Guanine Binding to Dirhodium Tetracarboxylate Anticancer Complexes: Quantum Chemical Calculations Unravel an Elusive Mechsnism

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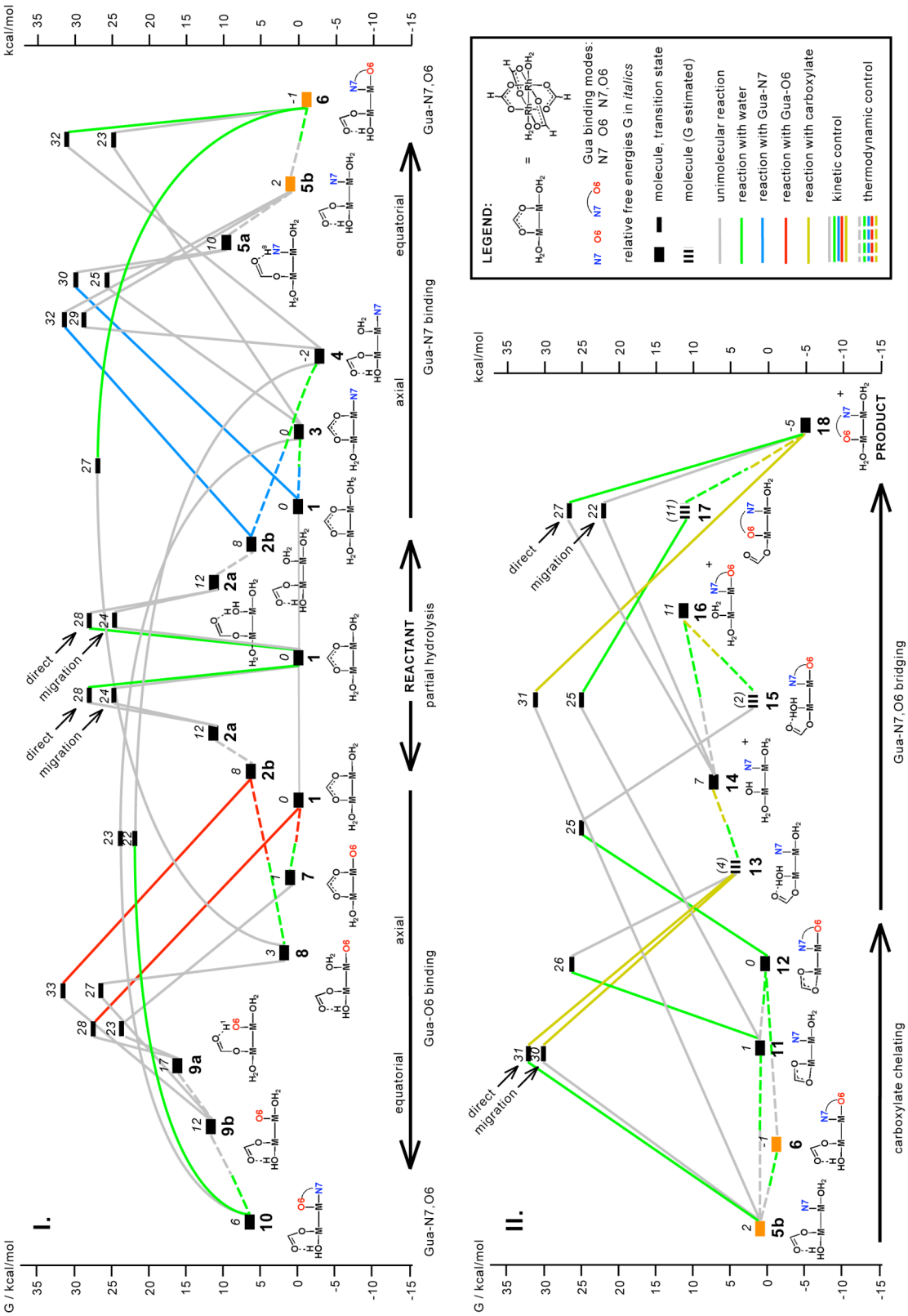

Figure S-1. Calculated reaction profile (B3LYP) of Gua binding to dirhodium tetraformate on a universal free energy scale. I. Formation of monodentate eq Gua adducts. II. Ring closure to afford the product with a bridging Gua ligand. Thick and thin bars represent molecules and transition states, respectively. Dashed and solid lines represent thermodynamically and kinetically controlled reactions, respectively. Gray and colored lines indicate unimolecular and bimolecular reactions, respectively, with co-reactants water (green), Gua-N7 (blue), Gua-O6 (red), and formate (olive). For molecules **1**-**18**, only one carboxylate group is shown; the other three bridging carboxylate groups are omitted. Gua is represented by N7 and/or O6.[1]

Computational Details

The geometries of the 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),[2,3] which includes the correlation functional of Lee, Yang, and Parr (LYP), as implemented in Gaussian 03.[4] The LANL2DZ ECP's[5] and valence-basis sets were used for platinum, and the 6-31G(d,p) basis sets were used for the other atoms.[6] 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 metal, but totally uncontracted and augmented with a set of f functions,[7] together with the 6-311+G(d,p) basis sets at the other atoms. This basis-set combination is denoted III+. Free energies 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 energies, which were calculated at the B3LYP/III+//II level.

