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Efficient Room-Temperature Oxidation of Hydrocarbons Mediated by Tricopper Cluster Complexes with Different Ligands

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Abstract: Six tricopper cluster complexes of the type $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ supported by a series of multidentate ligands (**L**) have been developed as oxidation catalysts. These complexes are capable of mediating the facile oxygen-atom transfer to hydrocarbon substrates like cyclohexane, benzene, and styrene (C_6H_{12}, C_6H_6 and C_8H_8) upon activation by hydrogen peroxide at room temperature. The processes are catalytic with high turnover frequencies (TOF), efficiently oxidizing the substrates to their corresponding alcohols, aldehydes, and ketones in moderate to high yields. The catalysts are robust with turnover numbers (TON) limited only by the availability of hydrogen peroxide used to drive the catalytic turnover. The TON is independent of the substrate concentration and the TOF depends linearly on the hydrogen peroxide concentration when the oxidation of the substrate mediated by the activated tricopper complex is rapid. At low substrate concentrations, the catalytic system exhibits abortive cycling resulting from competing reduction of the activated catalyst by hydrogen peroxide. This behaviour of the system is consistent with activation of the tricopper complex by hydrogen peroxide to generate a strong oxidizing intermediate capable of a facile direct "oxygen-atom" transfer to the substrate upon formation of a transient complex between the activated catalyst and the substrate. Some substrate specificity has also been noted by varying the ligand design. These properties of the tricopper catalyst are characteristic of many enzyme systems, such as cytochrome P450, which participate in biological oxidations.

Keywords: C–H activation; copper; epoxidation; homogeneous catalysis; hydroxylation

Introduction

Oxidation of unactivated C–H, C–C and C=C bonds in hydrocarbons is an important process in many applications, starting from the synthesis of fine chemicals in synthetic organic chemistry to the industrial conversion of basic building block materials. The vast reserve of naturally occurring hydrocarbons and basic synthetic hydrocarbons can be transformed to useful oxygenated derivatives and feedstocks through hydroxylation, epoxidation, or degradation of intermediates.[1–4] Catalytic processes[5] can offer a quick, economical, and environmentally friendly way over the conventional methods[6] that use high valent metal ions like permanganate or dichromate to accomplish the oxidation.[7–9] Towards this end, a number of efficient copper-based oxidation catalysts has been reported in recent years.[10–14]

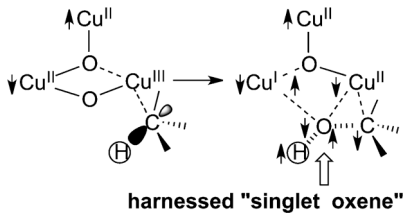
Nature has optimized this process with time through evolution to develop enzymes, which do the job efficiently at ambient temperatures and pressures with high turnover frequency (TOF) and without or minimal generation of undesirable by-products. Information on the active site structure and function of enzymes, especially metalloenzymes, can help in the development of efficient "bioinspired" catalysts with high TOF even at ambient conditions and with chemo- or regiospecificity and stereoselectivity.[15] These designed catalysts could be tuned to the need of a specific substrate or scale of production, and will find applications in the development of environmentally friendly catalytic processes, where there is the specific need to avoid undesirable by-products, use of expensive and potentially toxic metal reagents, oxidants, and solvents, and the reduction of high-energy-consuming multiple steps.[16]

Particulate methane monooxygenase (pMMO) is a membrane-bound enzyme that oxidizes methane to methanol in methanotrophic bacteria with ease even under ambient conditions. We have proposed, based on evidence derived from biochemical/biophysical data,[17–19] that the enzyme contains a $Cu^ICu^ICu^I$ cluster and dioxygen activation of this tricopper cluster produces a mixed-valence $[Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+}$ intermediate, which harnesses a highly reactive "singlet oxene" for facile concerted insertion into C–H and C=C bonds during the hydroxylation of simple alkanes and epoxidation of small alkenes, respectively.

Inspired by this suggestion, two $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ tricopper complexes based on the multidentate ligands (**L**) 3,3′-(1,4-diazepane-1,4-diyl)bis(1-{[2-(dimethylamino)ethyl](methyl)amino}propan-2-ol) (**7-Me**) and 3,3′-(1,4-diazepane-1,4-diyl)bis(1-{[2-(diethylamino)ethyl](ethyl)amino}propan-2-ol) (**7-Et**) have been developed and demonstrated to facilitate facile O-atom insertion into C–H and C–C bonds of small organic substrates such as benzil, 2,3-butanedione and CH_3CN under mild conditions.[20] On the basis of experiments using isotopically labeled oxygen ($^{18}O_2$) together with the examination of ESI-MS data on product distributions, it has been confirmed that the reaction proceeds according to a mechanism that involves concerted insertion of the harnessed "singlet oxene".

