Flavin-Mediated Photoactivation Of Pt(IV) Anticancer Complexes: Computational Insights On The Catalytic Mechanism

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Electronic Supplementary Material (ESI)

Table S1 Imaginary frequencies for all computed transition states.

NADH:Rf → NAD^+:RfH^-	
[1]TS	-1544.79
[3]TS	-506.97
RfH^-:Pt(IV) → Rf:Pt(II) – Complex 1	
TS (Pt–O1 attack)	-111.31
TS (acetyl O2 attack)	-592.10
RfH^-:Pt(IV) → Rf:Pt(II) – Complex 2	
TS (Pt–O1 attack)	-113.23
TS (acetyl O2 attack)	-113.15
NADH:Pt(IV) → NAD^+:Pt(II) – Complex 1	
TS (Pt–O1 attack)	-1265.22
TS (acetyl O2 attack)	-1194.61
NADH:Pt(IV) → NAD^+:Pt(II) – Complex 2	
TS (Pt–O1 attack)	-1352.04
TS (acetyl O2 attack)	-1139.99
$AscH^-$:Pt(IV) → $DHAsc^‡$:Pt(II) – Complex 1	
TS (Pt–O1 attack)	-1141.66
TS (acetyl O2 attack)	-189.16
$AscH^-$:Pt(IV) → $DHAsc^‡$:Pt(II) – Complex 2	
TS (Pt–O1 attack)	-655.29
TS (acetyl O2 attack)	-194.17

[‡] DHAsc = Dehydroascorbate

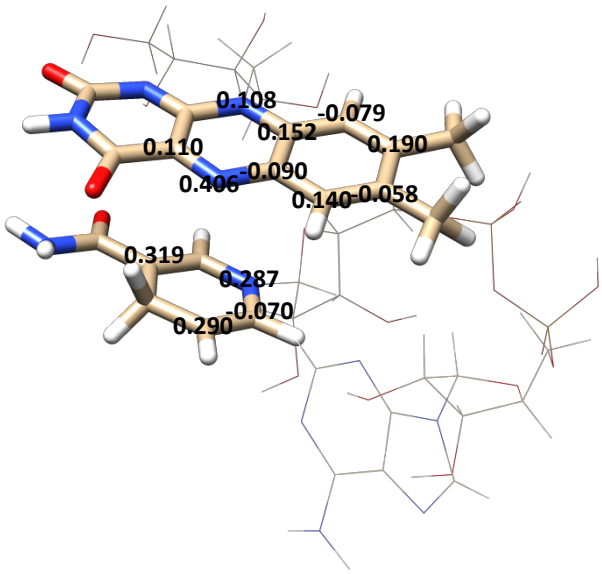

Fig. S1 Mulliken spin density of the initial adduct ^{3}[NADH:Rf] for atoms having values > 0.100 or < -0.050.

