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The divanadium-substituted phosphotungstate  $(Bu_4N)_4[\gamma-PW_{10}O_{38}V_2(\mu-O)(\mu-OH)]$  catalyzes aromatic oxidation of pseudocumene and 2-methylnaphthalene with  $H_2O_2$  demonstrating unusual regioselectivity.



# Selective oxidation of pseudocumene and 2-methylnaphthalene

# with aqueous hydrogen peroxide catalyzed by $\gamma$ -Keggin di-

## vanadium-substituted polyoxotungstate

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This paper is dedicated to the memory of Aleksandr Evgenievich Shilov (1930-2014).

#### Abstract

The catalytic performance of a  $\gamma$ -Keggin divanadium-substituted phosphotungstate, (Bu<sub>4</sub>N)<sub>4</sub>[ $\gamma$ -PW<sub>10</sub>O<sub>38</sub>V<sub>2</sub>( $\mu$ -O)( $\mu$ -OH)], has been evaluated in the selective oxidation of 1,2,4trimethylbenzene (pseudocumene, PC) and 2-methylnaphthalene with the green oxidant, 35% aqueous hydrogen peroxide. Under conditions of H<sub>2</sub>O<sub>2</sub> deficiency ([PC]/[H<sub>2</sub>O<sub>2</sub>] = 17–22), PC oxidation proceeded with unusually high chemo- and regioselectivity, producing exclusively 2,4,5-trimethylphenol (2,4,5-TMP) and 2,3,5-TMP in a molar ratio of 7.3/1 and a yield of 73% based on the oxidant. Isomeric 2,3,6-trimethylphenol was found in trace amounts. Under conditions of H<sub>2</sub>O<sub>2</sub> excess ([H<sub>2</sub>O<sub>2</sub>]/[PC] = 8), 2,3,5-trimethyl-1,4-benzoquinone (TMBQ, vitamin E key intermediate) formed with 41% selectivity at 41% substrate conversion. Atypical regioselectivity was also found in the oxidation of 2-methylnaphthalene which gave

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predominantly 6-methyl-1,4-naphthoquinone (6-MNQ) rather than isomeric 2-MNQ. The ratio between the isomers could be altered by varying the catalyst and oxidant amounts.

**Key words**: selective aromatic oxidation, pseudocumene, 2-methylnaphthalene, hydrogen peroxide, vanadium, homogeneous catalysis

#### 1. Introduction

The selective aromatic oxidation plays a central role in organic synthesis and biological systems [1, 2]. Phenols are important antioxidants and intermediates in the production of resins, plastics, fine chemical, and pharmaceuticals [1, 3, 4], while quinones serve as versatile building blocks of many biologically active compounds [2, 5-7]. The insertion of oxygen atom into aromatic rings, which are not activated by oxygen-containing electron-donating groups, is one of the most difficult transformations in the organic synthesis [8-11]. Alkyl substituents, from one hand, activate the aromatic nuclei toward oxygenation but, from another hand, they also undergo oxidation, resulting in poor aromatic oxidation selectivity.

Until recently, oxyfunctionalization of arenes was accomplished through multistage technologies, employing environmentally unfriendly reagents, such as  $CrO_3$ ,  $MnO_2$ ,  $OsO_4$ ,  $Pb(OAc)_4$ ,  $Tl(NO_3)_3$ , nitric acid, ceric ammonium nitrate (CAN), and others [1, 2, 5, 12]. However, the ever-increasing attention towards the economical and environmental sustainability is prompting the scientific community to develop chemical processes, which eliminate the use of hazardous reactants and reduce generation of waste [13-15]. Therefore, the selective catalytic oxidation of alkylsubstituted arenes to corresponding phenols and quinones with atom efficient and environmentally benign oxidants ( $O_2$ ,  $H_2O_2$ ) is a demanding task of the modern organic synthesis.

challenging goal aromatic oxidation of 1,2,4-trimethylbenzene А is the (pseudocumene), which is considered as an economically sound way to 2,3,5-trimethyl-1,4benzoquinone (vitamin E key intermediate) [16]. TMBO is currently produced in industry through oxidation of 2,3,6- and 2,3,5-trimethylphenol (hereinafter, TMP), by-products in the process of methylation of phenol to 2,6-dimethylphenol [17-19]. The direct aromatic oxidation of PC has been scarcely described in the literature. Non-catalytic procedures based on the use of *m*-chloroperbenzoic acid in CHCl<sub>3</sub> [20] and H<sub>2</sub>O<sub>2</sub> in formic acid [21] have been reported. The yield of TMBQ attained 16.5 and 19%, respectively. Beller and co-workers suggested oxidation of PC with a 4-fold excess of 50% H<sub>2</sub>O<sub>2</sub> in *t*-amyl alcohol in the presence of easily available iron complexes formed upon interaction of FeCl<sub>3</sub>·6H<sub>2</sub>O, pyridine-2,6-dicarboxylic acid, and benzylamine derivatives [17]. However, the yield of TMBQ did not exceed 26% at a substrate conversion of 69%. For now, the most efficient procedure for the direct oxidation of PC to TMBQ was reported for the catalytic system that employed methylrhenium trioxide (MTO,  $CH_3ReO_3$ ) as the catalyst and  $H_2O_2$  as the oxidant [16, 22, 23]. In acetic acid with a 20-fold excess of the oxidant, TMBQ could be obtained with the yield of 50% at 75% PC conversion [22]. A mild procedure (4-fold excess of H<sub>2</sub>O<sub>2</sub>, nitromethane) for the oxidation of PC based on the use of MTO and neutral amphiphile Brij 30 led to the TMBQ yield 22% at 28% conversion [23].