Oxene in its ^1D singlet state is a powerful oxidizing agent, but it is not the isolated naked "oxene" that is inserted into C–H and C–C bonds here. Rather the "singlet oxene" is "harnessed" by the activated tricopper complex and it is transferred in the transition state during the reaction between the activated $[Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+}$ intermediate and the substrate molecule. By design, the mixed-valence activated tricopper complex is created in an overall "singlet" state and the chemistry that ensues with the substrate proceeds over a "singlet" potential surface. This conservation of the overall spin-state of the system during the reaction pathway is important as it facilitates the concerted insertion of the oxene (Scheme 1).

Although only a single turnover is usually observed with these complexes in the presence of oxygen due to the formation of the dead-end product $[Cu^{II}Cu^{II}(\mu\text{-}O)Cu^{II}(\mathbf{L})]^{2+}$,[21] multi-turnovers are possible when H_2O_2 is employed as the oxidant. H_2O_2 is also a reductant and we have demonstrated that the "spent" tricopper catalyst is efficiently re-reduced by H_2O_2 to regenerate the $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ catalyst for successive cycles until the H_2O_2 in the solution is exhausted.[22] Hydrogen peroxide is the most useful oxygen source for homogeneous catalysis.[23] It can oxidize organic compounds with an atom efficiency of 47% generating water as the only co-product and is relatively cheap. Thus, our tricopper complexes offer an opportunity to evaluate their potential as oxidation catalysts for hydrocarbons under economically viable and environmentally friendly conditions.



Scheme 1. Facile "singlet oxene" transfer to methane from a dioxygen-activated tricopper cluster in the singlet state to form the transition state complex. ↑ and ↓ denote "up" and "down" directions of the electron spins.

In this paper, we report the design and synthesis of six additional tricopper clusters that are capable of mediating facile conversion of organic substrates like cyclohexane (C_6H_{12}), benzene (C_6H_6), and styrene (C_8H_8) to their corresponding alcohols, ketones, aldehydes and epoxides at room temperature with high turnover frequencies.

Results and Discussion

Ligand Design

The ligand environment of the tricopper complex affects the formation or stability of the activated tricopper complex as well as the approach of the substrate towards the active site of the catalyst. For productive oxo transfer, the substrate must form at least a weak transient complex with the catalyst to reach the appropriate transition state. For this reason, the tricopper complexes assembled by **7-Me** and **7-Et** are designed to allow the β-dicarbonyls of benzil or 2,3-butanedione to interact with the two copper ions at the base of the triad to facilitate "O-atom" insertion across the central C–C bond in these β-diketones. Similarly, the CH_3CN coordinates weakly to these copper ions, which allows the methyl group to approach the "harnessed" oxene provided that there is no steric hindrance from the alkyl substituents attached to the base of the tricopper complex.[20]

In this study, new ligands have been synthesized with different donor atoms (N, O, and S) and steric environments around the active site of the tricopper complexes for oxidation of hydrocarbons (Figure 1). The apical copper in the tricopper complexes with the new ligands **7-Dipy**, **7-Ethppz**, **7-Mehppz**, **7-Bn**, **7-Thio** and **7-Morph** shares the same environment as **7-Me** and **7-Et**, with two neutral amines and two hydroxy groups. However, the steric environment and molecular surface surrounding the two basal coppers are designed to suppress the coordination of CH_3CN (solvent) and to promote van der Waals interactions

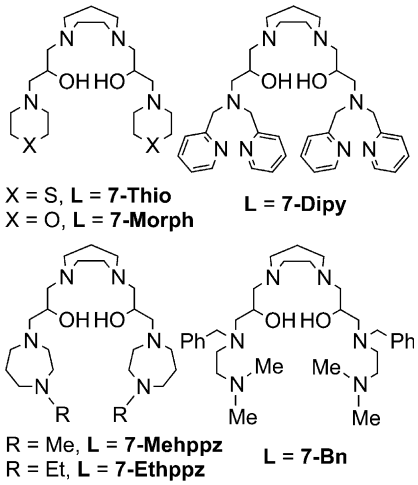


Figure 1. Ligands.

