

S-Se oxidative addition to auranofin derivatives: A theoretical DFT study

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Supplementary Information

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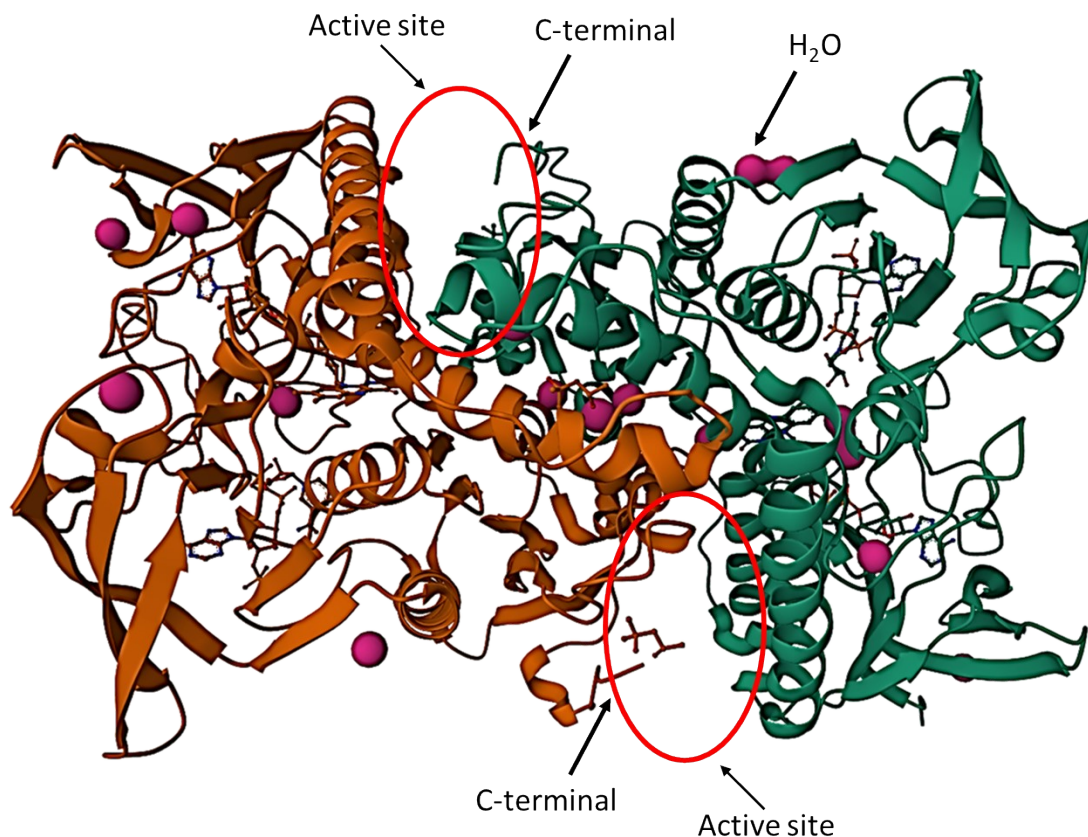


Figure S1. X-ray structure of the TrxR enzyme (PDB ID 2J3N).¹ The catalytic site is highlighted and the water molecules are represented as pink balls. From this snapshot it is possible to notice that the interior of the binding site is not accessible to water molecules.

Dispersion correction effect on the reaction energy profile

In order to assess the effect of dispersion correction on the oxidative addition reaction profile of auranofin (AF), single-point energy calculations were performed at the B3LYP-D3/BS1 and ω B97xD/BS1 levels (BS1 stands by the 6-31G(d) basis sets for light atoms and the ECP LANL2TZ(f) for heavy metal). The B3LYP-D3 includes the empirical D3 Grimme's dispersion terms on the B3LYP functional, while ω B97xD is a range-separated (RS) functional with an additional dispersion correction. Figure S2 illustrates the oxidative addition reaction profile for AF (**1**) where B3LYP results in gas phase and solution ($\epsilon = 4.0$) are included for reference.

