Reviews

Bioorganometallic Chemistry: Structural Diversity of Organometallic Complexes with Bioligands and Molecular Recognition Studies of Several Supramolecular Hosts with Biomolecules, Alkali-Metal Ions, and Organometallic Pharmaceuticals

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Bioorganometallic chemistry, a nascent area of organometallic chemistry, has recently provided significant advancements in structural diversity and molecular recognition studies. This review shows the various novel structures with bioligands of other colleagues, as well as those from our own studies. In addition, molecular recognition, the cornerstone of how biological systems operate, has now been extended to organometallic, supramolecular host molecules with biologically important guest compounds, including organometallic ionophores for selective recognition of alkali-metal ions. This host−guest molecular recognition chemistry with biologically important compounds occurs by noncovalent interactions, which encompass $\pi-\pi$, hydrophobic, and selective hydrogen bonding. The advent of organometallic pharmaceuticals has further provided unique molecular recognition/computer docking studies with hormone receptor sites that clearly delineate novel, noncovalent processes. The future looks extremely promising for bioorganometallic chemistry with regard to structural diversity and host−guest chemistry, including noncovalent interactions of organometallic pharmaceuticals with receptor site proteins to delineate mode of action.

Introduction

Bioorganometallic chemistry has now become an important subtopic in organometallic chemistry, in a manner similar to that for bioinorganic chemistry as a subtopic of inorganic chemistry.[1] However, unlike the many enzymatic inorganic complexes found necessary to sustain life on earth, bioorganometallic complexes, those with a definitive carbon−metal bond, are rarely seen in life-sustaining processes here on earth. The exception is methyl-B_{12} or methylcobalamin, one of the very few natural coenzymatic organometallic complexes that has been shown to exist, which contains a discrete CH_3-Co bond. One of its primary roles is the biomethylation of other environmentally important metals, such as Hg^{2+} and Sn^{4+} , which provides the toxic-to-man CH_3-HgX and CH_3-SnX_3 complexes.[2] Moreover, one recent exciting discovery that further shows the role of carbon−metal-bonded biocomplexes in enzymatic reactions is that of the structural findings and postulates related to the bifunctional carbon monoxide dehydrogenase/acetyl-CoA synthase. It was found that the critical Cu−Ni binuclear sites are in proximity to each other, Cu−CO and CH_3-Ni, to favorably affect a CH_3 group migration to provide a postulated $Cu-C(O)CH_3$ intermediate complex, which was thought to be crucial for the acetylation of CoA-SH.[3a] Interestingly, other enzymes with carbon−metal bonds have been found, such as NiFe hydrogenase and methyl reductase, and their active sites modeled, as were those of CO dehy-

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(1) (a) Jaouen, G.; Top, S.; Vessières, A.; Alberto, R. *J. Organomet. Chem*. **2000**, *600*, 25 and references therein. (b) Jaouen, G. *Chem. Br.* **2001**, 36. (c) Jaouen, G.; Vessières, A.; Butler, I. S. *Acc. Chem. Res.* **1993**, *26*, 361. (d) Ryabov, A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 931. (e) Köpf-Maier, P. *Eur. J. Chim. Pharmacol.* **1994**, *47*, 1. (f) Dagani, R. The Bio Side of Organometallics. *Chem. Eng. News* **2002**, *80* (Sept 16), 23.

(2) Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*; Wiley: New York, 1994; Chapter 3, p 39, and references therein.

(3) (a) Doukov, T. I.; Ivrerson, T. M.; Seravalli, J.; Ragsdale, S. W.; Drennan, C. L. *Science* **2002**, *298*, 567 and references therein. (b) Fontacilla-Camps, J. C.; Ragsdale, S. W. *Adv. Inorg. Chem*. **1999**, *47*, 283. (c) Riordan, C. G. Bioorganometallic Chemistry of Cobalt and Nickel. In *Comprehensive Coordination Chemistry II*; McCleverty, J. A., Meyer, T. J., Eds. (Que, L., Tolman, W. B., Volume Eds.), Pergamon Press: New York, 2003; Vol. 8, Chapter 8.26, p 1, and references therein. (d) Gloagueu, F.; Lawrence, J. D.; Rauchfuss, T. B. *J. Am. Chem. Soc.* **2001** *123*, 9476.

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drogenase/acetyl-CoA; this represents a future direction for bioorganometallic chemistry.[3b−d]

More importantly, in contrast to bioinorganic chemistry. which has developed a robust synthetic aspect focused on biomimetic models of active enzyme sites and their functional chemistry, recent studies in bioorganometallic chemistry have focused more on structural aspects of organometallic complexes that contain bioligands and that have been evaluated as pharmaceuticals for cancer therapy, radiopharmaceuticals for diagnotics and therapy, probes for biosensors, and novel supramolecular structures for molecular recognition studies, to name several representative examples.[1,4]

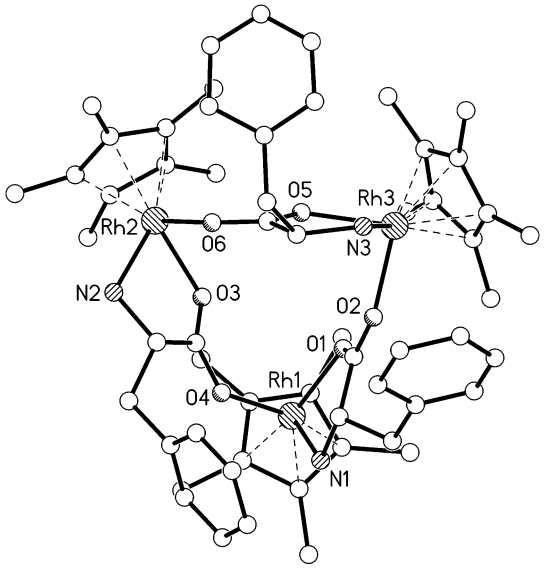
Therefore, the kind invitation by the editor of *Organometallics* has presented the authors with an opportunity to enlighten the community on some recent developments in this exciting area of organometallic chemistry. We also preface these comments with the fact that the first International Symposium on Bioorganometallic Chemistry (ISBOMC'02) was convened in Paris on July 18−20, 2002 and, furthermore, will meet every 2 years in different global venues; the 2004 meeting will be held in Zurich. This international symposium should further help promote bioorganometallic chemistry as a viable discipline focused on structure, reactivity, and biological applications, including the avant-garde topic of organometallic pharmaceuticals.

Thus, in this review, we want to focus on the unique structural diversity that has recently been discovered in the reactions of organometallic complexes with bioligands and then enlighten the community to the new area of molecular recognition with bioorganometallic host complexes and biologically relevant guests, in water, that defines noncovalent $\pi-\pi$, hydrophobic, and selective hydrogen bonding regimes. A new class of organometallic ionophores that selectively recognize alkali-metal ions will also be discussed. Moreover, we will present some exciting new results on computer docking experiments of the potential organometallic breast cancer drug Ferrocifen, in addition to a ruthenocene derivative of the estradiol ligand, with proteins associated with the estrogen receptor site, to define the noncovalent interactions that occur in this important molecular recognition process, and attempt to relate this process to biological activity.

Structural Diversity in Reactions of Organometallic Complexes with Bioligands

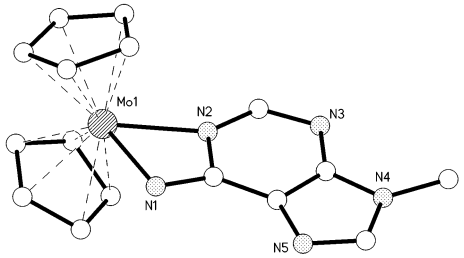
Wolfgang Beck, the first recipient of the Lavoisier Medal for seminal studies in bioorganometallic chemistry (instituted at ISBOMC'02, July 2002), and coworkers in Munich were among the first to study the reactions of organometallic complexes with bioligands.[5] They worked in methanol in most of their reactions with organometallic complexes and bioligands, which initially provided mononuclear complexes. For example, the reaction of [Cp*Rh(μ-Cl)$_2$Cl$_2$] with L-phenylalanine in methanol gave, after reaction of the initial mononuclear chloride complex with Ag^+ ions, a cyclic trimer, which was identified by single-crystal X-ray analysis (complex **1**; Figure 1) as one of several possible diastereomers with $S_CS_CS_CS_{Rh}S_{Rh}S_{Rh}$ stereochemistry. This is a pertinent example of self-assembly and chiral self-recognition providing a unique, thermodynamically favored cyclic trimer structure.[5a]

Marks and co-workers were some of the pioneers in the reactions of organometallic antitumor agents with nucleobases, conducted in water, for structural identity, including selective bonding modes.[6] For example, Cp$_2$-MoCl$_2$ with the nucleobase 9-methyladenine provided, at the time, the unusual bonding mode of a four-



1, $S_CS_CS_CS_{Rh}S_{Rh}S_{Rh}$

Figure 1. X-ray structures of one diastereomer of the cyclic trimer [(Cp*Rh)(μ-η^1(*OCO*):η^2(*N*,*OCO*)-L-phenylalanine)]$_3^{3+}$ (**1**).



