J. Chemtracks 27 (1&2) 317-322, 2025
Abstracted / Indexed in
A division of the American Chemical Society
Chemical Abstract U.S.A.
ISSN 0973-239X
CODEN:JCOHF7
IMPACT FACTOR : 7.866

Alkaline Earth Metal Complexes with Oxine derivatives : A Review

Anand Raj* and Ashok Kumar Yadav#
*Research Scholar, Dept. of Chemistry, B. Mandal University, Madheppura, Bihar -852128
#Professor & Head (Retd.) University Dept. of Chemistry, B. Mandal University, Madheppura
Email ID: yadavkrashok@yahoo.co.in

Manuscript received online 15 May 2025, accepted on 19 June 2025

Abstract : Oxine i.e. 8-hydroxyquinoline is a versatile heterocyclic compound as it exhibits numerous biological activities such as anti-fungal, anti-bacterial, anti-microbial, anti-cancer, anti-viral, etc. The molecule also exhibits excellent chelating properties and binds effectively to both transition metals and alkali and alkaline earth metals. This moiety has been drawn great attention of medicinal chemists due to its significant biological activities. Synthetic modification of 8-hydroxyquinoline is under exploration on large scale to develop more potent target-based broad spectrum drug molecules for the treatment of several life-threatening diseases such as anti-cancer, HIV, neurodegenerative disorders, etc. Metal chelation properties of 8-hydroxyquinoline and its derivatives also make these a potent drug candidate for the treatment of various diseases. The past two decades have witnessed the preparation of a huge number of transition metal-based 8-HQ complexes along with their incredible applications. However, no remarkable work has been reported in the field of alkali and alkaline earth metal-based complexes of 8-HQ and its derivatives. Since alkali and alkaline earth metals play a vital role in the biological system, we herein anticipate that alkali and alkaline earth metal complexes of 8-hydroxyquinoline may serve as models to understand the mechanism of uptake, transport, and storage of these metals in animals and plants. Owing to the numerous biological activity of the 8-HQ core structure, the synthesized complexes are also expected to show promising biological activities. Since drug resistance has emerged as the major problem after the prolonged usage of the same drug, the identification of new alternatives is the need of the hour and hence more and more lead compounds may prove beneficial to overcome the drug resistance that offers an unprecedented challenge to public health.

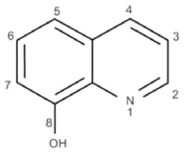
(Keywords : 8-Hydroxyqunoline (8-HQ), Biological activities, Alkaline earth metal complexes).

Introduction

8-Hydroxyquinoline (8-HQ) i.e. oxine is an important heteroaromatic compound that has attracted significant attention in coordination chemistry, medicinal chemistry, and materials science due to its excellent chelating ability and diverse biological activities[1-3]. The molecule contains a phenolic hydroxyl group and a ring nitrogen atom, which together act as a bidentate N,O-donor system capable of forming stable chelate rings with metal ions[4]. It is a significant heterocyclic scaffold in organic and analytical chemistry because of the properties of chromophore and is used to detect various metal ions and an ions. From the last two decades, this moiety has been drawn great attention of medicinal chemists due to its significant biological activities. Synthetic modification of 8-hydroquinoline is under exploration on large scale to develop more potent target based broad spectrum drug molecules for the treatment of several life threatening diseases such as cancer, HIV, neurodegenerative disorders, etc. Metal chelation properties of 8-hydroxyquinoline and its derivatives also make these potent drug candidates for the treatment of various diseases[5].

Transition metal complexes of 8-HQ i.e. oxine have been extensively investigated and reported to exhibit applications in catalysis, sensing, anticancer therapy, and antimicrobial formulations[6-8]. In contrast, alkali and alkaline earth metal complexes of oxine derivatives remain relatively underexplored, despite the critical biological importance of these metals. Magnesium and calcium, in particular, play indispensable roles in enzymatic catalysis, signal transduction, muscle contraction, and structural stabilization of biomolecules[9,10]. Therefore, understanding their interaction with biologically active ligands such as 8-HQ is of considerable importance.

