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Vanadium-Based, Extended Catalytic Lifetime Catechol Dioxygenases: Evidence for a Common Catalyst

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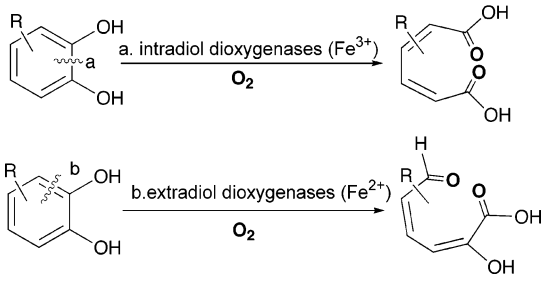
Abstract: In 1999, a catechol dioxygenase derived from a V-polyoxometalate was reported which was able to perform a record >100 000 total turnovers of 3,5-di-*tert*-butylcatechol oxygenation using O_2 as the oxidant (Weiner, H.; Finke, R. G. *J. Am. Chem. Soc.* **1999**, *121*, 9831). An important goal is to better understand this and *other* vanadium-based catechol dioxygenases. Scrutiny of 11 literature reports of vanadium-based catechol dioxygenases yielded the insight that they all proceed with *closely similar selectivities*. This, in turn, led to a "common catalyst hypothesis" for the broad range of vanadium based catechol dioxygenase precatalysts presently known. The following three classes of V-based compounds, 10 complexes total, have been explored to test the common catalyst hypothesis: (i) six vanadium-based polyoxometalate precatalysts, (n-$Bu_4N)_4H_5PV_{14}O_{42}$, (n-$Bu_4N)_7SiW_9V_3O_{40}$, (n-$Bu_4N)_5[(CH_3CN)_xFe^{II}{\cdot}SiW_9V_3O_{40}]$, ($n$-$Bu_4N)_9P_2W_{15}V_3O_{62}$, ($n$-$Bu_4N)_5Na_2[(CH_3CN)_xFe^{II}{\cdot}P_2W_{15}V_3O_{62}]$, and ($n$-$Bu_4N)_4H_2$-$\gamma$-$SiW_{10}V_2O_{40}$; (ii) three vanadium catecholate complexes, $[V^{V}O(DBSQ)(DTBC)]_2$, $[Et_3NH]_2[V^{IV}O(DBTC)_2]{\cdot}2CH_3OH$, and $[Na(CH_3OH)_2]_2[V^{V}(DTBC)_3]_2{\cdot}4CH_3OH$ (where DBSQ = 3,5-di-*tert*-butylsemiquinone anion and DTBC = 3,5-di-*tert*-butylcatecholate dianion), and (iii) simple $VO(acac)_2$. Product selectivity studies, catalytic lifetime tests, electron paramagnetic resonance spectroscopy (EPR), negative ion mode electrospray ionization-mass spectrometry (negative ion ESI-MS), and kinetic studies provided compelling evidence for a common catalyst or catalyst resting state, namely, Pierpont's structurally characterized vanadyl semiquinone catecholate dimer complex, $[VO(DBSQ)(DTBC)]_2$, formed from *V-leaching* from the precatalysts. The results provide a considerable simplification and unification of a previously disparate literature of V-based catechol dioxygenases.

Introduction

Oxygen activation for selective oxidation reactions continues to be a central and challenging subject in catalysis.[1−4] In nature, the discovery of dioxygenase enzymes, that is, enzymes catalyzing the incorporation of both oxygen atoms of O_2 into substrates with no added protons or electrons, dates back to the 1950s with the discovery of oxygen incorporation into catechol by pyrocatechase of *Pseudomonas* sp.[5] Since that time, mild, selective, and facile man-made dioxygenases have been the Holy Grail of biomimetic studies of oxidation catalysis.[3]

One important class of dioxygenase enzymes, catechol dioxygenases, catalyze the degradation of aromatic compounds.[6] Catechol dioxygenases have been classified into two groups, intradiol and extradiol dioxygenases (Scheme 1). Catechol dioxygenase enzymes containing non-heme $Fe^{II/III}$ or Mn^{II} have been discovered in nature.[7−10] Biomimetic model systems containing Fe(II/III),[8,10−19] V(IV/V) (Table 1), Ru(II),[20] Rh(III),[21,22] as well as several other metals[23] are known to catalyze catechol dioxygenation reactions.

Scheme 1. Definitions and Fe^{3+} versus Fe^{2+} Intradiol Catechol Dioxygenases (cleavage of the C−C bond between the two hydroxyl groups) versus Extradiol Catechol Dioxygenases (cleavage of one of the C−C bonds adjacent to the two hydroxyl groups)



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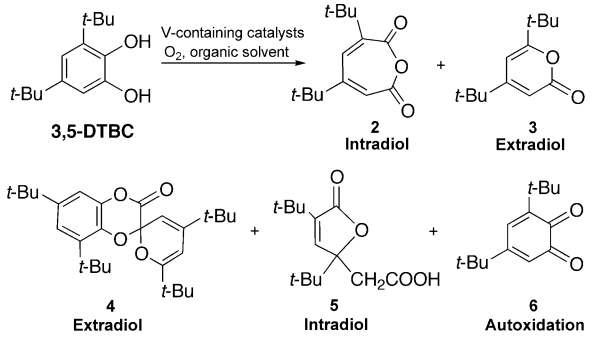
Scheme 2. Oxidative Cleavage of 3,5-DTBC by Vanadium-Based, Nonenzymatic Catechol Dioxygenase Catalysts



Vanadium-based nonenzymatic dioxygenase catalysts react with 3,5-di-*tert*-butylcatechol (hereafter 3,5-DTBC) to produce mixtures of three classes of products (Scheme 2):[24] intradiol cleavage products, 3,5-di-*tert*-butyl-1-oxacyclohepta-3,5-diene-2,7-dione (**2**) and 3,5-di-*tert*-butyl-5-(carboxymethyl)-2-furanone (**5**); extradiol cleavage products, 4,6-di-*tert*-butyl-2*H*-pyran-2-one (**3**) and spiro[1,4-benzodioxin-2(3*H*),2′(2*H*)-pyran]-3-one,4′,6,6′,8-tetrakis(1,1-dimethylethyl) (**4**); and the autoxidation product, 3,5-di-*tert*-butyl-1,2-benzoquinone (**6**). The product numbers in Scheme 2 will be used subsequently throughout this paper.

Previously, a survey of 28 vanadium-containing precatalysts revealed that the vanadium polyoxometalate plus Fe^{II} precatalyst, $(n\text{-}Bu_4N)_5[(CH_3CN)_xFe^{II}\cdot SiW_9V_3O_{40}]$, was able to accomplish 125 000 Total Turnovers (hereafter TTOs) of DTBC dioxygenation in ~300 h.[24] (For leading reviews on polyoxometalates, see elsewhere.[25−27]) This level of combined catalytic activity and lifetime is an improvement of *2 orders of magnitude* over the previous record of ~500 TTOs.[28] Practically, it means that a *few milligrams* of V-based precatalyst is able to convert *10 g* of DTBC into grams of isolable, pure products in ≤312 h.[24] Our prior work also shows that the O_2-uptake kinetics, beginning with V-based polyoxometalates, such as $SiW_9V_3O_{40}^{7-}$ or $P_2W_{15}V_3O_{62}^{9-}$, could be curve-fit with the two-step mechanism, A → B, then A + B → 2B, where the latter step is the kinetic definition of autocatalysis in which a product (B) is also a reactant.[29] Kinetics studies of four of the 28 precatalysts examined revealed that the true catalysts were *not* the starting vanadium complexes; rather, the V-based precatalysts reacted with a DTBC-derived product, B, to generate the true catalyst. This precatalyst conversion demands that understanding the nature of the true catalyst and eventually improving the broad selectivity seen with such V-based dioxygenase catalysts (Scheme 2) are important goals within the broader context of dioxygenase chemistry.

Tatsuno and co-workers reported catechol oxygenation catalysis using the heteropolyvanadates, $PV_{14}O_{42}^{9-}$, $MnV_{13}O_{38}^{7-}$, and $NiV_{13}O_{38}^{7-}$.[30] Isolation of the reaction intermediate afforded a blue compound, tentatively assigned as the dimer complex "$[V(DBSQ)(DBCatH)]_2$" by elemental analysis, IR, EPR results, and a cryoscopic measurement of the approximate molecular weight (DBCatH ≡ monoprotonated di-*tert*-butylcatecholate anion).[30]

The present contribution also builds off an important earlier observation by Professor C. G. Pierpont at the University of Colorado who, in his review of metal compounds containing catecholate and semiquinone ligands, noted that the "product distribution is rather similar" for catechol oxidations beginning with different sources of vanadium (see p 347 elsewhere).[31] Significantly, he also proposed that a mixed catecholate and semiquinone vanadium oxo compound, $[VO(DBSQ)(DTBC)]_2$, could be a soluble component of catechol oxidation by vanadium-based catalysts. Hence, the questions raised and addressed herein include the following: is there a common catalyst for the broad range of vanadium precursors employed for V-based catechol dioxygenases? Alternatively, do vanadium-based dioxygenases inherently lack selectivity for some as of yet unexplained reason(s)?

