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Is It True Dioxygenase or Classic Autoxidation Catalysis? Re-Investigation of a Claimed Dioxygenase Catalyst Based on a Ru_2-Incorporated, Polyoxometalate Precatalyst

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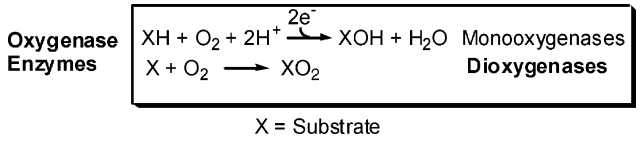
A 1997 *Nature* paper (*Nature* **1997**, *388,* 353–355) and a 1998 *J. Am. Chem. Soc.* paper (*J. Am. Chem. Soc.* **1998**, *120*, 11969–11976) reported that a novel Ru_2-incorporated sandwich-type polyoxometalate, $\{[WZnRu^{III}_2(OH)(H_2O)](ZnW_9O_{34})_2\}^{11-}$, is an all-inorganic dioxygenase catalyst for the hydroxylation of adamantane and the epoxidation of alkenes using molecular oxygen. Specifically, it was reported that the above Ru_2-containing polyoxometalate catalyzes the following reaction by a non-radical-chain, dioxygenase mechanism: $2RH + O_2 \rightarrow 2ROH$ (R = adamantane). A re-investigation of the above claim has been performed, resulting in the following findings: (1) iodometric analysis detects trace peroxides (0.5% relative to adamantane), the products of free-radical-chain autoxidation, at the end of the adamantane hydroxylation reaction; (2) a non-dioxygenase product, $H_2{}^{18}O$, is observed at the end of an adamantane hydroxylation reaction performed using $^{18}O_2$; (3) kinetic studies reveal a fractional rate law consistent with a classic radical-chain reaction; (4) a non-dioxygenase ~1:1 adamantane products/O_2 stoichiometry is observed in our hands (instead of the claimed 2:1 adamantane/O_2 dioxygenase stoichiometry); (5) adamantane hydroxylation is initiated by the free radical initiator, AIBN (2,2′-azobisisobutyronitrile), or the organic hydroperoxide, *t*-BuOOH; (6) four radical scavengers completely inhibit the reaction; and (7) $\{[WZnRu^{III}_2(OH)(H_2O)](ZnW_9O_{34})_2\}^{11-}$ is found to be an effective catalyst for cyclohexene free-radical-chain autoxidation. The above results are consistent with and strongly supportive of a free-radical-chain mechanism, not the previously claimed dioxygenase pathway.

Introduction

Dioxygenases are defined as a class of enzymes capable of catalyzing the insertion of both oxygen atoms of oxygen into a substrate (Scheme 1).[1−3] Dioxygenases are, therefore, unique and of central importance in oxygenation catalysis owing to their O_2 atom efficiency. No protons or electrons are needed for the reaction; hence, no H_2O byproduct—representing wasted $2e^-/2H^+$ or H_2 in comparison to monooxygenases—is generated. Dioxygenases are therefore key systems for biomimetic studies aimed at more efficient and selective oxygenation catalysts.

The first Ru-based nonenzymatic dioxygenase catalyst was reported by Groves and Quinn,[4] who found that dioxo-

Scheme 1. Monooxygenase- and Dioxygenase-Catalyzed Oxygenation Reactions



(tetramesitylporphyrinato)ruthenium(VI), [Ru(TMP)$(O)_2$] catalyzes the aerobic epoxidation of olefins at ambient temperature. Our group has reported that vanadium-containing polyoxoanions serve as all-inorganic catechol dioxygenases with record catalytic total turnovers of over 100 000.[5] Subsequent mechanistic studies provide evidence for a novel autoxidation-product-initiated dioxygenase,[6] in which the

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autoxidation of catechol generates quinone and H_2O_2, followed by release of vanadium from the vanadium-containing polyoxoanion to give a common,[7] V-based catalyst.[6] Mizuno and co-workers have reported that $[\gamma\text{-}SiW_{10}\{Fe^{3+}(OH_2)\}_2O_{38}]^{6-}$ catalyzes the epoxidation of cyclooctene in, it is believed, a dioxygenase manner.[8] There are of course a few catalytic, and many more stoichiometric, Fe-based dioxygenase model systems[3,9−11] that are important toward understanding nature's Fe-based dioxygenase enzymes. These interesting Fe systems[3,9−11] are, however, not the focus of the present work.

In 1997, a *Nature* paper reported that the Ru_2-incorporated sandwich-type polyoxometalate, $\{[WZnRu^{III}_2(OH)(H_2O)](ZnW_9O_{34})_2\}^{11-}$ (**1**), is an all-inorganic dioxygenase;[12] a full paper was published in *J. Am. Chem. Soc.* the next year.[13] Those papers are currently considered significant progress toward realizing an all-inorganic, and thus robust, dioxygenase catalyst.[14]

However, scrutiny of the data from the above two publications indicates that the evidence for the claimed dioxygenase is weak. First, organic-soluble Q_{11}-**1** (Q is tricaprylmethylammonium from QCl added as a phase-transfer reagent) gives rise to a 10 h induction period at 80 °C prior to the observation of any adamantane hydroxylation activity.[12] The observed induction period demands that the as-added Q_{11}-**1** is *not* the catalyst; instead **1** must be a *precatalyst*. Additionally, preincubation of the precatalyst Q_{11}-**1** with O_2 at 80 °C for 12 h is necessary to initiate the alkene epoxidation.[12] Second, when we attempted to fit the published observed rate constant versus oxygen pressure curve using the published rate equation,[13] the attempt failed (Figure 1). This demands that either (a) the proposed mechanism is wrong; (b) there are some errors in the kinetics versus pO_2 data; or (c) both (a) and (b). Third, in the proposed mechanism, ≥1 electron is needed to activate the precatalyst to a putative Ru(II) state, but our work does not support this claim (vide infra). Moreover, a well-known source of *reductant* under *oxidizing* (O_2) *conditions* is the initial autoxidation product ROOH, with the RO**O**−**H** bond serving as a reductant to strong enough oxidants in a classic Haber−Weiss fashion.[15−21] Fourth, the original work reported

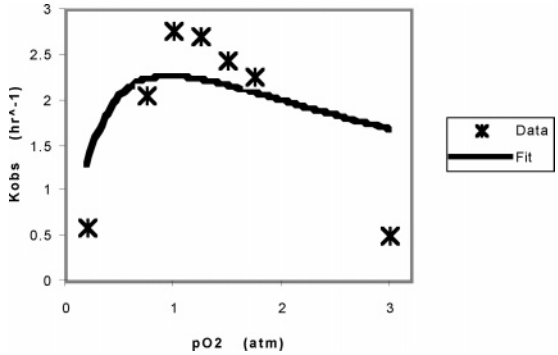

Figure 1. Kinetic data from Figure 4 of the prior work[13] plus our attempted fit using the published rate equation ($K_{obs} = K_1k_2[O_2]/(1 + K_1[O_2])^2$).[13] Both K_1 and k_2 were allowed to vary; the "best" fit is $K_1 = 1.0 \pm 0.5\ M^{-1}$ and $k_2 = 9 \pm 1\ M^{-1}\ h^{-1}$ [the (underestimated) error bars are from the fit, which is obviously poor ($R^2 = 0.55$)]. The curve-fit was accomplished with MacCurveFit ver 1.1.2. As a control we showed that an identical curve-fit as well as identical K_1, k_2, and R^2 values were obtained when we used Origin ver 7.0383 from OriginLabs.

that radical scavengers had no effect on the catalytic activity,[12,13] but this is *negative evidence*; in addition, it is well-known that conclusions based on such one-point radical-scavenger experiments are fraught with problems—the use of the wrong scavenger (typically with too low a scavenging rate constant)[22] or too low a concentration of scavenger being two common problems leading to such negative, sometimes very misleading results. In fact, we find that we can inhibit the adamantane oxidation reaction readily with four inhibitors (vide infra), positive evidence suggestive of a free-radical-based, classic autoxidation reaction and not the claimed dioxygenase. Rather clearly, then, this heralded claim[12,13] of a novel dioxygenase catalyst merits a careful re-investigation.

Herein we provide the following evidence inconsistent with the claimed dioxygenase but fully consistent with and supportive of a classic, radical-chain autoxidation reaction: (i) the detection of trace hydroperoxide by iodometric analysis; (ii) the detection of $H_2{}^{18}O$, a non-dioxygenase product, when labeled $^{18}O_2$ is used; (iii) kinetics of the maximum rate post the induction period and in the reaction's steady state, $d[product]/dt_{max} = k_{obs}[adamantane]^{3/2}[Q_{11}\text{-}\mathbf{1}]^{1/2}[O_2]^{\approx 1/2}$, kinetics diagnostic of a radical-chain reaction; (iv) a ∼1:1 adamantane products/O_2 (not the claimed 2:1) stoichiometry as expected for a non-dioxygenase; (v) the ability to initiate the chain reaction with AIBN or ROOH (the latter serving, presumably, as a RO**O**−**H** reductant for Ru^{III} in Q_{11}-**1**); (vi) the ability to inhibit the reaction with four radical scavengers; and (vii) the ability of Q_{11}-**1** to catalyze cyclohexene autoxidation efficiently along with its inability to perform catechol dioxygenase catalysis.

Experimental Section

Materials. All reaction solutions were prepared under oxygen- and moisture-free conditions in a Vacuum Atmosphere drybox (<5 ppm O_2, as continuously monitored by an oxygen sensor). 1,2-

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Dichloroethane (Aldrich, HPLC grade), *o*-dichlorobenzene (Aldrich, HPLC grade), and DMSO (Aldrich, anhydrous grade) were dried with preactivated 4 Å molecular sieves and stored in the drybox. Adamantane (Aldrich, 99+%) was dried under vacuum at room temperature overnight and stored in the drybox. 2,2′-Azobisisobutyronitrile (AIBN) (Aldrich, 98%), 2-phenyl-*N*-*tert*-butylnitrone (Aldrich, 98%, PBN hereafter), and galvinoxyl (Aldrich) were stored in a freezer; 4-*tert*-butylcatechol (Aldrich, 97%) and 2,6-di-*tert*-butyl-4-methylphenol (Aldrich, 99+%, BHT) were used as received. *tert*-Butyl hydroperoxide in decane with molecular sieves (Aldrich, ~5.5 M as labeled) was stored in a refrigerator. $Na_2WO_4 \cdot 2H_2O$ (Aldrich, 99%), $ZnNO_3 \cdot 6H_2O$ (Fisher chemicals), $RuCl_3 \cdot 3H_2O$ (Aldrich, 99.98%), and Aliquat 336 (Aldrich; hereafter Q^+Cl^-) were used as received. Zinc powder (Aldrich, −100 mesh, 99.998%) was washed with dilute acid (2% HCl), water, ethyl alcohol, and diethyl ether and then dried under vacuum overnight before use. Isotopic $^{18}O_2$ gas (95.6%) was purchased from Cambridge Isotope Lab, Inc. Chemicals used in the iodometric titration are NaI, $Na_2S_2O_3 \cdot 5H_2O$, and isopropyl alcohol (Fisher scientific); glacial acetic acid (Mallinckrodt); and KIO_3 (Mallinckrodt, analytical reagent). Deionized water was used for solution preparations. Cyclohexene (Aldrich, 99%) was distilled over sodium under argon and stored in the drybox. Prior to use, it was passed through a neutral alumina column under nitrogen to remove traces of hydroperoxides. $[Bu_4N]_5Na_3[(1,5\text{-COD})Ir \cdot P_2W_{15}Nb_3O_{62}]$ was made by our most recent method[23,24] (except that crystalline $[(1,5\text{-COD})Ir(CH_3CN)_2]BF_4$ was employed in the synthesis[25]) and then stored in the drybox.

