Inorganic Chemistry

Article

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Further Insight into the Lability of MeCN Ligands of Cytotoxic Cycloruthenated Compounds: Evidence for the Antisymbiotic Effect Trans to the Carbon Atom at the Ru Center

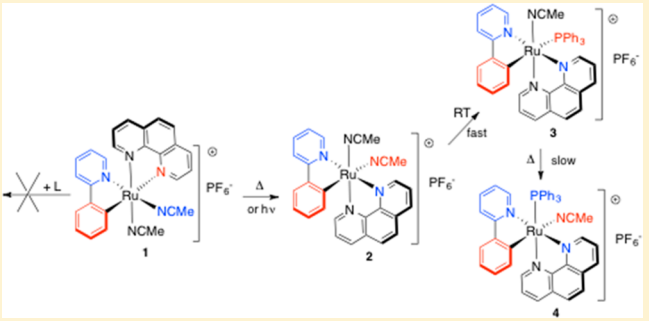
Ana Soraya Lima Barbosa,[†] Christophe Werlé,[†] Claudia Olivia Oliva Colunga,[§] Cecilia Franco Rodríguez,[§] Ruben Alfredo Toscano,[§] Ronan Le Lagadec,*[,§] and Michel Pfeffer*[,†]

[†]Laboratoire de Chimie & Systémique Organo-Métallique of the Institut de Chimie, UMR 7177, CNRS, Université de Strasbourg, 4, rue Blaise Pascal, 67000 Strasbourg, France

[§]Instituto de Química, UNAM, Circuito Exterior s/n, Ciudad Universitaria, Mexico, D. F. 04510, Mexico

Supporting Information

ABSTRACT: The two MeCN ligands in [Ru(2-C_6H_4-2′-Py-κC,N)(Phen, *trans*-C)$(MeCN)_2$]PF_6 (**1**), both *trans* to a sp^2 hybridized N atom, cannot be substituted by any other ligand. In contrast, the isomerized derivative [Ru(2-C_6H_4-2′-Py-κC,N)(Phen, *cis*-C)$(MeCN)_2$]PF_6 (**2**), in which one MeCN ligand is now *trans* to the C atom of the phenyl ring orthometalated to Ru, leads to fast and quantitative substitution reactions with several monodentate ligands. With PPh_3, **2** affords [Ru(2-C_6H_4-2′-Py-κC,N)(Phen, *cis*-C)$(PPh_3)(MeCN)$]PF_6 (**3**), in which PPh_3 is *trans* to the C σ bound to Ru. Compound **3** is not kinetically stable, because, under thermodynamic control, it leads to **4**, in which the PPh_3 is *trans* to a N atom of the Phen ligand. Dimethylsulfoxide (DMSO) can also substitute a MeCN ligand in **2**, leading to **5**, in which DMSO is coordinated to Ru via its S atom *trans* to the N atom of the Phen ligand, the isomer under thermodynamic control being the only compound observed. We also found evidence for the fast to very fast substitution of MeCN in **2** by water or a chloride anion by studying the electronic spectra of **2** in the presence of water or NBu_4Cl, respectively. An isomerization related to that observed between **3** and **4** is also found for the known monophosphine derivative [Ru(2-C_6H_4-2′-Py-κC,N)$(PPh_3$, *trans*-C)$(MeCN)_3$]PF_6 (**10**), in which the PPh_3 is located *trans* to the C of the cyclometalated 2-phenylpyridine, since, upon treatment by refluxing MeCN, it leads to its isomer **11**, [Ru(2-C_6H_4-2′-Py-κC,N)$(PPh_3$, *cis*-C)$(MeCN)_3$]PF_6. Further substitutions are also observed on **11**, whereby N^N chelates (N^N = 2,2′-bipyridine and phenanthroline) substitute two MeCN ligands, affording [Ru(2-C_6H_4-2′-Py-κC,N)$(PPh_3$, *cis*-C)(N^N)$(MeCN)$]PF_6 (**12a** and **12b**). Altogether, the behavior of the obtained complexes by ligand substitution reactions can be rationalized by an antisymbiotic effect on the Ru center, *trans* to the C atom of the cyclometalated unit, leading to compounds having the least nucleophilic ligand *trans* to C whenever an isomerization, involving either a monodentate or a bidentate ligand, is possible.



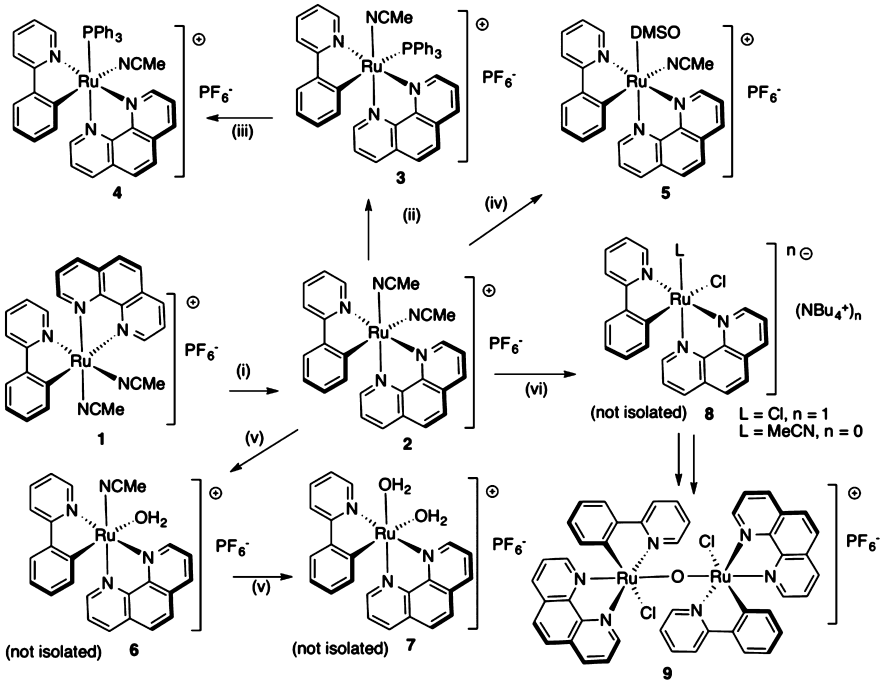
INTRODUCTION

The quest for identifying transition-metal-containing compounds that might display better anticancer activity and lower toxicity than those of cisplatin or oxaliplatin is currently still a very popular research theme. Indeed, thousands of coordination or organometallic compounds involving all metals and presenting many biologic activities against countless tumor cells have been tested throughout the world during the last decades, in the hope of identifying those that could display biologic activities that might be interesting enough so that they warrant further clinic studies.[1] Ruthenium compounds have been studied for this purpose for more than 30 years and two of them (Nami-A and KP1019) have indeed reached phase 2 clinical trials.[2] Among the huge variety of organometallic compounds that have been tested, it appeared already 35 years ago, that compounds where a genuine covalent carbon−metal σ-bond is present might be of special interest in this research area.[3] This is indeed the case of cyclometalated compounds in which the carbon−metal bond is stabilized by an intramolecular coordination bond. Several research groups have successfully used such cyclometalated derivatives for their cytotoxicity against a large variety of cancer cell lines. Recent published reviews[4] have highlighted this property, as well as many other useful applications that these compounds have displayed so far.[5] We chose to study such compounds based on ruthenium and, more recently, osmium, because of their structural resemblance with existing compounds that displayed interesting cytotoxicities against tumor cells and also because, after having extensively studied their reactivity, we had good evidence of

Received: June 1, 2015
Published: July 14, 2015

DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617−7626

Scheme 1. Reaction Conditions[a] (Complexes 1–9)



[a](i) $h\nu$ in acetone/MeCN (9:1) (2 h), Δ in CH_2Cl_2/MeCN (9:1) (72 h) or in $CHCl_2CH_3$/MeCN (9:1) (48 h); (ii) PPh_3 (2 equiv) in acetone, RT, 2 h; (iii) MeOH/MeCN (6:1), reflux, 48 h; (iv) DMSO (2 equiv), CH_2Cl_2/MeCN (6:1), reflux, 12 h; (v) 3 min in MeCN/H_2O (1:9); 30 min in MeCN/H_2O (1:9); (vi) NBu_4Cl (5 equiv) in CH_2Cl_2/MeCN (6:1), 10 min.