Herein, we test the specific hypothesis that there is, in fact, a common catalyst for the rather different vanadium-based catechol dioxygenase systems described in the literature. We report reaction selectivity, catalytic lifetime, EPR, MS, and kinetic evidence which support this "common vanadium catechol dioxygenases catalyst" hypothesis. Our evidence supports Pierpont's suggestion that $[VO(DBSQ)(DTBC)]_2$ is that common catalyst. A subsequent paper in this series presents kinetic studies which reveal how virtually any V-based precursors can yield the same V-based DTBC dioxygenase catalyst, via the novel concept of autoxidation-product-initiated dioxygenase catalysis.[32]

Experimental Section

Reagents. 3,5-DTBC (purchased from Aldrich, 99%, mp 96−99 °C) was recrystallized three times using *n*-pentane under argon (mp 99−100 °C) and stored in a Vacuum Atmosphere drybox (O_2 level ≤5

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ppm). (NB: it is important to recrystallize the 3,5-DTBC substrate more than one time to remove impurities such as 3,5-di-*tert*-butyl-1,2-benzoquinone.) The polyoxometalate precursors, $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$,[33] $(n\text{-}Bu_4N)_7SiW_9V_3O_{40}$,[34] $(n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$,[34,35] $(n\text{-}Bu_4N)_5Fe^{II}\cdot SiW_9V_3O_{40}$,[24] and $(n\text{-}Bu_4N)_5Na_2Fe^{II}\cdot P_2W_{15}V_3O_{62}$,[24] were synthesized according to the most recent literature procedures. $(n\text{-}Bu_4N)_4H_2\text{-}\gamma\text{-}SiW_{10}V_2O_{40}$, a gift from Prof. N. Mizuno, was prepared as described[36] and characterized by ^{183}W NMR. $VO(acac)_2$ (Aldrich, 95%) and VCl_3 (Aldrich) were stored in the drybox and used as received. $NaOCH_3$ (Fisher Scientific) was stored under N_2 and used as received. $[Co^{III}(3,5\text{-}DBSQ)(CN)_4]^{2-}$ crystals[37] were a gift from Prof. M. Wicholas. HPLC grade solvents (1,2-dichloroethane, acetonitrile, diethyl ether, and ethyl acetate) and anhydrous grade methanol were purchased from Aldrich and stored in the drybox; each of the above solvents was dried by standing for at least 48 h over ~5 vol % 3 or 4 Å molecular sieves that had been preactivated by heating at >170 °C under vacuum (≤1 Torr) for at least 12 h, then cooled under dry N_2 in the drybox. Anhydrous grade toluene was purchased from Aldrich, stored in the drybox, and used without further drying. Et_3N (Mallinckrodt) was distilled over BaO under Ar and stored in the drybox. Anhydrous certified ACS grade diethyl ether was purchased from Fisher Scientific and used as received. Argon gas was purchased from General Air (99.985%) and used as received.

Instrumentation. Air-sensitive samples were prepared in a drybox prior to analyses. GC analyses were performed on an HP (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: initial temperature, 200 °C (initial time, 2 min); heating rate, 2 °C/min; final temperature, 240 °C (final time, 3 min); injector temperature, 250 °C; FID detector temperature, 250 °C. GC-MS analyses were performed under the same temperature program on an Agilent 5973N/GC 6890 instrument equipped with a mass selective detector (70 eV) and an Agilent HP-5MS column (30 m). Negative ion electrospray ionization mass spectrometry (negative ion ESI-MS) analyses were performed on a Thermo Finnigan LCQ Advantage Duo MS directly coupled with a syringe pump (5 μL/min feeding speed and 15 μL/min at purging; spray voltage −4.5 kV, capillary voltage −(38−42) V, capillary temperature 180 °C) or on a Fisons VG Quattro-SQ spectrometer by directly injecting an acetonitrile solution (spray voltage −2.9 kV, sample cone voltage −25 V, source temperature 80 °C). NMR spectra were obtained in $CDCl_3$ or CD_3CN (Cambridge Isotope Lab). ^1H, ^{31}P, and ^{51}V NMR were recorded in 5 mm o.d. tubes on a Varian Inova (JS-300) NMR spectrometer. ^1H NMR was referenced to the residual impurity in the deuterated solvent; ^{31}P NMR was referenced to 85% H_3PO_4 in H_2O using the external substitution method, and ^{51}V NMR was referenced to neat $VOCl_3$ (Aldrich) using the external substitution method. Spectral parameters for ^{31}P NMR include: tip angle = 60° (pulse width 10 μs); acquisition time, 1.6 s; sweep width, 10 000 Hz. Spectral parameters for ^{51}V NMR include: ^{51}V tip angle = 90° (pulse width 3.1 μs); acquisition time, 0.096 s; sweep width, 83 682.0 Hz. Infrared spectra were obtained on a Nicolet 5DX spectrometer as KBr pellets (Aldrich, spectrophotometric grade) or in a CaF_2 cell (A = 0.1 mm). UV−visible spectra were obtained on an HP 8452A diode spectrophotometer in glass UV cells sealed by ground-glass stopcocks. Electron paramagnetic resonance (EPR) spectra were recorded on a Bruker EMX 200U EPR spectrometer. Quartz EPR tubes of 4 mm o.d. were used, and DPPH (2,2-diphenyl-1-picrylhydrazyl) was used as the reference compound (g = 2.0037). Single-crystal X-ray diffraction crystallography was performed on a Bruker SMART 1K CCD X-ray diffractometer. CHN elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, Georgia) or Galbraith Laboratories (Knoxville, Tennessee).

Preparation of Polyoxometalate Precursors. The polyoxometalate precursors, $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$,[33] $(n\text{-}Bu_4N)_7SiW_9V_3O_{40}$,[34] $(n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$,[34,35] $(n\text{-}Bu_4N)_5Fe^{II}\cdot SiW_9V_3O_{40}$,[24] and $(n\text{-}Bu_4N)_5Na_2Fe^{II}\cdot P_2W_{15}V_3O_{62}$,[24] were prepared according to the most recent literature procedures. Further details about the syntheses and characterizations are provided in the Supporting Information.

Preparation and Characterization of Vanadium−Catecholate Complexes. Three vanadium catecholate complexes, $[VO(DBSQ)(DTBC)]_2$,[38] $[Et_3NH]_2[VO(DTBC)_2]\cdot 2CH_3OH$,[39] and $[Na(CH_3OH)_2]_2[V(DTBC)_3]_2\cdot 4CH_3OH$,[40,41] were chosen from the literature as the best available examples of relatively simple, well-characterized vanadium-catecholate complexes that provide three alternative hypotheses as to common components in V-based catechol dioxygenase reactions. The details of their synthesis and characterization are provided in the Supporting Information.

Synthesis and Characterization of Deprotonated Di-*tert*-butylcatecholate Salt, Na_2(3,5-DTBC). The details of these experiments are recorded in the Supporting Information, including Figures S8 and S9.

Selectivity Experiments. The DTBC dioxygenase selectivities of the 10 vanadium model compounds which follow were examined with the same substrate-to-vanadium ratio to test whether they produce a similar product distribution: $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$, $(n\text{-}Bu_4N)_7SiW_9V_3O_{40}$, $(n\text{-}Bu_4N)_5[Fe^{II}\cdot SiW_9V_3O_{40}]$, $(n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$, $(n\text{-}Bu_4N)_5Na_2[Fe^{II}\cdot P_2W_{15}V_3O_{62}]$, $(n\text{-}Bu_4N)_4H_2\text{-}\gamma\text{-}SiW_{10}V_2O_{40}$, $[V^{V}O(DBSQ)(DTBC)]_2$, $[Et_3NH]_2[V^{IV}O(DBTC)_2]\cdot 2CH_3OH$, $[Na(CH_3OH)_2]_2[V^{V}(DTBC)_3]_2\cdot 4CH_3OH$, and $VO(acac)_2$. Oxygenation experiments were carried out on a volume-calibrated oxygen-uptake line, as detailed in the Supporting Information elsewhere.[24] The standard procedure used for these experiments is as follows: 400 ± 5 mg (ca. 1.8 mmol) of three-times-recrystallized 3,5-DTBC was weighed 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-coated magnetic stir bar. Using a 10 mL glass syringe, approximately 8 mL of predried HPLC grade 1,2-dichloroethane was transferred into the flask. Then, the flask was sealed with a Teflon stopcock and taken out of the drybox. The flask was connected to the oxygen-uptake line through an O-ring joint, and the reaction solution was frozen in a dry ice/ethanol bath (−76 °C). Two pump-and-fill cycles with O_2 as the refill gas were performed. Next, the dry ice bath was replaced with a temperature-controlled oil bath. The temperature of the flask was increased to 40 ± 0.7 °C and allowed to equilibrate with stirring for 25 min. In the drybox, 0.5−2.0 mg of a predetermined vanadium precatalyst (mole ratio of substrate to the vanadium in the precatalysts of ca. 1000:1) was weighed into a glass

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vial and dissolved in ca. 0.2 mL of 1,2-dichloroethane (0.2 mL toluene was used for $[Na(CH_3OH)_2]_2[V(DTBC)_3]_2 \cdot 4CH_3OH$ because of its greater solubility in toluene). The resultant precatalyst solution was drawn into a 1 mL gastight syringe and brought out of the drybox with its needle protected from air via its insertion into a septum-capped vial. This precatalyst solution was then injected through the sidearm of the reaction flask and $t = 0$ was set. Pressure readings from the manometer were used to follow the reaction (±1 Torr or ca. ±1% precision over a pressure loss of ca. 80−100 Torr). The reaction was stopped at 23.5 h unless noted otherwise, and the reacted mixture was diluted 21-fold using $1,2\text{-}C_2H_4Cl_2$ prior to GC analysis.

