TAML Activators: Green Chemistry Catalysts as Effective Small Molecule Mimics of the PeroxidaseEnzymes

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About the Author

Terry Collins, a New Zealander by birth, gained his chemistry education at Auckland University, completing his PhD under the guidance of Prof. Warren Roper in 1978. After a postdoctoral with James Collman at Stanford he was appointed Assistant Professor at CIT and then moved to Carnegie Mellon University in 1988, where he is now the Teresa Heinz Professor of Green Chemistry. Terry championed the field of green chemistry and gained international recognition for his work in creating a new class of oxidation catalysts with enormous potential and positive impact on the environment. Experts worldwide believe that Collins' commercializing systems can be used to effectively replace chlorine-based oxidants in large global technologies so that some of society's most toxic chlorinated residuals are not produced. The systems also enable valuable approaches for handling previously unsolved environmental and health problems. His honors include the EPA's 1999 Presidential Green Chemistry Challenge Award, the Pittsburgh Section Award of the ACS and Japan's Society of Pure and Applied Coordination Chemistry Award. Terry is an Honorary Professor and a Distinguished Alumni awardee of Auckland University. He was the inaugural recipient of the Kaufman Award of Pittsburgh Foundation and he received the 2010 Heinz Award for his green chemistry work. He was elected an Honorary Fellow of the RSNZ in 2008.
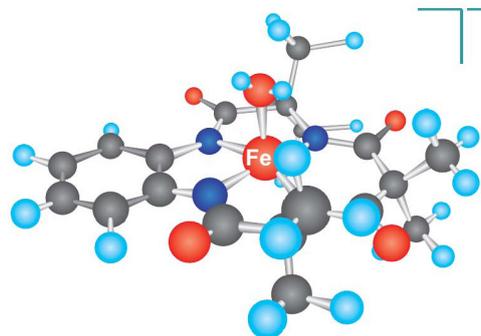
Terry learned of the insidious health damage caused by pollutants from paper and pulp mills and pesticides in his native New Zealand. He began exploring whether there could be an environmentally benign and cost-effective new technology to avoid or to destroy the pollutants. After a major breakthrough in homogeneous catalyst ligand design, Collins and his fellow researchers established the scientific basis for both goals and more. Laboratory studies show that oxidation processes employing hydrogen peroxide can now be used to avoid and eliminate pollutants in these and other industries. Commercialization is under way and there are application areas still to be discovered. The ongoing saga of deleterious health effects in New Plymouth is but one reason to bring him home fairly frequently.

Introduction

It is now over 30 years since I received my Ph.D. degree from the University of Auckland where I was privileged to receive a world-class training from Warren Roper, New Zealand's world-leading organometallic chemist, and to be a contemporary of current Auckland staff members, James Wright and Penny Brothers. We are a few of the lucky chemists to have been students of Professor Roper.

In this short review, I will give a perspective on my independent research that started in 1980 and led, in 1995, to TAML® activators (see Chart 1), the first effective small molecule mimics of the peroxidase enzymes. And I will sketch our ongoing studies of their further design, mechanisms of action and applications. In the last two decades, I have become increasingly inspired by the potential of green chemistry to help in building the technological dimension of a sustainable civilization and I will weave green chemistry into the discussion.

Green chemistry was launched at the US Environmental Protection Agency (USEPA) in 1991. Dr. Paul Anastas proposed the important definition a few years later, namely: *Green chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances*. When green chemistry arrived on the scene, my program to develop miniature peroxidase replicas fitted into the infant field perfectly. My long-term goal was to develop oxygen- or peroxide-based processes that could replace chlorine and metal-based oxidations in water and elsewhere. While these incumbent oxidation technologies bring us many benefits, they also come at the cost of adding carcinogens and/or other toxic pollutants to water and, thus, can be viewed as temporary rather than as sustainable solutions for the important process goals they meet.

