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Review

Harnessing the properties of cobalt coordination complexes for biological application

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ABSTRACT

Cobalt is an essential metal that is found in very low abundance in the body and the environment. Cobalt coordination complexes exhibit interesting redox and magnetic properties that make them suitable for a remarkable breadth of applications in biology and medicine. Here we review the diversity of uses of cobalt complexes in imaging and therapy, and highlight the most promising directions for future research.

Contents

1. Introduction

While cobalt-containing blue pigments have been found in ancient artifacts, the metal itself was not isolated until 1735 by the Swedish chemist, Brandt, as the first elemental metal discovered since ancient times, and it was only confirmed as an element

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in 1780 [1]. However, despite this slow start, it is commonly held that the first coordination complex discovered by Tassaert in 1798 was Co(III) hexamine, with cobalt complexes also being central to Werner's seminal work in 1893 [2]. Commonly used in alloys, catalysts and pigments, cobalt is found in low abundance compared to other first row transition metals, comprising only 0.0025% (w/w) of the Earth's crust, and 4×10^{-8}% (w/v) of seawater [3].

Cobalt is an essential element for life, although only approximately 1 mg is present in the body [4]. Cobalt is sourced from the diet, particularly green vegetables and cereals [5], and is also a common supplement in vitamins [6]. Key amongst its biological activity is its role in vitamin B_{12}, cobalamin [7], with a small number of other cobalt-containing enzymes identified to date [3].

While cobalt is an essential metal, it has systemic toxicity, including neurological, cardiovascular and endocrine impairment, attributed largely to free ionic Co(II), with blood concentrations of over 300 μg/L suggested to be of concern [8]. The toxicity of cobalt has been attributed to its redox activity, leading to the generation of ROS [9], and to its ability to substitute iron in metalloenzymes to form substitutionally-inert complexes. For example, cobalt substitution for iron in prolyl 4-hydroxylase inhibits the normal activity of the enzyme in activating hypoxia-responsive transcription, thus causing hypoxia in mammalian cells [10]. However, in contrast to toxic heavy metals to which cells have only been exposed since the industrial revolution, the body has evolved mechanisms to efflux excess cobalt from cells, including hijacking of iron export pathways [11].

Beyond the treatment of pernicious anaemia arising from cobalamin deficiency, the use of cobalt in medicine began in 1940 with the first metallic hip replacement, employing a cobalt–chrome alloy [12], in a protocol still widely used today [13]. 1951 saw the first Co-60 radiation therapy, which soon superseded X-ray radiation as the primary form of radiotherapy, and is still heavily used in developing countries [14]. Co-60, a beta-emitter with a half-life of 5.3 years, has also been used for brachytherapy, in which a sealed radiation source is implanted close to the tumour, although it has been largely replaced by Ir-192 [15].

In contrast, the study of cobalt coordination complexes for biological applications has flourished only more recently. The above-mentioned applications of cobalt in medicine harness its physical and nuclear properties. In coordination complexes, the cobalt ion also exhibits interesting redox and magnetic properties that make it suitable for a remarkable breadth of applications in biology and medicine. Most importantly, cobalt has a number of possible oxidations states from −1 to +4. Cobalt in biological systems exists almost exclusively as Co(II) or Co(III), though Co(I) (in cobalamin) and Co(IV) are known [16]. These two predominant oxidation states exhibit different properties: d^6 Co(III) complexes are generally octahedral and may be low spin or high spin [17]. The low spin d^6 configuration is diamagnetic and substitutionally inert. d^7 Co(II) ions can form four-, five- or six-coordinate complexes [18,19], all of which are substitutionally labile and paramagnetic. Based on these various properties, cobalt complexes have demonstrated therapeutic potential as reduction-activated complexes, or can be applied in imaging by MRI or fluorescence. Here we consider recent advances in the application of cobalt coordination complexes in biological systems.

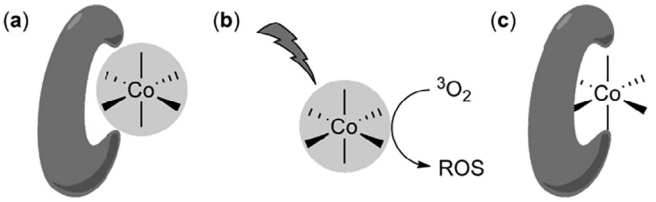

Fig. 2. Biologically-active cobalt systems can harness various properties of cobalt coordination complexes: (a) substitutionally-inert complex as a structural enzyme inhibitor; (b) substitutionally-inert complex as a photosensitiser for photodynamic therapy; and (c) labile complex that undergoes ligand exchange with biological ligands. ROS = reactive oxygen species.

2. Cobalt complexes in therapy

The biological activity of cobalt complexes was first reported by Dwyer et al. at the University of Sydney in 1952 [20]. The researchers studied Co(III) complexes with salicylidenamino-based ligands, such as **1** (Fig. 1), noting micromolar bacteriocidal activity but a low systemic toxicity in mice. Dwyer subsequently identified cobalt phenanthroline complexes with potent antibacterial activity [21], as well as complexes that could inhibit neuromuscular activity in animals [22].

Inorganic pharmaceuticals can be classed according to the active moiety [23], and cobalt complexes are no exception in this regard. Here we classify complexes according to whether the cobalt complex, or a cobalt-containing metabolite, is active; or whether the cobalt ion is a carrier for an active ligand. We will discuss each of these in turn.

2.1. Biologically-active cobalt complexes and metabolites

Various properties of cobalt coordination complexes can theoretically be harnessed in the preparation of systems that modulate biological function (Fig. 2). Examples of each are provided below.

2.1.1. Substitutionally-inert complexes

Much of organic drug design involves the preparation of structural inhibitors for enzyme active sites. Metal complexes offer a greater diversity of coordination numbers and geometries, and therefore can potentially provide tighter binding than existing organic inhibitors, or even be designed to inhibit active sites for which there is currently no organic inhibitor. In recent years, organometallic complexes of ruthenium, osmium and iridium with ligands that resemble enzyme substrates have been reported to

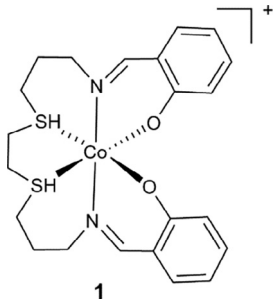

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Fig. 1. Dwyer's salicylidenamino-based Co(III) complex.

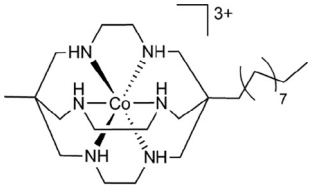

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Fig. 3. An example of a Co(III) sarcophagine with antiparasitic activity.

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