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# "Turning Over" Definitions in Catalytic Cycles

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## 1. INTRODUCTION

*"Indeed, the catalytic activity, for a valid comparison, must be referred to the number of exposed surface atoms of a specified kind. Thus a convenient way to express catalytic activity is by means of a turnover number equal to the number of reactant molecules converted per minute per catalytic site for given reaction conditions."*

With these words of Boudart<sup>1</sup> the first definition of what later was called the **Turnover Frequency (TOF)** entered into the realm of heterogeneous chemistry.<sup>2</sup> It was a term borrowed from enzymatic kinetics,<sup>3</sup> and slowly passed to homogeneous catalysis.

Nowadays it is a ubiquitous term, focusing strictly on the catalytic center,<sup>4</sup> as distinct from the classical term "rate of reaction", which emphasizes the generation of products or the consumption of reactants.

Despite its utility and common use,<sup>5–9</sup> the TOF concept is still not well-defined and leads to confusion. IUPAC's gold book,<sup>10</sup> the most authoritative source of chemical terminology, has a very concise definition of the turnover frequency:<sup>11</sup>

*"Commonly called the turnover number,  $N$ , and defined, as in enzyme catalysis, as molecules reacting per active site in unit time."*

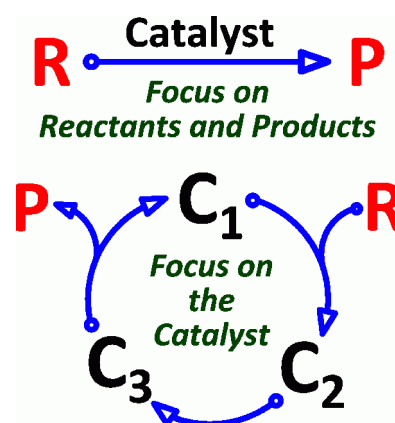
This description of the TOF has two main problems. The first is the difficulty of providing a one-to-one correspondence between name and function, since (as appeared in Boudart's paragraph<sup>1</sup>) the terms "turnover frequency" (TOF) and "turnover number" (TON) seem to have one and the same meaning. However, in typical catalytic jargon, both expressions have very different connotations. Sometimes also the terms "turnover rate" and "catalytic constant" ( $k_{\text{cat}}$ ) are used interchangeably in the literature with the same meaning.<sup>12,13</sup>

To make matters worse, the TOF is occasionally considered a rate-constant,<sup>14</sup> since the rate of reaction ( $r = \text{TOF} \times [\text{Cat}]$ ) depends on the catalysts concentration. However, the TOF itself can depend on the concentration of reactants and products even at saturation, and in this sense it is closer to a rate than to a kinetic constant. In spite of this, from a strict terminological stance the TOF is a frequency, with units of  $\text{time}^{-1}$ . All this debate evidently resembles the biblical story of the Tower of Babel and the confusion of languages.

The second problem of IUPAC's and Boudart's definitions is a recurring expression of the TOF as a function of the number of reactants consumed,<sup>4,5,12</sup> or even of the products generated.<sup>15</sup> In most cases it is indeed an accurate way to derive the TOF, but for instance in bimolecular reactions this is not the case. Moreover, and from a philosophical perspective, when expressing the TOF as a function of produced or consumed molecules, the focus of the measure goes back to

those molecules instead of emphasizing the role of the catalyst (see Scheme 1).

**Scheme 1. Two Representations of the Same Model Reaction, Focusing on Different Aspects of Their Chemistry**



As Gladysz points out:<sup>16</sup>

*"In judging quality, it is certainly possible for a given scientific community to become hypercritical. However, it is also important to avoid uncritical and semi-evangelical love-fests... New synthesis methods are constantly being developed with the idea of improving or replacing older non or less green technology. There are obvious questions such as: (a) Do the new methods constitute genuine improvements? (b) Which of several competing new technologies is the best, or how do the trade-offs compare? (c) Which evaluation criteria are most important?"*

In this "viewpoint" article, in an effort to answer these questions, we will propose a redefinition of the TOF and TON in an unambiguous form. It is not our aim to analyze the reasons for the effectiveness of a specific system, or to try to understand its intrinsic mechanisms and determining factors. It is possible to find numerous works on that matter, from the enzymatic kinetics textbooks that start with the Michaelis–Menten model,<sup>17,18</sup> to the homogeneous catalysis treatises that describe pathways and mechanisms,<sup>15,19,20</sup> or the microkinetic model for heterogeneous chemistry trying to reproduce the rate equations by analyzing how the elementary steps intermingle.<sup>3,21–24</sup> In all of them, the key issue and the final outcome of their formulations is the estimation of the efficiency of the catalysts, that is, to obtain the TOF and TON.

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Admittedly, this attempt to reformulate the TOF and TON will not produce such a simple, concise phrase as the current IUPAC definition, but it will be consistent with the spirit of the terms, that is, the comparison of the efficiency of different catalysts.<sup>3</sup> To this end, we will start by reviewing several sources of misunderstandings, most of them quite obvious but still important, as they are too widely seen in the catalytic literature.

## 2. TYPICAL MISUSES OF THE TOF

Considering the economy of words in its common definition, saying that the term “TOF” is incorrectly used is an overstatement. Most researchers calculate TOFs in ways that are still contemplated by its description, but make it impossible to compare their data to other studies. It is essential to point out the disadvantages of such a “free” use of the TOF to build a practical and universal quantity.

**2.1. TOF as a Function of the Turnovers, Not of the Reactants.** As stated before, the TOF should be a measure of turnovers,<sup>19</sup> and not of the consumed reactants or generated products (although the first can be derived from the others<sup>9</sup>). The SI units of the TOF are hertz, s<sup>-1</sup>, but if one reactant is involved in its formulation, then it should be M·s<sup>-1</sup>. This is fine for defining a rate of reaction, but not for a frequency. Moreover, if we have a catalyst that can attain the same frequency for two different reactions, for instance “R → P” and “2R → P”, the second will consume twice the reactant in the same time, even though the TOF should be the same (the TOF in this second case can be derived from  $-1/(2[\text{Cat}]) \cdot d[\text{R}]/dt$ ).