their apparent inertness toward ligand exchange processes. Indeed, we have shown ca. 10 years ago that cyclometalated ruthenium compounds displayed important *in vitro* and *in vivo*[6] activities that might be useful for the chemotherapy of cancers. Today, however, we are still lacking enough information about the mechanism of action of these compounds so that we can hardly increase their selectivity toward cancer cells. We recently felt that we should continue studying the chemical reactivity of our compounds in order to better control their behavior in cells *in vitro* and hopefully *in vivo*. This was highlighted by the following observations that we have made on one of our compounds, namely **RDC11** ([Ru(2-C_6H_4-2′-py-κC,N)(Phen, *trans*-C)$(MeCN)_2$]PF_6 (**1**) (where 2-C_6H_4-2′-py-κC,N = cyclometalated 2,2′-phenylpyridine = PhPy, Phen = phenanthroline), in which we have concentrated most of our biological studies so far. Not long ago, we discovered[7] that this compound, which has long been believed to be thermally stable and nonreactive (as no substitution reaction of the MeCN ligands have been observed), could in fact be isomerized either thermally or photochemically. Indeed, UV or visible light irradiation and/or thermal treatment of **RDC11**, obtained via the addition of Phen to [Ru(2-C_6H_4-2′-py-κC,N)$(MeCN)_4$]PF_6, had a dramatic consequence upon its stereochemistry as it isomerized to a new species **2**. In this new compound, one of the nitrogen atoms of Phen has moved from a position *trans* to C to a position *cis* to the same atom, with the freed position *trans* to C being occupied by an acetonitrile ligand. We have discovered that the MeCN ligands of the new species could be readily substituted by N^N chelates, thanks to the large *trans* effect of the C atom of the cycloruthenated PhPy ligand. This property led us to propose new ways to obtain trisheteroleptic compounds such as [Ru(PhPy)(Phen)(N^N)]-PF_6, in which one N atom of the incoming N^N ligand is always and exclusively *trans* to C. In the present article, we further investigate the reactivity of the recently identified isomer **2** and we confirm that it has a rich chemistry, in opposition to that of its precursor, which was apparently inert toward substitution reactions in the absence of heat or light. This investigation has been complemented by the study of phosphine ligands containing complexes that display a behavior analogous to that of **1**. It is obviously of great importance to control every chemical feature of potential drugs, especially when studying their mechanisms of action in biological media. We have thus embarked on a research aimed at satisfying our curiosity about the chemistry of **RDC11**, its stereoisomer and of the compounds derived from the latter.

RESULTS AND DISCUSSION

The presence of coordinating solvents such as MeCN or acetone is important in order to observe the different species that we are examining in the next sections. (See Scheme 1.) In the absence of such solvents, as we have already shown,[7] the decomposition of the isomerized products was fast, e.g., in pure dichloromethane. In the presence of small amounts of MeCN (CH_2Cl_2/MeCN or MeOH/MeCN = 6:1) or in acetone, the substitution of the coordinated acetonitrile ligand is obviously slower, but this avoids the occurrence of decomposition reactions that might take place if the concentration of the new ligand is low. We first checked that no reaction occurred between **1** and any of the nucleophiles used in this paper when the reactions were performed in darkness or at room temperature. However, as the isomerization of **1** may already proceed at room temperature (although very slowly), tiny amounts of the isomerized **2** could be observed if the reaction was performed during more than 48 h. If the reaction was performed at higher temperature and during a long enough time, the isomerization of **1** to **2** was observed in good yields, as

DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617–7626

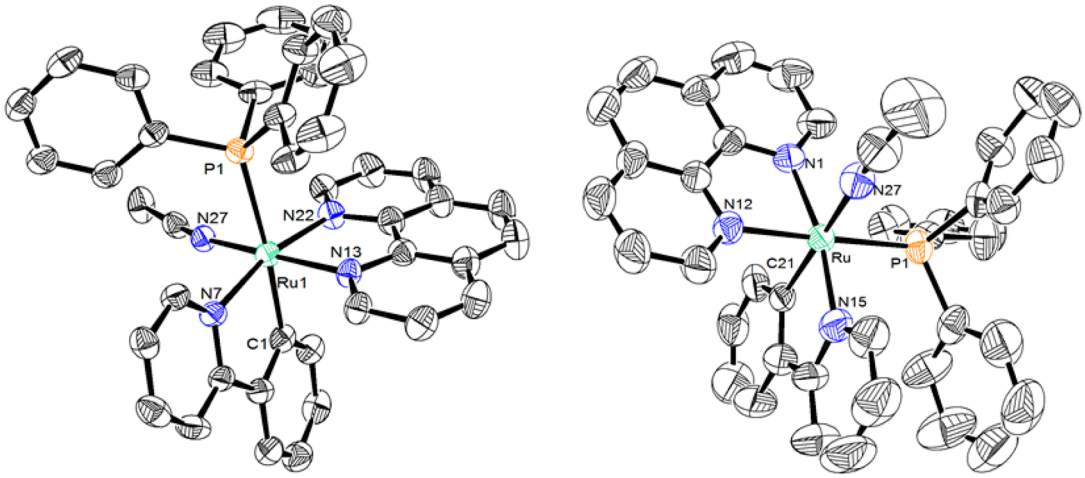


Figure 1. Perspective views of compounds **3** and **4**. Ellipsoids are drawn at a probability level of 50%. (H and PF_6^- omitted for the sake of clarity.)

the isomerization reaction occurred almost quantitatively and the corresponding amounts of substitution products were produced. These results led us to conclude that the obtained products are, in most cases, the result of the substitution of the MeCN on the isomerized product **2**, and not of a direct substitution of one MeCN on **1**.

Substitution of MeCN in 2 by PPh_3, DMSO, H_2O, and Cl^-. We first treated **2** with excess PPh_3 in refluxing MeOH/MeCN and, after 1 h, we observed the quantitative formation of **3**, together with minute amounts of **4**. The **3**:**4** ratio decreased with time, and it was soon clear that **3** was the compound obtained under kinetic control, whereas **4** was the compound formed under thermodynamic control of the substitution reaction of one MeCN by PPh_3. Indeed, after 24 h at the reflux temperature of the solvent, **4** appeared to be the major compound of the reaction. The ^{1}H NMR spectrum of **3** and **4** displayed characteristic features that were assigned to their structures: for instance, for **3**, the signal of the proton *ortho* to the C atom covalently bound to Ru (5.81 ppm) showed a $^4J_{PH}$ coupling constant of 3.6 Hz, whereas no such $^4J_{PH}$ coupling was visible for the corresponding proton of **4** that resonated at 5.84 ppm. In addition, the ^{31}P NMR spectra revealed that the chemical shifts of PPh_3 were of 24.46 and 52.64 ppm for **3** and **4**, respectively. These data are a strong indication that the PPh_3 was bound to Ru *trans* to the ruthenated phenyl group of PhPy in **3** and *trans* to one N of the phen ligand (i.e., *cis* to C) in **4**. We could grow crystals suitable for X-ray diffraction (XRD) studies of both compounds. The perspective views of **3** and **4** are given in Figure 1. The structures that were obtained fully confirmed our assignments based on the NMR spectra. Moreover, the Ru−P bond distances were indeed characteristic of PPh_3 *trans* to a phenyl group (2.4309(13) Å) and *trans* to a pyridine ligand (2.325(12) Å) for **3** and **4**, respectively, this being consistent with the well-known larger *trans* influence of a phenyl versus that of a pyridine ligand.[8]

When we added 2 equiv of DMSO in a CH_2Cl_2/MeCN solution of **2** under a strict absence of oxygen (i.e., in a glovebox), the formation of a new compound **5** was observed, whose ^{1}H NMR spectrum revealed the presence of diastereotopic methyl groups of DMSO (3.05 and 2.13 ppm) coordinated on a chiral ruthenium center. In addition, the aromatic region of the spectrum showed resonances at chemical shifts significantly different from those of **2**, for example, one of the *ortho* to N protons of the phenanthroline ligand resonated at lower field (10.5 vs 9.5 ppm). The crystal structure, which is depicted in Figure 2, indicated that the DMSO is indeed

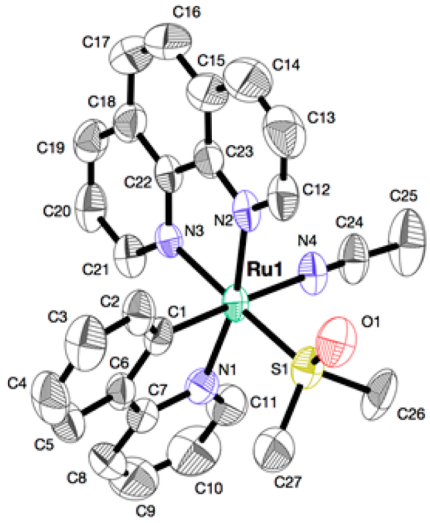


Figure 2. Perspective view of compound **5**. Ellipsoids are drawn at a probability level of 50%. (H and PF_6^- omitted for the sake of clarity.)

coordinated to Ru via its S atom and that this ligand is coordinated *trans* to one of the N atoms of the phenanthroline ligand. This result seemed to indicate that the substitution of the MeCN *trans* to the phen ligand was observed prior to the substitution of the MeCN *trans* to C. However, we cannot rule out the fact that this compound could arise from a too fast isomerization of an intermediate compound that would have the DMSO ligand *trans* to C.

