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# PAPER

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# Poly(*N*-vinylpyrrolidone) $-H_2O_2$ and poly(4-vinylpyridine) $-H_2O_2$ complexes: solid $H_2O_2$ equivalents for selective oxidation of sulfides to sulfoxides and ketones to *gem*-dihydroperoxides<sup>†</sup>

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Complexes of poly(*N*-vinylpyrrolidone) (PVD) and poly(4-vinylpyridine) (PVP) with hydrogen peroxide have been prepared and their synthetic utility as solid  $H_2O_2$  equivalents for the selective oxidation of sulfides to sulfoxides and ketones to *gem*-dihydroperoxides has been studied. These complexes are convenient and safe alternatives to  $H_2O_2$  solutions and it is found that various symmetric as well as unsymmetrical sulfides undergo oxidation under mild conditions to provide the respective sulfoxides in high yields. A series of *gem*-dihydroperoxides were obtained from the corresponding ketones in good yields under ambient conditions.

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# Introduction

Oxidation reactions play a vital part in both the natural and scientific world from cellular respiration to the oxidation of hydrocarbons as fuels. Oxidants themselves come in a great variety of forms but in synthetic applications, there has been a growing search for oxidants that more accurately mimic the environmentally friendly characteristics of natural ones. Apart from transition-metal based oxidants, some of the most accessible ones among these reagents are usually organic peroxides and related peroxy compounds. From very early on, however, it was well recognized that many peroxy compounds possess significant drawbacks that can make their use both limited and, at times very dangerous.

One of the most popular reagents, m-chloroperoxybenzoic acid (m-CPBA) for instance, is known to be shock sensitive and poor in terms of its oxygen content. Other peroxides such as *tert*-butyl hydroperoxide can become unstable and explosive making them difficult to both implement into a large scale process and dispose of after the reaction is completed. In response to these concerns, many have begun to look back to the "classic" use of simple hydrogen peroxide due to its high oxygen content, reliable reactivity and the formation of only water as the byproduct of its reactions.<sup>1</sup> However, even hydrogen peroxide poses risks due to its oxidative strength and reactivity.<sup>2</sup> It also, for instance, reacts violently with metals and reducing agents, can become explosive above certain concentrations, and acts as a strong bleaching agent. Hydrogen peroxide can also be destabilized by extreme pH's and form explosive mixtures with organics upon prolonged exposure. On the other hand, H<sub>2</sub>O<sub>2</sub> can also form extended hydrogenbonded complexes with organic bases and many see these compounds as a safer way to store and access the peroxides for oxidations. Indeed, such complexes can reduce the volatility of the hydrogen peroxide allowing its storage at higher concentrations for extended periods of time more safely without seriously affecting the reactivity.

Well before its molecular structure was agreed upon,<sup>3</sup> hydrogen peroxide was known to form adducts with various bases. Urea– $H_2O_2$  for instance, was the first such adduct discovered and for almost a century has been the model for subsequent peroxide complexes. Commercially available urea– $H_2O_2$  is a crystalline, white, hygroscopic solid that is generally stable at room temperature. With such favorable characteristics, it comes as no surprise that urea– $H_2O_2$  is known as a dependable, solid alternative to hydrogen peroxide with established utility in a range of oxidative applications.<sup>4</sup> Such reactions include epoxidations,<sup>5</sup> the oxidation of sulfides,<sup>6</sup> selenium compounds,<sup>7</sup> benzylic carbons<sup>8</sup> and many other reactions.<sup>9</sup> Hydrogen peroxide also forms a stable complex



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with 1,4-diazabicyclo[2.2.2]octane (DABCO),<sup>10</sup> though complexes with other tertiary amines have been known to degrade easily and are less useful.<sup>11</sup>

