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13. ABSTRACT (Maximum 200 words)

The proposed research focused on the detoxification of both *G*- and *V*-types nerve agents by chemical means. Two key objectives are (i) developing novel hetero-bimetallic Fe/Zn TACN complexes that facilitate efficient hydrolysis of both organophosphate esters and *G*-agents, and (ii) synthesizing Mn_2-complexes of TACN and probe their activities in catalyzing oxidative degradation of VX-simulants (sulfides) using either O_2 or H_2O_2. Early on, we succeeded in the preparation of the tethered bis-TACN ligands. However, clean synthesis of hetero-bimetallic Fe/Zn complexes remains a challenge. The effort during the later stage (2002-2004) was focused on the activation of H_2O_2 and $^tBuO_2H$ for the oxygenation of organic sulfides, which is the key step in V-agent degradation. Proficiency of bimetallic Mn-TACN system was explored and the effect of co-catalysts was evaluated. It is also found that the mononuclear Mn-TACN system can activate $^tBuO_2H$ and exhibits one of the highest TOFs (turn-over frequency) in the oxygenation of sulfides by $^tBuO_2H$. Also identified is an organic soluble polyoxometallate catalyst, $(Bu_4N)_4[\gamma\text{-}SiW_{10}O_{34}(H_2O)_2]$, which displays both a remarkable 100% utility of H_2O_2 in catalytic sulfide oxygenation and chemical selectivity for sulfoxide formation. Several graduate and undergraduate students (both female and underrepresented groups) participated all phases of ARO funded research.

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(**1**) LIST OF PAPERS submitted or published under ARO sponsorship during this reporting period:

1. Barker, J. E., Liu, Y., Martin, N. D. and Ren, T., *J. Am. Chem. Soc.*, **2003**, 125, 13332-13333.
   "Dicopper-[18]ane-N_6 Complex as the Platform for Phosphate Monoester Binding"
2. Liu, Y. and Ren, T., *Inorg. Chim. Acta*, **2003**, *348*, 279-282.
   "Preparation and Structural Studies of $(TACN)Cu(NO_3)_2$ and $[Cu(TACN)_2](PF_6)_2$"
3. Barker, J. E. and Ren, T., *Tetrahedron Lett.*, **2004**, *45*, 4681-4683
   "Facile Oxygenation of Organic Sulfides with H2O2 Catalyzed by Mn-Me3TACN Compounds"
4. Phan, T. D., Kinch, M. A., Barker, J. E. and Ren, T., *Tetrahedron Lett.*, **2005**, *46*, 397-400.
   "Highly Efficient Utilization of H2O2 for Oxygenation of Organic Sulfides Catalyzed by [g-SiW10O34(H2O)2]4-"

(**2**) SCIENTIFIC PERSONNEL supported by this project and HONORS/AWARDS/DEGREES received during this reporting period:

Dr. Tong Ren	Principal Investigator	12 weeks summer salary
Ms. Julia Barker	Graduate Student	2+ yr (26 months) stipend
Dr. Stephanie Hurst	Postdoctoral	3 month stipend
Dr. Yu Liu	Postdoctoral	6 month stipend
Ms. Nicole Martin (Hispanic)	Undergraduate	supported by a separate ONR grant
Ms. Vilma Rivera (Hispanic)	Undergraduate	supported by the University of Miami

(**3**) Report of INVENTIONS (By TITLE only)

US provisional patent "FOSSIL FUEL DESULFURIZATION", filed January 6, 2005

(**4**) SCIENCE PROGRESS AN ACCOMPLISHMENTS:

Main Scientific Milestones of ARO Funded Research

1. We demonstrated the proficiency of bimetallic Mn-TACN system in catalyzing the oxygenation of organic sulfides by H_2O_2 and the dramatic co-catalyst role of oxalate.

2. We uncovered that the mononuclear Mn-TACN system can activate $^tBuO_2H$ and exhibit one of the highest TOFs (turn-over frequency) in the oxygenation of sulfides by $^tBuO_2H$.

3. We identified an organic soluble polyoxometallate catalyst, $(Bu_4N)_4[\gamma\text{-}SiW_{10}O_{34}(H_2O)_2]$, that has both a remarkable 100% utility of H_2O_2 in sulfide oxygenation and selectivity for sulfoxide formation.