Activation of the $Cu^ICu^ICu^I$ cluster by O_2:

$$[Cu^ICu^ICu^I(\mathbf{L})]^{1+} + O_2 \xrightarrow[\text{fast}]{k_1} [Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+}$$

Activation of the $Cu^ICu^ICu^I$ cluster by H_2O_2:

$$[Cu^ICu^ICu^I(\mathbf{L})]^{1+} + H_2O_2 \xrightarrow[\text{fast}]{k_{1a}} [Cu^ICu^{II}(\mu\text{-}O)_2Cu^{II}(\mathbf{L})]^{1-} + 2H^+$$

$$[Cu^ICu^{II}(\mu\text{-}O)_2Cu^{II}(\mathbf{L})]^{1-} + H_2O_2 \xrightarrow[\text{fast}]{k_{1b}} [Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+} + 2OH^-$$

with hydrocarbon substrates. The ligands **7-Dipy**, **7-Ethppz**, **7-Mehppz** and **7-Bn** provide amine nitrogens along with the bridging hydroxy oxygens for coordination of the basal copper ions. In the case of **7-Thio** and **7-Morph**, there are coordinating sulfur or oxygen atoms from thioethers or ethers, in addition to the amine nitrogens and bridging hydroxy oxygens. In any case, all these various ligand scaffolds can trap three Cu^I ions to form an isosceles triad without the metal sites becoming coordinately saturated except for solvent molecules that might be readily displaced during activation of the complex by dioxygen.

Reaction of the Tricopper Complexes with Dioxygen and H_2O_2

As in our earlier work[20] with $[Cu^ICu^ICu^I(\mathbf{7\text{-}Me})]^{1+}$ and $[Cu^ICu^ICu^I(\mathbf{7\text{-}Et})]^{1+}$, bubbling dioxygen into solutions of $[Cu^ICu^ICu^I(\mathbf{L})](ClO_4)$, (**L** = **7-Thio**, **7-Morph**, **7-Dip**, **7-Ethppz**, **7-Mehppz**, and **7-Bn**) in CH_3CN at room temperature causes an instantaneous color change from pale yellow to deep green in each case. The spectroscopic features of the oxygen adducts are similar for all the $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ complexes (see the Supporting Information). Typically, in the absence of substrate, only the $[Cu^{II}Cu^{II}(\mu\text{-}O)Cu^{II}(\mathbf{L})]^{2+}$ oxygen adduct is formed.[21] The same results were obtained with H_2O_2 as the oxidant. This outcome indicates that H_2O_2 can also activate the $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ complexes to produce the $[Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+}$ intermediate. The two scenarios of activating the tricopper complexes, by dioxygen or H_2O_2, can be depicted by the following chemical equations:

Catalytic Oxidation of Substrates. Product Distributions

To assess the efficacy and chemo- and/or regioselectivity of the various $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ complexes as catalysts for hydrocarbon oxidation by H_2O_2, we have chosen three representative substrates C_6H_{12}, C_6H_6 and C_8H_8. The thiomorpholine, morpholine, picolylamine, ethylhomopiperazine, methylhomopiperazine, and benzyldimethylethylenediamine groups of **7-Thio**, **7-Morph**, **7-Dipy**, **7-Ethppz**, **7-Mehppz**, and **7-Bn**, respectively, are designed to provide a molecular surface to facilitate the binding of different substrates near the base of the triad of copper ions. Since the substrate oxidation occurs *via* an inner-sphere mechanism involving formation of a transient complex between the substrate and the activated tricopper complex, even the formation of a relatively weak complex would enhance the O-atom transfer and accelerate the overall catalytic process.

The results of catalytic oxidation of C_6H_{12}, C_6H_6, and C_8H_8 by the tricopper complexes constructed with the new ligands are summarized in Figure 2. The oxidation of these hydrocarbon substrates mediated by four of the tricopper complexes, $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ (**L** = **7-Thio**, **7- Morph**, **7-Dipy**, and **7-Ethppz**), in the presence of H_2O_2 as the O-atom source, has turned out to be extremely efficient (Scheme 2). To study the catalytic reaction, 200 equiv. of H_2O_2 from 35% aqueous solution, 500 equiv. of substrate, and one equiv. of $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ were mixed together in CH_3CN with a total volume of 3 mL at room temperature and examined for 1 h. According to GC- MS analysis, the products consist of a mixture of cyclohexanol and cyclohexanone in roughly equal amounts in the case of C_6H_{12}. With C_6H_6 as substrate, the products are phenol and hydroquinone with the latter as the major product. In the case of C_8H_8, the major product is

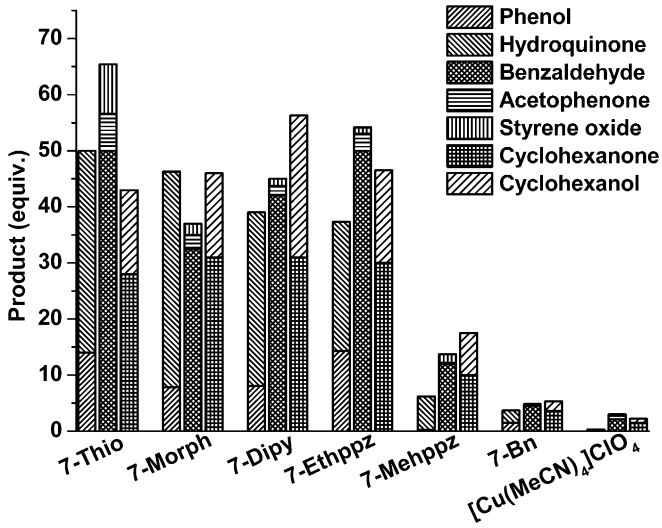
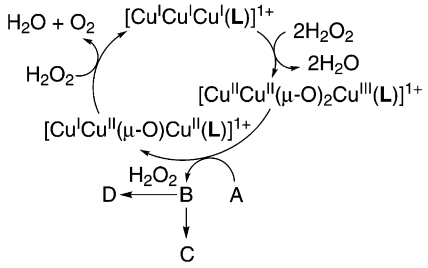