Interestingly, some of the more effective supports or carriers for hydrogen peroxide are polymeric bases and heterocycles. In particular, poly(N-vinylpyrrolidone) has been known to form stable, free flowing, solid complexes with various concentrations of hydrogen peroxide. Since their discovery during the 1960s,<sup>12</sup> PVD-H<sub>2</sub>O<sub>2</sub> complexes have been used as peroxide surrogates in many different capacities. Many differing formulations have been proposed<sup>13</sup> and most of them are used for surface sterilizations,<sup>14</sup> tissue preservations,<sup>15</sup> acne treatments,<sup>16</sup> tooth whiteners<sup>17</sup> and radical polymerization initiations.<sup>18</sup> However, while its industrial and cosmetic applications have been well documented, PVD-H<sub>2</sub>O<sub>2</sub> has only within the last few decades been shown useful in synthetic organic transformations. Unlike other complexes, hydrogen peroxide within PVD-H<sub>2</sub>O<sub>2</sub> has been shown to preferentially bond with the carbonyl moiety of the amido group.<sup>19</sup> Inevitably, this alternative bond site and the presence of a polymeric backbone have both led to interesting and new applications of these complexes.

PVD-H<sub>2</sub>O<sub>2</sub> for instance has been used by Pourali and associates in the production of iodinated arene.<sup>20</sup> The complex was used in conjunction with KI or molecular iodine and catalytic amounts of hydrated tungstophosphoric acid and produced a range of products in good yields. The complex was also used in the epoxidation of ketones and  $\alpha$ , $\beta$ -enones in the presence of sodium hydroxide<sup>21</sup> and Mn porphyrins<sup>22</sup> as catalysts. Recently, our group has sought to expand the synthetic role of hydrogen peroxide complexes. We have reported the use of both PVD-H<sub>2</sub>O<sub>2</sub> and the newly formed poly(4-vinylpyridine) hydrogen peroxide complex (PVP-H<sub>2</sub>O<sub>2</sub>).<sup>23</sup> PVP-H<sub>2</sub>O<sub>2</sub>, similar to other peroxide complexes, is formed by hydrogen bonds through the amine functionality and forms a free-flowing, light yellow solid. Both complexes were used in the synthesis of phenols and halophenols from arylboronic acids under very mild conditions (Scheme 1). Calculations were also performed to help elucidate the extended structure of the complexes and it was found that both PVD and PVP form stable, extended hydrogen bonded structures with a linear arrangement of



Scheme 1 Solid  $H_2O_2$  complexes and *ipso*-hydroxylation and halogenation of arylboronic acids.

3–5 molecules of hydrogen peroxide being preferred over a cyclic structure.<sup>28</sup> Compared to urea–H<sub>2</sub>O<sub>2</sub>, a 1:1 complex, PVD–H<sub>2</sub>O<sub>2</sub> (1:4.5) and PVP–H<sub>2</sub>O<sub>2</sub> (1:3.5) carry more equivalents of H<sub>2</sub>O<sub>2</sub> content making them better H<sub>2</sub>O<sub>2</sub> carriers.

Interestingly, it has been found that PVD– $H_2O_2$  performs significantly better than PVP– $H_2O_2$  in most applications though this may be simply a difference in  $H_2O_2$  loading between the two. Nonetheless, as efficient, solid forms of hydrogen peroxide, both complexes showed impressive promise as efficient oxidizing agents. In our efforts in exploring the applications of hydrogen peroxide complexes in oxygenation and oxidation reactions, we found that they are efficient oxidizing agents and our results are reported here in the selective partial oxidation of sulfides to sulfoxides as well as in preparation of *gem*-dihydroperoxides from the corresponding ketones.

## Results and discussion

#### Selective oxidation of sulfides to sulfoxides

The oxidation of sulfides to sulfoxides is one of the most simple, yet particularly important transformations in organic chemistry. Sulfoxides are indispensable as they appear in numerous natural products and drug molecules, act as chiral auxiliaries and C-C bond forming reagents, and even participate as intermediates in some molecular rearrangements and transformations. Because of this, numerous reagents and methods have been developed in an effort to produce sulfoxides as selectively and inexpensively as possible. Among these, the oxidation of sulfides has been proven as one of the most durable and pervasive methods in synthetic organic chemistry.<sup>24</sup> Sulfoxides have been made from sulfides using nitrates in combination with halogens,<sup>25</sup> hypervalent iodine or periodic acids,26 and peroxyacids and peroxides in conjunction with multiple transition metal catalysts.<sup>27</sup> However, with the growing emphasis on environmentally benign processes, more and more chemists have sought out ways to bring about this transformation with greater selectivity with minimal by-products and waste as possible. In many instances, overoxidation to sulfones hinder the selectivity of the process. The use of the many inorganic oxidants for instance is seen as less than optimal due to their tendency to over-oxidize sulfides and interfere with sensitive functional groups while peroxyacids can be hazardous and lead to excessive waste streams.

