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The Potential of Organometallic Complexes for Medicinal Chemistry

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Abstract

Organometallic complexes have unique physico-chemical properties, which have been widely used in homogenous catalysis, e.g. for the synthesis of lead compounds and drug candidates. Over the last two decades, a few scientists from all over the world have extended the use of the specific characteristics of these compounds (e.g. structural diversity, possibility of ligand exchange, redox and catalytic properties) for medicinal purposes. The results are stunning. A few organometallic compounds have already entered clinical trials and it can be anticipated that several more will follow in coming years. In this short review, we present the specific advantages that organometallic metal complexes have over purely organic and also coordination compounds. Furthermore, using specific examples, we illustrate how these particular properties can be put to good use in medicinal chemistry. The examples we present have an emphasis on, but are not restricted to, anti-cancer activity.

Introduction

Chemists and their compounds are without any doubt contributing tremendously to the breathtaking progress of medicine. A view at the periodic table reveals that there are 82 non-radioactive elements, of which more than 60 easily form air- and water-stable covalent, molecular compounds that could potentially be useful in medicinal chemistry. The great majority of all drugs, however, contain only ten of those >60 elements. Notably, very few drugs or drug candidates exist that contain any of the transition metals other than platinum.[1,2] On the other hand, it is obvious that organometallic chemistry, which can be classified as the chemistry studying chemical compounds containing at least one metal-carbon bond, is currently much more known for its many applications in catalysis, rather than for applications in medicine. Although the attention given to *medicinal organometallic chemistry,* which can be defined as the research field involving the use of organometallic compounds for medicinal purposes, has steadily grown over the last years, the importance and reputation of this area of research are still negligible compared to those of catalysis or even biosensing.[3]

We hope to demonstrate to the readers of this article that organometallic compounds possess remarkable physico-chemical properties, which are rather unique and of high interest in a medicinal chemistry context. As described in more detail below, spectacular advances have been recently made in this field of research despite only "polite" interest from both the pharmaceutical industry and academia. A few organometallic compounds have even entered into clinical trials and *metal-specific modes of action* have been lately uncovered![4] Importantly, these compounds have the potential in various areas of medicine to serve as anticancer, antimalarial, antimicrobial or diagnostic agents.

In this contribution, we will not review all the latest developments in medicinal organometallic chemistry as this has been recently performed.[5-9] We will rather highlight the specific properties / advantages (e.g. structural diversity, possibility of ligand exchange, redox and catalytic properties, etc...), that organometallics have over purely organic compounds and exemplify them with one or two concrete examples.

Structural Diversity

A carbon atom with four different substituents may occur in two different enantiomers, which are not superimposable. In contrast, an octahedral transition metal complex with six substituents has 30 different stereoisomers! If we take the central atom (carbon or transition metal) simply as a template that will orient its substituents in three-dimensional space then clearly, the structural diversity in typical transition metal complexes exceeds that of purely organic compounds. Parallel to organic compounds, racemization is unlikely to occur in kinetically inert transition metal complexes, i.e. the positioning of the ligands around the metal center must be stereochemically stable. This requirement is not equally well met by all transition metals, and conformational stability may in addition be a function of the oxidation state of the metal. In general, transition metals of the second and third row with closed electron shells are most suited, such as Ru(II), Os(II) or Ir(III) and therefore have been most frequently used in medicinal inorganic chemistry when structurally rigid compounds were required.