We also observed a fast reaction in darkness between **2** and water when studying solutions of **2** in MeCN/H_2O via ultraviolet−visible light (UV-vis) spectroscopy, provided however that the amount of water was large enough, with respect to the amount of MeCN. Indeed, whereas no reaction seemed to occur in MeCN/H_2O (1/1) even after 4 h, a different behavior was observed when the amount of water was superior to that of acetonitrile. For instance, when we examined the UV-vis spectrum of **2** in a solution containing 9 equiv of water and 1 equiv of MeCN, (MeCN/H_2O = 1/9), we could observe that three different reactions occurred successively, as shown on Figure 3. Whereas **1** had a strong absorption at 480

DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617−7626

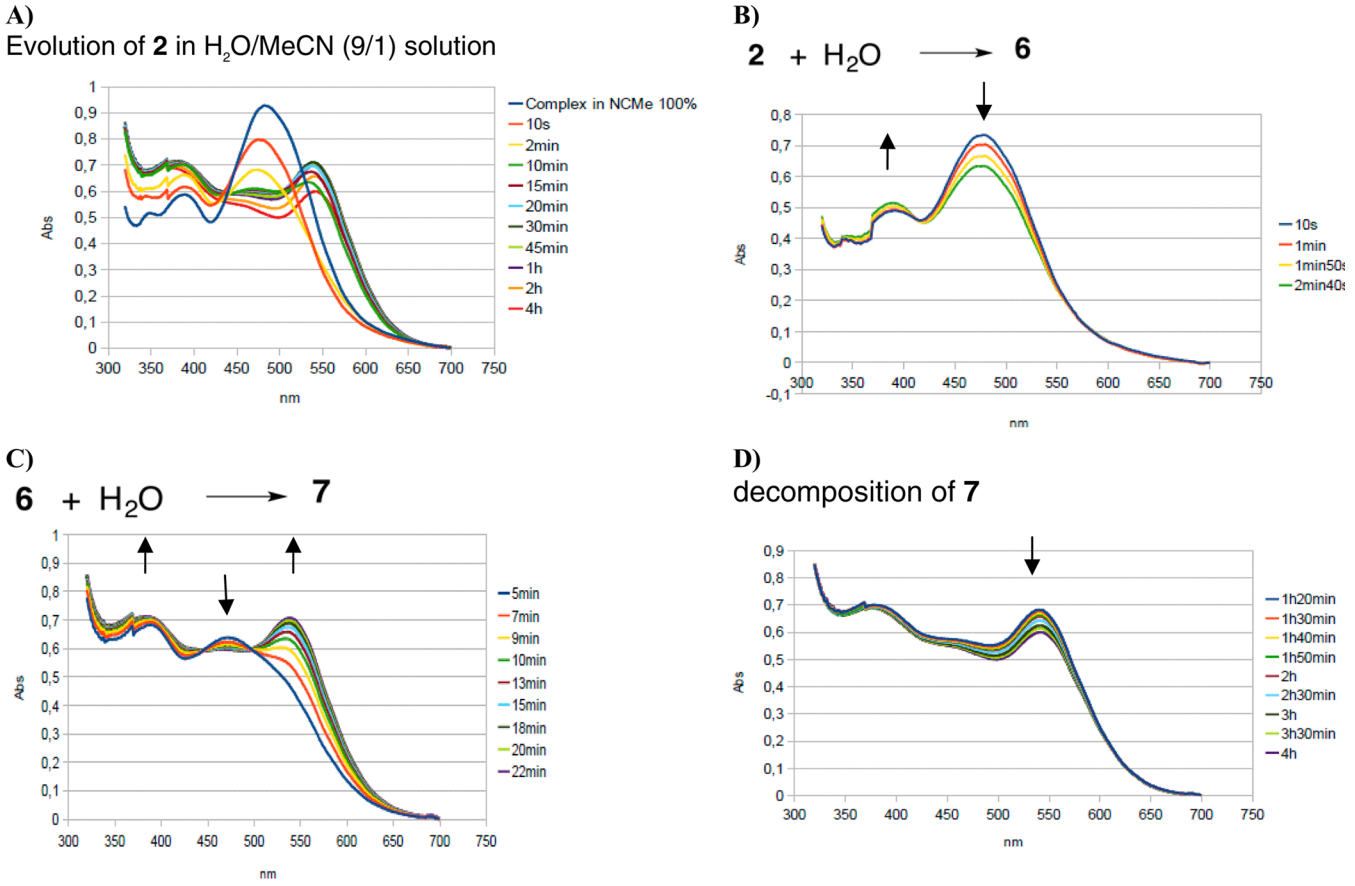


Figure 3. Electronic spectra of **2** in H_2O/MeCN (9:1) solution (10^{-4} M): (A) evolution from 10 s to 4 h, (B) evolution from 10 s to 160 s (isosbestic point at 412 nm), (C) evolution from 5 min to 22 min (isosbestic points: 455 and 498 nm), and (D) evolution after 80 min.

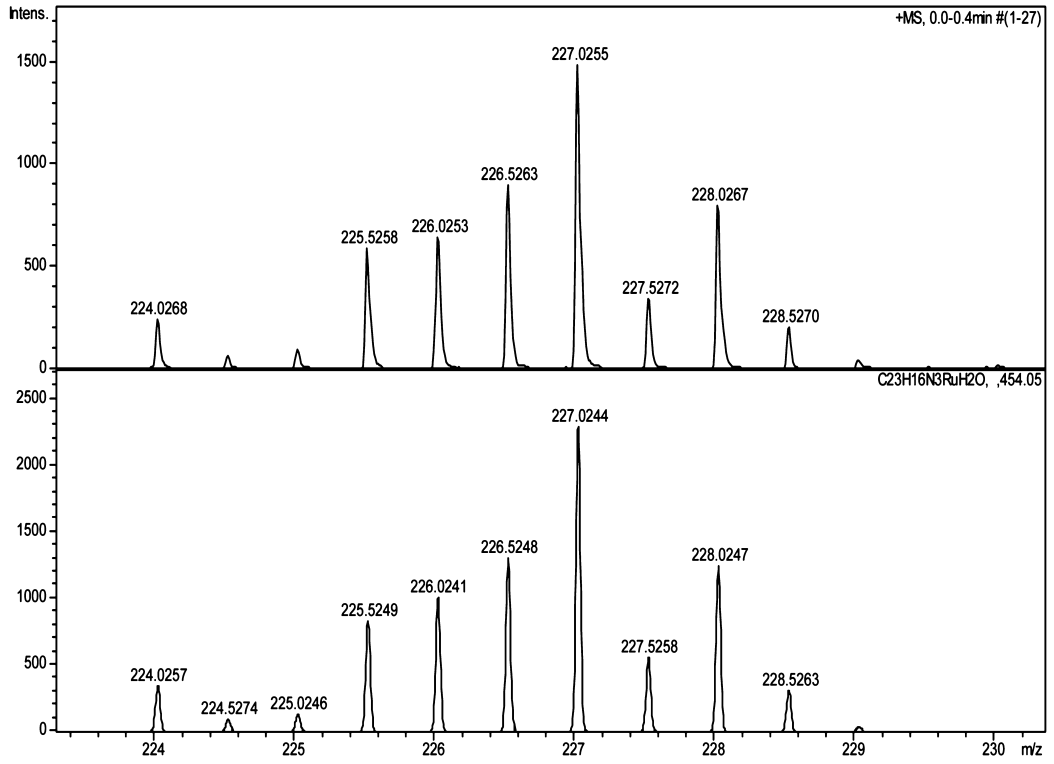


Figure 4. ESI-MS spectrum of **2** in a H_2O/MeCN solution showing the peak for $[Ru(2\text{-}C_6H_4\text{-}2'\text{-py-}\kappa C,N)(Phen)(H_2O)]^{2+}$. The upper trace shows the experimental spectrum, and the lower trace shows a simulated one.

DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617−7626

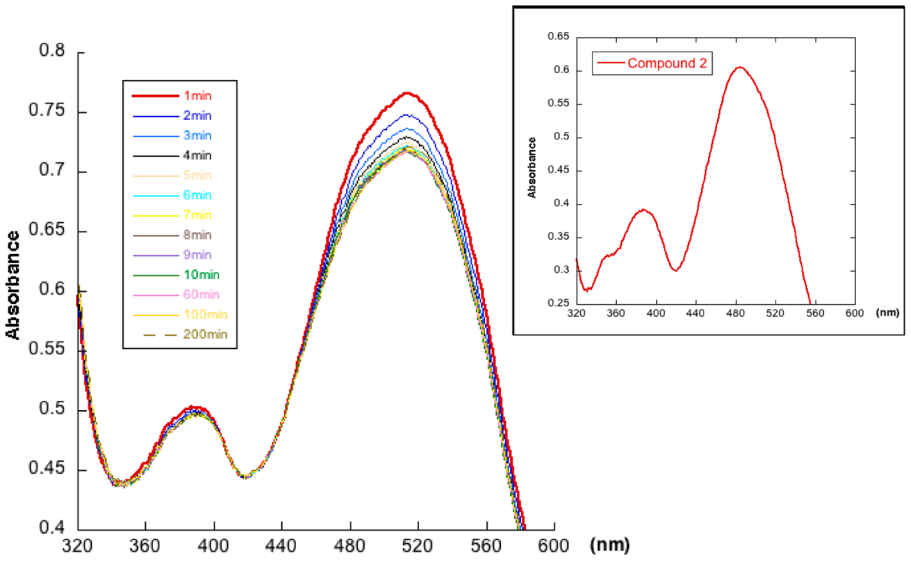


Figure 5. Behavior of **2** in a $MeCN/CH_2Cl_2$ solution in the presence of 5 equiv of Bu_4NCl. Inset shows the spectrum of **2** in the same solvent mixture (no change with time).

nm, which was shown to be a MLCT transition,[9] **2** had a maximum absorption at 484 nm. We saw a rapid evolution (within <3 min) of the spectrum of **2** in this $H_2O/MeCN$ solution with an isosbestic point, this pointing to the existence of only two species during this evolution. We suggest that one molecule of water substituted one MeCN ligand (probably the MeCN *trans* to the C atom, affording **6**) during this first process. A second reaction took place within a time interval of 20 min during which a new absorption arose at 546 nm with the occurrence of two isosbestic points. This result suggests that the second MeCN ligand was substituted by water, leading to **7**. The third reaction occurred after 80 min and the obtained spectra pointed to decomposition of the products, no isosbestic points being visible during the evolution. We could check the coordination of water at the Ru atom when dissolving **2** in a water/MeCN solution by running an electrospray-MS spectrum of **2** dissolved in these solvents. Indeed, we could detect (see Figure 4) a signal at m/z = 227.02 ($C_{23}H_{18}N_3ORu$) with an isotope pattern consistent with the simulation that corresponded to a dication of [**2** − 2MeCN + H_2O], i.e., [Ru(III)(2-C_6H_4-2′-py-κC,N)(phen)(H_2O)]$^{2+}$. Another signal was observed at 453.04 with a correct isotope pattern (the precision was 10 ppm) that we assigned to the monocation of [**2** − 2MeCN + OH] in which again the ruthenium has been oxidized. These results strengthen the hypothesis of the formation of aquo derivatives, however the Ru atom has probably been oxidized to Ru(III) prior or during the ionization of the compound.

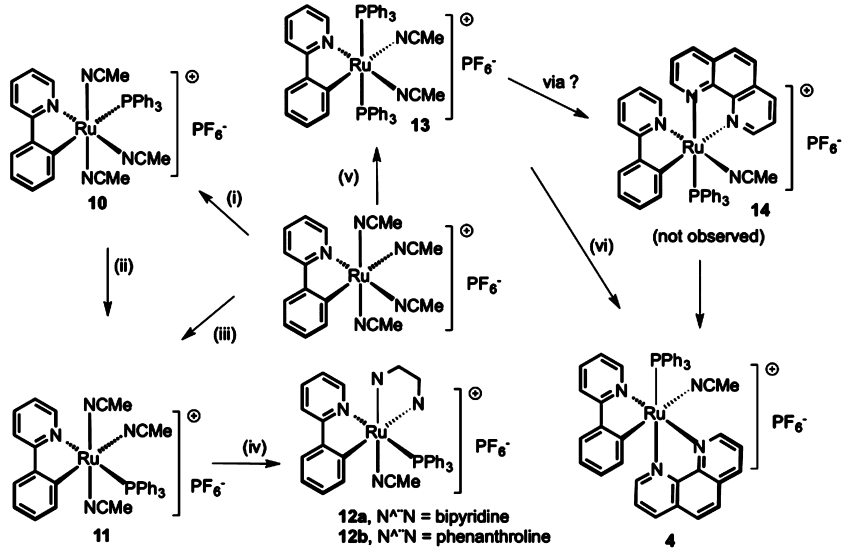
These results are somewhat consistent with those of a recent paper whose objective was to study the substitution of the MeCN ligands of **1** under visible light.[10] However, in this work, the substitution process in water only took place after at least 90 min and the first substitution reaction was over after 180 min. This can be rationalized by the fact that the first substitution only took place *after* the isomerization of **1** to **2** has occurred; in other words, the water ligand did not substitute a MeCN ligand as long as this ligand was *trans* to a pyridine or a phenanthroline ligand. The authors also saw isosbestic points for their reaction: the two species that are thus present in their reaction medium were likely to be **1** and **6** (since **2** should not be present, because it led to **6** within <3 min). The second substitution could then take place according to our present results.

When **2** was treated with an excess of Cl^- (from Bu_4NCl) in CH_2Cl_2/MeCN (6:1) in a glovebox, we observed the immediate formation of a new purple species that we could only analyze by UV-vis and NMR spectroscopy, because our efforts to get crystals of the products of this reaction failed. The UV-vis spectrum showed a new absorption (as compared to **2**) at 514 nm (see Figure 5). The ^1H NMR spectrum of this new species in CD_2Cl_2 displayed two signals, at 2.32 ppm and at 1.97 ppm, i.e., typical of MeCN coordinated to Ru trans to N of PhPy and of noncoordinated MeCN, respectively. A few changes in the aromatic region relevant to a different coordination around the Ru center were also identified (see the Experimental Section). We have unfortunately no data that could allow us to decide unambiguously whether the new compound (**8**) was a pure neutral compound with a Cl ligand *trans* to C of PhPy, or if it was a mixture of the latter and an anionic compound in which both MeCN have been substituted by Cl^-. Contrary to what we observed for the reaction with water, these latter results are remarkably different from those previously reported[10] for the substitution reaction of MeCN by chloride anion in the presence of visible light. The authors reported the formation of [Ru(PhPy)(Phen)(MeCN)Cl] based on the observation of two isosbestic points and the appearance of a strong absorption at ∼560 nm that we did not observe. Since this reaction was very fast (it seemed to be completed within 120 s), it is not possible that the isomerization of **1** to **2** had taken place as it requires at least 1−2 h to be identifiable. Therefore, it is likely that, in this specific reaction, the isomerization of **1** to **2** was not a prerequisite for the substitution of MeCN by Cl^- to take place and that a reaction product, different from ours (derived from **1** with a Cl *trans* to a phenanthroline ligand), might have been obtained by Turro and co-workers.[10]

Solutions of **8** in CH_2Cl_2 decomposed in air, probably by following a process that we have encountered earlier. We have previously found[11] that irradiation of a methanol solution of **1** led to an intermediate that (i) we did not characterize and (ii)

DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617−7626

Scheme 2. Reaction Conditions[a] (Complexes 10−14)



[a](i) PPh_3 (1 equiv) in MeOH/MeCN (6:1), RT, 4 h; (ii) MeCN, reflux, 24 h; (iii) PPh_3 (1 equiv) in MeOH/MeCN (6:1), reflux, 24 h; (iv) 2,2′-bipyridine or phenanthroline in MeCN, reflux, 45 h; (v) PPh_3 (2 equiv) in MeCN reflux, 24 h; and (vi) phenanthroline (2 equiv), MeCN, reflux 4 h.

was reacted with Cl^-, forming, after oxidation in air, a dinuclear species (**9**) having a bridging oxo unit between two Ru atoms, each of them linked to a Cl^- ion, an orthometalated PhPy, and a phenanthroline ligand. Based on the results that we have now obtained in the present study, it is reasonable to assume that the uncharacterized intermediate is a bis-methanol adduct analogue to **7** as the treatment of **1** by light should have isomerized **1** and the substitution of the MeCN ligand by MeOH should have occurred according to what we have seen in the present work. Therefore, it is very likely that the decomposition of **8** in air might lead to a compound similar to **9**.

