ACS Catalysis

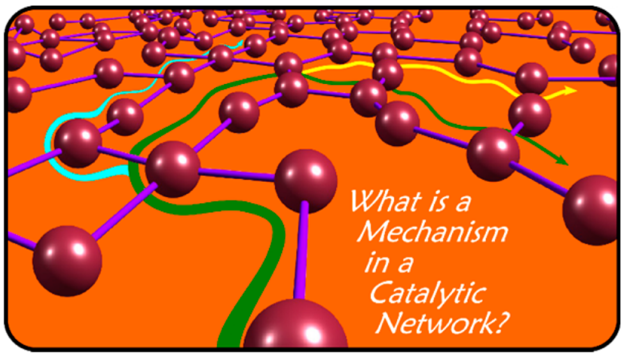
Research Article

pubs.acs.org/acscatalysis

Steady State Kinetics of Any Catalytic Network: Graph Theory, the Energy Span Model, the Analogy between Catalysis and Electrical Circuits, and the Meaning of "Mechanism"

Sebastian Kozuch*

Department of Chemistry, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel



ABSTRACT: As originally shown by King and Altman, graph theory, and specifically the use of spanning trees, provides the means to solve the kinetics of any catalytic network in a steady state regime, taking as input data all the rate constants. Herein, it is shown that the translation of the rate constants to Gibbs energies provides a simpler way to estimate the energy span (i.e., the apparent activation energy of the full reaction), the determining states, and the turnover frequency (TOF) of any and all catalytic networks. By re-examining the concepts of chemical kinetics through rigorous mathematical treatment, an alternative definition is suggested for the term "chemical mechanism". In addition, and in analogy to electrical circuits, the chemical resistor terms (called here "kinestors") are identified for parallel and series chemical circuits, providing a new Ohmic interpretation for catalysis.

KEYWORDS: *graph theory, energy span model, kinetics, catalysis, turnover frequency, network, mechanism*

■ INTRODUCTION

Since the original mathematical description of the simplest model for a catalytic reaction (in this case, for enzymes) by Michaelis and Menten in 1913,[1,2] more than a century of expansions has brought us to the vast array of expressions[3,4] for what should have been a simple problem: the formulation of a universal and straightforward equation to calculate the turnover frequency (TOF)[5−8] of any catalytic cycle in a steady state regime.

As a matter of fact, there are very simple procedures to calculate the rate of any steady state reaction (some of them discussed below). They are based on "algorithms" that start from the expression of the kinetic steady state equations and are solved by algebraic or graph theory methods. The problem resides in the size of the resulting formulas, which can be intractable for large networks. Although modelers can explain kinetic phenomena using different techniques, these expressions lack universality (as they may be completely different from case to case) and usually fail to bring a conceptual meaning for each term of the equation. Still, some of these procedures pioneered by Christiansen[9] and King and Altman[10] bring the possibility of answering the question of how to calculate *any* steady state catalytic network kinetics based on the knowledge of all the rate constants and therefore are a stepping stone for this paper (and previous works on the energy span model[11−16]).

In graph theory, graphs are diagrams made of points (vertices) with pairwise interactions between them (edges).[17] These diagrams not only are for the aesthetic or schematic depiction of complex networks (such as in electricity circuits, social networks and map drawing) but also provide powerful mathematical tools to solve specific questions on these networks. Graph theory has found two main niches in chemistry:[18] the enumeration of Lewis-style connectivity of molecules (in which the vertices are atoms and the edges are chemical bonds)[19,20] and in chemical kinetics (in which the vertices are intermediates and the edges are the elementary steps).

In this work we will consider four different types of graphs for chemical kinetics (*net flow*, *rate constant*, *energy*, and *circuit* graphs). Some of them are similar, some are not, but all of them bring a different kind of information on the kinetics of the catalytic network. With the aid of these graphs, we will find a simpler and more straightforward expression to calculate the TOF of any type of catalytic cycle when using as input data the Gibbs energies of all the intermediates and transition states (the *E*-representation,[12,13] in contrast to the equivalent *k*-representation, based on rate constants). This information will permit us to find the factors that define the kinetics of the network.

The classical definition of a chemical mechanism is "a detailed description of the process leading from the reactants to the products of a reaction, including a characterization as complete as possible of the composition, structure, energy and other properties of reaction intermediates, products and transition states".[5] We shall see in this work that, as opposed to this IUPAC definition, a complementary definition of "mechanism" naturally arises from the mathematical treatment of the steady state kinetics of the network. A mechanism will be defined here as *the*

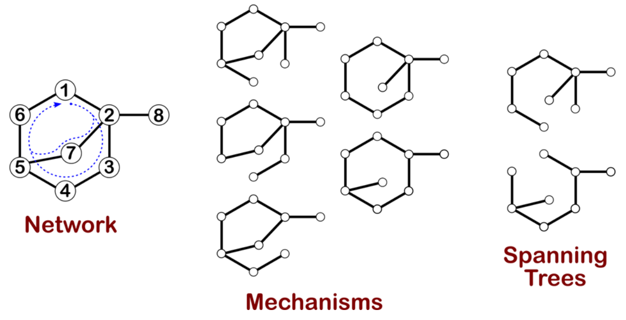
Received: April 2, 2015
Revised: May 21, 2015
Published: June 29, 2015

© 2015 American Chemical Society

DOI: 10.1021/acscatal.5b00694
ACS Catal. 2015, 5, 5242−5255

subgraph of the network that consists of only one cycle, but still includes all the intermediates, even if they are dead-ends of the cycle (see Scheme 1).

Scheme 1. Eight-Intermediate Model Kinetic Network with the Two Possible Catalytic Cycles (in blue), the Five Mechanisms That Can Arise from This Network[a], and Two of the 21 Possible Spanning Trees



[a]Note that all the intermediates are included on each mechanism, even if they appear as "dead-ends".

If we portray a blueprint of a complex catalytic network including many pathways, the detection of the most probable mechanism and the determining factors that shape the global rate are clearly the most important tasks of a kinetic study. Hopefully, this work will help in that task.

In light of the number of topics discussed in this conceptual paper, the most critical subjects are discussed in the body of the manuscript, and the most tedious derivations and off-topics (including a discussion on selectivity and on the driving force of catalytic systems) will be relegated to the appendices.

KINETICS IN THE *K*-REPRESENTATION

The Algebraic Method. The estimation of the TOF of a catalytic network is a known procedure that comes in several flavors when working in the *k*-representation (see, for instance, refs 16, 21, 22). One of the most traditional TOF derivations will be described here as a basis for the novel kinetic analysis in the *E*-representation.

In a network of reactions, the concentration change of each intermediate, C_i, is mathematically described as

$$\frac{\mathrm{d}[C_i]}{\mathrm{d}t} = \sum_m (k_{mi}[C_m] - k_{im}[C_i]) \tag{1}$$

where k_{mi} and k_{im} are the different rate constants directed to or emitted from intermediate *i*, respectively. In other words, the concentration of an intermediate grows according to the chemical flow going to or from it. Note that in the case of having a multisite catalytic mechanisms, more typical of heterogeneous catalysis, eq 1 is only an approximation; however, more than often it is still possible to approach the microkinetics of such a case to a simple stepwise network.[23] In a matricial form, we can write the kinetic master equation of this Markovian process as

$$\hat{K}\vec{c} = \frac{\mathrm{d}\vec{c}}{\mathrm{d}t} \tag{2}$$

where $\hat{K}$ is the rate constants matrix, and $\vec{c}$ is the intermediates concentration vector. The steady state regime is reached when the concentrations do not vary (or more accurately, when their variation is much slower than the net variation of the full chemical reaction).[5] This is simply written as

$$\hat{K}\vec{c} = 0 \tag{3}$$

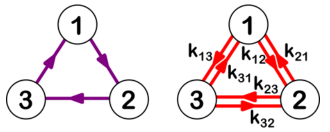
For example, in a simple three-step catalytic cycle, such as the one in Scheme 2, where the vertices are the different catalytic stages (intermediates), we will have

$$\begin{aligned} k_{21}[C_2] + k_{31}[C_3] - [C_1](k_{12} + k_{13}) &= 0 \\ k_{32}[C_3] + k_{12}[C_1] - [C_2](k_{23} + k_{21}) &= 0 \\ k_{13}[C_1] + k_{23}[C_2] - [C_3](k_{31} + k_{32}) &= 0 \end{aligned} \tag{4}$$

or, according to eq 3,

$$\begin{pmatrix} -(k_{12} + k_{13}) & k_{21} & k_{31} \\ k_{12} & -(k_{23} + k_{21}) & k_{32} \\ k_{13} & k_{23} & -(k_{31} + k_{32}) \end{pmatrix} \begin{pmatrix} [C_1] \\ [C_2] \\ [C_3] \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} \tag{5}$$

Scheme 2. ***Net Flow Graph*** **(in purple) and** ***Rate Constant Graph*** **(in red) for a Simple Three-Intermediate/Three-Step Model Catalytic Cycle[a]**



[a]Each red edge corresponds to a rate constant (thus two edges per elementary step). The net flow graph shows the direction of the chemical reaction; this information is not always obvious from the rate constant graph.

To estimate the TOF of the cycle, we must measure the net chemical flow through any one of the steps (all the steps must have the same net rate at a steady state regime). For instance, in the first step of the reaction (between intermediates C_1 and C_2):

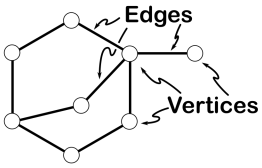
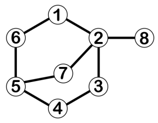
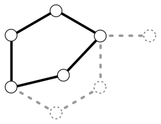
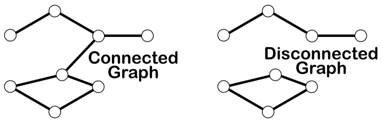
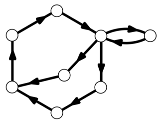
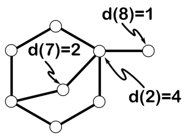
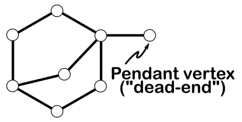
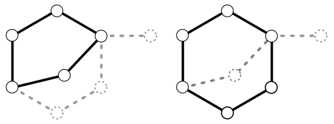
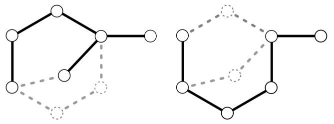
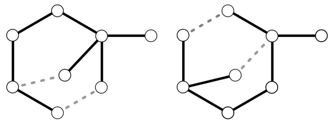
$$\mathrm{TOF} = \vec{r}_{12} - \vec{r}_{21} = \frac{k_{12}[C_1] - k_{21}[C_2]}{[C_t]} \tag{6}$$

where C_t is the total catalyst concentration. The concentrations can be calculated by Cramer's rule, but since $\hat{K}$ has linearly dependent terms, one more condition is necessary to solve the system. This can be achieved with a normalization condition to make "probability concentrations" ($\sum_i C_i = 1$, which makes sense considering that the TOF is defined as the derivative of the turnovers with respect to the time per active site[8]) and removal of any one of the rows of $\hat{K}$ to produce a linearly independent system. For instance, removing row 1 from eq 5 and adding at the end the normalization condition we have

$$\begin{pmatrix} k_{12} & -(k_{23} + k_{21}) & k_{32} \\ k_{13} & k_{23} & -(k_{31} + k_{32}) \\ 1 & 1 & 1 \end{pmatrix} \begin{pmatrix} [C_1] \\ [C_2] \\ [C_3] \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} \tag{7}$$

which can be written as $\hat{A}\cdot\vec{c} = \vec{I}$, where $\hat{A}$ can be considered the normalized rate constants matrix.[16] Now, Cramer's rule can be applied to obtain

