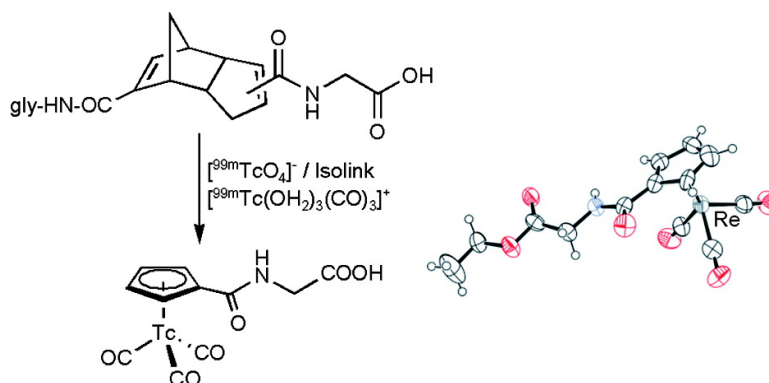


Metal-Mediated Retro Diels–Alder of Dicyclopentadiene Derivatives: A Convenient Synthesis of [(Cp-R)M(CO)] (M = Tc, Re) Complexes

Yu Liu, Bernhard Spingler, Paul Schmutz, and Roger Alberto

J. Am. Chem. Soc., **2008**, 130 (5), 1554-1555 • DOI: 10.1021/ja0777411

Downloaded from <http://pubs.acs.org> on February 8, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)



Metal-Mediated Retro Diels–Alder of Dicyclopentadiene Derivatives: A Convenient Synthesis of [(Cp-R)M(CO)₃] (M = ^{99m}Tc, Re) Complexes

Yu Liu, Bernhard Spingler, Paul Schmutz, and Roger Alberto*

University of Zürich, Institute of Inorganic Chemistry, Winterthurerstrasse 190, 8057 Zürich, Switzerland

Received October 16, 2007; E-mail: ariel@aci.unizh.ch

Site-specific targeting of receptors and overexpressed genes as related to cancer or neurodegenerative diseases is the basic concept of molecular imaging with radionuclides or contrast agents.¹ Achieving a high target/nontarget ratio within a short period of time is crucial for a precise diagnosis. In molecular radioimaging, ^{99m}Tc plays still a major role, but the design of a ^{99m}Tc bioconjugate fulfilling the “*conditio sine qua non*” mentioned before is very challenging. The size of the complex and chelator functionalities may govern the biological behavior of the vector, rather than the vector itself.² To optimize these parameters, the cyclopentadienyl (Cp) ligand is an obvious choice. Cp is one of the smallest “innocent” ligands and stably binds to the [^{99m}Tc(CO)₃]⁺ core. Notably, it mimics arene rings in pharmaceuticals or biomolecules such as amino acids. This structural analogy was successful in ferrocifen, the ferrocene (Fc) analogue of tamoxifen, as pioneered by Jaouen et al.^{3–6} or steroid hormones combined with [(Cp)Re(CO)₃].^{7,8} Recent results from our group indicated that amino acids derivatized with Fc or [(Cp)Re(CO)₃] are surrogates for natural amino acids.⁹

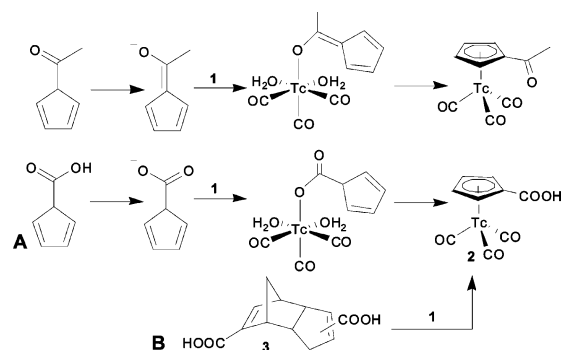
Whereas biomolecules with pendent [(Cp)Re(CO)₃] or Fc are accessible via classical organometallic methods, the ^{99m}Tc analogues must be prepared directly from aqueous buffer, apparently incompatible conditions for HCp which rapidly decomposes in water. Efforts by Katzenellenbogen et al. to prepare [(Cp-R)^{99m}Tc(CO)₃] by the so-called double ligand transfer reaction gave the desired piano-stool complexes but from organic solvents in autoclaves.^{10,11} Alternatively, the [Fe(Cp)]⁺ moiety in Fc-derivatized biomolecules could be replaced by [Tc(CO)₃]⁺ but still at *T* > 100 °C and in the presence of DMSO.¹² We reported an aqueous synthesis at *T* < 100 °C with biomolecules bound to the cyclopentadiene ring via an α-keto group. Still, all these Cp-derivatized compounds are sensitive and limit types of biomolecules and chemistry.^{13,14}

