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The insertion of ruthenium into porphyrins revisited and improved: proof of concept results with a Ru(II) mono-carbonyl compound, and the spectacular effect of propionic acid.

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Abstract

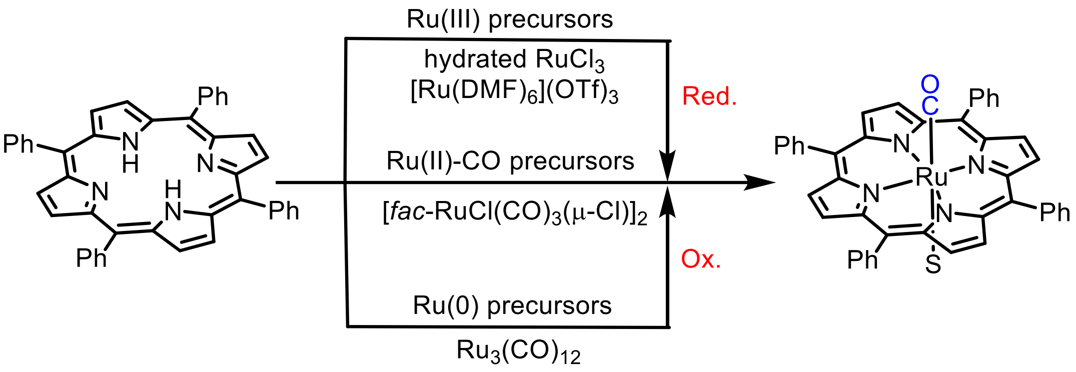
This contribution, that readdresses the insertion of the Ru(II)–CO fragment into model porphyrins (i.e. ruthenation), has a Janus character, with one speculative and one practical side. As a proof of concept we demonstrate that ruthenation of a porphyrin can be performed under relatively mild conditions using the Ru(II) monocarbonyl complex $[Ru(CO)(dmso)_5][PF_6]_2$ that – besides CO – features exclusively labile dmso ligands. Even though this finding might seem trivial, it is only the second example that uses a Ru(II) carbonyl for porphyrin ruthenation, the first one having been reported almost 50 years ago and then neglected. From a practical point of view, we show the spectacular effect of propionic acid as solvent for performing the ruthenation of neutral and anionic model porphyrins with $Ru_3(CO)_{12}$ (**1**). This process turned out to be extremely efficient and advantageous in terms of both reaction rates and yields (e.g. 100% ruthenation of TPP in 30 min at 140°C) compared to the procedures described in the literature.

Introduction

Metalation of porphyrins (Por) is typically accomplished by the reaction of the free-base analogue with a metal salt (or complex) in an organic solvent, such as chloroform, toluene, or DMF. The metalation is in general a slow process, with a high activation barrier attributed mainly to the distortion that the relatively rigid porphyrin ring must undergo to allow the formation of the first bond of an internal pyrrolenine nitrogen to the metal, which seems to be rate-limiting.[1] The insertion of ruthenium is no exception. Initially ruthenium porphyrins were prepared as low-spin air-stable biomimetic models of Fe(II) porphyrins: adducts and intermediates (e.g. with oxygen) are expected to be more stable and more inert for the ruthenium than for the iron compounds.[2-4] Later on they were also investigated as catalysts,[5] in particular for oxidation reactions,[6] and sensors.[7] For simple free-base neutral porphyrins (e.g. *meso*-tetraphenylporphyrin (TPP), octaethylporphyrin (OEP), and similar) the conditions for ruthenium insertion are much more demanding compared to iron, typically requiring high temperatures and long reaction times.[8] In addition, contrary to iron but similarly to osmium,[9] ruthenium is inserted into porphyrins *exclusively* as the Ru(II)–CO fragment, yielding neutral products of the type Ru(CO)(Por). No examples of the direct insertion either of “naked” Ru(II)/Ru(III) ions or other RuL or RuL_2 fragments are known. It might be argued that the presence of a strong π-acceptor ligand such as CO is necessary for removing from the relatively soft metal ion (Ru^{II} or Os^{II}) part of the charge density provided by the Por^{2-} macrocycle. Indeed, consistent with a strong π-back donation contribution, the CO stretching mode in Ru(CO)(TPP) occurs at rather low frequencies, e.g. ca. 1930-1945 cm^{-1}, depending on the report.[10-12] The axial coordination position *trans* to CO is typically occupied by a weak and labile solvent molecule deriving from the workup (e.g. ethanol),[11] which can be easily replaced by a stronger σ and/or π-donor ligand (e.g. pyridine, imidazole).[13-15] The axial Ru–N(pyridyl) bond is relatively strong and inert.[16] For this reason, ruthenium porphyrins and pyridyl ligands have been largely exploited as building blocks in the construction of supramolecular assemblies by us and by others.[17-19] The coordinated CO can be removed by prolonged photolysis in weakly coordinating solvents (S), affording $Ru(Por)(S)_2$ adducts.[20] Similarly, Ru(OEP)(CO)(py) in degassed pyridine solution is photochemically converted to $Ru(OEP)(py)_2$.[21] Conversely, strong σ-donor and π-acceptor ligands such as phosphines (P) readily displace the CO ligand from the parent Ru(CO)(Por) under mild conditions affording $Ru(Por)(P)_2$ derivatives.[22,23]

As users of ruthenium porphyrins, we have been surprised by the lack of a reliable, high yielding and widely adopted synthetic procedure for ruthenium insertion in the literature. More specifically, the ruthenation of free-base porphyrins uses one of the following precursors (Scheme 1): *i*) The