Solvation free energies 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 platinum and the 6-31G(d,p) basis set on the other atoms as implemented in the Jaguar 5 program package.[8] The

continuum boundary in the PB calculations was defined by a solvent-accessible molecular surface. The continuum boundary in the PB calculations was defined by a solvent-accessible molecular surface with a set of atomic radii[9] for H (1.150 Å), C (1.900 Å), N (1.600 Å), O (1.600 Å), and Rh (1.600 Å). The radius at Rh was determined by matching the calculated relative free energy in solution of several dirhodium complexes with one ax aqua ligand and one free ax coordination site to the calculated relative free energy in solution of the analogous complexes with two ax aqua ligands. We believe that continuum dielectric models do not properly describe the changes of solvation entropy in bimolecular reactions; comparisons with experimental values indicated that relative free energies reactions of Pt(II), Pd(II), and Ru(II) complexes with biomolecules are systematically approximately ~6 kcal/mol too high. According to Wertz and others,[10] various molecules lose a constant fraction (approximately 0.5) of their entropy, when they are dissolved in water. All free energies in solution were modified by an entropic term that is half (0.5) of the entropy in vacuo with the opposite sign. Activation free energies for the reactions of several anticancer complexes that are in good agreement with experimental values.[11]

ESI References

1 The relative free energy of the three compounds is considered an estimate rather than an accurate prediction for the following reasons: Geometry optimizations of **13** and **15** resulted in complexes containing an ax carboxylic acid and an eq hydroxo ligand. Subsequent manual assignment of the protonation state and calculation of the solvation free energy consistently lowered the relative free energy. Geometry optimization of **17** led to a displacement of the ax aqua ligand.

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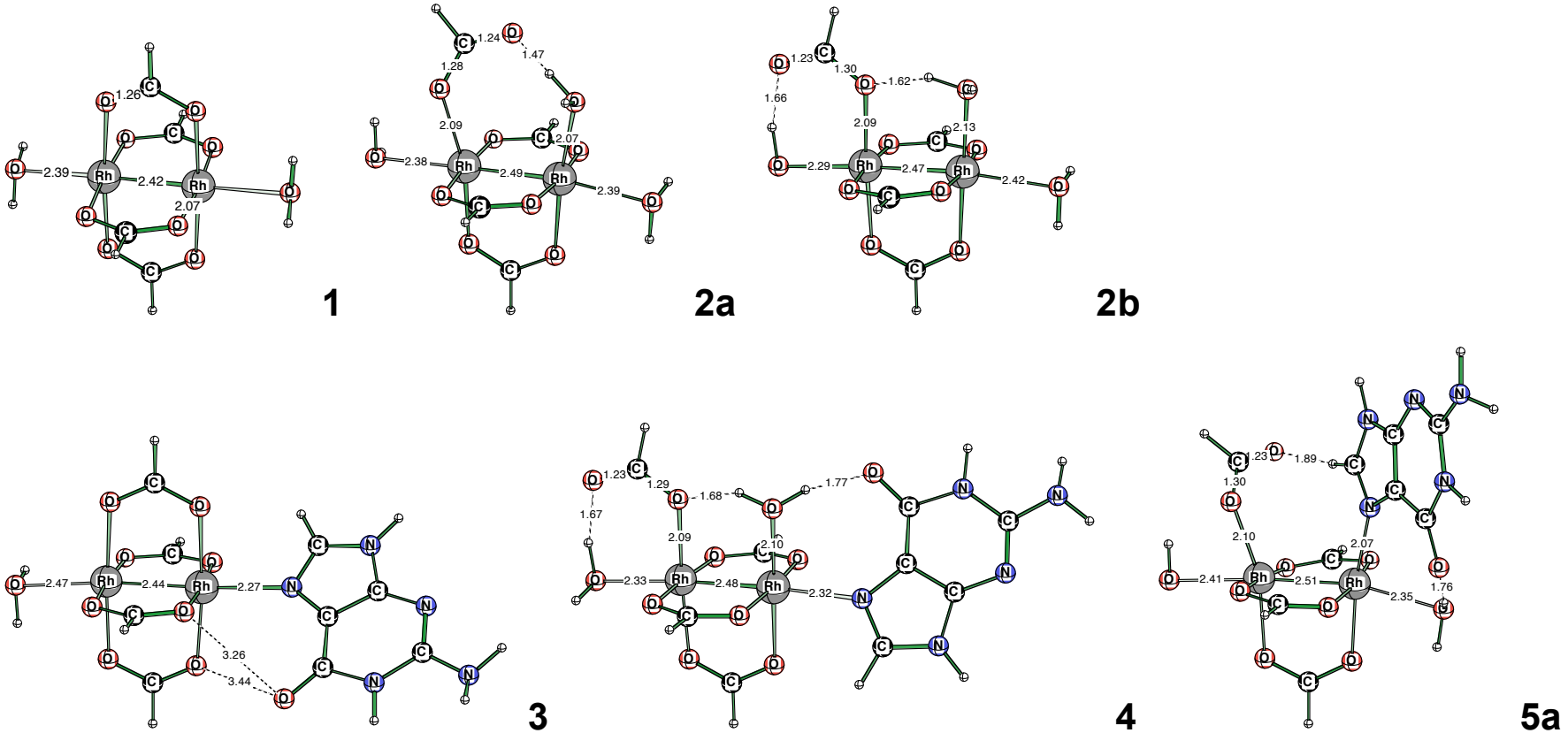
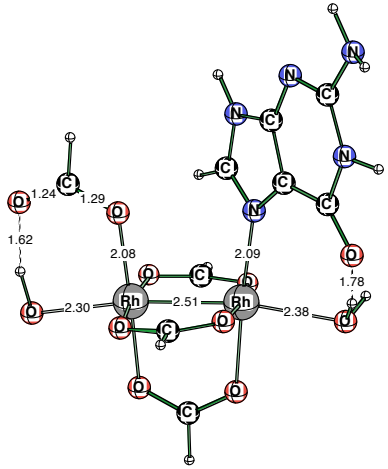
Figure S-2. Calculated structures of molecules and transition states (TS).





