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O,O′-Diester Methylenediphosphonotetrathioate: Synthesis, Characterization, and Potential Applications

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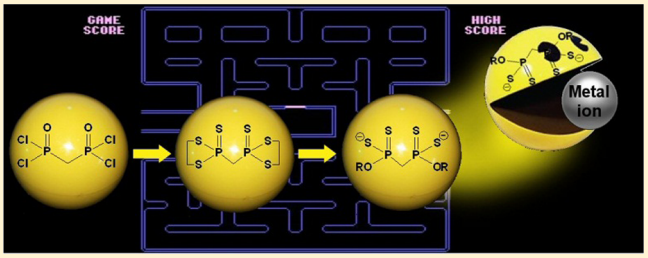
Supporting Information

ABSTRACT: A new transformation of methylene-bis(phosphonic dichloride) into tetrathiobisphosphonate derivatives is reported. The reaction of methylene-bis(phosphonic dichloride) with 1,2-ethanedithiol in bromoform in the presence of $AlCl_3$ formed methylene-bis(1,3,2-dithiaphospholane-2-sulfide), which gave rise to *O,O′*-diester-methylenediphosphonotetrathioate analogues **1a**–**k** upon reaction with phenols and alkyl alcohols in the presence of DBU. Reaction mechanisms are proposed, and all products were characterized by ^{31}P, ^{13}C, and ^{1}H NMR. An X-ray crystal structure was obtained for intermediate **2**. The potential of the novel scaffold for selective coordination of metal-ions was examined by coordination of Hg(II) and Pb(II) by **1f**, as determined by FT-IR, and chelation of Zn(II), but not Ca(II), by **1b**, as determined by $^{31}P/^{1}H$ NMR. UV–vis measurements of **1g**–Ni(II) mixture revealed a 2:1 ligand:metal complex. These derivatives are potential antioxidants, and their ability to inhibit ·OH formation in Fenton reactions was quantified by ESR measurements. Analogue **1g** proved to be a most potent antioxidant (IC_{50} 53 μM), inhibiting the Cu(I)-catalyzed Fenton reaction at lower concentrations than GSH, ascorbic acid, and EDTA. Analogue **1c** inhibited the Fe(II)-catalyzed Fenton reaction at about the same concentrations as ascorbic acid (IC_{50} 83 vs 93 μM). In summary, the novel compounds, **1a**–**k**, proved to chelate various borderline/soft Lewis acid metal-ions, and may be useful as antioxidants and metal extractors.



INTRODUCTION

Metal chelators containing sulfur are important agents in the treatment of heavy metal (e.g., Hg(II), Pb(II)) poisoning. Specifically, these agents chelate the metal-ion and induce its elimination through the urine.[1,2] Metal chelators containing sulfur have also been proposed as a treatment for Alzheimer's disease,[3,4] Wilson's disease,[5] and other physiological conditions caused by metal abnormalities. Furthermore, related metal chelators are important for industrial use as metal extractors[6] and lubricant additives.[7] For instance, the zinc complex of phosphorodithioic acid (ZDDP) is widely used as an antiwear agent and an antioxidant.[8]

Bisphosphonate analogues are known as hard/borderline[9−11] Lewis acid metal chelators and have been used for treating osteoporosis,[12] multiple myeloma,[13] and other bone abnormalities. By binding to Ca(II) ions they adsorb to bone and interfere with bone resorption.[14] The bisphosphonate scaffold is an enzymatically stable analogue of pyrophosphate.[15] Although bisphosphonate analogues are Ca(II) and Mg(II) ion-selective, they are not suitable for chelating borderline/soft metal-ion Lewis acids such as Cu(I) and Fe(II)-ions, and they are not effective for removing heavy metal ions from contaminated areas. For this purpose, we targeted the development of a novel scaffold bearing both a bisphosphonate-like moiety, to provide metabolic and chemical stability, and the replacement of oxygen atoms with four sulfur atoms, which confer a "soft-base" character. Analogues of tetrathiobisphosphonate diester **1** (Scheme 1) may be potential therapeutic agents for the removal of soft/borderline metal-ions, as well as useful industrial agents for metal extraction as in antiwear additives. Specifically, we describe the synthesis of a novel series of *O,O′*-diester-methylenediphosphonotetrathioate derivatives, their mechanism of formation, their characterization as metal-ion chelators, and their potential application as antioxidants.

RESULTS AND DISCUSSION

Synthesis of Methylene-bis(1,3,2-dithiaphospholane-2-sulfide), 2. We targeted the preparation of *O,O′*-diester-methylenediphosphonotetrathioate, **1**, from a commercially available starting material using a minimal number of synthetic steps. Our synthetic plan involved the intermediacy of **2**, synthesized from the commercially available methylene-bis(phosphonic dichloride), **3** (Scheme 1). We envisaged that bisphosphonate **2** would subsequently undergo ring-opening upon reaction with alcohol in the presence of DBU to form analogues **1** (Scheme 1).[16,17]

In our first attempt to obtain compound **2**, we reacted starting material **3** with Lawesson's reagent[18] hoping to replace

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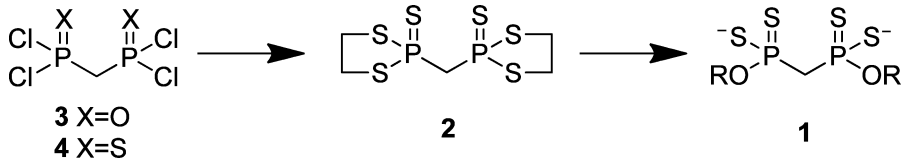
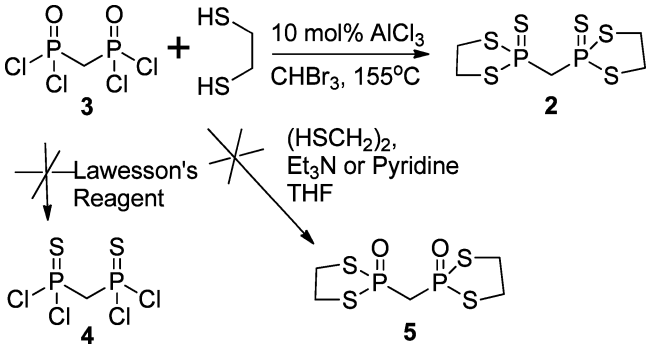
Scheme 1. *O,O′*-Diester-methylenediphosphonotetrathioate, 1



the phosphonate oxygen atoms with sulfur atoms to form compound **4** (Scheme 2). However, the reaction resulted in mixture of **4** and many side-products.

Scheme 2. Synthesis of Compound 2



In our second attempt we reacted **3** with 1,2-ethanedithiol in a first step to produce **5** and then used Lawesson's reagent in an attempt to produce compound **2**. Compound **3** was treated with 1,2-ethanedithiol under several conditions: in pyridine, THF/Et_3N, or heated under reflux in $CHCl_3$. However, no product **5** was obtained. When **3** was treated with 1,2-ethanedithiol in the presence of 10 mol % of $AlCl_3$ in hot $CHCl_3$ for 5 days, traces of compound **2** were formed.