Catalytic Lifetime Experiments. These experiments were performed to determine if the V complexes, $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$, $(n\text{-}Bu_4N)_7SiW_9V_3O_{40}$, $(n\text{-}Bu_4N)_5[Fe^{II}\cdot SiW_9V_3O_{40}]$, $(n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$, $(n\text{-}Bu_4N)_5Na_2[Fe^{II}\cdot P_2W_{15}V_3O_{62}]$, $[V^{V}O(DBSQ)(DTBC)]_2$, $[Et_3NH]_2[V^{IV}O(DBTC)_2]\cdot 2CH_3OH$, $[Na(CH_3OH)_2]_2[V^{V}(DTBC)_3]_2\cdot 4CH_3OH$, and $VO(acac)_2$, differ in their catalytic lifetimes. Experiments were performed with the apparatus described in the literature;[24] a catalytic lifetime experiment is briefly described below, in which about half the amount of substrate (~29 mmol), yielding ≤50 000 TTOs, is employed in comparison to the largest scale previously employed (~63 mmol substrate which yielded 100 000−150 000 TTOs[24]). The precatalyst amounts were in the range of 0.4−0.7 μmol for all the catalytic lifetime experiments.

The ≤50 000 TTO catalytic lifetime experiment proceeded as follows: ca. 6.50 g (29.2 mmol) of three-times-recrystallized 3,5-DTBC was weighed into a 250 mL round-bottom flask with a sidearm and an egg-shaped 1 in. × $^1/_2$ in. Teflon-coated magnetic stir bar. About 125 mL $1,2\text{-}C_2H_4Cl_2$, measured in a graduated cylinder, was added to the reaction flask. Then, 1.1−4.0 mg of a chosen precatalyst was weighed into a vial (the mole ratio of substrate to the catalyst is ca. 45000:1), dissolved in ca. 0.2 mL of $1,2\text{-}C_2H_4Cl_2$, and quantitatively transferred into the reaction flask via a pipet. The flask was sealed, brought out of the drybox, and frozen in a dry ice/ethanol bath (−76 °C) for 1 h. Next, the flask was connected to a condenser under an argon flow. Two pump-and-fill cycles with O_2 as the refill gas were performed, followed by heating the solution to 65 ± 1 °C via a temperature-controlled oil bath (this took ca. 30 min). Once a constant temperature was achieved, $t = 0$ was noted. The flask was connected to an oxygen tank through a bubbler, keeping a slow positive flow of O_2 (ca. 0−5 psig) atop the solution. An aliquot of ca. 0.15 mL was drawn from the solution every 24−48 h with a disposable polyethylene 1 mL syringe equipped with a predried stainless steel needle. The aliquot was diluted 21-fold using $1,2\text{-}C_2H_4Cl_2$, and then subjected to GC analysis.

The 100 000−150 000 TTO catalytic lifetime experiments were performed via the same procedures as above, except ca. 14 g of 3,5-DTBC was employed (substrate-to-precursor mole ratio within 100 000−150 000).

$VO(acac)_2$ Aging Studies. The effects of aging the $VO(acac)_2$ were tested due to our inability to reproduce the low TTOs observed (<6000) in the TTO catalytic lifetime experiment reported in our previous studies.[24] A putatively fresh sample was purchased from Aldrich (95%) and stored in the drybox upon receiving. One aged sample of $VO(acac)_2$ was prepared by placing the fresh $VO(acac)_2$ in a vial, taking the vial out of the drybox, and then exposing the sample to atmospheric oxygen for 2 months. The other sample was prepared by heating ground $VO(acac)_2$ (from a bottle which had been stored outside the drybox for over 2 years) in a 60 °C thermostatic oven in air for 6 days. During this time, the color darkened from green to green−black. The above two aged samples together with a fresh sample were examined by EPR in CH_2Cl_2 (the two aged samples did not totally dissolve, presumably due to the presence of insoluble decomposition products). Double-integrated EPR peak areas of the three compounds were compared, but no difference was found within experimental error. The first aged sample was also tested in a 100 000−150 000 TTO catalytic lifetime experiment and yields the same catalytic lifetime within experimental error as the fresh sample (Table S3 of the Supporting Information).

^{31}P NMR Following Oxygen-Uptake Using Precatalyst ($n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$. Results are shown in Figure S10; and the experimental details are included in the Supporting Information.

EPR Following Oxygen-Uptake Experiments. The procedure employed here is exactly as reported above in the "Selectivity Experiments", except that (i) the precatalyst amount was chosen so that the amount of vanadium from the precatalyst was ca. 6−8 μmol, (ii) toluene was employed as the solvent in place of 1,2-dichloroethane, with the toluene being frozen using liquid nitrogen instead of dry ice/acetone and (iii) the precatalyst was premixed with DTBC in the drybox instead of being injected into a stirred $DTBC/O_2$ solution. The oxygen pressure loss was monitored with a manometer. An aliquot of the reaction solution was drawn under an oxygen flow at ca. 0.5−2 h after the oxygen pressure started to decrease. The reaction solution was sampled again after no further pressure change was observed for >2 h.

Quantitative EPR Analysis. The standard solutions were prepared by dissolving an air-stable, semiquinone-containing crystal, $[Co^{III}(3,5\text{-}DBSQ)(CN)_4]^{2-}$,[37] into toluene (1.0 M) and serial diluting to concentrations of 0.10 and 0.010 M. The reaction solution (catalyzed by the precatalyst $VO(acac)_2$) was harvested ca. 2 h after oxygen-uptake ceased, as described above (in the section titled EPR Following Oxygen-Uptake Experiments). The double-integrated area of $[VO(DBSQ)(DTBC)]_2$ was compared to that of $[Co^{III}(3,5\text{-}DBSQ)(CN)_4]^{2-}$ to estimate the concentration of $[VO(DBSQ)(DTBC)]_2$.

Negative Ion ESI-MS Analysis. These experiments were performed on a mass spectrometer (Thermo Finnigan LCQ) directly coupled to a syringe pump. The solvent in the syringe serves as the matrix for the negative ion ESI-MS. Solid samples were diluted in the drybox using predried acetonitrile to ca. 10 μM (ca. 0.01−0.1 mg in 1 mL) and placed in a 2 mL septum screw-capped vial. The sample was then transferred into a rinsed 500 μL syringe outside the drybox; the syringe needle was inserted into the MS sampler hose as fast as possible to avoid oxygen contamination. The injection rate was controlled by a syringe pump. The MS peaks were observed ca. <1 min after the injection. The influence of water in the ESI-MS matrix was examined with a set of control experiments using $[VO(DBSQ)(DTBC)]_2$ as the sample and varying the ratio of $CH_3CN{:}H_2O$ from 1:0, 9:1, 1:1, 1:9, to 0:1 in the solvent. Although this instrument is not optimal for pure water samples (as shown by the lower signal level as the water ratio goes up), the same peaks were observed as in neat acetonitrile.

Kinetic Competence Experiments. The kinetic competence experiments were set up the same way as the selectivity experiments described above, except that a higher concentration (0.46−0.48 mM) of the precursor was used to increase the O_2-uptake rate.

Attempted Catalyst Isolations. Isolation and characterization of the actual catalyst, if possible, would of course provide direct evidence of the identity of the true catalyst, although the obvious caveat here is that good catalysts are often metastable transients that are not readily isolable (see "Halpern's Rules" as detailed elsewhere[50]). Nevertheless, it was important to attempt to isolate an active catalyst (or even a deactivated form of the active catalyst) from the vanadium-containing

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Table 1. A Compilation of the Product Distributions and Mass Balance of 11 Literature Reports of V-Based Oxidative Cleavage of 3,5-DTBC

		Product Distributions (%)				Mass Balance and TTOs				
	precatalyst(s)[a]	**2**	**3**	**4**	**6**	mass balance	TTO_{max}[b]	TTO_{conv}[c]	TTO_{yield}[d]	ref
1	$VO(acac)_2$, VO(salen), VCl(salen), VCl(saldpt)	39−43	6−15		22−28	≤83%	1000	1000	≤750	28
2	$[V(salen)(DbcatH)_2]\cdot 1/2CH_2Cl_2$, $[V(saldpt)(DBcatH)]\cdot CH_2Cl_2$[e]	42	11		24	77%	100		77	42
3	$[VO(acac)(OCH_3)]_2$, $[VO(tmh)(OCH_3)]_2$, $(VOaap)_2$, $(VOdmba)_2$, $(VOdba)_2$, $(VO(acac)OCH_3)_2$	46−48	7−10		22−25	≤82%	100	100	≤82	43
4	$[LVO(acac)]$, $[LVO(phen)]^+PF_6^-$, $[LVO(bipy)]^+PF_6^-$ (O_2 or H_2O_2 as oxidant)	<10[f]			70[f]	<80%				44
5	VO(acac)(TCCat)	45	6		24	75%	100		75	45
6	$PV_{14}O_{42}^{9-}$, $MnV_{13}O_{38}^{7-}$, $NiV_{13}O_{38}^{7-}$, $VO(acac)_2$	34−36	11−20	3−13	15−21	≤82%	100		≤82	30
7	[VO(acac)(DTBCat)]	45	6		24	75%				46
8	*cis*-$V_2W_4O_{19}^{4-}$, 1,4,9-$[PV_3W_9O_{40}]^{6-}$, $V_{10}O_{28}^{6-}$, $VO(acac)_2$	15−39			5−19	58%	100		≤58	47
9	$VO(HL)_2OH$, $(VO)_2L_2SO_4\cdot 4H_2O$	45−48	5−10		23−25	≤82%	100	100	≤82	48
10	TEA[VO(TEA)]	80[g]				≤82%	10		8.2	49
11	$SiW_9V_3O_{40}^{7-}$, $Fe^{II}\cdot SiW_9V_3O_{40}^{5-}$, $P_2W_{15}V_3O_{62}^{9-}$, $Fe^{II}\cdot P_2W_{15}V_3O_{62}^{7-}$, $PV_{14}O_{42}^{9-}$, $VO(acac)_2$, etc. (28 total)	40−57	6−15	10−18	9−25	≤94%	4500	4500	4230	24