Meggers and coworkers have used structurally inert Ru(II) complexes to design inhibitors of protein kinases.[10-12] These proteins are known to have a multitude of important functions in the body and are therefore valuable targets to modify e.g. signalling pathways within malignant cells. This work was inspired by the natural product staurosporin, which inhibits kinases by competitively binding to the ATP binding site. Figure 1 depicts the similar binding mode of metallo-pyridocarbazole complexes to the ATP binding site, and the structure of one Ru-based metal complex **1** (FL-411) as an example. Generally, the Ru-containing degradation products are assumed to have a low metal-based toxicity and the synthetic chemistry of these complexes is very well established, giving access to a huge variety of compounds. This provides great opportunities for the design of selective kinase inhibitors, which should target one of the 518 different kinases that are encoded in the human genome.[13] To date, almost a dozen co-crystal structures with metal complexes as inhibitors provide an excellent structural basis for the remarkable selectivity of the identified metal complexes, some of which have as low as pM affinity to one specific kinase *in vitro*. Since the Ru complexes described above are generally

stable to air and water, and even withstand exposure to mM concentrations of biological ligands such as glutathione, they can readily be tested *in vivo*. For example, the effect of inhibiting the kinase GSK-3 with complex **2**, which in turn switches on the wnt signalling pathway, has been demonstrated *in vivo* by the development of a hyperdorsalized phenotype in *Xenopus laevis* embryos.[14] Intriguingly, almost exactly the same anti-proliferative activity is observed for the complex DW12(Ru / Os) regardless of whether the central atom is Os or Ru.[15] This nicely emphasizes the purely structural role played by the metal centres in such complexes.