Several vanadium-based catalytic systems have been reported for the nuclear hydroxylation of alkylaromatics [24-29]. Recently, Mizuno and co-workers have discovered a very efficient homogeneous polyoxometalate (POM) catalyst,  $\gamma$ -Keggin divanadium-substituted phosphotungstate (see Figure 1 for the polyanion structure) (Bu<sub>4</sub>N)<sub>4</sub>[ $\gamma$ -PW<sub>10</sub>O<sub>38</sub>V<sub>2</sub>( $\mu$ -O)( $\mu$ -OH)] (shortly,  $\gamma$ -PW<sub>10</sub>V<sub>2</sub>) for the selective aromatic hydroxylation of a range of alkylarenes with H<sub>2</sub>O<sub>2</sub> as oxidant [29]. Additives of a mineral acid (HClO<sub>4</sub>) were required to activate the catalyst system.



Figure 1. γ-Keggin divanadium-phosphotungstate (Bu<sub>4</sub>N)<sub>4</sub>[γ-PW<sub>10</sub>O<sub>38</sub>V<sub>2</sub>(μ-O)(μ-OH)].

This finding has prompted us to explore the possibility of application of this POM as catalyst for the  $H_2O_2$ -based selective oxidation of pseudocumene to obtain either TMP or TMBQ. We also evaluated the catalytic performance of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> in the selective oxidation of 2-methylnaphthalene (2-MN), another industrially relevant arene substrate that could potentially lead to 2-methyl-1,4-naphthoquinone (2-MNQ, the so-called menadione or vitamin K<sub>3</sub>) [17, 18].

## 2. Experimental

#### 2.1. Materials

Pseudocumene (97+%) was obtained from Aldrich. 2,3,5-Trimethylphenol (2,3,5-TMP, 98%), 2,3,6-trimethylphenol (2,3,6-TMP, 98%), 2-methylnaphthalene (2-MN, 99%), and 2-methyl-1,4-naphthoquinone (2-MNQ, 98%) were purchased from Acros. 2,4,5-Trimethylphenol (2,4,5-TMP, 99%) was purchased from Alfa Aesar. Acetonitrile (Panreac, HPLC grade) was dried and stored over activated 4 Å molecular sieves. All the other compounds were the best available reagent grade and used without further purification. The concentration of  $H_2O_2$  (ca. 35 wt.% in water) was determined iodometrically prior to use.

#### 2.2. Catalyst preparation and characterization

The cesium salt of the dilacunary phosphotungstate  $C_{57}[\gamma-PW_{10}O_{36}]\cdot xH_2O$  was synthesized as described in the literature [30]. Polyoxometalate  $(Bu_4N)_4[\gamma-PW_{10}O_{38}V_2(\mu-O)(\mu-OH)]$  was prepared according to the procedure reported by Kamata et al. [31] with some modifications. NaVO<sub>3</sub>·2H<sub>2</sub>O (0.83 g) was dissolved in 50 mL of H<sub>2</sub>O and the pH of the solution was adjusted to 0.8 with 3 M HCl. Then  $C_{57}[\gamma-PW_{10}O_{36}]\cdot xH_2O$  (8 g) was added to the solution and a yellow precipitate was formed. The mixture was diluted with 150 mL of H<sub>2</sub>O and slightly heated to give a yellow solution to which 3 g of TBABr dissolved in water was added. A yellow precipitate of the TBA-salt was separated, washed with water, and dried at 100 °C. The crude  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> was purified by precipitation with H<sub>2</sub>O from a MeCN solution and dried again. Its spectroscopic characteristics were in accordance with the literature [29, 31]. <sup>51</sup>V NMR (MeCN): -579 ppm. <sup>31</sup>P NMR (MeCN): -14.0 ppm. IR (KBr): 1094, 1062, 1039, 953, 875, 806, 704, 533 cm<sup>-1</sup>.

Polyoxometalate  $(Bu_4N)_4[\gamma-SiW_{10}O_{38}V_2(\mu-OH)_2]$  ( $\gamma$ -SiW\_{10}V\_2) was synthesized as described in the literature [32]. <sup>51</sup>V NMR (MeCN): -564 ppm. IR (KBr): 1006, 995, 967, 914, 877, 840, 787, 692, 547 cm<sup>-1</sup>. The number of TBA cations was determined by ignition at 600 °C. Potentiometric titration with TBAOH was used to determine the number of acidic protons. Heteropolyacid H<sub>5</sub>PMo<sub>10</sub>V<sub>2</sub>O<sub>40</sub> was prepared according to the literature [33].