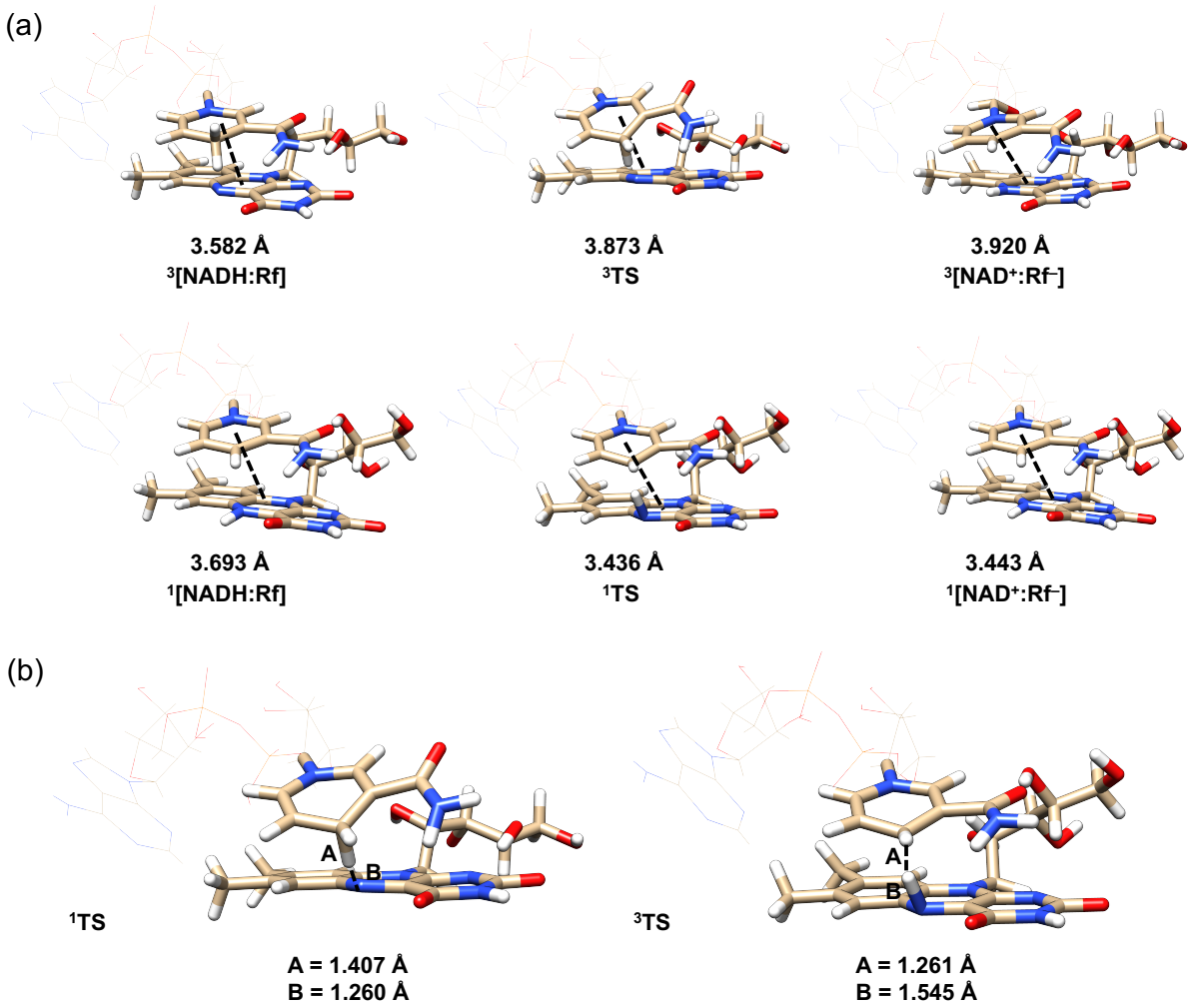

Fig. S2 Calculated models for the reaction between NADH and Rf in both singlet ground and triplet excited-states. Distances between the stacked adducts are shown in (a), while (b) reports the $C(6)_{NAD}$–H–$N(5)_{Rf}$ bond lengths.

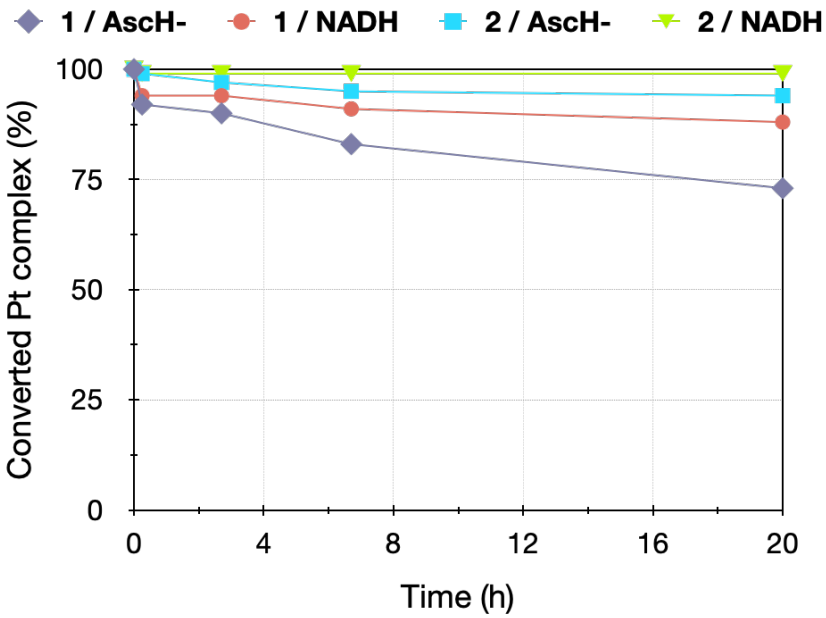

Fig. S3 Experimental reduction rates of **1** and **2** for AscH⁻ and NADH over 20 h in the dark. Reactions were performed in PB buffer (10 mM, pH 7.4) using 1 mM of reducing agent. Under similar experimental conditions, light-generated RfH⁻ (catalytic, 5% catalyst load) achieves full conversion of the two complexes in less than 4 min.[1]