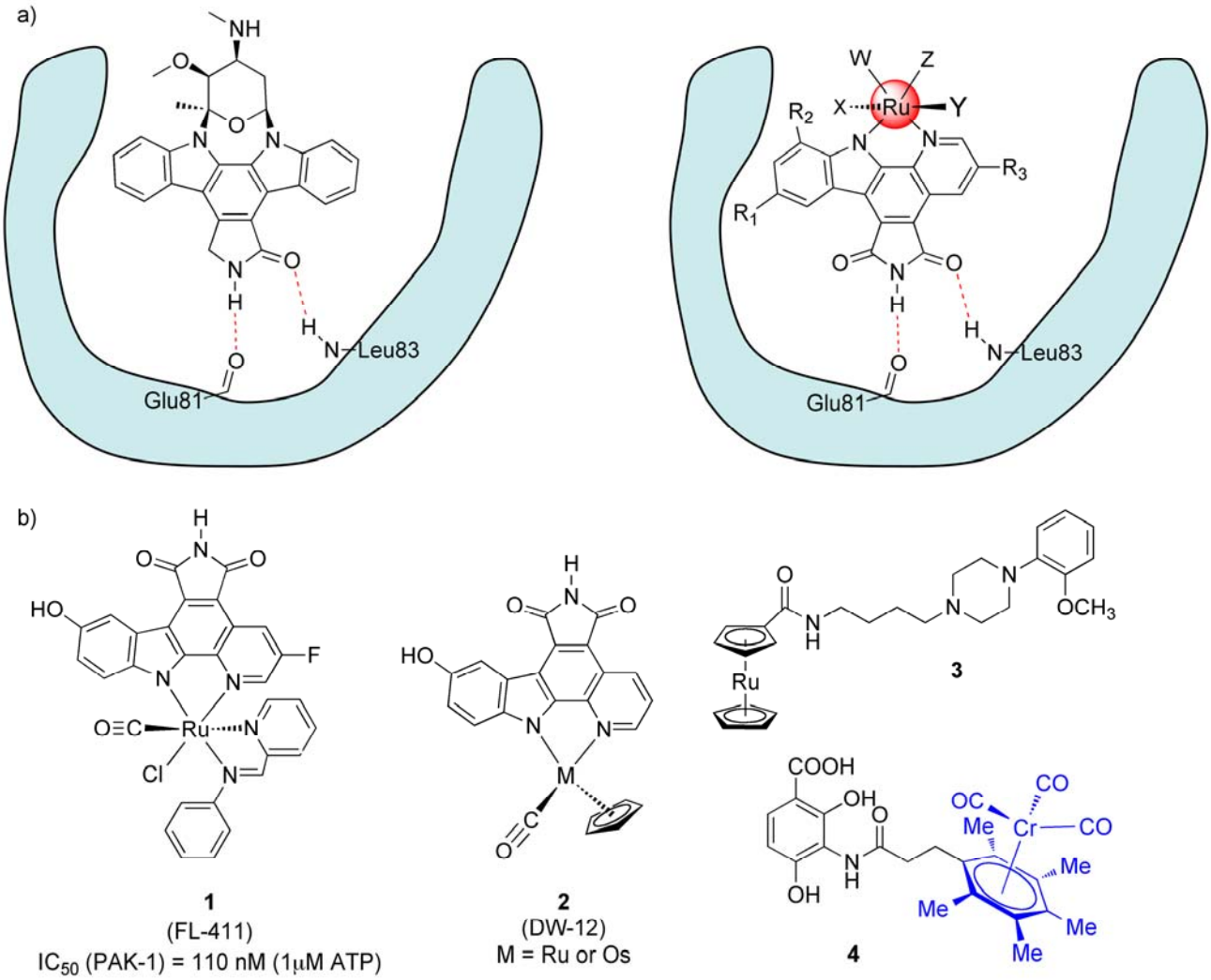


Figure 1. a) The binding motif of the natural product staurosporine to the ATP binding site in kinases (magenta), and the binding of octahedral metal complexes to the same site. b) Two metal-based kinase inhibitors from Meggers' group (**1** and **2**), a dopamine D4 subtype-specific agonist containing a

ruthenocene (**3**), and a chromium-containing platensimycin analogue (**4**). In **4**, the chromium tricarbonyl moiety in blue replaces a multi-cyclic organic group with six stereocenters.

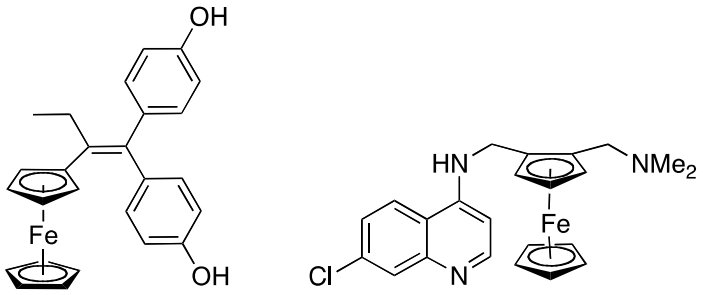
The concept of bio-isosteric replacement of organic groups with metal complexes has been used in other fields of medicinal organometallic chemistry as well. First, Gmeiner's group has exploited organometallic Ru complexes for dopamine receptor targeting. They found that a ruthenium metallocene derivative **3** (Figure 1) has a nM affinity for the G-protein coupled receptors such as dopamine and serotonin receptors, and provides unique D4-selective agonist properties.[16] In our work, different organometallic complexes were used as organometallic analogues of platensimycin, an interesting natural compound with anti-bacterial activity. The antibacterial activity of platensimycin is attributed to inhibition of fatty acid biosynthesis in bacteria, especially inhibition of FabF and FabH enzymes. While a range of ferrocene derivatives provided interesting insights into structure-activity relationships (SAR),[17,18] an arene chromium tricarbonyl derivative (**4**, Figure 1) was the most active compound.[19] Molecular docking experiments showed this compound to fit well into the active pocket of the FabF enzyme. Proteomic studies, on the other hand, indicated a mechanism of action for **4** that is different from inhibition of fatty acid biosynthesis and as yet has not been linked to a single molecular target.[20]

Redox Properties

In the previous section, we discussed metal complexes which were completely inert, and in which the metal center had a purely structural role. However, many metal complexes will readily undergo electron transfer reactions, as it is well known for many enzymes and cofactors, e.g. cytochromes and the Fe-S clusters. It has only recently been realized that such redox activity may be highly beneficial for the medicinal activity of the metal complex.