Instead, the use of hydrogen peroxide  $(H_2O_2)$  as a sulfide oxidant is seen as a more viable alternative due to its strong oxygen content, safety and low cost. Hydrogen peroxide also acts as a milder oxidant than other reagents and produces water as the only waste by-product. The molecule has been used to oxidize sulfides for decades both alone or in the presence of other catalysts.<sup>28</sup> Such additives can help increase reactivity, decrease reaction times and induce stereoselectivity though an increase in the amounts of sulfone produced may also occur as well. Khodaei and coworkers have, for instance, reported the use of triflic anhydride (Tf<sub>2</sub>O) in conjunction with H<sub>2</sub>O<sub>2</sub> where the peroxy acid generated *in situ* acts as the oxidizing agent.<sup>29</sup> In other cases, hydrogen-bonding additives can play a part in the activation of peroxide. For example, Varma and Naicker have shown that commercially available urea- $H_2O_2$  complexes are capable of such oxidations under solventfree conditions (Scheme 2).<sup>4</sup>

$$R_1^{S_R_2} \xrightarrow{Urea:H_2O_2} \qquad \begin{matrix} O \\ I \\ S \\ R_1^{S_R_2} \end{matrix}$$

Scheme 2 Oxidation of sulfides with urea- $H_2O_2$ .



Scheme 3 Oxidation of sulfides with PVD-H<sub>2</sub>O<sub>2</sub>.

Inspired by these successful examples, we decided to examine the use of PVD- $H_2O_2$  and PVP- $H_2O_2$  (both prepared with 50% aqueous  $H_2O_2$ ) as oxidants for arylsulfides. Initially, as with many oxidizing reagents, by using PVD- $H_2O_2$  we obtained mixtures of both sulfoxides and sulfones as products with sulfoxide being more predominant at lower temperatures while sulfone being the major one under prolonged heating at elevated temperatures (Scheme 3).

However, unlike many other oxidants,  $PVD-H_2O_2$  proved highly amenable to control and optimization making the reaction highly tunable. By monitoring the progress of reactions with thin layer chromatography and modifying the reaction temperature, selective formation of various sulfoxides derivatives were achieved (Table 1).

The relatively simple modifications led to excellent yields and diverse side groups like alkenes, amines and alkyl chlorides were tolerated. More importantly, by using a solid form of  $H_2O_2$ , we were able to eliminate the steps associated with workup as well as product separation and the amount of solvents used has been significantly reduced.

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			$R_{2} \xrightarrow{II} \overset{S}{\underset{U}{\cup}} \overset{S}{\underset{H_{1} \cup U_{2} \cup U_{2}}{(14.5) \text{ or }}}_{CH_{3} CN, 70 \text{ °C}} \qquad R_{2} \xrightarrow{II} \overset{Q}{\underset{U}{\cup}} \overset{S}{\underset{H_{3} \cup U_{2}}{(14.5) \text{ or }}}_{R_{1}}$			
Entry	Substrate <sup>a</sup>	Product	PVD-H <sub>2</sub> O <sub>2</sub> Time (h)	PVD-H <sub>2</sub> O <sub>2</sub> Yield (%)	PVD-H <sub>2</sub> O <sub>2</sub> Time (h)	PVD-H <sub>2</sub> O <sub>2</sub> Yield (%)
a	S~	OH S	3	99	24	72
b	C) <sup>s</sup> √	ol s	6	85	24	86
с	S_	OF S	3	82	24	82
d	H <sub>2</sub> N S	H <sub>2</sub> N S	3	88	24	95
e	MeO	Moo	5	83	24	71
f	CI S		24	84	24	74
g	Br		24	82	24	70
h		Š-s°	3	94	24	60
i	C) <sup>S</sup>	o s s	6	93	24	—
j	CI S	S CI	6	81	24	_

<sup>*a*</sup> Substrate to  $H_2O_2$  ratio is 1:2.75.