Instrumentation. Infrared spectra were obtained on a Nicolet 5DX spectrometer using KBr disks. The nuclear magnetic resonance spectra in D_2O or $CDCl_3$ (Cambridge Isotope Lab, Inc.) were obtained on a Varian Inova (JS-300) NMR spectrometer. A high precision (±0.02 psig at 14 psig or ±0.15%) oxygen pressure transducer was purchased from Omegadyne Inc., model PX02C1-100G10T-OX. (**CAUTION:** Standard pressure transducers need to be cleaned by the manufacturer before their use with oxygen, as any leftover oil from calibration or dirt inside the transducer is potentially flammable/explosive in the presence of O_2.) The automatic data collection was implemented by integration of the pressure transducer to an analog-to-digital converter; the data were collected electronically with LabView 6.1 software. A more detailed view of this apparatus is available elsewhere[26] (note that there it is used for H_2 and not O_2 reactions, however). GC analyses were performed on a Hewlett-Packard 5890 series II gas chromatograph equipped with a FID detector and a SPB-1 capillary column (30 m, 0.25 mm i.d.) with the following temperature program for adamantane hydroxylation products: initial temperature, 140 °C (initial time, 4 min); heating rate, 5 °C/min; final temperature, 180 °C (final time, 3 min); FID detector temperature, 250 °C; injector temperature, 250 °C. An injection volume of 1 μL was used. Product peaks were identified by comparison to authentic sample peaks; product amounts were quantitated by external calibration using authentic samples. GC−MS analyses were carried on an Agilent 6890 series GC system with a SPB-1 capillary column and an Agilent 5973 mass selective detector. The temperature program is the same as that used above in GC analyses. TGA−MS analyses were performed on a TGA 2950 thermogravimetric analyzer (TA Instruments, Inc.) coupled with a ThermoStar mass analyzer (Balzer Instrument). CHN elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Cyclic voltammetric data were obtained using a standard three-electrode cell with an EG&G PAR model 173 potentiostat/galvanostat controlled by a model 175 universal programmer. The reference electrode was Hg/Hg_2Cl_2 in saturated NaCl (0.236 V vs SHE). The auxiliary electrode was a 0.5 cm^2 platinum flag, and the working electrode was a glassy carbon electrode. Prior to use, the working electrode was polished on a felt pad with a water slurry of 0.3 μm alumina polishing powder, followed by rinsing with distilled water and dichloromethane.

Preparation of Precatalyst $\{[WZnRu^{III}_2(OH)(H_2O)](ZnW_9O_{34})_2\}^{11-}$. The precursors $Na_{12}[WZn_3(H_2O)_2(ZnW_9O_{34})_2] \cdot 46-48H_2O$ (precrystallization yield 71 g, 51%; lit. 90−95 g, 65−68%) and $[Ru^{II}(DMSO)_4]Cl_2$ (recrystallized yield ca. 4.0 g, 70−79%; lit. 72%) were both synthesized and recrystallized according to the literature.[27,28] The ^1H NMR of recrystallized $[Ru^{II}(DMSO)_4]Cl_2$ was identical to a recent published preparation by Nomiya et al.[29] ^1H NMR ($CDCl_3$): δ (major peaks) 2.63, 2.72, 3.30, 3.42, 3.48 and 3.51; literature ($CDCl_3$): δ (major peaks) 2.60, 2.72, 3.32, 3.43, 3.48, 3.50.[29] $K_{11}[WZnRu_2(ZnW_9O_{34})_2] \cdot 15H_2O$ was prepared and recrystallized twice from hot water according to the literature.[30] Yield 3.73 g, 16%; lit. 5.7 g, 24%. $K_{11}[WZnRu_2(ZnW_9O_{34})_2] \cdot 15H_2O$ was examined by ^1H NMR in D_2O: δ 4.8 (solvent peak only, no remaining DMSO). The UV−visible spectrum in water shows only one peak at 284 nm (ϵ = 24 000 M^{-1} cm^{-1}), different from the literature which reports two peaks at ~300 nm (ϵ = ~50 000 M^{-1} cm^{-1}) and 430 nm.[30] The 430 nm peak has been assigned a O→Ru charge transfer band.[30] TGA in the 50−250 °C range on a sample predried in a vacuum oven (at ca. 1 Torr) overnight at 40 °C showed a 2−3% weight loss corresponding to 7−10 waters, that is, $K_{11}[WZnRu(III)_2(OH)(H_2O)(ZnW_9O_{34})_2] \cdot 7-10H_2O$. The organic counterpart of this polyoxometalate salt $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$, Q_{11}-**1**, was synthesized via the published method[30] with the following additional steps: after drying over $MgSO_4$, the organic phase was separated from $MgSO_4$ by a filtration on a glass frit. The filtrate was then dried under vacuum overnight at room temperature. The yield of the gum-like, red-orange compound was ca. 50−65%; no literature yield has been reported. IR data (as a drop on KBr, as done previously[13]): 723 (s), 766 (s), 871 (m), 921 (m) cm^{-1} (see the Supporting Information, Figure S1); literature:[12,13] 765 (s) [a broad peak with a full width at half-maximum of ca. 80 cm^{-1} (720−800 cm^{-1}), two identifiable peaks within this range at ca. 730 and 750 cm^{-1}], 881 (m), 928 (m) cm^{-1}. The microanalysis data confirm the previous finding by another researcher in our labs (i.e., for an independent preparation)[5] that precatalyst **1** is impure. The composition is approximated by $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\} \cdot n$QCl; the value of n was estimated from the CHN analysis (n = 2−4 for three different batches of Q_{11}-**1**). Herein the value of $n \approx 2-3$ gives the "best" fit to the analysis; calculated (for the formulation shown above, and n = 2−3) [found; repeat found (i.e., repeat analysis)]: C, 39.51−40.88 [40.57, 40.68]; H, 7.16−7.41 [7.52, 7.38]; and N 1.84−1.91 [1.64, 1.55].[31] No elemental analysis was reported in the original paper[30] for comparison. Cyclic voltammogram of Q_{11}-**1** in 1,2-$C_2H_4Cl_2$ (with 0.1 M $TBAClO_4$, at a glassy carbon working

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electrode, vs SSCE at a sweep rate of 100 mV/s) shows two irreversible oxidation peaks at +0.94 and +1.22 V, but no reduction peaks out to even −1.0 V (Figure S5 in the Supporting Information).

General Procedures for Oxygen-Uptake Experiments. Adamantane hydroxylation was monitored either by the formation of 1-adamantanol (via periodic sampling and subsequent GC analysis) or by the oxygen pressure decrease (via the computer-interfaced oxygen pressure transducer, vide supra). The reaction flask is a pressurized Fischer−Porter bottle attached via Swagelock quick-connects and flexible stainless steel tubing to both an oxygen tank and to the pressure transducer (total volume 148 mL).[26] In the drybox, the adamantane substrate (typically 341−817 mg, 2.5−6.0 mmol) was weighed into a 22 mm × 175 mm Pyrex culture tube along with a 5/8 in. × 5/16 in. Teflon stir bar. The precatalyst (typically 25−60 mg, 2.5−6.0 μmol) was weighed into a 5 mL glass vial with a preweighed stainless steel spatula. Then the precatalyst was dissolved in 1,2-$C_2H_4Cl_2$ (unless stated otherwise) and quantitatively transferred into the culture tube with a disposable pipet. The culture tube was then placed inside the Fischer−Porter bottle, sealed, brought out of the drybox, placed in a temperature-controlled oil bath, and attached to the oxygen uptake apparatus via the quick-connects. Stirring was initiated, and the solution was equilibrated in the oil bath (80 °C) under N_2 (from the drybox gas) for 40 min. The Fischer−Porter bottle was then purged 15 times with ∼14 psig of O_2 (or ∼1.8 atm; the atmosphere pressure at the ca. 1 mile-high altitude of Fort Collins, CO, is around 632 Torr, or 0.83 atm); 15 s/purge, equilibrate 1 min 15 s; 5 min total time elapsed before the pressure recordings were started. The reaction vessel was then pressurized to 14 ± 1 psig and $t = 0$ was set. During GC sampling, a 500 μL syringe with a 20 in. stainless steel needle was used to sample 200−300 μL aliquots of the reaction solution under a positive oxygen flow. Following sampling, two additional purges with O_2 were performed. The sample solution was diluted with 1,2-$C_2H_4Cl_2$ (41-fold) and then analyzed by authentic sample-calibrated GC.

Pressure Control Experiment at 1 atm O_2. This control was performed to ensure that reaction products did not change when the reaction was run at 1.0 vs 1.8 atm O_2. To start, 6.0 mmol of adamantane, 6.0 μmol of precatalyst Q_{11}-**1**, and 12.0 mL of 1,2-dichloroethane were measured into a 22 mm × 175 mm Pyrex culture tube along with a 5/8 in. × 5/16 in. Teflon stir bar. The culture tube was then placed inside the Fischer−Porter bottle, sealed and brought out of the drybox. The Fischer−Porter bottle was placed in a dry ice/ethanol bath (−72 °C). After the reaction solution was frozen, two pump-and-fill cycles were performed with 1 atm O_2. Next, the dry ice/ethanol bath was replaced by a temperature-controlled oil bath (80.0 ± 0.5 °C) and stirring was initiated; $t = 0$ was set when the oil bath reached 80.0 °C (ca. 25 min). At the end of the reaction ($t = 24$ h), the product yields were determined by calibrated GC to be 13 ± 1% of 1-adamantanol and 2.5 ± 0.1% of 2-adamantanone. These values are the same within experimental error as the yields (12 ± 1% of 1-adamantanol and 2.2 ± 0.4% of 2-adamantanone) under the standard conditions employed (6.0 mmol of adamantane, 6.0 μmol of Q_{11}-**1**, 12.0 mL of 1,2-dichloroethane, and 1.8 atm O_2).

Reaction-Scale Control Experiment. A control was performed to make sure the reaction scale has no effect on the yields or selectivity. A run at the conditions used in the previous studies[12,13] (0.25 mmol of adamantane, 0.25 μmol of precatalyst Q_{11}-**1**, and 0.5 mL of 1,2-dichloroethane) was performed in a ca. 15 mL pressure tube (Ace Glassware) with a 3/8 in. × 3/16 in. Teflon stir bar. The reaction mixture was frozen by a dry ice/acetone bath (−79 °C) and subjected to two pump-and-fill cycles using O_2. The pressure tube was filled with ca. 1 atm oxygen gas through an opening on the plunger valve sealing the pressure tube, the opening was then closed, the dry ice bath was replaced by a temperature-controlled oil bath (80.0 ± 0.5 °C), and stirring was initiated; $t = 0$ was set when the oil bath reached 80.0 °C (ca. 15 min). At the end of the reaction (24 h), the product yields were determined by calibrated GC to be 15 ± 1% of 1-adamantanol and 2.7 ± 0.1% of 2-adamantanone. These values are the same within experimental error as the yields (12 ± 1% of 1-adamantanol and 2.2 ± 0.4% of 2-adamantanone) under the standard conditions we employ of a 24-fold increase: 6.0 mmol of adamantane, 6.0 μmol of Q_{11}-**1**, 12.0 mL of 1,2-dichloroethane, and 1.8 atm O_2. Trace products were also identified.[35]