1. Structure and Chelation Mode of 8-Hydroxyquinoline



Structure of 8-Hydroxyquinoline

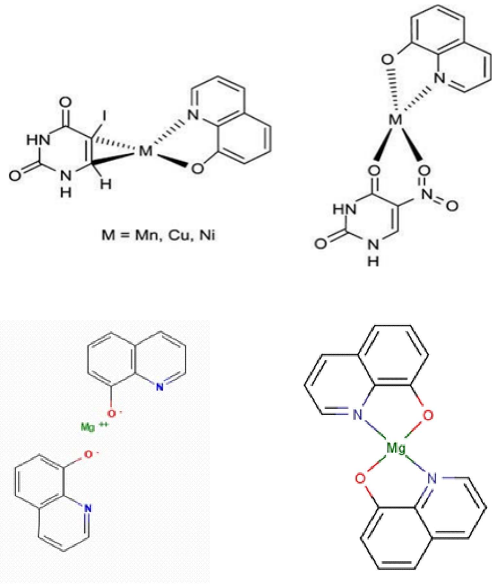


Figure 1.Molecular structure of 8-hydroxyquinoline and its typical bidentate coordination mode through quinoline nitrogen and deprotonated phenolic oxygen atoms.

The chelation of 8-hydroxyquinoline generally occurs after deprotonation of the hydroxyl group, resulting in a neutral or anionic chelate depending on the metal ion and reaction conditions[11]. Alkaline earth metal ions, owing to their larger ionic radii and preference for higher coordination numbers, often form complexes in which solvent molecules or counter-ions participate in completing the coordination sphere[12].

3. Alkaline Earth Metals and Their Biological Importance

Alkaline earth metals are characterized by their divalent oxidation state and preference for ionic interactions with hard donor atoms such as oxygen and nitrogen. Among them, magnesium and calcium are biologically essential and play crucial roles in maintaining cellular structure and function[9,13].

Magnesium is a key intracellular cation involved in stabilizing ATP, activating enzymes, and supporting nucleic acid structure. Its coordination behavior with oxygen- and nitrogen-donor ligands makes oxine derivatives suitable models for studying biologically relevant metal–ligand interactions[9]. Calcium, on the other hand, serves both regulatory and structural functions. Fluctuations in intracellular calcium concentrations act as signals controlling, muscle contraction, neurotransmission, and gene regulation, while calcium also contributes to bone mineralization[10,13].

Although strontium and barium are not essential elements, their chemical similarity to calcium allows partial substitution in biological systems. Strontium has attracted attention for its role in bone-related processes, whereas barium is mainly of toxicological interest[14]. From a bioinorganic perspective, alkaline earth metal–oxine complexes provide useful models for understanding metal binding, transport, and distribution under physiological conditions without complications arising from redox activity[13,23].

4. Synthesis of Alkaline Earth Metal–Oxine Complexes

Alkaline earth metal complexes of 8-hydroxyquinoline are generally prepared through straightforward solution-phase reactions involving metal salts such as chlorides, nitrates, or acetates and the oxine ligand or its substituted derivatives[15]. These reactions are commonly carried out in alcoholic or aqueous media, where both the metal salt and ligand exhibit sufficient solubility to promote efficient coordination.

Mildly basic conditions are essential for successful complex formation, as deprotonation of the phenolic hydroxyl group of 8-hydroxyquinoline facilitates binding through the oxygen atom. Bases such as sodium hydroxide, potassium hydroxide, or organic amines are often employed to assist ligand deprotonation and enhance metal–ligand interaction[15]. The stoichiometry of the reactants and the choice of solvent significantly influence the nuclearity and composition of the resulting complexes.

Reaction temperature and duration also play an important role in determining the structural features of the synthesized complexes. Reactions are typically performed at room temperature or under gentleheating to ensure complete coordination without decomposition of the ligand. Under appropriate conditions, both mononuclear and polynuclear complexes may form, depending on the metal ion size and coordination preference[15].

The resulting alkaline earth metal–oxine complexes are usually obtained as crystalline or microcrystalline solids following filtration and solvent evaporation. Purification is commonly achieved by repeated washing with suitable solvents to remove unreacted ligands or metal salts. The isolated products are generally stable under ambient conditions, allowing further spectroscopic and structural characterization[15]. The synthesis of alkaline earth metal–oxine complexes is influenced by:

- Nature of the metal salt and its counter-ion
- Choice of solvent and reaction medium
- Degree of ligand deprotonation under basic conditions
- Metal-to-ligand stoichiometric ratio
- Reaction temperature and time

5. Spectroscopic and Structural Characterization

Spectroscopic methods are fundamental for establishing the formation and coordination behavior of alkaline earth metal complexes with oxine derivatives. Since alkaline earth metals do not show characteristic d–d transitions, characterization mainly relies on changes in ligand-based spectral features supported by complementary analytical techniques[11,12].

Infrared spectroscopy provides clear evidence of metal coordination. Upon complex formation, noticeable shifts in the stretching frequencies of the phenolic C–O and quinoline C=N groups are observed, indicating the involvement of oxygen and nitrogen donor atoms in bonding. The weakening or disappearance of the O–H stretching vibration further supports deprotonation of the hydroxyl group during complexation[11,16].

