In Silico Evolution of Substrate Selectivity: Comparison of Organometallic Ruthenium Complexes with the Anticancer Drug Cisplatin

Dirk V. Deubel* and Justin Kai-Chi Lau

Supporting Information

Figure S-1. Charge transfer from L to the metal complex in the transition states (full symbols), and products (empty symbols), based on a natural population analysis (NPA). Charge transfer from OH_2 in the reactants (black symbols).

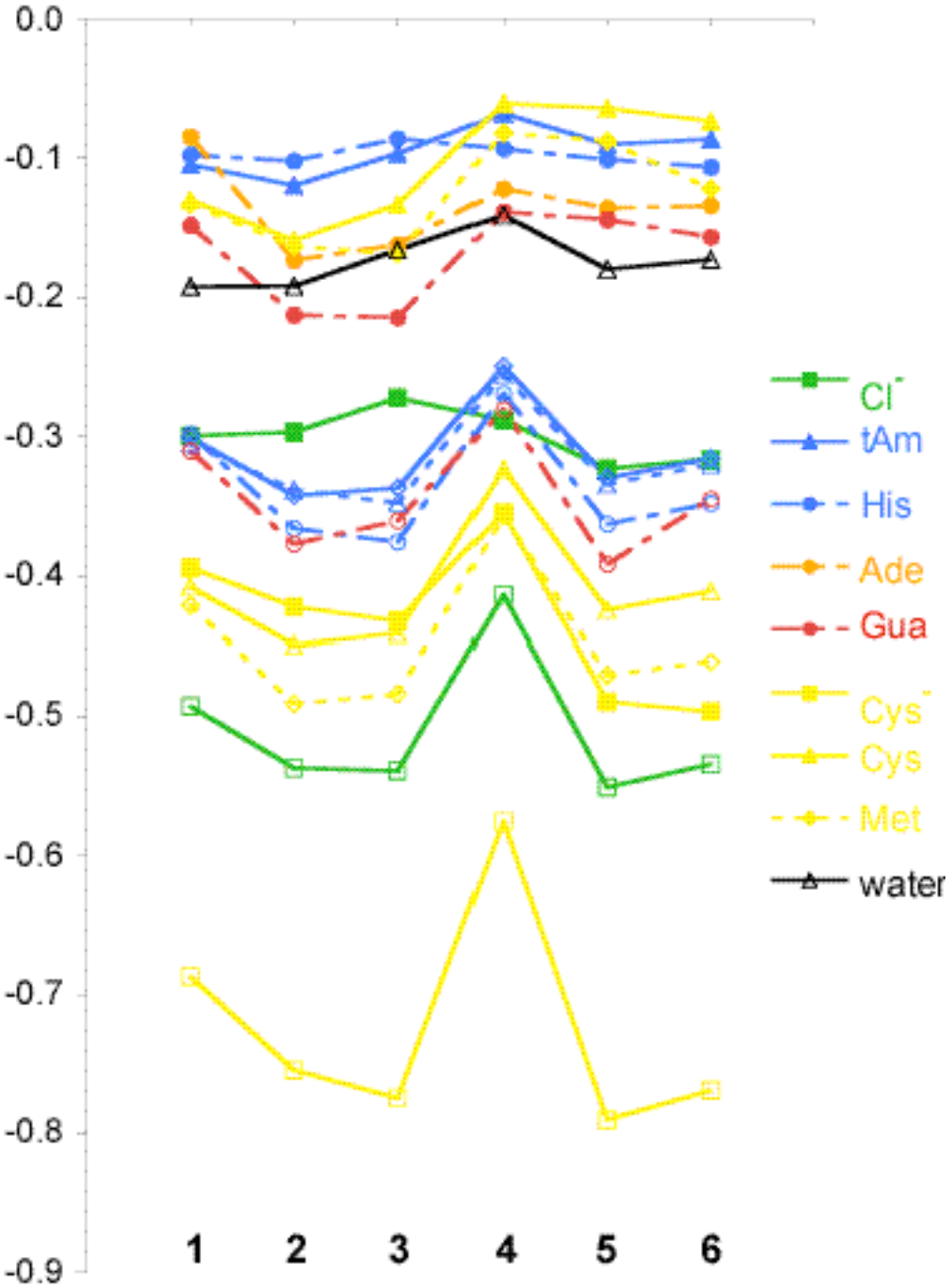


Figure S-2. Extent of reaction ξ and dissociative character δ of transition structures (see text below). Average values are given for each L and each metal complex (**1 – 6**).

