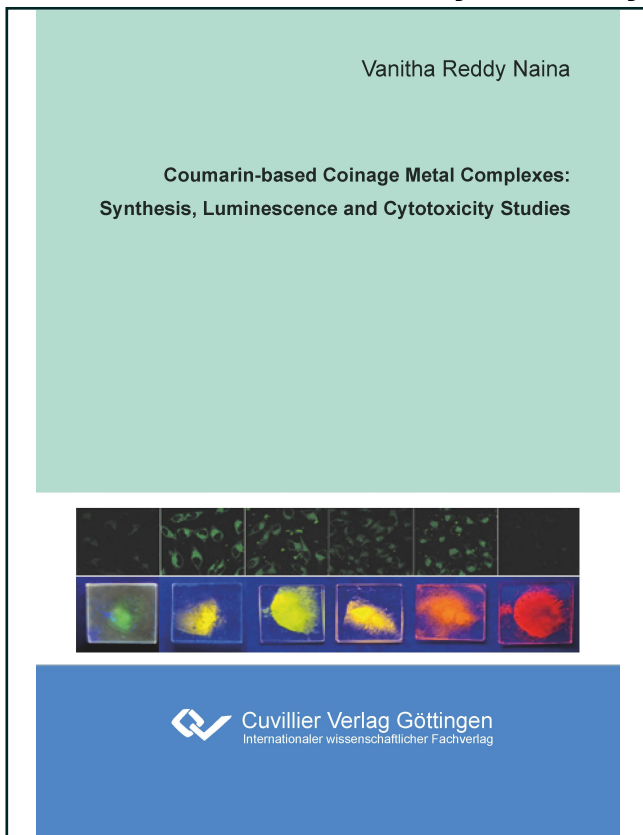




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Coumarin-based Coinage Metal Complexes: Synthesis, Luminescence and Cytotoxicity Studies



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1. INTRODUCTION

1.1 The coinage metals-copper, silver and gold

1.1.1 General

The coinage metals comprise of copper, silver and gold, the group 11 elements of the periodic table. The term coinage metal was used for these metals as they have been historically employed to mint coins by alloying them with other metals. Till date, these metals have found applications in various aspects of human life. Copper is the cheapest metal (US\$8.94 per kg)¹ when compared to silver (US\$798 per kg)² and gold (US\$65,051 per kg)². Since the industrial revolution, copper has been a critical component in several disciplines such as automotive, machinery or telecommunication due to its high conductivity and low price.³ Due to its high utility, the annual demand for copper raised to 28 million tons (2020), estimated by the United States Geological Survey (USGS).⁴ Copper is widely studied in coordination chemistry and its complexes have found potential applications in various fields. For instance, recently, copper complexes have emerged as promising organic light-emitting diodes (OLEDs) (Figure 1).⁵⁻⁶ Apart from applications in technology, copper complexes are also being investigated as anticancer agents.⁷

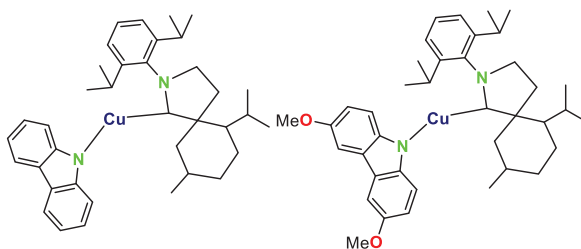


Figure 1: Copper complexes which were reported to exhibit >99 % quantum efficiency and used in the design of OLEDs.⁶

Although silver has the highest electrical conductivity of all metals, it is not profitable for the electronics industry due to its higher price and lower availability compared to copper. It is therefore only used for special applications. For example, sterling silver containing 92.5 % silver, is prominent in the jewelry industry because of its luster and corrosion resistance. Other applications include, for instance, dental treatments or electrical circuits. Apart from this,

silver is also known to exhibit antibacterial properties.⁸ Recently, silver sulfadiazine was certified as a topical cream to treat burns (Figure 2a).⁹

Gold, the heaviest and the rarest among the coinage metals, is a long sought-after and cherished metal due to its luster and color. It is used in jewelry and associated with wealth because of its high durability and rarity. Even today, it is used as a symbol of appreciation, for example, in designing Olympic medals, Oscars etc. In its elemental form, gold, the most malleable and ductile of all metals, can be rolled out thinly to just a few atomic layers, allowing a 30 m² area to be formed from just one ounce (~31.1 g).¹⁰ Ernest Rutherford exploited this property in the early 20th century when he irradiated a thin foil of gold with alpha particles that were partially backscattered, leading to the development of Rutherford's atomic model.¹¹