One prominent example comes from Jaouen's group. Using the idea of a "bio-isosteric" replacement of phenyl rings with metallocene fragments, they produced a series of derivatives of the well-known anti-cancer drug tamoxifen.[21] While most derivatives were rather inactive, the ferrocene derivatives (later called "ferrocifens", see compound **5** in Figure 2 as an example) did not only show an activity comparable to tamoxifen itself, but some additional, remarkable features.[22] Tamoxifen is the first-line treatment for breast cancer. The drug binds competitively to the estrogen receptor α subtype (ERα), thereby repressing estradiol-mediated DNA transcription in tumor cells. It follows that tamoxifen and related compounds will only be active against those types of breast cancer which overexpress the ERα. Unfortunately, this is not the case for about one third of all breast cancer patients and indeed, those without ERα overexpression have a significantly worse prognosis. Much to the surprise of the researchers, certain ferrocifens were similarly active against all breast cancer cell lines, including the ERα-negative ones. Careful further experiments revealed that the activity is linked to reversible redox behaviour of the iron center in these compounds. A mechanism was proposed by which oxidation of Fe(II) to Fe(III) in the ferrocene core initiates proton-coupled electron abstraction in the organic part, eventually leading to oxidation of the phenolic part to a quinone methide.[23] Already in tamoxifen, the formation of quinone methides, which are thought to react with thiols and nucleobases *in vivo*, has been proposed as vital for activity of the drug. Because of the fast and reversible formation of Fe(III) species, the metallocene is thought to act as a "redox antenna", thereby offering an alternative mode of action for the ferrocifens beyond estrogen receptor binding.[24]

Interesting experimental support for this proposal comes from Ru analogues of ferrocifen. These compounds do exhibit tamoxifen-type activity against ERα-positive cancer cells, but like tamoxifen itself are inactive against ERα-negative cell lines. While the overall size and shape of ruthenocene is indeed very similar to ferrocene, its electrochemistry is drastically different, with higher redox potential and most importantly, no reversibility for the electron transfer reaction. Hence, in contrast to the kinase inhibitors described above, where exchanging structurally similar metal ions supports the notion of a purely structural role for the metal ions, the ferrocifen story provides an example where indeed redox activity of the metal is crucial, and iso-structural replacement of metal ions may indeed kill the activity of the compound if it alters the redox properties of the compound.[25]



5 **6**

Figure 2. An active and more versatile analogue of the anti-tumor drug tamoxifen (ferrocifen, **5**), and ferroquine (**6**), an anti-malarial drug candidate in clinical trials that does not develop cross-resistance with chloroquine.

It seems that redox activity of iron in a ferrocene derivative also plays a role in an analogue of the well-known anti-malarial drug candidate chloroquine, namely ferroquine **6** (Figure 2), although other factors seem to play a role as well. The reader is referred to a rather comprehensive recent article on ferroquine, which at the moment is the most advanced organometallic drug candidate, soon to enter clinical phase III trials.[26]

