

# Role of Ligand Design on the Stability of Metal Complexes and Its Catalytic Properties - A Mini-Review

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**Abstract:** The role of ligand design is a serious criterion for forming metal complexes and their stability, as well as the catalytic properties. This has been a hot topic for at least 30 years. Nine electronic databases, including China National Knowledge Infrastructure (CNKI), Wan Fang Data, PubMed, Science Direct, Scopus, Web of Science, Springer Link, Sci Finder, and Google Scholar were searched from 2011 to 2023 and without language restrictions in this review. Based on the findings, the metal complex formation depends on the structure, bonding, and ligand design. Its stability corresponds to the ion's size and charge based on the hard and soft acid-base principle. Metal ions and complexes play important roles in applying biological living systems.

**Keywords:** ligand design; stability; metal complexes; catalytic properties.

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## 1. Introduction

Ligand design for the metal complex formation is important in catalysis, materials synthesis, photochemistry, and biological systems [1]. It is based on the s, d, and f blocks orbitals overlapping, and elements correspond to have different characteristics. The d-block metal is more predominant than the other because of its variable oxidation state with a low-lying orbital. Chelate and macrocyclic effects [2, 3] are rules for determining the stability of metal complexes. Ions decrease as the size of the chelate rings formed by open-chained polyamine ligands increases from the 5 to 6-membered rings. The thermodynamic stability of a metal complex with a cyclic polydentate ligand is more stable than the non-cyclic ligand.

Some inorganic elements produced in the metal complex formation, such as the dioxygen molecule O<sub>2</sub> that reacts with transition metals and its single or double bond in dioxygen molecule O<sub>2</sub>, would be reduced [4]. Enzymatic catalyst-like protein, which is connected to the peptide bonds, acts as a medium in the solvent. It reduces ionic attraction and the repulsion forces to form a protein complex [5].

Besides, carbohydrates, sugars, and nucleic acids can act as ligands to form metal complexes [6]. Since carbohydrates are very weak acids, they ionize free sugars. The metal complex is formed by mono- and disaccharides in acidic solutions. If sugar molecules are present in metal salts, these towards the cathode indicate the positive charge, resulting in stabilizing the metal complexes cations. Nucleic acids such as adenosine and adenine have different characteristics. They react with the alkali metal and alkaline earth metal ions to form a stable metal complex because of the chelate effect on 3d transition metal ions.

Several metal complexes have catalytic properties, including enzymes and redox catalysis [7]. Enzyme catalysis such as Carbonic anhydrase and Carboxypeptidases. These are the enzyme-containing  $Zn^{2+}$ , which catalyzes the dehydration of the bicarbonate ion and the hydration of  $CO_2$  and catalyzes the hydrolysis of the peptide bonds in a protein. Redox catalysis is the energy conversion process that catalyzes oxidation and reduction, for example, cytochromes and flavoproteins.

Thus, this review article aims to (i) discuss the processes of metal complex formation and rules for determining the stability of the metal complex, (ii) explain the biological functions of inorganic elements in the transport of dioxygen molecule  $O_2$  for enzymatic catalysis, (iii) describe the interaction between metal ions and carbohydrates or sugars type ligands, and nucleic acids, (iv) illustrate the role of inorganic elements in a biological system, e.g. enzymatic and redox catalysis.