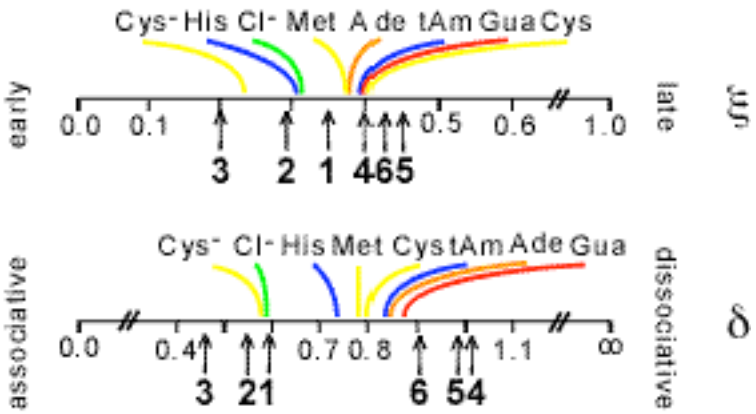
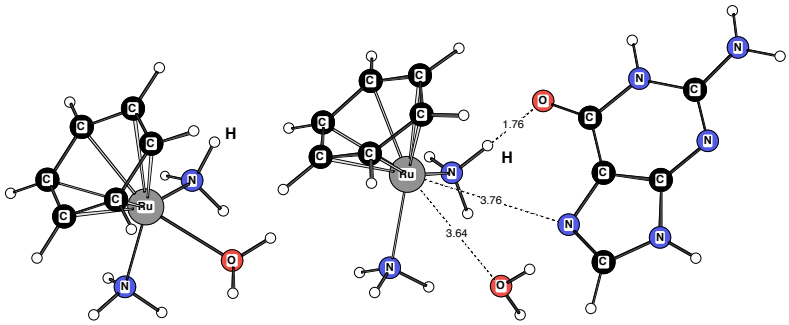
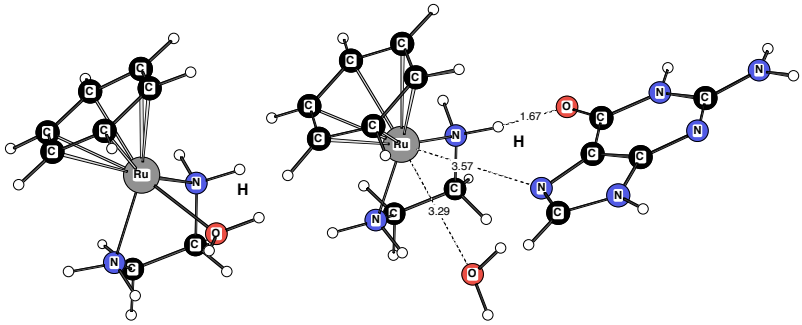


Figure S-3. Structure of the reactants and transition states for the reactions of 5-OH_2 and 6-OH_2 with Gua. In parentheses: H-N-Ru-N dihedral angle, indicating the conformational activation of 6-OH_2.

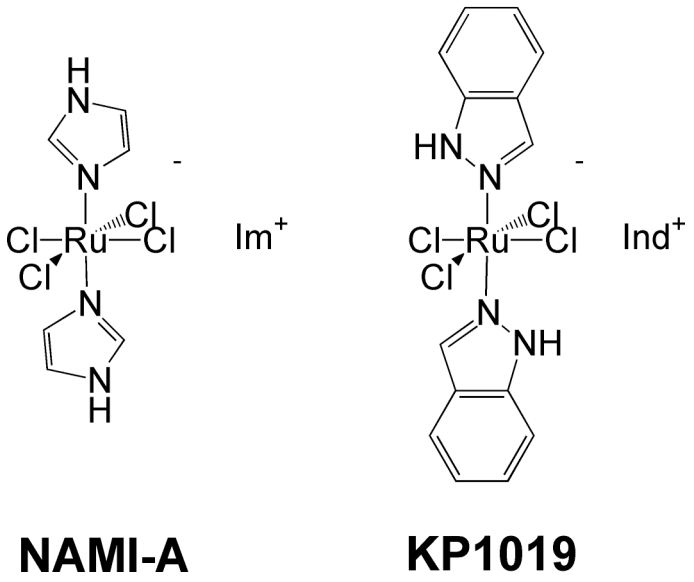


5-OH_2 (-176°) **TS 5-OH_2 Gua (-142°)**



6-OH_2 (-136°) **TS 6-OH_2 Gua (-132°)**

Figure S-4. Structures of NAMI-A and KP1019. Im = imidazole, ind = indazole.



