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C-H Activation by RuCo₃O₄ Oxo Cubanes: Effects of Oxyl Radical Character and Metal-Metal Cooperativity

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ABSTRACT: High-valent multimetallic-oxo/oxyl species have been implicated as intermediates in oxidative catalysis involving proton-coupled electron transfer (PCET) reactions, but the reactive nature of these oxo species has hindered the development of an in-depth understanding of their mechanisms and multimetallic character. The mechanism of C–H oxidation by previously reported RuCo₃O₄ cubane complexes bearing a terminal Ru^V-oxo ligand, with significant oxyl radical character, was investigated. The rate-determining step involves H atom abstraction (HAA) from an organic substrate to generate a Ru– OH species and a carbon-centered radical. Radical intermediates are subsequently trapped by another equivalent of the terminal oxo



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to afford isolable radical-trapped cubane complexes. Density functional theory (DFT) reveals a barrierless radical combination step that is more favorable than an oxygen-rebound mechanism by 12.3 kcal mol⁻¹. This HAA reactivity to generate organic products is influenced by steric congestion and the C–H bond dissociation energy of the substrate. Tuning the electronic properties of the cubane (i.e., spin density localized on terminal oxo, basicity, and redox potential) by varying the donor ability of ligands at the Co sites modulates C–H activations by the Ru^V–oxo fragment and enables construction of structure–activity relationships. These results reveal a mechanistic pathway for C–H activation by high-valent metal–oxo species with oxyl radical character and provide insights into cooperative effects of multimetallic centers in tuning PCET reactivity.

INTRODUCTION

Biological and synthetic oxidation processes often involve highvalent multimetallic-oxo species as reactive intermediates. Water oxidation catalyzed by the oxygen-evolving complex (OEC) in photosystem II, for example, employs a Mn₄CaO₄ cubane cluster (Scheme 1a), which converts water to O_2 through a stepwise oxidation mechanism.⁸ Current hypotheses invoke metal ion cooperativity in the requisite accumulation of redox equivalents in the OEC via a series of proton-coupled electron transfer (PCET) steps; the resultant high-valent metal-oxo/oxyl species directly catalyzes the formation of the relevant O-O bond.9-11 Oxo-diiron cores in nonheme hydroxylases highlight another key enzymatic example in which multimetallic-oxo complexes engage in oxidative reactions, specifically in the context of C-H hydroxylation (Scheme 1a).¹² The postulated mechanism involves an initial H atom abstraction (HAA) from a C-H bond by the $bis(\mu$ oxo)diiron(IV) core; a subsequent rapid radical rebound step occurs between the resultant $(\mu$ -oxo) $(\mu$ -hydroxo)diiron core and the substrate-derived radical to produce an alcohol (Scheme 1b).¹³ The importance of these biological oxidation processes has inspired significant interest in fully characterizing the mechanisms and probing the essence of metal-metal cooperativity.

While significant efforts have elucidated the mechanisms of metal-oxo mediated PCET reactions,¹⁴⁻¹⁶ a limited subset of these studies employ high-valent multimetallic-oxo complexes.¹⁷⁻²⁰ Indeed, reactive multimetallic-oxo species bearing well-characterized terminal metal-oxo/oxyl motifs are exceedingly rare despite their importance as key intermediates in oxidative catalysis.^{5,9,21-23} To date, few spectroscopically and computationally characterized high-valent multimetallic-oxo/oxyl species exist.²⁴ Meyer and co-workers have provided evidence for a dioxo-Ru^V intermediate, $[(bpy)_2(O)Ru^VO-Ru^V(O)(bpy)_2]^{4+}$ (bpy = 2,2'-bipyridine), derived from PCET reactions of the binuclear oxo "blue dimer" $[(bpy)_2(H_2O)-Ru^{III}ORu^{III}(H_2O)(bpy)_2]^{4+}$ (Scheme 1c).²⁵⁻²⁷ This dioxo-Ru^V intermediate appears to possess considerable spin density



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Scheme 1

a) Enzymatic multimetallic-oxo active sites



at the terminal oxo ligands, and a radical coupling between the two terminal Ru^V -oxo moieties has been proposed to mediate O-O bond formation.^{5,28} Indeed, transient intermediate Ru^V -oxo species are commonly invoked in water and organic oxidation catalysis.²⁹⁻³¹ Although metal-oxyl species are known to exhibit unique reactivity,²⁴ it is unclear how the spin density localized on oxo ligands contributes to the PCET reactivity of multimetallic-oxo clusters.^{32,33} Studies of high-valent multimetallic-oxo clusters bearing terminal oxo/oxyl moieties present an opportunity to probe the influence of metal-metal cooperativity and provide insight into the role of oxyl radical character in PCET reactions.

This laboratory recently reported a series of mixed-metal cubane clusters $\text{Ru}^{V}(O)\text{Co}^{III}_{3}(\mu_{3}-O)_{4}(OAc)_{4}(4-\text{R-py})_{3}$ (1-O-4-O, R = OMe, H, CF₃, and Me, respectively; Scheme 1c) featuring a rare terminal Ru^{V} -oxo and preliminary studies of their oxidative reactivity toward organic substrates.³⁴ Exper-

imental and computational analyses revealed radical character at the terminal oxo ligand, with significant electronic communication between the Co and Ru ions within the cluster. These interesting features and the reactive nature of this class of complexes prompted further mechanistic investigations into multimetallic effects and oxyl radical character in PCET reactions.

