

Activation Mechanisms for Organometallic Anticancer Complexes

Ana M. Pizarro, Abraha Habtemariam, and Peter J. Sadler

Abstract Organometallic complexes offer potential for design as anticancer drugs. They can act as inert scaffolds and specifically inhibit enzymes such as kinases, or as pro-drugs which undergo activation by various mechanisms. The activation of metallocenes, arene, alkyl or aryl complexes by hydrolysis, and metal- or ligand-based redox reactions is discussed.

Keywords Medicinal Organometallics · Photoactivation · Hydrolysis · Anticancer · Titanium · Ruthenium · Osmium · Ferrocene · Tin

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1 Introduction

Metal-based pharmaceuticals offer unprecedented versatility in medicinal chemistry because of the different building blocks from which they can be constructed, the variety of available interactions (H-bond, π -stacking, coordinative bond, spatial recognition), the combination of rigidity around the metal and flexibility in the ligands, the kinetics of ligand substitution when coordinative bonds with biomolecules are formed and because of their redox properties.

Recently, the benefits of these properties in medicinal chemistry have begun to emerge. The misconception that organometallic complexes lack stability under conditions in which living organisms thrive, has been one reason why they have not been considered as suitable candidates as pharmaceuticals until quite recently. However, in the last decade there has been a flurry of activity with regard to the development of organometallics in a biological context [1]. Organometallic complexes which are stable in physiological environments are now being developed as, for example, anticancer agents, radiopharmaceuticals for diagnosis and therapy, and biosensor probes.

Achieving aqueous stability is a prerequisite for metal-based drugs, as lack of control of speciation makes pharmacokinetic studies difficult, thus hindering, or, even excluding, progress towards clinical development. Titanocene dichloride (**1**) was the first organometallic anticancer drug to reach phase II trials. Its withdrawal from clinical evaluation epitomises the stability challenge which is inherent in organometallic complexes. The complicated hydrolysis of titanocene dichloride at physiological pH has made characterisation of the active species responsible for antitumour activity difficult. At pH values above 4, loss of the Cp ligands results in the formation of insoluble Ti oxo species [2, 3]. From this point of view, the development of organometallic drugs which can be activated in a controlled manner towards specific targets, with well characterised speciation behaviour, is of paramount importance.

In this chapter, we classify organometallic complexes with cytotoxic activity against cancer cells with regard to the chemical-physical processes that activate them towards interactions with biological targets. As we have noted previously in a classification of the biological activity of metal complexes [4], the activity can depend intimately on the metal and some or all of its ligands as an intact complex or fragment, on the metal itself and on the ligands themselves. This classification has recently been elaborated upon by Alessio and co-workers for both organometallic and coordination complexes [5].

In the emerging field of medicinal organometallic chemistry, various strategies for the activation of complexes have been employed. These can facilitate interactions with biomolecules either through the incorporation within the structure of a known pharmacophore, thus altering the reactivity profile of the organometallic fragment and thereby delivering enhanced cytotoxicity, or through the inclusion of labile groups with favourable ligand substitution characteristics. For example, for

complexes containing a labile group prone to substitution, such as the Ru arene piano stool complexes of the type $[\text{Ru}(\eta^6\text{-arene})(\text{XY})(\text{Z})]^{\text{n}+}$ (where XY = chelating ligand, and Z = labile halide), the activation can occur through hydrolysis of the Ru–Z bond, in a similar manner to cisplatin. Hydrolysis of the Pt–Cl bond in cisplatin inside the cells, where the chloride concentration drops from ca. 100 mM to ca. 23 and 4 mM in the cytoplasm and nucleus, respectively, is believed to generate active aqua species. The aqua adduct interacts with the biological target, DNA, and the drug exerts its cytotoxic effect.

Other pathways for activating organometallic complexes towards substitution reactions may be triggered inside the cells by internal sources such as oxidation of a less labile ligand, by chelate ring-opening, and even by an external source such as light of a certain wavelength.

The strategy used by, for example, Jaouen, Meggers and Metzler-Nolte, involves enhancing the biological activity of an already-active molecule such as tamoxifen, staurosporine or aspirin by incorporating an organometallic fragment into the structure. In the case of ferrocifens, however, the metal atom has been found not to be a mere spectator, but is involved in the anticancer activity of the drug through redox activity. Finally, there are studies which use organometallic cages as delivery vehicles.

These different modes of activation of organometallic complexes for anticancer activity are now discussed in more detail.

2 Activation Through Cleavage of M–X Bonds

In this section we review organometallic complexes in which the metal plays a functional role, i.e. the cytotoxic activity is believed to derive from direct binding of a fragment of the metal complex to the biological target. For this binding to occur, one or more of the original ligands on the metal must undergo a substitution reaction. Since the biological environment of the cell is aqueous, many of these substitutions occur through hydrolysis in first place, and a second substitution replaces the bound aqua ligand by the target biomolecule. Control of drug activity and refinement of the structures for these types of complexes requires that such substitution reactions proceed in a predictable way.

2.1 Titanocenes

Titanocene dichloride, $[\text{Ti}^{\text{IV}}(\eta^5\text{-C}_5\text{H}_5)_2\text{Cl}_2]$, will be remembered in the history of metal-based drugs as a pioneer in the field of organometallic complexes with anticancer activity.

In the late 1970s, Köpf-Maier et al. investigated the antitumour activity of a series of metallocenes, and in 1979 reported in detail the antitumour activity of titanocene dichloride (**1**) [6]. This complex is active against a diverse range of human carcinomas, including gastrointestinal and breast [7]. It progressed successfully through phase I clinical trials [8, 9] into phase II.

The Ti–Cl bond in titanocene dichloride undergoes fast hydrolysis. The hydrolysed forms of the organometallic complex appear to interact with DNA [10–17], with most of the biological studies suggesting that nuclear DNA is a potential intracellular target of $[\text{Ti}(\text{Cp})_2\text{Cl}_2]$. Moreover, Ti^{IV} binds strongly to human serum transferrin and this protein could be involved in the delivery of titanium(IV) into cancer cells [18]. The mechanism of transferrin-mediated uptake of the drug may involve cleavage of the Ti–Cp bonds (in addition to the hydrolysis of the Ti–Cl bonds) and binding of the Ti^{IV} to the specific iron sites of human transferrin (hTF), yielding the adduct $\text{Ti}_2\text{--hTF}$. Titanium(IV) binds very strongly to hTF, but ATP facilitates the release of Ti^{IV} from transferrin adducts (as might happen inside cells) [19].

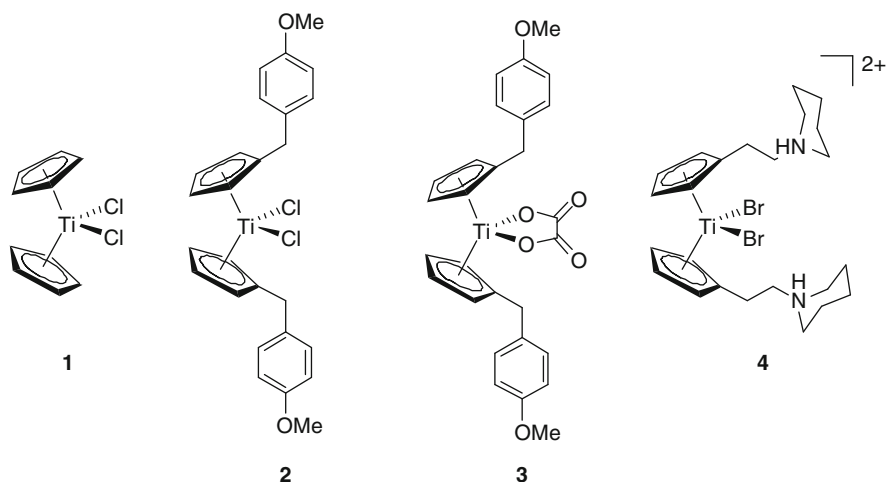
Ultimately, formulation problems as a result of rapid hydrolysis, i.e. instability, halted further evaluation of the drug [2, 20]. In addition, the efficacy rates of titanocene dichloride in Phase II clinical trials in patients with metastatic renal-cell carcinoma and metastatic breast cancer were too low to support further development [21, 22].

Although the progress of titanocene into the clinic has been hampered by the complicated characterisation of its metabolites [17, 20], the discovery of its cytotoxic activity has triggered the search for titanocene derivatives and other metallocenes ($[\text{M}(\text{Cp})_2\text{Cl}_2]$, where M is, e.g. V, Mo) that show similar or better antineoplastic activity [23–26] whilst controlling aqueous activity [3, 20, 27].

In the search for an improved aqueous stability, Tacke et al. have prepared titanocene derivatives with bridged-cyclopentadienyls, the so-called *ansa*-titanocenes. The same group has successfully optimised the substitution pattern on the Cp ring of titanocene dichloride derivatives developing the un-bridged organotitanium titanocene **Y** (**2**) [28, 29]. Compound **2** showed in vivo activity against A431 and PC-3 xenografts, models for epidermoid and human prostate cancer, respectively, similar to cisplatin [30, 31]. The authors have recently optimised the labile ligands, exchanging the chlorides for more suitable anions [32] and found that an oxalato derivative, oxali-titanocene **Y** (**3**), exhibits cytotoxicity in LLC-PK cell line (mimic of kidney carcinoma) with a potency similar to that of cisplatin. In vivo studies in CAKI-1 (renal cancer) tumour-bearing mice have shown a statistically-significant tumour growth reduction with respect to the control group [33].

