Aerobic hydroxylation of hydrocarbons catalysed by vanadate ion

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Abstract

Vanadate anion catalyses aerobic hydroxylation of hydrocarbons in acetonitrile in the presence of solid ascorbic acid or zinc and with obligatory participation of pyridine, pyrazine-2-carboxylic acid and acetic acid as mediators of proton and electron transfer. If sufficient amount of water is present in the reaction mixture, ascorbic acid is dissolved in aqueous acetonitrile and no hydroxylation occurs in this case. The dependencies of the product yields on the concentrations of the reactants have been studied and a mechanism of the formation of hydroxyl radicals has been proposed. These systems mimic generation of hydroxyl radicals in certain vanadium-dependent biological processes.
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1. Introduction

Vanadium complexes are known to catalyse many synthetically useful organic reactions [1–8], and they also play a very important role in living organisms [9–15]. For example, vanadium can mimic some of insulin's actions [16–18], its complexes with amino acids and phenanthroline derivatives have been proposed as anti-tumor and anti-leukemic agents [19], organometallic V(IV) compounds cause cessation of sperm motility [20]. On the other hand, vanadium derivatives are known as potent toxicants and carcinogens [21–27], which can act via generation of reactive oxygen species. Thus, hydroxyl radicals generated from molecular oxygen or hydrogen peroxide under the action of vanadium complexes in a living cell [28,29] attack various cell components leading to their damage and induce aerobic peroxidation of liposomal membranes [30].

Here we wish to report new vanadium-based systems which hydroxylate aromatic and saturated hydrocarbons with atmospheric oxygen under mild conditions. As these systems require reducing agents and nitrogen-containing bases and acids we can consider them as models of certain biological oxidising systems.

2. Results and discussion

We have found that stirring of a suspension of solid ascorbic acid in acetonitrile in air in the presence of benzene, $(n\text{-Bu})_4NVO_3$, pyrazine-2-carboxylic acid (PCA), pyridine and acetic acid gives rise to formation of phenol (Fig. 1). Soluble vanadate salt was used in catalytic amounts; no oxidation occurs in its absence (Fig. 2). The oxidation of toluene under the same

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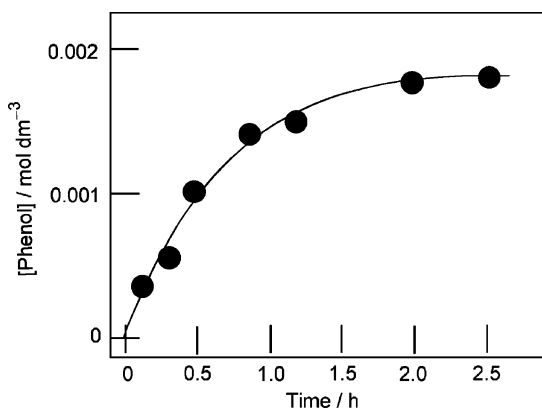*E-mail address:* shulpin@chph.ras.ru (G.B. Shul'pin).
URL: http://members.fortunecity.com/shulpin

Fig. 1. Concentration of phenol vs. time in the oxidation of benzene ($0.9 \, mol \, dm^{-3}$). Conditions: [PCA], $4.8 \times 10^{-3} \, mol \, dm^{-3}$; [py], $0.08 \, mol \, dm^{-3}$; [CH_3CO_2H], $0.67 \, mol \, dm^{-3}$; ascorbic acid, $0.57 \, mmol$; [VO_3^-], $2 \times 10^{-4} \, mol \, dm^{-3}$; $30 \,°C$; $2 \, h$.