There are quantities that are meant to work with reactants and can be mathematically equivalent through proper arithmetic translation, such as the conversion (*vide infra*), the extent of the reaction and the rate of conversion (its time derivative),<sup>10,11</sup> the conversion half-time,<sup>25</sup> the enzyme unit (μmol/min), and its SI successor, the katal (*kat*, or mol/s),<sup>26,27</sup> or simply the rate of the reaction ( $-\partial[\text{R}]/\partial t$ ). All of these have their merits but again, if we want a standard for catalysis, the TOF is an already widespread solution.

**2.2. TOF as a Function of the Conditions.** The TOF changes with the concentrations of reactants (see section 2.4) and sometimes also of the products.<sup>17,28–32</sup> Therefore, to express a TOF without describing the concentrations of the species involved is misleading, and should be discouraged.<sup>11,33,34</sup> The same goes for the temperature, since the TOF can grow almost exponentially with it.<sup>29,31,35</sup> To judge the efficiency of a catalytic system, all the conditions of the reaction must be clearly written down for comparative reasons and to be able to reproduce the kinetics.<sup>3</sup>

**2.3. TOF as a Function of Instantaneous Conditions.** As the TOF is defined as “molecules reacting per active site per time”, there is no clear description of how long must be considered for the measuring process.<sup>13</sup> In extreme cases the time considered is up to total disappearance of the reactant.<sup>7</sup> This is clearly confusing, as the total disappearance of a species will theoretically need an infinite time, making the TOF equal to zero for any reaction. But even if the time is calculated up to, for instance, 90% consumption of the reactant, the result will be very different from considering up to 10% consumption, since the TOF is usually a function of the reactant concentration.

From a mathematical perspective, the TOF (like any other rate-based quantity) must be defined as the *derivative* of the number of turnovers (*N*) with respect to the time (*t*).<sup>3,6</sup> If the TOF has a linear dependency on the reactant R (kinetics of order one), we can write

$$\text{TOF} = \frac{dN}{dt} = \text{TOF}^\circ \cdot \frac{[\text{R}]}{c^\circ} \quad (1)$$

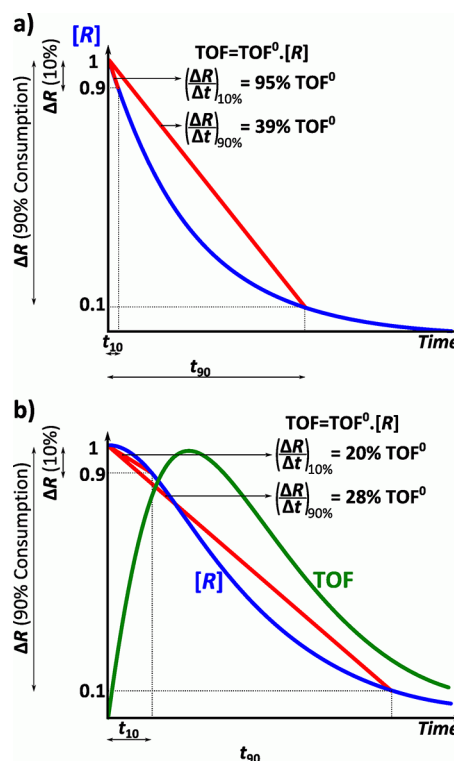
where TOF<sup>°</sup> is a “standard” TOF (see section 3.2), measured at a concentration of R equal to 1 M (*c*<sup>°</sup> is the standard concentration, 1 M, that maintains TOF and TOF<sup>°</sup> within frequency units, similar to the full expression of the equilibrium constant<sup>12</sup>). A simple integration gives an exponential depletion of R,

$$[\text{R}] = [\text{R}_0] \cdot e^{-\text{TOF}^\circ \cdot t} \quad (2)$$

with [R]<sub>0</sub> being the initial concentration of the reactant. If we want to measure the TOF as the consumed R divided by the reaction time at 90% consumption (*x* = 90), it can be proven that this “average” TOF is only 39% of the initial TOF (see Figure 1),

$$\frac{\Delta[\text{R}]}{\Delta t} = \frac{[\text{R}_0] - [\text{R}_x]}{t_x} = \text{TOF}^\circ \cdot [\text{R}_0] \cdot \frac{-\frac{x}{100}}{\ln\left(1 - \frac{x}{100}\right)} \quad (3)$$

Under these conditions, an unequivocal TOF value is only possible when declaring an instantaneous (derivative) TOF at specified concentrations; therefore, in an experimental analysis, the TOF should be taken as the slope of the curve of the graph



**Figure 1.** (a) With a first order dependency on the reactant for a reaction of the type “R → P”, calculating an “average” TOF at high reactant consumption underestimates the initial instantaneous TOF (see eq 3). (b) With a preactivation step involved any “average” TOF estimated at a finite time will be an underestimation of the TOF compared to the situation where all the catalyst is active; at the beginning of the reaction the active catalyst is at low concentration, and at the end the reactant will be too low. The graph corresponds to a model catalyst with an energetic span ( $\delta E$ , i.e., the apparent activation energy of the full cycle) equal to the preactivation barrier, calculated with the AUTOF program.<sup>29</sup>

of turnovers vs time. The only exception is the specific case of zero order kinetics (“saturation regime”, see section 2.4), where the TOF is constant until near disappearance of the reactant, plunging to zero at that point.