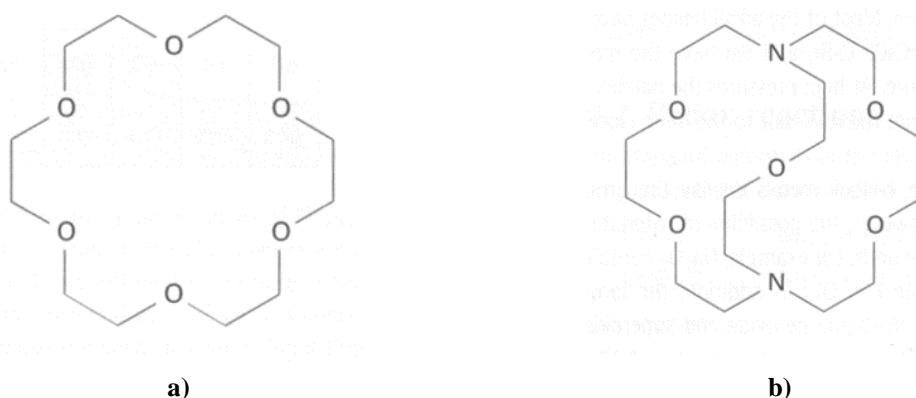
## 2. Materials and Methods

Nine electronic databases, including China National Knowledge Infrastructure (CNKI), Wan Fang Data, PubMed, Science Direct, Scopus, Web of Science, Springer Link, Sci Finder, and Google Scholar, were searched from 2011 to 2023 and without language restrictions. The searched keywords include "Metal complex and Ligand", "Metal complex and Stability", etc. All eligible studies are analyzed and summarized in this review.

## 3. Metal complexes and its stability

### 3.1. The formation of metal complexes.

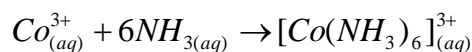
Elements are metals in the periodic table's s, d, and f blocks, which have high electrical and thermal conductivity because of their valence electrons and different oxidation states [8]. Metal ions are hard in s-block that interact with the small and hard donors such as O or N atoms to form a complex. The complex of cations in Group 1 is heavier than the Group 2 metal formed by the polydentate ligands. Monodentate ligands are weakly covalent bonded by the metal ions. Crown ethers (18-crown-6) (Fig.1a) form a complex with the alkali metal ion. Bicyclic cryptand ligands, 2.2.1 crypt (Fig. 1b), form a more stable metal complex. Group 2 metal ions form a more stable metal complex than Group 1 since the size of Group 1 metal ions is larger, and the alkali earth metal complex is in the order  $Ca^{2+} > Mg^{2+} > Sr^{2+} > Ba^{2+}$ . D-block metals form the most stable complexes because of their low-lying orbital with variable oxidation states.



**Figure 1. a)** Crown ethers (18-crown-6); **b)** bicyclic cryptand ligands, 2.2.1 crypt.

### 3.1.1. Structure and bonding in metal complexes.

The metal complex is a central metal atom or ion surrounded by ligands. It is an ion or molecule which is the combination of a Lewis acid (central metal atom) with Lewis bases (ligands). Lewis base ligands are called donor atoms, and the Lewis acid in the metal complex is called an acceptor atom (Fig. 2). The electron donor atom and acceptor atom have a positive or negative formal charge, respectively [9].



**Figure 2.** Example of Lewis acid and base for the metal complex formation.

### 3.2. Design of ligands.

Generally, two methods for designing ligands: Chelate, Macrocyclic rings, and Crown ethers using  $NH_3$ ,  $Cl^-$ , and  $H_2O$ .

#### 3.2.1. Chelate ring.

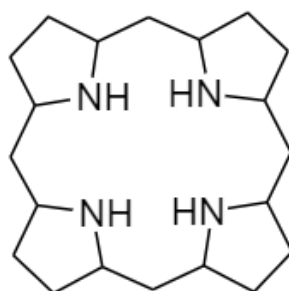
Coordination of a polydentate ligand from an ion to form 5 or 6-membered rings (Fig. 3a & 3b). The 6-membered ring is formed when it chelates to a metal ion. It is planar and is stabilized by delocalized  $\pi$ -bondings. Ligands such as pyridine and oxalate produce the planar chelate rings, interacting with the metal center. Small metal ions favor forming 6-membered rings, and large metal ions favor forming 5-membered rings. The metal ion replaces a  $sp^3$  hybridized C atom in a 6-membered chelate ring. The bite angle is close to  $109.5^\circ$  and the M-N bond length should be 160 pm, while the bite angle is  $69^\circ$  and the M-N bond length is 250 pm in a 5-membered chelate ring [10]. The stability complex of metal ions decreases as the size of the chelate rings formed by open-chained polyamine ligands increases from the 5 to 6-membered rings [11].



**Figure 3.** Structure of a) 5-membered ring; b) 6-membered ring.

#### 3.2.2. Macrocyclic ring.

Porphyrin (Fig. 4) is one of the cyclic polydentate ligands coordinated by the macrocyclic ring. It is occurring in hemoglobin and myoglobin. The metal ion fits inside the core, giving a planar, and occupies three *cis* positions to form an octahedral complex [12].