Ru(0) carbonyl cluster $Ru_3(CO)_{12}$ (**1**). This is the most widely adopted procedure, even though no two equal preparations can be found in the literature. The reaction is typically performed by refluxing the porphyrin and an excess of cluster (Ru/Por in the range 3-10) under an inert atmosphere for several hours (often days or even weeks). Hydrocarbon solvents (i.e. benzene (b.p. 80.1 °C),[10] toluene (b.p. 110.6 °C),[11,24-26] 1,2,4-trichlorobenzene (b.p. ca. 214°C),[27] or decalin (b.p. 190°C)[28,29]) are used for neutral porphyrins,[30] whereas DMF is preferred for water-soluble charged porphyrins.[31,32] In a single report acetic or propionic acid were used as solvent (see below).[33] To be noted that – regardless of the solvent – the reaction requires that ruthenium, besides breaking several Ru–Ru and Ru–CO bonds, is oxidized to Ru(II). *ii*) A Ru(III) species. The most common procedures involve the universal Ru(III) precursor $RuCl_3{\cdot}3H_2O$ and are typically performed in two steps. In the first step hydrated $RuCl_3$ is treated at high temperature (e.g. in refluxing ethylene glycol or 2-(2- methoxyethoxy)ethanol) with a source of CO, either a stream of CO or formaldehyde, that decomposes thermally and yields CO.[23,26,34] This procedure generates a yellow-orange solution containing an undefined "ruthenium carbonyl", later found to be an equilibrium mixture of the Ru(II) dimer [*fac*-$RuCl(CO)_3(\mu\text{-}Cl)]_2$ (**2**) and of the poorly characterized Ru(II) polymer $[RuCl_2(CO)_2]_n$ in which each unit is believed to feature two adjacent carbonyls and four bridging chlorides.[35] It is instead unlikely that this solution contains the Ru(0) cluster **1**, whose preparation under these conditions requires the addition of a base.[35] In the second step, the free-base porphyrin is added and the reaction mixture further heated at high temperature for hours. In some cases a one-pot procedure was also reported.[36] More recently James and co-workers have described a one-pot reaction in which the Ru(III) precursor $[Ru(DMF)_6](SO_3CF_3)_3$ is treated with the free-base porphyrin in refluxing DMF (that partially decomposes generating CO).[8] However, the generally good yields need to accommodate the preparation of the Ru(III) precursor from hydrated $RuCl_3$ that also requires the use of three equivalents of silver triflate.[37] In all these procedures, carbon monoxide has the double role of reductant and ligand. *iii*) A Ru(II) precursor (not prepared *in situ*). To the best of our knowledge, the one and only example of this type dates back to 1971, when Chow and Cohen reported the ruthenation of TPP with [*fac*-$RuCl(CO)_3(\mu\text{-}Cl)]_2$ (**2**) in refluxing propionic or acetic acid (24h).[33]



Scheme 1. Ruthenation procedures exemplified for the free-base *meso*-tetraphenylporphyrin (TPP); S is a molecule of solvent, typically EtOH or MeOH, from the workup procedure.

In all cases, the ruthenation reaction is followed by one or more purification steps, typically column chromatography and/or recrystallization. Yields (when reported) range from low (30-40%) to excellent (96%), depending on the porphyrin and the procedure, but it is often unclear if they concern the whole procedure or the purification step only.

The detailed literature survey leads to a quite obvious general conclusion: Regardless of the adopted procedure, the ruthenation of porphyrins is a very complex reaction. Mechanistic studies are missing and in no case the exact stoichiometry is known. It is typically assumed that the two inner H atoms are removed as protons (but formation of H_2 when **1** is used as precursor cannot be excluded). In addition, the reactions require that all the supporting ligands (except one CO in **1** and **2**) are replaced and – with a single exception – that ruthenium also changes its original oxidation state.

In this general picture that spans the last 50 years (the first Ru-porphyrin was reported in 1969, even though its formulation was incorrect),[38] we found particularly surprising that only in one case – quite old and apparently never repeated – the ruthenation of a porphyrin had been performed with a Ru(II) precursor, i.e. in the same oxidation state as in the final compound (Scheme 1).[33]

In the past we have described a number of neutral Ru(II)-dmso carbonyls of the general formula $RuCl_2(CO)_n(dmso)_{4-n}$ (n = 1-3).[39,40] More recently, cationic mono- and di-carbonyl Ru(II)-dmso compounds were obtained from the neutral ones by silver-assisted replacement of chlorides with dmso.[41,42] We reasoned that these carbonyls, that feature relatively labile Cl^- and/or dmso supporting ligands, might be good precursors for the ruthenation of porphyrins. Two neutral compounds, the monocarbonyl *fac*-$RuCl_2(dmso)_3(CO)$ (**3**) and the triscarbonyl *fac*-$RuCl_2(CO)_3$(dmso-O) (**4**) (that can be considered as the activated form of the dinuclear species **2**),[43] and the chloride-free $[Ru(CO)(dmso)_5][PF_6]_2$ (**5**) (Figure 1) were selected for testing.

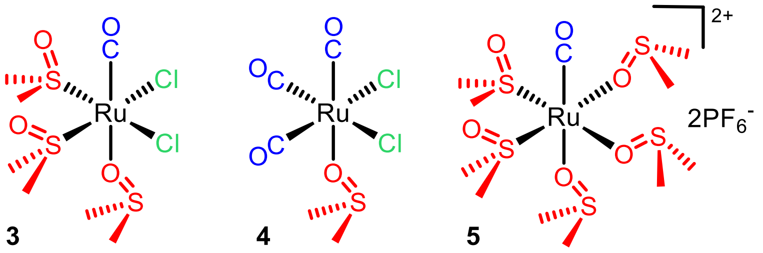


Figure 1. The three Ru(II) carbonyls selected for being tested in the ruthenation of porphyrins.

For comparison, we also reinvestigated the ruthenation procedures described in the literature for $Ru_3(CO)_{12}$, using TPP as model porphyrin. Given the unexpected findings when propionic acid was used as solvent, this investigation was extended to other neutral and charged porphyrins. Transmetalation reactions, with Zn·TPP and Ag·TPP as starting materials, were also investigated. The results of this systematic investigation are reported in this manuscript.