Organic Peroxide Detection and Quantitation. A qualitative test of peroxide presence was performed by shaking a 10% KI/starch solution with the final reaction mixture obtained from a standard, scaled-up run (6.0 mmol of adamantane, 6.0 μmol of Q_{11}-**1**, 12.0 mL of 1,2-dichloroethane, and 1.8 atm O_2) after 24 h of reaction time. The aqueous layer slowly turned violet. Quantitative analysis of organic peroxide was accomplished by the standard iodometric titration method[21,32] performed immediately following a standard run of adamantane hydroxylation. Specifically, 40 mL of isopropyl alcohol and a Teflon stir bar were introduced into a 250 mL Erlenmeyer flask. The flask was equipped with a gas inlet tube and a reflux condenser; 2 mL of glacial acetic acid and a 2 mL aliquot of the reaction solution (24 h) from the scaled-up reaction were then added into the flask. The mixture was purged to remove oxygen by bubbling with argon gas for 15 min through either a stainless steel syringe or a soft Teflon syringe needle (the latter as a control to avoid possible ROOH decomposition by the steel syringe needle). The experiments using different syringes gave equivalent results; hence the stainless steel syringe needle did not induce ROOH decomposition on the time scale and at the temperature of our experiments. The solution was heated to reflux and 10 mL of a saturated solution of sodium iodide in isopropyl alcohol (prepared by refluxing 25 g of sodium iodide in 100 mL of isopropyl alcohol) was added to the refluxing solution from the top of the condenser; the solution was then refluxed for 5 additional minutes. The mixture was removed from the heating plate and titrated immediately with aqueous 0.01 M standard sodium thiosulfate solution (standardized using a primary standard KIO_3 solution with H^+/KI through titration). A blank titration was performed for each peroxide titration using the same procedure as above, except that the sample solution was replaced by a 0.5 M adamantane solution in 1,2-$C_2H_4Cl_2$ (to mimic the reaction conditions). The results, which are described in the main text, are the

(31) The uncertainty in determining the exact value of n (±1) in Q_{11}-**1**·nQCl contributes to an error of ≤±4% in the estimation of the molecular weight of Q_{11}-**1** used throughout this work. However, this error will not change the major conclusions in this paper. This ≤±4% error is also smaller than the error (≥8% for $n \geq 2$) in the prior work where no such molecular weight correction was considered.[12,13]

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(35) Other trace products detected are ∼0.2−0.3% adamantane-1,3-diol ($m/z = 168$) and ∼0.4−0.5% 2-adamantanol ($m/z = 152$). The upper limit of these trace products is ∼0.5%, estimated by the Effective Carbon Numbers detailed elsewhere.[34] The order of GC elution of these products on a low-polarity column (SPB-1 in this study) is adamantane, 1-adamantanol, adamantane-1,3-diol, 2-adamantanone, and then 2-adamantanol.

average of four titrations of product solutions from two identical adamantane hydroxylation experiments. In addition, ca. 5.5 M of commerical *t*-BuOOH was titrated as a control experiment to check the titration method in our hands (observed 5.9 M in two repeat titrations, results in good agreement with the labeled value).

$H_2{}^{18}O$ Detection. The prior work claimed that "no $H_2{}^{18}O$ was observed" (see p 354 in ref 12) in the catalytic adamantane hydroxylation using $^{18}O_2$; however, no detection limit was given.[12] In our studies, a control was performed first using the cheaper (than $H_2{}^{18}O$) D_2O ($m/z = 20$) to mimic the $H_2{}^{18}O$ ($m/z = 20$) and to estimate our detection limit. In this control, D_2O (0.45 μL, 0.025 mmol, the same amount as the $H_2{}^{18}O$ generated from the reaction at 100 turnovers based on 0.25 μmol Q_{11}-**1**) was deliberately injected into 0.5 mL of 1,2-dichloroethane, and then this solution was added to ~100 mg of predried 4 Å molecular sieves (Mallinckrodt, Grade 514GT, predried at >250 °C under vacuum overnight, followed by cooling and then storage under vacuum before use in the air). The solution and mol sieves were swirled by hand for a ca. 1 min period (controls, vide infra, showed that longer mixing times (1 h vs 1 min) of the molecular sieves with sample solution did not give a stronger signal (at $m/z = 20$), that is, did not change the results). The solution was then removed by a disposable pipet. The molecular sieves were collected using a stainless steel spatula, placed into a glass vial, and then into an aluminum pan of a TGA apparatus (TGA 2950, TA Instruments) using a pair of stainless steel tweezers, all quickly as possible in the open air. Upon heating the molecular sieves at 10 °C/min or, separately, 50 °C/min up to 600 °C in the TGA apparatus, $D_2O^{\bullet+}$ ($m/z = 20$), $H_2O^{\bullet+}$ or $DO^{\bullet+}$ ($m/z = 18$), $HO^{\bullet+}$($m/z = 17$), and the deuterium-exchange product $H-O^{\bullet+}-D$ ($m/z = 19$) were detectable by the mass analyzer (resolution $\geq \pm 0.5$ amu) directly coupled to the TGA instrument. These controls demonstrate that our detection limit of D_2O (as a surrogate for $H_2{}^{18}O$ in the real run) is lower than ~0.025 mmol (<10% compared to the adamantane substrate) and assuming no major differences in the detectability of D_2O versus $H_2{}^{18}O$.

Next, we repeated the adamantane hydroxylation experiment using $^{18}O_2$. A run at the standard conditions (0.25 mmol of adamantane, 0.25 μmol of precatalyst Q_{11}-**1**, 0.5 mL of 1,2-dichloroethane) of the previous studies[12,13] was performed in a ca. 15 mL pressure tube (Ace Glassware) with a 3/8 in. × 3/16 in. Teflon stir bar. The reaction mixture was frozen by a dry ice/acetone bath (−79 °C) and subjected to two pump-and-fill cycles using $^{18}O_2$ (ca. 1 atm $^{18}O_2$ was introduced to the pressure tube through the opening on the plunger valve sealing the pressure tube). The opening was closed, and the dry ice bath was replaced by a temperature-controlled oil bath (80.0 ± 0.5 °C); $t = 0$ was set when the oil bath reached 80.0 °C (ca. 15 min). The reaction was stopped after 24 h. The reaction solution (~0.5 mL) was mixed for ca. 1 min with ~100 mg of Mallinckrodt, Grade 514GT 4 Å molecular sieves predried at at >250 °C under vacuum overnight as detailed above. Next, the solution was removed using a disposable pipet. The mol sieves were transferred into a closed vial with a stainless steel spatula and then quickly placed in the aluminum TGA pan in the open air using a pair of stainless steel tweezers (ramp 50 °C/min to 600 °C during TGA-MS analysis). Ion currents corresponding to $H_2{}^{18}O$ ($m/z = 20$ and 19 for $H^{18}O^{\bullet+}$) and H_2O ($m/z = 18$ and 17 for $HO^{\bullet+}$) were detected.

A blank control was also performed in the exact same manner as above, except that no precatalyst, Q_{11}-1, was added. In that control, preactivated mol sieves were mixed with 0.5 mL of 0.5 M adamantane solution that had been stirred under $^{18}O_2$ at 80 °C for 24 h. The expected, unavoidable background $H_2{}^{16}O^{\bullet+}$ peaks ($m/z = 18$ and 17) were observed; signals at $m/z = 20$ (due, apparently, to $m/z = 20$ $Ar^{\bullet2+}$ and/or *possibly* some $H_2{}^{18}O^{\bullet+}$ and $H^{18}O^{\bullet+}$ formed from $^{18}O_2$ in the EI detector) and $m/z = 19$ were also observed, but their level is less than one-third that of the signals from the run with Q_{11}-**1**. The observed mass spectra are given in Figure 2.

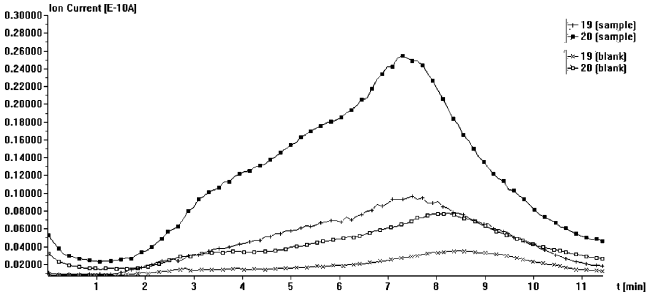


Figure 2. TGA-MS results of the molecular sieves added to and then harvested from the adamantane hydroxylation reaction solution under $^{18}O_2$ plus precatalyst Q_{11}-**1**. A blank consisting of the molecular sieves mixed with adamantane solution stirred under $^{18}O_2$ without Q_{11}-**1** is shown for comparison. The ion currents at 20 (m/z, $H_2{}^{18}O^{\bullet+}$) and 19 (m/z, $H^{18}O^{\bullet+}$) were followed by a mass analyzer (resolution $\geq \pm$ 0.5 amu) coupled to the TGA instrument. Note the high signal at the start of the heating (the leftmost part of the graph); this rise is due to the contamination of residual Ar gas (doubly charged $Ar^{\bullet2+}$, $m/z = 20$) present in the TGA instrument chamber at the start of the analysis.

In one TGA−MS control experiment, an opening on the TGA chamber was left unplugged during the heating (i.e., the molecular sieves were deliberately exposed to moist air). Higher signals of $H_2O^{\bullet+}$ ($m/z = 18$ and 17 for $HO^{\bullet+}$) were observed along with higher signals at $m/z = 20$ ($Ar^{\bullet2+}$) and 19; we interpret the latter as unresolved $m/z = 18$ from the large $H_2{}^{16}O^{\bullet+}$ peak due to a mass analyzer resolution of only around 1−0.5 amu. Hence, it is crucial for controls to be performed, such as the one above to establish the background signal.

H_2O Yield. The amount of H_2O produced was estimated by TGA from the weight loss during heating to 550 °C in two repeat experiments (e.g., from a 119 mg sample in one run produced from the 100 mg of original mol sieves) (Figure S2 in the Supporting Information). A total weight loss of 19% (18% from a 122 mg sample in the repeat run) was observed, 15% of that loss being observed in a sharp weight drop by 100 °C with the other 4% being more slowly evolved up to 550 °C. Concomitant MS analysis (e.g., Figure 2) confirms that H_2O is being evolved throughout this temperature range up to 550 °C. The ratio of $H_2{}^{16}O$ to $H_2{}^{18}O$ was calculated from the integral area of the ion currents of $(H_2{}^{16}O^{\bullet+} + H^{16}O^{\bullet+})/(H_2{}^{18}O^{\bullet+} + H^{18}O^{\bullet+})$ up to 550 °C.

Detection of ^{18}O-Containing Organic Products. In the adamantane hydroxylation experiment using $^{18}O_2$ under the procedure described in the above section, the organic products after 24 h were tested for $^{18}O_2$ inclusion by GC−MS. The reaction solution was diluted with 1,2-$C_2H_4Cl_2$ (41-fold) and then analyzed by GC−MS. The major product, 1-adamantan-^{18}O-ol ($m/z = 154$ as the molecular ion peak), exhibited an abundance of $^{18}O/(^{18}O + {}^{16}O)$ of ca. 96% once a correction for the 95.6% abundance of the $^{18}O_2$ used was made, vide infra). The 2-adamantan-^{18}O-one ($m/z = 152$) contains 39% ^{18}O. The other trace products (yield ≤0.5%) are adamantane-1,3-di-^{18}O-ol ($m/z = 172$) containing ^{18}O in 60% abundance (di-^{18}O-ol vs di-^{18}O,^{16}O-ol ratio of 1:4.4; no di-^{16}O-ol was detected) and 2-adamantan-^{18}O-ol ($m/z = 154$) containing ^{18}O in 55% abundance, all after correction for the 95.6% abundance of the $^{18}O_2$ used.

Attempted Preparation of 1-Adamantyl Peroxide. There is only one published preparation of 1-adamantyl peroxide, one with no experimental details.[33] Details of our three attempted preparations of this peroxide are provided in the Supporting Information.