From a chemical point of view, gold was assumed to be non-reactive due to its nobility and resistance. Even though several gold compounds were known prior to the 1980s, it was the discovery of gold as a catalyst by Bond *et al.*¹² and followed by Haruta¹³ and Hutchings¹⁴ which attracted a lot of attention in gold chemistry. Eventually, gold has gathered increasing interest in medicine and technology due to rapid advancement in nanotechnology. For instance, colloidal gold was employed to detect SARS-CoV-2 virus.¹⁵⁻¹⁶ In addition to nanoparticles, various gold(I) and gold(III) complexes have also been investigated and used for several years for the medication of various diseases.¹⁷⁻¹⁸ Since, both gold(I) and gold(III) compounds are highly reactive and prone to ligand exchange and disproportionation under physiological conditions, they need to be stabilized by appropriate ligands. Due to their lipophilicity, stability and binding affinity, phosphines, thiolates and N-heterocyclic carbenes (NHCs) are among the preferred ligand systems for Au(I) compounds and for the Au(III) ions, porphyrins are one of the suitable systems.¹⁸ For example, Auranofin constituted a milestone in the field of gold-based drugs and was approved to treat rheumatoid arthritis (Figure 2b).¹⁹⁻²⁰ Apart from medical applications, gold compounds were found suitable for optoelectronics. Recently Yam and co-workers have realized robust gold complexes for the fabrication of OLEDs (Figure 2c).²¹

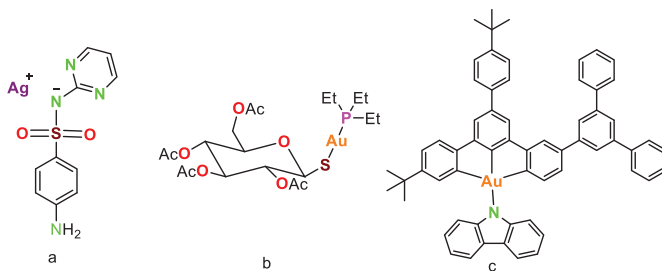


Figure 2: Molecular structures of a) Silver sulfadiazine⁹ b) Auranofin drug¹⁹ and c) Carbazolygold(III) complex for OLED fabrication.²¹

1.1.2 Chemical properties

The coinage metals, especially silver and gold, owe their designation as precious metals to their high corrosion resistance, due to the high positive standard potential. The standard potential increases downward in group 11 and reaches the highest values of all metals for gold ($E^0(\text{Au}/\text{Au}^+) = +1.69 \text{ V}$, $E^0(\text{Au}/\text{Au}^{3+}) = +1.50 \text{ V}$ and $E^0(\text{Au}^+/\text{Au}^{3+}) = +1.40 \text{ V}$). The group of coinage metals holds several records among the metals, including the highest thermal and electrical conductivity for silver and the highest electronegativity, most positive standard potential and most negative electron affinity of all metals for the element gold.²²

In addition to smaller native deposits, copper is mainly found in oxide and sulfide ores, with the latter playing the most crucial role in commercial production. The iron components are separated from chalcopyrite (CuFeS_2), copper pyrite (Cu_5FeS_3) and copper glance (Cu_2S) by the smelting metallurgical process, and the crude copper is then produced from the resulting Cu_2S utilizing a roasting process.²² This is followed by electrolytic purification to produce pure copper. Copper usually exists in oxidation states +I or +II in its compounds, with the latter being the more stable one. The rare oxidation states 0, +III and +IV of copper are also reported in the literature. The preferred coordination number of the $\text{Cu}(\text{I})$ ion is four, followed by three and two.²³⁻²⁴ Examples of tri- and dicoordinate copper complexes are shown in Figure 3.²³⁻²⁴

