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Communications

New Synthetic Pathways of *cis*- or *trans*-Hydroxytamoxifen Derivatives with in Situ Formed $[Cp^*Rh(solvent)_3]^{2+}$ Complexes: Kinetic and Thermodynamic Control, Including a Novel, Intramolecular N-π Rearrangement, and Relative Binding Affinities of the η^6 Complexes for the Estrogen Receptor

Siden Top,[†] Anne Vessières,[†] Gérard Jaouen,[†] and Richard H. Fish*[,‡]

Laboratoire de Chimie et Biochimie des Complexes Moléculaires, Ecole Nationale Supérieure De Chimie de Paris, 11 rue Pierre et Marie Curie, F 75213 Paris Cedex 05, France, and Lawrence Berkeley National Laboratory, University of California, Berkeley, California 94720

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*Summary: Reactions of hydroxytamoxifen derivatives, **1** and **2**, with $[Cp^*Rh(solvent)_3]^{2+}$ complexes (solvent = MeOH or CH_2Cl_2) initially provided the kinetically controlled η^1-N complexes, **4** and **5**, which undergo a novel intramolercular N-π rearrangement to give the regioselective η^6 products, **6** and **7**; molecular mechanics calculations showed a preferred ground state for both the η^1-N and η^6 complexes, while **6** had a higher relative binding affinity for the estrogen receptor, in competition with estradiol, than **7**.*

The research area of organometallic pharmaceuticals has now been shown to be a viable discipline for drug discovery.[1] Due to the pioneering studies of Jaouen et al., it has also been demonstrated that modification of the structures of the *cis* and *trans* isomers of derivatives of hydroxytamoxifen, **1** and **2**, with a ferrocenyl moiety, ferrocifen, **3**, provided an antagonist compound, which binds at the estrogen receptor in competition with the female hormone estradiol.[1g,h,2] In addition, **3** also demonstrated a cytotoxic effect, for a potential, future therapy for breast cancer, as well as a variety of other cancers.[1k,2] The important reason for further studying the derivatives of hydroxytamoxifen, **1** and **2**, with a three-spacer methylene, instead of the two-spacer methylene utilized in the actual breast cancer drug, was predicated on previous bioassay studies on compound **3**, where maximum bioactivity was achieved with the three-methylene tether.[2]

Furthermore, our continuing interest involving the bioorganometallic chemistry of organorhodium complexes[1a,3] led to new approaches for a strategy on modifying the basic structure of **1** and **2**, to capitalize on the eventual use of the Rh-105 radio-

* To whom all correspondence should be addressed. E-mail: rhfish@lbl.gov.
[†] Ecole Nationale Supérieure De Chimie de Paris.
[‡] University of California.

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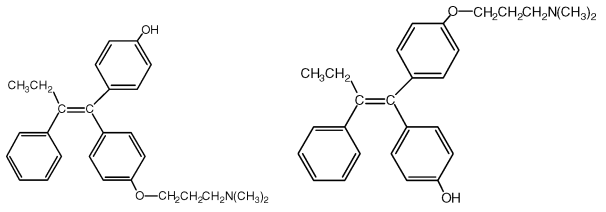

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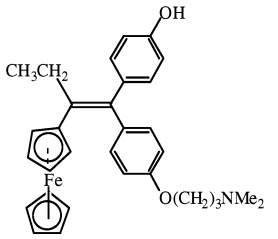

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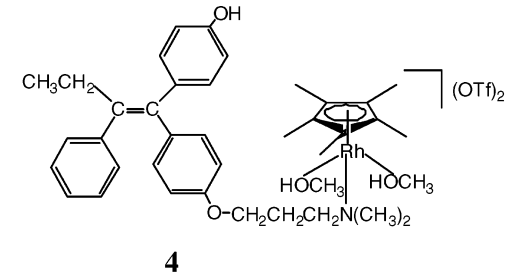
isotope, a beta emitter, as a potential radiopharmaceutical; as far as we are aware, no organorhodium complexes have been reported for the drug hydroxytamoxifen or its derivatives, **1** and **2**. The strategy we followed was dictated by the lack of solubility of **1** or **2** in water, including their ammonium salt derivatives. Thus, we initially studied, via ^{1}H NMR spectroscopy, the reactions of in situ formed [Cp*Rh(CH_3OH-d_4)$_3$](OTf)$_2$ with **1** or **2** at room temperature, in methanol-d_4. This afforded interesting results, in that the initial kinetically controlled product, from each individual *cis* or *trans* isomer, **1** or **2**, was the Cp*Rh η^1-N compounds [1-butenyl-2-phenyl-1-(*p*-phenol)-1′-*p*-phenyl-(oxotrimethylene-3-dimethylamino)(η^1-N-η^5-pentamethylcyclopentadienylrhodium)(η^1-O-(CH_3OH)$_2$](OTf)$_2$, *cis*-**4** and *trans*-**5**, which were elucidated from their ^{1}H NMR spectra and, particularly, from the dramatic downfield shifts of the $-N(CH_3)_2$ groups, 2.24/2.28 ppm (**1** and **2**) to 2.88/2.95 ppm (**4** and **5**), respectively.



