Activation of Light Alkanes by Earth-Abundant Metal-Oxo Catalysts
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Introduction: The heavy Group 6 transition metals, Mo and W, are important in enzymes relevant to C, N and S metabolism. One interesting molybdoenzyme is ethylbenzene dehydrogenase (EBDH) which belongs to subfamily II of the DMSO reductase family. It catalyzes oxygen-independent, stereospecific hydroxylation of a benzylic C–H bond of ethylbenzene to (S)-1-phenylethanol.

Results and Discussion: The B97D/(CEP-121G,6-311++G(d,p))/SMD-THF free energy profiles of the different substrates and activating complex models were based on mechanisms put forth by Szaleniec *et al.*, Scheme 1. The major goal of our ACS-PRF research is to assess how modification of EBDH active site mimics may permit facile oxidation of light alkanes such as methane.

Impact of Metal and Acid/Base Pair. The results for the model of the EBDH active site are collected in Figure 1 – Figure 4. When using ammonia as the base and methane as the substrate, the free energy profile follows a clear trend from low to high free energy barriers, Figure 1, in the order: Cr < Mo < W. The results indicate that for the C−H activation by the anionic Mo-oxo complex the hydrogen atom in the C−H activation transition state has substantial protic ($H^{\delta+}$) carácter. Therefore, the more basic the metal-oxo complex (Group 6) is, the lower activation energy barrier will be. Going up the Group 6, electronegativity of metals will be decreased (EN: Cr < Mo < W). We speculate that the oxo group attached to Cr has more electron density than that of Mo and W and generally the chromium-oxo complex will be more basic. Moreover, this generalization applies to both the initial C–H bond activation (**TS1**) as well as the subsequent functionalization (*i.e.*, C–O bond forming) step, **TS2**.

Scheme 1. Modeled reaction mechanism for hydroxylation of methane and toluene catalyzed by an EBDH model. Note additional tautomers may be relevant to the various stationary points.
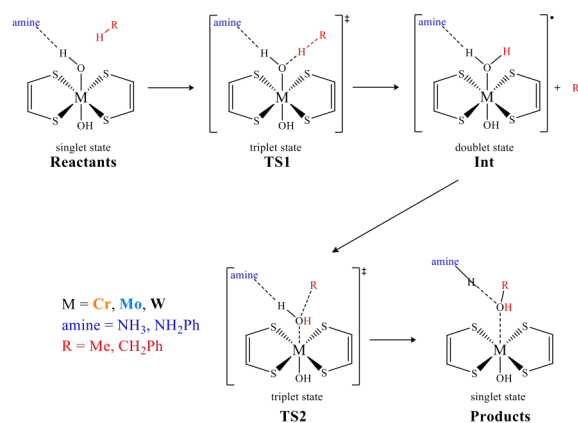
It is interesting that the second transition state, **TS2**, is higher in free energy for all Mo and W EBDH model complexes for all the systems in Figures 1 - 4, whereas it is generally switched to **TS1** for chromium. Energy barriers to go from **Int** to **TS2** are, however, modest at an average $\Delta G^{\ddagger}_{reb} \sim 14 \pm 3$ kcal/mol for the different metals. Thus, the higher relative free energy of **TS2** versus **TS1** largely reflects the instability of the aqua complex/hydrocarbyl radical intermediate.

The effect of altering the hydrocarbon substrate generally leads to more pronounced changes in the free energy barriers as compared to changing the acid/base pair. For example, for the activation of toluene by the Mo complex, $\Delta G^{\ddagger}_{HAA} = 25.7$ kcal/mol with aniline base (pK_a(anilinium) = 4.6), Figure 4, versus ammonia as the base (pK_a(ammonium) = 9.2), $\Delta G^{\ddagger}_{HAA} = 25.3$ kcal/mol, Figure 3. For methane, however, the impact of altering the acid/base pair is more dramatic, $\Delta G^{\ddagger}_{HAA} \sim 2$ (for W) and ~ 6 (for Mo) kcal/mol with a lower barrier for the ammonium/ammonia vs. anilinium/aniline, Figure 1 and Figure 2. Analysis of Figure 1 through Figure 4 suggests that the stabilization of the intermediate, **Int**, is key in facilitating the catalysis. Therefore, one may also presume that stabilizing of the aqua intermediate by "inorganic" means – metal and/or supporting ligand modification – can be achieved.