conditions gave a mixture of isomeric cresols with the ratio $o{:}m{:}p = 60{:}16{:}24$. Naphthalene gave isomeric naphthols ($\alpha{:}\beta = 4{:}1$). It follows from Figs. 3 and 4 that the system under consideration requires both pyridine and PCA (only very small amounts of the oxygenates are obtained in the absence of these com-
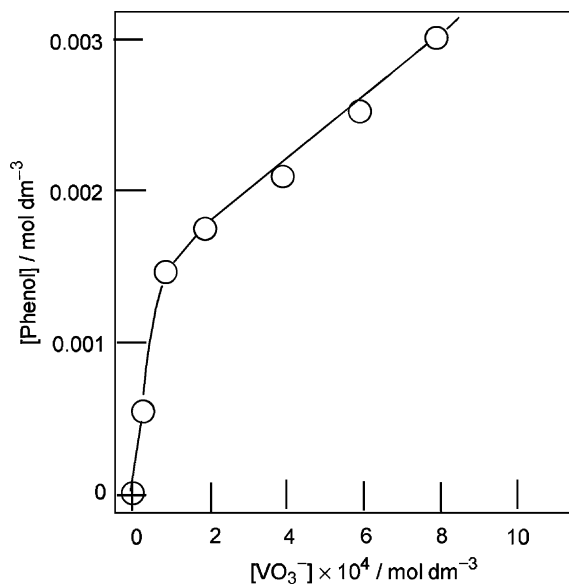

Fig. 2. Concentration of phenol vs. concentration of VO_3^- in the oxidation of benzene ($0.9 \, mol \, dm^{-3}$). Conditions: [PCA], $4.8 \times 10^{-3} \, mol \, dm^{-3}$; [py], $0.08 \, mol \, dm^{-3}$; [CH_3CO_2H], $0.67 \, mol \, dm^{-3}$; ascorbic acid, $0.57 \, mmol$; $30 \,°C$; $2 \, h$.
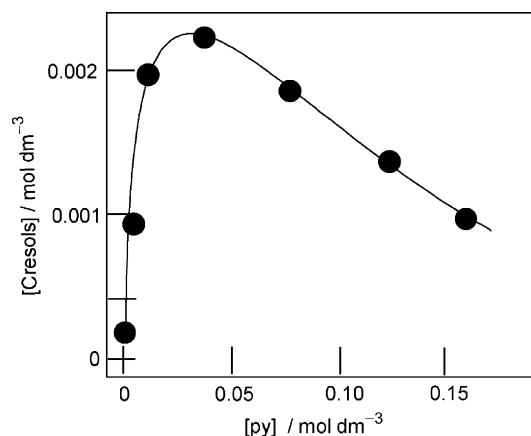

Fig. 3. Concentration of cresol isomers vs. concentration of pyridine in the oxidation of toluene ($0.9 \, mol \, dm^{-3}$). Conditions: [VO_3^-], $2 \times 10^{-4} \, mol \, dm^{-3}$; [PCA], $2.4 \times 10^{-3} \, mol \, dm^{-3}$; [py], [$CH_3CO_2H$], $0.67 \, mol \, dm^{-3}$; ascorbic acid, $0.57 \, mmol$; $30 \,°C$; $2 \, h$.

ponents). In the presence of acetic acid the yield of the oxygenates is 1.5 times higher. It is important to emphasise that if a relatively small amount of water (ca. 0.5 ml) is added, this leads to dissolution of ascorbic acid, and under homogeneous conditions no oxidation of aromatic hydrocarbons has been detected. We have found for the benzene oxidation that the phenol yield after $2 \, h$ is proportional to the amount of solid ascorbic acid (at its amount $<0.6 \, mmol$).
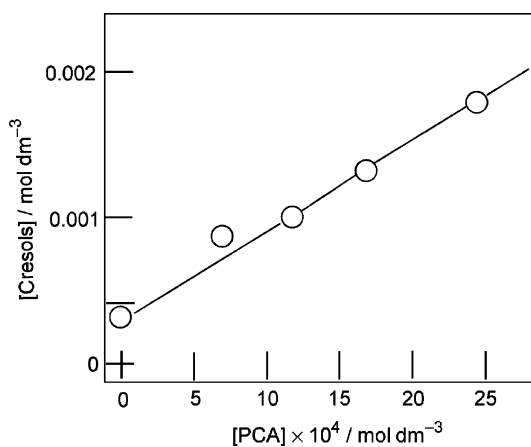

Fig. 4. Concentration of cresol isomers vs. concentration of PCA in the oxidation of toluene ($0.9 \, mol \, dm^{-3}$). Conditions: [VO_3^-], $2 \times 10^{-4} \, mol \, dm^{-3}$; [py], $0.08 \, mol \, dm^{-3}$; [CH_3CO_2H], $0.67 \, mol \, dm^{-3}$; ascorbic acid, $0.57 \, mmol$; $30 \,°C$; $2 \, h$.

