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Introductory Chapter: Phosphorus - Nature's Versatile Pentavalent and Tetrahedral Covalent Building Block and Agent for Energy, Disease and Health

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1. Introduction

It is extremely exciting to be involved with editing and discussing the recent developments of phosphorus (P, $[Ne]3s^23p^3$), an element that has one main isotope [1]. The element, its compounds, and its reactions (including emergent reactions) will certainly allow for some of “tomorrow’s” methods and molecules; this science will help to form an extremely wide swath of emergent technologies. In terms of inorganic chemistry, the element of phosphorus (electronegativity = 2.06) has many future prospects. In the chemistry classroom, we often first discuss allotropes. With well-known diversity known for the allotropes of P that exhibit diverse stability, color, and structural characteristics (atomic number 15, group 15), we are afforded a first look at the possibilities of rich *covalent* chemistry that the element affords; examples of extensive ionic bonding (e.g., Na_3P) are rare. P retains, as always, the chemistry that is extremely dynamic, diverse, and developing.

Phosphorus often takes on certain common forms (**Figure 1**), phosphines, as well as phosphites, and so forth are important classes of ligands in which the free lone pair offers a relatively π -acidic dative bonding interaction (in comparison to amines)

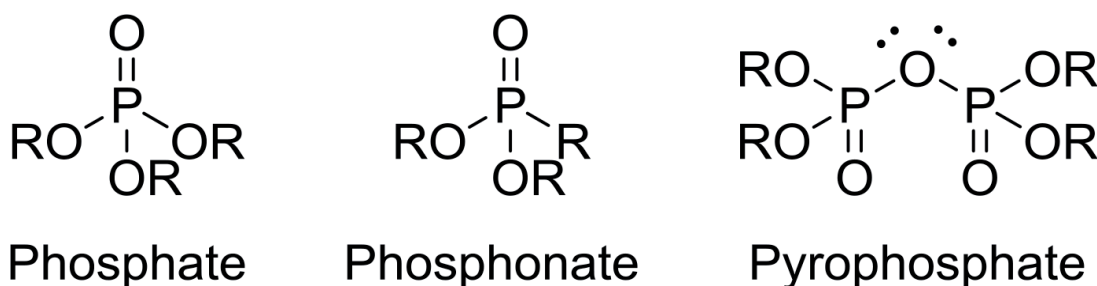


Figure 1.
Structures of simple selected oxygenated phosphorus (V) compounds: phosphate, phosphonate, and pyrophosphate.

with a range of metals [2, 3]. Reports and studies of molecules with the (V) oxides/hydroxides, etc., are rife in health; these species are essential for life as we know it; life sciences are full of such reports (**Table 1**); geochemistry too involves phosphates as expected, an initial literature search in the ISI web of science on the term “phosphate” gives 396,702 hits (since 1970) [4]. While not always the case, phosphorus, and especially its oxo chemistry, is found as a rule to be tetrahedral (pyramidal), and for that matter, pentavalent [5]. While in terms of valence states, there are also valencies of III, however, even when looking in the allotropic forms, we can appreciate the $MLX(Z)$ covalent bond classification, not the formal oxidation state model [6]. However, the trigonal bipyramidal form is an important transition state intermediate at play and does exist for molecules such as PF_5 , which bear certain well defined dynamic processes in solution (see Berry Pseudo rotation) [7]. If we add a fluoride, we can easily formally covert to PF_6^- , which is clearly octahedral and a ubiquitous non coordinating ion (anion). Therefore, as a starting point, we present the information from searches (**Figure 1**). Phosphine (PH_3), for example, is a common parent molecule that is rarely encountered in the lab; as a compound, it has three hydrides and is often considered theoretically when considering phosphine chemistry (see below).

In (bio)materials science terms, tetrahedral allow for bridging and networks and support. Ionic or hybrid materials, crystallization or not, can be encased, or spangled with phosphates; well-ordered materials from a crystalline perspective such as chains, rings, 2-D layers, and 3-D architectures are enabled. These larger molecules are, therefore, very important for materials chemistry. There is also the option for them to be involved with non-well-ordered materials such as glasses, glazes, coatings, etc. In further research, however, we hope that the community can go against the *plus ça change, plus c’est le meme chose* notion.

One P–O–P bond in ATP releases 7–9 kcal mol⁻¹ of energy upon hydrolytic scission [8]; analogously, phosphorylation of hydroxyl groups requires 6–9 kcal mol⁻¹ in Gibbs free energy [9]. There is, of course, much more to the story, especially the evolutionary story. Considering this chemical energy, chemists studying prebiotic chemistry claim that the recruitment of phosphates for energy in biological systems may have been absent; a predecessor system of energy storage was present (see thioesters) [10]. In other words, phosphate centers that are currently functional serve as a thioester-like center. In light of it being 2020, 1 year since the 450th anniversary of the discovery of the element, and considerations of this simple “light bearing” main group element having been discovered by H. Brand (1669), the same year when Stradivari built his first violin and when Mt. Aetna had a notable eruption, still offers an extremely important amount of contemporary information for today’s research community.