Impact of Substrate. On average, the transition states for methane activation/functionalization are roughly 13 kcal/mol higher than those for toluene. This largely reflects the difference in homolytic C-H bond enthalpies for the two hydrocarbons ($\Delta_{BDE} \sim 16$ kcal/mol). In general, there was a more dramatic effect when the electronics of the hydrocarbon were changed as compared to the base for these EBDH mimics.

Summary and Future Work: This research models active species of ethylbenzene dehydrogenase (EBDH), a molybdoenzyme, using DFT method to evaluate the impact of different factors including transition metals, Brønsted-Lowry acid/base conjugate pairs, the trans effect, and supporting ligands upon the relevant activation barriers for different hydrocarbon substrates (methane and toluene). Several important conclusions have emerged from this research; the most important are summarized here:

(1) The impact of metal upon kinetics and thermodynamics of the reaction follows the trend: Cr < Mo < W. On average, for all systems (Figures 1 - 4), there is a 10 kcal/mol stabilization of ΔG_{rxn} from W to Mo to Cr. Energy barriers were likewise reduced for Cr significantly in relation to its heavier congeners, and for Mo slightly versus related W complexes for both the initial C–H activation (**TS1**) and the subsequent radical rebound (**TS2**) reactions.
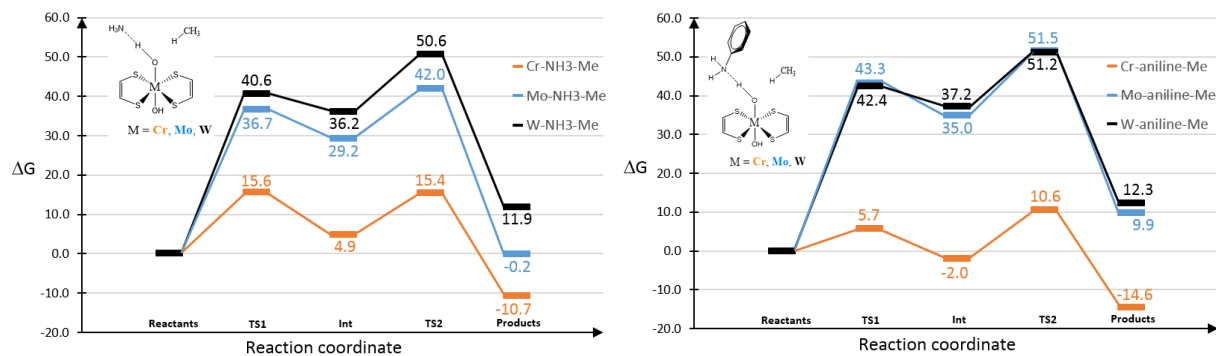
Figure 1 (left). Energy profile for ammonia-assisted hydroxylation of methane by *trans*-M(S$_2$C$_2$H$_2$)$_2$(OH)=O [M = Group 6 metal]. B97D/(CEP-121G,6-311++G(d,p))/SMD-THF level of theory. Relative free energies in kcal/mol.
Figure 2 (right). Energy profile for aniline-assisted hydroxylation of methane by *trans*-M(S$_2$C$_2$H$_2$)$_2$(OH)=O [M = Group 6 metal]. B97D/(CEP-121G,6-311++G(d,p))/SMD-THF level of theory. Relative free energies in kcal/mol.
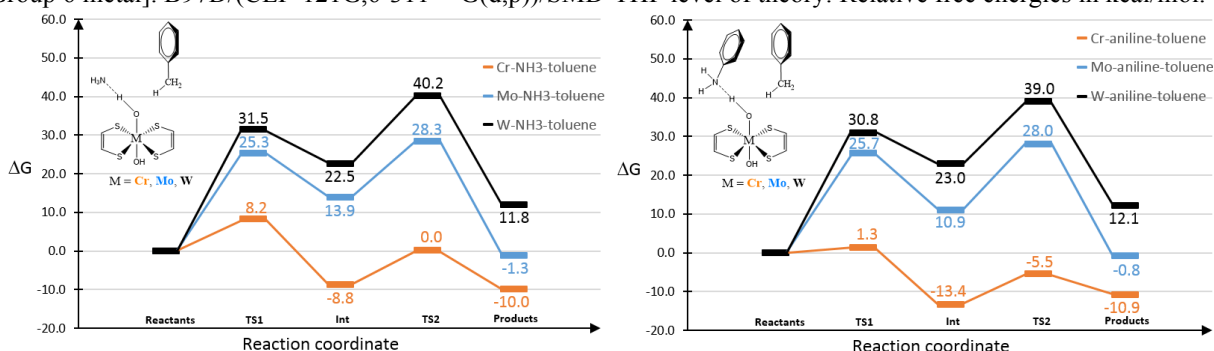
Figure 3 (left). Energy profile for ammonia-assisted hydroxylation of toluene by *trans*-M(S$_2$C$_2$H$_2$)$_2$(OH)=O [M = Group 6 metal]. B97D/(CEP-121G,6-311++G(d,p))/SMD-THF level of theory. Relative free energies in kcal/mol.
Figure 4 (right). Energy profile for aniline-assisted hydroxylation of toluene by *trans*-M(S$_2$C$_2$H$_2$)$_2$(OH)=O [M = group-6 metal]. B97D/(CEP-121G,6-311++G(d,p))/SMD-THF level of theory. Relative free energies in kcal/mol.