Table 1. Definitions of Some Graph Theory Terms Employed in Chemical Kinetics

	Term	Definition	Utility in chemical kinetics	Examples
1	Graph	Diagram consisting on points connected by lines.	Describes the network of the chemical reaction.	
2	Vertex	Point in the graph.	Corresponds to the intermediates of the reaction.	
3	Edge	Line connecting vertices.	In the *k*-rep, an edge corresponds to a rate constant. In the *E*-rep, it is the exponential of ± the Gibbs energy of a TS.	
4	Labeled graph	Graph with indexed vertices.	All chemical kinetic graphs are labeled, since the intermediates are identified.	
5	Subgraph	Graph whose vertices and edges belong to a greater, underlying graph.	A mechanism or a cycle are subgraphs of the network.	
6	Connected Graph	A one piece graph with all its vertices joined by edges.	A chemical kinetic network must always be connected.	
7	Digraph	A graph with directed edges (also called “arcs” or “arrows”).	The directed edges can indicate the net chemical flow of the step, or the direction of the rate constants.	
8	Degree of a vertex – **d**(**v**)	Number of edges converging in the vertex.	An intermediate from where the reaction splits in two different pathways will have **d**(**v**)=3. A dead-end will have **d**(**v**)=1. In a simple cycle, all the intermediates have **d**(**v**)=2.	
9	Pendant vertex	A vertex with degree 1. Sometimes called “terminal”, or “leaf” in trees terminology.	A dead-end, an intermediate out of the cycle but in equilibrium with it.	
10	Simple cycle	A closed trail, without branching and **d**(**v**)=2 for all vertices.	A mechanism of the network without dead-ends is a simple cycle. Walking the cycle is equivalent to one turnover.	
11	Tree	A connected subgraph without cycles.		
12	Spanning tree	A tree that includes all the vertices of the graph.	There is no physical utility for spanning trees in chemical kinetics, more than being a tool to obtain the TOF.	

$$[C_i] = \frac{|\hat{A}_i|}{|\hat{A}|} \tag{8}$$

where $|\hat{A}|$ is the determinant of $\hat{A}$, and matrix $\hat{A}_i$ is obtained by replacing column i of $\hat{A}$ by vector $\vec{I}$ (note that $|\hat{A}| = \sum_i |\hat{A}_i|$). In a certain sense, $|\hat{A}|$ is for catalysis what the partition function is for statistical thermodynamics. As a matter of fact, considering that according to transition state theory all the rate constants can be translated to Gibbs energies of activation, eq 8 can be considered as the Boltzmann distribution of a catalytic system.

From eqs 6 and 8, the solution for the steady state catalytic cycle of Scheme 2 is

$$\mathrm{TOF} = \vec{r}_{12} - \overleftarrow{r}_{21} = \frac{k_{12}|\hat{A}_1| - k_{21}|\hat{A}_2|}{|\hat{A}|} \tag{9}$$

Equation 9 can be easily extrapolated to any catalytic network by “reprogramming” matrix $\hat{A}$. The drawback resides in the complexity that the explicit formulation of the TOF can reach after the full determinant expansion. For the simple three-step cycle, the TOF is

$$\mathrm{TOF} = \frac{k_{12}k_{23}k_{31} - k_{13}k_{32}k_{21}}{k_{21}k_{31} + k_{23}k_{31} + k_{32}k_{21} + k_{31}k_{12} + k_{32}k_{13} + k_{32}k_{12} + k_{12}k_{23} + k_{13}k_{23} + k_{21}k_{13}} \tag{10}$$

In general, for a simple cycle (a catalytic reaction without alternative pathways or dead ends) with N intermediates, there are N^2 terms in the denominator, each one composed of $N - 1$

DOI: 10.1021/acscatal.5b00694
ACS Catal. 2015, 5, 5242−5255

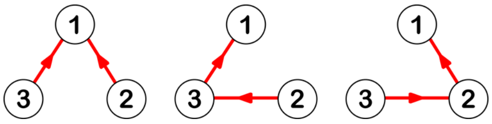
rate constants. Although the complexity of these equations can be dazing even with small networks, some tricks have been devised for how to write $|\hat{A}|$ for simple cycles.[9,21] With larger and more intricate networks, the number of terms can be monumental. By Cayley's theorem,[3,10,17] a "complete" catalytic network (in which all the intermediates are interconnected), the number of terms in $|\hat{A}|$ will be N^{N-1}. For instance, the complete graph of a four-intermediate network has 64 terms in $|\hat{A}|$, each one composed of three rate constants. Still, even after solving the full TOF expression, we are still no closer to comprehending the physical meaning of each term of the TOF equation.

The Graph Theory Method. King and Altman discovered that because a kinetic chemical network can be drawn as a graph (that is, dots connected by lines), then it can be described by graph theory.[3,4,10,24,25] We will make a short description of the methodology designed by them for steady state catalytic cycles, still working in the *k*-representation. For the sake of simplicity, Table 1 presents a short glossary of graph theory terms important for our case.

An important tool in graph theory must be introduced at this point: *spanning trees* are graphs that cover all the intermediates but do not close any cycle (however, any edge added to them will generate a cycle). Spanning trees are very useful tools in chemical kinetics, despite the fact that they do not possess any evident physical meaning, other than being parts of the "partition function" of catalytic concentrations, as $|\hat{A}_i|$ in eq 8. In Scheme 1, in addition to the eight-intermediate model network and all the possible mechanisms, two of the 21 possible[26] spanning trees for this system are shown.

Let us consider the catalytic network as a labeled digraph (Table 1, rows 4 and 7), in which each intermediate is a vertex and each rate constant is an edge (what we called a *rate constant graph* in Scheme 2). The key in the description of the kinetics in graph theory is to realize that every term of the determinant of the normalized rate constants matrix ($|\hat{A}|$; see eq 7) corresponds to a spanning tree (rows 11 and 12 of Table 1) of the digraph of the reaction. This set of directed spanning trees is divided into subsets according to their convergence to a specific intermediate. For instance, to obtain $|\hat{A}_1|$ of the three-step cycle of Scheme 2, we draw the three possible digraphs that connect all the vertices without closing any cycle and are directed to intermediate 1, as shown in Scheme 3.

Scheme 3. Spanning Trees of the Rate Constant Graph Directed to Intermediate 1, Equivalent to eq 11

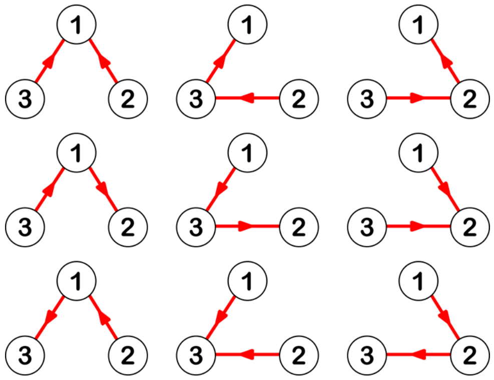


Because the directed edges symbolize rate constants, the sum of the three spanning trees will be the graph version of $|\hat{A}_1|$,

$$|\hat{A}_1| = k_{21}k_{31} + k_{23}k_{31} + k_{32}k_{21} \tag{11}$$

Because $\sum_i |\hat{A}_i| = |\hat{A}|$, the nine possible directed spanning trees will be composed of three subsets, each one with the same underlying nondirected subgraph but with varying direction of the edges, as shown in Scheme 4. In general, the number of these subsets will be equal to N (the number of intermediates), and the number of nondirected underlying subgraphs will go from N for simple cycles to N^{N-2} for complete graphs (that is, with all the vertices interconnected).[17]

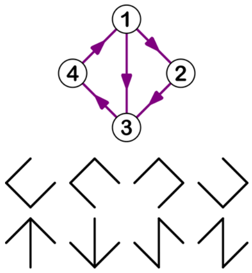
Scheme 4. The Nine Directed Spanning Trees for a Three-Step Cycle in a Rate Constant Graph[a]



[a]Their sum is equivalent to $|\hat{A}|$ in eq 7.

In this way, graph theory transformed the problem of expressing the TOF in an algebraic form (based on determinants) to devising a technique to draw all the possible spanning trees. For complex mechanisms, there are several algorithms to depict all the trees,[17] but for small networks, it is easy to do it by hand (for our chemical cases, we recommend the top-to-bottom approach of removing edges one by one from the starting graph until there are no cycles remaining). As an example, Scheme 5 shows the eight nondirected spanning trees of a four-vertices/five-edges net flow graph, which has two alternative cycles going through intermediates 1−2−3−4 and 1−3−4. In this system, the number of directed spanning trees (equal to the number of terms in $|\hat{A}|$) is 8 × 4 = 32. This graph will serve us as a model network for the following sections.

Scheme 5. The Eight Nondirected Spanning Trees of a Four-Vertices/Five-Edges *Net Flow Graph* (with purple edges)[a]



[a]The total number of directed spanning trees as used in the King and Altman[10] method is 32.