Occurrence of an Antisymbiotic Effect *trans* to C on a Phosphine Derivative. Intrigued by the facile isomerization of **1** upon thermal or photochemical conditions,[4] we decided to investigate the behavior of the compound **10** (see Scheme 2) that we described recently.[6b] Following the same path previously described for compound **3** that isomerized to **4** after several hours at higher temperatures, the coordination of PPh_3 *trans* to C is likely to be kinetically unstable, because of an expected antisymbiotic effect that should exist in these compounds at the position *trans* to C. The concept of antisymbiosis, which was first proposed by Pearson,[12] predicted that when a nucleophilic ligand such as a PPh_3 is coordinated to a metal of the second row *trans* to a soft atom such as a C from a phenyl unit, this ligand should be destabilized in such a way that it should isomerize to a position *trans* to a less nucleophilic atom.

We thus treated **10** under thermal conditions, i.e., under refluxing acetonitrile and found that, as expected, the compound totally isomerized after 24 h. The new structure of **11** was ascertained by a crystal structure determination, which unambiguously showed that PPh_3 was now located *trans* to N as the Ru−P distance (2.3102(7) Å) was significantly lower than in **10** (2.458(1) Å, as expected for a phosphine *trans* to a pyridine versus a phenyl ligand, respectively (see Figure 6).[8] On the other hand, the MeCN *trans* to C (Ru−N = 2.134(2) Å) is close to those of closely related compounds[6b] in which this ligand was *trans* to the same C atom. This

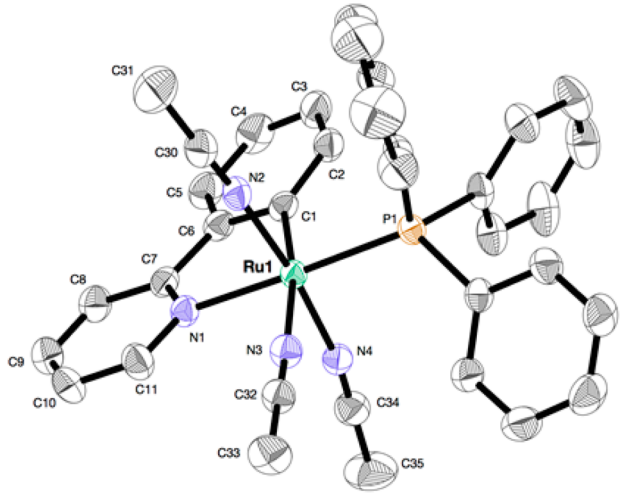


Figure 6. Perspective view of compound **11**. Ellipsoids are drawn at a probability level of 50%. (H and PF_6^- omitted for the sake of clarity.)

destabilization of a phosphine *trans* to a C−metal bond has been shown to also take place at the position *trans* to C in cyclopalladated complexes[13] and it recently led Vicente et al. to elaborate on the concept of transphobia for soft ligands coordinated *trans* to the C atoms of cyclopalladated compounds.[14] Interestingly, a similar behavior has been observed in a cycloplatinated 2-dimethylbenzylamine compound in which the triphenyl phosphine ligand was first coordinated *trans* to C of the cyclometalated ligand and then rapidly isomerized to the corresponding isomer in which the phosphine was *trans* to N.[15] The authors proposed that the tendency for isomerization of a ligand trans to C, which has a strong *trans* effect, is related to its own kinetic *trans* effect and its capacity of π back-bonding. Thus, a phosphine should be more destabilized *trans* to C, compared to MeCN, because of both its larger kinetic *trans* effect and its important π-acceptor capacities.

The new compound (**11**) with an acetonitrile ligand *trans* to C was, as expected, reactive toward 2,2′-bipyridine or

DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617−7626

phenanthroline, leading to **12a** (see Figure 7) and **12b** respectively. Note that this latter compound could not be obtained by treating **1** with PPh_3. Earlier, we also described the synthesis of compound **13**, by adding 2 equiv of PPh_3 on the starting compound $[Ru(PhPy)(MeCN)_4]PF_6$. In **13**, the MeCN *trans* to C was again susceptible to be substituted by a phenanthroline ligand to afford **14**. However, this did not occur, as we observed the formation of **4** only. Thus, as for the reaction of **2** with DMSO, the phen ligand was probably too destabilized at the position *trans* to C, because the reaction had to be performed at the refluxing temperature of MeCN to be effective. Again, we cannot rule out the formation of the transient **14**, which should quickly isomerize, placing the phen *trans* to N and not *trans* to C under thermodynamic control of the reaction.

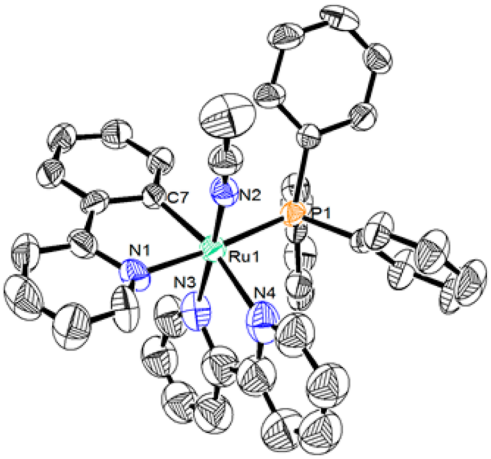


Figure 7. Perspective view of compound **12a**. Ellipsoids are drawn at a probability level of 50%. (H and PF_6^- omitted for clarity.)

Data regarding the bond distances and bond angles for selected complexes are given in Table 1.

CONCLUSION

This study has allowed us to confirm the huge *trans* effect displayed by a σ-bonded C atom linked to a Ru(II) center. Indeed, it may not only displace a MeCN or a PR_3 ligand but also (although less readily) a chelating ligand. This behavior must be taken into account when studying the behavior of these compounds in biological media. The displacements of ligands that we have studied here led, in most cases, to compounds thermodynamically stable with a MeCN ligand *trans* to a C atom (see **2**, **4**, **5**, or **11**). It may well be anticipated that this position should now be easily occupied by any more or less strongly coordinating ligands that are found in biological media (see the reaction of **2** with water). Indeed, it has already been shown[10] that the *in situ*-formed **2** by irradiating **1** with visible light, led to significantly improved cytotoxicity, with respect to **1**, and that the new photoproduct **2** showed much higher affinity for DNA than **1**.

EXPERIMENTAL SECTION

General Remarks. Experiments were carried out under an argon atmosphere, using a vacuum line. Diethyl ether and pentane were distilled over sodium/benzophenone, dichloromethane, and acetonitrile over calcium hydride and methanol and ethanol over magnesium under an argon atmosphere immediately before use. Chromatography columns were carried out on aluminum oxide (aluminum oxide 90, standardized, Merck). The other starting materials were purchased from Sigma–Aldrich, Alfa Aesar, or Strem Chemicals and used as received, without further purification.