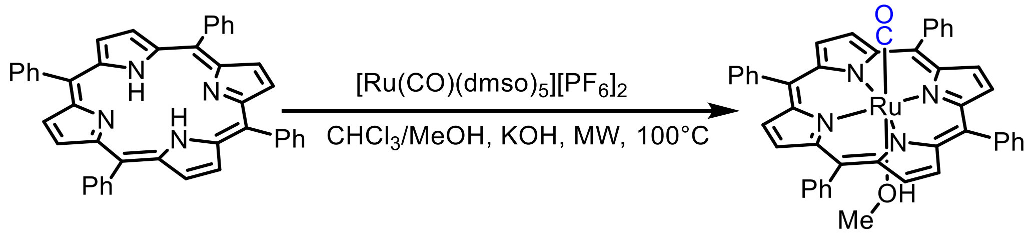
Results and Discussion

Ru(II)-dmso carbonyls as precursors.

After an extensive – and unsuccessful – investigation, in which treatment of TPP with the Ru(II) carbonyls **3** and **4** was systematically tested under different conditions, we eventually observed the formation of Ru(CO)(TPP) when the reaction was performed in a microwave reactor at 100°C in a 2:1 chloroform/methanol mixture (in which TPP is fully soluble), in the presence of a slight amount of KOH (presumably to either deprotonate the TPP or remove any H^+ that might be formed in the ruthenation process). Moreover, the insertion of Ru(CO) into TPP occurred only when an excess of a soluble silver salt (e.g. $AgPF_6$) was added to remove the chlorides from the Ru precursor. However, the addition of Ag^+ also led to the contemporary formation of Ag·TPP (evidenced by TLC analysis by comparison with a sample of pure Ag·TPP). Thus, we focused on the chloride-free precursor $[Ru(CO)(dmso)_5][PF_6]_2$ (**5**) and systematically investigated several parameters (Ru/TPP, KOH/TPP, temperature and reaction time) for optimizing the yield. It is noteworthy that, contrary to TPP, **5** is not fully soluble in the reaction medium, thus the initial system is an heterogeneous mixture. We found that best results were obtained at Ru/TPP = 4 and KOH/TPP = 2. Under these conditions, a moderate 21% yield of Ru(CO)(TPP) (established by ^1H NMR spectroscopy, see Experimental) was obtained after 1h reaction at 100°C in a MW reactor (Scheme 2). However, the final reaction mixture had a brown-green color, indicating that – despite the addition of the base – at least partial protonation of residual TPP, with formation of the deep-green $TPPH_2^{2+}$, had occurred.[44,45] The presence of $TPPH_2^{2+}$ was confirmed by the UV-vis and ^1H NMR spectra. We believe that during the reaction KOH, besides contributing to the removal of the inner TPP protons, is mainly consumed by reacting with the Ru(II) precursor, leading to its (partial) decomposition (e.g. through the formation of polymeric hydroxo- or oxo-bridged species).[46] In other words, the added base is insufficient for neutralizing the two equiv of protons that may be liberated per each equiv of inserted Ru.[47] The initial addition of larger amounts of KOH prevented the protonation of residual TPP (i.e. afforded purple final solutions), but lowered the conversion, presumably due to increased decomposition of **5**. We found that, if the "green" mixture obtained after 1h reaction (i.e. a mixture of Ru(CO)TPP, TPP, and $TPPH_2^{2+}$) was further heated in the MW reactor at 100°C, no increase – or even a moderate decrease – in the relative amount of Ru(CO)(TPP) vs TPP was observed. Consistent with this result, we investigated shorter reaction times and found that after 30 min the ruthenation of TPP is only slightly lower than after 1h. Eventually, improved conversion was obtained by performing the reaction in a stepwise manner. After each 30 min step, the purple color of the mixture was restored (i.e. the formed $TPPH_2^{2+}$ was converted back to TPP) – if necessary – with the addition of small amounts of a methanol solution of KOH. For example, we obtained 33% of Ru(CO)(TPP) when the ruthenation of TPP was performed in two subsequent steps of 30 min, compared to ca. 21% in a single step of 1h. A ca. 50% conversion was achieved in two additional steps.

By comparison, no formation of Ru(CO)(TPP) was observed when, under these reaction conditions, either Zn·TPP or Ag·TPP where used as substrate.

Since we are well aware that this ruthenation procedure – even though quite well reproducible – is impractical (in particular in view of the results reported below), the achievement of higher conversions was not further pursued.



Scheme 2. Ruthenation of TPP with the chloride-free Ru(II) carbonyl precursor $[Ru(CO)(dmso)_5][PF_6]_2$ (**5**). See text for reaction time and yields.

$Ru_3(CO)_{12}$ as precursor

When the ruthenation of TPP with **1** (Ru/TPP = 6) was performed in refluxing toluene or decalin, according to literature procedures, the best results were obtained – not surprisingly – in the solvent with the highest boiling point. Nevertheless, even after 36h of reflux in decalin (under an argon atmosphere), less than 50% conversion was estimated by TLC and UV-vis analysis, and the final isolated yield of Ru(CO)(TPP) after purification by column chromatography was even lower.

Trans-metallation reactions using Zn·TPP and Ag·TPP were also investigated. We reasoned that the replacement of Zn(II) by Ru(II) should be thermodynamically favored (the X-ray structures show that both ions have an excellent size match with the inner cavity of TPP, and Ru is expected to form stronger bonds with the macrocycle). The redox-induced *trans*-metalation of Ag(II) porphyrins is an established strategy:[48] Reduction of Ag(II) to Ag(I) involves a significant increase of the ionic radius that facilitates demetalation and subsequent replacement.[49] However, in neither case formation of Ru(CO)(TPP) was observed.

Ruthenation of TPP was not observed when the reaction in refluxing decalin was performed using the Ru(II) carbonyls **3**-**5**. In these cases, however, the initially purple mixture turned gradually brown-green, suggesting the partial formation of $TPPH_2^{2+}$, and a dark precipitate formed most likely due to the decomposition of the Ru complex. It should be noted that neither the porphyrins nor the Ru precursors are particularly soluble in decalin and each system remains heterogeneous throughout the procedure. No reactivity was observed also when the reaction between TPP and **5** was performed in refluxing DMF and DMSO, where the complex (but not TPP) is soluble.