[a] Inactive vanadium-containing precatalysts omitted from the above table, but listed here for the sake of completeness are $[V(salen)(cat)]\cdot 0.1CH_2Cl_2$ and $[V(salen)(4\text{-}Bcat)]\cdot H_2O$;[42] $Na[VO(DBcat)_2]$ and $Na_2[VO(OCH_3)(DBcat)_2]$;[30] VO(acac)(cat) and VO(acac)(3-Bcat);[46] $[VW_5O_{19}^{3-}]$;[47] VO(NTA);[49] and $[SiW_{11}VO_{40}^{5-}]$.[24] [b] $TTO_{max} = moles_{substrate}/moles_{precatalyst}$. [c] $TTO_{conv} = moles_{substrate,\ consumed}/moles_{precatalyst}$. [d] $TTO_{yield} = moles_{sum\ of\ products}/moles_{precatalyst}$. [e] The product distribution was not reported for the denoted precatalyst. [f] We speculate the reason for these different selectivities is that the bulky ligand (L) blocks the oxygen binding to the vanadium−catecholate compound. [g] This yield should be the sum of **2** and **6** due to its "red" color; the yield of **5** is 3%. Abbreviations: salen = ethylenebis(salicylideneaminato); saldpt = *N*,*N*′-(3,3′-dipropylamine)bis(salicylideneaminato); tmh = 2,2,6,6-tetramethylheptandione; H_2aap = *o*-hydroxyacetophenone; H_2dmba = 1,5-bis(*p*-methoxyphenyl)-1,3,5-pentanedione; H_2dba = 1,5-diphenyl-1,3,5-pentanetrione; L (entry 4) = [η-CpCo{P(O)$(OC_2H_5)_2$}$_3$]$^-$; bipy = 2,2′-bipyridine; TCCat = tetrachlorocatecholate; DBcat/DTBCat = 3,5-di-*tert*-butylcatecholate; H_2L (entry 9) = 2,2′-dihydroxy-3,3′-diacetyl-5,5′-dichlorodiphenylmethane; TEA = triethanolamine; cat = pyrocatecholate; Bcat = *tert*-butylcatechol; and NTA = nitrilotriacetic acid.

polyoxometalate precatalysts, especially in light of earlier indications that this *might* be possible.[24,30] However, in the end, we were not able to isolate analytically pure catalysts from these particular studies, so that we turned to the use of in situ spectroscopic studies (vide infra). Details of the attempted isolation studies are in the Supporting Information, along with figures showing IR, negative ion ESI-MS, or EPR of the resultant materials (Figures S11−S14).

Results and Discussion

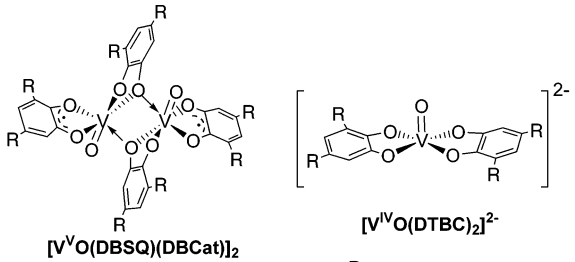
A Literature Survey of V-Based 3,5-Di-*tert*-butylcatechol Oxygenations. The published selectivity and lifetime data for the 11 reports of vanadium-based DTBC oxygenations are shown in Table 1. The tabulated data yield the following insights: muconic acid anhydride (**2**) is the major product (40−50%), followed in decreasing order by 3,5-di-*tert*-butylquinone (**6**, 20−30%), pyranone (**3**), the spiro product (**4**), and the furanone product (**5**); the last three products have a combined yield of 10−20%. *Clearly, the product selectivities are rather similar for all of the V-based DTBC precatalysts examined in the literature to date and which are active*, as Professor Pierpont had hinted.[31] A second, relevant insight comes from the literature for Fe catechol dioxygenase models;[13] the product distributions therein are often quite different compared to those in Table 1. For example, Fe(III) model complexes with tripodal N_4 donor ligands and catecholate ligands catalyze the intradiol cleavage of 10−100 equiv of 3,5-DTBC to product **2** in 30−84% yield (the yield of the autoxidation product **6** is less than 6%);[18] $[Fe^{III}(tacn)Cl(DTBC)]$ (where tacn = 1,4,7-triazacyclononane) reacts with O_2 to produce extradiol cleavage product **3** in up to 78% yield with the addition of 1 equiv of $AgBF_4$ and 20 equiv of 4-methylpyridine (the yield of an isomer of product **3**, 3,5-di-*tert*-butyl-2*H*-pyran-2-one, is 20%; the yield of product **6** is less than 1%).[17] These results show that, as one would expect, there is not an inherent insensitivity in the DTBC oxygenation product selectivities, at least when considering different metals.

The hypothesis for the remainder of this work then became the "common catalyst hypothesis", namely, that there is a common catalyst for the rather different vanadium-based catechol dioxygenase systems described in the literature, Table 1. The results in Table 1 are, of course, themselves consistent with and supportive of this hypothesis.

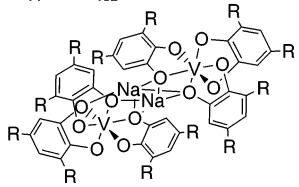
Choice of Three Simple, Well-Characterized Vanadium-Containing DTBC Complexes for Further Investigation. Given the data in Table 1 and the resultant common catalyst hypothesis, the next task was to identify vanadium-DTBC and/or -DBSQ complexes known in the literature that were logical starting points as either (i) precatalysts closer in composition and structure to the hypothesized true catalyst(s), or conceivably (ii) actual catalysts themselves. Three vanadium-DTBC or DTBC/DBSQ complexes quickly rose to the top of the list from a scrutiny of the literature: Pierpont and co-worker's[38] $[V^{V}O(DBSQ)(DTBC)]_2$, Raymond and co-worker's[39] $[Et_3NH]_2[V^{IV}O(DTBC)_2]\cdot 2CH_3OH$, and Luvena and co-worker's[40] $[Na(CH_3OH)_2]_2[V^{V}(DTBC)_3]_2\cdot 4CH_3OH$ (Chart 1). In addition, it proved to be productive to examine the simple $VO(acac)_2$ as an example of a well-known V-precatalyst without DTBC or DBSQ ligands. The $VO(acac)_2$ was purchased commercially (Aldrich, 95%), whereas the other three complexes were prepared according to the literature as detailed in the Supporting Information.

All three vanadium catecholate complexes were characterized by UV−visible spectroscopy, negative ion electrospray ionization mass spectrometry (ESI-MS), and elemental analysis (plus

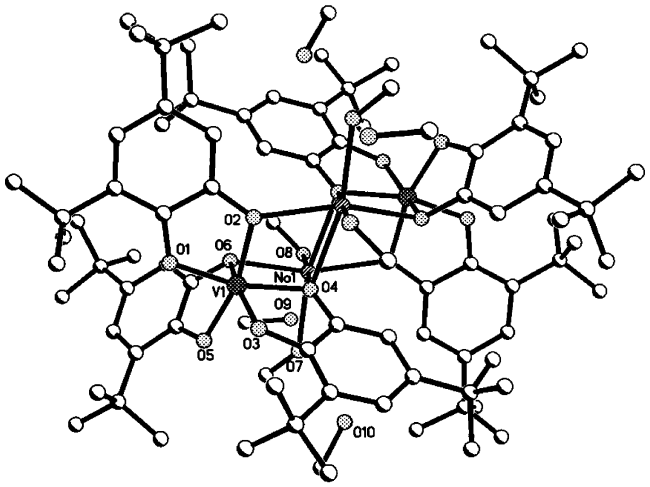
Chart 1. Structures of the Three Vanadium Catecholate Complexes Studied Herein (*tert*-butyl groups are shown as R, only one isomer of $[V^{IV}O(DTBC)_2]^{2-}$ is shown, and coordinated methanol is not shown in the middle structure for the sake of clarity). Also Shown Is the Structure of $[Na(CH_3OH)_2]_2[V(DTBC)_3]_2{\cdot}4CH_3OH$ Obtained through X-ray Single-Crystal Diffraction



$[V^{V}O(DBSQ)(DBCat)]_2$ $[V^{IV}O(DTBC)_2]^{2-}$



$[Na(CH_3OH)_2]_2[V^{V}(DTBC)_3]_2$



$[Na(CH_3OH)_2]_2[V^{V}(DTBC)_3]_2$ Crystal Structure

single-crystal X-ray crystallography in the case of $[Na(CH_3OH)_2]_2[V^{V}(DTBC)_3]_2{\cdot}4CH_3OH$). The elemental analysis results of different batches of $[VO(DBSQ)(DTBC)]_2$ show that a variable amount of methanol solvates are present in the compounds; hence, the difficulty in obtaining single crystals is ascribed to crystal deterioration due to solvate loss at room temperature.[38] In summary, analytically pure samples of each of the three literature vanadium DTBC/DBSQ complexes were prepared so that their DTBC oxygenation selectivities, kinetics, and catalytic lifetimes could be studied.

Confirmation of the Similar Selectivities For the Three Vanadium DTBC/DBSQ Complexes, $VO(acac)_2$, As Well As for Six V-Polyoxometalate Precatalysts. Selectivity experiments were carried out in 1,2-$C_2H_4Cl_2$ for the 10 complexes; studies of isolated, active components and control studies were also performed (entries 11−15, Table 2), for a total of 15 studies. The key results include the following: (i) The selectivities are the same for the three V-precatalysts, as well as for $VO(acac)_2$ (entries 1−4, Table 2). The O_2-uptake values are also the same, and interestingly, no induction periods are observed for $[VO(DBSQ)(DTBC)]_2$ or $VO(acac)_2$ (the absence of an induction period for $VO(acac)_2$ is as reported in the literature[24]). Note that the lack of an induction period is kinetic evidence that we are closer to the catalyst in these cases, if not at a true catalyst in the $[VO(DBSQ)(DTBC)]_2$ case, vide infra.