Herein, the mechanism of C–H bond oxidation reactions involving a terminal Ru–oxo/oxyl fragment of oxo cubane complexes is described. Mechanistic analyses, as well as DFT computational studies, implicate a rate-determining HAA step with a subsequent radical combination between the resulting carbon-centered radical and the terminal Ru^V–oxo of a second cubane complex. Steric congestion and the C–H bond energy of the substrate strongly influence the HAA reactivity of the oxo cubanes to form organic products. Additionally, the electronic properties of the multimetallic cubane core are shown to influence the reactivity toward C–H bond cleavage via metal–metal cooperativity.

RESULTS AND DISCUSSION

Stoichiometric Reactions with 9,10-Dihydroanthracene. This laboratory recently reported 2-O (Scheme 1c) as a versatile oxidant toward a range of organic substrates.³⁴ The current study focuses on the C-H activation chemistry of 1-O, a related derivative ligated by *p*-methoxypyridine. Significantly, the distinct ¹H NMR signature of the methoxy groups and the higher degree of crystallinity relative to other cubane derivatives make 1-O well suited for reactivity and mechanistic studies. We first examined stoichiometric reactions between 1-O and 9,10-dihydroanthracene (DHA) in chloroform-d (Table S4). With 1 equiv of DHA, full conversion of 1-O was observed after 22 h at 23 °C as determined by ¹H NMR spectroscopy; in contrast, only 51% of DHA was consumed to primarily produce a new paramagnetic species (54% yield with respect to 1-O). Interestingly, only a trace amount of anthracene was observed as an organic product. When an excess of cubane (2 equiv) was exposed to DHA (1 equiv), both reactants were fully consumed to afford the same paramagnetic species in 50% yield with respect to 1-O (Scheme 2).

Single crystals of the paramagnetic species were isolated and characterized as the radical-trapped cubane complex Ru- $(OC_{14}H_{11})Co_3(\mu_3-O)_4(OAc)_4(4-OMe-py)_3$, **1-OHAn**. This species exhibits ¹H NMR spectroscopic features consistent



Scheme 2. Synthesis of 1-OHAn^a

"Inset: solid-state molecular structure of 1-OHAn as determined by XRD. Solvents and hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at 50% probability.

with a C_s symmetric structure (Figure S43), in good agreement with the solid-state molecular structure as determined by single-crystal X-ray diffraction (XRD) (Scheme 2, inset). The Ru1–O1 distance of 1.928(2) Å is consistent with corresponding bond lengths for reported Ru^{IV}–OR alkoxide complexes.³⁴ An Evans method measurement of the magnetic moment of **1-OHAn** (3.2 μ_B) supports an S = 1 configuration for this formally Ru^{IV}Co^{III}₃O₄ cubane. Consistently, geometric optimization of various spin states of **1-OHAn** by DFT indicated that the triplet is the lowest energy spin state (see the Supporting Information).

The observed stoichiometry in Scheme 2 implies that a likely byproduct is the formally Ru^{IV}-OH species (1-OH), which accounts for the consumption of a second equivalent of 1-O as well as the loss of a hydrogen atom from DHA. Although this species could not be isolated, ¹H NMR spectroscopic monitoring of the reaction between 1-O and DHA indicated the production of 1-OH. Thus, in addition to proton resonances corresponding to 1-OHAn, a new set of peaks grew over 1 h and slowly decreased over the course of 4 h (Figure S44). The number of peaks (8) and their relative integration are consistent with the expected inequivalent protons of acetate and *p*-methoxypyridine ligands of a C_s symmetric cubane species which is tentatively assigned as 1-**OH** (a chemical shift for the Ru–OH could not be identified). Furthermore, analysis of an aliquot of the reaction mixture by HR-ESI-MS in acetonitrile after 4 h revealed the presence of the expected Ru^{IV}-OH species (m/z = 923.9091, [Ru(OH)- $Co_3(\mu_3-O)_4(OAc)_4(4-OMe-py)_3] \cdot H^+$, 1-OHAn, and formally Ru^{IV} species such as $[Ru(L)Co_3(\mu_3-O)_4(OAc)_4(4-OMe-py)_3]^+$ (L = MeCN, 4-OMe-py) (Table S22, Figures S45 and S46). The relatively weak signal of 1-OH disappeared within a few minutes after sample injection, suggesting that this compound is not persistent under the ionization conditions. Note that an O-H stretching frequency could not be identified by solutionstate IR measurements, indicating the instability of 1-OH under these conditions.

Mechanism of C–H Bond Activation by 1-O. Kinetic experiments using ¹H NMR spectroscopy were performed to elucidate the operative mechanism of this C–H activation process. Monitoring the reaction of **1-O** and DHA at 25 °C revealed that the initial decay rate of DHA (k_{init}) depends linearly on the concentrations of both reactants (i.e., first order with respect to each substrate; Figures 1a,b and Figures S16 and S17), and the overall second-order reaction proceeds with an observed rate constant of $(1.1 \pm 0.1) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$. An Eyring analysis elucidated the temperature dependency on the reaction and provided activation parameters of $\Delta H^{\ddagger} = 8 \pm 1$ kcal mol⁻¹ and $\Delta S^{\ddagger} = -41 \pm 4$ eu, which correspond to a $\Delta G^{\ddagger}(298 \text{ K})$ of 20 ± 3 kcal mol⁻¹ (Figure 1c). The negative entropy of activation is consistent with a bimolecular mechanism.

Kinetic isotope effects (KIEs) were determined to further probe the nature of the C–H activation.³⁵ The reaction of **1-O** with DHA- d_4 provided a large primary KIE value of 20 ± 2, which implicates a rate-limiting C–H bond cleavage in the operative mechanism.¹⁵ Indeed, KIE values greater than ca. 7 typically reflect a contribution from tunneling effects,¹⁴ which was corroborated by DFT calculations for this reaction. By treating only the electrons quantum mechanically (i.e., nuclei are treated classically, without tunneling effects), a significantly lower KIE value of 6.8 is predicted.