There are additional arguments in favor of the definition of the TOF as a derivative. First, there are preactivation and deactivation processes involved, which cannot be attested correctly when doing an “average” type of TOF measurement (Figure 1b). Second, it is possible to theoretically estimate the turnover frequencies from a computationally calculated catalytic cycle (for instance with the energetic span model<sup>29–32,35</sup>). This type of *in silico* estimations produces exclusively a derivative type of TOF. In fact, the only two reasons why the TOF is still considered at a finite time and reactant consumption are that it is sometimes easier to measure, and that the current definition of TOF loosely admits this meaning.

**2.4. TOF at Saturation Regime.** While the whole concept of “catalytic concentration” implies that the reactants and products are in much higher concentration than the catalyst, this is not explicitly declared in the TOF definition.

In fact, for enzymatic processes the Michaelis–Menten kinetic model<sup>12</sup> considers the rate of the reaction starting from a zero reactant concentration, while the famous<sup>36</sup> Lineweaver–Burk plot<sup>37</sup> makes use of the reactant concentration to derive  $V_{\max}$ , the maximum rate, and  $K_M$ , the Michaelis–Menten constant.<sup>18</sup> This is a suitable data treatment when the focus is set on the reactants, but not on the catalyst (the enzyme in this case). Accordingly, in biochemistry (and sometimes also in other branches of catalysis) the reactant is usually called “substrate”, which in IUPAC’s words means: “A chemical species, the reaction of which with some other chemical reagent is under observation (e.g. a compound that is transformed under the influence of a catalyst)”.<sup>10</sup> Because of this treatment of the kinetics and to avoid misunderstandings, some books expressly declare the turnover number (i.e., the TOF in our present nomenclature) as a function of the maximum rate:  $V_{\max}/[E_0]$ , with  $E_0$  being the total enzyme concentration.<sup>12,18</sup>

In heterogeneous catalysis  $\theta$ , the fractional coverage of the surface, is one of the most important variables. Similar to the Michaelis–Menten model, important kinetic information can be obtained considering low and high coverage, usually applying the Langmuir isotherm.<sup>12</sup> But again, unless a “saturation regime” is achieved (if possible), it will be problematic to express a useful TOF for comparative purposes.

Note that saturation kinetics does not mean that the TOF will be independent of all the reactants and products concentrations. In the Michaelis–Menten model (which considers only one reactant), saturation indeed means order zero on that species, but reaching saturation may be impossible for some reactions. Even more, if more reactants are consumed on other steps, it can be proven<sup>17,18,20,28,29,38–40</sup> that the TOF will probably be dependent on other reactants, no matter how high their concentrations are.

For instance, a catalytic system in a steady state regime that obeys a simple mechanism with two irreversible steps, such as



has a TOF of

$$\text{TOF} = \frac{k_1 k_2 [R]}{k_2 + k_1 [R]} \quad (5)$$

giving a saturation TOF (at high  $R_1$  concentration) of

$$\text{TOF}_{\text{sat}} = k_2 \quad (6)$$

which is the desired “order zero on the reactant” (i.e., saturation). However, if  $k_2$  is several orders of magnitude bigger than  $k_1$ , achieving saturation of  $R$  will be physically unattainable, and the TOF will be

$$\text{TOF} = k_1 [R] \quad (7)$$

at all concentrations. In cases like this finding the “ $V_{\max}$ ” term of the Michaelis–Menten model reaction only has a metaphysical value. In simple words, it is possible to have a catalytic system that cannot reach saturation.

In addition, a model reaction with two reactants such as



has a TOF of

$$\text{TOF} = \frac{k_1 k_2 [R_1][R_2]}{k_2 [R_2] + k_1 [R_1]} \quad (9)$$

which on saturation of  $R_1$  or  $R_2$  will have a TOF of

$$\begin{aligned} \text{TOF}_{\text{sat}(R_1)} &= k_2 [R_2] \\ \text{TOF}_{\text{sat}(R_2)} &= k_1 [R_1] \end{aligned} \quad (10)$$

respectively. It is clear from eq 10 that it is not possible to have saturation for both reactants in this model reaction. This issue can be usefully put to work as a way to find the rate determining zone of the cycle.<sup>41–44</sup>

From here we can conclude that the “saturation regime” is a complex issue, compatible with the fact of having a TOF dependent on the concentrations of reactants and products (a matter brought up by a constructive debate with the reviewers of the present manuscript). It is not only a thermodynamical (i.e., “Le Chatelier’s principle”) situation, but also a behavior coming from the cyclical nature of catalytic reactions (as in eqs 4 to 10).

Summarizing, the TOF should be expressed at saturation whenever possible, but still the concentrations must be declared if we are looking for a reproducible TOF.

**2.5. TOF at an Infinite Catalyst Dilution.** Sometimes it is considered that as the TOF is defined per active site, this is equivalent to expressing it as per one molar concentration of the catalyst.<sup>12</sup> In principle this is true, provided that all the concentrations and the turnovers are also expressed in molar units. While this may not be technically incorrect, intuitively the use of the molar scale for catalyst concentration feels awkward: a 1 M concentration of an enzyme hardly seems realistic. But more importantly, it is not possible to speak about catalyst concentrations in heterogeneous systems.

As always in chemistry, it is more correct to speak about the *activity* instead of the concentration, since the interactions between molecules of the depicted species affect their behavior at high concentrations (and 1 M is high concentration indeed!). For this reason IUPAC defines the standard state of a solute as: “For a solute in solution it is the (hypothetical) state of solute at the standard molality  $m^\circ$ , standard pressure  $p^\circ$  or standard



concentration  $c^\circ$  and exhibiting infinitely dilute solution behavior". A typical catalyst is used at a very low load (with substrate to catalyst ratio usually over 100), and thus can be considered infinitely dilute for practical purposes. However, for comparative purposes it may be suitable to explicitly test and declare the TOF at low catalyst concentration.

