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Unifying Evaluation of the Technical Performances of Iron-Tetra-amido Macrocyclic Ligand Oxidation Catalysts

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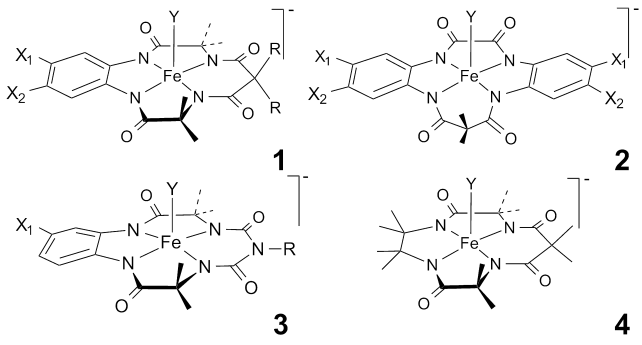
Supporting Information

ABSTRACT: The main features of iron-tetra-amido macrocyclic ligand complex (a sub-branch of TAML) catalysis of peroxide oxidations are rationalized by a two-step mechanism: $Fe^{III} + H_2O_2 \rightarrow$ Active catalyst (Ac) (k_I), and Ac + Substrate (S) $\rightarrow Fe^{III}$ + Product (k_{II}). TAML activators also undergo inactivation under catalytic conditions: Ac $\rightarrow$ Inactive catalyst (k_i). The recently developed relationship, $\ln(S_0/S_\infty) = (k_{II}/k_i)[Fe^{III}]_{tot}$, where S_0 and S_∞ are [S] at time $t = 0$ and ∞, respectively, gives access to k_i under any conditions. Analysis of the rate constants k_I, k_{II}, and k_i at the environmentally significant pH of 7 for a broad series of TAML activators has revealed a 6 orders of magnitude reactivity differential in both k_{II} and k_i and 3 orders differential in k_I. Linear free energy relationships linking k_{II} with k_i and k_I reveal that the reactivity toward substrates is related to the instability of the active TAML intermediates and suggest that the reactivity in all three processes derives from a common electronic origin. The reactivities of TAML activators and the horseradish peroxidase enzyme are critically compared.

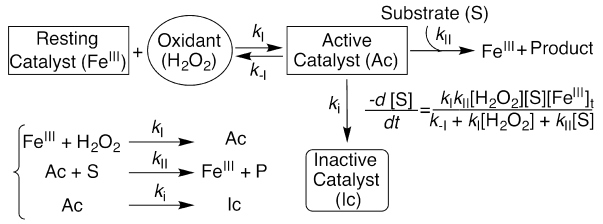
Understanding the origins of lifetime control in functional oxidation enzyme mimics is as useful for furthering catalyst design[1] as it is for advancing sustainable chemical technologies. The iterative design of the fully functional, small-molecule peroxidase enzyme mimics, iron-tetraamido macrocyclic ligand complexes (TAML activators, Chart 1), has driven our program for several decades. This has led to remarkably effective and efficient catalysts for oxidations by hydrogen peroxide, a prevalent reagent in both biochemistry and chemical technology.[2,3] All TAML catalysts to date have been found to adopt the same stoichiometric mechanism[4] in which the resting ferric catalyst reacts with the primary oxidant (k_I) to form the catalytically active species (Ac), which then either oxidizes a substrate (k_{II}) to regenerate the resting catalyst or undergoes inactivation (k_i) (Scheme 1, where k_{-I}, associated with the reverse of peroxide activation, is kinetically negligible[5] and all rate constants k_I, k_{II}, and k_i are pH dependent).

Chart 1. TAML Activators Employed (See Table 1 for X/R; Y is usually H_2O)[a]



[a]TAML is a registered trademark of Carnegie Mellon University, covering tetra-organic-amido-*N* macrocyclic ligand complexes.[6]

Scheme 1. General Mechanism of TAML Activator Catalysis Adopted for Mathematical Treatment



For TAML activators, the magnitudes of the second-order rate constants, k_I and k_{II}, that describe the catalytic activity, together with the first-order inactivation rate constant k_i that characterizes the lifetime, determine the comparative technical performance in each catalytic process. This study gives a unifying evaluation of these rate constants for 15 TAML activators over the generational ligand structures **1**−**4**. The results deliver the relative reactivity powers and limitations within the members of this suite of catalysts. Here we show that a remarkable preservation of the relationships between k_I, k_{II}, and k_i persists across the discovered million-fold ranges in k_{II} and k_i and thousand-fold range in k_I for all of the TAMLs studied.