Figure 1. (a) Plot of k_{init} vs $[DHA]_0$ ($[1-O]_0 = 9.0 \text{ mM}$, $k_{obs} = 7.8 \times 10^{-5} \text{ s}^{-1}$). (b) Plot of k_{init} vs $[1-O]_0$ ($[DHA]_0 = 9.0 \text{ mM}$). (c) Eyring analysis of the reaction of 1-O and DHA. (d) Plot of log k_{obs} vs BDE_{C-H} of organic substrates with linear regression ($R^2 = 0.9732$). Observed rate constants (k_{obs}) were obtained from the slope of the linear correlation between k_{init} and [substrate]₀.

To gain further information about the HAA mechanism, 1-O was treated with xanthene, fluorene, and 1,4-cyclohexadiene (CHD). Notably, the radical-trapped cubane species and 1-OH were observed in the reactions with each of these H atom donors (by ¹H NMR spectroscopy and HR-ESI-MS, Tables S4–S7 and Figures S1–S8). Kinetic analyses revealed a linear correlation between the reaction rates and the bond dissociation energy (BDE) values of the substrates¹⁵ (Figure 1d). The slope of -0.35 is within the reported range for H atom abstraction reactions mediated by several other mononuclear Ru-oxo complexes, -0.21 to -0.61.36-39 The absolute value of the slope (0.35) is reasonably close to the theoretical slope of 0.5 predicted by the Bell-Evans-Polanyi correlation between activation energy and enthalpic driving force, which indicates an H atom transfer mechanism.^{40,4} However, no apparent correlation between the reaction rates and the pK_a and ionization energies of the C-H substrates exists (Figures S47 and S48). Note that the reactivity of 1-O exhibits an inverse relationship with the pK_a values of fluorene, DHA, and CHD; namely, 1-O reacts faster with substrates having higher pK_a values. There is, however, a large rate difference of a half order of magnitude for DHA and xanthene despite the similarity in their pK_a values (30 and 30.1, respectively, in DMSO).⁴² These observations support a concerted HAA mechanism over a stepwise transfer of the proton and electron.⁴²

Given that 1-OH is not isolable, we sought to determine its bond dissociation free energy (BDFE) by evaluating reactions of 1-O with substrates of various C–H bond strengths and by carrying out DFT calculations. Compound 1-O reacted rapidly in stoichiometric reactions with substrates exhibiting BDFE_{C-H} ~ 70 kcal mol⁻¹ (e.g., xanthene and CHD)⁴² under ambient conditions. However, with a 1000-fold excess of THF (DFTpredicted BDFE_{C-H} ~ 78.5 kcal mol⁻¹) as a substrate, 1-O slowly activated the α -C–H position of THF to generate the radical-trapped cubane species Ru(OC₄H₇O)Co₃(μ_3 -O)₄(OAc)₄(4-OMe-py)₃ (1-OTHF) (by ¹H NMR spectroscopy and HR-ESI-MS; Table S8, Figures S9 and S10). This reaction sets the BDFE_{C-H} of THF as an approximate upper bound for the $BDFE_{O-H}$ of **1-OH**. Additionally, DFT calculations predict an H atom abstraction barrier of 27.1 kcal mol⁻¹ for the reaction between **1-O** and THF, which is at the upper limit under the conditions considered here. Consistently, DFT calculations predict a $BDFE_{O-H}$ value for **1-OH** of 65.5 kcal mol⁻¹ in acetonitrile at 23 °C.

Using the calculated BDFE_{0-H} and the Ru^V/Ru^{IV} cathodic peak potential ($E_{p,c}$) of **1-O** (-0.95 V vs Fc/Fc⁺ in acetonitrile)³⁴ as an approximation of $E_{1/2}$, a thermodynamic square scheme was constructed (Figure S40) to estimate a p K_a value of 25.4 for **1-OH** (see the Supporting Information for details). The BDFE_{0-H} of **1-OH** is comparatively lower than those of other well-studied mononuclear Ru–oxo/hydroxo complexes (Table 1). When compared to E^0 values of the

Table 1. Thermodynamic Parameters for Selected Ru–Oxo Complexes

Ru ⁿ⁺ -oxo complex	$E^0 (vs Fc/Fc^+)^a$	${pK_a \over (MeCN)^b}$	$BDFE_{O-H}$ (kcal mol ⁻¹) ^c	ref
$ \begin{array}{l} \text{Ru}^{V}(O)\text{Co}^{II}{}_{3}(\mu_{3}\text{-}\\ O)_{4}(OAc)_{4}(4\text{-}OMe\text{-}py)_{3}\\ (1\text{-}O) \end{array} $	-0.95	25.4	65.5	this work
$[RuIV(O)(TPA)(H_2O)]^{2+d}$	1.67	9.1	104	44
$ \begin{matrix} [\mathrm{Ru}^{\mathrm{IV}}(\mathrm{O})(\mathrm{N4Py}) \\ (\mathrm{H_2O}) \end{matrix} \rbrack^{2+e} \end{matrix} $	1.74	9.4	91.1	44
$trans-[Ru^{VI}(O)_2(14-TMC)]^{2+f}$	1.19	2.8	83.9	38
$trans$ - $[Ru^{VI}(O)_2(Me_2BAdC]^{2+g}]$	1.57	1.2	90.4	38