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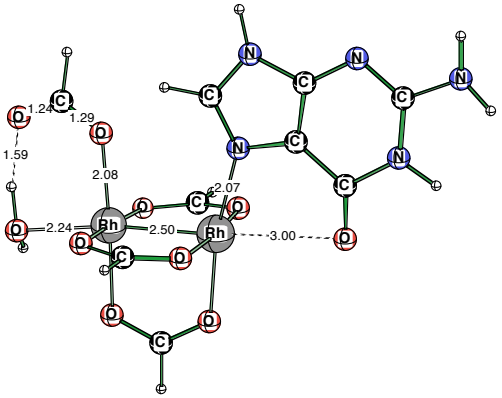

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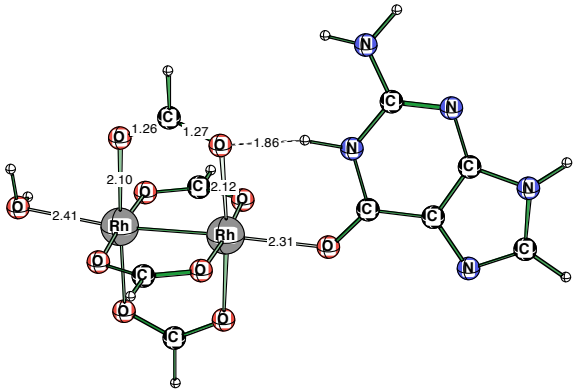

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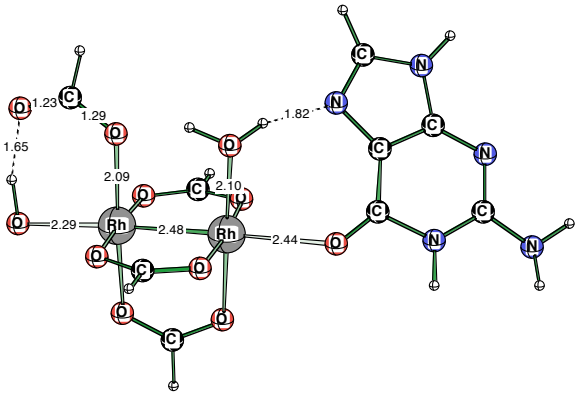

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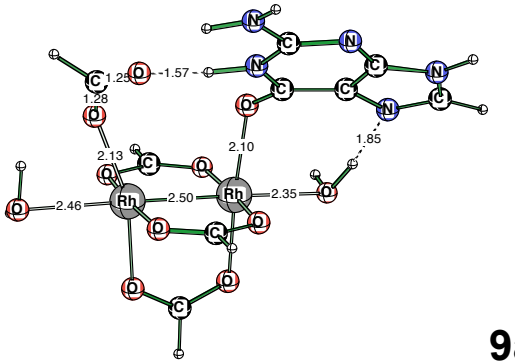