We optimized the latter reaction to obtain **2** in a reasonably good yield, applying various solvents and catalysts, and changing the number of reactant equivalents (Table 1). The optimal reaction time was found to be 5 days when using hot bromoform as a solvent.

As shown in Table 1, no detectable reaction occurred between **3** and 5 equiv of 1,2-ethanedithiol in the presence of 10 mol % $AlCl_3$ in THF under reflux conditions (entry 2), but the product was obtained in 24% yield when 1,1,2,2-tetrachloroethane was used as a solvent (at 145 °C) (entry 3). Triglyme at 155 °C gave a product that was highly contaminated (entry 4), as did the reaction in $CHBr_3$ at 170 °C when $AlCl_3$ was present (entry 5).

To reduce byproducts, **3** was treated with 6 equiv of 1,2-ethanedithiol in $CHBr_3$ at 155 °C without $AlCl_3$. This gave more pure product, but the yield was reduced to 17% (entry 6). Reaction of **3** with 10 mol % $AlCl_3$ and a reduced amount (2 equiv) of 1,2-ethanedithiol in $CHBr_3$ at 155 °C gave traces of the product along with methylenediphosphonic acid (entry 7), leading us to conclude that at least 4 equiv of 1,2-ethanedithiol were needed for the formation of **2**.

The role of $AlCl_3$ as a catalyst was investigated by replacing it with $TiCl_4$. The latter was less effective than $AlCl_3$ in $C_2H_4Cl_4$ (24%, entry 3), decreasing the yield to 10% (entry 8) with the same product purity. The role of $AlCl_3$ in the reaction was also evaluated by addition of 1 equiv of $AlCl_3$. Under this condition, compound **2** could not be recovered due to highly contaminated product (entry 9).

Table 1. Optimization of Reaction Conditions for the Synthesis of Compound 2 with 5 Day Reaction Times for All Experiments

entry	temp [°C]	solvent	catalyst/ additive	1,2-ethanedithiol [equiv]	isolated yield [%]
1	60	$CHCl_3$	10 mol % $AlCl_3$	5	traces
2	65	THF	10 mol % $AlCl_3$	5	
3	145	$C_2H_2Cl_4$	10 mol % $AlCl_3$	5	24
4	155	triglyme	10 mol % $AlCl_3$	6	
5	170	$CHBr_3$	10 mol % $AlCl_3$	6	
6	155	$CHBr_3$	none	6	17
7	155	$CHBr_3$	10 mol % $AlCl_3$	2	traces
8	155	$CHBr_3$	10 mol % $TiCl_4$	5	10
9	155	$CHBr_3$	1 eq $AlCl_3$	5	
10	155	triglyme	2 eq $CaCl_2$	6	24
11	155	$CHBr_3$	2 eq $CaCl_2$	6	24
12	155	$CHBr_3$	10 mol % $AlCl_3$	6	44
13[a]	145	$CHBr_3$	none	6	80

[a]A 2-step synthesis as depicted in Scheme 3.

Elimination of water in the reaction may decrease the yield of **2**. Therefore, $CaCl_2$ was used as both a desiccant and Lewis acid in either triglyme or $CHBr_3$. However, the yield was still low, 24% yield for each case (entries 10–11). Finally, the optimal yield of compound **2** (44%) was obtained in $CHBr_3$ with 10 mol % $AlCl_3$ and 6 equiv of 1,2-ethanedithiol at 155 °C for 5 days (entry 12). Although the reaction temperature in entry 12 was 15° lower than the reaction in entry 5, we obtained the product in a higher yield. Monitoring the reaction progress by ^{31}P NMR revealed that a reaction temperature higher than 160 °C leads to many other signals that do not appear in reactions conducted in lower temperatures. Thus, although ^{31}P NMR confirmed the formation of the product, the latter was inseparable from the byproducts. Moreover, extending the reaction time to 7 days at 155 °C did not result in a higher yield, and when the reaction time was shortened to 4 or 3 days, lower yields were obtained.

Mechanism of Formation of Compound 2. The mechanism of the reaction was investigated by analyzing aliquots from the reaction mixtures in $CDCl_3$ or DMSO-d_6 by ^{31}P NMR. In $CDCl_3$ solution, a signal at 50–52 ppm emerged several hours after the reaction had started. This signal implies the formation of intermediate **4**.[19] In wet DMSO-d_6 solution, a 50–52 ppm signal could not be observed, possibly due to hydrolysis of **4**. To validate the hypothesis that **4** is an intermediate in the reaction we synthesized **4** according to the literature.[20] Briefly, bis(dichlorophosphino)methane **6** (which is commercially available) was treated with neat $PSCl_3$ in the

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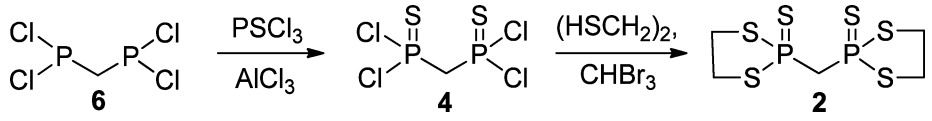
Scheme 3. Synthesis of Compound 2 Starting from Bis(dichlorophosphino)methane 6



Scheme 4. Proposed Mechanism for Formation of Compounds 2

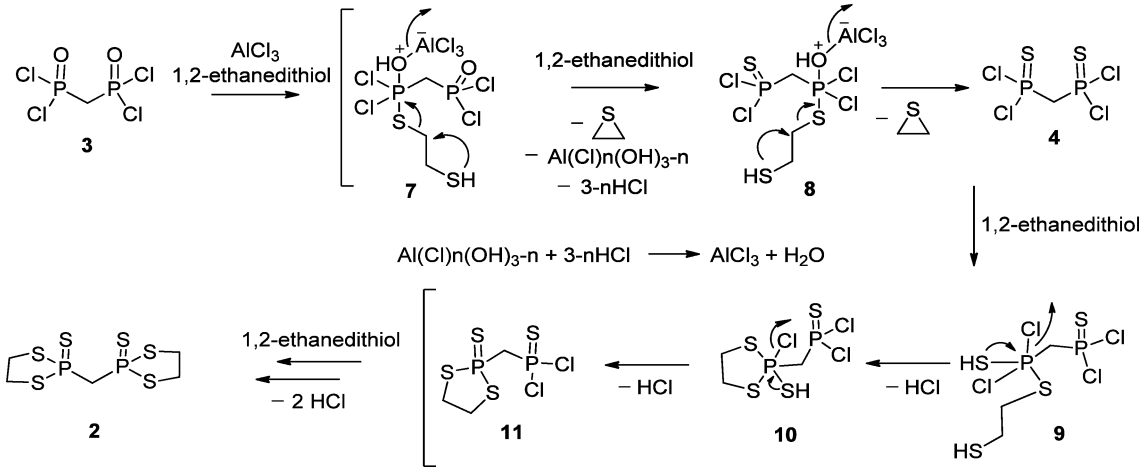
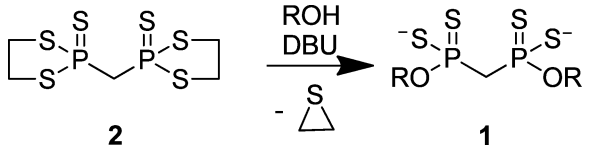
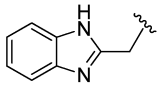