 ${}^{a}E^{0}$ for Ruⁿ⁺-oxo/Ru⁽ⁿ⁻¹⁾⁺-oxo adjusted vs Fc/Fc⁺ as necessary.⁴⁵ ${}^{b}pK_{a}$ in H₂O for Ru⁽ⁿ⁻¹⁾⁺-OH/Ru⁽ⁿ⁻¹⁾⁺-oxo converted to that in MeCN by using the correlation between pK_{a} values in H₂O and MeCN as necessary.⁴⁶ c BDFE_{O-H} in MeCN calculated by using Bordwell's equation with adjusted thermodynamic parameters and C_G value of 52.6 kcal mol⁻¹ as necessary.⁴⁷ d TPA = tris(2-pyridylmethyl)amine. e N4Py = N,N-(dipyridin-2-ylmethyl)bis(pyri-din-2-ylmethyl)amine. f 14-TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane. g Me₂BAdC = 1,12-dimethyl-3,4:9,10-dibenzo-1,12-diaza-5,8dioxacyclopentadecane.

Scheme 3. Possible Mechanisms for Formation of 1-OHAn

aforementioned reported complexes, **1-O** is far less oxidizing, likely a consequence of the lower overall charge of **1-O** and the strong π -electron donation from the Co₃O₄ fragment to the Ru^V-oxo moiety.³⁴ Nevertheless, the weak oxidizing ability of **1-O** is compensated by the high pK_a value of **1-OH** to afford a moderate BDFE_{O-H}. In fact, the pK_a of **1-OH** is one of the highest reported values among metal-oxo/hydroxo complexes.⁴³

Mechanism of O-C Bond Formation. The kinetic analyses indicate that the first and rate-determining step of the reaction between 1-O and DHA occurs via a concerted HAA mechanism. However, there are two plausible pathways after this rate-limiting step to account for formation of 1-OHAn (Scheme 3). After the HAA step (step 1), the corresponding 9-hydroanthracyl radical may be readily trapped by a second molecule of 1-O to form 1-OHAn (step 2A). Alternatively, the 9-hydroanthracyl radical may undergo rebound with 1-OH to form an anthracenol-bound Ru(III) intermediate that then acts as a hydrogen-atom donor to an unreacted equivalent of 1-O to give 1-OHAn and 1-OH (step 2B). Both mechanisms are possible as they provide the same overall net reaction described in Scheme 2. Note that the conventional oxygen rebound mechanism¹² (Scheme 1b) is discounted since 9-anthracenol and the formally Ru(III) cubane species were not observed.

DFT was employed to probe the degree of oxyl character in **1-O** and **1-OH** and to provide insight into which species couples more readily with 9-hydroanthracyl radical. Optimization of the doublet state of **1-O** yielded an energy minimum in which the spin density of the unpaired electron (ρ) is mostly located on Ru ($\rho = 0.56\alpha$) and the terminal oxo ligand ($\rho =$ 0.36α) (Figure 2a). Conversely, the hydroxyl ligand of **1-OH** in the triplet state contains a smaller portion of the spin density ($\rho = 0.25\alpha$) (Figure 2b). The stronger localization of the spin density on the terminal oxo of **1-O** than on the hydroxo ligand of **1-OH** suggested that the 9-hydroanthracyl radical preferentially couples with **1-O** to form **1-OHAn** in this





Figure 2. (a) Spin density of 1-O (ρ (Ru:O) = 0.56:0.36 α). (b) Spin density of 1-OH (ρ (Ru:O) = 1.4:0.25 α). Isovalue is 0.02 for both 1-O and 1-OH. All hydrogen atoms except that of the hydroxo ligand of 1-OH were removed for clarity.

reaction (Scheme 3, step 2A). This hypothesis was corroborated by computing the associated reaction pathways.

The DFT-calculated energy profiles of the plausible reaction mechanisms for formation of 1-OHAn solvated by chloroform (conductor-like polarizable continuum model, C-PCM)^{48,49} at 296.15 K are shown in Figure 3. The first step involves formation of 1-OH and 9-hydroanthracyl radical (HAn[•]) via HAA from DHA by 1-O (Figure 3, top). This reaction traverses the doublet transition state $^2T\dot{S}_{HAA}$ with a ratedetermining barrier of 18.9 kcal mol⁻¹. Over the course of the reaction, the spin density steadily accumulates on Ru (ρ = 0.56 α , 1.06 α , and 1.40 α in 1-O, ²TS_{HAA}, and 1-OH, respectively). In contrast, the spin density on the oxo decreases until the transition state, after which a slight increase of spin density occurs ($\rho = 0.36\alpha$, 0.12 α , and 0.25 α in 1-O, ²TS_{HAA} and 1-OH, respectively). β spin density originating from the increasing radical character of DHA is shared between the carbon undergoing HAA and the terminal oxo. The observed polarization of spin density toward the Ru-O…H…C moiety is consistent with a concerted HAA mechanism.

The oxygen rebound mechanism in the reaction of 1-OH with the 9-hydroanthracyl radical to yield the hypothesized anthracenol-bound Ru(III) intermediate $({}^{2}P_{OR})$ (step 2B in Scheme 3) was found to have a feasible energy barrier of 12.3 kcal mol⁻¹ (Figure 3, top). However, a competing reaction—a radical combination between starting material 1-O and the 9-hydroanthracyl radical to yield the observed 1-OHAn species (step 2A in Scheme 3)—was found to be essentially barrierless (*vide infra*) and should therefore outcompete the oxygen rebound pathway.