**Figures 4.** Structure of Porphyrin.

### 3.2.3. Crown ethers.

It is a subclass of the cyclic polydentate ligands. They form complexes with alkaline and alkaline earth metal ions, such as 15-crown-5 (Fig. 5a) and 18-crown-6 (Fig. 5b). Crown ether can have up to ten oxygen atoms [13].



**Figures 5.** Structure of a) 15-crown-5; b) 18-crown-6.

### 3.3. The stability of metal complexes.

#### 3.3.1. Determination of stability constants.

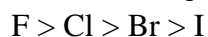
There should be a known concentration of metal ion ( $M^{2+}$ ) and ligand (L) in the aqueous solution. It only forms one coordination complex in the presence of a solution—the stability constant for determining the concentration of uncomplexed  $M^{2+}$ . The stability constant becomes smaller when ligands are introduced, decreasing the values of the equilibrium constant K [14].

#### 3.3.2. Ionic size and charge.

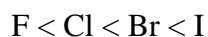
The stability of complexes in the non-d-block metal ions and their charge decrease with increasing the cation size, e.g.,  $Ca^{2+} > Sr^{2+} > Ba^{2+}$ . The stability of ligands with similar size ions increases when the ionic charge increases, e.g.,  $Li^+ < Mg^{2+} < Al^{3+}$  [15].

#### 3.3.3. Hard and soft metal centers.

The cations (Lewis acids) and ligands (Lewis bases) are classified as Hard or Soft. The hard and soft acid-base principle (HSAB) determines the stability of a complex. The complex formation between hard metal ions and ligands containing the donor atoms and the stability is:



However, the stability is conversely for the soft metal ions and ligands containing the donor atoms,



Hard and soft acids describe the polarization of the metal ions.

**Table 1.** Comparison of hard and soft acids.

Properties	Hard	Soft
Size of ion	Small	Large
Charge density	High	Low
Polarizable	Not easy	Easy

Thus, Hard acids (Hard Metal cations) form complexes preferred with Hard bases (Hard Ligands). Soft acids (Soft Metal cations) prefer soft bases (Soft Ligands) [16].

## 4. Biological Functions of Inorganic Elements

### 4.1. Dioxygen molecule $O_2$ .

Oxygen is a natural product. Dioxygen molecules are potentially reactive at high concentrations in the earth's atmosphere, about 21%. It has a strongly oxidizing character, which is partly reduced, and its highly reactive species are easily formed through catalysis by transition metals such as  $Fe^{2+}$ . The partially reduced oxygen intermediates are the reaction of oxygen molecules in different stages with different  $pK_a$ .

The unsaturated molecule  $O_2$  is  $\sigma$ ,  $\pi$  donor, or  $\pi$  acceptor ligand, and electron density is transferred to the electro-positive metal. Dioxygen ligand acts as bridging ligands between metal centers, contributing to the irreversibility of  $O_2$  coordination. The dioxygen ligand is mainly bound singly or doubly in reduced form [17]. Thus, Hard acids (Hard Metal cations) form complexes preferred with Hard bases (Hard Ligands). Soft acids (Soft Metal cations) prefer soft bases (Soft Ligands) [16].

### 4.2. Enzymatic catalysis.

Proteins can act as enzymes, consisting of  $\alpha$ -amino acids connected by the peptide bonds. The function of carboxamide is to provide a poor metal coordination site. Solvents such as N-methyl- or N, N-dimethylformamide with a high concentration of amide functions lead to a high dielectric constant, and protein acts as a medium, thus reducing ionic attraction and the repulsion forces within the protein and protein complexes [18].

