

To this, we must add the errors on E estimations. For example, using standard density functional theory, we underestimate dispersion forces or deal poorly with static correlation. Adding the fact that a small inaccuracy in TDTS/TDI corresponds to an exponential error on the TOF (eq 8), it is clear that accurate absolute TOF values are still unattainable computationally. Yet, because of error compensation, *relative* TOFs can be quantitatively useful if we use the same computational level for all the systems.

The last key factor to consider is the comparison of two competing cycles that share states, like in Figure 13A. This example shows a profile with two competing mechanisms in connected cycles that lead to the same final product. Calculating relative δE's for the alternative mechanisms will lead to an error. As in the Curtin–Hammett principle,[18] the TDI and the TDTS are shared states for both cycles and correspond to the most stable intermediates and TS. In the model of Figure 13, the TDI is I'_2 and the TDTS is T_3, thus mixing the red and the green pathways (Figure 13B).

10. Conclusion and Prospects

The energetic span model offers a straightforward method to calculate the TOF of catalytic cycles based on its computed energy profile (eqs 6 and 7). In most cases, the TOF is determined by one transition state, the TDTS, one intermediate, the TDI, and by the reaction energy, ΔG_r (eqs 8 and 9). The energy difference between the TDI and the TDTS (with due ΔG_r correction), so-called the *energetic span* (δE), is the apparent activation energy of the entire catalytic cycle that determines the catalytic efficiency.[6,14]

We exemplified herein the usage of the energetic span concept with two computed cross-coupling systems, based on palladium and nickel complexes.[5−8,35] Several significant notions in catalytic kinetics were reviewed in the light of the mathematical machinery of the energetic span model. The influence of reactant and product concentrations on the TOF and the degree of TOF control for energy states were also assessed.

The energetic span model constitutes a fundamental tool for the computational chemist in the world of catalysis. Alongside the quantitative aspect, it has a qualitative impact of changing kinetic concepts; based on the energy representation of the cycle's kinetics, we conclude that in catalytic cycles there are no rate determining *steps*, but rate determining *states* (and in many cases just two, the TDI and the TDTS).

Further developments of the model are currently being considered and include the calculations of turnover numbers (TONs), which consider poisoning of catalysts, and the treatment of a network of connected cycles.

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BIOGRAPHICAL INFORMATION

Sebastian Kozuch was born in Buenos Aires, Argentina, in 1976. He got his licentiate in chemistry from the University of Buenos Aires and immigrated to Israel in 2002. He received his M.Sc. and Ph.D. *summa cum laude* in the Hebrew University under the supervision of Sason Shaik. He is currently a postdoc of Jan (Gershom) Martin at the Weizmann Institute of Sciences. His theoretical interests include organometallic chemistry, catalysis, and kinetics.

Sason Shaik received his B.Sc. and M.Sc. in chemistry from Bar-Ilan University and his Ph.D. from the University of Washington. He spent a postdoctoral year with Roald Hoffmann. In 1980, he started as a Lecturer at Ben-Gurion University, and in 1992 he moved to the Hebrew University, where he is currently the director of The Lise-Meitner-Minerva Center for Computational Quantum Chemistry. Among his awards is the 2007 Schrödinger Medal. His research interests range from bonding in small molecules to structure and reactivity of metalloenzymes.

FOOTNOTES

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