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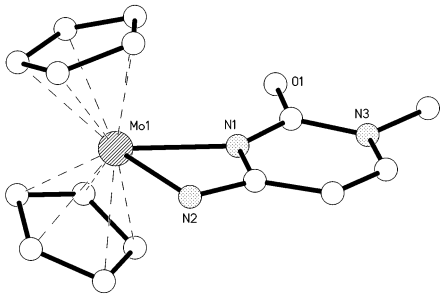

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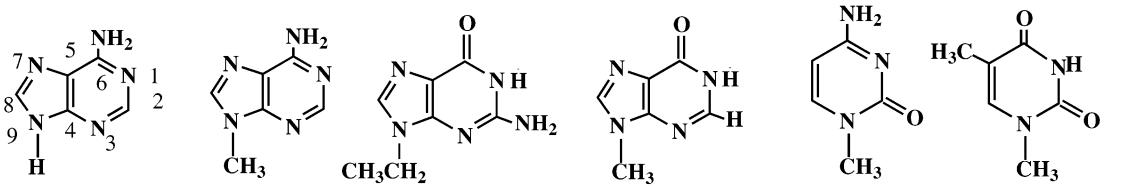
Figure 2. X-ray structures of bonding modes of [η^2-(*N1*,*N6*)-9-methyladenyl]dicyclopentadienylmolybdenum (HFP; **2**) and [η^2(N3,N4)-1-methylcytosyl]dicyclopentadienylmolybdenum (HFP; **3**).

(4) Fish, R. H. *Coord. Chem. Rev.* **1999**, *185/186*, 569.
(5) (a) Kramer, R.; Polborn, K.; Robl, C.; Beck, W. *Inorg. Chim. Acta* **1992**, *198−200*, 415. (b) Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1086 and references therein. (c) Beck, W.; Kottmair, N. *Chem. Ber.* **1976**, *109*, 970. (d) Singh, M. M.; Rosopulos, Y.; Beck, W. *Chem. Ber.* **1983**, *116*, 1364. (e) Krämer, R.; Polborn, K.; Beck, W. *J. Organomet. Chem.* **1991**, *410*, 111.

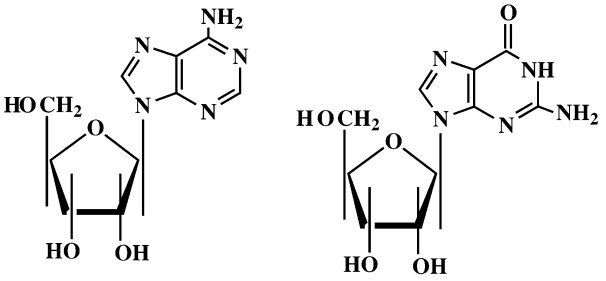
Chart 1

Nucleobases



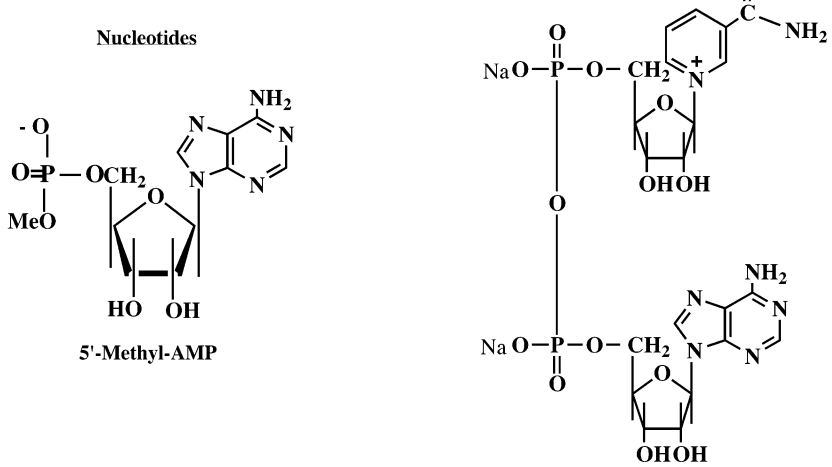
Adenine | 9-Methyladenine | 9-Ethylguanine | 9-Methylhypoxanthine | 1-Methylcytosine | 1-Methylthymine

Nucleosides



Adenosine | Guanosine

Nucleotides



5'-Methyl-AMP | NAD^+

membered ring with NH6 and N1 (ORTEP shows incorrect numbering of the nucleobase) in the coordination sphere (complex **2**; Figure 2). The nucleobase 1-methylcytosine also provided an unusual binding mode, with N3 and NH4 bonding to the Mo metal ion center also making a four-membered ring (complex **3**). Clearly, the NH_2 groups of both nucleobases studied dictate the bonding mode to the ring N atoms, which does not necessarily mean the most basic nitrogen site available but, rather, the plausible thermodynamic effect of forming the four-membered ring.[6a]

Cp*Rh Complexes of DNA/RNA Nucleobases

Thus, with the initial bonding studies of Beck and Marks and their co-workers on nucleobases and other relevant biomolecules, such as L-amino acids, Fish and co-workers, who were attempting to use the $[Cp^*Rh(H_2O)_3](OTf)_2$ synthon to bind large DNA molecules (λ-DNA, 50 000 base pairs; unpublished results with M. Maestre) to glass surfaces for a novel mapping and sequencing technique, decided to study individual nucleobases to further the structural/bonding studies of Beck and Marks, as a function of pH. Chart 1 provides the name and structures of many of the DNA/RNA bases Fish and co-workers utilized in their studies, as well as nicotinamide adenine dinucleotide (NAD^+), an important cofactor in biological redox reactions containing an adenine nucleus.

9-Substituted Adenine Cyclic Trimer Complexes

Fish and co-workers initiated the reactions of various nucleobases with 9-methyladenine and $[Cp^*Rh(H_2O)_3](OTf)_2$ in D_2O at pD 7.2 that provided, by ^1H NMR spectroscopy, evidence for the formation of a new complex with dramatic chemical shifts for H2 and H8 in comparison to those of free 9-methyladenine at 8.83 and 7.67 ppm, respectively. They later found that these

(6) (a) Kuo, L. Y.; Kanatzidis, M. G.; Sabat, M.; Tilton, A. L.; Marks, T. J. *J. Am. Chem. Soc.* **1991**, *113*, 9027. (b) Toney, J. H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 947. (c) Toney, J. H.; Brock, C. P.; Marks, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 7263. (d) Kuo, L. Y.; Kanatzidis, M. G.; Marks, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 7207. (e) Kuo, L. Y.; Kanatzdis, M. G.; Sabat, M.; Tipton, A. L.; Marks, T. J. In *Metal Ions in Biological Systems*; Sigel, H., Ed.; Marcel Dekker: New York, 1996; Vol. 33, p 53.

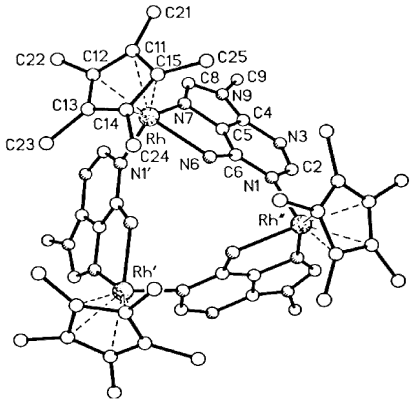


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Figure 3. X-ray structure of [Cp*Rh(μ-η^1(*N1*):η^2(*N6*,*N7*)-9-methyladenenyl]$_3$(OTf)$_3$ (**4**).

dramatic ^{1}H NMR chemical shifts for H8 and H2 were *a diagnostic characteristic for all Cp*Rh cyclic trimer structures* with 9-substituted adenine derivatives, which was verified by X-ray crystallography of the Cp*Rh−9-methyladenine cyclic trimer.[7]

The single-crystal X-ray structure of an enantiomer, [Cp*Rh(μ-η^1(*N1*):η^2(*N6*,*N7*)-9-methyladenenyl]$_3$(OTf)$_3$ (**4**), was shown to have a triangular domelike supramolecular structure, with three Cp* groups stretching out from the top of the dome, three Me groups pointing to the bottom, three adenine planes forming the surrounding shell, and three Rh atoms embedded in the top of the dome. This molecule also possesses a C3 axis, which passes from the top of the dome to the bottom. The distance between the adjacent methyl groups at the bottom of the dome, i.e., at the opening of this potential molecular receptor, is about 7.5 Å, while the cavity depth is a consequence of the substituent on N9 of the nucleobase, nucleoside, or nucleotide and was in the range of ∼4 Å (Figure 3). Both adenosine and the phosphate methyl ester of 5′-AMP, as further examples, also formed cyclic trimer structures, [Cp*Rh(μ-η^1(*N1*):η^2(*N6*,*N7*)-Ado/methyl-5′-AMP)]$_3$.[8]