Finally, the reaction between **1** and TPP was carried out in refluxing propionic acid, as in the work by Chow and Cohen.[33] We were rather skeptical about this procedure. In general, in metalation procedures, either the solvent is a good proton-acceptor or – when a metal salt is used – the anion is a mild base. For example, insertion of zinc is best performed at room temperature with zinc acetate.[4] Conversely, demetalation of metal-porphyrins is typically performed in acidic medium.[50] Thus, the choice of propionic acid for the ruthenation of TPP is counter-intuitive. In the original procedure described in 1971, TPP and either $Ru_3(CO)_{12}$ (**1**) or [*fac*-$RuCl(CO)_3(\mu\text{-}Cl)]_2$ (**2**) (Ru/TPP = 1.1) were refluxed under nitrogen in propionic acid (141°C) for 24h .[33] Thus, we were quite surprised to see that after refluxing **1** and TPP (Ru/TPP = 6) under Ar for barely 30m a clear red-orange solution was obtained from the original purple/brown mixture (the initial color suggests that partial protonation of TPP occurs) and no residual TPP (that is partially soluble in propionic acid at room temperature) remained according to TLC and UV-vis analysis.

Given these results, we analyzed in detail the ruthenation reaction in propionic acid and investigated how the yield of Ru(CO)(TPP) is affected by the nature of the precursors, the Ru/porphyrin ratio, time and temperature. The use of a microwave reactor was also investigated. Overall, the best performance in the ruthenation of TPP in propionic acid was obtained with **1**, that afforded 100% conversion after 30 min of reflux (or in MW reactor at 140 °C) at a Ru/TPP ratio = 1.5 (Figure 2).

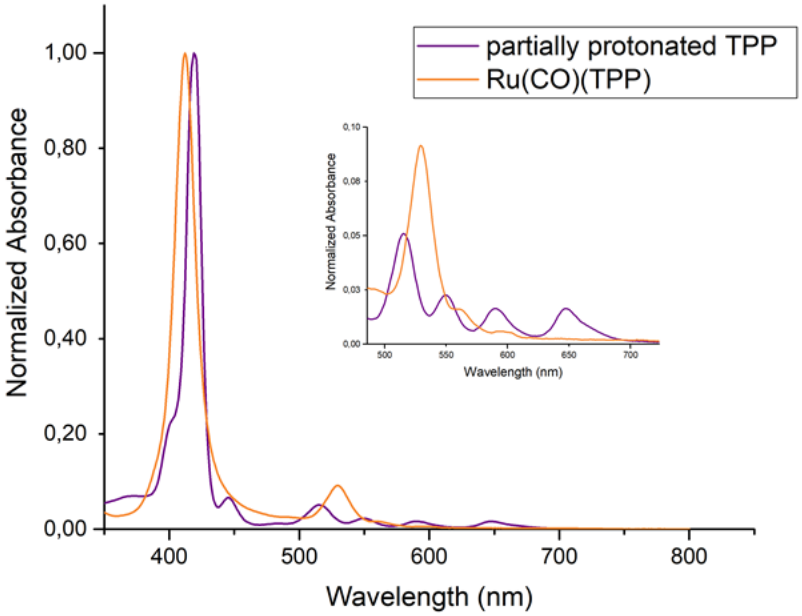


Figure 2. UV-vis spectra (propionic acid solutions diluted ca. 50× in $CHCl_3$) of TPP (purple) and after 30 min of reflux with **1** (Ru/TPP = 1.5). The initial spectrum corresponds to a mixture of TPP (major species) and $TPPH_2^{2+}$; the final spectrum (orange) corresponds to Ru(CO)(TPP).

When this reaction was performed on a larger scale, followed by chromatographic purification, a 92% isolated yield of Ru(CO)(TPP) was obtained (see Experimental). Systematic studies were carried out on the TPP concentration, and the properties of the acids used (both in terms of their pKa and boiling points). We found that, at constant Ru/TPP ratio, the concentration of TPP plays a relevant role: when the TPP concentration was lower than 0.6 mg/mL, the initial solution is deep-green, suggesting consistent formation of $TPPH_2^{2+}$, and no ruthenation occurred even after hours at refluxing conditions with **1**. Conversely, when the concentration of TPP was higher than 2.6 mg/mL, 100% conversion was obtained (see above) and within a few hours after the end of the reaction some Ru(CO)(TPP) precipitated spontaneously from the mother liquor kept at room temperature. A lower reactivity was found when **1** and TPP were refluxed in acetic acid (b.p. = 117.9 °C), whereas no reaction occurred, even after several hours, in refluxing trifluoroacetic acid (TFA, b.p. = 72.4 °C). The ruthenation of TPP with **1** in propionic acid was found to occur also at lower temperatures, obviously with lower rates (for example, at 100°C ca. 50% conversion according to TLC analysis was obtained after 1h, at Ru/TPP = 5.5). Performing a MW-assisted reaction at the same temperature brought no significant improvement in the yield of the product. The Ru(II) triscarbonyl complex *fac*-$RuCl_2(CO)_3$(dmso-O) (**4**) was slightly less active than **1** in propionic acid at reflux (90% conversion after 30min, and 100% after 1h), whereas the monocarbonyl *fac*-$RuCl_2(dmso)_3(CO)$ (**3**) was considerably less active (e.g. ca. 50% conversion in 1h at Ru/TPP = 6). This result is counterintuitive since, in principle, compound **3** has more labile ligands than **4** (two dmso’s vs two CO’s).[51] Conversely, the chloride-free carbonyl **5** in this case turned out inactive: When refluxed with TPP in propionic acid, the initially insoluble complex afforded a deep-green solution from which a dark precipitate gradually formed, most likely a Ru decomposition product.[52] Under the best conditions, ruthenation (*trans*-metalation) of Zn·TPP and Ag·TPP also occurred with both **1** and **4**, with the following order of activity: TPP > Ag·TPP » Zn·TPP.

Very similar results were obtained also with octaethylporphyrin (OEP, Figure 3), another commonly used neutral porphyrin: similarly to TPP, when OEP was treated with **1** in refluxing propionic acid (Ru/OEP = 1.5) 100% conversion to Ru(CO)(OEP) was obtained in 30 min according to UV-vis analysis (Figure 4).