Similarly, McGowan et al. have synthesised a number of new ionic titanocene organometallic complexes (e.g. **4**), which exhibit cytotoxicity against different human tumour cell lines including a cisplatin-resistant cell line [34].

Although hydrolysis may play an important role in the activation of titanocene derivatives as tumour inhibitors, few studies as yet support this postulate.



2.2 Ruthenium and Osmium Arenes

In the 1970s, Clarke et al. reported $[\text{Ru}(\text{NH}_3)_5(\text{purine})]^{3+}$ complexes capable of inhibiting DNA and protein synthesis in human nasopharyngeal carcinoma cells in vitro [35] and subsequently initiated interest in ruthenium complexes as potential anticancer pharmaceuticals [36]. During the following decade, Mestroni et al. developed hexacoordinated Ru^{II} complexes with dimethylsulfoxide and chloride ligands, particularly, *cis*- and *trans*- $[\text{RuCl}_2(\text{dimethylsulfoxide})_4]$, which exhibited anticancer activity and were shown to interact both in vitro and in vivo with DNA, their most likely target [37]. Today, there are two Ru-based anticancer drugs in clinical trials: NAMI-A [38–41], developed in Trieste by Mestroni, Alessio, and co-workers, and KP1019, developed by Keppler and co-workers in Vienna (Chart 1) [42–45].

Octahedral ruthenium(III) complexes are relatively inert towards ligand substitution. The reduction from ruthenium(III) to ruthenium(II) as an activation process prior to DNA binding was first suggested in the late 1970s by Clarke and co-workers [35, 46–50].

Consequently, organometallic ruthenium(II) and osmium(II) arene complexes have recently attracted interest as anticancer agents [51]. The presence of a π -bonded arene in Ru^{II} (and Os^{II}) complexes can have a dramatic influence on their chemical reactivity. There is a delicate balance between electron donation from the arene into the empty Ru 4d orbitals and back-donation from the filled 4d⁶ orbitals into vacant arene orbitals. This is influenced by the donor–acceptor power of the arene (e.g. hexamethylbenzene as a strong donor, in contrast to biphenyl which may act as acceptor) and by the other ligands on Ru^{II} which can influence the

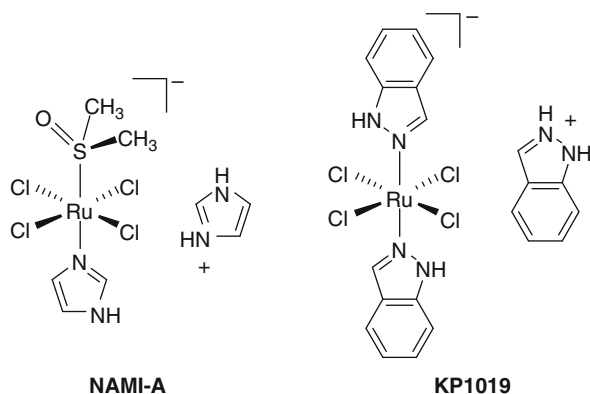


Chart 1 Structures of Ru^{III} complexes NAMI-A and KP1019

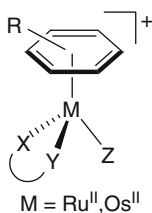


Chart 2 General structure of Ru^{II} and Os^{II} 'piano-stool' arene complexes

availability of the Ru 4d⁶ electrons, e.g. presence of strong π -acceptor chelating ligands such as bipyridine and azopyridine [52], or donor strength of monodentate ligands (e.g. iodide vs. chloride) [53].

The potential of Ru^{II} and Os^{II} η^6 -bound arene complexes of the type $[M^{II}(\eta^6\text{-arene})(X)(Y)(Z)]$ as antitumour drugs has been explored [54–57]. These complexes possess characteristic 'piano-stool' structures (Chart 2, where XY is a neutral chelating ligand, and Z a monoanionic ligand). In these complexes, the metals are already in their lower oxidation state, which may be important for the cytotoxicity of the drug in vivo [58]. The arene ligand, binding as an η^6 -electron donor and a π -acceptor, confers stability to the +2 oxidation state. The presence of a chelating ligand, XY, provides additional stability to the whole structure and the capability of tuning the electronic properties of the metal centre. The monodentate ligand Z allows activation of the molecule: if labile, such as halide, it can provide a vacant coordination site for biomolecules. Small variations of the arene and the 'legs of the stool' confer versatility to the molecule and the capability of fine-tuning their pharmacological properties [53, 59].

In general, Ru^{II} and Os^{II} arene complexes show promising cytotoxic activity against human ovarian cancer cell lines, some of them as potent as cisplatin and carboplatin. Some structure–activity relationships have been established

[51–55, 59–66]. As an example, when the chelating ligand is ethylenediamine and the leaving group is chloride, the cytotoxicity against A2780 human ovarian cancer cells increases with increasing size of the coordinated arene [60]. However, substitution of chloride by bromide or iodide has only a marginal effect on the cytotoxicity of ethylenediamine complexes [53]. Additionally, substitution of the chelating ligand by relatively labile monodentate ligands leads to less cytotoxic complexes [54]. The importance of the chelating ligand for moderating activity is evident when complexes such as $[\text{Ru}(\eta^6\text{-}p\text{-cymene})\text{Cl}(\text{CH}_3\text{CN})_2]\text{PF}_6$, and $[\text{Ru}(\eta^6\text{-}p\text{-cymene})\text{Cl}_2(\text{isonicotinamide})]$ are compared to $[\text{Ru}(\eta^6\text{-}p\text{-cymene})\text{Cl}(\text{en})]\text{PF}_6$. The Ru arene complexes with monodentate ligands show low or no activity (IC_{50} values $> 150\ \mu\text{M}$) while the chelated ligand-containing complex possesses high activity ($9\ \mu\text{M}$, compared to $0.5\ \mu\text{M}$ for cisplatin in these tests) [54]. A possible explanation for this lack of activity might be their high reactivity: they may be inactivated before reaching their target. Another example of the relevance of the ethylenediamine chelating ligand comes from a recent comparison of the activity of $[\text{Ru}(\eta^6\text{-}p\text{-cymene})\text{Cl}(\text{en})]\text{PF}_6$ with its non-chelated analogue $[\text{Ru}(\eta^6\text{-}p\text{-cymene})\text{Cl}(\text{NH}_3)_2]\text{PF}_6$. The latter showed only modest cytotoxicity in the three cell lines A549 (non-small cell lung carcinoma), CH1 (ovarian carcinoma), and SW480 (colon carcinoma), with IC_{50} values $293\text{--}542\ \mu\text{M}$, compared to $3.5\text{--}7.1\ \mu\text{M}$ for the former in the same cell lines [67]. This lack of activity may be related to rapid hydrolysis of both Cl^- and NH_3 ligands and subsequent formation of hydroxy-bridged dimers, as found in the solid state. The X-ray structure of the Os dimer: $[\{\text{Os}(\eta^6\text{-}p\text{-cymene})\}_2(\mu\text{-OCH}_3)_3]\text{PF}_6$ has been reported [67].

The effect of changing the three building blocks, i.e. $\eta^6\text{-arene}$, chelating ligand and monodentate group, in the activation of organometallic Ru^{II} and Os^{II} drugs is explored in more detail below.

2.2.1 Hydrolysis of the Ru–Z Bond

Activation through hydrolysis of the Ru–Z bond may be important for the mechanism of action of this class of drugs and their chemical behaviour in aqueous media has been extensively investigated [52, 53, 68–70]. Hydrolysis of $[\text{Ru}(\eta^6\text{-arene})\text{Cl}(\text{en})]^+$ is suppressed in the presence of 100 mM chloride ions [68]. The intracellular chloride concentration is significantly lower than the extracellular concentration (ca. 4 and 23 mM in nucleus and cytoplasm, respectively, vs. 103 mM outside the cell) [71]. Thus, although the chlorido form (Ru–Cl) of the complex probably resists aquation in the extracellular medium, hydrolysed products (Ru–OH₂/OH species) are likely to predominate inside cells under physiological conditions. In general, ruthenium arene complexes that hydrolyse also exhibit cancer cell cytotoxicity, whereas those which do not undergo aquation exhibit little or no activity [53]. This observation supports the assumption that this type of complex binds to biomolecules coordinatively to exert their cytotoxic activity.

The rate and extent of hydrolysis of the Ru–Z bond are highly dependent on the nature of Z, more labile leaving groups giving rise to faster hydrolysis [53].