Electronic (UV–Visible) spectroscopy offers additional confirmation of complex formation. Although alkaline earth metal ions are spectroscopically inactive, variations in absorption maxima and intensity compared to the free ligand arise from intraligand and ligand-to-metal charge-transfer transitions, reflecting changes in the electronic environment of the ligand upon coordination[17].

Nuclear magnetic resonance spectroscopy shows coordination-induced chemical shift changes and signal broadening, supporting metal–ligand interaction[17]. Structural information obtained from X-ray diffraction studies, when available, reveals coordination geometry, metal–ligand stoichiometry, and the presence of solvent molecules or counter-ions, while thermal and elemental analyses confirm composition and stability of the complexes[24].

The spectroscopic and structural characterization of alkaline earth metal–oxine complexes is typically supported by:

- Shifts in IR ν(C–O) and ν(C=N) stretching frequencies
- Changes in UV–Visible absorption spectra relative to the free ligand
- Coordination-related variations in NMR chemical shifts
- Structural parameters derived from X-ray crystallographic data
- Thermal stability and stoichiometry confirmed by TGA and elemental analysis

6. Biological Activities and Pharmacological Potential

8-Hydroxyquinoline and its derivatives are well recognized for their broad spectrum of biological activities, including antimicrobial, antifungal, antiviral, and anticancer properties[18]. These activities are largely attributed to their strong metal-chelating ability, which allows interference with essential metal-dependent biological processes. Coordination with metal ions often enhances the biological efficacy of oxine derivatives by modifying physicochemical properties such as lipophilicity, stability, and cellular permeability[19].

The formation of alkaline earth metal complexes with oxine derivatives may further influence pharmacological behavior by introducing biologically compatible metal ions into the molecular framework. Unlike many transition metals, alkaline earth metals are generally associated with lower toxicity and play natural roles in physiological systems[22]. Their complexes with oxine ligands may therefore provide improved therapeutic profiles while maintaining biological relevance. Although detailed biological evaluations of these complexes are limited, existing studies suggest that metal coordination can enhance activity compared to the free ligand through synergistic metal–ligand interactions[20].

The biological and pharmacological relevance of alkaline earth metal–oxine complexes may be associated with:

- Enhanced antimicrobial and antifungal activity due to improved membrane penetration[18,19]
- Modulation of metal-dependent enzymatic pathways through controlled metal chelation[13,18]
- Potential anticancer activity arising from disruption of cellular metal homeostasis[19,21]
- Neuroprotective and antioxidant effects linked to regulated metal ion transport[22]
- Reduced systemic toxicity owing to the endogenous nature of alkaline earth metal ions[22].

7. Role in Drug Resistance and Bioinorganic Relevance

The growing incidence of resistance to conventional therapeutics has emerged as one of the most serious challenges in modern medicine. Prolonged exposure to organic drugs often results in adaptive cellular responses such as reduced drug uptake, overexpression of efflux pumps, metabolic inactivation, and modification of molecular targets, ultimately leading to therapeutic failure[21,22]. These limitations have stimulated interest in alternative drug design strategies, including the development of metal-based bioactive compounds.

Coordination of 8-hydroxyquinoline derivatives with metal ions offers a distinctive approach to overcome resistance by altering the chemical and biological behavior of the parent ligand. Metal complexation can significantly influence parameters such as charge distribution, lipophilicity, and molecular geometry, thereby enhancing cellular internalization and reducing susceptibility to common resistance mechanisms[18-20]. In contrast to many transition metal systems, complexes of alkaline earth metals are generally associated with improved biological tolerance due to the endogenous nature of these metal ions[22].

From a bioinorganic standpoint, alkaline earth metal–oxine complexes provide important insight into physiologically relevant metal–ligand interactions. Magnesium and calcium are essential cofactors in numerous metabolic and signaling pathways, and their association with oxine derivatives may modulate metal availability and distribution at the cellular level[9,13]. Such modulation is particularly relevant in disease states where metal ion imbalance plays a role in pathogenesis, including cancer and neurodegenerative disorders[23].

Oxine derivatives are also recognized for their ionophoric properties, enabling regulated transport of metal ions across biological membranes. Complexes incorporating alkaline earth metals may therefore function as controlled metal delivery systems, influencing intracellular metal-dependent biochemical processes and potentially disrupting survival pathways in resistant cells[18-20]. This mechanism provides an additional advantage over conventional drugs that rely on single molecular targets.

Moreover, metal-based complexes often exhibit a multi-site mode of action, interacting with proteins, nucleic acids, and membrane components simultaneously. Such multifaceted interactions decrease the likelihood of resistance development compared to single-target organic therapeutics[21]. Consequently, alkaline earth metal–oxine complexes hold significant bioinorganic relevance not only as potential therapeutic agents but also as molecular probes for understanding metal-regulated biological functions[13,25].