## 5. Carbohydrates, Sugars Type Ligands, and Nucleic Acids

### 5.1. Sugar (small molecular carbohydrate) complexes.

Carbohydrates are very weak acids; the first acidity constants fall in the range of  $10^{-14}$  to  $10^{-12}$  mol  $dm^{-3}$ . Several investigations have been published on the ionization of free sugars (among them pentoses, hexoses, and sugar derivatives) and acyclic polyhydroxy alcohols. There are some exceptional cases, e.g., it has been made the hydroxy group, which deprotonates in the system. An OH group is the most acidic in glycopyranosides. The acidities of methyl arabinose, ribose-, Xylo-, and lyxofuranosides comprise two groups. *Trans*-1,2-glycosides have acidity constants 2 to 4 times larger than those of *cis* counterparts. A possible explanation for this acidity difference is the stronger solvation of the 2-oxyanion than that of the neutral hydroxy group, and a neighboring *cis*-methoxy group impedes solvation more effectively than does the *trans* group. Each pair of anomers having the *cis*-1,2-configuration is the weaker acid. Because of the low acidity of sugar molecules, the metal complexes formed by mono- and disaccharides are usually weak in acidic and slightly alkaline solutions. This is the reason for the lack of equilibrium data for such systems. Just the opposite can be said about complexes formed with sugar acids or sugar derivatives containing stronger donor groups than the alcoholic oxygens [19].

One of the first convincing pieces of evidence on the metal ion coordination of sugar molecules stems found that in the presence of metal salts, some sugar molecules migrate, even at pH  $\sim 7$ , toward the cathode, indicating the positive charge of the sugar-containing species in the system. This behavior could be understood only by assuming that the neutral sugars

coordinate metal ions, resulting in metal complex cations. The extent of migration could be considered to be a rough measure of the complexity of ability [20].

The electrophoretic migration and the NMP spectra of some sugars were investigated in the presence of calcium chloride. The results indicated a clear-out correlation between the migration and the NMR shifts due to the presence of calcium ions in the case of sugars carrying hydroxy oxygens in the axial-equatorial-axial sequence. Some other less pronounced but still significant complexing groupings were also identified as a consequence of these investigations. These results were confirmed in a large number of independent studies that showed the metal ion-binding ability of sugar molecules is determined by the steric situation of their hydroxy groups [21].

The complexing sites of monosaccharides in descending sequence of their strengths are as follows: axial-equatorial-axial triol grouping on a six-membered ring > cis-cis triol grouping on a five-membered ring > acyclic threo-threo triol grouping > acyclic threo pair adjacent to a primary hydroxy group > acyclic erythro-threo triol grouping > cis diol grouping on a five-membered ring > cis diol grouping on a six-membered ring > trans diol grouping on a six-membered ring [22].

In cyclic monosaccharides, no more than three hydroxy oxygens can coordinate to the same metal ion, but in molecules containing more than one monosaccharide moiety, complexing can occur at more than three oxygen atoms. Two monosaccharide moieties,  $\alpha$ -D-allopyranosyl or  $\alpha$ -D-allopyranose, with an axial-equatorial-axial-sequence of hydroxy groups and form a pentadentate complex with calcium ions [23].

### 5.2. Amino sugar complexes.

Amino sugars, which are the most abundant natural organic compounds, are known to bind metal ions. The amino sugar complexes of copper(II) usually have outstanding stability. The complex formation of different metal ions was investigated using pH-metric titrations. The stability constants of the metal complexes decreased in the sequence  $\text{Cu}^{2+} > \text{Pb}^{2+} > \text{Zn}^{2+} > \text{Ni}^{2+} > \text{Cd}^{2+} > \text{Ca}^{2+} \sim \text{Mg}^{2+}$ . The stabilities of the copper(II) complexes increased in the above sequence of ligands. Recent potentiometric and spectroscopic studies on the coordination ability of D-mannosamine have shown that this amino sugar is a more effective ligand than D-glucosamine or D-galactosamine. All monomeric amino sugars act as bidentate ligands, with their amino group as a main donor toward metal ions. The second donor center derives from one of the amino-sugar hydroxyl groups. e.g., 2-Amino-2-deoxy-D-gluconic acid forms complexes with higher stability than those of D-glucosamine, owing to the presence of the carboxylate group indicating the coordination of the latter oxygen in the system [24].

### 5.3. Adenosine complexes.

Alkali metal and alkaline earth metal ions do not interact with the basic part of adenosine, whereas 3d transition metal ions form comparably stable complexes. Based on the linear stability-basicity correlation for adenosine, Cu(II) and Ni(II) ions prefer N1 rather than N7, but Zn(II) ions can bind with both sites theoretically. However, the experimental results showed that the microscopic  $\log(K/M^{-1})$  values of N1 and N7 coordination were 0.28 and 0.59 with Ni(II) and 0.59 and 0.87 with Cu(II). This is because the stability complexes were based on m- and p-substituted pyridines. However, in adenosine, there is an amino group that is large

in the ortho position. So steric hindrance plays an important role in adenosine binding with Ni(II) at the 6-amino group to form a complex; thus, N7 coordination is favored [25].