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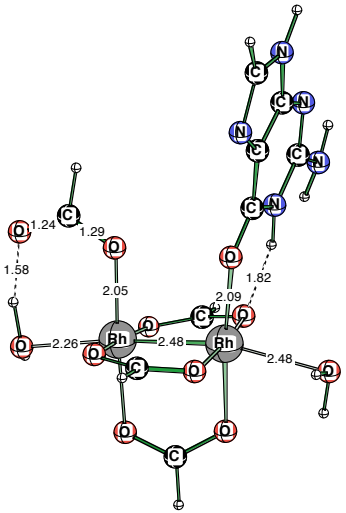

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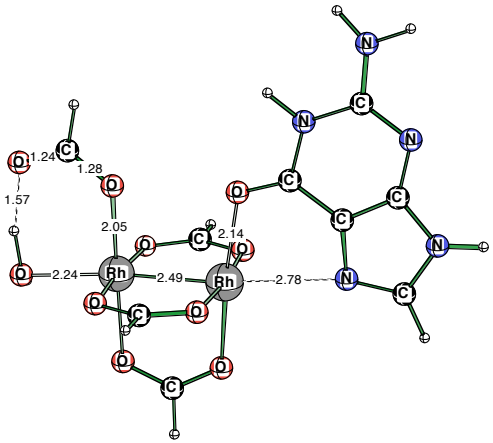

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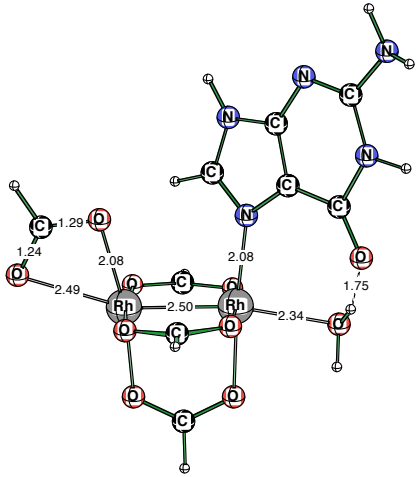

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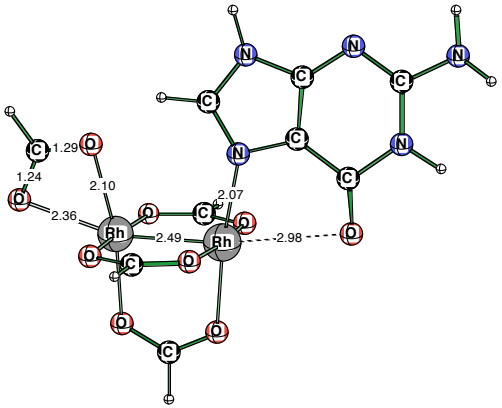

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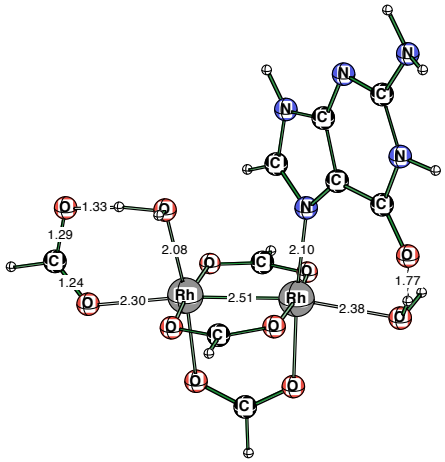

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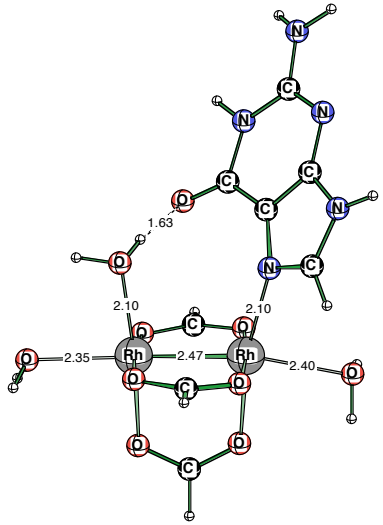

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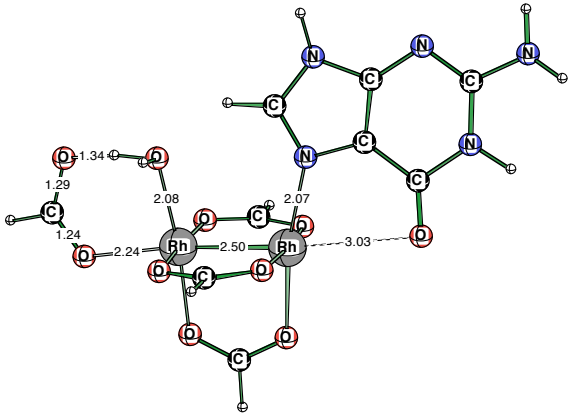