## 2.3. General procedure for PC oxidation

Catalytic oxidations of PC with  $H_2O_2$  in the presence of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> were carried out in temperature-controlled glass vessels at 30–80 °C under vigorous stirring (500 rpm). In case of  $H_2O_2$  deficiency, concentrations of the reactants were in the range of [PC] = 0.8–2.4, [ $\gamma$ -PW<sub>10</sub>V<sub>2</sub>] = 0.0009–0.0045, [HClO<sub>4</sub>] = 0.0009–0.0045, and [H<sub>2</sub>O<sub>2</sub>] = 0.036–0.180 M. In case of H<sub>2</sub>O<sub>2</sub> excess, the concentrations were as follows: [PC] = 0.1–0.5, [ $\gamma$ -PW<sub>10</sub>V<sub>2</sub>] = 0.0025–

0.0125,  $[\text{HClO}_4] = 0.0025-0.0125$ , and  $[\text{H}_2\text{O}_2] = 0.8-2$  M. Typically, the reactions were initiated by the addition of  $\text{H}_2\text{O}_2$  either in one portion or stepwise to a mixture containing aromatic substrate,  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> catalyst and HClO<sub>4</sub> in 1 mL of a solvent mixture MeCN/*t*-BuOH (1:1 v/v). Samples were taken during the reaction course by a syringe and analyzed by GC, GC-MS, HPLC and <sup>1</sup>H NMR. Before HPLC and <sup>1</sup>H NMR measurement, the catalyst was separated by precipitation with diethyl ether; the reaction mixture was concentrated on a rotary evaporator and then diluted with iPrOH/H<sub>2</sub>O and CDCl<sub>3</sub>, respectively.

#### 2.4. General procedure for 2-MN oxidation

Catalytic oxidations of 2-methylnaphthalene with  $H_2O_2$  in the presence of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> were carried out in temperature-controlled glass vessels at 60 °C under vigorous stirring. The reaction was initiated by addition of 0.3 mmol of  $H_2O_2$  to the mixture containing 0.1 mmol of 2-MN, 0.0039 mmol of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> and HClO<sub>4</sub> in 1 mL of MeCN/*t*-BuOH (1:1 v/v). Samples were taken during the reaction course by a syringe and analyzed by GC and GC–MS.

#### 2.5. Product analysis

The oxidation products were identified by GC, GC–MS and <sup>1</sup>H NMR using authentic samples. The substrate conversions and product yields were quantified by GC using biphenyl as the internal standard. Each experiment was reproduced at least two times. The experimental error in the determination of the substrate conversions and product yields by GC normally did not exceed 2%. The ratio of 2,3,5- and 2,4,5-TMP isomers, which could not be distinguished by GC, was determined by <sup>1</sup>H NMR and HPLC (270 nm, eluent *i*PrOH/H<sub>2</sub>O = 67/33, isocratic flow, 1 mL/min) using authentic samples for comparison. The amount of H<sub>2</sub>O<sub>2</sub> at the end of the reaction was estimated using semiquantitative test sticks "Peroxide 100".

2,4,5-Trimethylphenol (2,4,5-TMP)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 25 °C, 400 MHz): 6.87 (s, 1H, Ar-H); 6.58 (s, 1H, Ar-H); 4.39 (s, 1H, OH);

2.184 (s, 3H, Ar-CH<sub>3</sub>); 2.180 (s, 3H, Ar-CH<sub>3</sub>); 2.16 (s, 3H, Ar-CH<sub>3</sub>).

GC-MS (EI): m/z (relative int.): 136 (77)  $[M]^+$ , 121 (100)  $[M - CH_3]^+$ , 91 (21)  $[M - 3CH_3]^+$ .

2,3,5-Trimethylphenol (2,3,5-TMP)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 25 °C, 400 MHz): 6.59 (s, 1H, Ar-H); 6.47 (s, 1H, Ar-H); 4.51 (s, 1H, OH);

2.23 (s, 6H, Ar-CH<sub>3</sub>); 2.12 (s, 3H, Ar-CH<sub>3</sub>).

2,3,5-Trimethyl-1,4-benzoquinone (TMBQ)

GC-MS (EI): *m*/*z* (relative int.): 150 (100) [M]<sup>+</sup>, 122 (47) [M - CO]<sup>+</sup>, 107 (64) [M - CO, -

 $CH_3]^+$ , 79 (48)  $[M - 2CO, -CH_3]^+$ .

2-Hydroxy-3,5,6-trimethyl-1,4-benzoquinone (OH-TMBQ)

GC-MS (EI): m/z (relative int.): 166 (100) [M]<sup>+</sup>, 137 (13) [M - COH]<sup>+</sup>, 136 (13) [M - CO]<sup>+</sup>,

123 (13)  $[M - CH_3, -CO]^+$ , 109 (15)  $[M - CCH_3, -2CH_3]^+$ , 95 (22)  $[M - CCH_3, -CH_3, -CH_3, -COH_3]^+$ .