Kinetic Experiments. Kinetic experiments were performed under the same conditions as the previous researchers performed their kinetic runs (2.5 mmol of adamantane, 2.5 μmol of precatalyst Q_{11}-**1,** 5.0 mL of 1,2-dichloroethane, 80 °C);[13] the only exception is the higher pressure 1.8 atm employed herein versus the 1 atm used in the prior work.[13] The start-up procedures are the same as stated in the General Procedures for Oxygen-Uptake Experiments section. The kinetics of 1-adamantanol formation were followed by authentic sample-calibrated GC. Steady-state/maximum rates, post-induction period, were measured as shown in Figure S3 of the Supporting Information. Kinetic derivations were done, therefore, under the steady-state assumption as detailed in the Supporting Information.

Kinetic Results Fitting By Mackinetics. Mackinetics (a free software designed by Walter S. Leipold III for chemical reaction kinetics modeling; product information is at http://members.dca.net/leipold/mk/advert.html) was used to curve-fit the kinetic results in Figure 5. To start, a set of chemical equations together with experimental data were written into Mackinetics (the exact reactions used in Mackinetics are listed in the Supporting Information). Next, a grid search was performed to fit the kinetic parameters to one or more sets of experimental data. Specifically, the kinetic parameter search was performed first in a broad range of the parameters ($10^{-9}-10^{9}$) by the grid search command in Mackinetics. Then, the grid search was narrowed down to a bit more than half the previous range (e.g., if the first search gave $k_1 = 0.01$ and $k_2 = 0.1$ as the best fit in the range of $10^{-9}-10^{9}$, then the second search was performed in the range of $10^{-7}-10^{3}$ for k_1 and $10^{-6}-10^{4}$ for k_2); the center of the new range was always set to equal the result from last grid search as in the above examples. The search was deemed finished once a grid search was performed in a range no larger than 2 orders of magnitude. The data for curve-fits shown (in Figure 5) are those obtained by performing a final integration, using the best set of kinetic parameters, and then co-plotting that data with the observed, experimental data.

Determination of the Reaction Stoichiometry. Two different methods were applied in the stoichiometry studies: a two-point method to mimic that used in the original work[13] and a more precise and more reliable multi-point, real-time method employing a ±0.15% high-precision pressure transducer. The reaction conditions employed for the two-point method were 1.5 mmol of adamantane, 1.5 μmol of Q_{11}-**1**, 3 mL of 1,2-dichloroethane, and 80 °C in the first two runs (6-fold higher than the scale used in the previous studies[13]); reaction conditions in a third, repeat run were (24-fold higher than before[13]): 6.0 mmol of adamantane, 6.0 μmol of Q_{11}-**1**, 12 mL of 1,2-dichloroethane, and 80 °C. The specific details of the two-point method mimicking the literature[13] are as follows: after introducing 1 atm of O_2 into the reaction flask at room temperature, the pressure was recorded (by a mercury manometer or, in the third run, the oxygen pressure transducer was used), and then the reaction flask was sealed and heated in a 80 °C oil bath ($t = 0$ was set when the oil bath reached 80.0 °C; this took ca. 10−30 min). After 24 h, the reaction flask was removed from the oil bath and cooled to ambient temperature over 30 min. Then, the second pressure point was recorded by reopening the valve connected to the manometer (or, in the third run, the O_2 pressure transducer).

The multi-point, real-time method allows collection of data by the oxygen pressure transducer connected to the reaction flask as described in the Instrumentation section. The reaction conditions for the real-time method employed a 24-fold increase in the absolute amounts, vide supra: 6.0 mmol of adamantane, 6.0 μmol of Q_{11}-**1**, 12 mL of 1,2-dichloroethane, and 80 °C in the first run; then 6.0 mmol of adamantane, 6.0 μmol of Q_{11}-**1**, 6 mL of 1,2-dichloroethane, and 80 °C in the remaining four runs (a 24-fold increase in reagents and a 12-fold increase in the amount of solvent). The other procedures employed are the same as described in the General Procedures for Oxygen-Uptake Experiments section. Data points were taken every 10 min. The results are shown in Table 1 and Figure 4. The ΔpO_2 data collected in Table 1 were obtained by first correcting the initial part of the data for the vapor pressure due to the solvent (i.e., the rise in the pressure due to the solvent's vapor pressure as is apparent for the one run shown in Figure 4). The solvent vapor pressure was measured in an independent experiment in which solvent only was present. The resulting $\Delta P(O_2) = P(O_2, \text{initial}) - P(O_2, \text{final})$ proved to be the same within experimental error as the ΔpO_2 determined from the uncorrected data as shown for the one run in Figure 4.

Initiation and Inhibition Experiments. Initiation and inhibition experiments were performed with a slight variation of the General Procedures for Oxygen-Uptake Experiments section. The initiation experiments employing the addition of H_2O_2 (0.2 mmol, 20 μL, 30% wt H_2O_2) or H_2O (0.9 mmol, ∼17 μL, as a control in a separate run) were started as normal experiments except, after 12 purges of oxygen, the initiator was added into the reaction flask via a 1 mL airtight syringe, and the reaction flask was then purged 3 more times with O_2. The other initiation and inhibition experiments were all started with the additives premixed with the reaction mixture in the drybox (0.2 mmol of AIBN, ∼0.2 mmol of *t*-BuOOH, 6 μmol of Zn, 0.2 mmol of PBN, 0.2 of mmol galvinoxyl, 0.21 mmol of 4-*tert*-butylcatechol, or 0.2 mmol of BHT in nine separate runs). The formation of 1-adamantanol was followed by GC.

Cyclohexene Autoxidation Experiments. This control was performed to see if Q_{11}-**1** is a good autoxidation catalyst for readily autoxidized substrates, such as cyclohexene, and in comparison to known autoxidation precatalysts such as the $[Bu_4N]_5Na_3[(1,5\text{-COD})Ir{\cdot}P_2W_{15}Nb_3O_{62}]$ complex.[21] First, ∼9 μmol of precatalyst ($[Bu_4N]_5Na_3[(1,5\text{-COD})Ir{\cdot}P_2W_{15}Nb_3O_{62}]$ or Q_{11}-**1** in two independent runs**)** were weighed out in the drybox into a 50 mL round-bottom reaction flask equipped with an egg-shaped 3/4 in. × 3/8 in. Teflon stirring bar. Next, 6 mL of predried HPLC grade 1,2-dichloroethane and 1 mL of distilled cyclohexene (chromatographed through an 8 cm × 1 cm neutral alumina column in the drybox prior to use to remove trace peroxides) were transferred into the flask, and then the flask was sealed with a Teflon stopcock and taken out of the drybox. The flask was connected to an oxygen-uptake line through an O-ring joint, the reaction solution was frozen in a dry ice-ethanol bath (−72 °C) for 10 min, and two pump-and-fill cycles with ∼1 atm O_2 were performed. Next, the dry ice bath was replaced with a temperature-controlled oil bath, the flask was brought up to 40 ± 0.4 °C, and $t = 0$ was set. The reaction was stopped after 24 h, and the product solution was diluted with 1,2-$C_2H_4Cl_2$ (41-fold) for GC analysis (SPB-1 capillary column): temperature program, initial temperature, 50 °C (initial time, 4 min); heating rate, 10 °C/min; final temperature, 160 °C (final time, 5 min); injector temperature, 250 °C; detector temperature, 250 °C. The results are presented in Table 3; GC traces are shown as Figure S6 in the Supporting Information.

Attempted Catechol Oxygenation Reactions. This experiment was performed to see if Q_{11}-**1** could serve as a precatalyst for known catechol dioxygenase reactions.[5,9] To start, ∼400 mg of 3,5-di-*tert*-butylcatechol that had been recrystallized three times (from pentane under Ar, mp = 99−100 °C) was weighed out in the drybox into a 50 mL round-bottom reaction flask equipped with a septum, sidearm and an egg-shaped 3/4 in. × 3/8 in. Teflon stirring bar. (Note: It is important to recrystallize the 3,5-di-*tert*-butylcatechol ≥3 times to remove impurities such as 3,5-di-*tert*-butylsemiquinone.)[5,6] Approximately 8 mL of predried HPLC grade 1,2-

dichloroethane was transferred into the flask using a 10-mL glass syringe, the flask was sealed with a Teflon stopcock and then taken out of the drybox. The flask was connected to the oxygen-uptake line through its O-ring joint, and the reaction solution was frozen in a dry ice/ethanol bath (−72 °C) for 10 min after which two pump-and-fill cycles with ∼1 atm O_2 were performed. Next, the dry ice bath was replaced with a temperature-controlled oil bath, the flask was brought up to 40 ± 0.4 °C and allowed to equilibrate with stirring for 25 min during which a solution of precatalyst Q_{11}-**1** was prepared as follows. In the drybox, 47.2 mg of Q_{11}-**1** (ca. 7.3 μmol) was weighed into a glass vial and dissolved in ca. 0.2 mL of 1,2-dichloroethane. The catalyst solution was drawn into a gastight syringe and brought out of the drybox with its needle protected from air in a septum-capped-vial. The catalyst was then injected through the sidearm of the 40 °C reaction flask and $t = 0$ was set. The pressure reading from the manometer was used to follow the reaction. The reaction was stopped at 133 h, and the product solution was diluted (21-fold) with 1,2-$C_2H_4Cl_2$ prior to GC analysis. The final product is the autoxidation product 3,5-di-*tert*-butylbenzoquinone (17%); no dioxygenase cleavage products[5] were detected despite our ability to routinely detect ≥1% of those products.[7]

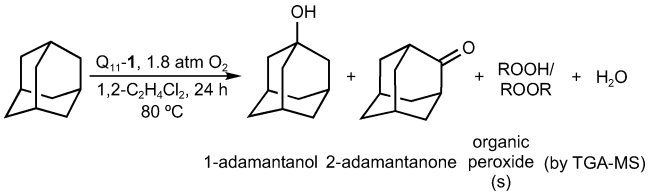
Results and Discussion

A Choice of Standard Reaction Conditions. The standard conditions in the previous work[12,13] are 0.25 mmol of adamantane, 0.25 μmol of precatalyst (**1**), 0.5 mL of 1,2-dichloroethane, 1 atm of oxygen, and 80 °C. In the previous *kinetic* studies, the above amounts of reagents were scaled up 10-fold (except O_2).[13] We have employed these exact same conditions and concentrations, including the 10-fold scale-up for kinetic studies, except that we have scaled up the product studies by 24-fold in the absolute amounts of reagents used (i.e., while keeping the absolute concentrations the same) in order to achieve better precision in especially the O_2-uptake studies. Additionally, the slightly higher O_2 pressure we applied (1.8 atm of O_2 vs 1 atm in the prior work[12,13]) was found to exhibit little effect on the reaction kinetics (which are ca. half-order in O_2, see Figure 3C, vide infra) and no detectable effect on the product yields as demonstrated in the following control experiment: the yields at 1 atm O_2 (of 13 ± 1% of 1-adamantanol and 2.5 ± 0.1% of 2-adamantanone) are the same within experimental error as the yields at 1.8 atm O_2 (where 12 ± 1% of 1-adamantanol and 2.2 ± 0.4% of 2-adamantanone are formed).

Moreover, under our (scaled-up) standard conditions (namely, 6.0 mmol of adamantane, 6.0 μmol of precatalyst, 12.0 mL of 1,2-dichloroethane, 1.8 atm of oxygen, and 80 °C), the yield of the main product[35] (1-adamantanol, 12 ± 1% after 24 h) is identical within experimental error to that reported in the prior work, 12.3% at 24 h.[13] The minor product (2-adamantanone) was detected at a yield of 2.2 ± 0.4% (Scheme 2) as compared to none in the prior work. Mass balance in our studies averaged 95 ± 5% with a range of 92−99% (mass balance was not reported in the previous work[12,13]).