Also, in light of the recent novel coronavirus outbreak and the ongoing COVID pandemic, we mention at least one phosphate-based molecule that has been discussed extensively within the research community in the context of enzymatic inhibition;

Topic	Numerical results of articles (hits)
(Phosphorus or phosphate) and “biochemistry”	2475
(Phosphorus or phosphate) and “organic chemistry”	270
(Phosphorus or phosphate) and “analytical chemistry”	168
(Phosphorus or phosphate) and “physical chemistry”	91
(Phosphorus or phosphate) and “inorganic chemistry”	65

Table 1. ISI Web of Science search terms related to chemistry subfields presented in descending number of research articles (hits since 1970) [4].

other important biomolecules that contain phosphates, etc., are also briefly discussed. Here, in this *e-book*, with nine different contributions from institutes worldwide, we can regard new (bio)chemistry considerations and new materials.

1.1 Selected contemporary research fields, industrial workings, and the economy

The involvement of phosphorus in the chemical sciences is truly extensive. It “runs the gamut” from the theoretical chemical sciences and physics through engineering and including all of biology and the life sciences; this breadth and the current access to search the literature enables researchers in one field to access which is working well, or not, in other scientific (technological) fields. We can behold various cycles. There is what is known as the *phosphorus/phosphate cycle* and the *phosphorus/phosphate economy*; phosphorus is traded on the stock exchange [11, 12]; there is the *phosphate metabolism* in the human body. Moreover, there is a great deal in terms of materials/biomaterials to cover and derive as research; with regard to natural bone, teeth, and tissue (*vide infra*); entire journals are dedicated to these research topics (e.g., *Bone*, *Journal of Bone Oncology*, *The Journal of the American Dental Association*, *Journal of Dental Research*, *Journal of Dentistry*, *Journal of Dentistry for Children*, and *International Journal of Oral and Dental Health*). With a tremendous amount of industrial, agricultural (herbicide), and even military importance (white phosphorus and nerve agents), exploration and utility of this element continue to flourish. Therefore, initial key search terms unveil a lot of research activity as found in **Table 2**; these terms, however, do not necessarily articulate the exact research fields involved; therefore, a secondary search was performed and its results are shown below to give a breakdown by research area (**Table 1**).

2. Agriculture

There exists the phosphate cycle; phosphorus, while a macronutrient for plants and animals is centrally important in biology and required in the food chain (*vide infra*). There are always new ways to explore phosphorus-based agriculture agents in the future, however. Of contemporary concern might be, how a heavily used chemical agent such as *Roundup* can be understood fully in terms of its biochemistry; because of some recent controversy, there have been unsubstantiated allegations while prevalent use of the pesticide is ongoing. In the future, we believe that its biological workings will be confirmed fully in molecular detail; our current scientific position is it is *neither* a cancer causing agent *nor* an agent that creates adverse health effects within reason. This exploration of chemical science that is strongly coupled with biology will continue to play out in other examples too.

3. Biochemistry

ATP is an energy storage molecule for life; related molecules also possess the same energy in the anhydride P–O–P bonds; as seen in **Table 1**, considering the number of hits (articles), and looking a little deeper suggesting there may be a lot of research momentum in the field. Furthermore, post-translational modifications (PTM's), for example in the form of phosphorylation, are exceptionally interesting and important; research with this chemistry continues (**Table 2**); the Park laboratory at KAIST for example, has found ways to explore phosphoserine “stop codon” chemistry and to apply this biosynthesis to various problems in molecular biology [13–16]; Additionally, the Lashuel group at EPFL and other researchers

(e.g., E. Mandelkow) have been involved with detailed studies of phosphorylation, specifically in the context of neurodegenerative disease research [17–20]. The presence of a phosphorylated serine, threonine, tyrosine, etc., reveals the evident workings of kinases and anticipation of the workings of phosphatases. Among the