4-Hydroxy-2,4,5-trimethyl-2,5-cyclohexadien-1-one (TMQL)

GC-MS (EI): m/z (relative int.): 152 (44)  $[M]^+$ , 137 (100)  $[M - CH_3]^+$ , 124 (32)  $[M - CO]^+$ , 109 (60)  $[M - CH_3, -CO]^+$ .

2-Methyl-1,4-naphthoquinone

GC–MS (EI): *m/z* (relative int.): 172 (100) [M]<sup>+</sup>, 144 (19) [M – CO]<sup>+</sup>, 116 (42) [M – 2CO]<sup>+</sup>.

6-Methyl-1,4-naphthoquinone

GC–MS (EI): *m*/*z* (relative int.): 172 (100) [M]<sup>+</sup>, 157 (11) [M-CH<sub>3</sub>]<sup>+</sup>, 144 (31) [M – CO]<sup>+</sup>, 118 (39) [M – CO; -CH=CH]<sup>+</sup>, 116 (38) [M – 2CO]<sup>+</sup>.

#### 2.4. Instrumentation

GC analyses were performed using a gas chromatograph Chromos GC-1000 equipped with a flame ionization detector and a quartz capillary column BPX5 (30 m × 0.25 mm). GC–MS analyses were carried out using an Agilent 7000B system with the triple-quadrupole mass-selective detector Agilent 7000 (HP-5ms quartz capillary column 30 m × 0.25 mm). HPLC measurements were carried out using an Agilent Technologies 1220 Infinity LC (ZORBAX Eclipse plus C18). <sup>1</sup>H, <sup>31</sup>P and <sup>51</sup>V NMR spectra were recorded on a Brüker AVANCE-400 spectrometer at 400.130, 161.67 and 105.24 MHz, respectively. Chemical shifts,  $\delta$ , were determined relative to tetramethylsilane, 85% H<sub>3</sub>PO<sub>4</sub> and VOCl<sub>3</sub>, respectively. Infrared spectra were recorded for 0.5-1.0 wt.% samples in KBr pellets on an Agilent 660 FTIR spectrometer.

#### 3. Results and discussion

#### 3.1. Oxidation of pseudocumene

One of the difficulties in the selective oxidation of hydrocarbons is high reactivity of the oxygenated products, which rapidly undergo further oxidation. To prevent overoxidation processes, oxidant is often taken in a deficiency. Following the work of Mizuno [29], we first evaluated the catalytic performance of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> in pseudocumene oxidation under the conditions of a high substrate excess: [PC] = 1.9 M, [H<sub>2</sub>O<sub>2</sub>] = 0.036 M, [ $\gamma$ -PW<sub>10</sub>V<sub>2</sub>] = 0.9 mM, [HClO<sub>4</sub>] = 0.9 mM, MeCN/*t*-BuOH = 1:1, 60 °C. <sup>1</sup>H NMR and HPLC studies with authentic samples identified 2,4,5-TMP as the principal oxidation product that formed along with minor amounts of 2,3,5-TMP (Scheme 1).



Scheme 1. PC oxidation with  $H_2O_2$  catalyzed by  $(Bu_4N)_4[\gamma - PW_{10}O_{38}V_2(\mu - O)(\mu - OH)]$ .

The main results acquired on the PC oxidation in the presence of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> are presented in Table 1. Under standard Mizuno's conditions, TMP yield (sum of 2,4,5- and 2,3,5-isomers in the ratio of ca. 7.3/1) attained 64% based on H<sub>2</sub>O<sub>2</sub> added (Table 1, entry 1). The reaction was fast and completed within 10 min. The isomeric 2,3,6-TMP was formed in negligible amounts (< 2%). Importantly, only traces of products of the oxidation of methyl groups (corresponding isomeric benzylic alcohols and benzaldehydes) were found, thus indicating electrophilic hydroxylation mechanism. The lack of 2,3,6-TMP is consistent with the observation of Mizuno and co-workers, who found high regioselectivity in the hydroxylation of methoxy(methyl)- and dimethoxy(methyl)benzenes producing less sterically hindered phenols [29]. Note that variation of the reaction conditions within the diapason indicated in Table 1 had very minor influence on the ratio of TMP isomers that remained ca. 7.3/1/<0.15.

With high excess of PC, further oxidation of the phenolic products was insignificant and the yield of TMBQ and TMQL, the quinone and quinol formed presumably from 2,3,5and 2,4,5-TMP, respectively, did not exceed 2%. Hence, the phenol selectivity, i.e. TMP yield based on the aromatic substrate consumed, was high (>95%). On the other hand, we may conclude that some unproductive decomposition of the oxidant occurred parallel to the hydroxylation process since no  $H_2O_2$  was found in the reaction mixture after the TMP yield reached the maximal value of 64%.