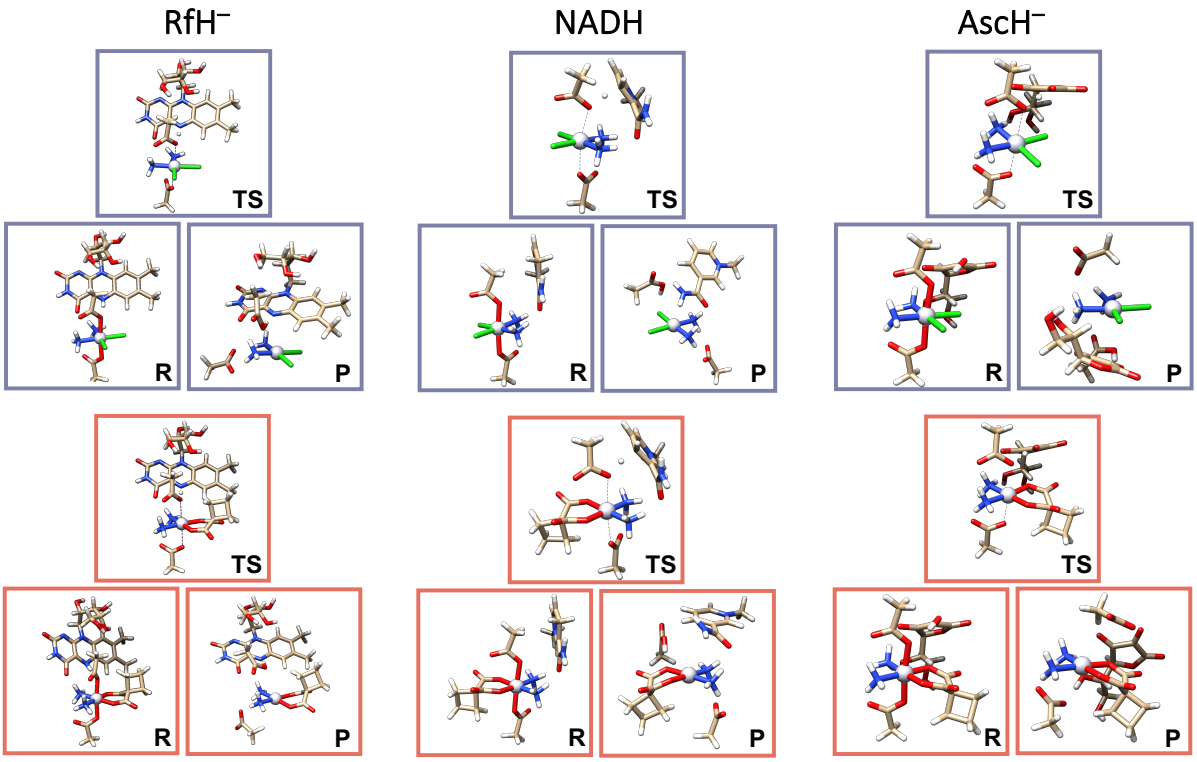

Fig. S4 Models of initial adduct (R), transition state (TS) and product (P) for the reduction of complexes **1** (violet) and **2** (red) by RfH^-, NADH and $AscH^-$. Optimized geometries were obtained assuming that the Pt-coordinated O(1) atom of an axial acetato ligands of **1** and **2** interacts with the hydride donating moiety of the donor.