In this case, the chemical flow is divided at intermediate 1, and therefore, there are four completely equivalent ways to calculate the TOF:

$$\mathrm{TOF} = r_{12} + r_{13} = r_{23} + r_{13} = r_{34} = r_{41} \tag{12}$$

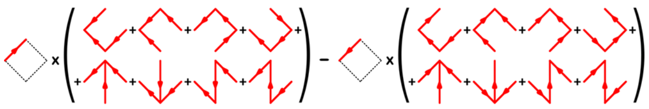
For simplicity we will use only r_{41} to calculate the TOF:

$$\mathrm{TOF} = r_{41} = k_{41}[C_4] - k_{14}[C_1] = \frac{k_{41}|\hat{A}_4| - k_{14}|\hat{A}_1|}{|\hat{A}|} = \frac{\Delta}{|\hat{A}|} \tag{13}$$

The denominator of eq 13 will be composed of the 32 directed spanning trees identified before in Scheme 5 and will not be drawn here, but as an example of how to work with these graphs, let us explicitly write the numerator, called Δ according to

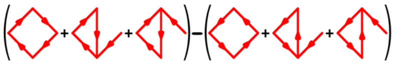
Christiansen notation,[9] where each red edge symbolizes a rate constant, and a graph is the product of those constants:

$$\Delta = k_{41}|\hat{A}_4| - k_{14}|\hat{A}_1| =$$



(14)

Most of the terms in these trees cancel, appearing in both the right and left terms, and therefore,

$\Delta =$  (15)

Equation 15 has two components: one positive, and the second negative, which have the same underlying graphs but vary in the directionality of the edges. It can be postulated that each one of these graph depicts a chemical *mechanism* (see also Scheme 1), forming the three possible pathways that can close the catalytic cycle. They are the ones that go through intermediates 1−2−3−4 and through intermediates 1−3−4 (with two possible ways to have intermediate 2 as a dead end in equilibrium, also called “pendant vertex”; see Table 1, row 9).

What we have here is a novel conceptual interpretation of some of the terms that form the TOF expression of any steady state system: *each term of Δ (a subgraph of the network that consists of only one cycle but still includes all the intermediates) represents a possible mechanism for the catalytic cycle.* This is the first time that, to the best of our knowledge, a mathematical definition of a “chemical mechanism” is proposed. As stated before, this definition naturally arises from the algebraic treatment of the steady state kinetics of a catalytic network. Note the difference between this interpretation and the standard use of the term “mechanism”. In the usual sense, a mechanism is considered as one simple cycle (1−2−3−4 or 1−3−4 in the example of Scheme 5, which in real life can be, for instance, a radical vs anionic pathway, a concerted vs nonconcerted mechanism, or via an S_N2 vs an S_N1 substitution). In the definition proposed here, a mechanism is still a simple cycle, but it also includes all the intermediates of alternative cycles as possible states in fast equilibrium with the main cycle. As we shall see later, these out-of-the-cycle intermediates can be a critical part of the TOF expression and therefore cannot be neglected when describing the mechanism. In other words, a stable intermediate of one pathway can be a determining factor in another pathway (see ref 15 for some examples).

Let us see a practical illustration. Figure 1A,B shows the energy profile and the network flow graph of two possible pathways for a Pd-catalyzed heterocoupling of two nonactivated arenes, benzene and indole, computed by Meir et al.[27] Naïvely, one would say that there are two mechanisms, going through one of two paths: 1−2R−3R−4R−5−6−7−1 (the “red” path), or 1−2B−3B−4B−5−6−7−1 (the “blue” path), as depicted in the flow graph network in Figure 1B. However, both paths are intertwined, and the intermediates of one can affect the other. According to the working definition postulated here, there are actually eight possible mechanisms that will be obtained via the procedure of eqs 12−15, four of which are shown in Figure 1C (because the blue path has a very high transition state with low probabilities of being crossed, the mechanisms with a closed cycle going through this path were neglected). Note that the low-energy intermediate I_{2B} from the blue path is in fast equilibrium with the second path, and completely disregarding it from the “red mechanism” will be a huge kinetic mistake (this intermediate is actually the TOF-determining intermediate[27]). If we have to identify the more probable mechanism, then taking into account that the high energy of T_{45B} hinders the fast equilibrium between the red and blue paths, then mechanism  will be it (see later the discussion regarding Scheme 13).

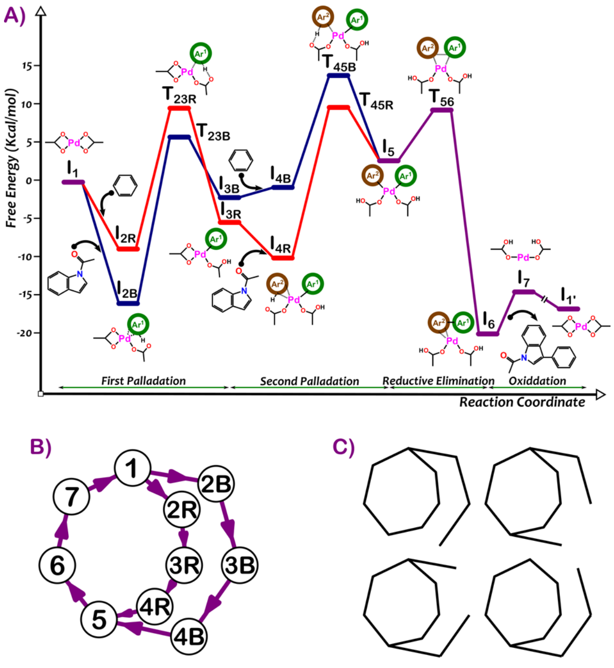


Figure 1. (A) Computed energy profile for two possible pathways (blue and red) of a Pd-catalyzed heterocoupling of two nonactivated arenes, benzene and indole, computed by Meir et al. (Adapted with permission from ref 27). (B) Flow graph of the network. (C) Four of the eight possible mechanisms.

The negative components of Δ in eq 15 depict the possibility of having a backward flow through the same mechanisms; they are usually negligible compared with the positive terms, but in the case of exergonic or nearly isergonic reactions, they can be a major part of the kinetics.[12] In the following sections, we will try to make sense of all the other components of the TOF equation.

KINETICS IN THE *E*-REPRESENTATION

Solving Kinetics of Simple Cycles. As stated above, there is a direct translation between Gibbs energies and rate constants, at least under transition state theory (TST). In principle, this means a total mathematical equivalence between the *k*-representation and *E*-representation of the kinetics, although in practice, there can be significant conceptual differences.[13]

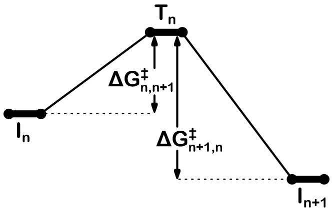
Let us see, as an example, what would be the translation from *k*- to *E*-representation of eq 10, the three-step simple cycle of Scheme 2 (for the general derivation, see refs 11−13). According to TST, we have for forward and backward rate constants the following relations (Scheme 6):

$$k_{n,n+1} = \frac{k_B T}{h} e^{-\Delta G^{\ddagger}_{n,n+1}/RT} = \frac{k_B T}{h} e^{(I_n - T_n)/RT}$$

$$k_{n+1,n} = \frac{k_B T}{h} e^{-\Delta G^{\ddagger}_{n+1,n}/RT} = \frac{k_B T}{h} e^{(I_{n+1} - T_n)/RT} \qquad (16)$$

where I_n and T_n are the Gibbs energies of intermediate and transition state n, respectively. Inserting eq 16 into eq 10, we obtain equation 17.

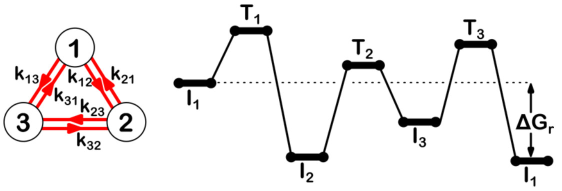
Scheme 6. Forward and Backward Gibbs Energies of Activation



$$\begin{aligned}\mathrm{TOF}&=\frac{k_{12}k_{23}k_{31}-k_{13}k_{32}k_{21}}{k_{21}k_{31}+k_{23}k_{31}+k_{32}k_{21}+k_{31}k_{12}+k_{32}k_{13}+k_{32}k_{12}+k_{12}k_{23}+k_{13}k_{23}+k_{21}k_{13}}\\&=\frac{\left(\frac{k_BT}{h}\right)^3\left[e^{-(T_1-I_1+T_2-I_2+T_3-I_3)/RT}-e^{-(T_3-I_1+\Delta G_r+T_2-I_3+T_1-I_2)/RT}\right]}{\left(\frac{k_BT}{h}\right)^2\left[e^{-(T_1-I_2+T_3-I_3)/RT}+e^{-(T_2-I_2+T_3-I_3)/RT}+\ldots+e^{-(T_1-I_2+T_3-I_1+\Delta G_r)/RT}\right]}\end{aligned}\tag{17}$$

In eq 17, we converted k_{13} to $\exp[-(T_3-I_1+\Delta G_r)/RT]$, with ΔG_r being the global reaction Gibbs energy (negative for exergonic cycles). Intermediate 1 in this term is not only the end point of the first cycle but also the starting point of a second cycle and has a lower energy compared with the first appearance of intermediate 1, as shown in Scheme 7.

Scheme 7. Rate Constants Graph and Energy Profile of the Three-Step Simple Cycle[a])



[a] Intermediate 1 appears twice in the energy representation, the second time being lower in energy by ΔG_r (the Gibbs energy of reaction, that is, the difference between products and reactants, not shown in the rate constant graph.

Because each term includes most of the intermediates and TS energies, we can take all these energies as a common factor, obtaining eq 18.

$$\begin{aligned}\mathrm{TOF}&=\frac{k_BT}{h}\frac{e^{\sum_{i=1}^{3}(I_i-T_i)/RT}.[1-e^{\Delta G_r/RT}]}{e^{\sum_{i=1}^{3}(I_i-T_i)/RT}.[e^{(T_2-I_1)/RT}+e^{(T_1-I_1)/RT}+\ldots+e^{(T_2-I_3+\Delta G_r)/RT}]}\\&=\frac{k_BT}{h}\frac{1-e^{\Delta G_r/RT}}{e^{(T_2-I_1)/RT}+e^{(T_1-I_1)/RT}+\ldots+e^{(T_2-I_3+\Delta G_r)/RT}}\end{aligned}\tag{18}$$

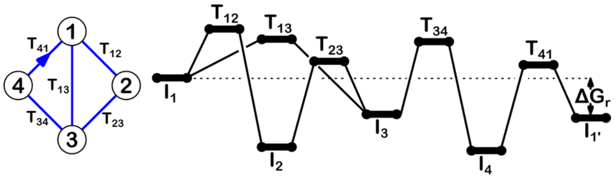
This can be extrapolated to any simple cycle (i.e., without alternative pathways or dead ends; see Table 1, row 10), resulting in[11−16]

$$\mathrm{TOF}=\frac{k_BT}{h}\frac{1-e^{\Delta G_r/RT}}{\sum_{i,j=1}^{N}e^{(T_i-I_j+\delta G_{ij})/RT}}\tag{19}$$

where $\delta G_{ij}=\Delta G_r$ if the transition state i comes *before* the intermediate j, or zero otherwise.[28] This equation and derivations for simple cycles were previously described in refs 11−16 and 29 as part of the energy span model.