In the radical-combination pathway, two different electronic states, singlet and triplet, were considered; the spin state depended on whether the spins at the terminal oxo and the carbon-centered radical were aligned antiparallel or parallel (Figure 3, bottom). The energy barrier required for the triplet transition state ${}^{3}TS_{RC}$ was found to be 9.3 kcal mol⁻¹. The singlet transition, however, was found to be barrierless due to spin coupling toward bond formation.

Because of the small energy difference between the singlet and triplet states in the reactant complexes of the radicalcombination pathway ($\Delta G({}^{1}\mathbf{R}_{RC}) - \Delta G({}^{3}\mathbf{R}_{RC}) = 0.6$ kcal mol⁻¹), the reaction may take place in the singlet state, without an energy barrier, and yield the most stable triplet product, ³1-OHAn, after spin crossover (SCO). Alternatively, the reaction pubs.acs.org/JACS

may take place in the triplet state—either way, the radical coupling is faster than the rebound, which has a higher energy barrier of 12.3 kcal mol⁻¹. In ³TS_{RC}, the Ru–O distance is slightly longer than that of 1-O (1.74 vs 1.70 Å), and the O–C distance is rather long (2.56 Å). The reactant-like nature of ³TS_{RC} indicates that it should be easily accessible without significant changes to the structure of the cubane. However, the barrier height (9.3 kcal mol⁻¹) and the significant amount of α spin density localized on both O and C ($\rho = 0.33\alpha$ and 0.38α , respectively) suggest electronic repulsion between these two moieties and provide a plausible explanation for the greater barrier height of the triplet state relative to the lack of barrier in the singlet.

The lack of anthracene formation prompted an investigation into the free energy barriers for possible pathways to generate anthracene. DFT predicts an energy barrier of 13.5 kcal mol⁻¹ for an HAA reaction between **1-OH** and 9-hydroanthracyl radical, which is slightly higher than the barrier height of the radical rebound (12.3 kcal mol⁻¹). Because the formation of anthracene is not an experimentally observed pathway, the small energy difference between the two processes (1.2 kcal mol⁻¹) implies that the radical rebound is also unfavorable, further strengthening the proposed radical combination mechanism.

Additionally, the HAA reaction between 1-O and 9hydroanthracyl radical to form anthracene was found to have a barrier of 7.2 kcal mol⁻¹ in the triplet state. Because this reaction is not observed experimentally, the fact that the barrier is lower than that of the triplet radical combination (9.3 kcal mol⁻¹) implies that the latter pathway can be discounted. Note that the singlet transition for the HAA reaction between 1-O and 9-hydroanthracyl radical was found to be barrierless, but this possibility is not preferred since the triplet state transition is lower in energy (Figure S56). Taken together, DFT calculations reveal a barrierless radical combination step between 1-O and 9-hydroanthracyl radical in the singlet state and a subsequent singlet-to-triplet SCO yielding ³1-OHAn.

The divergence in mechanism from a conventional oxygen rebound is reminiscent of several reports on mononuclear nonheme metal—oxo complexes.^{50–52} In these systems, the oxygen rebound mechanism is disfavored in preference for a pathway involving dissociation of the substrate radical from the metal—hydroxo intermediate and further reaction with an oxidizing metal center or a radical trap.⁵³ Consistent with the latter scenario, **1**-**O** may be regarded as a radical trap that intercepts the diffusing 9-hydroanthracyl radical to form **1**-**OHAn**. An analogous radical coupling reaction was observed in the HAA reaction of methane with a Zn^{II} —oxyl species stabilized in an MFI-type zeolite.⁵⁴ In this system, after a Zn^{II} —OH species and a methyl radical are generated in the HAA step, another site of Zn^{II} —oxyl readily traps the methyl radical to form a Zn^{II} —OCH₃ species.

To further support the dissociation of the free radical from **1-OH**, a 2:1 reaction of **1-O** with DHA was performed under an atmosphere of O_2 , a commonly used radical trap.⁵³ In contrast to the identical reaction performed in an N_2 atmosphere (*vide supra*), anthraquinone was observed as a major product (66%) while only a small amount of **1-OHAn** (15%) was observed after 22 h as determined by ¹H NMR spectroscopy (Table S4). The interference of O_2 with this reaction resulted in the formation of anthraquinone and the reduction in yield of **1-OHAn**. These observations suggest that the substrate radical likely diffuses away from **1-OH** and is

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Figure 3. Free energy profiles for the plausible reaction pathways, including the HAA and oxygen rebound steps in the doublet state (top), and the radical combination step in the singlet and triplet states (bottom). Reaction coordinate, ξ , is given on the *x*-axis, and the relative free energy, ΔG , is given in kcal mol⁻¹ on the *y*-axis. The labels R, TS, and P refer to reactant complex, transition state, and product complex, respectively. Spin multiplicities are given as superscripts preceding the labels, whereas subscripts following the labels describe the reaction mechanism, with HAA, OR, and RC referring to H atom abstraction, oxygen rebound, and radical combination mechanisms, respectively.

subsequently intercepted by O_2 and 1-O, which lend support to the radical combination mechanism in this chemistry.

Given that 1-O is present in much higher concentrations than the substrate-based radicals generated in these stoichiometric reactions, it is of interest to determine whether substantially decreasing the concentration of 1-O could favor the rebound of organic radicals at 1-OH or the dimerization of substrate radicals. Notably, a reaction with a 20:1 ratio of DHA to 1-O in CDCl₃ afforded 1-OHAn in ~50% yield with respect to 1-O after 24 h as determined by ¹H NMR spectroscopy. Additionally, neither 9-anthracenol nor 9,9'-bianthracene was observed. The exclusive formation of 1-OHAn in the highly diluted solution of 1-O indicates a strong propensity of 1-O for coupling with a substrate radical.