While in New Zealand, I learned a lot about the controversial subject of dioxin toxicity. My evaluation as a young
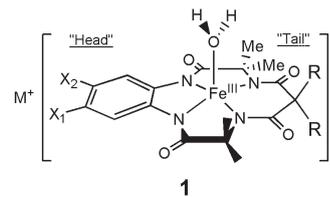
scientist, listening to and reading the dioxin debates of the 1970s, was that what I will call the environmentalist point of view (for want of a better terminology) was probably correct—dioxin contamination of the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) was leading to exposures resulting in much human illness and even severe developmental abnormalities in NZ infants. Over the years, more and more information concerning dioxin toxicity has come to light about what was known and when it was known. While this is not the right place to air all the details, the well-documented history is both a sorry story and an emblem of what needs to be avoided in industrial chemistry if we are going to build a sustainable civilization. We are burdened today with large-scale, unsustainable products because *dioxin* (or more appropriately *dioxins* to capture all the toxic dioxins and dioxin-like compounds) has been poorly handled since the 1960s. And I have come to realize that how each generation responds to challenges like dioxins plays a large role in determining whether our civilization gets more sustainable or less sustainable on that generation's watch.

As soon as green chemistry emerged, my team and I were happy to call ourselves *green chemists* and to join with Dr. Anastas and other colleagues to help expand our own and general understanding of what this field, which is so critical to a good future for mankind, has to become. You can learn more about important concepts of green chemistry and especially (at this stage of development) about introductory materials on the multidisciplinary understanding that is vital to green chemistry's success by visiting Carnegie Mellon's open-source green science education website (see: *http://igs.chem.cmu.edu/*).

The Design Problem for Peroxidase Mimics and Green Chemistry Connections

In biochemistry, oxidation processes are largely carried out by oxygen or its reduced derivative, hydrogen peroxide (which living things produce from oxygen). Oxygen and hydrogen peroxide possess very complex chemistries that are mostly marshalled by iron-based enzymes. These enzymes have proven to be particularly difficult to mimic with small molecule catalysts, in large part because the reactive intermediates produced when peroxide is mixed with activating metal species are aggressively oxidizing and readily destroy oxidizable ligands. Enzymes use their proteins to provide protection to metalloprotein ligands in various ways. For large-scale water purification processes, toxicity has to be avoided and this severely restricts the metals that can be used. Iron is ideal. It is widely used in biochemistry and, coincidentally, it is the least toxic transition metal. By following an iterative design protocol for fifteen years that was aimed at slowing down oxidative and hydrolytic ligand degradations in potential small molecule catalysts, we were able to develop TAML® activators with iron as the active metal (Chart 1). TAML activators have genuinely useful lifetimes and we have since shown that they are quite faithful mimics of the peroxidase enzymes.[1,2] In the process, we produced a set of rules to guide co-ordination chemists wanting to produce oxidation resistant ligand systems.[3]

Chart 1. First generation TAML activators with iron as the active metal.

1	X_1	X_2	R
a	H	H	Me
b	Me	Me	Me
c	Me	H	Me
d	MeO	MeO	Me
e	NO_2	H	Me
f	COOMe	H	Me
g	COOH	H	Me
h	$CONH(CH_2)_2NMe^{3+}$	H	Me
i	Cl	Cl	Me
j	Cl	Cl	Et
k	Cl	Cl	F
l	H	H	F
m	H	H	
n	Cl	Cl	

Catalytic Properties of TAML Activators

TAML activators are able to mimic peroxidase processes very well for two key reasons. Firstly, anionic amido-*N* ligands possess a high donor capacity. With four such Lewis bases, the TAML macrocycle shifts iron's redox chemistry with hydrogen peroxide away from the outer sphere processes called *Fenton chemistry* to inner sphere processes in which the metal is relatively easily oxidized by one and two units above the ferric (Fe[III]) state with concomitant formation of oxo ligands. So for example, in terms of reduction potentials, iron(IV) in the TAML environment looks like iron(III) in the porphyrin environment. Secondly, the macrocycles have been iteratively designed to resist the oxidative degradation pressure that has probably terminated prior attempts to mimic peroxodase-like catalysis—this designed-in resistance to oxidative destruction is the real key to the functional lifetime of TAML activators.[4,5]

TAML activators catalyze peroxide processes typically at room temperature under ambient conditions. The five coordinate structures isolated in the solid state from the syntheses (Chart 1) – sometimes axial chloride complexes are produced – form six-coordinated species in water with two axial water ligands. The very high donor capacity of the macrocycles significantly quenches the axial Lewis acidity of the iron and this has the benefit of making the axial ligands particularly labile to deliver a significant advantage for catalysis. Luckily, our use of high donor capacity ligands with iron did not overly mute the oxidizing properties (a perceived risk at the outset of the project),

but instead produced very reactive catalysts. In contrast, we made the first manganese(V)-oxo complexes many years ago and found these to be remarkably inactive. We attributed the low reactivity to the high donor capacities of the polyanionic chelating ligand systems we were developing at that time.[6-8]