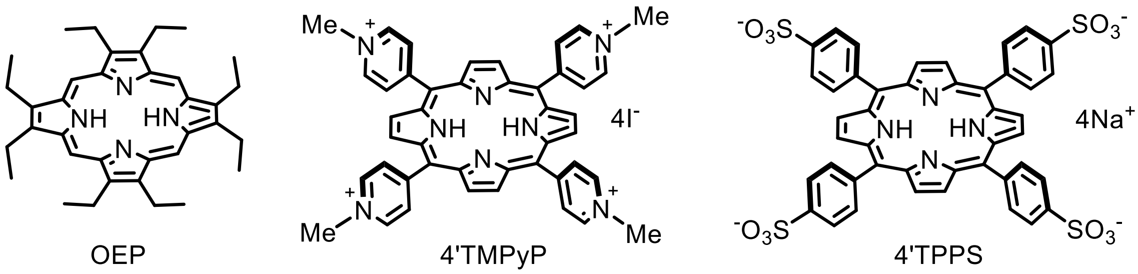


Figure 3. Additional neutral and charged model porphyrins investigated in this work besides TPP.

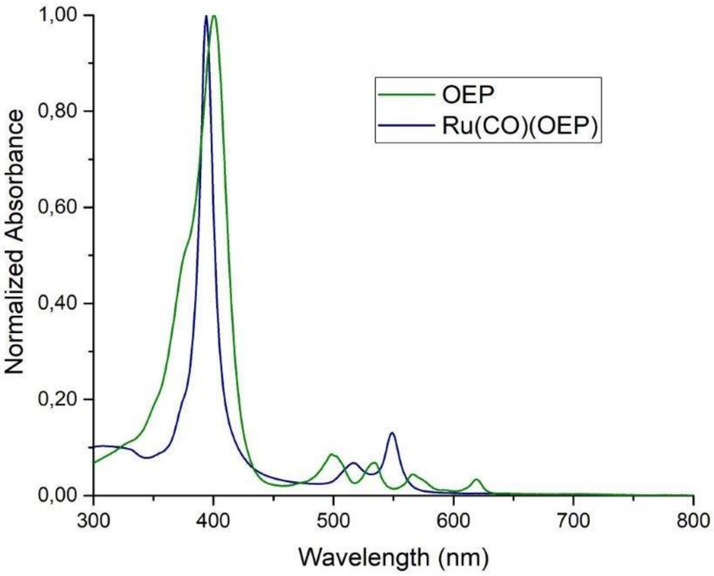


Figure 4. UV-vis spectra (propionic acid solutions diluted ca. 50× in $CHCl_3$) of OEP (green) and after 30 min of reflux with **1** (Ru/OEP = 1.5). The initial spectrum corresponds to a mixture of OEP (major species) and $OEPH_2^{2+}$; the final spectrum (purple) corresponds to Ru(CO)(OEP).

Charged model porphyrins

Given the above reported results, the investigation was extended to model cationic and anionic porphyrins: *meso*-tetrakis(4′-*N*-methylpyridiniumyl)porphyrin (4′TMPyP, iodide salt) and *meso*-tetrakis(4′-sulfonatophenyl)porphyrin (4′TPPS, sodium salt), respectively (Figure 3).

In the literature, ruthenation of the charged porphyrins 4′TMPyP and 4′TPPS was performed with **1** in refluxing DMF (Ru/Por = 15), in the presence of 2,4,6-trimethylpyridine (presumably as a non-coordinating proton acceptor).[31] Interestingly, ruthenium insertion into the tetra-cationic 4′TMPyP was reported to occur in a much shorter time and with higher yield than into the tetra-anionic 4′TPPS (2h at 110°C vs 24h at 140°C; yield 57 vs 36%). Apparently, in the absence of 2,4,6-trimethylpyridine, the ruthenation of 4′TPPS (unknown Ru/porphyrin ratio) in refluxing DMF required much longer times, from 1 to 3 weeks.[32] When the Ru(III) complex $[Ru(DMF)_6](SO_3CF_3)_3$ was used as precursor, ruthenation of 4′TMPyP in refluxing DMF was found to depend strongly on the nature of the counter-ion: metalation of the tosilate salt occurred in 17h, whereas the chloride salt was totally unreactive.[8]

In our hands, MW-assisted ruthenation of 4′TPPS with **1** was best performed in 1:3 water/propionic acid mixtures, where a good compromise of the solubility of the two reactants was found.[53] Working at Ru/4′TPPS = 6, 100% conversion to Ru(CO)(4′TPPS) was obtained in 1.5h at 140°C, as assessed by UV-vis spectroscopy (Figure 5). A very similar result was obtained using the tricarbonyl complex **4** as ruthenium source, however at lower temperatures **4** proved again to be less reactive than **1** (for example at 100°C **4** – unlike **1** – was basically unreactive). No reaction was found with **5**. Remarkably, no ruthenation was observed under the same conditions when the reaction between 4′TPPS and **1** was performed in DMF (where both reactants are soluble), thus stressing the role of propionic acid.

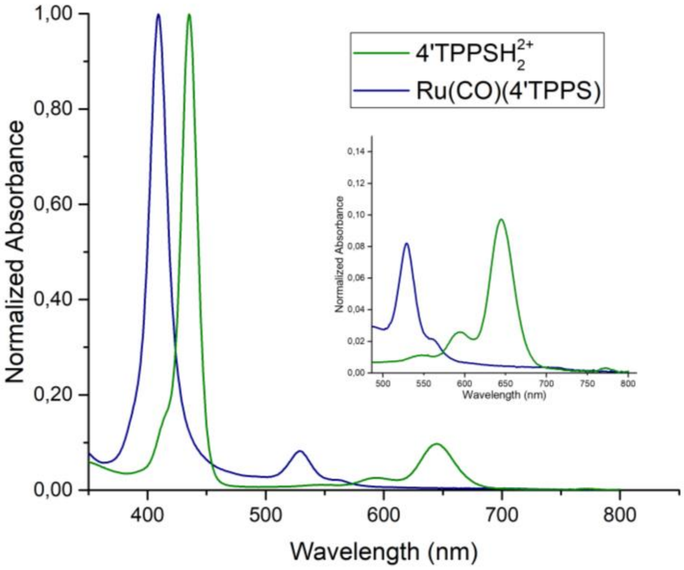


Figure 5. UV-vis spectra (1:3 water/propionic acid mixture diluted ca. 50× in water) of 4′TPPS (green), fully protonated to 4′$TPPSH_2^{2+}$ in the reaction conditions, and after treatment with **1** (Ru/4′TPPS = 6, 2h at 140°C in a MW reactor of reflux). The final spectrum (blue) corresponds to Ru(CO)(4′TPPS).