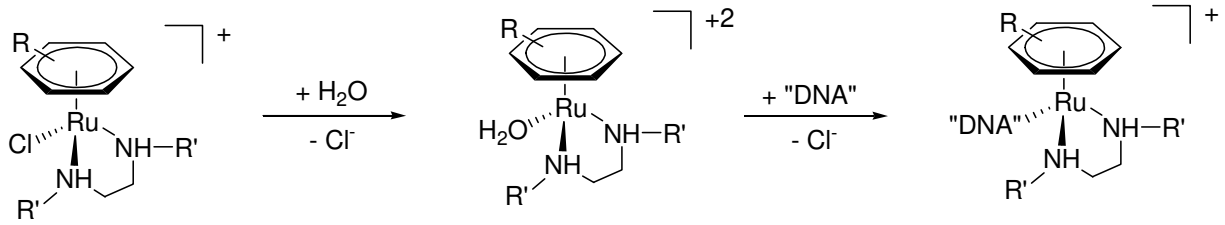
Ligand Exchange

The ability of metal complexes to undergo ligand exchange "for medicinal purposes" is notorious and cisplatin is probably the best example to illustrate it.[27,28] This aptitude towards ligand exchange is not limited to coordination complexes alone. Organometallic compounds can undergo a similar ligand exchange. As outlined below, this leads to applications in diverse areas of medicinal chemistry, but predominantly for the preparation of novel chemotherapeutic agents. Indeed, several organometallic compounds are thought to exert, at least partially, their antiproliferative activity through a ligand exchange mechanism.[3,6,29-31] In this section, we will only highlight two examples where the cellular targets of the organometallic anticancer compounds are different despite the fact that the mode of action of both derivatives seems to involve a related ligand exchange process. To date, besides the ferrocifens mentioned above,[22] organogold compounds [32] and titanocene derivatives,[33] the most studied examples of organometallic anticancer compounds are Ru-arene derivatives. These compounds are developed independently by the Sadler[34] (Scheme 1a) and Dyson[35] (Scheme 1c) research groups. Interestingly, despite their strong structural resemblance and the ability of both derivatives to (potentially) undergo ligand exchange, it is believed that these two types of half-sandwich "piano-stool" organometallics have a very different mechanism of action. The one for compounds of the type $[(\eta^6\text{-arene})Ru(en)(Cl)]^+$ (en = ethylenediamine) is reminiscent of that of cisplatin and involves, first, the substitution of the chloride anion by a water molecule (Scheme 1a). The new aqua species formed then binds to nuclear DNA with a high affinity for the N7 position of guanine bases.[3,36-38] The similarity to the mode of action of cisplatin stops at this point as only monoadducts with DNA can be formed with these derivatives, contrasting to cisplatin which forms bifunctional adducts and DNA cross-links. It is also important to highlight the fact that these $[(\eta^6\text{-arene})Ru(en)(Cl)]^+$ derivatives are active against cisplatin-resistant cell lines suggesting that at least the detoxification mechanism is different that of cisplatin.[3,39] By comparison, the *in vivo* behaviour of RAPTA-C and RAPTA-T (RA stands for Ruthenium-Arene and PTA for the 1,3,4-triaza-7-phosphatricyclo-[3.3.1.1]decane

ligand, see Scheme 1c) is strongly different. They can indeed selectively reduce the weight and number of lung metastases of CBA mice bearing the MCa mammary carcinoma with only mild effects on the primary tumour. Interestingly, hydrolysis does not seem to be required for these compounds to exert their activity, although ligand exchange still occurs and seems to contribute to their cytotoxic activity. It has been indeed demonstrated that even in blood plasma, where the chloride concentration is high enough to avoid the hydrolysis of the dichloride-containing RAPTA compounds, these Ru complexes bind to serum protein.[30] Other experimental observations provide strong evidence that the hydrolysis step is not required: RAPTA compounds, whose chloride ligands have been replaced with dicarboxylate ligands and which resist hydrolysis (e.g. oxalo-RAPTA-C in Scheme 1c), still exerts a similar *in vitro* activity as the parent compound RAPTA-C! All evidence taken together, it is now thought that RAPTA complexes bind not to DNA but rather to proteins and particularly to cathepsin B (cat B) by different interactions, notably by binding to the sulphur atom of a cysteine present in the active site of the enzyme (Scheme 1b). It seems that the particular properties of the PTA ligand do also contribute to these notable differences.

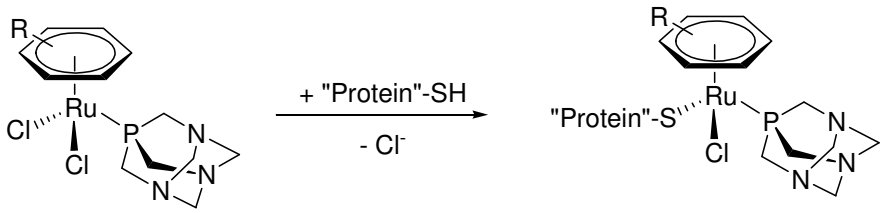
It is worth mentioning that the ability of organometallics to undergo ligand exchange has found application in areas other than chemotherapeutic treatment. Hence, different metal (e.g. Au, Ag, Rh and Ru) carbene compounds have very promising antimicrobial activity.[40-43] All in all, the examples shown above demonstrate clearly that organometallic compounds possess outstanding properties to be used in medicinal chemistry development due, notably, to their ability to strongly bind target through a coordinative bond.