#### 5.4. Adenine complexes.

A direct chelate formation of adenosine with 3d transition metal ions through hydrogen bonding of the 6-amino group to the N7 atom is not possible. Since the chelate structure complex- 1, N6-ethanoadenosine is several orders of magnitude more stable than those of the purine riboside. The complexes of neutral adenine are more stable than those of adenosine, most probably because of the availability of an additional binding site. N9 coordination of adenine would form complexes with metal ions. Cu(II) metal ion may display monodentate binding to the N9 atom of either the adeninate ion, neutral (N7H) adenine, or the (N1H, N7H) adeninium cation. The formation of a Ni(II) complex of the adenine anion is abnormally slow. It is assumed that the metal ion initially attacks neutral adenine, and the complex then undergoes deprotonation. The rate-determining step is the ring closure to a bidentate chelate. In addition, the initial hydrogen bonding of neutral adenine through the N1 atom to a water molecule of the inner sphere of the Ni(II) ion results in a misorientation [26].

## 6. Inorganic Elements of a living system

### 6.1. The biological roles of metal ions.

The chemistry of life involves at least twenty-five essential elements. There are another nine elements that are required in relatively large quantities, called macronutrients in humans [27, 28]. These elements are Na, K, Mg, Ca, S, P, Cl, Si, and Fe, while V, Cr, Mn, Co, Ni, Cu, Zn, Mo, W, Se, and F are required in relatively small quantities. Some are toxic, such as beryllium, thallium, and uranium, which are not used in the biochemical processes. These metallic elements play a variety of roles in the living system, including:

- (i) Regulatory action is exercised by  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ , and  $\text{Ca}^{2+}$ . The influx and rush out of these ions through the cell membrane maintain the concentration gradients and regulate the metabolism activity [29, 30].
- (ii) Structural role of calcium in bone, teeth, and blood clotting, which makes the teeth and bone more rigid and initiates blood clotting in wounds in the presence of metal ions [31, 32].
- (iii) Electron transfer depends on metal-containing electron-transfer agents, such as cytochromes, and ferredoxins (Fe) [33, 34].
- (iv) Metalloenzymes or Metallocoenzymes are involved in enzymatic activity, depending on the presence of metal ions; both have the active site of the enzyme or co-enzyme. Metallocoenzyme includes carbonic anhydrase, carboxypeptidase, and cytochrome P450 [35, 36].
- (v) Oxygen carries the molecules from the lung to tissue used in oxidative processes to generate energy, e.g., ATP. Oxygen carriers also contain metal ions that provide the active sites for the  $\text{O}_2$  molecules. Typical oxygen carriers are hemoglobin and myoglobin [37, 38].

## 7. Conclusion

The metal complex formation depends on the structure, bonding, and ligand design. Its stability corresponds to the ion's size and charge based on the hard and soft acid-base principle. Dioxygen molecule O<sub>2</sub> and enzymatic catalysis are the major biological functions of inorganic elements. Carbohydrates, sugars-type ligands, and nucleic acids are commonly used to form complexes. The biological roles of metal ions play important roles in the living system.

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## Conflicts of Interest

The author declares no conflict of interest. This manuscript's contents originated and modified from Siu Kan Law, BSc in Applied Sciences (Biology and Chemistry), Course: AS 310F Final Year Project (OUHK in 2008).