It would be highly desirable to find a general approach to [(Cp-R)^{99m}Tc(CO)₃]-type complexes from stable precursors, conjugated to biomolecules and generating the active cyclopentadiene *in situ*. We present in this paper the unexpected formation of [(Cp-R)^{99m}Tc(CO)₃]-type complexes from their Diels–Alder dimerized precursors (HCp-R)₂. Since a thermal *retro* Diels–Alder reaction, (HCp-R)₂ → HCp-R, did not occur to a measurable extent under our conditions, monomerization and coordination to [^{99m}Tc(CO)₃]⁺ are concerted; hence, cleavage is metal-mediated.

Originally, we supposed that the mechanism of the aqueous synthesis of [(Cp-COCH₃)^{99m}Tc(CO)₃] involved deprotonation at the cyclopentadiene ring followed by direct coordination to [^{99m}Tc(OH₂)₃(CO)₃]⁺, **1**.¹³ Initial coordination to the enolate followed by an intramolecular recoordination to η⁵-Cp seemed less likely. On a mechanistic base, no complex formation was expected with cyclopentadiene carboxylic acid (HCp-COOH) since acidity of C–H is too low in aqueous solution.¹⁵ We found that **1** still reacted with HCp-COOH in aqueous buffer at almost the same rate as with HCp-COCH₃ to yield [(Cp-COOH)^{99m}Tc(CO)₃], **2**, in high

yield. Since alkenes do not coordinate to **1** in water (i.e., no reaction with HCp at all) and [HCp-COO[−]] did not ring-deprotonate, the formation of **2** must consist in initial σ-binding to carboxylate with subsequent or concerted coordination to cyclopentadiene (path A in Scheme 1).

Scheme 1. Stepwise Reaction of **1** with HCp-R and Thiele's Acid **3**, Respectively

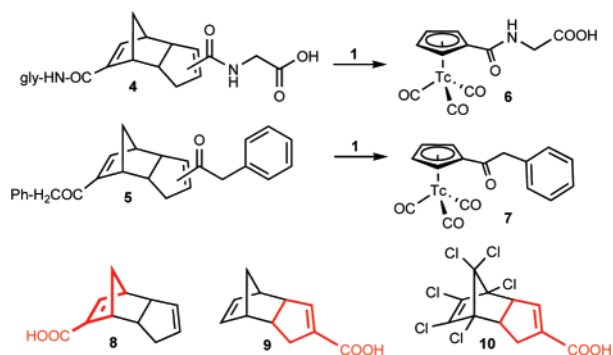


The formation of Cp complexes is a thermodynamic driving force. After carboxylate coordination, the Lewis acid [^{99m}Tc(CO)₃]⁺ exerts a strong electronic interaction with the adjacent cyclopentadiene. This distinct affinity for the formation of {(η⁵-Cp)Tc} implied the use of a “pre-cyclopentadiene” instead of the comparably reactive HCp-R itself. Evidently, the Diels–Alder dimer (HCp-COOH)₂, **3** (Thiele’s acid), is such a “protected” cyclopentadiene. Although thermal cracking of **3** requires *T* > 160 °C, reaction of **3** with **1** at 95 °C for 30 min in buffer resulted in the quantitative formation of **2** (path B).