a)



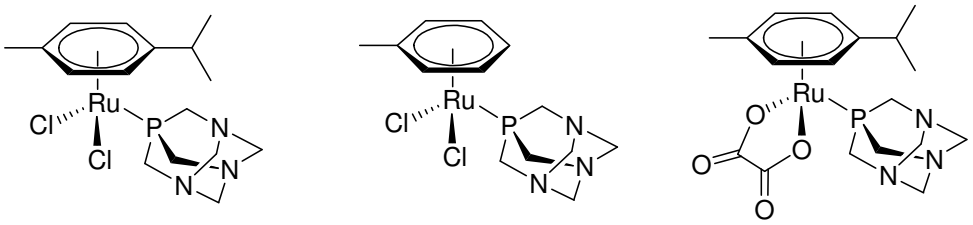
Ru^{II} arene ethylenediamine derivatives

b)



RAPTA Derivatives

c)



RAPTA-C **RAPTA-T** **oxalo-RAPTA-C**

Scheme 1. a) Simplistic representation of the mechanism of action of Ru^{II} arene ethylenediamine and b) RAPTA derivatives, highlighting the different biological targets of the two types of compounds; c) Structures of RAPTA-C, RAPTA-T and oxalo-RAPTA-C.

Beside the examples described above, the ability of organometallics to undergo ligand exchange can lead to further interesting applications in medicine. Indeed, instead of exchanging a "useless" ligand (e.g. Cl^-, etc...) by a biomolecule (e.g. DNA, protein, etc...) to form a novel metal adduct, which will interrupt the proper function of this precise biomolecule, the released ligand can be actually a molecule

with a medicinal effect of its own, as for example, carbon monoxide (CO).[44] Indeed, despite its bad reputation as the “silent killer", the beneficial therapeutic effects of CO as a small messenger molecule similar to NO are extremely diverse. They include, for example, the reduction of inflammation, the suppression of organ graft rejection or the protection of the heart during reperfusion after cardiopulmonary bypass surgery.[45-47] Naturally, the use of gaseous CO causes obvious problems linked to its safe handling as well as its selective and specific delivery to a specific part of the body.[47] CO-releasing molecules, often abbreviated CORMs, are therefore an attractive alternative to the administration of CO gas. However, as emphasised by Motterlini and Otterbein in 2010, the chances to see any of the CORMs reported so far to reach the clinic are low.[46] These compounds lack the drug-like properties necessary for a pharmaceutically acceptable medicine.[46] In this context, Zobi *et al*. envisaged the use of cyanocobalamine (vitamin B_{12}) as a biocompatible scaffold for rhenium-containing CORMs. An important argument for the use of such organometallic complexes is that the resulting oxidised product after CO release, namely rhenium pertechnetate ReO_4^-, is one of the least toxic of the rarest inorganic compounds.[47] Their two Re-vitamin B_{12} bioconjugates (e.g. **B_{12}-$ReBr_2(CO)_2H_2O$**, Figure 3) were shown to have favourable half-lives for biological/medicinal applications and to protect heart tissue from ischaemia-reperfusion injury.[47] As outlined by the authors, all Re bioconjugates in this paper have better features than their parent complexes.[48] They are more water soluble, more stable in aqueous aerobic media and biocompatible.[47] Furthermore, the therapeutic potential of these compounds seems extremely large. As Vitamin B_{12} is stored and processed in the liver, one could think that these rhenium bioconjugates could be useful for the treatment of liver inflammation. They could also be given to patients with liver transplants as it has been shown that CO helps to suppress organ rejections.[45,46]