Hydrolytic Stability

The hydrolytic stability of any catalyst intended for use in water is a critical property. The prototype TAML activator, **1a**, is stable in water under neutral pH. However, under acid conditions, H^{+}-promoted demetalation occurs that follows the rate law:[9]

$$k_{obs} = k_1*[H^+] + k_3*[H^+]^3.$$

This rate law is consistent with the mechanism in Scheme 1 provided that K_{a1} and K_{a2} are high, ensuring $K_{a1}K_{a2} >> (K_{a2}[H^+] + [H^+]^2)$ and k_2 is negligible compared to k_1 and k_3.[9]
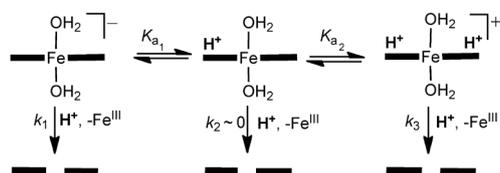

Scheme 1. Suggested mechanism of the H+-induced demetalation; ▬▬ ▬▬ = macrocyclic ligand; see ref. 9

So we had to ask where the protons might be attaching to the TAML activator in the demetalation processes and we concluded that amide ligand nitrogen and oxygen atoms were the likely binding sites. The third order term is intriguing as it requires three protons to attach somewhere before the metal is liberated. We suspected that protonation of the tail amide oxygen atoms (see Chart 1) was involved. This suggested that we could slow the rate of demetalation by reducing the basicity of the tail region. We achieved this by replacing the methyl substituents on the six-membered chelate ring with fluorine groups and were able to dramatically lower the demetalation rate constants validating a strategy for producing acid-tolerant TAML activators.[9]

We also found that in the pH 4–9 region, certain buffer ions would lead to the slow demetalation of acid-intolerant TAML activators and others would not. A mechanistic study led us to the conclusion that if a buffer ion can bind to the axial site of the TAML catalyst to set up a six-membered ring for delivery of a proton to an amide nitrogen atom, then an enhanced rate of demetalation will occur (Scheme 2).[10] The message for applications chemistry is that if solutions of TAML activators are to be stored for long periods, buffer ions that can form these proton-delivering rings should not be present.

The Mechanisms of TAML Activator Catalysis

TAML activators catalyze the reactions of hydrogen peroxide to oxidize a broad range of substrates. We have spent much time studying the mechanisms and this work has been reviewed recently.[11,12] The overall mechanism is summarized in Scheme 3.
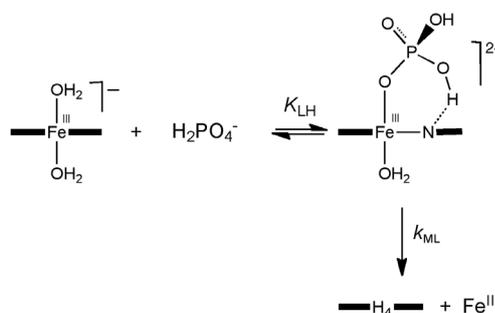
Scheme 2. Mechanism of dihydrogenphosphate-induced demetalation of TAML activators.
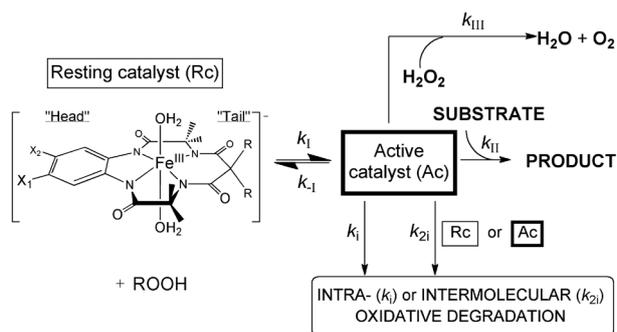
Scheme 3. Overall mechanism of peroxide catalysis by TAML activators.