Topic (entered search term)	Numerical results (hits)	Notes	People, places and research fields
Phosphorus	207,800	Highly Cited in Field (1198) Hot Papers in Field (27) Open Access (36,011)	—
Phosphate	397,854	Highly Cited in Field (1530) Hot Papers in Field (21) Open Access (91,329)	Centre National de la Recherche Scientifique (CNRS) (10,095) University of California System (8822) Chinese Academy of Sciences (8317) Russian Academy of Sciences (5055) National Institutes of Health (NIH, USA) (3995)
Phosphate and material	41,569	Highly Cited in Field (292) Hot Papers in Field (6) Open Access (7409)	—
Phosphate and NMR	14,062	—	—
Phosphon*	45,743	—	—
Phosphonate	12,975	—	—
Roundup	2530	—	—
Phosph* and virus	36,004	—	—
Phosphorus and organometal*	1045	—	—
Phosphate and inhibitor	24,237	—	—
Phosphate and inhibitor and enzyme	7967	Highly Cited in Field (27) Open Access (2720)	Centre National de la Recherche Scientifique (CNRS) (248) University of California System (218) National Institutes of Health (NIH USA) (143) University Of Texas System (135) Russian Academy of Sciences (119)
Phosphate and dementia	346	Highly Cited in Field (3) Open Access (120)	Neurosciences (137) Clinical Neurology (57) Biochemistry Molecular Biology (55) Pharmacology Pharmacy (34) Geriatrics Gerontology (22)
Phosphoryl* and dementia	3897	Highly Cited in Field (65) Hot Papers in Field (2) Open Access (1794)	Blennow K (166) Zetterberg H (128) Trojanowski JQ (106) Scheltens P (68) Lee VMY (66)
The asterisk (*) serves to truncate the search term and thus broaden the search.			

Table 2.
ISI Web of Science search on terms related to phosphorus and the number of articles (hits since 1970).

other recent findings of import involves biochemistry involving pyrophosphate as a type of PTM, a related phosphate-based species (**Figure 1**) [21–24].

4. Enzyme inhibitors and the COVID outbreak

In recent months, there has been a great emphasis on the possibility of small molecules that can serve as emergent molecular treatments for the novel corona virus (COVID-19). While vaccine research continues, some potential pharmaceutical treatments have recently come to light. Unfortunately, many molecules have been “bandied about” in the news and social media and overly discussed in an unprofessional way by non-experts, and dangerously so, in some cases. However, there has been special and recent attention paid to specific novel drugs that, while still in their early days, are strongly considered by the research community and officials at NIH and elsewhere. Remdesivir, for example (Gilead Sciences, Inc.), was involved in a recently completed trial regarding COVID; some promise was evident (**Figure 2**). The molecule is provided here because it incorporates a phosphate and a description of how it works is important to be illustrated for the readership of our book.

4.1 Remdesivir

4.1.1 How It Works

Remdesivir (**Figure 2**) is a known synthetic molecule developed by Gilead Sciences, USSCD, and USAMRIID. Remdesivir's working chemical mechanism is that of an antiviral nature; it is nucleoside-modified based drug that without such modification has poor cell permeability. The process of transcription of RNA polymerase is blocked in a patient (human subject). Specifically, although Remdesivir still has its 3'hydroxyl site that can form phosphodiester bond, the steric 1'-position containing a cyano group (–CN) prevents any further elongation of the polymerase polymer. Thus, the production of the polymer is halted with this monophosphate, ester, and phosphoramidate-based drug [25]. It is also important to consider the prescribed human dosage currently being considered. Administration of remdesivir is through intravenous injection (IV); the loading dose on the first day is in the amount of 200 mg for an adult with weight adjustment required; following this is maintenance for up to 10 days with a daily dosage amount being 100 mg for an adult.

When considering living cells, (eukaryotic) cells, the known intended mode of action of Remdesivir can be discussed. Remdesivir undergoes hydrolysis at

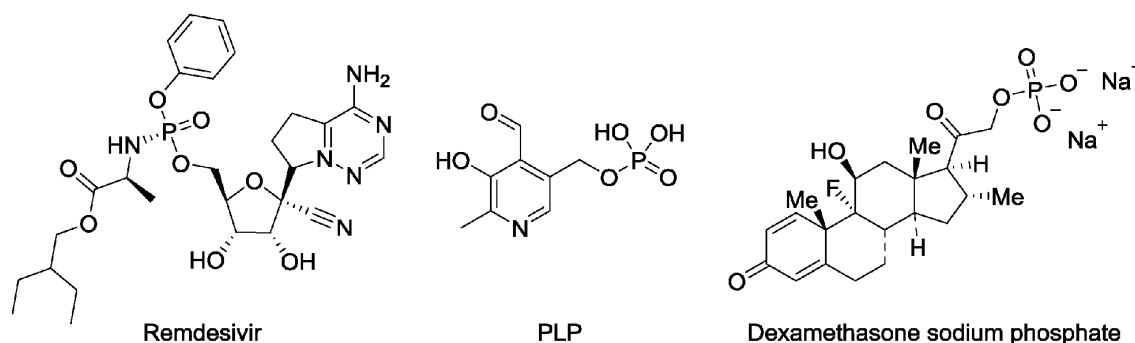


Figure 2.
(Left) Structure of the synthetic Remdesivir proposed as a treatment for the continuing corona outbreak (COVID-19). (Right) The structure of PLP, a naturally occurring small molecule and aldehyde that is phosphorylated.

its aryloxy phosphoramidite; this affords a cyclic anhydride; hydrolysis of such groups is readily obtained through the action of esterases in biology. This cyclic anhydride functionality undergoes reaction with water easily to give the analine. Then, a subsequent hydrolysis event allows for the P–N bond to be cleaved; here, a *phosphoramidase*-type enzyme is at play.