Figure 2. Product analysis after a 1 hr catalytic oxidation of C_6H_6, C_8H_8 and C_6H_{12} by H_2O_2 in CH_3CN mediated by various tricopper complexes at room temperature. The products are given in equivalents produced. Reaction mixture: 500 equiv. of substrate, 200 equiv. of H_2O_2 and one equiv. (24 μmol) of $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$. As a control, with the complex $[Cu(CH_3CN)_4]ClO_4$ as the catalyst, only very low levels of substrate oxidation are obtained, if any.



Scheme 2. The catalytic mechanism proposed for the activation of $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ by H_2O_2 to generate the $[Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+}$ for the oxidation of substrate **A** to the oxo-substrate **B**, followed by rearrangement to give product **C** or further direct oxidation by H_2O_2 to produce **D**.

benzaldehyde, with acetophenone and styrene oxide (small or trace amounts, if any) as minor products (Table 1). For all three substrates, the extent of product formation varies with the starting level of H_2O_2 with the overall turnover numbers limited by the H_2O_2 available. The distribution of products for each of the three substrates is summarized in Table S1, Table S2 and Table S3 in the Supporting Information.

Pathways of the Catalytic Oxidations

We have studied the time course of formation of the products for each tricopper complex. The results for C_6H_6 catalyzed by $[Cu^ICu^ICu^I(\mathbf{7\text{-}Thio})]^{1+}$ are summarized in Figure 3. Based on these data, it is evident that the reaction is completed within 30–45 min when

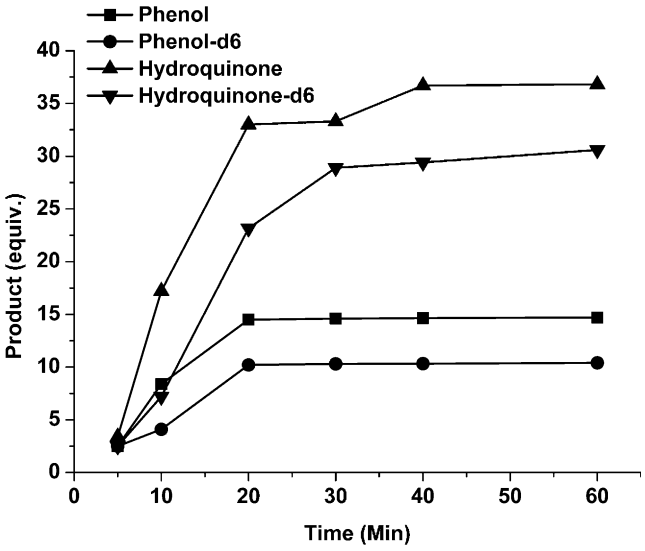
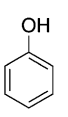
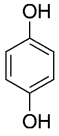
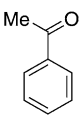
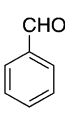
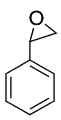
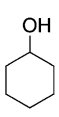
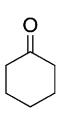
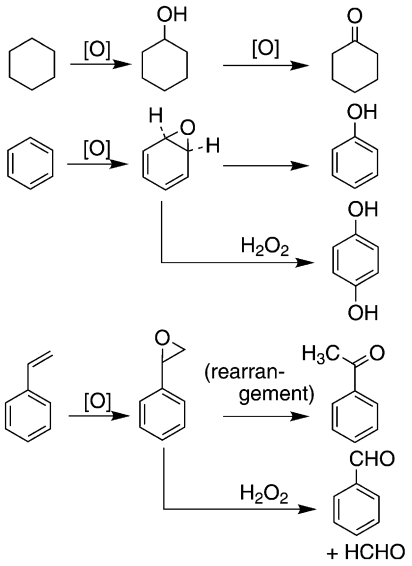


Figure 3. Time course of product formation in the catalytic turnover of the $[Cu^ICu^ICu^I(\mathbf{7\text{-}Thio})]^{1+}$ complex during the oxidation of C_6H_6 and C_6D_6 to the corresponding phenol and hydroquinone by 200 equiv. of H_2O_2 at the start.

