Review

Interaction of dioxygen with the electronic excited state of Ir(III) and Ru(II) complexes: Principles and biomedical applications

Albert Ruggi [a], Fijs W.B. van Leeuwen [b], Aldrik H. Velders [a,c,*]

[a] Supramolecular Chemistry and Technology, MESA+ Institute for Nanotechnology, University of Twente, Enschede, The Netherlands
[b] Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands
[c] Biomedical Chemistry, MIRA Institute of Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands

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ABSTRACT

Luminescent transition metal complexes are enjoying a growing interest because of their ubiquitous applications in, e.g., the fields of material science, sensors and (biomedical) diagnostics, and iridium(III) and ruthenium(II) complexes are among the best studied. Due to their long-living excited states, these complexes can have a strong interaction with dioxygen, resulting in luminescence quenching. This oxygen quenching might be regarded as an unwanted effect in luminescence imaging, but, on the other hand, it can be exploited for diagnostic and therapeutic applications as well. After a theoretical introduction concerning the dioxygen quenching mechanism and the parameters involved, in the second part of this review we focus on the possibility of tailoring this quenching by modifying selected properties of a complex (triplet energy, oxidation potential, localization and shielding of the excited state) in order to obtain systems with higher or lower oxygen quenching compared to the archetypical complexes. In the third part of this review an overview of the applications of oxygen quenching of luminescence is offered, with particular attention to biomedical use: diagnostic oxygen sensing, imaging and therapy.

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1. Introduction

1.1. Overview

Luminescent transition metal complexes have recently shown to be a potentially good alternative to the more widespread organic luminophores (e.g. phenalenone, fluorescein, rhodamine and Alexa® dyes) in diagnostic imaging [1–5]. However, the interaction of the relatively long-lived excited state of transition-metal luminophores with dioxygen readily results in luminescence quenching and production of highly reactive species, i.e. singlet oxygen and/or superoxide radical. Dioxygen quenching of excited states does not necessarily represent a disadvantage that has to be avoided, and can, in fact, also be exploited, for instance in luminescence imaging for sensing and quantification of dioxygen levels. In particular the generation of singlet oxygen has been an attractive

field of research since the first observations of the phenomenon back in the 1960s [6,7]. In more recent times, the study of oxygen quenching of the excited state of fluorophores like porphyrins and phthalocyanines with the consequent generation of the cytotoxic singlet oxygen, has even demonstrated potential applications in so-called PhotoDynamic Therapy (PDT) [8,9]. Herein the local interaction of photoactivated transition metal complexes and dioxygen is used to damage e.g. DNA and cell membranes in tumor tissue [2].

Ruthenium(II), and iridium(III) complexes have been extensively studied for their rich photochemistry and remarkable photophysical properties. Due to their chemical stability and the possibility of inducing different cell localization by changing the substituents on the (usually chelating di- or tridentate) ligands these two types of complexes have also been studied for biological applications [1]. In fact, diagnostic-related applications of dioxygen sensing have been recently described and many of them are based on Ru(II) or Ir(III) complexes [10], and their dioxygen quenching has been studied both from a theoretical point of view and for its potential applications. In this review we aim to offer a comprehensive summary of the different strategies that can be used to either increase or decrease oxygen quenching of Ru(II) and Ir(III) complexes, depending on the application, in order to provide a guideline for the future development of optimized luminophores. After a theoretical introduction summarizing the dioxygen quenching mechanisms and the parameters involved in this processes (this section), we describe the different strategies used for tailoring the oxygen quenching of ruthenium(II) and iridium(III) complexes, and finally report some relevant examples of applications of oxygen quenching in the biomedical field: oxygen sensing, imaging and therapy.

1.2. Theoretical considerations

Luminescent molecules can interact with a quencher molecule, thus altering their photophysical properties. In this section the oxygen quenching mechanism and the molecular parameters involved in this process are described. Both singlet and triplet excited states might be quenched by molecular oxygen [11], however, the oxygen quenching of triplet states is usually more efficient than the quenching of singlet states. Moreover, Ru(II) and Ir(III) complexes usually show excited states with a pronounced triplet character due to the high degree of spin–orbit coupling usually observed for heavy metals. Therefore, in this review only the quenching mechanism of triplet excited states will be considered.