For example, the differences between Cl^- and Br^- in complexes of the type $[\text{Ru}(\eta^6\text{-arene})(\text{en})\text{Z}]^+$, where arene is biphenyl, indane or benzene, is not dramatic, however, when $\text{Z} = \text{I}^-$ the hydrolysis is slower (3- to 7-fold). Other leaving groups such as pyridine or pyridine derivatives can slow down the hydrolysis further and even block it almost completely on biologically-relevant time scales. Such complexes are not cytotoxic towards cancer cells within 24-h drug exposures. There are a few exceptions such as $[\text{Ru}(\eta^6\text{-hexamethylbenzene})(\text{en})(\text{SPh})]\text{PF}_6$, where the monodentate ligand is thiophenolate. This complex does not hydrolyse, but intriguingly is active. The mechanism of activation of this complex is different (vide infra).

Changing the arene can also have a significant effect on the rate and extent of hydrolysis. For example, there is a 2-fold difference in the hydrolysis rate between the biphenyl complex $[\text{Ru}(\eta^6\text{-biphenyl})\text{Cl}(\text{en})]\text{PF}_6$, and the tetrahydroanthracene complex $[\text{Ru}(\eta^6\text{-5,8,9,10-tetrahydroanthracene})\text{Cl}(\text{en})]\text{PF}_6$ or the dihydroanthracene complex $[\text{Ru}(\eta^6\text{-9,10-dihydroanthracene})\text{Cl}(\text{en})]\text{PF}_6$, demonstrating that variations in the steric and electronic effects of arene ligands can modulate the aquation rate [68].

The chelating ligand can also exert a strong effect on the hydrolysis rate and equilibrium constant, attributable not only to electronic (strength of π interactions) but also steric effects (competitive binding of Z and water). Density functional calculations have suggested that aquation occurs by a concerted ligand exchange mechanism (more associative character in the substitution of Z by H_2O) [53]. An example of the effect of the chelating ligand on the rate of hydrolysis is represented by the series $[\text{Ru}(\eta^6\text{-indan})\text{Cl}(\text{N,N})]\text{PF}_6$ where $\text{N,N} = 2,2'$ -bipyridine, 4,4'-dimethyl-2,2'-bipyridine, and phenanthroline, with values for the pseudo first-order rate constants of 121.0 ± 1.0 , 113.0 ± 2.0 , and $75.1 \pm 1.2 (\times 10^3 \text{ min}^{-1})$ (determined by UV-vis spectroscopy for 50 μM solutions in 95% H_2O , 5% MeOH) [61]. In general, the reported half-lives for aquation of the chlorido ethylenediamine Ru^{II} arene complexes are shorter than those for bipyridine analogues [68].

As important as the rate of hydrolysis for drug activation is the pK_a of the coordinated water molecule of the activated aqua adduct. The pK_a value determines whether the active species containing the more labile $\text{Ru}-\text{OH}_2$ bond or the less reactive deprotonated form $\text{Ru}-\text{OH}$ prevails in solution at a given pH [72]. pK_a values for the coordinated water ligand in most of Ru arene complexes are around 8, therefore, at pH 7 aqua adducts should predominate. It has also been observed that control over the pK_a of the bound water molecule has an impact on the reactivity of the complex, with a pK_a higher than 7 leading to an active complex, while a pK_a lower than the physiological pH (ca. 7) resulting in an inactive species, since the hydroxo form would dominate rendering the complexes non-cytotoxic [68]. It has been found that the pK_a of the aqua adduct is as tuneable as the hydrolysis rate. It can be affected by the nature of the arene (8.3 for $[\text{Ru}(\eta^6\text{-}p\text{-cym})\text{Cl}(\text{en})]\text{PF}_6$, 7.9 for $[\text{Ru}(\eta^6\text{-bz})\text{Cl}(\text{en})]\text{PF}_6$ and 7.7 for $[\text{Ru}(\eta^6\text{-biph})\text{Cl}(\text{en})]\text{PF}_6$, for example) and the chelating ligand, since more electron withdrawing groups (better π -acceptors arenes) will divert the electron density away from the metal centre leaving it more

depleted of negative charge and making the bound water molecule more acidic (lower pK_a ; Table 1).

The nature of the chelating ligand (N,N or N,O or O,O) can have a major influence on the pK_a values of the $Ru-OH_2$ group (Table 1). Replacement of ethylenediamine by anionic acetylacetonate (acac) as the chelating ligand, raises the pK_a of the aqua adduct [69]. A neutral ethylenediamine ligand, however, increases the acidity of a bound water molecule. This reasoning also explains the relatively higher basicity of the bound water molecule of the glycinate aqua adduct in comparison to the ethylenediamine aqua adduct. Within a series of O,O - negatively charged ligands with different substituents and aromaticities, the trend becomes more complicated.

Ruthenium(II) arene complexes of general formula $[Ru(\eta^6\text{-arene})Cl_2(PTA)]$ ($PTA = 1,3,5\text{-triaza-7-phosphatricyclo}[3.3.1.1]$ decane) which possess antitumour activity have been reported by Dyson and co-workers (5, RAPTA-C) [74–76]. The RAPTA compounds showed pH-dependent DNA-damaging properties. These complexes were originally believed to be activated by the protonation of the PTA ligand at pH values close to physiological pH [77]. However, further studies rationalised the pH-dependent DNA binding by the aqua/hydroxo equilibrium for $[Ru(\eta^6\text{-arene})Cl(OH_2)(PTA)]^+$ [78], and the activation of the organometallic complex is

Table 1 pK_a data for Ru and Os organometallic complexes with different arenes and chelating ligands

Arene	Metal (M)	Chelating ligand (XY)	pK_a	Reference
<i>p</i> -cym	Ru	acac	9.4	[69]
<i>p</i> -cym	Ru	maltol	9.2	[73]
<i>p</i> -cym	Ru	trop	9.1	[70]
<i>p</i> -cym	Ru	gly	8.7	[60]
<i>p</i> -cym	Ru	en	8.2	[72]
bz	Ru	en	7.9	[59]
biph	Ru	en	7.7	[68]
<i>p</i> -cym	Os	maltol	7.6	[73]
<i>p</i> -cym	Os	acac	7.6	[59]
bz	Os	acac	7.3	[59]
biph	Os	acac	7.1	[59]
bz	Os	en	6.3	[59]
biph	Os	en	6.3	[59]
<i>p</i> -cym	Os	bipy	5.8	[63]
<i>p</i> -cym	Os	phen	5.8	[63]

p-cym *para*-cymene; bz benzene; biph biphenyl; acac acetylacetonate; maltol maltolate; trop tropolonate; gly glycinate; en ethylenediamine; bipy bipyridine; phen phenanthroline

When comparing two transition metals from the same group in the periodic table but from different rows, much lower ligand exchange rates are often associated with the heavier congener (osmium complexes in comparison with those of ruthenium). The hydrolysis of chlorido $\text{Os}^{\text{II}}-(\eta^6\text{-arene})$ complexes containing ethylenediamine as the chelating ligand is very slow (ca. $100\times$ slower than that of the analogous active ruthenium complexes) [59] (Fig. 1). Additionally, the pK_{a} of the water molecule bound to Os^{II} -en complexes is ca. 1.5 units lower, i.e. more acidic, than for the Ru^{II} complexes (Table 1). Therefore at physiological pH the osmium complexes can exist largely in the less reactive Os-OH form [63]. Changing the chelating ligand from en to acac in Os^{II} arene complexes has a marked effect on increasing the rate and extent of hydrolysis [69], becoming so fast for complexes such as $[\text{Os}(\eta^6\text{-arene})(\text{acac})\text{Cl}]$, where the arene is *p*-cymene, benzene or biphenyl, that the rate constant cannot be determined by NMR (hydrolysis occurring in less than 10 min) [59]. Moreover, replacement of en by acac has the expected effect on the acidity of the coordinated water, raising the pK_{a} by ca. one unit, attributable to the increased electron-density on the metal centre. However, dissociation of oxygen-chelating ligands from osmium at micromolar concentrations deactivates the complexes under biological testing conditions [59]. The acac complexes were unstable in aqueous solution due to the formation of inert hydroxo-bridged species, which could explain their lack of cytotoxicity.