Catalytic Networks in the *E*-Representation. Let us introduce here a new type of graph, the *energy graph*, which looks very similar to the classical net flow network graph (Scheme 5), but we will identify the edges as the Gibbs energies of the transition states connecting the pairs of intermediates, as can be seen in blue in Scheme 8.

Scheme 8. Energy graph, and its energy profile[a]



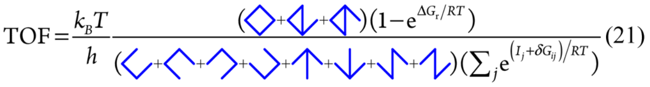
[a] Each blue edge corresponds to $\exp(-T_{lm}/RT)$, with T_{lm} being the transition state Gibbs energy of the step between intermediates l and m.

The energy graph is not, strictly speaking, a digraph (that is, with directed edges; see Table 1, row 7) because there is no intrinsic directionality in the edges. The edges are representations of transition states, and as such, they are the fixed values for the forward and backward elementary reactions; however, the last edge appears to include directionality. The arrow indicates that in this step the cycle is closed, and the energy of the ending intermediate is not the energy of the starting point but the beginning of a second cycle, which is lower by ΔG_r (or, as shown in Scheme 8, $I_{1'}=I_1+\Delta G_r$).

What would be the TOF expression in this *E*-representation? The full mathematical development of this new method to calculate catalytic rates is relegated to Appendix 1. Here, we show the final result:

$$\mathrm{TOF}=\frac{k_BT}{h}\frac{(\sum_n\mu_n)(1-e^{\Delta G_r/RT})}{(\sum_i\tau_i)(\sum_j e^{(I_j+\delta G_{ij})/RT})}\tag{20}$$

In eq 20, μ_n represents mechanism n (or, more accurately, the exponential of the sum of the transition states of this mechanism), and τ_i corresponds to the spanning tree i (the exponentials of minus its transition states). Equation 20 provides a novel way to calculate the TOF of any and all catalytic networks in the E-representation, as long as we are working in a steady state regime with fast relaxation, under transition state theory, and without multisite kinetics. In other words, it should work for almost all homogeneous and enzymatic catalysis in ordinary conditions and, if they can be written as a network graph, also for heterogeneous cases. For instance, for the four-intermediate/five-step system of Schemes 5 and 9, the TOF will be written as (see Appendix 1):



$$\mathrm{TOF}=\frac{k_BT}{h}\frac{(\quad)(1-e^{\Delta G_r/RT})}{(\quad)(\sum_j e^{(I_j+\delta G_{ij})/RT})}\tag{21}$$

with each edge corresponding to the exponentials of minus the Gibbs energy of a TS, for example:

$$=e^{(-T_{23}-T_{34}-T_{41})/RT}\tag{22}$$

and $\delta G_{ij}=\Delta G_r$ if the edge that closes a cycle of the spanning tree i comes before intermediate j (as explained in Appendix 1). Comparing the TOF expressions in the *E*- and *k*-representations, we can see that in the energy form (eqs 20 and 21), the number of graphs involved is much smaller because we have only nondirected spanning trees. Expressing the kinetics of a network in terms of energies is therefore simpler compared with rate constants. Still, eq 20 for complex networks is much more cumbersome than eq 19 for simple cycles, and the evaluation of

δG_{ij} on each term is not straightforward. Therefore, we will try to simplify the TOF to a more digestible form with more physical meaning.

Because each graph of the numerator of eqs 20 and 21 (Δ) corresponds to a different chemical mechanism, it will be useful to distribute the TOF according to them,

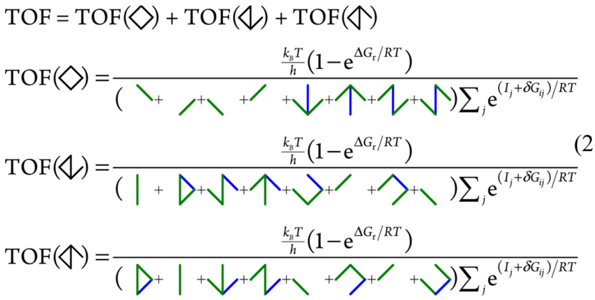
$$\mathrm{TOF} = \sum_n \mathrm{TOF}_n = \frac{k_\mathrm{B}T}{h}\sum_n \frac{\mu_n(1 - \mathrm{e}^{\Delta G_\mathrm{r}/RT})}{(\sum_i \tau_i)(\sum_j \mathrm{e}^{(I_j+\delta G_{ij})/RT})} \tag{23}$$

where TOF_n is the turnover frequency when the reaction goes through mechanism n. If we rearrange μ_n into the denominator, we obtain

$$\mathrm{TOF} = \frac{k_\mathrm{B}T}{h}\sum_n \frac{1 - \mathrm{e}^{\Delta G_\mathrm{r}/RT}}{\left(\frac{\sum_i \tau_i}{\mu_n}\right)(\sum_j \mathrm{e}^{(I_j+\delta G_{ij})/RT})} \tag{24}$$

This equation is similar to eq 19, but now describes any type of catalytic network. Indeed, if we have only a simple catalytic cycle, then $\mu = \exp(\sum_i -T_i/RT)$, and $(\sum_i \tau_i)/\mu = \sum_i \exp(T_i/RT)$, resulting in eq 19.

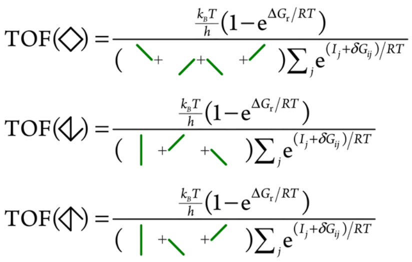
If we explicitly write eq 24 for a system such as the one in Scheme 5 and eq 21, we will obtain a rather tortuous expression:


(25)

Equation 25 was divided into its three mechanisms, the first one going through intermediates 1−2−3−4−1, and the second and third through 1−3−4−1, one with intermediate 2 in fast equilibrium with intermediate 3 and the other with intermediate 1. Each TOF provides the weight of each mechanism in the complete reaction.

In eq 25, the edges of two colors appear: blue edges corresponding to $\exp(-T_{lm}/RT)$, and green edges for the inverse, $\exp(T_{lm}/RT)$. Admittedly, if we wanted to provide a simple analytic formula with clear physical meaning to solve any catalytic network, we are not doing a good job with this equation; however, we may find a good approximation that can help in the simplification process.

There are two types of graphs in eqs 24 and 25: the ones with one single green edge and the ones with mixed green and blue edges. Evidently, the latter are the complex ones, and get only more complex with bigger networks. We will call them *returning* graphs, and luckily, they are almost always negligible (except for the rare cases when several mechanisms have the same probability and the determining states are shared, as shown in Appendix 3), in such a way that we can write eq 25 as:


(26a)

(26b)

(26c)

or, extrapolating to any catalytic network:

$$\mathrm{TOF} \approx \frac{k_\mathrm{B}T}{h}\sum_n \frac{1 - \mathrm{e}^{\Delta G_\mathrm{r}/RT}}{\sum_{i\in \mathrm{cycle}_n, j} \mathrm{e}^{(T_i - I_j + \delta G_{ij})/RT}} \tag{27}$$

in which the transition state energies (T_i) are the ones involved in the cycle of mechanism n (and not in dead ends). Any TS appearing in a mechanism but not appearing in the cycle of that mechanism is ignored in the TOF equation because the elementary steps of dead ends must be in a fast equilibrium in a steady state regime.[15,30] For example, in the ◁ mechanism, intermediate 2 is in fast equilibrium with intermediate 3, and T_{23} does not appear in eq 26b (but T_{13}, T_{34}, and T_{41}, being part of the cycle of the sequence, do appear in that specific TOF expression). Again, if we have only one simple cycle, eq 27 falls into the already established eq 19. Note that in the vast majority of catalytic cycles, the driving force is effectively equal to 1 (see Appendix 4), and therefore, eq 27 can be reduced to

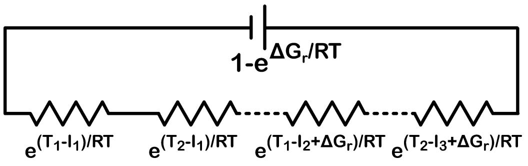
$$\mathrm{TOF} \approx \frac{k_\mathrm{B}T}{h}\sum_n \frac{1}{\sum_{i\in \mathrm{cycle}_{n,j}} \mathrm{e}^{(T_i - I_j + \delta G_{ij})/RT}} \tag{28}$$

The $\delta G_{i,j}$ term deserves some further clarifications because it differs from the case of eq 20. The division of τ_i/μ_n proposed in eq 24 leads to $\delta G_{ij} = \Delta G_\mathrm{r}$ if T_i comes before I_j, or zero otherwise, for eqs 26, 27, and 28. In the case that intermediate j is not part of the cycle but a dead end of the mechanism (a pendant vertex), then the δG_{ij} must be considered as if intermediate j was in the position of the intermediate from where the branching started. This means that a particular combination of intermediate−transition state may include ΔG_r for one mechanism and not for another. For instance, in the ◁ mechanism, intermediate 2 is a pendant vertex departing from intermediate 1, and therefore, the exponential term with T_{13} will be $\exp[(T_{13} - I_2)/RT]$; but in the ◁ mechanism, T_{13} comes before intermediate 3 (from where intermediate 2 departs), and therefore, the term for this latter pathway will be $\exp[(T_{13} - I_2 + \Delta G_\mathrm{r})/RT]$. This may sound confusing, but it actually has a clear physical meaning, as we shall see later.

Catalytic Flux Law and the Analogy with Electrical Circuits. As explained in ref 13, eq 19 (the expression of the TOF for simple cycles) can be considered as the catalytic equivalent of Ohm's law for electrical series circuits. The idea of having a flux law in chemical kinetics can be traced directly to Nernst almost a century ago[9,31] and followed much more recently[25,32−37] in the k-representation of catalytic cycles. Interestingly, the depiction of the catalytic cycle as an electricity circuit is also a graph in which each kinestor is an edge.[17] We will continue and expand the development of this concept in the E-representation, which tends to be mathematically and conceptually simpler.[13]

If the TOF is the catalytic "current", then the numerator of eq 19, being the thermodynamic driving force[9,36] of the cycle (dependent on only the reaction energy), is the catalytic "potential", and the denominator is the "resistance".[13] As in electricity series circuits, the total resistance is equal to the sum of the resistance of each component. In our catalytic system in the *E*-representation, each kinetic resistor (let us call them "kinestors") was defined as the exponential difference between TSs and intermediates, or in mathematical terms, $\exp[(T_i - I_j + \delta G_{ij})/RT]$.[13] Therefore, for a simple cycle of N elementary steps, we will have N^2 kinestors in series, as illustrated in Scheme 9.