To further support the feasibility of the radical combination step, 1-O was treated with Gomberg's dimer as a source of

trityl radical to quantitatively produce a radical-trapped cubane complex, $Ru(OC_{19}H_{15})Co_3(\mu_3-O)_4(OAc)_4(4-OMe-py)_3$ (1-OT), after 1 h at 23 °C (Scheme 4). Single-crystal XRD analysis, as well as other characterization techniques (i.e., elemental analysis, ¹H NMR spectroscopy, and HR-ESI-MS), confirmed the identity of the product as 1-OT (Figures S49 and S50). This type of radical coupling reaction where organic radicals are readily intercepted with the terminal oxyl of 2-O has been demonstrated previously by this laboratory.³⁴ Separately, treatment of 1-O (2 equiv) with triphenylmethane (1 equiv) afforded 1-OT in quantitative yield with respect to triphenylmethane (50% yield with respect to 1-O) as indicated by ¹H NMR spectroscopy (Scheme 4). The observed product distribution is consistent with the stoichiometry established for the reaction with DHA. Taken together, these results provide strong evidence that coupling of the substrate radicals with the

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Scheme 4. Synthesis of 1-OT and Subsequent Protonolysis^a



^aInset: solid-state molecular structure of 1-OT as determined by single-crystal XRD. Solvents and hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at 50% probability.

terminal oxo/oxyl of 1-O may be the operative mechanism in this chemistry.

Interestingly, an overall C–H hydroxylation reaction was achieved by protonolysis of **1-OT** with bistriflimidic acid, resulting in quantitative formation of triphenylmethanol and a formally Ru^{IV} species, $[Ru(L)Co_3(\mu_3-O)_4(OAc)_4(py)_3]^+$ (L = 4-OMe-py) as determined by ¹H NMR spectroscopy and HR-ESI-MS (Scheme 4 and Figure S51). Note that formation of the *p*-methoxypyridine adduct observed by HR-ESI-MS is likely a consequence of fragmentation of cubane species under ionization conditions. This experiment demonstrates that the radical-trapped cubane species may be viable intermediates for conversion of hydrocarbons to alcohols.

Influence of Steric Congestion and C–H Bond Energy of Radical Substrates on Formation of Organic Products. Previous work from this laboratory demonstrated the oxidation of 1,4-cyclohexadiene (CHD) by 2-O to afford benzene and the reduced Ru^{III}Co₃O₄ cubane with a 1:1 reaction stoichiometry.³⁴ Similarly, compound 1-O reacts cleanly with CHD to produce benzene in quantitative yield (by ¹H NMR spectroscopy) and a formal Ru^{III} species, detected by HR-ESI-MS after 24 h at 23 °C as $[Ru(L)Co_3(\mu_3 O_4(OAc)_4(4-OMe-py)_3] \cdot H^+$ (L = MeCN, 4-OMe-py). With 2 equiv of 1-O for each equivalent of CHD, 53% of 1-O was consumed to fully convert CHD to benzene; thus, this result stands in contrast to that observed under analogous conditions with DHA. These observations raise two important mechanistic questions. First, what is the origin of the discrepancy between the stoichiometries used to fully convert reactants in the oxidations of CHD (1:1; cubane:CHD) vs other substrates (2:1; cubane:substrate)? Second, why is benzene formed quantitatively in the reaction with CHD, but with other substrates only trace amounts of organic products are detected?

To answer these questions, a stoichiometric reaction of 1-O with CHD was monitored by ¹H NMR spectroscopy. After 1 h at 23 °C, 62% and 59% of 1-O and CHD, respectively, had

been consumed to produce benzene in 57% yield. Additional proton resonances consistent with formation of **1-OH** were also observed (Figure S7). HR-ESI-MS analysis of the reaction mixture in acetonitrile revealed the presence of a [Ru- $(OC_6H_7)Co_3(\mu_3-O)_4(OAc)_4(4-OMe-py)_3]\cdot H^+$ ion (**1-OCHD**, m/z = 1001.8933) though only a trace amount of this radical-trapped species was observed by ¹H NMR spectroscopy (Figure S8).

The formation of 1-OH and 1-OCHD suggests that the first step of this reaction is abstraction of a hydrogen atom from CHD followed by radical combination involving the cyclohexadienyl radical (*CHD) and a second molecule of 1-O (eqs 1 and 2), in a manner similar to that observed in the reaction with DHA. However, it appears that a second HAA reaction at 1-OCHD occurs to produce benzene. The most likely H atom abstractor for the latter step is 1-OH to form a Ru^{III}-OH₂ cubane species $(1-OH_2)$ (eq 3). This is consistent with the Ru^{III}-cubane species observed by HR-ESI-MS. Taken together, these steps give the overall reaction depicted in eq 4, which is consistent with the observed stoichiometry. This implies that 1-OCHD is a reactive intermediate in the C-H activation reaction of CHD and functions as an H atom donor to 1-OH. Nevertheless, a HAA reaction between 1-OH and •CHD cannot be ruled out and may be a competing pathway to produce benzene.

$$1-O + CHD \xrightarrow{RDS} 1-OH + {}^{\bullet}CHD$$
(1)

$$1-O + ^{\bullet}CHD \rightarrow 1-OCHD$$
(2)

$$1-OH + 1-OCHD \rightarrow 1-O + C_6H_6 + 1-OH_2$$
 (3)

net:
$$\mathbf{1-O} + \text{CHD} \rightarrow \text{C}_6\text{H}_6 + \mathbf{1-OH}_2$$
 (4)

The above observations imply that **1-OH** might also undergo a HAA reaction with **1-OHAn** or 9-hydroanthracyl radical to generate anthracene. However, as mentioned above, only a small amount of anthracene (<5%) was produced in the reaction between **1-O** and DHA after 22 h at 23 °C. At 50 °C,

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this reaction slowly converted to anthracene and anthraquinone in 16% and 30% yield, respectively, after 24 h (by 1 H NMR spectroscopy). The greater quantities of organic products formed with increasing temperature suggest that the pathways leading to anthracene and anthraquinone occur at relatively slow rates.