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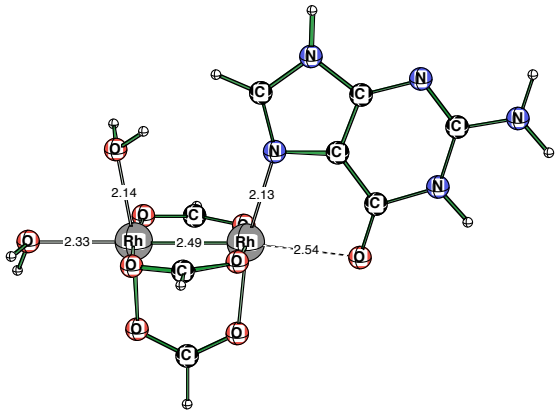

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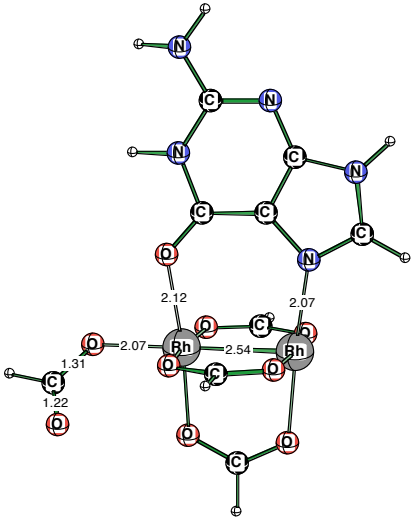

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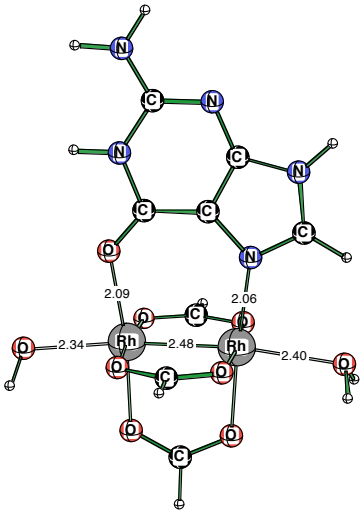

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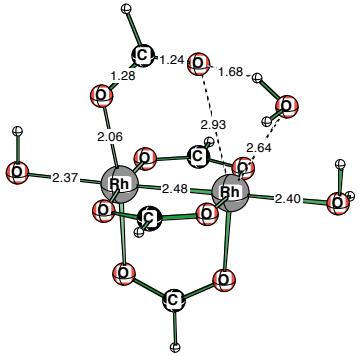

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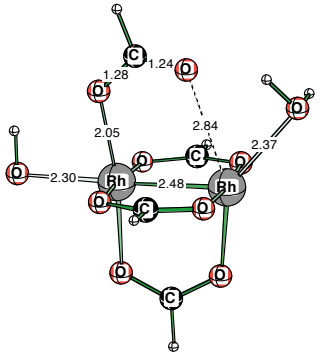

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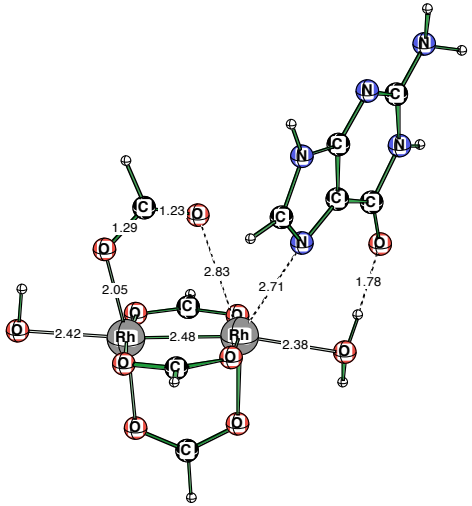

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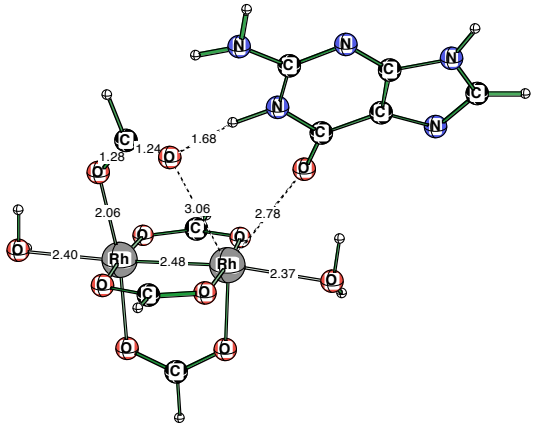