More recently, it became apparent that no organometallic complex of an important cofactor, nicotinamideadenine dinucleotide (NAD$^+$), containing the adenosine monophosphate group, had been assigned a definitive structure. Therefore, the reinvestigation of this interesting reaction with cofactor NAD$^+$ and [Cp*Rh(H$_2$O)]$_3$(OTf), using ^{1}H NMR spectroscopy from pH 3 to 9.5, showed the presence of the definitive diastereomeric, cyclic trimer complex [Cp*Rh(μ-η^1(*N1*):η^2(*N6*,*N7*)-NAD)]$_3$(OTf)$_3$ (**5**), with an extremely narrow range of stability: i.e., pH 6.0. Again, the ^{1}H NMR spectrum provided clear evidence for the cyclic trimer structure with a dramatic downfield shift for H8 (in comparison to free NAD$^+$) of δ 0.35 ppm and an upfield shift for H2 of δ 0.48 ppm (Figure 4).[9]

Guanine and Hypoxanthine Complexes

In contrast to cyclic trimer formation for 9-substituted adenine compounds, Fish and co-workers found that the

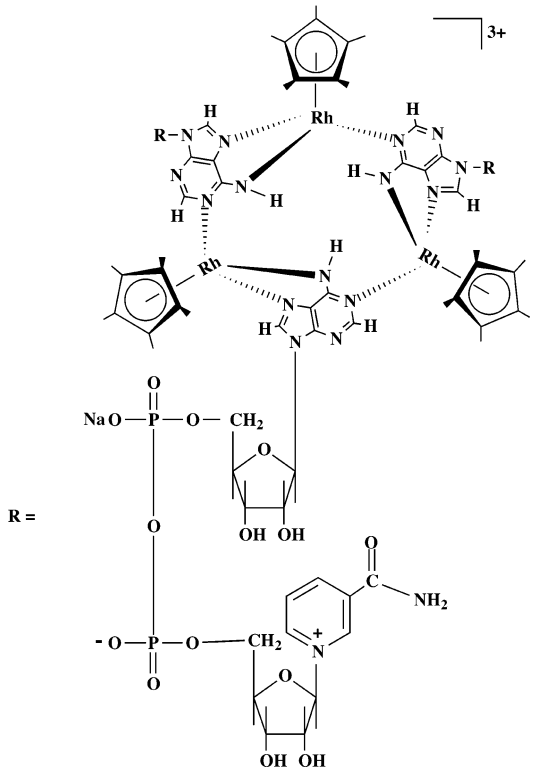

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Figure 4. [Cp*Rh(μ-η^1(*N1*):η^2(*N6*,*N7*)NAD)]$_3$(OTf)$_3$ (**5**).

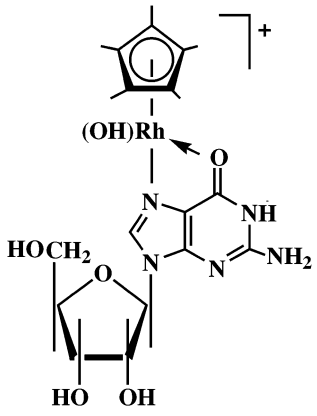

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Figure 5. [Cp*Rh(μ-η^1(*N1*,*O6*)-Guo)(OH)] (**6**).

nucleoside guanosine reacted with [Cp*Rh(H$_2$O)]$_3$(OTf)$_2$ at pH 5.4 to provide an isolated product that by elemental analysis and FAB-MS (*m*/*z* 670.1, [Cp*Rh(Guo)(OTf)]; *m*/*z* 556.1, [Cp*Rh(Guo)(OH)]) was a monomer with the formula [Cp*Rh(μ-η^1(*N1*,*O6*)-Guo)(OH)](OTf) (**6**). The tentative structure was elucidated by 500 MHz ^{1}H NMR spectroscopy in DMSO-d_6 to show a substantial downfield shift for H8 at 8.93 ppm ($\Delta\delta$ = 1.01 ppm), which is consistent with N7 binding to the guanine nucleus. The NH1 group was also shifted downfield ($\Delta\delta$ = 0.53 ppm), and this may be indicative of the 6-C=O group interacting with the Cp*Rh metal center as shown (Figure 5).[7,10a]

Moreover, an ^{1}H NMR spectroscopy study was performed with 9-methylhypoxanthine and the ethyl ana-

(7) Smith, D. P.; Baralt, E.; Morales, B.; Olmstead, M. M.; Maestre, M. F.; Fish, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 10647.

(8) Smith, D. P.; Kohen, E.; Maestre, M. F.; Fish, R. H. *Inorg. Chem.* **1993**, *32*, 4119.

(9) Ogo, S.; Buriez, O.; Kerr, J. B.; Fish, R. H. *J. Organomet. Chem.* **1999**, *589*, 66 (special issue of JOMC on Bioorganometallic Chemistry).

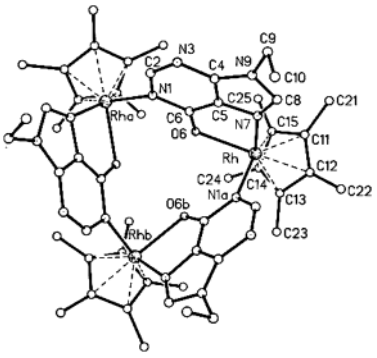


Figure 6. [Cp*Rh(μ-η^1(*N1*):(η^2(*O6,N7*)-9-ethylhypoxanthyl)]$_3^{3+}$ (**8**).

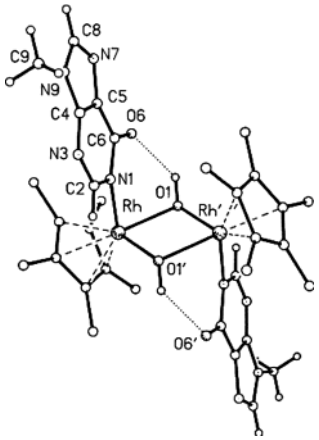


Figure 7. [(Cp*Rh)(η^1(*N1*)-9-MH)(μ-OH)]$_2$ (**9**).

logue, since this would also allow determination of the steric role, if any, of the NH_2 group at C2 of the guanine nucleus (9-ethylguanine) and the bonding mode of NH1. The pH profile of the Cp*Rh complex of 9-methylhypoxanthine was studied by ^{1}H NMR spectroscopy in D_2O. At pD 2.45−5.13, the downfield chemical shifts for both H8 (8.48 ppm, $\Delta\delta = 0.44$ ppm) and H2 (8.35 ppm, $\Delta\delta = 0.17$ ppm) compared to those for free 9-methylhypoxanthineand (H8, 8.04 ppm; H2, 8.18 ppm) are consistent with exclusive N7 binding. However, at pD 6.45, the Cp*Rh−9-methylhypoxanthine complex provides the dramatic chemical shifts we have found to be diagnostic for cyclic trimer formation, especially for H8 (downfield shift) and H2 (upfield shift) at 8.60 ppm (H8, $\Delta\delta = 0.56$ ppm) and 7.78 ppm (H2, $\Delta\delta = 0.40$ ppm), as well at 3.73 ppm (9-CH_3, $\Delta\delta = 0.09$ ppm) and 1.84 ppm (Cp*), and strongly suggested the presence, at that time, of the unusual and unprecedented structure [Cp*Rh(μ-η^1(*N1*):η^2(*O6,N7*)-9-methylhypoxanthyl)]$_3^{3+}$ (**7**), as unequivocally determined by single-crystal X-ray analysis of the ethyl analogue **8** (Figure 6).[10b]

Two structural features of the ethyl analogue [Cp*Rh(μ-η^1(*N1*):η^2(*O6,N7*)-9-ethylhypoxanthyl)]$_3^{3+}$ (**8**) merit comment. First, the cationic portion had the similar triangular domelike cavity, with three Cp* groups stretching out from the top of the dome, three ethyl groups pointing to the bottom, three hypoxanthine planes forming the surrounding shell, and three Rh atoms embedded on the top of the dome. The cation also possesses a C_3 axis, which passes from the top of the dome to the bottom. Second, the C6−O6 bond distance of 1.296(24) Å falls between the single-bond distance of 1.42 Å, found in an alcohol, and the double-bond distances of 1.233(4) and 1.230(7) Å, which were observed in inosine. This result suggests that a significant amount of multiple-bond character still exists in the C6−O6 bond. It is important to note that when 9-ethylguanine was also studied from pD 2.45 to 6.45, only N7 binding was evident, with no diagnostic chemical shifts for a cyclic trimer structure.

Interestingly, at pD 10.50, a new Cp*Rh complex of 9-methylhypoxanthine was formed and showed significant upfield shifts of H8 and H2 that were reminiscent of a [Cp*Rh(μ-OH)(L)]$_2$ dimer complex, where L = 1-methylcytosine.[11] The single-crystal X-ray structure of the orange dimer [(Cp*Rh)(η^1(*N1*)-9-methylhypoxanthinyl)(μ-OH)]$_2$ (**9**), isolated from its aqueous reaction mixture at pH 10.2, is shown in Figure 7.[10b] The main structural features of interest are the unique η^1(N1), rather than η^1(N7) or η^2(N7,O6), binding mode of 9-methylhypoxanthine and the intramolecular H-bonding between the μ-OH groups and O6 of this nucleobase.

