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Review article

Transition metal carbonyl clusters in biology: A futile or niche research area?

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ABSTRACT

Transition metal carbonyl clusters (TMCCs) have seldom been considered in a biological perspective. Albeit generally flawed with low water-solubility and poor air-stability, drawbacks typical of all the organometallic complexes, selected TMCCs, designed by consolidated synthetic chemical routes, have so far encountered applications in few carefully selected biological fields, thus representing a very niche research area. This paper presents a brief overview of the applications of TMCCs in protein structural characterization, in hormone labelling, in carbonyl metallo-immunoassay (CMIA), as carbon monoxide releasing molecules (CORM) and, finally, as antiproliferative (antitumor) agents.

Contents

1. Introduction

Bioinorganic chemistry is a mature field of research dealing with the role of metals in biology, including both naturally occurring ones as in metallo-enzymes (structure, mechanism and inhibition), as well as artificial ones (toxicology and pharmacology). Transition metal coordination complexes undoubtedly predominate the bioinorganic area, being the anticancer drug cisplatin the most successful example [1]. The study of biologically active transition metal complexes containing at least one metal-carbon bond, i.e. bioorganometallic chemistry, represents a valuable and flourishing subarea of the bioinorganic scenario [2–4]. An important subset of bioorganometallic chemistry is represented by the family of metal carbonyl complexes, characterized by carbon monoxide molecules as ancillary ligands. These complexes may be homoleptic, i.e. containing only CO ligands, or, more commonly, in biological applications, heteroleptic, i.e. containing a mixture of ligands. The peripheral carbonyl ligands impart additional properties to these complexes, such as analytical cooperation (carbonyl metallo-immunoassay, CMIA) [5–8], or controlled, low-dose CO

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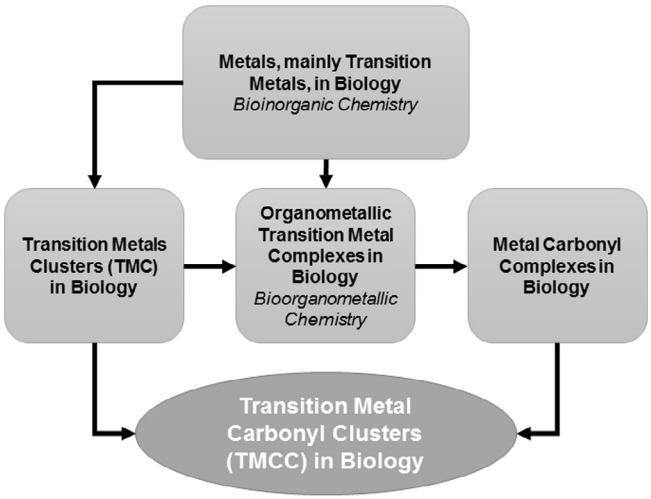

Scheme 1. Flow chart of the transition metal compounds used in biological applications.

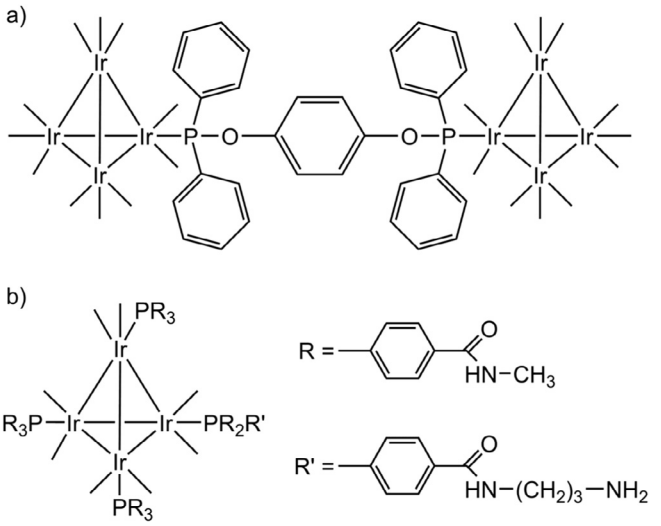

Fig. 2. The rigid dimer $[(CO)_{11}Ir_4(\mu\text{-}Ph_2PO\text{-}C_6H_4\text{-}OPPh_2)Ir_4(CO)_{11}]$ (a) and the TMCC $[Ir_4(CO_8)(PR_3)_3(PR_2R')]$ (b) used for electron microscopy applications.

freeing in targeted tissues having beneficial effects in some pathologies (carbon monoxide releasing molecules, CORM) [9,10].