5. Bone mineralization

Bone is crucial and has a multi-important role for any organism. In the next two paragraphs, we want to discuss bone because of its overwhelming importance and the complex process involved in its formation.

Bone is able to help other body organs; also, the process of hemostasis, and the glands of the endocrine system are assisted. The materials comprising bone can be considered in different molecular classifications; there is (i) hydroxyapatite ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$), (ii) collagen, and (iii) water, consistent by weight (65%, 20–30%, 10%, respectively). Collagen is a three-stranded wrapped biomolecule (triple helical structure); bone consists mainly (90%) of collagen type I. Water exists within the hard materials as almost a solvent of crystallization, as well as free water molecules. The process of bone mineralization, therefore, will relate to the ability of the water molecules to move freely during this process. The authors of this text do go into more details. Stiffness relates to the greater percentage of mineral content of bone versus amount of water. The implementation of carbonate is also important; in the beginning of bone formation, mineral in bone consists of both calcium carbonate and calcium phosphate. Through a so called “maturation process,” the carbonate fraction is lowered. The entire process of bone growth has molecular aspects that are still not fully appreciated. The growth of bone involves “medallion” shaped crystals that grow both in the same direction as, and perpendicular to, the fibrils of collagen. The role of carbonate and details of collagen and the microfibrils and related proteins will be discussed in this process and is also explored in this book.

Therefore, phosphate and hydroxyapatite do not come together to compose bone alone; rather it is biosynthesized; the process involves a lot of factors, enzymes and cofactors. For these reasons, research of bone continues and relates significantly to materials chemistry in contemporary research.

6. Synthetic organoelement chemistry

Representative element and organometallic chemistry are rich areas of research. Organometallic chemistry as a discipline is broad; it often encompasses organoelement chemistry and the various reactions by which, e.g., small molecules can be brought into existence. Much emphasis deals with the chemistry industry as well. We can refer to a text such as *Advanced Inorganic Chemistry* 5th edition [2], and *Chemistry of the Elements* [3]. There are also dedicated texts and journals to this main group chemistry topic, journals such as *Phosphorus Sulfur* and *Silicon and the Related Elements* (Publisher: Taylor & Francis). The journal *Organometallics* (ACS) is also an excellent source of new research in organoelement chemistry as well as the journal *Main Group Chemistry*. A couple of recent organoelement and organometallic examples are of note are provided as illustrative examples: the Cummins (MIT) *phosphatetrahedrane* (tri-tert-butyl phosphatetrahedrane, $\text{P}(\text{C}^t\text{Bu})_3$), for example, involves a central unit that resembles a saturated cyclopropane type ring bearing an apical *trivalent* P (**Figure 3**) [5]. Bond strain is apparent. The small organometallic systems also help us to set up a discussion of symmetry and electronics as well as macromolecular possibilities.