The above-mentioned result suggests that the NH_2 group at C2 on the guanine nucleus (9-ethylguanine), whose steric and electronic effects had not been previously well defined during the metal coordination process, *plays a significant steric role*, in this instance, in preventing cyclic trimer formation at pD 6.45; this is a steric rather than electronic effect due to NH1 pK_a similarities for 9-ethylguanine and 9-methylhypoxanthine.

Cytosine Complex

To further establish the reactivity of an exocyclic NH_2 group (in comparison to C6-NH_2-adenine derivatives), Fish and co-workers studied the reaction of [Cp*Rh(H_2O)]$_3$(OTf)$_2$ with 1-methylcytosine at pH 5.4, which was found to provide, by ^{1}H NMR, FAB/MS, elemental analysis, and single-crystal X-ray crystallography, a trans-μ-hydroxy dimer with the formula *trans*-[Cp*Rh(η^1(*N3*)-1-methylcytosine)(μ-OH)]$_2$(OTf)$_2$ (**10**) (Figure 8).[11] The 1-methylcytosine group binds at N3 and forms intramolecular hydrogen bonds to the μ-OH with the NH_2 group and to the μ-OH with the C═O group but does not form a four-membered chelate with N3/NH_2; clearly the extensive intramolecular hydrogen bonding of the donor and acceptor μ-OH groups with the NH_2 groups and the C═O groups overrides any four-membered chelate that may form.

Thymine Complex

Reaction of [Cp*Rh(H_2O)]$_3$(OTf)$_2$ and 1-methylthymine (1-MT) at pH 10 provided one of the most unusual and novel structures discovered in all of the bioorganometallic studies conducted by the Fish group.[12] Figure 9 shows the reported X-ray crystal structure of the anionic and cationic components, and *a key feature is*

(10) (a) Smith, D. P.; Griffin, M. T.; Maestre, M. F.; Fish, R. H. *Inorg. Chem.* **1993** *32*, 4677. (b) Chen, H.; Olmstead, M. M.; Smith, D. P.; Maestre, M. F.; Fish, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1514.

(11) Smith, D. P.; Olmstead, M. M.; Noll, B. C.; Maestre, M. F.; Fish, R. H. *Organometallics* **1993**, *12*, 593.

(12) Chen, H.; Olmstead, M. M.; Maestre, M. F.; Fish, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 9097.

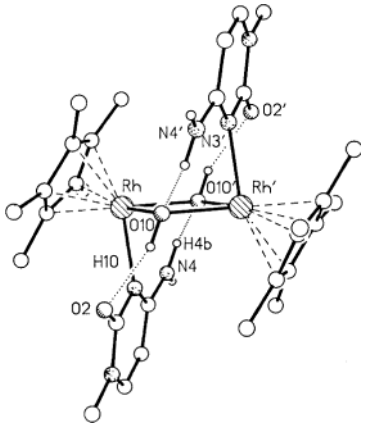


Figure 8. X-ray structure of *trans*-[Cp*Rh(η^1(*N3*)-1-methylcytosine)(μ-OH)]$_2$(OTf)$_2$ (**10**).

the linear, N1−Rh4−N3 grouping ([Rh(η^1(N3)-1-MT)$_2$]$^-$), with a bond angle of 178.2(3)°, and a near-staggered (98.8°) configuration of two thymine planes with respect to one another. Indeed, the two thymine planes are eclipsed, as required by its inversion symmetry. In addition, the perpendicular geometry of the two thymine rings gives rise to an interesting stacking arrangement where the two thymine planes are π-stacked either to a Cp* ring of [(Cp*Rh)$_2$(μ-OH)$_3$]$^+$ (three such interactions) or to a centrosymmetrically related thymine ring of another anion, which allows the Rh4 center to be shielded by a hydrophobic cavity generated from the five Cp* methyl hydrogens (Rh4−H distances range from 2.93 to 3.16 Å).

Shielding by the carbonyl oxygen lone pair electrons of the 1-MT ligands may also be of some importance;

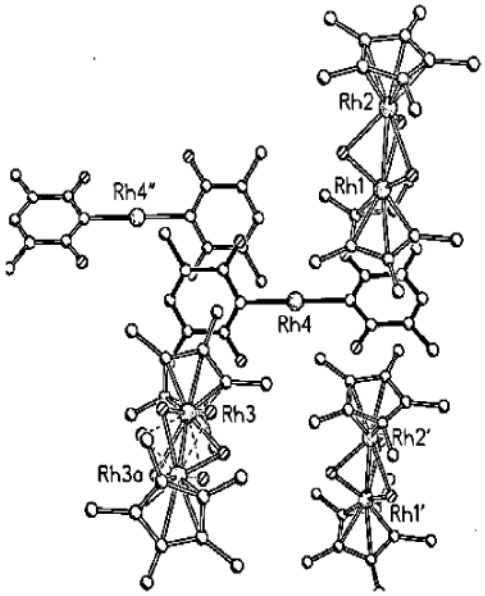
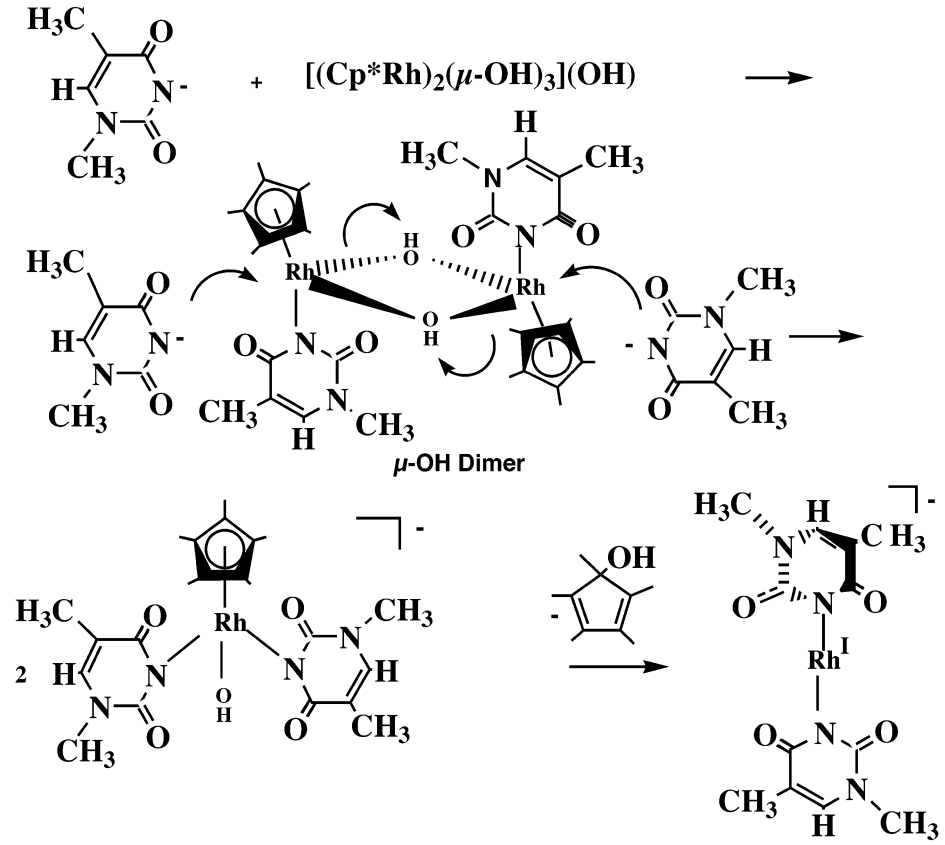


Figure 9. 2[Rh(η^1(*N3*)-1-MT)$_2$]$^-$·3[(Cp*Rh)$_2$(μ-OH)$_3$](OH) (**11**).

however, the four carbonyl oxygen atoms are hydrogen-bonded to H_2O molecules and none of these interactions are near the Rh4 atom. Moreover, the distances between the least-squares adjacent planes of the Cp* groups and the 1-MT ligands range from 3.45 to 3.58 Å and the angles from 0.0 to 2.9°, which agrees well with reported $\pi-\pi$ aromatic ring molecular recognition interaction.