Computational Details

Structures and free energies in vacuo. The geometries of molecules and transition states (TS) were optimized at the gradient-corrected DFT level using the 3-parameter fit of exchange and correlation functionals of Becke (B3LYP),[1] which includes the correlation functional of Lee, Yang, and Parr (LYP),[2] as implemented in Gaussian 98.[3] The LANL2DZ ECP's[4] and valence-basis sets were used at the metals, and the 6-31G(d,p) basis sets were used at the other atoms.[5] This basis-set combination is denoted II. Vibrational frequencies were also calculated at B3LYP/II. The structures reported are either minima (NIMAG = 0) or transition states (NIMAG = 1) on the potential energy surfaces. Improved total energies were calculated at the B3LYP level using the same ECP and valence-basis set at the metals, but totally uncontracted and augmented with Frenking's set of f functions,[6] together with the 6-311+G(3d) basis sets at sulfur and chlorine and the 6-311+G(d,p) basis sets at the other atoms. This basis-set combination is denoted III+. Activation and reaction free energies (ΔG_a, ΔG_r) were calculated by adding corrections from unscaled zero-point energy (ZPE), thermal energy, work, and entropy evaluated at the B3LYP/II level at 298.15 K, 1 atm to the activation and reaction energies (ΔE_a, ΔE_r), which were

calculated at the B3LYP/III+//II level. A similar computational approach was successfully used for investigating $[M(p\text{-cymene})Cl_2(pta)]^+$ complexes (M = Ru, Os).[7] Slight improvements of the structures but, most importantly, very little changes in relative free energies were observed when the basis set III+ was used for geometry optimization (Table S-3). Selected molecules have been optimized at the Becke-Perdew (BP)[8,9] level with a TZ2P basis set at the metal and a TZP basis set at the other atoms, as implemented in the Amsterdam Density Functional (ADF) package.[10] Non-relativistic and ZORA-scalar-relativistic calculations[11,12] have been compared at this level to explore the relativistic stabilization of strong and weak bonds as well as partial bonds in the TS.

Solvation free energies. Solvation free energies G_{solv}^{ε} of the structures optimized at the B3LYP/II level were calculated by Poisson-Boltzmann (PB) calculations with a dielectric constant ε of the dielectric continuum that represents the solvent. The PB calculations were performed at the B3LYP level using the LACVP** basis set on the metals, the 6-31G+* basis set at oxygen and nitrogen, and the 6-31G** basis set on the other atoms as implemented in the Jaguar 5 program package.[13] The continuum boundary in the PB calculations was defined by a solvent-accessible molecular surface with a set of atomic radii for H (1.150 Å), C (1.900 Å), N (1.500 Å), O (1.400 Å), S (1.900 Å), Cl (1.974 Å), Ru (1.481 Å), Pd (1.450 Å), and Pt (1.377 Å).[14] pK_a predictions were carried out using a thermodynamic cycle,[15] $\Delta G^{\varepsilon} = \Delta G^{1} + G_{solv}^{\varepsilon}(H^+) + G_{solv}^{\varepsilon}(A^-) - G_{solv}^{\varepsilon}(A)$ and $pK_a^{\varepsilon} = \Delta G^{\varepsilon}/ RTln10$, where ΔG^{1} and ΔG^{ε} are the reaction free energies of the reaction, $AH \rightarrow A^- + H^+$, in vacuo and at a dielectric constant ε = 80.37 for water, respectively, $G_{solv}^{\varepsilon}(X)$ is the solvation free energy of species AH or A^- at ε obtained via PB calculations, R is the ideal gas constant, and T is the temperature (298.15 K). Experimental values have been used for the hydration free energy $G_{solv}^{\varepsilon}(X)$ of small molecules and ions.[16] We believe that continuum dielectric models do not consider properly the changes of solvation entropy in bimolecular reactions; comparisons with experimental values indicate that that reactions of platinum complexes and palladium complexes are systematically ~6 kcal/mol too high. According to Wertz and others,[17] various molecules loose a constant fraction (approx. 0.5) of their entropy, when they are dissolved in water. All free energies in solution except that of the H^+ ion were modified by an entropic term