Table 1. Product formation (in equivalents) during catalytic oxidation of different substrates (500 equiv.) by tricopper complexes (1 equiv.) in the presence of H_2O_2 (200 equiv.).

Ligands supporting tricopper complex	Products Benzene oxidation		Styrene oxidation			Cyclohexane oxidation	
							
7-Thio	14	36	6.6	50	8.8	28	15
7-Morph	7.8	38.5	2.5	32.5	2	31.5	14.4
7-Dipy	8	31	1.7	41.8	1.3	30.9	25.3
7-Ethppz	14.3	23	3	49.5	1.2	30	16.2
7-Mehppz	0.1	6	0.2	11.4	1.5	10	7.5
7-Bn	1.5	2.3	0.32	4.5	0.1	3.6	1.6



Scheme 3. Oxidation schemes for the various substrates.

the H_2O_2 is exhausted. The products formed in this reaction are phenol and hydroquinone. The product distribution is consistent with initial activation of the π-system by *cis*-addition of an O-atom across one of the C=C bonds followed by rapid 1,2 hydride shift rearrangement to form phenol (Scheme 3). We surmise that this initial activation step involves O-atom transfer from the mixed-valence $[Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+}$ species, the intermediate that harnesses the highly reactive "singlet oxene". In the absence of the tricopper complex, no phenol is detected under otherwise identical conditions. Although resonance stabilization of the aromatic nucleus renders the benzene ring resistant to oxidation, π-electron activation is more favorable than direct σ-activation of one of the C–H bonds. Evidently, hydroquinone is also derived from the π-activated intermediate (Scheme 3), as phenol is not converted directly to hydroquinone by H_2O_2 over a 2-h period at room temperature without the tricopper catalyst. Finally, since activation of the $[Cu^ICu^ICu^I(\mathbf{7\text{-}Thio})]^{1+}$ consumes three molecules of H_2O_2 per turnover of the catalyst whereas the formation of the hydroquinone requires an additional H_2O_2, the total amount of H_2O_2 consumed at any given time should be given by [3 × phenol + 4 × hydroquinone], in agreement with experiment.

The oxidation of C_8H_8 mediated by the $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ catalysts in the presence of H_2O_2 at room temperature begins with epoxidation of the C=C bond. The main product, however, is benzaldehyde, accounting for 75% of the H_2O_2 consumed over the 45 min reaction (see Figure S8 in the Supporting Information). A reaction scenario that is consistent with the products and product distribution is given in Scheme 3. First, styrene oxide is produced by epoxidation of styrene by the activated catalyst. We surmise that benzaldehyde results from the nucleophilic attack of the epoxide by a molecule of H_2O_2. A simple rearrangement of the epoxide would give acetophenone, the other minor product. This scenario predicts an H_2O_2 consumption of [4 × benzaldehyde + 3 × (styrene oxide + acetophenone)], in good agreement with experiment.

The oxidation of C_6H_{12} is straightforward, with cyclohexanol and cyclohexanone as the products. Based on the consumption of H_2O_2, both steps of the oxidation require insertion of an O-atom into the two C–H bonds, with the formation of cyclohexanone coupled to the loss of an H_2O molecule (Scheme 3). This scenario predicts an H_2O_2 consumption of [3 × cyclohexanol + 6 × cyclohexanone)], in excellent accord with experiment. It is interesting that the different tricopper catalysts yield somewhat different distributions of cyclohexanol and cyclohexanone. Presumably the observed product distributions reflect the different affinity of the various tricopper catalysts for the two substrates cyclohexane and cyclohexanol.

Catalytic Mechanism

From our earlier studies on the reactivity of the tricopper complexes $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$, **L = 7-Me** and **7-Et**, as well as a recent in-depth study on the dioxygen chemistry of these complexes,[20,21] we have concluded that the catalytic reaction proceeds by way of a putative $[Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+}$ believed to be the active oxidizing species. This transient species transfers the "singlet oxene" to the substrate in the transition state when it forms a bimolecular complex with the substrate. However, because of the high redox potential of the $[Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+}$, it can also be readily deactivated by reduction with a molecule of H_2O_2 present in the reaction mixture. This is an abortive process that competes with productive transfer of the harnessed "singlet oxene" to a substrate molecule to form product. These competing processes can be described by the following two chemical equations:

"O-atom" transfer from the activated catalyst to substrate:

$$[Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+} + S \xrightarrow[\text{fast}]{k_2 \text{ or } k_{OT}} [Cu^{I}Cu^{II}(\mu\text{-}O)Cu^{II}(\mathbf{L})]^{1+} + SO$$

