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Review Article

Transition metal salen complexes in bioinorganic and medicinal chemistry

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ABSTRACT

Salen is a common abbreviation for tetradentate N_2O_2 bis-Schiff base bis-phenolate ligands. Due to the ease of their synthesis, rich coordination chemistry and photophysical properties, biological and catalytic activity, salen complexes are widely employed in materials science, catalysis and biomedical science with applications ranging from enzyme models to therapeutics and biosensors to bioinspired nanotechnology. This review gives an overview of the role of metallosalens in bioinorganic and medicinal chemistry and discusses their applications as enzyme mimics, artificial enzyme cofactors, therapeutics, sensors, DNA cleavage and footprinting agents, quadruplex DNA binders and artificial DNA base pairs.

Contents

Abbreviations: ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid; DMF, dimethylformamide; ds-DNA, double-stranded DNA; ER, endoplasmic reticulum; EDTA, ethylenediaminetetraacetic acid; fla, flavonolate; GO, galactose oxidase; NHE, normal hydrogen electrode; ICT, intramolecular charge transfer; MPO, myeloperoxidase; PET, photoinduced electron transfer; PCET, proton-coupled electron transfer; py, pyridine; salalen, partially reduced salen; SOD, superoxide dismutase.

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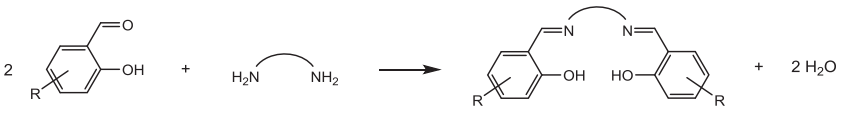

Fig. 1. Synthesis of salens by condensation of a diamine with salicylaldehyde.

1. Introduction

Salen is the acronym for *N,N*-bis(salicylidene)ethylenediamine and its derivatives. The first salen complex was described by Pfeiffer et al. in 1933 [1] and today salens are undoubtedly one of the most widely used ligand classes. Their popularity is largely due to their rich coordination chemistry, diverse properties and ease of synthesis [2,3]. Salens are readily accessible from inexpensive precursors by condensation of a diamine with two equivalents of salicylaldehyde (Fig. 1). The reaction is acid catalyzed, but in the case of aliphatic amines usually does not require the addition of acid. When the diamine is *o*-phenylenediamine or an analogue thereof, the condensation products are often referred to as salophens. However, for the sake of simplicity, throughout this review 'salen' will be used irrespective of the nature of the bridge between the imine nitrogens.

After deprotonation, the dianionic, tetradentate N_2O_2 salen ligands form relatively stable complexes with many transition and main group metals, with different oxidation states, coordination numbers and geometries. The coordination behavior can be tuned through the rigidity and length of the bridge between the two imine nitrogens. A rigid linker, for example, enforces a square-planar binding, while a longer carbon chain can lead to an almost tetrahedral coordination sphere in some Cu salens [4]. The introduction of a synthetic procedure for salens containing differently substituted phenolates 15 years ago further increased the structural diversity and the possibilities to fine-tune the electronic and geometric properties [5]. Most salens are notoriously poorly soluble in water, but dissolve readily in organic solvents such as DMF, ethanol, acetonitrile and dichloromethane.

Metallosalens are highly versatile coordination compounds with a wide range of applications. As their ligating groups resemble those in metalloproteins and enzymes, they are popular bioinorganic model compounds and functional enzyme mimics. Their biological activity and rich photophysical properties has led to numerous studies on their potential as therapeutics and biosensors. Certain metallosalens are able to induce specific damage to DNA or RNA and have been proposed as footprinting agents. Salen complexes are versatile (biomimetic) catalysts for important organic transformations. As stereogenic carbons can be easily introduced in proximity to the metal center there is continuous and ever growing interest in their application in asymmetric catalysis. The ability of the two phenolate oxygen atoms to bridge metal centers is well known and a large number of multinuclear complexes have been synthesized that are useful for studying magnetic exchange interactions between bridged paramagnetic metal ions. Various aspects of Schiff base complexes, their properties and applications have been reviewed previously [2,6–11]. This review focuses on the role and potential of metallosalens in bioinorganic and medicinal inorganic chemistry and summarizes the most important developments in the field.