Conversely, ruthenation of 4′TMPyP with **1** under similar conditions used for 4′TPPS proved unsuccessful. It is noteworthy that the tetra-cationic porphyrin, even though fully soluble in the 1:3 water/propionic acid mixture, according to the UV-vis spectrum, undergoes no protonation. Consistent with previous reports,[31.32] full conversion to Ru(CO)(4′TMPyP) was obtained in 1h when 4′TMPyP was treated with **1** in DMF at 140°C in a MW reactor (Ru/4′TMPyP = 6, Figure 6).

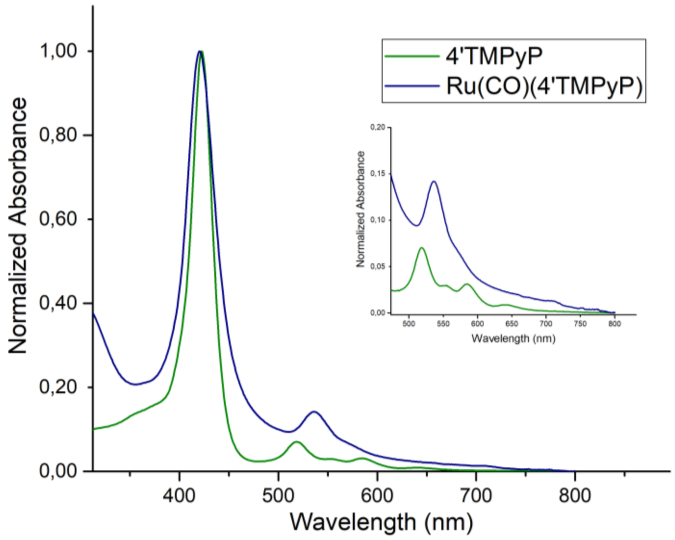


Figure 6. UV-vis spectra (DMF diluted ca. 50× in water) of 4′TMPyP (green), and after treatment with **1** (DMF, Ru/4′TMPyP = 6, 1h at 140°C in a MW reactor). The final spectrum (blue) corresponds to Ru(CO)(4′TMPyP).

Conclusions

The results obtained for the ruthenation of TPP with the Ru(II) carbonyl complex $[Ru(CO)(dmso)_5][PF_6]_2$ (**5**) are of moderate practical impact. Nevertheless, we believe that they establish a proof of concept: for the first time, almost 50 years after the single experimental report by Chow and Cohen,[33] we demonstrated that the Ru(II)–CO fragment can be inserted into a porphyrin under relatively moderate conditions using a well-defined Ru(II) monocarbonyl precursor that – besides CO – features exclusively labile dmso ligands (Scheme 2). We believe that this or similar complexes might turn out useful for performing a mechanistic investigation, both from the experimental and computational point of view.

On the other hand, from a practical point of view, the use of propionic acid as solvent for the ruthenation of neutral and anionic model porphyrins with $Ru_3(CO)_{12}$ (**1**) – suprisingly – turned out be extremely efficient and advantageous in terms of both reaction rates and yields compared to the procedures described in the literature. The Ru(0) cluster is commercially available or easily prepared from hydrated $RuCl_3$,[35, 54] the ruthenation reaction is fast at 140°C but can be performed also at lower temperatures and does not require an inert atmosphere, its workup is very simple and the yield of isolated pure product is excellent.

Table 1 summarizes the best results for the insertion of Ru(CO) into the model neutral (TPP, OEP), tetra-anionic (4′TPPS), and tetra-cationic (4′TMPyP) porphyrins with different Ru precursors.

Table 1. Best reaction conditions for the 100% ruthenation (based on spectroscopic analysis) of model porphyrins.

Porphyrin (porp)	Ru precursor	Ru/Por	T (°C)	Time (h)
TPP[a]	**1**	1.5	141[d]	0.5
TPP[a]	**4**	1.5	141[d]	1
OEP[a]	**1**	1.5	141[d]	0.5
4′TPPS[b]	**1**	6	140[e]	1.5
4′TPPS[b]	**4**	6	140[e]	1.5
4′TMPyP[c]	**1**	6	140[e]	1

[a] in propionic acid; [b] in 1:3 water/propionic acid mixture; [c] in DMF; [d] either at reflux or in MW reactor at 140°C; [e] in MW reactor.

From a mechanistic point of view, since both the Ru(0) cluster **1** and the (less practical) Ru(II) tricarbonyl precursor *fac*-$RuCl_2(CO)_3$(dmso-O) (**4**) gave similar ruthenation performances, the needed change in oxidation state from Ru(0) to Ru(II) in the case of **1** does not seem to play a very relevant role. Nevertheless, the combination of high yield and fast rate of metalation in an acidic medium is rather surprising. Indeed in the first part of this work we observed that the ruthenation of TPP with **5** required the addition of a base and did not occur at all in acidic conditions.