### 3. "TURNING OVER" DEFINITIONS

**3.1. Turnover Frequency (TOF).** Learning from the previous section, it is not only a philosophical exercise to compose a stricter and more complete definition of the TOF. It has the advantage of providing a standard for comparison of different catalysts without falling into the proverbial error of comparing apples to oranges. We presently propose such a definition as an extension of the classical one (but leaving room for discussion and amendments from the catalytic "gurus"):

*"The turnover frequency (TOF) is a measure of the instantaneous efficiency of a catalyst, calculated as the derivative of the number of turnovers of the catalytic cycle with respect of the time per active site, at such a low concentration of the catalyst that exhibits infinite dilution behavior and the reactants and products are (if possible) at a saturation regime. All the influencing conditions should be properly declared, such as the concentrations and temperature."*

Probably the most obvious complication resides in defining the active sites in heterogeneous catalysis, as several surface positions may exhibit different activity.<sup>3,21,34</sup> Experimentally the observed TOF corresponds to the weighted sum of the reactivity of each type of sites, much similar to the case of having several pathways of similar potential energies in homogeneous chemistry. There is still a hot ongoing debate on this issue, but most commonly the number of sites is estimated by a prior titration or another characterization method.<sup>9,40,45,46</sup> In the case of nanoparticles, where the line between homogeneous and heterogeneous catalysis becomes blurry,<sup>47,48</sup> an imaginative use of the magic numbers was proposed by Umpierre, de Jesús, and Dupont to count the sites.<sup>6</sup> The number of sites acting simultaneously to achieve the reaction may also be debated; for instance, in a Langmuir–Hinshelwood mechanism, the reaction includes two adsorbed molecules,<sup>12</sup> and therefore the "active site" should be considered as two surface sites. Homogeneous catalysis is not totally immune to this problem: multinuclear complexes,<sup>49</sup> enzymes with complex quaternary structure, or cascade reactions<sup>50</sup> can obscure the concept of a single active site. Alas, all of these are beyond the scope of the present manuscript.

An alternative, albeit criticized,<sup>40</sup> especially intended for comparison of catalysts based on similar chemistry, is to define a rate as a function of the mass instead of the number of sites ("TOF<sub>mass</sub>").<sup>3</sup> Such a measure is arguably biased against enzymes, which may have huge TOFs but also enormous masses per active site. For heterogeneous catalysis it is possible to set the rate as a function of the surface area ("TOF<sub>area</sub>").<sup>3</sup> From an economic viewpoint it is also possible to set a rate as a function of the price of the catalyst ("TOF<sub>\$</sub>"),<sup>8</sup> since this is the ultimate information that the industry require. Several other useful TOF options may be conceived for specific uses.<sup>6,11,46</sup>

At the reviewing stage of this article, one referee proposed the convenient measure of "TOF<sub>max</sub>", the maximum TOF attainable for a catalyst at the highest temperature at which the catalyst is still stable. Although this quantity cannot compare

catalysts at the same conditions, it can be useful for the understanding of the maximum potential of them.

From a pragmatic viewpoint, it is understandable that to obtain an accurate TOF is a problematic business both for the experimental and for the theoretical teams. Estimating it with an accuracy smaller than an order of magnitude can be sometimes challenging. A debate on whether the TOF should be a derivative or a simple "delta" measure may have in these cases only an academic value. Nonetheless, even in these circumstances it is important to acknowledge that we should be working with an approximation for a physically correct measure (the derivative version of the TOF), and not with an accurate result for a questionable measure (a "delta" quantity).

**3.2. Standard Turnover Frequency (TOF°).** As it is provided here, the TOF definition is useful for the assessment of a catalyst at certain specific conditions, but not for comparing different catalysts.<sup>33</sup> Evidently the TOF for a reaction in a 1 M reactant solution at 400 K will be much higher than with 1 mM concentrations at 250 K. Therefore, it would be appropriate to define a new quantity that "standardizes" the conditions so that only the efficiency of the catalyst is tested. In analogy to thermodynamical standard quantities (for instance the Gibbs energy of reaction,  $\Delta_r G^\circ$ , the enthalpy of formation,  $\Delta_f H^\circ$ , the entropy of activation,  $\Delta^\ddagger S^\circ$ , the equilibrium constant,  $K^\circ$ , or the electrode potential,  $E^\circ$ ),<sup>10</sup> a **standard TOF** can be formulated ("TOF°"), where the reactants and products concentrations are set to 1 M, or 10<sup>5</sup> Pa (1 bar) for gases. The temperature should be set at 273.15 K, in accordance to STP conditions (standard temperature and pressure), as IUPAC recommends.

The temperature is not defined for thermodynamical standard measures (unless explicitly declared as STP), but kinetics are too dependent on this variable to leave the TOF° without it. Arguably a temperature of 0 °C is too low for most reactions (especially for heterogeneous catalysis), but that is an issue only when looking at absolute rates. The argument here is about relative values, to evaluate competing catalysts.<sup>11,51,52</sup> In this way, even though the low values of the standard TOF may give the false impression of describing a useless catalyst, it has the ability to objectively distinguish the genuinely efficient catalysts vis-à-vis an "artificially" efficient one (for instance a species that only works at extremely high temperature), without the need to consider the conditions of the reaction.

Evidently this measure is not intended for comparison between totally different fields of catalysis. There is no point on trying to judge an industrial heterogeneous catalyst (which typically requires hundreds of Kelvin to operate) taking as a yardstick the enviable high TOF° of an enzyme. However, this standard measure can be used as a tool for judging different catalysts from the same field, or to have an unbiased picture of what to expect from a certain family of catalysts. In this way the TOF° (and the TON°, see below) are universal quantities for all branches of catalysis, with tangible practical value as all the other standard reaction quantities.