4. We have obtained preliminary data that suggest (i) sodium perborate is an excellent stoichiometric oxidant for organic sulfides in aqueous solution; (ii) both sodium perborate and sodium borate catalyze H_2O_2 oxygenation of organic sulfides; (iii) $Ru_2(OAc)_4Cl$ catalyzes sulfide oxygenation by ^tBuOOH in CH_3CN/H_2O solution.

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1. Forward

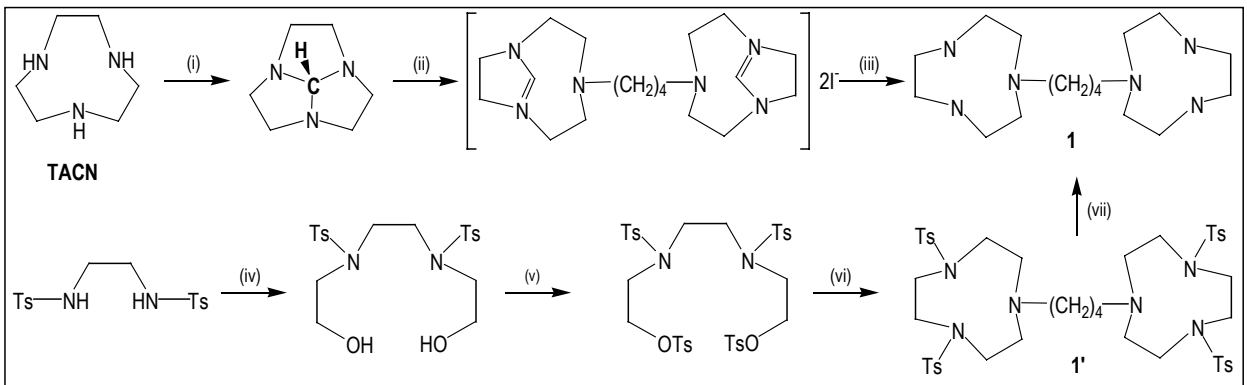
With the detoxification of both *G*- and *V*-types nerve agents as the focus, we outlined two key objectives for the funded project: (i) developing novel hetero-bimetallic Fe/Zn complexes supported by TACN (1,4,7-triazacyclononane) type ligands that facilitate efficient hydrolysis of both organophosphate esters and *G*-agents, and (ii) synthesizing Mn_2-complexes of TACN and probe their activities in catalyzing oxidative degradation of VX-simulants (phosphonothioates) using either O_2 or H_2O_2 as the oxidants. While we succeeded in the preparation of the desired TACN ligands, clean synthesis of hetero-bimetallic Fe/Zn complexes remains a challenge. It also became clear during the initial phase of the project that the degradation of chemical warfare agents (CWA) using peroxy-based chemicals is a more attractive route.[1-3] Hence, we narrowed the focus on the activation of H_2O_2 and $^tBuO_2H$ for the oxygenation of organic sulfides, which is the key step in V-agent degradation. Proficiency of bimetallic Mn-TACN system was explored and the effect of co-catalysts was evaluated.[4] It is also found that the mononuclear Mn-TACN system can activate $^tBuO_2H$ and exhibits one of the highest TOFs (turn-over frequency) in the oxygenation of sulfides by $^tBuO_2H$.[5] Subsequently, we identified an organic soluble polyoxometallate species, $(Bu_4N)_4[\gamma\text{-}SiW_{10}O_{34}(H_2O)_2]$, that displays both a remarkable 100% utility of H_2O_2 in catalytic sulfide oxygenation and chemical selectivity for sulfoxide formation.[6] These catalysts possess some of most desired features for a green Decon system: low cost, ease of transport and aqueous-based chemistry, and their catalytic chemistry are still subject to intense study in our laboratory. Originated from early interests in phosphate esters and TACN compounds, we also published on the research of TACN-Cu complexes, [18]ane-N_6 Cu compounds and their phosphate monoester binding events.[7-9]

More recently, our laboratory made two discoveries that bear great significances with Decon chemistry. First, we found that (i) sodium perborate is an excellent stoichiometric oxidant for organic sulfides in aqueous solution or aqueous/organic solution, and both the low cost and convenient transport/storage of sodium perborate should make it a lead candidate for battlefield decontamination; (ii) both sodium perborate and sodium borate catalyze H_2O_2 oxygenation of organic sulfides and our preliminary test appears to indicate the reaction initial rate with borate is much faster than that catalyzed by peroxycarbonate, on which the DECON GREEN was based,[1] under comparable experimental conditions. We also found that $Ru_2(OAc)_4Cl$, a readily prepared coordination compound, catalyzes sulfide oxygenation by ^tBuOOH in CH_3CN/H_2O solution, and this reaction system may provide the basis of a detoxification

system of long effective dates due to the long shelf life of ^{t}BuOOH. These discoveries remain at the preliminary stages and will be disclosed in detail at a later time.