Relatively recent papers – through both experimental and computational approaches – postulated (with simpler metal ions such as Zn^{2+}, Mg^{2+} and Fe^{2+}), that the processes of protonation and metalation of a porphyrin share common mechanistic intermediates.[1,55] In the presence of an acid, protonation of the pyrrolenine nitrogen atoms induces a distortion in the macrocycle (tilting of the diagonally opposing core N-rings) that, with the assistance of the acid-conjugate anion, favors metal coordination. The process is completed by the expulsion of the core protons with concomitant return to planarity of the metalated porphyrin and release of the strain. Our experimental results indicate that, in the moderately acidic environment provided by propionic acid, the large enthalpic driving force for the ruthenation of TPP is not particularly affected by the competition with the double protonation leading to $TPPH_2^{2+}$. It is likely that for neutral and anionic porphyrins propionic acid provides a good combination of solubilizing properties, moderate acidity (pK_a 4.87), boiling point and that – at least in the case of **1** and **4** – the kinetic effect (acid-induced acceleration) largely prevails over equilibrium considerations (i.e. ruthenation vs double protonation). It is arguable that acetic acid, with a comparable pK_a value, is less effective because of its lower boiling point (i.e. slower kinetics at reflux temperature), whereas TFA is much more acidic (pK_a = –0.25, i.e. stronger competition for protonation) and also has a lower boiling point. As noticed above, in propionic acid also the concentration of TPP is relevant for the performance of the reaction, since formation of $TPPH_2^{2+}$ occurs to a larger extent in diluted TPP solutions. With other Ru precursors such as **3** and **5** other factors must prevail and the ruthenation process is either much slower (**3**) or does not occur at all (**5**). Among such factors, solubility of the Ru compound and its stability in that environment are likely to be particularly relevant. Finally, propionic acid is unable to protonate the tetra-cationic porphyrin 4′TMPyP and its ruthenation with **1** is best performed in DMF.

Experimental Section

Materials

All chemicals were purchased from Sigma-Aldrich and used as received. Solvents were of reagent grade. The Ru precursors *cis*-$RuCl_2(dmso)_4$,[56] $Ru_3(CO)_{12}$ (**1**),[35] *fac*-$RuCl_2(dmso)_3(CO)$ (**3**),[39] *fac*-$RuCl_2(CO)_3$(dmso-O) (**4**),[41] Zn·TPP,[4] Ag·TPP,[57] and $[Na]_4$[4′TPPS][58] were synthesized as described in the literature. $[4'TMPyP][I]_4$ was a gift from Dr. Rita De Zorzi, Department of Chemical and Pharmaceutical Sciences, University of Trieste.

Instrumental methods.

^{1}H NMR spectra were recorded at room temperature on a Varian 400 or 500 spectrometer (^{1}H: 400 or 500 MHz). ^{1}H chemical shifts were referenced to the peak of residual non-deuterated solvent (δ = 7.26 for $CDCl_3$). The UV-vis spectra were obtained on an Agilent Cary 60 spectrophotometer, using 1.0 cm path-length quartz cuvettes (3.0 mL). ESI mass spectra were collected in the positive mode on a Perkin-Elmer APII spectrometer at 5600 eV. A thermostatted Berghof stainless steel vessel (autoclave), equipped with a 100 mL Teflon liner, was used for the reactions with CO under pressure. A CEM Discover microwave reactor was used for the microwave-assisted reactions performed in 10 mL vessels. Elemental analyses were performed on a Thermo Flash 2000 CHNS/O analyzer in the Department of Chemistry of the University of Bologna (Italy).

Synthesis

$Ru_3(CO)_{12}$ (1).

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In the course of this work, we developed two alternative synthetic procedures for **1**. In both cases the spectroscopic and analytical features of the isolated compound were coincident with those previously reported.[35,54]

1) as a proof of concept, we demonstrated that *fac*-$RuCl_2(CO)_3$(dmso-O) (**3**) affords **1** in moderate yield when treated with a stream of CO in refluxing ethanol in the presence of a base. This procedure confirms what reported by Lavigne and coworkers,[35] i.e. that the dinuclear species [*fac*-$RuCl(CO)_3(\mu\text{-}Cl)]_2$ (of which **3** is the activated form)[43] is an intermediate in the two-step preparation of **1** from hydrated $RuCl_3$. Even though **3** is certainly a less practical precursor compared to $RuCl_3 \cdot 3H_2O$,[35] the following procedure occurs in a single step and uses the easily available ethanol instead of 2-ethoxyethanol. A 401.0 mg amount of **3** (1.20 mmol) was partially dissolved in 20 mL of ethanol in a two-necked flask connected to a condenser. The system was deaerated (first connected to a vacuum line and then to a reservoir of CO for 3 times), and then warmed to 80°C under a stream of CO. Addition of 2 equiv of KOH (conc. aqueous solution) induced the deep-yellow solution to turn progressively darker and an orange-brown precipitate of **1** formed. After 45 min at 80°C, the mixture was allowed to cool under the CO stream. The precipitate was removed by filtration, washed with water and cold methanol and vacuum dried at room temperature (Yield: 100 mg, 39%). The raw solid was recrystallized from *n*-hexane (22 mL).

2) Reductive carbonylation of the chloride-free Ru(II)-dmso precursor $[Ru(dmso)_6][CF_3SO_3]_2$. The Ru(0) cluster **1** was obtained as the result of an unsuccessful attempt to perform the ruthenation of TPP by treating the porphyrin with $[Ru(dmso)_6][CF_3SO_3]_2$ under a CO pressure. Thus we developed the following procedure: A 100.0 mg amount of $[Ru(dmso)_6][CF_3SO_3]_2$ (0.115 mmol) was partially dissolved in 20 mL of methanol and treated with CO (30 atm, 60°C) in an autoclave for 24h. The resulting yellow solution was rotary evaporated to an oil. Addition of water (5 mL) induced the formation of an orange solid that was removed by filtration and redissolved in dichloromethane. The DCM solution was treated with anhydrous Na_2SO_4 and then evaporated to dryness, affording pure **1** (according to the IR spectrum) as an orange solid that was vacuum dried (Yield: 15.0 mg, 61%).

$[Ru(CO)(dmso)_5][PF_6]_2$ (5).