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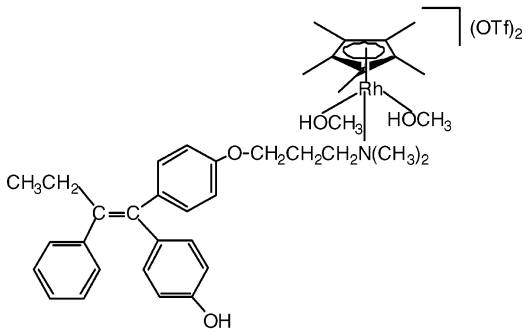

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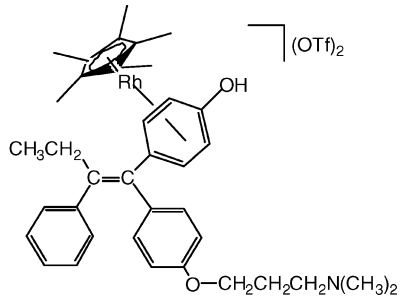
More importantly, and in a serendipitous manner, we found upon individually heating complex **4** or **5** in methanol-d_4 at 60 °C, a novel and unprecedented N-π rearrangement occurred that gave, after in-depth COSY and NOESY correlation NMR studies (see the Supporting Information), *cis*- or *trans*-[1-butenyl-2-phenyl-1-(η^5-pentamethylcyclopentadienyl-η^6-*p*-phenol)rhodium)-1′-*p*-phenyl(oxotrimethylene-3-dimethylamino)]-(OTf)$_2$, respectively, complex **6** or **7**. In addition, we found that at 60 °C in methanol-d_4 the η^1-N complexes, **4** or **5**, isomerized to a *cis* and *trans* mixture, during the N-π rearrangement, but since both simultaneously undergo the N-π rearrangement, it was difficult to obtain an accurate ratio for **4**/**5** after reaction. For example, after heating **4** for 40 h at 60 °C, the ratio **4**/**5** was 10:1, while a similar experiment starting with complex **5** gave a **4**/**5** ratio of 1:1. For a comparison to the isomerization of *cis* and *trans* derivatives of hydroxytamoxifen and ferrocifen, where a two-methylene tether was present, in various solvents, see the studies of Jaouen et al.[2a]



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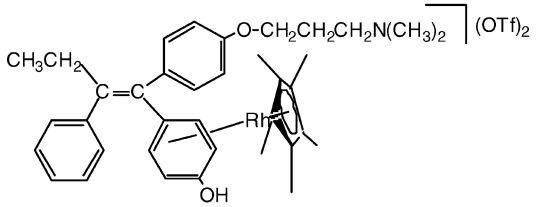

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It appeared qualitatively from our ^{1}H NMR studies that this N-π rearrangement was more favorable with the *trans* isomer, **5** (with the aromatic ether tether *cis* to the ethyl on the double bond) rather than the corresponding *cis* isomer, **4**, on possible steric grounds. Moreover, we found that starting with *cis*-**4**, we observed the two η^6-Cp*Rh complexes, *cis*-**6** and *trans*-**7**, via NMR analysis of the new dimethylamino signals that appeared at 2.97 and 2.95 ppm, respectively, in the ratio of ~83:17, after 17 h of heating in methanol-d_4 , reflecting the isomerization of **4** to **5** prior to the N-π rearrangement, as stated above.