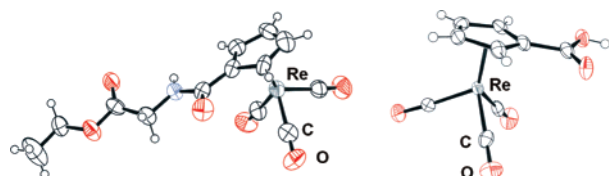
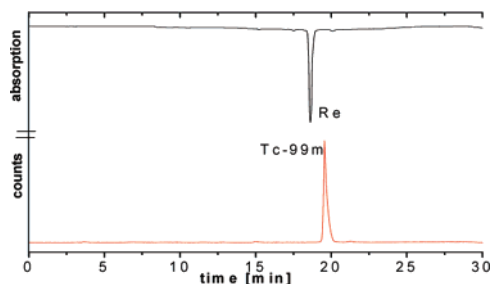
No free HCp-COOH was detected, excluding an *in situ* thermal *retro* Diels–Alder reaction and subsequent entry into path A. Complex **2** was also prepared directly from [^{99m}TcO₄][−] in the presence of **3** and under the same conditions as used for the preparation of **1** (Supporting Information [SI]).¹⁶ To our knowledge, this is the first evidence of a metal-mediated *retro* Diels–Alder reaction with concerted formation of the corresponding Cp complex. It can be hypothesized that other metal centers will behave similarly and new mixed Cp-H₂O complexes will become accessible.

A metal-mediated *retro* Diels–Alder reaction implies a general approach to [(Cp-R)^{99m}Tc(CO)₃] with more complex functionalities, “R”, bound to the dicyclopentadiene building block. Synthetically, biomolecules can be conjugated to precursors such as **3** via, for example, amide formation as exemplified with **4** (Scheme 2). Alternatively, NaCp is first reacted with, for example phenyl-acetic acid ethyl ester, and then dimerized to yield **5**.

Compounds **4** and **5** reacted directly with [^{99m}TcO₄][−] or **1** to give **6** and **7** after 30–120 min at 95 °C in quantitative yield. We emphasize that no measurable amounts of the respective monomers of **4** and **5** were observed. Further derivatives behaved comparably (SI). For all reactions, one HCp-R per ^{99m}Tc must be released but

Scheme 2. Reaction of **1** or $[\text{}^{99\text{m}}\text{TcO}_4]^-$ (Isolink Kit) with $(\text{HCp-R})_2^a$ 

^a $\text{Na}[\text{H}_3\text{BCO}_2\text{H}]$ (4 mg), $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$ (7 mg), $\text{Na}_2\text{tartrate} \cdot 2\text{H}_2\text{O}$ (7 mg) and, e.g., **4** (10^{-3} M), 30–60 min, 95 °C.

**Figure 1.** ORTEP presentations of complexes **6** (ethyl ester) and **2**.**Figure 2.** HPLC traces of macrocyclic **6** (Re) and the corresponding $^{99\text{m}}\text{Tc}$ complex prepared from $[\text{}^{99\text{m}}\text{TcO}_4]^-$. Time difference due to detector separation.

does not play a role since $^{99\text{m}}\text{Tc}$ is present at concentrations 10^{-8} – 10^{-7} M. To assess the authenticity of the $^{99\text{m}}\text{Tc}$ complexes **2**, **6**, and **7**, we applied the reaction to “cold” Re and ^{99}Tc . Since Re is much more robust than Tc, reactions of $[\text{Re}(\text{OH})_2(\text{CO})_3]^+$ with **3** require longer times or higher temperatures. A hydrothermal reaction at 160 °C gave the Re analogue of **2**. The X-ray structures of the Re surrogates of **2** and **6** (ethyl ester) (Figure 1) and a comparison of the HPLC retention times (Figure 2 and SI) confirmed their authenticity. Other $(\text{HCp-R})_2$ compounds reacted analogously, indicating that the reaction is general, regardless of the pendent group R.

Diels–Alder reactions with HCp-R produce homodimers such as **3**. It was therefore of interest if the former diene or dienophile was the source for Cp-COOH in **2**. We synthesized and separated the two Diels–Alder heterodimers **8** and **9** (Scheme 2) in a ratio of about 1 to 3.¹⁷ Surprisingly, **8** or **9** reacted only very slowly with $[\text{}^{99\text{m}}\text{TcO}_4]^-$ or **1** with yields of <5% under conditions as above. This implies that two binding or activating groups are required for

metal-mediated retro Diels–Alder reactions. Furthermore, a strong leaving group effect has been demonstrated in thermal retro Diels–Alder reactions with HCp .¹⁸ To probe this effect qualitatively, we prepared the heterodimers **10** from C_5Cl_6 and HCp-COOH . Again, the desired product was not received. We conclude that potentially coordinating functionalities such as keto-, amide-, or carboxylate groups should be present on the former diene and the dienophile in the Diels–Alder product. Since concentrations are extremely low, the presence of two biologically active groups is not impairing labeling reactions or applicability.