While the values of k_I and k_{II} can be obtained directly from kinetic data, the determination of k_i is much more complicated—two approaches have been developed. The earlier approach[7] rests upon ensuring a pure competition between substrate oxidation and catalyst inactivation, requiring catalyst activation to be fast and substrate oxidation to be rate-determining (i.e., $k_I[H_2O_2] \gg k_{II}[S]$, Scheme 1). This reactivity

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Table 1. Rate Constants k_I, k_{II}, and k_i for TAMLs 1−4 (Chart 1) at pH 7 and 25 °C[a]

TAML	$X_1/X_2/R$	k_I	$10^{-4} \times k_{II}$	$10^3 \times k_i$[b]
1a	H/H/Et	1.8 ± 0.1	0.28 ± 0.01	0.09 ± 0.01
1b	NH_2/H/Me	28 ± 2	0.42 ± 0.02	1.15 ± 0.07
1c	H/H/Me	31.4 ± 0.1	0.495 ± 0.002	0.30 ± 0.01
1d	CO_2Me/H/Me	38 ± 1	0.73 ± 0.01	0.11 ± 0.01
1e	Me/Me/Me	49 ± 3	0.90 ± 0.05	0.42 ± 0.01
1f	NO_2/H/Me	152 ± 5	2.7 ± 0.2	0.34 ± 0.02
1g	NO_2/H/F	350 ± 2	4.1 ± 0.1	1.1 ± 0.3
1h	Cl/Cl/F	361 ± 1	12 ± 1	2.50 ± 0.03
2a	Cl/Cl/Me	1490 ± 20	4.0 ± 0.2	11.0 ± 0.4
2b	CN/H/Me	1850 ± 90	26 ± 1	20 ± 1
2c	NO_2/H/Me	1900 ± 100	52 ± 7	85 ± 6
3a[c]	H/H/Ph	85 ± 3	0.19 ± 0.01	0.23 ± 0.05
3b[c]	H/H/Me	140 ± 20	2.3 ± 0.2	3.0 ± 0.4
3c[c]	NO_2/H/Me	1500 ± 30	6.8 ± 0.7	2.2 ± 0.3
4	−/−/Me	0.63 ± 0.02	(1.19 ± 0.03) × 10^{-4}	(4.1 ± 0.1) × 10^{-4}

[a] k_I and k_{II} are in M^{-1} s^{-1}; k_i is in s^{-1}. [b] All k_i values determined using eq 4. [c] Rate constants for **3** have been published.[19]

regime is generally found for peroxidase enzymes.[4] However, it can rarely be enforced for synthetic oxidation catalysts because catalyst activation (k_I) is usually rate-determining instead. Fortunately, for TAML activators, the regime can be imposed, allowing k_i to be captured, by setting the experimental conditions: (i) pH > 10, (ii) high $[H_2O_2]$, (iii) low [S], and (iv) slow-reacting S.[7]

This reactivity regime is often unattainable at pH 7 ($k_I[H_2O_2] \gg k_{II}[S]$ does not hold), which is by far the most important pH for understanding the relative catalytic behavior. This is because TAML catalysts enable, *inter alia*, the high performance mitigation of micropollutants in water where practical considerations require the pH to be near neutral.[8−17] Nevertheless, by setting the above conditions at higher pH, the analytic expression $\ln(\ln[S_t/S_\infty]) = \ln(k_{II}[Fe]_{tot}/k_i) - k_i t$ can be employed to determine k_i (where S_t and S_∞ are substrate concentrations at time t and $t = \infty$, respectively, and $[Fe^{III}]_{tot}$ is the total catalyst concentration). It follows that the condition $S_\infty > 0$ must hold for the analysis to be applicable. This is easily achieved by resorting to low catalyst loadings.

In order to assess k_i at pH 7, a second approach was devised.[18] A system of three differential equations (eqs 1−3) was developed to permit the treatment of the three rate constants in a single kinetic analysis where there is no analytic solution. Therefore, mathematical and chemical teams collaborated to develop a procedure that, remarkably, requires minimal data for evaluating k_i and applies under all conditions.[18] The important expression, eq 4, indicates that the amount of unreacted substrate (S_∞) is a function of the rate constants k_{II} and k_i, as well as the total catalyst concentration ($[Fe^{III}]_{tot}$). The elusive k_i can thus be evaluated, provided the oxidant is used in excess and the precise value of k_{II} is known.[18] Note that S_∞ does not depend on k_I.

$$\frac{d[Fe^{III}]}{dt} = -k_I[Fe^{III}][H_2O_2] + k_{II}[Ac][S] \quad (1)$$

$$\frac{d[Ac]}{dt} = k_I[Fe^{III}][H_2O_2] - k_{II}[Ac][S] - k_i[Ac] \quad (2)$$

$$\frac{d[S]}{dt} = -k_{II}[Ac][S] \quad (3)$$

$$\ln\frac{S_0}{S_\infty} = \frac{k_{II}}{k_i}[Fe^{III}]_{tot} \quad (4)$$

By adding eq 4 to standard kinetic tools, we have been able to determine the values of the effective rate constants k_I, k_{II}, and k_i for 15 TAML catalysts that vary widely in ligand structure and reactivity (Chart 1 and Table 1). The substrate-independent k_I values can be of great utility to any researcher using TAML activators at pH 7, as they will usually dictate the rate of substrate oxidation and are available for assessing k_{II} values when $k_I[H_2O_2] \approx k_{II}[S]$.