We also examined the use of PVP-H<sub>2</sub>O<sub>2</sub> as an oxidant and found the results similar to those obtained by the use of PVD-H<sub>2</sub>O<sub>2</sub>. PVP-H<sub>2</sub>O<sub>2</sub> was also found to selectively oxidize arylsulfides to sulfoxides, however, reaction rates were generally much slower and required much higher H<sub>2</sub>O<sub>2</sub> loading than expected (Table 1). Yields were generally lower than those observed in PVD-H<sub>2</sub>O<sub>2</sub> reactions. Interestingly, a few substrates such as **3i** and **3j** possessing sensitive groups seemed to undergo side reactions leading to complex mixtures when reaction was conducted with PVP-H<sub>2</sub>O<sub>2</sub>. Nonetheless, PVP-H<sub>2</sub>O<sub>2</sub> still proved effective as an environmentally friendly H<sub>2</sub>O<sub>2</sub> surrogate in oxidizing a range of sulfides.

#### Oxidation of ketones to gem-dihydroperoxides

With hundreds of millions of cases leading to over a million deaths every year, malaria unfortunately continues to be one of the most widespread and potent threats to lives and communities within the tropics.<sup>30</sup> As a result, there has been a concerted effort to discover newer, more potent molecules for the treatment of malaria.

One of the most promising of these is the naturally occurring artemisinin, isolated by Chinese scientists in 1971 from *Artemisia annua*.<sup>31</sup> Artemisinin is toxic to malaria parasites at micro and even nanomolar concentrations and the prime factor behind its activity has been shown to be its characteristic endoperoxide structure. However, while its antimalarial properties cannot be denied, artemisinin is still only slightly soluble in oil and water and has a very short half-life. This means that complex formulations must be administered repeatedly over several days. The other drawback is most of the artemisinin is still isolated directly from natural sources.

Thus many synthetic variants of artemisinin were and are still being developed for easy administration, longer lasting effects and greater lipophilicity while retaining the all-important peroxide linkage in active form.<sup>32</sup> These include a range of molecules from those closely mimicking the original artemisinin framework with simpler structures that are easier to synthesize. As is evident from looking at their structures (Fig. 1, **5a-h**), one of the best synthetic paths to many of these compounds could be through the use of *gem*-diperoxides.

*gem*-Diperoxides have been encountered as byproducts of various oxidation reactions for a very long time but were very rarely explored because of their perceived instability.<sup>33</sup> Though

Fig. 1 Artemisinin and related anti-malarial compounds with peroxy linkages.

many of the derivatives can indeed be explosive,<sup>34</sup> the continued search for better pharmaceuticals and the abundance of peroxide containing targets have made *gem*-dihydroperoxides more attractive and sought after targets for synthetic chemists. The molecules, for instance, have been used as starting materials or intermediates for a number of pharmaceuticals including 1,2-dioxolanes<sup>35</sup> and 1,2,4,5-tetroxanes<sup>36</sup> and by themselves as oxidizing reagents in epoxidation reactions.<sup>37</sup>

In terms of their own synthesis, *gem*-dihydroperoxides have been made in only a few primary ways. Dihydroperoxides can be synthesized through the ozonolysis of enol ethers as described by McCullough and others although the reaction is not general as ozone sensitive functionalities are not well tolerated.<sup>38</sup> Hydroperoxidation of ketals<sup>39</sup> has also been shown in some cases to lead to *gem*-dihydroperoxides though, one is limited to ketals as starting materials.<sup>40</sup> In contrast to these two paths, the mildest and most general route to *gem*-dihydroperoxides appears to be through the H<sub>2</sub>O<sub>2</sub> oxidation of ketones in the presence of an acid catalyst.

Several different acids have been used in such a process including the original acid of choice, formic acid<sup>33,41</sup> and, more recently, phosphomolybdic<sup>42</sup> and camphorsulfonic acids.<sup>43</sup> However, in terms of both strength and ease of use, the most intriguing acid for such reactions could be sulfuric acid.<sup>44</sup> Terent'ev and co-workers for example, have shown that acid activation of ketones can successfully lead to geminal bishydroperoxides in good yields (Scheme 4).