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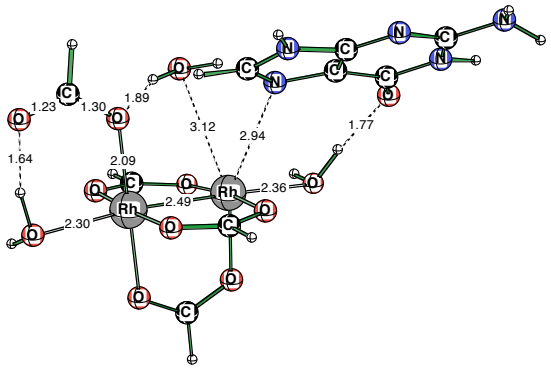

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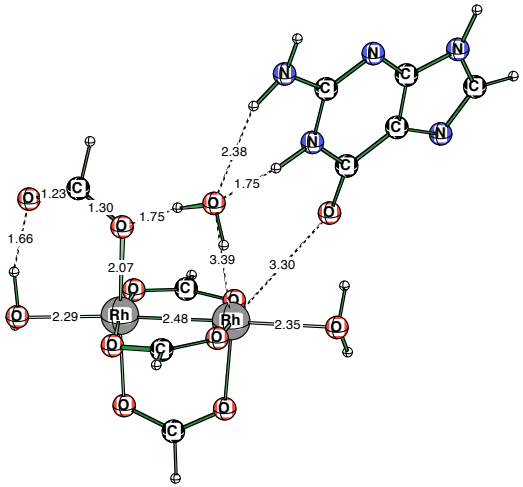

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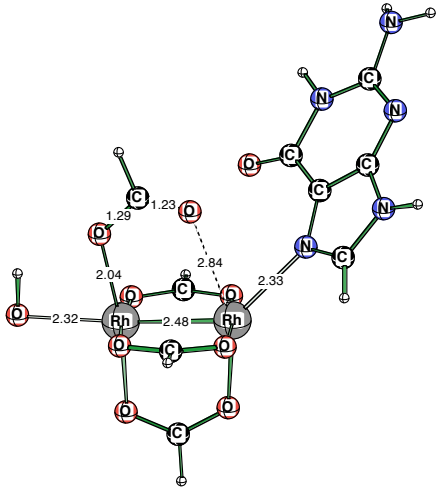

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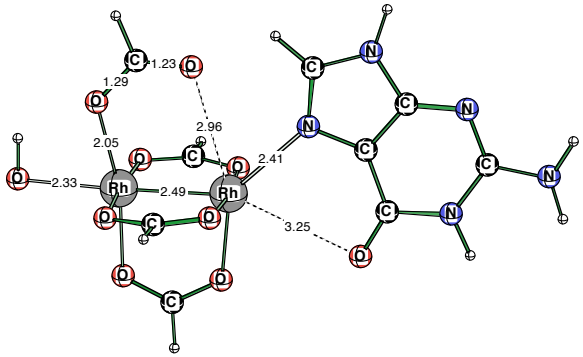

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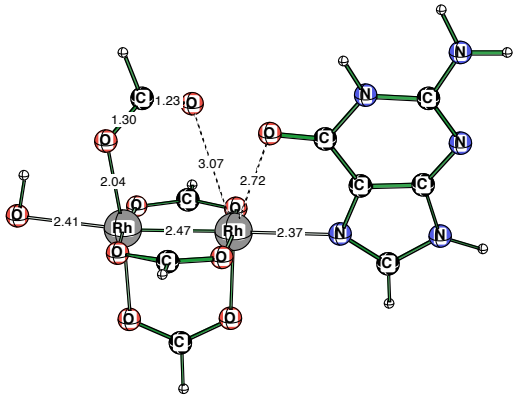

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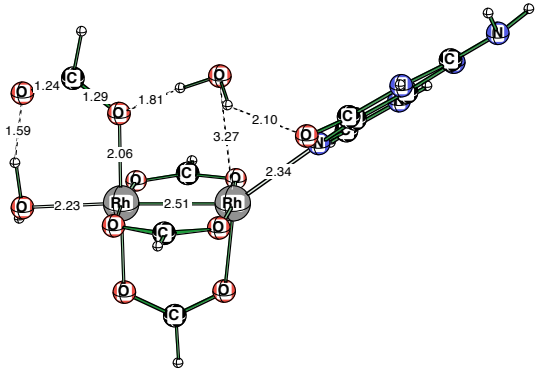