(ii) The vanadium-containing polyoxometalates are all the same within experimental error in their selectivities and O_2-uptake values.[51] Interestingly, there are no discernible induction periods for two of the polyoxometalates, $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$ and $(n\text{-}Bu_4N)_4H_2\text{-}\gamma\text{-}SiW_{10}V_2O_{40}$. This, plus knowledge of the properties of these particular polyoxometalates,[33,36] suggests the release of $V^{V}O_2^{+}$ or possibly $V^{IV}O^{2+}$ from the polyoxometalate structure,[52] as supported by the thermogravimetric studies on $H_2(V^{V}O_2)PW_{12}O_{40}$ and by the structure of $Na_2(V^{IV}O)[SiW_{12}O_{40}]{\cdot}13H_2O$.[52a]

(iii) Note that Fe is not needed for the oxygenation catalysis activity, *only V is required for facile dioxygenase catalysis* from the 15 entries in Table 2. A control using $(n\text{-}Bu_4N)_4SiW_{12}O_{40}$ confirms that polyoxometalates lacking V are *inactive* toward catechol oxygenation.[24]

(iv) The control using $(n\text{-}Bu_4N)_5SiW_{11}VO_{40}$ (Table 2, entry 11 (data from our previous study[24])) reveals *the inactivity of this single vanadium-containing polyoxometalate*. This inactivity is consistent with either its stability and/or the possibility that more than one vanadium is needed for oxygenation catalysis.

(v) The two active species isolated from $(n\text{-}Bu_4N)_5[Fe^{II}{\cdot}SiW_9V_3O_{40}]$[24] (grayish black, in the presence of DTBC under O_2) and $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$[30] (blue, in the presence of DTBC under N_2) give the same selectivities within experimental error as the other species in Table 2. The blue species was tentatively assigned by Tatsuno and co-workers as "$[V(DBSQ)(DBCatH)]_2$" (DBCatH, monoprotonated di-*tert*-butylcatecholate anion).[30]

(vi) The (no vanadium) control of $Na_2(DTBC)$ alone was also examined under our conditions. Previously, deprotonated 3,5-DTBC was reported to react with dissolved oxygen in ether.[53] Depending on the amount of H_2O present, 3,5-di-*tert*-butyl-5-(carboxymethyl)-2-furanone (product **5**) can be obtained in 20−60% yield.[53] In our hands, the light blue disodium salt of 3,5-DTBC in diethyl ether plus O_2 yields furanone **5** in 13−21% yield (following acidifying the product mixture with 5% HCl and then extracting with 1,2-$C_2H_4Cl_2$). The major product in the vanadium-catalyzed reactions, muconic acid anhydride (product **2**), is barely detectable by GC (<0.01%). If the above reaction is carried out in 1,2-$C_2H_4Cl_2$ (i.e., in the solvent used for most of our selectivity experiments,) instead of in Et_2O, then the major products are 3,5-di-*tert*-butyl-1,2-benzoquinone (30% yield) and an unknown compound (m/z = 248, yield ∼57% estimated from the area ratio to 3,5-di-*tert*-butyl-1,2-benzoquinone). All other products (i.e., **2**−**5**) are less than 1%. A

(51) Ca. 14−18% less of product **4** in the cases of the vanadium-based polyoxometalate precatalysts and $VO(acac)_2$ compared to our literature[24] is seen, due presumably to the instability of product **4** in the reaction solution (higher yields of product **4** can be obtained if sampled immediately after the O_2-uptake ceases).

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Table 2. Catalytic Selectivity Experiments, as well as O_2-Uptake and Induction-Period Observations, for the Three Classes of Vanadium-Based Compounds[a]

		Products Yield (%)					
		2	**3**	**4**	**6**	induction period?	$\Delta mol_{O2}/mol_{DTBC}$
				Four Simple V Complexes			
1	$[VO(DBSQ)(DTBC)]_2$	40 ± 2	12 ± 1	-	18 ± 1	no	0.64
2	$[Et_3NH]_2[VO(DTBC)_2]\cdot 2CH_3OH$	38 ± 1	12 ± 1	-	18 ± 1	yes	0.63
3	$[Na(CH_3OH)_2]_2$ $[V(DTBC)_3]_2\cdot 4CH_3OH$	38 ± 1	14 ± 1	1 ± 1	18 ± 1	yes	0.62
4	$VO(acac)_2$	42 ± 1	11 ± 1	-	16 ± 1	no	0.63
				V−Based Polyoxometalate Precatalysts			
5	$(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$	46 ± 2	13 ± 1	-	16 ± 1	no	0.64
6	$(n\text{-}Bu_4N)_7[SiW_9V_3O_{40}]$	49 ± 1	17 ± 1	2 ± 1	11 ± 1	yes	0.61
7	$(n\text{-}Bu_4N)_5[Fe^{II}\cdot SiW_9V_3O_{40}]$	40 ± 1	13 ± 1	3 ± 1	12 ± 1	yes	0.59
8	$(n\text{-}Bu_4N)_9[P_2W_{15}V_3O_{62}]^b$	40 ± 2	14 ± 1	3 ± 1	18 ± 1	yes	0.49
9	$(n\text{-}Bu_4N)_7[Fe^{II}\cdot P_2W_{15}V_3O_{62}]^b$	42 ± 2	13 ± 1	4 ± 1	22 ± 1	yes	0.55
10	$(n\text{-}Bu_4N)_4H_2\text{-}\gamma\text{-}SiW_{10}V_2O_{40}$	43 ± 1	13 ± 1	-	18 ± 1	no	0.66
11	$(n\text{-}Bu_4N)_5SiW_{11}VO_{40}$ (control; data from literature[24])	~1					
				Isolated Active Components			
12	isolated active species from $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$	39 ± 2	13 ± 1		19 ± 1	no	0.61
13	isolated active species from $(n\text{-}Bu_4N)_5[Fe^{II}\cdot SiW_9V_3O_{40}]^c$	40 ± 2	7 ± 1		13 ± 1	no	0.45
				Controls			
14	$Na_2(DTBC)^d$				30 ± 3		
15	$[Co^{II}(CH_3CN)_6](BF_4)_2^e$				2 ± 1		

[a] Experimental conditions: ca. 400 mg of 3,5-di-*tert*-butylcatechol, ca. 1000:1 mole ratio of substrate to vanadium in the precatalysts, 40.0 ± 0.7 °C, 9 mL of 1,2-$C_2H_4Cl_2$ solvent; reaction stopped at 23.5 h; product yields obtained by GC. [b] These two reactions were stopped at ca. 42 and 24 h, respectively. [c] This reaction was stopped at ca. 94 h; the exact number of moles of the precatalyst are not known for this incompletely characterized compound. [d] This experiment was run with ca. 410 mg of Na_2DTBC (1.55 mmol), 2 equiv of $(n\text{-}Bu_4N)Br$ (1 g, 3.l mmol, to facilitate the phase-transfer of Na_2DTBC into the organic phase), 8 mL of 1,2-$C_2H_4Cl_2$ solvent; reaction stopped at 161 h; product mixture was concentrated, acidified with 5% HCl, and then extracted into 1,2-$C_2H_4Cl_2$ and analyzed by GC. [e] Substrate to precatalyst mole ratio is ca. 700:1.

control experiment showed that the GC product yields are identical for the original product solution compared to the extracted solution acidified with 5% HCl. In short, the major intradiol cleavage dioxygenase reaction product **2** is obtained *only* upon interaction with a metal, in our case vanadium.

(vii) The control experiment using $[Co^{II}(CH_3CN)_6](BF_6)_2$ produces only 2% of benzoquinone product **6**, showing that the vanadium-based systems do give very different products and selectivities than such slow autoxidation systems.

In summary, *the 12 vanadium precursors in Table 2 all give the same selectivities within experimental error in DTBC oxygenation catalysis.*

Catalytic Lifetimes of the Four Simple V-Complexes and Five V-Polyoxometalate Precatalysts. (A) ≤50 000 Total Turnover (TTO) Experiments.[54] A series of catalytic lifetime experiments (≤50 000 TTOs) were carried out with ca. 29 mmol 3,5-DTBC and ca. 0.7 μmol precatalyst to determine if the catalyst lifetimes vary or are similar. The four simple vanadium complexes and five vanadium polyoxometalate complexes *show the same catalytic lifetimes within experimental error* (Figure 1). The product selectivities are also the same within experimental error for these nine precatalysts examined in the catalytic lifetime experiments. (Full details are provided in Table S2 of the Supporting Information.) Rather clearly, the true catalyst cannot be polyoxometalate-based. In short, the results offer further support for the hypothesis that a common catalyst is generated regardless of the V-based precursor employed.