2. Synthesis of TACN Type Ligands and Their Bimetallic Complexes

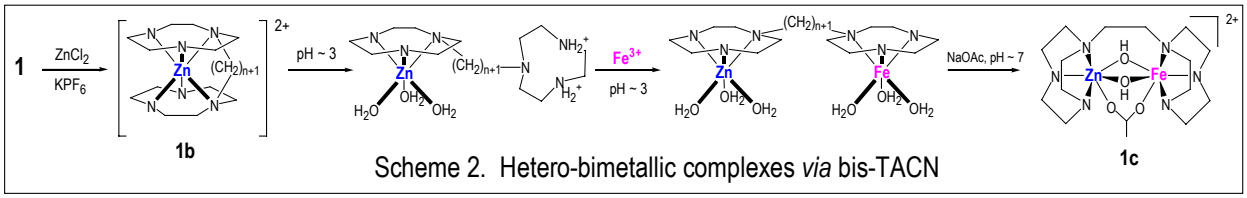
With the early effort focused on the assembly of heterometallic Fe/Zn complexes supported by two triazacyclononane (TACN) rings covalently linked by a -$(CH_2)_n$- chain, namely complex **1**, we explored several synthetic routes. Two successful preparations are shown in Scheme 1. The first route begins with treating TACN with *N*,*N'*-dimethylacetamide dimethyl acetal in anhydrous acetonitrile (step i), which results in the orthoamide of TACN in quantitative yield. Reaction between orthoamide and $I(CH_2)_4I$ in anhydrous acetonitrile affords the linked dication in *ca.* 60% yield (step ii), which is converted to bicyclic TACN (**1**) via base hydrolysis (step iii). In the second preparation, $TsNHCH_2CH_2NHTs$ reacts with 3 equiv of ethylene carbonate under weak alkaline conditions to afford 3,6-di(tosyl)-3,6-diazaoctane-1,8-diol (step iv). The latter was readily converted to the corresponding tosyltate, 3,6-di(tosyl)-3,6-diazaoctane-1,8-di(toluene-4-sulfonate) (step v), which reacts with α,ω-diamine to yield the tethered bis-TACN in its tosylated form (**1**', step vi). Hydrolysis of **1'** in concentrated sulfuric acid, followed by neutralization and extraction results in **1**. While both routes provide **1** in usable percentile yields, the second can be run on the scale of 10 - 100 g and provides the bis-TACN **1** on a multigram scale.



Scheme 1. Synthesis of covalently-tethered bis-TACN ligands

We extended our effort toward heterometallic Fe/Zn complex **1c** using the procedure outlined in Scheme 2. Reaction between **1** and one equiv $ZnCl_2$ in the presence of KPF_6 afforded colorless crystals that exhibit ^{1}H NMR signature of complex ion **1b**. Preliminary X-ray diffraction study confirmed the coordination geometry of **1b** shown in Scheme 2, although the data quality was insufficient for publication. Treating the acidified aqueous solution of **1b** with $FeCl_3$ and subsequent addition of sodium acetate

resulted in a brownish compound exhibiting charge transfer band characteristic of Fe/Zn mixed metal complex. However, the paramagnetism of the complex prevents its characterization by NMR spectroscopy and attempts to obtain crystals of X-ray quality have been futile so far. Nevertheless, pursuit in this regard is continued in our laboratory.



Scheme 2. Hetero-bimetallic complexes *via* bis-TACN

3. Sulfide Oxygenation by H_2O_2 or ^{t}BuOOH Activated with Mn-TACN Complexes

Mn(II/III/IV) complexes supported by multidentate nitrogen-based ligands are known to catalyze both the oxo-transfer reaction from peroxy chemicals and disproportionation reaction of hydrogen peroxide (analogous to *catalase*). Both $\{[(Me_3TACN)Mn]_2(\mu\text{-}O)_3\}(PF_6)_2$ (Me_3TACN = 1,4,7-trimethyl-1,4,7-triazacyclononane) (**3a**) and $[(Me_3TACN\text{-}Mn)_2(\mu\text{-}O)(\mu\text{-}O,O'\text{-}O_2CMe)_2](PF_6)_2$ (**3b**), shown in Figure 1, are among the best olefin epoxidation catalysts.[10-12] Catalyst **3a** was effective in promoting the conversion of organic sulfides to sulfones with periodic acid as the oxygen donor.[13]