The resting catalyst is a six coordinate ferric species. It interacts with peroxides (usually hydrogen peroxide is employed) to produce the active catalyst (**Ac**). By performing syntheses in liquid organic solvents at low temperature (-60 °C), we have produced an iron(V)-mono-oxo complex in almost pure form.[13] It is the first such species to be discovered and is low spin with one unpaired electron residing in a π* orbital of the iron-oxo bond. The oxo complex decays at higher temperatures such that we are not able to look for its possible formation in water, the key solvent for most of our studies and the vital medium for environmental applications. Iron(IV)-oxo complexes have also been produced in aqueous solution[14,15] and these are clearly involved as intermediates in catalysis to varying degrees depending upon the conditions. At this stage of our understanding, **Ac** should be considered to represent a number of possible reactive intermediates that form singly or multiply depending on the reactions conditions. Once formed, the **Ac** species then engage in a series of reaction processes that determine the effectiveness of the catalysis. Many reactions come into play in the catalytic cycle.

Firstly, there is a peroxidase-like reaction pathway in which **Ac** interacts with an oxidizable substrate. Depending on the substituents on the TAML macrocycle, the catalysts provide relatively more or relatively less aggressive peroxidase-like oxidizing systems. Secondly, **Ac** may catalyze a catalase-like process in which the peroxide is decomposed.[16] Hydrogen peroxide is more sensitive to this reaction channel than organic peroxides and it is decomposed to oxygen and water. Fortunately, the catalase-like chemistry, which is wasteful of hydrogen peroxide, does not dominate over the peroxidase-like chemistry, at least for the many substrates we have studied in detail to date. But when TAML/peroxide media do not attack

hard-to-oxidize oxidizable substrates, competition from the catalase process might be significantly responsible for the inactivity.

Thirdly, **Ac** engages in catalyst degradation processes. Two classes of degradations, intramolecular (k_i) and intermolecular (k_{2i}), have been identified. The rates of two separate intramolecular processes have been determined and some level of mechanistic insight has been obtained.[17] The bimolecular process(es) is(are) the subject of ongoing studies. The fact that TAML activators degrade in use is a plus for the environmental performance. Nature has developed enzymes to possess limited lifetimes. Industrial catalysts that are to be released to the environment as part of the operation of a technology should be designed similarly. Other reactions occurring, either before or after the production of **Ac**, also exert an influence on the catalysis. Thus, fourthly, a series of dimeric complexes have been detected and one of these, an oxo-bridged Fe(IV)–O–Fe(IV) dimer, has been reported.[14] The Fe(IV)–O–Fe(IV) reversibly hydrolyzes into two Fe(IV)(O) complexes depending upon the pH. There is much that remains to be understood about the significance of these various species in the overall catalytic cycle. Remarkably, in non-coordinating solvents, the Fe(IV)–O–Fe(IV) complex forms rapidly and completely from the ferric TAML activator and dioxygen. This opens the possibility of using TAML activators in oxygen-based oxidation processes.[18] Indeed, the ferric TAML activator does slowly catalyze oxygen-based oxidations of organic substrates in non-coordinating solvents, but heating is required and the challenge has become one of redesigning the TAML activator such that the same high quality of catalytic performance can be enabled for oxygen as has been found for peroxide. Oxygen chemistry is receiving much attention in my group at present.

Fifthly, one of the most interesting properties of the catalytic behaviour is its pH dependence, an effect that is manifested in the production of **Ac**.[16] Under conditions where the formation of **Ac** is rate determining, the peroxidase-like activity at room temperature changes by a factor of more than 10 over a range of 5 to 6 pH units. As the pH is increased from neutral, the rate soon begins to increase. It reaches a maximum value at about one half a pH unit above the pK_a of the TAML activator [an iron(III)bis(aqua) complex] that is being used. After reaching a maximum, the rate then declines as the pH is raised further. The catalase-like activity similarly varies with pH and reaches a maximum at the same pH value as the peroxidase-like activity. The pKa values for first generation TAML activators lie between 9.5 and 10.5.[16] Similar behaviour is found for organic hydroperoxides, but the curve shifts as the peroxide is changed, with the maximum rate moving to higher pH as the pK_a of the peroxide increases.[15] Following much mechanistic analysis of numerous catalysts, we have interpreted the data to mean that the rate of formation of the reactive intermediates depends on the state of deprotonation of both the iron(III)bis(aqua) complexes and the peroxides. The greatest rate occurs when the mono-deprotonated catalyst interacts with the neutral peroxide. For use in real-world processes, the closer the maximum rate is to neutral pH, the more useful the catalyst is likely to be. Therefore, we are designing TAML activators to have lower pK_a values for deprotonation of the aqua ligands to move the maximum catalytic activity closer to neutral pH. In the family of first generation TAML activators, the most reactive oxidizers have geminal fluorine atoms on the tail six membered chelate ring (R, Chart 1).[20] So if these were to be employed in large scale water treatment, fluoride or persistent organofluorine fragments could be added to water with possible implications for adverse health and environmental effects. In second generation TAML activators, we have learned how to achieve the high reactivity without using fluorine.[20]