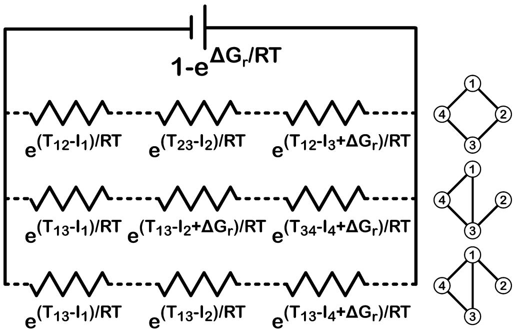
Scheme 9. A Circuit Graph, An Electrical Equivalent to the Catalytic Flux (the TOF, eq 19), Showing Some of the N^2 Kinetic Resistors Terms (Kinestors) for a Simple Cycle, Working As a Series Circuit[13]



In electrical circuits, Kirchhoff's and Ohm's laws explain that resistors in series comply with the formula $I = V/\sum_i R_i$, whereas in parallel, $I = \sum_n V/R_n$, with I being the current, V the voltage, and R the resistance of each resistor. This means that in a series circuit, more resistors lower the current, but for parallel circuits it is the opposite. We will see here an innovative way to look at complete kinetic networks based on these electrical circuit laws.

A simple catalytic cycle (eq 19) works as a series electrical circuit in which each kinestor is the exponential of a combination of one intermediate and one transition state (Scheme 9). In a complex network, on the basis of eqs 24−27, we will have a structure similar to a series circuit, with the only difference that now *each mechanism will work as a parallel circuit* (Scheme 10).

Scheme 10. Parallel Electrical Circuit Equivalent to the Catalytic Flux of the Four-Intermediates/Five-Steps Network of Scheme 5[a]



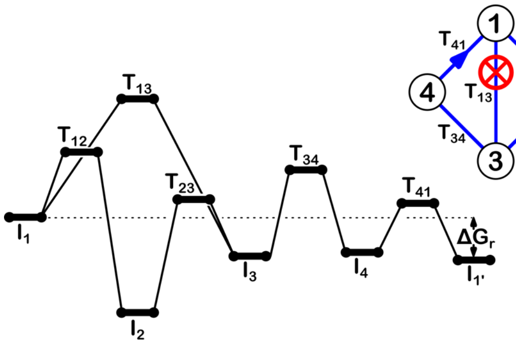
[a]Each of the three possible mechanisms (shown on the right) generates a parallel set of kinestors (in this example, only 9 of the 40 kinestors of eq 26 are shown).

Energy Span Approximation for Complex Networks. Most of the kinestors of any network have negligible influence on the kinetics. Moreover, usually (but not always!), only one kinestor determines the kinetics of the full catalytic system. In a simple cycle (series circuit), the largest kinestor will be determining, and the associated intermediate and transition state are called the TOF-determining intermediate (TDI) and TOF-determining transition state (TDTS),[12,13,29] terms that form the energy span (δE, the apparent activation energy of the whole cycle[11,13,38]). As a consequence, it was stated[13,15,16] that there are no rate-determining *steps*, but only rate-determining *states*.

In parallel circuits, the different mechanisms are competing with each other, and the one with the lower sum of kinestors will be the most efficient. Still, within each mechanism, the largest kinestor will determine the TOF of that particular pathway. As a corollary, from eq 27 we can conclude that the TDI and TDTS of a complex kinetic network will be the ones that form the smallest kinestor from the set of maximal kinestors within each mechanism. Let us see some simple examples of how to find the determining states on a model reaction.

On the basis of eq 27, in Scheme 11 the largest kinestor of mechanism ⇧ is $\exp[(T_{13} - I_2)/RT]$; of ⇩ is $\exp[(T_{13} - I_2 + \Delta G_r)/RT]$ (note that intermediate 2 branches out from intermediate 3 in this mechanism, and because T_{13} comes before I_3, this kinestor includes ΔG_r); and in mechanism ◇, the largest kinestor is $\exp[(T_{34} - I_2)/RT]$. Because T_{13} is much higher than both T_{12} and T_{23}, the first two kinestors are larger than the latter, and mechanism ◇ will be the most traversed by the catalyst, with T_{34} being the TDTS and I_2 the TDI (this conclusion is rather obvious for chemists with keen eyes). From eq 27, the TOF in this case will be

Scheme 11. Model Four-Intermediate/Five-Step Reaction[a]



[a]Because $T_{13} > T_{12} \sim T_{23}$, the only viable mechanism will be ◇.

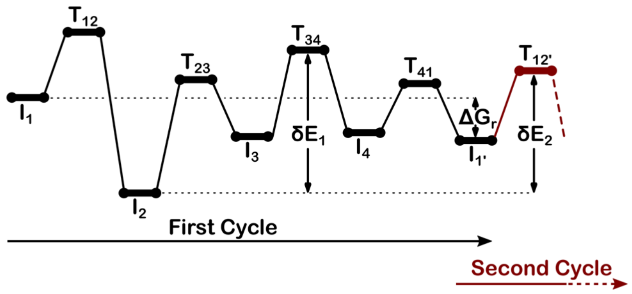
$$\mathrm{TOF} \approx \frac{k_B T}{h} \frac{1 - e^{\Delta G_r/RT}}{e^{(T_{34}-I_2)/RT}} \approx \frac{k_B T}{h} e^{-(T_{34}-I_2)/RT} \qquad (29)$$

$T_{34} - I_2$ is the energy span, appearing in an equation parallel to Eyring's TST. The energy span contains the most important information for the catalytic network's kinetics, and it is formed by the determining states (from where the determining kinestor is obtained).

One may wonder why in a model reaction such as the one in Scheme 11, T_{12} (being the highest point of the most probable mechanism) is not important for the kinetics, but T_{34} is. The answer is rooted on the fact that T_{12} comes before I_2, and therefore, that kinestor includes ΔG_r, making it smaller than the determining kinestor; or mathematically, $\exp[(T_{12} - I_2 + \Delta G_r)/RT] \ll \exp[(T_{34} - I_2)/RT]$. This effect was explained[12,13] by the cyclical nature of the catalytic process, in which we must always look in the forward direction to describe the kinestors, even if that means looking at the transition states of a second cycle, as illustrated in Scheme 12.

This concept of "never look back" in catalytic cycles can help us understand some intriguing outcomes of the kinestors, and it is the reason to include ΔG_r in some of them, a fact that has a strong impact on the energy span of the network. Let us consider

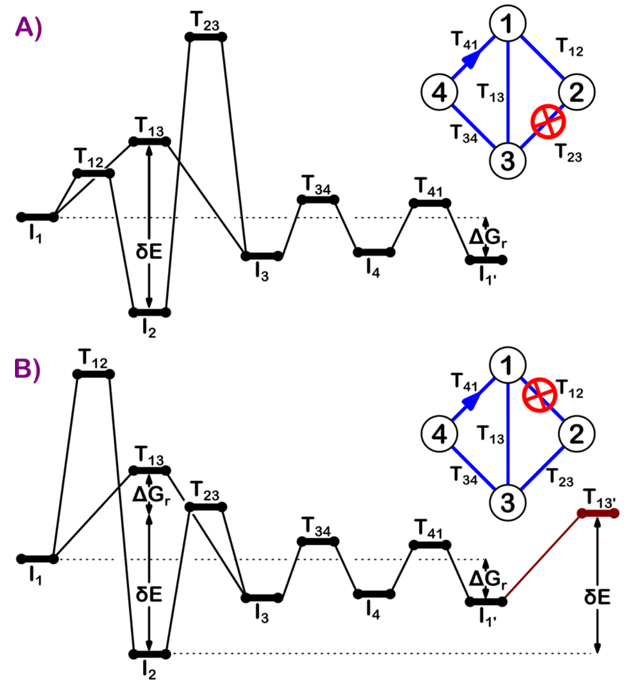
Scheme 12[a]



[a]Since the energy span (δE) must be measured going in the direction of the reaction from the intermediate to the transition state (even if the TS is in a second cycle), $\delta E_1 = T_{34} - I_2 > \delta E_2 = T_{12} - I_2 + \Delta G_r = T_{12'} - I_2$, and therefore, T_{34} is the TDTS of this model system, despite not being the highest point of the cycle (note that if the cycle starts at I_2, then T_{34} will be the highest point).

two other model reactions (Scheme 13). In both cases, the energy span involves I_2 and T_{23}.

Scheme 13. Two Model Systems in Which the Most Efficient Mechanisms Are (A) ◁↗ and (B) ◁↘



In Scheme 13A, because of the high energy of T_{23}, the only accessible mechanism is ◁↗. Similarly, because of a high T_{12} energy, in Scheme 13B, only ◁↘ is possible. Mechanism ◇ is negligible either way. We can compute the different TOFs as

$$\mathrm{TOF}(\triangleleft\!\nearrow) \approx \frac{k_BT}{h} e^{-(T_{13}-I_2)/RT} \tag{30a}$$

$$\mathrm{TOF}(\triangleleft\!\searrow) \approx \frac{k_BT}{h} e^{-(T_{13}-I_2+\Delta G_r)/RT} \tag{30b}$$

In eq 30a (corresponding to Scheme 13A), intermediate 2 is in equilibrium with intermediate 1, which comes before T_{13} (the TDTS) and therefore does not include ΔG_r. In eq 30b and Scheme 13B, I_2 branches out from I_3, and if we look only forward, we must compute the kinestor with respect to $T_{13'}$ in the second cycle (equal to $T_{13} + \Delta G_r$). We can see from these equations that the δG_{ij} term is a necessary factor that transpires from the cyclic, forward flowing nature of a catalyst. In a similar analysis of the reaction of Figure 1, we can easily deduce that for this particular cross-coupling reaction, the energy span will be $T_{23R} - I_{2B}$, where the red and blue paths are mixed in the ◯ mechanism.[27]

A question that may arise looking at Scheme 13 is, considering the high values of T_{12} and T_{23}, whether intermediate 2 will be accessible at all. Because I_2 is the TDI, this question is critical to understanding the kinetics of such a reaction. The answer is that the mathematics describe a system running in a full steady state regime, meaning that I_2 must be in complete equilibrium with intermediates 1 and 3 for mechanisms ◁↗ or ◁↘, respectively. If we indeed have these species in chemical equilibrium, it means that the barriers of the elementary steps 1−2 and 2−3 (the ones forming dead ends) are inconsequential. This may not be the reality; if the cited barriers are high enough, intermediate 2 will be completely inaccessible. Or worse, if these barriers are moderately high, then a steady-state regime will not be reached, and the catalyst will slowly deactivate if intermediate 2 is too stable. In that case, we must also consider calculating the turnover number (TON).[8,15] How high should the barriers be to neglect intermediate 2 will depend on the conditions of the reaction and the global potential energy surface. In such a case, some "chemical criteria" is required from the researcher to define this issue. Note that to neglect mechanism ◁↘ from Scheme 13A and mechanism ◁↗ from Scheme 13B, we had to use this criteria, since the steady state TOF equation will not tell us that these pathways are forbidden, no matter how high T_{12} and T_{23} are. As a rule of thumb, if the activation barrier of the branching to the dead end is ≲20 kJ/mol lower than the energy span, then it should be in equilibrium; if it is ≳20 kJ/mol higher, then the dead end should be relatively inaccessible.