## References

1. Ravinderpal, K.S.; Satya, P. Metal Complexes in Medicine: An Overview and Update from Drug Design Perspective. *Cancer Therapy Oncol. Int. J.* **2019**, *14*, 25-32, <https://doi.org/10.19080/CTOIJ.2019.14.555883>.
2. Esteruelas, M.A.; Moreno-Blázquez, S.; Oliván, M.; Oñate, E. Competition between N,C,N-Pincer and N,N-Chelate Ligands in Platinum(II). *Inorg. Chem.* **2023**, *62*, 10152-10170, <https://doi.org/10.1021/acs.inorgchem.3c00694>.
3. Yamamoto, K.; Higuchi, K.; Ogawa, M.; Sogawa, H.; Kuwata, S.; Hayashi, Y.; Kawauchi, S.; Takata, T. Macrocyclic Metal Complexes Bearing Rigid Polyaromatic Ligands: Synthesis and Catalytic Activity. *Chem. Asian J.* **2020**, *15*, 356-359, <https://doi.org/10.1002/asia.201901561>.
4. Pająk, M.; Woźniczka, M.; Lichawska, M.E.; Czerwiński, B.; Włodarczyk, J.; Fichna, J. Oxygen Binding by Co(II) Complexes with Oxime-Containing Schiff Bases in Solution. *Int. J. Mol. Sci.* **2022**, *23*, 5492, <https://doi.org/10.3390/ijms23105492>.
5. Zubi, Y.S.; Seki, K.; Li, Y.; Hunt, A.C.; Liu, B.; Roux, B.; Jewett, M.C.; Lewis, J.C. Metal-responsive regulation of enzyme catalysis using genetically encoded chemical switches. *Nat. Commun.* **2022**, *13*, 1864, <https://doi.org/10.1038/s41467-022-29239-y>.
6. Canner, S.W.; Shanker, S.; Gray, J.J. Structure-Based Neural Network Protein-Carbohydrate Interaction Predictions at the Residue Level. *Front. Bioinform.* **2023**, *3*, 1186531, <https://doi.org/10.1101/2023.03.14.531382>.
7. Madec, H.; Figueiredo, F.; Cariou, K.; Roland, S.; Sollogoub, M.; Gasser, G. Metal complexes for catalytic and photocatalytic reactions in living cells and organisms. *Chem. Sci.* **2022**, *14*, 409-442, <https://doi.org/10.1039/d2sc05672k>.
8. Liao, X.; Denk, J.; Tran, T.; Miyajima, N.; Benker, L.; Rosenfeldt, S.; Schafföner, S.; Retsch, M.; Greiner, A.; Motz, G.; Agarwal, S. Extremely low thermal conductivity and high electrical conductivity of sustainable carbon-ceramic electrospun nonwoven materials. *Sci. Adv.* **2023**, *9*, eade6066, <https://doi.org/10.1126/sciadv.ade6066>.
9. Liu, R.; Cui, J.; Ding, T.; Liu, Y.; Liang, H. Research Progress on the Biological Activities of Metal Complexes Bearing Polycyclic Aromatic Hydrazones. *Molecules* **2022**, *27*, 8393, <https://doi.org/10.3390/molecules27238393>.
10. Vasilyev, K.A.; Antonova, A.S.; Volchkov, N.S.; Logvinenko, N.A.; Nikitina, E.V.; Grigoriev, M.S.; Novikov, A.P.; Kouznetsov, V.V.; Polyanskii, K.B.; Zubkov, F.I. Influence of Substituents in a Six-