The hydroxylation reaction did not proceed in the absence of any catalyst (Table 1, entry 2) or with the addition of only HClO<sub>4</sub> (Table 1, entry 3). Therefore, in agreement with the results of Mizuno and co-workers [29], the catalytic performance of the combination of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> and HClO<sub>4</sub> was found to be unique. Conventional heteropoly acids H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> (Table 1, entry 4) and divanadium-substituted H<sub>5</sub>PMo<sub>10</sub>V<sub>2</sub>O<sub>40</sub> (Table 1, entry 5) with two vanadium atoms statistically distributed over 12 positions of the  $\alpha$ -Keggin structure produced TMP in 0 and 5% yield, respectively, indicating that namely the presence of the dimeric vanadium core in the  $\gamma$ -Keggin POM is crucial for the selective aromatic hydroxylation. The nature of the POM central atom (Si or P) had a strong impact on the catalytic activity: silicotungstate  $\gamma$ -SiW<sub>10</sub>V<sub>2</sub> was significantly less active than phosphotungstate  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> (Table 1, compare entry 6 with entry 1).

The solvent nature played important role in the title reaction. In MeCN, the yield of TMP was only 4% (Table 1, entry 7), but the addition of *tert*-butanol (*t*-BuOH/MeCN 1:2 v/v) increased the yield up to 44% (Table 1, entry 8). At *t*-BuOH/MeCN ratio of 1:1, the phenol yield reached 64% and remained constant upon further increase of the *t*-BuOH/MeCN ratio (2:1) (Table 1, entry 9). In neat *t*-BuOH, the POM catalyst was not soluble.

Based on the results of the Mizuno group [29], we started investigation of PC hydroxylation using 1 equiv. of H<sup>+</sup> (in form of HClO<sub>4</sub>) relative to  $\gamma$ -PW<sub>10</sub>V<sub>2</sub>. Then we varied the amount of HClO<sub>4</sub> relative to  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> and confirmed that the maximum TMP yield corresponds to 1 equiv. of H<sup>+</sup>, irregardless the other reaction conditions (Figure 2). In the absence HClO<sub>4</sub>, only 24% yield of TMP was attained (Table 1, entry 10). This contrasts with the selective H<sub>2</sub>O<sub>2</sub>-based oxidation of 2,3,6-TMP to TMBQ catalyzed by  $\gamma$ -PW<sub>10</sub>V<sub>2</sub>, for which the impact of protons on the product yield was found to be insignificant [34].



**Figure 2.** TMP yield versus amount of HClO<sub>4</sub>. Reaction conditions: PC 2.4 mmol,  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> 0.9 µmol, H<sub>2</sub>O<sub>2</sub> 0.036 mmol, 1 mL MeCN/*t*-BuOH (1/1), 60 °C (**■**) and PC 0.8 mmol,  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> 1.8 µmol, H<sub>2</sub>O<sub>2</sub> 0.036 mmol, 1 mL (MeCN/*t*-BuOH (1/1), 40 °C (**●**).

We also assessed effects of the reaction temperature and amounts of catalyst, substrate, oxidant and water on the yield of TMP. The decrease in the temperature to 30 °C (Table 1, entry 11) or, oppositely, its increase to 80 °C (Table 1, entry 12) led to the change of the reaction rate but did not strongly affect the yield of TMP, which attained 56 and 61% at 30 and 80 °C, respectively. The phenol yield grew up and reached 74% when the concentration of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> was increased four times (Table 1, entry 14). Further increase in POM concentration resulted in reduction of TMP yield (Table 1, entry 15). At a lower concentration of PC (0.8 M), TMP was obtained in a similar yield as at [PC] = 1.9 M (Table 1, entry 16). However, when substrate concentration was enlarged to 2.4 M, the yield of phenol dropped to 50% (Table 1, entry 17).

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We tried to get a higher PC conversion and TMP volume yield (which is the amount of product formed per L of reaction mixture) by increasing the amount of  $H_2O_2$  introduced into the reaction mixture. However, this resulted in a significant decrease of the TMP yield based on the oxidant (Table 1, compare entries 18 and 19 with entry 1). Apparently, phenol overoxidation could compete with its formation from PC when higher oxidant concentrations are employed. However, the amount of TMP overoxidation products, such as TMBQ and TMQL, remained at the same level as in entry 1 (below 2%). Another reason for the lower TMP yield could be a higher rate of unproductive decomposition of  $H_2O_2$  relative to the target oxygenation reaction. In fact, the amount of products related to the oxidation of the methyl groups of PC increased in entries 18 and 19 as compared with entry 1.

A standard method that often helps to enhance the oxidant utilization efficiency is a stepwise addition of  $H_2O_2$  into reaction mixture. Indeed, we found that addition of  $H_2O_2$  by small portions (5.5 µmol every 5 min) enabled improvement of the product yield from 64 to 73% (Table 1, compare entry 20 and entry 1). Moreover, the stepwise mode of the oxidant introduction made possible a 3-fold enlargement of the amount of  $H_2O_2$  used without an evident deterioration of TMP yield, which maintained at the level of 70–73% based on the oxidant (Table 1, entry 20). As a result, the volume yield of the phenolic product could be increased from 3.6 to 10.5 g/L.