By the strictest definition, a metal cluster is an aggregate having at least three direct metal-metal bonds [11,12]. Rare examples of biological applications of transition metal clusters (TMC), bearing cyclopentadienyl and hydrido ligands, have been so far reported [13,14].

Transition metal carbonyl clusters (TMCCs) contain CO as the exclusive or predominant ligand, able to stabilize the low oxidation state (mainly zero) of metals involved in the cluster assembly. TMCCs are featured by low water-solubility and poor air-stability, drawbacks typical of all the organometallic complexes. This prevents any straightforward application of TMCCs in the biological area. In Scheme 1, the domain classification of TMCCs in the comprehensive applications of metal complexes in biology is illustrated.

Usually, in TMCCs some peripheral carbonyls are replaced by specifically designed ligands to impart better water-solubility and to establish covalent or non-covalent interactions with the desired biological target. Moreover, by using polydentate ligands as alkynes, able to clasp the metal atoms, the overall stability of the TMCCs is enormously enhanced [15,16]. In Fig. 1 the synthesis of a triruthenium TMCC is reported as an example, along with its coordination modes to a prototypal biologic ligand (i.e. ethynylestradiol, EE).

In this mini-review, examples of application of TMCCs in biology are showed in protein characterization [17,18], including aims at determining specific sites [19–21], in CMIA [5–8], as CORMs [9,10], and finally as antiproliferative (antitumor) agents [12,13].

2. TMCCs in protein structural determination

Starting from the first methodological report in literature [16], different experimental attempts at better solving protein structures have exploited the 'labelling' application of transition metals [17]. The interaction of a transition metal with the protein active site may help a better understanding of its partial structure [18], which is the main interest in molecular biology [22,23]. Successful efforts have been dedicated to label proteins with single transition metal carbonyl fragments (e.g. $W(CO)_3$) [24].

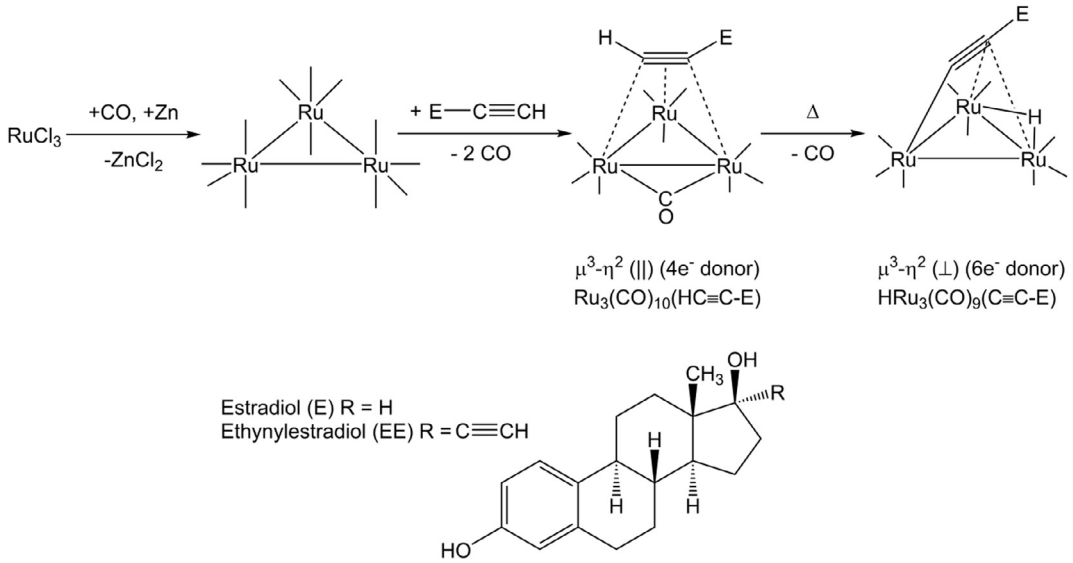

Fig. 1. Synthesis of triruthenium clusters containing ethynylestradiol. Its coordination modes to the bioligand are illustrated (carbonyls are only sketched for clarity).