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Biological labelling reagents and probes derived from luminescent transition metal polypyridine complexes

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Contents

Abstract

Many transition metal polypyridine complexes display intense and long-lived metal-to-ligand charge-transfer emission with a large Stokes' shift. This property renders them promising candidates as luminescent labelling reagents and probes for biological molecules. In view of this, we have designed various biological labels that are derived from luminescent rhenium(I) and iridium(III) polypyridine complexes. These complexes contain various functional groups that can react with the amine and sulfhydryl groups of biomolecules such as oligonucleotides, peptides and protein molecules to form luminescent bioconjugates. In other studies, we have incorporated biotin into luminescent rhenium(I) polypyridine complexes to form new probes for the protein avidin. These new luminescent conjugates and biological probes have been utilised in the development of various bioassays.

Keywords: Labelling reagents; Polypyridine complexes; Bioassays; Luminescence; Rhenium(I); Iridium(III)

Abbreviations: bpy-CHO, 4-carboxy-4′-methyl-2,2′-bipyridine; bpy-IAA, 4-iodoacetamido-2,2′-bipyridine; bpy-ITC, 4-isothiocyanato-2,2′-bipyridine; bpy-NH$_2$, 4-amino-2,2′-bipyridine; BSA, bovine serum albumin; dppn, benzo[*i*]dipyrido[3,2–*a*:2′,3′–c]phenazine; dppz, dipyrido[3,2–*a*:2′,3′–c]phenazine; HABA, 4′-hydroxyazobenzene-2-carboxylic acid; Hmppz, 3-methyl-1-phenylpyrazole; Hpba, 4-(2-pyridyl)benzaldehyde; Hpq, 2-phenylquinoline; HSA, human serum albumin; IL, intra-ligand; MLCT, metal-to-ligand charge-transfer; phen-IAA, 5-iodoacetamido-1,10-phenanthroline; phen-ITC, 5-isothiocyanato-1,10-phenanthroline; phen-NH$_2$, 5-amino-1,10-phenanthroline; py-3-mal, 3-maleimidopyridine; py-3-NCS, 3-isothiocyanatopyridine; py-3-NH$_2$, 3-aminopyridine; py-CH$_2$─NH-biotin, *N*-((4-pyridyl)methyl)biotinamide

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1. Introduction

Traditionally, radioactive isotopes have been commonly used for labelling of biomolecules for DNA sequencing, hybridisation studies and immunological applications owing to their high detection sensitivity. However, due to the relatively long experimental time, short shelf-lives of expensive reagents and increasing concern about the potential hazards of radioactive materials, alternative reagents derived from organic fluorophores and luminescent lanthanide chelates have been developed [1]. A number of fluorescent organic compounds have been designed and labelling of oligonucleotides, amino acids, peptides, proteins, antibodies and biological tissues with these fluorophores has been well documented [2]. However, the use of many organic dyes has general limitations including their high photobleaching rates, strong pH dependence, short fluorescence lifetimes and small Stokes' shifts. Thus, various lanthanide chelates have been employed as biological labelling reagents owing to their intense and extraordinarily long-lived luminescence [1]. However, the design of new lanthanide chelates is a challenge because the chelate must (i) protect the luminescent lanthanide centre from quenching by water molecules and (ii) act as an energy sensitiser to enable energy transfer to the lanthanide centre [1].

By virtue of their variable oxidation states, flexible coordinating geometry, and rich photophysical and electrochemical properties, many transition metal complexes have been covalently linked to biomolecules for various purposes [3–9]. The studies include photo-induced electron transfer in metalloproteins [3]; recognition, photocleavage and cross-linking of nucleic acids [4,5]; automated synthesis of metal-containing oligonucleotides [6]; investigations of protein hydrodynamics using anisotropy probes [7]; development of artificial nucleases [8]; and folding kinetics and thermodynamics of proteins [9].

We are interested in the possibility of using luminescent transition metal complexes, such as rhenium(I) and iridium(III) polypyridines, as biological labels and probes because many of these complexes show intense and long-lived photoluminescence in the visible region, and the emission energy of these complexes can be controlled using various diimine and/or cyclometallating ligands. Attachment of reactive functional groups or biologically important molecules to these luminescent complexes is anticipated to generate a new class of labelling reagents and probes for biomolecules.

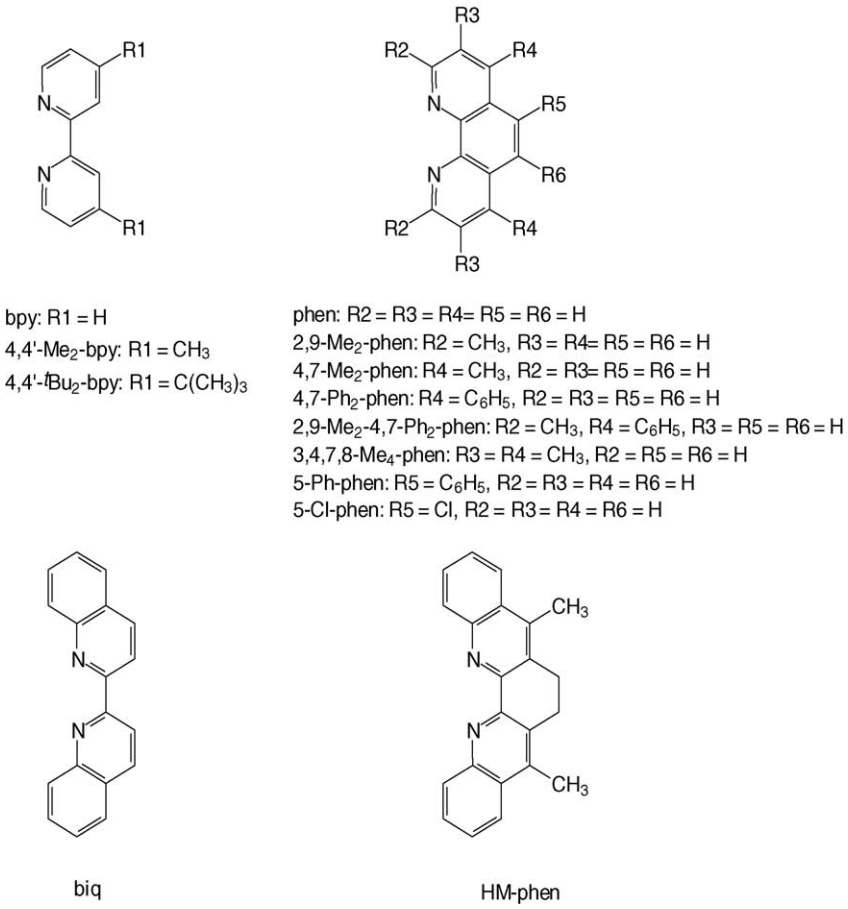

Fig. 1. Structures of the diimine ligands (N─N) of the rhenium(I) polypyridine complexes $[Re(N{-}N)(CO)_3(py\text{-}3\text{-}NCS)](CF_3SO_3)$ and $[Re(N{-}N)(CO)_3(py\text{-}3\text{-}mal)](CF_3SO_3)$.