(2) Interestingly, for all the systems reported in Figures 1 - 4, the hydrocarbyl radical rebound transition state (**TS2**) has the higher free energy for all of the Mo and W EBDH model (average $\Delta\Delta G^{\ddagger} \sim 7$ kcal/mol), whereas it is generally switched to **TS1** for Cr models (average $\Delta\Delta G^{\ddagger} \sim -3$ kcal/mol).

(3) In general, the effect of altering the hydrocarbon substrate (in this study: methane vs. toluene) leads to more pronounced changes in the barriers as compared to changing the acid/base pair.

(4) The magnitude of the trans ligand influence is larger than those calculated for the alteration of the hydrocarbon substrate and acid/base pair, and less than the impact of metal modification.

(5) The impact of the supporting ligand for the Mo complex results in no significant changes on the activation free energy for abstracting a hydrogen atom (**TS1**) from toluene, while the free energy barrier for the rebounding tolyl radical (**TS2**) dropped by 6 kcal/mol.

(6) On average, TSs for methane activation/functionalization are ~13 kcal/mol higher than those for toluene. This largely reflects the difference in homolytic C-H bond enthalpies for the two hydrocarbons ($\Delta_{BDE} \sim 16$ kcal/mol). The lowest free energy barrier of methane hydroxylation (**TS2**) by Mo-oxo model was $\Delta G^{\ddagger} = 42.0$ kcal/mol. This is higher than desirable for a low-temperature, homogeneous, methane-to-methanol catalyst. An analysis of the free energies indicates that the relative free energies of the two transition states and the intermediate that lies between them are all positively correlated, so that synthetic strategies to reduce one barrier should positively impact to the other.

Impact: The research outlined herein was initiated by Prof. J. O. C. Jimenez-Halla, a former protégé, and now on the faculty of the University of Guanajuato. Initial results were encouraging enough that Ms. Azadeh Nazemi followed this project up as part of her doctoral research. This ACS-PRF grant has impacted the PI's research program, and revealed the critical importance of acid/base properties (of both the C—H bond of the substrate and the metal-ligand active site) in activating light alkanes by metal complexes. The ACS-PRF-spnsored research has initiated new research thrusts in the PI's group to quantify the extent to which coordination to a metal impacts the pKa of aliphatic C—H bonds and how this correlates with catalyst activity and selectivity.