Figure 3 shows how TMP yield depends on the amount of  $H_2O_2$  added. One can see that in the range of 0.03–0.09 mmol  $H_2O_2$  the yield is kept quasi constant (71–73 %), but further addition of the oxidant eventually leads to decreasing yield, most probably, because overoxidation processes become significant.



**Figure 3.** Dependence of TMP yield on  $H_2O_2$  amount. Reaction conditions: PC 1.9 mmol,  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> 0.9 µmol, HClO<sub>4</sub> 0.9 µmol, 1 mL MeCN/*t*-BuOH (1/1), 60 °C. H<sub>2</sub>O<sub>2</sub> was added by portions of 5.5 µmol every 5 min. TMP yield is based on H<sub>2</sub>O<sub>2</sub> added.

Since  $H_2O_2$  was introduced into the reaction mixture as an aqueous solution (35 wt.%), the increasing amount of water during the reaction course could affect the catalytic activity. This prompted us to evaluate the effect of water concentration in the system on the catalytic performance. We found that in the range of  $[H_2O] = 0.002-0.03$  M, where the reaction mixture remained homogeneous, TMP yield was quasi constant.

The stability of POMs under turnover conditions is a key issue that have to be addressed when hydrogen peroxide is employed as the oxidant [35, 36]. Under the conditions of the oxidant deficiency relative to the substrate (Table 1),  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> was rather stable as confirmed by IR and <sup>31</sup>P and <sup>51</sup>V NMR spectra of the catalyst recovered from the reaction mixture. Furthermore, the POM catalyst could be reused under the conditions of Entry 1, Table 1, showing a similar reaction rate and TMP yield.

The oxidation of PC was also studied under conditions of the oxidant excess with respect to the arene substrate, when formation of TMBQ could be expected (Scheme 2).



Scheme 2. Pseudocumene oxidation with excess of  $H_2O_2$ 

The main results are presented in Table 2. In contrast to the conditions of  $H_2O_2$  deficiency (Table 1, entry 1), practically no conversion of PC was observed when an 8-fold excess of  $H_2O_2$  was added in one portion (Table 2, entry 1). A possible reason for that could be completely different ratios of the reactants in the two cases: cat/Ox/PC = 1/40/2100 (Table 1) and 1/320/40 (Table 2). <sup>31</sup>P and <sup>51</sup>V NMR spectroscopic studies revealed that under the high oxidant excess conditions, POM destruction occurred and the mode of the oxidant addition affected this process. We may tentatively suppose that the addition of  $H_2O_2$  in one portion led to the fast formation of forms, which are not active in PC oxidation. A stepwise addition of  $H_2O_2$  changed the situation drastically and PC was easily converted to afford TMP (sum of 2,4,5- and 2,3,5-isomers) and TMBQ as the main oxidation products. The yield of TMBQ increased with increasing amount of the oxidant and PC conversion (Table 2, entry 2).

4-Hydroxy-2,4,5-trimethyl-2,5-cyclohexadien-1-one and 2-hydroxy-3,5,6-trimethyl-1,4-benzoquinone were the main by-products. The former, most likely, derived from 2,4,5-TMP while the latter could be a product of TMBQ overoxidation. Figure 4 shows kinetic curves for PC conversion and product accumulation, which confirm that TMP is the primary oxidation product on the way from PC to TMBQ. While the carbon mass balance is >99% at the initial stages of the reaction, then it becomes poor because of overoxidation processes. At the end of the reaction, the selectivity to quinone attained 39% at PC conversion of 46% (Table 1, entry 2).



**Figure 4.** PC conversion and product yields versus time. Reaction conditions: PC 0.1 M,  $H_2O_2$  0.8 M,  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> 2.5 mM, HClO<sub>4</sub> 2.5 mM, MeCN/*t*-BuOH (1/1), 60 °C.

The amount of  $H_2O_2$  added in one step could be redoubled without significant deterioration of the results (Table 2, entry 3). An attempt to increase loading of all the reactants (Table 2, entry 4) led to some decrease in TMBQ selectivity (32% versus 38% in entry 2, 4-fold excess of  $H_2O_2$ ) but the yield of TMBQ based on PC remained similar. As a result, the volume yield of TMBQ could attain 9 g/L. Further increase in the initial PC concentration was not possible because of the restricted solubility of the POM catalyst.

#### 3.1. Oxidation of 2-methylnaphthalene

To estimate further the reaction scope, we assessed catalytic properties of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> in the oxidation of 2-methylnaphthalene. With three equivalents of H<sub>2</sub>O<sub>2</sub> ([2-MN] = 0.1 M, [ $\gamma$ -PW<sub>10</sub>V<sub>2</sub>] = [HClO<sub>4</sub>] = 8 mM) conversion of 2-MN reached 72% after 10 min at 60 °C in

MeCN/*t*-BuOH (1/1). The reaction products were two isomeric quinones, 2- and 6-MNQ formed with the yields of 7 and 27%, respectively (Scheme 3).