Table 2. Yields and ^{31}P NMR Data of Derivatives 1[a]



Entry	Compound	R	% Yield Procedure A	% Yield Procedure B	^{31}P-NMR (ppm)[b]
1	**1a**	CH_3	60	20	105.4
2	**1b**	$CH_3(CH_2)_3$	83	N/O	101.9
3	**1c**	$CH_3(CH_2)_7$	19	10	101.8
4	**1d**	$(CH_3)_2CH$	N/O	N/O	--
5	**1e**	$(CH_3)_3C$	N/O	N/O	--
6	**1f**	$(CH_3CH_2)_2CHCH_2$	N/O	12	101.9
7	**1g**	$PhCH_2$	75	17	103.4
8	**1h**	2-$OMePhCH_2$	37	2	103.6
9	**1i**	2,4-$(OMe)_2PhCH_2$	N/O	N/O	--
10	**1j**		N/A	36	106.5
11	**1k**	L-Bz-Tyr-OEt	N/A	54	104.6

[a]N/O: not obtained. N/A: not applicable. Procedure A is not applicable. [b]The given ^{31}P NMR data are for products as the corresponding disodium salts.

presence of $AlCl_3$ at 110 °C for 2 h and then at 140 °C for 4 h. The product was obtained as a liquid upon high vacuum distillation which then solidified to give a white solid in 89% yield. Compound **4** was further reacted with 1,2-ethanedithiol in the absence of $AlCl_3$ in $CHBr_3$ at 145 °C resulting in the formation of compound **2** in 90% yield. The overall yield of **2** from compound **6** was 80% (Scheme 3) (Table 1, entry 13).

We concluded that formation of **2** from **3** involves first replacement of oxygen atoms by sulfur atoms, and then P−Cl bonds are broken upon reaction with 1,2-ethanedithiol to form dithiophospholane rings.

Although the bond energy of P═O is higher than that of P═S (120 kcal/mol for P═O in $POCl_3$ vs 76 kcal/mol for P═S in $PSCl_3$),[21] we hypothesized that formation of thiirane as a leaving group can trigger the transformation of P═O bond to

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P═S (Scheme 4). To corroborate this hypothesis we used PPh_3 as a scavenger of thiirane. PPh_3 can react with thiirane to form triphenylphosphine sulfide and ethylene.[22] Thus, compound **3** was treated with 6 equiv of 1,2-ethanedithiol and 2 equiv of PPh_3 in $CHBr_3$ at 155 °C. After 19 h, compound **2**, triphenylphosphine sulfide (^{31}P NMR: 43.9 ppm), and ethylene were formed. Almost no PPh_3 remained which led us conclude that the driving force for the formation of **2** is indeed thiirane elimination.

The role of $AlCl_3$ as a catalyst is described in Scheme 4. $AlCl_3$ probably coordinates the phosphonate oxygen atom in **3** resulting in a more electrophilic phosphorus atom susceptible to nucleophilic reaction with 1,2-ethanedithiol. Consequently, a pentavalent phosphorus intermediate **7**/**8** is formed with the concomitant elimination of $AlCl_3$, thiirane, and water to form intermediate **4**. Next, **4** reacts with an additional equivalent of 1,2-ethanedithiol to form the dithiaphospholane ring **10**/**11** followed by elimination of HCl and formation of P═S bond. $AlCl_3$ catalyst is possibly recycled by the reaction of HCl with $Al(Cl)_n(OH)_{3-n}$.

The structure of product **2** was verified by X-ray diffraction of crystals obtained by slow evaporation of $CHBr_3$ solution of **2** (Figure S50).[23] Compound **2** demonstrates a *gauche* conformation between the two rings. Selected bond lengths and angles are presented in Table S1.

Synthesis of *O,O′*-Diester-methylenediphosphonotetrathioate, 1. To obtain derivatives **1**, compound **2** was treated with various alcohols in the presence of DBU (Table 2). The reaction was performed, either in neat alcohol for 0.45−2.5 h (reaction procedure A), or in $CHCl_3$ with 4 equiv of alcohol for 24 h (reaction procedure B) (Table 2). In both procedures the solutions were heated at 60 °C.

The reaction yield depended on the properties of the alcohol. When the reactions were carried out in neat and relatively low molecular weight primary alcohols, yields ranged from 60% to 83% (entries 1−2). When the reactions were carried out in $CHCl_3$ with 4 equiv of alcohol, yields were reduced considerably. Furthermore, with secondary or tertiary alcohols, no reaction was observed (entries 4−5). When **2** was reacted with long alkyl chain alcohols, the reaction yield decreased dramatically, e.g., from 83% for butanol to 19% for octanol (entries 2 and 3). It is noteworthy that compound **1b** was obtained via procedure A in 83% versus 60% yield of **1a**. This is probably due to the low solubility of both the reactant **2** and product **1a** in methanol giving rise to a suspension, while the reaction to form **1b** results in a clear mixture.

The reaction progression could be easily monitored by ^{31}P NMR, since the signal of starting material **2** appeared at ∼90.5 ppm and the products were observed at 101−107 ppm.

Compound **2** was also treated with thiols and primary amines in the presence of DBU (Figure 1). With thiols (e.g., benzylthiol), product **12** was obtained, as observed by ^{31}P NMR (76 ppm). However, it completely decomposed during silica gel column separation. No product was detected upon treatment of **2** with primary amine (e.g., benzylamine) **13**.

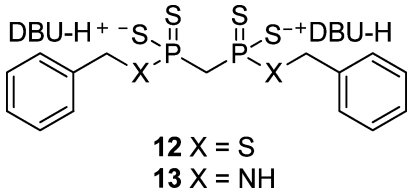

Figure 1. Products **12** and **13** (not isolated).

Products **1a−j** were separated over silica gel with $CHCl_3$:MeOH (0−20%), and $CHCl_3$:iPrOH (91:9%) for compound **1k**, and obtained as the corresponding $DBUH^+$ salts. The exchange of ($DBUH^+$) counterion with Na^+ or pyridinium ions, using Dowex 50W, -Na^+ or -pyridinium form, did not proceed well, resulting in a contaminated product. Alternatively, the ($DBUH^+$) counterion was replaced with Na^+ on Sephadex CM-Na^+ form column. The ammonium salt of **1** was obtained by washing a $CHCl_3$ solution of **1** with 0.25 M HCl to get the neutral product, which was then extracted with 3 M NH_4OH, followed by freeze-drying to give **1** as a white powder of the ammonium salt.