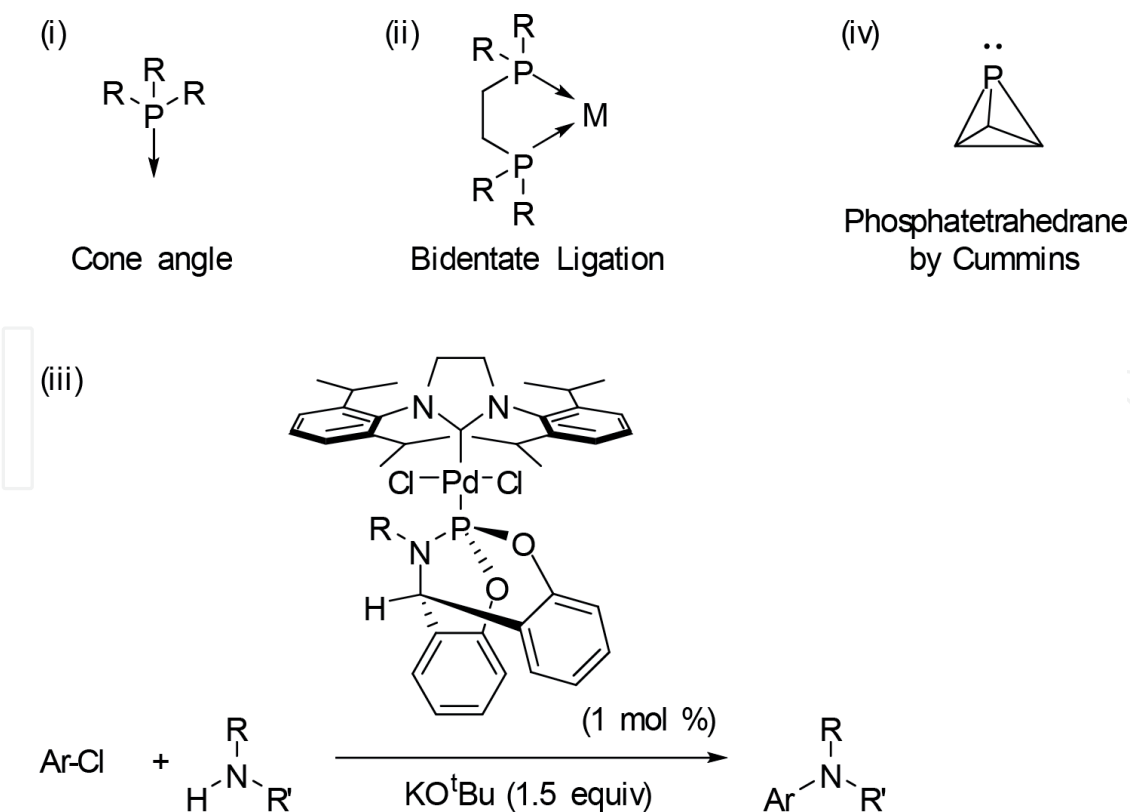


Figure 3.
 (i) Monophosphine form that inspired the Tolman cone angle analysis [26]; (ii) the well-known bidentate ligation from diphosphines (e.g., 1,2-bis(diphenylphosphino)ethane); (iii) the recent phosphatetrahedrane core brought synthetically into reality; and (iv) the important mixed bismonodentate ligation in a recent Pd structure by Kim et al. [27].

Examples, such as the *phosphatetrahedrane*, continue to show us how different chemistries can be blended to afford creative main group organometallic examples that can factor into current catalysis, also be pursued in current and emergent applications.

7. Catalysis

Phosphorus chemistry afforded phosphine ligands; the corpus of monophosphine ligand research eventually lent itself to a steric bulk analysis known as “cone angle” measurement analysis (Tolman cone angle) (**Figure 3**). Lewis acidic metal centers are often the sites for homogeneous catalysis. The phosphine ligand provides a single soft donor atom; the ligand can be styled frequently as monodentate and bidentate. Other common ligand options are phosphites and phosphoramides and combinations. Phosphines, historically ubiquitous as the *de facto* go-to ancillary ligand, have given way to other ligand families such as carbenes (i.e., *N*-heterocyclic carbenes, NHCs); but there is some very intriguing research on phosphorus-based ligands. A recent intriguing example from KAIST involved a monodentate phosphine analog ligand paired trans with a single *N*-heterocyclic carbene (NHC) ligand (**Figure 3**) [27]. There is also an important issue of how phosphorus, reduced or oxidized phosphorus is involved in catalyst poisoning or inhibition [28, 29]. Therefore, having P(III) in substrates such as inhibitors, etc., in biochemistry is also an important issue.

8. Characterization

NMR spectroscopy dominates solution characterization in the chemical sciences; it is especially convenient when a (soluble) molecular sample contains P can

be subjected to ^{31}P NMR spectroscopy (^{31}P isotope is 100% abundant). To think how spectroscopic characterization can be more extensively organized, phosphorus-31 is uniquely situated in this research field; we can briefly think about both heavier and lighter congeners of group 15 in which the situation is much less convenient. For antimony, the ^{121}Sb isotope and its chemistry can be studied with Mossbauer spectroscopy. Nitrogen 15 (^{14}N is naturally abundant) needs to be introduced into biology as an enriched component (^{15}N -labeled nutrients, etc.) to afford 2-D NMR studies; beautiful solution NMR spectroscopy characterization using ^1H - ^{15}N HSQC experiments are found in many biochemistry and protein-related articles [30].

9. Materials and biomaterials

As shown in **Table 2**, there are a lot of chemistry topics we could delve into here; there are health-related and biomaterial-related issues with phosphorus. Physical properties such as NMR spectroscopy (as just discussed), thermochemistry, pK_a , solubility, thermogravimetric analysis (TGA) etc., purification also comes into play. Therefore, this general tetrahedral (sometimes pyramidal) nature and the pentavalent nature serve it well; these boundaries do bear some flexibility. Further, the nature of the intermediates, and some stable compounds keep our mind occupied with how P centers be employed in emergent applications by geometrically tweaking what is apparently preferable based on knowledge of the most stable confirmations of P in a given molecule.