Ascorbic acid can be replaced with zinc powder. The oxidation ($[VO_3^-]$, 1×10^{-4} mol dm^{-3}; [PCA], 4.8×10^{-3} mol dm^{-3}; [py], 0.08 mol dm^{-3}; [CH$_3$CO$_2$H], 0.67 mol dm^{-3}; Zn, 1.5 mmol) of benzene and toluene (0.9 mol dm^{-3}) gave after 40 min, respectively, phenol (0.63 mmol dm^{-3}) and a mixture of cresols (0.4 mmol dm^{-3}, o:m:p = 47:28:25) and benzyl alcohol (0.12 mmol dm^{-3}). The zinc-based system can hydroxylate not only methyl group in toluene but also C–H bonds in cyclohexane. This oxidation ([cyclohexane], 0.74 mol dm^{-3}; $[VO_3^-]$, 1×10^{-4} mol dm^{-3}; [PCA], 2.4×10^{-3} mol dm^{-3}; [py], 0.32 mol dm^{-3}; [CH$_3$CO$_2$H], 0.67 mol dm^{-3}; Zn, 1.5 mmol) gave after 2 h cyclohexanol (5.5 mmol dm^{-3}) and cyclohexanone (0.4 mmol dm^{-3}) with total turnover number being 78 (see Section 3) [31–36]. In the presence of phenanthroline or imidazole the oxidation occurs less efficiently. The cyclohexane oxidation under the same conditions in the presence of pyridine and 2,6-di-*tert*-butyl-4-methylphenol (1.6 mmol dm^{-3}) gave rise to only 20% decrease of the product yield. Thus, it can be concluded that this reaction does not proceed via a chain mechanism. Figs. 5–7 clearly show that not only vanadate anion but also both pyridine and PCA are necessary compo-
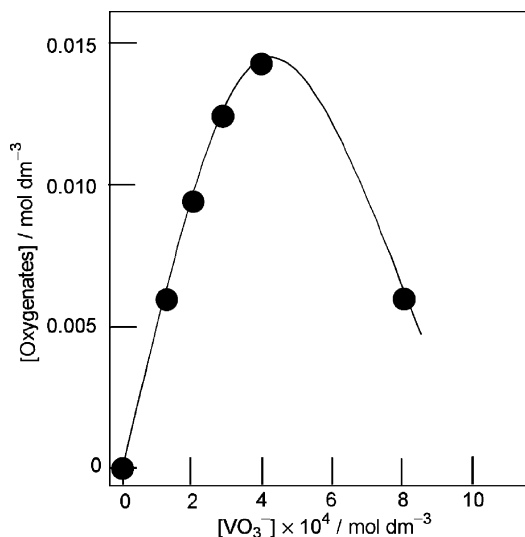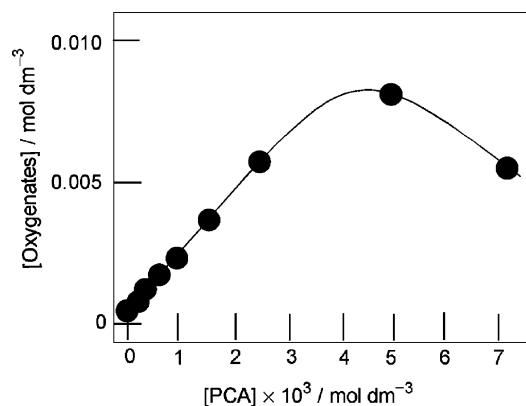