The integration of biologically compatible alkaline earth metals into oxine-based frameworks represents a promising strategy to mitigate drug resistance while maintaining favorable safety profiles. Continued investigation of these systems may contribute to the development of next-generation metal-based therapeutics with improved efficacy and reduced resistance potential[22,23].

8. Future Perspectives

Further systematic studies focusing on structure–activity relationships, biological evaluation, and mechanistic understanding of alkaline earth metal–oxine complexes are required. Advanced characterization techniques and computational studies may provide deeper insight into their coordination behavior and biological interactions[23-26].

9. Conclusion

Alkaline earth metal complexes of 8-hydroxyquinoline (oxine) represents an underexplored yet promising class of coordination compounds. Their study not only enhances understanding of bioinorganic metal–ligand interactions but also opens new avenues for the development of biologically relevant metal-based therapeutics.

References

1. A. Albert, Selective toxicity, Methuen, London, pp. 1 (1951).
2. R. Cheluvappa, R. Shimmon, M. Dawson, and S. N. Hilmer, *Biochimie*, **91**, 1089 (2009).
3. S. Tardito, and L. Marchiò, *Current Medicinal Chemistry*, **16**, 1325 (2009).

4. A. E. Martell, and R. D. Hancock, Metal Complexes in Aqueous Solutions, *Springer, New York*, pp. **1** (1996).
5. Rohini Gupta, Vijay Luxami and Kamaldeep Paul, *Bioinorganic Chemistry, Elsevier*, **108**, 104633 (2021).
6. K. Singh, M. S. Barwa, and P. Tyagi, *European Journal of Medicinal Chemistry*, **41**, 147 (2006).
7. P. G. Cozzi, *Chemical Society Reviews*, 33, 410 (2004).
8. K. C. Gupta, and A. K. Sutar, *Coordination Chemistry Reviews*, **252,** 1420 (2008).
9. J. A. Cowan, *Chemical Reviews*, **98**, 1067 (1998).
10. D. E. Clapham, *Cell*, **131**, 1047 (2007).
11. K. Nakamoto,Infrared and Raman Spectra of Inorganic and Coordination Compounds, *Wiley, New York*, pp. 1-420 (2009).
12. F. A. Cotton, G. Wilkinson, C. A. Murillo, and M. Bochmann, Advanced Inorganic Chemistry, 6th ed.*Wiley, New York*, pp.1-1350 (1999).
13. I. Bertini, H. B. Gray, E. I. Stiefel, and J. S. Valentine, Biological Inorganic Chemistry: Structure and Reactivity,*University Science Books, Sausalito*, 2007, pp. 1-739 (2007).
14. K. L. Haas, and K. J. Franz, *Chemical Reviews*, **109**, 4921 (2009).
15. D. Kovala-Demertzi, M. A. Demertzis, E. Filiou, and A. Pantazaki, *Polyhedron*, **23**, 153 (2004).
16. L. J. Bellamy, The Infrared Spectra of Complex Molecules, *Chapman and Hall, London*, pp. **1**–433 (1975).
17. A. B. P. Lever, *Elsevier, Amsterdam*, pp. 1 (1984).
18. W. Q. Ding, and S. E. Lind, *Biochemical Pharmacology*, **78**, 1368 (2009).
19. C. Orvig, and M. J. Abrams, *Chemical Reviews*, **99**, 2201 (1999).
20. H. Sakurai, Y. Kojima, Y. Yoshikawa, K. Kawabe, and H. Yasui, *Journal of Inorganic Biochemistry*, **90**, 9 (2002).
21. N. P. E. Barry, and P. J. Sadler, *Chemical Communications*, **49**, 5106 (2013).
22. I. Kostova, *Current Medicinal Chemistry*, **13**, 1085 (2006).
23. A. S. Pithadia, M. H. Lim, *Current Opinion in Chemical Biology*, 16, 67 (2012).
24. F. H. Allen, *ActaCrystallographica Section B*, **58**, 380 (2002).
25. A. Sigel, H. Sigel, and R. K. Sigel, Metal Ions in Life Sciences, Vol. 13, *Wiley, Chichester*, pp. 1–530 (2013).
26. J. M. Mc Cord, and I. Fridovich, *Journal of Biological Chemistry*, **244**, 6049 (1969).

An International Peer Reviewed Research Journal of Chemistry
Abstracted / Indexed in : Chemical Abstract U.S.A.
JC- 1662/2K25 (ISSN:0973-239X), INDIA
Journal Chemtracks Vol. 27 (1&2), 317-322, January to December 2025