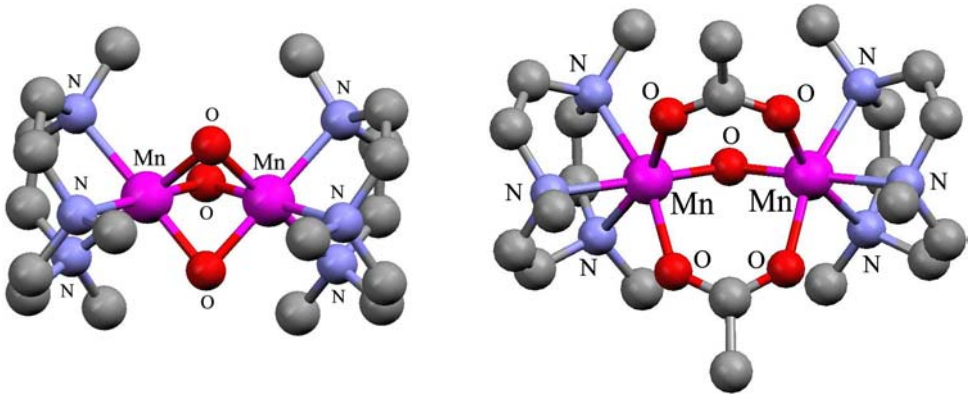
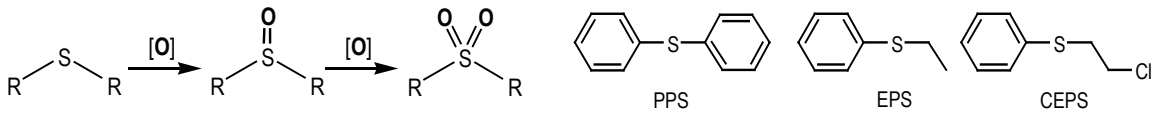


Figure 1. Ball-and-stick representation of catalysts **3a** (left) and **3b** with counter ions omitted.

Three organic sulfides were selected for the assessment of oxygenation potency of catalytic systems: phenyl sulfide (PPS), ethyl phenyl sulfide (EPS) and 2-chloroethylphenyl sulfide (CEPS) (Scheme 3), the latter of which is often used as the simulant of mustard gas.[2] Both ascorbate and oxalate were examined as potential co-catalysts. As shown by entries in Table 1, both **3a** and **3b** are very effective in catalyzing sulfide oxygenation by H_2O_2 with TOFs ranging from 100 – 300. Remarkably, the addition of oxalate/oxalic acid (1:1) resulted in up to 40-fold increase in the TOF for both **3a** and **3b**. On the other

hand, the addition of ascorbate actually inhibits the sulfide oxygenation (entry 14). Noting that efficient epoxidation was achieved using catalyst generated from mixing free Me_3TACN and Mn(II) salt *in situ*,[14] we also tested sulfur oxygenation under similar conditions (entry 15), which did not result in detectable amount of sulfoxide. This result underlines the significance of the use of pre-formed catalysts. With CEPS as the substrate, substantial formation of sulfone(s) was always the case regardless the nature of catalyst and co-catalyst (entries 9 – 13). Clearly, the Me_3TACN-Mn system is not desirable for mustard detoxification, since the sulfone of mustard is also very toxic and should be avoided.[2]



Scheme 3. Oxygenation of organic sulfide(left) and sulfides studied

Table 1. Oxidation products of organic sulfides with H_2O_2 in the presence of either **3a** or **3b**[a]