(B) 100 000−150 000 TTO Experiments. Several larger-scale catalytic lifetime experiments were carried out with mole ratios of substrate to catalyst (3,5-DTBC to $(n\text{-}Bu_4N)_7SiW_9V_3O_{40}$ or $(n\text{-}Bu_4N)_5Fe^{II}\cdot SiW_9V_3O_{40}$) from 100 000:1 to

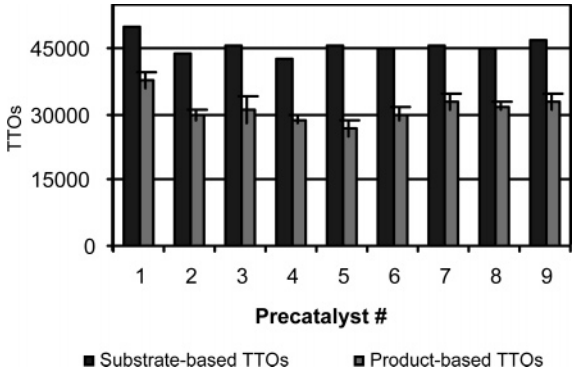
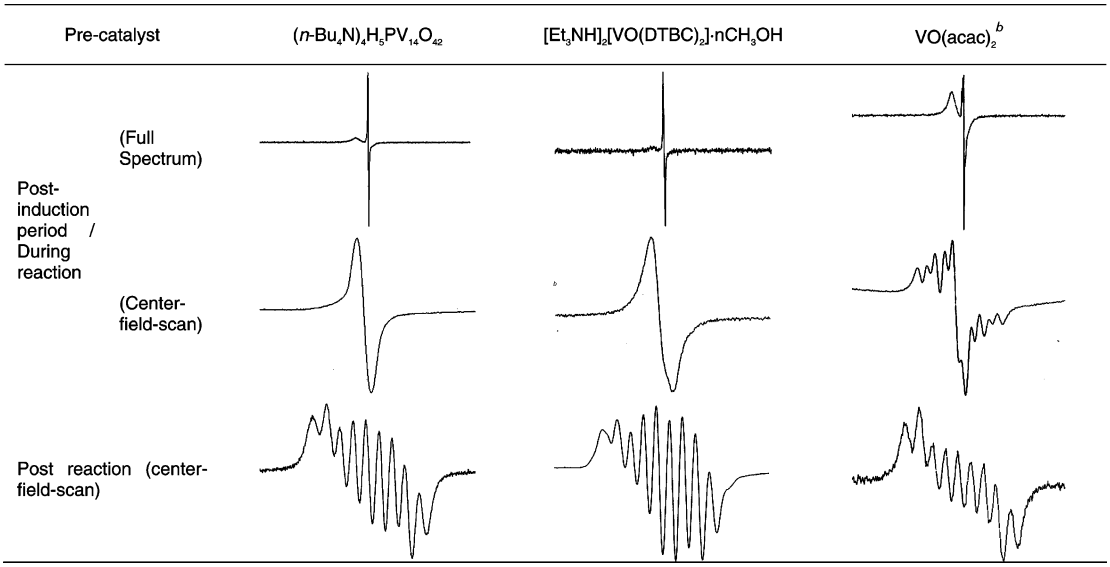


Figure 1. Catalytic lifetime study using nine different vanadium-based precatalysts. **1** = $[VO(DBSQ)(DTBC)]_2$; **2** = $[Et_3NH]_2[VO(DTBC)_2]\cdot 2CH_3OH$; **3** = $[Na(CH_3OH)_2]_2[V^V(DTBC)_3]_2\cdot 4CH_3OH$; **4** = $VO(acac)_2$; **5** = $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$; **6** = $(n\text{-}Bu_4N)_7SiW_9V_3O_{40}$; **7** = $(n\text{-}Bu_4N)_5[Fe\cdot SiW_9V_3O_{40}]$; **8** = $(n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$; **9** = $(n\text{-}Bu_4N)_5Na_2[Fe\cdot P_2W_{15}V_3O_{62}]$. Error bars for the substrate-based TTOs are not available due to the complete conversion (>99%) of the substrate at the end of each reaction.

150 000:1 to verify the prior record TTOs of ca. 100 000. The results show the product-based TTO catalytic lifetimes of the above two precursors of 60 000−80 000 (±5000) are comparable with the previous results employing $(n\text{-}Bu_4N)_5Fe^{II}\cdot SiW_9V_3O_{40}$ of 90 000−100 000 (±10 000) product-based TTOs.[24] Details of the results are provided in Table S3 of the Supporting Information.

Before our previous studies,[24] the highest reported catalytic lifetime of $VO(acac)_2$ was only ~500 TTOs.[28] Our previous result of the modest TTOs (<6000) exhibited by $VO(acac)_2$[24] was >10-fold better than that in the literature,[28] so that the <6000 TTOs seemed to be reliable at the time. However, given

Table 3. EPR Spectra of O_2-Uptake Solutions of Three Disparate Kinds of Precatalysts during and after the Reaction[a]



[a] The full spectra were scanned at a magnetic field width of 1000 G while the center-field scans were obtained at 50 G. [b] The spectra of the oxygenation reaction solution using $VO(acac)_2$ are different from those of $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$ or $[Et_3NH]_2[VO(DTBC)_2]\cdot n CH_3OH$. The reason for the lack of hyperfine coupling in the center-field-scan spectra is not known, but may result from interference from the additional ligands present in those two cases.

that our current experimental data show that all the vanadium-based precatalysts exhibit the same, high catalytic lifetimes within experimental error, a re-examination of the maximum TTOs exhibited by $VO(acac)_2$ seemed in order. Those experiments reveal that $VO(acac)_2$ exhibits the same 29 000 ($\pm$1000) TTOs of DTBC oxygenation as do all the other V-precatalysts within experimental error. Even after deliberately exposing the somewhat O_2-sensitive $VO(acac)_2$ to atmospheric oxygen, neither the double-integrated EPR area nor the catalytic lifetime result of aged $VO(acac)_2$ differ from those obtained from a fresh sample (details of the aging procedure are in the Experimental Section; lifetime results are provided in Table S3, Supporting Information). Hence, despite the fact that the underlying cause of the lower TTO performance of $VO(acac)_2$ in previous studies including ours is not clear,[24] the present reproducible result (three experiments) is that $VO(acac)_2$ behaves as a prototypical V−DTBC dioxygenase catalyst. In addition and although $VO(acac)_2$ oxidation is slow (by EPR), we suggest that this precatalyst be treated as oxygen-sensitive.

^{31}P NMR Control Confirming the Expected $(n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$ Precatalyst's Degradation under Catalytic Conditions. Because a clear prediction of our results so far is that polyoxometalate structures are at least partially degraded under DTBC/O_2 dioxygenase catalysis, an important control was to confirm this prediction by a direct method, such as ^{31}P NMR. As the further information and Figure S10 of the Supporting Information detail, a paramagnetic species is formed in the "V_3 cap" of $(n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$ upon the addition of just 3,5-DTBC (i.e., no O_2). Following the addition of O_2 and catalysis, the ^{31}P NMR peak shifts and loss of intensity confirm that the polyoxoanion structure has been at least somewhat degraded as predicted (Figure S10).

EPR Detection of A Common Active Species, $[VO(DBSQ)(DTBC)]_2$. EPR of reaction solutions employing three representative precursors, $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$, $[Et_3NH]_2[VO(DTBC)_2]\cdot 2CH_3OH$, and $VO(acac)_2$, all show an EPR signal at center field (g = 2.003−2.004) and a weak broad signal at g = 2.036−2.038. A clear, resolved view at the center signal (g = 2.003−2.004) was obtained by scanning at a magnetic field of 50 G instead of the whole field, 1000 G. The reaction solution employing $VO(acac)_2$ shows a 10 line signal (g = 2.006−2.007, A_{51V} = 2.1 G; Table 3) as reported in the literature.[38] We speculate that the EPR detected during the O_2-uptake reactions is a binary or ternary complex between the catalyst, the substrate, and O_2.[55]

The postreaction, center-field-scan results show that the *same* EPR spectrum is observed for the three disparate vanadium precatalysts shown in Table 3 following 3,5-DTBC oxygenation in toluene. A nine line spectrum centered at g = 2.004−2.006 ($\pm$0.002) with an average hyperfine coupling value (A_{51V}) of 3.04−3.08 ($\pm$0.1) G is observed in the EPR spectra of all three postreaction solutions. Significantly, the literature[38] reports a nine line EPR spectrum for $[VO(DBSQ)(DTBC)]_2$ centered at g = 2.004 with A_{51V} = 2.85 G (this coupling constant was obtained by simulation[38]), *a spectrum within experimental error of the EPR we observed* (Table 3 and Figure 2). This small coupling constant signifies the weak coordination of the semiquinone ligand DBSQ to the single diamagnetic vanadium(V). This EPR spectrum serves as a signature of $[VO(DBSQ)(DTBC)]_2$[38] since most V^{IV} compounds show an eight line spectrum with hyperfine coupling, $A_{51V} \sim$ 100 G. Given that we know that $[VO(DBSQ)(DTBC)]_2$ is as active as any complex tested, reacts without an induction period (vide infra), displays the maximum O_2-uptake rate of −0.5 mmol O_2/h (vide infra), and also gives a high TTO value, it follows from this EPR and other evidence that $[VO(DBSQ)(DTBC)]_2$ is at least a resting state of the true catalyst.

(54) The catalytic lifetime experiments at $\leq$50 000 TTOs (with 29 mmol 3,5-DTBC) are ca. half the largest scale used in the previous work[24] (with ca. 63 mmol 3,5-DTBC). All other conditions are the same, 0.5−0.7 μmol precatalyst, ca. 125 mL of 1,2-$C_2H_4Cl_2$, 65 °C, and 1 atm O_2.

(55) The compound exhibiting the 10 line EPR spectrum is tentatively assigned to $V(DBSQ)_3$ in the literature[38] via a parent ion at m/z = 712. In our experience, many different compounds can give this 712 peak (see Table 5 in the main text), so that the identity of the compound responsible for the 10 line EPR spectrum remains unclear, a point confirmed by Prof. Pierpont.