We have shown that $[\text{}^{99\text{m}}\text{Tc}(\text{OH})_2(\text{CO})_3]^+$ mediates the retro Diels–Alder reaction of dicyclopentadiene derivatives with concomitant formation of corresponding piano-stool complexes. A weakly coordinating, Cp pendent group binds to the metal and initiates a retro Diels–Alder reaction and coordinative shift. This opens an avenue to the versatile preparation of $[(\text{Cp-R})^{99\text{m}}\text{Tc}(\text{CO})_3]$ complexes with attached targeting molecules “R”, avoiding thereby reactive organic precursors. Solid-phase bound Diels–Alder products will yield no carrier-added complexes.

In conclusion, labeling of biomolecules with piano-stool-like $^{99\text{m}}\text{Tc}$ and Re complexes from water is now to become an option in the development toward novel radiopharmaceuticals.

Acknowledgment. This research was supported in part by a Eureka project and Mallinckrodt Med. B.V.

Supporting Information Available: Labeling and synthetic procedures, HPLC conditions, and crystallographic data for **2**, **6** and **10** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Weissleder, R. *Science* **2006**, *312*, 1168–1171.
- Liu, S. *Chem. Soc. Rev.* **2004**, *33*, 445–461.
- Top, S.; Dauer, B.; Vaissermann, J.; Jaouen, G. *J. Organomet. Chem.* **1997**, *541*, 355–361.
- Jaouen, G.; Top, S.; Vessières, A.; Alberto, R. *J. Organomet. Chem.* **2000**, *600*, 23–36.
- Jaouen, G. *Chem. Br.* **2001**, 36–38.
- Jaouen, G.; Top, S.; Vessières, A.; Pigeon, P.; Leclercq, G.; Laios, I. *Chem. Commun.* **2001**, 383–384.
- Top, S.; Hafa, H. E.; Vessières, A.; Quivy, J.; Vaissermann, J.; Hughes, D. D.; McGlinchey, M. J.; Mornon, J.-P.; Thoreau, E.; Jaouen, G. *J. Am. Chem. Soc.* **1995**, *117*, 8372–8380.
- Top, S.; Vessières, A.; Pigeon, P.; Rager, M. N.; Huche, M.; Salomon, E.; Cabestaing, C.; Vaissermann, J.; Jaouen, G. *ChemBioChem* **2004**, *5*, 1104–1113.
- K_d values of Fc-gly and $[(\text{Cp-R})\text{Re}(\text{CO})_3]$ with $\text{R} = -(\text{CH}_2)_3\text{CH}(\text{NH}_2)-(\text{COOH})$ with LAT1 are 33 and 16 μM respectively.
- Spradau, T. W.; Katzenellenbogen, J. A. *Organometallics* **1998**, *17*, 2009–2017.
- Minutolo, F.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 13264–13265.
- Masi, S.; Top, S.; Boubekeur, L.; Jaouen, G.; Mundwiler, S.; Spingler, B.; Alberto, R. *Eur. J. Inorg. Chem.* **2004**, 2013–2017.
- Wald, J.; Alberto, R.; Ortner, K.; Candrea, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3062–3066.
- Bernard, J.; Ortner, K.; Spingler, B.; Pietzsch, H. J.; Alberto, R. *Inorg. Chem.* **2003**, *42*, 1014–1022.
- Top, S.; Lehn, J.-S.; Morel, P.; Jaouen, G. *J. Organomet. Chem.* **1999**, *583*, 63–68.
- Alberto, R.; Ortner, K.; Wheatley, N.; Schibli, R.; Schubiger, A. P. *J. Am. Chem. Soc.* **2001**, *123*, 3135–3136.
- Peters, D. *J. Chem. Soc.* **1961**, 1037–1042.
- Birney, D.; Lim, T. K.; Koh, J. H. P.; Pool, B. R.; White, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 5091–5099.

JA077741L