Entry	Substrate	Catalyst	Oxalate Present	Reaction Time	Sulfide	Sulfoxide	Sulfone	Other	TOF[b]
1	PPS	**A**	None	4h	0	0	100	0	333
2	PPS	**A**	Yes	15min	0	0	100	0	5,330
3	PPS	**B**	None	4h	<1	50	50	0	250
				6h	0	26	74	0	190
4	PPS	**B**	Yes	30min	0	0	100	0	2,660
5	EPS	**A**	None	5h	0	11	70	19	200
				7h	0	12	78	11	160
6	EPS	**A**	Yes	20min	0	0	100	0	4,000
7	EPS	**B**	None	4h	32	25	23	20	120
8	EPS	**B**	Yes	30min	0	0	100	0	2,660
9	CEPS	**A**	None	8h	10	0	83	7	140
10	CEPS	**A**	Yes	20min	0	0	100	0	4,000
11	CEPS	**B**	None	7h	52	0	39	13	74
				16h	20	0	38	42	32
12	CEPS	**B**	Yes	25min	0	0	100	0	3,200
13	CEPS	**A**	Yes	15min	4	1	74	21	4,000
				30min	0	0	98	2	2,600
14	PPS	**A**	ascorbate	2 days	<100	Trace	0	0	0
15	PPS	Me_3TACN + $MnSO_4$	No	45min	100	0	0	0	0

[a] See Ref 4 for experimental conditions; [b] Turn-over-frequency ($hour^{-1}$) = {[RR'SO] + 2[RR'SO_2]}/{[Cat]*time (hour)}

Like many other groups working on Decon chemistry, we are also interested in using ^{t}BuOOH as the oxidant because of its thermal stability and transportability. Unsurprisingly, few catalysts facilitating oxygenation of organic sulfides by TBHP have been reported since ^{t}BuOOH is a far more difficult oxidant to activate due to the size and electron donation from its *tert*-butyl group. Among these examples, MeReO(mtp)PPh_3 (mtp = 2-(mercaptomethyl)thiophenol)) by Espensen catalyzes the oxygenation of methyl phenyl sulfide by TBHP with a remarkable turnover frequency (TOF) of 100 at room temperature,[15] although the use of chlorinated solvent and the cost of Re-based activator make the system less practical for Decon chemistry.

We initially tested the efficacy of both **3a** and **3b** in activating ^{t}BuOOH and found they were inactive with or without oxolate. We were pleasantly surprised that several mononuclear compounds, (Me_3TACN)MnX_3 with X as Cl (**3c**), Br (**3d**), and N_3 (**3e**), facilitates sulfide oxygenation by ^{t}BuOOH in CH_3CN. Some results obtained with phenyl sulfide (PPS) as the model compound is shown in Table 2, from which it is clear that **3c** is the most active catalyst and **3e** the least. The best TOF for **3c** is the same as that of MeReO(mtp)PPh_3. In addition, oxygenation reactions catalyzed by both **3c** and **3d** proceed in a stepwise fashion (entries 1 and 3), indicating the possibility of stopping the reaction at the sulfoxide formation. Figure 2 shows the time course of product distribution from the reaction between PPS and two equiv of ^{t}BuOOH in the presence of 1 mol% of **3c** monitored by GC-MS over a period of 3 h, where it is clear that the sufone product was not present until the complete disappearance of sulfide. The step-wise feature of (Me_3TACN)MnX_3 catalysts implies their potential application in the mustard detoxification.

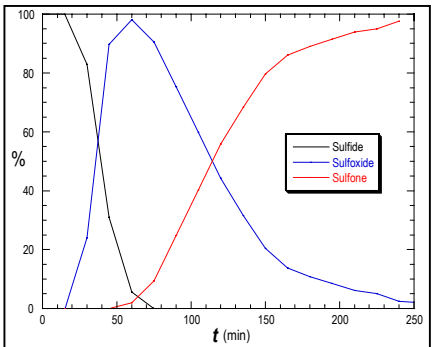


Figure 2

Table 2. Oxygenation of PPS with Catalysts **3c-3e** using ^{t}BuOOH

	Cat.	TBHP	Time	Sulfide	Sulfoxide	Sulfone	TOF
1	**3c**	4	1 h	0	99	1	101
			4h	0	2	98	50
2	**3c**	8	1h	0	0	100	200
3	**3d**	8	1.5h	1	99	0	66
			24h	0	6	94	8
4	**3e**	4	2h	>99	Trace	0	0