In most cases a good approximation of the TOF at a specified temperature can be obtained by applying the energetic span approximation:<sup>29–32,35</sup>

$$\text{TOF} = \frac{k_b T}{h} e^{-\delta E/RT} \quad (11)$$

$$\text{TOF}(x) = \text{TOF}^\circ \frac{T(x)}{T^\circ} e^{-\delta E/R(\frac{1}{T(x)} - \frac{1}{T^\circ})} \quad (12)$$

with  $x$  being the temperature in Kelvin and  $T^\circ = 273.15$  K, presenting an almost exponential tendency in the spirit of the transition state theory. For instance, a reaction that shows a very good TOF(100 °C) of  $200 \text{ s}^{-1}$  ( $\delta E = 18 \text{ kcal/mol}$ ) will only show a small TOF $^\circ$  of  $0.02 \text{ s}^{-1}$ . Still, in spite of the huge difference between both values, for comparative purposes TOF $^\circ$  is easier to tabulate and maintains the same kinetic information.

Note that  $\delta E$  (the energetic span), being the apparent activation Gibbs energy of the cycle, can be decomposed to  $\delta E = \Delta H^\ddagger - T\Delta S^\ddagger$  and, similar to the van't Hoff equation, the entropic term is canceled in eq 12. Therefore, the only variable is the apparent activation enthalpy of the cycle. As a result, the molecularity of the reaction does not affect eq 12, making the extrapolation to different temperatures easier from both experimental and theoretical perspectives.

Like before, all other conditions must be taken into account, such as the solvent, the pH, or any cocatalyst that enhances the reaction. These parameters, as they are not changed through the process, can be considered as external characteristics of the catalyst and should not be constrained to the standard 1 M concentration rule for the TOF $^\circ$ .

One last issue that can severely affect the TOF is the preactivation and deactivation of the catalyst. These processes must be taken into account for a proper kinetic analysis, but as they can mask the real TOF of the active catalytic cycle, they should be removed from the TOF $^\circ$  analysis. The nonstandard TOF should not neglect the pre- and deactivation, since these steps can be analyzed by looking at the TOF, as graphed in Figure 1b. But for the comparative purpose of TOF $^\circ$ , the catalyst must be fully functional. With a similar reasoning the system should be running at a steady state regime, since the TOF has no meaning with fluctuating rates (as in autocatalytic systems).

At this point it is appropriate to finally present the proposed definition of this TOF $^\circ$ :

*"The standard turnover frequency, TOF $^\circ$ , is the TOF measured at a hypothetical 1 M standard concentration of reactants and products (or  $10^5$  Pa in case of gases) at 273.15 K, in a steady state regime and with all the catalyst active. All the influencing conditions should be properly declared, such as the solvent and co-catalysts."*

This standard TOF is not meant to be a universal archetype of catalytic efficiency, immune to any specific circumstance of the measurement. Several difficulties may hinder its absolute comparative power, most of them related to nonlinearity in the concentrations. For instance, systems that show zero-order dependency (saturation regime) on a certain reactant may exhibit first order kinetics when going to low concentrations,<sup>41,42</sup> something that cannot be expressed in a single TOF number.

It is worth noting that in multistep reactions integer order kinetics are not the rule,<sup>53</sup> and unless there is one clear determining intermediate and one determining transition state, fractional orders can appear (or, in more precise terms, the TOF equation will not be a simple power law).<sup>29–32,35,38,39,44,54,55</sup>

There are other sources of inaccuracies when trying to summarize all the kinetic information in one value. For example the possibility of a product inhibiting the reaction at high concentration (usually when the reaction is only slightly exergonic, as in the Haber–Bosch ammonia synthesis<sup>30</sup>) will show that the TOF $^\circ$  may even be negative! Inhibition can also

appear at high reactant concentrations, due to stable off-cycle intermediates.<sup>53</sup> In addition, the efficiency of a catalyst is somewhat dependent on the extent of the reaction.<sup>30</sup> In all these specific cases, researchers can be excused if they do not want to follow the standard TOF protocol.

**3.3. What about the Turnover Number (TON)?** In biochemistry the term TON is still, regretfully, used with the same meaning as TOF.<sup>18</sup> Although this old definition of TON predates the current use by the homogeneous and heterogeneous community, the confusion should be avoided by taking into account the name of the quantity: the TOF is a frequency, with units of  $[\text{time}^{-1}]$ , while the TON is a dimensionless number.<sup>3,56</sup>

If the TOF is the measure of the instantaneous efficiency of the catalyst, the TON deals with its lifetime robustness. It corresponds to the total number of turnovers the catalyst can achieve until its total decay, regardless of time.<sup>46</sup> In enzymatic catalysis it is commonly known as *total turnover number* (TTN),<sup>14</sup> to distinguish it from the TON in the biochemical sense.

The catalyst can "die" by decomposition or poisoning. In both cases an energetic barrier that leads to very stable inactive states is slowly crossed, mining the average activity of the catalyst.<sup>29,57,58</sup>

There is no IUPAC definition for the TON (so far), but it appears in modern chemistry literature, for instance in the encyclopedic book "Catalysis from A to Z":<sup>9</sup>

*"Turnover number (TON) specifies the maximum use that can be made of a catalyst for a special reaction under defined reaction conditions by the number of molecular reactions or reaction cycles occurring at the reactive center up to the decay of activity. In this respect, the TON represents the maximum yield of products attainable from a catalytic center. The TON results from multiplication of the turnover frequency (TOF)  $[\text{time}^{-1}]$  and the lifetime of the catalyst  $[\text{time}]$ ."*

Most of the questions discussed in Section 2 for the TOF also apply to the TON. Two specific issues must be dealt with in this case. First, sometimes the TON is considered merely as the number of turnovers completed; so, if the reactant is totally converted, the TON will be exactly the original number of reactant molecules per active site,<sup>7</sup> in spite of still having active catalyst. This is a naïve interpretation of the term since it does not mean that the catalyst became degraded (simply adding more reactant will increase the TON), and therefore it is not a measure of its efficiency.<sup>6</sup> Let us remember that the focus of the TOF and TON must be placed on the catalyst and not on the reactant.