It is worth noting that in this *E*-representation, there is no need for a complex series of rate constants. Suppose we find that the TOF of the reaction is defined by $\delta E = T_{13} - I_2 + \Delta G_r$, as in Scheme 13B, which can be simply expressed as eq 30b. In the *k*-representation, eq 13, we can track this equation to the expression

$$\mathrm{TOF} \approx \frac{\triangleleft\!\searrow}{\triangleleft\!\swarrow} = \frac{k_{23}k_{13}k_{34}k_{41}}{k_{32}k_{43}k_{14}} = K_{23}K_{34}K_{41}k_{13} \tag{31}$$

where $K_{nl} = k_{nl}/k_{ln}$ are the equilibrium constants for each elementary step. According to TST and Boltzmann distribution, eqs 31 and 30b are too sides of the same coin and should exhibit the same TOF. All the equilibria of eq 31 (which can be much more complex in bigger networks) indicate that all the intermediates between the TDI and the TDTS (the rate-determining *zone*[29,39]) are irrelevant to the kinetics; however, in the *k*-representation we cannot neglect any one of them because only their multiplication provides the proper kinetic information on the reaction. The *E*-representation and the energy span model inherently recognize that all the states residing inside the rate-determining zone are unimportant to the full kinetics of the network, and therein lies their strength.

■ CONCLUSIONS

As originally shown by King and Altman, graph theory, and specifically the concept of spanning trees, provides the means to solve the kinetics of any catalytic network in a steady state regime.[3,4,10,24,25] It was shown here that, in addition to providing raw numbers, this approach also brings in some common but up to now vague concepts of chemical kinetics, especially when the original equations based on rate constants are translated into energies by transition state theory.

Within these concepts, it was shown that *a chemical mechanism of a catalytic network can be unequivocally and mathematically defined from the TOF equation as the subgraph of the network that consists of only one cycle, but still includes all the intermediates*. In addition, and in analogy to an Ohmic electrical circuit, the chemical resistor terms (called here kinestors, on the basis of Gibbs energies of intermediates and transition states) were identified for networks, showing that simple cycles work as series circuits, and multiple mechanisms act as parallel circuits. This information sets the table to find the TOF, the apparent activation energy (i.e., the energy span) and the determining states of any and all catalytic networks, as long as they operate in a steady state regime.

We can conclude, as was done before for simple catalytic cycles,[13,15] that the E-representation can provide simpler and more physically sound terms than the k-representation for complex catalytic networks (and probably for stoichiometric cases as well[40]), despite both representations being formally equivalent. The application of the concepts and the mathematical framework presented in this work may bring a fresh look to understand and solve catalytic systems of any size and shape.

APPENDIX 1

Spanning Trees and the TOF with Energy Graphs

In the k-representation, all the terms of the $|\hat{A}|$ determinant (eq 7) are defined by the directed spanning trees of the rate constant digraph, as shown in Scheme 4 for a three-step cycle. If we convert them to the E-representation, we will still require the spanning tree, but only of the undirected graph, severely lowering the complexity of the TOF equation.

Let us write the normalized rate constant matrix ($\hat{A}$) of the four-intermediate/five-step cycle of Schemes 5 and 9, and transform it into energies (for convenience, we will express here the TOF in k_BT/h units, and the energies in dimensionless units, i.e., already divided by RT):

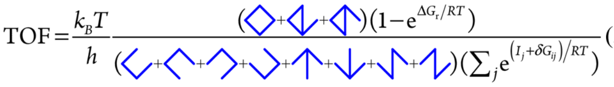
$$\hat{A}=\begin{pmatrix} -(k_{12}+k_{13}+k_{14}) & k_{21} & k_{31} & k_{41} \\ k_{12} & -(k_{21}+k_{23}) & k_{32} & 0 \\ k_{13} & k_{23} & -(k_{31}+k_{32}+k_{34}) & k_{43} \\ 1 & 1 & 1 & 1 \end{pmatrix}$$
$$\hat{A}=\begin{pmatrix} -(e^{I_1-T_{12}}+e^{I_1-T_{13}}+e^{I_1+\Delta G_r-T_{41}}) & e^{I_2-T_{12}} & e^{I_3-T_{13}} & e^{I_4-T_{14}} \\ e^{I_1-T_{12}} & -(e^{I_2-T_{12}}+e^{I_2-T_{23}}) & e^{I_3-T_{23}} & 0 \\ e^{I_1-T_{13}} & e^{I_2-T_{23}} & -(e^{I_3-T_{13}}+e^{I_3-T_{23}}+e^{I_3-T_{34}}) & e^{I_4-T_{34}} \\ 1 & 1 & 1 & 1 \end{pmatrix} \quad (32)$$

In eq 32, it is possible to see that when $\hat{A}$ is translated to energies, in all the terms of a column the intermediate with the same index number (I_j) appears. Therefore, each term of $|\hat{A}|$ will include $\exp(\sum_j I_j)$, and each term of $|\hat{A}_i|$ (eq 8) will include $\exp(\sum_{j\neq i} I_j)$, as can also be deduced from the directed spanning trees of the rate constant graph (e.g. Scheme 4 for a three step cycle). Therefore, we will have the possibility to simplify the TOF equation by taking out as a common factor $\exp(\sum_j I_j)$ in the numerator and denominator of the TOF equation, as was done in eq 18. This will reduce each $\exp(\sum_{j\neq i} I_j)$ term of $|\hat{A}_i|$ to only $\exp(-I_j)$ and completely eliminate the intermediate energies from the numerator. For simple catalytic cycles, it is also possible to simplify the TOF by taking out the TS energies [$\exp(\sum_i T_i)$] producing eq 19,[11] but for more complex networks, this simplification is not possible.

The transition state energies included in the terms of $|\hat{A}_i|$ are easy to find, because each rate constant k_{lm} or k_{ml} will include T_{lm} in it. If we consider each blue edge of the energy graph as a representation of $\exp(-T_i)$, then these energy graphs will be equal to the underlying undirected spanning tree of the rate-constant directed spanning trees.

As seen in eq 15, Δ (the numerator of the TOF) is expressed as a sum of graphs in the k-representation. In the E-representation, we leave the underlying undirected graphs expressing the exponentials of the transition states. Because we removed $\exp(\sum_j I_j)$ from each term, what we have left is the driving force, $1 - \exp(\Delta G_r)$, in which the "1" corresponds to the forward chemical flow, and "$-\exp(\Delta G_r)$" to the possibility of having a backward reaction.[12]

With this in mind, we can write the TOF of the four-intermediate/five-step network of Scheme 5 in the E-representation as (see also eq 21):



(33)

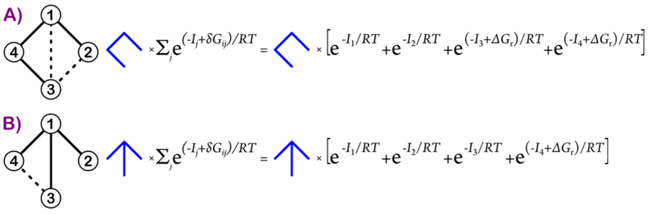
in which each blue edge symbolizes the exponential of minus a TS, in such a way that each graph is a product of those exponentials. We see in eq 33 that the numerator (Δ in eq 15) is composed of the driving force multiplied by the different "mechanisms" expressed in transition states energies (three mechanisms in this case), and the denominator combines the spanning trees of the TSs and the intermediates' energies (eq 20). This is a general method to calculate the TOF of any network of reactions in the E-representation at a steady state regime and is equivalent to the k-representation expression of King and Altman.[10]

The last component of eq 33 that needs to be defined is δG_{ij}. In eq 19 we saw that *for simple cycles*, $\delta G_{ij} = \Delta G_r$ if the transition state i comes before the intermediate j, or zero otherwise. However, this comes after taking as a common factor $\exp(\sum_i T_i)$, which, as stated above, cannot be considered for more complex systems such as the one in Scheme 5.

A spanning tree is an open graph that requires one and only one edge to close a cycle. The key to check if δG_{ij} is ΔG_r or zero for a term in eq 33 is to check if there is an edge that closes a kinetic cycle that comes before the intermediate I_j. As an example, in Scheme 14 two spanning trees and the TOF terms that result from them are shown.

In Scheme 14A (which includes the transition states T_{12}, T_{34}, and T_{41}), two edges can close a kinetic cycle (shown with dotted lines), and they come before intermediates 3 and 4; therefore, the

Scheme 14. Two Spanning Trees (A and B) from the Reaction Network of Scheme 5, and the TOF Terms That Result from Them eq 33[a]



[a] The dotted lines show the edges that close a valid kinetic cycle.

combination of these TSs and intermediates are the ones that include the ΔG_r value. Note that intermediate 2 is a pendant vertex, but because it is connected with intermediate 1, it can be considered that it comes before T_{13} (and T_{23}). For the case of Scheme 14B, there is only one edge that closes a valid kinetic cycle, T_{34} (T_{23} does not generate a full chemical cycle for the reaction of Scheme 5, and therefore does not close a valid cycle). Because of that, only intermediate 4 comes after the closing edge and includes the reaction energy.

When having simple cycles, it can be easily proven that this TOF expression, including the δG_{ij} definition, is completely equivalent to eq 19.

APPENDIX 2

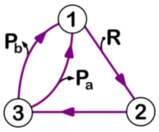
Selectivity

The TOF is not the only important information that can be extracted from the TOF equation; another important outcome is the selectivity. There are several ways to characterize the selectivity. Probably the most popular is the enantiomeric excess (at least for enantiomers), rooted in the measurement of optical rotation of enantiomeric mixtures [ee = $(R - S)/(R + S) \times 100$, with R and S being the fractions of each enantiomer]. For more general use, it is more convenient to calculate the selectivity simply as $S = [P_a]/[P_b]$,[5] where P_a and P_b are the concentrations of the two possible products of the reaction (with the assumption that there are only two products). For active catalytic cycles, if there are two possible mechanisms, each of them producing a different product, then

$$S = \frac{[P_a]}{[P_b]} = \frac{\mathrm{TOF_a}}{\mathrm{TOF_b}} \tag{34}$$

It is typically assumed that the selectivity is defined by the classical Curtin−Hammett principle (CHP, $S = \exp(\Delta T)$, with ΔT being the difference in Gibbs energy of the *selectivity-determining* TS for both mechanisms),[41−43] but catalytic networks may provide kinetic complications that might thwart this assumption. As we shall see now, there is no reason for concern because the CHP is an excellent approximation, even for complex networks.