More importantly, there was a dramatic solvent effect on the rate of the N-π rearrangement.[4] We discovered that in methylene chloride the N-π rearrangement was complete in 15 h at 22 °C for both **4** and **5** to either **6** or **7**, while in methanol *no reaction* occurred at 22 °C; under these mild reaction conditions in methylene chloride, neither **4** nor **5** was isomerized to a *cis* and *trans* mixture of both starting complexes. We believe that this

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(3) (a) Fish, R. H. *Coord. Chem. Rev.* **1999**, *185/186*, 569, and references therein. (b) Fish, R. H. In *Bioorganometallics*; Jaouen, G., Ed.; Wiley-VCH: New York, 2005; Chapter 10, p 321.

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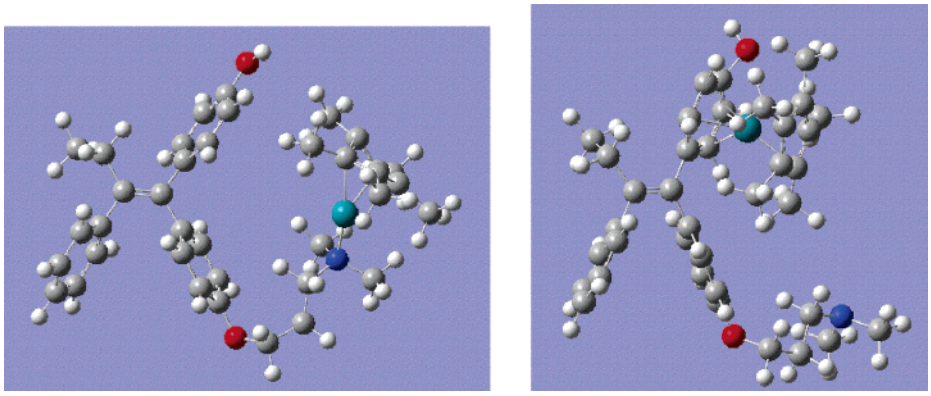


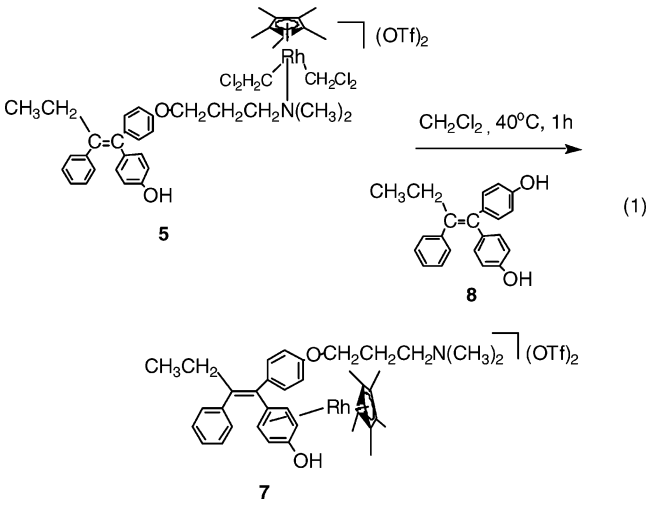
Figure 1. Optimized ground state conformations for the N-π conversion of **4** (left view) to **6** (right view); both images were obtained with the GAUSSIAN03 package. C (gray); H (white); N (blue); O (red); Rh (green).

was conceivably due to the weaker binding methylene chloride (CH_2Cl_2) solvato complex of **4**; that is, CH_2Cl_2 is a better leaving group for the N-π rearrangement in comparison to MeOH.[4] Interestingly, complex **6** was less stable to isomerization than **7**. Thus, in CH_2Cl_2, complex **6** gave a 9:1 ratio of **6**:**7** after being heated for 1 h at 40 °C and then kept at 22 °C for 15 h, while complex **7** did not show this isomerization propensity, under the same reaction conditions.

It was also found that the η^6-Cp*Rh complexes, **6** and **7**, were *water soluble*, via extraction of the reaction mixture, after removing methanol-d_4, with D_2O, while the Cp*Rh-N-bound, kinetically controlled compounds, **4** and **5**, were *water insoluble, even though both are dications*. This represents a rather facile technique for the separation of the Cp*Rh-η^1-N-bound, kinetically controlled product from the thermodynamically controlled η^6 complex and, moreover, provides the first water-soluble organometallic complexes of hydroxytamoxifen derivatives, **1** and **2**, to be synthesized, as far as we were able to ascertain, and bodes well for possible increased biological compatibility.