One of the most important challenges green chemists must face in designing safer products and processes is to learn how to avoid endocrine disruptors (EDs) or endocrine disrupting chemicals (EDCs)—both names are commonly used. There are several definitions and the following is that of the International Program on Chemical Safety (IPCS; March, 1998): *An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.* Endocrine disruptors can alter development at environmentally relevant concentrations, concentrations to which people are being exposed, to result in impaired organisms. An excellent expanded explanation can be found in the Scientific Statement on EDs by the Endocrine Society.[19] Thus, to explore the possibility that TAML activators might have endocrine activity (more precisely, the hope that they would not) we have begun to collaborate with the group of Bruce Blumberg in the Department of Developmental and Cell Biology at UC-Irvine. In the first studies, our colleagues have found that over a wide concentration range (1×10^{-5} M, 1×10^{-6} M, …, 1×10^{-11} M) three different TAML activators do not activate any of three nuclear hormone receptors, *viz.*, human thyroid receptor (TRβ), human estrogen (ERα), and rat androgen receptor (AR), suggesting that the catalysts do not bind to the receptors and reducing concerns that the catalysts might have endocrine-disrupting activity.[20]

The Science of TAML Activator Applications

TAML activators have a wide range of laboratory-demonstrated applications several of which are being deployed commercially. In the following discussion, I will sketch a few examples and the reader is referred to a larger recent review for more details and specifics of other systems.[11] The Carnegie Mellon University spin-off company, GreenOx Catalysts, Inc., is leading the commercial development efforts. Groups led by James Wright at Auckland University and Trevor Stuthridge at the Scion Crown Research Institute in Rotorua are among those involved in developing commercial applications.

Because of my interests in the hazard reduction goals of green chemistry, we have focused in research significantly on the remarkable ability of the catalysts to activate hydrogen peroxide to degrade recalcitrant oxidizable pollutants in water and to kill hardy pathogens. A long list

of compounds has been shown to be readily degradable. To date, a range of toxicity tests have shown no toxicity problems: luminescent bacterial toxicity assays, tests with Daphnia magna, tests with human cancer cells, and endocrine disruption assays. The studies were conducted, where appropriate, on TAML activators, their degradation products, and aqueous TAML-peroxide reaction solutions after the process of decomposing a pollutant had been completed. However, as time goes on and resources permit, we hope to expand our toxicity testing to more elaborate assays to further consolidate our understanding and to keep checking up on our hopes that the systems are free of toxic properties.

We have tested scores of dyes, including members of each of the main classes; all are degraded. Organophosphorus (OP) triesters account for an estimated 34% of worldwide insecticide sales and are linked to human health and environmental concerns associated with cholinergic toxicity. Some OP insecticides are EDCs. Hydrolytic detoxification approaches for OP insecticides are inadequate, because these do not satisfactorily eliminate the toxicity of the hydrolysates. The complete degradation of a series of widely used OP pesticides has been achieved using TAML/peroxide in a controlled, rapid, versatile, and environmentally friendly manner (on the basis of aquatic toxicity assays).[21] The organophosphorus chemical warfare agents, Soman and VX, are also subject to efficient degradation by TAML/peroxide. Experiments with the *live agents* were conducted at the US Navy's Surface Warfare Center in Dahlgren, VA, when TAML activators demonstrated the highest reactivity and stability in an evaluation of over a dozen different catalysts in combination with several different peroxygen compounds.[22]

The synthetic estrogen, 17α-ethinylestradiol (EE$_2$, Chart 2), is an active ingredient in the birth control pill. It is excreted to give an important source of estrogenicity in water. Farm animals excrete natural estrogens. When large numbers are grouped together in concentrated animal feeding operations (CAFOs) increased estrogenic activity in the surrounding surface waters can result.[23] The commercially available prototype TAML activator 1a (a relatively less aggressive oxidizer in the TAML activator family) at 83 nM with hydrogen peroxide at 4 mM (<2 times the mineralization requirement) has been shown to rapidly degrade 17α- and 17β-estradiol (E$_2$), estriol (E$_3$), estrone (E$_1$) and 17α-ethinylestradiol (EE$_2$) (all at 80 μM, Chart 2), with half-lives of approximately five minutes coinciding with the removal of estrogenic activity.[24] Under these conditions, a kilogram of 1a could be used to treat more than 20,000 tonnes of water.