A quencher molecule (viz. dioxygen) colliding with a luminophore in its excited state causes a collision-dependent decrease of luminescence. The quenching process can be illustrated by using a Jablonski diagram (Fig. 1) and it can be described by the Stern–Volmer equation (Eq. (1)):

$$\frac{I_0}{I} = \frac{\tau_0}{\tau} = 1 + K_{SV}[O_2] = 1 + k_q \tau_0 [O_2] \tag{1}$$

where I_0 and I are the luminescence intensities without and with quencher (dioxygen), respectively, and τ_0 and τ are the corresponding luminescence lifetimes. K_{SV} is the Stern–Volmer constant and k_q is the kinetic quenching constant [12], that reflects the efficiency of the quenching process and can be used to compare luminophores with different lifetimes but with similar size.

The kinetic constant k_q is proportional to the diffusion-controlled rate constant k_d as shown in Eq. (2):

$$k_q = f_Q k_d \tag{2}$$

In which f_Q is the quenching efficiency, and k_d is defined according to the Smoluchowski equation (Eq. (3)):

$$k_d = \frac{4\pi N}{1000}(R_f + R_q)(D_f + D_q) \tag{3}$$
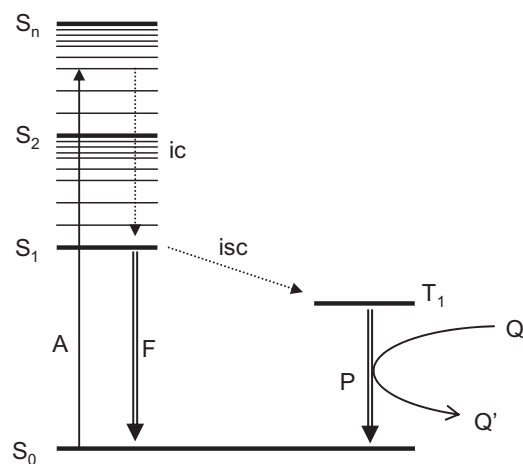
Fig. 1. Simplified Jablonski diagram for a generic luminophore showing the possible pathways of excitation and relaxation. S_0, S_1, S_2, S_n = singlet states, T_1 = triplet state, ic = internal conversion, isc = intersystem crossing, A = absorption, F = fluorescence, and P = phosphorescence. The collisional quenching process by a generic quencher Q – giving the product Q' – is shown. For sake of clarity, only the quenching of a triplet state is depicted.

where N is the Avogadro number, and R_f and R_q are the radii of the luminophore and quencher, respectively, and D_f and D_q the diffusion coefficients of the luminophore and quencher, respectively. The diffusion coefficients can be obtained from the Stokes–Einstein equation (Eq. (4)):

$$D = \frac{k_B T}{6\pi \eta R} \tag{4}$$

where k_B is the Boltzman's constant, T the temperature, η the viscosity of the solvent and R the molecular radius. It should be pointed out that the diffusion constants evaluated through Eq. (4) are frequently underestimated (up to a factor of 3) when the quencher species has a smaller radius than the solvent molecules, which is usually the case for molecular oxygen [12].

In heterogeneous media, fluorophores are usually located in different environments, which causes different quencher accessibility, i.e. different quenching degrees. Under these conditions, the Stern–Volmer plot is not linear anymore. Several models have been elaborated in order to treat these cases. We concisely report here about Lehrer's and Demas' models.

Lehrer reported first a modified Stern–Volmer equation which takes into account the different environment of each fluorophore [13]. For a series of n fluorophores (for instance bound to a protein), the modified Stern–Volmer equation in the quantum yield form is reported in Eq. (5)

$$\frac{\phi_0}{\Delta\phi} = \left[\sum_{i=0}^{n} \frac{K_{SVi}[Q](\phi_{0i}/\phi_0)}{1 + K_{SVi}[Q]}\right]^{-1} \tag{5}$$

ϕ_0 is the fluorescence quantum yield in the absence of quencher, ϕ_{0i} is the quantum yield of the ith fluorophore in absence of quencher, K_{SVi} the Stern–Volmer quenching constant of the ith fluorophore and $[Q]$ the molar concentration of quencher. Plots of the ratio $\phi_0/\Delta\phi$ vs. $[Q]$ are often linear in the case of fluorophores in different environments, whereas in these conditions the classic Stern–Volmer plot (according to Eq. (1)) usually fails.

A similar approach has been developed by Demas et al. This model is based on the analysis of the multiexponential decays usually shown by fluorophores with different environments [14]. A