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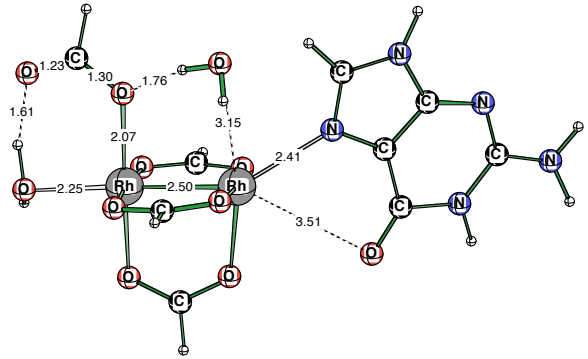

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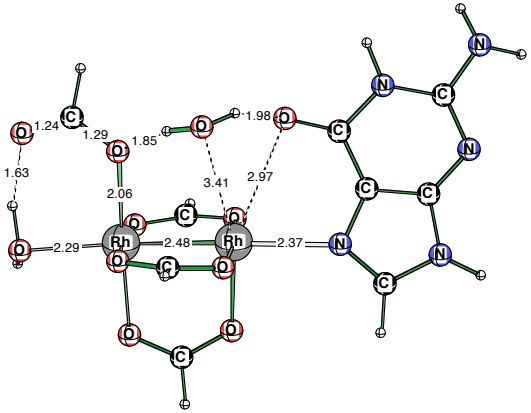

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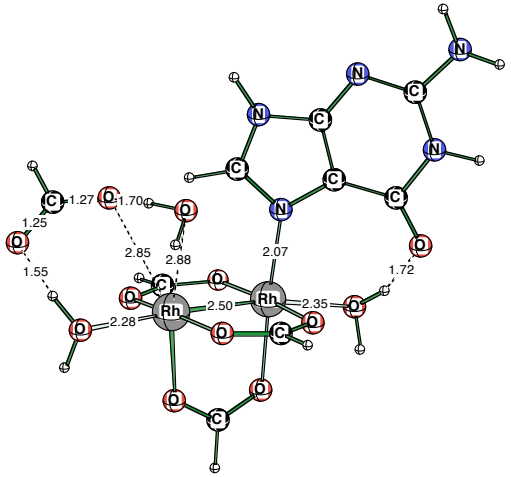

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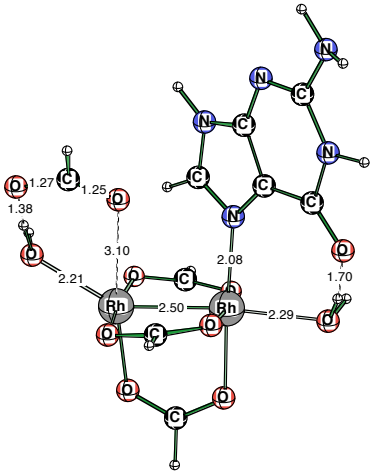

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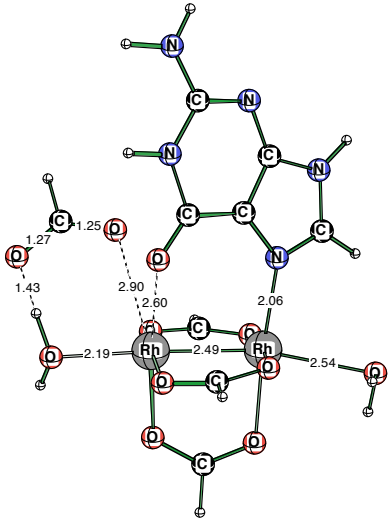

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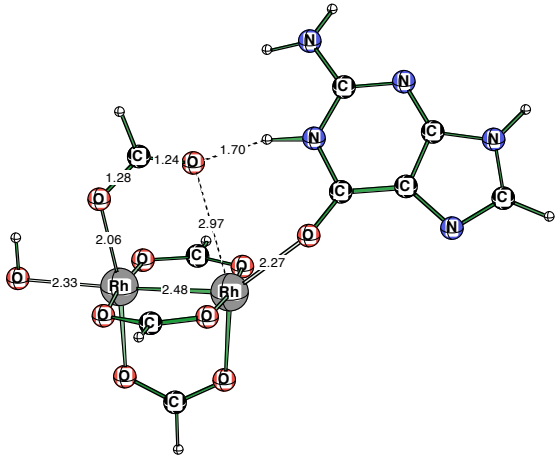

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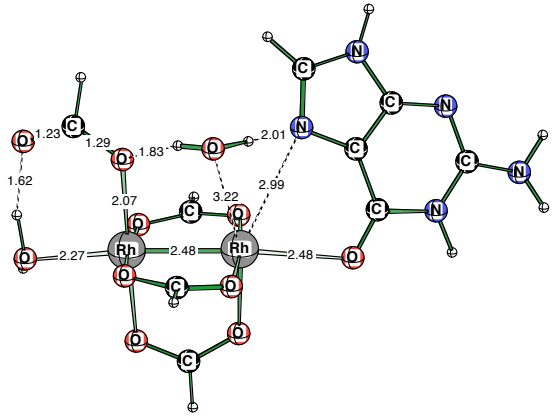