The second issue falls on the way it is calculated. *The TON is not the TOF multiplied by the lifetime.*<sup>7,9,15,46,56</sup> This treatment again lacks the time precision that we saw in section 2.3. What is the lifetime of the catalyst? In theory it is infinite, as an exponential decay does not have a definite end. Should it be taken up to 90% disappearance of the active species? Perhaps 99%? Also the TOF is misleading in this equation, as it implies an average instead of a derivative value. Regretfully, the TON needs a more complex treatment, as it is in fact the time integral of the TOF:<sup>14,29</sup>

$$\text{TON} = \frac{N^\circ_{\text{cycles}}}{N^\circ_{\text{sites}}} = \int_0^\infty \text{TOF}(t) \cdot dt \quad (13)$$

The TOF is constantly affected by the variation of the reactants concentrations (and sometimes of the products as well), by the deactivation of the catalyst and its preactivation.<sup>57</sup>

The TON can be experimentally gauged by the consumed reactant at the infinite time asymptote (taking into account that the reactant must not run out). This will give the total number of turnovers at the experimental conditions, which include all the fluctuations of the TOF. For qualitative analysis it may be enough, but for comparative purposes a **standard TON** ("TON°") may be needed.

As for the TOF°, to define a TON° the concentrations should be maintained at 1 M (or 10<sup>5</sup> Pa), at a steady state regime and at 273.15 K. The temperature may be less critical, since high temperature will increase both the TOF and the deactivation; but at the same time the mathematical conversion from one temperature to another will not be as easy as in eq 12. To calculate TOF° all the catalyst must be active, but for the TON° this is not the case, as it must pass through a deactivation to have a finite TON. However, the preactivation process should still be avoided.

From all these concerns, it seems that obtaining an accurate TON° is a thorny business. It may be estimated experimentally if the concentrations of reactants and products are artificially held constant (for instance in a continuous stirred-tank reactor), while at the same time the conversion is being monitored until no more reaction is observed. However, a much simpler way is to estimate the half-life of the catalyst. If the deactivation is a first order reaction and we already know the TOF°, the resulting equation is<sup>14,29</sup>

$$\text{TON}^\circ = \frac{\text{TOF}^\circ \cdot t_{1/2}}{\ln 2} \quad (14)$$

The limit of what can be considered a good TON depends on the application. For development and small scale synthesis, a TON of 100 may be enough. For industrial applications, a high turnover catalyst (HTC)<sup>8</sup> should have a TON of no less than 1000 (and ideally over 10<sup>5</sup>) to minimize the recovery of the active species, to avoid preactivation steps and the contamination of the product, and from economic reasons.<sup>8,16</sup> TONs as high as 10<sup>8</sup> have only been reached for very specific reactions.

#### 4. BEYOND THE TURNOVER MEASURES

For the sake of completeness, let us check some other quantities and their relation with the turnover-based kinetic measures.

One of the most employed measures is the yield (*Y*), the fraction of the desired product respective to the initial reactant (or the theoretical maximum):<sup>20,59</sup>

$$Y(t) = \frac{[P(t)]}{[R_0]} \quad (15)$$

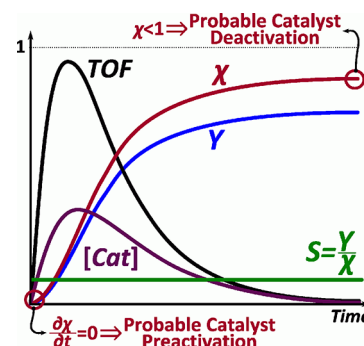
Although the yield is a function of time, it is usually implied that it is estimated at  $t = \infty$ , since it is mostly employed in synthetic chemistry without kinetic considerations. It is also implied that  $Y(\infty)$  is reached because the reactant was totally consumed (or at least it reached thermodynamical equilibrium), and not because the catalyst has been deactivated. In this way  $Y(t)$  is connected to the TOF, but  $Y(\infty)$  is not. What makes the yield lower than 100% is a selectivity problem (apart from the experimental errors, which of course may be quite severe).

The conversion ( $\chi$ ) is not affected by the selectivity. It measures the reactant consumption, regardless of the final product composition (the desired and undesired ones):<sup>20,46,59</sup>

$$\chi(t) = \left(1 - \frac{[R(t)]}{[R_0]}\right) \quad (16)$$

This quantity is strongly connected to the TON and TOF since, unlike the yield, it is mostly considered as a function of time. As  $\chi(\infty)$  is supposed to asymptotically reach 1 (unless the reaction is only slightly exergonic and reaches equilibrium), to find that the conversion gets "stuck" at a lower value is a sign of an expired catalyst, thus providing a way to calculate the TON (but not the TON°, since there was a variation of the reactant concentration).

From the slope of the conversion curve the rate of the reaction and the TOF can be easily deduced at each point of the reaction. For instance, a zero slope at the beginning can indicate a preactivation step (see Figure 2).



**Figure 2.** Conversion percentage ( $\chi$ ), yield ( $Y$ ), selectivity ( $S$ ), TOF, and active catalyst concentration for a model reaction with preactivation and deactivation.

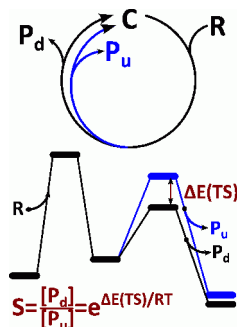
It is open to debate whether a full turnover must be counted only when the desired reaction products have been reached, or when any cyclic mechanism is completed regardless of the products generated. In the first case the TOF can be derived from the yield, in the second from the conversion. However, from the catalyst point of view it does not really matter what the final products are to close a turnover, so it can be argued that the conversion is a more appropriate quantity to this purpose.

