Methylmercury chalcogenolates ligand exchange: insight from DFT into a very fast reaction[1]

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Introduction

Methylmercury (CH_3Hg^+) binding to thiol- and selenol- based enzymes is a key-element to explain its high toxicity. CH_3Hg^+ is not found in its free form in biological environment, it is present as a chalcogenolate complex.[2] Thus, **chalcogen-mercury bond reactivity** is implicated in the distribution of this toxicant in the human body.[3] (Scheme 1)

Methodology and scope

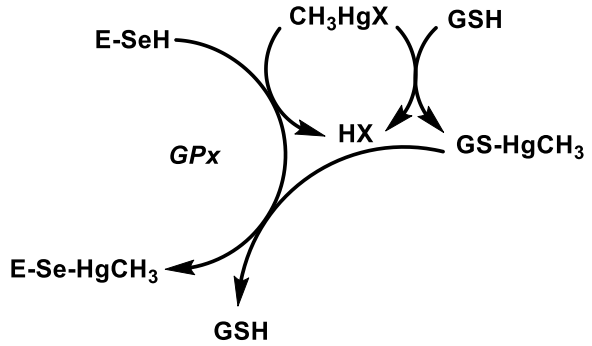
State-of-the-art *DFT calculations* have been employed to investigate trends and mechanism of nine model **ligand exchange reactions** involving methylmercury chalcogenolates (**X, X**=S, Se, Te) i.e. $CH_3Hg\text{-}\mathbf{X}CH_3 + CH_3\mathbf{X}^- \rightleftarrows CH_3Hg\text{-}\mathbf{X}CH_3 + CH_3\mathbf{X}^-$

Level of theory (COSMO)-ZORA-BLYP-D3(BJ)/TZ2P.

References

[1] A. Madabeni, M. Dalla Tiezza, O. B. Folorunsho, P. A. Nogara, M. Bortoli, J. B. Rocha, L. Orian, *J. Comput. Chem.* **2020**, 41, 2045-2059. [2] P. A. Nogara, C. S. Oliveira, G. L. Schmitz, P. C. Piquini, M. Farina, M. Aschner, J. B. T. Rocha, *Biochim. Biophys. Acta - Gen. Subj.* **2019**, *1863*, 129284. [3] D. L. Rabenstein, R. S. Reid, *Inorg. Chem.* **1984**, *23*, 1246–1250. [4] T. A. Hamlin, M. Swart, F. M. Bickelhaupt, *ChemPhysChem* **2018**, *19*, 1315–1330.

Results and discussion



Scheme 1. Schematic representation of chalcogen-mercury bonds formation and disruption involved in methylmercury delivery to GPx. X can be a thiolate or Cl^-. GSH stands for glutathione.

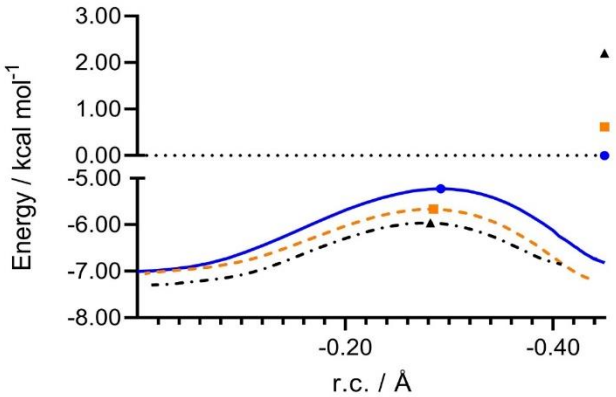


Fig. 1. IRC reaction profiles computed for the exchange of $CH_3\mathbf{S}^-$ with $CH_3Hg\text{-}\mathbf{X}CH_3$ (X=**S, Se, Te**). Dots represent the position of transition states and free products for each reaction.

While in gas phase all reactions proceed through a stable intermediate, in water (COSMO) all reactions display a concerted mechanism (**Fig. 1**), with a transition state (TS) connecting a pre-coordinated reactant complex (RC) to a product complex (PC). (**Fig. 2**)

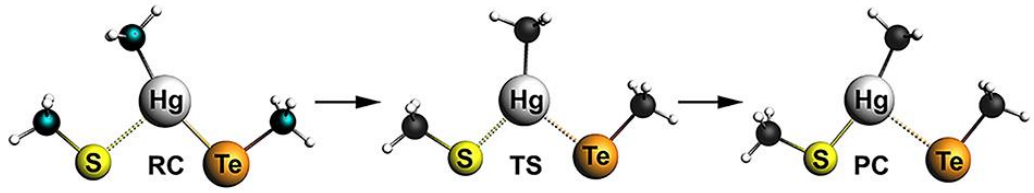


Fig. 2. Stationary points along the r.c. for $CH_3\mathbf{S}^-$ with $CH_3Hg\text{-}\mathbf{Te}CH_3$

- Trends in agreement with **nucleophilicity and leaving group capabilities** of chalcogenolates, both in gas phase and in water.
- **Switch to a concerted mechanism** when going from gas phase to water in line with previous studies on **S_N2 reactions at heavy center atoms.**[4]

Conclusions

All **activation energies** in solution are lower than 2 kcal mol^{-1} (**Fig. 1**) *Almost-diffusive reactions*

S_N2 @ Hg

Stable gas phase **intermediates** converged as **TSs** when including solvation

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