Interestingly, the reactions were carried out in tetrahydrofuran as a solvent, which the authors claim helps the solvation of the products preventing further reaction. We sought therefore, to use hydrogen peroxide complexes in such a manner. For the activation of ketone, instead of using a liquid acid, we decided to use 1:5 PVP-H<sub>2</sub>SO<sub>4</sub>, the complex of poly(4-vinyl pyridine) with 83 wt% H<sub>2</sub>SO<sub>4</sub> as a convenient solid equivalent of H<sub>2</sub>SO<sub>4</sub> (Fig. 2b and 3c), which makes the reaction more ecofriendly. We prepared PVP-H<sub>2</sub>SO<sub>4</sub> (1:5) and by combining



Scheme 4 Synthesis of gem-dihydroperoxides under acidic conditions.



Fig. 2 SEM images of (a) PVP and (b) PVP-H<sub>2</sub>SO<sub>4</sub> (1:5).



Fig. 3 (a)  $PVD-H_2O_2$  (1:4.5), (b)  $PVP-H_2O_2$  (1:3.5), and (c)  $PVP-H_2SO_4$  (1:5).

both the solid polymeric complexes  $PVD-H_2O_2$  and  $PVP-H_2SO_4$ , *gem*-dihydroperoxides of several cyclic and acyclic ketones have been synthesized.

Reactions were generally carried out by first stirring the substrate of choice and our acid catalyst in tetrahydrofuran at 0 °C. PVD-H<sub>2</sub>O<sub>2</sub> was then added followed by warming the entire mixture to room temperature and allowing it to stir for 24 h (Table 2). We found that the yields for the reaction are

Table 2 Acid catalyzed synthesis of gem-dihydroperoxides

	6 a-j	H2O <sub>2</sub> (1:4.5), 24 h H2O <sub>2</sub> (1:4.5), 24 h <b>H</b> 2O <sub>2</sub> (1:4.5), 24 h	ЮН R2 i
Entry	Substrate <sup>a</sup>	Product	Yield (%)
a	°	ноо оон	57
b	0	HOO	77
с	0	HOO	80
d	°	HOO	72
e	0	HOO	70
f	₽ <b>°</b>	ООН	65
g		HOOOH	51
h	Ph Ph	HOO OOH Ph Ph	42
i		ноо оон	64
j	() ) o	OOH OOH	71

<sup>*a*</sup> Substrate to  $H_2O_2$  ratio is 1 : 2.75.

generally better for cyclic ketones such as cyclohexanone derivatives though ring size also appeared to play an important role. Benzylic ketones were found to be very resistant to reactions though such difficulties have been noted by other groups as well. Results were also dependent upon the amount of acid used. Though Terent'ev and co-workers have described ratios between 8:0.3 and 4:0.3 for hydrogen peroxide to acid as optimal, we found most reactions to progress well with a 2:1 ratio of peroxide to acid. This may be due entirely to the nature of our solid oxidant system compared to liquid systems. Even though these systems have been found to exhibit slight  $H_2O_2$  leaching in solvents, their reactivity is still somewhat tempered by the strong bonds between polymer and oxidant molecules.

All products were isolated, purified by crystallization or chromatographic separation and characterized by NMR spectroscopy comparing their spectral data with those of the authentic samples.<sup>45</sup>

# Conclusion

The present study unveils an important application of the solid H<sub>2</sub>O<sub>2</sub> equivalents PVD-H<sub>2</sub>O<sub>2</sub> and PVP-H<sub>2</sub>O<sub>2</sub> for the selective oxidation of the sulfides to sulfoxides with much safer and more convenient handling of the oxidant H2O2 while reducing the amount of side products. Conversion of aryl alkyl sulfides to their corresponding sulfoxides was achieved in good to excellent yields. Additionally, we found that these stable complexes can be very useful for the preparation of the gemdihydroperoxy compounds from corresponding ketones in good yields. Reaction methodology, workup procedure and purification of the products are safe and the reagents can be easily handled compared to the one involving the use of other oxidants such as tert-butyl hydroperoxide and peracids such as *m*-CPBA or liquid H<sub>2</sub>O<sub>2</sub>. Moreover, the complexes are more environmentally benign than other oxidants as they have the potential to be recycled and reused (with the remaining amount of H<sub>2</sub>O<sub>2</sub> or enhancing the H<sub>2</sub>O<sub>2</sub> content by additional complexation) and water is the by-product. This, in fact, prompts us to test the efficacy of these solid oxidizing reagents for many selective oxidation/oxygenation reactions in the future.

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