Peroxide Detection and Quantitation. Since adamantyl hydroperoxide (Adm-OOH) should be the primary, at least initial product generated from a free-radical-chain autoxidation reaction and since the peroxide Adm-OO-Adm is expected as part of termination of a Adm-OO$^\bullet$ radical chain, we performed experiments to see if these ROOH/ROOR could be detected in the reaction products. Iodometric titration of a freshly reacted solution (24 h reaction time) revealed a small, but nonzero, amount (0.5%, relative to the substrate) of organic peroxide products ROOH and/or ROOR. Note that the conversion is relatively low, and it is known in the literature that ROOR products are typically under-detected in autoxidation reactions,[36,37] so that we regard the 0.5% peroxide as a lower limit on the amount of peroxides actually present. Three attempts were made to prepare authentic 1-adamantyl hydroperoxide following the ambiguous procedures available in the literature,[33] but all failed. Nevertheless, detection of any peroxide is inconsistent with published claim of solely a dioxygenase[12,13] and demands at least *some* contribution from an autoxidation route. Furthermore, in the Kinetic Studies section presented next, we will show that the rate law provides compelling support for an autoxidation pathway.

Scheme 2. Adamantane Hydroxylation under Standard Conditions[a]



	1-adamantanol	2-adamantanone	organic peroxide (s)	(by TGA-MS)
Previous work	12.3%	-	-	-
Current study	12 ± 1%	2.2 ± 0.4%	0.5%	~8%

[a] Product yields (the average of five runs) were determined by authentic sample-calibrated GC.

$^{18}O_2$ Labeling Studies and $H_2{}^{18}O$ Detection. The prior work claimed that "no $H_2{}^{18}O$ was observed" when the reaction was run under $^{18}O_2$ (see p 354 of ref 12) but failed to give a $H_2{}^{18}O$ detection limit.[12] On the other hand, the autoxidation mechanism predicts that $H_2{}^{18}O$ will be formed if $^{18}O_2$ is used. Hence, whether H_2O is formed is a clear test to distinguish between the claimed dioxygenase pathway vs a well-precedented, classic autoxidation mechanism.

First, control experiments were performed to confirm our ability to detect trace amounts of $H_2{}^{18}O$ (D_2O was used instead here as a $m/z = 20$ surrogate for the $m/z = 20$ $H_2{}^{18}O^{\bullet+}$ formed from the more expensive $^{18}O_2$). Our detection limit is ≤0.025 mmol (≤10% yield); details are available in the Experimental Section.

Next, an adamantane hydroxylation reaction (Scheme 2) was performed at the smaller scale of 0.25 mmol of adamantane, 0.25 μmol of Q_{11}-**1**, 0.5 mL of 1,2-$C_2H_4Cl_2$, and 1 atm $^{18}O_2$ (i.e., 1/24 of our normal scale to reduce the amount of $^{18}O_2$ required). After 24 h (ca. 150 turnovers), preactivated 4 Å molecular sieves were added to the reaction solution. The reaction solution was removed by a pipet. Next, the molecular sieves were collected and then subjected to TGA−MS analysis. Besides the unavoidable $H_2{}^{16}O^{\bullet+}$ back-

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ground peaks ($m/z = 18$, plus a fragment peak due to $HO^{\bullet+}$ at $m/z = 17$), the results reveal the presence of $H_2{}^{18}O^{\bullet+}$ ($m/z = 20$ with its fragment peak of $H^{18}O^{\bullet+}$ at $m/z = 19$). In a control, 0.5 mL of adamantane solution was stirred under $^{18}O_2$ for 24 h at 80 °C and subsequently treated as above with preactivated 4 Å molecular sieves. A lower level of signals at $m/z = 20$ or 19 was observed which was less than one-third that with the precatalyst, **1** (Figure 2). The background peaks are due, apparently, mostly to $m/z = 20$ $Ar^{\bullet 2+}$ and the limited ability of the 0.5−1.0 amu resolution mass analyzer to deal with the background of $Ar^{\bullet 2+}$ or $H_2{}^{16}O^{\bullet+}$. These results alone argue strongly against the prior dioxygenase mechanism as the *sole* pathway as previously claimed, as that pathway does not produce H_2O.

The GC−MS of the organic products and their ^{18}O content was also examined. GC−MS of the reaction solution after 24 h shows a 96% abundance of ^{18}O in the main product: 1-adamantan-^{18}O-ol. Interestingly, the 2-adamantan-^{18}O-one contains only 39% ^{18}O, while the trace products (yield ≤0.5%) also incorporate less than 100% ^{18}O: adamantane-1,3-di-^{18}O-ol contains ^{18}O in 60% abundance (the di-^{18}O-ol/di-^{18}O,^{16}O-ol ratio is 1/4.4; no di-^{16}O-ol was detected), and 2-adamantanol contains ^{18}O in only 55% abundance. Reflection on these data yield the following insights: (i) a dioxygenase mechanism cannot account for these results; instead, an intermediate such as $R^{18}O^{18}OH$, which can exchange ^{18}O with ^{16}O in the polyoxometalate *seems* to be required; and (ii) the ^{16}O observed in the ketone product (2-adamantanone) could also be due to an ^{18}O exchange with $H_2{}^{16}O$ in the solvent via a gem−diol intermediate.[38,39] We did confirm that the ^{16}O content of the $\{[WZnRu^{III}{}_2(OH)(H_2O)](ZnW_9O_{34})_2\}^{11-}$ polyoxoanion, **1** (17.5 μmol for 70 ^{16}O atoms in 0.25 μmol of **1**), is sufficient to account for the observed total ^{16}O incorporation (5.7 μmol) into all the products. That is not to say that this previously undetected, putative O-exchange pathway is anything approaching well-understood, however.

Kinetic Studies. A series of kinetic experiments were performed to determine the reaction orders of adamantane, oxygen, and precatalyst **1**. The formation of the main product, 1-adamantanol, was followed by GC (as was done in the prior kinetic studies[13]), which necessitated the use of the post-induction period, steady-state, maximum rate of the reaction[40] (i.e., since the initial rate of 1-adamantanol production is zero during the induction period[41]). The steady-state rate law we observed is listed below; it is a fractional-order rate law, one diagnostic of a free-radical-chain reaction (Scheme 3) in the reaction's steady-state:

$$\left\{\frac{\mathrm{d[1\text{-}adamantanol]}}{\mathrm{d}t}\right\}_{\text{max, steady state}} = k_{\text{obs}}[\text{adamantane}]^{3/2}[Q_{11}\text{-}\mathbf{1}]^{1/2}[O_2]^{\approx 1/2}$$

The logarithmic plot of the substrate dependence is shown in Figure 3A. The logarithmic plot of the precatalyst

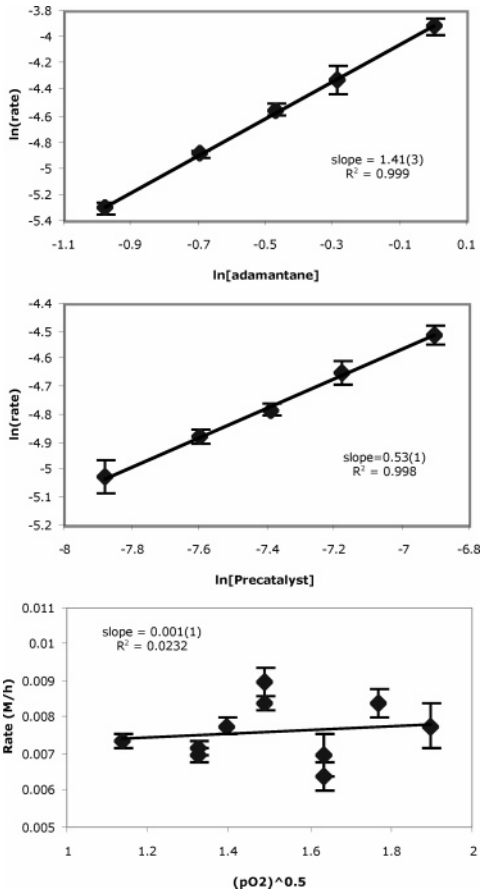


Figure 3. (A) Logarithmic plot of the post-induction period, steady-state, maximum rate $[(d[1\text{-adamantanol}]/dt)_{max}]$ vs the substrate concentration. Reaction conditions: 1.9−5.0 mmol of adamantane, 2.5 μmol of precatalyst Q_{11}-**1**, 5 mL of 1,2-$C_2H_4Cl_2$, and 1.8 atm of oxygen. The reaction order in the substrate is 1.5 within ±0.1 (i.e., within ±7%). (B) Logarithmic plot of the post-induction period, steady-state, maximum rate $[(d[1\text{-adamantanol}]/dt)_{max}]$ vs the precatalyst concentration. Reaction conditions: 2.5 mmol of adamantane, 1.9−5.0 μmol of precatalyst Q_{11}-**1**, 5 mL of 1,2-$C_2H_4Cl_2$, and 1.8 atm of oxygen. The order with respect to the polyoxometalate, $Q_{11}\{[WZnRu^{III}{}_2(OH)(H_2O)](ZnW_9O_{34})_2\}$, is 0.5 within ±0.03 (i.e., within ±6%). (C) Plot of the post-induction period, steady-state, maximum rate $[(d[1\text{-adamantanol}]/dt)_{max}]$ vs the square root of the oxygen pressure, $pO_2{}^{1/2}$. Reaction conditions: 2.5 mmol of adamantane, 2.5 μmol of precatalyst Q_{11}-**1**, 5 mL of 1,2-$C_2H_4Cl_2$, and 1−3.6 atm of oxygen. The reaction order is ca. 0.5 within the observed experimental error; note that the small range of the *y* or rate axis makes the data appear noisier than they really are (±≤14% error bars, similar to the error in panels A and B, ±≤13%). A zero-order plot of the oxygen pressure, pO_2, is provided in the Supporting Information but does not yield a better fit to the data. (The direct $Ru_2{}^{III}$ (**1**) + RH → $Ru_2{}^{II/III}$ + R$^\bullet$ + H$^+$ implied by a zero-order pO_2 was further ruled out on the basis of electrochemical data and thermodynamic grounds; see Figure S4 and Figure S5 provided in the Supporting Information.)

dependence is shown in Figure 3B, and the somewhat scattered plot of the rate versus $p[O_2]^{1/2}$ is given in Figure 3C. A typical kinetic curve (from which the maximum rate at steady state was determined) is shown in the Supporting Information (Figure S3). We also performed a control

(38) Samuel, D.; Silver, B. L. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic Press: London and New York, 1965; Vol. 3, pp 123−186.
(39) Cohn, M.; Urey, H. C. *J. Am. Chem. Soc.* **1938**, *60*, 679−687.
(40) Howard, J. A. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley & Sons: New York, 1973; Vol. 2, pp 3−62.
(41) Under our conditions, the induction period of adamantane hydroxylation reaction is less than 1 h, much shorter than the 10 h in the prior work.[12,13] The difference is expected for a radical-chain autoxidation reaction: different grades of solvent, adventitious ROOH, other initiators, or inhibitors are well-known to change the observed length of such induction period.[21]

Scheme 3. Proposed, Minimalistic, Radical-Chain-Initiated Adamantane Hydroperoxylation plus Concurrent Ru_2-Catalyzed, ROOH-Based Adamantane Reaction Consistent with the Observed Stoichiometry and Rate Law[a]

Initiation

(1) $Adm-H + Ru_2^{III} + O_2 \xrightarrow{k_1} Ru_2^{III/IV}OOH + \underset{\text{(mostly 1-adm•; but some 2-adm•)}}{Adm\bullet}$

Propagation

(2) $Adm\bullet + O_2 \xrightarrow[\text{fast}]{k_2} AdmOO\bullet$

(3) $AdmOO\bullet + Adm-H \xrightarrow{k_3} \underset{\text{(primary autoxidation product)}}{AdmOOH} + Adm\bullet$