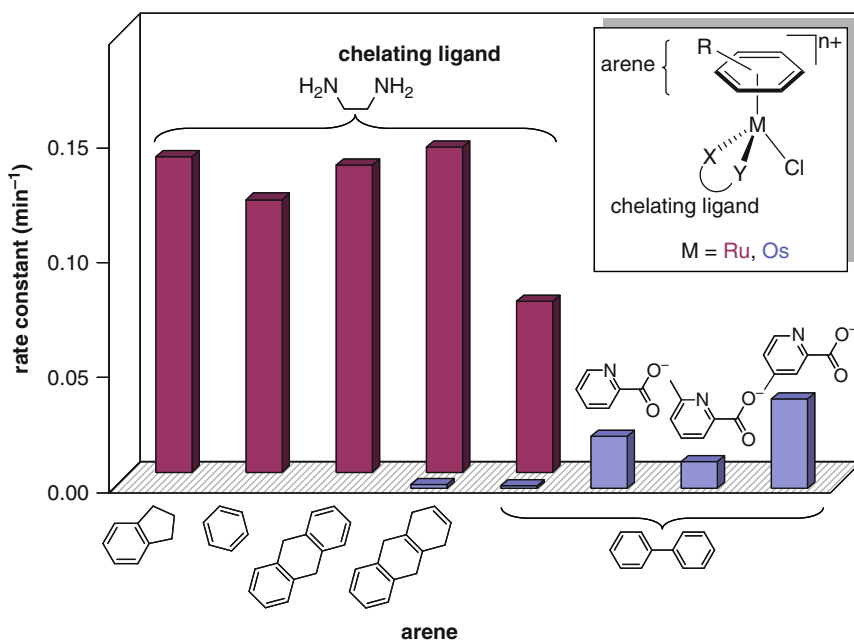
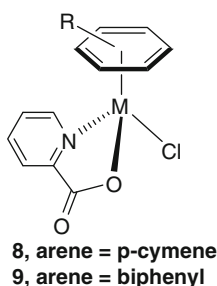


Fig. 1 Hydrolysis data for Ru and Os organometallic complexes with different arenes and chelating ligands. Data from [53, 63, 64, 66]

The inert hydroxo-bridged species were also a product of (very fast) hydrolysis of *p*-cymene osmium complexes with glycinate, L-alanine, α -aminobutyrate and β -alaninate. However, complexes with picolinate as the chelating ligand, $[\text{Os}(\eta^6\text{-}p\text{-cym})\text{Cl}(\text{pic})]$ **8** and $[\text{Os}(\eta^6\text{-biph})\text{Cl}(\text{pic})]$ **9**, with pyridine as *N*-donor and carboxylate as *O*-donor, hydrolyzed with half-lives of 0.20 and 0.52 h (298 K), and aqua adduct $\text{p}K_{\text{a}}^*$ values ($\text{p}K_{\text{a}}$ value for solutions in D_2O) of 6.67 and 6.33, respectively. Complexes **8** and **9** were cytotoxic towards A2780 human ovarian cancer cells, with IC_{50} values of 8 and 4.2 μM , respectively [64].



Novel picolinate derivatives have been synthesised that show hydrolysis rates intermediate between the slow values for the complexes with *N,N*-chelating ligands, and the rapidly-hydrolysing complexes with *O,O*- or *N,O*- amino acid-like chelating ligands. For these organometallic osmium complexes, the hydrolysis rates fall into the range of the ‘active’ ruthenium-arene relatives (Fig.1) [66].

Organometallic osmium-carbonyl clusters such as $[\text{Os}_3(\text{CO})_{10}(\text{NCCH}_3)_2]$ are apoptosis-inducing agents with anticancer therapeutic potential. The mechanism appears to involve the loss of the labile acetonitrile ligand [85].

Once the ruthenium or osmium arene organometallic complex is activated with the formation of the aqua species, $[\text{Ru}/\text{Os}(\eta^6\text{-arene})(\text{OH}_2)(\text{X})(\text{Y})]$ (Chart 3), the metal becomes a potential centre for nucleophilic attack by biomolecules. The binding of $\text{Ru}^{\text{II}}/\text{Os}^{\text{II}}$ arene complexes to nucleobases is of special interest, since DNA could be the ultimate target for this class of organometallic complexes. A number of studies have confirmed this postulate [86, 87] and investigated in detail such interactions [53, 54, 72, 88–93]. DNA interactions of Ru and Os arene complexes have recently been reviewed [94].

Ruthenium arene en complexes interact preferentially to guanine residues in double helical DNA. In addition to coordination to guanine, non-covalent,

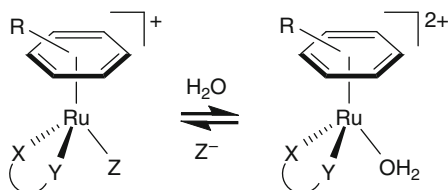


Chart 3 Hydrolysis of Ru^{II} arene complexes.

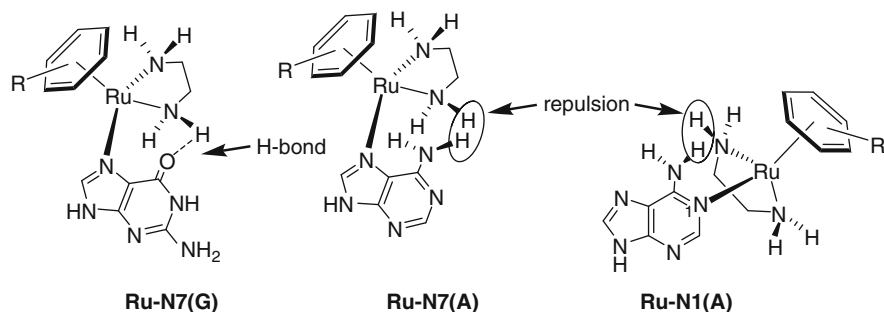


Chart 4 Interactions within guanine (G) and adenine (A) adducts of arene Ru-en anticancer complexes

hydrophobic interactions between the arene ligand and the DNA bases, such as π -stacking, arene intercalation and minor groove binding can occur [86]. The above observations clearly suggest a mechanism of action of Ru^{II} arene complexes different from that of cisplatin [87]. This is also true for osmium arene complexes [65].

The interaction between $[\text{Ru}(\eta^6\text{-arene})\text{Cl}(\text{en})]^+$ complexes and guanine, thymine, cytosine and adenine derivatives has been investigated in aqueous solution [72]. The reactivity of the various binding sites of nucleobases towards Ru^{II} at neutral pH decreases in the order $\text{G}(\text{N}7) > \text{T}(\text{N}3) > \text{C}(\text{N}3) > \text{A}(\text{N}7), \text{A}(\text{N}1)$ (with binding to cytosine being very weak and almost none to adenine derivatives). This base-selectivity appears to be enhanced by the ethylenediamine NH_2 groups, which form hydrogen bonds with exocyclic oxygens (e.g. $\text{C}6\text{O}$ of G) but are non-bonding and repulsive towards exocyclic amino groups of the nucleobases (e.g. $\text{C}6\text{NH}_2$ of A) (Chart 4) [72]. Density Functional Theory (DFT) calculations on these complexes with isolated nucleobases show good agreement with experimental data, which indicated preference for binding to guanine over any other base (ca. 100 kJ/mol) [95].

Nucleoside selectivity is altered by exchanging the H-bond donor *N,N*-chelating ligand, such as ethylenediamine, for an H-bond acceptor *O,O*-chelating ligand, such as acetylacetonate. The *acac*-type complexes show similar affinity for adenosine (N1- and N7-bound) and for guanosine and there is little binding to cytidine or thymidine [69, 70]. This work demonstrates how the more versatile octahedral organometallic Ru^{II} complexes can acquire different biomolecular recognition features in comparison with square-planar complexes such as cisplatin. Recently, Liu et al. studied the interaction of the monofunctional fragment $\{\text{Ru}(\eta^6\text{-biphenyl})(\text{en})\}^{2+}$ with the 14-mer $\text{d}(\text{ATACATGGTACATA})\cdot\text{d}(\text{TAT}^{17}\text{G}^{18}\text{TACCATGTAT})$ by HPLC-ESI-MS and 2D NOESY NMR [92]. When the duplex is annealed at high temperature, ruthenation occurs at N7 of every guanine residue of the oligonucleotide, and at one site (G^{18}), two different conformers were identified involving intercalation of the arene between G^{18} and adjacent T^{17} in one, and in the second the arene is non-intercalated but stacked on a tilted adjacent thymine lying on the surface of the major groove (Fig. 2).

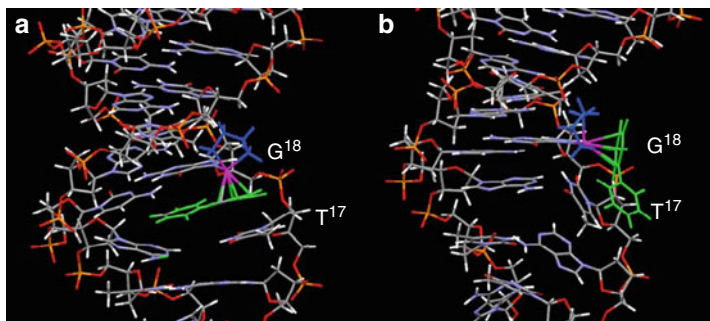


Fig. 2 Molecular models of two conformers of the 14-mer duplex d(ATACATGGTACATA) · d(TAT¹⁷G¹⁸TACCATGTAT) ruthenated at N7 of G¹⁸ with monofunctional fragment {Ru(η^6 -biphenyl)(en)}²⁺: (a) showing the intercalation of the arene between G¹⁸ and T¹⁷; (b) the arene is non-intercalated but stacked on a tilted T¹⁷. Colour code: Ru *purple*; en *blue*; biphenyl *green*. Adapted from [92]

2.2.3 Sulfur Oxidation

Redox reaction pathways can activate Ru^{II} arene thiolate complexes towards biomolecules. In unbuffered solutions (pH 3), the reaction of the complex [Ru(η^6 -biph)Cl(en)]⁺ with the tripeptide glutathione (γ -L-Glu-L-Cys-Gly, GSH) results in the loss of the chelating ligand (en), and the formation of the dinuclear sulphur-bridged dimer [{Ru(η^6 -biph)}₂(GS- μ -S)₃]²⁻ as the major product. However, in phosphate buffer (pH 7) and under physiologically-relevant conditions, the thiolato complex [Ru(η^6 -biph)(en)(GS-S)] is formed which subsequently undergoes oxidation to give the sulfenato complex [Ru(η^6 -biph)(en)(GS(O)-S)] quite readily. In the presence of cGMP (guanosine-3',5'-cyclic monophosphate), the cGMP adduct [Ru(η^6 -biph)(en)(cGMP-N7)]⁺ is formed as the major product even in the presence of a large molar excess of GSH [96]. These results demonstrate that oxidation of coordinated glutathione in the thiolato complex [Ru(η^6 -biph)(en)(GS-S)] to the sulfenato [Ru(η^6 -biph)(en)(GS(O)-S)] provides a facile route for the displacement of S-bound glutathione by guanine N7, a route for RNA and DNA ruthenation (Chart 5). FT-ICR MS studies with ¹⁸O-labelled water as solvent have suggest that oxygen atoms in sulfenato and sulfinate products may originate from water [97].