that is half (0.5) of the entropy in vacuo with the opposite sign. This empirical correction has led to predicted pK_a values of aqua complexes as well as reaction and activation free energies for the hydrolysis of Pt(II) and Ru(II) complexes that agree within ~4 kcal/mol with experimental values.[18,19] Starting with the approach in ref. 14e for investigating the reactions of cisplatin derivatives with Gua vs Ade, we have tried very hard to improve the computational protocol further toward a better prediction of relative free energies of reactions involving various different metal complexes and substrates. We noticed that diffuse functions together with a decrease of the effective radius at oxygen and nitrogen improve the agreement with experimental solvation free energies and acidity constants significantly. Despite this success, we recommend to focus on the trends rather than on absolute numbers. For example, experiments with free amino acids suggested binding constants of $[Ru(arene)(en)(OH_2)]^{2+}$ decreasing in the order cysteine > methionine > histidine[20] within one order of magnitude, while we predict deprotonated Cys^- > His > Met > protonated Cys with larger free energy differences than those suggested by the binding constants. Deviations between experimental and computational data might be attributed to the intrinsic accuracy of the computational approach (~4 kcal/mol)[18] and to the difference of computational and experimental models. While free amino acids were used in experiments, we have considered the primary functional groups, e.g., imidazole as a model for His residues in proteins, in which peptide bonds have replaced the free carboxylate and ammonium ionic functional groups of free amino acids. The presence of ionic groups already changes the experimental pK_a of imidazolium (7.0) vs protonated histidine (6.0) and methanethiol (10.3) vs cysteine (8.3), possibly by interaction of the ionic functional groups with the functional group that becomes deprotonated. The ionic groups of metal-bonded amino acids may also interact strongly via hydrogen bonding with other first-shell ligands in the metal complexes.

Analysis of transition states. To explore the mechanism of the reactions in eq. 1, we have performed a comparative analysis of the transition structures. Despite sophisticated experimental and computational techniques, the clarification of ligand substitution mechanisms remains a challenging task.[21] To facilitate a meaningful comparison of the transition structures for the ligand substitutions involving various metal complexes and substrates, we introduce[22] (i) the *extent of reaction* ξ on a scale

from 0 (reactant-like, "early") to 1 (product-like, "late") and (ii) the *dissociative character* δ on a scale from 0 (associative) to ∞ (dissociative). A δ value of 0.5 [1.0] means that the sum of the elongations of the M-OH_2 and M-L bonds in the TS relative to the corresponding distances in the reactants and products, respectively, is 50% [100%]. This simple concept[22] is based on relative bond-length elongations in the transition structures and allows for a general analysis of ligand-substitution mechanisms. In contrast, the traditional computation-based analysis of water-exchange reactions[23] considers absolute bond-length changes (Rotzinger's ΔΣd(M-O) criterion) and requires the calculation of second-shell reactant adducts. The "reactant adduct" approach is justified for water-exchange reactions, but it would be less meaningful for many other reactions studied in the current work.