Scheme 15. Net Flow Graph of a Simple Catalytic Network with Two Possible Products



Let us consider a simple three-intermediate/four-step catalytic network, in which in the last step there is a bifurcation with the possibility of generating two products (P_a or P_b; see Scheme 15).

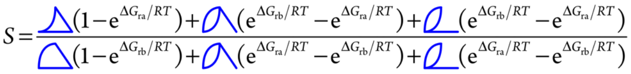
In reactions with selectivity issues, the total TOF will be equal to the sum of the TOFs for the generation of all the products (in this case, TOF = $\mathrm{TOF_a} + \mathrm{TOF_b}$). The fact that we have individual TOFs for each product forces us to roll back to eq 9, in which we worked in the k-representation. According to this, we can find $\mathrm{TOF_a}$ and $\mathrm{TOF_b}$ from

$$\mathrm{TOF_a} = \frac{k_{31a}|\hat{A}_3| - k_{13a}|\hat{A}_1|}{|\hat{A}|}$$
$$\mathrm{TOF_b} = \frac{k_{31b}|\hat{A}_3| - k_{13b}|\hat{A}_1|}{|\hat{A}|} \tag{35}$$

The selectivity will therefore be

$$S = \frac{\mathrm{TOF_a}}{\mathrm{TOF_b}} = \frac{k_{31a}|\hat{A}_3| - k_{13a}|\hat{A}_1|}{k_{31b}|\hat{A}_3| - k_{13b}|\hat{A}_1|} \tag{36}$$

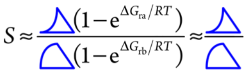
Converting all the rate constants to energies and taking into account that each product has its own reaction energy, eq 36 reduces to



$$S = \frac{\triangle(1 - e^{\Delta G_{ra}/RT}) + \wedge(e^{\Delta G_{rb}/RT} - e^{\Delta G_{ra}/RT}) + \angle(e^{\Delta G_{rb}/RT} - e^{\Delta G_{ra}/RT})}{\triangle(1 - e^{\Delta G_{rb}/RT}) + \wedge(e^{\Delta G_{ra}/RT} - e^{\Delta G_{rb}/RT}) + \angle(e^{\Delta G_{ra}/RT} - e^{\Delta G_{rb}/RT})} \tag{37}$$

Note that in this equation, we distinguish the exergonicity between both products ($\Delta G_{ra} \neq \Delta G_{rb}$), but obviously, for enantioselective processes, $\Delta G_{ra} = \Delta G_{rb}$.

Going from eq 36 to 37, all the energies of the intermediates are cancelled (taken out as a common factor). Recalling that the blue edges are equivalent to $\exp(-T_i/RT)$, what we have left is a series of "selectivity mechanisms", in which △ and △ represent the generation of P_a and P_b from the reactant, and ∧ and ∠ denote thermodynamical generation of one product from the other product (note that these terms disappear in the full TOF equation). Although these two thermodynamical mechanisms seem to be at odds with the idea of an ongoing catalytic reaction (which is by definition out of equilibrium), they actually represent the small possibility that one product of high energy will reenter into the cycle and fall into the second more stable product during the reaction. However, the $\exp(\Delta G_r/RT)$ terms are so small for typical exergonic reactions that these product-to-product cycles are virtually inaccessible (and in enantioselective reactions, they are completely cancelled). The selectivity can then be approximated to



$$S \approx \frac{\triangle(1 - e^{\Delta G_{ra}/RT})}{\triangle(1 - e^{\Delta G_{rb}/RT})} \approx \frac{\triangle}{\triangle} \tag{38}$$

We can further simplify eq 38, dividing all the graphs by $\exp(\sum_i T_i/RT)$, obtaining

$$S \approx \frac{e^{T_{31b}}}{e^{T_{31a}}} = e^{\Delta T} \tag{39}$$

which is nothing more than the Curtin−Hammett principle! Therefore, for the vast majority of catalytic cycles, indeed, the CHP is a valid approximation (unless other dynamical issues arise[44]).

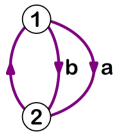
APPENDIX 3

Returning Graphs

In eq 25, we saw that the TOF may include compound green and blue graphs, which we called "returning". It was stated that those graphs are almost always negligible; herein, it will be shown why and when that occurs. For that, let us consider a very simple network composed of two intermediates and three steps (Scheme 16), in which there are two routes from intermediate 1 to 2.

According to eqs 24 and 25, we can write the kinetics of the two mechanisms as

Scheme 16. Net Flow Graph for a Simple Two-Intermediate/Three-Step Network

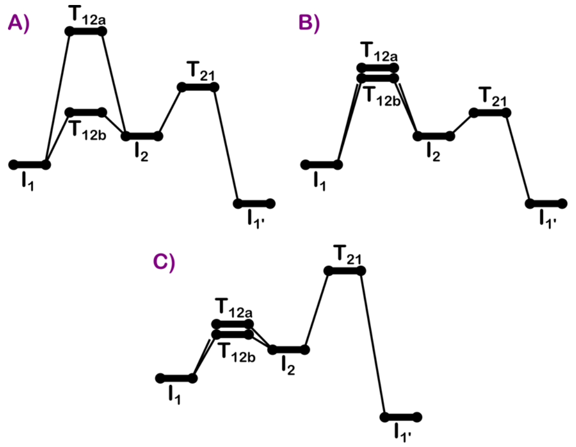


$$\mathrm{TOF_a}=\frac{k_BT}{h}\frac{1-\mathrm{e}^{\Delta G_\mathrm{r}/RT}}{(\textcolor{green}{)})+(\textcolor{green}{(}\;+\textcolor{green}{(}\textcolor{blue}{)}\textcolor{green}{)})\sum_j\mathrm{e}^{(I_j+\delta G_{ij})/RT}}$$
$$\mathrm{TOF_b}=\frac{k_BT}{h}\frac{1-\mathrm{e}^{\Delta G_\mathrm{r}/RT}}{(\textcolor{green}{)})\;+(\textcolor{green}{(}\;+\textcolor{green}{(}\textcolor{green}{)}\textcolor{blue}{)})\sum_j\mathrm{e}^{(I_j+\delta G_{ij})/RT}} \tag{40}$$

where the green edges are equivalent to $\exp(T_i/RT)$, and blue edges to $\exp(-T_i/RT)$. We will show with two typical cases why the returning graphs (i.e., the ones that have both blue and green edges) are usually not significant.

Case A: If $T_{12\mathrm{a}}$ is much higher than the other transition states (Scheme 17A), $\mathrm{TOF_a}$ will be negligible compared with $\mathrm{TOF_b}$, and $\textcolor{green}{(}\textcolor{green}{)}\textcolor{blue}{)}$ will be much smaller than $\textcolor{green}{(}$ or $\textcolor{green}{)}$. The determining TS can be only $T_{12\mathrm{b}}$ or T_{21}, and the returning graph will be unimportant to the kinetics. In a case like this, if one returning graph is bigger than the other terms in the same mechanism, then the second mechanism will be more significant to the kinetics, and the entire first mechanism (including the returning graph) can be neglected.

Scheme 17. Three Possible Energy Profiles (A, B, and C) for the Reaction of Scheme 16



Case B: If $T_{12\mathrm{a}} \approx T_{12\mathrm{b}} > T_{21}$ (Scheme 17B), the returning graphs will be negligible because, for instance, in the b mechanism, $\textcolor{green}{(}\textcolor{green}{)}\textcolor{blue}{)} \sim \textcolor{green}{(} \ll \textcolor{green}{)}$, or equivalently, $\exp[(T_{12b}+T_{21}-T_{12a})/RT] \sim \exp(T_{21}/RT) \ll \exp(T_{12a}/RT)$. In this case, we can disregard the returning graphs because the other terms of the same mechanism will be more significant.

Almost all networks will be of the type "A" or "B", and therefore, in most cases, the returning graphs are negligible. Is there a situation in which they are not negligible? Scheme 17C shows the extreme case when for accurate results, one cannot neglect any term, even though the returning graphs will not change the overall picture. In this example $T_{21} > T_{12\mathrm{a}} = T_{12\mathrm{b}}$ and I_1 is the TDI, with the resulting TOF of

$$\mathrm{TOF}=\mathrm{TOF_a}+\mathrm{TOF_b}=2.\mathrm{TOF_a}$$
$$\mathrm{TOF}\approx 2\frac{k_BT}{h}\frac{1-\mathrm{e}^{\Delta G_\mathrm{r}/RT}}{((\textcolor{green}{(}\;+\textcolor{green}{(}\textcolor{blue}{)}\textcolor{green}{)})\mathrm{e}^{-I_1/RT}}=\frac{k_BT}{h}\frac{1-\mathrm{e}^{\Delta G_\mathrm{r}/RT}}{\mathrm{e}^{(-I_1+T_{21})/RT}} \tag{41}$$

For this model reaction (Scheme 17C and eq 41), the energy span is clearly defined by I_1 and T_{21}, states that appear in both mechanisms. The reaction will have the same TOF, no matter which pathway the system takes, and with $T_{12\mathrm{a}} = T_{12\mathrm{b}}$, both mechanisms have exactly the same probability of being crossed. Because the total TOF is twice the TOF of any one of the mechanisms, eq 41 requires two identical kinestors for each mechanism to account for the factor of 2. In other words, if we neglect the returning graphs, it will appear that the overall rate is twice the actual TOF. The returning kinestors are a mathematical "necessary evil" for the specific cases that several mechanisms have the same probability, and the determining states are shared. Luckily, this means not only that the error of neglecting the returning graphs has a maximum value not higher than the TOF itself, but also that it is easy to spot those rare cases for which the returning graphs are not completely negligible.

Regarding the reason for calling them "returning" graphs, let us consider the $\textcolor{green}{(}\textcolor{green}{)}\textcolor{blue}{)}$ term of mechanism b in eq 40. The only way this graph can be significant is if the transition states $T_{12\mathrm{b}}$ and T_{21} are high, and $T_{12\mathrm{a}}$ is low. In other words, low energy transition states outside a mechanism drain the forward flow of the original mechanism, as if the chemical flow "returns" through the transition states that are outside the mechanism in question.

In more intricate networks, the returning graphs grow in complexity, but still, in the vast majority of cases, they are negligible for the total TOF.

■ APPENDIX 4

On the Driving Force, Reaction Irreversibility, BEP Principle, and Nonlinearity of Kinestors

In electrical circuits, the resistance of a linear (Ohmic) resistor is independent of the voltage, thus complying with Ohm's law ($V = I \times R$). Nonlinear (non-Ohmic) resistors, whose resistance is a function of the voltage, include diodes and varistors. For the chemical case, are the kinestors linear or not?