The N-π rearrangement was somewhat reminiscent of previous studies by Fish et al.[4] and Grotjahn et al.[5] with CpRu- and Cp*Ru-substituted pyridine/quinoline/benzothiophene (Fish et al.)/aliphatic amino and thio aromatic compounds (Grotjahn et al.) that undergo a N-π or S-π rearrangement. However, the N-π rearrangement we have observed with **4** and **5** was unprecedented, as far as the current literature is concerned, since the Cp*Rh group has a choice between two geminal, electron-rich, oxygen-substituted phenyl groups on the double bond; i.e., the phenyl group with the ether, dimethylamino tether containing the η^1-N-Cp*Rh moiety or the geminal phenol. Interestingly, we *exclusively* see the regioselective η^6-Cp*Rh phenol complexes, **6** or **7**, being formed from **4** and **5**, respectively.

To prove the intramolecular nature of the N-π rearrangement, we conducted a crossover experiment with complex **5** in the presence of compound **8**, and in methylene chloride at 40 °C for 1 h, followed by 6 h at room temperature. If the N-π rearrangement, **5** to **7**, was *intramolecular*, we should see no Cp*Rh complexes of compound **8** (eq 1); an NMR control experiment with **8** and $[Cp^*Rh(CH_2Cl_2\text{-}d_2)_3](OTf)_2$ showed instantaneous reaction with only one product formed, that being the η^6-Cp*Rh phenol complex *cis* to the ethyl group. This was exactly what transpired with the conversion of **5** to **7** as the *only* reaction that occurs in the presence of **8** and provides clear proof that the *N-π rearrangement, **4** to **6**, or **5** to **7**, was intramolecular and highly regioselective*. This latter result also provides added validity for a preferred ground state conformation, from initial molecular mechanics calculations, which clearly demonstrates the close proximity of the Cp*Rh group to the face of the geminal phenol ring, to ultimately form the η^6-Cp*Rh complex, **6** (Figure 1); this is possibly the only option the Cp*Rh group has to eleviate the steric constraints in the ground/transition state of the kinetically controlled product, complex **4**, and form the thermodynamically controlled product, complex **6**.



Relative Binding Affinities of Complexes 6 and 7 for the Estrogen Receptor. The relative binding affinities (RBA) of **6** and **7** for the estrogen receptor (ERα, 4 °C, 3 h) were determined by competiton with [^{3}H]-estradiol and provided values of 4.7% and 1%, respectively.[6] Thus, a significant difference between the two geometrical isomers, **6** and **7**, was clear, which suggests differences in the conformation at the estrogen receptor. For comparison, ferrocifen, **3**, has an RBA of 11.5% (4 °C, 3 h).[2] Clearly, *cis* complex **6** is moderately competitive with estradiol for binding to the ERα site. We are now studying the in vitro activity of **6** and **7** on MCF 7 hormone-dependent breast cancer cells to determine any antihormonal effect that has been shown to be connected to the presence of the dimethylamino side chain on the hydroxytamoxifen derivative nucleus, which has been reported to be responsible for this bioactivity.

In conclusion, we have prepared the first Cp*Rh complexes of hydroxytamoxifen derivatives, **1** and **2**, and in this process, we have discovered an unprecedented, intramolecular N-π

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rearrangement that was highly regiospecific for the geminal phenol group on the nucleus of complexes **4** and **5**; molecular mechanics calculations verify the optimized ground state conformation for the N-π rearrangement from complex **4** to **6**. Moreover, *cis* complex **6** shows moderate competitive behavior toward estradiol at the ERα site versus its *trans* isomer, **7**. Studies on the docking of **6** and **7** at the estrogen receptor site, in the future, will provide conformational information and explicit hydrogen bonding regimes for these noncovalent interactions. We will also pursue the anticancer/antiproliferative behavior of **6** and **7** and the synthetic quest for their corresponding Rh-105 radiopharmaceutical analogues.

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Supporting Information Available: Synthetic procedures for complexes **4** and **6**, including ^{1}H and ^{13}C NMR, MS, and elemental analysis data. NOESY and COSY correlation NMR spectra for complex **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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