- Membered Chelate Ring of HG-Type Complexes Containing an N→Ru Bond on Their Stability and Catalytic Activity. *Molecules* **2023**, *28*, 1188, <https://doi.org/10.3390/molecules28031188>.
11. Lavrenova, L.G.; Sukhikh, T.S.; Glinskaya, L.A.; Trubina, S.V.; Zvereva, V.V.; Lavrov, A.N.; Klyushova, L.S.; Artem'ev, A.V. Synthesis, Structure, and Magnetic and Biological Properties of Copper(II) Complexes with 1,3,4-Thiadiazole Derivatives. *Int. J. Mol. Sci.* **2023**, *24*, 13024, <https://doi.org/10.3390/ijms241613024>.
  12. Xu, W.; Nagata, Y.; Kumagai, N. TEtraQuinolines: A Missing Link in the Family of Porphyrinoid Macrocycles. *J. Am. Chem. Soc.* **2023**, *145*, 2609-2618, <https://doi.org/10.1021/jacs.2c12582>.
  13. Ullah, F.; Khan, T.A.; Iltaf, J.; Anwar, S.; Khan, M.F.A.; Khan, M.R.; Ullah, S.; Fayyaz ur Rehman, M.; Mustaqeem, M.; Kotwica-Mojzych, K.; Mojzych, M. Heterocyclic Crown Ethers with Potential Biological and Pharmacological Properties: From Synthesis to Applications. *Appl. Sci.* **2022**, *12*, 1102, <https://doi.org/10.3390/app12031102>.
  14. Gutten, O.; Rulíšek, L. Predicting the Stability Constants of Metal-Ion Complexes from First Principles. *Inorg. Chem.* **2013**, *52*, 10347-10355, <https://doi.org/10.1021/ic401037x>.
  15. de Souza, J.P.; Pivnic, K.; Bazant, M.Z.; Urbakh, M.; Kornyshev, A.A. Structural Forces in Ionic Liquids: The Role of Ionic Size Asymmetry. *J. Phys. Chem. B.* **2022**, *126*, 1242-1253, <https://doi.org/10.1021/acs.jpcc.1c09441>.
  16. Zheng, S.; Sun, Y.; Xue, H.; Braunstein, P.; Huang, W.; Pang, H. Dual-ligand and hard-soft-acid-base strategies to optimize metal-organic framework nanocrystals for stable electrochemical cycling performance. *Natl. Sci. Rev.* **2021**, *9*, nwab197, <https://doi.org/10.1093/nsr/nwab197>.
  17. Liu, X.; Feng, L.; Li, Y.; Xia, T.; Sui, Z.; Chen, Q. Covalent Organic Frameworks Composites Containing Bipyridine Metal Complex for Oxygen Evolution and Methane Conversion. *Molecules* **2022**, *27*, 5193, <https://doi.org/10.3390/molecules27165193>.
  18. Wang, L.; Wang, B.; Dong, R. Editorial: Enzymatic Catalysis and Applications. *Chem. Asian J.* **2022**, *17*, e202200875, <https://doi.org/10.1002/asia.202200875>.
  19. Holesh, J.E.; Aslam, S.; Martin, A. Physiology, carbohydrates. In StatPearls [Internet]; StatPearls Publishing: **2023**.
  20. Sohrabi, M.; Binaeizadeh, M.R.; Iraj, A.; Larijani, B.; Saeedi, M., Mahdavi, M. A review on  $\alpha$ -glucosidase inhibitory activity of first row transition metal complexes: a futuristic strategy for treatment of type 2 diabetes. *RSC Adv.* **2022**, *12*, 12011-12052, <https://doi.org/10.1039/d2ra00067a>.
  21. Lokajová, J.; Porras, S.; Elovaara, E.; Wiedmer, S. Determination of N-methyl-2-pyrrolidone and its metabolites in urine by micellar electrokinetic chromatography. *Open Chem.* **2011**, *9*, 825-833, <https://doi.org/10.2478/s11532-011-0062-2>.
  22. Li, Q.; Levi, S.M.; Wagen, C.C.; Wendlandt, A.E.; Jacobsen, E.N. Site-selective, stereocontrolled glycosylation of minimally protected sugars. *Nature* **2022**, *608*, 74-79, <https://doi.org/10.1038/s41586-022-04958-w>.
  23. Kamitori, S.; Ueda, A.; Tahara, Y.; Yoshida, H.; Ishii, T.; Uenishi, J. Crystal structures of rare disaccharides,  $\alpha$ -D-glucopyranosyl  $\beta$ -D-psicofuranoside, and  $\alpha$ -D-galactopyranosyl  $\beta$ -D-psicofuranoside. *Carbohydr. Res.* **2011**, *346*, 1182-1185, <https://doi.org/10.1016/j.carres.2011.04.003>.
  24. Yang, J.; Xie, D.; Ma, X. Recent Advances in Chemical Synthesis of Amino Sugars. *Molecules* **2023**, *28*, 4724, <https://doi.org/10.3390/molecules28124724>.
  25. Cai, H.; Xu, Y.; Guo, S.; He, X.; Sun, J.; Li, X.; Li, C.; Yin, W.; Cheng, X.; Jiang, H.; Xu, H.E.; Xie, X.; Jiang, Y. Structures of adenosine receptor A<sub>2B</sub>R bound to endogenous and synthetic agonists. *Cell Discov.* **2022**, *8*, 140, <https://doi.org/10.1038/s41421-022-00503-1>.
  26. Bamidele, N.; Zhang, H.; Dong, X.; Gaston, N.; Cheng, H.; Kelly, K.; Watts, J.K.; Xie, J.; Gao, G.; Sontheimer, E.J. Engineering Nme2Cas9 Adenine Base Editors with Improved Activity and Targeting Scope. *bioRxiv* **2023**, 2023.04, <https://doi.org/10.1101/2023.04.14.536905>.
  27. Moustakas, M. The Role of Metal Ions in Biology, Biochemistry and Medicine. *Materials* **2021**, *14*, 549, <https://doi.org/10.3390/ma14030549>.
  28. Farag, M.A.; Abib, B.; Qin, Z.; Ze, X.; Ali, S.E. Dietary macrominerals: Updated review of their role and orchestration in human nutrition throughout the life cycle with sex differences. *Curr. Res. Food Sci.* **2023**, *6*, 100450, <https://doi.org/10.1016/j.crfs.2023.100450>.
  29. Missirlis, F. Regulation and biological function of metal ions in *Drosophila*. *Curr. Opin. Insect. Sci.* **2021**, *47*, 18-24, <https://doi.org/10.1016/j.cois.2021.02.002>.