A plausible mechanism for formation of the unique complex [Rh(η^1(*N3*)-1-MT)$_2$]$^-$, is shown in Scheme 1. The mechanism can be tentatively rationalized by the fol-

Scheme 1. Plausible Mechanism for the Formation of [Rh(η^1(*N3*)-1-MT)$_2$]$^-$



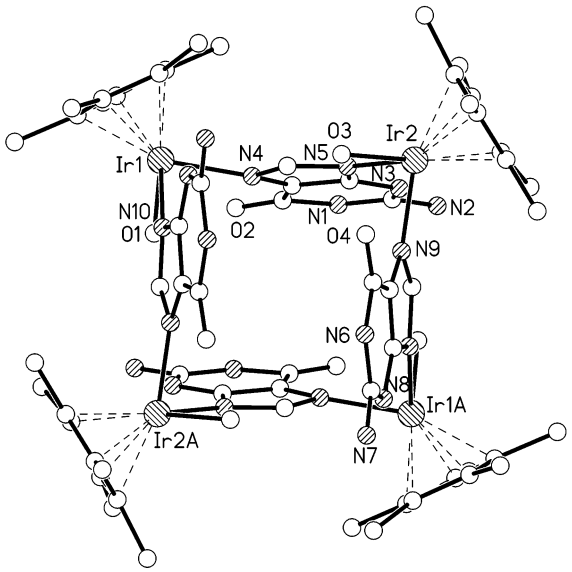


Figure 10. X-ray structure of [CpIr(μ-η^1(*N7,N9*)-guaninyl]$_4^{4+}$ (**12**).

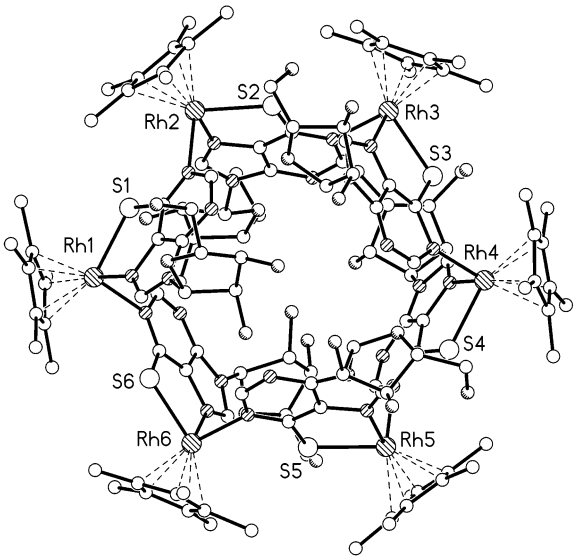


Figure 11. X-ray structure of complex **13**.

lowing observations: the distillate of the reaction mixture was analyzed by GC/MS techniques and provided information that Cp*OH was formed (*m/z* 151 and 135, for $[M - H]^+$ and $[M - OH]^+$) during the reaction; this is clear evidence for the loss of the Cp* ligand from Rh^{3+}. Thus, we speculate that reductive elimination of Cp*OH from the putative mononuclear [Cp*Rh(1-MT)$_2$(OH)]$^-$ complex provided [Rh(η^1(*N3*)-1-MT)$_2$]$^-$. This former complex, [Cp*Rh(1-MT)$_2$(OH)]$^-$, was thought to form via nucleophilic substitution of 1-MT$^-$ ($pK_a = 9.7$) on the plausible and similarly precedented intermediate *trans*-[Cp*Rh(μ-OH)(η^1(*N3*)-1-MT)]$_2$, the presumed initial product from the reaction of 1-MT$^-$ with [(Cp*Rh)$_2$(μ-OH)$_3$](OH).[4]

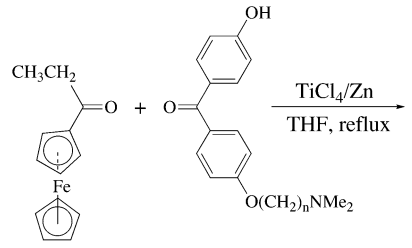
Other Novel Organometallic−Nucleobase Cyclic Complexes

Sheldrick and co-workers[13] extended the nucleobase bonding studies of Fish et al. with, for example, the Cp*Ir aqua complex and reported a novel cyclic tetramer structure with guanine, adenine, or hypoxanthine itself (no substituent at the 9-position). An example shown is the X-ray structure of the tetranuclear [CpIr(μ-η^1-(*N7,N9*)-guaninyl]$_4^{4+}$ complex (**12**; Figure 10),[13a] while adenine afforded the μ-η^1(N9):η^2(N6,N7) bonding mode.[13b]

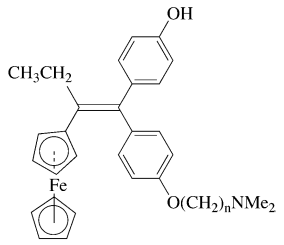
Moreover, Yamanari and co-workers reported that replacement of the NH_2 group in the adenosine nucleus with a C═S group provided an unprecedented cyclic hexamer, rather then the cyclic trimer found by Fish and co-workers with adenosine. This compound was analyzed by X-ray crystallography to provide unequivocal evidence for complex **13** (Figure 11) with μ-η^1(N1):η^2(S6,N7) bonding.[14]

Structures of Organometallic Pharmaceuticals

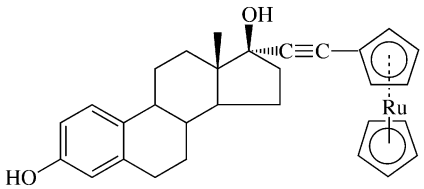
Recently, Jaouen and co-workers have defined novel synthetic pathways to several important organometallic derivatives of the breast cancer drug Tamoxifen, where the phenyl group was replaced by a ferrocenyl group.[1a,b,15] The synthesis and structure of several Ferrocifen derivatives are shown: for example, complex **14**, where *n* = 2, 3, 5, 8. In addition, ruthenocene and cyclopenta-



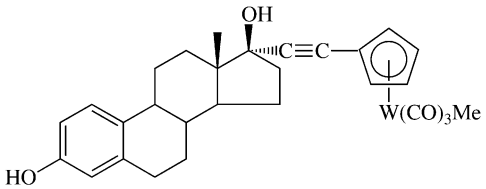
n = 2, 3, 5, 8



Ferrocifen Derivatives, **14**



Estradiol Ruthenocene Complex, **15**



Estradiol CpW(CO)Me Complex, **16**

dienyltungsten derivatives of estradiol provided new

(13) (a) Annen, P.; Schildberg, S.; Sheldrick, W. S. *Inorg. Chim. Acta* **2000**, *307*, 115. (b) Korn, S.; Sheldrick, W. S. *Inorg. Chem. Acta* **1997**, *254*, 85. (c) Korn, S.; Sheldrick, W. S. *J. Chem. Soc., Dalton Trans.* **1997**, 2191. (d) Sheldrick, W. S.; Hagen-Eckard, H. S.; Heeb, S. *Inorg. Chem. Acta* **1993**, *206*, 15.

(14) Yamanari, K.; Yamamoto, S. Ito, R.; Kushi, Y.; Fuyuhiro, A.; Kubota, N.; Fukuo, T.; Arakawa, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2268.

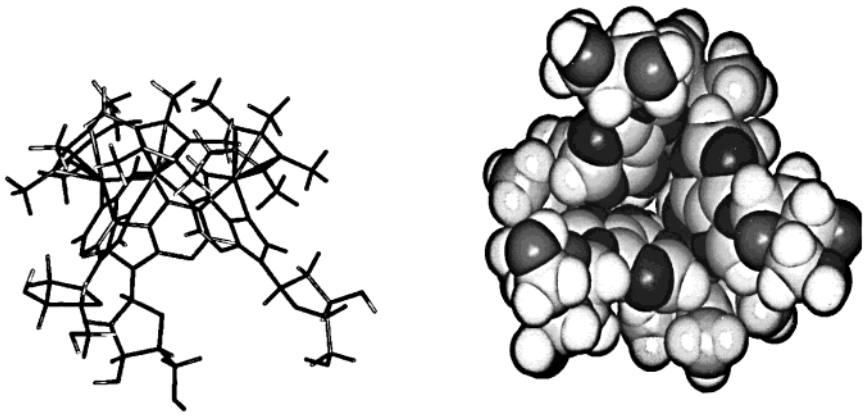


Figure 12. Dreiding model (left) and CPK model (right) of the host [Cp*Rh(2′-deoxyadenosine)]$_3$(OTF)$_3$ (**17**).

synthetic pathways to these organometallic pharmaceuticals.[19a] The critical focus of these synthetic studies was to ascertain the biological effect of an organometallic moiety at the known hormone receptor binding site for efficacious drug therapy. This seminal finding, which appends an organometallic complex to the now modified drug structure, was successful in providing a new scenario for drug discovery and has given credence to the new field of organometallic pharmaceuticals.[1a,b]

Molecular Recognition Studies with Cyclic Trimer Bioorganometallic Hosts and Biological Guests in Water

Host [Cp*Rh(2′-deoxyadenosine)]$_3$(OTf)$_3$. When Fish and co-workers discovered the 9-substituted adenine cyclic trimer structures, for example complex **4**, having C_3 symmetry, they found that the X-ray/computer-generated molecular models conveyed a supramolecular, bowl structure to this potential host and considered the possibilities of noncovalent $\pi-\pi$, hydrophobic, and subtle hydrogen bonding interactions with biologically important guest molecules.[4,7] Indeed, this was the case; moreover, they found that the [Cp*Rh(2′-deoxyadenosine)]$_3$(OTf)$_3$ complex (**17**) was the best host available (Figure 12).[16]