In addition to the desired *O,O′*-diester-methylenediphosphono-tetrathioate derivative, **1**, two byproducts were usually obtained. This is exemplified by **1k**. The reaction to form **1k** took place in acetonitrile at RT for 18 h. Besides bisphosphonate **1k** (14% yield), product **14** (33% yield) and product **15** (9% yield) were obtained (Figure 2). Side product

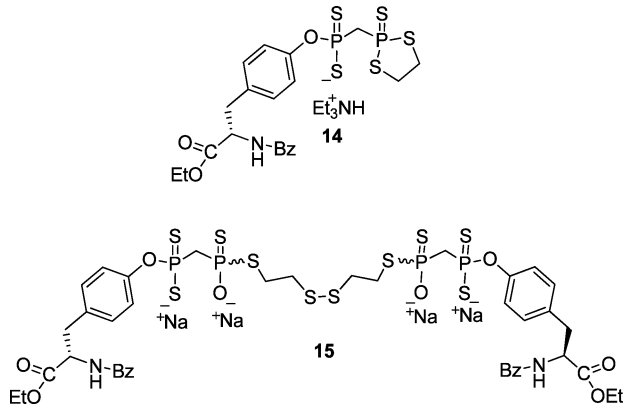

Figure 2. Byproducts formed in the reaction of **2** with *N*-benzoyl-L-tyrosine ethyl ester.

14 is due to reaction of tyrosine at one dithiophospholane ring, while side product **15** is due to reaction of H_2O molecule at the dithiophospholane ring in side-product **14** during workup, followed by air oxidation to form the disulfide product. However, by applying procedure B, compound **1k** was formed in 54% yield.

Characterization of Compounds 1 as Metal-Ion Chelators. In order to demonstrate the ability of compounds **1** to bind borderline metal-ions we titrated compound **1b** with 0.45 and 1.45 equiv of $ZnCl_2$. Titration was monitored by $^{31}P/^{1}H$ NMR in DMSO-d_6 (Figure 3). When 0.45 equiv of $ZnCl_2$ was added to **1b** (Figure 3b) the PCH_2P triplet signal in ^{1}H NMR spectrum shifted from 3.16 to 3.03 ppm and the ^{31}P NMR signal at 102.4 shifted to 98.6 ppm. When **1b** was treated with 1.45 equiv of $ZnCl_2$ the PCH_2P triplet signal (3.13 ppm) significantly broadened. Likewise, the ^{31}P NMR signal at 97.9 ppm further shifted and significantly broadened.

To establish the metal-ion selectivity of analogues **1**, we repeated the above NMR-monitored metal-ion titration, this time with $CaCl_2$. Addition of up to 2 equiv of $CaCl_2$ did not change at all the chemical shift of the PCH_2P signal, thus indicating no binding of Ca(II) ion by analogue **1b** (Figure S2).

Next, we demonstrated the ability of compound **1** to bind heavy metal-ions, e.g., Hg(II) and Pb(II). For this purpose we

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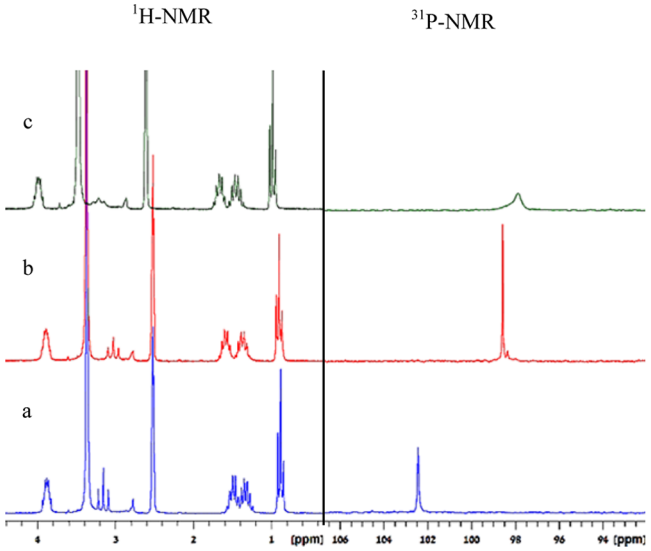

Figure 3. ^{31}P/^{1}H NMR spectra in DMSO-d_6 of **1b**–Zn(II) complex at (81 and 200 MHz): (a) **1b**; (b) **1b** with 0.45 equiv of Zn(II); (c) **1b** with 1.45 equiv of Zn(II).

prepared the corresponding complexes as follows: The **1f**–M(II) complex was obtained by addition of methanol dissolved $HgCl_2$ or $PbCl_2$ into **1f** in water at 2:1 ligand:metal ratio. The complex precipitated as a white solid, and the solvent was removed by decantation. The solid was washed with methanol and dried under vacuum.

The binding properties of compound **1f** with Hg(II) and Pb(II) were assayed using FT-IR (Figure 4). The P═S

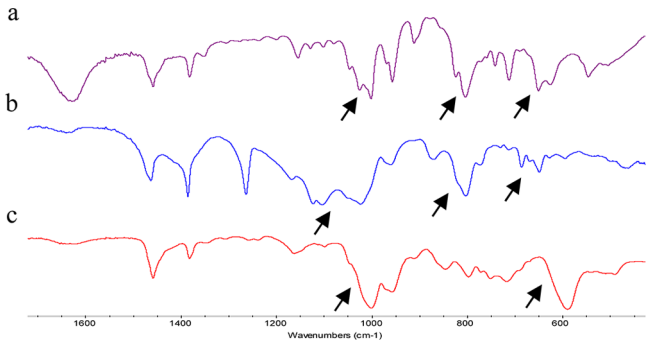

Figure 4. FT-IR (KBr plates) region 1900–560 cm^{-1} of (a) compound **1f**, (b) **1f**–Pb(II) 2:1, (c) **1f**–Hg(II) 2:1.

stretching bands[24,25] of **1f** lie at 804 and 650 cm^{-1} (Figure 4a), while the stretching band of the **1f**–Pb(II) complex (800 cm^{-1}) became wider and more intense, implying Pb(II)-binding (Figure 4b). P═S stretching bands for the **1f**–Hg(II) complex shifted from 804/650 cm^{-1} to a lower frequency, 590 cm^{-1}, and became wider and more intense, indicating coordination of sulfur with Hg(II) ion. Yet, S–Hg–S absorptions were not observed, possibly because they are weak and appear at frequencies below 400 cm^{-1} (Figure 4c).[26] The P–O–(C) stretching bands of **1f**–Pb(II) and **1f**–Hg(II), 1100–1000 and 1001–958 cm^{-1}, respectively, exhibit greater intensity versus the P–O–(C) bands in free **1f** (1025–1002 cm^{-1}).

The metal-binding stoichiometry and metal extractive properties of analogues **1** with Ni(II) were assayed using UV–vis measurements. The Ni(II) complexes of many organic molecules are colored. Hence, complex detection and discrimination from the signal of compound **1** at 230 nm is expected. Thus, solutions of $Ni(BF_4)_2$ dissolved in EtOH and **1g**–DBU dissolved in DCM were mixed, and the organic phase turned yellow. DBU salt of **1g** was diluted, and $Ni(BF_4)_2$ was added. After each addition the absorbance was measured at 321 nm (Figure 5a). The complex absorbance was metal-concentration dependent up to 2:1 ligand:metal ratio (Figure 5b).