Concurrent Ru_2 - Catalyzed AdmOOH - Based Reaction

(4) $AdmOOH + Ru_2^{III/IV} \xrightarrow{k_4} AdmOO\bullet + H^+ + Ru_2^{III}$

(5) $AdmOOH + Ru_2^{III} \xrightarrow{k_5} AdmO\bullet + OH^- + Ru_2^{III/IV}$

(6) $OH^- + H^+ \xrightarrow[\text{fast}]{k_6} H_2O$

(7) $AdmO\bullet + AdmOOH \xrightarrow{k_7} AdmOH + AdmOO\bullet$

(8) $AdmO\bullet + Adm-H \xrightarrow{k_8} AdmOH + Adm\bullet$

(9) $2AdmOO\bullet \xrightarrow{k_9} 2AdmO\bullet + O_2$

Termination

(10a) $2AdmOO\bullet \xrightarrow{k_{10}} AdmOOAdm + O_2$

(10b) $2AdmOO\bullet \xrightarrow[\text{(possible when one AdmOO• is 2-AdmOO•)}]{k'_{10}} 1\text{-}AdmOH + 2\text{-}Adm{=}O + O_2$

[a] Adm = adamantane; AdmOH = 1-adamantanol; Adm=O = 2-adamantanone; AdmOOH = 1-adamantyl peroxide; Ru_2^{III} = **1** (precatalyst); $Ru_2^{III/IV}$ = oxidized **1**.

showing that the $ClCH_2CH_2Cl$ solvent does *not* appear to be involved in the autoxidation reaction.[42−45]

The rate law derived for the radical-chain in Scheme 3 mechanism using the steady-state approximation (see the derivation in the Supporting Information) gives:

$$d[product]/dt = k_{obs}[adamantane]^{3/2}[precatalyst]^{1/2}[O_2]^{1/2}$$

Such fractional rate laws are typically highly diagnostic of radical-chain mechanisms,[18,20] since they are virtually impossible to rationalize by other, precedented mechanisms. In short, the radical-chain mechanism in Scheme 3 is consistent with, and overall strongly supported by[46] the observed kinetics.[47,48]

Our observed $[O_2]^{\approx 1/2}$ oxygen dependence, $[precatalyst]^{1/2}$ and $[adamantane]^{3/2}$ observations are obviously quite different from $[O_2]^{\sim 1\rightarrow 0}$, second-order $[precatalyst]^2$, and zero-order substrate, $[adamantane]^0$, kinetics reported in the previous work.[13] It is not exactly clear how the prior workers obtained the rate law they reported; at times during our studies it seemed as if we were studying a different system. But our identical precatalyst synthesis, properties (save the $\lambda = 430$ peak), and product yields, would seem to ensure the systems are, in fact, the same. Also, the following comments seem relevant to the previously reported kinetics: (a) the earlier work used post-induction period rates derived from obviously nonlinear, bi-phasic kinetic data (see the plots in Figure 2 in ref 13); (b) we have shown in Figure 1 that the prior authors' own O_2-dependence data rule out their proposed dioxygenase mechanism; and (c) in the final analysis, our kinetic results are repeatable and, we believe, reliable. Of course, only the prior authors can repeat and support or refute and retract their prior 2:1 O_2-uptake, H_2O nonformation, and kinetic work; something that we physically cannot do.

There is, of course, extensive precedent for the autoxidation of hydrocarbons by oxygen in the presence of metal catalysts dating back to the 1950s (see the references summarized in ref 21). Labinger's recent excellent work on isobutane autoxidation, and the references therein, provide specific, excellent precedent for the mechanism in Scheme 3 past the initiation step.[37] Interestingly, in both that case and in Scheme 3, the facile consumption of the initial ROOH product is a key, precedented,[37] feature of the system. Labinger's work also makes clear that fairly high selectivity reactions are possible from even such multistep autoxidation schemes.[37] In short, the observed products, kinetics, and extant literature provide strong support for the proposed, classic autoxidation mechanism (Scheme 3) as do the additional experiments that follow.

O_2-Uptake Stoichiometry Studies. We performed several trials at different scales (6- or 24-fold) either by two-point pressure readings of a manometer (i.e., a reproduction of the literature method[13]) or by higher precision, more reliable, multi-point, real-time pressure readings through the use of a high-precision oxygen pressure transducer (±0.02 psig at 14 psig, i.e., ±0.15%).[49] The average stoichiometric ratio

(42) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493−532.

(43) Lide, D. R. *CRC Handbook of Chemistry and Physics*, 85th ed.; CRC Press: Chelsea, MI, 2004−5.

(44) Kruppa, G. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 2162−2169.

(45) We wondered if the $ClCH_2CH_2Cl$ solvent could serve as a H radical source in the autoxidation, since the C−H BDE of $ClCH_2CH_2Cl$ is ca. 101 kcal/mol[42] (as estimated from the data listed in Table 9-66 elsewhere[43]) vs that of adamantane of 99 kcal/mol.[44] Hence, we performed a control experiment using *o*-dichlorobenzene (C−H BDE ca. 111 kcal/mol[43]) instead of 1,2-dichloroethane as the solvent. Identical product yields and reaction rates rule out the possibility that 1,2-dichloroethane is a major player in the radical reactions, despite the relative concentration of the two, 13 M $ClCH_2CH_2Cl$ vs 0.5 M adamantane, a factor of 26:1.

(46) The R^2 value (0.023) of our $pO_2^{ca.1/2}$ fit in Figure 3C is poor. It is, then, the $[adamantane]^{3/2}$ and $[precatalyst]^{1/2}$ dependences (Figure 3A,B) more than the $pO_2^{ca.1/2}$ fit that offer the main kinetic support for the radical-chain mechanism.

(47) Bravo, A.; Bjorsvik, H.-R.; Fontana, F.; Minisci, F.; Serri, A. *J. Org. Chem.* **1996**, *61*, 9409−9416.

(48) Note that we did consider in detail the alternative, O_2-free, direct initiation step of Adm-H + $Ru_2^{III} \rightarrow Adm\bullet + Ru_2^{II/III}$, since it is consistent with a $[pO_2]^0$ treatment of our kinetic data (Figure S4 of the Supporting Information) and since it has some general precedent[40]—albeit for ∼+1.8 V (vs NHE) oxidants such as Co^{3+}/Co^{2+}. The lower—but still, overall, high!—oxidation potential of adamantane (E_{ox} = 2.72 V vs SCE) compared to a noncyclic alkane (2,3-dimethylbutane, E_{ox} = 3.45 V vs SCE)[47] is at least somewhat consistent with this alternative step. To test this alternative route thermodynamically, cyclic voltammetry of the Q_{11}-**1** (i.e., Ru_2^{III} in Scheme 3) in dichloroethane was performed: the absence of any well-defined Ru^{III}/Ru^{II} peak (Figure S5 in the Supporting Information) argues against this alternative initiation step. (NB: the $Ru_2^{III} + e^- \rightarrow Ru_2^{II/III}$ reduction potential of +0.13 V in H_2O vs SCE claimed in the prior work[30] is at best not obvious from the unlabeled cyclic voltammogram provided, one which shows no obviously chemical reversible peaks and one in which it is not even possible to tell where the CV scan was initiated.) Finally, and as the literature notes,[40] autoxidation's initiation step is the least understood of the elementary reactions in autoxidation despite more than 60 years of research in autoxidation.[40]

Table 1. O_2-Uptake Stoichiometry for Adamantane Hydroxylation Reaction Run on Different Scales[a]

O_2 consumed (mmol)	1-adamantanol yield (mmol)	2-adamantanone yield (mmol)	ratio of Σproducts:O_2
	Two-Point Method		
0.4 ± 0.1[b]	0.31 ± 0.02	0.08 ± 0.01	**1.0** $\pm$ 0.3
0.5 ± 0.1[b]	0.40 ± 0.02	0.08 ± 0.01	**1.0** $\pm$ 0.2
0.96 ± 0.06	0.73 ± 0.02	0.14 ± 0.01	**0.9** $\pm$ 0.1
	Multi-Point, Real-Time Method		
0.8 ± 0.1	0.77 ± 0.06	0.14 ± 0.01	**1.1** $\pm$ 0.1
1.2 ± 0.1	1.09 ± 0.03	0.21 ± 0.07	**1.1** $\pm$ 0.1
1.4 ± 0.1	1.17 ± 0.04	0.22 ± 0.01	**1.0** $\pm$ 0.1
1.5 ± 0.1	1.12 ± 0.06	0.21 ± 0.01	**0.9** $\pm$ 0.1
1.1 ± 0.2[c]	0.82 ± 0.02	0.27 ± 0.01	**1.0** $\pm$ 0.2

[a] Reaction conditions are scaled up proportionally (6 or 24 times) from the conditions used in the literature[12,13] to increase the precision of our results: 0.25 mmol of substrate, 0.25 μmol of precatalyst, 80 °C, reaction time 24 h. The solvent volume (1,2-dichloroethane) is scaled up by factors of 6, 12, or 24 in the various experiments. [b] Reaction time 72 h. [c] This run was performed in *o*-dichlorobenzene rather than the normal solvent (1,2-dichloroethane).

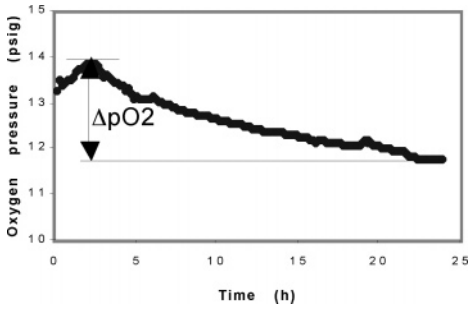


Figure 4. Full oxygen pressure vs time curve recorded by an oxygen pressure transducer. The pressure rise for the first 2 h is due to solvent pressure equilibration following the introduction of O_2 into the reaction flask via a cycle of 15 purges, a procedure that initially cools the system some and unavoidably sweeps solvent vapor out of the system, thereby initially lowing the pressure recorded at $t = 0$.

of adamantane products:oxygen we observe (Table 1) is 1.0($\pm$0.3):1 (the $\pm$0.3 error bar refers to 3σ). Our observed 1:1 stoichiometry is completely at odds with the previously claimed 2:1 dioxygenase stoichiometry.[13]

A representative oxygen-uptake curve obtained via the O_2 pressure transducer is shown in Figure 4. This specific experiment, repeated four times, yields a stoichiometry of $\sim$1.0 equiv of adamantane per O_2. The 24-fold smaller scale (i.e., 24-fold lower O_2-consumed volume available for measurement) is one problem with the prior studies.[13,50] The lack of a detailed experimental section (e.g., one noting the precision of the pressure readings in the prior O_2-uptake experiments) is another problem with the previous work.[13] Obviously, any two-point O_2-uptake experiment is another potential problem in light of the full, complex curve in Figure 4.

A detailed comparison of the observed stoichiometry versus that predicted by the mechanism in Scheme 3, and as a function of time (i.e., of the chain length), is possible only via a numerical integration computer model of Scheme 3 analogous to what Labinger has so nicely done for isobutane autoxidation, a system fairly close to that in Scheme 3 except for different initiation steps.[37] Although we are continuing to work on a version of Scheme 3 complete with the needed rate constants, so far it appears that an insufficient number of the required rate constants are known in the literature to allow any more detailed, meaningful computer model (i.e., more detailed than the minimum numerical integration model already in the Supporting Information). However, the main point for the present work is that the experimentally observed stoichiometry is *not* the previously claimed 2:1 value, at least in our hands. Instead, it is closer to $\sim$1:1($\pm$0.3) findings consistent with the autoxidation pathway in Scheme 3.