4. Organic Sulfide Oxygenation Catalyzed by Polyoxometallate (POM)

Polyoxometallates (POMs) are well known for their capacity in activating oxidants such as H_2O_2 and O_2, and many significant results have been covered in excellent reviews by Hill and Neumann.[16,17] Recently, Mizuno and co-workers reported the synthesis of $(Bu_4N)_4[\gamma\text{-}SiW_{10}O_{34}(H_2O)_2]$ (**4**, Figure 3), which displays remarkable regioselectivity in olefin epoxidation and quantitative utility of hydrogen peroxide.[18,19] The latter feature of **4** prompted us to consider its utility in the oxygenation of sulfides by H_2O_2, since the selectivity for sulfoxide over sulfone (Scheme 3) may be achieved by controlling the stoichiometry of H_2O_2.[6] Organic sulfides studied include phenyl sulfide (PPS), methyl phenyl sulfide (MPS), ethyl phenyl sulfide (EPS) and 2-chloro-ethylphenyl sulfide (CEPS). Since additives such as cyclic imines and carboxylates have been shown to increase reaction rates for catalytic olefin epoxidation,[20] six additives, namely benzoate, ascorbate, oxalate, phosphate, acetate and imidazole, were evaluated for their effects on the oxygenation of organic sufides.

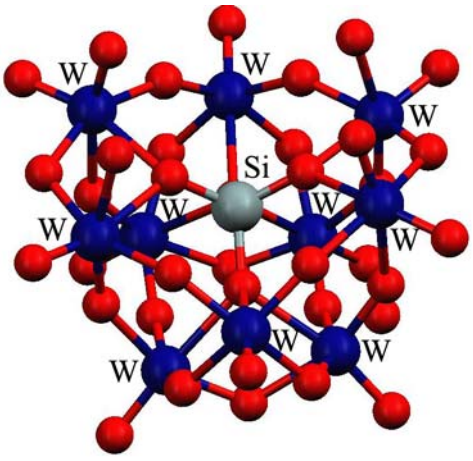


Figure 3. Ball-and-stick representation of **4** (cation)

Table 3 lists the results obtained from the oxygenation of PPS with hydrogen peroxide catalyzed by **4** both with and without additives. In the absence of an additive, conversion of PPS to the corresponding sulfoxide is slow (entry 1), while the use of 2 equiv of H_2O_2 resulted in a quantitative conversion to sulfoxide in 4h (entry 8) followed by a slower conversion to sulfone (19% in 6 hours, entry 15). In comparison, all six additives significantly accelerate the conversion of PPS to sulfoxide or sulfone with 1 or 2 equiv of H_2O_2, respectively (entries 2-7, 9-14 and 16-21). The addition of imidazole resulted in 100% sulfoxide or sulfone formation using either 1 or 2 equiv of H_2O_2, respectively, demonstrating a 100% utility of active oxygen from H_2O_2 in each case (entries 7 and 21). Oxygenation of PPS catalyzed by **4** also proceeds in a well-defined stepwise fashion: no sulfone product was detected prior to the complete sulfoxide formation with the use of 2 equiv of H_2O_2, even in the presence of an additive (entries 8 – 14). Addition of 2 equiv of H_2O_2 resulted in the partial conversion to sulfone within 6 hours without (entry 15) or with additives other than imidazole (entries 16 – 20). In contrast, the use of imidazole led to the complete conversion to sulfone (entry 21), reaffirming the efficiency in utilizing H_2O_2 by **4** in conjunction with imidazole.

Table 3. Results for oxygenation of phenyl sulfide (PPS) in CH_3CN catalyzed by **4**[a]

Entry	Additive	H_2O_2 equiv	Reaction time (h)	Sulfide	Sulfoxide	Sulfone
1	None	1	3.0	62	38	0
2	Benzoate	1	3.0	49	51	0
3	Ascorbate	1	3.0	39	61	0
4	Oxalate/oxalic acid	1	3.0	19	81	0
5	$(NH_4)_3PO_4$	1	3.0	14	86	0
6	Acetate	1	3.0	12	88	0
7	Imidazole	1	3.0	0	100	0
8	None	2	4.0	1	99	0
9	Benzoate	2	3.5	0	100	0
10	Ascorbate	2	3.0	2	98	0
11	Oxalate/oxalic acid	2	2.5	2	98	0
12	$(NH_4)_3PO_4$	2	2.5	2	98	0
13	Acetate	2	2.0	0	100	0
14	Imidazole	2	1.5	0	100	0
15	None	2	6.0	0	81	19
16	Benzoate	2	6.0	0	68	32
17	Ascorbate	2	6.0	0	53	47
18	Oxalate/oxalic acid	2	6.0	0	39	61
19	$(NH_4)_3PO_4$	2	6.0	0	34	66
20	Acetate	2	6.0	0	16	84
21	Imidazole	2	6.0	0	0	100

[a] See Ref. 6 for experimental conditions

Table 4. Results for oxygenation of 2-chloro-ethylphenyl sulfide (CEPS) catalyzed by **4**[a]