10. Contributions for this *Intechopen* book project

In this work supported by *Intechopen*, we feature the recent advances in phosphates and materials and related studies.

- There is a contribution by Sayantan et al. (CHRIST University, India) discussing about the effect of phosphorus on plants and agriculture. They discuss phosphate in the environment. The types of P-containing species dissolved readily observed in nature. He describes P well as an element. Sayantan explains heavy metals such as Cr and As are taken up by plants causing toxicity; phosphorus mitigates too. In fact, the concentration of P and As in root and shoot tissues of *A. viridis* showed a negative correlation [31]. Plant species such as *Pistia stratiotes* (water lettuce) were also introduced. The combined involvement of Cr and As in the context of phosphate (phosphorus in the environment) help frame important chemical remediation issues.
- The chapter by Kalka et al. (Wrocław University) deals with the proteins that enable biomineralization which involve phosphates [32]. These key processes in biology help afford composition of bone and teeth (tooth, enamel, dentin, cementum, etc.) (see above section). The authors therefore explain nature's structural building materials and their construction therefore are extremely diverse; this is an especially great reference for those biochemists interested in expanding their research into the biomaterials area.
- The chapter by Bienek (Research Division, American Dental Association Foundation) discusses the application of amorphous calcium phosphate composites (ACP) in dental materials. ACP composites can regenerate tooth material through the release of Ca^{2+} and PO_4^{3-} (HPO_4^{2-} , H_2PO_4^-) ions, making them good candidates for dental restoratives (Research Division, American Dental Association Foundation) [33].

- The reference by Omrani et al. (National Center For Research in Materials Sciences, Tunisia) discusses glasses, material categorically separate from crystalline solids [34, 35]. The sought values of T_g , as well as the NMR spectroscopy, as well as calorimetry were employed (the value T_g is defined as the glass transition temperature) are listed and discussed.
- The chapter by Rosenthal et al. (Georgetown University) deals with *PolyP*; this amazing species is the polymeric form of phosphate [36]. Consider pyrophosphate being elongated to make an enormous polymeric and relatively energetic chain (chemical energy in the P–O–P anhydride bond); these molecules exist and are fascinating. They are prebiotic molecules, and of course, vary in length. They would be naturally quite difficult to study, even by ^{31}P NMR. There is an excellent discussion of the concentration levels of these *PolyP* species in eukaryotes. From studies of rats and mice, *PolyP* concentration appears high in brain tissue (~100 μM) and *PolyP* is known for regulation of protein translation, and normal osmolarity [37].
- The chapter by Kafarski (Wrocław University) involves a discussion of the biological use of phosphonates; these are phosphates groups in which there is one carbon attachment (see **Figure 1**) [38]. Biogeochemistry and phosphorus cycling is discussed. Peptides that contain phosphonate groups, specifically phosphonopeptides which can be used as antibiotics and their mechanism of action, are shown. The authors show the biosynthesis of phosphonates. Structures of fosmidomycin analogs are also shown and discussed. Phosphonates can help form methane [38].
- The contribution by Graça et al. (University of Aveiro, Portugal) deals with materials, and calcium phosphate bone cements, abbreviated as CPC's. These species will involve solution chemistry, a dissolution and precipitation (nucleation) processes; this will require RT or physiological temperature [39]. There is microporosity and considerations of optimum concentrations of additives—quite a long discussion of apatite cements and brushite cements is provided. Applications such as drug delivery were discussed; there is a nice scheme showing the interrelated papers. There are also sections for applications dealing with growth factor addition, ion addition and 3D printing is also included.
- The article by Dey et al. (National Institute of Technology, India) deals with bone materialization. As we began to explain above, the complex bone matrix has important roles for bone mineralization [40]. To help make deposition of mineral and for it to become ordered in patterns, nucleation is necessary and made possible by this apparatus. Beside the physiological mineralization, about which the normal mechanisms are described below, pathological bone mineralization also occurs; disabling conditions such as *osteomalacia* and *osteodystrophy*. Further, the concept of mineralization has been brought to many applications such polymer science, bio-ceramics, bio-active glasses. While research is still ongoing, there are two models to explain the mechanism of bone mineralization [40] (i) collagen-moderated mineralization and (ii) matrix-vesicle moderated mineralization.
 - In the first proposed mechanism, collagen provides a molecular template for the nucleating mineral that is accumulating. To create nucleation, calcium triphosphate formation emerges from acidic polypeptide pre-nucleation. This molecule is negatively charged; because of its charge, calcium triphosphate interacts with the positively charged regions of the structural collagen template and transforms into a solid phase.