Fig. 6. Dependence of concentration cyclohexanol + cyclohexanone (after 2 h at 30 °C) on concentration of PCA in the oxidation of cyclohexane (0.74 mol dm^{-3}). Conditions: $[VO_3^-]$, 1×10^{-4} mol dm^{-3}; [py], 0.32 mol dm^{-3}; [CH$_3$CO$_2$H], 0.67 mol dm^{-3}; Zn, 1.5 mmol.
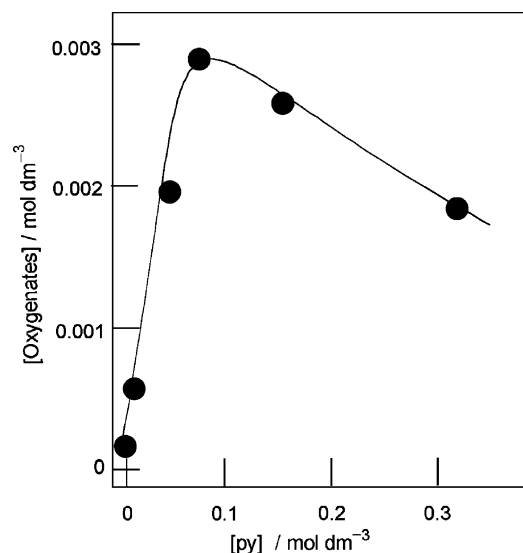

Fig. 7. Dependence of concentration cyclohexanol + cyclohexanone (after 2 h at 30 °C) on concentration of pyridine in the oxidation of cyclohexane (0.74 mol dm^{-3}). Conditions: $[VO_3^-]$, 1×10^{-4} mol dm^{-3}; [PCA], 4×10^{-4} mol dm^{-3}; [CH$_3$CO$_2$H], 0.67 mol dm^{-3}; Zn, 1.5 mmol.

Fig. 5. Dependence of concentration cyclohexanol + cyclohexanone (after 2 h at 30 °C) on concentration of VO_3^- in the oxidation of cyclohexane (0.74 mol dm^{-3}). Conditions: [PCA], 2.4×10^{-3} mol dm^{-3}; [py], 0.32 mol dm^{-3}; [CH$_3$CO$_2$H], 0.67 mol dm^{-3}; Zn, 1.5 mmol.

nents of the oxidising system. It is interesting that the three curves pass through maximum testifying that only relatively low concentrations of vanadium complex, pyridine and PCA lead to the efficient oxidation.

We propose for these systems a mechanism which is shown with simplifications in Scheme 1. Initial vana-
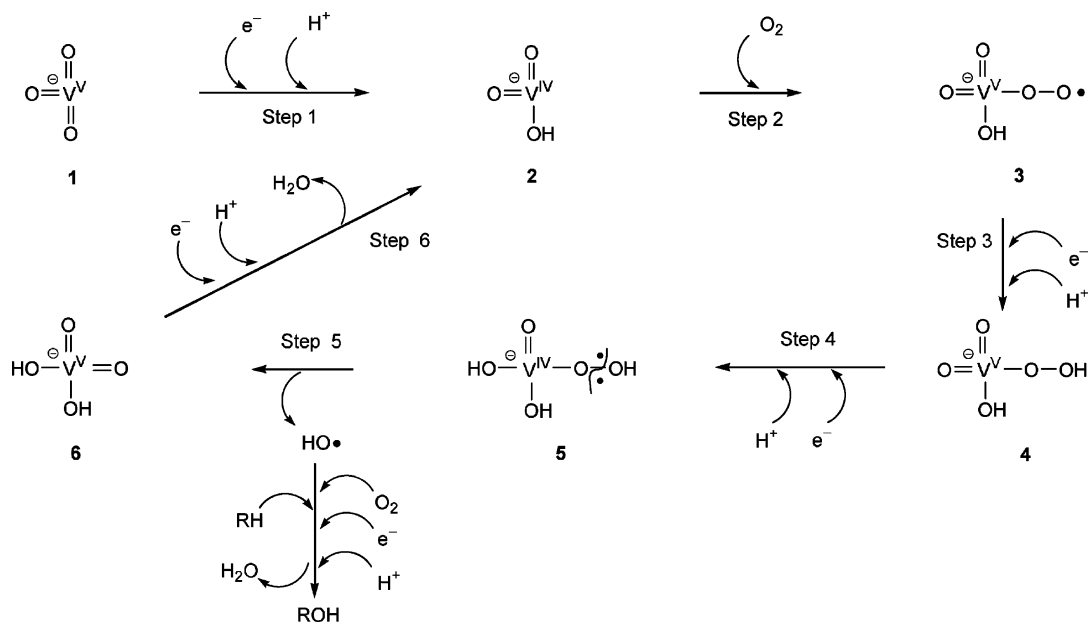
Scheme 1.