Scheme 3. 2-MN oxidation with  $H_2O_2$  catalyzed by  $(Bu_4N)_4[\gamma - PW_{10}O_{38}V_2(\mu - O)(\mu - OH)]$ .

Note that such isomer distribution is not typical for catalytic oxidation of 2-MN where 2-MNQ generally prevails over 6-MNQ because the methyl group activates the aromatic ring towards oxidation [17, 37-42]. Typical ratios of 2-MNQ/6-MNQ are, for example, 7:1 (CH<sub>3</sub>ReO<sub>3</sub>/H<sub>2</sub>O<sub>2</sub>) [37], 4:1 (FeCl<sub>3</sub>·6H<sub>2</sub>O/H<sub>2</sub>O<sub>2</sub>) [17] and (FePcS-SiO<sub>2</sub>/t-BuOOH) [38], 2:1  $(Fe(ClO_4)_3 \text{ or } (CH_3COO)_3Fe/H_2O_2)$  [39], 8:1  $(H_2SO_4/H_2O_2)$  [40], 5:1 or 10:1 (Ru(II)(terpyridine)(2,6-pyridinedicarboxylate)/H<sub>2</sub>O<sub>2</sub>) depending on reaction conditions [41, 42]. The only exception found in the literature, where 6-MNQ dominated over 2-MNQ with the ratio of 2.5:1, was 2-MN oxidation with FeTDCPPS/KHSO<sub>5</sub> catalyst system (FeTDCPPS = tetrasodium *meso*-tetrakis(2,6-dichloro-3-sulfonatophenyl)porphyrin) [43]. On the other hand, the unusually high regioselectivity toward 6-MNQ in the oxidation of 2-MN in the presence of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> is consistent with the results reported by Mizuno and co-workers for dimethoxy- and dimethyl-substituted benzenes [29] and the results acquired by us in this work for the oxidation of PC. Although the oxidation of 2-MN with  $H_2O_2$  catalyzed by  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> gives the quinone isomer (6-MNQ) which is not industrially relevant, this reaction provides one more confirmation that steric effects rather than electronic ones govern the arene oxidation regioselectivity over  $\gamma$ -PW<sub>10</sub>V<sub>2</sub>.

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In addition, we studied the influence of different reaction parameters on the distribution of MNQ isomers. Variation of temperature in the range of 30–80 °C and H<sub>2</sub>O concentration in the range of 0.06–5 M, as well as substitution of MeCN/*t*-BuOH solvent for MeCN did not affect the ratio of 6- and 2-MNQ. However, interesting dependences were found upon varying the amounts of HClO<sub>4</sub>, POM and H<sub>2</sub>O<sub>2</sub> (Figure 5). The increase in the number of HClO<sub>4</sub> equivalents relative to  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> (Figure 5A) as well as the increase in  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> concentration (Figure 5B) led to enlargement of 6-MNQ selectivity at the expense of 2-MNQ. An opposite effect was found when the amount of the oxidant was increased: the 6-/2-MNQ ratio was reduced in this case (Figure 5C).





**Figure 5.** Effect of reaction conditions on 2-MN conversion and selectivities toward 2- and 6-MNQ: (**A**)  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> 8 mM, H<sub>2</sub>O<sub>2</sub> 0.3 M, H<sub>2</sub>O 1.15 M; (**B**) HClO<sub>4</sub> 1 equiv. to  $\gamma$ -PW<sub>10</sub>V<sub>2</sub>, H<sub>2</sub>O<sub>2</sub> 0.3 M, H<sub>2</sub>O 1.15 M; (**C**)  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> 8 mM, HClO<sub>4</sub> 8 mM, H<sub>2</sub>O 0.15 M (90% H<sub>2</sub>O<sub>2</sub> was used). In all experiments: 2-MN 0.1 M, MeCN/*t*-BuOH (1/1), 60 °C, 10 min.

#### 4. Conclusions

The divanadium-substituted phosphotungstate  $(Bu_4N)_4[\gamma-PW_{10}O_{38}V_2(\mu-O)(\mu-OH)]$  catalyzes the selective oxidation of pseudocumene with aqueous  $H_2O_2$  to produce either 2,4,5-/2,3,5trimethylphenols (ca. 7:1) or 2,3,5-trimethyl-1,4-benzoquinone along with some other phenol overoxidation products, depending on the substrate to oxidant ratio. The lack of products of the oxidation of methyl groups certainly indicates electrophilic hydroxylation mechanism and argues against electron transfer or hydrogen atom transfer mechanisms. The presence of mineral acid (HClO<sub>4</sub>) is crucial for the catalytic activity. Under the conditions of  $H_2O_2$ deficiency, the reaction revealed unusually high chemo- and regioselectivity towards 2,4,5trimethylphenol, indicating that steric factors most likely control the oxidation process. This was also corroborated by the atypical regioselectivity observed in the oxidation of 2methylnaphthalene where 6-methylnaphthoquinone prevailed over 2-methylnaphthoquinone (ca. 4:1). Kinetic and DFT studies are in progress in our group to get further insight into the mechanism of this unusual oxygenation reaction.