Entry	Imidazole present	H_2O_2 equiv.	Reaction time (h)	Sulfide	Sulfoxide	2-Chloro-ethylphenyl sulfone	Phenyl vinyl sulfone	Others
1	No	1	6	0	67	0	0	33[b]
2	Yes	1	2	0	73	0	0	27[b]
3	No	2	6	0	0	82	13	5[c]
4	Yes	2	3	0	0	72	27	1[c]
5	No	2	24	0	0	75	25	0
6	Yes	2	24	0	0	70	30	0

[a] See Ref. 6 for experimental conditions

As shown by the entries in Table 4, catalyst **4** is also effective in the H_2O_2 oxygenation of 2-chloro-ethylphenyl sulfide (CEPS), a model compound for mustard gas.[1,2] Notably, use of 1 equiv of H_2O_2 both

without and with imidazole resulted in the complete consumption of CEPS in 6 h (entry 1) and 2 h (entry 2), respectively, while sulfones were not detected among the products. Prevention of sulfone formation is significant in the decontamination of mustard gas since its sulfone is also highly toxic.[2] Similar product distribution was observed in both the presence and absence of imidazole, although a longer reaction time is required for quantitative conversion for the latter. In summary, $(Bu_4N)_4[\gamma\text{-}SiW_{10}O_{34}(H_2O)_2]$ (**4**) is remarkably efficient with its utilization of hydrogen peroxide in the oxygenation of organic sulfides. Results reported herein reveal a 100% utilization of H_2O_2 by catalyst **4,** enabling synthetic control of organic sulfide oxygenation to form either sulfoxide or sulfones with 1 or 2 equiv of H_2O_2, respectively.

5. Binding of Phosphate Monoesters by Cu Complexes

We are interested in both mono- and bi-metallic complexes supported by TACN and its *N*-alkylated surrogates, since they often exhibit labile coordination sites, and are hence capable of facilitating the degradation of phosphate esters through both the hydrolytic and oxidative pathways. During the course of this work, we uncovered two new TACN-Cu complexes, $(TACN)Cu(\eta^1\text{-}ONO_2)_2$ (**5a**) and $[Cu(TACN)_2](PF_6)_2$ (**5b**), and their syntheses and structures (Figure 4) are reported herein.[8] Although **5b** is inactive towards phosphate ester hydrolysis, **5a** is an active catalyst for the hydrolysis of BNP (bis(*p*-nitrophenol)phosphate). In addition, the presence of two labile sites in **5a** facilitates the formation of various phosphate ester adducts on (TACN)Cu, which may offer structural insights of phosphate ester activation.

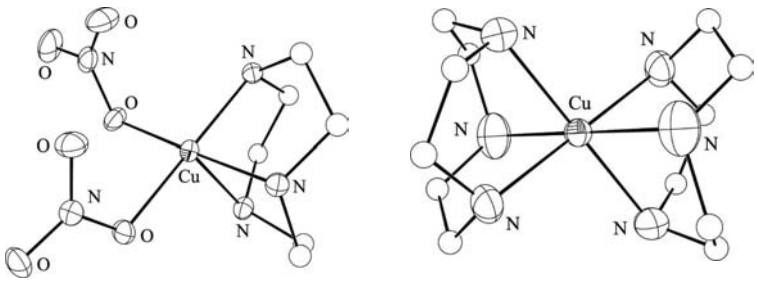
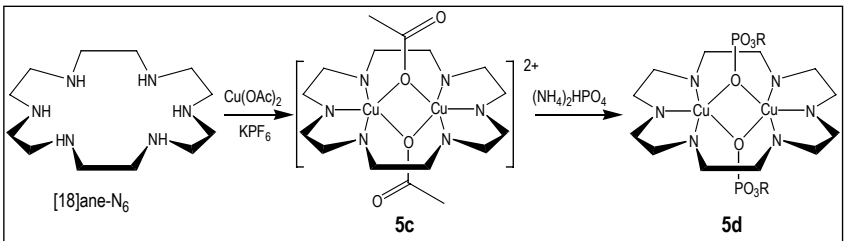


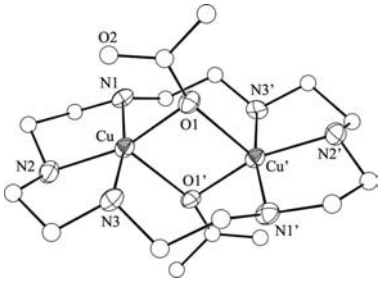
Figure 4. ORTEP plots of compound $Cu(TACN)(NO_3)_2$ (**5a**, left) and $Cu(TACN)_2^{2+}$ (**5b**) at 30% probability level.