Abortion of the activated catalyst:

$$[Cu^{II}Cu^{II}(\mu\text{-}O)_2Cu^{III}(\mathbf{L})]^{1+} + H_2O_2 \xrightarrow{k_{abortive}} [Cu^{I}Cu^{II}(\mu\text{-}O)Cu^{II}(\mathbf{L})]^{1+} + H_2O + O_2$$

Thus, unless $k_2\,[\text{substrate}] = k_{OT}\,[\text{substrate}] \gg k_{abortive}\,[H_2O_2]$, abortive cycling will compete effectively with

productive cycling. These two parallel reaction pathways consume H_2O_2 differently. In the oxidation of cyclohexane, 3 equivalents of H_2O_2 will be consumed during a productive cycle, two molecules of H_2O_2 to activate the tricopper complex and another H_2O_2 molecule to regenerate the "spent" catalyst:

Regeneration of the "spent" catalyst:

$$[Cu^{I}Cu^{II}(\mu\text{-}O)Cu^{II}(\mathbf{L})]^{1+} + H_2O_2 \xrightarrow[\text{rate-limiting}]{k_3} [Cu^{I}Cu^{I}Cu^{I}(\mathbf{L})]^{1+} + H_2O + O_2$$

As expected, the regeneration of the "spent" catalyst is the rate-limiting step, and the turnover frequencies of the catalysts are found to depend linearly on the H_2O_2 concentration with a second-order rate constant of *ca.* $2\times10^{-1}\,M^{-1}s^{-1}$ regardless of the catalyst or the substrate. An abortive cycle will consume an additional H_2O_2 molecule. In effect the tricopper complex is acting merely as a catalyst to disproportionate the four molecules of H_2O_2 to produce two O_2 and four H_2O. In practice, the two pathways are tightly linked, with substrate oxidation predominating at very high substrate concentrations relative to the H_2O_2 concentration present in the reaction mixture, but abortive cycling prevailing at high H_2O_2 and low substrate concentrations.

To test these ideas, we have studied the TON as a function of substrate concentration in the oxidation of C_6H_{12}, C_6H_6, as well as C_8H_8 by the $[Cu^{I}Cu^{I}Cu^{I}(\mathbf{7\text{-}Thio})]^{1+}$ complex. The results obtained are shown in Figure 4. In these experiments, the substrate concentration has been varied from 20 equiv. to 500 equiv. with the turnover driven by an initial H_2O_2 concentration of 200 equiv. It is evident that the TON is essentially independent of the substrate concentration when the starting substrate concentration is greater than 200 equiv. Presumably there is no abortive cycling of the catalyst at these substrate concentrations. However, the TON begins to fall off at lower substrate concentrations, and at $[substrate]_0 \approx 100$ equiv. the TON becomes *ca.* 50% of the maximum TON observed. A precipitous drop-off in the TON will be manifested when $k_{OT}\,[substrate] \approx k_{abortive}\,[H_2O_2]$.

Another scenario where abortive cycling might become evident is when the rate constant of "O-atom" transfer, namely, k_{OT}, is reduced by isotope substitution, as when the C–H bond is replaced by C–D in the oxidation of cyclohexane or benzene. We have examined the impact of the H/D isotope effect on the TON for both of these substrates when they are oxidized by the $[Cu^{I}Cu^{I}Cu^{I}(\mathbf{7\text{-}Thio})]^{1+}$ complex. The time courses of product formation in the catalytic turnover of the $[Cu^{I}Cu^{I}Cu^{I}(\mathbf{7\text{-}Thio})]^{1+}$ complex during

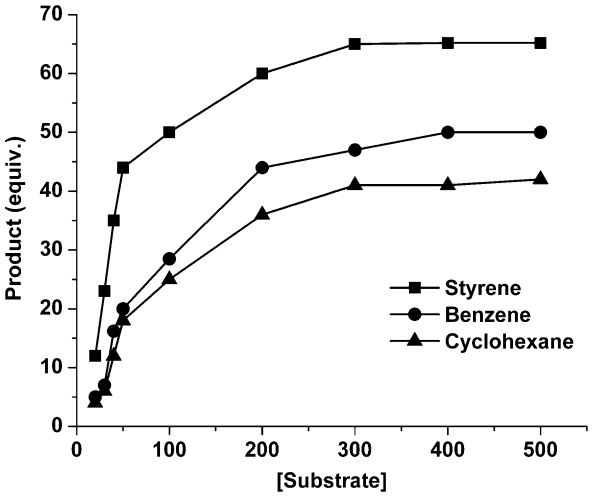


Figure 4. Total product formation (equiv.) as a function of the starting substrate concentration determined after one hour of incubation of the three substrates, C_6H_6, C_6H_{12}, and C_8H_8, in the presence of 1 equiv. of the $[Cu^{I}Cu^{I}Cu^{I}(\mathbf{7\text{-}Thio})]^{1+}$ complex and 200 equiv. of H_2O_2 at room temperature. The turnovers are H_2O_2-limited in these experiments, except possibly at the lowest substrate concentrations (below 50 equiv.).