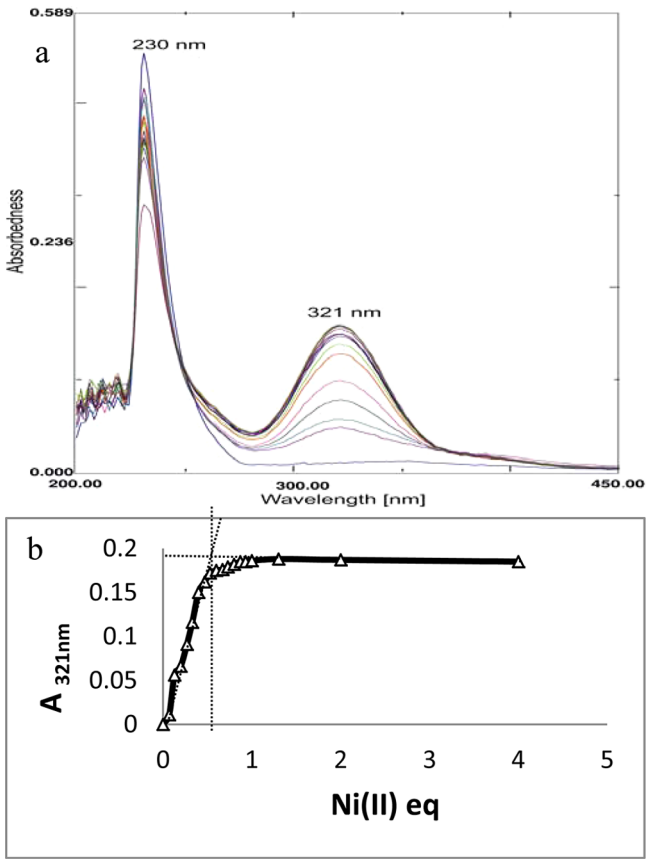

Figure 5. Titrations of **1g** with Ni(II) as monitored by UV–vis spectra: (a) UV–vis spectra of **1g**–Ni(II), (b) UV–vis cross-section at 321 nm of the nickel titration of **1g**.

The ability of derivatives **1** to chelate borderline/soft metal-ions was further demonstrated by measuring inhibition of Cu(I) and Fe(II) induced Fenton reactions. Specifically, we measured the antioxidant effect of compounds **1** by quantifying the formation of OH radical from H_2O_2 induced by Cu(I) or Fe(II) ions. OH radicals formed in the reaction were trapped by 5,5′-dimethyl-1-pyrroline-*N*-oxide (DMPO), and the amount of DMPO–OH adduct was then measured by ESR. Generally, addition of chelators to Fe(II)/Cu(I)–H_2O_2 mixture lowers DMPO–OH signal due to metal-ion chelation and radical scavenging.[27]

Our data (Table 3) demonstrate the high ability of the tested compounds to reduce the amount of OH radical in the Cu(I)-induced Fenton reaction. Compounds **1a**/**g**/**k** were found to be superior antioxidants as compared to EDTA. In the Fe(II)–H_2O_2 system, compound **1c** was the most promising antioxidant, IC_{50} 83 μM versus 61.5 μM for EDTA. The greater ability of compounds **1a**,**g**,**c**,**k** to lower the radical formation in Cu(I)–H_2O_2 versus Fe(II)–H_2O_2 system is attributed to the presence of tetrathio groups, making these

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Table 3. Antioxidant Capacity of Derivatives 1 As Compared to Standard Metal Ion Chelators/Antioxidants[a]

	IC_{50} μM		IC_{90} μM	
compd	Fe(II)	Cu(I)	Fe(II)	Cu(I)
EDTA	61.5 ± 1	64.0 ± 2	98.0 ± 1	110.0 ± 8
ascorbic acid	92.5 ± 8	N/A	N/A	N/A
GSH	63.0 ± 5	216.0 ± 40	N/A	490.5 ± 6
1a	114.5 ± 3	56.0 ± 1	374.5 ± 22	83.0 ± 1
1g	115.5 ± 2	53.0 ± 5	287.0 ± 28	80.5 ± 4
1c	83.0 ± 2	67.5 ± 1	209.0 ± 6	97.0 ± 6
1k	94.5 ± 7	59.5 ± 1	330.5 ± 15	86.5 ± 1

[a]N/A = not available, the minimal amount of radical production exceeds 50% (IC_{50}) or 10% (IC_{90}).

compounds soft chelators that preferably chelate Cu(I) over Fe(II) ions.

CONCLUSIONS

We synthesized a novel family of *O,O′*-diester-methylenediphosphonotetrathioate analogues, **1a−h**, by a two-step process from commercially available methylene-bis(phosphonic-dichloride) or a three-step process from bis(dichlorophosphino)methane in reasonable to good yields. Formation of **1** involved the intermediacy of methylene-bis(1,3,2-dithiaphospholane 2-sulfide), **2**, the mechanism of formation of which was elucidated. Compounds **1a,b,c,d,g,h** were found to selectively chelate soft/borderline metal-ions, i.e., Zn(II), Ni(II), Cu(I), and Fe(II) ions, and to function as potent antioxidants, superior to EDTA, ascorbic acid, and GSH in Cu(I)−H_2O_2 system. In addition, compound **1f** chelated heavy metal-ions, e.g., Pb(II) and Hg(II) ions. Compound **1g** was found to efficiently bind Ni(II) in a 2:1 stoichiometry by UV−vis monitored titrations. Our studies on the application of derivatives **1** as extreme pressure lubrication additives will be published in due course.

EXPERIMENTAL SECTION

Precautions must be taken when synthesizing these phosphorus products due to their resemblance to neurotoxins.

Methylene-bis(1,3,2-dithiaphospholane-2-sulfide), 2. Methylene-bis(phosphonic dichloride) **3** (5 g, 20 mmol) was dissolved in dry $CHBr_3$ (48 mL). 1,2-Ethanedithiol (11.42 g, 121 mmol) was added via syringe followed by addition of anhydrous $AlCl_3$ (0.25 g, 1.87 mmol). The reaction mixture was heated to 155 °C for 5 days. The resulting yellow mixture contained brown greenish precipitate, which was hot filtered. An additional amount of hot $CHBr_3$ (20 mL) was added for rinsing. The mixture was left at rt for several hours until turquoise needles formed. The needles were collected by vacuum filtration and washed with methanol, water, and methanol again, and were left to dry. The dry needles were dissolved in hot DMSO. After cooling down to rt, water was added until a white precipitate formed. The precipitate was collected by vacuum filtration, washed with water and methanol, and dried under vacuum to give product **2** (2.86 g, 44% yield) as a white solid. Suitable crystals for X-ray diffraction were obtained by slow evaporation of the white product from $CHBr_3$.