While the novel complex $(TACN)Cu(NO_3)_2$ (**5a**) catalyzes the hydrolysis of BNP, the rate enhancement is generally in line with other mononuclear TACNCu complexes. We noted that a pre-formed dimetallic center may lead to significantly enhanced hydrolytic rates, as alluded in the acclaimed *two-metal-ion mechanism* by Steitz & Steitz.[21] Since many *homo*-dinuclear complexes supported with TACN have

been reported by laboratories around the world, we decided to focus on dicopper complexes supported by a different macrocyclic ligand: 1,4,7,10,13,16-hexaazacyclooctadecane (**[18]ane-N_6**, Scheme 4).



Scheme 4. Synthesis of dicopper-[18]ane-N_6 complexes **5c** and **5d**; Structure of **5c** shown to the right



Complex $\{Cu_2(\mu\text{-}O\text{-}OAc)_2([18]ane\text{-}N_6])\}(PF_6)_2$ (**5c**) was initially isolated from a prolonged reaction between $(TACN)CuCl_2$ and excessive AgOAc in aqueous solution in *ca.* 40% yield. Rational synthesis based on treating an aqueous solution of [18]ane-N_6 with two equivalents of $Cu(OAc)_2$ resulted in **5c** with a better yield (60%).[7,9] The lability of bridging acetates in **5c** enables their facile displacement by a number of phosphate monoester anions, including $(HPO_4)^{2-}$, $(PO_4Ph)^{2-}$, glycerol 2-phosphate, and α-D-glucose phosphate. Many phosphate monoester adducts have been characterized with X-ray single crystal diffraction (Figure 5), and these results may be significant in understanding metal-containing phosphate monoesterases. In addition to establishing the binding mode of phosphate monoesters *via* X-ray study, the affinity of $Cu_2([18]ane\text{-}N_6)$ unit towards phosphate monoester in solution was determined through optical titration in both buffered and unbuffered solutions. The *apparent association constants* relative to acetate ($K_{rel} = K_{phosphate}/K_{acetate}$) are on the order of 10^3 - 10^4 for all phosphate monoesters at physiological pH (7.4, buffered with HEPES).[7,9]

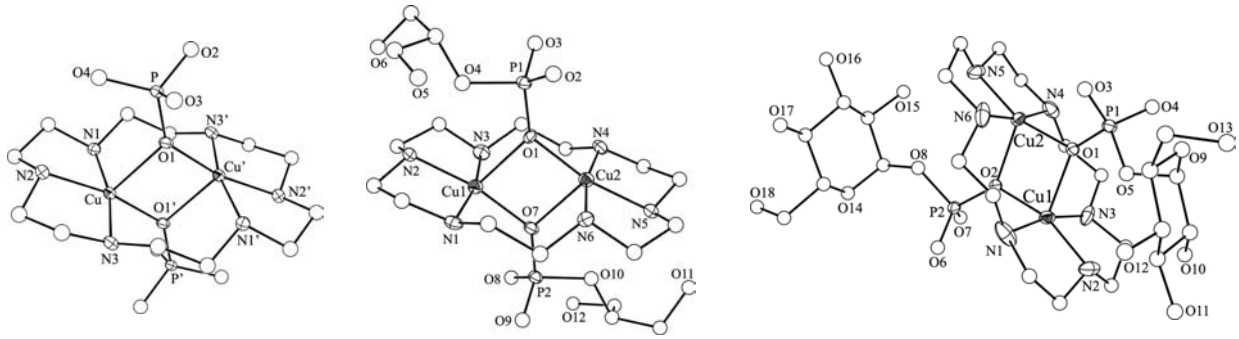


Figure **5.** ORTEP plots of $Cu_2(\mu\text{-}O\text{-}HPO_4)_2([18]ane\text{-}N_6)$ (left), $Cu_2(\mu\text{-}O\text{-}glycerolphosphate)_2([18]ane\text{-}N_6)$, and $Cu_2(\mu\text{-}O\text{-}\alpha\text{-}D\text{-}glucosephosphate)_2([18]ane\text{-}N_6)$ (right) at 30% probability level.

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