Therefore, a variety of guest aromatic and aliphatic amino acids, substituted aromatic carboxylic acids, and aliphatic carboxylic acids, including examples such as L-phenylalanine, L-tryptophan (L-**Trp**), and phenylacetic and cyclohexylacetic (**CAA**) acids, were studied by ^{1}H NMR spectroscopy (association constants (K_a) and free energies of complexation ($\Delta G°$)) for their noncovalent interactions with the host, [Cp*Rh(2′-deoxyadenosine)]$_3$-(OTf)$_3$. Apparently, the aromatic groups interact by a classical $\pi-\pi$ mechanism, while the aliphatic guests engage in classical hydrophobic interactions. The computer-generated molecular recognition process of L-**Trp** with [Cp*Rh(2′-deoxyadenosine)]$_3$(OTf)$_3$ was shown in the energy-minimized, space-filling host and the docking of L-**Trp** (Figure 13).[16,17] These overall results suggest that the molecular recognition of L-**Trp** with [Cp*Rh-

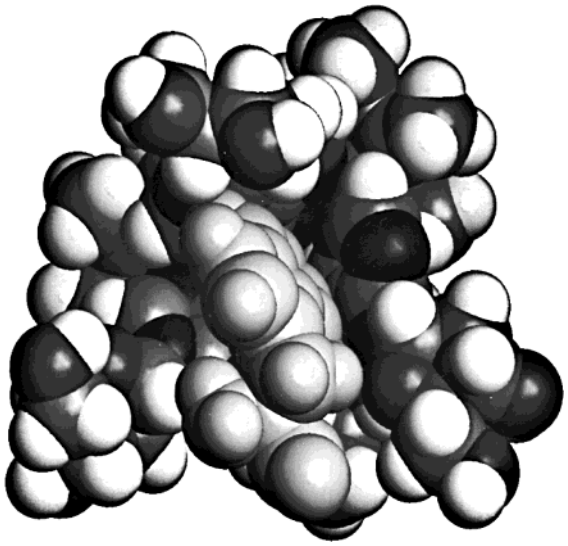


Figure 13. Host−guest [Cp*Rh(2′-deoxyadenosine)]$_3$(OTf)$_3$·L-tryptophan docking experiment.

(2′-deoxyadenosine)]$_3$(OTf)$_3$ can be described in a way that places the L-**Trp** aromatic rings inside of the host cavity with the aromatic plane, or more specifically, the line which bisects the C−H(a) and C−H(a′) bonds parallel to the C3 axis of the host. Similar Dreiding and CPK models for the [Cp*Rh(2′-deoxyadenosine)]$_3$(OTf)$_3$ hydrophobic interaction with **CAA** are shown in Figure 14.

A New Biorganometallic Host−Guest Process: Selective Hydrogen Bonding. Furthermore, the X-ray structure of potential host **10** (Figure 8) clearly shows the unique intramolecular H-bonding aspects of the ligand, 1-methylcytosine, with the $Rh_2(\mu\text{-}OH)_2$ core that were previously reported.[11] Thus, the μ-OH groups act as both H-donors and H-acceptors with the 2-carbonyl (OH- - -OC = 1.96(1) Å) and NH_2 groups (HO- - -HNH = 1.93(1) Å), respectively. Moreover, we thought that an intermolecular recognition process also based on H-bonding to the μ-OH groups and the cytosine NH_2 and C=O functionalities might be possible with the aromatic amino acid NH_3^+ and COO^- groups, without disrupting the intramolecular hydrogen bonding regime shown in Figure 8.

By analyzing complexation-induced ^{1}H NMR chemical shifts (CICS), we were able to discern a new molecular recognition process based on selective hydrogen bonding between host **10** and the guests L-tryptophan and

(15) Top, S.; Dauer, B.; Vaissermann, J.; Jaouen, G. *J. Organomet. Chem.* **1997**, *541*, 355.
(16) (a) Chen, H.; Maestre, M. F.; Fish, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 3631. (b) Chen, H.; Ogo, S.; Fish, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 4993.
(17) Ogo, S.; Nakamura, S.; Chen, H.; Isobe, Y.; Watanabe, Y.; Fish, R. H. *J. Org. Chem.* **1998**, *63*, 7151.

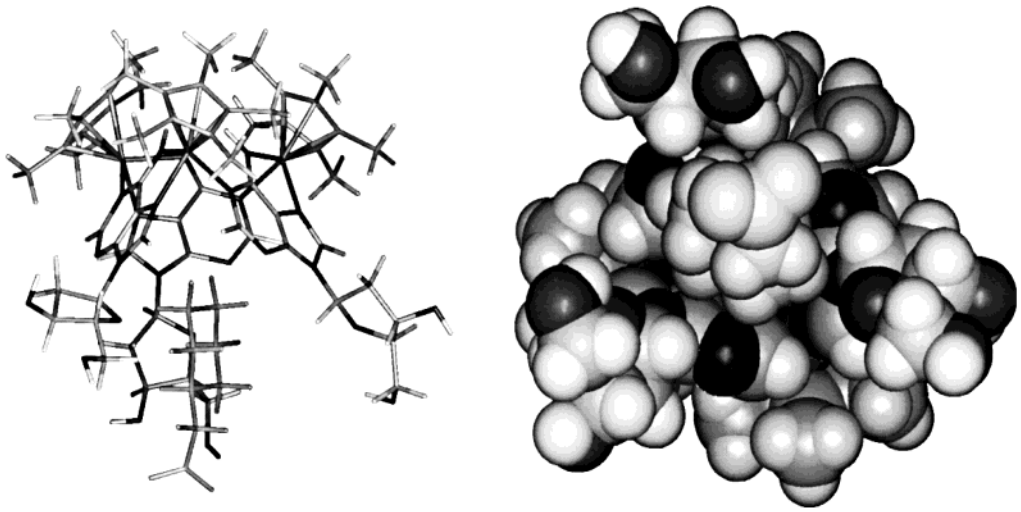


Figure 14. Host−guest, $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3 \cdot CAA$ docking experiment.

L-phenylalanine. Thus, it appeared plausible that the primary host−guest interaction of **10** with L-tryptophan was from a H-bonding process of the NH_3^+ and COO^- groups with the 1-methylcytosine ligand.

To better understand these H-bonding and noncovalent interactions between host and guest, we conducted computer docking experiments to provide the energy-minimized, space-filling/ball-and-stick model of **10** with a ball-and-stick model of the guest L-tryptophan, as shown in Figure 15. The top view in Figure 15 demonstrates the H-bonding of the NH_3^+ group to one μ-O and to the C═O group of one of the 1-methylcytosine ligands, while the COO^- group H-bonds to a NH_2 group of the other 1-methylcytosine ligand. This H-bonding scheme then provides that the remaining structure of the guest is fixed in relation to the host, as shown in the top and bottom views of Figure 15.[18a] This represents a new molecular recognition process for a bioorganometallic host−aromatic amino acid guest interaction and is reminiscent of similar interactions of biologically significant compounds with metalloenzymes or DNA/RNA oligomers.[18b]

Computer Docking Experiments of Organometallic Pharmaceuticals at Estrogen Receptor Binding Sites: Selective, Noncovalent Interactions with Hormone Proteins

The recent exciting find, as elaborated on earlier in the synthetic aspects of this review, by Jaouen and coworkers that an organometallic derivative of the known breast cancer drug Tamoxifen, namely, Ferrocifen and its derivatives, were potentially candidates for breast cancer therapy as well as other cancers has created a new paradigm: namely, the field of organometallic pharmaceuticals.[1e] Since the X-ray structure of the estradiol hormone receptor site has been accomplished, which is thought to be the major receptor protein implicated in hormone-dependent breast cancers, it is now possible to conduct computer docking/energy minimization experiments at the receptor site to discern the conformation and noncovalent interactions of Ferrocifen, and other organometallic drug derivatives, with the surrounding simplified protein structure.[1,19]