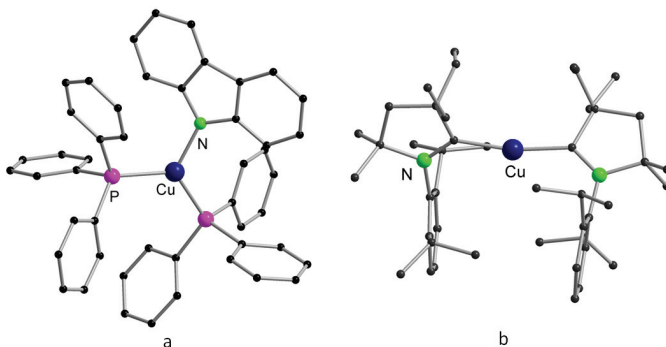
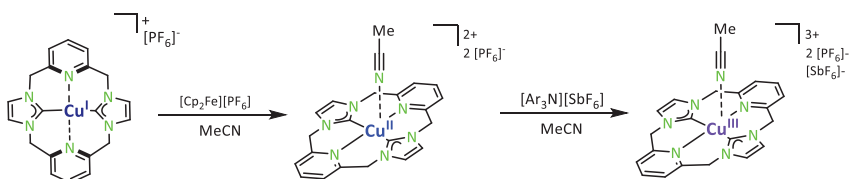


Figure 3: Molecular structures of a) tricoordinate copper(I) complex²³ and b) dicoordinate copper(0) complex²⁴.

The copper complex with a formal oxidation state zero was successfully isolated by Bertrand, Roesky, Kaim, and Frenking *et al.* using cyclic alkyl amino carbene ligands (CAACs). CAAC ligands are especially useful for forming strong bonds with metal centers and are good π -acceptors. The two-coordinate Cu(0) complex can be isolated either by the reduction of a cationic Cu(I) complex with Na or by the reduction of CuCl₂ with KC₈ in the presence of a CAAC ligand.²⁴

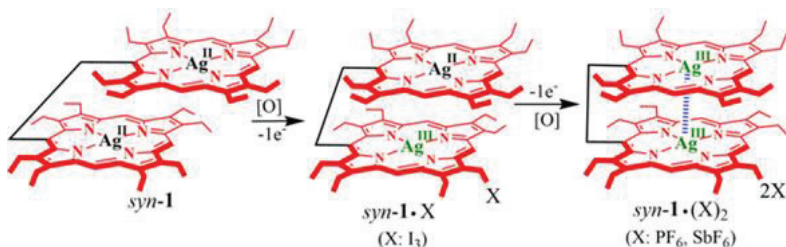
Although +III is an unusual oxidation state for copper, it has been reported several times recently.²⁵⁻²⁶ In particular, chelating cyclic NHC or pyridine-containing ligand systems are suitable for this purpose. Meyer *et al.* have isolated copper complexes in +I, +II and +III oxidation states by stepwise oxidation of Cu(I), which is depicted in Scheme 1.²⁷ Copper in the +IV oxidation state is poorly known and was first reported in the octahedral complex Cs₂[CuF₆] by Hoppe *et al.* in 1988 which is structurally analogous to K₂[PtCl₆].²⁸



Scheme 1: Systematic oxidation of a copper(I) ion in a pyridyl-NHC ligand system published by Meyer *et al.* Adapted with permission from John Wiley and Sons (license number 5521800347289).²⁷

The next heavier congener of group 11 elements, silver, occurs naturally in the form of pure silver or predominantly in the form of sulfide ores. Raw silver can be extracted from the latter, for example, by cyanide leaching, and subsequently can be purified electrochemically. Similar

to its lighter homologue, silver also occurs in the oxidation states from +I to +III. However, unlike copper, the +I oxidation state is the most stable for silver. In addition, low-valent compounds with oxidation states <1, for example, in silver subfluoride Ag_2F , are also known.²⁹ The monovalent silver cation usually prefers a linear or tetrahedral geometry.²² However, in recent times, several silver complexes with trigonal planar³⁰⁻³¹ and octahedral geometry³² were also reported. The +II and +III oxidation states are also unusual for silver but can be stabilized with, for example, nitrogen-containing cyclic ligands.³³ Rath and co-workers successfully isolated silver in the +III oxidation state by stepwise oxidation using porphyrin-based ligands. Apart from that, they also reported the existence of d^8-d^8 argentophilic interactions between silver cations.³⁴⁻³⁵



Scheme 2: Schematic representation of stepwise oxidation of silver cation in the porphyrin rings reported by Rath and co-workers. Adapted with permission from John Wiley and Sons (license number 55224006237359).³⁵