30. Blayney, E.-L.; Chennath, M.; Cranfield, C.G.; Clarke, R.J. Bioinformatic Analysis of Na<sup>+</sup>, K<sup>+</sup>-ATPase Regulation through Phosphorylation of the Alpha-Subunit N-Terminus. *Int. J. Mol. Sci.* **2022**, *24*, 67, <https://doi.org/10.3390/ijms24010067>.
31. He, L.; Yu, Z.; Geng, Z.; Huang, Z.; Zhang, C.; Dong, Y.; Gao, Y.; Wang, Y.; Chen, Q.; Sun, L.; Ma, X.; Huang, B.; Wang, X.; Zhao, Y. Structure, gating, and pharmacology of human Ca<sub>v</sub>3.3 channel. *Nat. Commun.* **2022**, *13*, 2084, <https://doi.org/10.1038/s41467-022-29728-0>.
32. Fouhy, L.E.; Mangano, K.M.; Zhang, X.; Hughes, B.D.; Tucker, K.L.; Noel, S.E. Association between a Calcium-to-Magnesium Ratio and Osteoporosis among Puerto Rican Adults. *J. Nutr.* **2023**, *153*, 2642-2650, <https://doi.org/10.1016/j.tjnut.2023.05.009>.
33. Iyanagi, T. Roles of Ferredoxin-NADP<sup>+</sup> Oxidoreductase and Flavodoxin in NAD(P)H-Dependent Electron Transfer Systems. *Antioxidants* **2022**, *11*, 2143, <https://doi.org/10.3390/antiox11112143>.
34. Wieferig, J.P.; Kühlbrandt, W. Analysis of the conformational heterogeneity of the Rieske iron-sulfur protein in complex III<sub>2</sub> by cryo-EM. *IUCrJ* **2023**, *10*, 27-37, <https://doi.org/10.1107/S2052252522010570>.
35. Jarvis, A.G. Designer metalloenzymes for synthetic biology: Enzyme hybrids for catalysis. *Curr. Opin. Chem. Biol.* **2020**, *58*, 63-71, <https://doi.org/10.1016/j.cbpa.2020.06.004>.
36. Pan, Y.; Li, G.; Liu, R.; Guo, J.; Liu, Y.; Liu, M.; Zhang, X.; Chi, L.; Xu, K.; Wu, R.; Zhang, Y.; Li, Y.; Gao, X.; Li, S. Unnatural activities and mechanistic insights of cytochrome P450 PikC gained from site-specific mutagenesis by non-canonical amino acids. *Nat. Commun.* **2023**, *14*, 1669, <https://doi.org/10.1038/s41467-023-37288-0>.
37. Boyette, L.C.; Manna, B. Physiology, Myocardial Oxygen Demand. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing **2022**.
38. Chen, L.; Yang, Z.; Liu, H. Hemoglobin-Based Oxygen Carriers: Where Are We Now in 2023? *Medicina* **2023**, *59*, 396, <https://doi.org/10.3390/medicina59020396>.