Ruthenium complexes listed hereafter were synthesized following already reported procedures: $[Ru(2\text{-}C_6H_4\text{-}2'\text{-}py\text{-}\kappa C,N)(NCMe)_4]PF_6$,[16] $[Ru(2\text{-}C_6H_4\text{-}2'\text{-}py\text{-}\kappa C,N)(phen, trans\text{-}C)(NCMe)_2]PF_6$ (**1**),[11] $[Ru(2\text{-}C_6H_4\text{-}2'\text{-}py\text{-}\kappa C,N)(phen, cis\text{-}C)(NCMe)_2]PF_6$ (**2**),[7] $[Ru(2\text{-}C_6H_4\text{-}2'\text{-}py\text{-}\kappa C,N)(PPh_3, trans\text{-}C)(NCMe)_3]PF_6$ (**10**),[6b] and $[trans\text{-}Ru(2\text{-}C_6H_4\text{-}2'\text{-}py\text{-}\kappa C,N)\text{-}(PPh_3)_2(NCMe)_2]PF_6$ (**13**).[6b]

The NMR spectra were obtained at room temperature on Bruker or JEOL spectrometers. ^1H NMR spectra were recorded at 300.13 MHz (Model AC-300), 300.53 MHz (Model GX300), 400.13 MHz (Model AM-400), or 500.13 MHz (Bruker, Model Avance I 500). The chemical shifts are referenced to the residual solvent peak. $^{13}C\{^1H\}$ NMR spectra were recorded at 75.48 MHz (Model AC-300), 75.56 MHz (Model GX300), or 100.62 MHz (Model AC-400) and referenced to $SiMe_4$. ^{31}P NMR spectra were recorded at 161.98 MHz (Model AC-400) or at 121.5 MHz (Model GX300) and referenced to H_3PO_4. The NMR assignments were supported by COSY spectra for ^1H NMR. Chemical shifts (δ) and coupling constants (J) are expressed in units of ppm and Hz, respectively. (Multiplicity: s = singulet, d = doublet, t = triplet, q = quadruplet, h = heptuplet, m = multiplet.) Electronic absorption spectra were recorded using an Uvikon XL spectrophotometer from Bio-Tek Instruments with quartz cells of 1 cm wide. Mass spectra (FAB^+) were obtained using a JEOL Model JMS-SX102A instrument with *m*-nitrobenzyl alcohol as a matrix. ESI-MS measurements were performed on a Bruker Daltonics microTOF spectrometer equipped with

Table 1. Bond Distances and Bond Angles for Selected Crystal Structures

complex **3**		complex **4**		complex **5**		complex **11**		complex **12a**	
Bond Distances (Å)									
C1–Ru	2.061(5)	C21–Ru	2.042(4)	N1–Ru	2.076(2)	N1–Ru	2.124(2)	C7–Ru	2.053(8)
N7–Ru	2.103(4)	N15–Ru	2.070(4)	N2–Ru	2.088(2)	C1–Ru	2.055(2)	N1–Ru	2.078(6)
N13–Ru	2.063(3)	N1–Ru	2.099(4)	N3–Ru	2.106(2)	N2–Ru	2.006(2)	N2–Ru	2.013(7)
N22–Ru	2.051(4)	N12–Ru	2.112(4)	N4–Ru	2.135(2)	N3–Ru	2.134(2)	N3–Ru	2.051(8)
N27–Ru	2.028(4)	N27–Ru	2.117(4)	C1–Ru	2.022(2)	N4–Ru	2.026(2)	N4–Ru	2.191(2)
P1–Ru	2.4309(13)	P1–Ru	2.325(12)	S1–Ru	2.2421(8)	P1–Ru	2.3102(7)	P1–Ru	2.308(2)
Bond Angles (deg)									
C1–Ru–N7	79.2(2)	N1–Ru–N12	78.5(1)	C1–Ru–N1	80.26(11)	C1–Ru–N1	79.55(7)	N3–Ru–C7	89.2(3)
N13–Ru–N22	80.4(1)	C21–Ru–N15	79.8(2)	C1–Ru–S1	88.54(8)	N4–Ru–N2	172.6(1)	N3–Ru–N4	81.6(4)
C1–Ru–P1	174.9(1)	N12–Ru–P1	178.7(1)	N3–Ru–S1	178.38(7)	N1–Ru–P1	177.5(1)	C7–Ru–P1	96.9(2)

DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617–7626

an orthogonal electrospray (ESI) interface. Infrared spectra were recorded on a Nicolet FTIR Magna 750 instrument in KBr disks or on a Bruker-Alpha ATR apparatus.

Synthesis. *[Ru(2-C_6H_4-2′-py-κC,N)(phen)(PPh_3, trans-C)(NCMe)]PF_6 (**3**).* A solution of 100 mg (0.15 mmol) of **2** and 80 mg (0.3 mmol) of PPh_3 in 15 mL of acetone was stirred at room temperature for 2 h. The mixture was evaporated to dryness under vacuum, washed with Et_2O to remove excess of PPh_3 and the residue purified through Al_2O_3 using dichloromethane as eluent. Crystallization from dichloromethane/diethyl ether gave red crystals (53 mg, 40%) suitable for X-ray analysis, which were washed with diethyl ether and dried under vacuum.

^{1}H NMR (400.13 MHz, CD_3CN): 9.02 (d, 1H, ^3J = 5.3 Hz), 8.97 (d, 1H, ^3J = 5.3 Hz), 8.31 (d, 1H, ^3J = 8 Hz), 8.17 (d, 1H, ^3J = 8 Hz), 8.09 (d, 1H, ^3J = 8 Hz), 7.95 and 7.91 (AB pattern, 2H, ^3J = 8.8 Hz), 7.88−7.83 (m, 2H), 7.78 (d, 1H, ^3J = 8 Hz), 7.68−7.56 (m, 3H), 7.38 (m, 2H), 7.28 (m, 4H), 7.19 (m, 2H) 7.13 (m, 3H), 7.03 (td, 1H, ^3J = 6.8, ^4J = 1.8 Hz), 6.95 (m, 3H), 6.80 (td, 1H,^3J = 7.6, ^4J = 1.1 Hz), 6.54 (td, 1H, ^3J = 7.3, ^4J = 1.4 Hz), 5.81 (ddd, 1H, ^3J = 7.3, ^4J = 1, $^4J_{PH}$ = 3.6 Hz) 2.18 (d, 3H, $^5J_{PH}$ = 3.5 Hz). ^{13}C{^{1}H} NMR (100.62 MHz, acetone-d_6): 186.64, 185.63, 168.55, 156.72, 156.61, 152.27, 151.15, 159.81, 147.52, 147.06, 145.34, 136.93, 133.69, 132.97, 132.82, 132.66, 132.32, 131.84 129.32, 128.42, 128.31, 127.47, 127.15, 125.61, 124.73, 121.97, 119.34, 3.54.

^{31}P{^{1}H} NMR (121.5 MHz, acetone-d_6): 24.46 (s, PPh_3), −144.21 (h, J_{P-F} = 705.97 Hz, PF_6).

IR (FTR) [cm^{-1}]: 2257 (m, νCN), 833 cm^{-1} (s, νPF_6^-).

M/S FAB$^+$: 698 [(M+H) − MeCN], 436 [(M+H) − (MeCN + PPh_3)], 282 [(M+H) − (MeCN + PPh_3 + phpy)]$^+$. Anal. Calculated for $C_{43}H_{34}N_4F_6P_2Ru{\cdot}0.2CH_2Cl_2$: C, 57.60; H, 3.85; N, 6.22. Found C, 57.68; H, 3.50; N, 6.26.

*Ru(2-C_6H_4-2′-py-κC,N)(phen)(PPh_3)(NCMe, trans-C)]PF_6 (**4**).* A solution of 200 mg (0.20 mmol) of [*trans*-Ru(Phpy)(PPh_3)$_2$(NCMe)$_2$]PF_6 (**13**) and 72 mg (0.40 mmol) of 1,10-phenanthroline in 15 mL of acetonitrile was heated to reflux for 4 h. The mixture was evaporated to dryness under vacuum and the residue purified through Al_2O_3 using dichloromethane as an eluent. Crystallization from dichloromethane/diethyl ether gave red crystals (120 mg, 68%) suitable for X-ray analysis, which were washed with diethyl ether and dried under vacuum.

^{1}H NMR (300.53 MHz, CD_3CN): 9.24 (dd, 1H, ^3J = 5.2 Hz, ^4J = 1.1 Hz), 8.67 (dd, 1H, ^3J = 5.2 Hz, ^4J = 1.1 Hz), 8.51 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.1 Hz), 8.38 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.2 Hz), 8.12 (d, 1H, ^3J = 8.9 Hz), 8.04 (d, 1H, ^3J = 8.9 Hz), 7.64−7.47 (m, 6H), 7.33−7.25 (m, 3H), 7.20−7.15 (m, 12H), 6.94 (td, 1H, ^3J = 5.7 Hz, ^4J = 1.7 Hz), 6.66 (td, 1H, ^3J = 7.4 Hz, ^4J = 1.1 Hz), 6.35 (td, 1H, ^3J = 7.4 Hz, ^4J = 1.1 Hz), 5.84 (d, 1H, ^3J = 7.4 Hz), 2.08 (s, 3H, NCMe).