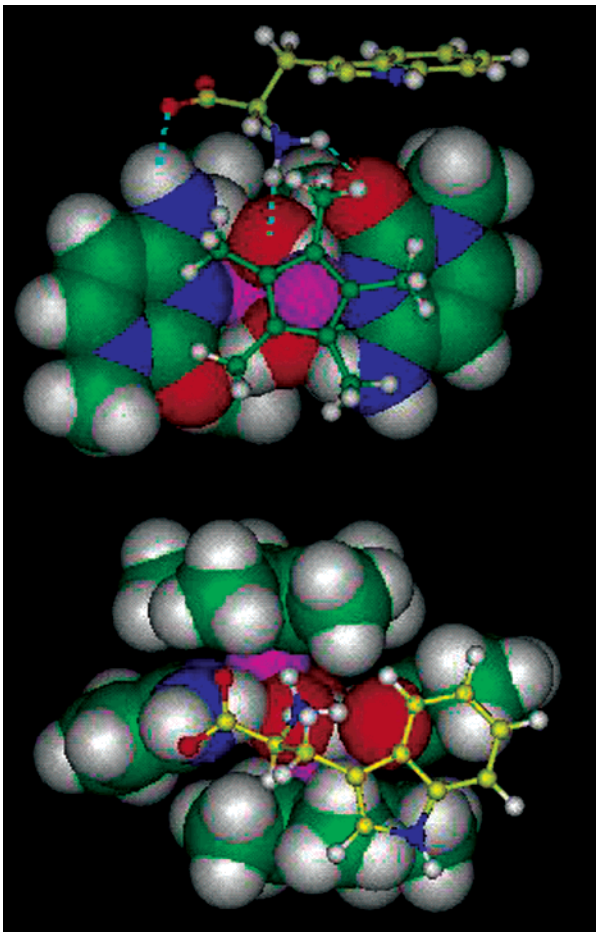
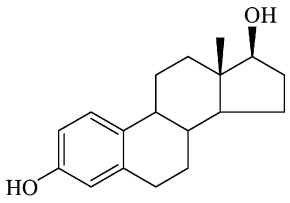


Figure 15. (top) Host **10** with L-tryptophan, showing selective H-bonding of the amino acid CO_2^- to NH_2 of one 1-methylcytosine ligand and NH_3^+ of the amino acid to Rh−μ-OH and C═O of the other 1-methylcytosine ligand. (bottom) Same as top view, turned 90°.

(18) (a) Elduque, A.; Carmona, D.; Oro, L. A.; Eisenstein, M.; Fish, R. H. *J. Organomet. Chem.* **2003**, *668*, 123 (special issue of JOMC on Bioorganometallic Chemistry emanating from ISBOMC'02). (b) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 90.

(19) (a) Top, S.; El Hafa, H.; Vessières, A.; Huché, M.; Vaissermann, J.; Jaouen, G. *Chem. Eur. J.* **2002**, *8*, 5241. (b) Top, S.; Vessières, A.; Cabestaing, C.; Laios, I.; Leclercq, G.; Provot, C.; Jaouen, G. *J. Organomet. Chem.* **2001**, *639*, 500.

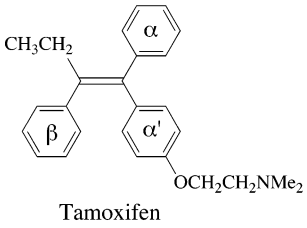
Moreover, the identification of novel targets of estrogen action provides an increasing degree of complexity to the understanding of mechanisms by which this hormone elicits many of its normal, as well as pathological, effects. Estradiol (**18**), the archetype of estro-



Estradiol, **18**

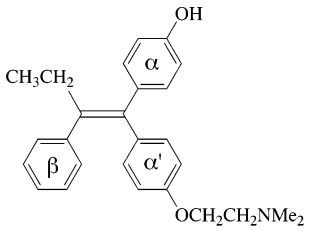
gens, has been implicated in a number of problems from fertility questions to several types of cancer, including frequent diseases such as osteoporosis and cardiovascular and metabolic disorders. It is well-known that the effect of estradiol (**18**) is mediated through its ability to bind to the estradiol hormone receptor site.

A molecular view of the binding modes existing with both an agonist (**18**) and an antagonist (**19** (TAM) and **20** (OH-TAM) block estrogen from the receptor site) with



Tamoxifen

19



4-Hydroxytamoxifen (Z)

20

similar nanometer distances, on the basis of these X-ray determinations, can now be utilized to examine the consequences of the attachment of an organometallic moiety, for example compound **14** ($n = 3$), to a modified drug structure, i.e. drug **20** modified to **14**, with respect to the receptor binding site. Since we have two groups of organometallic drug derivatives based on an estrogenic (complex **15**) or an anti-estrogenic (complex **14**) structural effect, we will illustrate the different noncovalent binding regimes with an example of each type of behavior.

Figure 16 defines the anti-estrogenic, organometallic complex **14** ($n = 3$) as to its conformation in computer docking/energy minimization experiments with the estrogen receptor site proteins and demonstrates important noncovalent interactions with the amino acids depicted in the figure. Thus, several hydrogen-bonding regimes are discernible: for example, between aspartic acid carboxylate 353 (1.868 Å) and one of the $N-CH_3$ groups of the ether side chain, $O(CH_2)_3N(CH_3)_2$, the carboxylate of glutamic acid 351 and the phenolic hydrogen (1.577 Å), and the arginine 394 NH with the phenolic oxygen (2.061 Å). Moreover, one of the Cp ligands of the ferrocene group has a noncovalent $CH-\pi$ interaction with the histidine 524 imidazole ring.

In contrast to the anti-estrogenic **14** ($n = 3$; *Z* isomer) binding mode to the estrogen protein receptor site, the ligand binding domain for estrogenic **15** was similar to that of estradiol (**18**), with the exception of the ru-

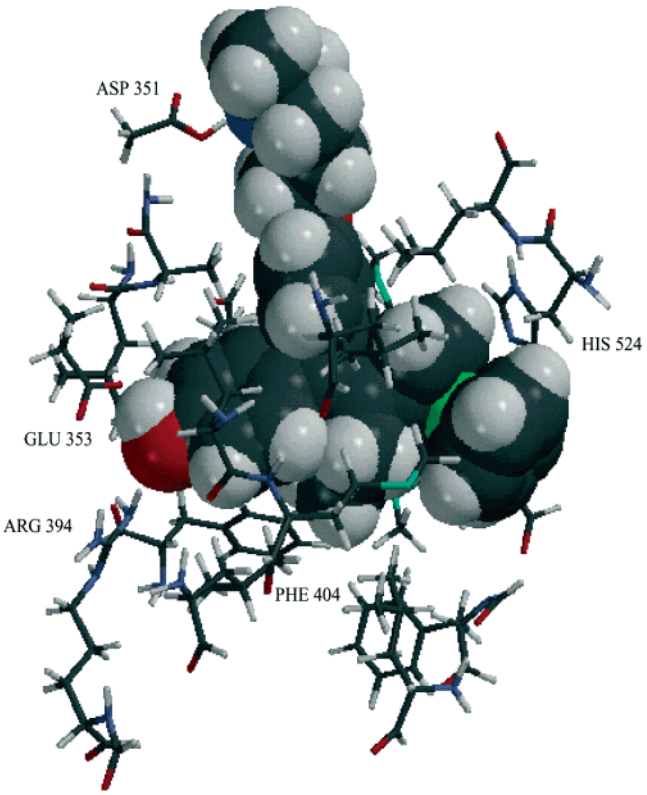


Figure 16. Ferrocifen derivative (*Z* isomer) **14** ($n = 3$), docked at the estrogen protein receptor site, showing the organometallic complex inside the antagonist binding site of the estrogen receptor.

thenocene Cp ligand, attached to a rigid acetylenic linkage. Clearly, Figure 17 shows dramatic conformational and noncovalent bonding differences with the estrogen protein binding site between the two organometallic modified drugs **14** and **15**. Significantly, one of the Cp rings of the ruthenocene group is now in a noncovalent $\pi-\pi$ interaction (3.211 Å) with the histidine 524 imidazole group, while the imidazole ring NH group forms a hydrogen bond (2.722 Å) to the 17α-OH group. Other pertinent hydrogen bonds are those with the A ring phenolic OH with both the glutamic acid carboxylate 353 (2.722 Å) and the arginine 394 NH (3.101 Å).

Therefore, the exciting finding from bioassay results of possibly why the organometallic pharmaceutical **14** ($n = 3$) is a potential anticancer agent,[1a,b] while the organometallic modified estradiol **15** is not, could be related to the conformational changes in the estrogen receptor protein upon binding of the drug. This can be depicted in the more complex receptor protein site with **14** ($n = 3$) (Figure 18), where the apparent steric effects of the $O(CH_2)_3N(CH_3)_2$ side chain appear to cause helix 4 and helix 12 to leave a gap between them. This factor is opposite to that of complex **15**, where there is no gap (similar to a mouse trap) between helix 4 and helix 12, and this plausible reason, among others, may explain why **14** is a potential cancer drug for breast cancer and **15** is not. Another important aspect is the fact that **14**, with a ferrocenyl ligand, can be readily oxidized to a ferrocenium ion and, in the process of degradation to Cp and Fe(III), can generate an oxygen radical species that can provide the cytotoxic effect, by possibly reacting