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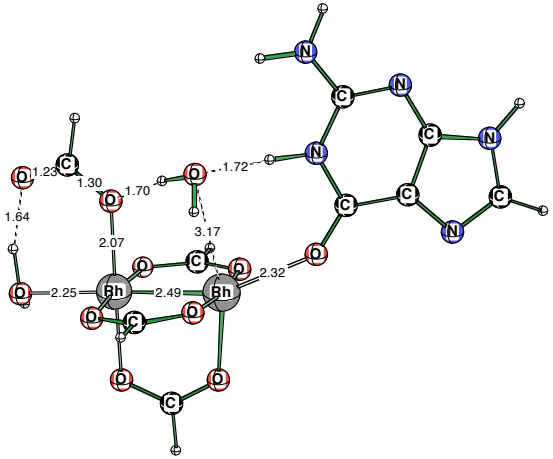

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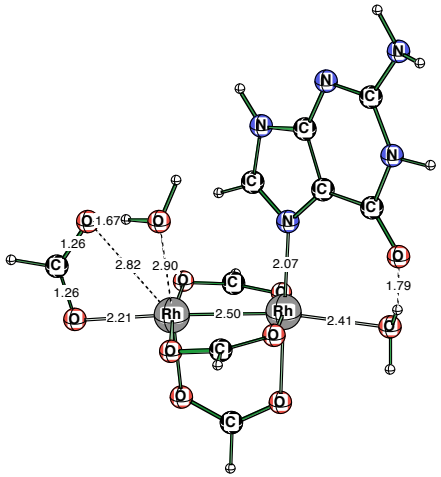

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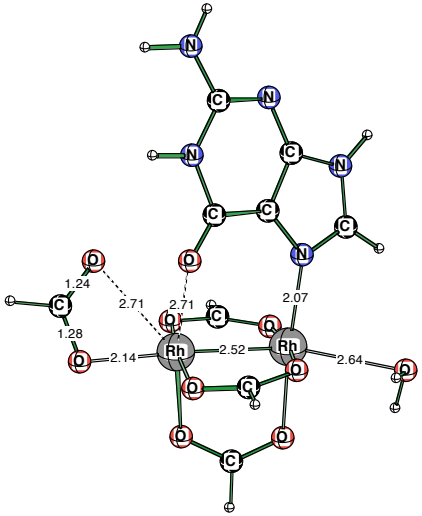

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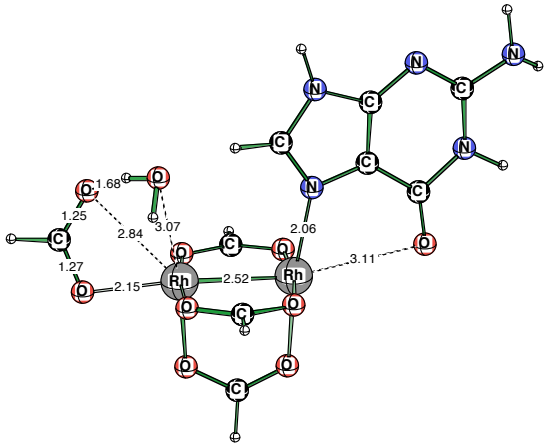

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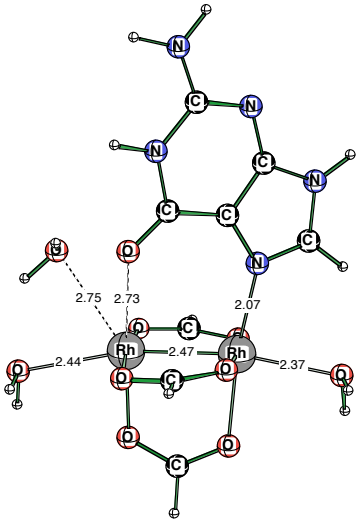

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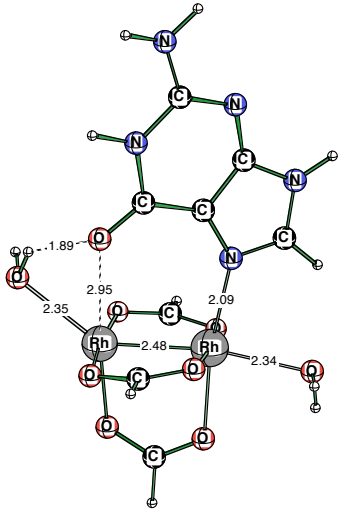

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