^{31}P{^{1}H} NMR (121.5 MHz, CD_3CN,): 52.64 (s, Ph_3P), −144.02 (h, J_{P-F} = 706.87 Hz, PF_6).

IR KBr [cm^{-1}]: 2271 (m, νNCMe), 840 (s, νPF_6),

M/S [FAB$^+$, *m*/*z* (%)]: 739 (3) [M+H]$^+$, 698 (100) [M+H − NCMe]$^+$, 518 (3) [M+H − NCMe − phen]$^+$, 436 (65) [M +H − NCMe − PPh_3]$^+$, 256 (6) [M+H − NCMe − PPh_3 − phen]$^+$.

Anal. Calcd for $C_{43}H_{34}F_6N_4P_2Ru$: C, 58.88; H, 3.88; N, 6.34. Found: C, 59.09; H, 3.63; N, 6.33.

*[Ru(2-C_6H_4-2′-py-κC,N)(phen)(DMSO)(NCMe, trans-C)]PF_6 (**5**).* A solution of **2** (100 mg, 0.15 mmol) and DMSO (0.022 mL, 0.30 mmol) in a mixture of dry CH_2Cl_2:acetonitrile 6:1 (15 mL) was refluxed for 12 h under vigorous stirring. After reduction of the volume of the orange/red solution, the solution was immediately filtered through alumina, using a 90:10 CH_2Cl_2/NCMe mixture as an eluent. The dark red fraction was collected and evaporated to dryness under vacuum. Flash chromatography in CH_2Cl_2/MeCN (9:1) allowed the elimination of the remaining **2**. Crystallization from dichloromethane/pentane gave orange microcrystals (0.086 mg, 81%), which were found to be suitable for X-ray analysis.

^{1}H NMR (500.13 MHz, CD_2Cl_2) δ: 10.51 (dd, *J* = 5.3, 1.4 Hz, 1H), 9.08 (dt, *J* = 5.5, 1.2 Hz, 1H), 8.50 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.33 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 8.03−7.86 (m, 4H), 7.65 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.60 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.53 (ddd, *J* = 6.4, 5.3, 2.3 Hz, 2H), 6.81 (td, *J* = 7.5, 1.3 Hz, 1H), 6.59 (td, *J* = 7.4, 1.3 Hz, 1H), 6.29 (dd, *J* = 7.6, 1.3 Hz, 1H), 3.44 (q, Et_2O), 3.05 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 1.16 (t, Et_2O).

^{13}C NMR (126 MHz, CD_2Cl_2) δ: 181.27, 167.06, 155.44, 152.39, 148.94, 147.92, 145.98, 145.27, 137.52, 136.08, 135.98, 135.02, 130.29, 129.73, 128.62, 127.75, 126.83, 125.22, 124.71, 124.18, 123.58, 121.76, 121.51, 119.55, 46.74, 44.02, 3.44.

HRMS (ESI, *m*/*z*): Calcd for $C_{27}H_{25}N_4ORuS$ (M): 555.0793. Found: 555.0751.

Anal. Calcd for $C_{27}H_{25}F_6N_4OPRuS{\cdot}0.5Et_2O$: C, 47.28; H, 4.10; N, 7.61. Found: C, 46.91; H, 4.48; N, 7.35.

*Ru(2-C_6H_4-2′-py-κC,N)(phen)(NCMe)Cl and/or [Ru(2-C_6H_4-2′-py-κC,N)(phen)Cl_2]Bu_4N (**8**).* A solution of **2** (10 mg, 0.015 mmol) and NBu_4Cl (77 mg, 0.075 mmol) in a mixture of dry CH_2Cl_2:CH_3CN 6:1 (15 mL) was stirred for ca. 10 min at room temperature, affording a dark purple solution. No purification of these compounds could be performed, because of their instability.

^{1}H NMR (400.13 MHz, CD_2Cl_2) δ: 10.04 (d, *J* = 5.3 Hz, 1H), 9.63 (d, *J* = 5.0 Hz, 1H), 8.28−8.21 (m, 1H), 7.92 (m, 4H), 7.85−7.73 (m, 3H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.33−7.18 (m, 2H), 6.63 (t, *J* = 7.4 Hz, 1H), 6.44 (t, *J* = 7.3 Hz, 1H), 6.19 (d, *J* = 7.8 Hz, 1H), 3.26−3.16 (m, NBu_4), 2.32 (s, 3H), 1.71−1.58 (m, NBu_4), 1.43 (h, *J* = 7.4 Hz, NBu_4), 1.97 (s, 3H), 1.02 (t, *J* = 7.3 Hz, NBu_4).

*[Ru(2-C_6H_4-2′-py-κC,N)(NCMe)$_3$(PPh_3, cis-C)]PF_6 (**11**).* A solution of [Ru(2-C_6H_4-2′-py-κC,N)(NCMe)$_4$]PF_6 (692 mg, 1.23 mmol) and PPh_3 (323 mg, 1.23 mmol) in MeOH/CH_3CN (6/1) (50 mL) was refluxed for 24 h under vigorous stirring. After reduction of the volume of the orange/red solution, the solution was filtered through alumina using a 90:10 CH_2Cl_2/MeCN mixture as an eluent. The yellow orange fraction was collected and evaporated to dryness under vacuum. Flash chromatography in CH_2Cl_2/MeCN (9:1) allowed the elimination of the remaining [Ru(2-C_6H_4-2′-py-κC,N)(NCMe)$_4$]PF_6. Crystallization from dichloromethane/Et_2O/pentane gave orange microcrystals (450 mg, 47%), which were found to be suitable for XRD analysis.

^{1}H NMR (400.13 MHz, CD_3CN) δ 9.03 (m, 1H), 8.07 (dd, 1H, *J* = 8.2, 1.2 Hz), 7.93 (ddd, 1H, *J* = 8.2, 7.4, 1.6 Hz), 7.66 (dd, 1H, *J* = 7.8, 1.4 Hz), 7.67−7.60 (m, 6H), 7.51 (d, 1H, *J* = 7.6 Hz), 7.48−7.37 (m, 9H), 7.35−7.30 (m, 1H), 6.89 (t, 1H, J = 7.6 Hz), 6.68 (td, 1H, *J* = 7.4, 1.4 Hz), 1.96 (s, 3H), 1.62 (s, 6H).

^{31}P NMR (161.98 MHz, CD_3CN): 57.01 (s, Ph_3P), −144.7 (h, J_{P-F} = 685 Hz, PF_6).

Anal. Calcd for $C_{35}H_{32}F_6N_4P_2Ru$: C, 53.51; H, 4.11; N, 7.13. Found: C, 53.29; H, 4.38; N, 7.12.

*[Ru(2-C_6H_4-2′-py-κC,N)(bipy)(PPh_3, cis-C)(NCMe)]PF_6 (**12a**) and [Ru(2-C_6H_4-2′-py-κC,N)(phen)(PPh_3, cis-C)(NCMe)] PF_6*

DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617−7626

Table 2. Details for the X-ray Crystal Structure Determinations

	3	4	5	11	12a
chemical formula	$C_{45}H_{39}F_6N_4O_{0.5}P_2Ru$	$C_{45}H_{39}F_6N_4O_{0.5}P_2Ru$	$C_{31}H_{55}F_6N_4O_2RuSP$	$C_{36}H_{34}Cl_2N_4PRuF_6P$	$C_{41}H_{34}F_6N_4P_2Ru$
formula mass	920.81	920.81	773.73	870.58	959.73
crystal system	monoclinic	triclinic	triclinic	monoclinic	orthorhombic
a (Å)	14.807(2)	10.5548(7)	9.5091(4)	8.9301(3)	17.9446(15)
b (Å)	14.232(2)	13.0455(8)	12.5594(5)	18.1083(6)	18.7673(15)
c (Å)	21.532(3)	15.4633(10)	14.4211(4)	25.6637(8)	24.048(2)
α (°)	90	85.8168(13)	97.045(2)	90	90
β (°)	106.085(4)	86.5947(13)	104.120(2)	97.5720(10)	90
γ (°)	90	72.1131(13)	96.500(2)	90	90
unit cell volume (Å^3)	4360.1(11)	2019.3(2)	1639.21(11)	4113.9(2)	8098.6(12)
temperature (K)	150(2)	298(2)	173(2)	173	298(2)
space group	$P\,2_1/c$	$P\bar{1}$	$P\bar{1}$	$P\,2_1/c$	$Pbca$
No. of formula units per unit cell, Z	4	2	2	4	8
No. of reflections measured	49 323	20 305	14 376	39 712	65 183
No. of independent reflections	9553 [R(int) = 0.0695]	9223 [R(int) = 0.0354]	7468 [R(int) = 0.059]	13 142 [R(int) = 0.0354]	7456 [R(int) = 0.165]
final R_1 values ($I > 2\sigma(I)$)	0.0663	0.0487	0.0582	0.0403	0.0758
final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1177	0.1278	0.1510	0.0943	0.1874
final R_1 values (all data)	0.1093	0.0568	0.0687	0.0490	0.1462
final $wR(F^2)$ values (all data)	0.1360	0.1333	0.1649	0.0912	0.2101