- In the second proposed mechanism, this involves carbonic anhydrase. This allows for the intervesicular environment to become more basic (high pH). The primary crystal material therefore becomes stable. After the hydroxyapatite forms, it becomes in contact with the extracellular fluid vesicle breaks; next, the calcium ion and phosphate ion concentration allow for proliferation of the new hydroxyapatite crystal. What caused the rupture of the vesicle needs further investigation; it is believed that proteases and phospholipases are involved. Mineral transfer is enabled by metalloproteinases. Channeling for mineral transfer is made through the help of collagen types II and X and the outside surface of the matrix vesicle.
- Catalysis involves instances where there is a decrease in efficiency upon contact with unwanted additives (think thermodynamic sink); therefore, inhibition or poisoning can occur [28, 29]. Inhibition, however, might be a good prospect when the reaction is that which deals with metal oxidation (corrosion). With steel (girders and reinforcement) and cement-based construction [41] being what they are in the world today, and the need for industrial reinforcement, Dr. Sail (Abou Bekr Belkaid University) studied the effects of different phosphates; albeit closely related phosphates, were used as corrosion inhibitors [42]. Gravimetric tests were performed; corrosion rates and inhibitor efficiencies were obtained by direct measurements. Assays involving steel corrosion inhibition were measured at variable temperature. While these projects are outstanding and essential to consider in engineering, on a chemical level, the exact mechanistic details at the molecular level are eventually necessary to achieve a full understanding. As part of the proposed mechanism, chlorides were discussed to migrate through pores in the concrete material to reach the steel surface and act to promote corrosion. Steel simply corrodes faster in salt water (sea water) (electrolytes).

11. Research of the Churchill lab at KAIST

As a laboratory involved with synthesis and since ca. 2009 trying to carry forward a big picture of neurodegenerative disease research and chemosensing [44], we have had a chance to publish research that deals with phosphorus chemistry. We have been involved in work that deals with phosphine ligands [45, 46], phosphate metal binding [47–49] (**Figure 4**), phosphyl cleavages in chemical sensor constructs,

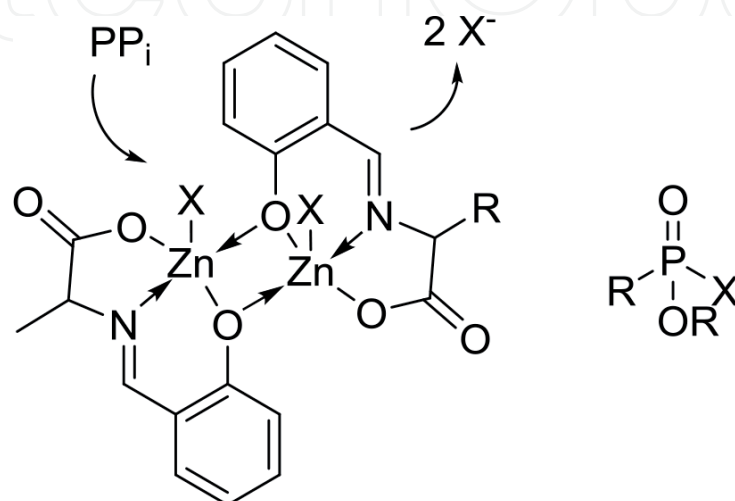


Figure 4. Dizinc Schiff base dimer synthesized, characterized, and tested in the context of PP_i detection [43].

and also reviewed the organophosphonate pesticides and CWA literature among other work [24]. Research also extended to theoretical studies as well and porphyrin derivatives. This research involved the themes of characterization, molecular sensing, molecular logic gating and neurodegenerative disease research aspects, and live cell imaging. Recently, while on sabbatical at IIT Technion (Israel), Churchill with Professor Zeev Gross was involved with the synthesis, derivatization and characterization of phosphorus-centered porphyrinoids (corroles); these were studied as important analogs and isomers of beta-position trifluoromethyl substitution [49].

12. Further comments and outlook

There is a relative wide “storm” of other findings related to phosphorus chemistry every year which help expands currently existing research; they are interconnected with other aspects of elements in biology as seen in both **Tables 1** and **2**. We have touched on just a few topics that we currently find interesting, but there is a host of others.

12.1 Molecular sensing

Phosphorus can be a constituent of an analyte, probe, or construct, as well as a connecting or bridging chemical motif (MS-325, MRI contrast agent). In many cases, phosphate has been used as the analyte for such research. There is no perfect sensor; our interests are reminiscent and seated in the goals spelled out by the Sessler et al. review [50, 51] and the Yoon et al. review [50, 51]; our *Molecular Logic Gate Laboratory* yearns for progress relating to synthetic systems that are elaborate optical imaging driven by ATP and GTP and alternations of optical or chemical outputs. Our vision of the chemistry is to address both usable components of analytes themselves as endogenous targets, as well as the novel synthetic pursuits of preparing sensing components.