This leaves room for the third measure of efficiency for a catalytic cycle, the selectivity ( $S = Y/\chi$ , or the ratio between the desired and the total product).<sup>20</sup> There are several flavors of this matter: chemoselectivity, regioselectivity, or stereoselectivity (which can be enantio- or diastereoselectivity).<sup>15</sup> When dealing with enantioselectivity it is also common to speak about the enantiomeric excess (e.e.), an uncomfortable quantity<sup>60</sup> with roots in polarimetry and difficult to work with from a theoretical perspective.

The selectivity is most often defined by the selectivity-determining transition state, which may or may not coincide with the TOF determining transition state (see Figure 3). Hence, the selectivity is usually not a function of the time or the conversion, unless the products (or the intermediates on the different pathways) can slowly reach thermodynamic equilibrium.<sup>20</sup> However, the selectivity is a function of the temperature and of the initial concentrations. Therefore, for comparative purposes it is advisable to express it as a standard quantity, in the same line as the TOF° and TON°.

It can be said that the TON itself is a selectivity issue, but not from the product perspective. The catalyst is deactivated by a





**Figure 3.** Selectivity between a desired ( $P_d$ ) and an undesired ( $P_u$ ) product. In most cases this selectivity corresponds to a bifurcation of the pathways. The selectivity depends exponentially on the difference of energy between the selectivity determining transition states.

reaction whose barrier competes with the transition states of the active cycle.<sup>29</sup> In this way the catalyst can cross to a dead species or continue “turning over”, with a ratio dependent on the exponential of  $\Delta T$ , akin to the product selectivity.

A recurrent observation that can be seen from all these quantities (rooted in the work of Boltzmann, Arrhenius, and others) is that all the experimental “observables” have an exponential dependency on the energy:  $\delta E$  for the TOF,  $\Delta T$  for the TON and the selectivity. At the same time, the dependency on the concentrations is only linear. In other words, tinkering with the catalyst’s molecular nature brings more profound chemical changes than altering the concentrations.

## 5. CONCLUSION

The turnover frequency (TOF) and number (TON) have been revisited with the objective of forming a common ground to compare different catalysts. As Laidler wrote<sup>33</sup>

“However, the turnover number varies with the temperature, the concentration of substrate... and other conditions.

Therefore it is not a useful quantity in kinetic work...”

In this “viewpoint” article we propose a definition for a standard TOF (“TOF°”) and TON (“TON°”), which may cure these deficiencies and can provide a real measure of the efficiency of a catalyst. These standard kinetic values, inspired by the classical standard thermodynamic functions such as  $\Delta_r G^\circ$ , should be estimated at 1 M or 10<sup>5</sup> Pa and 273.15 K, that is, at standard conditions of temperature, pressure, and concentrations.

In addition, we reviewed some common errors in the use of the turnover-based quantities. Most of them are matters overlooked by current definitions, so extended definitions were proposed to avoid confusions and to allow a more accurate comparison of catalysts. Lastly, we revised the connection between the TOF, TON, and other typical quantities (conversion, yield and selectivity).

The debate is far from finished, but it may come the day when the catalyst will be neatly tabulated according to their kinetic behavior, much like the standard thermodynamic tables.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

- (1) Boudart, M.; Aldag, A.; Benson, J. E.; Dougharty, N. A.; Girvin Harkins, C. J. *Catal.* **1966**, 6, 92–99.
- (2) Interestingly, in his book edited just two years after (Boudart, M. *Kinetics of Chemical Processes*; Prentice Hall: Englewood Cliffs, NJ, 1968) Boudart does not mention the TON or the TOF. It seems the concept took some time to take off.
- (3) Dumesic, J. A.; Huber, G. W.; Boudart, M. In *Handbook of Heterogeneous Catalysis*; Ertl, G., H. Knözinger, F. Schüth, Weitkamp, J., Eds.; Wiley-VCH: Weinheim, Germany, 2008; pp 1445–1462.
- (4) *Catalysis looks to the future*; National Academy Press: Washington, DC, 1992.
- (5) Chorkendorff, I.; Niemantsverdriet, J. W. *Concepts of modern catalysis and kinetics*; Wiley-VCH: Weinheim, Germany, 2003.
- (6) Umpierre, A. P.; de Jesús, E.; Dupont, J. *ChemCatChem* **2011**, 3, 1413–1418.
- (7) Arai, N.; Ohkuma, T. *Chem. Rec.* **2011**, 12, 284–289.
- (8) Farina, V. *Adv. Synth. Catal.* **2004**, 346, 1553–1582.
- (9) *Catalysis from A to Z: a concise encyclopedia*; Wiley-VCH: Weinheim, Germany, 2006.
- (10) *IUPAC Compendium of Chemical Terminology - the Gold Book*; International Union of Pure and Applied Chemistry, 2005–2012; <http://goldbook.iupac.org>.
- (11) Burwell, R. L. *Pure Appl. Chem.* **1976**, 46, 71–90.
- (12) Levine, I. N. *Physical chemistry*; McGraw-Hill: Boston, MA, 2008.
- (13) Atkins, P. W.; De Paula, J. *Physical chemistry*, 9th ed.; W. H. Freeman and Co.: New York, 2010.
- (14) Rogers, T. A.; Bommarius, A. S. *Chem. Eng. Sci.* **2010**, 65, 2118–2124.
- (15) Bhaduri, S.; Mukesh, D. *Homogeneous catalysis: mechanisms and industrial applications*; Wiley: New York, 2000.
- (16) Gladysz, J. A. *Pure Appl. Chem.* **2001**, 73, 1319–1324.
- (17) Segel, I. *Enzyme kinetics: behavior and analysis of rapid equilibrium and steady state enzyme systems*; Wiley Classics Library ed.; Wiley: New York, 1993.
- (18) Leskovac, V. *Comprehensive enzyme kinetics*; Kluwer Academic/Plenum Publishers: New York, 2003.
- (19) Crabtree, R. *The organometallic chemistry of the transition metals*; 4th ed.; John Wiley: Hoboken NJ, 2005.
- (20) Helfferich, F. G. *Kinetics of homogeneous multistep reactions*; Comprehensive Chemical Kinetics; Elsevier: Amsterdam, The Netherlands, 2001; Vol. 38.
- (21) Dumesic, J. A.; Rudd, D. F.; Aparicio, L. M.; Rekoske, J. E.; Treviño, A. A. *The microkinetics of heterogeneous catalysis*; ACS professional reference book; American Chemical Society: Washington, DC, 1993.
- (22) Davis, M. E.; Davis, R. J. *Fundamentals of chemical reaction engineering*; McGraw-Hill: Boston, MA, 2003.
- (23) Hansen, A.; van Well, W.; Stoltz, P. *Top. Catal.* **2007**, 45, 219–222.
- (24) Ertl, G.; Knözinger, H.; Schüth, F.; Weitkamp, J. *Handbook of heterogeneous catalysis*; 2nd ed.; Wiley-VCH: Weinheim, Germany, 2008.
- (25) Held, I.; Larionov, E.; Bozler, C.; Wagner, F.; Zipse, H. *Synthesis* **2009**, 2009, 2267–2277.
- (26) Dybkær, R. *Clin. Chem.* **2002**, 48, 586–590.
- (27) *Eur. J. Biochem.* **1979**, 97, 319–320.