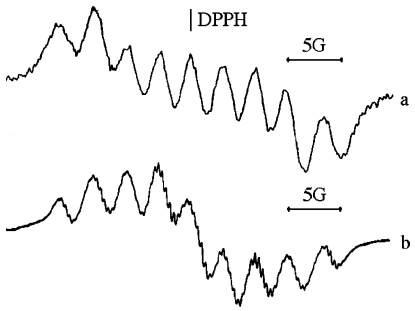


Figure 2. Center-field EPR spectrum of the postreaction solution of 3,5-DTBC and $VO(acac)_2$ in toluene (a). This resonance is identical within experimental error to those of postreaction solutions using precatalysts (n-$Bu_4N)_4H_5PV_{14}O_{42}$ and $[Et_3NH]_2[VO(DTBC)_2]\cdot nCH_3OH$, as shown in Table 3, as well as the authentic $[VO(DBSQ)(DTBC)]_2$ in toluene (b).[38]

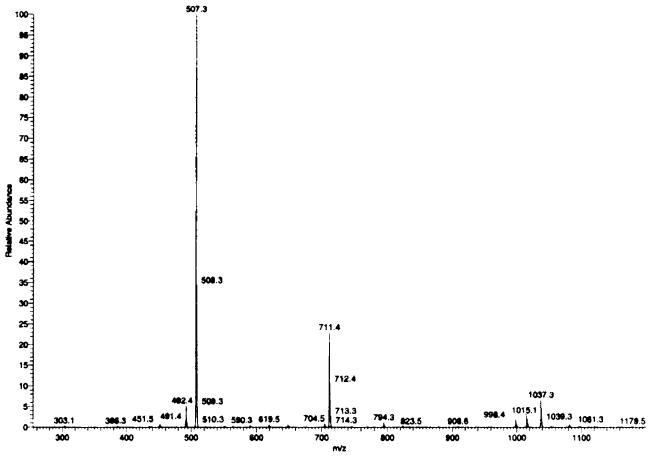


Figure 3. Negative ion ESI-MS spectrum of crystalline $[VO(DBSQ)(DTBC)]_2$. The parent ion peak is at $m/z = 1015$; the additional peak at $m/z = 1037$ is due to an exchange of two H^+ with Mg^{2+} of $MgSO_4$ from the distillation step. The base peak, at $m/z = 507$, is due to $[VO(DTBC)_2]^-$.

Importantly, if additional substrate was added to the post-reaction solution of 3,5-DTBC and $VO(acac)_2$ under O_2, the oxygen-uptake continued and the EPR changed back to the EPR observed during reaction. Additionally, the identical EPR diagnostic of $[VO(DBSQ)(DTBC)]_2$ was observed again once all the substrate was consumed (Figure S15 of the Supporting Information). These additional EPR experiments show that the vanadium species we observe in the three postreaction solutions (Table 3) with its characteristic nine line EPR spectrum is intimately connected to the catalytic cycle of DTBC oxygenation. Since that nine line spectrum is seen for authentic $[VO(DBSQ)(DTBC)]_2$, it follows that $[VO(DBSQ)(DTBC)]_2$ is an intimate part of the catalytic cycle.

Quantitation of the $[VO(DBSQ)(DTBC)]_2$ EPR Signal. Given the high sensitivity of EPR, it was important to determine whether $[VO(DBSQ)(DTBC)]_2$ is present more than at a trace level. Hence, the amount of the vanadyl semiquinone dimer complex in the postreaction solution was compared by double integration to the air-stable free-radical in crystalline $[Co^{III}(3,5\text{-}DBSQ)(CN)_4]^{2-}$,[37] a sample generously provided by Professor M. Wicholas. This comparison indicates that the $[VO(DBSQ)(DTBC)]_2$ semiquinone complex is present at ca. 5 mol % of the precatalyst ($VO(acac)_2$) concentration (ca. 0.035 mM), an estimate that is necessarily an approximation since $[VO(DBSQ)(DTBC)]_2$ is oxygen-sensitive and slowly degrades under aerobic conditions. The results, again, support $[VO(DBSQ)(DTBC)]_2$ as a key species intimately connected to the catalytic cycle.

Negative Ion ESI-MS Evidence of a Common Catalyst, $[VO(DBSQ)(DTBC)]_2$. When crystalline $[VO(DBSQ)(DTBC)]_2$ is dissolved in acetonitrile, the molecular ion peak at $m/z = 1015$ is observable, together with two main fragment peaks at $m/z = 507$, assigned to $[VO(DTBC)_2]^-$, and at $m/z = 711.4$, assigned to $[V(DTBC)_3]^-$ (Figure 3). When MS−MS was applied to the molecular ion peak, a peak attributable to $[VO(DTBC)_2]^-$ ($m/z = 507$) was observed.

The $m/z = 507$, 711, and 1015 peaks were simulated using the Isotope Viewer software (version 1.0; in the Qual Browser of the Thermo Finnigan MS). The corresponding formulas reproducing the observed molecular weights and isotopic abundances are $VO(C_{14}H_{20}O_2)_2$ corresponding to $[VO(DTBC)_2]^-$, $V(C_{14}H_{20}O_2)_3$ corresponding to $[V(DTBC)_3]^-$, and $[V_2O_2(C_{14}H_{20}O_2)_3(C_{14}H_{21}O_2)]$ corresponding to $[V_2O_2(DBSQ)(DBSQ\text{-}H)(DTBC)_2]^-$ (where $C_{14}H_{20}O_2$ corresponds to 3,5-di-*tert*-butylcatecholate dianion or 3,5-di-*tert*-butylsemiquinone anion, and $C_{14}H_{21}O_2$ corresponds to protonated 3,5-di-*tert*-butylsemiquinone (3,5-DBSQ-H) radical). The observed MS spectra and simulations are shown in Table 4; the match between the observed and simulated spectra is excellent.

As a semiquantitative method, ESI-MS is capable of identifying the main species in solution.[56−58] Significantly, two common major peaks $(VO(DTBC)_2^-$ of m/z 507, and $V(DTBC)_3^-$ of m/z 711.5) are detected in the mass spectra for two of the three vanadium catecholate compounds and the two isolated active components from the vanadium polyoxometalates (Table 5).

The possibility of either hydrolysis or oxygenation during the process of electrospray ionization needs to be considered. Oxygenation was minimized by sealing the sample in the drybox and exposing it to air only briefly just before injection. The effect of water was tested with several controls detailed in the Experimental Section; these experiments show the two common peaks $(VO(DTBC)_2^-$ and $V(DTBC)_3^-)$ are *not* generated through a reaction with water. Overall, the mass spectral data further support the hypothesis that the active species in the reaction solution is $[VO(DBSQ)(DTBC)]_2$ since its diagnostic fragment peak $VO(DTBC)_2^-$ at $m/z = 507$, as seen from authentic material $[VO(DBSQ)(DTBC)]_2$, is observed in the postreaction solution from disparate vanadium precatalysts, including active components isolated from two different V-containing polyoxometalate precatalysts.

Kinetic Competence of $[VO(DBSQ)(DTBC)]_2$ But Not of $[Na(CH_3OH)_2]_2[V(DTBC)_3]_2\cdot 4CH_3OH$. In oxygen-uptake experiments (Figure 4), $[VO(DBSQ)(DTBC)]_2$ was shown to be an active oxygenation catalyst with no induction period. Moreover, its rate is as fast as that of any catechol oxygenation catalysis we have observed for our conditions herein,[59] $d[O_2]/dt_{max} \sim -0.5$ mmol/h. This establishes $[VO(DBSQ)(DTBC)]_2$ as a kinetically competent catalyst or catalyst resting state.

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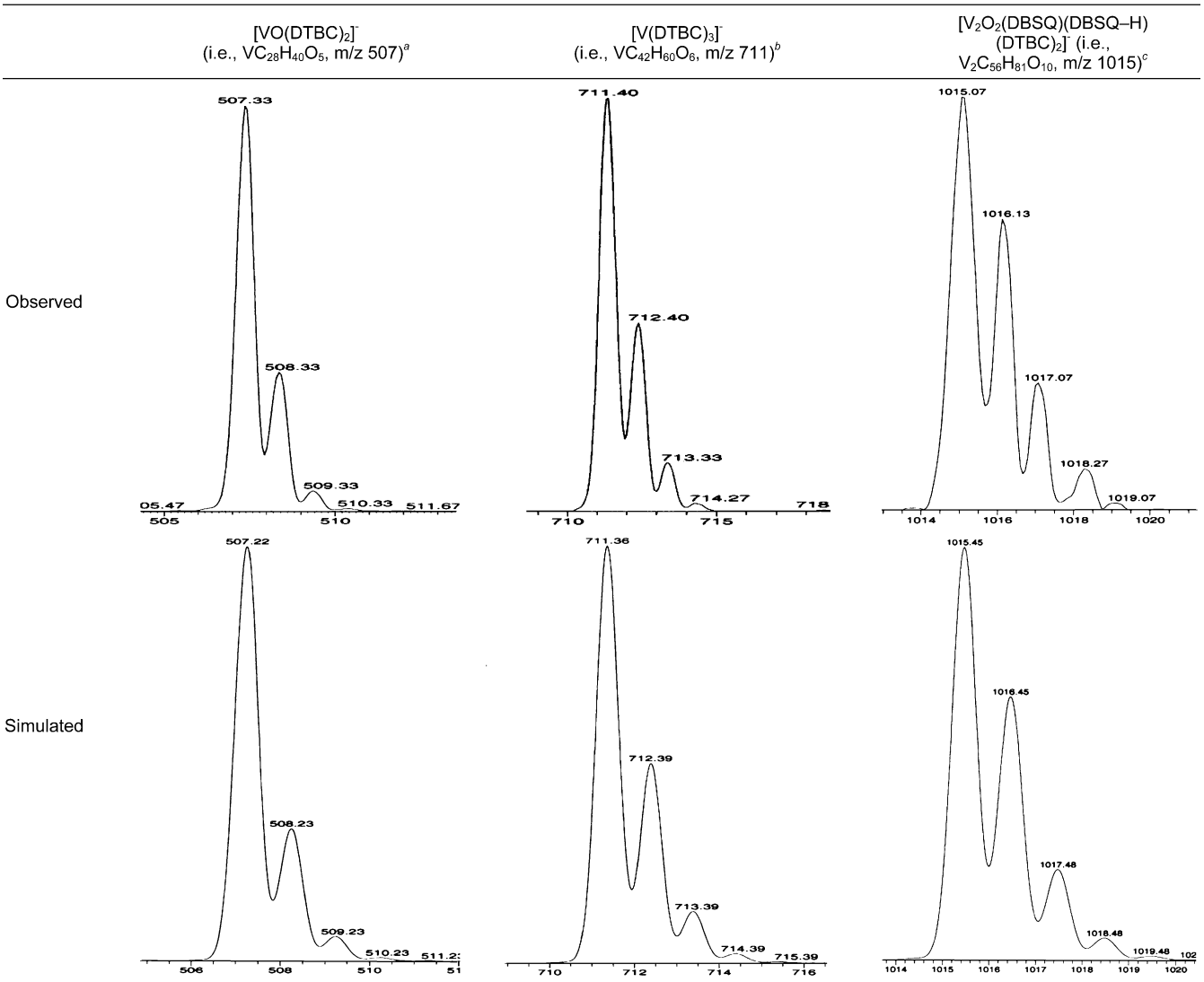
Table 4. Observed versus Computer-Simulated Parent Peaks and Isotopic Abundance Patterns for $[VO(DTBC)_2]^-$, $[V(DTBC)_3]^-$, and $[V_2O_2(DBSQ)(DBSQ\text{-}H)(DTBC)_2]^-$