12.2 Ligands for catalysis

Phosphorus is a reliable donor atom in a range of ligands. Next would be their use as ligands: Phosphines have enjoyed decades as the mainstay ligand type in inorganic chemistry (homogenous catalysis) these have given way to new types of ligation systems such as those with redox action involvement; non-innocent ligand platforms continue to be considered. These and other efforts require the continued attention of synthetic chemists (organometallic chemistry etc.)

12.3 NMR spectroscopy

The solution chemistry is easily accounted for by NMR spectroscopy, therefore, the future is bright for NMR spectroscopy in small molecule work, protein chemistry, materials, electronics applications, etc., that contain phosphorus in one form or another (see above).

12.4 “Roundup” herbicide

The agent glyphosate has the trivial commercial name “roundup” and is an extremely heavily used and a very successful herbicide. In the fullness of time, efforts in biological science will be able to establish any and all positive or negative effects with respect to herbicides, some of which appear to be under some recent scrutiny. We feel that “roundup” will be fully “acquitted” in the near future.

Future research and further development into mild but effective, pesticides and agents are important and surely will be conducted in the future. Among other biological science angles, pesticides, and herbicides that are phosphorus-based, there is the connection to health and, e.g., immune system which can be investigated; this area will be of urgent interest to pursue.

12.5 Prebiotic chemistry

As mentioned in the introduction, the chemistry of phosphates is sometimes theorized through either prebiotic chemistry or future chemical research as a replacement to the chemistry of thioesters; these $(RC(O)SR')$ groups may have been in operation as forerunners to the present-day phosphates. How phosphates (ATP and GTP and others) were brought in to replace this alleged previous ancient chemistry is fascinating; research will help shine light on how life comes into being, and how this can relate to the possibility of extraterrestrial life; and what could shape future life extrapolating forward. The extremely interesting topics of poly-phosphates, which are also prebiotic, can also be investigated.

12.6 Phosphorus(III) and switchable chiral centers

Recent research by the Feringa Laboratory for example, involves phosphorus species that are involved with chiral switching. In these cases, there is a “trivalent” phosphorus at play. Please see examples of this recent work [52]. How light can be used as an external stimulus and allow for switching of multiple chiral molecular logic gating centers is an important issue where the scientific community can establish certain “world records”: (i) most number of chiral centers, (ii) weakest effective wavelength, (iii) most convenient multiplexing, etc.

13. Conclusion

In conclusion, we have used this introductory chapter, to primarily introduce the authors' nine focused chapters. We have also tried to create optimism and describe some semblance of an interconnected foundation for future research; research areas and their connectivity and some examples were laid out. Perceived areas of activity, enthusiasm, and hope for phosphate chemistry, including organoelement chemistry, was brought forth. While we are excited and proud to introduce the topics shown here, from our own laboratory, we delved into some aspects of organoelement chemistry of phosphorus and phosphates. Through the contributions by our authors from Algeria, India, Poland, Portugal, Tunisia, and the USA, and we see how the literature of P-containing molecules continues to expand itself [53, 54]. As reflected from our own experience and publication trajectory, too, here we are looking at the oxidized P(V) chemistry almost exclusively. We introduced each chapter's emphasis. Phosphorus offers an extremely wide palate of chemistry and from a prebiotic point of view too; it, despite tetrahedral/pentavalent disposition, could still be thought of as a visionary futuristic element with research that is “dynamic and interdisciplinary.” In some circles, phosphates are best known as being involved on storing energy in the P–O bond (9 kcal mol^{-1}). Because of its affinity to O, yet covalent, phosphates, feature as a macronutrient element for health. There are main group research findings all the time. Regarding future collaboration there is an interesting story about the collaboration, in dentistry and bone research regarding the compound etidronic acid, 1,1-diphosphonic acid (EHDP), a collaboration that was fueled by a coffee meeting [55, 56]. An interesting story about scientists

serendipitously initiating work together like this is to help unlock more important findings and utility about the element in the future. Phosphorus is, and for that matter phosphates are, chemical species for life on planet Earth and beyond.

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Conflicts of interest

DGC currently has no commercial interests in the manufacture, use, etc., of Roundup or other agrochemicals or related agents, or in concrete, its production, and related chemical additives.

Notes

In memory of: Dr. Helga Füredi Milhofer.

Abbreviations

Ar	arsenic
COVID	corona virus diseases
Cr	chromium
DNA	deoxyribonucleic acid
EHDP	etidronic acid, 1,1-diphosphonic acid
EPFL	Ecole Polytechnique Fédérale de Lausanne
ISI	Institute for Scientific Information
Na	sodium
Ne	neon
NMR	nuclear magnetic resonance
PLP	pyridoxal 5'-phosphate
PolyP	polyphosphate
PTM	posttranslational modifications
RNA	ribonucleic acid
SN2	nucleophilic substitution second order

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