These ruthenium arene complexes can also induce oxygenation of cysteine residues in proteins. For example, when complexes [Ru(η^6 -*p*-cym)Cl(en)]⁺ and [Ru(η^6 -biph)Cl(en)]⁺ react with human serum albumin both bind to surface histidine (His128, His247, His510) and methionine (Met298) residues, but only the *p*-cymene complex gains entry to the cleft containing the free cysteine thiolate (Cys34) and induces oxidation to the sulfinate [98], indicating the critical role the arene plays in these interactions. Oxidation of the cysteine results in the weakening of the Ru–S bond and can trigger transfer of ruthenium to other protein sites or nucleobases.

There is a wider general interest in understanding the oxidation of cysteine thiolates in proteins since they are involved in redox-sensing reactions [99]. Therefore, such oxidation reactions of thiols induced by Ru coordination may also play a more general role in the pharmacological activity of Ru-arene complexes by coupling Ru coordinative binding to redox processes both outside and inside cells.

The oxidation of the non-chelated thiolato group to a sulfenato group in the complex $[\text{Ru}(\eta^6\text{-arene})(\text{en})\text{SR}]^+$ (arene = hexamethylbenzene, or *p*-cymene and $R = {}^i\text{Pr}$, Ph) has been reported by Holm et al. [100]. The arene and the hydrogen donor ethylenediamine play a significant role in controlling the stability and reactivity of the Ru-bound sulfenato. Moreover, the sulfenato complexes are readily protonated with $\text{p}K_{\text{a}}$ values of 3.37 and 3.61, respectively. The protonated complexes can easily hydrolyse to form reactive aqua or chlorido species (Chart 6). This is in contrast to the thiolato complex which does not hydrolyse. Thus the oxidation of the thiolato to the sulfenato group by the Ru arene complexes generates a labile leaving group, paving the way for interactions with biomolecules [100].

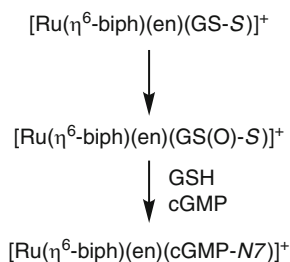


Chart 5 Activation of a thiolato ruthenium complex by ligand oxidation

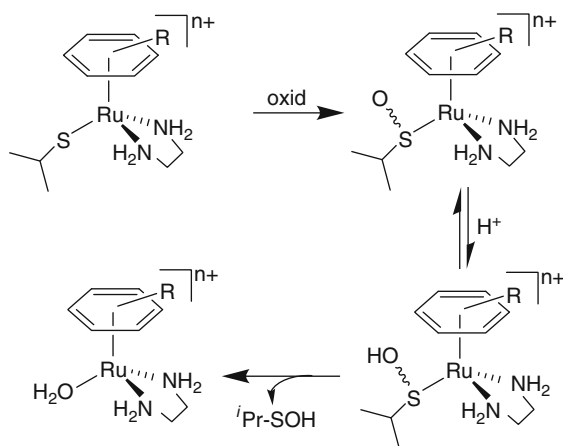


Chart 6 Activation of ruthenium thiolato complexes by oxidation followed by hydrolysis

It is interesting to note that cysteine sulfenates are found in catalytic centres of enzymes [101] and are of much interest in biological signalling processes [102–107]. An important feature of the sulfenato group compared to the thiolates and sulfinates is that it can exert high trans effects [101, 108, 109] and can exist in either oxidised [110] or reduced [111, 112] forms, in addition sulfenates have a negatively charged oxygen that forms strong hydrogen bonds [113, 114].

The thiolato complex $[\text{Ru}(\eta^6\text{-hmb})(\text{en})\text{SR}]^+$ (hmb = hexamethylbenzene, $R = \text{iPr}$) can also undergo activation by ligand-based redox reactions involving a remarkably efficient oxygen-GSH couple under physiological conditions [115]. In these reactions GSH is almost completely oxidised to form GSSG and the thiolato complex is oxidised to the sulfenato complex $[\text{Ru}(\eta^6\text{-hmb})(\text{en})\text{S}(\text{O})\text{R}]^+$.

A combined XAS and DFT study of the complexes $[\text{Ru}(\eta^6\text{-arene})(\text{en})\text{SR}]^+$, where arene is *p*-cymene or hexamethylbenzene and R is isopropyl or phenyl, has shown that the Ru–S bond is susceptible to ligand oxygenation and the influence of substituents on the sulfur and arene [116]. Sulfur K-edge XAS indicates that S_{3p} donation into the Ru_{4d} manifold depends strongly on the oxidation state of the sulfur atom, whereas Ru K-edge data suggest little change at the metal centre. DFT results are in agreement with the experimental data. Oxygenation of the thioate sulfur has little effect on the strength of the Ru–S/Ru–SO/RuSO₂ bond. In sulfenato complexes, the terminal oxo group makes a large contribution to charge donation making it more susceptible to ligand exchange, but only if protonation of the terminal oxo group occurs. These results are consistent with the observed hydrolysis of the sulfenato complexes under acidic conditions [100], and further indicate that modifications to the arene group and the thiolato group have a measurable impact on the Ru–S bond.

2.2.4 Bifunctional Ru Arenes

In an attempt to achieve a stable bifunctional ruthenium arene complex Melchart et al. prepared the tethered complexes $[\text{Ru}(\eta^6:\eta^1\text{-arene})\text{Cl}_2]$, where two of the three legs of the piano-stool are chlorides and the third is a NH_2 group from a tethered arm pendant from the π -bonded arene [117]. This complex contains two *cis* reactive Ru–Cl bonds, as does cisplatin which is known to form intrastrand crosslinks in DNA as a major lesion leading to cell death, and also maintains the presence of an H-bond donor, directed towards nucleobase interaction [89, 118]. However, these complexes hydrolyse very rapidly yielding mainly mono-aqua mono-chlorido species. In spite of the apparent formation of bi-functional adducts with model nucleobases such as 9-ethylguanine, they failed to give evidence of cross-linking with calf thymus DNA. The second G is bound only weakly, which together with the rapid hydrolysis, might explain their lack of cytotoxic activity.

2.2.5 Chelate Ring Redox

The diamine complex $[\text{Ru}(\eta^6\text{-}p\text{-cym})\text{Cl}(\text{o-pda})]\text{PF}_6$ (*o-pda* = *o*-phenylenediamine), undergoes concomitant ligand-based oxidation and hydrolysis (38% after 24 h) in water [119]. The oxidation also occurs in methanol. The iodido diimine complex $[\text{Ru}(\eta^6\text{-}p\text{-cym})\text{I}(\text{o-bqdi})]\text{I}$ (*o-bqdi* = *o*-benzoquinonediimine) does not undergo hydrolysis, whereas the chlorido complex hydrolyses relatively rapidly ($t_{1/2} = 7.5$ min). Loss of cytotoxic activity was observed upon oxidation of the amine ligand to an imine (e.g. $\text{IC}_{50} = 11 \mu\text{M}$ for $[\text{Ru}(\eta^6\text{-}p\text{-cym})\text{Cl}(\text{o-pda})]\text{PF}_6$ vs. $\text{IC}_{50} > 100 \mu\text{M}$ for $[\text{Ru}(\eta^6\text{-hmb})\text{Cl}(\text{o-bqdi})]\text{Cl}$ against A2780 ovarian cancer cells). This oxidation can be controlled through changes in electronic properties of the other ligands (arene and monodentate ligands) in the complex. The loss of activity in this series of complexes may be related to the absence of hydrolysis as well as to the formation of less stable adducts with guanine, which would lead to weaker binding to DNA. Interestingly the diimine (*o-bqdi*) complexes can be reduced by the tripeptide glutathione but readily undergoes re-oxidation in air.