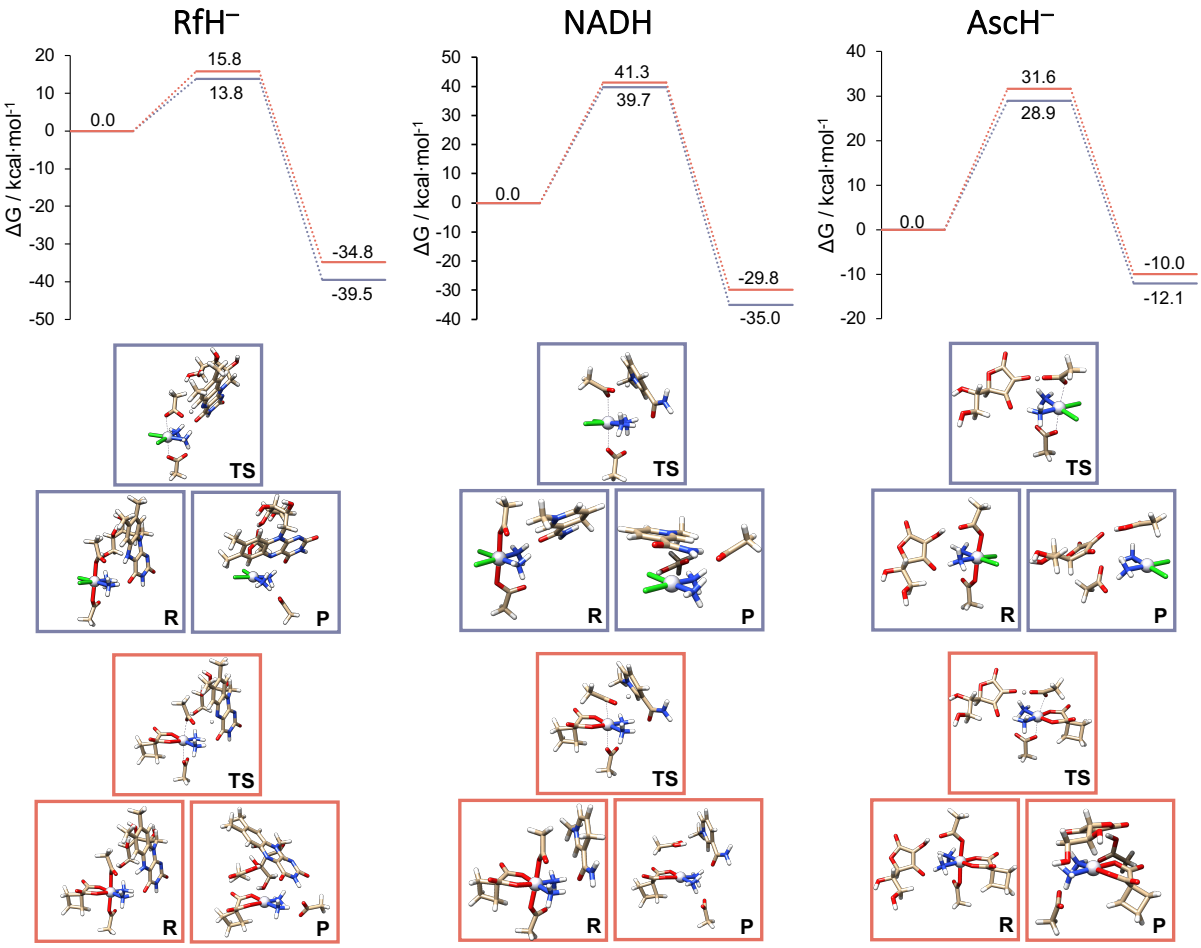

Fig. S5 Free energy profiles describing the ligand-bridged-H-transfer mechanism for the reduction of complexes **1** (violet) and **2** (red) by RfH^-, NADH and $AscH^-$. Models of initial adduct (R), transition state (TS) and product (P) were obtained assuming that the carbonyl O(2) atom of an axial acetato ligands of **1** and **2** interacts with the hydride donating moiety of the donor. Relative energies are expressed in kcal mol^{-1} and calculated with respect to the zero-reference energy of the initial adduct (in the singlet ground state).

References

1 J. Gurruchaga-Pereda, V. Martínez-Martínez, E. Rezabal, X. Lopez, C. Garino, F. Mancin, A. L. Cortajarena and L. Salassa, *ACS Catal.*, 2020, **10**, 187–196.