dium(V) compound **1** is reduced to a catalytically active V(IV) species **2** by ascorbic acid or Zn^0 (which give e^-). The latter species adds molecular oxygen and after reduction is converted to hydroperoxy V(IV) derivative **5**. A homolytic splitting O–O bond in this species gives rise to more stable oxo derivative **6** of V(V) and hydroxyl radical. The latter will attack a substrate. If this is an alkane, RH, hydroxyl radical abstracts the hydrogen atom to produce the alkyl radical:

$$HO^\bullet + RH \rightarrow H_2O + R^\bullet$$
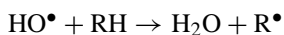
It is well known that alkyl radicals react very rapidly with atmospheric molecular oxygen to afford alkylperoxy radicals:

$$R^\bullet + O_2 \rightarrow ROO^\bullet$$
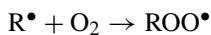
Reduction of these radicals leads to the formation of the corresponding alcohol:

$$ROO^\bullet + e^- \rightarrow ROO^-$$

$$ROO^- + H^+ \rightarrow ROOH$$

$$ROOH + 2H^+ + 2e^- \rightarrow ROH + H_2O$$
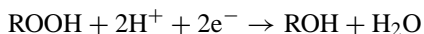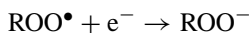
We assume that ascorbic acid transfers its electrons from solid to dissolved vanadium(V)-containing oxo

species (via electron transfer reagent, protonated pyridine; see below). It is important that ascorbic acid (being in other phase) does not take part further in the catalytic cycle. If ascorbic acid is present in the solution, hydroxyl radicals formed at vanadium-containing catalytic center, will attack not a hydrocarbon but preferentially ascorbic acid. This explains why no oxygenates were obtained under completely homogeneous conditions. There is principal difference in the interaction of hydroxyl radicals with aromatic and saturated hydrocarbons. In the first case $HO^\bullet$ radicals can be added to the unsaturated systems, in the second case $HO^\bullet$ radicals abstract hydrogen atoms from much less reactive sp^3-C–H bonds. The system based on ascorbic acid does not hydroxylate cyclohexane which is possibly due to the competition between ascorbic acid (even in solid state) and cyclohexane for hydroxyl radicals. When we use the Zn/CH_3COOH system situation is different. In this case, hydroxyl radicals do not react with metallic Zn and attack only cyclohexane.