Melting point 244−245 °C (dec). ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.64 (t, J = 12.3 Hz, 2H), 3.8−3.6 (m, 8H) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ 60.3 (t, J = 41.23 Hz), 41.9 ppm. ^{31}P NMR (81 MHz, DMSO-d_6): δ 90.5 ppm. HRMS (MALDI) m/z: calcd for $C_5H_{10}NaP_2S_6$ $[M + Na]^+$ 346.847, found 346.844. IR (ATR): 2950w, 2914w, 2890w, 1403w, 1344w, 1272w, 1239w, 1151w, 937w, 847w, 775m, 750m, 719m, 628s, 548s cm^{-1}.

Methylene-bis(1,3,2-dithiaphospholane-2-sulfide), 2. Methylene-bis(phosphonothioic dichloride) **4** (0.1 g, 0.35 mmol) was dissolved in dry $CHBr_3$ (1.5 mL) followed by addition of 1,2-ethanedithiol (0.23 g, 2.4 mmol). The mixture was heated to 145 °C for 3 days. The mixture was hot filtered, and another portion of $CHBr_3$ (2 mL) was used for rinsing. After the mixture cooled down to rt, n-hexane was added, and the product was precipitated. The white precipitate was collected by vacuum filtration and washed with n-hexane to give compound **2** as a white solid (0.11g, 90% yield).

O,O′-Diester-methylenediphosphonotetrathioate, 1, Typical Procedure A. Compound **2** (100 mg, 0.31 mmol) was suspended in dry alcohol (3 mL) followed by the addition of DBU (100 mg, 0.66 mmol). The reaction mixture was heated in an oil bath set to 60 °C for 0.45−2.5 h (reaction time was determined by monitoring the reaction by ^{31}P NMR). After cooling to rt the reaction mixture was separated by flash chromatography ($CHCl_3$ to $CHCl_3$:MeOH 80:20) to give a colorless oil. The colorless oil was dissolved in a water:THF 6:4 mixture and passed through CM Sephadex Na^+. THF was evaporated, and the remaining aqueous solution was freeze-dried to give a white solid. In cases where further purification was needed, the crude product was separated over RP-flash chromatography eluting with 0.1 M triethylammonium acetate−acetonitrile (TEAA−ACN) 40:60. The solvent mixture was freeze-dried several times until a constant weight was attained. Triethyl ammonium counterion was replaced by sodium by passing the triethyl ammonium salt solution through CM Sephadex Na^+ or Dowex 50wx8−20 Na^+ form resin and freeze-drying again to obtain **1** as white products.

O,O′-Diester-methylenediphosphonotetrathioate, 1, Typical Procedure B. Compound **2** (100 mg, 0.31 mmol) was suspended in dry $CHCl_3$ (3 mL). The alcohol (1.86 mmol) was added followed by the addition of DBU (100 mg, 0.66 mmol). The reaction mixture was heated under reflux for 0.45−24 h (reaction time was determined by monitoring the reaction by ^{31}P NMR). After cooling, the mixture was loaded on a flash chromatography column ($CHCl_3$ to $CHCl_3$:MeOH 80:20 for compounds **1a−j** or $CHCl_3$ to $CHCl_3$:iPrOH 91:9 for compound **1k**) to give a colorless oil. The colorless oil was dissolved in a water:THF 6:4 mixture and passed through CM Sephadex Na^+. THF was evaporated, and the remaining aqueous solution was freeze-dried to give a white solid. In cases where further purification was needed, the crude product was separated over RP-flash chromatography eluting with 0.1 M TEAA−ACN 40:60. The solvent mixture was freeze-dried several times until a constant weight was attained. Triethyl ammonium counterion was replaced by sodium by passing the triethyl ammonium salt solution through CM Sephadex Na^+ or Dowex 50wx8−20 Na^+ form resin and freeze-drying again to obtain **1** as white products.

Disodium-*O,O′*-dimethyl-methylenediphosphonotetrathioate, 1a. Product **1a** was obtained from reaction of **2** (100 mg, 0.31 mmol) with methanol (3 mL, procedure A) (or 60 mg, 1.86 mmol, procedure B) as a white solid (58 mg, 60% and 19 mg, 20% yield via procedure A and B, respectively). Melting point 200−202 °C (dec). ^{1}H NMR (200 MHz, D_2O): δ 3.65 (second order $A_3A'_3XX'$, 6H), 3.48 (t, J = 13.73 Hz, 2H) ppm. ^{13}C NMR (50 MHz, D_2O): δ 56.2 (t, J = 64.2 Hz), 50.7 (t, J = 3.4 Hz) ppm. ^{31}P NMR (81 MHz, D_2O): δ 105 ppm. HRMS (MALDI) m/z: calcd for $C_3H_9O_2P_2S_4^-$ $[M - H]^-$ 266.896, found 266.893. FT-IR(ATR): 2994w, 2938w, 2832w, 1453w, 1433w, 1351w, 1143w, 1007s, 992s, 755s, 742s, 637s cm^{-1}.

Disodium-*O,O′*-dibutyl-methylenediphosphonotetrathioate, 1b. Product **1b** was obtained from reaction of **2** (100 mg, 0.31 mmol) with n-butanol (3 mL, procedure A) as a white solid (102 mg, 83% yield via procedure A). Melting point 195−198 °C (dec). ^{1}H NMR (200 MHz, D_2O): δ 4.1−4.06 (m, 4H), 3.51 (t, J = 13.5 Hz, 2H), 1.8−1.66 (m, 4H), 1.57−1.39 (m, 4H), 0.99 (t, J = 7.47 Hz, 6H) ppm. ^{13}C NMR (50 MHz, D_2O): δ 64.6 (t, J = 3.8 Hz), 56.9 (t, J = 63.4 Hz), 31.8 (t, J = 4.2 Hz), 18.4, 13 ppm. ^{31}P NMR (81 MHz, D_2O): δ 101.9 ppm. HRMS (MALDI) m/z: calcd for $C_9H_{21}O_2P_2S_4^-$ $[M-H]^-$ 350.989, found 350.988. FT-IR (ATR): 2958m, 2900m, 1467w, 1381w, 1230w, 1065m, 1057m, 978m, 883w, 790m, 765s, 617s cm^{-1}.

Disodium-*O,O′*-dioctyl-methylenediphosphonotetrathioate, 1c. Product **1c** was obtained from reaction of **2** (100 mg, 0.31 mmol) with octanol (3 mL, procedure A) (or 242 mg, 1.86 mmol, procedure B) as a white solid (30 mg, 19%, and 16 mg, 10% yield via procedure A and B, respectively). Melting point 168−170 °C (dec). ^{1}H NMR (200

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MHz, D_2O): δ 4.07−3.96 (m. 4H), 3.48 (t, J = 13.22 Hz, 2H), 1.76−1.63 (m, 4H), 1.44−1.27 (m, 20H), 0.94−0.87 (m, 6H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 65.4, 60.1 (t, J = 62.2 Hz), 33.1, 31.7 (t, J = 4.2 Hz), 30.7, 30.5, 27.1, 23.7, 14.4 ppm. ^{31}P NMR (81 MHz, D_2O): δ 101.8 ppm. HRMS (MALDI) m/z: calcd for $C_{17}H_{37}O_2P_2S_4^-$ $[M\text{-}H]^-$ 463.115, found 463.116. FT-IR(ATR): 2920s, 2852m, 1467w, 983s, 776s, 762s, 742s, 637s cm^{-1}.