2.2.6 Irradiation

Photodynamic therapy is currently used in the clinic as a method for treating cancer. Irradiation of a photosensitizer, such as a porphyrin, with light leads to conversion of ground-state triplet oxygen into excited state and highly reactive singlet oxygen which damages DNA and kills the cells. However tumours are often deficient in oxygen and therefore the prospect of using excited state transition metal complexes that could kill cancer cells by an oxygen-independent mechanism is an attractive one. For example, some organometallic ruthenium arene complexes are capable of undergoing photo-induced reactions with DNA bases [120].

UV or visible irradiation of $[\{\text{Ru}(\eta^6\text{-indane})\text{Cl}\}_2(\mu\text{-}2,3\text{-dpp})](\text{PF}_6)_2$ (2,3-dpp = 2,3-bis(2-pyridyl)pyrazine) in aqueous (or methanolic) solution leads to arene loss, and the DNA binding of this organometallic ruthenium dimer increases after irradiation. The non-irradiated dinuclear complex forms DNA adducts that only weakly block RNA polymerase, while irradiation transforms adducts into stronger blocks for RNA polymerase. Irradiation of $[\{\text{Ru}(\eta^6\text{-indane})\text{Cl}\}_2(\mu\text{-}2,3\text{-dpp})](\text{PF}_6)_2$ in the presence of DNA leads to an increased frequency of cross-linking. In addition, there is a 40-fold increase in fluorescence of the unbound compared to bound arene. These results show that photoactivation of dinuclear Ru^{II} arene complexes can simultaneously produce a highly reactive ruthenium species that can bind to DNA and a fluorescent marker (the free arene). Importantly, the mechanism of photoreactivity is also independent of oxygen. These complexes, therefore, have the potential to combine both photo-induced cell death and fluorescence imaging of the location and efficiency of the photoactivation process [121].

An example of a piano-stool Ru^{II} arene complex, $[\text{Ru}(\eta^6\text{-}p\text{-cym})(\text{bpm})(\text{py})](\text{PF}_6)_2$ (where bpm = 2,2'-bipyrimidine and py = pyridine) that can be activated

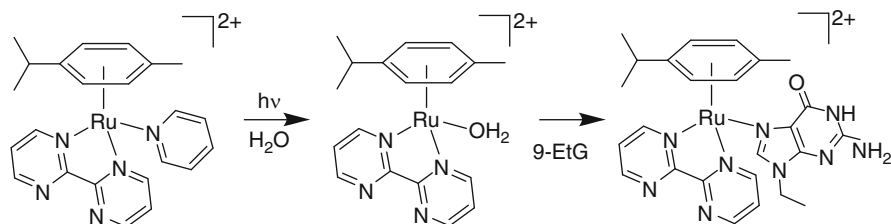


Chart 7 Photoactivation of a ruthenium arene complex

by visible light to photo-dissociate selectively a monodentate ligand (py), conventionally non-labile (on a timescale and under conditions relevant for biological reactivity) has been reported recently (Chart 7). Irradiation generates a reactive aqua species, able to bind to a DNA base. Such behaviour creates a platform for control of the hydrolysis reaction of the complex and phototriggered binding of an anticancer pro-drug to biomolecules [122].

2.3 Other Transition Metal Complexes

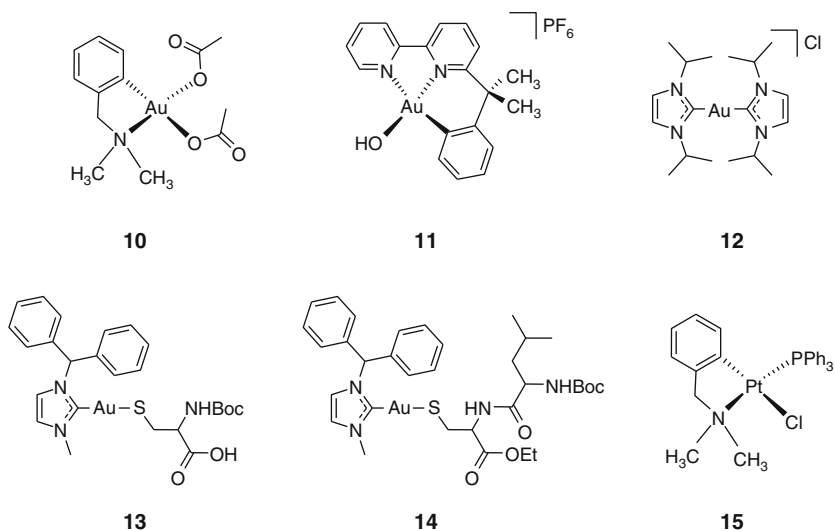
Gold(III) organometallics are isoelectronic with cisplatin-like Pt^{II} complexes. For example, complex **10** hydrolyses in water [123] and has shown activity in human tumour xenograft models [124]. However, its mechanism of action is different from that of cisplatin [124, 125]. The role of hydrolysis as an activation step for this class of compounds is not yet clear.

Other examples of organogolds with cytotoxic activity are complexes such as **11**, $[\text{Au}(\text{bipy}^{\text{c}}\text{-H})(\text{OH})]\text{PF}_6$ [126], and analogues in which the OH has been substituted by bulkier ligands such as: 2,6-xylylidine-H and *p*-toluidine-H [127]. For these analogues, hydrolysis may represent an activation step.

Very recently, the mitochondria-targeted antitumour agents gold(I) *N*-heterocyclic carbenes (NHC) have been reported that combine both selective mitochondria targeting and selective thioredoxin reductase inhibition properties [128]. The lipophilic cationic organogold(I) complex $[\text{Au}((^i\text{Pr})_2\text{Im})_2]\text{Cl}$ (**12**) induces caspase-9 and caspase-3 activation in human breast adenocarcinoma cells suggesting that this class of complexes causes selective cancer cell death through a mitochondrial apoptotic pathway. Additionally, promising gold NHC complexes such as the gold(I) cysteine derivatives **13** and **14** have been recently reported that exert antiproliferative activity in cancer cell lines comparable to that of cisplatin [129].

Moreno et al. have developed highly active platinum(II) and palladium(II) organometallic complexes derived from the *N,C*-chelating ligand 2-(dimethylamino)methyl)phenyl (dmmba) (e.g. **15**) or pentafluorophenyl ligands and studied reactions with representative model nucleobases, namely, 1-methylthymine, 1-methyluracil, and 1-methylcytosine [130–133]. The complexes interact strongly with DNA. Values of IC_{50} were also determined for these new organometallic platinum complexes against the tumour cell lines (HL-60, A2780, A2780cisR,

NCI-H460 and T47D), and all were more active than cisplatin. Given the success enjoyed by cisplatin-like platinum coordination complexes, this appears to be a promising area of research.



3 Metal Complexes as Catalytic Drugs

Here we describe an example of metal-based catalysis is described followed by an example of ligand-based catalysis.

Ruthenium(II) arene anticancer complexes, for example $[\text{Ru}(\eta^6\text{-C}_6\text{Me}_6)(\text{H}_2\text{O})(\text{en})]^{2+}$, can catalyse regioselective reduction of NAD^+ in the presence of formate as hydride donor in vitro [134], although the reaction rates are ca. $50\times$ slower than those catalysed by rhodium(III) pentamethylcyclopentadienyl complexes [135]. Interestingly A549 human lung cancer cells appear to tolerate high (millimolar) levels of formate well and so the possibility arises of exploring the catalytic activity of organometallic metal complexes in cells. Recent work has shown that the efficiency of such catalysts can be greatly improved by appropriate choice of the chelated *N,N*-ligand [136].

The presence of a π -bonded arene ligand together with a strongly chelated σ -donor/ π -acceptor azopyridine ligand and iodide as a strong monodentate ligand, produces Ru^{II} arene complexes $[\text{Ru}(\eta^6\text{-arene})(\text{azpy})\text{I}]^+$ (where arene = *p*-cymene or biphenyl, and azpy = *N,N*-dimethylphenyl- or hydroxyphenyl-azopyridine) which are relatively inert toward activation by hydrolysis in aqueous solution. Surprisingly, despite this inertness, these complexes are highly cytotoxic to human ovarian A2780 and human lung A549 cancer cells. Fluorescence trapping experiments in A549 cells suggest that the cytotoxicity arises from an increase in reactive oxygen species. These azopyridine complexes undergo activation by reduction of the ligand. While