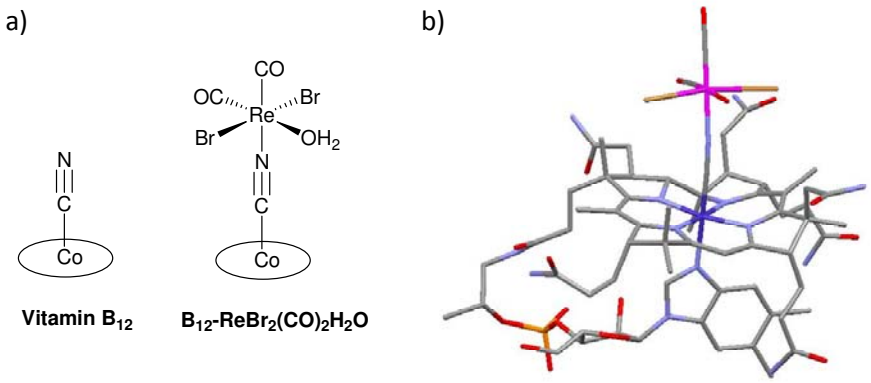
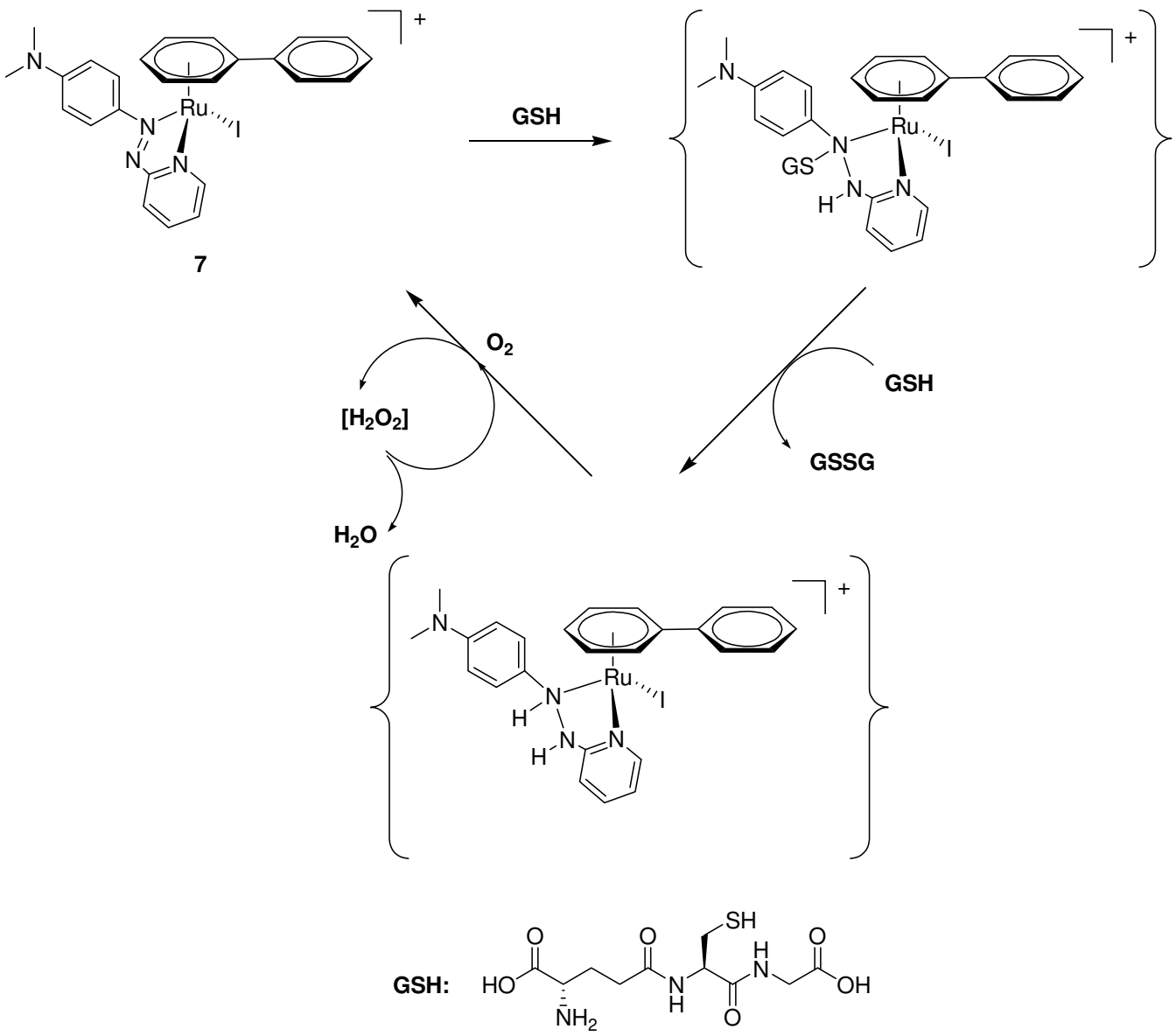