The lower reactivity of 1-OHAn with respect to 1-OCHD in HAA reactions indicates that interactions with 1-OH are influenced by the steric bulk of the trapped substrate radical (Ru-alkoxide cubane). For 1-OHAn, the steric congestion introduced by the tricyclic 9-hydroanthracyl moiety may hinder the approach of 1-OH as an H atom acceptor. The persistence of the radical-trapped cubane species Ru- $(OC_{13}H_9O)Co_3(\mu_3-O)_4(OAc)_4(4-OMe-py)_3$ (1-OX) and Ru- $(OC_{13}H_9)Co_3(\mu_3-O)_4(OAc)_4(4-OMe-py)_3$ (1-OFl) in the reactions with related tricyclic substrates, xanthene, and fluorene further supports this hypothesis (Figures S1-S8). However, in a 2:1 reaction of 1-O with xanthene, 1-OX slowly converted to xanthone in 15% yield after 25 h at 23 °C (by ¹H NMR spectroscopy). Xanthene possesses a relatively weaker C–H bond $(\Delta BDE_{C-H} \sim 0.8 \text{ kcal mol}^{-1})$ but is more sterically demanding than CHD. The slow conversion of 1-OX therefore implies that steric hindrance and C-H bond energies of the bound substrates are competing factors that contribute to the formation rates of organic products.

To further characterize the steric and electronic effects, **1-O** was treated with an excess of cyclohexene (20 equiv), a relatively small allylic C–H substrate with a relatively strong C–H bond (BDE_{C–H} = 87 ± 3 kcal mol⁻¹),⁵⁵ in chloroform-*d* (Scheme 5). After 23 h at 23 °C, no organic products were

Scheme 5. Synthesis of 1-OCH^a



^aInset: Solid-state molecular structure of **1-OCH** as determined by single-crystal XRD. Solvents and hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at 50% probability.

observed; however, new resonances consistent with formation of 1-OH and a new radical-trapped cubane species were observed by ¹H NMR spectroscopy (Figures S11 and S12). The resulting cyclohexenyl complex, Ru(OC₆H₉)Co₃(μ_3 -O)₄(OAc)₄(4-OMe-py)₃ (1-OCH), was isolated in moderate yield (22%) compared to the theoretical yield (50%) with respect to 1-O as the limiting reactant. Recrystallization from dichloromethane/hexamethyldisiloxane afforded X-ray quality single crystals of 1-OCH (Scheme 5, inset). The C–C single bond lengths of the cyclohexenyl moiety span the range of 1.482(5)–1.523(5) Å, while the short C28–C29 bond length (1.310(5) Å) is consistent with the presence of a cyclohexenyl moiety.

The isolation of **1-OCH** and its persistence further suggest that steric effects are not solely responsible for the observed

reactivity. Relative bond energies of the radical-trapped cubane intermediates vs those in $1-OH_2$ may also play a pivotal role in determining the rates of subsequent HAA and formation of organic products.

Influence of Oxyl Radical Character and Metal–Metal Cooperativity on C–H Bond Activations. Significant metal–metal interactions within the RuCo₃O₄ cubane clusters give rise to redox properties that can be tuned through modulation of the electron-donating properties of the Cobound pyridine ligands.³⁴ These cooperative interactions also influence the C–H activation reactivity of these cubane clusters. Notably, in reactions between DHA and Ru(O)-Co₃(μ_3 -O)₄(OAc)₄(4-R-py)₃ cubanes (1-O–4-O, R = OMe, H, CF₃, and Me), the HAA reaction rate decreases linearly with the conjugate acid pK_a values of the 4-R-pyridine ligand in water (Figure 4a).⁵⁶ To probe the origin of this variable reactivity, the electronic properties of the cubanes as a function of substituents were investigated by using DFT calculations.



Figure 4. (a) Plot of $\log(k_{obs})$ of reactions between Ru(O)Co₃(μ_3 -O)₄(OAc)₄(4-R-py)₃ cubanes (1-O-4-O, R = OMe, H, CF₃, and Me) and DHA vs conjugate acid pK_a value of 4-R-pyridine with R^2 = 0.9993. (b) Plot of $\log(k_{obs})$ vs spin density at terminal oxo ligand with R^2 = 0.9939. (c) Plot of $\log(k_{obs})$ vs local natural charge of terminal oxo ligand with R^2 = 0.9916. (d) Plot of $\log(k_{obs})$ vs reduction potential (in o-C₆H₄F₂) with R^2 = 0.9939. The observed rate constants (k_{obs}) were obtained from the slope of the linear correlation between k_{init} and [substrate]₀.