- (28) Yablonskii, G. S.; Bykov, V. I.; Elokhin, V. I.; Gorban, A. N. *Kinetic models of catalytic reactions*; Comprehensive Chemical Kinetics; Elsevier: Amsterdam, The Netherlands, 1991; Vol. 32.
- (29) Kozuch, S. *WIREs Comput. Mol. Sci.* **2012**, *2*, 795–815.
- (30) Kozuch, S.; Shaik, S. *J. Phys. Chem. A* **2008**, *112*, 6032–6041.
- (31) Kozuch, S.; Shaik, S. *Acc. Chem. Res.* **2011**, *44*, 101–110.
- (32) Uhe, A.; Kozuch, S.; Shaik, S. *J. Comput. Chem.* **2011**, *32*, 978–985.
- (33) Laidler, K. J. *Chemical Kinetics*, 3rd ed.; Prentice Hall: Englewood Cliffs, NJ, 1987.
- (34) Vannice, M. *Kinetics of catalytic reactions*; Springer: New York, 2005.
- (35) Kozuch, S.; Shaik, S. *J. Am. Chem. Soc.* **2006**, *128*, 3355–3365.
- (36) Dagani, R. *C&EN* **2003**, *81*, 26.
- (37) Lineweaver, H.; Burk, D. *J. Am. Chem. Soc.* **1934**, *56*, 658–666.
- (38) Christiansen, J. A. *Adv. Catal.* **1953**, *5*, 311–353.
- (39) King, E. L.; Altman, C. *J. Phys. Chem.* **1956**, *60*, 1375–1378.
- (40) Goodwin, J. G.; Kim, S.; Rhodes, W. D. In *Catalysis*; Spivey, J. J., Roberts, G. W., Eds.; Royal Society of Chemistry: Cambridge, U.K., 2004; Vol. 17, pp 320–348.
- (41) Johnson, J. B.; Bercot, E. A.; Rowley, J. M.; Coates, G. W.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 2718–2725.
- (42) Kozuch, S.; Lee, S. E.; Shaik, S. *Organometallics* **2009**, *28*, 1303–1308.
- (43) Yagisawa, S. *Biochem. J.* **1995**, *308*, 305–311.
- (44) Kozuch, S.; Martin, J. M. L. *ChemPhysChem* **2011**, *12*, 1413–1418.
- (45) Boudart, M.; McDonald, M. A. *J. Phys. Chem.* **1984**, *88*, 2185–2195.
- (46) Hagen, J. *Industrial catalysis: a practical approach*; 2nd ed.; Wiley-VCH: Weinheim, 2006.
- (47) Crabtree, R. H. *Chem. Rev.* **2011**, *112*, 1536–1554.
- (48) Precht, M. H. G.; Scholten, J. D.; Dupont, J. *Molecules* **2010**, *15*, 3441–3461.
- (49) Jain, V. K.; Jain, L. *Coord. Chem. Rev.* **2005**, *249*, 3075–3197.
- (50) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167–178.
- (51) Wolfenden, R. *Chem. Rev.* **2006**, *106*, 3379–3396.
- (52) Wolfenden, R. *Annu. Rev. Biochem.* **2011**, *80*, 645–667.
- (53) Baxter, R. D.; Sale, D.; Engle, K. M.; Yu, J.-Q.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 4600–4606.
- (54) Stegelmann, C.; Andreasen, A.; Campbell, C. T. *J. Am. Chem. Soc.* **2009**, *131*, 8077–8082.
- (55) Stegelmann, C.; Andreasen, A.; Campbell, C. T. *J. Am. Chem. Soc.* **2009**, *131*, 13563–13563.
- (56) Rothenberg, G. *Catalysis: concepts and green applications*; Wiley-VCH: Weinheim, Germany, 2008.
- (57) Ostrovskii, N. M. *Chem. Eng. J.* **2006**, *120*, 73–82.
- (58) Kozuch, S.; Martin, J. M. L. *ACS Catal.* **2011**, *1*, 246–253.
- (59) Missen, R. W.; Mims, C. A.; Saville, B. A. *Introduction to chemical reaction engineering and kinetics*; J. Wiley: New York, 1999.
- (60) Gibb, B. C. *Nat. Chem.* **2012**, *4*, 237–238.