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Entry	[POM] (mM)	[HClO <sub>4</sub> ] (mM)	[H <sub>2</sub> O <sub>2</sub> ] (mM)	Time (min)	TMP yield <sup>b</sup> (%)
1	0.9	0.9	36	10	64
2	-	-	36	60	0
3	-	0.9	36	60	0
4	0.9 <sup>c</sup>	0.9	36	60	0
5	0.9 <sup>d</sup>	0.9	36	60	5
6	0.9 <sup>e</sup>	0.9	36	60	15
7 <sup>f</sup>	0.9	0.9	36	180	4
8 <sup>g</sup>	0.9	0.9	36	10	44
9 <sup>h</sup>	0.9	0.9	36	10	63
10	0.9	-	36	60	24
11 <sup>i</sup>	0.9	0.9	36	240	56
12 <sup>j</sup>	0.9	0.9	36	10	61
13	1.8	1.8	36	10	70
14	3.6	3.6	36	10	74
15	4.5	4.5	36	10	63
16 <sup>k</sup>	0.9	0.9	36	10	61
$17^{1}$	0.9	0.9	36	10	50
18	0.9	0.9	110	10	35
19	0.9	0.9	180	10	17
20	0.9	0.9	36 <sup>m</sup>	35	73
		<u>ک</u>	88	80	73
			110	100	70

Table 1. PC oxidation in the presence of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> in conditions of H<sub>2</sub>O<sub>2</sub> deficiency <sup>a</sup>

<sup>a</sup> Reaction conditions: PC 1.9 M, POM =  $\gamma$ -PW<sub>10</sub>V<sub>2</sub>, MeCN/*t*-BuOH (v/v=1/1), 60 °C. <sup>b</sup> GC yield of 2,4,5- and 2,3,5-TMP (7:1) based on H<sub>2</sub>O<sub>2</sub> added. <sup>c</sup> POM = H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>. <sup>d</sup> POM = H<sub>5</sub>PMo<sub>10</sub>V<sub>2</sub>O<sub>40</sub>. <sup>e</sup> POM =  $\gamma$ -SiW<sub>10</sub>V<sub>2</sub>. <sup>f</sup> Without *t*-BuOH. <sup>g</sup> MeCN/*t*-BuOH (v/v=2/1). <sup>h</sup> MeCN/*t*-BuOH (v/v=1/2). <sup>i</sup> 30 °C. <sup>j</sup> 80 °C. <sup>k</sup> PC 0.8 M. <sup>1</sup> PC 2.4 M. <sup>m</sup> Stepwise addition of H<sub>2</sub>O<sub>2</sub>: 5.5 µmol every 5 min.

entry	[PC] (M)	[POM] (mM)	[H <sub>2</sub> O <sub>2</sub> ] (M)	Time (h)	PC conversion (%)	TMP yield (%) <sup>b</sup>	TMBQ yield (%) <sup>b</sup>
1	0.1	2.5	0.8	0.5	<1	-	_
2 °	0.1	2.5	0.13	1	17	12 (71)	3.5 (21)
			0.4	3	32	7.5 (23)	12 (38)
			0.8	6	46	4 (9)	18 (39)
3 <sup>d</sup>	0.1	2.5	0.13	0.5	17	12 (71)	3 (18)
			0.8	3	41	1 (2)	17 (41)
4 <sup>e</sup>	0.5	12.5	0.7	1	23	12 (52)	6 (26)
			2	3	37	2 (5)	12 (32)

Table 2. Pseudocumene oxidation in the presence of  $\gamma$ -PW<sub>10</sub>V<sub>2</sub> in conditions of H<sub>2</sub>O<sub>2</sub> excess <sup>a</sup>

<sup>a</sup> Reaction conditions: HClO<sub>4</sub> 1 equiv. to POM, MeCN/*t*-BuOH (1/1), 60 °C. <sup>b</sup> Yield based on initial PC; selectivity is given in parentheses. <sup>c-e</sup>  $H_2O_2$  was added stepwise: <sup>c</sup> 11 µmol every 5 min; <sup>d</sup> 22 µmol every 5 min; <sup>e</sup> 55 µmol every 5 min.

# Highlights

- Polyoxometalate  $(Bu_4N)_4[\gamma$ -PW $_{10}O_{38}V_2(\mu$ -O)( $\mu$ -OH)] catalyzes oxidation of pseudocumene and 2-methylnaphthalene with  $H_2O_2$ .
- Pseudocumene is converted to 2,4,5-trimethylphenol with unusually high regioselectivity.
- 2,3,5-Trimethyl-1,4-benzoquinone becomes the main product under excess of  $H_2O_2$ .
- 2-Methylnaphthalene gives predominantly 6-methyl-1,4-naphthoquinone.

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