Gold occurs in nature mainly in the native state, for example, in gold-bearing quartz SiO_2 and pyrite FeS_2 . Common extraction processes of gold include amalgamation or cyanide leaching. The obtained gold is further purified electrochemically to isolate pure gold.²² The physical and chemical properties of gold are sometimes very different from those of its lighter homologues, silver and copper.³⁶ Some of the exceptional properties can be rationalized when considering the influence of relativistic effects, which become more important in the periodic table as the atomic number increases. Approximately, the relativistic effects increase in proportion to the square of the atomic number, but only become noticeable for elements heavier than the lanthanides. For a simplified understanding of the effect, an electron is considered as a particle. According to Einstein's theory of relativity, with increasing atomic number, the *s*-electrons near the nucleus move at higher velocities, in the case of gold at about 58 % of the speed of light resulting in an increase of relativistic mass by 22 %.³⁶⁻³⁷

$$m_{rel}(v) = \frac{m_0}{\sqrt{1 - \frac{v^2}{c^2}}}$$

where m_{rel} - relativistic mass, m_0 - rest mass, v - velocity of the particle and c - speed of light.

This reduces the radius of the 1s orbital, by the same factor according to the following formula

$$a_0 = \frac{4\pi\epsilon_0\hbar^2}{m_e Z e^2}$$

where a_0 - Bohr's radius, ϵ_0 - the electric field constant in vacuum, $\hbar = (h/2\pi)$ - reduced Planck's quantum of action, m_e - the electron mass, Z - the nuclear charge number and e - the elementary charge.

All the higher-lying s-orbitals up to the valence shell contract in a similar way. The electrons in the p orbitals are also affected by this effect, however, to a lesser extent. This contraction of the orbitals close to the nucleus is referred as the direct relativistic effect. As a consequence of s- and p- orbital contraction, the nuclear charge is better shielded, leading to an expansion and concomitant destabilization of the d and f orbitals. This effect is termed as the relativistic expansion or indirect relativistic effect.³⁸⁻³⁹ This leads to the fact that the 6s-electrons have an increased ionization energy, compared to the non-relativistic case, and are thus relatively inert. Therefore, this effect is referred as the "inert-pair effect".⁴⁰

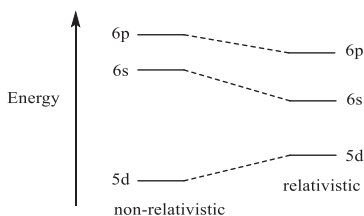


Figure 4: Schematic representation of the influence of relativistic effects on the energetic position of the gold atomic orbitals.³⁹

These relativistic effects have a strong influence on the properties of gold. One of the most obvious effects is the characteristic color of metallic gold. In the non-relativistic case, the excitation energy starting from the 5d band into the half-filled 6s band (Fermi level) would be about 3.6 eV, which is in the ultraviolet region of the light spectrum. This would result in visible light being mainly being reflected and the metal would have the typical white-gray color, such as silver. However, the excitation energy decreases to about 2.4 eV because the relativistic effects destabilize the 5d orbital and stabilize the 6s orbital (Figure 4).⁴¹ This energy

corresponds to the wavelength of blue-green light, so the red and yellow colors are strongly reflected, giving the metal its golden color.¹⁰

Although gold is characterized by the highest standard potential of the coinage metals, it shows diverse redox chemistry. Besides elemental gold, +I and +III are the most stable oxidation states. The destabilization of 5d orbitals, as explained above, also enables access to the higher +IV and +V oxidation states.⁴²⁻⁴³

With the electron configuration $[\text{Xe}]4f^{14}5d^{10}$, the Au(I) cation has a closed valence shell and usually prefers near-linear coordination. For several years, molecular gold(0) compounds have been the focus of research. Their preparation has proved to be a significant synthetic challenge due to their tendency to agglomerate, resulting in the formation of nanoparticles.⁴⁴ The CAAC ligands used to stabilize copper in zero oxidation state were also employed to access mononuclear and dinuclear gold complexes in zero oxidation state. This work was reported by Bertrand and co-workers and the structures are depicted in Figure 5.⁴⁵