(12b). A solution of 200 mg (0.25 mmol) of **11** and 80 mg (0.50 mmol) of 2′2-bipyridine (for **12a**) or 91 mg (0.50 mmol) of 1,10-phenanthroline (for **12b**) in 15 mL of acetonitrile was heated to reflux for 45 h. The mixture was evaporated to dryness under vacuum and the residue purified through alumina using dichloromethane as an eluent. Crystallization from dichloromethane/diethyl ether gave red microcrystals, which were washed with diethyl ether and dried under vacuum. Recrystallization from dichloromethane−acetonitrile/diethyl ether gave crystal of **12a** suitable for for XRD analysis.

***12a** NMR Data*. Yield: 39% (84 mg). ^{1}H NMR (300.53 MHz, CD_3CN): 8.86 (d, 1H, ^3J = 5.2 Hz), 8.46 (d, 1H, ^3J = 8.2 Hz), 8.40 (d, 1H, ^3J = 8.9 Hz), 8.10 (d, 1H, ^3J = 8.2 Hz), 8.04 (td, 1H, ^3J = 7.2 Hz, ^4J = 1.4 Hz), 7.97 (td, 1H, ^3J = 7.2 Hz, ^4J = 1.4 Hz), 7.92 (dd, 1H, ^3J = 8.0, Hz, ^4J = 1.4 Hz), 7.82−7.73 (m, 2H), 7.56 (d, 1H, ^3J = 5.8), 7.43 (td, 1H, ^3J = 7.2 Hz, ^4J = 1.1 Hz), 7.32−7.19 (m, 15H), 7.02 (td, 1H, ^3J = 7.2 Hz, ^4J = 1.1 Hz), 6.97 (m, 4H), 2.37 (s, 3H).

^{31}P{^{1}H} NMR (121.5 MHz, CD_3CN): 55.04 (s, Ph_3P), −144.02 (h, J_{P-F} = 706.87 Hz, PF_6).

IR KBr [cm^{-1}]: 843 (s, PF_6), 2268 (m, NCMe).

M/S [FAB$^+$, m/z (%)]: 715 (10) [M+H]$^+$, 674 (59) [M+H − NCMe]$^+$, 518 (100) [M+H − NCMe − bpy]$^+$, 412 (38) [M +H − NCMe − PPh_3]$^+$, 256 (13) [M+H − NCMe − PPh_3 − bpy]$^+$.

Anal. Calcd for $C_{41}H_{34}F_6N_4P_2Ru{\cdot}0.25CH_2Cl_2$: C, 56.24; H, 3.95; N, 6.36. Found: C, 56.13; H, 3.77; N 6.51.

***12b** NMR Data*. Yield 62% (137 mg). ^{1}H NMR (300.53 MHz, CD_3CN): 9.03 (dd, 1H, ^3J = 5.22 Hz, ^4J = 1.1 Hz), 8.47 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.4 Hz), 8.18 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.4 Hz), 8.05 (d, 1H, ^3J = 8.8 Hz), 7.97 (d, 1H, ^3J = 8.8 Hz), 7.95 (m, 2H), 7.86 (dd, 1H, ^3J = 7.7 Hz, ^4J = 1.4 Hz), 7.72−7.66 (m, 2H), 7.58 (td, 1H, ^3J = 7.4 Hz, ^4J = 1.7 Hz), 7.27−7.21 (m, 3H), 7.12−7.75 (m, 15H), 6.92 (td, 1H, ^3J = 7.4 Hz, ^4J = 1.4 Hz), 6.66 (t, 1H, ^3J = 6.6 Hz), 2.21 (s, 3H).

^{31}P{^{1}H} NMR (121.5 MHz, CD_3CN): 55.30 (s, Ph_3P), −143.63 (h, J_{P-F} = 706.87 Hz, PF_6).

IR KBr [cm^{-1}]: 842 (s, PF_6), 2263 (m, NCMe).

M/S [FAB$^+$, m/z (%)]: 739 (21) [M+H]$^+$, 698 (100) [M+H − NCMe]$^+$, 518 (4) [M+H − NCMe − phen]$^+$, 436 (71) [M +H − NCMe − PPh_3]$^+$, 256 (6) [M+H − NCMe − PPh_3 − phen]$^+$.

Anal. Calcd for $C_{43}H_{34}F_6N_4P_2Ru{\cdot}0.4CH_2Cl_2$: C, 56.80; H, 3.82; N, 6.10. Found: C, 56.33; H, 3.72; N, 6.69.

Crystal Structure Determinations. ***5** and **11***. Acquisition and processing parameters are displayed in Table 2. Reflections were collected with a Nonius Kappa CCD system and with an APEX diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Mo Kα radiation (λ = 0.71073 Å). The crystal detector distance was 38 mm. The cell parameters were determined (APEX2 software[17a]) from reflections taken from three sets of 12 frames, each at 10 s exposures. The structures were solved by direct methods using the program SHELXS-97.[17b] The refinement and all further calculations were carried out using SHELXL-97.[17c] The crystal structures acquired with the Nonius Kappa CCD were solved using SIR-97[17d] and refined with SHELXL-97. The refinement and all further calculations were carried out using SHELXL-97. The H atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2. A semiempirical absorption correction was applied using SADABS in APEX2.

3**, **4**, and **12a. X-ray intensities were measured on a Bruker Smart Apex diffractometer (**4**, **12a**) and a Bruker D8 Venture κ-geometry diffractometer (**3**) with a sealed tube and a microfocus X-ray source (λ = 0.71073 A), respectively. The intensities were integrated using SAINT.[18a] Absorption correction and scaling was performed with SADABS.[18b] The structures were solved with Direct Methods using the program SHELXS-97.[18c] Least-squares refinement was performed with SHELXL-2014[18d] against the F^2 values of all reflections. Non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located in difference Fourier maps. H atoms were positioned geometrically and refined using a riding model with isotropic displacement parameters tied to the parent C atoms. The three compounds display some type of disorder, affecting the cations, anions, and/or solvent included, which were modeled with SIMU and DELU restraints on anisotropic displacement parameters and

DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617−7626

SADI and SAME geometrical restraints. In addition, for compounds **3** and **12a**, the interstitial solvent is highly disordered and could not be modeled successfully; its contribution was removed from the refinement, using the SQUEEZE routine in the PLATON program.[18d]

■ ASSOCIATED CONTENT

Supporting Information

CIF files giving detailed experimental procedures for the determination of the structures of complexes **3**, **4**, **5**, **11**, and **12a**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.5b01236.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ronan@unam.mx (R. Le Lagadec).
*E-mail: pfeffer@unistra.fr (M. Pfeffer).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Laboratory of Excellence (LABEX) "Chemistry of Complex Systems" (UdS), the FRC (UdS) through the project "synergie" are gratefully acknowledged for partial support of this work. CAPES is gratefully acknowledged for a fellowship to A. S. Lima Barbosa. Financial support from DGAPA-UNAM (PAPIIT Project No. IN204812) and CONACyT (Project No. 153151 and Scholarship No. 273495 to C.O.O.C.) is acknowledged. We are grateful to Lydia Brelot and Corinne Bailly (UdS) for determining the crystal structures of compounds **5** and **11** and Dr. C. Perret (UdS) for the analysis of **2** in a H_2O/MeCN solution by electrospray.

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DOI: 10.1021/acs.inorgchem.5b01236
Inorg. Chem. 2015, 54, 7617−7626