Disodium-*O*,*O*′-bis(2-(ethyl)butyl)-methylenediphosphonotetrathioate, 1f. Product **1f** was obtained from reaction of **2** (100 mg, 0.31 mmol) with 2-ethylbutanol (172 mg, 1.86 mmol) as a white solid (17 mg, 12% yield via procedure B). Melting point 170−173 °C (dec). ^1H NMR (200 MHz, D_2O): δ 4.0−3.85 (m, 4H), 3.47 (t, J = 13.62 Hz), 1.67−1.18 (m, 10H), 0.89 (t, J = 7.26 Hz) ppm. ^{13}C NMR (50 MHz, D_2O): δ 66.7 (t, J = 3.9 Hz), 57.1 (t, J = 64.5 Hz), 40.8 (t, J = 4 Hz), 22.2, 10.1 ppm. ^{31}P NMR (81 MHz, D_2O): δ 101.9 ppm. HRMS (MALDI) m/z: calcd for $C_{13}H_{29}O_2P_2S_4^-$ $[M\text{-}H]^-$ 407.052, found 407.050. FT-IR(ATR): 2960m, 2932m, 2874w, 1458w, 1378w, 1000s, 956s, 794s, 756s, 621s cm^{-1}.

Disodium-*O*,*O*′-dibenzyl-methylenediphosphonotetrathioate, 1g. Product **1g** was obtained from reaction of **2** (100 mg, 0.31 mmol) with benzyl alcohol (3 mL, procedure A) (or 201 mg, 1.86 mmol, procedure B) as a white solid (108 mg, 75% and 24.5 mg, 17% yield via procedures A and B, respectively). Melting point 248−249 (dec). ^1H NMR (200 MHz, D_2O): δ 7.49−7.36 (m, 10H), 5.07−5.03 (m, 4H), 3.59 (t, J = 13.4 Hz, 2H) ppm. ^{13}C NMR (50 MHz, D_2O): δ 137.5, 128.3, 127.9, 127.8, 65.7 (t, J = 3.3 Hz), 57.3 (t, J = 63.5 Hz) ppm. ^{31}P NMR (81 MHz, D_2O): δ 103.4 ppm. HRMS (MALDI) m/z: calcd for $C_{15}H_{17}O_2P_2S_4^-$ $[M - H]^-$ 418.958, found 418.954. FT-IR (ATR): 2922w, 1496w, 1454w, 1373w, 1210w, 1123w, 977m, 949m, 761s, 725s, 693s, 617s cm^{-1}.

Disodium-*O*,*O*′-[2-(methoxybenzyl)]-methylenediphosphonotetrathioate, 1h. Product **1h** was obtained from reaction of **2** (100 mg, 0.31 mmol) with 2-methoxybenzyl alcohol (3 mL, procedure A) (or 257 mg, 1.86 mmol, procedure B) as a white solid (60 mg, 37%, and 3 mg, 2% yield, for procedures A and B, respectively). Melting point 249−250 °C (dec). ^1H NMR (200 MHz, D_2O): δ 7.50 (d, J = 7.47 Hz, 4H), 7.32 (t, J = 8.04 Hz, 4H), 7.05−6.90 (m, 4H), 5.09−5.00 (m, 4H), 3.80 (s, 6H), 3.60 (t, J = 13.58 Hz, 2H) ppm. ^{13}C NMR (75 MHz, D_2O): δ 156.6, 129.4, 129.2, 125.8 (t, J = 4.6 Hz), 120.8, 61.4 (t, J = 2.9 Hz), 57.6 (t, J = 63.2 Hz), 55.7 ppm. ^{31}P NMR (81 MHz, D_2O): δ 103.6 ppm. HRMS (MALDI) m/z: calcd for $C_{17}H_{21}O_4P_2S_4^-$ $[M - H]^-$ 478.979, found: 478.976. FT-IR(ATR): 2937w, 2836w, 2360w, 1493m, 1463w, 1244m, 1121s, 1025m, 981m, 955m, 754s, 727m, 637m cm^{-1}.

Disodium-*O*,*O*′-bis((1*H*-benzo[*d*]imidazol-2-yl)methyl)-methylenediphosphonotetrathioate, 1j. Product **1j** was obtained from reaction of **2** (100 mg, 0.31 mmol) with 2-benzimidazolemethanol (276 mg, 1.86 mmol), as a white solid (56 mg, 36% yield via procedure B). Melting point 210−212 °C (dec). ^1H NMR (200 MHz, D_2O): δ 7.24−7.19 (m, 4H), 7.07−7.02 (m, 4H), 5.28−5.23 (m, 4H), 3.82 (t, J = 13.06 Hz, 2H) ppm. ^{13}C NMR (50 MHz, D_2O): δ 151.1 (t, J = 5.5 Hz), 122.2, 114.1, 58.3, 57.6 (t, J = 63.3 Hz) ppm. ^{31}P NMR (81 MHz, D_2O): δ 106.7 ppm. HRMS (MALDI) m/z: calcd for $C_{17}H_{17}N_4O_2P_2S_4^-$ $[M - H]^-$ 498.970, found 498.968. FT-IR(ATR): 2924w, 1435w, 1043m, 995w, 740s, 632s.

Disodium-*O*,*O*′-bis(4-((S)-2-benzamido-3-ethoxy-3-oxopropyl)phenyl)-methylenediphosphonotetrathioate, 1k. Product **1k** was obtained from reaction of **2** (100 mg, 0.31 mmol) with *s*-ethyl-2-benzamido-3-(4-hydroxyphenyl)propanoate (583 mg, 1.86 mmol, procedures B), as a white solid (146 mg, 54% yield via procedure B). Melting point >175 °C (slow decomposition). ^1H NMR (600 MHz, D_2O): δ 7.63 (d, J = 7.53 Hz, 4H), 7.59 (t, J = 7.18 Hz, 2H), 7.47 (t, J = 7.18 Hz, 4H), 7.32 (d, J = 8.11 Hz, 4H), 7.19 (d, J = 7.53 Hz, 4H), 4.27−4.19 (m, 4H), 3.79 (t, J = 13.06 Hz, 2H), 3.30 (dd, J = 14.22 Hz, 5.90 Hz, 2H), 3.16 (dd, J = 14.22 Hz, 9.4 Hz, 2H), 1.25 (t, J = 7.08 Hz, 6H) ppm. ^{13}C NMR (150 MHz, D_2O): δ. 173.2, 170.7, 150.5, 132.9, 132.4, 132.2, 129.7, 128.6, 127.1, 122.5, 62.6, 58.7 (t, J = 64.8 Hz), 54.8, 35.6, 13.2 ppm. ^{31}P NMR (243 MHz, D_2O): δ 104.7 ppm. ESI-MS m/z: 829 $[M - H]^-$. HRMS (MALDI) m/z: calcd for $C_{37}H_{39}N_2O_8P_2S_4^-$ $[M]^-$ 829.106, found 829.107.