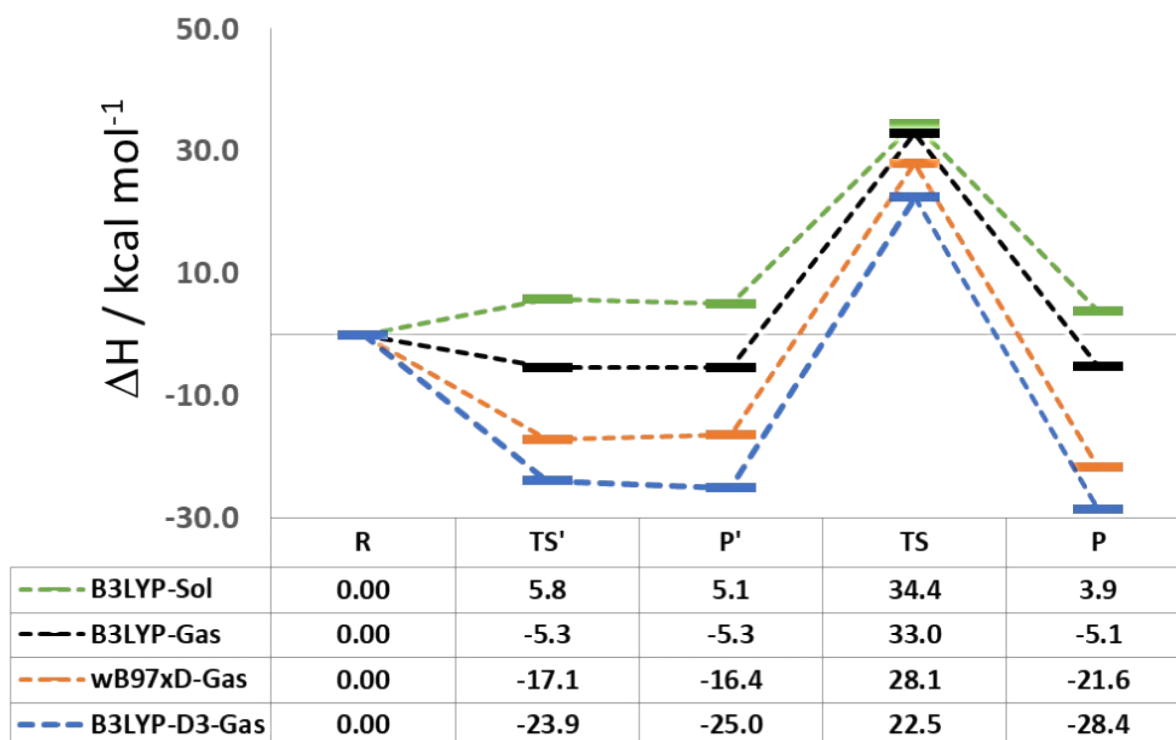


Figure S2. Oxidative addition energy profile calculated for AF (see Figure 1 in the main text).

Analyzing the data in gas phase, we note that the dispersion forces stabilize significantly the TS', P' and P species, with the effect being more pronounced for B3LYP-D3. This was previously observed for Pt(IV) → Pt(II) reduction process, for which the stability of Pt(IV) species were highly overestimated at B3LYP-D3.² When it comes to TS and the overall activation barrier, the values decrease from 33 kcal mol⁻¹ (B3LYP, gas phase) to 28.1 and 22.4 kcal mol⁻¹ with ωB97xD and B3LYP-D3, respectively. Certainly, it would affect significantly the reaction kinetics, favoring even more the overall process. However, if the dispersion correction is applied for the series of AF derivatives, the effects are similar for all analogues, keeping the reactivity order predicted from B3LYP level (Figure S3).

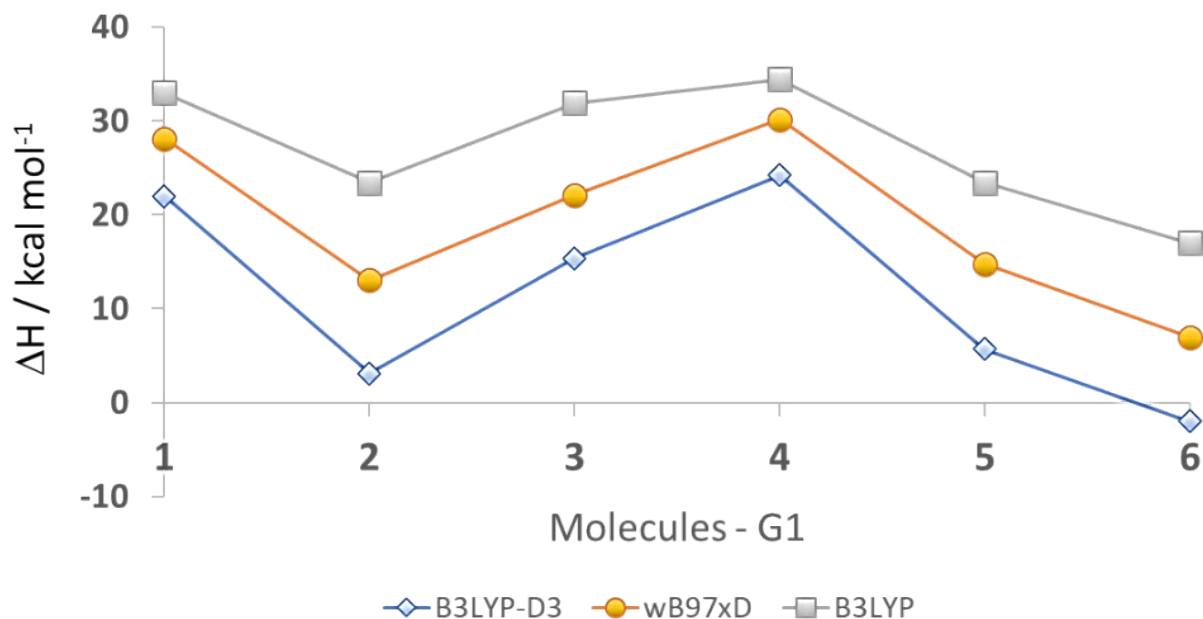


Figure S3. Activation barrier for oxidative addition reaction of AF derivatives (**1** to **6** from group G1 – Figure 4 in the main text).

As mentioned earlier, B3LYP-D3 tends to overestimate the dispersion effect (indicated by the blue line in Figure S3) and the ω B97xD decreases the activation energy by $\sim 15\%$, regardless of the AF analogue. In summary, the dispersion correction seems to play a significant role in the kinetics of the oxidative addition reaction for AF derivatives, decreasing the energy barrier by $\sim 15\%$ (ω B97xD); however, at least for analogue molecules, the dispersion terms exhibit similar effects, and the predicted reactivity order remains consistent, even without corrections. Finally, it is worth mentioning that for absolute prediction, a deeper benchmarking should be done, including distinct approaches.²

References

1. K. Fritz-Wolf, S. Urig and K. Becker, *J. Mol. Biol.*, 2007, **370**, 116-127.

2. L. P. N. M. Pinto, G. Y. Sánchez Delgado, H. F. Dos Santos and D. F. S. Paschoal, *Comput. Theor. Chem.*, 2023, **1225**, 114132.