[a] Observed peaks: 507.3, 508.3, and 509.3; simulated peaks: 507.2, 508.2, and 509.2. [b] Observed peaks: 711.4, 712.4, and 713.3; simulated peaks: 711.4, 712.4, and 713.4. [c] Observed peaks: 1015.1, 1016.1, 1017.1, and 1018.3; simulated peaks: 1015.5, 1016.5, 1017.5, and 1018.3.

Table 5. Negative Ion Electrospray Ionization Mass Spectrometry Identified Peaks of Various Precursors

	Relative Abundance					
ESI-MS peaks, *m/z*	451.4	491.4	507.3	711.4	998.4	1015.1
simple V-catecholate complexes						
$[VO(DBSQ)(DTBC)]_2$	<5	<5	100	25	<5	<5
$[Et_3NH]_2[VO(DTBC)_2]\cdot 2CH_3OH$			86	100	30	<10
$[Na(CH_3OH)_2]_2[V(DTBC)_3]_2\cdot 4CH_3OH$		<10	<5[a]	100		
Isolated Active Components						
isolated active species from $(n\text{-}Bu_4N)_5[Fe^{II}\cdot SiW_9V_3O_{40}]$	93		100	17		
isolated active species from $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$	25	<5	30	100		

[a] $[Na(CH_3OH)_2]_2[V(DTBC)_3]_2\cdot 4CH_3OH$ only shows a trace amount of $[VO(DTBC)_2]^-$ in its negative ion ESI-MS, as expected since it lacks an oxo ligand.

The remaining question is whether the other common MS peak (m/z = 711.5, $V(DTBC)_3^-$) is one of the catalytic species. In kinetic trials, an induction period of about 10 min is observed when $[Na(CH_3OH)_2]_2[V(DTBC)_3]_2\cdot 4CH_3OH$ is used as the precatalyst. Therefore, $V(DTBC)_3^-$ can be ruled out as a dominant catalyst.

In summary, $[VO(DBSQ)(DTBC)]_2$ is a kinetically competent catalyst or catalyst resting state. It is proposed as an active

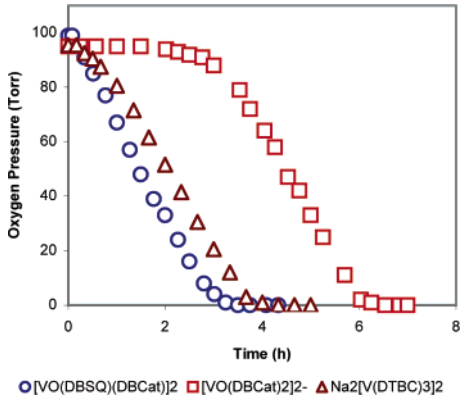


Figure 4. Kinetic competence or incompetence of the three vanadium catecholate complexes. Experimental conditions: 400 mg (1.8 mmol) of DTBC, 0.46−0.48 mM precatalyst/catalyst, ca. 9 mL of 1,2-$C_2H_4Cl_2$, 40 (±0.7) °C, and 1 atm O_2.

catalyst component, in (at least) the 11 tabulated vanadium catechol dioxygenases, based on the observation of its signature EPR spectrum in the postreaction solution of three different classes of precatalysts and the observation of its diagnostic half-fragment ($VO(DTBC)_2^-$) in the negative ion ESI-MS spectra of postreaction solutions beginning with disparate precatalysts, including vanadium catecholate complexes and polyoxometalates. The EPR and negative ion ESI-MS signatures reported herein can now be used to expand or refute the common catalyst finding herein with any other vanadium-based DTBC dioxygenase system.

Conclusions

In conclusion, we have (i) shown that a survey of 11 literature reports of vanadium-based catechol dioxygenases reveal that they all give very similar product ratios, an insight which, in turn, implies that a common catalyst is present; (ii) shown that 10 vanadium compounds that we have tested to date behave remarkably similar in their DTBC oxygenation catalysis selectivities and TTOs, again implying the existence of a common active catalyst; and (iii) provided EPR, negative ion ESI-MS, and kinetic data which all point to a common resting form of the catalyst, namely, Pierpont's novel $[VO(DBSQ)(DTBC)]_2$ complex.

This study also provides an excellent example of the phenomenon of "leaching" of a soluble form of the true catalyst from both heterogeneous[60] and homogeneous precatalysts. Combined with previous work,[60] our results indicate, for example, that the task of preparing single-site, supported V_x catalysts[61,62] (e.g., $x = 1,2$), which stay firmly supported and do not leach, is an important but probably very difficult challenge. Put in different terms, facile ligand substitution and leaching, especially in the presence of H_2O_2[32] and powerfully chelating ligands, such as DTBC dianion, is hereby established as the dominant hypothesis to be disproved for future V-based oxygenation catalysis.

In a subsequent paper, we provide further evidence that $[VO(DBSQ)(DTBC)]_2$ is a catalyst resting state that reversibly fragments to its reactive monomer, [VO(DBSQ)(DTBC)], as well as evidence for a novel autoxidation-product-initiated mechanism producing H_2O_2 for the release of V from V-based precatalysts to form $[VO(DBSQ)(DTBC)]_2$, that is, for a novel autoxidation-initiated dioxygenase.[32]

Acknowledgment. We thank Professor Cort G. Pierpont for multiple insightful discussions relevant to this work, and Professor Mark Wicholas for his generous gift of air-stable cobalt semiquione crystals employed in the quantitative EPR analysis. We thank Mr. Don Dick for his expert assistance with the GC-MS and negative ion ESI-MS experiments, Mr. Don Heyse for his expert assistance with the EPR experiments, and Dr. Susie Miller for her expert assistance with the single-crystal X-ray crystallography. This research is supported by NSF fund 9531110.

Supporting Information Available: Preparation of polyoxometalate precursors; preparation and characterization of $[VO(DBSQ)(DTBC)]_2$, $[Et_3NH]_2[VO(DTBC)_2]\cdot n CH_3OH$, and $[Na(CH_3OH)_2]_2[V(DTBC)_3]_2\cdot 4CH_3OH$; preparation and characterization of deprotonated 3,5-di-*tert*-butylcatecholate salt, Na_2(3,5-DTBC), and $[Et_3NH][V(DTBC)_3]\cdot 1.5CH_3OH$; ^{31}P NMR following oxygen-uptake using $(n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$; catalyst isolation attempts; spectroscopic information (UV−visible, negative ion ESI-MS, or ^{1}H NMR) of $[VO(DBSQ)(DTBC)]_2$, $[Et_3NH]_2[VO(DTBC)_2]\cdot n CH_3OH$, and $[Na(CH_3OH)_2]_2[V(DTBC)_3]_2\cdot 4CH_3OH$; EPR spectrum of Zn(Cat-N-SQ)(BQ-N-SQ); crystal data for $[Na(CH_3OH)_2]_2[V(DTBC)_3]_2\cdot 4CH_3OH$; IR spectrum of Na_2(3,5-DTBC) and 3,5-DTBC; ^{31}P NMR following the O_2-uptake of $(n\text{-}Bu_4N)_9P_2W_{15}V_3O_{62}$ with DTBC; IR spectrum of $(n\text{-}Bu_4N)_5Fe^{II}\cdot SiW_9V_3O_{40}$ and the isolated active species from $(n\text{-}Bu_4N)_5Fe^{II}\cdot SiW_9V_3O_{40}$; negative ion ESI-MS spectrum of isolated catalyst from $(n\text{-}Bu_4N)_5Fe^{II}\cdot SiW_9V_3O_{40}$; solid EPR of the material isolated from $(n\text{-}Bu_4N)_4H_5PV_{14}O_{42}$; center field, nine line EPR spectrum of a postreaction solution of 3,5-DTBC and $VO(acac)_2$ in toluene, which had additional fresh DTBC and O_2 added; tabulated literature overview of vanadium catecholate organometallic complexes relevant to dioxygenase catalysis; details for ≤50 000 TTO catalytic lifetime experiments (data for Figure 1 in the main text) and 100 000−150 000 TTO catalytic lifetime experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(59) The maximum rate, measured from the post-induction period (or initial rate in the case of $[VO(DBSQ)(DTBC)]_2$), is approaching the O_2 gas-to-solution mass transfer limit under our experimental conditions of 400 mg (1.8 mmol) of DTBC, 0.46−0.48 mM precatalyst/catalyst, ca. 9 mL of 1,2-$C_2H_4Cl_2$, 40 (±0.7) °C, 1 atm O_2, and stirring rate of ca. 700−800 rpm.

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