Figure S-2 displays the predicted average values of ξ and δ for the reactions of each L and each aqua complex (**1-OH_2** – **6-OH_2**). The reactions with the anionic L = Cys^- have both the lowest ξ (earliest TS) and the lowest δ (most associative), while the Gua metalations are among the reactions with the highest ξ and δ. It is particularly interesting to note that the dissociative character δ increases in the order **3** < **2** < **1** << **6** < **5** < **4** (Figure S-2, bottom). In former experimental and computational studies of water-exchange reactions at Ru(II),[24] the following data were reported: (a) $[Ru(OH_2)_6]^{2+}$. ΔS_a = +16.1±15 J/molK. ΔV_a = -0.7±0.4 cm^3/mol.[24a] Conclusion: I mechanism. (b) $[Ru(\eta^6\text{-benzene})(OH_2)]_3^{2+}$. ΔS_a = +1.5±0.4 J/molK. ΔV_a = -0.7±0.4 cm^3/mol. Conclusion: I mechanism.[24b] (c) $[Ru(OH_2)_6]^{2+}$. ΔΣd(M-O) = +1.25 Å: Conclusion: I_d or D mechanism.[24c] Negative ΔS_a values of Ru-Cl hydrolysis and Ru-OH_2 anation reactions of most $[Ru(\eta^6\text{-arene})(en)(Cl/OH_2)]^{+/2+}$ complexes suggested an I_a mechanism.[25] Remarkably, the comparative analysis of transition structures (Figure S-2) indicates that the reactions of the en-arene Ru(II) complex **6-OH_2** are only slightly less dissociative (or slightly more associative) than those of the inorganic Ru(II) complex **4-OH_2**, whereas the reactions of all Ru(II) complexes (δ ~ 1.0) have a much more dissociative character than the reactions of cisplatin derivatives **1-OH_2** and **2-OH_2** and their cispalladium analog **3-OH_2** (δ ~ 0.5). One should note that the transition structures predicted in vacuo provide an important information about the intrinsic mechanism, while experimental activation entropies ΔS_a and volumes ΔV_a, the sign and magnitude of which have been the basis of the D,

I_d, I, I_a, A classification, are determined to a considerable extent by explicit solvation effects. CDM approaches change the interatomic distances in calculated TS less strongly than does the addition of a few water molecules.[26] The geometric changes in the TS strongly depend on the number of explicit water molecules and on where they are placed, as demonstrated for cisplatin hydrolysis in the presence of 6 vs 10 water molecules.[27] In contrast to the TS structures, the activation barriers are relatively insensitive to explicit hydration.[27] Others advised caution in the use a CDM in combination with explicit solvent molecules and even considered CDM-solvated reactant fragments like *cis*-$\{Pt(NH_3)_2Cl\}^+_{solv}$ rather than *cis*-$[Pt(NH_3)_2(OH_2)Cl]^+$ for calculating the reaction free energies of reactions of aqua complexes.[28]

References SI

1. Becke, A. D. *J. Chem. Phys.* 1993, **98**, 5648.
2. Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* 1988, **37**, 785.
3. Gaussian 98: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich. S.; Milliam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomberts, R.; Martin, R. L.; Fox, D. J.; Keith, T. A.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1998.
4. Hay, P. J.; Wadt W. R. *J. Chem. Phys.* 1985, **82**, 299.
5. Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* 1980, **102**, 939. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* 1972, **56**, 2257.
6. Ehlers, A. W.; Böhme, M.; Dapprich, S.; Gobbi, A.; Höllwarth, A.; Jonas, V.; Köhler, K. F.; Stegmann, R.; Veldkamp A.; Frenking, G. *Chem. Phys. Lett.* 1993, **208**, 111.