The synthetic protocol previously reported by us for the preparation of **5**,[41] turned out to be scarcely reproducible. Thus, a modified procedure was developed for the efficient preparation of **5**, that used pure DMSO instead of the original acetone/DMSO solvent mixture. A 191.3 mg amount of *cis,fac*-$RuCl_2(dmso)_3(CO)$ (**3**) (0.44 mmol) was dissolved in 1 mL of DMSO. To the colorless solution a slight excess of $AgPF_6$ (257.1 mg, 1.0 mmol) was added and the solution warmed to 80°C for 1h, during which time a greyish precipitate of AgCl formed. After cooling, the precipitate was removed by filtration on a celite pad that was then thoroughly washed with acetone. The solvent mixture (DMSO + acetone) was completely evaporated under vacuum, yielding a yellow solid, that was dissolved in 3 mL of acetone. Additional undissolved AgCl was removed by filtration as above. The yellow acetone solution was concentrated to ca. 2 mL. Dropwise addition of diethyl ether until cloudiness induced the slow precipitation of the product as pale-yellow crystals, that were recovered by filtration, washed with diethyl ether and vacuum dried at room temperature. Yield: 227 mg (64%). The spectroscopic features of the complex were coincident with those previously reported.[41] Elemental analysis calcd for [$C_{11}H_{30}F_{12}O_6P_2RuS_5$] ($M_w$: 809.64): C 16.32; H 3.73. Found: C 16.5; H 3.89.

Methods for qualitative and quantitative assessment of the ruthenation of the model porphyrins.

The formation of the ruthenated porphyrins was qualitatively monitored by UV-vis spectroscopy. TLC analysis was also used for the neutral porphyrins Ru(CO)(TPP) or Ru(CO)(OEP). The ^{1}H NMR, IR (*ν*CO), ESI-MS, and UV-vis data for Ru(CO)(TPP), Ru(CO)(OEP),[25] Ru(CO)(4′TPPS),[31,32] and Ru(CO)(4′TMPyP)[31] – obtained from solutions where, according to the UV-vis spectra, the full conversion of the free-base porphyrin was achieved – were consistent with those previously reported in the literature for those compounds.

In the case of the most deeply investigated TPP, **t**he UV-vis spectra (a drop of original solution was diluted in ca. 2 mL of chloroform into the cuvette) were useful for quantitatively assessing conversions >90%, but less practical and informative for lower conversion rates, due to the partial overlap of the Q bands of the product with those of the corresponding free base (Figure 2). Thus, in particular for the reactions performed in the MW reactor with **5** as Ru precursor, quantitative analysis was performed by ^{1}H NMR spectroscopy. The following procedure was adopted to treat the sample: 1/3 of the solution was removed from the MW vial and rotary-evaporated to dryness. The purple-greenish solid (depending on the reaction conditions) was washed with a small amount of water, thoroughly dryed under vacuum, and then dissolved in $CDCl_3$. The percentage of ruthenation was obtained through the integration of the well-resolved βH singlets of TPP (8.84 ppm), $TPPH_2^{2+}$ (if present) (8.75 ppm), and Ru(CO)(TPP) (8.69 ppm).[45]

Procedures for the ruthenation of TPP.

The protocols that afforded the best results, both using compound **5** in $CHCl_3$/methanol mixtures and **1** in propionic acid, are reported.

Synthesis of Ru(CO)(TPP) from [Ru(CO)(dmso)$_5$][PF$_6$]$_2$ (5) in the MW reactor.

In a MW vial, a 5.0 mg amount of TPP (0.0074 mmol) was completely dissolved in 3.0 mL of a 2:1 chloroform/methanol mixture. Four equiv of **5** (24.0 mg, 0.030 mmol, only partially soluble) and two equiv of KOH (21 μL of a 0.7 M methanol solution) were added to the purple solution and the mixture was heated at 100°C for the desired time (typically 30 or 60 min) in the MW reactor, yielding a dark green solution with a grayish precipitate (undissolved and/or decomposed complex). At this stage, either the amount of Ru(CO)(TPP) was quantitatively assessed by NMR spectroscopy (and the reaction was terminated), or it was qualitatively assessed by TLC analysis and then, after addition of 2-3 equiv of KOH until the solution turned purple, the mixture was further reacted as above. With this stepwise protocol, a 33% of Ru(CO)(TPP) was obtained in two 30 min steps, whereas a 50% in four 60 min steps.

Preparative synthesis of Ru(CO)(TPP) from $Ru_3(CO)_{12}$ (1) in refluxing propionic acid or in MW reactor.

In a 10 mL MW vial, a 20.0 mg amount of TPP (0.0326 mmol) was partially dissolved in 4 mL of propionic acid. Half equivalent of **1** (8.25 mg) was added to the mixture and heated in a microwave reactor at 140°C for 1h. Conversion was quantitative according to the UV-vis spectrum. The solvent was then removed *in vacuo* and the Ru(CO)(TPP) was purified, in order to remove traces of propionic acid and Ru compounds, by passage through a small column of silica gel eluted with $CHCl_3$. A single red-orange band was collected. To this solution 10 mL of EtOH were added and then the solvent was removed and the solid residue of Ru(CO)(TPP) was vacuum dried. (Isolated yield: 23.7 mg, 92%).

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Keywords

Ruthenium, Porphyrin, Metalation, Propionic acid, Carbonyl

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[53] In this solvent mixture the initial solution is deep green, indicating extensive protonation of the porphyrin to 4′$TPPSH_2^{2+}$. No reaction occurred in pure propionic acid (where 4′TPPS is insoluble) or in water (where **1** is not soluble).

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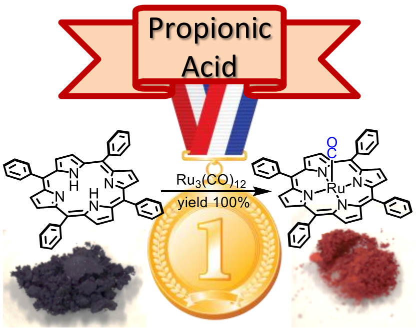
Graphic for Table of Contents



Text for Table of Contents:

As a proof of concept we demonstrate that porphyrin ruthenation can be performed under relatively mild conditions using the Ru(II) monocarbonyl complex $[Ru(CO)(dmso)_5][PF_6]_2$. From a practical point of view, we show the spectacular effect of propionic acid as solvent for performing the ruthenation of neutral and anionic porphyrins with $Ru_3(CO)_{12}$.

Key Topic: Ruthenation of porphyrins