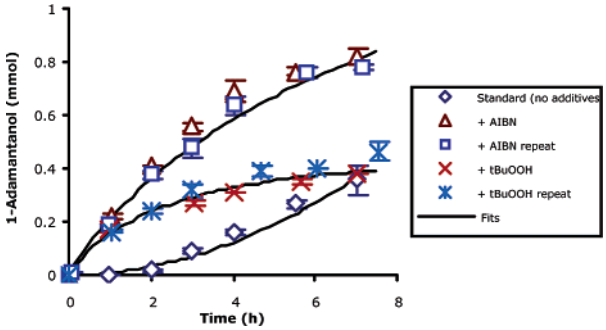


Figure 5. Effects of adding the radical initiator (AIBN) (0.2 mmol) or anhydrous TBHP (ca. 0.2 mmol) at the start of the adamantane hydroxylation reaction. The kinetic model used in Mackinetics for the fit under standard conditions is basically the k_1-k_3 and k_{10} steps of the radical-chain mechanism in Scheme 3; see the Supporting Information for further details.

Effects of Radical Initiators and Hydroperoxides. We also studied the effects of several additives introduced at the start of the reaction: the radical initiator AIBN (2,2′-azobisisobutyronitrile), *tert*-butyl hydroperoxide (TBHP), H_2O_2, and, following the earlier report,[12] zinc powder. In the case of AIBN, TBHP, or H_2O_2, 0.2 mmol was added, which is ca. 33 equiv versus the amount of the precatalyst Q_{11}-**1**. The amount of Zn powder added was chosen to reproduce the literature[12] (ca. 5 equiv of Zn vs the amount of Q_{11}-**1**). Two identical runs for the first two additives were performed, and the repeatability proved good (Figure 5).

The radical initiators AIBN and TBHP eliminate the induction period, and the initial rates of product formation increase ca. 20-fold from $\sim$0.01 mmol/h to $\sim$0.2 mmol/h with AIBN and $\sim$0.17 mmol/h with added TBHP. The major product yield with TBHP is essentially the same as the standard conditions yield (13 $\pm$ 1% 1-adamantanol), while the run with AIBN increases the 1-adamantanol yield to 19 $\pm$ 1% after 24 h. The selectivities (the 3°/2° ratio, ratio of 1-adamantanol to 2-adamantanone times a statistical factor

(49) The sensitivity of manometer vs pressure transducer is actually about the same ($\pm$0.13% vs $\pm$0.15%, respectively), but the pressure transducer is capable of handling pressure readings in a broader range (0−100 psig compared to the <1 psig range of the manometer). Hence, with the pressure transducer we were able to scale-up the reaction, thereby allowing real-time pressure readings over a ca. 12 psig range, ca. 12-fold better than our manometer allows.

(50) Given the scale used for the stoichiometry study in the previous work,[13] the uncertainty in pressure readings might be sizable in comparison to the actual pressure loss. The amount of oxygen consumed is estimated to be 0.025 mmol (0.25 mmol of adamantane, assuming 20% conversion at 48 h and a 2:1 ratio). With an assumed 100 mL total volume, only a 5 ($\pm$0.1) mmHg pressure change would have been observed at room temperature, so that a reading error of $\pm$1 mmHg would introduce an error of $\pm$20%.

Table 2. Estimated Rate Constants Obtained from Fitting the Radical-Chain Mechanism in Scheme 3 to the Kinetic Data in Figure 5[a]

	$k_{initiation}$ or k_1 ($M^{-1}\,h^{-1}$)	$k_{H-abstraction}$ or k_3[b] ($M^{-1}\,h^{-1}$)	$k_{termination}$ or ($k_{10} + k_{10}'$) ($M^{-1}\,h^{-1}$)	$k_{propagation}$ ($M^{-1}\,h^{-1}$)[c]	
				experimental	related literature[51]
standard conditions	~0.0015	~3.5	~1		
standard conditions + AIBN	~10 (in h^{-1})	~1	~2	k_3' ~80 at 80 °C[d]	0.288 at 30 °C
standard conditions + *t*-BuOOH	~20 (in h^{-1})	~0.1	~1.5	k_2'' ~100 at 80 °C[e]	0.0162 at 30 °C

[a] The rate constants refer to 80 °C. The observed rate constants from a three- or four-parameter fit are not expected to be accurate to better than $10^{\pm 1}$. [b] AdmOO• + Adm-H → AdmOOH + Adm•; the absolute rate constant for reaction of cumene toward its own peroxy radical is 10.8 $M^{-1}\,h^{-1}$ (or 0.18 $M^{-1}\,s^{-1}$) at 30 °C.[40] [c] $k_{propagation}$ equals the k_3' or k_2'' for the reactions defined in footnotes *d* and *e* below (and discussed more in the Supporting Information), rate constants which should not be confused with the k_2 and k_3 of Scheme 3. [d] (CN)Me_2COO• + Adm-H → (CN)Me_2COOH + Adm•. [e] *t*-BuOO• + Adm-H → *t*-BuOOH + Adm•.

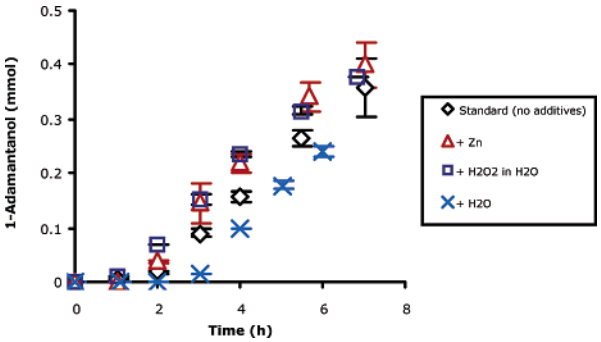
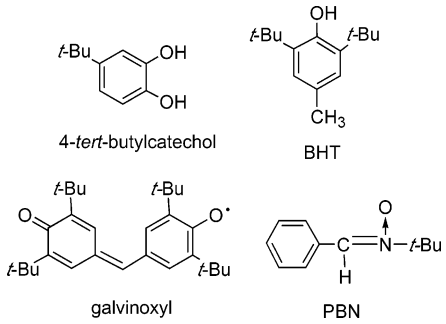


Figure 6. Lack of any significant effects upon adding Zn (0.028 mmol) or 30% H_2O_2 (0.2 mmol) in H_2O and the inhibition effect upon adding H_2O at the start of the adamantane hydroxylation reaction.

Chart 1. Radical Inhibitors Used in the Present Studies[a]



[a] Two of the inhibitors, 4-*tert*-butylcatechol and BHT, are the identical scavengers used in the prior work.[12,13]

of 3 to correct for the number of available 3°/2 °C−H bonds) with or without the radical initiator are same within experimental error: 16(±3):1 versus 14(±1):1, providing evidence that the deliberately initiated and normal reactions are one and the same, namely, autoxidation.

Mackinetics was used to fit the kinetic curves following the formation of 1-adamantanol. The elementary steps entered into the program are the appropriate steps from the autoxidation mechanism in Scheme 3 as detailed in the Supporting Information. A grid search was performed on the independent rate constants to generate the best-fit rate via numerical integration; the resulting rate constants are given in Table 2. The good fits provide additional kinetic evidence in support of the mechanism in Scheme 3.

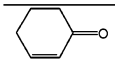
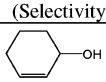
Neither H_2O_2 (30% in H_2O) nor Zn (−100 mesh, 99.998%, prewashed with dilute HCl to activate the surface and dried under vacuum at RT) has a measurable effect on the induction period or the resultant kinetic curve (Figure 6). The product yields after 24 h with 33 equiv (vs precatalyst Q_{11}-**1**) of added 30% H_2O_2 (in H_2O) are the same as the normal yields within experimental error. A control of adding H_2O only (the same amount as added in the 30% H_2O_2 experiment) shows that the addition of H_2O alone leads to a longer induction period (~2.5 h vs ~1 h for the addition of 30% H_2O_2 in H_2O). Therefore, pure hydrogen peroxide would be expected to eliminate the induction period in the absence of the masking, inhibiting effect of added H_2O. The product yields for the run with added Zn are reduced to 7 ± 1% 1-adamantanol as compared with our standard yield of 12 ± 1%, zinc apparently serving as an (inefficient) radical inhibitor. Although we do not see a large reduction of the induction period (from 10 h to ~1 h) as seen in the previous work,[12] our result with added Zn is actually similar in that a 1 h induction period results in both cases. Restated, it appears that added Zn serves primarily to remove inhibitors present in the prior reaction conditions.[12] This shows just how misleading the interpretation of such "additive" experiments can be in the absence of reliable kinetic studies supporting a reliable mechanism from which to interpret such inhibitor (i.e., such single-point kinetic) experiments.

In summary, organic hydroperoxide (ROOH), organic hydroperoxide radicals (ROO•, derived from AIBN plus O_2), or hydrogen peroxide (HOOH) have a significant effect on the reaction as expected for the presence of free radicals in the adamantane hydroxylation reaction. The higher stability of the 3° radical over the 2° radical also explains the selectivity observed for 1-adamantanol over 2-adamantanol/2-adamantanone.

Effects of Radical Inhibitors. Four radical scavengers, 4-*tert*-butylcatechol, 2,6-di-*tert*-butyl-4-methylphenol (BHT or butylated hydroxyltoluene), galvinoxyl, or 2-phenyl-*N*-*tert*-butylnitrone (PBN hereafter) were added at the start of the reaction (0.2 mmol vs 6 mmol substrate) in four independent experiments. All four runs gave 0% 1-adamantanol after 24 h (detection limit 0.001−0.01 mmol, or 0.02−0.2%). These inhibition results further support the free-radical-initiated mechanism of adamantane hydroxylation with Q_{11}-**1**. Note that we have used the same two radical scavengers (*tert*-butylcatechol and BHT) used in the previous studies, but which were claimed to have no effect.[12,13,52] Moreover, positive inhibition results were obtained in our hands even with a 30-fold lower inhibitor concentration than that employed in the prior work.[12,13]

(51) Hendry, D. G.; Mill, T.; Piszkiewicz, L.; Howard, J. A.; Eigenmann, H. K. *J. Phys. Chem. Ref. Data* **1974**, *3*, 937−978.

Table 3. Autoxidation of Cyclohexene in 1,2-dichloroethane at 38 °C and 1 Atm O_2[a]

Precatalyst	Yield (%) (Selectivity[b])		
			
$Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$	19 ± 1 (11 ± 1)	9.4 ± 0.5 (5.2 ± 0.4)	1.8 ± 0.1 (1)
$[Bu_4N]_5Na_3[(1,5\text{-}COD)Ir{\bullet}P_2W_{15}Nb_3O_{62}]$[c]	6.6 ± 0.4 (7 ± 1)	3.3 ± 0.2 (3.3 ± 0.4)	1.0 ± 0.1 (1)

[a] Reaction conditions: 1.0 mL of cyclohexene, 6.0 mL of 1,2-dichloroethane, 8.6−8.8 μmol of precatalyst, 38 °C, 1 atm O_2, reaction time 48 h. [b] Selectivity was calculated as the ratio of the product to cyclohexene oxide. [c] This precatalyst is not totally soluble in the 1,2-dichloroethane solvent, but we did not wish to introduce an additional variable by changing the solvent.

Our ability to inhibit or initiate (vide supra) the reaction with known, free-radical inhibitors or initiators provides disproof of the claim in the prior work that "... the induction period is related to the activation of the ruthenium polyoxometalate with molecular oxygen".[12] Instead, the induction period is fully accounted for by classic, free-radical autoxidation chemistry.

Cyclohexene Autoxidation and Catechol Dioxygenase Control Experiments. Our previous study of the polyoxometalate-supported transition metal precatalyst, $[(1,5\text{-COD})Ir{\bullet}P_2W_{15}Nb_3O_{62}]^{8-}$, showed it initiates autoxidation with O_2 leading to ~70 products, 27 of which were identified.[21] That paper also points out the ca. 70 products in the GC trace is a simple but powerful method to detect autoxidation catalysis. Hence, we tested Q_{11}-**1** for its ability to catalyze cyclohexene autoxidation in comparison to a control with $[(1,5\text{-COD})Ir{\bullet}P_2W_{15}Nb_3O_{62}]^{8-}$. The prediction is, of course, that it will.