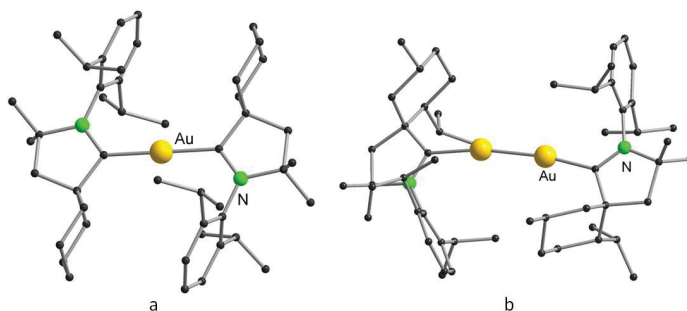


Figure 5: a) Mono- and b) dinuclear gold complexes with gold in the oxidation state zero.⁴⁵

Due to the disproportionation of gold into the more stable oxidation states +I and +III, only handful of works are reported with divalent gold. One of the earliest divalent gold compounds was published by Schröder and co-workers in 1990 with gold in an octahedral environment surrounded by two bis(1,4,7-trithiacyclononane) ligands.⁴⁶ The cationic complex is presented in Figure 6a. This work was followed by the well-known first gold(II) xenon compound $[\text{AuXe}_4]^{2+}([\text{Sb}_2\text{F}_{11}]^-)_2$ which was reported by Seppelt and Seidl in 2000.⁴⁷ In recent times, Heinze *et al.* successfully proved that porphyrins could be potent ligands to stabilize gold in +II oxidation state (Figure 6b).⁴⁸

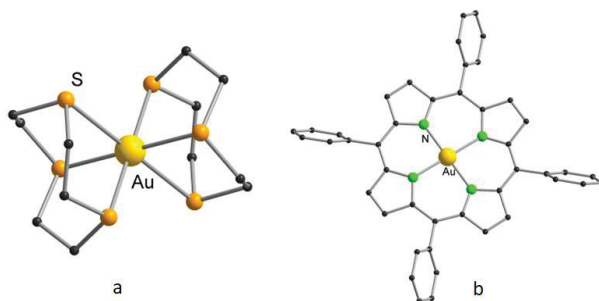


Figure 6: Molecular structures illustrating the divalent gold complexes a) $[\text{Au}(\text{bis}(1,4,7\text{-trithiacyclononane}))]^{2+}$ and b) $[\text{Au}(\text{meso-tetraphenylporphyrin})]$.^{46,48}

Due to its high electron affinity, gold is also known in the -I oxidation state, which is obtained, for example, in the presence of strong reducing agents such as cesium.⁴⁹⁻⁵⁰ However, the first example of a nucleophilic molecular gold complex was only reported recently in 2019 by Goicoechea and Aldridge *et al.*⁵¹ The molecular gold complex was synthesized using a NON ligand, where NON is 4,5-bis(2,6-diisopropylanilido)-2,7-di-*tert*-butyl-9,9-dimethylxantheno and the molecular structure is displayed in Figure 7a. Further, they have also explored its reactivity. For example, when the complex was reacted with carbon dioxide, the CO_2 moiety inserts between the gold and the aluminium bond (Figure 7b).⁵¹

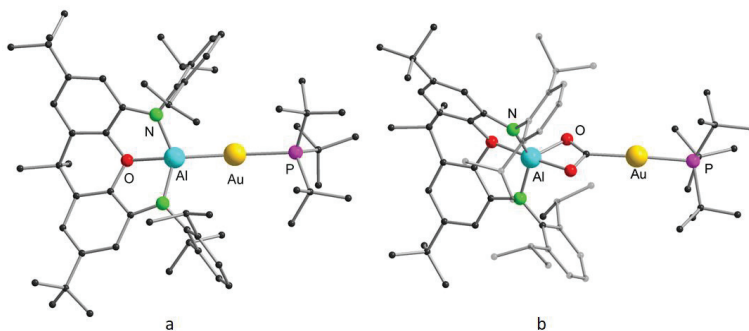


Figure 7: a) Nucleophilic gold complex reported by Aldridge and co-workers and b) gold complex with a CO_2 moiety inserted between Al-Au bond.⁵¹