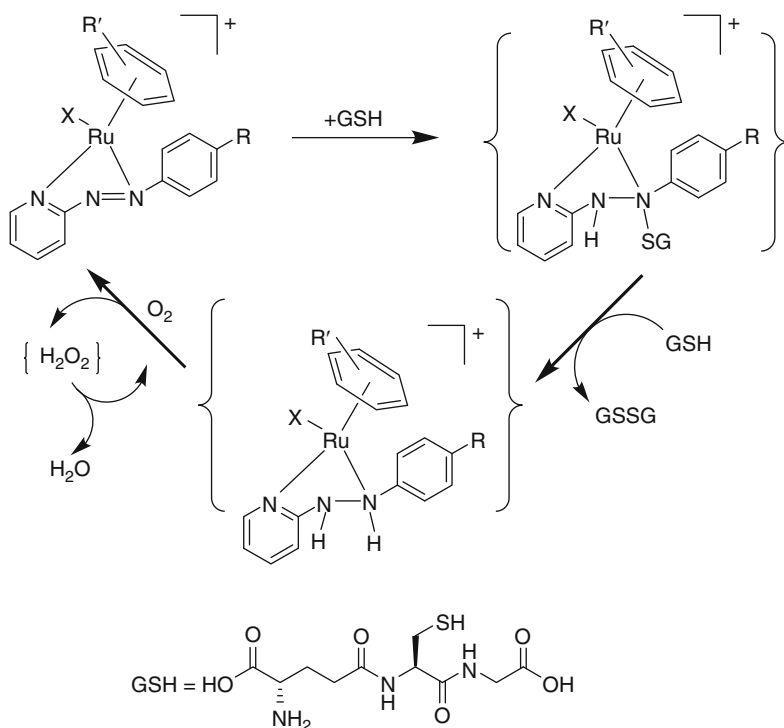


Chart 8 Possible scheme for catalytic activity of ruthenium azopyridine complexes

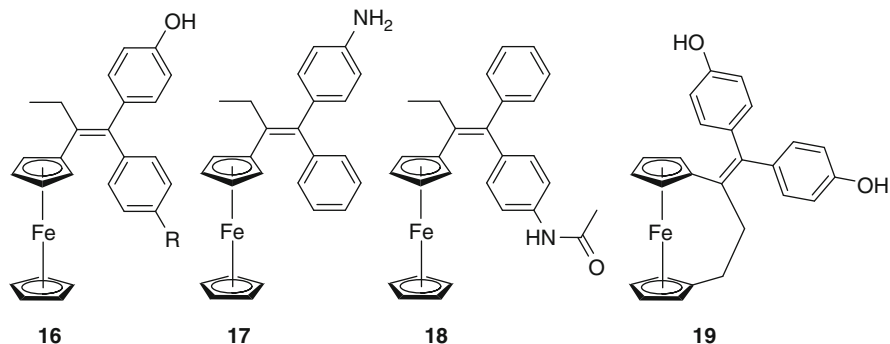
azopyridine ligands alone are difficult to reduce, the reduction potentials are biologically accessible when the azopyridine is coordinated to Ru^{II} [137]. Intriguingly the ruthenium complex appears to act as a catalyst in reactions with GSH; millimolar amounts of GSH can be oxidised to GSSG in the presence of micromolar ruthenium concentrations in a cycle which appears to involve ligand-centred reduction of the azo bond by GSH forming a hydrazo intermediate, followed by formation of GSSG and regeneration of the azo bond (Chart 8). Such ligand-based redox reactions provide new concepts for the design of catalytic drugs.

4 Structural Scaffolds

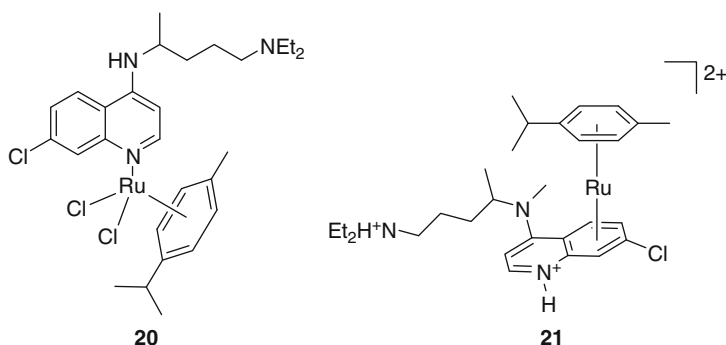
4.1 Ferrocenes and Ferrocenyl Derivatives

Depending on the presence or absence of the oestrogen receptor in the cells, breast cancer is often treated by endocrine therapy (tamoxifen) or chemotherapy, respectively. Organometallic derivatives of hydroxytamoxifen (e.g. ferrocifen, **16**, and its

derivatives) have been explored as a potential therapy for breast cancer and other cancers by Jaouen and co-workers. The presence of an organometallic fragment (ferrocene), and a pharmacophore (hydroxytamoxifen), generates compounds which display a new therapeutic spectrum consisting of anti-oestrogenicity and cytotoxicity. A structure-activity relationship (SAR) study has shown that a ferrocene group linked to a *para*-phenol group by a conjugated spacer, is a necessary motif for strong cytotoxic effects against both the hormone-dependent MCF-7 and hormone-independent MDA-MB-231 breast cancer cell lines, involving oxidative quinone methide formation [138]. Ferrocenyl quinone methides, potentially cytotoxic species, are formed by metabolic and chemical oxidation of ferrocenyl phenols [139]. The binding of ferrocifen to the oestrogen receptor is believed to produce an enhanced antiproliferative effect together with additional cytotoxicity induced by the redox properties of ferrocene [138]. It is interesting to note that the isostructural ruthenocene derivative is also active in hormone-dependent breast cancer cells but lacks the antiproliferative effect of ferrocifen against hormone-independent cells [140]. Electrochemical experiments suggest that on replacement of the phenol group by analogous amine and acetamide complexes **17** and **18**, both complexes can be transformed to oxidised quinoid-type species, analogous to those observed previously for the ferrocene phenols [141]. New ferrocenophane compounds have been reported recently, one of which (**19**) has an anti-proliferate effect seven times greater than the corresponding noncyclic species, with IC₅₀ values of 90 and 94 nM towards hormone-independent MDA-MB-231 breast and PC-3 prostate cancer cell lines [142].



In a strategy which involves incorporation of a biologically active compound into a metal fragment, to achieve enhanced activity and possibly with a different mode of action, Sanchez-Delgado et al. have synthesised complexes containing a Ru^{II} arene fragment and the anti-malarial drug chloroquine (**20**) and chloroquine diphosphate (**21**). These complexes display activity against chloroquine-resistant parasites and also inhibit the growth of colon cancer cells, especially **21**, for which an IC₅₀ value of 8 μ M was observed. Chloroquine binds to ruthenium preferentially through the quinoline nitrogen atom, whereas chloroquine diphosphate is π -bonded through the carbocyclic ring [143].



4.2 Glutathione-S-Transferase Inhibitors

Organometallic ruthenium-arene complexes conjugated to ethacrynic acid have been prepared as part of a strategy to develop novel glutathione-S-transferase (GST) inhibitors with alternate modes of activity through the organometallic fragment (binding at Cys47 and to a lesser extent Cys101) and hence potentially enhanced antiproliferative activity.

The dichloro-Ru^{II}-arene complex conjugated to ethacrynic acid [Ru(η⁶-*p*-cymene)Cl₂(EA-imidazole)] more rapidly inactivated GST P1-1 than the carboxylato analogues, suggesting that the ruthenium centre plays a role in the inactivation of the enzyme [144].

4.3 Kinase Inhibitors

Meggers and co-workers have pioneered the use of inert organometallic Ru^{II} and Os^{II} complexes as scaffolds bearing organic compounds with biological activity, such as staurosporine (Chart 9), a known kinase inhibitor [145–147]. The creation of unique and defined molecular structures based on metal scaffolds tailored to fit (and inhibit) the active sites of kinase enzymes is an active area of research. Kinases are important therapeutic targets since their mutations and deregulation are linked to diseases. They have a highly conserved ATP binding site for which the design of organic inhibitors is challenging [148].

This strategy has resulted in the discovery of nanomolar and even picomolar ATP-competitive ruthenium-based inhibitors for different protein kinases [146]. In particular one of these complexes DW1/2 (Chart 9) has shown remarkable anticancer properties in several cancer cell lines (300 nM of the complex maximally inhibited cell growth in most of the melanoma cell lines tested) [149].

Recent structural studies confirm that these complexes bind to the ATP-binding site of protein kinase [150]. Superimposition of the co-crystal structures of Pim-1

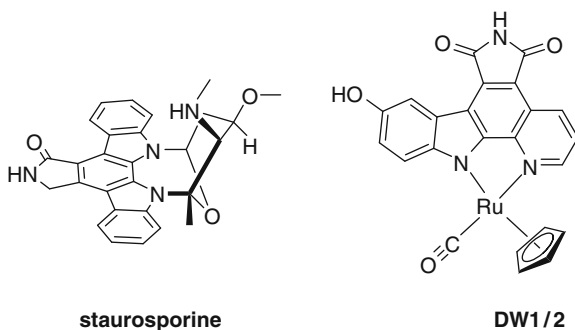


Chart 9 The kinase inhibitor staurosporine and the ruthenium complex DW1/2

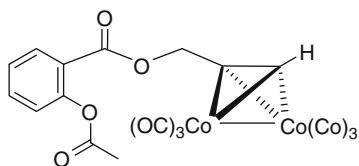
with (S)-Os and (S)-Ru (PDB: 3BWF and 2BZI, respectively) showed virtually identical structures [151]. Unlike ruthenium and osmium-arene relatives, where substitution reactions appear to have an essential role in their cytotoxic activity, it was found that the isostructural Ru^{II} and Os^{II} complexes display almost indistinguishable biological activities and identical modes of action as protein kinase inhibitors.