Finally the catalytic cycle step 6 leads (after water extrusion from species **6** and its reduction) to species **2**. In this sequence of stages, PCA can facilitate proton transfer [37–40], for example, intramolecular transfer between two HO groups (step 6) or between proton
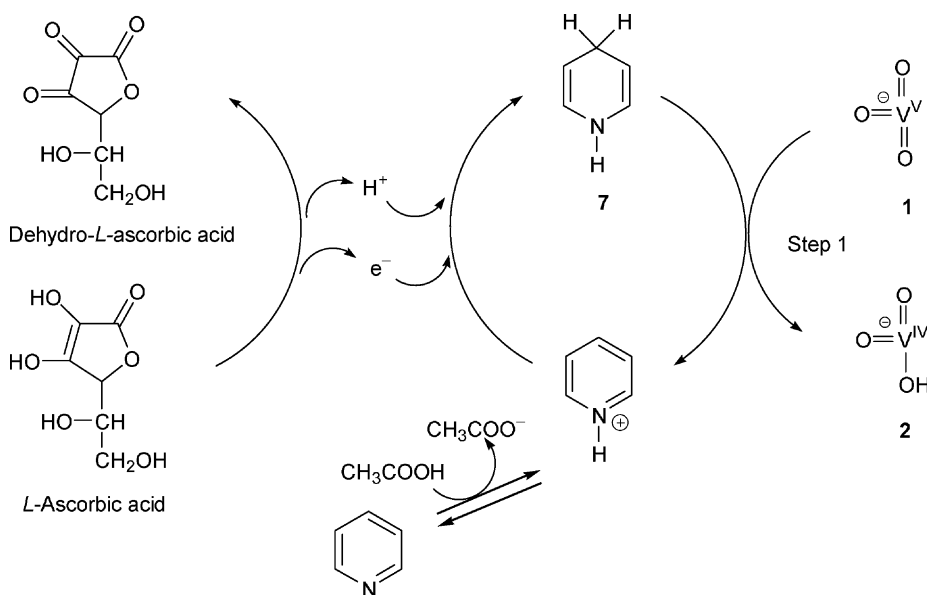
Scheme 2.

donors from the reaction media and oxo or hydroxy groups at vanadium ion.

Protonated pyridine apparently plays a role of a hydrogen atom mediator. In this case, a reduced protonated pyridine (species **7** in Scheme 2) is a model of NADH. Reduction of V(V) by NADH in biological systems is known [41,42]. It has also been shown that the NADH microsomal reduction of vanadate produces hydroxyl radicals [43].

Alternatively, one can assume that in the first step of the process, molecular oxygen is reduced in a vanadium-catalysed reaction to afford hydrogen peroxide. The latter under the action of a vanadium complex and PCA generates hydroxyl radicals [3,6,32,35,37–39] which attack the hydrocarbon molecule. This route looks, however, less probable because the hydrogen peroxide should be produces in relatively high concentration and due to this in the beginning of the process the reaction rate would be negligible. Moreover, we have found that the oxidation of hydrocarbons with the "H$_2$O$_2$–vanadium complex–PCA" in acetonitrile is less efficient in the presence of pyridine.

In summary, we assume that in our systems pyridine and PCA are models of NADH and amino acid residues. Hydroxyl radicals formed in our systems at-

tack hydrocarbons [36–38] present in the solution to produce finally hydroxylated derivatives.

3. Experimental

Reactions were carried out in air in MeCN at 30 °C in thermostated Pyrex vessels with vigorous stirring. The total volume of the reaction solution was 5 ml. Phenol and cresols in the samples of the reaction solutions (after treatment with triphenylphosphine to decompose hydrogen peroxide) were quantitatively determined by GC (instruments CG MASTER with fused silica capillary column 48 m × 0.25 mm × 0.25 μm, CARBOWAX 20 M, and VARIAN 3800 equipped with a capillary column VA-5, 30 m).

In order to determine the concentrations of all possible cyclohexane oxidation products, the samples of reaction solutions were analysed twice, before and after their treatment with PPh$_3$, by GC measuring concentrations of cyclohexanol and cyclohexanone. This very simple method proposed and described by us earlier [31–35] allows to detect alkyl hydroperoxides and to measure also the real concentrations of alkyl hydroperoxide, alcohol and aldehyde (ketone) present in the reaction solution (usually alkyl hydroperoxides

are decomposed in the gas chromatograph to produce mainly the corresponding ketone and alcohol). Such analysis of the reaction mixture obtained from the oxidation in the presence of Zn showed that cyclohexyl hydroperoxide is present only in negligible concentration.

Acknowledgements

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