For many years, the azo dye Orange II has served us as a reference substrate for kinetic analyses. The pH 7 rate constants k_I and k_{II} were obtained by measuring the initial rates of bleaching of Orange II by H_2O_2 in the presence of **1**−**4** as described elsewhere.[5,7,20−22] The lifetimes of TAML activators are known to be influenced by $[H_2O_2]$. This was first noted a decade ago,[17] confirmed quantitatively,[7] and then exploited practically by generating H_2O_2 enzymatically in situ.[23] Therefore, effective k_i values were determined in the presence of a low constant $[H_2O_2] = 2.5 \times 10^{-3}$ M. All k_i values were calculated using eq 4, where $S_\infty > 0$ was achieved by using very low [TAML] (ca. 10^{-8}, 10^{-9}, and 10^{-7} M for **1**, **2**, and **4**, respectively). Importantly, in the test case of **1c**, the k_i at pH 7 depends very weakly on [**1c**] (Figure 1S, Supporting Information (SI)), as was found at pH 11.[7] Projecting reasonably to the entire suite, these inactivation processes are unimolecular in catalyst under the specified conditions. The kinetic information is presented in Table 1, and useful linear free energy relationships (LFERs) derived therefrom are shown graphically in Figures 1 and 2. The synthesis, characterization, and catalytic evaluation of the new TAML activator **4** are described in SI. This body of work allows us to make the following conclusions concerning TAML activator-catalyzed oxidations at pH 7.

First, the line in Figure 1 establishes the rule for this TAML class that, at neutral pH, higher catalytic activity (k_{II}) is accompanied by lower operational stability (k_i), even over the diverse range of structural motifs and reactivities of **1**−**4**. This trend agrees with the general observation that catalysts displaying increased reactivity are more prone to inactivation.[1] Equation 5 provides an analytical expression for the straight line of Figure 1 giving a slope of approximately 1. Under these

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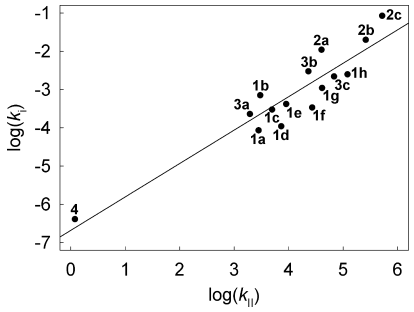

Figure 1. LFER between log k_i and log k_{II} of TAML activators at 25 °C and pH 7; k_{II} refers to the bleaching of Orange II dye.

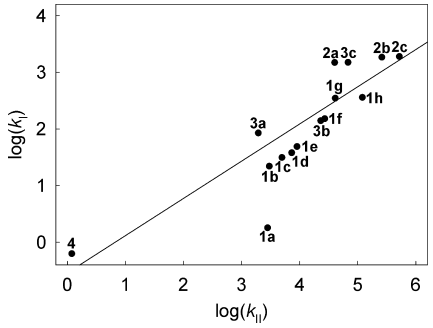

Figure 2. LFER between log k_I and log k_{II} of TAML activators at 25 °C and pH 7; k_{II} refers to the bleaching of Orange II dye.

$$\log k_i = (0.9 \pm 0.1) \log k_{II} - (6.7 \pm 0.4) \quad (5)$$

conditions, faster-reacting TAML catalysts will not do a great deal more work over time because the degradation rates track the substrate oxidation rates closely. Thus, factors that enhance the aggressiveness of TAML activators with respect to target molecules decrease their operational stability.

The slope being near 1 in Figure 1 supports the hypothesis of Scheme 1 that a common intermediate, Ac, participates in both the k_{II} and k_i processes. As for the exact nature of Ac, very reactive iron(V)oxo species have been characterized for various TAML activators in organic solvents.[24−26] We have to date been unable to observe or capture such species in aqueous H_2O_2 systems. In electron transfer processes, which are among the possible pathways for subject bleaching of Orange II,[5] the kinetics in water is dominated by iron(IV) species which are likely formed by fast reduction of iron(V)oxo primary intermediates. Iron(IV) intermediates, the exact speciation of which depends on pH, have been implicated in TAML/H_2O_2 catalytic oxidation of one electron transfer agents.[27]

Both rate constants k_{II} and k_i vary remarkably by 6 orders of magnitude. The new-generation TAML activator **4** (first reported herein) is particularly valuable for this broad study, as it extends k_{II} and k_i by 3 orders of magnitude to anchor and improve confidence in the observed trend, although it is markedly less active than earlier generations represented by **1**−**3** (Table 1, Figure 1). For **4** at pH 7, the rate constants k_I and k_{II} are almost identical. However, at pH 11, **4** conforms to the general relationship $k_I < k_{II}$ that holds for all other TAML activators, with k_I and k_{II} of 660 ± 10 and (7.5 ± 0.3) × 10^3 M^{-1} s^{-1}, respectively.