1.1.3 Metallophilicity

The term “metallophilicity” or “metallophilic interactions” was coined by Pyykkö in 1994 and generally refers to the propensity of metal atoms to come into close proximity to each other where the distance between the metal centers is less than the sum of their Van der Waals

radii.⁵² With the advent of single crystal X-ray diffraction (SCXRD) for structure elucidation in chemistry, many compounds with these closed shell interactions that were not compatible with the previously established understanding of chemical bonding were discovered. Although no interactions were expected for closed-shell systems and two cations repel each other according to Coulomb's law, stabilization of metal cations in spatial proximity, often below the sum of van der Waals radii, was observed. The metallophilic interactions are now commonly reported among metals with d^{10} - d^{10} , d^{10} - d^8 , and d^8 - d^8 electronic configurations.⁵³⁻
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Mostly, these interactions were reported for gold(I) cations with d^{10} electronic configuration, which can be traced back to the early 1970s. Later, in 1988, these interactions were termed "aurophilic" interactions by H. Schmidbaur when the Au-Au separation is below 3.5 Å.⁵⁹⁻⁶⁰ Depending on the distance r , these are of the order of strong hydrogen bonds.

$$D_e = 1.27 \cdot 10^6 \cdot \exp(-3.5 r_{Au-Au}),$$

where D_e - Interaction energy in kJ/mol; r_{Au-Au} - equilibrium distance in Å.⁶¹

According to this formula, with a gold-gold distance of $r_{e^{Au-Au}} = 3.0 \text{ \AA}$, a binding energy of about 35 kJ mol⁻¹ is expected.⁶¹

The cause of these aurophilic interactions is now mainly attributed to van der Waals interactions between gold metal centers, but these are particularly pronounced because of the strong relativistic effects. One of the main indicators for this is that they follow the laws of the London dispersion force, according to which the force field between neighboring particles decreases with the sixth power of the distance.⁶²⁻⁶³ Furthermore, the literature contains arguments stating that aurophilicity is a combination of relativistic and correlation effects, in which an ionic contribution is also assumed in addition to exclusively dispersive interactions.⁶⁴⁻⁶⁶ It should be noted that for theoretical calculations, dispersion, induction, electrostatic, and di- or multipole interactions must be included, which are equally dependent on the symmetry and nature of the neighboring atoms as ligands.⁶⁷⁻⁶⁸ Therefore, to describe and analyze metallophilic interactions, the entire system must always be considered; focusing on the metals is insufficient.

Metallophilic interactions between other congeners of group 11 have been widely reported in recent times.⁶⁹⁻⁷⁰ Attractive interactions between silver(I) cations are referred to as

“argentophilic” interactions when the distance between the cations is less than 3.4 Å, and their strength is similar to that of aurophilic interactions.⁷¹ Among the group 11 metals, the weakest metallophilic interactions are observed for copper cations. These are known as “cuprophilic” interactions ($r_{(\text{Cu-Cu})} < 2.8 \text{ \AA}$), and their strength is approximately 15 kJ/mol.⁷²⁻⁷³

1.2 Photoluminescence

1.2.1 Fluorescence, phosphorescence and thermally activated delayed fluorescence (TADF)

Absorption of light promotes a chemical system into a higher energy excited state from which relaxation back to the ground state can occur *via* radiative or non-radiative pathways. Mechanisms for radiative decay include fluorescence, phosphorescence or thermally activated delayed fluorescence (TADF).⁷⁴ Such emission processes can be described using a Jablonski diagram (Figure 8). Apart from the radiative processes, the excited molecule can also undergo non-radiative transitions. This proceeds either by internal conversion (IC) from the first excited electronic singlet state, S_1 or by intersystem crossing, starting from the first excited electronic triplet state, T_1 , into excited vibrational states of the electronic ground state, S_0 , followed by vibrational relaxation (VR). The VR is caused, for example, by collisions with other molecules, such as solvent molecules. The efficiency of photoluminescence is defined as the ratio of radiative and non-radiative deactivation and is also referred to as quantum yield or quantum efficiency.⁷⁵

Fluorescence was first observed by Sir John Frederick William Herschel in a quinine solution in 1845, which emits blue color upon UV irradiation.^{74,76} Fluorescence occurs when a molecule absorbs light with suitable energy, promoting an electron from S_0 into S_1 (in principle, an excitation into higher vibrational states, e.g. S_2 , can also take place) which is followed by the relaxation of the excited molecule to the lowest vibrational level of S_1 on a timescale of 10^{-11} - 10^{-13} s by vibrational relaxation and subsequently, fluorescence occurs by emission of photons on a time scale of 10^{-8} - 10^{-9} s. The energy released in this process corresponds to the difference between the relaxed excited state and the excited vibrational levels of the ground state.