7. (a) Dorcier, A.; Dyson, P. J.; Gossens, C.; Rothlisberger, U.; Scopelliti, R.; Tavernelli, I. *Organometallics* 2005, **24**, 2114. (b) Gossens, C.; Tavernelli, I.; Rothlisberger, U. *Chimia* 2005, **59**, 81.
8. Becke, A. D. *Phys. Rev. A* 1988, **38**, 3098.
9. (a) Perdew, J. P. *Phys. Rev. B* 1986, **33**, 8822. (b) Perdew, J. P. *Phys. Rev. B* 1986, **34**, 7406.
10. ADF 2004.01; SCM, Amsterdam, The Netherlands. www.scm.com
11. ZORA: (a) Van Lenthe, E.; Van Leeuwen, R.; Baerends, E. J.; Snijders, J. G. *Int. J. Quantum. Chem.* 1996, **57**, 281. (b) Van Lenthe, E.; Ehlers, A.; Baerends, E. J. *J. Chem. Phys.* 1999, **110**, 8943.
12. Cf. Tai, H. C.; Krossing, I.; Seth, M.; Deubel, D. V. *Organometallics* 2004, **23**, 2343.
13. Jaguar 5.0; Schrodinger, Inc.: Portland, OR, 2000. See: Vacek, G.; Perry, J. K.; Langlois, J.-M. *Chem. Phys. Lett.* 1999, **310**, 189. www.schrodinger.com
14. Cf. (a) Rashin, A. A.; Honig, B. *J. Phys. Chem.* 1985, **89**, 5588. (b) Gilbert, T. M.; Hristov, I.; Ziegler, T. *Organometallics* 2001, **20**, 1183. (c) Cooper, J.; Ziegler, T. *Inorg. Chem.* 2002, **41**, 6614. (d) Baik, M. H.; Friesner, R. A. *J. Phys. Chem. A* 2002**, 106***,* 7407. (e) Baik, M. H.; Friesner, R. A.; Lippard, S. J. *J. Am. Chem. Soc.* 2002, **124**, 4495.
15. (a) Jorgensen, W. L.; Briggs, J. M.; Gao, J. *J. Am. Chem. Soc.* 1987, **109**, 6857. (b) Jensen, J. H.; Li, H.; Robertson, A. D.; Molina, P. A. *J. Phys. Chem.* 2005, **109**, 6634.
16. (a) Barone, V.; Cossi, M. *J. Chem. Phys*. 1997, **107**, 3210. H_2O: –6.3 kcal/mol, Cl^-: –77.0 kcal/mol. (b) Chambers, C. C.; Hawkins, G. D.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem.* 1996, **100**, 16385. H^+: –260.9 kcal/mol.
17. (a) Wertz, D. H. *J. Am. Chem. Soc.* 1980, **102**, 5316. (b) Abraham, M. H. *J. Am. Chem. Soc.* 1981, **103**, 6742.
18. Lau, J. K.-C.; Deubel, D. V. *J. Chem. Theory Comput.* 2006, **2**, 103.
19. Deubel, D. V. *J. Am. Chem. Soc.* 2006, **128**, in press.
20. Yan, Y. K.; Melchart, M.; Habtemariam, A.; Sadler, P. J. *Chem. Commun.* 2005, 4764.
21. (a) van Eldik, R. *Chem. Rev.* 2005, **105**, 1917. (b) Helm, L.; Merbach, A. E. *Chem. Rev.* 2005, **105**, 1923. (c) Rotzinger, F. P. *Chem. Rev.* 2005, **105**, 2003.

22. We define ξ and δ as follows: $\xi = \lambda / \delta$. $\delta = \lambda + \nu$.
With $\lambda = ((M\text{-}O)_{TS}/(M\text{-}O)_{Re}) - 1$. $\nu = ((M\text{-}L)_{TS}/(M\text{-}L)_{Pr}) - 1$.
(M-O) = distance between the metal and the oxygen of the aqua ligand in the transition state (TS) and reactant (Re). (M-L) = distance between the metal and the metal-bound donor atom of L in the TS and product (Pr).

23. (a) Rotzinger, F. P. *J. Am. Chem. Soc.* 1996, **118**, 6760. (b) Rotzinger, F. P. *J. Am. Chem. Soc.* 1997, **119**, 5230.

24. (a) Rapaport, I.; Helm, L.; Merbach, A. E.; Bernhard, P.; Ludi, A. *Inorg. Chem.* 1988, **27**, 873. (b) Stebler-Roethlisberger, M.; Hummel, W.; Pittet, P. A.; Buergi, H. B.; Ludi, L.; Merbach, A. E. *Inorg. Chem.* 1988, **27**, 1358. (c) De Vito, D.; Sidorenkova, H.; Rotzinger, F. P.; Weber, J.; Merbach, A. E. *Inorg. Chem.* 2000, **39**, 5547.

25. F. Wang, H. M. Chen, S. Parsons, L. D. H. Oswald, J. E. Davidson, P. J. Sadler, *Chem. Eur. J.* 2003, **9**, 5810.

26. Cf. Rotzinger, F. P. *J. Phys. Chem. B* 2005, **109**, 1510.

27. (a) Raber, J.; Zhu, C.; Eriksson, L. A. *Mol. Phys.* 2004, **102**, 2537. (b) Robertazzi, A.; Platts, J. A. *J. Comput. Chem.* 2004, **25**, 1060.

28. Baik, M.-H.; Friesner, R. A.; Lippard, S. J. *J. Am. Chem. Soc.* 2003, **125**, 14082.