The electronic tunability of the cubane clusters, and hypotheses concerning the possible roles of oxyl radical character in C–H activation of metal–oxo complexes, ^{32,33,57–61} prompted a study of the effect of spin density on HAA reactivity. Metal–oxyl species are thought to be more reactive than closed-shell systems in C–H bond activation since less energy is required to reorganize spins prior to accepting an H atom. ^{32,59,62} An alternative perspective suggests that spin density at the oxo ligand can influence the reactivity but cannot be a dominant factor. ³³ Significantly, the influence of spin density may be investigated with a metal–oxo system in which the degree of ground-state oxyl radical character can be fine-tuned and correlated to C–H activation reactivity. Notably, the spin density localized on the terminal oxo moiety (ρ_0) of the RuCo₃O₄ cubanes increases linearly with the electron-withdrawing ability of the pyridine ligand set (Figure S53) and with the rates of the reactions between 1-O–4-O and

DHA (1-O, R = OMe < 4-O, R = Me < 2-O, R = H < 3-O, R = CF_3) (Figure 4b). The total increase in spin density over this series ($\Delta \rho_{\Omega} = 0.05 \alpha$) is relatively small, which is consistent with the small change in free energy of activation ($\Delta\Delta G^{\ddagger} \sim 1.1$ kcal/mol) at 298 K. The increase in spin density may be rationalized based on simplified π -bonding interactions of the Ru-oxo moiety (Figure S54). The reduction of π -electron donation from the $[Co_3O_4]$ framework induced by electron-withdrawing substituents³⁴ lowers the energies of the π - $\operatorname{Ru}(d_{xz}/d_{yz})$ orbitals. This results in a net decrease in energy for the antibonding π^* -Ru-oxo(d-p) orbital (SOMO), in turn increasing the contribution of $O(p_x/p_y)$ orbitals to the SOMO. This explanation is consistent with the lower SOMO energy³⁴ and stronger oxyl radical character of the more electrondeficient clusters. Notably, enhanced oxyl radical character may provide a stronger driving force for H atom transfer from DHA to the Ru-oxo center, consistent with the observed reactivity trend and the influence for spin density contribution in increasing C-H oxidation reactivity.

While the spin density descriptor applies to metal-oxyl systems or organic radicals undergoing H atom transfer reactions in which the proton and electron travel in concert,⁶³ more general PCET reactivity determinants for metal-oxo complexes are the charge on the proton-receiving oxo ligand (basicity) and the reduction potential at the metal center (oxidizing power).^{62,64} Because the cubanes belong to an intermediate class where the spin is delocalized over the Ruoxo bond, their oxidizing power and/or the basicity should also contribute to the observed reactivity. In fact, the rates of reactions between 1-O-4-O and DHA are linearly dependent on both the local natural charges of the terminal oxo (q_0) and the experimentally determined reduction potentials $(E_{\rm p,c})$ in odifluorobenzene³⁴ (Figures 4c,d). The local natural charges predicted by DFT reveal a decrease ($\Delta q_0 \sim 0.02e$) as the cluster becomes more electron deficient (i.e., less basic), which should result in a lower driving force for proton transfer in a HAA reaction. Therefore, the increase in reactivity is predicted to be dominated by the decrease in reduction potential ($\Delta E_{p,c}$ ~ 0.13 V vs Fc/Fc⁺) as the reduction is rendered more facile by electron-withdrawing ligands. Note that the locus of reduction in these complexes is centered at the Ru-oxo as evidenced by the LUMOs located upon the Ru-oxo moieties (Figure S55).

The strong dependence of the reaction rates on the electronic properties of the cubanes demonstrates that simple modifications to the distal ligands bound at Co directly modulates the reactivity at the Ru–oxo moiety. Significantly, electronic changes at the ligand set are transmitted through all three Co centers to the Ru–oxo moiety, indicating that the metal centers are working cooperatively as an assembly in oxidizing C–H substrates. Similar multimetallic cooperative effects have been predicted by DFT in the C–H activation study of the related Co₄O₄ cubane.¹⁸ These studies indicate a direct influence of the electronic communication within the cubane clusters on C–H activation reactivity.

CONCLUDING REMARKS

Mechanistic insights described above highlight the importance of two structural features that contribute to the reactivity of $RuCo_3O_4$ cubanes in oxidative catalysis: high-valent metal oxyl moieties and multimetallic oxo frameworks. These clusters abstract H atoms from a range of C–H substrates to generate substrate radicals that are readily trapped by available (and radical-like) Ru–oxo moieties. DFT calculations predict a barrierless radical combination between 9-hydroanthracyl radical and the terminal Ru–oxo whereas the radical rebound at the Ru–hydroxo species is less favorable, consistent with the higher spin density localized upon oxygen of the terminal Ru–oxo vs Ru–hydroxo. These results suggest that the degree of oxyl character could be a critical factor in determining the preferred pathway(s) for C–H activation by high-valent metal–oxo/oxyl species, and such a radical combination reaction may be a common pathway in other metal–oxyl mediated PCET reactions.

The strong electronic communication within the cubane core allows for establishing structure-function relationships. The reactivity of the terminal Ru-oxo moiety is readily manipulated by the donating properties of the pyridine ligand set for the Co sites. Notably, it was found that electrondeficient clusters exhibit faster reaction rates toward C-H cleavage. The origins of the observed reactivity may be attributed to the reduction potential and the spin density localized upon the terminal oxo ligand as important properties that can be tuned in these cubane clusters. Such relationships may be important in other multimetallic oxo systems wherein the PCET reactivity of the terminal oxo/oxyl can be fine-tuned without changing the formal oxidation state of the supporting metal center; however, subtle electronic changes of nearby metals directly influence the electronic properties and thus reactivity of the overall cluster. This cooperativity may also play a role in enzymatic multimetallic catalysts in which the highly dynamic local environments and ligand binding to the active sites could greatly affect the reactivity of the reactive oxo moiety.⁶⁵ The fundamental understanding developed in this study regarding multimetallic cooperative effects should prove useful in designing and evaluating multimetallic oxo catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04069.

Experimental and computational details (PDF)

Accession Codes

CCDC 2081075–2081077 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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