The targeting of proteins with metal complexes, both organometallic and coordinative metal-based compounds, has been recently reviewed by Meggers [148].

Keppler et al. have synthesised Ru^{II} and Os^{II} arene complexes with paullones as ligands to confer solubility on these otherwise insoluble cyclin-dependent kinase (CDK) inhibitors [152]. No dramatic differences between the ruthenium and the osmium complexes were found in the IC_{50} values against A549, CH1 and SW480 cancer cell lines.

4.4 COX Inhibitors

The cobalt-alkyne analogue **22** of the non-steroidal anti-inflammatory drug aspirin (acetylsalicylic acid) exhibits antiproliferative activity against human breast cancer cell lines [153]. The cytotoxicity is related to cyclooxygenase (COX) inhibition, which retards the growth of established tumours and enhances their response to conventional therapies [154]. COX is involved in eicosanoid metabolism and targeting this pathway is a viable strategy for the development of new anticancer agents. It has been speculated that **22** binds to cyclooxygenase in a fashion similar to aspirin followed by an acetylation of a surface residue.



22

5 Metal as a Carrier for Active Ligands

In order to target drug delivery, it is very important to study the distribution of the drug within the body. For example radiolabelling of the anticancer complex $[\text{Ru}(\eta^6\text{-fluorene})\text{Cl}(\text{en})]\text{PF}_6$ with the β -emitter ^{106}Ru (half-life = 1.01 y) has allowed its biodistribution to be studied; 0.25 h post i.v. injection at a dose of 25 mg kg^{-1} , ^{106}Ru is well distributed throughout the tissues of a rat [155].

Various other strategies for investigating biodistributions of metallodrugs are being developed by different groups.

5.1 Side-Chain Hydrolysis

A fluorescent complex $[\text{Ru}(\eta^6\text{-}p\text{-cym})\text{Cl}(\text{L})]\text{Cl}$ ($\text{L} = 2\text{-}[(2\text{-aminoethyl})\text{amino}]\text{ethyl-2-(methylamino)benzoate}$) has been synthesised by tagging a small fluorogenic reporter onto the chelating ligand. The interaction of this complex with porcine liver esterase (PLE) showed that esterase-catalysed hydrolysis reactions can liberate methylisatoic acid (MIAH) from the ruthenium complex suggesting a possible use of similar derivatives in esterase-activated Ru-based prodrug delivery systems. The hydrolysis reaction appears to be slow [156].

5.2 Ruthenium Cages

Stable ruthenium arene cages consisting of a cationic hexanuclear metalla-prism $[\text{Ru}_6(p\text{-}^i\text{PrC}_6\text{H}_4\text{Me})_6(\text{tpt})_2\text{-(dhbq)}_3]^{6+}$ (which incorporates *p*-cymene ruthenium building blocks and is bridged by 2,5-dihydroxy-1,4-benzoquinonato (dhbq) ligands and connected by two tpt subunits (tpt = trigonal 2,4,6-tris(pyridin-4-yl)-1,3,5-triazine)) have been synthesised. The cages can encapsulate and deliver $\text{Pd}^{\text{II}}(\text{acac})_2$ or $\text{Pt}^{\text{II}}(\text{acac})_2$ complexes in a Trojan-horse manner. The encapsulated Pd and Pt complexes are insoluble in water and therefore inactive. The capsule itself showed cytotoxicity which was remarkably enhanced by encapsulating the acac complexes (IC_{50} of $23 \text{ }\mu\text{M}$ decreased to 12 and $1 \text{ }\mu\text{M}$, respectively) [157]. A review article on the synthetic strategies to obtain metalla-rectangles, triangular metalla-prisms and metalla-boxes with arene ruthenium complexes has been recently published [158].

6 Photoactivation and Photosensitizers

Therrien et al. have developed organometallic ruthenium porphyrin compounds for anticancer photodynamic therapy. These combine synergistically the photodynamic action of porphyrins with the DNA damage-related cytotoxicity of Ru^{II} -arene

complexes. Porphyrin arene-ruthenium(II) and osmium derivatives and cyclopentadienyl-iridium and -rhodium analogues have been prepared as potential photosensitising chemotherapeutic agents. The ruthenium complexes showed good photo-toxicities toward melanoma cells when exposed to red laser light at 652 nm [159].

The organometallic ruthenium-arene fragments improved the aqueous solubility of the otherwise insoluble porphyrins without modifying the photophysical properties of the photosensitizer. Additionally, the presence of the ruthenium on the porphyrins facilitated uptake into melanoma cells [160].

7 Organotins

Since the early finding in 1972 that triphenyltin acetate (but not the corresponding chloride) retards tumour growth in mice [161], a number of organotin derivatives have been prepared and tested in vitro and in vivo [162–166].

It has been suggested that, in solution, triorganotin compounds may undergo spontaneous disproportionation into the corresponding diorganotin and tetraorganotin derivatives [167] while, in vivo, the loss of one alkyl or aryl group may occur through the intervention of enzymes such as aromatase [168].

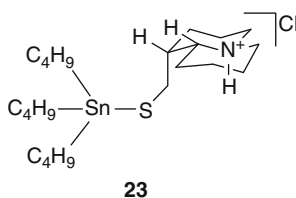
On the basis of the above consideration, diorganotin compounds might be considered to be the ultimate cytotoxic agents and the frequently observed higher activity of triorganotins may be related to their pharmacokinetic behaviour.

Inhibition of macromolecular synthesis, mitochondrial energy metabolism, and reduction of DNA synthesis, as well as direct interaction with the cell membrane (increase in cytosolic Ca^{2+} concentration), have been implicated in organotin-induced cytotoxicity [169, 170]. Promotion of oxidative and DNA damage in vivo has been detected [171]. Oxidative damage and increased concentration of intracellular calcium ions seem to be the major factors contributing to triorganotin-induced apoptosis in many cell lines [172].

Sn^{IV} organometallic compounds can induce apoptosis [163, 173, 174]. However, the exact mechanism of anti-tumour action of organotin(IV) compounds remains unknown. Although the mechanism of this antiproliferative activity is not well established, it has been suggested [175] that organotin(IV) compounds wield antiproliferative effects through binding to thiol groups of the proteins hence differing from the behaviour of several cytotoxic complexes of other metals.

A comprehensive review of recent advances on organotin anticancer therapeutics has been recently published [172].

Interesting are recent findings for the tributyl complex tri-*n*-butyltin(IV) lupinylsulfide hydrogen fumarate (IST-FS 35, **23**) which inhibits both the P388 myelomonocytic leukaemia and the B16-F10 melanoma, implanted subcutaneously in BDF1 mice. The mechanism is not understood [166, 176].



Triorganotin carboxylates may exist in monomeric or polymeric forms, while diorganotin derivatives may exist as true dicarboxylates or as distannooxane salts $[(R_2SnO-COR')_2O]$ and may further aggregate in a number of ways that influence both solubility and bioavailability. More work on the molecular basis for the activity of tin complexes is needed.

8 The Future for Medicinal Organometallics

Organometallic complexes provide versatile platforms for drug design. Metal-carbon bonds can exert major electronic and steric effects, which in turn can be used to control their biological activity. In particular such complexes offer the possibility of novel mechanisms of action compared to purely organic drugs and have the potential for combating drug resistance as well as treating currently intractable conditions.

Some organometallic complexes are inert enough to act as scaffolds which can be designed to interact stereospecifically with biomolecular targets and act, for example, as enzyme inhibitors. In general though, most are 'pro-drugs' which can undergo ligand exchange and/or redox reactions before they reach the target site, it is important to demonstrate that such reactions can be controlled so as to maximise activity and minimise unwanted side-effects.

In this chapter, we have illustrated how π -bonded metal arene complexes can undergo activation by hydrolysis, by metal-based or ligand-based redox reactions, or by irradiation with light. The choice of not only the arene (benzene and cyclopentadienyl derivatives) but also the other ligands in the complex is crucial for determining both thermodynamic and kinetic stability and biological activity. This is well illustrated by the first organometallic complex to enter clinical trials as an anticancer agent titanocene dichloride [177]. Variations to both the Cp substituents and to the monodentate ligands can change the aqueous reactivity and perhaps help prevent the complicated hydrolysis reactions which made clinical formulation of this compound difficult.

Some organometallic complexes are well known to possess catalytic activity and it is interesting to consider the possibility that catalytic drugs could be developed. The problem of catalyst poisoning may be difficult to overcome in a biological medium but perhaps this can be used to switch off the activity when required.

There are major challenges to be tackled relating to the chemical and biochemical mechanisms of action of organometallic complexes, for example involving the mechanism of displacement and release of coordinated arenes and cyclopentadienyl ligands which can expose several reactive coordination positions on a metal ion. Also the metabolism of coordinated arene and Cp ligands (e.g. modification by P450 enzymes in the liver) may have a major effect on the biodistribution and excretion of complexes.

We can expect to see new organometallic complexes become candidates for clinical trials as anticancer drugs in the near future and they will also find applications in other fields of therapy. Medicinal organometallic chemistry is in its infancy but shows much promise for future developments.

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