the oxidation of C_6H_6 and C_6D_6 to their corresponding phenol and hydroquinone by 200 equiv. of H_2O_2 at the start are shown in Figure 3. Only a small H/D kinetic isotope effect (KIE) (k_H/k_D of ~1.5) is observed for the formation of the two products. At the concentration of C_6H_6 and C_6D_6 (500 equiv.) employed in these experiments, it is evident that the overall process is rate-limited by regeneration of the catalyst by H_2O_2 rather than by the kinetic steps leading to the formation of the observed products. Thus, the observed KIE must arise from $k_{OT}^{C-H}/k_{OT}^{C-D}$ upon deuterium substitution of the C–H bond. An isotope effect on TON is expected if $k_{OT}^{C-D}\,[C_6D_6]_0$ becomes comparable to $k_{abortive}\,[H_2O_2]_0$ under the conditions of our experiment, namely, $[C_6D_6]_0 = 500$ equiv. and $[H_2O_2]_0 = 200$ equiv. In case of C_6H_6, the onset of abortive cycling does not become apparent until $[C_6H_6]_0 \approx 100$ equiv. Thus, the KIE on the substrate oxidation, namely $k_{OT}^{C-H}/k_{OT}^{C-D}$, is not large, no more than 5, which would rule out any mechanism involving hydrogen abstraction from the hydrocarbon. This conclusion holds for cyclohexane as well as benzene.

The behavior of the catalytic system to varying levels of H_2O_2 and C_6H_6, and to C_6D_6 is consistent with a process in which the tricopper complex is activated by H_2O_2 to generate a transient intermediate capable of facile "O-atom" transfer to substrate rather than a mechanism involving the participation of freely diffusing radical species produced by the reaction between the tricopper complex and H_2O_2. In support of this conclusion, no characteristic EPR signals are detected in the presence of 5,5-dimethylpyr-

roline *N*-oxide (DMPO), a nitrone spin trap that becomes converted to the persistent nitroxide radical with its distinctive EPR signal at room temperature in the presence of $^{\bullet}OH$ or $^{\bullet}OOH$.[24] If $^{\bullet}OOH$ radicals are involved, the primary product would be cyclohexyl hydroperoxide if the substrate is cyclohexane,[25] but no evidence was found for any involvement of this hydroperoxide during the catalytic cycle of any of our tricopper complexes.

Conclusions

In summary, we have demonstrated here that the tricopper cluster system is an active and robust oxidation catalyst capable of mediating the efficient oxidation of both aliphatics and aromatics at room temperature. Our $Cu^ICu^ICu^I$ complexes are the first catalysts that can be activated by H_2O_2 to harness a "singlet oxene" for direct transfer to a hydrocarbon substrate upon complex formation.

Experimental Section

General Remarks

All chemicals were purchased from commercial sources as reagent grade quality and used as received unless stated otherwise. Acetonitrile (CH_3CN) was distilled under nitrogen from CaH_2 or P_2O_5; and stored in dried, N_2-filled flasks over 4 Å molecular sieves. Nitrogen was purged through these solvents before use. Oxygen gas (99.8%, Fong Ming), used for oxygenation, was dried by passing it through two short columns in succession of P_2O_5 and Drierite. Manipulations, reactions, and transfers were conducted under nitrogen according to Schlenk techniques or in a glove box (nitrogen gas).

Physical Measurements

NMR spectra were recorded on a Bruker 400 spectrometer. Chemical shifts (in ppm) were referenced either to an internal standard of Me_4Si, or to the residual solvent peak. UV-visible spectra were recorded on an HP 8453 diode array spectrometer. Electrospray ionization (ESI) mass spectra were collected on a Finnigan LCQ mass spectrometer (Thermo Finnigan, San Jose, CA, USA). FAB mass spectra were collected on a JMS 700 double focusing mass spectrometer (JEOL, Tokyo, Japan) with a resolution of 8000 (3000) (5% valley definition). For FAB mass spectra, the source accelerating voltage was operated at 10 kV with a Xe gun, using 3-nitrobenzyl alcohol (NBA) as the matrix. EPR spectra were recorded on a Bruker E-500 spectrometer equipped with a Bruker TE102 cavity. In the EPR experiments, the sample temperature was maintained at 77 K by using a liquid nitrogen finger Dewar. GC analyses were carried out on an HP 6890 plus analyzer equipped with an HP5 column (60 m × 0.25 mm × 0.25 micron). Splitless injection at an injector temperature of 280 °C was used. The column temperature was maintained at 120 °C for the 10 min duration of the analysis. The flow rate used was 1.9 mL min^{-1}. GC-MS analysis were carried out on an HP 6890 Plus (GC) with HP 5973 (MS) analyzer equipped with a DB-1MS column (60 m × 0.25 mm × 0.25 micron). Split injection was conducted with split ratio of 35:1 and split flow 28 mL min^{-1} at an injector temperature of 300 °C. The column temperature was maintained at 120 °C for the 15 min duration of the analysis. The flow rate used was 1.4 mL min^{-1}.