2. Metal salen complexes as enzyme mimics

2.1. Superoxide dismutase, catalase and peroxidase mimics

Superoxide dismutases (SODs) protect cells against toxic superoxide radicals by catalyzing the reaction

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2 \quad (1)$$

They are classified according to their metal ion cofactor as CuZn-SODs, Mn-SODs, Fe-SODs and Ni-SODs [12,13]. Mammals have CuZn- and Mn-SODs with the former ones being located in the cytoplasm, nucleus, intermembrane space of the mitochondria and in the intracellular space, while the latter ones are found in the mitochondrial matrix [14–17]. Under physiological conditions SOD activity is coupled to catalase systems that eliminate the H_2O_2 produced in reaction (1):

$$2H_2O_2 \rightarrow O_2 + 2H_2O \quad (2)$$

Overproduction of superoxide radicals is associated with various pathological conditions and diseases such as cardiovascular disease, chronic and acute inflammation, disorders of the central nervous system and cancer [18]. Metal complexes that mimic SOD and catalases and that catalyze the disproportionation of superoxide and H_2O_2 are therefore extensively studied as potential therapeutics and antioxidants [19]. The SOD mimetic properties of Mn^{III} salen complexes were first reported by Malfroy, Jacobson and coworkers in 1993 [20]. Since then Mn salen derivatives have been extensively investigated as antioxidants, as they reportedly scavenge superoxide as well as H_2O_2 [21,22]. Similar to the mechanism of Mn-SOD, Mn^{III} in the complex is reduced by O_2^- to Mn^{II} which is subsequently oxidized back to Mn^{III} by a second O_2^-, sometimes referred to as 'ping-pong' mechanism.

$$Mn^{III}(salen) + O_2^- \rightarrow Mn^{II}(salen) + O_2 \quad (3)$$

$$Mn^{II}(salen) + O_2^- + 2H^+ \rightarrow Mn^{III}(salen) + H_2O_2 \quad (4)$$

The catalase activity of Mn^{III}(salen) involves the formation of an oxomanganese-salen intermediate in the presence of H_2O_2 which in a subsequent two-electron redox process breaks down H_2O_2 to O_2 and H_2O:

$$Mn^{III}(salen) + H_2O_2 \rightarrow (salen)Mn^V = O + H_2O \quad (5)$$

$$(salen)Mn^V = O + H_2O_2 \rightarrow Mn^{III}(salen) + H_2O + O_2 \quad (6)$$

The bioactive properties of the prototype Mn salen EUK-8 and some of its more active derivatives (Fig. 2) were demonstrated in various *in vitro* and *in vivo* studies [21,23–29]. EUK-8 and EUK-134 were shown to protect tissue and cells from radiation injury [30] and from oxidative stress in animal models for Alzheimer's disease [23], multiple sclerosis [31], Parkinson's disease [32], stroke [33], motor neurone disease [27], excitotoxic neuronal injury [25] and ischemia/reperfusion in heart and kidney tissue [34,35]. Melov et al. found that Mn salen complexes can increase the life-span of nematodes by up to 50% [26]. The SOD- and catalase-like activity of Mn salens is probably not the only reason for their neuroprotective properties. Besides reactive oxygen species, reactive nitrogen species and nitrosative stress have been associated with a range of neurodegenerative disease states. Sharpe et al. reported that Mn salen complexes also break down peroxynitrite and nitric oxide to more benign species [36]. In the presence of H_2O_2, $ONOO^-$, peracetate or persulfate, EUK-8 and EUK-134 are oxidized to the oxomanganese(V) species which react with NO and NO_2 to give NO_2^- and NO_3^-:

$$(salen)Mn^V = O + NO \rightarrow Mn^{III}(salen) + NO_2 \quad (7)$$