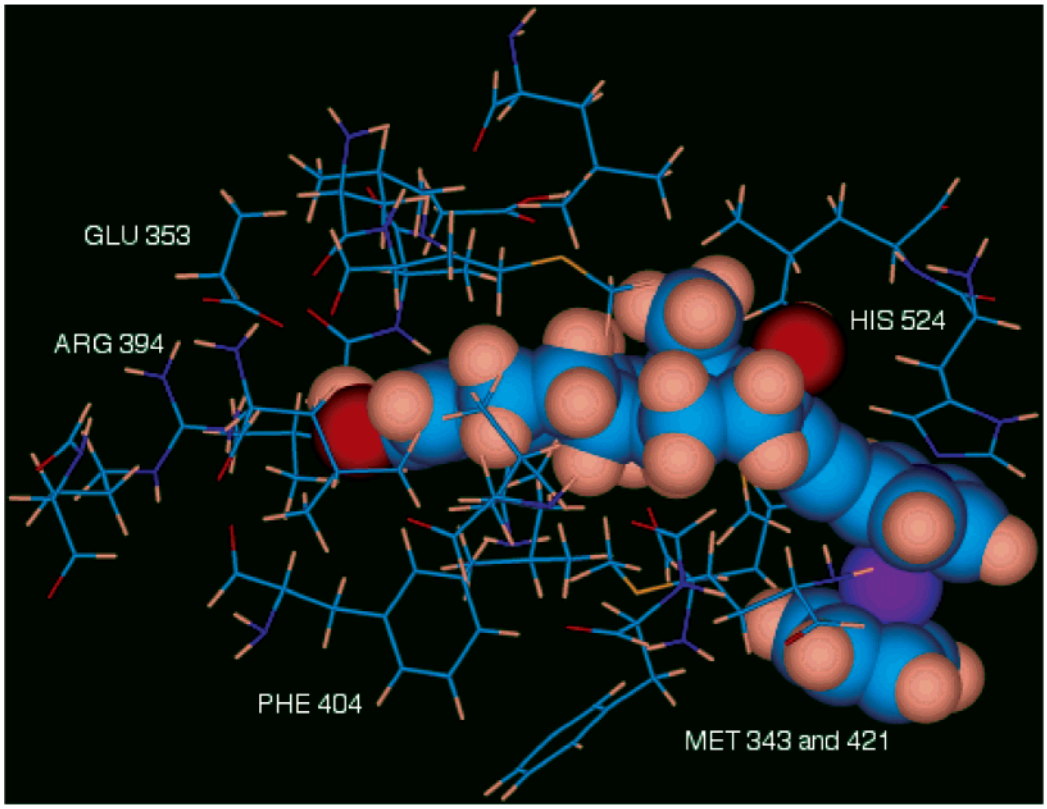


Figure 17. 17α-ruthenocenylethynylestradiol (**15**), docked at the estrogen protein receptor site. The ethynyruthenocenyl group is also bordered on its lower side by the two hydrophobic amino acid residues Met 343 and Met 421. A shrinkage, which is well adapted to accommodate the rigid ethynyl group, can be clearly seen in front of the 17α-position of the hormone. This allows the ruthenocenyl group to avoid steric constraints inside the cavity.

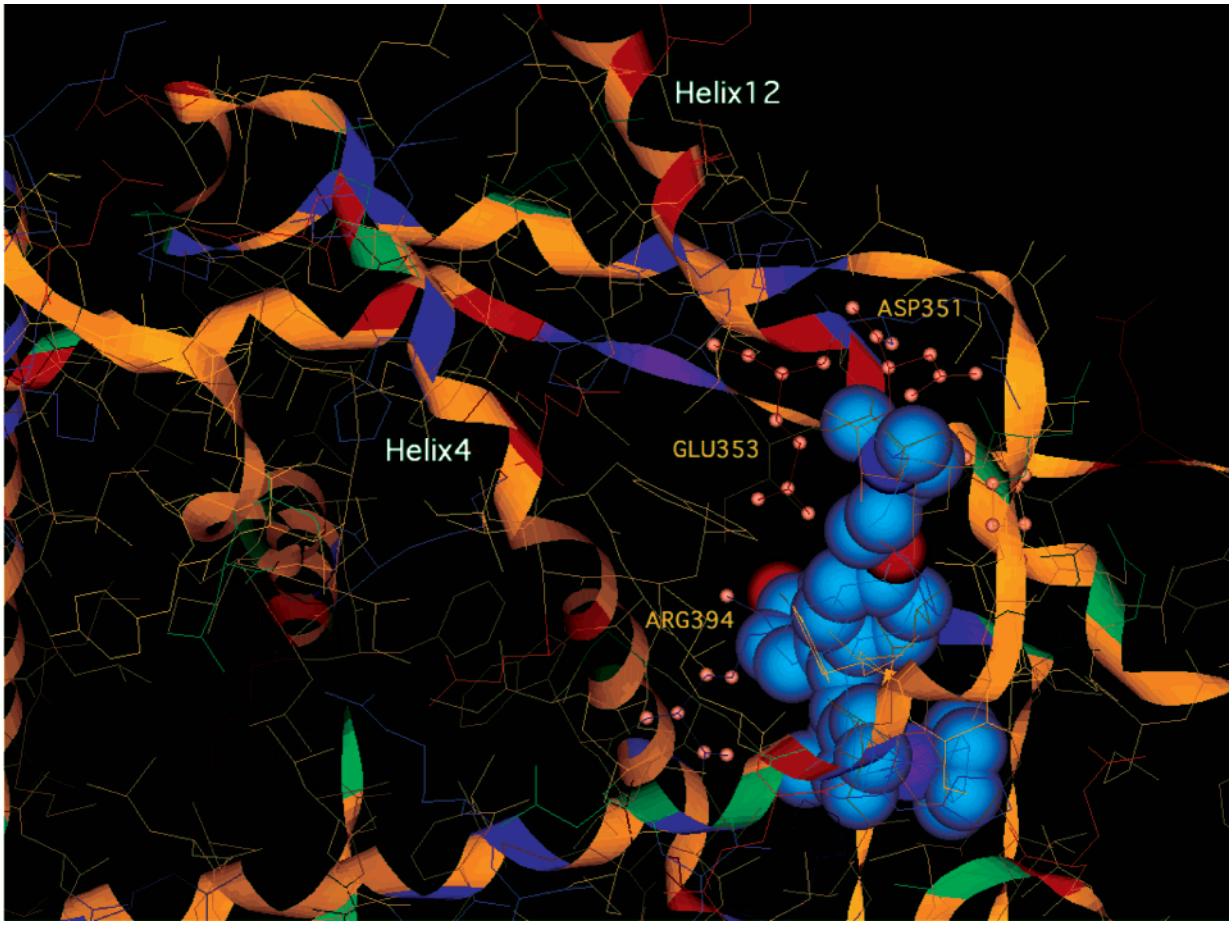


Figure 18. Ligand binding domain at the estrogen receptor site of the potential organometallic pharmaceutical **14**.

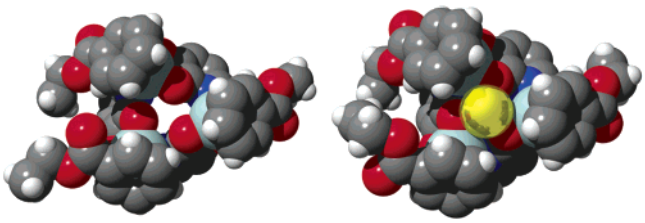


Figure 19. Organometallic ionophore **21** (left) and Li complex **22** (right).

with DNA in proximity to the binding domain at the estrogen receptor site.[20]

Organometallic Ionophores: Selectivity for Li^+ Ions

In the quest for more selective ionophores, biomolecular metallomacrocycles that selectively sequester alkali-metal ions, several groups have used the self-assembly approach to these synthetic targets that are useful for medical and analytical applications. Taking a synthetic approach similar to that for the self-assembled Cp*Rh cyclic trimer structures, such as **4**, that were used as hosts for biomolecules, Severin and co-workers developed a novel organometallic ionophore, by reaction of 3-hydroxypyridone with $[(C_6H_5CO_2Et)\text{-}RuCl_2]_2$, which is highly selective for Li^+ ions over the more highly concentrated Na^+ ions.[21] This is significant, since Li^+ ion concentrations are strictly monitored for a variety of medical applications related to mental disorders. The CPK models of the organometallic ionophere **21** and that of the Li complex **22** (Cl omitted for clarity) are shown in Figure 19.

Conclusions

In this mini-review of the bioorganometallic chemistry discipline, focused on structural diversity and molecular recognition, we hope to have enlightened the organometallic community to these new directions and to have envisioned the exciting possibilities for future directions. Clearly, as organometallic chemists, we have a vital role at the interface of chemistry and biology to create new paradigms for basic research and, for example, medical applications, for the betterment of the global society.

Acknowledgment. R.H.F. thanks the CNRS for a visiting professorship at ENSCP, where the initial writing of the review took place, and all the students and colleagues named in the references who carried out these exciting studies. The studies at LBNL were supported by the LBNL Laboratory Directed Research and Development Funds and the Department of Energy under Contract No. DE-ACO3-76SF00098. G.J. thanks the CNRS for support of the ENSCP Bioorganometallic Chemistry programs as well as students and colleagues named in the references.

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(21) (a) Piotrowski, H.; Polborn, K.; Hilt, G.; Severin, K. *J. Am. Chem. Soc.* **2001**, *123*, 2699. (b) Piotrowski, H.; Severin, K. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4997 and references therein.