We may approach this question with a simple one-step stoichiometric reaction. If the rate of the reaction, r, is the chemical current, and considering a standard concentrations of 1 M, we can write

$$r = \vec{r} - \overleftarrow{r} = \vec{k} - \overleftarrow{k} = \vec{k}\left(1 - \frac{1}{K}\right) \tag{42}$$

The last equality can be obtained by considering the equilibrium constant equal to the ratio of the forward and backward rate constants ($K = \vec{k}/\overleftarrow{k}$). The term between parentheses is the driving force (equal to $1 - \exp(\Delta G_\mathrm{r}/RT)$, as in the catalytic eqs 19 and 24), and $1/\vec{k}$ is the resistance (the kinestor, equal to $(k_\mathrm{B}T/h)\cdot\exp(-\Delta G^{\ddagger}/RT)$, according to TST).[36,37]

In a linear (Ohmic) kinetic system, the rate has a linear trend as a function of the driving force. However, because of the exponential dependence on the Gibbs energy of reaction, almost all exergonic reactions ($\Delta G_\mathrm{r} < 0$) will have a driving force effectively equal to 1, since $1 \gg \exp(-\Delta G_\mathrm{r}/RT)$, resulting in $r \simeq \vec{k}$. As a consequence, the kinetics of most exergonic reactions will be in a kinetic regime, that is, virtually independent of the reaction Gibbs energy. In this regime, reactions are irreversible.

Only when the reaction approaches equilibrium the driving force can vary significantly (from 0 to 1) and the rate can be considered to be in a mixed kinetic−thermodynamic regime (and obviously, at complete equilibrium, the rate is completely cancelled out).[45] Because of the limited values that the chemical driving force can take, it is difficult to make a one-to-one comparison between the voltage of electrical circuits and the rate for chemical reactions, but the complexities in the electrical−chemical comparison do not end here.

For chemical "circuits", it is not easy to find purely linear kinestors because they are not independent devices, such as electrical resistors (at least under the "lumped element model"), from which we can assemble a full chemical gadget. All the states of the chemical network are interconnected, and only by a thought experiment can we tinker with one state and keep all other states unaffected. This is especially clear considering the Bell−Evans−Polanyi (BEP) principle,[46,47] in which it is physically impossible to change the energy of an intermediate (for example, by a ligand substitution in homogeneous catalysis or a change in the metal substrate in heterogeneous systems) and maintain the neighbor transition states fixed. The BEP principle states that there is a linear dependency between the activation energy and the energy of reaction, which for our one-step reaction of eq 41 can be written as

$$\Delta G^{\ddagger} \approx \alpha \cdot \Delta G_r + \beta \tag{43}$$

with $\alpha \gtrsim 0.5$ for a late transition state and $\alpha \lesssim 0.5$ for an early TS, according to Hammond's postulate. With this dependency, we obtain that the rate constant will be

$$\vec{k} = \frac{k_B T}{h} e^{-(\alpha . \Delta G_r + \beta)/RT} \tag{44}$$

Because now $\vec{k}$ depends on the reaction energy and, therefore, on the driving force, $1/\vec{k}$ must be considered a nonlinear resistor. To define the BEP principle for complete catalytic cycles as a function of ΔG_r is much more problematic; however, the principle has been observed multiple times as a function of the adsorption energy in heterogeneous catalysis.[48]

Even without considering the BEP principle, the δG_{ij} values in the kinestors of eqs 19 and 24 seem to be at odds with the idea of having linearity in the TOF as a function of the reaction energy. Yet, the same energy span can be obtained with $\delta G_{ij} = 0$ or ΔG_r, when a different starting point of the cycle is selected. In one case, the determining kinestor seems to be linear, whereas in the other case, it seems to be nonlinear.

In light of all these kinetic complications, chemical systems cannot, in principle, be considered linear.

Abbreviations

δE, energy span; ΔG_r, Gibbs energy of reaction; BEP, Bell−Evans−Polanyi; CHP, Curtin−Hammett principle; TDI, TOF-determining intermediate; TDTS, TOF-determining transition state; TOF, turnover frequency; TST, transition state theory

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kozuch@bgu.ac.il.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Michaelis, L.; Menten, M. L. *Biochem. Z.* **1913**, *49*, 333−369.

(2) Johnson, K. A.; Goody, R. S. *Biochemistry* **2011**, *50*, 8264−8269.

(3) Segel, I. *Enzyme kinetics: Behavior and analysis of rapid equilibrium and steady state enzyme systems*; Wiley Classics Library; Wiley: New York, 1993.

(4) Bisswanger, H. *Enzyme kinetics principles and methods*; Wiley-VCH: Weinheim, 2008; pp 59−190.

(5) IUPAC Gold Book. http://goldbook.iupac.org.

(6) Boudart, M.; Aldag, A.; Benson, J. E.; Dougharty, N. A.; Girvin Harkins, C. *J. Catal.* **1966**, *6*, 92−99.

(7) Cornils, B.; Hermann, W. A.; Schlögl, R.; Wong, C.-H. *Catalysis from A to Z: A concise encyclopedia*, 2nd ed.; Wiley-VCH: Weinheim, 2003.

(8) Kozuch, S.; Martin, J. M. L. *ACS Catal.* **2012**, *2*, 2787−2794.

(9) Christiansen, J. A. *Adv. Catal.* **1953**, *5*, 311−353.

(10) King, E. L.; Altman, C. *J. Phys. Chem.* **1956**, *60*, 1375−1378.

(11) Kozuch, S.; Shaik, S. *J. Am. Chem. Soc.* **2006**, *128*, 3355−3365.

(12) Kozuch, S.; Shaik, S. *J. Phys. Chem. A* **2008**, *112*, 6032−6041.

(13) Kozuch, S.; Shaik, S. *Acc. Chem. Res.* **2011**, *44*, 101−110.

(14) Uhe, A.; Kozuch, S.; Shaik, S. *J. Comput. Chem.* **2011**, *32*, 978−985.

(15) Kozuch, S. *WIREs Comput. Mol. Sci.* **2012**, *2*, 795−815.

(16) Kozuch, S. In *Understanding Organometallic Reaction Mechanisms and Catalysis*; Ananikov, V. P., Ed.; Wiley-VCH: Weinheim, 2014; pp 217−248.

(17) Wilson, R. J. *Graphs: An introductory approach: A first course in discrete mathematics*; Wiley: New York, 1990.

(18) Garcia-Domenech, R.; Galvez, J.; de Julian-Ortiz, J. V.; Pogliani, L. *Chem. Rev.* **2008**, *108*, 1127−1169.

(19) Balaban, A. T. *J. Chem. Inf. Model.* **1985**, *25*, 334−343.

(20) Balaban, A. T. *J. Chem. Inf. Model.* **1995**, *35*, 339−350.

(21) Boudart, M. *Kinetics of chemical processes*; Prentice-Hall: Englewood Cliffs, New Jersey, 1968.

(22) Helfferich, F. G. Kinetics of homogeneous multistep reactions. In *Comprehensive Chemical Kinetics*; Elsevier: New York, 2001; Vol. *38*; pp 6−260.

(23) Logadóttir, Á.; Nørskov, J. K. *J. Catal.* **2003**, *220*, 273−279.

(24) Yablonskii, G. S.; Bykov, V. I.; Elokhin, V. I.; Gorban, A. N. Kinetic models of catalytic reactions. In *Comprehensive Chemical Kinetics*; Elsevier: New York, 1991; Vol. *32*, pp 185−257.

(25) Marin, G. B.; Yablonsky, G. S. *Kinetics of chemical reactions: Decoding complexity*; Wiley-VCH Verlag: Weinheim, Germany, 2011.

(26) Merris, R. *Linear Algebra Appl.* **1994**, *197−198*, 143−176.

(27) Meir, R.; Kozuch, S.; Uhe, A.; Shaik, S. *Chem. - Eur. J.* **2011**, *17*, 7623−7631.

(28) Note that in previous papers[11−13] eq 19 was written in a slightly different but equivalent way because it was considered that the reaction starts with intermediate zero instead of one. The resulting equation was

$$\mathrm{TOF} = \frac{k_B T}{h} \frac{e^{-\Delta G_r/RT} - 1}{\sum_{i,j=1}^{N} e^{(T_i - I_j - \delta G'_{ij})/RT}}$$

where now $\delta G'_{ij} = \Delta G_r$ if the TS is *after* the intermediate, or zero otherwise. This equation can be obtained by dividing both the upper and lower parts of eq 19 by $\exp(\Delta G_r/RT)$.

(29) Kozuch, S.; Martin, J. M. L. *ChemPhysChem* **2011**, *12*, 1413−1418.

(30) Kozuch, S.; Martin, J. M. L. *ACS Catal.* **2011**, *1*, 246−253.

(31) Nernst, W. *Theoretische Chemie*; Ferdinand Enke: Stuttgart, 1926; p 766.

(32) Fishtik, I.; Callaghan, C. A.; Datta, R. *J. Phys. Chem. B* **2004**, *108*, 5671−5682.

(33) Fishtik, I.; Callaghan, C. A.; Datta, R. *J. Phys. Chem. B* **2004**, *108*, 5683−5697.

(34) Fishtik, I.; Callaghan, C. A.; Datta, R. *J. Phys. Chem. B* **2005**, *109*, 2710−2722.

(35) Fishtik, I.; Callaghan, C. A.; Datta, R. *Ind. Eng. Chem. Res.* **2006**, *45*, 6468−6476.

(36) Vilekar, S. A.; Fishtik, I.; Datta, R. *Chem. Eng. Sci.* **2009**, *64*, 1968−1979.

(37) Vilekar, S. A.; Fishtik, I.; Datta, R. *Chem. Eng. Sci.* **2010**, *65*, 2921−2933.

(38) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254−278.

(39) Yagisawa, S. *Biochem. J.* **1995**, *308*, 305−311.

(40) Murdoch, J. R. *J. Chem. Educ.* **1981**, *58*, 32−36.

(41) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111−128.

(42) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.

(43) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741−6750.

(44) Rehbein, J.; Carpenter, B. K. *Phys. Chem. Chem. Phys.* **2011**, *13*, 20906−20922.

(45) Pekař, M. *ChemPhysChem* **2015**, *16*, 884−885.

(46) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1938**, *34*, 11−24.

(47) Masel, R. I. *Chemical Kinetics and Catalysis*, 1st ed.; Wiley-Interscience: New York, 2001; pp 633−652.

(48) Bligaard, T.; Nørskov, J. K.; Dahl, S.; Matthiesen, J.; Christensen, C. H.; Sehested, J. *J. Catal.* **2004**, *224*, 206−217.