Chlorophenols are significant pollutants. The EPA has listed five chlorophenols as priority pollutants, including 2,4,6-trichlorophenol (2,4,6-TCP) and pentachlorophenol (PCP)—pollutants regulated under the Clean Water Act are classified as *priority* pollutants in the US. Chlorinated phenols are resistant to microbiological degradation and can persist for decades in the environment.[25] TAML activators 1a and 1k (a relatively aggressive oxidizer in the TAML activator family) were used to catalyze the H$_2$O$_2$ treatment of 2,4,6-trichlorophenol and pentachlophenol.[26]
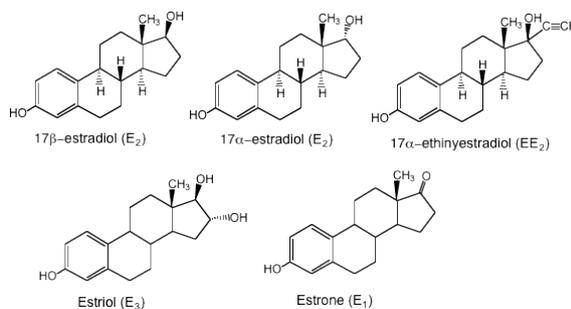

Chart 2. 1a/H$_2$O$_2$ treatment of estrogenic steroid hormones results in their degradation with associated loss of estrogenic activity.

Both compounds were degraded completely in minutes, even by 1a. The conditions for pentachlorophenol (PCP) were: 1a (7 μM), PCP (715 equiv., 5 mM), H$_2$O$_2$ (100,000 equiv., 0.5 M). The peroxide quantity was not optimized, but at the end of the reaction, the remaining peroxide was assayed for both PCP and TCP and it was found that only slightly more than the mineralization requirement was consumed. The mineralization of PCP requires nine equivalents of hydrogen peroxide. The 25 °C reaction was stopped at 9 minutes by adding acid to eject iron from 1a. All the pentachlorphenol was gone. Approximately half the carbon was mineralized. The chloride was mineralized to 87±4%. The remainder of the material was mostly small molecule diacids, chlorinated and nonchlorinated. No dioxins were produced within the limits of detection of the mass spectrometers at the Institut für Ökologische Chemie in Neuherberg, Germany.

Among pathogenic microbes, bacterial spores are the hardiest. Most of us know that certain bacterial spores can be extremely dangerous because of the extensive media coverage of the anthrax attacks in the United States in 2001 and their aftermath. We have studied the ability of TAML activator/peroxide to deactivate spores of *Bacillus atrophaeus*, common non-toxigenic surrogates of *B. anthracis* that also serve as indicators for water-borne protozoa such as *Cryptosporidium parvum*. This protozoan is a bane of drinking water treatment plants. Treatment of *B. atrophaeus* with 1k (50 μM) in the presence of *t*-butylhydroperoxide (TBHP, 0.5 M) and cetyl trimethyl ammonium bromide (CTAB, 0.03%) at pH 10 achieved the military performance goal of a 7 log kill in 15 min.[27] The ability of TAML catalysts to activate TBHP in the presence of CTAB for the decontamination of bacterial spores was studied independently by the Setlow Group at the University of Connecticut employing *Bacillus subtilis* spores where similarly efficient (and lethal) deactivation was observed.[28]

Conclusion

At nanomolar catalyst concentrations, TAML® activators effectively and efficiently mimic the activity of peroxidase enzymes. The catalysts represent a case study in green chemistry because they activate hydrogen peroxide, an oxidant that is used profusely in biochemistry, to decompose persistent pollutants and hardy pathogens in water. Many applications for cleaning water of recalcitrant pollutants and hardy pathogens have been demonstrated

in the laboratory. The mechanisms of action are becoming well understood. Based on the toxicity data collected to date, it is appropriate to call TAML® activators *green oxidation catalysts*. Several applications are in commercial use. The catalysts possess the technical properties to offer a potent new tool for water-based oxidations and advanced water purification processes.

Acknowledgment

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