Second, the activation of peroxide (k_I) is related to the oxidation of substrate (k_{II}), and the data shown in Figure 2 can be fitted by the linear analytical expression of eq 6. Since the

$$\log k_I = (0.7 \pm 0.1) \times \log k_{II} - (0.8 \pm 0.5) \quad (6)$$

point for **1a** deviates from the trend-line by greater than 1 order of magnitude (the sole case of steric modulation), the data for this catalyst was excluded from the fit—**1a** uniquely contains a *gem*-diethyl-substituted carbon in the six-membered tail ring in place of *gem*-dimethyl or difluoro substitution patterns.

The approximately linear trend lines of Figures 1 and 2 are consistent with the Lewis acidity at iron playing an important role in all three processes. Following this rationalization, it is noteworthy that the peroxide activation process (an oxidation at iron) is accelerated by increased Lewis acidity at iron, which could seem counterintuitive. We have long interpreted this feature as evidence for heterolysis of the peroxide O−O bond, as this would be faster with increasing acidity of the coordinated water and, especially, the H_2O_2 ligands.[28,29]

It is interesting to consider the relative rate behavior of TAML activators and peroxidase enzymes as catalysts for peroxide oxidation of organic substrates in water. For the enzymes, catalyst activation is fast, i.e. $k_I \gg k_{II}$. For TAML activators, catalyst activation is typically rate limiting ($k_I \ll k_{II}$), as is the case with Orange II. The small, 44 000 Da horseradish peroxidase (HRP)[30] is among the fastest activators of peroxide in the peroxidase family with $k_I = 2 \times 10^7$ M^{-1} s^{-1}.[31] By comparison, at pH 7 **2c** has the highest TAML k_I value of (1.9 ± 0.1) × 10^3 M^{-1} s^{-1}. This leads to a catalyst design question—can the iterative design protocol that led to TAML activators[2,3] be extended to give new catalysts with k_I increased by 4 orders of magnitude to rival HRP? One can foresee what this challenge might entail from the proportionality between log k_I and log k_{II}. Based on eq 6, if k_{II} for the oxidation of Orange II (25 °C and pH 7) could be increased in a future TAML activator to the diffusion-controlled limit ($k_{II} \approx 10^{10}$ M^{-1} s^{-1}),[32] the corresponding k_I value would be ∼10^6 M^{-1} s^{-1}. If this challenge seems forbidding, consider that the **2c** k_I value is ca. 2 orders of magnitude greater than that of the prototype **1c** and more than 3 orders of magnitude greater than that of the least active **4**. The data in Figure 2 provide additional insight into the design of this more ideal TAML. Replacement of the geminal ethyls of **1a** with methyls in **1c** produces an increase in k_I relative to k_{II} indicating that steric bulk in this location hinders the H_2O_2 activation pathway. A design venture to further improve the kinetic rate constants of TAML activators relative to the peroxidase enzymes is academically enticing. However, in comparing the utility of TAML activators and peroxidases, it is important to recognize that a typical TAML activator enjoys a large advantage in terms of atom economy, comprising ∼1% the mass of HRP, a particularly light peroxidase enzyme.[30]

Third, since both catalyst inactivation (k_i) and the activation of peroxide (k_I) vary directly with substrate oxidation (k_{II}), k_i and k_I are also directly related. Again, at neutral pH, catalyst activation is typically rate-determining in TAML processes. Here too, activators capable of greater overall rates of substrate oxidation controlled by the catalyst activation step display proportionally increased rates of inactivation providing further evidence that all three "proportionalities" derive from a common electronic origin.

In conclusion, this general evaluation of peroxide oxidation processes delivers considerable insight into how TAML catalysis works. The study exemplifies the well-established approach of using knowledge of the key rate constants, k_I, k_{II},

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and k_i here, that we call "technical performance parameters", to generate robust LFER analyses that give valuable insight into the forces underlying each while bolstering the limited literature of catalyst inactivation.[1] In principle, this approach could have wider utility for probing the reactivity of other synthetic catalysts in oxidation, reduction or other processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13087.

Synthesis of **4** and details of kinetic data collection (PDF)

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Notes

The authors declare no competing financial interest.

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