Figure 3. a) Schematic structures of vitamin B_{12} and its rhenium complex **B_{12}-$ReBr_2(CO)_2H_2O$**; b) DFT calculated structure of **B_{12}-$ReBr_2(CO)_2H_2O$.** H atoms are omitted for clarity. Line drawing structure created from data provided by Dr. Fabio Zobi with the help of the Mercury Program.

Catalytic Properties

A physico-chemical property of organometallic compounds which has been certainly, up to now, underestimated for its potential in medicinal chemistry and chemical biology is the ability of such derivatives to catalyse chemical reactions. In this perspective, the recent results obtained by Sadler and co-workers with half-sandwich "piano-stool" ruthenium arene complexes are definitively a step forward towards the design of catalytic drugs. Indeed, they found that relatively hydrolytically inert Ru organometallics complexes such as **7** (Scheme 2) were still highly toxic towards human ovarian A2780 and human lung A549 cancer cells.[49] The mechanism of action of these compounds has been associated with an increase of reactive oxidative species (ROS). The authors have proposed a redox catalytic cycle involving gluthatione attack on the azo bond of coordinated azopyridine to explain the cytotoxic effect of these Ru complexes (Scheme 2).[49] Of note, the azopyridine ligand alone is difficult to reduce. However, upon coordination to the Ru centre, the reduction potential of the ligand becomes biologically accessible. It should also be pointed out that the ferrocenyl moiety of the antimalarial compound ferroquine (see above) has been also found to be responsible of the formation of ROS. All in all, we strongly believe that these examples will pioneer a new area in the design of organometallic anticancer compounds.



Scheme 2. Proposed redox catalytic cycle explaining the cytotoxic effect of inert Ru-arene complexes using **7** as an example. Scheme adapted from ref.[29,49].

Conclusions

Although spectacular advances have been recently made in medicinal organometallic chemistry, we do think that the full potential of these compounds has not yet been realized. One area which was not mentioned above is metal-based radiopharmaceuticals. Across the periodic table, several isotopes exist of all transition metals, of which some can be used for both radioimaging and radiotherapy.[50] Even beyond radiopharmaceuticals, it seems that the specific properties of organometallic drug candidates have by far not been fully exploited. Organometallics provide a great structural variety (ranging from linear to octahedral and even beyond) and a far more diverse stereochemistry than organic compounds, as described in the section on structural variations above. Rational ligand design offers to the medicinal chemist control over kinetic properties, such as the rate of ligand exchange (see above). Furthermore, they are kinetically stable, usually uncharged with the metal atom in a low oxidation state, relatively lipophilic, and amenable to a host of standard chemical transformations. Once the full potential of organometallics unfolds in the hands of medicinal chemists, we can expect some further stunning discoveries, which, once translated into drugs, will ultimately benefit patients as well.

Acknowledgments

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