Ligand Synthesis

The ligands (**L**) 3,3′-[1,4-diazepane-1,4-diyl]bis(1-thiomorpholinopropan-2-ol) (**7-Thio**), 3,3′-[1,4-diazepane-1,4-diyl]-bis(1-morpholinopropan-2-ol) (**7-Morph**), 3,3′-(1,4-diazepane-1,4-diyl)bis{1-[bis(pyridin-2-yl)methyl]amino}propan-2-ol) (**7-Dipy**), 3,3′-(1,4-diazepane-1,4-diyl)bis[1-(4-ethyl-1,4-diazepan-1,4-diyl)propan-2-ol] (**7-Ethppz**), 3,3′-(1,4-diazepane-1,4-diyl)bis[1-(4-methyl-1,4-diazepan-1-yl)propan-2-ol] (**7-Mehppz**), and 3,3′-(1,4-diazepane-1,4-diyl)bis{1-[2-benzyl-(2-dimethylethylene)amino]propan-2-ol} (**7-Bn**) were synthesized according to established procedures. Details on the synthesis and characterization of the ligands are given in the Supporting Information (Figure S1, Figure S2, and Figure S3).

Formation of the Tricopper Cluster

The ligands (**L**) form $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ complexes in CH_3CN, as previously described for **7-Et** and **7-Me**.[20,21] The nuclearity of the $[Cu^ICu^ICu^I(\mathbf{7\text{-}Dipy})]^{1+}$ complex was established by electrospray ionization (ESI) mass analysis of the $[Cu^ICu^ICu^I(\mathbf{7\text{-}Dipy})(CO)_2(CH_3CN)_2](X)$ complex formed by purging CO into a solution of the $[Cu^ICu^ICu^I(\mathbf{7\text{-}Dipy})](X)$, X = BF_4 or ClO_4 in CH_3CN (Supporting Information, Figure S4 A and B) and by ^1H NMR.

Catalytic Oxidation of Substrates

We have carried out the catalytic oxidation of the substrates benzene, styrene and cyclohexane with 50, 100, and 200 equiv. of H_2O_2 as 35% aqueous solution, 500 equiv. of substrate, and one equiv of $[Cu^ICu^ICu^I(\mathbf{L})]^{1+}$ (**L** = **7-Thio**, **7-Morph**, **7-Dipy**, **7-Ethppz**, **7-Mehppz** and **7-Bn**) in CH_3CN (total volume 3 mL) at room temperature for 1 h. According to GC-MS analysis, the products consisted of a mixture of cyclohexanol and cyclohexanone when cyclohexane was used as the substrate. For benzene as substrate, we obtained phenol and hydroquinone as products. For styrene, the major product was benzaldehyde, with acetophenone and styrene oxide as minor products. GC chromatograms are shown for three starting H_2O_2 concentrations in the Supporting Information (Figure S5 A, B, and C). With benzene as the substrate, peaks were observed at retention time (t_R) 3.23 for the substrate (benzene), t_R 4.76 min for phenol, and t_R 4.4 min for hydroquinone. For cyclohexane, GC peaks were observed at t_R 3.4, 4.1, and 4.2 min for cyclohexane, cyclohexanol, and cyclohexanone, respectively. In the case of styrene, the GC peaks were at t_R 4.2 min for the styrene substrate, t_R 4.9 min for benzaldehyde, t_R 6.0 min for styrene oxide, and t_R 6.39 min for acetophenone. Nitrobenzene (t_R 6.8 min) was used as an internal standard in all the GC experiments. The extents of product formation with different

starting H_2O_2 concentrations are summarized in Table S1, Table S2 and Table S3 (Supporting Information) for the three substrates examined in this study.

Product Yields as a Function of Substrate Concentrations

To study the turnover of the tricopper catalysts, we have purposely carried out the catalytic oxidation of the substrates at a sufficiently high substrate concentration (500 equiv.) so that the O-atom transfer process is not limiting the rate of formation of the products. Accordingly, the product yields are fairly low, typically ~10% of the starting substrates. However, the product yields could be increased to almost 50% without substantially compromising the rate of product formation simply by reducing the starting substrate concentration to 100 equiv. At lower substrate concentrations, the rate of O-atom transfer becomes comparable to the rate of abortion of the activated tricopper catalyst.

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