GC traces of both precatalyst's oxidation mixtures show similar product profiles (Figure S6 of the Supporting Information). Table 3 shows the yields of the three major products of the two runs (not including cyclohexen-1-yl hydroperoxide). The results in Table 3 demonstrate that Q_{11}-**1** is an efficient precatalyst for the facile autoxidation of cyclohexene.

Precatalyst Q_{11}-**1** was also tested in the catechol dioxygenase reaction[5,9] of 3,5-di-*tert*-butylcatechol (3,5-DTBC hereafter) oxygenation. As expected, precatalyst **1**, $\{[WZnRu^{III}_2(OH)(H_2O)](ZnW_9O_{34})_2\}^{11-}$, is inactive over 133 h for the 3,5-DTBC dioxygenase reaction, a result consistent with the same result[5] by another researcher from our group using an earlier, separate batch of **1**. The inability to catalyze the catechol dioxygenase catalysis plus the ability to catalyze cyclohexene autoxidation further refutes the claim that inorganic precatalyst Q_{11}-**1** acts as an inorganic dioxygenase.

Some Additional Control Experiments. We performed the following additional experiments in part in response to issues raised by Professor Neumann to whom we provided a preprint of this paper; details are reported in the Supporting Information. We thank Prof. Neumann for raising the issues that follow. A control experiment testing the possible effects of excess Q^+Cl^- in the precatalyst **1** as an initiator to the autoxidation as well as the catalytic ability of Q^+Cl^- without precatalyst **1** showed that there is no discernible effect within experimental error of changing the amount of Q^+Cl^- present. In addition, changing the solvent pretreatment to exactly that used in the prior work had no effect. Our attempt to repeat the prior report of *trans*-cyclooctene epoxidation failed, the *cis*-oxide being the primary product in our hands.

The results of these additional controls offer no evidence for a dioxygenase pathway but, rather, are consistent with the autoxidation pathway in Scheme 3. We also requested a sample of $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$ from Prof. Neumann (i.e., a sample made in his labs) for a control experiment to see how it behaves in our hands but, unfortunately, never received a response to that specific request.

Critical Reanalysis of the Other Data Previously Claimed in Support of a Dioxygenase Mechanism. For the sake of completeness, it is important to analyze the other prior data previously interpreted in terms of a dioxygenase pathway[12,13] to be sure that the mechanism in Scheme 3 can explain *all* of the available data. This is done in the Supporting Information for the interested reader. The end result is that the autoxidation mechanism in Scheme 3 is consistent with all of the available data.

Summary and Conclusions

We have re-investigated the interesting, *albeit impure* as *reported*,[5] sandwich-type polyoxometalate precatalyst, $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$, for its adamantane[53−62] hydroxylation reaction. Trace amounts of peroxide could be

(52) There are at least two possibilities for lack of positive results in the prior work: (i) the radical inhibitors used previously degraded;and/or (ii) the inhibitors were not concentrated enough to inhibit the radical reaction. There is literature precedent of BHT giving negative inhibition results due to the use of too low a concentration.[22] However, at a 30-fold lower inhibitor concentration than the previous studies, we found that (16 mM) *tert*-butylcatechol, BHT, galvinoxyl, or PBN completely inhibited adamantane hydroxylation, while *tert*-butylcatechol, BHT, or BHA (used previously at 500 mM) showed no effect in the previous work.[12,13] Hence, the inhibitor concentration is not the reason for the literature report of noninhibition. It is quite possible that the inhibitors the authors used had degraded, but no details on the source or purity of the inhibitors used are available. Unfortunately, these scavenging results, along with the reported 2:1 adamantane:O_2 stoichiometry, the reported rate law, and the claimed nonreactivity of cyclohexene—which is easily autoxidized as expected in our experiments—are aspects of the prior work that proved unrepeatable in our hands while following the previously published experimental details.

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detected at the end of the reactions. $H_2{}^{18}O$ is shown to be formed from $^{18}O_2$, refuting the prior negative evidence, presented without stated detection limits, that no $H_2{}^{18}O$ was observed.[12] Kinetic studies yield a fractional rate law that is readily and quantitatively—if not only—explained by a radical-chain reaction. The stoichiometry of adamantane products/O_2 determined by two different methods is a net ~1:1 autoxidation stoichiometry in our hands instead of the previously reported 2:1 dioxygenase stoichiometry. The radical initiator AIBN and the organic hydroperoxide *t*-BuOOH eliminate the induction period completely, increasing the initial rate about 20-fold. Four radical scavengers completely inhibited the adamantane hydroxylation reaction, including two inhibitors previously reported to have no effect but which completely inhibit the reaction in our hands at 1/30 the prior, reported concentrations. A further analysis and critique of the previous work[12,13] has also been included as part of the Supporting Information.

The clear conclusion of this work is that the polyoxometalate precatalyst $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$ prepared as previously described is a classic autoxidation catalyst, at least in our hands. There is no compelling evidence for, and now strong evidence against, the prior claim of a novel dioxygenase catalyst for adamantane hydroxylation based on the precatalyst $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$. Significant parts of the prior work (the adamantane products/O_2 stoichiometry; the rate law; the results with radical inhibitors; the claimed nonreactivity of cyclohexene[63] despite its weak and thus reactive allylic C−H bond) have not proved repeatable from the sometimes inadequate experimental details provided, again at least in our hands. A main component of the present work is that we have emphasized Platt's scientific method involving the disproof of alternative hypotheses.[64,65] The significance of Platt's method is impossible to overemphasize: "for exploring the unknown, there is no faster method".[64] Moreover, Platt's method with its emphasis on disproof helps shield us as fallible, human researchers against the well-established but still flourishing, insidious problem in science of "experimenter expectancy",[66] that is, of our seeing what we wish to see in our results (i.e., rationalizing our results in terms of our initial hypothesis or beliefs and/or attempting the impossibility of "proving" something rather than focusing on disproof). In the present case, our attempted disproof focused on the key hypothesis in oxidation catalysis, one apparent in Ingold's recent work[22] and one stated concisely in the conclusion section of Limburg's 2003 review: "Radicals are far more frequently involved in oxygenation reactions than originally assumed; in fact, they appear almost omnipresent".[67] We could not disprove the radical catalysis hypothesis in the present case; instead, our results strongly support it. Certainly any future claim of new dioxygenase catalysis must thoroughly test for and attempt to disprove rigorously the omnipresent autoxidation catalysis hypothesis: the well-established existence of classic, often facile, free-radical-chain autoxidation.

Note Added in Proof. Nomiya and co-workers have independently checked the preparation of $K_{11}[WZnRu(III)_2(OH)(H_2O)(ZnW_9O_{34})_2]$, K_{11}-**1**, reported by Neumann and co-workers;[30] they find a yellow-brown material results that is sometimes a mixture of crystals.[29,68] They also find that the UV−visible absorption spectrum of K_{11}-**1** does not exhibit the reported 430 nm peak,[68] analogous to the findings reported herein. Nomiya and co-workers also find no reversible $Ru^{III/II}$ or $Ru^{IV/III}$ redox peaks at positive potentials,[68] results again consistent with our findings for Q_{11}-**1**. Overall, Nomiya reports[29,68] that they find it very difficult to reproduce the reported preparation[30] of K_{11}-**1** as a primary product when *cis*-$[RuCl_2(DMSO)_4]$ is used as the ruthenium source, even though they followed the original synthesis "as closely as possible".[29]

Acknowledgment. We thank Jeremy J. Nelson in Professor C. Michael Elliott's Group at Colorado State University for performing the electrochemistry experiments on **1** reported in the Supporting Information. Each of the following persons read the paper and provided comments that led to

(62) A question we considered is whether adamantane is a substrate unusually susceptible for autoxidation from this work and prior work.[53−61] Its 99 kcal/mol C−H BDE[44] argues "no". However, our opinion is that adamantane should not be used as the *only* substrate for any type of oxidation catalysis. Substrates such as cyclohexene or propene are much tougher tests of any claim of dioxygenase catalysis.

(63) The previous work reported that cyclohexene (with its 87 kcal/mol allylic C−H BDE) gave "no products" (see p 11974 in fnt 13; no detection limits were provided) even though adamantane with its stronger 99 kcal/mol C−H BDE does react. We find it hard to accept this observation as supporting a dioxygenase as previously proposed since (i) the evidence is negative and (ii) the result is unprecedented and counter-intuitive; that is, to our knowledge there is no known oxidant of any type that will preferentially activate adamantane's 99 kcal/mol C−H bonds but leave untouched the weaker 87 kcal/mol allylic C−H bond of cyclohexene. Of course there is also (iii) our finding that cyclohexene is in fact readily autoxidized under the same conditions which autoxidize adamantane.

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(65) A lingering, alternative hypothesis that is difficult to disprove completely is the "magic ingredient or impurity" hypothesis: that is, that there is some ingredient or impurity present in one study and one lab only, which is a key to the claimed dioxygenase chemistry (i.e., and despite our attempt to reproduce the previously published work as closely as possible). *If* correct and *if* such a putative magic ingredient were identified, then that would of course be a profound finding—a "magic bullet" that would be a key to turning on (or off) dioxygenase vs autoxidation catalysis for at least $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$. *However*, the one reasonable and logical possibility here that we can see, namely, an adventitious radical-chain initiator in our studies, can be ruled out by our observed kinetics. Those kinetics implicate a reasonably reproducible initiation step that depends on the polyoxoanion precatalyst complex plus dioxygen and adamantane. In short, the magic ingredient hypothesis has no support at present as well as the following evidence squarely against it: (i) the reaction's reproducibility in our hands; (ii) our kinetics and the implied initiation step; (iii) the fact that our $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$ precatalyst is made by the published prescription and has the spectroscopic signatures indicated in the prior work (save the $\lambda =$ 430 nm band); and (iv) the *identical* 12% yield of the main product, 1-adamantol. *The latter is a powerful piece of evidence, as it places the restriction on the dioxygenase mechanism that it must coincidentally provide the same yield of the product as the now documented autoxidation mechanism!* Accordingly, the burden of support of the "magic ingredient" hypothesis is left to its proponents.

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revisions that strengthened the paper: the Associate Editor of *Inorganic Chemistry* who handled the paper and an anonymous referee who shared his or her expertise with radical autoxidation chemistry, its mechanisms, and possible stoichiometries. This work was supported by NSF Grant 0314678.

Supporting Information Available: IR spectrum of $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$; a TGA curve from the molecular sieves/$H_2{}^{18}O$ experiment; a typical kinetic curve following the formation of 1-adamantanol showing how the maximum, steady-state rate measurements were made; plot of the maximum rate versus pO_2; cyclic voltammgram of $Q_{11}\{[WZnRu_2(OH)(H_2O)](ZnW_9O_{34})_2\}$; rate law derivation for the proposed mechanism in Scheme 3 of the main text at the steady-state; rate law derivation for the mechanism with the alternative initiation step not involving O_2 (and leading to a zero-order pO_2 dependence) at the steady-state; kinetic models used in Mackinetics to fit the observed kinetic curves in Figure 5; attempted synthesis of 1-adamantyl peroxide; GC traces of cyclohexene autoxidation catalyzed by Q_{11}-1 and $[Bu_4N]_5Na_3[(1,5\text{-COD})Ir{\cdot}P_2W_{15}Nb_3O_{62}]$; control experiments testing the effect of excess Q^+Cl^- in the precatalyst **1**; control experiment testing the catalytic ability of Q^+Cl^- without precatalyst **1**; control experiment testing for any effects of solvent pretreatment; control experiment testing for the reported *trans*-cyclooctene epoxidation reaction; discussions of the other putative evidence in the prior work;[12,13] tabulated literature overview of adamantane oxidation by ruthenium complexes and different oxidants (O_2, hydroperoxides, etc.). This material is available free of charge via the Internet at http://pubs.acs.org.

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