Triethylammonium-*O*-(4-((*S*)-2-benzamido-3-ethoxy-3-oxopropyl)phenyl)((2-sulfido-1,3,2-dithiaphospholan-2-yl)-methyl)phosphonodithioate, 14. Compound **2** (100 mg, 0.31 mmol) was suspended in dry ACN (10 mL). *N*-Benzoyl-L-tyrosine ethyl ester (1.86 mmol) was added followed by the addition of DBU (100 mg, 0.66 mmol). The crude products were separated over semipreparative RP-C18-HPLC eluting with 0.1 M TEAA-ACN 65:35 for 5 min then with a linear gradient of 40:60 up to 16 min (t_R = 12.5 min). The relevant fraction was freeze-dried several times until a constant weight was attained. Product **14** was obtained as a clear oily solid (59 mg, 33% yield). ^1H NMR (600 MHz, $CDCl_3$): δ 9.41 (br, s, 1H), 7.70 (d, J = 7.9 Hz, 2H), 7.51 (t, J = 7 Hz, 1H), 7.45−7.40 (m, 4H), 7.06 (d, J = 8.16 Hz, 2H), 6.56 (d, J = 7.44 Hz, 1H), 5.03−4.97 (m, 1H), 4.21 (q, J = 7.19 Hz, 2H), 4.06 (t, J = 13.08 Hz, 2H), 3.70−3.60 (m, 2H), 3.55−3.45 (m, 2H), 3.21 (ddd, J = 29.4, 14.08, 5.44 Hz, 2H), 3.11 (q, J = 7.16 Hz, 6H), 1.29 (t, J = 7.19 Hz, 3H), 1.24 (t, 7.16 Hz, 9H) ppm. ^{13}C NMR (150 MHz, D_2O): δ 171.7, 167, 150.86 (d, J = 10.2 Hz), 134.1, 131.9, 131.5, 130.7, 129.76, 128.8, 127.17, 123.6, 123.5, 115.6, 61.8, 60.7 (dd, J = 66.9, 42.8 Hz), 53.7, 46.2, 41.6, 37.4, 14.4, 8.6 ppm. ^{31}P NMR (243 MHz, $CDCl_3$) 100.9 (d, J = 12.68 Hz), 89.8 (d, J = 12.68 Hz) ppm. ESI-MS m/z: 576 $[M - H]^-$. HRMS (MALDI) m/z: calcd for $C_{21}H_{24}NO_4P_2S_5$ $[M]^-$ 575.978, found 575.978

Tetrasodium-*O*,*O*′-bis(4-((*S*)-2-benzamido-3-ethoxy-3-oxopropyl)phenyl)((oxido((2-((2((oxidohydrophosphorothioatothio)thio)ethyl)disulfanyl)ethyl)thio)phosphorothioyl)bis(methylene))diphosphonodithioate, 15. Product **15** was obtained by the same procedure as for **14**. After the HPLC separation (t_R= 6 min), product **15** triethylammonium salt was exchanged to the corresponding sodium salt by passing through CM Sephadex Na^+. Product **15** was obtained as a white-yellowish solid (35 mg, 9% yield) (exists with 10% of the thiol). Melting point 206−212 °C (dec). ^1H NMR (600 MHz, D_2O): δ 7.64 (d, J = 7.68 Hz, 4H), 7.60 (t, J = 7.31 Hz, 2H), 7.48 (t, J = 7.48 Hz, 4H), 7.38 (d, J = 7.83 Hz, 4H), 7.26 (d, J = 8.15 Hz, 4H), 4.27−4.21 (m, 4H), 3.57 (t, J = 13.84 Hz, 4H), 3.34−3.30 (m, 2H), 3.20−3.14 (m, 6H), 2.90−2.85 (m, 4H), 1.27 (t, J = 7.15 Hz, 6H) ppm. ^{13}C NMR (150 MHz, D_2O): δ 173.2, 170.67, 150.4, 150.3, 132.8, 132.5, 132.3, 129.8, 129.6, 128.7, 122.6, 122.5, 62.6, 57.4 (t, J = 65.71 Hz), 54.8, 38, 35.7, 32, 13.3 ppm. ^{31}P NMR (243 MHz, D_2O): δ 104.6 (d, J = 20.7 Hz), 67.5−67.3 (m) ppm. ESI-MS m/z: 1187 $[M - H]^-$. HRMS (MALDI): m/z: calcd for $C_{42}H_{49}K_1N_2Na_1O_{10}P_4S_{10}^{-1}$ $[M + K + Na - H]^-$ 1246.907, found 1246.905.

Coordination of Zn(II)/Ca(II) by 1b Monitored by $^1H/^{31}P$ NMR. Compound **1b** (3.4 mg, 0.0086 mmol) was dissolved in DMSO-d_6 (0.6 mL), and $^1H/^{31}P$ NMR spectra were measured at 200 and 81 MHz, respectively. $ZnCl_2$ (0.52 mg, 0.0038 mmol, 0.45 equiv, and then 1.2 mg, 0.0088, overall 1.45 equiv) was added, and the $^1H/^{31}P$ NMR spectra were measured.

Compound **1b** (2 mg, 0.005 mmol) was dissolved in D_2O (0.6 mL), and $^1H/^{31}P$ NMR spectra were measured at 200 and 81 MHz, respectively. $CaCl_2$ (0.75 mg, 0.005 mmol, 1 equiv and then additional 0.75 mg, overall 2 equiv) was added, and the $^1H/^{31}P$ NMR spectra were measured.

UV−Vis Measurements of 1g−Ni(II) Complex. A 0.05 mM DCM solution of DBU **1g** salt was titrated by 5 mM $Ni(BF_4)_2$ in EtOH; 1 μL of the Ni(II) solution was added each time. After each addition the absorbance was measured at 321 nm.

ESR OH Radical Assay. ESR settings for OH radicals detection were as follows: microwave frequency, 9.76 GHz; modulation frequency, 100 kHz; microwave power, 6.35 mW; modulation amplitude, 1.2 G; time constant, 655.36 ms; sweep time 83.89 s; and receiver gain 2×10^5 in experiments with Cu(I) and Fe(II).

A 1 mM $Cu(CH_3CN)_4PF_6$ solution in acetonitrile (10 μL) or 1 mM $FeSO_4$ (10 μL) was added to 5−500 μM of tested compound (10 μL) solutions. All final solutions of $Cu(CH_3CN)_4PF_6$ contained 10% v/v acetonitrile. Afterward, 1 mM Tris buffer, pH 7.4, (10 μL) was added to the mixture. After mixing for 2 s, 100 mM DMPO (10 μL) was quickly added followed by the addition of 100 mM H_2O_2 (10 μL). Final sample pH values for the Cu(I) and Fe(II) systems ranged

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between 7.2 and 7.4. Each ESR measurement was performed 150 s after the addition of H_2O_2. All experiments were performed at room temperature, in a final volume of 100 μL.

■ ASSOCIATED CONTENT

Supporting Information

Drawing of the system used to synthesize **2**, copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra, copies of FT-IR spectra of the compounds, and X-ray data for compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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